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Epidemiology of Adenomyosis

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Abstract

Adenomyosis, characterized by the presence of endometrial glands and stroma within the myometrium, can have a substantial impact on the quality of women's lives. Despite this, the epidemiologic research on this condition lags considerably behind that of other non-cancerous reproductive health conditions. The lack of progress and knowledge is due in part to the challenges in designing valid epidemiologic studies, since the diagnosis of adenomyosis historically has been limited to examination of uterine specimens from hysterectomy. This review describes the available data on the frequency of this condition and the epidemiologic investigation thus far into the risk factors for disease – highlighting the methodologic and inference challenges primarily around study sample selection. We conclude with providing recommendations for approaches to future epidemiologic study that capitalize on the advancements in imaging technology to detect adenomyosis and provide a fuller picture of the occurrence and risk factors for disease.

Keywords

adenomyosis; epidemiology; risk factors; prevalence; hysterectomy

Description of adenomyosis and its impact

Adenomyosis is characterized by the presence of endometrial glands and stroma within the myometrium, surrounded by smooth muscle hyperplasia. Although adenomyosis was first described by pathologist Carl von Rokitansky in 1860,[1] and recognized as an "elusive disease" by gynecologist Ludwig Emge in 1962,[2] the etiology of adenomyosis remains enigmatic more than a half-century later. The two most common theories of adenomyosis pathogenesis postulate it occurs from the invagination of basalis endometrium into the myometrium[3] or arises *de novo* from the metaplasia of embryonic Müllerian remnants.[4] A unifying mechanism postulates tissue damage or injury at the endometrial-myometrial

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junction leads to inflammation and local estrogen production, perpetuating oxytocin-mediated uterine activity and chronic peristaltic myometrial contractions that is exacerbated with repetitive cycles, leading to endometrial cell migration into the myometrium and disease establishment.[5,6] (See Antero et al and also Zhai et al in this issue for details on pathogenesis).

Progress on understanding the epidemiology of adenomyosis lags considerably behind other benign reproductive conditions. This stems largely from the historic reliance on histopathologic examination of uterine specimens after hysterectomy for disease diagnosis, and the past lack of reliable pre-operative diagnosis. Since adenomyosis is also cured by hysterectomy, this likely limited both the perceived importance and the ability to further investigate the associated symptomatology, co-morbidities, and impact on quality of life. As a result, the impact of adenomyosis on women's health has not been adequately studied.

The surgical removal of the uterus, warranted by serious medical indications or severe symptoms including heavy menstrual bleeding and pelvic pain, indicates that adenomyosis has a substantial impact on the quality of women's lives. However, only one study to date has qualitatively evaluated women's experiences with the condition;[7] it was conducted after the advancement in imaging technologies permitting non-invasive diagnosis. That study, a qualitative report of 31 women with adenomyosis diagnosed by transvaginal ultrasound (TVUS) or magnetic resonance imaging (MRI), found a considerable impact of the disease on many aspects of life, including activities of daily living, physical activities, sleep, work/school, and personal relationships. Participants frequently reported burdensome self-care hygiene related to heavy menstrual bleeding as well as fatigue and low energy due to adenomyosis-associated pain.[7]

Adenomyosis appears to have an adverse impact on the risk of other health outcomes, including obstetrical outcomes. Studies using imaging to diagnose adenomyosis have reported an association between adenomyosis and an increased risk of preterm birth, small for gestational age, and pre-eclampsia among pregnant women who conceive spontaneously.[8] Among women undergoing in vitro fertilization and intracytoplasmic sperm injection treatment, adenomyosis is associated with a reduced rate of pregnancy and live births as well as an increased risk of miscarriage.[9–11]

Little information is available on the relationship between adenomyosis and non-malignant chronic conditions.[12] With regard to cancer risk, a few large, population-based epidemiologic studies have linked adenomyosis with an increased risk of cancer (all cancers combined).[13,14] Some of these studies have also suggested specific associations with cancers of the endometrium,[14,15] thyroid,[13,15] ovary,[14] breast,[13] and non-Hodgkin's lymphoma,[13] although the number of cancer cases with adenomyosis were small.

Frequency of adenomyosis occurrence

Prevalence at hysterectomy

The true prevalence of adenomyosis, defined as the proportion of a defined population with existing disease at a given time,[16] is unknown. Since the gold standard for diagnosis has

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been histopathologic examination of the uterus after hysterectomy,[17] most prevalence estimates are restricted to the highly select population of women undergoing hysterectomy (Figure 1). Women requiring major surgery and removal of the uterus have medical indications for doing so, including severe symptoms that impact quality of life and that may not have responded to conservative treatment, surgical repair (i.e., pelvic organ prolapse), or removal of malignant tissue. Thus, the study population of hysterectomy patients is oversampled with regard to uterine pathologies overall, which may overestimate the prevalence. Yet, the prevalence may be underestimated from missed adenomyosis cases that do not come to clinical attention or are not managed by hysterectomy.

The estimated prevalence among consecutive hysterectomy patients over the past 50 years has ranged from 8.8% to 61.5% (Table 1).[18–47] The wide range frequently has been attributed to the lack of standard histopathologic criteria for diagnosis, variable number of histologic tissue samples evaluated per hysterectomy, and differing levels of provider awareness. At least 9 different histopathologic diagnostic criteria have been used to diagnose adenomyosis in uterine samples.[1] Bergholt et al (2001) reported a prevalence of 10% with the diagnostic criteria of ≥5 mm distance between endometrial glands and the endo-myometrial junction and the presence of myometrial hyperplasia.[38] The prevalence was higher at 18% with a less strict definition: depth of only ≥1 mm depth and no myometrial hyperplasia.[38] A more striking variation has been observed when comparing the prevalence using a “routine” pathologic examination with the section of 3 blocks of uterine wall (31%) to that using six extra uterine tissue blocks, and including adenomyosis subbasalis (61.5%).[19] Based on these findings, Bird et al (1972) suggested that nearly half of adenomyosis present in extirpated uteri remains undiagnosed. A study of women undergoing hysterectomy at hospitals in Maryland, USA, highlights the contribution of provider and hospital factors to the wide range of prevalence estimates. Across 15 hospitals that issued at least 30 reports and 25 pathologists that signed at least 20 reports, the prevalence of adenomyosis diagnosis ranged from 12% to 58% across hospitals and from 10% to 88% across pathologists.[35]

The reliance on hysterectomy for the diagnosis of adenomyosis has precluded the assessment of the prevalence of adenomyosis by age. The age at which adenomyosis develops cannot be determined by hysterectomy, only the age at surgical diagnosis. In addition, hysterectomy studies of adenomyosis prevalence have not been restricted to premenopausal women. These studies were conducted among women with a broad range of age, including women in their 80s (Table 1). As such, the median age at surgical diagnosis is between 40 and 50 years (Table 1), mirroring the age-distribution for hysterectomy. In the US in years 2000–2004, the highest incidence of hysterectomy was among women ages 40–44, followed by women ages 45–49.[48] Hence, the common perception that adenomyosis affects older reproductive-age women based on hysterectomy data misses the experience of younger women with the condition.

Prevalence at imaging

To date, screening by imaging has not been conducted in the general population. The few studies that have reported on the prevalence of adenomyosis at imaging were conducted

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among women referred by healthcare providers for TVUS. The first study was conducted among 985 women attending a general UK gynecology clinic and undergoing TVUS for indications including menorrhagia, pelvic pain, infertility, irregular bleeding or amenorrhea, and postmenopausal bleeding; the prevalence of adenomyosis was 20.9%.[49] A subsequent study of the same population, further restricted to premenopausal women with menses in the prior 60 days, reported a prevalence of 21.9%.[50] Another study was conducted in Italy among 18–30 year-old nulligravid women attending a gynecology clinic for contraceptive care and referred for ultrasound evaluation.[51] Although the medical indications warranting TVUS referral were not provided, strict inclusion criteria were employed, including the presence of regular menstrual cycles, no use of hormonal medications that affect the menstrual cycle, no history of infertility nor sonographic evidence of endometriosis or leiomyomas. In that study population of 156 women, the prevalence of adenomyosis was 34%.[51] In addition, the mean age of adenomyosis cases was 26 years. These data, although collected among women obtaining care with indications warranting imaging, do suggest that adenomyosis may be common and may develop early during the reproductive years.

