DR AKIKO YAMAGUCHI (Orcid ID : 0000-0002-5331-5490)

DR HYO KYOZUKA (Orcid ID : 0000-0001-7782-3396)

DR KEIYA FUJIMORI (Orcid ID : 0000-0001-8618-4063)

Article type : Original Research Article

Risk of preterm birth, low birthweight, and small-for-gestational-age infants in pregnancies with adenomyosis: a cohort study of the Japan Environment and Children's Study

Akiko Yamaguchi[1], Hyo Kyozuka[1,2], Keiya Fujimori[1,2], Mitsuaki Hosoya[2,3], Seiji Yasumura,[2,4], Tadahiko Yokoyama[2], Akiko Sato[2], Koichi Hashimoto[2,3], The Japan Environment and Children's Study Group

[1]Department of Obstetrics and Gynecology, School of Medicine, Fukushima Medical University, Fukushima, Japan, [2]Fukushima Regional Center for the Japan Environmental and Children's Study, Fukushima, Japan, [3]Department of Pediatrics, School of Medicine, Fukushima Medical University, Fukushima, Japan, [4]Department of Public Health, School of Medicine, Fukushima Medical University, Fukushima, Japan

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/aogs.13498

Corresponding author
Akiko Yamaguchi
Department of Obstetrics and Gynecology, School of Medicine, Fukushima Medical University, 1 Hikarigaoka, Fukushima, 960-1295, Japan
E-mail: akiko-y@fmu.ac.jp

Conflicts of Interest statement
The authors report no conflicts of interest.

Funding
The Japan Environment and Children's Study was supported by the Ministry of the Environment Japan.

ABSTRACT

Introduction. This study evaluated the risk of preterm birth, low birthweight, and small-for-gestational-age neonates born to mothers with adenomyosis during pregnancy. **Material and methods.** We used the results of a Japanese nationwide prospective birth cohort study, identifying 93 668 singleton deliveries from 2011 to 2014. We identified 314 pregnancies with adenomyosis using self-reported questionnaires. Multiple logistic regression analyses were conducted to examine whether adenomyosis was associated with adverse pregnancy outcome. Maternal age, smoking status, method of conception, history of parity, fibroids, endometriosis and body mass index before pregnancy were analyzed as confounding factors. **Results**. Multiple logistic regression analysis showed that pregnancy with adenomyosis was a risk factor for preterm birth < 37 weeks (adjusted odds ratio (aOR): 2.49, 95% confidence interval (CI); 1.89 to 3.41), preterm birth < 34 weeks (aOR: 1.91, 95% CI; 1.02 to 3.55), low birthweight < 2500 g (aOR: 1.83, 95% CI; 1.36 to 2.45), low birthweight < 1500 g (aOR: 2.39, 95% CI; 1.20 to 4.77), and small-for-gestational-age neonates (aOR: 1.68, 95% CI; 1.13 to 2.51). **Conclusions.** This study found that pregnancy with adenomyosis was associated with preterm birth, low birthweight, and small-for-gestational-age neonates.

Keywords
Adenomyosis, obstetric outcome, birth cohort study, preterm birth, low birthweight infant, small-for-gestational-age, multiple logistic regression analysis

Abbreviations
PTB, preterm birth;
LBW, low birthweight;
SGA, small-for-gestational-age;
JECS, Japan environment and children's study;
BMI, body mass index;
aOR, adjusted odds ratio
CI confidence interval

Key message
We evaluated the risk of preterm birth, low birthweight and small-for-gestational-age in pregnancy with adenomyosis using the results of a Japanese nationwide birth cohort study. Multiple logistic regression analysis revealed adenomyosis to be a risk factor for preterm birth, low birthweight and small-for-gestational-age neonates.

INTRODUCTION

Adenomyosis is defined as the ectopic proliferation of endometrial glands and stroma within the myometrium of the uterus. Therefore, the uterus becomes edematous and enlarged.[1,2] Adenomyosis affects up to 10–20% of women of reproductive age,[3-5] and often results in severe dysmenorrhea and/or hypermenorrhea. The disease occurs more often in women between the ages of 30 and 40 years.[1]

It is widely accepted that adenomyosis is related to reproductive disorders. Several studies have reported that adenomyosis affects fertility, spontaneous abortionand second-trimester miscarriage.[1,6-10] However, obstetric and neonatal outcomes in patients with adenomyosis have not yet been thoroughly investigated.

