BREASTFEEDING HISTORY AND ADENOMYOSIS RISK USING A NOVEL CASE-CONTROL STUDY DESIGN

By

Mandy Sue Hall

A THESIS

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

Epidemiology ─ Master of Science

2022

ABSTRACT

BREASTFEEDING HISTORY AND ADENOMYOSIS RISK
USING A NOVEL CASE-CONTROL STUDY DESIGN

By

Mandy Sue Hall

Adenomyosis is characterized by presence of endometrial tissue within the muscular wall of the uterus and is associated with substantial morbidity. While etiology of adenomyosis remains unknown, an estrogenic milieu contributes to disease pathogenesis. We hypothesize that lactation, wherein infant suckling inhibits ovulation and induces a hypoestrogenic state, is associated with decreased adenomyosis risk. We investigated this hypothesis using data from a case-control study of adenomyosis conducted among female enrollees of a large healthcare system in Washington State. In that study, incident, pathology-confirmed adenomyosis cases diagnosed 2001-2006 were identified and two control groups were employed: randomly selected age-matched enrollees with intact uteri ("population controls") and hysterectomy controls. Breastfeeding history of initiation and duration for each live birth reported were collected by in-person interview. We restricted the analytic sample to those with at least one live birth (330 cases, 246 population controls, and 198 hysterectomy controls) and used logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for associations between adenomyosis and breastfeeding, adjusting for age, reference year, smoking, education, and parity. Using population controls, history of ever breastfeeding or ever breastfeeding an infant for ≥ eight weeks were associated with a 40% decreased risk of adenomyosis (ever breastfed: OR 0.6, 95% CI: 0.3, 1.0; ever breastfed an infant ≥ eight weeks: OR 0.6, 95% CI: 0.4, 0.8). The magnitude of association was stronger with longer lifetime breastfeeding duration (≥12 months vs. 0-<3 months: OR 0.4, 95% CI: 0.2, 0.6) and exclusive breastfeeding (≥12 months vs. 0-<3 months: OR 0.4, 95% CI: 0.2, 0.6). Using hysterectomy controls, we observed similar patterns of associations that were attenuated in magnitude. Our results indicate that a potentially modifiable factor, breastfeeding, may decrease adenomyosis risk among parous women.

This thesis is dedicated to my parents.
Thank you for encouraging me to reach my goals.

ACKNOWLEDGEMENTS

The completion of this thesis would not have been possible without the support of many. I would like to thank my thesis committee members, Dr. Kristen Upson (chair), Dr. Claudia Holzman, and Dr. Ana Vazquez. To Dr. Upson, thank you dearly for your guidance and support as I navigated my graduate studies. Through your expertise in reproductive health, I have been exposed to new knowledge and interests that I will carry forward throughout my career in epidemiology. To Dr. Holzman, thank you for your valuable insight and lending your expertise in perinatal and reproductive health throughout my thesis process. To Dr. Vazquez, thank you for knowledge and commitment and for instilling in me biostatistical methods during my graduate studies.

To my parents, thank you for your unwavering support and encouragement in everything I have done. I would like to thank my siblings and nephews for the times of laughter and lightheartedness when I needed it the most. I thank my love, Brad, for his active commitment to me as I pursue my goals and education.

Lastly, thank you to the Department of Epidemiology and Biostatistics for the invaluable experiences in support of my professional development, and thank you to Michigan State University for being a home for the last five years.

Thank you.

TABLE OF CONTENTS

LIST OF TABLES

INTRODUCTION

Adenomyosis is characterized by the presence of endometrial tissue within the muscular wall of the uterus, the myometrium (Vannuccini et al., 2017). This condition is associated with substantial morbidity, including painful menstruation, chronic pelvic pain, abnormal uterine bleeding, and pain with urination (Harada et al., 2016). Surgical removal of the uterus through hysterectomy is the only cure (Upson & Missmer, 2020). While the etiology of adenomyosis remains unknown, it is established that an estrogenic milieu contributes to disease pathogenesis. Estradiol is a critical antecedent of disease pathogenesis, as presence of a hyperestrogenic state initiates endometrial proliferation, inflammation, and endometrial invagination of the myometrium (García-Solares, Donnez, Donnez, & Dolmans, 2018). Given the central role of estrogen, breastfeeding is an exposure that may decrease the risk of adenomyosis. Breastfeeding induces a hypoestrogenic state and suppresses ovulation (Mcneilly, 1997). The impact of breastfeeding on estrogen deficiency depends on the daily frequency and months of lactation, and whether breastfeeding is the only source of infant nutrition (Heinig & Dewey, 1997).

Only two previous studies have investigated the association between breastfeeding history and adenomyosis risk (Naftalin et al., 2012; Templeman et al., 2008). Neither of those studies investigated breastfeeding duration, particularly exclusive breastfeeding duration, and those studies reported conflicting results (Naftalin et al., 2012; Templeman et al., 2008). The discrepant results are likely due to the challenges in designing valid epidemiologic studies of adenomyosis. Adenomyosis has been historically diagnosed through histopathologic examination post-hysterectomy (Upson & Missmer, 2020), making the selection of appropriate controls difficult. Although histopathology can confirm absence of adenomyosis among women undergoing hysterectomy, hysterectomy controls may not represent the frequency of exposure in the population that gave rise to cases. A control group comprising randomly selected women from the underlying source population would allow for a valid study design; however, confounding can arise from differences in measured and unmeasured factors between cases and population controls related to the cases' willingness to undergo hysterectomy. Given these challenges, the

purpose of the present study was to investigate the association between breastfeeding history, including exclusive breastfeeding and duration, and adenomyosis risk, comparing cases to both hysterectomy and population controls.

METHODS

Study design and population

We used data from a case-control study conducted among pre- and postmenopausal female enrollees ages 18-59 years of a large, integrated healthcare system, Kaiser Permanente Washington, in Washington State. At the time of the case-control study, the healthcare system was known as Group Health Cooperative (GH). Cases were women diagnosed for the first time with pathology-confirmed adenomyosis by hysterectomy between April 1, 2001 and March 31, 2006. Cases were identified by review of GH electronic databases of hospitalizations, inpatient and outpatient surgery, and medical visits for the ICD 9th revision diagnostic codes 617.0, "endometriosis of uterus". Since this ICD-9 code includes diagnoses of endometriosis and adenomyosis, record review was conducted to identify women diagnosed with adenomyosis, and women only diagnosed with endometriosis were excluded from the case group.

For comparison, this study design consisted of two control groups who were also ascertained via GH enrollment database. Hysterectomy controls were women who had confirmed absence of adenomyosis on pathology report by hysterectomy for benign disease during the same period that cases were diagnosed. Population controls were women with an intact uterus, who had no history of adenomyosis diagnosis, and had been enrolled in GH at some point between April 1, 2001 and March 31, 2006. Population controls were randomly selected from the health plan database and were frequency matched to cases by 5-year age groups. These two control groups were selected as each comparison group has different advantages and disadvantages. The hysterectomy controls are similar to cases with respect to factors related to having a hysterectomy, including their willingness to undergo this procedure. However, the reasons for which the hysterectomy controls underwent hysterectomy may be associated with the exposure of interest, and hysterectomy controls may therefore not represent the frequency of exposure in the underlying population that gave rise to cases. On the other hand, population controls were randomly selected from the underlying population that gave rise to cases. Although the population controls may represent the

frequency of exposure in the underlying population, they may differ from cases on factors related to undergoing hysterectomy. The comparison of cases to each control group allowed for a comprehensive investigation of our research question.

