The ADENO study

OBSTETRICS

The ADENO study: ADenomyosis and its Effect on Neonatal and Obstetric outcomes: a retrospective population-based study

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BACKGROUND: Adenomyosis is a benign gynecologic condition arising from the uterine junctional zone. Recent studies suggest a relationship between adenomyosis and adverse obstetrical outcomes, but evidence remains conflicting. There is no large-scale study investigating obstetrical outcomes in women with adenomyosis using the gold standard of histopathologic diagnosis.

OBJECTIVE: This study aimed to investigate the prevalence of adverse obstetrical and neonatal outcomes in women with histopathologic adenomyosis and that of the general (Dutch) population.

STUDY DESIGN: This retrospective population-based study used 2 Dutch national databases (Perined, the perinatal registry, and the nationwide pathology databank [Pathologisch Anatomisch Landelijk Geautomiseerd Archief], from 1995 to 2018) to compare obstetrical outcomes in women before histopathologic adenomyosis diagnosis to the general Dutch population without registered histopathologic adenomyosis. The adjusted odds ratios (95% confidence interval) were calculated for adverse obstetrical outcomes. The outcomes were adjusted for maternal age, parity, ethnicity, year of registered birth, induction of labor, hypertensive disorders in previous pregnancies, multiple gestation, and low socioeconomic status.

RESULTS: The pregnancy outcomes of 7925 women with histopathologic adenomyosis were compared with that of 4,615,803 women without registered adenomyosis. When adjusted for confounders, women with adenomyosis had adjusted odds ratios of 1.37 (95% confidence interval, 1.25—1.50) for hypertensive disorders, 1.37 (95% confidence interval, 1.25—1.51) for preeclampsia, 1.15 (95% confidence interval, 1.07—1.25) for small-for-gestational-age infants, 1.54 (95% confidence interval, 1.41—1.68) for emergency cesarean delivery, 1.24 (95% confidence interval, 1.12—1.37) for failure to progress, 1.29 (95% confidence interval, 1.10—1.48) for placental retention, and 1.23 (95% confidence interval, 1.10—1.38) for postpartum hemorrhage. No increased risk of HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome, placental abruption, or operative vaginal delivery or need for oxytocin stimulation was found.

CONCLUSION: Women with a histopathologic diagnosis of adenomyosis showed an increased prevalence of hypertensive disorders of pregnancy and small-for-gestational-age infants, failure to progress in labor, and placental retention compared with the general population in previous pregnancies. This suggests that uterine (contractile) function in labor and during pregnancy is impaired in women with adenomyosis.

Key words: adenomyosis, adverse obstetrical outcomes, fetal growth restriction, histopathology, hypertensive disorders, neonatal outcomes, obstetrical complications, placental abnormalities, population study, preeclampsia, progress of labor, small for gestational age

Introduction

Adenomyosis is a uterine condition closely linked to endometriosis, characterized by myometrial invasion of endometrial tissue. It is associated with dysmenorrhea, abnormal uterine bleeding, and chronic pelvic pain. Further evidence gathered identifies it as a cause for adverse reproductive outcomes.[1—3] Its prevalence is debated, with some estimates as high as 20% of women in the fertile phase of life.[4] Although most studies have investigated the relationship between adenomyosis and fertility, recent literature also proposes that the presence of adenomyosis may lead to a higher risk of obstetrical complications, such as preterm birth (PTB), fetal growth restriction (FGR), and hypertensive disorders of pregnancy (HDPs).[5—8]

The elements of the pathophysiology of adenomyosis—namely, its disruption of the uterine junctional zone and thereby uterine contractility—have been hypothesized to influence the obstetrical function of the uterus. HDPs are thought to arise from impaired spiral artery development and placentation in this same junctional zone. Furthermore, the junctional zone has an important role in uterine contractile function,[9—11] which is arguably most well known in the onset and progress of labor. Common obstetrical complications, such as failure to progress, uterine hyperstimulation and atony, and placental retention, are likewise associated with aberrant uterine contractility.

Part of the problem in gaining consensus regarding the (obstetrical) consequences of adenomyosis lies in its diagnosis in the first place. Adenomyosis is often underdiagnosed because one-third of women remain asymptomatic (or not consulting a gynecologist for their symptoms), alongside a lack of uniform diagnostic criteria.[12,13] Although adenomyosis can be relatively accurately diagnosed using imaging techniques, such as transvaginal ultrasound (TVUS) and magnetic resonance imaging (MRI), the diagnostic criteria vary, and there is a high level of interobserver variability.[14—20] For this reason, the gold standard for adenomyosis diagnosis remains histopathology. With biopsy also not being sufficiently

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AJOG at a Glance

Why was this study conducted?

This study aimed to assess the prevalence rates of obstetrical and neonatal complications between women with subsequent histologic adenomyosis diagnosis and women without reported histological adenomyosis diagnosis, at population level.

Key findings

Women with histologic adenomyosis showed higher rates of hypertensive disorders, fetal growth restriction, placental issues, and labor progression issues than women without histologic adenomyosis.

What does this add to what is known?

