Nationwide population-based cohort study of adverse obstetric outcomes in pregnancies with myoma or following myomectomy: Retrospective cohort study

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Abstract

Background Our objective was to evaluate risks of adverse obstetric outcomes in pregnancies with myoma(s) or in pregnancies following myomectomy.

Methods We analyzed the national health insurance database, which covers almost the entire Korean population, between 2004 and 2015. The risks of adverse pregnancy outcomes in pregnancies with myoma(s) or in pregnancies following myomectomy, compared to those in women without a diagnosed myoma, were analyzed in multivariate logistic regression analysis

Results During the study period, 38,402 women with diagnosed myoma(s), 9,890 women with a history of myomectomy, and 740,675 women without a diagnosed myoma gave birth. Women with a history of diagnosed myoma(s) and women with a history of myomectomy had significantly higher risks of cesarean section (aOR 1.13, 95% CI 1.1-1.16, p = 0.042; and aOR 7.46, 95% CI 6.97-7.98, p < 0.001, respectively) and placenta previa (aOR 1.41, 95% CI 1.29-1.54, p = 0.042; and aOR 1.58, 95% CI 1.35-1.83, p < 0.001, respectively), compared to women without a diagnosed myoma. And the risks of uterine rupture, preterm birth, and low birth weight were significantly higher in women with previous myomectomy but not in women with diagnosed myoma(s), compared to women without a diagnosed myoma (aOR 12.78, 95% CI 6.5-25.13, p < 0.001; aOR 1.64, 95% CI 1.47-1.84, p < 0.001; and aOR 1.53, 95% CI 1.39-1.68, p < 0.001, respectively). The incidence of uterine rupture was the highest at delivery within one year after myomectomy and decreased over time after myomectomy.

Conclusions When a woman who might become pregnant later on is diagnosed with uterine myoma, she should be counseled about the risk of myoma(s) and myomectomy on obstetric complications, especially including the significant risk of uterine rupture in pregnancies following myomectomy.

Background

Uterine myomas (leiomyomata, fibroids) are the most common tumor of the reproductive tract, with a prevalence of 20–25%[1] and a cumulative incidence of 70% in women of reproductive age.[2]

It has been reported that the presence of fibroids is associated with infertility, spontaneous abortion, fetal malpresentation, placenta previa, preterm birth, cesarean section, and peripartum hemorrhage.[3] Although surgical interventions such as myomectomy have been tried in infertile women without specific causes, it is unclear whether the treatment of uterine fibroids can improve pregnancy outcomes, except for cavity-distorting myomas (submucosal, or intramural with a submucosal component).[4] The most serious concern in pregnancies after myomectomy is the risk of uterine rupture, which can result in significant increased morbidity and mortality for both the mother and the fetus. The incidence of uterine rupture after prior myomectomy has been reported to range from 0.2 to 3.7% in women with prior myomectomy.[5] There is no consensus on the optimal interval between myomectomy and conception.

In US Census Bureau population projections, it was estimated that myomectomies are predicted to increase 31% between 2007 and 2050.[6] In Korea, the number of women who underwent myomectomy have increased 37.3% between 2006 and 2010.[7] Women in their 30 s and 40 s, who are a major population for pregnancy, have been major candidates for myomectomy. Because there is insufficient evidence that myomectomy improves pregnancy outcomes, a practice committee of the American Society for Reproductive Medicine (ASRM) reported that myomectomy is generally not advised for improving pregnancy outcomes in asymptomatic women with non-cavity-distorting myomas.[8] The Society of Obstetricians and Gynaecologists of Canada (SOGC) also recommended against myomectomy in women with intramural fibroids (hysteroscopically confirmed intact endometrium) and otherwise unexplained infertility, regardless of their size.[9]

The purpose of this study was to evaluate adverse pregnancy outcomes in women with a history of diagnosed myoma or myomectomy, including prevalence of uterine rupture in women with myomectomy, according to the time interval after myomectomy.