Similar to histologic diagnosis, there is a lack of consensus on imaging diagnostic criteria for the diagnosis of adenomyosis which could affect the estimation of prevalence. In addition, the use of hormonal or gonadotropin releasing hormone (GnRH) treatments may affect the diagnostic quality of these imaging modalities and the detection of adenomyosis by TVUS can be highly operator dependent.[52] Despite these limitations, the recent advancements in noninvasive imaging methods have allowed for the detection of adenomyosis outside the setting of hysterectomy.[17] The aggregated diagnostic qualities of TVUS and MRI reported in a recent systematic review and meta-analysis of high-quality studies suggests TVUS and MRI comparably perform reasonably well in the diagnosis of adenomyosis; in aggregate, MRI, 2-dimensional TVUS, and 3-dimensional TVUS had a sensitivity of 78%, 74% and 84% and a specificity of 88%, 76%, and 84%.[52] Diagnosis by imaging is addressed in more detail by O'Shea and colleagues in this issue.

Prevalence in women with other uterine-related conditions

Given the wide range of adenomyosis prevalence estimates, data from hysterectomy and imaging studies have not revealed a clear pattern of disease prevalence among women with other uterine-related conditions, including leiomyomas, pelvic organ prolapse, menorrhagia/abnormal uterine bleeding, infertility, and endometriosis. Among women with leiomyomas, the reported prevalence of adenomyosis varies widely from 16% to 62% in women undergoing hysterectomy or other surgery.[30,33,37,41,45,53,54] The prevalence of adenomyosis at hysterectomy ranges from 20–31% for pelvic organ prolapse[33,36,37,41,42,45] and 26–49% for menorrhagia/abnormal uterine bleeding.[45,55–57] The few studies evaluating the frequency of adenomyosis among women experiencing infertility report a prevalence of 8% and 24% with TVUS.[58,59]

Among women with endometriosis, the prevalence of adenomyosis also substantially varies. Although the prevalence of adenomyosis diagnosed by histopathology at surgery in women with endometriosis ranges from 15–31%,[60,61] the prevalence of adenomyosis varies between 22% and 89% with TVUS[49,62,63] and between 27% and 65% with MRI.[64,65] Higher

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prevalence of adenomyosis has been observed among women with endometriosis and concurrent infertility (35–79%)[59,66,67] or with endometriosis and concurrent pelvic pain/dysmenorrhea (38%−87%).[68,69] Restricting to women with deep infiltrating endometriosis, overall adenomyosis prevalence is similarly high (35%−78%),[65,70,71] with the highest prevalence reported for focal adenomyosis of the outer myometrium (49%−97%).[65,72,73]

Incidence

The true incidence of adenomyosis, or the frequency at which at-risk individuals become adenomyosis cases over a specified time period, is also unknown. Two population-based studies have reported on adenomyosis incidence. The first study estimated the cumulative incidence of adenomyosis using data from an automated centralized record system in a region of Italy with a population of approximately 1.22 million people.[74] Among women residing in the region aged 15–50 without an adenomyosis diagnosis in the prior decade, the incidence of newly diagnosed adenomyosis in years 2011–2013 based on hospital discharge data with accompanying hysterectomy was 0.027%. The other study used electronic health care data from a large US health insurance and care delivery system in western Washington state.[75] The study cohort comprised women aged 16–60 who were enrolled in the integrated healthcare system for at least two years, had at least one health visit, and did not have a record of hysterectomy in the two preceding months nor diagnosis of adenomyosis two years before cohort entry (January 1, 2006 through December 31, 2015). Incident adenomyosis cases were identified using the International Classification of Diseases 9th or 10th revision codes (codes 617.0 and N80.0, respectively) from either an inpatient stay or outpatient visit. The overall cumulative incidence and incidence rate of adenomyosis in the 10-year interval from 2006–2015 was 1.03% and 28.9 per 10,000 woman-years, respectively. The estimated prevalence in year 2015 was 0.8%.[75] Using these methods, the incidence of adenomyosis is likely underestimated. The extent of the under-estimation is unknown given the inconsistent histologic and imaging diagnostic standards, reliance primarily on diagnosis at hysterectomy, and lack of screening for adenomyosis in the general population.

Symptomatology

Although abnormal uterine bleeding (AUB) is currently the preferred terminology,[76] this section uses the terms presented in the original studies, for example metrorrhagia, rather than updating to current vernacular.

Menorrhagia and dysmenorrhea have long been considered the classic symptoms of adenomyosis.[77] However, adenomyosis as the source of symptoms was brought into question in earlier studies conducted only among adenomyosis cases diagnosed at hysterectomy.[18,77,78] In those studies, approximately one-third of patients were reported as asymptomatic, a statistic that is frequently cited in the current literature. Several aspects of this determination bring the statistic into question. First, patients in these studies were considered asymptomatic if the indication for hysterectomy was prolapse[18,77,78] or carcinoma in situ.[18] However, the possibility exists that prior to development or recognition of these conditions, patients may have experienced menorrhagia and dysmenorrhea. Second, it appears that the absence of the classic symptoms of menorrhagia and/or dysmenorrhea

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may have been the authors' definition of "asymptomatic", so other symptoms may have been present. Third, it is not stated in these studies how data on symptoms were collected and the point in time they reflect. Since there is no mention of interviewing patients or administering a survey, these studies may have relied on record review. The presence and absence of symptoms such as dysmenorrhea, dyspareunia, pelvic pain, and pelvic pressure are frequently not queried and recorded by clinicians.[79] If the symptoms reflect those at the time of hysterectomy, then studies including postmenopausal women[18,77] would overestimate the prevalence of asymptomatic disease, as postmenopausal women would not be at risk for menorrhagia or dysmenorrhea. In the study by Israel et al (1959), 28% of adenomyosis cases were postmenopausal. In contrast, a recent study reporting on symptoms among 710 premenopausal adenomyosis cases diagnosed by hysterectomy, only 4.5% had none of the four complaints of dysmenorrhea, menorrhagia, chronic pelvic pain, or metrorrhagia.[47]

Since menorrhagia and dysmenorrhea are common to other uterine pathologies that can also be indications for hysterectomy, adenomyosis is frequently described as not having symptoms specifically characteristic of this disease. However, most studies on the symptomatology of adenomyosis have been conducted among women undergoing hysterectomy, a population oversampled with regard to uterine pathologies. The potential to attribute symptoms to another condition that can be reliably detected pre-operatively, particularly a common condition such as leiomyomas, is possible. The pre-operative diagnosis of adenomyosis, on the other hand, has historically been low. Before the advent of improved imaging technologies, the percent of hysterectomy adenomyosis cases diagnosed preoperatively with the condition generally ranged from 0–23%.[18–22,27,29,30]

The study design employed may also affect the ability to detect an association between symptoms and adenomyosis. Early studies compared hysterectomy-confirmed symptomatic adenomyosis cases with and without other uterine pathology.[18–20,77,78] It was not until the mid-1980s when the first study using a comparison group of hysterectomy patients without adenomyosis was published.[25] Since this time, most studies comparing hysterectomy patients with and without adenomyosis have generally reported a positive association with the classic symptoms.[25,36–38,41,42,80,81] Recent studies conducted among patients undergoing TVUS as part of diagnostic work-up have also reported an association between heavy menstrual bleeding, menstrual pain, and adenomyosis.[50,51,82] Beyond the classic symptoms, other TVUS studies have reported associations between adenomyosis and overactive bladder symptoms.[83–85]

The results for menorrhagia and dysmenorrhea have been less consistent when adenomyosis, or adenomyosis with leiomyomas, have been compared to those with pathology-confirmed leiomyomas.[12,43,86–93] Although in several of these studies, patients with adenomyosis with or without leiomyomas appear to experience a greater frequency of dysmenorrhea than patients with leiomyomas.[12,86,87,90,92]

One frequently cited study has suggested that adenomyosis is an incidental finding and not a source of symptoms. That interpretation was based on a lack of association observed between abnormal uterine bleeding and chronic pelvic pain symptoms and adenomyosis in 137 women who had hysterectomies (data on estimated adjusted odds ratios not provided).

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These women were participants in a large, community-based study and were being followed through the menopausal transition; they comprised the subset who reported hysterectomies over nine years of follow-up.[94] However, the eligibility criteria for entry into the longitudinal cohort included being ages 42–52 years, having an intact uterus, and, in the prior three months, having had at least one menstrual period and not using reproductive hormones. Women with substantial symptoms that were managed by hysterectomy or hormonal medications were excluded from entering the study. In addition, data on abnormal uterine bleeding and chronic pelvic pain were abstracted from medical records. Both the selection of participants and collection of symptom data would decrease the sensitivity of the study to detect an association between abnormal uterine bleeding and chronic pelvic pain symptoms and adenomyosis.