This was the largest study to link adenomyosis to obstetrical outcomes using undisputable and reliable diagnosis in a broad population. Our findings should inform clinical practice and motivate further research into potential obstetrical management of women with likely adenomyosis.

accurate,[21] adenomyosis is most reliably diagnosed after hysterectomy in women after having completed their childbearing wish. This poses a clinical challenge as it is now commonly accepted that adenomyosis may be highly prevalent in younger, nulliparous women.[4,12,22,23]

Despite most published studies reporting convincing evidence associating adenomyosis with obstetrical complications, the common weaknesses of these studies limited their generalizability. First, they have relatively small sample sizes, with the largest study consisting of 245 women with adenomyosis.[24,25] Previous studies have made use of less reliable diagnostic methods, such as TVUS[8] and MRI,[26,27] with the larger published studies relying on self-reported diagnosis.[5,25] Nevertheless, no study exists on obstetrical outcomes in combination with histopathologic adenomyosis diagnosis. Hence, women with adenomyosis are not generally considered as having high-risk or complicated pregnancies. Consequently, no guideline exists for the management of pregnant women diagnosed with adenomyosis. Large-scale studies are needed to yield unambiguous results that can influence the clinical practice and (obstetrical) management of women, preferably using the diagnostic gold standard of histopathology.

Materials and Methods

Study objective

This study aimed to investigate the prevalence of adverse obstetrical and neonatal outcomes in women with histopathologic adenomyosis compared with that of the general (Dutch) population.

Study design

This was a retrospective observational population-based cohort study using Dutch population-level data from 1995 to 2018.

Population

Inclusion criteria

Women in the study group included women between the ages of 18 and 50 years histologically diagnosed with adenomyosis, from the Dutch nationwide pathology databank (Pathologisch Anatomisch Landelijk Geautomiseerd Archief [PALGA]) between 1995 and 2018, with pregnancy outcomes registered in the Dutch national perinatal registry (Perined).

Women in the control group included women between the ages of 18 and 50 with registered pregnancy outcomes in the Perined registry between the years 1995 and 2018, without reported histopathologic adenomyosis diagnosis.

Exclusion criteria

There was no pseudonymized personal identifier in the perinatal registry, meaning that data linkage could not be facilitated.

Sample size calculation

Because of the still disputed prevalence of adenomyosis[28] and the risk of adverse pregnancy outcomes in women with adenomyosis, a sample size calculation was not performed. However, because of this study, using population-level data was assumed that the power of the results is sufficient to yield clinically meaningful results.

Study outcomes

The prevalence of adverse obstetrical outcomes in women with adenomyosis was compared with that of women without reported histopathologic adenomyosis from the general Dutch population.

The primary outcomes of this study are summarized in Supplemental Table 1. The primary outcomes for this study included a variety of adverse obstetrical outcomes: mode of delivery, PTB (delivery at <37 weeks of gestation), failure to progress, placental retention, postpartum hemorrhage (PPH), HDPs, FGR (biometry <10th percentile), and small for gestational age (SGA, birthweight <10th percentile). Neonatal outcomes assessed included perinatal mortality, low Apgar scores (<7), neonatal asphyxia (umbilical artery pH of <7.00), and need for neonatal intensive care unit (NICU) admission.

A full list of patient and obstetrical characteristics as secondary outcomes is summarized in Supplemental Tables 1 and 2. In the context of this study, we extracted the following information from the pathologic reports: patient age at the time of hysterectomy, year of hysterectomy, and previous diagnosis of endometriosis.

Data sources

Pathologisch Anatomisch Landelijk Geautomiseerd Archief: Dutch nationwide pathology databank

The Pathologisch Anatomisch Landelijk Geautomiseerd Archief (PALGA; Houten, The Netherlands) database has existed since 1971, functioning as a data- and biobank for histopathologic material collected from Dutch pathology laboratories. Since 1991, it has achieved national coverage and currently holds the data of approximately 12 million patients. All women who received a diagnosis of

adenomyosis based on histopathology were collected from this database. These women were selected by performing a systematic search, with support from a pathologist. Appendix B provides details of the search strategy used.

Perined: Dutch National Perinatal Database

Perined (Utrecht, The Netherlands) is the Dutch national perinatal database that records pregnancy outcomes of all women giving birth under the supervision of a registered midwife or gynecologist in the home, outpatient, or clinical setting (generally from 22 weeks of gestation). Perined has achieved national coverage of pregnancy outcome registration since 2000 and holds information on more than 5 million pregnancies. The relevant characteristics of all women who gave birth within the study period (1995−2018) were requested. A full list of the pregnancy and patient outcomes available from the database is shown in Appendix D.

Data linkage between the Pathologisch Anatomisch Landelijk Geautomiseerd Archief and Perined

The women identified in the PALGA database with adenomyosis who have reported pregnancy outcomes in the Perined database were matched on the basis of the identification number. The combination and linkage of these 2 databases were facilitated using a trusted third party (TTP) at Statistics Netherlands (Central Bureau of Statistics [CBS]). All data were fully anonymized with each woman assigned a pseudonymized identification. The study had to adhere stringently to the privacy guidelines of the CBS to avoid reporting revealing data. This indicated that we were unable to report absolute values in certain situations, namely, for outcomes occurring in fewer than 10 women and any outcomes occurring with a prevalence of under 10% and/or more than 90%. Furthermore, we were unable to report minimum or maximum values. Consequently, a large fraction of the results were reported as a relative difference in prevalence (%) between groups rather than their absolute values (eg, +2%, as opposed to 6% and 8%).

Statistical analysis

Statistical analysis was performed using SPSS (version 26; IBM Corporation, Armonk, NY). The outcomes were compared between women diagnosed with adenomyosis and those without registered adenomyosis diagnosis. The dichotomous outcomes were compared using chi-square analysis. For continuous variables, the independent *t* test was used if normally distributed, and the Mann-Whitney *U* test was used if abnormally distributed. A multivariate regression analysis was performed to calculate the adjusted odds ratios (aORs) for relevant outcomes and 95% confidence intervals (CIs). The outcomes were corrected for potential confounders: maternal age (at time of delivery), parity (at time of delivery), ethnicity, year of registered birth, induction of labor, multiple gestation, and low socioeconomic status. Women who gave birth multiple times during the study could be included more than once in the analysis. The Bonferroni correction was used, where appropriate, to account for multiple comparisons and repeated measures. A P value of $<.05$ was considered statistically significant for all variables. This study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[29] (Appendix G). Figures were created using Miro and SPSS.