Methods

The characteristics of the dataset

In Korea, 97% of the population is enrolled in the Korea National Health Insurance (KNHI) program. All claims information for these individuals is contained within the KNHI claims database. Nearly all information about the prevalence of different diseases and procedures can be obtained from this centralized database, with the exception of procedures not covered by insurance. As part of the KNHI system, children aged 4–80 months are eligible for a National Health Screening Program for Infants and Children (NHSP-IC). An NHSP-IC is composed of seven consecutive health examinations based on age groupings. The first to the seventh health examinations are performed at ages 4–9, 9–18, 18–30, 30–42, 42–54, 54–66, and 66–80 months. An NHSP-IC consists of history taking, physical examination, anthropometric examination, developmental screening, and visual acuity testing based on the child's age. Women's data in the KNHI claims database were linked to the data of their offspring contained within the NHSP-IC database.

Data on women's health conditions including obstetric diagnosis were obtained from the KNHI claims database using ICD-10 codes. Data on preterm birth and birth weight were corrected from the NHSP-IC database. We have obtained the approval of this study by the Institutional Review Board (no. 2020GR0012).

Outcomes

Using the KNHI claims database, we identified all women who had given birth between January 1, 2014, and December 31, 2015. We also identified whether these women had a diagnosis of uterine myoma based on ICD-10 codes before pregnancy and whether these women had a myomectomy using procedure codes from the Health Insurance Medical Care Expenses.

The flow chart of study participants' enrollment is presented in Fig. 1. For pregnancy outcomes, we extracted information on delivery mode, nulliparity, multiple pregnancy, preeclampsia, PPH, placental abruption, placenta previa, and uterine rupture using the KNHI claims database (dataset 1). For the other outcomes, the KNHI claims database and the NHSP-IC database were merged. Because data on preterm birth and birth weight were corrected from the NHSP-IC database, women were excluded from analysis if their offspring did not undergo at least one of the seven consecutive NHSP-IC examinations or had missing data (dataset 2). Data on preterm birth, low birth weight (LBW), and large for gestational age (LGA) were extracted from dataset 2. Preterm birth was defined as gestational age < 37 weeks. LBW was defined as birth weight < 2.5 kg. LGA was defined as birth weight > 4.0 kg.

Statistical analysis

Continuous and categorical variables are expressed as the mean $\pm$ standard deviation and percentages, respectively. Clinical characteristics were compared using the ANOVA for continuous variables and the chi-square test for categorical variables. Multivariate logistic regression analysis was used to estimate the adjusted odd ratio (aOR) and the 95% confidence interval (CI)s for the association of a presence of leiomyoma and myomectomy with adverse pregnancy outcomes. For multivariate analyses, a fixed set of known risk factors for adverse pregnancy outcomes was adjusted for potential confounding: maternal age (continuous variable), and nulliparity (categorical variable). Statistical analyses were done using SAS for Windows v9.4 (SAS, Inc., Cary, NC). The study protocol was approved by the Institutional Review Board of the Korea University Medical Center

Results

From 2014 to 2015, 789,482 women delivered in Korea. After excluding women with missing data ($n = 515$), 788,967 remaining women were included in dataset 1. Among them, 740,675 (93.88%) women had no diagnosed myoma, 38,402 (4.88%) had diagnosed myoma(s) but no history of myomectomy, and 9,890 (1.25%) women had a history of myomectomy before pregnancy. Dataset 2 included 534,259 women, excluding women whose infants did not receive infant screening ($n = 254,693$) or showed missing values ($n = 15$). There were 502,209 (94.00%) women who had never been diagnosed with myoma, 25,408 (4.76%) women who had diagnosed myoma(s) but no history of myomectomy, and 6,642 (1.24%) women who had a history of myomectomy, in dataset 2.

Maternal characteristics and adverse pregnancy outcomes of the study population in dataset 1 as described in Table 1. There were significant differences in maternal age, rates of nulliparity, multiple pregnancy, cesarean section, and complications of preeclampsia, postpartum hemorrhage, placenta previa, and uterine rupture, between the groups. However, there was no significant difference in placental abruption between the three groups.

Obstetric characteristics in dataset 2 are presented in Table 2. There were significant differences in neonatal birth weight and sex, and rates of preterm birth, LBW, and LGA.

