＜特集「医学系研究における画像解析と臨床への応用」＞

Association Between Uterine Adenomyosis and Infertility: Role of Axonemal Alteration in Apical Endometria

Khaleque N Khan *

Department of Obstetrics and Gynecology,
Kyoto Prefectural University of Medicine Graduate School of Medical Science
The Clinical and Translational Research Center, University Hospital,
Kyoto Prefectural University of Medicine (CTREC)

Abstract

Uterine adenomyosis is an estrogen-dependent chronic inflammatory condition and may cause painful symptoms, abnormal uterine bleeding and/or subfertility/infertility. It is characterized by the presence of endometrial glands and stroma within the myometrium causing enlargement of the uterus as a result of reactive hyperplastic and/or hypertrophic change of the surrounding myometrium. Similar to endometriosis, adenomyosis has a negative impact on female fertility. Abnormal utero-tubal sperm transport, tissue inflammation, and toxic effect of chemical mediators have been proposed as contributing factors. Inflammation-induced damage of mucosal cilia in the Fallopian tube has been reported. Besides other proposed mechanisms, our most recent study with transmission election microscopic (TEM) analysis indicated that microvilli damage and an axonemal alteration in the apical endometria occur in response to endometrial inflammation. This may be involved in the negative fertility outcome in women with adenomyosis. We present a critical analysis of the literature data concerning the mechanistic basis of infertility in women with adenomyosis and its impact on fertility outcome.

Key Words: Uterine adenomyosis, Infertility, Inflammation, Microvilli, Microtubule.

Introduction

Uterine adenomyosis is a benign estrogen-dependent gynecological disease characterized by the presence of endometrial glands and stroma within the myometrium and may cause painful symptoms, abnormal uterine bleeding and/or subfertility/infertility[1)2)]. Although exact pathogenesis is still controversial, it is a common understanding that while endometriosis originates from the functionalis endometrium, adenomyosis develops as a down-growth and invagination of the basalis endometrium into the myometrium[3)4)]. A panel of mechanisms has been reported indicating tissue damage or injury at the endometrial-myometrial interface (EMI), leading to inflammation, local estrogen production and development of adenomyosis[5-8)]. Adenomyosis

Received: September 12, 2022. Accepted: September 13, 2022
* Correspondence address: Khaleque N Khan Department of Obstetrics and Gynecology The Clinical and Translational Research Center Graduate School of Medical Science Kyoto Prefectural University of Medicine 465 Kajii-cho, Kamigyo-ku, Kyoto 602-8566, Japan
nemokhan@koto.kpu-m.ac.jp
doi:10.32206/jkpum.131.12.985

commonly occurs during the fourth and fifth decades of life and after the completion of childbearing activity, however, recent imaging modalities such as trans-vaginal ultrasonography and magnetic resonance imaging (MRI) have indicated that adenomyosis may occur in women of younger ages[9)10)]. Endometriosis and adenomyosis are closely related diseases with variable coexistence rates depending on the endometriosis phenotype involved[11-13)]. Endometriosis and adenomyosis share a number of features in terms of symptomatology, histology, and molecular alterations[14-16)], albeit, they are several differences in their pathogenesis and pathogenic mediators[17)].

The incidence rate adenomyosis is widely variable. Histological examination of hysterectomy specimens revealed that the prevalence of adenomyosis varies between 5% and 70%. This variation may be due to the difference in diagnostic criteria used and the techniques used to procure myometrial samples[18-20)]. In a separate study with data over the last 50 years demonstrated that the estimated prevalence of adenomyosis among consecutive hysterectomy patients ranged from 8.8% to 61.5%[5)]. Adenomyosis appears in different configuration such as diffuse, focal and rare cases of cystic adenomyoma and is better detected by MRI[1)21)22)]. Recently, four subtypes of adenomyosis is proposed based on the clinical experience and assessment by MRI/histology. Among them, intrinsic adenomyosis (subtype I) is considered as a product of direct endometrial invasion involving inner-mid myometrium and extrinsic adenomyosis (subtype II) as endometriotic lesion coming from outside involving outer myometrium and is confirmed by separate study from our laboratory[23)24)]. Despite its prevalence and the severity of symptoms, little information is available on the etiology/pathogenesis of adenomyosis and our knowledge is insufficient on the factors related to negative fertility outcome in women with adenomyosis. An updated information on the etiology and pathogenesis of adenomyosis is reported elsewhere (1). In this review article, we aim to summarize our current understanding on factors that might be associated with infertility. In this article, a comprehensive review was performed with a literature search using PubMed for all publications in English, related to adenomyosis and infertility, from inception to April 2021.

Association with infertility

Female infertility and subfertility are clinical conditions associated with a significant economic and psychosocial impact[25-27)]. There are many gynecological diseases that influence infertility including endometriosis[28)], ovulatory dysfunction[29)], tubal factor[30)], endocrine disruption[31)], reduced endometrial receptivity[32)33)], and age-related infertility[34)]. The infertility is highly prevalent among women with endometriosis (25-50%), its etiology is ambiguous and the exact mechanisms driving infertility are unclear, as the majority of women with endometriosis are able to conceive but with reduced fertility[28)35)]. Similarly the mechanisms causing infertility or subfertility in women with adenomyosis are elusive, because majority of women with adenomyosis are multiparous. Approximately, 20% of cases of adenomyosis involve women younger than 40 and 80% are aged 40 to 50 years, when they almost complete their childbearing activity[36)]. Recently, however, an association between adenomyosis and infertility has emerged. With the advent of non-invasive diagnosis with MRI and TVUS, the role of adenomyosis in infertility and early pregnancy was better recognized[37)38)].

