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Menstrual blood VEGF, IL-6, TGF and nerve fibre as markers of adenomyosis: a literature review

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ABSTRACT

Background. Adenomyosis is a benign uterine disease characterized by the presence of endometrial glands and stroma in the myometrium. It lacks classic physical or laboratory examination findings, which hinders clinical diagnosis. Although unlikely to replace hysterectomy, transvaginal ultrasound, or MRI, menstrual blood based-biomarker testing is expected to aid in early adenomyosis detection and consequently earlier initiation of clinical management strategies.

Objective. This literature review aims to review and summarize the expression of VEGF, IL-6, TGF, and menstrual blood nerve fibre as biomarkers of adenomyosis.

Methods. We searched for literature using four database sources, published in English within the last 10 years using the following keywords: "adenomyosis" AND "VEGF" AND "IL-6" AND "TGF" AND "Nerve fiber". Data was extracted independently by the authors and then selected based on specified inclusion and exclusion criteria.

Results. Expression of VEGF, IL-6, TGF, and endomyometrial nerve fibres in patients with adenomyosis were significantly increased in patients with adenomyosis.

Conclusions. Most research results point to the expression of VEGF, IL-6, TGF, and endomyometrial nerve fibres as potential biomarkers for adenomyosis. However, future research with better methodology still needs to be conducted before routine clinical implementation.

BACKGROUND

Adenomyosis is a benign uterine disease marked by endometrial glands and stroma embedded in the myometrium, which surrounded by smooth muscle hyperplasia [1, 2]. The true prevalence of adenomyosis is unknown, as a definitive diagnosis requires histopathological examination via hysterectomy. Current estimates of prevalence range from 8.8-61.5% in patients undergoing consecutive hysterectomies over the past 50 years. Another study conducted involving 985 women undergoing

transvaginal ultrasound in the UK found that the prevalence of adenomyosis was 20.9%. It is also reported to coexist in a number of other gynaecological conditions: leiomyoma, pelvic organ prolapse, and abnormal uterine bleeding Differences in histopathologic criteria for diagnosis, different numbers of histologic tissue samples for each hysterectomy, and providers' level of awareness contribute to this broad estimation [1].

Diagnosis of adenomyosis typically begins with clinical suspicion and is confirmed through transvaginal ultrasound and pelvic MRI. Around one-third of patients with adenomyosis are asymptomatic, while others may experience heavy menstrual bleeding (most common symptom), infertility, or pelvic pain. It also lacks any classic physical examination findings or laboratory studies that would identify it as a possible diagnosis. Furthermore, sonographic assessment of adenomyosis is hindered by low reproducibility [3, 4]. Therefore, the diagnosis of adenomyosis can be challenging and ambiguous as it requires a combination of clinical evaluation, imaging, and histopathological examination, much like other uterine conditions [5-7]. Meanwhile, prompt diagnosis of adenomyosis is critical as delays may result in disease progression, increased morbidity, and impaired fertility.

Menstrual blood based-biomarker testing could enable earlier detection of adenomyosis compared to current diagnostic methods, enabling prompt initiation of clinical management strategies and fertility treatments. While unlikely to replace hysterectomy as the gold standard or imaging tools such as transvaginal ultrasound and MRI, biomarkers could still be used as adjunct in clinical decision-making [5, 8, 9]. With an understanding of molecular and clinical pathogenesis of adenomyosis, numerous potential biomarkers can be used to detect adenomyosis. This narrative review aims to examine the current evidence four adenomyosis biomarkers that have great potential which are not yet used routinely in clinical practice, namely VEGF, IL-6, TGF, and endometrial nerve fibres. These biomarkers are expected to be applied in the future in clinical practice.