Ethical considerations

No informed consent was requested from the patients included as only anonymized data that were already publicly available were used. For the correlation between databases, a TTP was used to deanonymize and link the databases. Ethical approval from the regional ethical committee was obtained with local study number nWMO-2020.0015.

Results

Our initial search in the PALGA registry resulted in a total of 36,168 women between the ages of 18 and 50 years who received the histopathologic diagnosis of adenomyosis after hysterectomy between 1995 and 2018. Of this pool of women, 7925 could be linked to obstetrical outcomes in the Perined registry. Supplemental Table S5 shows patient characteristic of adenomyosis patients linked to pregnancy outcomes versus those without. Table 1 gives an overview of the demographic characteristics of patients with adenomyosis who had pregnancy outcomes compared with the general population. The Perined registry was subsequently referred to identify the obstetrical outcomes of the general Dutch population in the same period, giving outcomes of 4,615,803 pregnancies of women without histologically confirmed adenomyosis. A total of 548,852 patients were excluded because of insufficient data to facilitate linkage between databases (eg, because of missing patient identifiers). See Supplemental Table 4 for full search results. Patient selection is visualized in Figure 1.

Relevant demographic obstetrical characteristics and outcomes available were compared between the pregnancies in women with histologically diagnosed adenomyosis and those of the general Dutch population. All available obstetric characteristics as registered in the Perined registry are shown in Supplemental Table 3. Obstetrical characteristics are summarized in Table 1, maternal and obstetrical outcomes are summarized in Table 2, and neonatal outcomes are summarized in Table 3.

Obstetrical characteristics were compared between groups (Table 1). Several significant differences were found between the adenomyosis patient pregnancies and those of the general Dutch population. Women with histopathologic adenomyosis were more often primiparous (65.8% vs 55.0%), had more reported subfertility (+4.7%), and subsequently were more often pregnant after undergoing assisted reproductive technology (ART).

Table 2 shows a descriptive analysis of all obstetrical and maternal outcomes. Multivariate binary logistic regression analysis was performed for obstetrical and neonatal outcomes. All outcomes were corrected for potential confounders:

TABLE 1
Demographic and obstetrical characteristics of patients with adenomyosis vs the general Dutch population

Characteristic	Total Dutch population (n=4,615,803)	Patients with adenomyosis (n=7925)	*P* value[a]
Low-income area, n (%)	587,058 (12.8)	959 (12.1)	.078
Age of women at the time of pregnancy (y), mean (SD)	30.42 (4.87)	29.15 (4.43)	<.001
Registered year of pregnancy, mean (SD)	2006 (6.80)	1999 (4.35)	<.001
Ethnicity			<.001
Dutch or White	3,056,539 (79.6)	5024 (87.1)	
Mediterranean, Creole, Hindustani, or Asian	431,571 (11.3)	<10%	
Other	<10%	—	
Unknown	776,448 (20.2)	2158 (37.4)	
Obstetrical characteristics			
Gravidity, median (IQR)	2 (2)	2 (2)	<.001
Multiple gestation	—	−0.9%[b]	<.001
History of miscarriage or abortion, n (%)	1,226,139 (26.4)	2420 (30.4)	<.001
Number of previous miscarriages, median (IQR)	0 (1)	0 (1)	
Parity			<.001
Median (IQR)	1 (1)	0 (1)	
Primiparous	2,098,078 (45.7)	4928 (62.2)	
Multiparous	—	2997 (37.8)	
Grande multiparity (>5)	—	−0.4%	
Mode of conception, n (%)			<.001
Spontaneous	2,536,563 (55.0)	5217 (65.8)	
Ovulation induction	—	+1.1%	
Intrauterine insemination	—	+0.3%	
IVF or ICSI	—	+1.4%	
Other	—	+0.1%	
Unknown	1,921,094 (41.6)	2201 (27.8)	
Reported subfertility	—	+4.7%	<.001
Gestational age at time of first consultation, (wk), median (IQR)	10 (5)	11 (4)	<.001
Diagnosis of uterine fibroids before pregnancy	—	+0.4%	<.001
Pregnancy setting at the start of pregnancy, n (%)			<.001
Midwife	3,955,220 (85.7)	6040 (76.2)	
Hospital or clinical	638,368 (13.8)	1834 (23.1)	
Unknown	—	−0.3%	
History of HDP	—	+0.1%	.444
Hyperemesis gravidarum	—	+0.3%	<.001

HDP, hypertensive disorder of pregnancy; *ICSI*, intracytoplasmic sperm injection; *IQR*, interquartile range; *IVF*, in vitro fertilization; *PIH*, pregnancy-induced hypertension; *SD*, standard deviation.

[a] *P* values were calculated using the chi-square analysis for dichotomous outcomes, the independent *t* test for normally distributed continuous variables, and the Mann-Whitney *U* test for abnormally distributed continuous variables; [b] Some outcomes were reported only as a relative percentage difference between patient groups instead of absolute values, because of the Central Bureau of Statistics data privacy restrictions. In some cases, this led to percentages not adding up to 100%.