To be eligible for the case-control study, participants needed to be enrolled in GH for at least six months before the reference date. The reference date for cases was the date of their first visit to GH for symptoms leading to adenomyosis diagnosis. The reference date for hysterectomy controls was the date of their first visit to GH for symptoms leading to hysterectomy. Reference dates were assigned to population controls corresponding to the distribution of reference dates among cases. The potential cases and controls (598 cases, 431 hysterectomy controls, and 726 population cases) received a letter of invitation for the case-control study followed by a phone call from GH personnel for the woman's name and telephone number that could be forwarded to Fred Hutchinson Cancer Research Center. Of those invited, 449 cases, 291 hysterectomy controls, and 707 population controls agreed to be contacted. After additional eligibility screening and completing the informed consent process, which included consenting to medical record review, 402 cases, 241 hysterectomy controls, and 354 population controls were enrolled. We restricted the study population to those for whom abstracted medical record data were available, including pathology confirmation of adenomyosis in cases or its absence in hysterectomy controls. Data for 386 cases, 233 hysterectomy controls, and 323 population controls were available for the present analyses.

Breastfeeding exposure

The main study activity in the case-control study was a structured, in-person interview conducted by a trained, female interviewer. Study participants were asked about a range of topics, from lifestyle behaviors to medical and pregnancy history, including history of live births and breastfeeding. For each live birth reported, participants were asked if they had breastfed this infant at all (no, yes) and if they had breastfed this infant for at least two weeks (no, yes). Participants were also asked the age (weeks or months) at which the infant began to take food, formula, or milk other than breast milk, regularly. Each participant was then asked the age (weeks or months) when the infant stopped breastfeeding altogether.

Using this information, we created binary variables characterizing a history of ever breastfeeding (no, yes) and ever breastfeeding an infant for at least eight weeks (no, yes). The duration of eight weeks aligns with the hypothesized minimum amount of time needed for lactation to induce lactational amenorrhea, as return to ovulation for non-lactating women is commonly after six weeks postpartum (Heinig, Nommsen-Rivers, Peerson, & Dewey, 1994; Jackson & Glasier, 2011). The selection of the eight weeks duration also corresponds with the time period during which breastfeeding may be the sole source of infant nutrition, based on recommendations on the introduction of solid foods that were in place when most participants gave birth. In the 1970s, guidelines recommended the delayed introduction of solid foods to four months of age; in the early 1990s, the recommended infant age for the introduction of solid foods was extended to six months (Koplin & Allen, 2013). We estimated the total months of lifetime breastfeeding by summing the reported months of breastfeeding across all livebirths. For use in analyses, we categorized total months of lifetime breastfeeding as 0- < 3, 3- < 6, 6- < 9, 9- < 12, and ≥12 months. We also estimated the lifetime duration of exclusive breastfeeding, defined as duration of breastfeeding before the reported regular feeding of food, formula, or milk other than breast milk, by summing the reported time of exclusive breastfeeding across all livebirths. We categorized the lifetime duration of exclusive breastfeeding as 0- < 3, 3- < 6, 6- < 9, 9- < 12, and ≥12 months.

Only participants who ever had a livebirth had the opportunity to breastfeed. For this reason, we restricted the analytic sample to parous participants (330 cases, 198 hysterectomy controls, and 246 population controls).

Statistical analyses

We used descriptive statistics to compare sociodemographic and reproductive characteristics between the cases and two control groups. We examined the association between breastfeeding and adenomyosis risk using the breastfeeding variables of ever breastfed, ever breastfed an infant at least eight weeks, lifetime

breastfeeding, and lifetime exclusive breastfeeding. We estimated the odds ratio (ORs) and 95% confidence intervals (CI) using unconditional multivariable logistic regression, comparing cases to hysterectomy controls and population controls in separate analyses. To test the trend across lifetime breastfeeding and exclusive breastfeeding categories, we created a continuous variable, assigning to cases and controls the median category value identified among controls in each category, and included that variable in the adjusted logistic regression model. Test of trend analyses were conducted separately when comparing cases to hysterectomy and population controls. We selected covariates *a priori* for adjustment based on associations with adenomyosis reported in the literature (Upson & Missmer, 2020) and their sociological impact on breastfeeding (Medicine, 1991). All analyses were adjusted for age at reference date (20-39, 40-44, 45-49, 50-59 years), cigarette smoking (never, current, former), education (high school graduate or general equivalency diploma (GED), some college/vocational/technical college, college graduate, post-graduate), and parity (1, 2, 3, ≥4 livebirths). Since population controls were assigned a reference date based on the distribution of reference dates in cases, analyses comparing cases to population controls were additionally adjusted for reference year (continuous).

We conducted several sensitivity analyses. First, we repeated the analyses adjusting for gravity instead of parity. Pregnancy history is a risk factor for adenomyosis, and it is hypothesized that the trophoblast invasion of the inner myometrium that occurs in early pregnancy is associated with increased adenomyosis risk (Pijnenborg, 1998). The adjustment for gravidity instead of number of live births allowed us to evaluate whether residual confounding may exist with the use of live births for adjustment in the main analyses. Second, we repeated the analyses additionally adjusting for body mass index (BMI). Adenomyosis and BMI are positively associated (Upson & Missmer, 2020), and higher BMI levels negatively impact initiation and duration of breastfeeding (Wojcicki, 2011). In this sensitivity analysis, we used the estimated BMI when the participants were in their 20s to best approximate BMI prior to breastfeeding and adenomyosis development; we estimated BMI using the average weight participants reported when they were in their 20s and height reported at the in-person interview. Third, we restricted

the study population to participants with two livebirths (138 cases, 96 hysterectomy controls, 126 population controls), the mode of live births in the sample, and adjusted for gravidity. This sensitivity analysis was conducted to further control for confounding due to pregnancy history as increasing parity provides a greater opportunity to breastfeed, and pregnancy history is associated with increased adenomyosis risk (Upson & Missmer, 2020). Fourth, for analyses comparing cases to population controls, we repeated the analyses after restricting the population controls to those who reported they would "probably" or "definitely" allow for hysterectomy if it was recommended to them if they "developed severe menstrual bleeding, severe menstrual pain, or severe pelvic pain every month for six months or more" (n = 126). As population controls may differ from cases on factors related to undergoing hysterectomy, this sensitivity analysis sought to make the population controls more representative of the population that gave rise to cases. Finally, we conducted a sensitivity analysis in which we additionally adjusted for duration of oral contraceptive use (0, ≤ 2, >2 - 8, >8 years). We were interested in accounting for use of oral contraceptives as an indirect measure for socioeconomic and reproductive factors, such as pregnancy intention (Soto-Ramírez & Karmaus, 2008). As oral contraceptives lower estrogen levels to a consistently low state (Dufau et al., 1970; Mishell, Thorneycroft, Nakamura, Nagata, & Stone, 1972), oral contraceptives can be used as first line of treatment for menstrual pain and pelvic pain due to undiagnosed adenomyosis (Pontis et al., 2016). For this reason, we did not adjust for duration of oral contraceptive use in the main analyses.