A potential concern exists in the majority of reported studies to find an association between adenomyosis and infertility as adenomyosis commonly coexists with other pathologic processes linked to infertility such as endometriosis, polyps or leiomyomas[39)]. Endometriosis is reported to occur in 54-90% of cases with adenomyosis[40)41)].

Therefore, we cannot avoid the bias that cause of infertility is due to concurrent endometriosis rather than adenomyosis, because endometriosis is a well-known condition to cause infertility[42]. However, a study with baboons showed a strong association between histological adenomyosis and lifelong infertility even in cases when coexisting endometriosis was excluded[43]. This was confirmed in another study of women who received embryos created through oocyte donation. In this study, the miscarriage rate was significantly higher in groups of women who had adenomyosis alone versus those with co-existing endometriosis or controls[44]. A recent meta-analysis further concluded that adenomyosis has a detrimental effect on clinical outcomes of in vitro fertilization[45].

Proposed mechanisms

A recent trend is that women delay their first pregnancy until they are aged in their late 30s or early 40s and as such adenomyosis has been diagnosed with increasing frequency in infertile women[46]. Although the exact mechanism behind the relationship between adenomyosis and infertility is still unclear, a number of factors has been proposed and focused on four putative pathways: (i) Intrauterine abnormities and increased uterine peristalsis causing abnormal utero-tubal sperm transport. Intrauterine anatomical distortion caused by uterine hyperperistalsis and inflammation-induced adnexal adhesion may block the tubal ostia and potentially impair sperm migration and embryo transport. The abnormal myometrial contraction waves leads to abnormal sperm transport through the uterine cavity and may also lead to intrauterine pressure[46-48]. (ii) Abnormal endometrial steroid metabolism, increased inflammatory response, and increased intrauterine oxidative stress environment leading to altered endometrial function and receptivity[32)33)]. The increased density of macrophages (Mϕ) increases inflammatory response of the endometrium and release of reactive oxygen species that are thought to be embryotoxic[49]. (iii) Impairment of implantation may result from inflammation, a lack of adequate expression of adhesion molecules (integrins), reduced expression of implantation markers such as leukemia inhibitory factor (LIF), and altered function of the gene for embryonic development (HOXA10)[50]. (iv) Occurrence of chronic endometritis (CE) resulting from intrauterine microbial infection may be associated with negative fertility outcome in women with adenomyosis[51].

Recent studies have shown a correlation between CE and reproductive failures such as recurrent implantation failures (RIF) after IVF-ET, recurrent miscarriage and unexplained infertility[52)53)]. The major cause of CE is microbial infection in the uterine cavity. This is supported by the fact that treatment with antibiotics is effective to eliminate plasma cells in the affected patients[53-55]. A multicenter cohort study in Japan reported higher incidence of uterine infection in patients with diffuse adenomyosis that may result in the occurrence of chronic endometritis (CE) in these women[56]. Although it is controversial about the causality between CE and embryo implantation failure, reports suggest that CE negatively affects reproductive outcome. A recent study provides the first piece of clinical evidence that a variable rate of chronic endometritis (CE) occurs in women with different types of adenomyosis such as focal/diffuse adenomyosis and intrinsic/extrinsic adenomyosis[51]. These findings indicated that a variable occurrence of CE in different types of adenomyosis may be involved in negative fertility outcome.

Similar to endometriosis where inflammation is a common factor associated with infertility and chronic pelvic pain, a similar inflammatory response of the endometrium may play a significant role in the adverse reproductive outcome in women with adenomyosis[44-48]. In contrast to

women with endometriosis, adenomyosis has not yet been shown to have an adverse influence on oocyte function or folliculogenesis[57]. In patients with endometriosis, different inflammatory markers (macrophages, prostaglandins, IL-1, IL-6, TNF α) were increased in the peritoneal fluid and their high concentrations may negatively affect oocyte function[58-60]. However, no association has been found so far between adenomyosis and oocyte quality and/or function.

Role of microvilli and axonemal alteration

A successful spontaneous conception requires normal function of endometrium and Fallopian tube and this contributes to a physiologically optimized environment for fertilization and early embryonic development. This provides a conduit for the gametes to convene and for the embryo to reach the uterine cavity[61]. The successful capture and/or migration of sperm and embryo may be achieved by the efficient microtubule-mediated movement of microvilli in the apical surface of endometrium[62]. Adenomyosis-induced local inflammation is one of the biological bases for a negative impact of adenomyosis on fertility[63]. Negative fertility outcome in women with adenomyosis could be due to tissue inflammation of the endometrium and/or toxic effect of chemical mediators as released by different immune cells[58-60]. If these embryotoxic chemical mediators diffuse to the apical endometrial cells, they may cause structural damage to the apical microvilli and its core bundles of microtubules[62]. In fact, inflammation-induced damage of mucosal cilia in the Fallopian tube has been described in women with ectopic pregnancy and salpingitis[61].

A longitudinal bundle of microtubules is encased at the core of the microvilli ultra-structure, known as axoneme. Similar to Fallopian tube, these microtubules are arranged in a 9+2 pattern in which nine peripheral microtubule doublets surround a core of two central single microtubules[64-67]. Each doublet microtubule consists of an A and a B component. Extending from each A microtubule to the B microtubule of the adjacent doublet, is a dynein arm; these dynein arms, depending on whether they anchor to the inner or outer side of the A microtubule, are called inner dynein arm (IDA) or outer dynein arm (ODA), respectively. The energy required for microvilli or cilia movement is derived from ATP hydrolysis through ATPs activity of ODA causing transformation of chemical energy from ATP into a mechanical movement of the single microvillus[61)68]. The sliding movements between peripheral doublets are transmitted through a different ultra-structural component, called radial spokes, to the central part of the axoneme (central microtubules), resulting in microvilli bending[68]. It can be noted that any abnormality in the 9+2 arrangement of microtubules in the microvilli or its core component may impair ciliary/microvilli movement of Fallopian tube or endometrium. An ultra-structural diagrammatic representation of an axoneme with 9+2 arrangement of microtubules (A) and axonemal arrangement in the apical endometria collected from a control woman (B) and a woman with diffuse adenomyosis (C), as detected by transmission electron microscopy (TEM), are shown in Fig. 1.