Recently, some studies have reported obstetric complications in pregnancies with adenomyosis. Preterm birth (PTB), which may cause low birthweight (LBW) in neonates, is a common obstetric complication, leading to significant neonatal morbidity and mortality.

Previous studies have reported that pregnancy with adenomyosis is related to PTB,[9-12] and/or fetal growth restriction, both of which may cause LBW in neonates.[9,12] However, previous studies were conducted using retrospective reviews of patients from just one or only a few tertiary medical institutions.[9-12] Such studies have potential limitations, including a lack of statistical power and non-representation of the general population.

Therefore, the aim of this study was to examine the risk of PTB, LBW, and small-for-gestational-age (SGA) neonates born to mothers with adenomyosis using data from a nationwide Japanese birth cohort study.

MATERIAL AND METHODS

Data sources

In the present study, we used the results of the Japan Environment and Children's Study (JECS), a nationwide, government-funded birth cohort study.[13] Enrollment in this study started in January 2011 and ended in March 2014, and it evaluated the effects of various environmental factors on children's health. The eligibility criteria for JECS participants (expectant mothers) were as follows: (1) prospective participants should have been residing in the study areas at the time of recruitment and were expected to reside continually in Japan for the foreseeable future, (2) the expected delivery date was between August 1, 2011 and mid-2014, and (3) individuals should have been capable of participating in the study without difficulty (i.e., they must have been able to comprehend the Japanese language and complete the self-administered questionnaire).

The target recruitment rate was more than 50% of all eligible mothers. Either or both of the following two recruitment protocols were applied: (1) recruitment at the time of the first prenatal examination at cooperating obstetric facilities and/or (2) recruitment at local government offices issuing pregnancy journals, namely the Mother-Child Health Handbook, which is given to all expecting mothers in Japan before receiving municipal services for pregnancy, delivery, and childcare. Written informed consent was obtained from all participating women.

Data collection

Data for the current analysis were extracted from the dataset released in June 2016 (dataset: jecs-ag-20160424). From this dataset, we used two types of data: 1) T1, obtained from a self-reported questionnaire collected during the pregnancy (the first questionnaire) and 2) M0, obtained from the medical records provided by each woman's institution. Women who delivered before 22 weeks, had a multiple pregnancy, or with insufficient data for maternal background or obstetrics outcome were excluded from this analysis.

Maternal medical background

Maternal medical background information was obtained from two sources: M0 data (maternal age at the time of delivery, body mass index [BMI] before pregnancy, primiparity or multiparity, and methods of conception) and T1 data (maternal smoking status and the presence of adenomyosis and/or fibroids and/or endometriosis before pregnancy). Maternal participants were requested to provide information about the presence of adenomyosis (or fibroids or endometriosis). "Have you ever diagnosed as adenomyosis (or fibroids or endometriosis) at medical institution?" The maternal participants who answered "Yes" were classified into the presence of adenomyosis (or fibroids or endometriosis). The mothers were categorized into six age groups: < 20, 20–24, 25–29, 30–34, 35–39, or ≥ 40 years. BMI was calculated according to World Health Organization standards (body weight [kg]/height $[m]^2$). We categorized the women into three groups according to BMI: < 18.5 (lean), 18.5–25.0 (normal), and ≥ 25.0 kg/m^2 (obese). The methods of conception were categorized as conception with or without medically assisted reproduction. Maternal participants were also classified as smoking or non-smoking.

Obstetric outcome

Obstetric outcomes were obtained from the M0 data. Obstetric outcomes included: gestational age at birth, PTB, birthweight, LBW, and mode of delivery. PTB was classified into two categories: PTB before 37 weeks inclusive and PTB before 34 weeks. LBW was classified into two categories: LBW < 2500 g inclusive and LBW < 1500 g. SGA was defined as a birthweight below -1.5 standard deviations, corrected for gestational age and sex according to the "New Japanese neonatal anthropometric charts".[13] The mode of delivery was categorized as either vaginal or cesarean.