Multivariate logistic regression analysis for adverse obstetric outcomes in pregnancies with myoma or following myomectomy

Both groups of women with a history of diagnosed myoma(s) and women with a history of myomectomy had significantly higher risks of cesarean section (aOR 1.13, 95% CI 1.1–1.16, $p = 0.042$; and aOR 7.46, 95% CI 6.97–7.98, $p < 0.001$, respectively) and placenta previa (aOR 1.41, 95% CI 1.29–1.54, $p = 0.042$; and aOR 1.58, 95% CI 1.35–1.83, $p < 0.001$, respectively), compared to women without a diagnosed myoma (Table 3). However, women with a history of myomectomy had a significantly higher risk of uterine rupture (aOR 12.78, 95% CI 6.5-25.13, $p < 0.001$). We evaluated incidences of uterine rupture in women with myomectomy, according to the time interval after myomectomy (Fig. 2). The incidence of uterine rupture was significantly higher at delivery within one year after myomectomy (0.71%) compared to any longer delivery interval after myomectomy.

Finally, we compared obstetric outcomes in dataset 2 (Table 4). The group of women with a history of myomectomy had significantly higher risks of preterm birth (aOR 1.64, 95% CI 1.47–1.84, $p < 0.001$) and LBW (aOR 1.53, 95% CI 1.39–1.68, $p < 0.001$) than did women without a diagnosed myoma. However, women with diagnosed myoma(s) and women with a history of myomectomy had a significantly lower risk of LGA (aOR 0.97, 95% CI 0.90–1.04, $p = 0.002$; and aOR 0.68, 95% CI 0.597–0.79, $p < 0.001$, respectively).

Discussion

Main Findings

The principal findings of this study are as follows: (1) In the study population (dataset 2), 25,408 (4.76%) women had a history of diagnosed myoma(s) but no myomectomy, and 6,642 (1.24%) women received myomectomy before pregnancy.; (2) Women who have had a myomectomy had significantly higher risks of cesarean section, placenta previa, preterm birth, LBW, and uterine rupture, but a lower risk of LGA, than did women without a history of diagnosed myoma.; (3) The incidence of uterine rupture was significantly higher at delivery within one year after myomectomy (0.71%) than during any longer delivery interval after myomectomy.; (4) Women with a history of diagnosed myoma had significantly higher risks of cesarean section and placenta previa, but no significantly increased risks of preterm birth, LBW, or uterine rupture, compared to women without a history of diagnosed myoma.

Interpretation

Previous studies have also reported increased adverse pregnancy outcomes, including abnormal placentation, such as placenta previa or placenta accreta,[10-12] preterm delivery, cesarean delivery, uterine rupture, and

postpartum bleeding, in women with a history of myomectomy.[13–16] The true incidence of uterine rupture during subsequent pregnancy following myomectomy is difficult to establish, because most of the studies have been cases, case series, or small retrospective cohort studies that do not account for the total number of pregnancies achieved after myomectomy and their consequent outcomes. The incidences of preterm birth and uterine rupture after myomectomy have been variously reported to range from 3.1–35% and from 0.2 to 3.7%, respectively.[17, 18] The previous systematic review including all cohort studies with at least five cases demonstrated that the overall incidence of uterine rupture after myomectomy was 0.93% (0.45–1.92%) (n = 7/756); specifically, it was 0.47% (0.13–1.70%) (n = 2/426) in women undergoing a trial of labor after myomectomy, and 1.52% (0.65–3.51%) (n = 5/330) in women before the onset of labor.[5] However, the number of pregnancies and viable deliveries after prior myomectomy were 2,367 and 1,284, respectively, from a total of 23 studies. In our study, pregnancy outcomes were available for 9,890 women with a history of myomectomy, which was the largest population. In the previous studies, although uterine rupture occurred at various gestation, it occurred more often before the onset of labor, with a high rate of fetal loss. [18].[5] In this study, the incidence of uterine rupture in women with a history of myomectomy was 0.22%, which is less than the reported incidence of uterine rupture (0.4–0.7%) in a trial of labor after cesarean Sect. [19,20] Possible reasons can be a missing diagnosis when uterine rupture is combined with abruptio placenta or antepartum/postpartum bleeding in the middle of pregnancy. Also, uterine dehiscence can be underdiagnosed, based on the data from diagnostic code. However, in this study, women with a history of myomectomy had more than a 12-fold risk of uterine rupture over that of women without a diagnosed myoma. Therefore, counseling for myomectomy in women who desire a pregnancy in the future should discuss the risk of adverse pregnancy outcomes, especially uterine rupture during pregnancy, which can be associated with fetal loss.