RESULTS

In this analytic sample, majority of study participants at the reference date were ages 45-49 years, white, and non-Hispanic. Adenomyosis cases more frequently reported lower educational attainment (some college or less) compared to population controls, but not hysterectomy controls (Table 1). However, cases were more likely to report a lower household annual income (<$50,000), history of ever smoking cigarettes, were more likely to have a BMI ≥ 30 kg/m^2 and were more likely to report a BMI 20 - <25 kg/m^2 in their 20's, compared to both hysterectomy and population controls. In addition, compared to both hysterectomy and population controls, cases more frequently reported an earlier age at menarche (≤ 11 years), history of five or more pregnancies, and history of ever using oral contraceptives (>2 – 8 years).

Among population controls, those who had a history of ever breastfeeding an infant at least eight weeks were more likely to report higher educational attainment (college graduate or more) and history of never smoking, compared to those who never breastfed an infant at least eight weeks (Supplemental Table I). Additionally, population controls who breastfed an infant at least eight weeks were more likely to report a history of four or more pregnancies and greater duration of oral contraceptive use (>8 years).

Majority of the study participants reported ever breastfeeding as observed across cases (85%), hysterectomy controls (88%), and population controls (91%) (Table II). We observed cases were less likely to have ever breastfed an infant compared to either hysterectomy controls (OR 0.7, 95% CI: 0.4, 1.2) or population controls (OR 0.6, 95% CI: 0.3, 1.0) (Table II). When we required at least eight weeks of breastfeeding an infant to be considered exposed, we observed similar associations (cases vs. hysterectomy controls: OR 0.7, 95% CI: 0.5, 1.0; cases vs. population controls: OR 0.6, 95% CI: 0.4, 0.8).

With regard to lifetime months of breastfeeding, increased duration of breastfeeding was associated with decreased risk of adenomyosis, comparing cases to hysterectomy (*P*-value for tend, P=0.07) and

population controls (*P*-value for trend, P<0.0001). The association was strongest with ≥ 12 months of lifetime breastfeeding (vs. < 3 months), comparing cases to population controls (OR 0.4, 95% CI: 0.2, 0.6). The association was attenuated when comparing cases to hysterectomy controls (≥ 12 months of lifetime breastfeeding vs. < 3 months OR 0.6, 95% CI: 0.4, 0.9). When we considered duration of exclusive breastfeeding over the lifetime, we similarly observed the strongest association with ≥12 months of lifetime exclusive breastfeeding (vs. < 3 months), when comparing cases to population controls (OR 0.4, 95% CI: 0.2, 0.6) and hysterectomy controls (OR 0.5, 95% CI: 0.3, 0.9). In addition, the tests for trend were statistically significant with increasing categories of exclusive breastfeeding duration.

In our sensitivity analyses, we observed results similar to those in the main analyses after adjusting for gravidity instead of parity (Supplemental Table II) and additionally adjusting for BMI (Supplemental Table III). In our sensitivity analyses restricting the analytic sample to women with two live births, we observed associations stronger in magnitude than in the main analyses when comparing cases to population controls, whereas the results parallel the main analyses when comparing cases to hysterectomy controls, although the ORs were accompanied by wide confidence intervals due to small cell sizes (Supplemental Table IV). In our sensitivity analyses comparing cases to population controls restricted to those who would allow for a hysterectomy if warranted, we observed results that were generally comparable to results observed from the main analyses (Supplemental Table V). When we additionally adjusted for duration of oral contraceptive use, we observed associations stronger in magnitude compared to the main analyses when comparing cases to population controls but similar results to the main analyses comparing cases to hysterectomy controls (Supplemental Table VI).

DISCUSSION

In the present analysis using data from a population-based case-control study of adenomyosis employing two control groups, we observed that breastfeeding was associated with decreased adenomyosis risk. The magnitude of the association was stronger with increasing lifetime breastfeeding and exclusive breastfeeding duration.

There is no established etiology of adenomyosis. One theory of adenomyosis pathogenesis postulates that a hyperestrogenic state promotes increased endometrial basalis proliferation and tissue microtrauma in the junctional zone leading to the invagination of basalis endometrium into the myometrium (García-Solares et al., 2018; Vannuccini et al., 2017). Evidence for the hyperestrogenic state includes the increased local and ovarian estrogen production among women with adenomyosis (Rizner, 2016; Urabe, Yamamoto, Kitawaki, Honjo, & Okada, 1989). Since estrogen is central to adenomyosis pathogenesis, breastfeeding could reduce the risk of adenomyosis through prolonged anovulation and the subsequent reduction of estradiol levels. When not lactating, the luteinizing hormone (LH) stimulates the ovarian follicle to produce estradiol and induces ovulation (Mcneilly, 2001). In contrast, when lactating, the infant suckling stimulus is detected by the hypothalamus and inhibits the pulsatile secretion of the gonadotropin releasing hormone (GnRH), leading to the inhibition of LH and the follicle-stimulating hormone (FSH) from the pituitary (Heinig & Dewey, 1997). The suppression of LH prevents stimulation of the ovarian follicle, resulting in anovulation and the lack of estradiol production (Mcneilly, 1997). As the infant suckling stimulus is removed or diminished in frequency, the pulsatile release of LH returns to normal levels over time and ovulation returns (Heinig & Dewey, 1997). Therefore, the impact of a breastfeeding-induced hypoestrogenic state on adenomyosis is dependent on duration and exclusivity of breastfeeding.

Our observation of an inverse relationship contrasts that observed in a cross-sectional study among pre- and post-menopausal women undergoing a transvaginal ultrasound examination for a medical indication at a gynecologic clinic (Naftalin et al., 2012). That study reported the suggestion of a positive association

between a history of breastfeeding for >6 months (vs. ≤ 6 months) and adenomyosis prevalence among parous women (unadjusted OR 1.19, 95% CI: 0.76, 1.87). The reported association was not adjusted for confounding factors. However, our finding is consistent to that observed in a large cohort study of over 80,000 female teachers in California that were followed for inpatient hospitalization with the diagnosis of adenomyosis (Templeman et al., 2008). That study reported a 26% decrease in the prevalence of surgically-confirmed adenomyosis with a history of ever breastfeeding (prevalence odds ratio 0.74, 95% CI: 0.62, 0.88) among parous women. The discrepant results across studies are likely due to the differences in sampling frames, method of adenomyosis diagnosis, and adjustment for confounding.

Our study benefitted from the utilization of two control groups and a sampling frame based on health plan enrollees. The use of hysterectomy and population controls allowed us to comprehensively evaluate the association between breastfeeding history and adenomyosis, as there is no perfect control group for adenomyosis cases identified by hysterectomy. Histopathology confirmation of adenomyosis through hysterectomy is the gold standard for diagnosis. Hence, the use of hysterectomy controls allowed for the histopathologic confirmation of disease absence. Additionally, hysterectomy controls are similar to cases on their willingness to undergo this procedure and factors related to having a hysterectomy. Despite these advantages, the reasons for which hysterectomy controls underwent hysterectomy may be associated with the exposure of interest and introduce selection bias. For this reason, cases were also compared to population controls who were randomly selected from the underlying population that gave rise to cases. Although the comparison of cases to population controls minimizes selection bias, this comparison may be susceptible to confounding as population controls may differ from cases on factors related to undergoing hysterectomy. However, the results from our sensitivity analysis comparing cases to population controls restricted to those who would “probably” or “definitely” have a hysterectomy if needed suggested that potential bias from this source of confounding was minimal; we observed results that were similar to those in the main analysis. In addition to the use of two control groups, the health plan enrollee population strengthened our study as all cases and controls were sampled from the same

population. Therefore, for example, we can assume controls would have been sampled as cases if they were diagnosed with adenomyosis.