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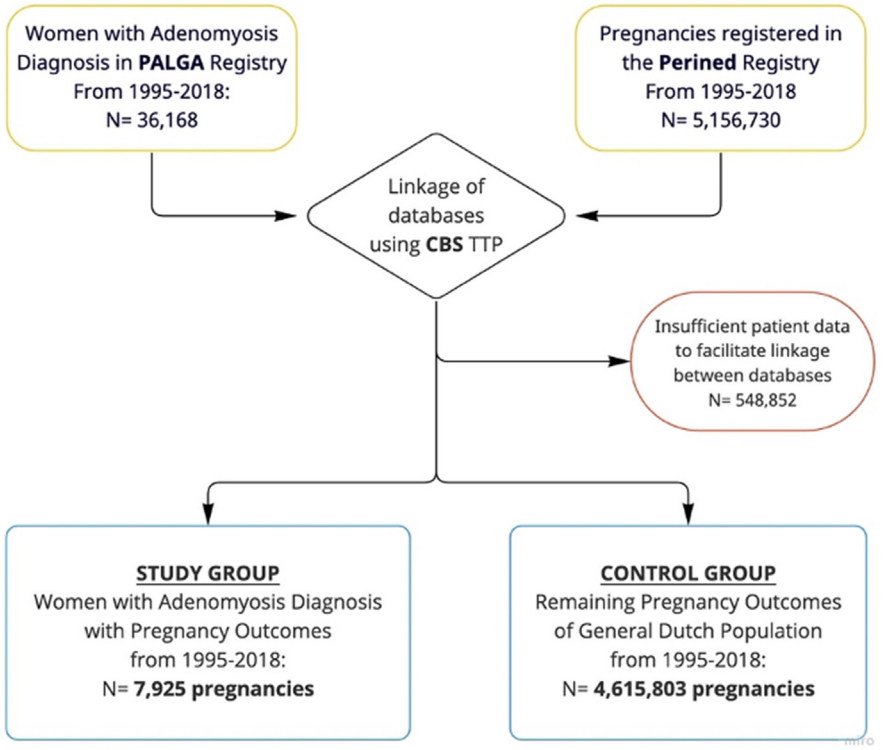
FIGURE 1
Flowchart of patient selection from Dutch National Databases



Linkage of the anonymized databases was performed using the services of a TTP via the Dutch CBS.
CBS, Central Bureau of Statistics; *PALGA*, Pathologisch Anatomisch Landelijk Geautomatiseerd Archief; *TTP*, trusted third party.
Rees. ADenomyosis and its Effect on Neonatal and Obstetric outcomes study. Am J Obstet Gynecol 2023.

parity, age, year of birth, multiple gestation, induction of labor, low-income area, ethnicity, gestational diabetes mellitus, and history of hypertensive disorder. Univariate analysis for relevant outcomes can be found in Table S6. Table S7 shows the full outcomes of multivariate regression analysis.

No significant difference was found in maternal mortality between groups $P>.05$. The outcomes of multivariate logistic regression are summarized in Figure 2 (presented aOR [95% CI]) for most obstetrical and neonatal outcomes.

Adenomyosis was found to have an increased prevalence of signs of premature labor (including cervical insufficiency, preterm premature rupture of membranes [PPROM], and premature contractions) during pregnancy with 2.2% more women in the group with adenomyosis diagnosed with premature labor or threatened prematurity compared with the general Dutch population. Moreover, there was a higher incidence (+0.5%) of PPROM and cervical insufficiency (an increase of 0.5%; all $P<.001$). However, the prevalence of cervical insufficiency did not differ statistically significantly $P=.113$. When adjusting for confounders, we found an aOR of 1.47 (95% CI, 1.33−1.63) for an episode of premature labor in general and an aOR of 1.41 (95% CI, 1.16−1.72) for PPROM. Unexpectedly, women with adenomyosis showed a lower prevalence of PTB (<37 weeks of gestation) with an aOR of 0.76 (95% CI, 0.69−0.84) for PTB than the general Dutch population.

There was a significantly ($P<.001$) higher prevalence of HDPs in patients with adenomyosis than in the general Dutch population. Patients with adenomyosis had a higher prevalence of all forms of HDPs, including pregnancy-induced hypertension, preeclampsia, and HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome or eclampsia. The aOR for all HDPs combined was 1.37 (95% CI, 1.25−1.50).

Women with adenomyosis showed a higher prevalence of FGR (0.5% more prevalent in the adenomyosis groups, $P<.001$) and SGA infants (14.3% vs 10.8%, respectively; $P<.001$) than the general Dutch population. An aOR of 1.15 (95% CI, 1.07−1.25) was found for an SGA fetus.

Women with adenomyosis showed significantly different outcomes concerning the progress of labor and mode of delivery. Women with adenomyosis had an aOR of 1.24 (95% CI, 1.12−1.37) for failure to progress in labor in general when corrected for confounders. When stratifying this by stage of labor, failure to progress in the second stage of labor remained statistically significant with an aOR of 1.24 (95% CI, 1.12−1.37). Similarly, women with adenomyosis had a higher prevalence of premature rupture of membranes (>24 hours) than the general population (aOR, 1.35; 95% CI, 1.23−1.48). No significantly higher prevalence for the need for oxytocin stimulation was found, with similarly insignificant results for failure to progress in the first stage of labor.

In addition, the mode of delivery differed significantly between groups. Women with adenomyosis diagnosis had an aOR of 1.73 (95% CI, 1.61−1.85) for cesarean delivery (CD) in general and aOR of 1.54 (95% CI, 1.41−1.70) for emergency CD. Most emergency CDs (59.9% for patients with adenomyosis vs 53.4% for the general population) were performed because of failure to progress. No significant difference was found for instrumental delivery.

There was a lower prevalence of antepartum hemorrhage in the group with adenomyosis than in the general Dutch population (1.5% lower in prevalence, $P<.001$). Women with adenomyosis showed an increased risk of hyperemesis gravidarum (aOR, 2.07; 95% CI, 1.52−2.82). Furthermore, women with adenomyosis experienced more miscarriages (30.4% vs 26.4%; aOR, 1.53; 95% CI, 1.44−1.62).