Statistical analyses

First, maternal medical background and obstetric outcomes were compared between pregnancies with and without adenomyosis. A chi-square test was used to compare the categorical variables, and a *t*-test was used to compare continuous variables between the two groups. An adjusted odds ratio (aOR) and 95% confidence interval (95% CI) for PTB < 37 weeks and < 34 weeks, LBW < 2500 g and < 1500 g, and SGA were calculated using a multiple logistic regression model. The odds ratios were adjusted for maternal age (categorical variable), smoking status, method of conception (with or without medically assisted reproduction), primiparity, coexistence of fibroids or endometriosis and BMI before pregnancy. In the analysis, maternal age 20–24 years and BMI 18.5–25.0 were used as references. SPSS version 21 (IBM Corp., Armonk, NY) was used for the statistical analyses. A *p*-value < 0.05 indicated statistical significance.

Ethical approval

The JECS protocol was reviewed and approved by the Ministry of the Environment's Institutional Review Board on Epidemiological Studies and by the Ethics Committees of all participating institutions (Programme Office [National Institute for Environmental Studies], The National Center for Child Health and Development, Hokkaido University, Sapporo Medical University, Asahikawa Medical College, Japanese Red Cross Hokkaido College of Nursing, Tohoku University, Fukushima Medical University, Chiba University, Yokohama City University, University of Yamanashi, Shinshu University, University of Toyama, Nagoya City University, Kyoto University, Doshisha University, Osaka University, Osaka Medical Center and Research Institution for Maternal and Child Health, Kyushu University, University of Occupational and Environment Health, Kumamoto University, University of Miyazaki, and University of Ryukyu). The JECS was conducted in accordance with the Helsinki Declaration and other nationally validated regulations and guidelines. This study was approved by the Ethical Committee of Fukushima Medical University (approval number 1165); the date of approval was December 20, 2010.

RESULTS

The total number of pregnancies in the JECS was 103 099. Of these, 93 521 maternal cases were eligible for the present study according to the exclusion criteria. The study consisted of 311 pregnancies with adenomyosis (adenomyosis group) and 93 210 pregnancies without adenomyosis (reference group) (Figure 1). The prevalence of pregnancy with adenomyosis was 0.33% (311/93 521).

Table 1 summarizes the maternal medical background and obstetric outcomes in pregnancies with and without adenomyosis. In the adenomyosis group, the mean maternal age at delivery was significantly older than that of the reference group. Moreover, the rate of primiparity and the rate of assisted reproductive technology pregnancy were also significantly higher than those in the reference group.

In the adenomyosis group, gestational age at delivery was significantly earlier than that in the reference group, and the frequencies of PTB < 37 weeks and PTB < 34 weeks were also significantly higher than those in the reference group. Moreover, the differences between the adenomyosis and reference groups were significant with regard to birthweight, LBW < 2500 g, LBW < 1500 g, cesarean delivery, and SGA, respectively.

Table 2 shows the results of logistic regression analyses for PTB and LBW. An adjustment by multiple logistic regression revealed that adenomyosis was a significant risk factor for PTB < 37 weeks, PTB < 34 weeks, LBW < 2500 g, LBW < 1500 g, and SGA. When we compared the aORs between PTB < 37 weeks and < 34 weeks, a higher aOR was observed in the < 37 weeks group. On the other hand, a higher aOR was observed in the < 1500 g group compared to the < 2500 g group.

DISCUSSION

In the present study, we demonstrated that adenomyosis was associated with an increased risk of PTB and of LBW using logistic regression analysis. This study also analyzed subcategories of PTB or LBW that represented more severe adverse outcomes (< 34 weeks and < 1500 g). We also found that adenomyosis was especially related to severe LBW in neonates (< 1500 g, aOR: 2.39) compared to LBW (< 2500 g, aOR: 1.83). Furthermore, adenomyosis was also significantly associated with SGA. Therefore, these data suggest that severe LBW (< 1500 g) in neonates born to women with adenomyosis during pregnancy

might not only be the result of PTB but also might be due to growth restriction caused by adenomyosis.

To date, several investigators have reported the influence of adenomyosis on pregnancy outcomes in retrospective studies using relatively small sample sizes. Adenomyosis was associated with an increased risk of PTB,[9-12] and fetal growth restriction.[12,15] In our study, the risk of PTB and SGA was significantly increased in women with adenomyosis, which was consistent with previous data. Unlike previous studies, we used data from a prospective study with a large number of participants. As a result, we could clarify the prevalence of pregnancy with adenomyosis in Japan and the risk of PTB, LBW, and SGA by the use of aORs.