Our study had several limitations. First, we relied on recall to ascertain information on breastfeeding history, including duration, for each livebirth a participant reported. Data from a prospective study of pregnant Norwegian women (Natland, Andersen, Nilsen, Forsmo, & Jacobsen, 2012) suggests that the exposure misclassification due to recall is minimal. That study compared information on breastfeeding initiation and duration recorded during the child's first year to that recalled 20 years later and observed that maternal recall of breastfeeding decades later was strongly correlated with recorded breastfeeding (intraclass correlation coefficient = 0.82) (Natland et al., 2012). Second, we also relied on recall for body weight ascertainment for when the participant was in their 20's. In a retrospective study on breast cancer detection among women ages 33-77 years, participants were asked to recall their height and weight in 10-year intervals starting at age 20 (Muñoz et al., 1996). The study compared information on recalled BMI and measured BMI for decades of 40-49, 50-59, and 60-69 and observed a strong correlation (Pearson correlation coefficient = 0.89) (Muñoz et al., 1996). Third, information was not collected during the in-person interview on the timing of return to menses while breastfeeding. Information on return to menses after birth would have allowed for the estimation of lactational amenorrhea that is indicative of the hypoestrogenic state experienced with breastfeeding. That said, we had available information on the timing of regular supplementary feeding to estimate the duration of exclusive breastfeeding. The time of supplementary feeding has been observed to be correlated with the time of menstrual resumption (Pearson correlation coefficient = 0.56, $P < 0.01$) in lactating postpartum women (Li & Qiu, 2007).

Fourth, it is possible that some population controls may have undiagnosed adenomyosis as they did not have confirmation of disease absence through hysterectomy. Although the prevalence of adenomyosis is not known in the general population, Naftalin et al. observed an adenomyosis prevalence of 21% using transvaginal ultrasound imaging among women with a medical indication, including pelvic pain. Among

the population controls in the present study (n = 246), 53 (22%) reported experiencing pelvic pain when not menstruating. Hence, if adenomyosis was present in 21% of these population controls with pelvic pain, then an estimated 5% of population controls could have undiagnosed adenomyosis. This suggests that outcome misclassification among the population controls is likely to be low.

Fifth, trained female interviewers were not blinded to participant assignment during the interview. As the trained interviewers used a structured interview format and information was collected comparably between cases and controls, the potential for the interviewer to introduce bias would be minimal. Sixth, there is potential for incomplete adjustment as breastfeeding is strongly associated with other behaviors and socioeconomic factors (Medicine, 1991; Odar Stough, Khalsa, Nabors, Merianos, & Peugh, 2019); however, we conducted sensitivity analyses to understand the effect of other factors such as BMI and oral contraceptives, and our results were consistent with the main analyses.

Lastly, few women in our study population of parous health plan enrollees in the Pacific Northwest reported never breastfeeding. Although our observed high breastfeeding rates mirror what is known about breastfeeding frequency in the Pacific Northwest (Medicine, 1991), the results from our study may not be generalizable to other parous populations. Conversely, due to the high frequency of breastfeeding history and collection of detailed breastfeeding data, we were able to investigate the relationship between adenomyosis and duration of breastfeeding.

The challenges in conducting a valid epidemiologic study of adenomyosis originates from the historic reliance on histopathologic confirmation of disease after hysterectomy, the gold standard for adenomyosis diagnosis. Recent advancements in imaging technology now allow for the detection of adenomyosis in the general population. The screening of the general population through imaging would provide a fuller picture of the association between breastfeeding history and adenomyosis risk in future studies.

CONCLUSION

In our analyses using data from a case-control study among female enrollees of a large, integrated healthcare system in western Washington state, we observed that breastfeeding initiation and duration were associated with decreased adenomyosis risk. If replicated, our findings would not only provide support for another maternal benefit of breastfeeding but would also inform approaches to modify the risk of adenomyosis - a condition that can be associated with substantial pain symptoms and that lacks a cure other than hysterectomy.

APPENDICES

APPENDIX A

Tables

Table I. Participant characteristics by case status, Kaiser Permanente Washington, 2001-2006. [a]

Participant characteristic[b]	Cases (n = 330) n (%)[c]	Hysterectomy Controls (n = 198) n (%)[c]	Population Controls (n = 246) n (%)[c]
Age at reference date, years			
< 35	15 (5)	5 (3)	8 (3)
35-39	29 (9)	26 (13)	26 (11)
40-44	89 (27)	47 (24)	67 (27)
45-49	103 (31)	64 (32)	84 (34)
50-59	94 (29)	56 (28)	61 (25)
Race			
White	282 (86)	171 (86)	219 (89)
Black or African-American	15 (5)	12 (6)	5 (2)
Asian, Native Hawaiian, other Pacific Islander	11 (3)	4 (2)	12 (5)
American Indian, Native American, Alaskan Native	5 (2)	0 (0)	2 (1)
More than one race	15 (5)	11 (6)	6 (2)
Hispanic			
No	312 (95)	191 (97)	234 (95)
Yes	17 (5)	7 (4)	7 (3)
Education			
≤HS graduate or GED	95 (29)	46 (23)	53 (22)
Some college/ vocational/technical college	153 (46)	96 (49)	89 (36)
College graduate	55 (17)	34 (17)	63 (26)
Post-graduate	27 (8)	22 (11)	41 (17)
Household income ($US)			
<35,000	58 (18)	24 (12)	31 (13)
35-<50,000	66 (20)	28 (14)	41 (17)
50-<70,000	72 (22)	55 (28)	63 (26)
70-<90,000	71 (22)	42 (21)	57 (23)
≥90,000	54 (16)	40 (20)	49 (20)

Table I. (cont'd)

Smoking status			
Never	152 (46)	112 (57)	140 (57)
Former	104 (32)	57 (29)	72 (29)
Current	73 (22)	29 (15)	32 (13)
Alcohol consumption			
Never	130 (39)	73 (37)	82 (33)
Former	57 (17)	38 (19)	59 (24)
Current	141 (43)	87 (44)	102 (42)
BMI (kg/m^2)[d]			
<25	76 (23)	60 (30)	99 (40)
25-<30	103 (31)	61 (31)	66 (27)
30-<35	83 (25)	39 (20)	39 (16)
≥35	64 (19)	35 (18)	38 (15)
BMI (kg/m^2)[e] in 20s			
<20	65 (20)	55 (28)	47 (19)
20-<25	201 (61)	100 (51)	142 (58)
25-<30	44 (13)	29 (15)	38 (15)
30+	19 (6)	14 (7)	16 (7)
Menarche age (years)			
≤10	52 (16)	20 (10)	25 (10)
11	66 (20)	40 (20)	37 (15)
12	93 (28)	57 (29)	77 (31)
13	66 (20)	48 (24)	55 (22)
≥14	53 (16)	32 (16)	50 (20)
Number of pregnancies			
1	34 (10)	27 (14)	24 (10)
2	70 (21)	65 (33)	78 (32)
3	97 (29)	52 (26)	70 (29)
4	62 (19)	32 (16)	44 (18)
≥5	67 (20)	22 (11)	30 (12)
Number of live births			