MATERIALS AND METHODS

We searched the literature using four database sources: PubMed, Cochrane, Medline, and ScienceDirect that published in English between 2014 and 2024 using the following keywords: "adenomyosis" AND "VEGF" AND "IL-6" AND "TGF" AND "Nerve fiber". Additionally, snowballing and hand searching were also done. The authors independently extracted data, starting with an initial screening of titles and abstracts (**Figure 1**). If the eligibility of an article could not be determined from the title and abstract alone, they reviewed the full text to make a final assessment. The studies obtained were then selected based on the specified inclusion and exclusion criteria. The inclusion criteria of our studies were: 1) Studies investigating the basic and clinical molecular pathogenesis of adenomyosis use human specimens, 2) Expression VEGF, IL6, TGF, and endometrium blood nerve in adenomyosis. The exclusion criteria for this study include inaccessible full text forms, narrative text, or research design. Study selection and data extraction was done by all authors, with discrepancies being resolved through discussion.

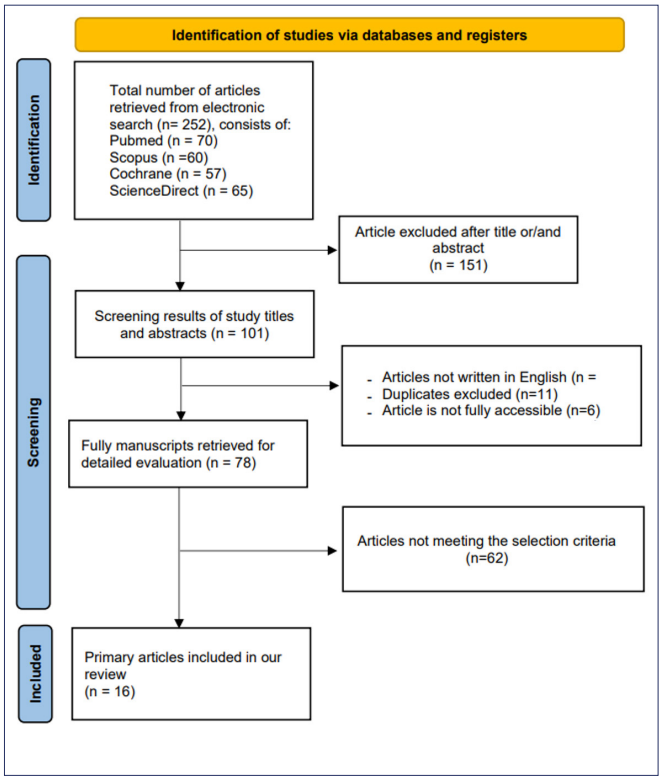

Figure 1. *Study selection process.*

RESULTS

A total of 16 articles met the research criteria and were used in this literature review study as the main findings, consisting of 6 articles discussing VEGF (**Table 1**), 3 articles discussing IL-6 (T**able 2**),

5 articles discussing TGF (**Table 3**), and 3 articles discussing endomyometrial nerve fibre (**Table 4**).

DISCUSSION

Pathogenesis of adenomyosis

There are several theories regarding the pathogenesis of adenomyosis (**Figure 2**). According to the most popular theory, adenomyosis arises from the invagination of the basalis endometrium into the myometrium, triggered by the myometrium's contractions, which cause trauma to the endometrial-myometrial junction zone (JZ), a structure that highly specialized hormone-responsive, located in the inner third of the myometrium. Persistent peristaltic myometrial contractions may induce constant microtrauma to the JZ, leading to inflammation, which in turn promotes local increases in oestrogen production and the recruitment of inflammatory mediators. Recent studies have also discovered that physiopathological mechanisms, including abnormalities in sex steroid hormones, inflammation, fibrosis, and neuroangiogenesis, may be associated to the pathogenesis of adenomyosis [10-13].

Angiogenesis is a mechanism of forming new capillaries from pre-existing blood vessels, which naturally occurs during the proliferative phase. Oestrogen plays an important role in this event through increasing cell mobilization and microvascular integration. Numerous studies have shown that increased neoangiogenesis is present in adenomyosis, as indicated by abnormalities and higher microvessel density in both ectopic and eutopic endometrium. Vascular endothelial growth factor (VEGF), a potent mitogen for endothelial cells, is highly secreted by endometrial epithelial, stromal, and perivascular cells in adenomyosis and plays a key role in angiogenesis mechanism. While VEGF is crucial for regenerating the endometrial lining after menstruation, its levels may be excessive in patients with adenomyosis [14, 15].

