Clinical characteristics and outcomes of women with adenomyosis pain during pregnancy: a retrospective cohort study

Seisuke Sayama[1], Takayuki Iriyama[1], Yotaro Takeiri[1], Ayako Hashimoto[1], Masatake Toshimitsu[1], Mari Ichinose[1], Takahiro Seyama[1], Kenbun Sone[1], Keiichi Kumasawa[1], Takeshi Nagamatsu[1], Kaori Koga[1], and Yutaka Osuga[1]

[1]The University of Tokyo Hospital

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Abstract

Objective To clarify the clinical characteristics of pain developing in adenomyosis lesions during pregnancy and the perinatal outcomes associated with this phenomenon. Study Design Retrospective cohort study. Setting A tertiary hospital in Japan. Patients and methods Ninety one singleton pregnancies with adenomyosis who delivered between 2011 and 2021 were retrospectively analyzed. Pain during pregnancy was defined as persistent pain at the adenomyosis site with analgesics administration, and its association with perinatal outcomes was analyzed. Main outcome measures Pain at the adenomyosis lesion and its onset and duration, maximum C-reactive protein level during pain, and perinatal outcomes such as preterm delivery, preeclampsia, and blood loss. Results Among 91 singleton pregnancies with adenomyosis, 12 pregnancies (13.2%) presented with pain at the adenomyosis site. In total, 5 of the 12 pregnancies (41.7%) developed preeclampsia, which resulted in preterm delivery. The incidence of preeclampsia and preterm delivery was higher in those who experienced pain than in those without (41.7% vs. 13.9%; $p<0.05$, and 66.7% vs. 31.7%; $p<0.05$, respectively). Among women with pain during pregnancy, the maximum C-reactive protein level was significantly higher in women who developed preeclampsia than in those without (5.45 vs. 0.12 mg/dL, $p<0.05$). Conclusion Adenomyosis can cause pain in over one of eight pregnancies with adenomyosis, which may be associated with the increased incidence of preeclampsia resulting in preterm delivery. Women with pain at the adenomyosis lesion, especially those with high C-reactive protein levels, may be at high risk for the future development of preeclampsia.

Title

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Authors

Seisuke SAYAMA, MD, PhD 1),

Takayuki IRIYAMA, MD, PhD 1),

Yotaro TAKEIRI, MD 1)

Ayako HASHIMOTO, MD, PhD 1),

Masatake TOSHIMITSU, MD, PhD 1),

Mari ICHINOSE, MD, PhD 1),

Takahiro SEYAMA, MD, PhD 1),

Kenbun SONE, MD, PhD 1),

Keiichi KUMASAWA, MD, PhD 1),

Takeshi NAGAMATSU, MD, PhD 1),

Kaori KOGA, MD, PhD 1),

Yutaka OSUGA, MD, PhD 1).

1) Department of Obstetrics and Gynecology, Faculty of Medicine, The University of Tokyo, Bunkyo-ku, Tokyo, JAPAN

Correspondence to: Takayuki Iriyama, Department of Obstetrics and Gynecology, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo, 113-8655, Japan. Tel: +81-3-5800-8657, Fax +81-3-3816-2017, E-mail:*iriyama-tky@umin.ac.jp*

Running title: Adenomyosis pain during pregnancy

Abstract

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Study Design

Retrospective cohort study.

Setting

A tertiary hospital in Japan.

Patients and methods

Ninety one singleton pregnancies with adenomyosis who delivered between 2011 and 2021 were retrospectively analyzed. Pain during pregnancy was defined as persistent pain at the adenomyosis site with analgesics administration, and its association with perinatal outcomes was analyzed.

Main outcome measures

Pain at the adenomyosis lesion and its onset and duration, maximum C-reactive protein level during pain, and perinatal outcomes such as preterm delivery, preeclampsia, and blood loss.