Table I. (cont'd)

1	67 (20)	38 (19)	58 (24)
2	138 (42)	96 (49)	126 (51)
3	88 (27)	46 (23)	41 (17)
≥4	37 (11)	18 (9)	21 (9)
Oral contraceptive duration, years			
Never	16 (5)	20 (10)	34 (14)
≤2	132 (40)	90 (46)	90 (37)
>2- 8	95 (29)	37 (19)	55 (22)
>8	85 (26)	50 (25)	65 (26)
Menopausal Status			
No	248 (75)	152 (77)	178 (72)
Yes	79 (24)	45 (23)	65 (26)

Abbreviations: BMI, body mass index; GED, general equivalency diploma; HS, high school.
[a]Among participants who ever had a livebirth.
[b]At reference date.
[c]May not add to 100% due to missing data.
[d]Using height and weight self-reported at in-person interview.
[e]Using height measured at structured interview and average weight participants reported when they were in their 20s.

Table II. Adjusted odds ratios (aOR) and 95% CI comparing adenomyosis cases with hysterectomy controls and population controls in relation to breastfeeding history, Kaiser Permanente Washington, 2001-2006.[a]

Breastfeeding characteristics	Cases (n=330) n (%)	Hysterectomy controls (n=198) n (%)	OR (95% CI)[b]	Population controls (n=246) n (%)	OR (95% CI)[c]
Ever breastfed					
No	51 (15)	23 (12)	1.0 Reference	23 (9)	1.0 Reference
Yes	279 (85)	175 (88)	0.7 (0.4, 1.2)	223 (91)	0.6 (0.3, 1.0)
Ever breastfed an infant ≥ 8 weeks					
No	115 (35)	53 (27)	1.0 Reference	54 (22)	1.0 Reference
Yes	215 (65)	145 (73)	0.7 (0.5, 1.0)	192 (78)	0.6 (0.4, 0.8)
Lifetime breastfeeding (months)					
0 - < 3	127 (38)	53 (27)	1.0 Reference	53 (22)	1.0 Reference
3 - < 6	28 (8)	22 (11)	0.5 (0.3, 1.0)	22 (9)	0.5 (0.3, 1.1)
6 - < 9	32 (10)	25 (12)	0.5 (0.3, 1.0)	27 (11)	0.5 (0.3, 1.0)
9 - < 12	30 (9)	20 (10)	0.6 (0.3, 1.3)	23 (9)	0.6 (0.3, 1.1)
≥12	113 (34)	78 (39)	0.6 (0.4, 0.9)	121 (49)	0.4 (0.2, 0.6)
P value for trend		*P* = 0.07		*P*< 0.0001	
Lifetime exclusive breastfeeding (months)					
0 - < 3	141 (43)	65 (33)	1.0 Reference	69 (28)	1.0 Reference
3 - < 6	57 (17)	39 (20)	0.6 (0.4, 1.1)	41 (17)	0.7 (0.4, 1.2)
6 - < 9	57 (17)	30 (15)	0.9 (0.5, 1.5)	46 (19)	0.6 (0.4, 1.0)
9 - < 12	21 (6)	23 (12)	0.4 (0.2, 0.8)	30 (12)	0.3 (0.2, 0.6)
≥12	54 (16)	41 (21)	0.5 (0.3, 0.9)	60 (24)	0.4 (0.2, 0.6)
P value for trend		*P* = 0.01		*P*< 0.0001	

[a] Among participants who ever had a livebirth.
[b] Adjusted for age at reference date (20-39, 40-44, 45-49, 50-59 years), smoking (never, current, former), education (HS graduate or GED, some, college/vocational/technical college, college graduate, post-graduate), and parity (1, 2, 3, ≥4 live births).
[c] Adjusted for age at reference date (20-39, 40-44, 45-49, 50-59 years), reference year (continuous), smoking (never, current, former), education (≤ HS graduate or GED, some, college/vocational/technical college, college graduate, post-graduate), and parity (1, 2, 3, ≥4 live births).

APPENDIX B

Supplemental Tables

Supplemental Table I. Participant characteristics among population controls by status of having ever breastfed an infant at least eight weeks, Kaiser Permanente Washington, 2001-2006.[a]

	Population Controls (n=246)	
Participant characteristic[b]	Never breastfed an infant at least 8 weeks (n= 54) n (%)[c]	Ever breastfed an infant at least 8 weeks (n=192) n (%)[c]
Age at reference date, years		
20-39	7 (13)	27 (14)
40-44	15 (28)	52 (27)
45-49	17 (32)	67 (35)
50-59	15 (28)	46 (24)
Race		
White	49 (91)	170 (89)
Black or African-American	2 (4)	3 (2)
Asian, Native Hawaiian, other Pacific Islander	2 (4)	10 (5)
American Indian, Native American, Alaskan Native	0 (0)	2 (1)
More than one race	1 (2)	5 (3)
Hispanic		
No	53 (98)	181 (94)
Yes	1 (2)	6 (3)
Education		
≤HS graduate or GED	20 (37)	33 (17)
Some college/ vocational/technical college	22 (41)	67 (35)
College graduate	6 (11)	57 (30)
Post-graduate	6 (11)	35 (18)
Household income ($US)		
<35,000	9 (17)	22 (12)
35-<50,000	10 (19)	31 (16)

Supplemental Table I. (cont'd)

50-<70,000	15 (28)	48 (25)
70-<90,000	10 (19)	47 (25)
≥90,000	9 (17)	40 (21)
Smoking status		
Never	24 (44)	116 (60)
Former	17 (32)	55 (29)
Current	13 (24)	19 (10)
Alcohol consumption		
Never	22 (41)	60 (31)
Former	11 (20)	48 (25)
Current	21 (39)	81 (42)
BMI (kg/m^2)[d]		
<25	16 (30)	83 (43)
25-<30	14 (26)	52 (27)
30-<35	10 (19)	29 (15)
≥35	13 (24)	25 (13)
BMI (kg/m^2)[e] in 20s		
<20	11 (20)	36 (19)
20-<25	26 (48)	116 (60)
25-<30	10 (19)	28 (15)
30+	7 (13)	9 (5)
Menarche age (years)		
≤10	6 (11)	19 (10)
11	7 (13)	30 (16)
12	17 (32)	60 (31)
13	11 (20)	44 (23)
≥14	13 (24)	37 (19)
Number of pregnancies		
1	10 (19)	14 (7)
2	21 (39)	57 (30)
3	16 (30)	54 (28)

Supplemental Table I. (cont'd)

4	5 (9)	39 (20)
5+	2 (4)	28 (15)
Number of livebirths		
1	18 (33)	40 (21)
2	23 (43)	103 (54)
3	10 (19)	31 (16)
4+	3 (6)	18 (9)
Oral contraceptive duration, years		
Never	11 (20)	23 (12)
≤2	20 (37)	79 (37)
>2- 8	12 (22)	43 (22)
>8	11 (20)	54 (28)
Menopausal Status		
No	36 (67)	142 (74)
Yes	18 (33)	47 (25)

Abbreviations: BMI, body mass index; GED, general equivalency diploma; HS, high school.
[a]Among participants who ever had a livebirth.
[b]At reference date.
[c]May not add to 100% due to missing data.
[d]Using height and weight self-reported at in-person interview.
[e]Using height measured at structured interview and average weight participants reported when they were in their 20s.