In an attempt to find an association between endometrial inflammation, microvilli damage and an axonemal alteration in the apical endometria, a recent prospective cohort study was performed using endometria derived from women with and without adenomyosis[62]. An in-depth evaluation with TEM found that comparing to control endometria, number of microvilli on the apical epithelial cells of endometria collected from women with focal and diffuse adenomyosis was significantly decreased in response to endometrial inflammation[62]. A separate analysis showed that number of microvilli on the apical endometria

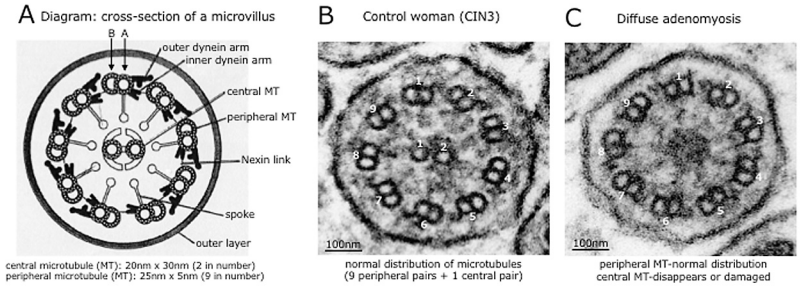

Figure 1. Transmission electron microscopy (TEM) shows distribution of microtubules (MT) after cross section of a single microvillus. (A) Diagrammatic representation of normal arrangement of microtubules (9 pairs of peripheral microtubules+1 separated central pair). (B) Distribution of microtubules in endometria of control women. Normal distribution of 9 pairs of peripheral MT and one pair of central MT (marked by numbers) in a microvillus of endometria collected from control women (CIN3). (C) Distribution of microtubules in endometria of adenomyosis. Abnormal distribution of MT in a microvillus collected from the endometria of diffuse adenomyosis showing that central pair of MT is either disappeared or damaged.

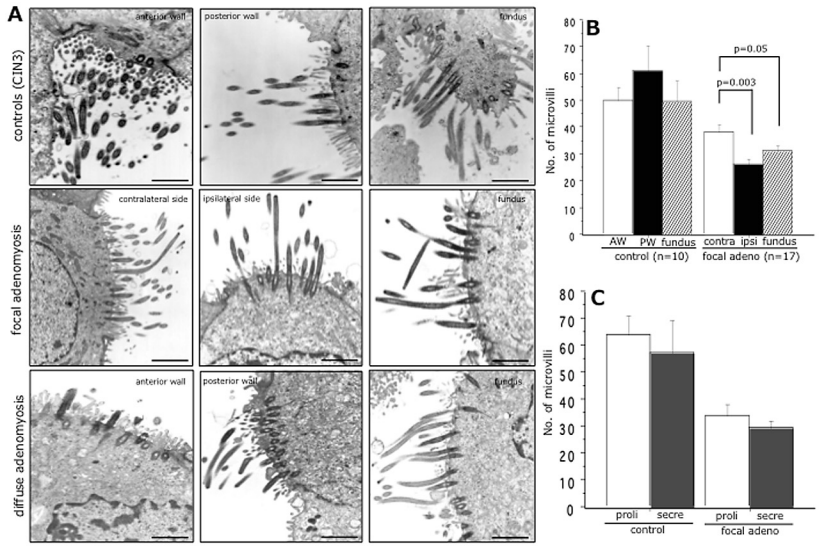

Figure 2. (A) Transmission electron microscopic analysis of microvilli in apical endometria. Transmission electron microscopy (TEM) shows distribution of microvilli in the different anatomical sites of endometria collected from control women with CIN3 (upper row)), focal adenomyosis (middle row), and diffuse adenomyosis (lower row). (B) Number of microvilli in each anatomical sites of control women and women with focal adenomyosis. (C) Distribution of microvilli based on phases of the menstrual cycle of women with CIN3 and focal adenomyosis. There was no significant difference in the number of microvili between proliferative phase and secretory phase of these two groups of women. Scale bar=1 μm for each slide (A). The results are expressed as mean ± SEM.

was significantly decreased on the ipsilateral side of focal adenomyosis than that on the contralateral side (Fig. 2 A, B). There was no significant difference in the distribution of microvilli in any anatomical site of endometria collected from control women and these findings were independent of the phases of the menstrual cycle (Fig. 2 B, C)).