Additionally, two growth factors, follistatin and activin A (both part of the TGF-β family), are involved in new blood vessel formation. In adenomyosis, these factors act as proangiogenic agents by promoting the formation of new capillaries and expanding the surface area of existing ones compared to controls. Specifically, Activin A enhances VEGF production by endometrial stromal cells, altering vascularization and cause formation of

Table 1. *Summary of studies discussing VEGF as adenomyosis marker.*

Author	Year	Study Design	Sample Size	Results
Harmsen *et al.* [23]	2022	Retrospective matched case-control study	19 specimen diagnosed with adenomyosis and 19 specimen controls with unrelated pathology	There was no difference in the intensity of VEGF staining between adenomyosis and control patients
Kwack *et al.* [24]	2022	Retrospective study	A uterine sample was taken from 22 premenopausal patients with focal uterine adenomyosis. Samples were collected from three specific areas: the adenomyosis lesion, the unaffected myometrium, and the endometrial tissue just beneath the unaffected myometrium	VEGF expression was significantly higher in adenomyotic lesions and the myometrium compared to the eutopic endometrium
Yalaza *et al.* [26]	2020	Retrospective study	90 paraffin-embedded archival tissues that categorized into three groups: Group I (ectopic endometrial tissues of adenomyosis patients), (n = 35); Group II (eutopic endometrial tissues of adenomyosis patients), (n = 35); Control Group (endometrial tissues of individuals without adenomyosis), (n = 20)	There was significant difference in the level of VEGF gene expression between Group I–Group II (p = 0.036) and Group I–Control Group (p = 0.001), and there was no significant difference between Group II and Control Group (p = 0.275)
Wang *et al.* [27]	2016	Retrospective study	30 ectopic and eutopic endometrial tissues of adenomyosis patients and 10 endometrial tissues of patients without adenomyosis as control	The staining levels of VEGF in the ectopic and eutopic endometrial of patients with adenomyosis were significantly higher than in the controls
Orazov *et al.* [28]	2016	Retrospective study	Uterus specimens from 30 patients with diffuse adenomyosis accompanied by severe pelvic pain syndrome and 30 biopsies of adenomyosis patients with a painless syndrome	VEGF expression in perivascular compartment cells was found to be higher in adenomyosis patients with the painful form compared to those with the painless form
Liu *et al.* [25]	2016	Cross sectional study	Endometrial tissue specimens from 34 women with adenomyosis (excluding endometriosis) and 20 women without adenomyosis (controls)	IHC result show that staining of VEGF, were highly significantly increased in ectopic endometrium from adenomyosis patients compared to controls

VEGF: vascular endothelial growth factor; IHC: immunohistochemistry.

Table 2. *Summary of studies discussing IL-6 as adenomyosis marker.*

Author	Year	Study Design	Sample Size	Results
Jiang *et al.* [22]	2023	Retrospective study	Biopsy specimens from 10 adenomyosis patients	IL-6 expressions were detected and enhanced in adenomyosis myometrium cells that were exposed to exosomes
Kim *et al.* [30]	2019	Retrospective cohort study	Blood samples of 59 infertile women with adenomyosis	Serum IL-6 levels on the day of hCG injection were markedly higher in infertile women with adenomyosis compared to those without adenomyosis who were undergoing IVF at the same time (p = 0.01). (p = 0.01)
Jiang *et al.* [31]	2017	Retrospective study	Eutopic endometrial (EU) and Ectopic endometrial (EC) samples were derived from 30 adenomyosis patients, and endometrium samples without adenomyosis (CE) from 30 healthy patients as controls	RT-PCR analysis showed that IL-6 mRNA expression levels in EC and EU were significantly higher than in CE, with EC showing significantly higher expression than EU (p < 0.01)

IL-6: interleukin-6; hCG: human chorionic gonadotropin; IVF: in vitro fertilization; RT-PCR: reverse transcription-polymerase chain reaction; mRNA: messenger ribonucleic acid.