Methodologic challenges in the epidemiologic study of adenomyosis

Sample selection

The major challenge in the epidemiologic study of adenomyosis has historically been and remains the identification of cases and its impact on the subsequent selection of non-cases for comparison. Given that the current gold standard for the diagnosis is histologic confirmation after hysterectomy and the poor performance of early imaging technologies, most epidemiologic studies have been conducted among women undergoing hysterectomy (Table 2). The advantage of this approach for selecting study participants is that cases and controls are evaluated for the presence of disease in the same manner and are more similar with regard to factors leading to the decision to have a hysterectomy. However, women undergoing hysterectomy are a highly selected population (Figure 1). The study base of women undergoing hysterectomy does not represent the underlying population that gave rise to adenomyosis cases. Women undergoing hysterectomy differ from the underlying population in terms of completion of childbearing, access to medical care, economic status, education, and age at menarche.[95,96] Women undergoing hysterectomy are also oversampled with regard to conditions that are indications for the procedure.

Ramifications of hysterectomy controls

Although most studies conducted among a sample of hysterectomy patients were not identified by the authors as case-control studies (Table 2), these studies are being considered in the context of this study design since the comparison groups were formed according to adenomyosis case status, and the exposure histories were compared.

The selection of controls among women undergoing hysterectomy can compromise the validity of a case-control study. The comparison group of women undergoing hysterectomy without a pathology-confirmed diagnosis of adenomyosis are not sampled from the identified study base, or source population that gave rise to cases. As such, hysterectomy controls may not represent the distribution of exposure, or risk factors, within the population from which the cases arose (which is the first rule of valid control selection),[97] resulting in biased estimates of associations.[16] The selection of controls from the underlying population source for the cases is essential to ensure that the selection of non-cases is independent of

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exposure.[98] This is a key principle of valid case-control study design; violation of this key principle can result in wrong results.[97,98]

Bias from the selection of hysterectomy controls may be considerable when investigating exposures, such as those related to estrogen, that may be associated with the indications for hysterectomy. In the U.S., the leading indications for hysterectomy include uterine leiomyomas, followed by uterine bleeding, prolapse, endometriosis, and cancer.[99] However, all of these indications are associated with an altered endogenous hormonal milieu. This means that hysterectomy controls are not selected independent of exposure and this will bias the estimation of the association. In addition, the extent of bias will differ with variations in comparison group selection.[100] With increasing age, the leading indications for hysterectomy change from leiomyomas, bleeding and endometriosis among women ages 18–44 to uterine prolapse and cancer among women ages 65 and older.[99] These indications may have different magnitudes of associations with factors that affect the endogenous hormonal milieu.

Risk factors for adenomyosis

Thirty-two epidemiologic studies investigating risk factors for adenomyosis have been published (Table 2).[12,33,36–43,49,59,80,86,87,89–93,100–111] These studies have investigated a variety of risk factors with discrepant results. Some of the discrepancy may be due to study design, sophistication of statistical analyses, sample size of the epidemiologic investigations, and consequences of the methodologic challenges described above. To help identify risk factors consistently associated with adenomyosis, the following review of risk factors in relation to adenomyosis is restricted to the subset of studies (n=16)[33,36,38–40,42,49,87,89,90,92,93,100,102,105,111] that met the following criteria: (1) employed a cross-sectional, case-control, or cohort study design, (2) provided a measure of association and precision (e.g., odds ratio and 95% confidence interval), (3) adjusted for confounding factors that were specified, and (4) included at least 30 adenomyosis cases and 30 non-cases. The last requirement was included to allow for more statistically stable estimates of associations to be compared across studies; it is not intended as a recommendation for the minimum number of participants in an epidemiologic study. If a study reported both unadjusted and adjusted odds ratios, only adjusted odds ratios were considered in the review.

Demographic factors

Race/ethnicity—Most studies of adenomyosis have not evaluated race or ethnicity. Structural racism is a key determinant of population health[112] and could contribute to adenomyosis risk. Two U.S. studies have reported mixed results. A large cohort study of over 80,000 female teachers in California reported a greater prevalence of surgically-confirmed diagnosis of adenomyosis among Latinas compared to white women (prevalence odds ratio (POR) 1.26, 95% CI: 0.96–1.66).[102] The number of adenomyosis cases among non-white women was small, impeding the evaluation of the association between women identifying as black or Asian or Pacific Islander and adenomyosis risk. In contrast, in a study of women undergoing hysterectomy in New York, black women were more likely to have a

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pathologic finding of adenomyosis and leiomyomas (versus leiomyomas alone; too few cases had adenomyosis alone for meaningful comparisons) than Hispanic women (OR 2.72, 95% CI: 1.11–6.68).[90]

Education—As a social determinant of health, higher educational attainment is related to higher wages and income and access to health-related resources, including healthcare, healthy food, and safe environment.[113] Thus, it is plausible that lower educational attainment could adversely affect the risk of adenomyosis. Two studies conducted among women undergoing hysterectomy that evaluated this association have reported inconsistent results. Data from a cross-sectional study of Italian women undergoing hysterectomy at a university hospital suggested a lower risk of adenomyosis with seven or more years of education compared to less than seven years (OR 0.7, 0.4–1.0).[36] In contrast, a subsequent study of women undergoing hysterectomy at 18 hospitals in Italy indicated an increased risk of adenomyosis with greater education, except for those with 16 years or more education (7–10 years: OR 1.5, 1.0–1.20; 11–15 years: OR 1.3, 0.8–2.3; 16+ years: 0.7, 0.3–1.6; <7 years as the reference group).[42]

Menstrual characteristics

Age at menarche—Several pathways exist by which earlier menarche could increase the risk of adenomyosis. This includes increased exposure to estrogen from a longer duration of ovulatory cycling over the reproductive years and greater parity from a decreased age at sexual debut.[114] Alternatively, early menarche could be a marker for earlier life disruption of reproductive system development[115] that also increases the risk of adenomyosis. However, the hypothesized association between early age at menarche and increased adenomyosis risk has not been borne out in epidemiologic studies conducted among women undergoing hysterectomy. Instead, these studies have reported no association.[33,36,42] The one study to observe an association was a large, population-based study that followed a cohort of over 80,000 female teachers in California for in-patient hospitalizations with the diagnosis of adenomyosis. In that study, menarche on or before age 10 compared to age 13 was associated with a 59% increased prevalence of surgically-confirmed diagnosis of adenomyosis (POR 1.59, 95%CI: 1.26–2.01).[102] The discrepant results across studies is likely related to the selection of study participants. Women undergoing hysterectomy are more likely to have an earlier age at menarche,[96] and earlier age at menarche is an established risk factor for uterine fibroids,[115] and is associated with endometriosis,[116] common indications for hysterectomy.[99] Thus, the relationship between age at menarche and indications for hysterectomy could decrease the sensitivity of a study restricted to women undergoing hysterectomy to detect an association with adenomyosis.

Menstrual cycle frequency—Shorter menstrual cycles confer increased exposure to ovarian steroid hormones, including estrogen. In alignment with the role of hyper-estrogenism on disease risk, two studies have reported greater adenomyosis risk with shorter menstrual cycles. Data from a study conducted among women undergoing hysterectomy suggested that those with lifelong menstrual patterns of 26–30 days and ≥31 days had a decreased risk of adenomyosis compared to those with cycle lengths of ≤25 days (OR 0.6, 95% CI: 0.3–1.1 and OR 0.5 95% CI: 0.1–1.6, respectively).[36] A large, prospective cohort

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study using data from the California Teachers Study reported that participants whose usual menstrual cycle length was ≤24 days had a 46% increased prevalence of surgically-confirmed adenomyosis (OR 1.46, 95% CI: 1.13–1.89) compared with those with a usual cycle length of 27–28 days.[102] In contrast, one hysterectomy study that defined lifelong irregular menstrual cycles as those either ≤21 days or ≥32 days in length reported no association.[42]

Breastfeeding—Breastfeeding is associated with the absence of ovulatory cycles and estrogen-deficiency.[117,118] It is plausible that among parous women, breastfeeding could be associated with a decreased risk of adenomyosis. This was observed in the cohort of California teachers in which parous women who reported ever breastfeeding had a lower prevalence of surgically-confirmed adenomyosis compared to parous women who never breastfed (POR 0.74, 95% CI: 0.62–0.88).[102]

Menopause—Given estrogen deficiency after menopause,[119] premenopausal women are generally considered to be at increased risk for adenomyosis due to greater circulating estradiol levels. Consistent with this hypothesis, in a large cohort of female teachers in California, premenopausal and perimenopausal women at baseline had an increased prevalence of surgically-confirmed adenomyosis compared with postmenopausal women not using hormone therapy (POR 4.72, 95% CI: 3.22–6.91 and 3.40 95% CI: 2.10–5.51, respectively).[102] Interestingly, postmenopausal women using estrogen-only preparations, combined estrogen and progestin preparations, and mixed use of estrogen-only and combined preparations had a greater prevalence of adenomyosis diagnosis as well (estrogen-only: POR 2.09, 95% CI: 1.27–3.43; combined estrogen and progestin: POR 2.87, 95% CI: 2.04–4.02; mixed use of preparations: POR 4.93, 3.37−−7.21).[102] Among patients undergoing hysterectomy, a record review study reported that pathology-confirmed adenomyosis patients were less likely to be menopausal than patients without this diagnosis (OR 0.7, 95% CI: 0.5–1.0).[33] However, another hysterectomy study did not report an association.[36] Both of these studies did not report on hormone therapy at the time of hysterectomy, which could contribute to the discrepancy in results across studies.