While contralateral side displayed significantly less abnormal microtubules, ipsilateral side of focal adenomyosis showed significantly higher abnormal comparing to normal patterns of microtubules (Fig. 3, middle and lower row). In three cases of control women with CIN3, there was no abnormal microtubule as detected by TEM (Fig. 3, upper row). These findings were consistent with strong tissue inflammatory reaction in endometria collected from women with focal and diffuse adenomyosis comparing to that of control women with both fibroids and CIN3[62]. In fact, significantly less tissue infiltration macrophages was observed in the endometria of women with CIN3 than in endometria of women with focal adenomyosis and difuse adenomyosis[62]. Interestingly, endometria collected from symptomatic women with focal adenomyosis showed significantly increased tissue inflammatory reaction comparing to that of asymptomatic women[62]. These biological and ultra-structural abnormal findings in the endometria may be associated with negative fertility outcome in women with adenomyosis. The distribution of abnormal axonemal arrangements was more frequently observed in women with symptomatic adenomyosis than that in asymptomatic women. The detail distribution of normal and

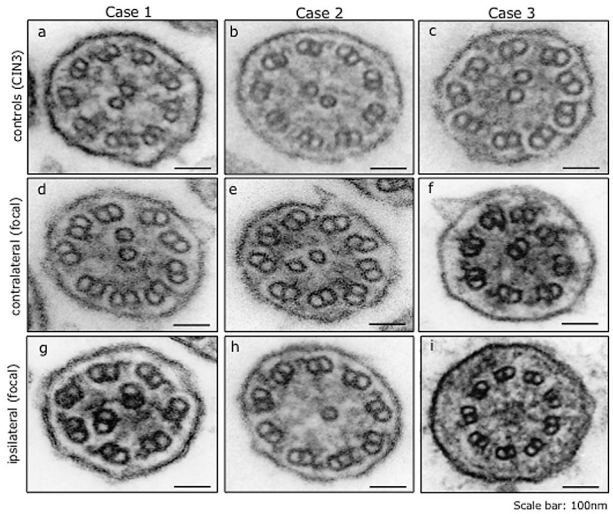

Figure 3. Shows distribution of microtubules in different cases with CIN3 and adenomyosis. Transmission electron microscopy (TEM) shows distribution of microtubules (MT) in the microvilli of endometria collected from three different cases of control women (CIN3) (upper row), contralateral side (middle row) and ipsilateral side (lower row) of focal adenomyosis. All 3 cases from control women (a, b, c) showed normal distribution of MT (9 peripheral pairs+1 separated central pair). Two cases from contralateral side showed normal distribution of MT (d, e) and one case (f) shows abnormal distribution (distorted alignment of peripheral MT and central MT disappears). All 3 cases from ipsilateral side showed abnormal distribution of MT (g, alignment distorted in peripheral MT; h, peripheral MT-intact but one arm of central MT disappears; i, peripheral MT-intact but central MT is disappeared or damaged). Scale bar=100nm for each slide.

Table 1. Distribution of normal and abnormal microtubules

	normal microtubules	abnormal microtubules	P value
Controls (CIN3) (n=10), n (%)	10 (100)	0 (0)	0.0000
Adenomyosis (n=20), n (%)	5 (25)	15 (75)	0.0016
Focal adenomyosis (n=17):			
contralateral side, n (%)	14 (82.3)	3 (17.7)	0.0002
ipsilateral side, n (%)	5 (29.4)	12 (70.6)	0.0164
Diffuse adenomyosis (n=3)			
anterior wall, n (%)	0 (0)	3 (100)	0.1336
posterior wall, n (%)	0 (0)	3 (100)	0.1336
Symptomatic (n=16), n (%)	3 (18.7)	13 (81.3)	0.0004
Asymptomatic (n=4), n (%)	3 (75)	1 (25)	0.1573

Data were analyzed by Chi-squared test. CIN3, cervical intraepithelial neoplasia grade 3

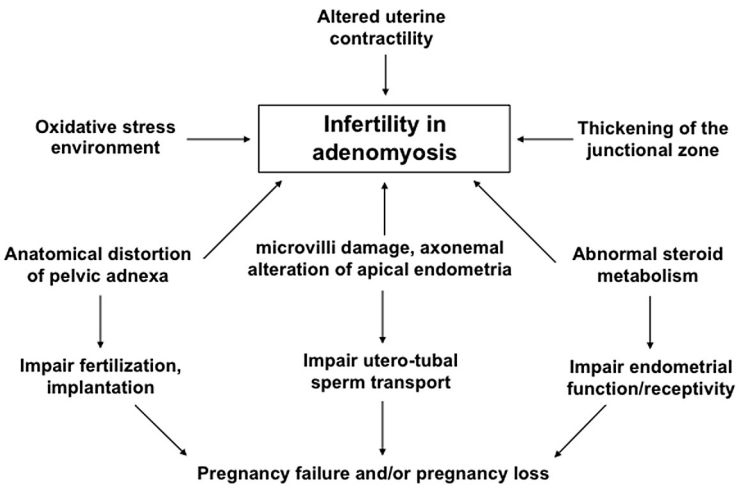

Figure 4. Represents different mechanistic bases that have been proposed and may be involved in the occurrence of negative fertility outcome in women with adenomyosis.

abnormal microtubules in the apical endometria of women with and without adenomyosis is shown in Table 1.

An Italian study demonstrated that clinical pregnancy rate, implantation rate, and live birth rate are not impaired in asymptomatic women with adenomyosis comparing to groups of women without adenomyosis in IVF cycles[69]. On the other hand, a systemic review and meta-analysis targeting IVF outcome suggested that women with symptomatic adenomyosis have a 28% reduction in the likelihood of clinical pregnancy rate

(RR=0.72; 95% CI, 0.55-0.95) and two fold increase in the risk of miscarriage (RR=2.12; 95% CI, 1.20-3.75)[70]. These findings indicate that complain of symptoms may be associated with a causal link between adenomyosis and infertility. Our findings may support the mechanistic basis of these ART clinical trials[69][70]. In addition to other mechanistic links as mentioned above, the ultra-structural abnormalities of microvilli and microtubules in the apical endometria in response to tissue inflammatory reaction may clarify the possible association between negative fertility outcome and adenomyosis. The possible mechanisms that might be involved in infertility in women with adenomyosis are shown in Fig. 4.

