# Is a history of cesarean section a risk factor for abnormal uterine bleeding in patients with uterine leiomyoma?

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## ABSTRACT

**الأهداف:** تحديد فيما إذا كان تاريخ الولادة القيصرية أحد عوامل الخطر لنزيف الرحم غير الطبيعي لدى المرضى الذين يعانون من العضلات الملساء في الرحم، وتحديد عوامل الخطر الأخرى لهذا العرض .

**الطريقة:** أجريت دراسة بأثر رجعي وتحليل السجلات الطبية للمرضى الذين خضعوا لاستئصال الرحم بسبب وجود العضلات الملساء في الرحم خلال فترة 6 سنوات مابين 2009 و 2014 في مستشفى أطلق زبيدة هانم لصحة المرأة والتدريب والأبحاث، أنقرة، تركيا. تم تشخيص الورم العضلي الأملس الرحمي على أساس فحص الأنسجة من عينات استئصال الرحم. وتمت مقارنة الخصائص الديموغرافية، ونتائج المختبر والتغيرات النسيجية المرضية بين المرضى الذين يعانون من الورم العضلي الأملس الرحمي مع وبدون نزيف الرحم غير طبيعي.

**النتائج:** بلغ مجموع المرضى الذين يعانون من نزيف الرحم غير الطبيعي 501 (57.9%) و 364 (42.1%) أعراض أخرى. كان تاريخ العملية القيصرية أكثر شيوعاً لدى المرضى الذين يعانون من نزيف الرحم غير طبيعي من الذين يعانون من أعراض أخرى 17.6 مقابل9.3%، p=0.001، ونسبة احتمالات 2.1 ؛ فاصل الثقة 95% (1.4–3.3) CI. و يرتبط أيضا مع نزيف الرحم غير طبيعي وجود الورم العضلي الأملس تحت المخاطية 95% CI؛ OR: 2.1 (1.5–3.1) و العضال الغديه عامل مشارك95% CI؛ OR: 1.6 (1.1–2.4).

**الخاتمة:** كان تاريخ العملية القيصرية عامل خطر مستقل لنزيف الرحم غير الطبيعي لدى المرضى الذين يعانون من العضلات الملساء في الرحم . كان الورم العضلي الأملس تحت المخاطية والعضال الغدية أيضاً عوامل خطر مستقلة مشتركة.

**Objectives:** To determine whether a history of cesarean section was a risk factor for abnormal uterine bleeding in patients with uterine leiomyomas, and to identify other risk factors for this symptom.

**Methods:** We analyzed retrospectively, the medical records of patients who underwent hysterectomies due to the presence of uterine leiomyomas during a 6-year period (2009 and 2014) at Etlik Zubeyde Hanim Women's Health Training and Research Hospital, Ankara, Turkey. Uterine leiomyoma was diagnosed based on histopathological examination of hysterectomy specimens. Demographic characteristics, and laboratory and histopathological findings were compared between patients with uterine leiomyoma with and without abnormal uterine bleeding.

**Results:** In total, 501 (57.9%) patients had abnormal uterine bleeding and 364 (42.1%) patients had other symptoms. A history of cesarean section was more common in patients with abnormal uterine bleeding than in those with other symptoms (17.6% versus 9.3%, *p*=0.001; odds ratio [OR]: 2.1; 95% confidence interval [CI]: 1.4-3.3). The presence of a submucosal leiomyoma (OR: 2.1; 95% CI: 1.5-3.1) and coexistent adenomyosis (OR: 1.6; 95% CI: 1.1-2.4) were also associated with abnormal uterine bleeding.

**Conclusion:** A history of cesarean section was an independent risk factor for abnormal uterine bleeding in patients with uterine leiomyomas; submucosal leiomyoma and coexisting adenomyosis were also independent risk factors.

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Uterine leiomyoma is the most common gynecological tumor in women of reproductive age.[1] The incidence of uterine leiomyoma is 60% in the reproductive years and 80% during the lifetime.[2] Most leiomyomas are benign tumors that principally cause significant morbidity; they rarely transform into malignant tumors. Abnormal uterine bleeding is the most common symptom of a uterine leiomyoma; however, most leiomyomas are asymptomatic.[2] Why some of these tumors are asymptomatic and others are not remains unknown. The number, size, and location of leiomyomas have been suggested to be associated with the onset of symptoms; however, these factors cannot explain the etiopathogenesis of symptoms in all cases. Abnormal uterine bleeding is more common in patients with submucosal leiomyomas, but asymptomatic submucosal leiomyomas have also been reported. Some patients with multiple leiomyomas are asymptomatic, whereas a single leiomyoma can cause severe symptoms.[3] Conditions such as adenomyosis, endometriosis, cesarean scar defects, and gastrointestinal and genitourinary pathologies can cause abnormal uterine bleeding and/or pain symptoms attributed to leiomyoma; leiomyoma can actually be an incidental finding.