Reproductive history

Gravidity and parity—Trophoblast invasion of the inner myometrium with pregnancy may disrupt the endometrial-myometrial border, increasing the risk of adenomyosis.[120,121] Parity, or the number of births, is the most studied risk factor for adenomyosis. Among studies conducted in hysterectomy patients, a positive association between parity and adenomyosis was reported in most,[33,36,87,89,90,100,102] but not all studies. Two hysterectomy studies reported no association.[38,42] However, these two studies simultaneously adjusted for method of delivery for birth (cesarean delivery) which may limit the ability to detect an association. A challenge to examining parity among women undergoing hysterectomy is that the leading indication for hysterectomy is leiomyomas; a well-established protective factor for leiomyoma risk is parity.[122] This raises concerns about bias contributing to the positive association observed in hysterectomy studies, particularly those in which the comparison group is composed of patients with leiomyomas.[87,89,90]

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The two studies using a population-based sampling frame also observed a positive association between parity and adenomyosis.[100,102] Using this study design, there is concern for bias from not being able to disentangle parity from the willingness to undergo hysterectomy by adenomyosis cases. However, the study conducted by Trabert et al (2011) used two control groups.[100] In addition to the population-based controls comprising randomly selected health plan enrollees, a comparison group of women who underwent hysterectomy was employed. The analyses comparing adenomyosis cases to the two control groups, conducted separately, both yielded positive associations. These results suggest that the association observed when using population-based controls was not solely due to confounding.

Since trophoblast invasion with pregnancy peaks at 9–12 weeks,[120] pregnancies lasting 9 weeks or longer may be most likely to affect the risk of adenomyosis. The number of pregnancies (gravidity) may capture more pregnancies lasting 9 weeks or longer than the number of births (parity), which is limited to pregnancies lasting more than 20–24 weeks.[123] Yet, fewer studies have investigated gravidity as a risk factor, and all observed a positive association with adenomyosis.[40,49,92,93,100] One of the studies, conducted among 985 women undergoing TVUS, reported increased adenomyosis risk with increasing number of pregnancies (1 pregnancy: OR 1.83, 95% CI: 1.09–3.06; 2 pregnancies: 2.46, 95% CI: 1.44–4.30; 3–5 pregnancies: 2.66, 95% CI: 1.62–4.28; ≥6 pregnancies: 4.90, 95% CI: 2.57–9.35; 0 pregnancies as reference category).[49]

Spontaneous abortion, induced abortion, evacuation, and dilatation and curettage (D&C)—Given the timing of peak trophoblast invasion (9–12 weeks gestation),[120] spontaneous and induced abortion may also contribute to disruption of the endometrial-myometrial border if the pregnancy lasts longer than 9 weeks. The studies included in the review had mixed results. Three studies that investigated spontaneous abortion were conducted in Italy among women undergoing hysterectomy.[33,36,42] Two studies reported a strong association between spontaneous abortion (both studies reported OR 1.6, 95% CI: 1.0–2.4),[33,36] whereas the other study reported a null association.[42] Of the studies that examined induced abortion,[33,36,39,42] all but one study reported a strong, positive association with adenomyosis. With regard to evacuation, one study included in the review investigated this procedure used for induced abortions in the second trimester. That study reported no association.[38]

Uterine dilatation and curettage (D&C) is performed for both pregnancy-related and non-pregnancy reasons. One study conducted among women undergoing hysterectomy in Denmark, which did not report the indication for endometrial curettage, reported no association between the history of the procedure and adenomyosis.[38] In contrast, another hysterectomy study conducted in Italy reported a strong association between D&C performed for “gynecological indication only” and adenomyosis (OR 2.1, 95% CI: 1.1–3.8).[36] The one study to specify the use of D&C not related to pregnancy observed no association with adenomyosis.[39] The possibility exists that an observed association between D&C and adenomyosis may be due to the use of D&C for symptoms (e.g. abnormal uterine bleeding or postmenopausal bleeding) related to adenomyosis.

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Considering the conflicting results for D&C in concert with the associations observed with induced abortion and gravidity, and that sharp curettage has rarely been used to terminate pregnancies in the U.S. since the mid-1970s,[39] the increased risk of adenomyosis observed with induced abortion may be due to trophoblast invasion with pregnancy, rather than the D&C procedure itself.

Cesarean delivery—Since cesarean delivery involves disruption of the endometrial-myometrial interface by both the trophoblast invasion of pregnancy and surgery, one would expect that this surgical procedure would be associated with an increased frequency of adenomyosis. However, studies of the history of cesarean delivery and adenomyosis have reported no association,[38,39,42,100] although the odds ratio from one study suggested a modest association.[39] All of the studies adjusted for parity or gravidity, which may suggest that the impact of surgery on adenomyosis risk may be minimal above and beyond the risk from pregnancy.

Other uterine surgery—Studies examining any uterine surgery and adenomyosis have reported mixed results. Data from two studies conducted among hysterectomy patients suggested a positive association.[40,42] One study defined “any uterine surgery” as a history of cesarean delivery, myomectomy, endometrial ablation, dilatation and evacuation, and dilatation and curettage.[40] The other study evaluated “previous abdominal surgery” and types of surgeries were not specified. In contrast, a study conducted among health plan enrollees in the US Pacific Northwest using two control groups reported conflicting results. An inverse association was observed when comparing adenomyosis cases to hysterectomy controls whereas a null association was observed when using population-based controls (randomly selected health plan enrollees matched on age to cases).[100] That study examined uterine trauma as the exposure, and considered history of induced abortion and/or uterine surgery, such as D&C, cesarean delivery, myomectomy, or endometrial ablation. An inverse association could be observed if exposure is driven by surgeries not related to pregnancy.

Medications

Contraception—Use of oral contraceptives (OCs) that include an estrogen component in the formulation could increase exogenous exposure to estrogen and contribute to the increased risk of adenomyosis. On the other hand, OC use could be associated with a decrease in disease risk through the suppression of ovarian steroidogenesis and prevention of pregnancy. However, if the reason for use is for symptoms such as heavy menstrual bleeding or menstrual pain, then an observed association could be a result of reverse causation. That is to say, symptoms related to adenomyosis could lead to OC use, rather than OC use being a risk factor for adenomyosis. Studies that evaluated OC use in relation to adenomyosis have reported mixed results. Two studies conducted among women undergoing hysterectomy reported no association between ever use of oral contraceptives and adenomyosis.[36,42] However, a large population-based cohort study of teachers in California observed that past use of oral contraceptive was associated with a 54% greater prevalence of surgically-confirmed adenomyosis (POR 1.54, 95% CI: 1.28–1.85) whereas current oral contraceptive use at baseline was not associated with adenomyosis prevalence.[102]

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The same two hysterectomy studies that investigated oral contraceptive use also examined history of IUD use. Similar to that observed for oral contraception, no association was observed with IUD use. [36,42]

Tamoxifen—None of the studies that met the criteria for inclusion in the review of risk factors evaluated tamoxifen use. Given that this medication has been mentioned in other reviews as a risk factor for adenomyosis,[124,125] we have provided a brief review from the epidemiologic perspective. Tamoxifen is a selective estrogen receptor modulator that has anti-estrogenic properties on breast tissue, but weakly estrogenic properties in the reproductive tract. As such, use of tamoxifen has been associated with endometrial carcinoma, endometrial hyperplasia and polyps.[126] Data linking tamoxifen use to adenomyosis come from a case report,[127], two case series studies, [128,129] and one small analytic study of postmenopausal women with a history of breast cancer.[130] In the case report and case series studies, all of the women were treated with tamoxifen and underwent hysterectomy or MRI, allowing for the detection of adenomyosis, if present. In the analytic study, postmenopausal women with breast cancer treated with tamoxifen (n=28) were compared to those not receiving this treatment (n=11) and who underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy.[130] The frequency of adenomyosis in the treated group (54%) was greater than that of the non-treated group (18%). However, the study did not account for potential confounding factors that may bias the association. For example, 57% of treated women had a history of 4 or more pregnancies compared with 27% of the women not treated with tamoxifen.