Conclusion and future perspective

With the elapse of more than one hundred and fifty years since the report of Von Rokitanski in 1860, most of the literatures still claim that the pathogenesis and pathophysiology of endometriosis and adenomyosis is unclear. Despite abundant publications, lack of standardized histopathologic criteria for diagnosis and variable number of histologic tissue samples evaluated per hysterectomy lags behind exact information on the true incidence rate of adenomyosis. However, the bulk of recent evidence has improved our knowledge greatly on the pathogenesis and supports that among many hypotheses, adenomyosis most commonly results from direct invasion of gland cells of endometrial basalis layer deep into the myometrium by repeated tissue injury and repair at the endo-mymetrial interface[3].

Most of the studies investigating adenomyosis as a possible cause of infertility have focused on the comparison of clinical outcomes of ART procedures between affected and non-affected infertile women. The rationale for this approach is that it allows evaluating the influence of adenomyosis on embryo implantation. The biological basis for a negative impact of adenomyosis on fertility may include one of the followings: adenomyosis-induced local inflammation, impairment of utero-tubal sperm transport, altered endometrial function/receptivity, dysregulation of local hormonal metabolism leading to hyperestrogenic mileu. According to our most recent information, an endometrial inflammation-induced microvilli damage and an axonemal alteration in the apical endometria may clarify a link between adenomyosis and negative fertility outcome. These recent findings may be clinically useful during counseling with symptomatic patients with adenomyosis who are planning for future pregnancy.

Unfortunately, there are several factors that make it difficult to investigate the relationship between adenomyosis and infertility: (i) the incidence of adenomyosis is not correctly known, (ii) universally accepted diagnostic criteria for adenomyosis are still lacking, (iii) adenomyosis often coexists with endometriosis and/or uterine fibroids. There is an unmet need for adequately designed prospective studies in order to improving our knowledge of this polymorphic disease, consequently establish more effective therapeutic strategies and to evaluate the cause-effect relationship between adenomyosis and infertility.

Acknowledgement

The authors thank Dr. Akira Fujishita of Saiseikai Nagasaki Hospital, Nagasaki and Prof. Taisuke Mori/Dr. Akemi Koshiba of Kyoto Prefectural University of Medicine, Kyoto or their kind assistance in collecting biopsy samples and stimulating discussion. The authors thank Prof. Masahiro Nakashima and Dr. Katsuya Matsuda of Department of Molecular and Diagnostic Pathology, Atomic Bomb Disease Institute, Nagasaki University School of Medicine, Nagasaki, Japan for their kind assistance in sample preparation, experiments and discussion. The authors thank Dr. Takashi Suematsu of Central

Electron Microscopy Laboratory, Nagasaki University Graduate School of Biomedical Sciences in Nagasaki for kind assistance in sample preparation and electron microscopic study. The authors thank Prof. Satoshi Teramukai and Dr. Go Horiguchi of Department of Biostatistics, Kyoto Prefectural University of Medicine for their excellent assistance in data analysis and interpretation. The authors also thank Prof. Kyoko Itoh and Ms. Miyuki Mori of the Department of Pathology and Applied Neurobiology, Kyoto Prefectural University of Medicine for their excellent technical assistance and discussion on histological and immunohistological findings.

Author contributions

KNK contributes to conceptualization, study design, supervision, data interpretation and manuscript writing and editing.

Funding

This work was supported in part by Grants-in-aid for Scientific Research (Grant Nos. 24592474, 15K10675, 18K09268 to KNK) from the Japan Society for the Promotion of Science (JSPS).

Disclosure statement

The author declares no conflict of interests related to this article.

References

1) Khan KN, Fujishita A, Mori T. Pathogenesis of human adenomyosis: current understanding and its association with infertility. J Clin. Med. 11: 4057, 2022. (doi.org/10.3390/jcm11144057)
2) Ferenczy A. Pathophysiology of adenomyosis. Hum Reprod Update 4: 312-322, 1998.
3) Khan KN, Kitajima M, Hiraki K, Fujishita A, Nakashima M, Masuzaki H. Involvement of hepatocyte growth factor-induced epithelial-mesenchymal transition in human adenomyosis. Biol Reprod 92(2): 35, 1-11,2015.
4) Khan KN, Fujishita A, Kitajima M, Masuzaki H, Nakashima M, Kitawaki J. Biological differences between functionalis and basalis endometria in women with and without adenomyosis. Eur J Obstet Gynecol Reprod Biol. 203: 49-55, 2016.
5) Upson K, Missmer SA. Epidemiology of adenomyosis. Semin Reprod Med. 38: 89-107, 2020.
6) Guo SW. The pathogenesis of adenomyosis vis-à-vis endometriosis. J Clin Med. 9: 845-863, 2020.
7) Garcia-Solares J, Donnez J, Donnez O, Dolmans MM. Pathogenesis of uterine adenomyosis: invagination or metaplasia? Fertil Steril 109: 371-379, 2018.
8) Zhai J, Vannuccini S, Petralgia F, Giuduce LC. Adenomyosis: mechanisms and pathogenesisi. Semin Reprod Med. 38: 129-143, 2020.
9) Bergeron C, Amant F, Ferenczy A. The pathology and physiopathology of adenomyosis. Best Pract Res Clin Obstet Gynecol 20: 511-521, 2006.
10) Exacoustos C, Manganaro L, Zupi E. Imaging for the evaluation of endometriosis and adenomyosis. Best Pract Res Clin Obstet Gynecol 28: 655-681, 2014.
11) Chapron C, Tosti C, Marcellin L, Bourdon M, Lafay-Pillet MC, Millscher AE, Streuli I, Borghese B, Petralgia F, Santulli P. Relationship between the magnetic resonance imaging appearance of adenomyosis and endometriosis phenotypes. Hum Reprod 32: 1393-1401, 2017.
12) Leyendecker G, Bilgicyildirim A, Inacker M, Stalf T, Huppert P, Mall G, Bottcher B, Wildt L. Adenomyosis and endometriosis. Re-visiting their association and further insights into the mechanisms of auto-traumatisation. An MRI study. Arch Gynecol Obstet. 291: 917-932, 2015.
13) Kunz G, Beil D, Huppert P, Noe M, Kissler S, Leyendecker G. Adenomyosis in endometriosis-prevalence and impact on fertility. Evidence from magnetic resonance imaging. Hum Reprod 20: 2309-2316, 2005.
14) Li B, Chen M, Liu X, Guo SW. Constitutive and tumor necrosis factor-alpha induced activation of nuclear factor kappa-B in adenomyosis and its inhibition by andrographolide. Fertil Steril 100: 568-577, 2013.
15) Donnez O, Van Langendonckt A, Defrere S, Colette S, Van Kerk O, Dehoux JP, Suifflet J, Donnez J.