TABLE 2
Obstetrical outcomes for patients with adenomyosis vs the general Dutch population

Outcomes	Total Dutch population (n=4,615,803)	Patients with adenomyosis (n=7925)	*P* value[a]
Gestational age at birth (d), median (IQR)	279 (14)	277 (15)	<.001
Gestational age at birth (wk), median (IQR)	39 (2)	39 (2)	<.001
Gestational diabetes mellitus	—	−0.1%[b]	.593
Antepartum hemorrhage	—	−1.5%	<.001
Preterm premature rupture of membranes	—	+0.5%	<.001
Threatened prematurity[c]	—	+2.2%	<.001
Cervical insufficiency	—	+0.1%	.113
HDP in current pregnancy, n (%)	—	+3.8%	<.001
Gestational hypertension or PIH	—	+3.7%	
Preeclampsia	—	+0.6%	
HELLP or eclampsia	—	+0.1%	
Proteinuria	—	+1.0%	<.001
Degree of proteinuria (mg/L), median (IQR)	581.00 (1190)	600.00 (1360)	.124
Mode of start of labor, n (%)			<.001
Spontaneous	3,145,799 (68.2)	5556 (70.1)	
Induction of labor	790,130 (17.0)	1698 (21.4)	
Elective CD	—	−1.3%	
Pregnancy setting at start of labor, n (%)			<.001
Midwife	2,248,806 (48.7)	3509 (44.3)	
Hospital or clinical	2,067,261 (44.8)	4353 (54.9)	
Unknown	—	−0.8%	
NA	—	−4.9%	
Delivery setting, n (%)			<.001
Home delivery	855,114 (18.5)	1222 (15.4)	
Birthing center	98,489 (64.7)	−0.6%	
Hospital delivery under supervision of midwife	—	−1.3%	
Hospital delivery under supervision of a gynecologist	—	5991 (75.6)	
Unknown	—	−0.1%	
Mode of delivery, n (%)			<.001
Vaginal	3,114,932 (67.5)	5677 (71.6)	
Spontaneous vaginal	628,496 (13.6)	5243 (66.2)	
Instrumental delivery	—	+2.8%	
CD	—	1567 (19.8)	
Elective CD	—	+1.9%	
Emergency CD	—	+4.4%	
Unknown	—	−7.2%	

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(continued)

TABLE 2
Obstetrical outcomes for patients with adenomyosis vs the general Dutch population *(continued)*

Outcomes	Total Dutch population (n=4,615,803)	Patients with adenomyosis (n=7925)	*P* value[a]
Indication for labor induction or elective CD, n (%)	1,025,775 (22.2)	2324 (29.3)	<.001
Elective	419,887 (40.9)	1016 (43.7)	
Fetal condition	256,783 (25.0)	464 (20.0)	
Maternal condition	199,489 (19.4)	511 (22.0)	
Maternal and fetal conditions	149,616 (14.6)	333 (14.3)	
Indication for instrumental delivery or emergency CD, n (%)	842,981 (18.3)	2083 (26.2)	<.001
Fetal distress	234,881 (27.9)	479 (23.0)	
Failure to progress	454,012 (53.9)	1248 (59.9)	
Fetal distress and failure to progress	—	−0.5%	
Other	—	−0.8%	
Postpartum hemorrhage (>1 L)	—	+0.4%	.194
Placental issues (composite)	—	+0.4%	.028
Placental abruption	—	+0.1%	.082
Placental retention	—	+0.3%	.135
Placenta previa	—	+0.1%	.152
Meconium-stained amniotic fluid, n (%)	496,331 (10.8)	842 (10.6)	.729
Nonvertex lie, n (%)	536,804 (11.6)	1248 (15.7)	<.001
Cephalopelvic disproportion	—	+0.7%	<.001
Fetal distress	—	+1.6%	<.001
Duration of ruptured membranes until delivery (h), median (IQR)	2.00 (7)	3.00 (8)	<.001
Prolonged rupture of membranes (>24 h), n (%)	318,453 (6.9)	733 (9.2)	<.001
Duration of second stage of labor (min), median (IQR)	18 (37)	27 (46)	<.001
Failure to progress in the second stage of labor	—	+0.7%	<.001
Failure to progress in the first stage of labor	—	+1.3%	<.001
Need for oxytocin stimulation	933,786 (39.9)	1029 (37.8)	<.001
Pain relief during labor (epidural or morphinomimetics)	1,081,218 (23.4)	2044 (25.8)	<.001
Episiotomy	1,084,463 (23.5)	2357 (29.7)	<.001
Hospital admission Duration of hospital stay (d), median (IQR)	2,498,476 (53.9) 1.00 (2)	5350 (67.5) 2.00 (3)	<.001
Maternal mortality	—	±0.0%	<.001
Uterine rupture	—	±0.0%	.544
Endometritis or puerperal fever	—	+0.1%	.002

CD, cesarean delivery; *HDP*, hypertensive disorder of pregnancy; *HELLP*, hemolysis, elevated liver enzymes, and low platelet count; *IQR*, interquartile range; *NA, not available*; *PIH*, pregnancy-induced hypertension.

[a] *P* values were calculated using the chi-square analysis for dichotomous outcomes, the *t* test for normally distributed continuous variables, and the Mann-Whitney *U* test for abnormally distributed continuous variables; [b] In some cases, no absolute value was reported because of data privacy restrictions. Alternatively, the relative difference in percentages was shown between the population with adenomyosis vs the general population. In some cases, this led to percentages not adding up to 100%; [c] Threatened prematurity: admittance because of suspicion of threatened premature delivery because of either cervical insufficiency, premature contractions, or preterm premature rupture of membranes.