Results

Among 91 singleton pregnancies with adenomyosis, 12 pregnancies (13.2%) presented with pain at the adenomyosis site. In total, 5 of the 12 pregnancies (41.7%) developed preeclampsia, which resulted in preterm delivery. The incidence of preeclampsia and preterm delivery was higher in those who experienced pain than in those without (41.7% vs. 13.9%;p <0.05, and 66.7% vs. 31.7%; p <0.05, respectively). Among women with pain during pregnancy, the maximum C-reactive protein level was significantly higher in women who developed preeclampsia than in those without (5.45 vs. 0.12 mg/dL,p <0.05).

Conclusion

Adenomyosis can cause pain in over one of eight pregnancies with adenomyosis, which may be associated with the increased incidence of preeclampsia resulting in preterm delivery. Women with pain at the adenomyosis lesion, especially those with high C-reactive protein levels, may be at high risk for the future development of preeclampsia.

Key words: pregnancy, adenomyosis, degeneration, preeclampsia, preterm delivery

Introduction

Uterine adenomyosis is a benign disorder in which endometrial tissues are present within the myometrium, and it is associated with abnormal uterine bleeding, dysmenorrhea, pelvic pain, and infertility.(1) (2) Moreover, adenomyosis is also known to be associated with unfavorable perinatal outcomes, with increased incidence of preterm delivery, preeclampsia (PE), cesarean delivery, postpartum hemorrhage (PPH), and small for gestational age infants. (3-8) However, the pathophysiology underlying this etiology remains to be elucidated, along with the clinical factors associated with adenomyosis that are responsible for these outcomes.

Several cases of adenomyosis accompanied by severe pain and enhanced inflammatory response during pregnancy that showed degenerative changes, which were confirmed with magnetic resonance imaging, have been reported since 2006, including one from our institution.(9) (10) (11) Intriguingly, all of the cases developed either preterm delivery, miscarriage, preeclampsia, or non-reassuring fetal status. Although fibroids are reported to degenerate during pregnancy and cause pain and enhanced inflammation in 12.6-28.0% of these women,(12),(13) the incidence of pain and enhanced inflammation during pregnancy among women with adenomyosis has not been reported, nor has its degeneration during pregnancy and its impact on perinatal outcomes.

Our main objective was to evaluate the clinical characteristics of pain at the adenomyosis site during pregnancy. We also compared perinatal outcomes between those who experienced pain and those who did not among pregnant women with adenomyosis to investigate whether this pain, suggesting degeneration during pregnancy, affects perinatal outcomes.

Methods

This was a retrospective cohort study of 91 singleton pregnancies in 73 women with adenomyosis, who were managed at a single institution. Clinical information was retrospectively obtained from the medical records of pregnant women with adenomyosis who were managed and delivered after 12 weeks of gestation at the University of Tokyo Hospital between January 2011 and December 2021. Women with artificial abortions, multiple gestations, fetal abnormalities, or uterine malformations were excluded from this study. Pain during pregnancy was judged based on medical records as those having persisting pain at the adenomyosis site with administration of analgesics for pain relief during pregnancy; C-reactive protein (CRP) was measured while the pain persisted.

Outcomes

The following maternal background information and perinatal outcomes were reviewed for those who experienced pain at the adenomyosis site: maternal age, parity, mode of conception, maximum CRP during pain, duration of pain, delivery week, onset of PE, spontaneous preterm delivery, delivery method, blood loss, PPH, neonatal weight, and light for gestational age (LGA) infants. Spontaneous preterm delivery was defined as delivery followed by spontaneous onset of labor or prelabor rupture of the membrane.(14) The duration of pain was judged by the time period in which the analgesics were prescribed and the patient's claim of the pain from the medical record. PPH was defined as blood loss of [?]500 g for vaginal delivery and [?]1000 g for cesarean delivery. LGA was defined as an infant with a birth weight below the 10th percentile. PE was diagnosed based on the diagnostic criteria of the International Society for the Study of Hypertension in Pregnancy.(15)