With regard to the etiology of PTB in adenomyosis, there are three interrelated etiologies: the presence of inflammation, increased prostaglandin levels, and increased intrauterine pressure. Recently, the causes of endometriosis have been recognized to involve not only hormonal factors but also inflammatory factors. Inflammation is present in the inner myometrium in adenomyosis, and it is present in peritoneal cavity in endometriosis.[2] Thus, adenomyosis is similar to endometriosis in terms of its pathologic status. In several previous studies, endometriosis also increased the risk of PTB.[16-18] Juang et al. reported that severe menstrual pain was more prevalent in the PTB cases than in the term delivery cases.[10] Moreover, in women with dysmenorrhea, elevated prostaglandin levels found in the endometrial fluid were correlated with the degree of menstrual pain.[19] Therefore, it is reasonable to hypothesize that patients with adenomyosis who have dysmenorrhea have increased endometrial prostaglandin production, affecting decidualization and altering the collagen structure of the fetal membranes, and this may lead to PTB.[11] Adenomyosis lesions present deep within the myometrium. The myometrium has an important role in maintaining pregnancy, and lesions within the myometrium may lead to uterine contractions. Ferenczy et al. reported that adenomyosis increased the intrauterine pressure and led to cervical changes, as seen in PTB.[20]

The pathology of SGA in adenomyosis is assumed to be impairment of placentation and reduced blood flow to the placenta. Adenomyosis is a thickened and disrupted junctional zone, which is associated with deep placentation.[9,15,16] Yorifuji et al. reported that blood flow to the placenta was diminished in women with adenomyosis and fetal growth restriction.[21] Hashimoto et al. noted that adenomyosis lesions are within the myometrium; therefore, adenomyosis might be blood flow diverted from the placenta.[12]

This study has potential limitations to be considered. In this study, the presence of adenomyosis was identified by a self-reported questionnaire. Therefore, the information about the existence of adenomyosis in each case was somewhat subjective. In clinical practice, adenomyosis is diagnosed by magnetic resonance imaging and ultrasonography, which confirms the type or severity classification.[22] Hasdemir et al. noted that not only the presence of adenomyosis but also the type of adenomyosis might be related to fetal growth restriction.[15] Therefore, further research that considers the type or severity of adenomyosis is required.

Despite these limitations, the present study has several strengths. JECS is the first large, nationwide study in Japan combining medical records and biological samples managed by the Japanese government with meticulous attention to data precision. Additionally, JECS included not only tertiary medical institutions but also a rather broad selection of other medical institutions.[23]

CONCLUSION

Adenomyosis was associated with an increased risk of PTB and SGA, resulting in an increase of severe LBW. In addition, women with adenomyosis tend to need sterility treatments. Therefore, this study can contribute to appropriate preconception counseling for women with adenomyosis expecting to become pregnant and can also lead to improved obstetric management for pregnant women with adenomyosis. More extensive research, including attention to specific types of adenomyosis, is needed to clarify the correlation between pregnancy with adenomyosis and obstetric outcomes.

Acknowledgments

The findings and conclusions of this article are solely the responsibility of the authors and do not represent the official views of the Ministry of the Environment. The authors are grateful to the director of the Programme Office who leads the JECS. The members of the Japan Environment and Children's Study (JECS) as of 2017 (principal investigator, Toshihiro Kawamoto) are: Hirohisa Saito (National Center for Child Health and Development, Tokyo, Japan), Reiko Kishi (Hokkaido University, Sapporo, Japan), Nobuo Yaegashi (Tohoku University, Sendai, Japan), Koichi Hashimoto (Fukushima Medical University, Fukushima, Japan), Chisato Mori (Chiba University, Chiba, Japan), Shuichi Ito (Yokohama City University, Yokohama, Japan), Zentaro Yamagata (University of Yamanashi, Chuo, Japan),

Hidekuni Inadera (University of Toyama, Toyama, Japan), Michihiro Kamijima (Nagoya City University, Nagoya, Japan), Takeo Nakayama (Kyoto University, Kyoto, Japan), Hiroyasu Iso (Osaka University, Suita, Japan), Masayuki Shima (Hyogo College of Medicine, Nishinomiya, Japan), Yasuaki Hirooka (Tottori University, Yonago, Japan), Narufumi Suganuma (Kochi University, Nankoku, Japan), Koichi Kusuhara (University of Occupational and Environmental Health, Kitakyushu, Japan), and Takahiro Katoh (Kumamoto University, Kumamoto, Japan).