Supplemental Table II. Adjusted odds ratios (aOR) and 95% CI for the association between breastfeeding and adenomyosis, adjusting for gravidity instead of parity in multivariable analyses, Kaiser Permanente Washington, 2001-2006.[a]

Breastfeeding characteristics	Cases (n=330) n (%)	Hysterectomy controls (n=198) n (%)	OR (95% CI)[b]	Population controls (n=246) n (%)	OR (95% CI)[c]
Ever breastfed					
No	51 (15)	23 (12)	1.0 Reference	23 (9)	1.0 Reference
Yes	279 (85)	175 (88)	0.7 (0.4, 1.1)	223 (91)	0.6 (0.4, 1.1)
Ever breastfed an infant ≥ 8 weeks					
No	115 (35)	53 (27)	1.0 Reference	54 (22)	1.0 Reference
Yes	215 (65)	145 (73)	0.6 (0.4, 0.9)	192 (78)	0.5 (0.4, 0.8)
Lifetime breastfeeding (months)					
0 - < 3	127 (38)	53 (27)	1.0 Reference	53 (22)	1.0 Reference
3 - < 6	28 (8)	22 (11)	0.4 (0.2, 0.9)	22 (9)	0.5 (0.3, 1.0)
6 - < 9	32 (10)	25 (12)	0.5 (0.3, 0.9)	27 (11)	0.5 (0.3, 0.9)
9 - < 12	30 (9)	20 (10)	0.5 (0.3, 1.1)	23 (9)	0.6 (0.3, 1.1)
≥12	113 (34)	78 (39)	0.5 (0.3, 0.8)	121 (49)	0.4 (0.2, 0.6)
P value for trend		*P* = 0.03		*P*= 0.0001	
Lifetime exclusive breastfeeding (months)					
0 - < 3	141 (43)	65 (33)	1.0 Reference	69 (28)	1.0 Reference
3 - < 6	57 (17)	39 (20)	0.6 (0.3, 1.0)	41 (17)	0.7 (0.4, 1.2)
6 - < 9	57 (17)	30 (15)	0.8 (0.5, 1.4)	46 (19)	0.6 (0.3, 0.9)
9 - < 12	21 (6)	23 (12)	0.3 (0.2, 0.7)	30 (12)	0.4 (0.2, 0.7)
≥12	54 (16)	41 (21)	0.4 (0.3, 0.8)	60 (24)	0.4 (0.3, 0.7)
P value for trend		*P*= 0.002		*P*= 0.0003	

[a] Among participants who ever had a livebirth.
[b] Adjusted for age at reference date (20-39, 40-44, 45-49, 50-59 years), smoking (never, current, former), education (HS graduate or GED, some, college/vocational/technical college, college graduate, post-graduate), and gravidity (1, 2, 3, 4, ≥5 pregnancies).
[c] Adjusted for age at reference date (20-39, 40-44, 45-49, 50-59 years), reference year (continuous), smoking (never, current, former), education (≤ HS graduate or GED, some, college/vocational/technical college, college graduate, post-graduate), and gravidity (1, 2, 3, 4, ≥5 pregnancies).

Supplemental Table III. Adjusted odds ratios (aOR) and 95% CI for the association between breastfeeding and adenomyosis, additionally adjusting for body mass index (BMI),[a] Kaiser Permanente Washington, 2001-2006.[b]

Breastfeeding characteristics	Cases (n=330) n (%)	Hysterectomy controls (n=198) n (%)	OR (95% CI)[c]	Population controls (n=246) n (%)	OR (95% CI)[d]
Ever breastfed					
No	51 (15)	23 (12)	1.0 Reference	23 (9)	1.0 Reference
Yes	279 (85)	175 (88)	0.7 (0.4, 1.2)	223 (91)	0.6 (0.3, 1.0)
Ever breastfed an infant ≥ 8 weeks					
No	115 (35)	53 (27)	1.0 Reference	54 (22)	1.0 Reference
Yes	215 (65)	145 (73)	0.7 (0.4, 1.0)	192 (78)	0.5 (0.4, 0.8)
Lifetime breastfeeding (months)					
0 - < 3	127 (38)	53 (27)	1.0 Reference	53 (22)	1.0 Reference
3 - < 6	28 (8)	22 (11)	0.5 (0.2, 0.9)	22 (9)	0.5 (0.3, 1.1)
6 - < 9	32 (10)	25 (12)	0.5 (0.3, 1.0)	27 (11)	0.5 (0.3, 1.0)
9 - < 12	30 (9)	20 (10)	0.7 (0.3, 1.3)	23 (9)	0.6 (0.3, 1.1)
≥12	113 (34)	78 (39)	0.6 (0.4, 0.9)	121 (49)	0.4 (0.2, 0.6)
P value for trend		*P* = 0.07		*P*< 0.0001	
Lifetime exclusive breastfeeding (months)					
0 - < 3	141 (43)	65 (33)	1.0 Reference	69 (28)	1.0 Reference
3 - < 6	57 (17)	39 (20)	0.6 (0.4, 1.1)	41 (17)	0.7 (0.4, 1.3)
6 - < 9	57 (17)	30 (15)	0.9 (0.5, 1.5)	46 (19)	0.6 (0.3, 0.9)
9 - < 12	21 (6)	23 (12)	0.4 (0.2, 0.8)	30 (12)	0.3 (0.2, 0.6)
≥12	54 (16)	41 (21)	0.5 (0.3, 0.9)	60 (24)	0.4 (0.2, 0.6)
P value for trend		*P*= 0.008		*P*< 0.0001	

[a] Estimated body mass index using average weight participants reported when they were in their 20s and height reported at structured interview.
[b] Among participants who ever had a livebirth.
[c] Adjusted for age at reference date (20-39, 40-44, 45-49, 50-59 years), smoking (never, current, former), education (HS graduate or GED, some, college/vocational/technical college, college graduate, post-graduate), parity (1, 2, 3, , ≥4 live births) and average BMI in 20s (< 20, 20-<25, 25-<30, ≥30 kg/m^2).
[d] Adjusted for age at reference date (20-39, 40-44, 45-49, 50-59 years), reference year (continuous), smoking (never, current, former), education (≤ HS graduate or GED, some, college/vocational/technical college, college graduate, post-graduate), parity (1, 2, 3, ≥4 live births), and average BMI in 20s (< 20, 20-<25, 25-<30, ≥30 kg/m^2).