Table 3. *Summary of studies discussing TGF as adenomyosis marker.*

Author	Year	Study Design	Sample Size	Results
Juárez-Barber, *et al.* [34]	2022	Retrospective study	Human endometrial biopsy specimens from adenomyosis women (n = 6) and healthy women (n = 6)	Adenomyosis organoids (self-organized in vitro in 3D structures) showed there was higher expression of TGF-β2
Cheong *et al.* [37]	2019	Experimental design	Endometrium samples at secretory phase of menstrual cycle from 25 patients with adenomyosis	Expression of TGF-β1 in the stroma of adenomyotic endometrium induce collagen production in endometrium-derived fibroblasts
Cai *et al.* [36]	2019	Experimental design	Ectopic endometrial tissue samples from 40 premenopausal women with adenomyosis (28 with diffuse adenomyosis, 12 with focal adenomyosis) and endometrial samples from 40 women without endometriosis, adenomyosis, uterine fibroids	Expression of TGF-β1 was significantly elevated in adenomyosis group compared to control
Kishi *et al.* [20]	2017	Retrospective study	Biopsy specimens from 18 adenomyosis patients (8 cases occur at the inner myometrium and 10 cases occur at outer myometrium)	A significant staining of TGF-β were found only at the smooth muscle cells of subtype II adenomyosis (occur at outer myometrium)
Liu *et al.* [25]	2016	Cross sectional study	Endometrial tissue specimens from 34 women with adenomyosis (excluding endometriosis) and 20 women without adenomyosis (controls)	Adenomyotic lesions had a significantly increased staining for TGF-β1 compared to control (p < 0.001)

TGF: tumour growth factor.

Table 4. *Summary of studies discussing endomyometrial nerve fibre as adenomyosis marker.*

Author	Year	Study Design	Sample Size	Results
Yadav *et al.* [39]	2021	Prospective study	Endometrial tissue specimens of 190 patients with endometriosis, adenomyosis, or uterine fibroids (73 patients had adenomyosis) and 30 patients without endometriosis, adenomyosis, uterine fibroids	There were 10/73 (13.7%) patients in the adenomyosis group who had endomyometrial nerve fibres and a significant difference was observed in the presence of nerve fibres among these groups (endometriosis, adenomyosis, or uterine fibroid, p <0.001)
Takeuchi *et al.* [40]	2016	Experimental Design	Adenomyosis tissue samples from 12 patients divided into 6 patients who received dienogest and 6 patients who did not receive hormonal treatment for ≥3 months as the control group	The density of nerve fibres in adenomyosis lesions was significantly reduced in the dienogest group compared to the control group
Lertvikool *et al.* [42]	2014	Cross sectional study	Uterine samples from 23 reproductive age women with adenomyosis that divided into two groups, VAS ≥ 5 (moderated and severe pain) and VAS < 5 (less pain)	Nerve fibres density was significantly higher in adenomyosis patients with moderate and severe pain compared to less pain group

VAS: visual analogue scale.