Diagnosis of adenomyosis

The diagnosis of adenomyosis was based on transvaginal ultrasound and/or magnetic resonance imaging (MRI) performed before conception and/or during the first or second trimester of pregnancy. On transvaginal ultrasound, adenomyosis was diagnosed based on the Morphological Uterus Sonographic Assessment (MUSA) criteria established in 2019: asymmetrical thickening, cysts, hyperechoic islands, fan-shaped shadowing, echogenic subendometrial lines and buds, translesional vascularity, irregular junctional zone, and interrupted junctional zone.(16) On MRI, adenomyosis was diagnosed when one of the following two diagnostic criteria were met: 1) presence of a myometrial mass with indistinct margins with primarily low signal intensity, or 2) diffuse or focal thickening of the junctional zone forming an ill-defined area of low signal intensity on

T2-weighted images.(17)

Statistical analysis

Statistical analyses were performed using the JMP Pro 16 software (SAS Institute Inc.). Frequencies of obstetric complications and other categorical variables were analyzed using Fisher's exact test, while blood loss and other continuous variables were analyzed using the Mann-Whitney U test. For these tests, $p < 0.05$ was considered to indicate a significant difference.

Results

Study population

There were 91 pregnancies in 73 women with adenomyosis during the study period of 11 years. Among these 91 pregnancies, 12 pregnancies (11 women) (13.2%) presented with pain at the adenomyosis site during pregnancy, and were given oral acetaminophen. None of the 12 pregnancies had coexisting fibroids. Maternal background and perinatal outcomes of the 12 pregnancies are shown in Table 1. In total, 5 pregnancies (41.7%) developed PE, which resulted in preterm delivery, and only 3 out of 12 pregnancies (25.0%) achieved term delivery. To quantitatively assess inflammation, CRP level was measured in each of the 12 pregnancies who developed pain during the onset of pain, and the maximum CRP level is shown in Table 1. The median value of the maximum CRP level in the 12 pregnancies was 1.67 mg/dL (interquartile range [IQR]: 0.11-4.89 mg/dL). Among the 12 pregnancies with pain, the median gestational week at which the pain started was 19 weeks (IQR: 14-23 weeks), and the median duration of the pain was 42 days (IQR: 28-148 days) (Fig. 1).

Comparison between those who did and did not develop pain during pregnancy

To assess the impact of pain during pregnancy on perinatal outcomes, we compared the maternal backgrounds and pregnancy outcomes between those who did and did not develop pain at the adenomyosis site among 91 pregnancies with adenomyosis, as shown in Table 2. There was no difference in the maternal backgrounds, but those who experienced pain during pregnancy had a significantly higher incidence of PE (41.7% vs. 13.9%; p <0.05). The cesarean section and preterm delivery rates were also significantly higher in those with pain (91.7% vs. 51.9%; p <0.05, and 66.7% vs. 31.7%;p <0.05, respectively), but the rate of spontaneous preterm delivery was not significantly higher in women who experienced pain than that in those who did not (25.0% vs. 11.9%; p =0.19).

To assess whether the extent of inflammation was associated with the onset of PE, we compared the maximum CRP level, which was measured before the onset of PE, among the 12 pregnancies who developed pain during pregnancy. The median maximum CRP level was significantly higher in patients with PE than that in those without PE (5.45 vs. 0.12 mg/dL,p <0.05) (Fig. 2). Among the 5 cases who developed PE, the maximum CRP level preceded the onset of PE as early as 6 days and as late as 47 days, with the median time from the maximum CRP level to the onset of PE being 15 days (IQR: 9-45 days).

Discussion

Main findings

The current study revealed that pain at the adenomyosis site occurred in 13.2% of all pregnancies with adenomyosis. Moreover, the onset of adenomyosis pain was associated with adverse perinatal outcomes, including PE that resulted in preterm delivery and a high cesarean delivery rate. Among women with adenomyosis pain, the maximum CRP level was significantly high among those who developed PE, which preceded the onset of PE for a median of 15 days.

Strengths and limitations

A strength of our study is that, to the best of our knowledge, this is the first report to show the clinical characteristics of pain at the adenomyosis site during pregnancy. Another limitation is that we did not confirm the imaging findings that are linked to the manifestation of adenomyosis pain. However, as with degeneration

in fibroids, diagnosis of adenomyosis pain during pregnancy seems sufficient to confirm the tenderness over the adenomyosis lesion with ultrasound after carefully excluding the possibility of intra-amniotic infection (IAI). Moreover, to elucidate the pathophysiology of pain at the adenomyosis site, pathological confirmation of the histological change in adenomyosis is warranted in future studies.