Induction of endometriosis nodules in an experimental baboon model mimicking human deep nodular lesions. Fertil Steril. 99: 783-789.e3, 2013.
16) Donnez O, Orellana R, Van Kerk O, Dehoux JP, Donnez J, Dolmans MM. Invasion process of induced deep nodular endometriosis in an experimental baboon model: similarities with collective cell migration? Fertil Steril. 104: 491-497.e2, 2015.
17) Benagiano G, Brosens I, Habiba M. Structural and molecular features of the endomyometrium in endometriosis and adenomyosis. Hum Reprod Update 20: 386-402, 2014.
18) Azziz R. Adenomyosis: current perspectives. *Obstet Gynecol Clin North Am* 16: 221-235, 1998.
19) Vercellini P, Vigano P, Somigliana E, Daguati R, Abbiati A, Fedele L. Ademonyosis: epidemiological factors. Best Pract. Res. Clin. Obstet. Gynecol. 20: 465-477, 2006.
20) Bergholt T, Eriksen L, Berendt N, Jacobsen M, Hertz JB. Prevalence and risk factors of adenomyosis at hysterectomy. Hum Reprod 16: 2418-2421, 2002.
21) Khan KN, Fujishita A, Koshiba A, et al. Biological differences between focal and diffuse adenomyosis and response to hormonal treatment. Reprod Biomed Online 38: 634-646, 2019.
22) Gordts S, Brosens JJ, Fusi L, Benagiano G, Brosens I. Uterine adenomyosis: a need for uniform terminology and consensus classification. Reprod Biomed Online 17: 244-248, 2008.
23) Kishi Y, Suginami H, Kumamori R, Yabuta M, Suginami R, Taniguchi F. Four syptypes of adenomyosis assessed by magnetic resonance imaging and their specification. Am J Obstet Gynecol 207: 114, e1-7, 2012.
24) Khan KN, Fujishita A, Koshiba A, et al. Biological differences between intrinsic and extrinsic adenomyosis with coexisting deep infiltrating endometriosis. Reprod Biomed Online 39: 343-353, 2019.
25) Hasanpoor-Azghdy SB, Simber M, Vedadhir A. The emotional-psychological consequences of infertility among infertile women seeking treatment: results of a qualitative study. Iran J Reprod Med 12: 131-138, 2014.
26) ESHRE Capri Workshop Group. Economic aspects of infertility care: a challenge for researchers and clinicians. Hum Reprod 30: 2243-2248, 2015.
27) Njagi P, Groot W, Arsenijevic J, Dyer S, Mburu G, Kiarie J. Economic costs of infertility care for patients in low-income and middle-income countries: a systematic review protocol. BMJ Open 10: e042951, 2020.
28) Bulletti C, Coccia ME, Battistoni S, Borini A. Endometriosis and infertility. J Assist Reprod Genet. 27: 441-447, 2010.
29) Urman B, Yakin K, Ovulatory disorders and infertility. J Reprod Med. 51: 267-282, 2006.
30) Briceag I, Costache A, Purcarea VL, Cergan R, Dumitru M, Briceag I, Sajin M, Ispas AT. Current management of tubal infertility: from hysterosalpingography to ultrasonography and surgery. J Med Life 8: 157-159, 2015.
31) Kairo BN. Impaired fertility caused by endocrine dysfunction in women. Endocrinol Metab Clin North Am. 32: 573-592, 2003.
32) Lessey BA, Palomino WA, Apparao KBC, Young SL, Lininger RA. Estrogen-receptor-alpha (ER-alpha) and defects in uterine receptivity in women. Reprod Biol Endocrinol. 4: S9, 2006.
33) Tremellen KP, Russell P. The distribution of immune cells and macrophages in the endometrium of women with recurrent reproductive failure II: adenomyosis and macrophages. J Reprod Immunol 93: 58-63, 2012.
34) Zegars-Hochschild F, Adamson GD, Dyer S, Racowsky C, de Mouzon J, Sokol R, Rienzi L, Sunde A, Schmidt L, Cooke ID, Simpson JL, van der Poel S. The international glossary on infertility and fertility care, 2017. Hum Reprod 32: 1786-1801, 2017.
35) Prescott J, Farland LV, Tobias DK, Gaskins AJ, Spiegeiman D, Chavarro JE, Rich-Edwards JW, Barbieri RL, Missmer SA. A prospective cohort study of endometriosis and subsequent risk of infertility. Hum Reprod 7: 1475-1482, 2016.
36) Bird CC, McElin TW, Manalo-Estrella P. The elusive adenomyosis of the uterus-revisited. Am J Obstet Gynecol. 112: 583-593, 1972.
37) Dueholm M, Lundorf E, Hansen ES, Sorensen JS, Ledertoug S, Olesen F. Magnetic resonance imaging and transvaginal ultrasonography for the diagnosis of adenomyosis. Fertil and Steril 76: 588-594, 2001.
38) Devlieger R, D'Hooghe T, Timmerman D. Uterine adenomyosis in the infertility clinic. Hum Reprod Update 9: 139-147, 2003.
39) Pervez SN, Javed K. Adenomyosis among samples from hysterectomy due to abnormal uterine bleeding. J Ayub Med Coll Abbottabad 25: 68-70, 2013.
40) De Souza NM, Brosens JJ, Schwieso JE, Paraschos T, Winston RM. The potential value of magnetic resonance