Anthropometric characteristics

Increasing evidence suggests that estrogens influence body fat distribution.[131] However, the only anthropometric characteristic evaluated in adulthood in relation to adenomyosis is body mass index (BMI). BMI can serve as a proxy for body adiposity, but it does not indicate the distribution of fat in the body.[131] The results across studies conducted among hysterectomy patients have been mixed, with studies reporting a positive,[100] inverse,[87] and no association. [42] Since BMI is associated with the risk of hysterectomy and weight gain during adulthood has been linked with uterine fibroid risk,[132–134] its relationship with adenomyosis may be additionally challenging to study using the sampling frame of hysterectomy patients. Conversely, two population-based studies reported a positive association between BMI and adenomyosis with odds ratios ranging from 1.4 to 3.8 comparing women with a BMI ≥ 30 kg/m^2 to those with a BMI <25.0 kg/m^2.[100,102] Both studies used data on BMI collected before adenomyosis diagnosis. The temporal sequence of exposure and outcome provides support for the hypothesis that higher BMI increases the risk of adenomyosis. When an exposure (here BMI) is measured at the time of outcome diagnosis, it is not possible to infer that the exposure contributes to the causal pathway, i.e. the exposure could in truth be coincidental with the outcome or it may be a consequence of the outcome (reverse causation described above).

Smoking

Cigarette smoking is associated with an earlier age at menopause through its toxic effects on ovarian follicles, which affects the production of gonadotropins and estrogen.[135] In addition,

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smoking may have anti-estrogenic effects through increased metabolism of estradiol and inhibiting aromatase conversion of androgens into estrogens.[136,137] Consistent with these findings, the first study of smoking and adenomyosis reported that current smoking of 10 or more cigarettes per day was associated with a decreased risk of adenomyosis (OR 0.5, 95% CI: 0.3–0.9).[36] However, subsequent studies have not observed a decreased risk in disease. Instead, these studies have reported a positive association with ever smoking[89] or no association.[42,100] Contributing to the discrepant results are the different characterizations of smoking across studies.

Endocrine-disruptive environmental exposures

Given the involvement of estrogen in the pathogenesis of adenomyosis, it is biologically plausible that environmental chemicals that interfere with hormonal action could alter the risk of adenomyosis.[138] Phthalates are non-persistent chemicals for which the developmental and reproductive effects have been documented, including altered steroidogenesis in women.[139] These chemicals are used as plasticizers or additives in a wide array of consumer products, and the contamination of food and beverages from the leaching of phthalates in packaging contributes to widespread exposure in the general population.[139] Among women undergoing laparoscopy at a university hospital in Taiwan, women with pathology-confirmed adenomyosis or endometriosis (n=44) and leiomyomas (n=36) were compared with those with none of these conditions (n=69). The researchers observed that urinary concentrations of the phthalate metabolite monomethyl phthalate (MMP) greater than the median were associated with decreased risk of adenomyosis or endometriosis (OR 0.122, 95% CI: 0.021–0.699), although the confidence interval is quite wide.[105]

Early-life risk factors

The theory of pathogenesis that postulates the development of adenomyosis from the metaplasia of Müllerian remnants suggests that exposures *in utero* or during childhood could contribute to the risk of disease.[4] A population-based study conducted in Denmark linked childhood school examination data from the Copenhagen School Health Records Register to the Danish National Patient Health Register to evaluate childhood body size and adenomyosis risk in adulthood.[111] Among the study population of 171,447 females, 1410 cases of adenomyosis were ascertained. The early-life body size exposures of birth weight, childhood BMI z-scores at ages 7 and 13 and height z-scores from ages 7–13 were evaluated. No associations were observed with birthweight or childhood height and the authors reported only very limited evidence of associations between childhood BMI and adenomyosis risk.[111] Additional studies are needed to better understand the role of early-life factors on disease risk.

Co-existing conditions

Some of the studies included in the review reported on the association between subfertility, endometriosis, endometrial hyperplasia, leiomyomas, and adenomyosis, inferring causal relations beyond the adenomyosis prevalence estimates in women with other uterine-related conditions summarized above. Although these conditions may not be risk factors for the development of adenomyosis, they may share common etiologic pathways with adenomyosis. The association between subfertility and adenomyosis was investigated in one

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population-based prospective cohort study among teachers in California. That study suggested only modest associations between ever experiencing difficulty becoming pregnant, ever use of fertility drugs for pregnancy, and adenomyosis.[102] Studies of the remaining conditions were conducted among women undergoing hysterectomy. The four studies that investigated endometriosis and adenomyosis reported mixed results.[33,36,38,42] Two studies reported a positive association (OR 1.4, 95% CI 0.9–2.2 and OR 1.5, 95% CI: 0.8–2.9)[33,36] whereas one study with substantial missing data on endometriosis observed a null association[42] and another study reported inconclusive results, likely owing to small numbers of women with both adenomyosis and endometriosis.[38] Two studies investigating endometrial hyperplasia reported a strong positive association with adenomyosis, with odds ratios ranging from 2.5 to 3.0.[36,38]

Unlike the positive associations generally reported between adenomyosis and subfertility, endometriosis, and endometrial hyperplasia, an inverse association has been observed with larger leiomyomas.[40,87] In one study, the presence of a uterine leiomyoma at least 2 cm in diameter was associated with a 67% lower odds of adenomyosis (OR 0.33, 95% CI: 0.25–0.44).[40] In another study comparing women with both leiomyomas and adenomyosis to those with only leiomyomas, each doubling in size of the largest fibroid was associated with 39% lower odds of having a concomitant diagnosis of adenomyosis (OR 0.61, 95% CI: 0.48–0.77).[87] Panganamamula et al (2004) speculated that the inverse association may be due to a more thorough investigation by the pathologist of the hysterectomy specimen that does not otherwise have a histopathologic diagnosis.[40] It is also possible that if parity both increases the risk of adenomyosis through disruption of the endometrial-myometrial border and is protective for uterine leiomyomas by the process of postpartum uterine involution,[122] fewer and smaller leiomyomas would be observed among adenomyosis cases.[122] Although, both studies adjusted for parity or gravidity in the analyses.

Heritability and Genetic Risk

There have been no twin studies of adenomyosis and no estimation of heritability to date. There also have been no genome-wide association studies that could yield agnostically identified loci associated with adenomyosis. The methodologic issues raised also apply to GWAS or candidate gene studies of adenomyosis, which would also be biased when restricted to only women who undergo hysterectomy as it would not be possible to tease apart the genes associated with adenomyosis and those associated with most common indications for hysterectomy or the characteristics of women most likely to undergo hysterectomy, each of which themselves have been associated with polymorphisms.[140–143]

Current state of epidemiologic research

Impact of selection bias

The ramifications of selection bias have been borne out in this review in the form of inconsistent results across studies. Most of the studies that met the criteria for review (N = 11 of 16) were conducted among women undergoing hysterectomy. As previously mentioned, the ability to reach valid conclusions is compromised when non-cases are not sampled from the source population that gave rise to cases (not sampled independent of

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exposure). Exposures, such as those related to estrogen, may also be associated with the indications for hysterectomy. As such, inconsistent results were observed for factors proposed to affect disease risk through an estrogenic pathway (e.g. early menarche, short menstrual cycle length, menopausal status, smoking, BMI, OC use, etc.). The consistent results for gravidity may be due to the proposed mechanism involving mechanical injury, and not an altered hormonal profile.

Other issues in conduct of epidemiologic research

In addition to study population sampling issues, the following issues fundamental to the conduct of epidemiologic research to investigate risk factors were observed during this review: (1) lack of reported study design or incorrect use of study design terminology. Epidemiologic observational studies typically use a cohort, case-control, or cross-sectional study design, and there are specific design elements that place studies into these types; (2) reliance on statistical significance to determine the presence of an association with some studies not reporting measures of association and precision (e.g., odds ratios and 95% confidence intervals); (3) cross-sectional ascertainment of exposures at the time of hysterectomy or the lack of information on the source of exposure data and the timeframe characterized. This limits the readers' understanding whether the exposure was characterized in the etiologically-relevant window for disease risk; (4) lack of adjustment for potential confounding factors or inappropriate selection of confounders based on statistical significance in univariate analyses or stepwise procedures. In several studies, these approaches resulted in correlated exposures, such as parity and gravidity, being included in the same multivariable model; and (5) absence of investigation for several potential risk factors commonly explored for gynecologic conditions and non-reproductive chronic diseases. No studies were found that investigated exposures such as physical activity, diet, or alcohol use. In addition, few studies explored early-life factors and endocrine-disrupting chemicals in relation to adenomyosis risk. Overall, the literature exploring a range of risk factors is very sparse.