In recent years, the cesarean section rate has increased worldwide. In 2015, the rate in developed countries was reported to exceed the 10-15% recommended by the World Health Organization.[4,5] Although cesarean section can be life saving for the mother and baby, it is associated with short- and long-term maternal morbidity, and high cost.[6] Post menstrual spotting, pelvic pain, cesarean scar pregnancy, and abnormal placentation are among the long-term complications.[7,8] In the present study, we investigated another possible long-term complication of cesarean section, abnormal uterine bleeding, in patients with uterine leiomyomas. Our aims were to determine whether a history of cesarean section was a risk factor for abnormal uterine bleeding in patients with uterine leiomyomas and to identify other risk factors for abnormal uterine bleeding in such patients.

**Methods.** This retrospective case-control study included patients who underwent hysterectomies due to the presence of uterine leiomyomas at Etlik Zubeyde Hanim Women's Health Training and Research Hospital, Ankara, Turkey, between January 2009 and December 2014. The study was approved by our local institutional review board and the principles of Helsinki Declaration were followed. Medical records were reviewed retrospectively; ethics committee approval was not required. All patients provided written informed consent.

The exclusion criteria were hysterectomy triggered by gynecological malignancy, benign ovarian neoplasm, uterine prolapse, performance of myomectomy, and postmenopausal status. All participants were evaluated preoperatively via bimanual examination and transvaginal ultrasonography. To exclude endometrial malignancy, preoperative endometrial biopsies were performed on all patients with abnormal uterine bleeding. A definitive diagnosis of uterine leiomyoma was based on postoperative histopathological examination of hysterectomy specimens. Patient age, body mass index, gravidity, parity, use of an intrauterine device,the preoperative hemoglobin level, and any history of diabetes mellitus, hypertension, smoking, or cesarean section were obtained from medical records. The number, location, and size of leiomyomas, and data on coexisting uterine pathologies causing abnormal uterine bleeding, including adenomyosis, endometrial polyps, endocervical polyps, and endometrial hyperplasia, were obtained from preoperative endometrial biopsy reports and postoperative histopathological reports on hysterectomy specimens.

Irregular menstruation, heavy prolonged bleeding (blood loss >80 mL and bleeding for >7 days), and intermenstrual bleeding were considered abnormal uterine bleeding. The patients were divided into 2 groups according to their symptoms: the case group had abnormal uterine bleeding and the control group did not. Patients with abnormal uterine bleeding and other symptoms, such as pelvic pain, pelvic pressure, dysmenorrhea, and/or urinary and bowel symptoms, together were included in the case group. Demographic, clinical, laboratory, and histopathological findings were compared between groups. Possible associations between a history of cesarean section and abnormal uterine bleeding, and between other risk factors and such bleeding, were investigated.

Data analysis was performed using the Statistical Package for Social Sciences version 21.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics are presented as means ± standard deviations for numerical variables and as frequencies with percentages for categorical variables. The independent samples t-test was used to compare means between the 2 groups. The Chi-squared test was used to compare differences in categorical

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variables between the groups. Multivariate logistic regression was performed to identify independent risk factors for abnormal uterine bleeding. Associations between independent variables (a history of cesarean section, adenomyosis, endometrial polyps, endometrial hyperplasia, endocervical polyps, submucosal leiomyoma, and intramural leiomyoma) and the binary dependent variable (abnormal uterine bleeding) were modeled using logistic regression analysis. Based on the logistic models, odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. The level of statistical significance was set at $p$=0.05.

**Results.** The medical records of 947 patients diagnosed preoperatively with uterine leiomyomas via transvaginal ultrasonography who then underwent hysterectomies were reviewed. Case and control group data are shown in **Figure 1**. Patients for whom the diagnoses changed after histopathological examination of hysterectomy specimens, and those for whom data were incomplete/missing, were excluded from the study. In total, 501 (57.9%) patients with abnormal uterine bleeding and 364 (42.1%) patients with other symptoms (pelvic pain, pelvic pressure, dysmenorrhea, and/or urinary and bowel symptoms) were included.