imaging in infertility. Clin Radiol 50: 75-79, 1995.
41) Kunz G, Beil D, Huppert P, Noe M, Kissler S, Leyendecker G. Adenomyosis in endometriosis-prevalence and impact on infertility: evidence from magnetic resonance imaging. Hum Reprod. 20: 2309-2316, 2005.
42) Tomassetti C, Meuleman C, Timmerman D, D' Hooghe T. Adenomyosis and subfertility: evidence of association and causation. Semin Reprod Med. 31(102): 101-108, 2013.
43) Barrier BF, Malinowski MJ, Dick EJ Jr., Hubbard GB, Bates GW. Adenomyosis in the baboon is associated with primary infertility. Fertil Steril 82 (Suppl. 3): 1091-1094, 2004.
44) MartAnez-Conejero JA. Morgan M, Montesinos M, Fortunio S, Meseguer M, Simon C, Horcajadas J, Pellicer A. Adenomyosis does not affect implantation, but is associated with miscarriage in patients undergoing oocyte donation. Fertil Steril 96: 943-950, 2011.
45) Younes G, Tulandi T. Effects of adenomyosis on in vitro fertilization treatment outcomes: a meta-analysis. Fertil Steril 108: 483-490, 2017.
46) Harada T, Khine YM, Kaponis A, Nikellis T, Decavalas G, Taniguchi F. The impact of adenomyosis on women's fertility. Obstet Gynecol Surv. 71: 557-568, 2016.
47) Kunz G, Beil D, Hupert P, Leyendecker G. Structural abnormalities of the uterine wall in women with endometriosis and infertility visualized by vaginal sonography and magnetic resonance imaging. Hum Reprod. 15: 76-82, 2000.
48) Brosens J, Verhoeven H, Campo R, Gianaroli L< Gordt S, Hazekamp J, Hagglund L, Mardesic T, Varila E, Zech J, Brosens I. High endometrial aromatase P450 mRNA expression is associated with poor IVF outcome. Hum Reprod 19: 352-356, 2004.
49) Noda Y, Matsumoto H, Umaoka Y, Tatsumi K, Kishi J, Mori T. Involvement of superoxide radicals in the mouse two-cell block. Mol Reprod Dev. 28: 356-360, 1991.
50) Fischer CP, Kayisili U, Taylor HS. HOXA10 expression is decreased in endometrium of women with adenomyosis. Fertil Steril 95: 1133-1136, 2011.
51) Khan KN, Fujishita A, Ogawa K, Koshiba A, Mori T, Itoh K, Nakashima M, Kitawaki J. Occurrence of chronic endometritis in different types of human adenomyosis. Reprod Med Biol. 1: e12421, 2022.
52) McQueen DB, Perfetto CO, Hazard FK, Lathi RB. Pregnancy outcomes in women with chronic endometritis and recurrent pregnancy loss. Fertil Steril 104(4): 927-931; 2015.
53) Cicinelli E, Matteo M, Trojano G, et al. Chronic endometritis in patients with unexplained infertility: prevalence and effects of antibiotic treatment on spontaneous conception. Am J Immunol. 79: e12782, 2018.
54) Cicinelli E, Matteo M, Tinelli R, et al. Prevalence of chronic endometritis in repeated unexplained implantation failure and IVF success rate after antibiotic therapy. Hum Reprod. 30: 323-330, 2015.
55) Kitaya K, Mastubayashi H, Yamaguchi K, et al. Chronic endometritis: potential cause of infertility and obstetric and neonatal complications. Am J Reprod Immunol. 75: 13-22, 2016.
56) Tamura H, Kishi H, Mitade M, et al. Complications and outcomes of pregnant women with adenomyosis in Japan. Reprod Med Biol 16: 330-336, 2017.
57) Sanchez AM, Vanni VS, Bartiromo L, Papaleo E, Ziberberg E, Candiani M, Orvieto R, Vigano P. Is the oocyte quality affected by endometriosis? A review of the literature. J Ovarian Res. 10: 43, 2017.
58) Khan KN, Kitajima M, Hiraki K, Fujishita A, Sekine I, Ishimaru T, Masuzaki H. Changes in tissue inflammation, angiogenesis and apoptosis in endometriosis, adenomyosis and uterine myoma after GnRH agonist therapy. Hum Reprod. 25, 642-53, 2010.
59) Cheong YC, Shelton JB, Laird SM et al. IL-1, IL-6 and TNF-alpha concentrations in the peritoneal fluid of women with pelvic adhesions. Hum Reprod. 17: 69-75, 2002.
60) Khan KN, Masuzaki H, Fujishita A, Kitajima M, Sekine I, Ishimaru T. Differential macrophage infiltration in early and advanced endometriosis and adjacent peritoneum. Fertil Steril. 81: 652-661, 2004.
61) Ezzati M, Djahanbakhch O, Arian S, Carr BR. Tubal transport of gametes and embryos: in review of physiology and pathophysiology. J Assist Reprod Genet 31: 1337-1347, 2014.
62) Khan KN, Fujishita A, Suematsu T, Ogawa K, Koshiba A, Mori T, Itoh K, Teramukai S, Matsuda K, Nakashima M, Kitawaki J. An axonemal alteration in apical endometria of human adenomyosis. Hum Reprod. 36: 1574-1589, 2021.
63) Vercellini P, Bonfanti I, Berlanda N. Adenomyosis and infertility: is there a causal link? Exp. Rev. Endocrinol Metab. 14: 365-367, 2019.
64) Kamiya R. Microtubules. In: Ishikawa H, Kondo H, Shibata Y eds. Standard cell biology. 1st ed. Tokyo,