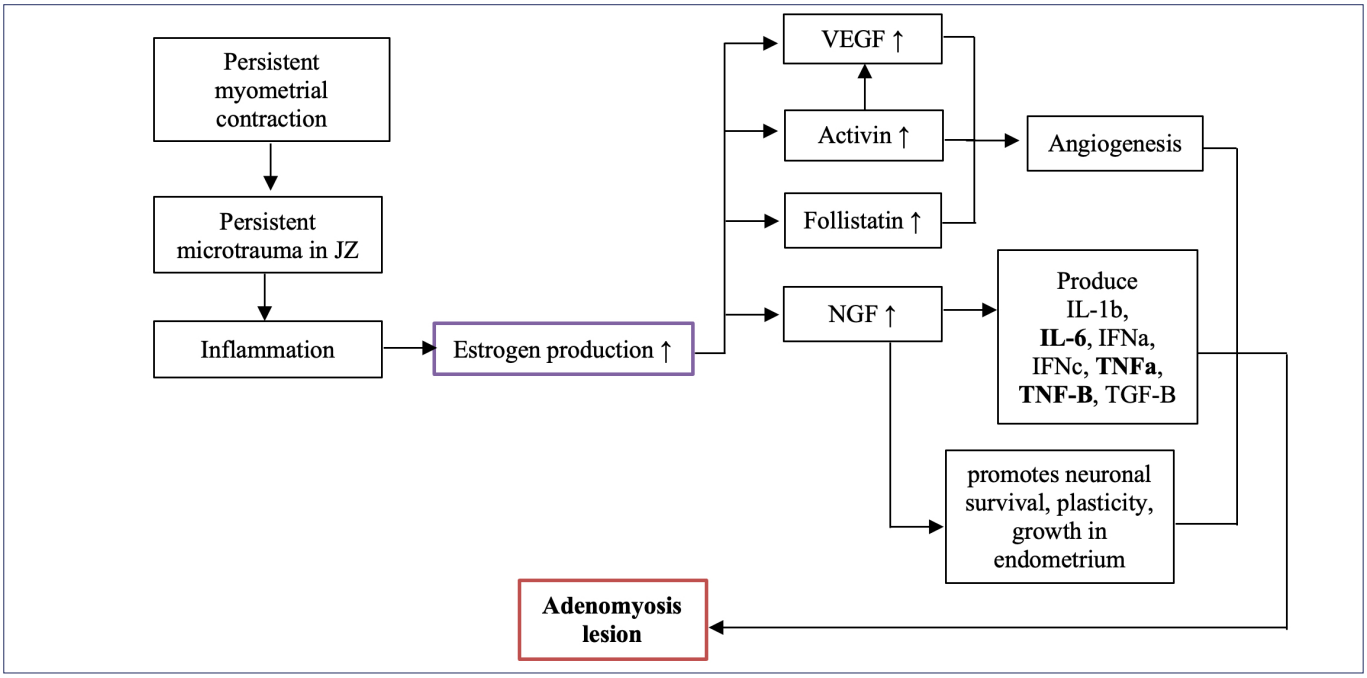

Figure 2. *Overview of pathogenesis of adenomyosis.*

new capillary. Furthermore, the mRNA expression levels of follistatin and activin type II receptors are elevated in adenomyotic nodules [11].

The increasing expression of oestrogen and TNF also trigger adenomyotic tissues to produce elevated levels of neurogenic factors, like nerve growth factors (NGF), which control the secretion of inflammatory factors, leading to mast cell growth and degranulation, producing inflammatory mediators, including IL-1b, IFNa, IFNc, IL-6, TNFa, TNF-B, TGF-B.28,30 Additionally, NGF promotes neuronal survival, plasticity, growth, and differentiation of catecholamine production in a manner that depends on the dose. Zhang *et al*. reported finding nerve fibres in the functional layer of the endometrium in women with adenomyosis who experienced pain symptoms. These nerve fibres were absent in women with asymptomatic adenomyosis. NGF may be related to these findings [11].