Supplemental Table IV. Adjusted odds ratios (aOR) and 95% CI for the association between breastfeeding and adenomyosis restricted to participants with two livebirths, Kaiser Permanente Washington, 2001-2006.[a]

Breastfeeding characteristics	Cases (n=138) n (%)	Hysterectomy controls (n=96) n (%)	OR (95% CI)[b]	Population controls (n=126) n (%)	OR (95% CI)[c]
Ever breastfed					
No	23 (17)	12 (12)	1.0 Reference	11 (9)	1.0 Reference
Yes	115 (83)	84 (88)	0.8 (0.4, 1.7)	115 (91)	0.5 (0.2, 1.2)
Ever breastfed an infant ≥ 8 weeks					
No	50 (36)	31 (32)	1.0 Reference	23 (18)	1.0 Reference
Yes	88 (64)	65 (68)	0.8 (0.4, 1.4)	103 (82)	0.4 (0.2, 0.8)
Lifetime breastfeeding (months)					
0 - < 3	55 (40)	31 (32)	1.0 Reference	20 (16)	1.0 Reference
3 - < 6	16 (12)	10 (10)	0.7 (0.3, 1.8)	13 (10)	0.4 (0.2, 1.1)
6 - < 9	16 (12)	11 (11)	0.8 (0.3, 1.9)	13 (10)	0.4 (0.2, 1.1)
9 - < 12	12 (9)	11 (11)	0.5 (0.2, 1.3)	17 (13)	0.3 (0.1, 0.7)
≥12	39 (28)	33 (34)	0.7 (0.4, 1.4)	63 (50)	0.2 (0.1, 0.5)
P value for trend		*P* = 0.37		*P*= 0.0002	
Lifetime exclusive breastfeeding (months)					
0 - < 3	63 (46)	33 (34)	1.0 Reference	29 (23)	1.0 Reference
3 - < 6	26 (19)	16 (17)	0.7 (0.3, 1.5)	24 (19)	0.5 (0.3, 1.1)
6 - < 9	24 (17)	21 (22)	0.6 (0.3, 1.2)	22 (17)	0.5 (0.2, 1.1)
9 - < 12	9 (7)	14 (15)	0.3 (0.1, 0.8)	21 (17)	0.2 (0.1, 0.5)
≥12	16 (12)	12 (13)	0.8 (0.3, 1.9)	30 (24)	0.3 (0.1, 0.6)
P value for trend		*P* = 0.13		*P*= 0.0001	

[a] Among participants who ever had a livebirth.
[b] Adjusted for age at reference date (20-39, 40-44, 45-49, 50-59 years), smoking (never, current, former), education (HS graduate or GED, some, college/vocational/technical college, college graduate, post-graduate), and gravidity (1, 2, 3, 4, ≥5 pregnancies).
[c] Adjusted for age at reference date (20-39, 40-44, 45-49, 50-59 years), reference year (continuous), smoking (never, current, former), education (≤ HS graduate or GED, some, college/vocational/technical college, college graduate, post-graduate), and gravidity (1, 2, 3, 4, ≥5 pregnancies).

Supplemental Table V. Adjusted odds ratios (aOR) and 95% CI for the association between breastfeeding and adenomyosis, comparing adenomyosis cases with population controls who would allow hysterectomy,[a] Kaiser Permanente Washington, 2001-2006.[b]

Breastfeeding characteristics	Cases (n=330) n (%)	Population controls (n=126) n (%)	OR (95% CI)[c]
Ever breastfed			
No	51 (15)	14 (11)	1.0 Reference
Yes	279 (85)	112 (89)	0.7 (0.4, 1.3)
Ever breastfed an infant ≥ 8 weeks			
No	115 (35)	31 (25)	1.0 Reference
Yes	215 (65)	95 (75)	0.6 (0.4, 1.1)
Lifetime breastfeeding (months)			
0 - < 3	127 (38)	32 (25)	1.0 Reference
3 - < 6	28 (8)	8 (6)	1.0 (0.4, 2.4)
6 - < 9	32 (10)	18 (14)	0.5 (0.2, 1.0)
9 - < 12	30 (9)	9 (7)	0.8 (0.3, 2.0)
≥12	113 (34)	59 (47)	0.5 (0.3, 0.8)
P value for trend		*P*= 0.008	
Lifetime exclusive breastfeeding (months)			
0 - < 3	141 (43)	39 (31)	1.0 Reference
3 - < 6	57 (17)	23 (18)	0.8 (0.4, 1.5)
6 - < 9	57 (17)	21 (17)	0.8 (0.4, 1.4)
9 - < 12	21 (6)	13 (10)	0.4 (0.2, 1.0)
≥12	54 (16)	30 (24)	0.4 (0.2, 0.8)
P value for trend		*P*= 0.007	

[a] Population controls restricted to those who reported they would "probably" or "definitely" allow for hysterectomy if it was recommended to them if they "developed severe menstrual bleeding, severe menstrual pain, or severe pelvic pain every month for six months or more".

[b] Among participants who ever had a livebirth.

[c] Adjusted for age at reference date (20-39, 40-44, 45-49, 50-59 years), reference year (continuous), smoking (never, current, former), education (≤ HS graduate or GED, some, college/vocational/technical college, college graduate, post-graduate), and parity (1, 2, 3, ≥4 live births).

Supplemental Table VI. Adjusted odds ratios (aOR) and 95% CI for the association between breastfeeding and adenomyosis, additionally adjusting for duration of oral contraception use, Kaiser Permanente Washington, 2001-2006.[a]

Breastfeeding characteristics	Cases (n=330) n (%)	Hysterectomy controls (n=198) n (%)	OR (95% CI)[b]	Population controls (n=246) n (%)	OR (95% CI)[c]
Ever breastfed					
No	51 (15)	23 (12)	1.0 Reference	23 (9)	1.0 Reference
Yes	279 (85)	175 (88)	0.7 (0.4, 1.2)	223 (91)	0.5 (0.3, 1.0)
Ever breastfed an infant ≥ 8 weeks					
No	115 (35)	53 (27)	1.0 Reference	54 (22)	1.0 Reference
Yes	215 (65)	145 (73)	0.7 (0.5, 1.0)	192 (78)	0.5 (0.3, 0.8)
Lifetime breastfeeding (months)					
0 - < 3	127 (38)	53 (27)	1.0 Reference	53 (22)	1.0 Reference
3 - < 6	28 (8)	22 (11)	0.5 (0.2, 0.9)	22 (9)	0.5 (0.2, 0.9)
6 - < 9	32 (10)	25 (12)	0.6 (0.3, 1.1)	27 (11)	0.5 (0.3, 0.9)
9 - < 12	30 (9)	20 (10)	0.6 (0.3, 1.2)	23 (9)	0.5 (0.2, 1.0)
≥12	113 (34)	78 (39)	0.6 (0.4, 0.9)	121 (49)	0.3 (0.2, 0.5)
P value for trend		*P* = 0.07		*P*< 0.0001	
Lifetime exclusive breastfeeding (months)					
0 - < 3	141 (43)	65 (33)	1.0 Reference	69 (28)	1.0 Reference
3 - < 6	57 (17)	39 (20)	0.6 (0.4, 1.1)	41 (17)	0.7 (0.4, 1.1)
6 - < 9	57 (17)	30 (15)	0.9 (0.5, 1.6)	46 (19)	0.5 (0.3, 0.9)
9 - < 12	21 (6)	23 (12)	0.4 (0.2, 0.8)	30 (12)	0.3 (0.1, 0.6)
≥12	54 (16)	41 (21)	0.5 (0.3, 0.9)	60 (24)	0.4 (0.2, 0.6)
P value for trend		*P* = 0.01		*P*< 0.0001	

[a] Among participants who ever had a livebirth.
[b] Adjusted for age at reference date (20-39, 40-44, 45-49, 50-59 years), smoking (never, current, former), education (HS graduate or GED, some, college/vocational/technical college, college graduate, post-graduate), parity (1, 2, 3, ≥4 live births), and oral contraception duration (0, ≤ 2, >2 - 8, >8 years).
[c] Adjusted for age at reference date (20-39, 40-44, 45-49, 50-59 years), reference year (continuous), smoking (never, current, former), education (≤ HS graduate or GED, some, college/vocational/technical college, college graduate, post-graduate), parity (1, 2, 3, ≥4 live births), and oral contraception duration (0, ≤ 2, >2 - 8, >8 years).