In a previous comparison study about delivery outcomes between pregnancies following myomectomy and myoma-complicated pregnancies, the latter showed better outcomes, including fewer cesarean sections, preterm births, and less blood loss, than did pregnancies after myomectomy, which were similar to the results of this study[21] A prospective, randomized, multicenter study in couples with unexplained infertility demonstrated no significant difference in conception, placenta previa, preterm labor, postpartum hemorrhage, or live birth rates in women with non-cavity distorting myomas and those without myomas.[22] A recent retrospective cohort study[23] revealed that women with a history of myomectomy were associated with a 180% increased risk of intraoperative transfusion, were 713% more likely to experience a bowel injury, and were 243% more likely to undergo a cesarean hysterectomy. These findings provide reassurance that pregnancy success is not affected in couples with non-cavity distorting myomas undergoing assisted reproductive treatment (ART) for unexplained infertility.

Previously, ACOG stated that myomectomy should be considered for a woman with uterine leiomyomas who has undergone several unsuccessful IVF cycles despite appropriate ovarian response and good-quality embryos.[24] SOGC, ASRM, and French guideline also stated that intramural myomas may have a negative effect on fertility, but treating them does not improve fertility, and myomectomy is therefore indicated only for symptomatic myomas,[8,24,25] They emphasized that information should be provided about the risk of uterine rupture during a future pregnancy, before planning a myomectomy in women who might become pregnant later on.

Strengths and Limitations

A limitation of this study was our lack of data on number, size, or type of myomas, type of closure after myomectomy, number of suture layers, and use of electrocauterization, which may have important clinical significance. Also, there was no information on the type of myomectomy (laparoscopic, open, hysteroscopic, or robot-assisted) or type of conception (natural, OS, OS-IUI, or IVF). Last, data about gestational age at uterine rupture was not available.

However, this study included the largest population in the group with a history of diagnosed myoma(s) with and without myomectomy. In addition, the nationwide design of the original database can provide more generalized outcomes in pregnancies with diagnosed myoma(s) and with previous myomectomy. In addition, to our

knowledge, this is the first study about incidence of uterine rupture in women with myomectomy, according to delivery time interval after myomectomy. The incidence of uterine rupture was highest within one year after surgery, which suggests that pregnancy with or without ART should be delayed at least 3–6 months. Last, we compared pregnancy outcomes in three groups: women with diagnosed myoma(s), with previous myomectomy, and without a diagnosed myoma or myomectomy. Although both groups of women with myoma and women with previous myomectomy showed adverse pregnancy outcomes, women with a previous myomectomy demonstrated more risks of adverse pregnancy outcomes, including preterm birth, low birth weight, cesarean section, and uterine rupture. These results might be useful in counseling when a woman, who might become pregnant later on, is diagnosed with uterine myoma.

Conclusion

When a woman is diagnosed as having asymptomatic non-cavity distorting myoma(s) before pregnancy, counseling should include information about the risks of pregnancies with myoma(s) and after myomectomy. Especially, if myomectomy is considered before pregnancy, a woman should be counseled that her risk of uterine rupture, which can be accompanied with fetal loss, during pregnancies after myomectomy can be increased. In addition, pregnancy with or without ART after myomectomy should be delayed at least 3–6 months.

Abbreviations

ASRM, American Society for Reproductive Medicine

SOGC, Society of Obstetricians and Gynaecologists of Canada

KNHI, Korea National Health Insurance

NHSP-IC, National Health Screening Program for Infants and Children

LBW, Low birth weight

LGA, Large for gestational age

ART, Assisted reproductive treatment

PPH, Postpartum hemorrhage

Declarations

Ethics approval and consent to participate

The institutional review board of Korea University Guro Hospital approved the collection and use of clinical information for research purposes (No. 2020GR0012; Approval date, January 9, 2020). This study is in compliance with the 2013 Helsinki World Medical Association Declaration.

Consent for publication

This work has not been published before nor is it under consideration for publication elsewhere. The contents of this manuscript will not be copyrighted, or published elsewhere while acceptance by your journal is under consideration.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

SJL, HSK, GJC and IYP conceived the study and designed the experiment. SJL, HSK, SHN, JYB, WJS, JWK, JES, HJC, KYC, GJC and IYP contributed the collection of data and performed the experiment. HSK, GJC and IYP analyzed the data and contributed to the statistical analysis. SJL, HSK, GJC and IYP wrote the article. All authors critically revised the article and gave approval of the version to be published.