Menstrual blood-based biomarker

Several biomarkers have been investigated in research for diagnosing adenomyosis, but none have been implemented in clinical practice. Menstruation is the process of shedding the functional layer of the uterine lining following the luteal phase of the ovarian cycle. Endometrium is a multicellular and dynamic uterine tissue that is highly responsive to sex steroid hormones [16]. Menstrual blood offers a promising non-invasive diagnostic tool because layers of the endometrium are shed during menstruation and returned to the pelvic cavity during menstruation, simplifying and accelerating the diagnostic process [17]. Some of these biomarkers can be found in menstrual blood, including VEGF. VEGF protein is expressed in normal endometrial stromal cells, with levels rising in response to oestrogen and progesterone, which are elevated in adenomyosis [18]. Sex hormones that regulate the menstrual cycle also induce the secretion of various cytokines (such as interleukin and TGF) in the uterine endometrium, which are essential for angiogenesis, the proliferation of natural killer (NK) and T cells, decidualization, and implantation [19]. Thus, these cytokines can thus be found in menstrual blood. Additionally, nerve fibres can be detected in menstrual blood, both under physiological and pathological conditions. In pathological conditions like adenomyosis, where endometrial tissue infiltrates the muscular layer of the uterus, nerve fibres can also be released during menstruation [20]. While still under research, evidence for menstrual blood biomarkers may one day be as robust as that for biomarkers used in cervical cancer [21].

Study by Burghaus *et al*. also revealed there are other potential biomarkers for adenomyosis. Burghaus *et al*. found compared to 5 other blood-based biomarkers (HGF.aAB, Prokineticin-1, NSE, S100-A12, DNASE2.aAB), sFRP-4 was the best performing univariate biomarker with a sensitivity of 56.4% for

comparison *versus* "all symptom controls". For comparison *versus* "pathology-free symptom control", S100-A12 was the best performing univariate biomarker with a sensitivity of 74.6% [8].

VEGF as biomarker of adenomyosis

In adenomyosis, tissue injury and repair result in the accumulation of myofibroblasts in the affected myometrium, causing myometrial hypertrophy. VEGF plays a significant role in stimulating the growth of new blood vessels, supplying oxygen and nutrients to the proliferating tissue. In adenomyosis, additionally, repetitive tissue injury causes local vascular disruption and blood extravasation, leading to platelet aggregation, the formation of clots, and consequent hypoxia. In response to hypoxic stimuli, hypoxia-inducible factor-1alpha (HIF-1α), a main mediator of cellular adaptation to hypoxia, is activated [18, 22].

Macrophages also recruited to the wounding site, secrete chemotactic factors and several growth factors, including VEGF. This factor is important for cell migration and proliferation, which mediates tissue repair and is enhanced by activation of platelets releasing a series of cell growth factors and angiogenic factors, such as PDGF and VEGF. VEGF plays a crucial role in regenerating the endometrial layer after menstruation; however, it is overexpressed in patients with adenomyosis. Consequently, an increase in VEGF expression is anticipated in the myometrium of adenomyosis patients [18, 22]. While studies utilizing immunochemistry (IHC) and RT-PCR have demonstrated increased VEGF expression in adenomyotic lesions, inconsistencies remain. For instance, Harmsen *et al*. reported no difference in myometrial VEGF levels between patients with adenomyosis and control. The study also found that IHC score of VEGF was highest in the myometrium, followed by endometrial glands, and lowest in the endometrial stroma. While their study was the first to utilize multiplex IHC, the limited number of sample is a clear limitation. The samples were also only analysed based on areas of interest, which may not be representative [23]. In contrast to the result by Harmsen [23], Kwack *et al*. [24], Liu *et al*. [25], and Yalaza *et al*. [26] all also found VEGF expression levels to be elevated in adenomyotic and myometrial lesions compared with eutopic endometrium, whether from normal subjects or those with adenomyosis.

Wang *et al*. also reported similar findings, with notably higher levels of VEGF in the endometrial glandular epithelial cells of adenomyotic lesions. Additionally, the study found that the immunoreactivity of GRIM-19, a novel protein which regulates apoptosis and the formation of new blood vessels, was markedly reduced in the adenomyosis group. In adenomyosis, deficiency in expression of GRIM-19 results in decreased apoptosis and increased angiogenesis [27]. Orazov *et al*. also added that VEGF levels were significantly higher in ectopic endometrial epithelial cell and in the myometrial smooth muscle cells and stromal cells. VEGF levels were also reported to be higher than those found in abnormal uterine bleeding. These findings suggest that the neovascularization process, which is promoted by VEGF, plays a significant role in the development of pelvic pain associated with adenomyosis [28]. Future studies should further study the role of VEGF in the pathophysiology of adenomyosis, along with the role of novel proteins, such as GRIM-19. Utilization of advanced techniques such as multiplex IHC is also promising. However, retrospective design of the studies may introduce selection bias and should be addressed in subsequent studies.