The demographic, clinical, and histopathological findings in the case and control groups are shown in **Tables 1 and 2**. The mean age was significantly lower in the case group (46.6 ± 3.7 years versus 47.5 ± 5.4 years, $p$=0.010), whereas a history of diabetes (13.2% versus 7.4%, $p$=0.005) and hypertension (22.5% versus 16.4%, $p$=0.022) were more common in the control group. In addition, the mean hemoglobin level was significantly lower in the case group (10.6 ± 2.2 g $dL^{-1}$ versus 12.2 ± 1.9 g $dL^{-1}$, $p$<0.001). A history of cesarean section was associated with abnormal uterine bleeding.

**Table 1 -** Demographic, clinical, and laboratory findings of 865 patients diagnosed preoperatively with uterine leiomyomas via transvaginal ultrasonography who underwent hysterectomies.

| Demographic characteristics | Case Group n=501 | Control Group n=364 | *P*-value |
|---|---|---|---|
| Age (years)[a] | 46.6 ± 3.7 | 47.5 ± 5.4 | 0.010 |
| BMI (kg $m^{-2}$)[a] | 29.9 ± 5.1 | 30.2 ± 5.3 | 0.686 |
| *Gravidity* | | | 0.285 |
| 0 | 16 (3.2) | 17 (4.7) | |
| ≥1 | 484 (96.8) | 347 (95.3) | |
| *Parity* | | | 0.507 |
| 0 | 20 (4.0) | 18 (4.9) | |
| ≥1 | 480 (96) | 346 (95.1) | |
| *Diabetes mellitus* | | | 0.005 |
| No | 464 (92.6) | 316 (86.8) | |
| Yes | 37 (7.4) | 48 (13.2) | |
| *Smoking* | | | 0.714 |
| No | 432 (86.2) | 317 (87.1) | |
| Yes | 69 (13.8) | 47 (12.9) | |
| *Hypertension* | | | 0.022 |
| No | 419 (83.6) | 282 (77.5) | |
| Yes | 82 (16.4) | 82 (22.5) | |
| *IUD use* | | | 0.365 |
| No | 454 (90.6) | 323 (88.7) | |
| Yes | 47 (9.4) | 41 (11.3) | |
| *History of cesarean section* | | | 0.001 |
| No | 413 (82.4) | 330 (90.7) | |
| Yes | 88 (17.6) | 34 (9.3) | |
| Hb (g $dL^{-1}$)[a] | 10.6 ± 2.2 | 12.2 ± 1.9 | <0.001 |

BMI - body mass index, IUD - intrauterine device, Hb - hemoglobin

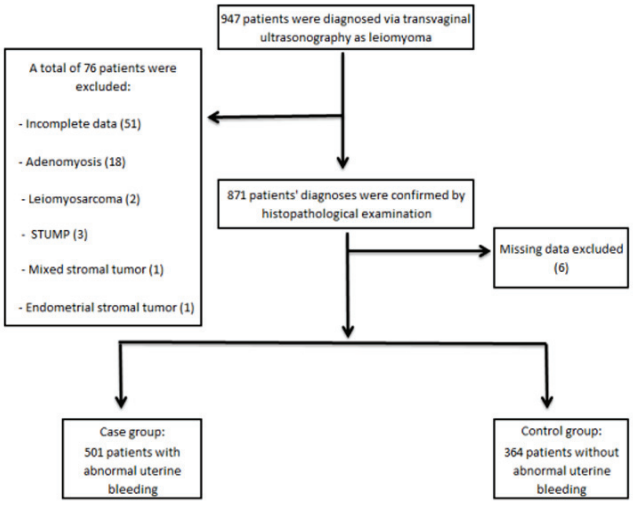


**Figure 1 -** Case and control group enrollment of 947 patients diagnosed preoperatively with uterine leiomyomas via transvaginal ultrasonography who underwent hysterectomies.