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Tables

Table 1. Demographics and birth outcomes of study population (Dataset 1)

	Group A* (N = 740,675)	Group B* (N = 38,402)	Group C* (N = 9,890)
Age	31.62 ± 3.96	33.87 ± 3.50	34.63 ± 3.42
Nulliparity	385,663 (52.07)	19,541 (50.89)	5,380 (54.40)
Multiple pregnancy	12,495 (1.69)	1,074 (2.80)	432 (4.37)
Cesarean section	286,946 (38.74)	17,547 (45.69)	8,447 (85.41)
Preeclampsia	16,033 (2.16)	1,063 (2.77)	327 (3.31)
PPH	72,501 (9.79)	3,946 (10.28)	1,007 (10.18)
Placental abruption	2,728 (0.37)	170 (0.44)	40 (0.40)
Placenta previa	9,365 (1.26)	848 (2.21)	289 (2.92)
Uterine rupture	107 (0.01)	12 (0.03)	22 (0.22)

*Group A, Women who had never been diagnosed with myoma; Group B, Women who had diagnosed myoma(s) but no history of myomectomy; Group C, Women who had a history of myomectomy

PPH, Postpartum hemorrhage

Values are given as mean ± standard deviation or number (%).

Table 2. Demographics and birth outcomes of study population (Dataset 2)

	Group A* (N = 502,209)	Group B* (N = 25,408)	Group C* (N = 6,642)
Preterm birth	13,470 (2.68)	1,018 (4.01)	327 (4.92)
Neonatal sex–male	258,518 (51.48)	13,066 (51.42)	3,430 (51.64)
Birth weight (kg)	3.20 ± 0.46	3.17 ± 0.50	3.11 ± 0.50
LBW	20,203 (4.02)	1,452 (5.71)	459 (6.91)
LGA	17,390 (3.46)	885 (3.48)	165 (2.48)

*Group A, Women who had never been diagnosed with myoma; Group B, Women who had diagnosed myoma(s) but no history of myomectomy; Group C, Women who had a history of myomectomy

LBW, Low birth weight; LGA, Large for gestational age

Values are given as mean ± standard deviation or number (%).

Table 3. The obstetric outcomes in women with diagnosed myoma(s) or a history of myomectomy (Dataset 1)

Obstetric outcomes	Odds ratio (95% confidence interval)	
	Unadjusted	Adjusted [a]
Cesarean section		
Group A	1	1
Group B	1.312 (1.279 – 1.346)	1.129 (1.100 – 1.159)
Group C	8.992 (8.408 – 9.617)	7.459 (6.971 – 7.980)
Preeclampsia		
Group A	1	1
Group B	1.326 (1.227 – 1.433)	1.176 (1.087 – 1.272)
Group C	1.360 (1.175 – 1.574)	1.121 (0.968 – 1.299)
PPH		
Group A	1	1
Group B	1.048 (1.005 – 1.092)	1.052 (1.008 – 1.097)
Group C	1.064 (0.983 – 1.152)	1.065 (0.983 – 1.154)
Placental abruption		
Group A	1	1
Group B	1.185 (0.970 – 1.448)	1.060 (0.866 – 1.298)
Group C	1.156 (0.784 – 1.704)	0.971 (0.657 – 1.434)
Placenta previa		
Group A	1	1
Group B	1.797 (1.646 – 1.962)	1.411 (1.291 – 1.542)
Group C	2.223 (1.912 – 2.584)	1.575 (1.352 – 1.833)
Uterine rupture		
Group A	1	1
Group B	2.421 (1.037 – 5.651)	1.927 (0.818 – 4.536)
Group C	17.00 (8.836 – 32.708)	12.784 (6.503 – 25.132)

*Group A, Women who had never been diagnosed with myoma; Group B, Women who had diagnosed

myoma(s) but no history of myomectomy; Group C, Women who had a history of myomectomy

PPH, Postpartum hemorrhage

[a] Adjusted for age and parity

Table 4. The obstetric outcomes in women with diagnosed myoma(s) or a history of myomectomy (Dataset 2)