IL-6 as biomarker of adenomyosis

IL-6 is a growth regulator of human endometrial stromal cells. When bound to its receptor, it activates JAK2, leading to the phosphorylation and nuclear localization of signal transducer and activation of transcription 3 (STAT3). This signalling pathway is crucial for the growth and progression of various human cancers, including endometrial carcinoma. Hyperactivation of this signalling pathway may enhance the invasive behaviour of endometrial cells in adenomyosis. Exosomes, a subtype of extracellular vesicles, function as carriers for transferring molecules such as DNA, RNA, proteins, and lipids from parental cells to recipient cells. Thus, endometrial cell-derived exosomes could facilitate communication between the endometrium and myometrium via IL-6 signalling, playing a role in the development of adenomyosis [22, 29].

Jiang *et al*. found that IL-6 expressions were enhanced in adenomyosis myometrium cells that were exposed to exosomes. Western blotting also revealed that endometrial cell exosomes are significantly increased the protein expression of IL-6, p-JAK2, JAK2, p-STAT3, STAT3, which influenced the effect of endometrial cell exosomes on AM cells. Reflecting on this, exosome inhibitors may be a future therapeutic modality in adenomyosis. IL-6

may also be directly targeted in future treatment of adenomyosis. Adenomyotic myometrium cells exposed to tocilizumab, an IL-6 inhibitor, were also observed to display apoptotic characteristics and significant reduction in survivability during the MTT assay [22]. However, there are still questions to be answered with regards to the precise mechanisms of tocilizumab and its dynamics on immune cells in adenomyosis.

Study by Kim *et al*. in patients undergoing IVF revealed higher baseline IL-6 levels in infertile adenomyosis patients with clinical pregnancy rate being significantly lower in those with higher IL-6 levels [30]. It would be interesting to explore the prognostic role of IL-6 in pregnancy and fertility among patients with adenomyosis.

Jiang *et al*. also reported RT-PCR results that showed IL-6 mRNA expression levels in ectopic and eutopic were significantly higher than in control group. Jiang *et al*. also found a significant positive correlation between IL-6 mRNA expression and TLR-1,4,5, and 9 in eutopic tissue. In EC, IL-6 mRNA expression was positively correlated with TLR-1, 2, 4, 5, 6, and 9, but did not show any significant correlation with other TLRs. These findings suggest that TLRs might potentially play a role in the inflammatory development of adenomyosis through the NK-κB-mediated signalling pathway [31, 32].

TGF as biomarker of adenomyosis

The Epithelial-mesenchymal transition (EMT) is a physiological process where epithelial cells gain the motile and invasive properties of mesenchymal cells. During embryonic development, EMT is an expected and coordinated process which involves interactions among various cells and tissues [33]. However, microenvironmental changes and abnormal stimuli may improperly activate the EMT process, contributing to the pathogenesis of adenomyosis. Transforming growth factor (TGF)-β1 and TGF-β2 may play an important role in the induction and regulation of EMT. The upregulation of these factors in the endometrium of patients with adenomyosis indicate a dysfunction during the secretory phase [34, 35].

Research conducted by Juárez-Barber *et al*. supported this notion as they reported significantly increased TGF-β2 expression in adenomyosis when evaluated by IHC [34], with Cai *et al*. and Liu *et al*. reporting comparable results [25, 36]. Furthermore, the experiment by Cai *et al*. found a negative correlation between the level of eIF3e staining and TGF-β1. According to recent research, decreased expression of eIF3e is associated with the epithelial-mesenchymal transition (EMT) process. The phenomena of EMT may be a widespread occurrence in disease progression and requires an active and ongoing TGF-β signalling pathway, which may also be a future therapeutic target with antibodies or small molecule inhibitors [36].