Contributions of population-based studies

Although this review has highlighted the challenges in conducting epidemiologic research on adenomyosis, there have also been advancements in study design in the past decade with the development of population-based study designs.[100,102,110,111] Three of these studies were conducted among established cohorts linked to other data sources.[102,110,111] The remaining study was a population-based case-control study conducted among enrollees of an integrated health plan. By selecting population controls from a defined study base of health plan enrollees, this case-control study allowed population controls to be selected independent of exposure. Recognizing the difficulty in disentangling the risk factors for hysterectomy from the pathology-confirmed diagnosis of adenomyosis, Trabert et al (2011) also employed a hysterectomy control group. The researchers reasoned that the use of both population and hysterectomy controls allowed for a realistic range of associations to be estimated.

Although these population-based studies have moved the field forward in understanding risk factors for adenomyosis, the possibility exists for misclassification of disease from

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undiagnosed disease or disease not leading to clinical attention or surgical management. The extent of this misclassification is not known due to the lack of data on the prevalence of adenomyosis in the general population. However, the impact of systematic error from case under-ascertainment and disease misclassification on the estimate of association can be evaluated using quantitative bias analyses.[144,145] A valid study design with some disease misclassification is preferable to a design, such as a study population restricted to hysterectomy patients, which may yield wholly invalid conclusions.

Contributions of imaging-based studies

One study that contributed information to this review of disease risk factors was conducted among women undergoing imaging as part of a diagnostic work-up.[49] The restriction to women with medical indications warranting imaging makes this study design prone to selection bias. However, unlike studies restricted to patients undergoing hysterectomy, the selection factors related to willingness to undergo major surgery with the removal of the uterus are not at play.

Recommendations for future research

Population-based study design and participant sampling

To promote valid inference, epidemiologic studies of adenomyosis should not rely on case series and the selection of convenience samples, but rather use population-based case-control and cohort study designs. In addition, the temporality of risk factors, or exposures, in relation to adenomyosis should be taken into account. The use of TVUS or MRI imaging for future adenomyosis research will be critical in this regard. First, imaging allows for the study of adenomyosis in the general population of women, and not just those with medical indications seeking health care. Second, the screening of the general population across the lifespan would facilitate the estimation of disease prevalence that more closely approximates the true prevalence. This would allow the prevalence estimate to include undiagnosed disease that has not come to medical attention. Third, screening would permit the prospective follow-up of women across the reproductive years to understand vital aspects of adenomyosis - including the natural history of disease, symptomatology, and disease progression, and risk factors for disease incidence. Fourth, screening would support the investigation of the impact of adenomyosis in adolescents and young women – a population for whom adenomyosis has not been well-characterized. Thus, screening for adenomyosis in the general population would provide a fuller picture of the occurrence and risk factors for disease.

The use of TVUS or MRI imaging is supported by the substantial advancement in imaging technology, increase in non-invasive treatment options, and concurrent decrease in utilization of hysterectomy. However, consensus on the sonographic features for adenomyosis diagnosis is still needed. Imaging of adenomyosis is presented in more detail by O’Shea et al, in this issue.

For future studies employing innovative study designs using data linkages within large health systems or national registries, care will be needed when relying on the International

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Classification of Diseases (ICD) to capture and define adenomyosis cases. For example, the 9th revision (ICD-9) and 10th revision (ICD-10) use codes 617.0 and N80.0, respectively, named “endometriosis of uterus”.[146] As such, there is the potential for misclassification of both adenomyosis and endometriosis. This issue is anticipated to improve with the 11th revision (ICD-11) that is scheduled to come into effect on 1 January 2022 that will include code GA11 named “adenomyosis.”[147]

Best practices in epidemiologic research

Future research would benefit from collaboration between epidemiologists, biostatisticians, and clinicians to optimize study validity and accurate reporting of results. This includes the movement away from statistical significance testing and towards estimating and reporting measures of association (e.g., odds ratio (OR) or hazard ratios (HR)) and precision (95% confidence interval).[148,149] It is also expected that adjustment for confounding factors transpires when estimating associations, a practice essential to valid inference. In addition, modern epidemiologic methods (e.g., directed acyclic graphs), informed by the relationship between factors and adenomyosis and not statistical significance testing, should be employed in the selection of potential confounding factors for adjustment.[150,151] Furthermore, greater emphasis is needed on exposure measurement, with particular attention to the timing of exposure in relation to disease development and approaches to more accurately ascertain exposure.[152] Lastly, guidelines for the reporting of observational studies, such as Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines,[153] should be used in the reporting on observational studies in manuscripts. This would help to ensure that the approaches and methods used to conduct the study, including the ascertainment of exposure data, are transparent to the reader.

Summary and conclusions

The epidemiologic study of adenomyosis has lagged behind the study of other non-cancerous reproductive conditions such as endometriosis and uterine leiomyomas. In part, the lack of progress stems from the challenges in designing valid epidemiologic studies of adenomyosis given its diagnosis has historically relied on specimens from hysterectomy. This has precluded the determination of the prevalence of adenomyosis in the general population as well as inference regarding risk factors for disease, as hysterectomy controls are not selected independent of exposure. Hence, firm conclusions about the epidemiology of adenomyosis, including its prevalence, symptomatology, and risk factors, cannot be drawn from the results of existing studies. However, the substantial improvements in imaging technologies now allows the epidemiologic study of adenomyosis to extend beyond the setting of hysterectomy patients and into the general population. Imaging-based detection of disease and population-based study designs will facilitate a greater understanding of a disease that may be more prevalent across the lifespan than currently documented, and that can substantially affect the quality of women’s lives.

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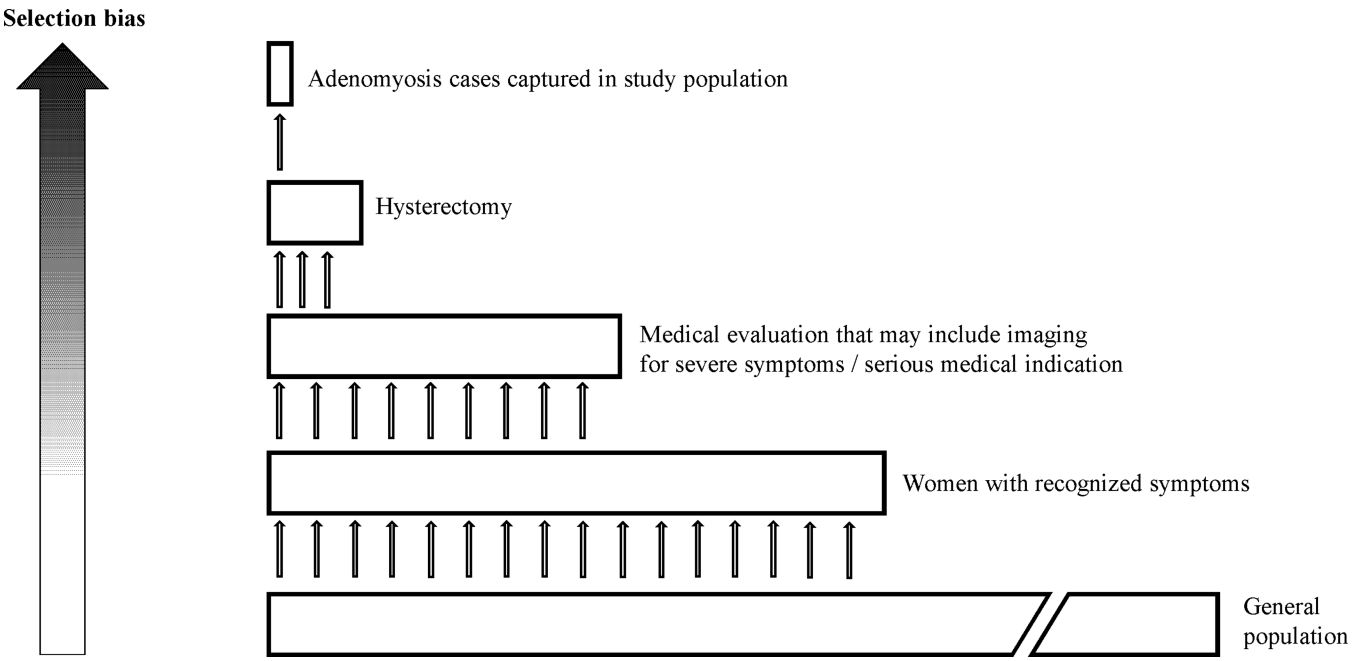

Figure 1.

Sample selection, from the general population to the highly selected population of women undergoing hysterectomy.

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Table 1.