References

1. Harada T, Khine YM, Kaponis A, Nikellis T, Decavalas G, Taniguchi F. The impact of adenomyosis on women's fertility. *Obstet Gynecol Surv*. 2016;71:557-568.
2. Leyendecker G, Wildt L, Mall G. The pathophysiology of endometriosis and adenomyosis: tissue injury and repair. *Arch Gynecol Obstet*. 2009;280:529-538.
3. Di Donato N, Montanari G, Benfenati A, et al. Prevalence of adenomyosis in women undergoing surgery for endometriosis. *Eur J Obstet Gynecol Reprod Biol*. 2014;181:289-293.
4. Bergholt T, Eriksen L, Berendt N, Jacobsen M, Hertz JB. Prevalence and risk factors of adenomyosis at hysterectomy. *Hum Reprod*. 2001;16:2418-2421.
5. Vavilis D, Agorastos T, Tzafetas J, et al. Adenomyosis at hysterectomy: prevalence and relationship to operative findings and reproductive and menstrual factors. *Clin Exp Obstet Gynecol*. 1997;24:36-38.
6. Younes G, Tulandi T. Effects of adenomyosis on in vitro fertilization treatment outcomes: a meta-analysis. *Fertil Steril*. 2017;108:483-490.
7. Vercellini P, Consonni D, Dridi D, Bracco B, Frattaruolo MP, Somigliana E. Uterine adenomyosis and in vitro fertilization outcome: a systematic review and meta-analysis. *Hum Reprod*. 2014;29:964-977.
8. Vlahos NF, Theodoridis TD, Partsinevelos GA. Myomas and adenomyosis; Impact on reproductive outcome. *Biomed Res Int*. 2017;2017:5926470.
9. Hashimoto A, Iriyama T, Sayama S, et al. Adenomyosis and adverse perinatal outcomes: increased risk of second trimester miscarriage, preeclampsia, and placental malposition. *J Matern Fetal Neonatal Med*. 2018;31:364-369.

10. Juang CM, Chou P, Yen MS, Twu NF, Horng HC, Hsu WL. Adenomyosis and risk of preterm delivery. *BJOG*. 2007;114:165-169.
11. Tamura H, Kishi H, Kitade M, et al. Complications and outcomes of pregnant women with adenomyosis in Japan. *Reprod Med Biol.* 2017; 16: 330-336.
12. Mochimaru A, Aoki S, Oba MS, Kurasawa K, Takahashi T, Hirahara F. Adverse pregnancy outcomes associated with adenomyosis with uterine enlargement. *J Obstet Gynaecol Res*. 2015;41:529-533.
13. Kawamoto T, Nitta H, Murata K, et al. Rational and study design of the Japan Environment and Children's Study (JECS). *BMC Public Health*. 2014;14:25.
14. Itabashi K, Miura F, Uehara R, Nakamura Y. New Japanese neonatal anthropometric charts for gestational age at birth. *Pediatr Int*. 2014;56:702-708.
15. Hasdemir M, Farasat M, Aydin C, Ozyurt BC, Guvenal T, Pekindil G. The role of adenomyosis in the pathogenesis of preeclampsia. *Geburtshilfe Frauenheilkd*. 2016;76:882-887.
16. Vannuccini S, Clifton VL, Fraser IS, et al. Infertility and reproductive disorders: impact of hormonal and inflammatory mechanisms on pregnancy outcome. *Hum Reprod Update*. 2016;22:104-115.
17. Conti N, Cevenini G, Vannuccini S, et al. Women with endometriosis at first pregnancy have an increased risk of adverse obstetrics outcome. *J Matern Fetal Neonatal Med*. 2015;28:1795-1798.
18. Harada T, Taniguchi F, Onishi K, et al. Obstetrical complications in women with endometriosis: a cohort study in Japan. *PLoS One*. 2016;11:e0168476.
19. Bieglmayer C, Hofer G, Kainz C, Reinthaller A, Kopp B, Janisch H. Concentrations of various arachidonic acid metabolites in menstrual fluid are associated with menstrual pain and are influenced by hormonal contraceptives. *Gynecol Endocrinol*. 1995;9:307-312.
20. Ferenczy A. Pathophysiology of adenomyosis. *Hum Reprod Update*. 1998;4:312-322.
21. Yorifuji T, Makino S, Yamamoto Y, Sugimura M, Kuwatsuru R, Takeda S. Time spatial labeling inversion pulse magnetic resonance angiography in pregnancy with adenomyosis. *J Obstet Gynaecol Res*. 2013;39:1480-1483.
22. Maheshwari A, Gurunath S, Fatima F, Bhattacharya S. Adenomyosis and subfertility: A systematic review of prevalence, diagnosis, treatment and fertility outcomes. *Hum Reprod Update*. 2012;18:374-392.