Results from the experiment by Cheong *et al*. suggested that TGFβ1 influences collagen production by inducing CTGF, a protein classified within the CCN family of matricellular proteins. It is a key regulator of tissue remodelling and fibrosis where impairment causes excessive extracellular matrix (ECM) synthesis which is implicated in various fibrotic conditions [37]. Elevated levels of CTGF may promote the development and fibrotic advancement of adenomyosis, which consequently lead to dysmenorrhea [38].

Endomyometrial nerve fibre as biomarker of adenomyosis

Recent research has identified fine and unmyelinated sensory nerve fibres in the functional layer of the eutopic endometrium in women with endometriosis. These nerve fibres have subsequently been observed in the peritoneal endometrioses. Study by Yadav *et al*. reported that 10 out of 73 patients (13.7%) in the adenomyosis group had nerve fibres, as indicated by positive PGP 9.5 staining. However, the percentage of women with endomyometrial nerve fibres is significantly higher in the endometriosis group [39].

Research by Takeuchi *et al.* in adenomyosis patients found significantly lower density of nerve fibres and lower NGF immunoreactivity in those receiving dienogest [40]. Dienogest, a novel progestin derived from 19-norsteroid, is highly selective for progesterone receptors and exhibits antiproliferative, immunologic, and antiangiogenic effects on endometrial tissue. It also significantly reduces chronic pelvic pain and menorrhagia in patients with adenomyosis [41]. Furthermore, Lertvikool *et al*. reported significantly increased number of nerve fibres identified by PGP9.5 staining in the myometrium of adenomyosis patients experiencing moderate to severe pain when compared to those with less pain. NGF and its receptors are crucial in mediating both neuropathological and non-neuropathological pain by promoting the growth, survival, and maintenance of sensory neurons. Studies in a mouse model have also shown that NGF-beta

is a key factor in the pathogenic mechanisms of adenomyosis [42]. These findings shed a light on the possible mechanism on how dienogest may reduce pain in adenomyosis.

Clinical implications

There are three primary ways in which measuring a biomarker in clinical care can enhance health: it can help the patients in understanding their disease, which enhances their quality of life and mental health; it can motivate patients to adopt healthier behaviours, such as better diet, increased exercise, or improved adherence to prescribed treatments; and it can assist clinicians in making better clinical decisions, such as determining appropriate treatments, which leads to better patient health. However, biomarker measurements can also have negative health outcomes through these same mechanisms (for example causing depressed mood from unfavourable news). Furthermore, these biomarkers may also have the potential to provide gynaecologic and obstetric prognostic value in the holistic management of adenomyosis. Therefore, before ordering a biomarker test, clinicians should have a clear expectation that, on average, the test will lead to improved health through one or more of these mechanisms.

CONCLUSIONS

Most of the research results point to the possibility of VEGF, IL-6, TGF, and endomyometrial nerve fibres as potential biomarkers for adenomyosis. In summary, we found these expressions were significantly increased in patients with adenomyosis compared to the control group (without adenomyosis). VEGF and endomyometrial nerve fibres may play an important role in pain in adenomyosis [43,44]. However, more evidence backed by better research methodology is still necessary before routine clinical application, such as by employing an experimental design and blinding. This would also better resolve the conflicting findings seen between authors.

COMPLIANCE WITH ETHICAL STANDARDS

Authors' contribution

A.R.: Conceptualization. Y.I.A.: Data curation, formal analysis, investigation, project administration, resources, software, visualization, writing - original draft, writing - review & editing. D.T.: Methodology. A.R., D.T.: Supervision, validation.

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Study registration

N/A.

Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

N/A.

Informed consent

N/A.

Data sharing

N/A.

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