Adenomyosis prevalence at hysterectomy

Author	Country	Years	# Hysterectomies	% Adenomyosis	Case median age	Sample age range
Molitor[18]	USA	1960–1969	3207	8.8	40–49 (peak)	27–85[a]
Bird[19]	USA	1969–1970	200	31.0–61.5[b]	45.5 (mean)	18–77
Owolabi[20]	Canada	1971–1974	1619	9.9	45 (mean)	NR
Blum[21]	Israel	1975–1977	920	9.7[c]	44.5 (mean)	31–67[a]
Pendse[22]	India	1970–1979	1476	10.7	41–50 (peak)	24–65[a]
Rao[23]	Jamaica	1966–1980	1947	16.4	46–50 (peak)	20–75[a]
Fukamatsu[24]	Japan	1977–1981	418	12.2	44.8 (mean)	NR
Kilkku[25]	Finland	1978–1979	212	13.2	46.7 (mean)	35–51[a]
Harris[26]	USA	1978–1982	3129[d]	15.5	40–50 (peak)	NR
Thompson[27]	USA	1972–1981	702	16.0[c]	37 (mean)[e]	19–65[a]
Raju[28]	Trinidad, W. Indies	1976–1982	2616	15.9	30–49 (peak)	24–82[a]
Thomas[29]	USA	1982–1983	174	26.4[c]	30–39 (peak)	NR
Shaikh[30]	Pakistan	1986–1989	419	56.6[c]	40–59 (peak)	31–74[a]
Chrysostomou[31]	Greece	1985–1989	646	25.1[c]	40–49 (peak)	33–74
Bocker[32]	Israel	1970–1989	1434	12.1[c]	50 (mean)[f]	33–84[f]
Vercellini[33]	Italy	1990–1992	1334	24.9	50[g]	31–82
Reinhold[34]	Canada[h]	1992–1994	119	23.5	51[g]	29–83
Seidman[35]	USA	NR	1252	39.0	NR	NR
Parazinni[36]	Italy	1993–1994	707	21.2	52.9 (mean)	19–84
Vavilis[37]	Greece	1991–1995	594	19.5	NR	NR
Bergholt[38]	Denmark	1990–1991	549	10.0–18.2[i]	54 (mean)[j]	23–88
Curtis[39]	USA	1978–1981	1850	19.9	NR	NR
Panganamamula[40]	USA	1995–2002	873	47.2[c]	47.1 (mean)	25–89

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Author	Country	Years	# Hysterectomies	% Adenomyosis	Case median age	Sample age range
Yeniel[41]	Turkey	2003–2004	298	34.6[c]	50.0 (mean)	38–86
Parazzini[42]	Italy	2006	820	28.2	51.2 (mean)	NR
Ozkan[43]	Turkey	2005–2009	1680	12.0[k]	NR	NR
Saleh[44]	Jordan	2008–2009	137	27.7	49.1 (mean)[j]	35–76
Shrestha[45]	Nepal	2009–2010	256	23.4	45 (mean)[j]	26–76
Pervez[46]	Pakistan	2008–2012	861	34.4	44.5 (mean)[j]	27–62
Li[47]	China	2007	1697	43.3	45[l]	21–75

Abbreviation: NR, not reported.

[a]Among adenomyosis cases.

[b]Prevalence using 3 and 9 sections.

[c]Prevalence estimated using data provided in study.

[d]Total number of hysterectomies estimated using available data.

[e]Mean reported as “slightly over 37 years”.

[f]Mean age and range reported among adenomyosis and endometriosis patients.

[g]Median age of patients undergoing hysterectomy.

[h]Author location; location of study not reported.

[i]Prevalence varied with diagnostic criteria; 10.0% reported when stricter criteria was applied (≥5 mm between endometrial glands and endomyometrial junction and presence of myometrial hyperplasia) and 18.2% prevalence when less strict criteria applied (≥1 mm between endometrial glands and endomyometrial junction and no myometrial hyperplasia). Number of adenomyosis cases not provided in manuscript.

[j]Mean age of patients undergoing hysterectomy.

[k]Prevalence estimate provided in the manuscript.

[l]Median age among premenopausal adenomyosis cases (96.7% of all adenomyosis cases).

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Table 2.

Characteristics of epidemiologic studies of adenomyosis.

First author	Location	Years	Reported study design	Design defined in review	Study population	Case ascertainment	Cases	Controls or non-cases	Exposure measurement	Report OR (95% CI)	Confounder Adjustment
Vercellini[33]	Italy	1990–1992	NR	Cross-sectional	Hysterectomy	Pathology records	332	1002	Record review	Yes	Yes[a]
Parazzini[36]	Italy	1993–1994	Cross-sectional	Cross-sectional	Hysterectomy	Pathology records	150	557	Patient report, record review	Yes	Yes[b]
Vavilis[37]	Greece	1991–1995	Retrospective study	Cross-sectional	Hysterectomy	Pathology records	116	478	Record review	Yes	No
Levgur[101]	USA	1994–1997	Retrospective study	Cross-sectional	Hysterectomy[c]	Specimen section re-evaluation	17 AD 19AD +L 39 L	36 no AD, no L	Record review	Yes	Yes[d]
Bergholt[38]	Denmark	1990–1991	NR	Cross-sectional	Hysterectomy	Specimen re-examination	NR	549 (total)	Record review	Yes	Yes[e]
Curtis[39]	USA	1978–1981	NR	Cross-sectional	Hysterectomy[f]	Pathology records	368	1482	Interview, record review	Yes	Yes[g]
Panganamamula[40]	USA	1995–2002	Retrospective study	Case-control	Hysterectomy[h]	Pathology records	412	461	Record review	Yes	Yes[i]
Yeniel[41]	Turkey	2003–2004	Prospective study[j]	Case-control	Hysterectomy	Not specified[k]	103	195	NR	No	No
Templeman[102]	USA	1995–1996 (Baseline) Study entry to 12/31/2003 (follow-up)	Prospective cohort	Prospective cohort	California Teachers Study[l]	ICD-9 code 617.0 inpatient hospitalization	961	79,329 (total)	Questionnaire	Yes	Yes
Parazzini[42]	Italy	2006	Cross-sectional	Cross-sectional	Hysterectomy[m]	Pathology data not specified[n]	231	589	Interview[o]	Yes[p]	Yes[q]
Huang[103]	Taiwan	2005–2007	Case-control	Case-control	Laparoscopy[r]	Pathology records	16 AD 28 EN 36 L	29 no AD, EN, L	Urinary measurement	Yes	Yes
Romanek[86]	Poland	2003–2007	Retrospective study[s]	Case-control	Hysterectomy	Pathology records	135 AD+L	176 L	Record review	Yes[t]	No
Taran[12]	USA	2000–2007	Retrospective case-control	Matched case-control	Hysterectomy[u]	Pathology records	76 AD, no L	152 L, no AD	Record review	Yes[v]	No[w]

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First author	Location	Years	Reported study design	Design defined in review	Study population	Case ascertainment	Cases	Controls or non-cases	Exposure measurement	Report OR (95% CI)	Confounder Adjustment
Taran[87]	USA	2000–2007	Retrospective matched case-control	Matched case-control	Hysterectomy[u]	Pathology records	85 AD +L	170 L, no AD	Record review	Yes[v]	Yes[x]
Trabert[100]	USA	1996–2001	Case-control	Case-control (two control groups)[y]	Health plan enrollees	Hysterectomy pathology record	174 AD[z]	149 population 106 hysterectomy	Record review	Yes	Yes[aa]
Naftalin[49]	UK	2009–2010	Prospective observational study	Cross-sectional	General gynecology clinic	TVUS	206	779	Not specified[bb]	Yes	Yes[cc]
Ozkan[43]	Turkey	2005–2009	Retrospective study	Case-control	Hysterectomy[dd]	Pathology records	98	106 L	Not specified[ee]	Yes[ff]	No
Shrestha[104]	Nepal	2010–2012	Cross-sectional	Cross-sectional	Hysterectomy	Pathology records	69	91	Not specified[ee]	Yes	Yes[gg]
Taran[89]	Germany	2003–2006	Retrospective study	Case-control	Hysterectomy[hh]	Pathology records	38 AD 56 AD +L	197 L	Record review	Yes[ii]	Yes
Jean-Baptiste[90]	USA	2007–2010	Retrospective chart review	Case-control	Hysterectomy or myomectomy[jj]	Pathology record	21 AD 37 AD +L	148 L	Record review	Yes	Yes[kk]
Boeer[91]	Germany	2007–2010	Retrospective and questionnaire-based study	Case-control	Hysterectomy[hh]	Pathology record	52	402 L	Record review[ll]	No	No
Brucker[92]	Germany	2007–2010	Retrospective questionnaire-based study	Case-control	Hysterectomy[hh]	Pathology record	159 AD+L	401 L	Record review[mm]	Yes[nn]	Yes[oo]
Huang[105]	Taiwan	2005–2007	Case-control	Case-control	Laparoscopy[r]	Pathology record	44 EN/AD 36 L	69 No EN, AD, L	Urinary measurement	Yes	Yes
Kazemi[106]	Iran	2001–2011	Cross-sectional	Cross-sectional	Hysterectomy[pp]	Pathology record	72	119	Record review	No	No
Riggs[107]	USA	2003–2007	Case-control	Case-control	Hysterectomy[qq]	Pathology record	189	178	Record review	Yes	No
Bodur[80]	Turkey	2005–2008	Retrospective analysis	Case-control	Hysterectomy	Specimen re-evaluation	56	43	Record review	Yes[rr]	Yes[ss]