Interpretation

We have provided a new insight that adenomyosis can trigger abdominal pain during pregnancy. Fibroids cause abdominal pain in up to 28% of cases during pregnancy,(12) but whether the same physiologic changes occur in adenomyosis during pregnancy is not well understood. The pathophysiology underlying pain mechanism in fibroids is degeneration, which occurs predominantly during the second and early third trimesters.(18),(19) It is generally diagnosed by confirming the presence of pain directly over the fibroid correlating with ultrasound examination findings, and further accurate diagnosis can be made with MRI.(20, 21) The degeneration of fibroids is often accompanied by enhanced inflammation and an increase in CRP levels,(12),(13) which decrease with the amelioration of pain, usually within two weeks.(12),(20) However, whether this phenomenon is linked to adverse perinatal outcomes has not been conclusive.(22) Considering the similarity between fibroids and adenomyosis, the timing of pain onset that we reported in this study and the past reports of degeneration of adenomyosis during pregnancy indicate that the pain followed by the enhanced inflammatory response observed in our cohort mimics the degeneration of fibroids.(11, 23, 24) Nevertheless, it seems unquestionable that some proportion of women with adenomyosis develop pain during pregnancy.

A recent meta-analysis showed that women with adenomyosis had an increased likelihood of PE (odds ratio [OR]: 4.35; 95% confidence interval [CI], 1.07–17.72; p <0.05), although the pathophysiology underlying this result is unknown.(5) In our study, the adenomyosis pain onset was associated with the onset of PE, which intriguingly was more conspicuous in patients with elevated CRP levels. Interestingly, the median time from the maximum CRP level to the onset of PE was 15 days, and the CRP level decreased in the days before PE development. Several mouse models of PE have been reported that were induced by inflammatory cytokines.(25-28) Although CRP cannot be used as a marker for predicting the onset of PE, circulating CRP is reported to be elevated in some groups of women, such as those with periodontal disease or obesity, before the onset of PE. (29-31) Although the number of cases is limited, considering that the maximum CRP preceded the onset of PE in our cohort and that previous reports show an association with inflammation and the onset of PE, enhanced inflammation at the utero-placental unit may be the key factor to induce the onset of PE in women with adenomyosis pain.

Practical and clinical recommendations

Our findings suggest that adenomyosis can trigger abdominal pain during pregnancy, but as with fibroid degeneration, it is essential to rule out other diseases when uterine tenderness and enhanced inflammation are observed among pregnant women, especially threatened preterm labor with IAI. In the case with prominent inflammation and severe pain at onset (#3 in Table 1), IAI was initially suspected when the patient presented with acute abdominal pain and an enhanced inflammatory response. Therefore, we performed amniocentesis to rule out IAI, followed by MRI, which showed hemorrhagic degeneration of the adenomyosis, as previously reported.(11) In the other 11 cases, the patients had confined pain at the adenomyosis site on primary presentation without shortening of the cervix; therefore, we clinically diagnosed these patients with adenomyosis pain. Moreover, all placentae from 15 pregnancies underwent pathological examination, of which only two cases (#2 and #3 in Table 1) showed histological chorioamnionitis of stage 1 based on Blanc's classification(32) in the absence of any sign suggestive of clinical IAI, which implies that the pain observed in 12 pregnancies is likely to be distinct from IAI. Consequently, we believe that the diagnosis of adenomyosis pain should be based on clinical symptoms by carefully excluding IAI. Of note, even after the pain resolves and a decrease in CRP level is confirmed, women with adenomyosis pain accompanied by elevated CRP levels warrant close follow-up for the onset of PE as a high-risk group of patients.