Rees. ADenomyosis and its Effect on Neonatal and Obstetric outcomes study. Am J Obstet Gynecol 2023.

TABLE 3
Neonatal outcomes for patients with adenomyosis vs general Dutch population

Outcome	Total Dutch population (n=4,615,803)	Patients with adenomyosis (n=7925)	*P* value[a]
Birthweight (g), mean (SD)	3372.27 (670.73)	3308.83 (665.25)	<.001
Birthweight percentile (%), mean (SD)	50.06 (28.83)	50.65 (29.35)	<.001
Prematurity (wk)			
<37	725,856 (15.7)	867 (10.9)	<.001
<34	—	+0.6%[b]	.006
<32	—	−0.3%	.158
<28	—	−1.0%	<.001
Postterm pregnancy (>42 wk gestational age)	—	+0.6%	.003
Apgar score at 5 min, median (IQR)	10 (0)	10 (1)	1.000
Low Apgar score (<7 at 5 min)	—	±0.0%	.974
Neonatal asphyxia (umbilical artery pH<7.00)	—	−0.1%	.036
Congenital defects	—	−0.1%	.002
Intrauterine fetal death (antepartum and intrapartum)	—	−0.3%	.022
Neonatal mortality	—	+0.1%	.348
Perinatal mortality (antepartum, intrapartum, and postpartum)	—	+0.2%	.017
Small for gestational age (birthweight<10th percentile)	499,324 (10.8)	1134 (14.3)	<.001
Large for gestational age (birthweight>95th percentile)	—	+0.8%	.001
Fetal growth restriction	—	+0.5%	.012
NICU admission, n (%)	792,275 (17.2)	1290 (16.3)	.037
Pediatrician consultation after birth, n (%)	1,984,374 (43.0)	4233 (53.4)	<.001

IQR, interquartile range; *NICU*, neonatal intensive care unit; *SD*, standard deviation.

[a] *P* values were calculated using the chi-square analysis for dichotomous outcomes, the *t* test for normally distributed continuous variables, and the Mann-Whitney *U* test for abnormally distributed continuous variables; [b] In some cases, no absolute value was reported because of data privacy restrictions. Alternatively, the relative difference in percentages was shown between the population with adenomyosis vs the general population.

Rees. ADenomyosis and its Effect on Neonatal and Obstetric outcomes study. Am J Obstet Gynecol 2023.

When looking at absolute values, no significantly increased prevalence of PPH could be found in the group with adenomyosis (*P*=.194). However, when correcting for confounders, a slightly increased risk of PPH was found in patients with adenomyosis (aOR, 1.23; 95% CI, 1.10−1.38). Moreover, the prevalence of endometritis was increased in the group with adenomyosis (aOR, 1.70; 95% CI, 1.02−2.82).

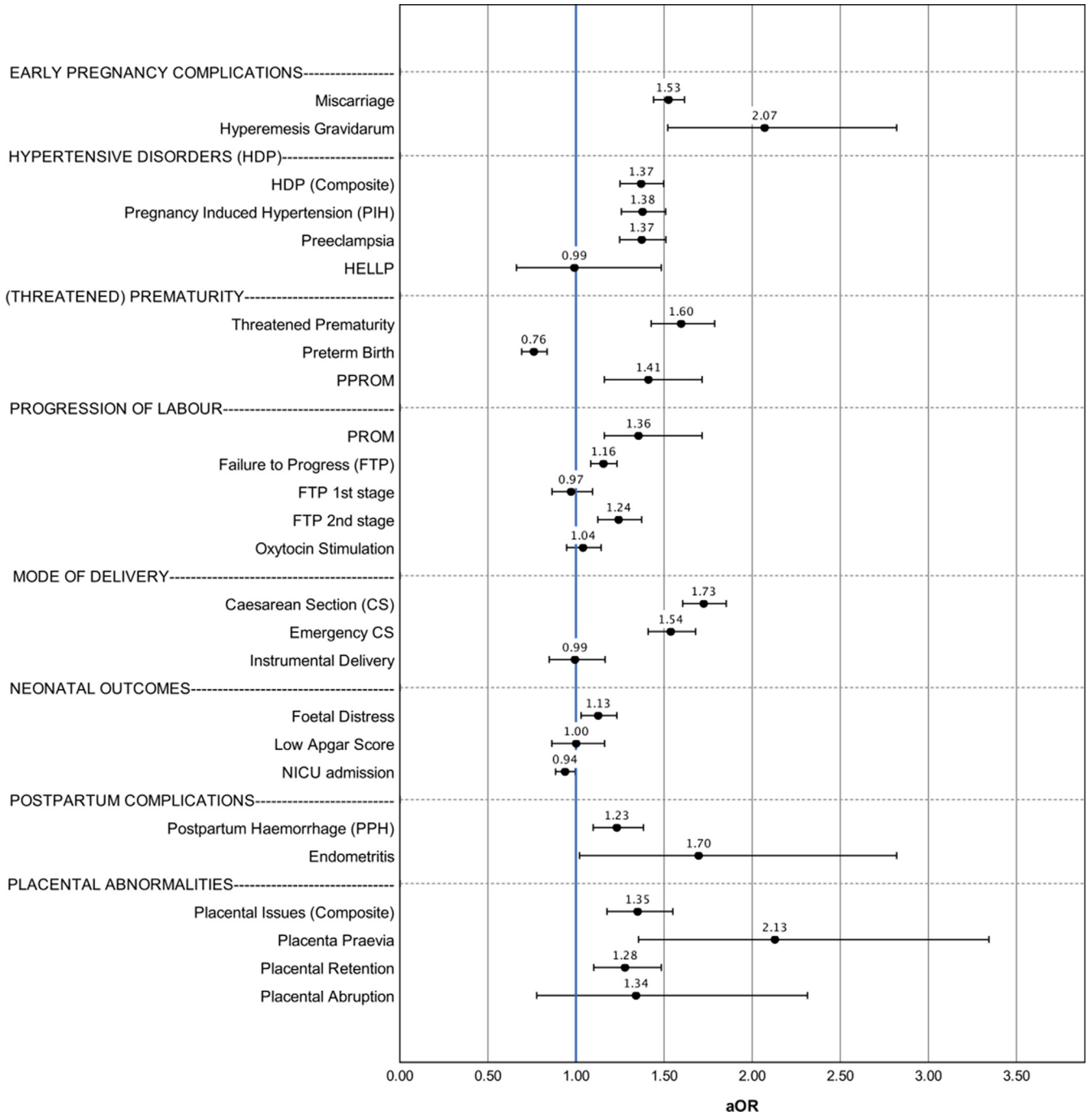
Women with adenomyosis showed an increased prevalence of placental retention, placenta previa, and placental abruption (Table 2); however, only placenta previa (aOR, 2.13; 95% CI, 1.36−3.34) and placental retention (aOR, 1.28; 95% CI, 1.10−1.48) showed statistically significantly increased aORs when adjusting for confounders. When combining placental issues into a composite outcome, statistical significance remained, with a reported aOR of 1.35 (95% CI, 1.18−1.55).