Obstetric outcomes	Odds ratio (95% confidence interval)	
	Unadjusted	Adjusted [a]
Preterm birth		
Group A	1	1
Group B	1.514 (1.419 – 1.616)	1.386 (1.297 – 1.480)
Group C	1.879 (1.679 – 2.103)	1.644 (1.468 – 1.841)
LBW		
Group A	1	1
Group B	1.446 (1.369 – 1.528)	1.313 (1.242 – 1.388)
Group C	1.771 (1.609 – 1.949)	1.525 (1.385 – 1.680)
LGA		
Group A	1	1
Group B	1.006 (0.939 – 1.078)	0.967 (0.902 – 1.036)
Group C	0.711 (0.609 – 0.830)	0.676 (0.578 – 0.790)

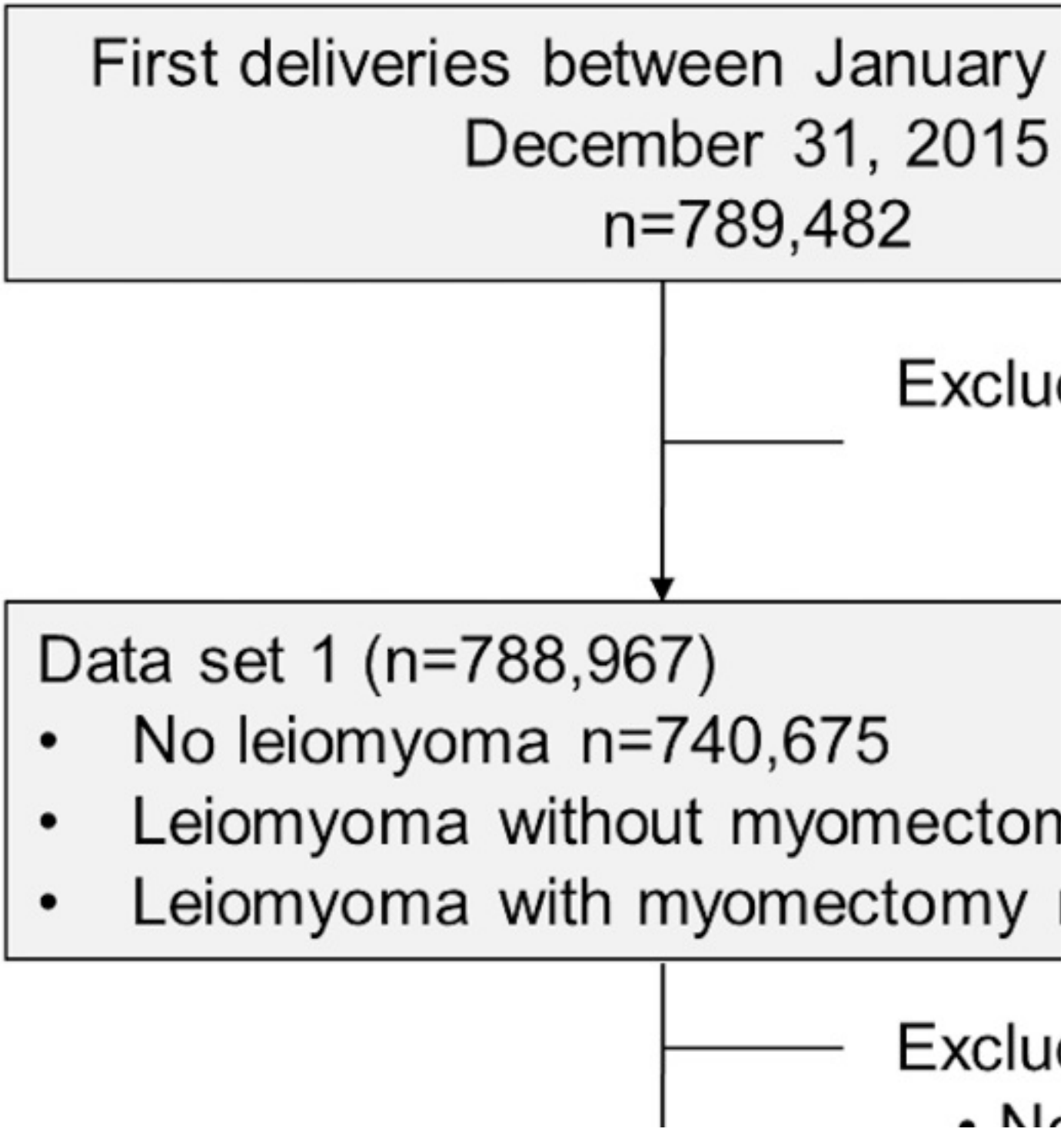
*Group A, Women who had never been diagnosed with myoma; Group B, Women who had diagnosed

myoma(s) but no history of myomectomy; Group C, Women who had a history of myomectomy