REFERENCES

REFERENCES

1. Dufau, M., Dulmanis, A., Hudson, B., Catt, K. J., Fullerton, M., & Burger, H. G. (1970). Suppression of oestradiol secretion and luteinising-hormone release during oestrogen-progestagen oral contraceptive therapy. *Lancet, 1*(7641), 271-274. doi:10.1016/s0140-6736(70)90638-0

2. García-Solares, J., Donnez, J., Donnez, O., & Dolmans, M.-M. (2018). Pathogenesis of uterine adenomyosis: invagination or metaplasia? *Fertility and Sterility, 109*(3), 371-379. doi:10.1016/j.fertnstert.2017.12.030

3. Harada, T., Khine, Y. M., Kaponis, A., Nikellis, T., Decavalas, G., & Taniguchi, F. (2016). The Impact of Adenomyosis on Women's Fertility. *Obstetrical & Gynecological Survey, 71*(9), 557-568. doi:10.1097/ogx.0000000000000346

4. Heinig, M. J., & Dewey, K. G. (1997). Health effects of breast feeding for mothers: a critical review. *Nutrition Research Reviews, 10*(1), 35-56. doi:10.1079/nrr19970004

5. Heinig, M. J., Nommsen-Rivers, L. A., Peerson, J. M., & Dewey, K. G. (1994). Factors related to duration of postpartum amenorrhoea among USA women with prolonged lactation. *Journal of Biosocial Science, 26*(4), 517-527.

6. Jackson, E., & Glasier, A. (2011). Return of ovulation and menses in postpartum nonlactating women: a systematic review. *Obstet Gynecol, 117*(3), 657-662. doi:10.1097/AOG.0b013e31820ce18c

7. Koplin, J. J., & Allen, K. J. (2013). Optimal timing for solids introduction - why are the guidelines always changing? *Clin Exp Allergy, 43*(8), 826-834. doi:10.1111/cea.12090

8. Li, W., & Qiu, Y. (2007). Relation of supplementary feeding to resumptions of menstruation and ovulation in lactating postpartum women. *Chin Med J (Engl), 120*(10), 868-870.

9. Mcneilly, A. S. (1997). Lactation and Fertility. *Journal of Mammary Gland Biology and Neoplasia, 2*(3), 291-298. doi:10.1023/a:1026340606252

10. Mcneilly, A. S. (2001). Lactational control of reproduction. *Reproduction, Fertility and Development, 13*(8), 583. doi:10.1071/rd01056

11. Medicine, I. o. (1991). *Nutrition During Lactation*. Washington, DC: The National Academies Press.

12. Mishell, D. R., Jr., Thorneycroft, I. H., Nakamura, R. M., Nagata, Y., & Stone, S. C. (1972). Serum estradiol in women ingesting combination oral contraceptive steroids. *Am J Obstet Gynecol, 114*(7), 923-928. doi:10.1016/0002-9378(72)90098-1

13. Muñoz, K. A., Ballard-Barbash, R., Graubard, B., Swanson, C. A., Schairer, C., & Kahle, L. L. (1996). Recall of body weight and body size estimation in women enrolled in the breast cancer detection and demonstration project (BCDDP). *Int J Obes Relat Metab Disord, 20*(9), 854-859.

14. Naftalin, J., Hoo, W., Pateman, K., Mavrelos, D., Holland, T., & Jurkovic, D. (2012). How common is adenomyosis? A prospective study of prevalence using transvaginal ultrasound in a gynaecology clinic. *Human Reproduction, 27*(12), 3432-3439. doi:10.1093/humrep/des332

15. Natland, S. T., Andersen, L. F., Nilsen, T. I. L., Forsmo, S., & Jacobsen, G. W. (2012). Maternal recall of breastfeeding duration twenty years after delivery. *BMC Medical Research Methodology, 12*(1), 179. doi:10.1186/1471-2288-12-179

16. Odar Stough, C., Khalsa, A. S., Nabors, L. A., Merianos, A. L., & Peugh, J. (2019). Predictors of Exclusive Breastfeeding for 6 Months in a National Sample of US Children. *American Journal of Health Promotion, 33*(1), 48-56. doi:10.1177/0890117118774208

17. Pijnenborg, R. (1998). The human decidua as a passage-way for trophoblast invasion. *Placenta, 19*, 229-241. doi:10.1016/s0143-4004(98)80017-9

18. Pontis, A., D'Alterio, M. N., Pirarba, S., De Angelis, C., Tinelli, R., & Angioni, S. (2016). Adenomyosis: a systematic review of medical treatment. *Gynecological Endocrinology, 32*(9), 696-700. doi:10.1080/09513590.2016.1197200

19. Rizner, T. L. (2016). The important roles of steroid sulfatase and sulfotransferases in gynecological diseases. *Front Pharmacol, 7*, 16.

20. Soto-Ramírez, N., & Karmaus, W. (2008). The use of oral contraceptive before pregnancy and breastfeeding duration: A cross-sectional study with retrospective ascertainment. *International Breastfeeding Journal, 3*(1), 29. doi:10.1186/1746-4358-3-29

21. Templeman, C., Marshall, S. F., Ursin, G., Horn-Ross, P. L., Clarke, C. A., Allen, M., . . . Bernstein, L. (2008). Adenomyosis and endometriosis in the California Teachers Study. *Fertility and Sterility, 90*(2), 415-424. doi:10.1016/j.fertnstert.2007.06.027

22. Upson, K., & Missmer, S. A. (2020). Epidemiology of Adenomyosis. *Seminars in Reproductive Medicine, 38*(02/03), 089-107. doi:10.1055/s-0040-1718920

23. Urabe, M., Yamamoto, T., Kitawaki, J., Honjo, H., & Okada, H. (1989). Estrogen biosynthesis in human uterine adenomyosis. *Acta Endocrinol, 121*(2), 259-264.

24. Vannuccini, S., Tosti, C., Carmona, F., Huang, S. J., Chapron, C., Guo, S.-W., & Petraglia, F. (2017). Pathogenesis of adenomyosis: an update on molecular mechanisms. *Reproductive BioMedicine Online, 35*(5), 592-601. doi:10.1016/j.rbmo.2017.06.016

25. Wojcicki, J. M. (2011). Maternal Prepregnancy Body Mass Index and Initiation and Duration of Breastfeeding: A Review of the Literature. *Journal of Women's Health, 20*(3), 341-347. doi:10.1089/jwh.2010.2248