Several additional statistically significant differences were found between groups for other obstetrical outcomes. An increased prevalence of fetal malposition (ie, nonvertex lie) was seen in the group with adenomyosis vs the general population (aOR, 1.37; 95% CI, 1.27−1.47). Moreover, women with adenomyosis showed a higher prevalence of pain relief during labor (aOR, 1.38; 95% CI, 1.30−1.47).

Several significant differences between the group with adenomyosis and the general population were also found concerning neonatal outcomes (Table 3 and Figure 2). Children born from women with adenomyosis diagnosis showed a slightly lower birthweight (3308 g (±670 g) than the general population (3372 g) (*P*<.001); however, the median birthweight percentile was still within normal range (50.06 vs 50.67; *P*<.001).

Women with adenomyosis showed a slightly increased prevalence of fetal distress during labor with an aOR of 1.13 (95% CI, 1.03−1.23). No significant difference was found for the presence of meconium-stained amniotic fluid (*P*=.729). Moreover, no increased

FIGURE 2
aORs for pregnancy outcomes for adenomyosis patients (n = 7925) versus the general population (n = 4,615,803)



The aORs were corrected for maternal age, parity, ethnicity, year of registered birth, induction of labor, multiple gestation, and low socioeconomic status. Error bars signify 95% confidence interval.

aOR, adjusted odds ratio; CD, cesarean delivery; FTP, failure to progress; HDP, hypertensive disorder of pregnancy; HELLP, hemolysis, elevated liver enzymes, and low platelet count; NICU, neonatal intensive care unit; PIH, pregnancy-induced hypertension; PPH, postpartum hemorrhage; PPROM, preterm premature rupture of membranes; PROM, premature rupture of membranes.

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prevalence was found for neonatal mortality or low Apgar scores at birth ($P>.05$), with neonates of women with adenomyosis also showing a lower prevalence of neonatal asphyxia ($P=.036$). NICU admission was more common in the general population than in patients with adenomyosis (17.2% vs 16.3%, respectively; $P=.037$).

Discussion

Principal findings

Here, previous pregnancy outcomes of 7925 women with a histopathologic diagnosis of adenomyosis were compared with the pregnancy outcomes of 4,615,803 women of the general Dutch population without adenomyosis. When adjusted for common confounders, women with histopathologic adenomyosis had an increased prevalence of HDPs and SGA infants. Furthermore, women with adenomyosis more often had an emergency CD, failure to progress, and placental retention. There was no increased risk of HELLP syndrome, eclampsia, placental abruption, or operative vaginal delivery or need for oxytocin stimulation.

Results in the context of what is known

No previous study has investigated the progress of labor in women with histologically proven adenomyosis. Adenomyosis is thought to affect uterine contractile function because of the associated disruption of the junctional zone, leading to symptoms, such as dysmenorrhea and infertility.[30,31] Uterine contractile function is arguably most well known in the context of the onset and progress of labor, where common obstetrical complications may be associated with ineffectual contractions. Therefore, it can be hypothesized that adenomyosis in pregnancy leads to a higher risk of these obstetrical outcomes.

Aberrant (specifically, premature) uterine contractile function during pregnancy can also be related to PTB. Past reported ORs for PTB in women with adenomyosis have ranged from 1.96[27] to as high as 24.53.[6] Strikingly, our study cannot confirm this finding, with a lower risk of PTB in the group with adenomyosis than in the general population (aOR, 0.76; 95% CI, 0.69−0.84). However, the group with adenomyosis did show an increased risk of threatened PTB, including PPROM and cervical insufficiency. Potentially, this discrepancy lies in differences in (past) Dutch management protocols of PPROM and premature labor compared with previously published studies, leading to a later gestational age at birth. Another potential explanation for the difference in the results is that most existing studies included mainly patients undergoing ART in their populations,[32,33] in contrast to our study. This may be a confounding factor leading to a higher incidence of PTB in previous studies (although most studies did adjust for mode of conception).