Japan: Igaku Shoin publishing Co. 137-151,1999 (in Japanese).
65) Satir P, Mechanisms of ciliary movement: contributions from electron microscopy. Scanning Microsc. 6: 573-579, 1992.
66) Satir P. The role of axonemal components in ciliary motility. Comp Biochem Physiol A Comp Physiol. 94: 351-357, 1989.
67) Satir P. Structural basis of ciliary movement. Environ Health Perspect. 35: 77-82, 1980.
68) Sale WS, Satir P. Detection of active sliding of microtubules in Tetrahymena cilia. Pros. Natl. Acad Sci USA 74: 2045-2049, 1977.
69) Benaglia L, Cardellicchio L, Leonardi M, Faulisi S, Vercellini P, Paffoni A, Somigliana E, Fedele L. Asymptomatic adenomyosis and embryo implantation in IVF cycles. Reprod Biomed Online 29: 606-611, 2014.
70) Vercellini P, Consonni D, Dridi D, Bracco B, Frattaruolo MP, Somigliana E. Uterine adenomyosis and in vitro fertilization outcome: a systematic review and meta-analysis. Hum Reprod 29: 964-977, 2014.

〈和文抄録〉

子宮腺筋症と不妊症の関連：子宮内膜上皮先端の微絨毛における微小管の変化

カ ー ン　カ レ ク

京都府立医科大学大学院医学研究科女性生涯医科学
京都府立医科大学附属病院臨床研究推進センター（CTREC）

子宮腺筋症は，エストロゲン依存性の慢性炎症性疾患であり，疼痛症状，異常子宮出血，不妊症の原因となる．子宮腺筋症は，子宮筋層内に子宮内膜腺および間質が存在し，周囲の子宮筋層の反応性過形成および肥大の結果として子宮の増大を引き起こすことを特徴とする．子宮腺筋症は，子宮内膜症と同様に女性の生殖機能に悪影響を及ぼす．子宮から卵管内への精子輸送の異常，組織の炎症，およびケミカルメディエーターによる毒性作用がその要因として提唱されている．また，炎症による卵管粘膜繊毛の損傷も報告されている．他の提唱されたメカニズムに加えて，透過型電子顕微鏡法（TEM）を用いた我々の最新の研究では，子宮内膜の炎症に反応して，子宮内膜上皮細胞に存在する微絨毛の損傷と微絨毛内の微小管に変化が生じることを示唆した．このことは，子宮腺筋症の女性における不妊の病態に関与している可能性がある．我々は，子宮腺筋症の女性における不妊症のメカニズムをそれが不妊治療成績に及ぼす影響に関する文献データの分析と合わせて報告する．

キーワード：子宮腺筋症，不妊症，子宮内膜の炎症，微絨毛（microvilli），微小管（microtubule）．

著者プロフィール

Khaleque N Khan　カーン　カレク

Associate Professor, Department of Obstetrics and Gynecology, The Clinical and Translational Research Center (CTREC), Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

Ambassador: World Endometriosis Society (WES)
Asian Society of Endometriosis and Adenomyosis (ASEA)

1984年 3 月　Obtained MD from Dhaka University, Bangladesh

1986年 4 月-1988年 3 月
Clinical Training in King's College, London

1991年 8 月　Obtained Diploma in Tropical Medicine (DTM) from Nagasaki University, Japan

1993年 3 月　Obtained PhD from Nagasaki University, Japan

2016年 6 月-2016年 8 月
Visiting Professor of Mahidol University in Bangkok, Thailand

As an Ambassador of ASEA and WES, Dr. Khan has established multinational/multicenter collaboration study on endometriosis awareness promotion project (EAPP) and organized international congresses and master class symposia/workshops on endometriosis/adenomyosis in different Asian countries.

ACADEMIC AWARDS:

2020: Recipient of 72nd Congress Award by the Japan Society of Obstetrics and Gynecology
2017: Recipient of 18th Royan International Research Award (Tehran, Iran)
2010: Best Paper Award at ICIR/ISIR joint meeting (Osaka)
2004: Best Presentation Award at 9th World Congress of Gynecol Endocrinol (Florence, Italy)
2003: Presidential Award at 23rd Endometriosis Meeting (Tokyo)

OTHER CONGRESS AFFILIATIONS:

Counselor: Japan Society of Reproductive Immunology (JSRI)
Counselor: European Society of Reproductive Immunology (ESRI)
Members: Japan Society of Obstetrics and Gynecology/ Japan Society of Endometriosis/ASRM/JSRM

EDITORS:
Managing Editor: Frontiers in Bioscience (FBS)
Associate Editor: Journal of Obstetrics and Gynecological Research (JOGR)
Associate Editor: International Journal of Women's Health (IJWH)
Editorial Board: Journal of Endometriosis and Pelvic Pain Disorders (JEPPD)

PUBLICATIONS IN ENGLISH:

(1) Original articles (first author): more than 100 (peer reviewed)
(2) Review articles: 20, (3) Book chapter: 16