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First author	Location	Years	Reported study design	Design defined in review	Study population	Case ascertainment	Cases	Controls or non-cases	Exposure measurement	Report OR (95% CI)	Confounder Adjustment
Genc[108]	Turkey	2005–2013	Retrospective analysis	Case-control	Hysterectomy	Not specified[k]	327	618	Not specified[ee]	Yes[tt]	Yes[uu]
Guzel[109]	Turkey	2009–2014	Retrospective study	Case-control	Hysterectomy[vv]	Not specified[k]	33 AD +L 26 AD 48 L	22 No AD, no L	Not specified[ee]	Yes	Yes[ww]
Ates[93]	Turkey	2011–2014	Retrospective study	Case-control	Hysterectomy[xx]	Pathology records	75AD +L	218 L	Record review	Yes	Yes[yy]
Puente[59]	Spain	2009–2013	Cross-sectional study	Cross-sectional study	Infertility patients with diagnostic imaging	TVUS, stored 3D volumes	248	767	Record review	Yes[zz]	No
Gao[110]	Sweden	1933–1972 (born) 1968–2008 (follow-up)	Population-based cohort study	Population-based cohort study	Uppsala Birth Cohort Multigenerational Study Cohort female offspring	Swedish inpatient and outpatient registers	24	3406 (total)	Archived obstetric records	Yes[aaa]	Yes
Aarestrup[111]	Denmark	1930–1996 (born) 1977–2017 (follow-up)	Population-based cohort	Population-based cohort study	Copenhagen School Health Register	Danish National Patient Health Register	1410	171,477 (total)	School health examination records	Yes[aaa]	Yes

Abbreviations: AD, adenomyosis; AD+L, both adenomyosis and leiomyomas; EN, endometriosis; L, leiomyomas; NR, not reported; TVUS, transvaginal ultrasound.

Studies included in the review of risk factors are denoted with first author's name in bold.

[a] Adjusted for age using Mantel-Haenszel procedure.

[b] Adjusted for more than one pregnancy-related factor in the same multivariable model (parity, spontaneous abortion)

[c] Women undergoing hysterectomy for benign uterine enlargement with uteri <280g.

[d] Adjusted for multiple pregnancy-related factors in the same multivariable model (parity, cesarean delivery, pregnancy termination).

[e] Adjusted for multiple pregnancy-related factors in the same multivariable model (cesarean delivery, evacuation, parity).

[f] Data from retrospective cohort study.

[g] Adjusted for gravidity when examining pregnancy-related factors including abortion and cesarean delivery.

[h] Patients undergoing peripartum hysterectomy and hysterectomy patients with endometriosis reported on pathology report were excluded.

[j] Multivariable analysis conducted only for subset of risk factors investigated; assumed factors used for adjustment were those reported in the data table.

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[j] Hysterectomy patients with and without adenomyosis are referred to as study and control groups, respectively.

[k] Uterine specimens obtained during hysterectomy were histopathologically examined. Not specified if data collected from pathology report or direct examination of specimens by the researchers.

[l] Excluded participants diagnosed with incident endometriosis during follow-up.

[m] Restricted the study population to patients undergoing hysterectomy for benign gynecological conditions.

[n] Pathology data were collected, but not specified if data collected from pathology report and direct examination of specimens by researchers.

[o] Interview conducted using questionnaire at time of hospitalization, prior to hysterectomy; medical records used to check patient responses regarding medical history.

[p] Odds ratio was used to approximate rate ratio, despite outcome being common (identified in 28% of participants).

[q] Adjusted for multiple pregnancy-related factors in the same multivariable model (parity, spontaneous abortions, induced abortions, cesarean delivery).

[r] laparoscopy patients previously diagnosed with estrogen-dependent conditions were excluded.

[s] Hysterectomy patients with leiomyomas with and without adenomyosis are referred to as study and control groups, respectively.

[t] "RR (95%CI)" reported in data table; RR not defined in manuscript.

[u] Study population restricted to premenopausal hysterectomy patients, ages <55 years, residing in Olmsted County, Minnesota, without gynecologic cancer on pathologic examination.

[v] No accounting for matching in estimation of odds ratio.

[w] Multivariable regression analyses conducted on subset of participants with disease-specific symptoms or uterine weight ≥150g and only select factors were evaluated.

[x] Adjusted odds ratios and 95% CIs provided for subset of factors investigated, with stepwise selection procedures used to select adjustment variables; variables entered into the stepwise model were selected based on statistical significance in univariate analyses.

[y] Two control groups were used: hysterectomy controls and population-based controls. Hysterectomy controls were health plan enrollees who underwent hysterectomy and not found to have endometriosis, adenomyosis, or gynecologic cancer. Randomly selected health plan enrollees without a history of hysterectomy, frequency matched to cases on age served as population-based controls. Neither control group had a history of endometriosis.

[z] Cases of adenomyosis without endometriosis or gynecologic cancer.

[aa] In analyses of cesarean delivery, adjusted for parity, age, and reference year.

[bb] Data collected at time of ultrasound examination. Not specified if data collected using standardized research methods or as part of clinical care.

[cc] Adjusted odds ratios and 95% CIs provided for subset of factors investigated; assumed factors used for adjustment were those reported in the data table.

[dd] Study population restricted to hysterectomy patients undergoing hysterectomy for benign pathologies; patients with the presence of gynecologic cancer on pathologic examination were excluded.

[ee] Information not provided on how data collected.

[ff] RR and 95% CI estimated for subset of factors. No information is provided about the adjustment for confounding factors in analyses.

[gg] No information on confounding factors used for adjustment in the analysis.

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[hh] Study population restricted to patients undergoing hysterectomy for benign uterine disease, premenopausal, ages <55 years, and no presence of gynecologic cancer on pathologic examination.

[ii] Results from multivariable analysis provided only in manuscript text, not in tabular form.

[jj] Patients with a history of gynecologic malignancies or undergoing hysterectomy for benign conditions other than adenomyosis and fibroids were excluded.

[kk] Factors selected for adjustment based on statistical significance in univariate analysis; assumed factors used for adjustment were those reported in the data table.

[ll] Questionnaire data collected on disease-specific symptoms and therapeutic impact of surgical procedure.

[mm] Questionnaire collected data on symptoms and their impact on quality of life.

[nn] Odds ratios and 95% CIs estimated for subset of factors

[oo] Adjustment factors selected using stepwise selection procedures.

[pp] Study population restricted to patients undergoing hysterectomy for benign and non-emergency gynecologic conditions; excluded those with endometriosis and uterine malignancies on pathologic examination.

[qq] Excluded hysterectomy patients without adenomyosis who had no history of prior gynecologic surgeries.

[rr] For some odds ratios, the odds ratio estimate is outside the confidence interval.

[ss] Multivariable analysis conducted only for subset of risk factors investigated, with backward stepwise procedure used to select adjustment variables in logistic regression.

[tt] Odd ratio estimated for each category of exposure, when exposure had more than two categories (no single exposure category served as the reference category).

[uu] Adjustment using Mantel-Haenzel. Adjustment factors not specified.

[vv] Hysterectomy patients who did not respond to medical treatment for metrorrhagia or menorrhagia. Excluded patients who underwent hysterectomy for malignant conditions or prolapse of the uterus.

[ww] Variables statistically significantly associated with adenomyosis in univariate analysis were included in multivariable regression model. Multiple pregnancy-related factors were included in the same model (gravidity, parity, spontaneous abortion).

[xx] Study population restricted to patients undergoing hysterectomy for benign uterine diseases.

[yy] Adjusted odds ratios and 95% CIs provided for subset of factors investigated. Factors selected based on statistical significance in univariate analyses. Two pregnancy-related factors were included in the same model (parity and gravidity).

[zz] For several exposures, odds ratio calculated for each category of exposure (no single exposure category served as the reference category).

[aaa] Hazard ratio and 95% confidence intervals were estimated.