**Table 2 -** Histopathological findings of 865 patients diagnosed preoperatively with uterine leiomyomas via transvaginal ultrasonography who underwent hysterectomies.

| Histopathological findings | Case Group n = 501 | Control Group n = 364 | *P*-value |
|---|---|---|---|
| *Number of leiomyomas* | | | 0.275 |
| 1 | 161 (32.1) | 130 (35.7) | |
| ≥2 | 340 (67.9) | 234 (64.3) | |
| *Size of largest leiomyoma* | | | <0.001 |
| ≥8 cm | 165 (32.9) | 194 (53.4) | |
| <8 cm | 336 (67.1) | 169 (46.6) | |
| *Localization of all leiomyomas* | | | |
| Submucosal | 127 (25.3) | 55 (15.1) | <0.001 |
| Intramural | 451 (90.0) | 322 (88.5) | 0.503 |
| Subserous | 193 (38.5) | 189 (51.5) | <0.001 |
| *Localization of largest leiomyoma* | | | |
| Submucosal | 63 (12.6) | 14 (3.8) | <0.001 |
| Intramural | 403 (80.4) | 281 (77.2) | 0.271 |
| Subserous | 35 (7.0) | 69 (19.0) | <0.001 |
| *Adenomyosis* | | | 0.016 |
| No | 405 (80.8) | 317 (87.1) | |
| Yes | 96 (19.2) | 47 (12.9) | |
| *Endometrial polyp* | | | 0.730 |
| No | 404 (80.6) | 290 (79.7) | |
| Yes | 97 (19.4) | 74 (20.3) | |
| *Endometrial hyperplasia* | | | 0.143 |
| No | 478 (95.4) | 355 (97.5) | |
| Yes | 23 (4.6) | 9 (2.5) | |
| *Endocervical polyp* | | | 0.394 |
| No | 473 (94.4) | 338 (92.9) | |
| Yes | 28 (5.6) | 26 (7.1) | |

In all, 8 of 88 (9.1%) patients with such histories had intermenstrual spotting and the remaining 80 (90.9%) patients had regular or irregular heavy bleeding. Although the number of leiomyomas (3.4±2.7 versus 3.4± 2.6, $p$=0.936), their location (submucosal: 11.4% versus 8.4%, $p$=0.303; intramural: 74% versus 79.8%, $p$=0.152; subserous: 14.6% versus 11.8%, $p$=0.372), and the mean maximum dimension of the largest leiomyoma (7.1 ± 2.8 versus 7.4 ± 4.6 cm, $p$=0.447) were similar in patients with and without a history of cesarean section, such a history was significantly more common in the case group (17.6% versus 9.3%, $p$=0.001). We found no association between abnormal uterine bleeding and the number of leiomyomas ($p$=0.275); however, the size of the largest leiomyoma and leiomyoma location differed significantly between the groups. The mean maximum dimension of the largest leiomyoma was smaller in the case group (6.3 ± 2.9 versus 7.9 ± 3.5 cm, $p$<0.001). Submucosal leiomyomas were associated significantly with a higher rate of abnormal uterine bleeding ($p$<0.001), and subserous leiomyomas were more common in the control group ($p$<0.001). Analysis of the relationships between abnormal uterine bleeding and other pathologies coexisting with uterine leiomyoma, such as adenomyosis, endometrial polyps, endocervical polyps, and endometrial hyperplasia, showed that only adenomyosis was significantly more common in the case group (19.2% versus 12.9%, $p$=0.016).

**Table 3 -** Multivariate logistic regression analysis of the risk factors for abnormal uterine bleeding in patients with uterine leiomyomas.

| Variables | Adjusted OR | 95% CI | *P*-value |
|---|---|---|---|
| History of cesarean section | 2.1 | 1.4- 3.3 | 0.001 |
| Adenomyosis | 1.6 | 1.1-2.4 | 0.016 |
| Endometrial polyps | 0.9 | 0.65-1.3 | 0.633 |
| Endometrial hyperplasia | 1.85 | 0.8-4.1 | 0.134 |
| Endocervical polyps | 0.8 | 0.5-1.5 | 0.505 |
| Submucosal leiomyoma | 2.1 | 1.5-3.1 | <0.001 |
| Intramural leiomyoma | 1.54 | 0.97-2.46 | 0.070 |

OR - odds ratio, 95% CI - 95% confidence intervals

Multivariate logistic regression showed that a history of cesarean section was an independent risk factor for abnormal uterine bleeding in leiomyoma cases, increasing the bleeding rate of 2-fold (95% CI: 1.4-3.3). Coexistent adenomyosis (OR: 1.6; 95% CI: 1.1-2.4) and the presence of a submucosal leiomyoma (OR: 2.1; 95% CI: 1.5-3.1) were also independent risk factors for abnormal uterine bleeding (**Table 3**).