HDPs are thought to arise from impaired implantation and placentation because of defective spiral artery development and remodeling in this same junctional zone. Recent studies have suggested a link between adenomyosis and HDPs.[2,3,26,33] Our study confirmed this finding, with consistently higher aORs for most patients with HDPs than the general population. In addition, we reported a higher prevalence of FGR and SGA infants in the population with adenomyosis. This could be simultaneously attributed to impaired placental implantation in adenomyotic uteri, with subsequent placental insufficiency affecting fetal growth.

Our results showed increased prevalence of placental issues overall, be it malposition (ie, previa) or problems with adherence (ie, retention or abruption). The higher prevalence of placenta previa (aOR, 2.129; 95% CI, 1.355−3.344) may be explained by placental implantation being impaired at the site of adenomyotic lesions (most often in the corpus of the uterus), leading to aberrant localization of placental tissue. Interestingly however, despite the increased prevalence of placenta previa, women with adenomyosis did not show an increased prevalence of antepartum hemorrhage. Possibly, this was underreported. Alternatively, aberrant placental localization and implantation could also have formed the impetus for adenomyosis development in conjunction with the Tissue Injury and Active Repair theory as proposed by Leyendecker et al.[34]

Furthermore, previous studies support our results for neonatal outcomes, with comparable studies investigating neonatal outcomes reporting mildly significant or statistically insignificant results.[3,35] Therefore, it seems that adenomyosis affects mostly the maternal and obstetrical outcomes, without a clinically relevant effect on neonatal outcomes.

Clinical implications

The results of our study supported that women with subsequently proven adenomyosis more often experienced (previous) adverse obstetrical outcomes. Of course, the diagnostic method referred to in this study—histopathologic diagnosis mostly after hysterectomy—cannot be applied to pregnant women prospectively. However, the noninvasive diagnostic methods of TVUS and MRI can fairly accurately diagnose adenomyosis in the nonpregnant uterus.[13,14,18,36] Whether adenomyosis is present at the time of the pregnancy is not proven by our study and warrants future studies using MRI and ultrasound to shed light on the directionality and causality of these relationships. Nevertheless, if clear signs of adenomyosis are present, it is worth contemplating the high-risk obstetrical management of these patients. One could advocate for these patients needing more frequent fetal growth monitoring or aspirin use from the first trimester of pregnancy for instance.

Research implications

Further studies should investigate the effect of severity and type of adenomyosis on obstetrical outcomes. Our study has confirmed that women with adenomyosis experience more obstetrical and neonatal adverse outcomes, but this needs to be confirmed in prospective clinical studies. Subsequently, appropriate follow-up and adenomyosis treatments (hormonal, surgical, or otherwise) can be assessed for their effect on obstetrical complications.

Strengths and limitations

Our study has several important strengths. First, the use of large population-based cohorts spanning several years enabled us to conduct the largest study investigating this topic up to now. Moreover, this study used the gold standard of histologically confirmed adenomyosis. This gives our study a clear advantage because of the undisputed presence of adenomyosis in our study population. Third, contrary to most existing studies, our study

population included both women who conceived naturally and used ART, making our conclusions more widely generalizable.

Despite its strengths, this study did not have important limitations, which should be considered. First, when conducting studies with a large (imbalanced) population, there is a higher chance of receiving statistically significant results. As such, one has to consider whether this statistical significance immediately translates to clinical significance. Nevertheless, as our results were generally in line with the existing literature and remain significant after correction for a large number of confounders, they should be taken as clinically relevant.

Second, as only women with histologically confirmed adenomyosis were included, a potential bias may have been introduced. It is possible that women with more severe adenomyosis (symptoms) opt for operative over hormonal treatment and are thereby able to receive histologically confirmed diagnosis. Moreover, as not all women with adenomyosis undergo histologic examination, the control group likely contains a substantial proportion of women with imaging-diagnosed adenomyosis. Hence, our results could be an over- or underestimation of adenomyosis' true association with (adverse) pregnancy outcomes. However, we believe that because of the (much) larger size of our control group vs the group with adenomyosis, this effect will have been sufficiently minimized. We purposefully selected a broad control group to, as far as possible, reflect obstetrical outcomes in the general population vs those with certain adenomyosis (as opposed to, eg, controls without adenomyosis at hysterectomy, as this group would represent a selected population with an indication for hysterectomy in the first place).

Despite the obvious benefits of using large and anonymized national databases, their use did introduce several constraints to the amount of patient information available. First, as visible in Figure 1, a large proportion of women with adenomyosis could not be linked to pregnancy outcomes. This is most likely because of limits regarding the years of available data and missing patient information. It is plausible that many women did experience pregnancies but fell outside the study period. Moreover, one could hypothesize that as adenomyosis is linked to infertility,[1,2,37] a large number of women with adenomyosis may not have been able to become pregnant in the first place, although this is purely speculative.

In addition, pathologic reports gave little to no information on the type of adenomyosis, making it difficult to conclude the effect of adenomyosis severity on obstetrical outcomes. Moreover, in the Perined registry, certain potential confounding factors, such as body mass index and smoking were not (well) reported. We attempted to adjust for these confounders by using the proxy of low socioeconomic background. Other potentially relevant patient characteristics, such as miscarriages and mode of conception, were also not well reported.

Conclusions

This was the largest study to assess adverse obstetrical outcomes in women with adenomyosis diagnosis based on histopathology. Our results confirmed that women with histologically proven adenomyosis exhibit a higher prevalence of adverse obstetrical outcomes, particularly for hypertensive disorders, failure to progress in labor, and placental issues. Future prospective studies should investigate the extent to which noninvasive methods of adenomyosis diagnosis can be associated with adverse obstetrical outcomes and which treatments of adenomyosis adequately reduce the risk of obstetrical complications. ■

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