23. Michikawa T, Nitta H, Nakayama SF, et al. Baseline profile of participants in the Japan Environment and Children's Study (JECS). *J Epidemiol*. 2018;28:99-104.

Legends of figures and tables

Table 1. Maternal medical background and obstetric outcomes of participants based on adenomyosis.

Table 2. Correlation between adenomyosis and risk of preterm birth, low birthweight, or small-for-gestational-age neonates.

Figure 1. The flow chart for select research participants.

Table 1. Maternal medical background and obstetric outcomes of participants based on adenomyosis.

Variable	Total participants 93 521	Adenomyosis 311	*p-value
Maternal medical background			
Maternal age, years mean (SD)	31.2 (5.0)	35.0 (4.4)	< 0.001
Maternal age category, years % (n)			
< 20	0.8 (749)	0.0 (0)	
20 - 24	8.9 (8333)	1.3 (4)	
25 - 29	27.5 (25 723)	10.6 (33)	< 0.001
30 - 34	35.5(33 206)	31.8 (99)	
35 - 39	22.6 (21 182)	42.1 (131)	
over 40	4.6 (4328)	14.1 (44)	
BMI before pregnancy, % (n)			
< 18.5	16.1 (15 056)	12.2 (38)	
18.5 - 25.0	73.1 (68 396)	77.5 (241)	0.150
> 25	10.8 (10 069)	10.3 (32)	
Primiparity, % (n)	40.3 (37 713)	48.6 (151)	0.003
Sterility treatment, % (n)	6.6 (6206)	28.9 (90)	<0.001

ART, % (n)	3.0 (2816)	19.3 (60)	< 0.001
Smoking during pregnancy, % (n)	4.8 (4518)	3.5 (11)	0.286
Fibroids, % (n)	6.1(5715)	28.6(89)	<0.001
Endometriosis, % (n)	3.6(3412)	41.2(128)	<0.001
Obstetric outcome			
Gestational age, weeks mean (SD)	38.8 (1.7)	37.9 (2.4)	< 0.001
Preterm birth < 37 weeks, % (n)	5.2 (4909)	15.8 (49)	< 0.001
Preterm birth < 34 weeks, % (n)	1.2 (1129)	3.5 (11)	<0.001
Birthweight, g, mean (SD)	3014 (433)	2845 (552)	< 0.001
LBW < 2500 g, % (n)	8.8(8189)	18.3 (57)	< 0.001
LBW < 1500 g, % (n)	0.7 (701)	2.9 (9)	< 0.001
SGA, % (n)	5.2 (4883)	8.7 (27)	0.006
Cesarean section, % (n)	19.5 (18 197)	36.7 (114)	< 0.001

ART, assisted reproductive technology; BMI, body mass index; LBW, low birthweight; SD, standard deviation; SGA, small-for-gestational-age

* Each *p*-value were calculated between the group with and without adenomyosis

Table 2. Correlation between adenomyosis and risk of preterm birth, low birthweight, or small-for-gestational-age neonates

Adenomyosis		Preterm birth		Low birthweight		Small for gestational age
		< 37 weeks	< 34 weeks	< 2500 g	< 1500 g	
-	aOR	Ref	ref	ref	ref	ref
	95% CI[a]	ref	ref	ref	ref	ref
+	aOR	2.49	1.91	1.83	2.39	1.68
	95% CI[a]	1.81 to 3.41	1.02 to 3.55	1.36 to 2.45	1.20 to 4.77	1.13 to 2.51

[a]Adjusted for maternal age, smoking status, method of conception, primiparity, fibroids, endometriosis, and body mass index before pregnancy

aOR, adjusted odds ratio; CI, confidence interval; ref, reference