Research recommendations

Future studies are warranted to delineate the pathophysiology by which pain is induced in adenomyosis lesion during pregnancy. Confirming the histologic features of adenomyosis lesion during pregnancy may aid in elucidating the underlying pathophysiology, although the pathology of the uterus and the adenomyosis lesion during pregnancy is difficult to determine owing to the nature of the disease. Considering the difficulty of obtaining diagnostic confirmation based on histologic features, confirmation of the adenomyosis lesion with serial MRIs before conception and during adenomyosis pain, as shown previously, (11) (24) may aid in delineating the pathophysiology of the adenomyosis pain during pregnancy; therefore, more reports based on serial MRI findings are awaited. After accumulation of these data, it may be possible to unravel the characteristic findings of adenomyosis which lead to adenomyosis pain during pregnancy.

Future research should aim to elucidate the pain mechanism in adenomyosis as associated with the onset of PE. PE is a multifactorial disease, and one of the known pathophysiology that may trigger the onset of PE is enhanced inflammation.(33, 34) However, the precise mechanism by which the inflammation induces PE is yet to be elucidated. Moreover, the type of adenomyosis or the maternal background associated with the onset of the adenomyosis pain during pregnancy and subsequent PE cannot be concluded from our small sample size; therefore, more reports on this phenomenon are warranted for further evaluation. Elucidating the mechanism by which PE is induced from adenomyosis pain may in turn unravel one aspect of the pathophysiology of PE.

Conclusions

We have delineated one aspect of the perinatal pathophysiology of adenomyosis that can cause pain in more than one of eight pregnancies with adenomyosis, which may be associated with an increased incidence of PE resulting in preterm delivery. The risk of adverse perinatal outcomes in a patient population with adenomyosis is not well known, but our findings have provided new insights, indicating that those who develop adenomyosis pain during pregnancy, especially those with high CRP levels, may be at high risk for the later development of PE and consequently warrant special attention in perinatal care.

Disclosure of Interests

The authors report no conflict of interest.

Contribution to authorship

SS collected data, conducted statistical analysis, and drafted the article. TI conceived the study, drafted the article, and reviewed the final version. YT and AH assisted in collecting data. MT, MI, TS, KS, KK, TN, KK, and YO supervised and reviewed the final version.

Details of Ethics Approval

This study was approved by the Institutional Review Board of the University of Tokyo (approval number: 3053-1). This study was a retrospective cohort study, and patient consent was achieved using the opt-out method of our hospital website, in accordance with the request of the ethics committee and guidelines.

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Table 1

Maternal background and pregnancy outcomes of 12 pregnancies with adenomyosis pain during pregnancy

#	age	Parity	Mode of conception	Max CRP (mg/dL)	Delivery week	PE	Delivery method	Blood loss (ml)	PPH	Neonatal weight (g)
1	41	1	natural	2.37	17	no	VD	1722	yes	180
2	43	0	ART	5.45	23	yes	CS	780	no	293
3	39	1	ART	25.9	27	yes	CS	940	no	1000
4	38	0	ART	3.1	33	yes	CS	1140	yes	1351
5	39	0	ART	10.29	33	yes	CS	2730	yes	1639
6	38	0	ART	0.97	34	yes	CS	1480	yes	2750
7	40	0	ART	0.46	35	no	CS	1090	yes	2066

#	age	Parity	Mode of conception	Max CRP (mg/dL)	Delivery week	PE	Delivery method	Blood loss (ml)	PPH	Neonatal weight (g)
8	34	0	natural	0.12	36	no	CS	1390	yes	2416
9	36	0	natural	3.2	36	no	CS	750	no	2164
10	39	0	ART	0.04	37	no	CS	1550	yes	1847
11	36	1	natural	0.53	37	no	CS	1520	yes	2446
12	38	0	ART	0.11	37	no	CS	1755	yes	3126

ART, assisted reproductive technology; CRP, C-reactive protein; CS, cesarean delivery; Max, maximum; PE, preeclampsia; PPH, postpartum hemorrhage; LGA, light for gestational age infants; VD, vaginal delivery

Table 2

Maternal background and pregnancy outcomes of 91 pregnancies with adenomyosis

	pain + (12)	pain – (79)	p value
Age, median, years (IQR)	38.5 (36.5-39.8)	37.0 (34.0-40.0)	0.27
primiparity	75.0 (%)	67.1 (%	

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