LBW, Low birth weight; LGA, Large for gestational age

[a] Adjusted for age and parity

Figures



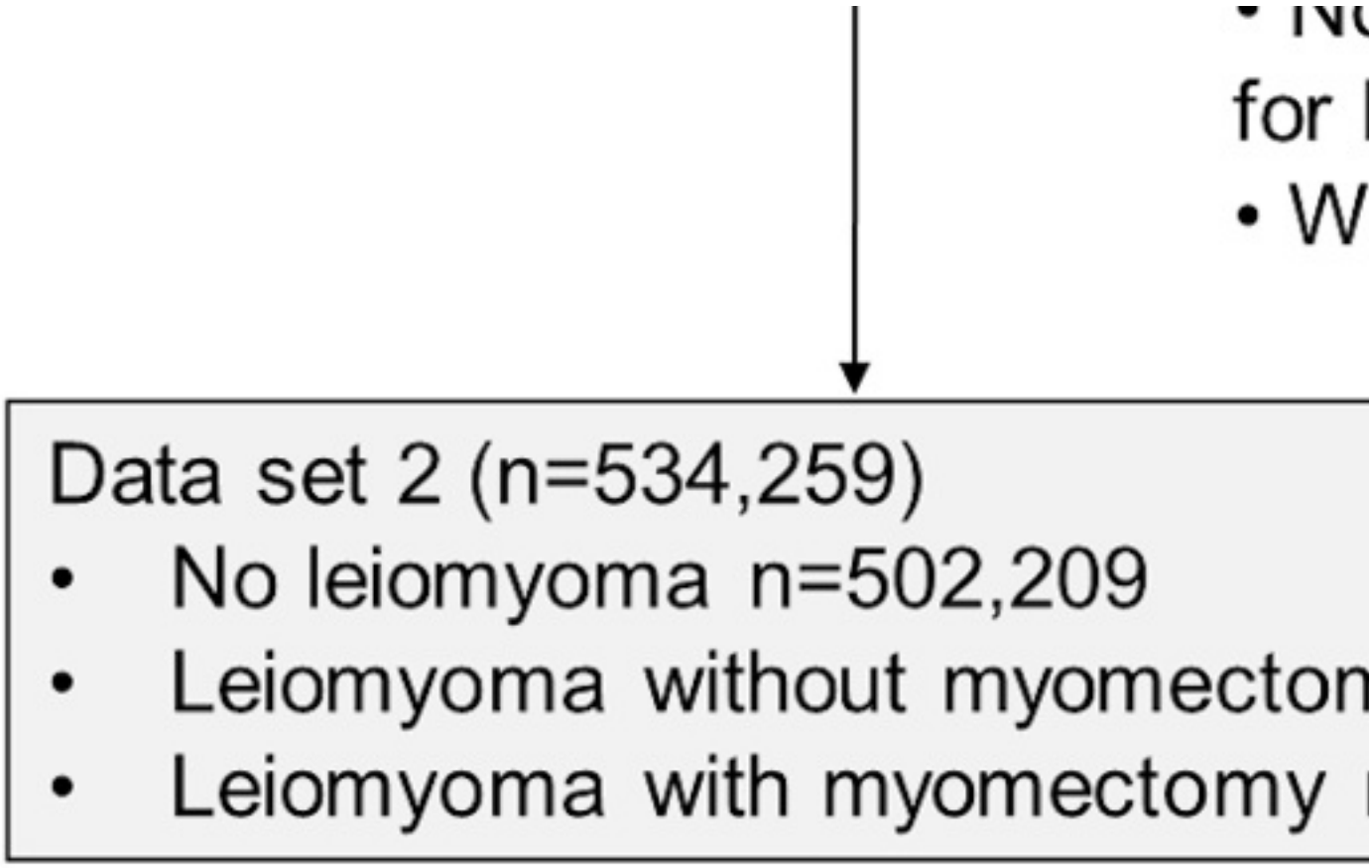


Figure 1

Flow chart of study participants' enrollment

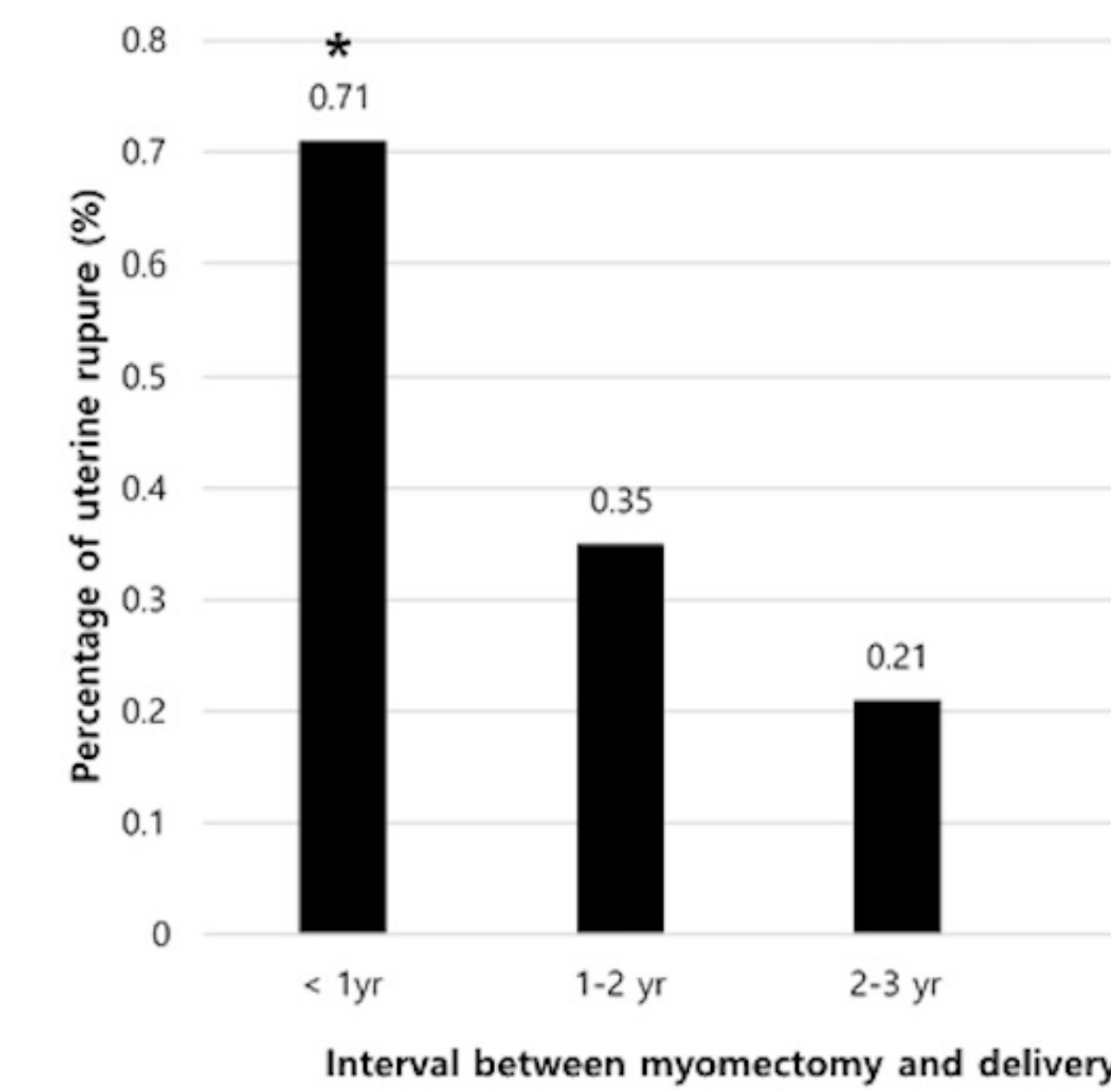

0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Percentage of uterine rupure (%)
*
0.71
0.35
0.21
< 1yr
1-2 yr
2-3 yr
Interval between myomectomy and delivery

Figure 2

Incidence of uterine rupture in women with myomectomy, according to time interval after myomectomy.