**Discussion.** Uterine leiomyoma is the most common benign pelvic tumor in women. The incidence of leiomyoma is approximately 70% in women aged >30 years.[9] Abnormal uterine bleeding is the most common symptom, occurring in 30% of cases.[2] Abnormal uterine bleeding caused by a uterine leiomyoma is classified as AUB-L in the Federation Internationale de Gynecologie et d'Obstetrique classification system,[10] it presents in most cases as heavy prolonged bleeding and can cause iron-deficiency anemia. Intermenstrual bleeding, dysmenorrhea, pelvic pain, increased urinary frequency, bowel disturbance, and pelvic pressure are other symptoms associated with uterine leiomyoma.[11]

The pathophysiological mechanisms of and risk factors for symptoms in patients with uterine leiomyoma remain unclear. Numerous studies have investigated the relationships among disease incidence, the severity of symptoms, and tumor location and size. Clevenger-Hoeft et al[12] reported a higher prevalence of submucosal (21% versus 1%) and intramural (58% versus 13%) leiomyomas in patients with abnormal uterine bleeding than in asymptomatic patients. In contrast, a population-based study that included 341

patients aged 30-60 years found no association among the number, volume, and location of leiomyomas and menstrual cycle length, bleeding severity, or duration of bleeding.[13] Moreover, Bachmann et al[14] reported that the rates of heavy bleeding and anemia were similar in patients with and without submucosal leiomyomas. In the present study, the submucosal leiomyoma rate was higher in the case group than in the control group, but no association was evident between the number of leiomyomas and symptoms. In addition, leiomyomas were smaller in patients with abnormal uterine bleeding than in those with other symptoms. Based on our present findings, we suggest that the pathophysiological mechanism underlying abnormal uterine bleeding is independent of leiomyoma size, and that leiomyomas causing uterine bleeding become symptomatic earlier without the need for excessive growth.

Cesarean section affords unquestionable benefits to the mother and newborn when it is actually necessary. Currently, the cesarean section rate based on maternal request (with no medical indication) is increasing,[6] however, unnecessary cesarean sections are associated with increased risks of maternal and neonatal morbidity.[15,16] In addition to short-term complications, a cesarean section can cause long-term maternal complications, including abnormal placentation, uterine rupture during a subsequent pregnancy, cesarean scar pregnancy, and intermenstrual bleeding.[17,18] The present study identified another potential long-term complication of cesarean section: an increased risk of abnormal uterine bleeding in patients with uterine leiomyomas. Abnormal uterine bleeding was twice as common in our patients with histories of cesarean section.

The pathophysiology of abnormal uterine bleeding associated with a uterine leiomyoma is not known in detail. Increased endometrial surface area, increased uterine vascularity, inhibition of uterine contractility, endometrial ulceration caused by a submucosal leiomyoma, and congestion of the myometrium and endometrium have all been posited to play a role in the pathophysiology of abnormal uterine bleeding.[11] Deficient healing of a cesarean scar and formation of a niche in the lower uterine segment may cause abnormal uterine bleeding in patients with uterine leiomyomas. The prevalence of cesarean scar defects ranges from 19.4-88%.[7] Cesarean scar defects have been reported to cause abnormal uterine bleeding; in particular, post menstrual spotting.[7,18] Menstrual debris collects in the niche and leaks from the cervix after cessation of menstrual bleeding.[18] In the present study, a history of cesarean section was associated not only with increased intermenstrual spotting in patients with uterine leiomyoma, but also with regular or irregular heavy bleeding in 90.9% of patients. Prevention of normal uterine contractility by the cesarean section scar and the uterine leiomyoma together may play a pathophysiological role in heavy bleeding.

Endometrial polyps, endometrial hyperplasia, adenomyosis, and endocervical polyps are other uterine pathologies causing abnormal uterine bleeding.[10] In the present study, we also investigated whether the risk of abnormal uterine bleeding increased when these pathologies coexisted with leiomyoma. We found that only the coexistence of adenomyosis and uterine leiomyoma increased the risk of abnormal uterine bleeding. We found no association between coexistent endometrial polyps, endometrial hyperplasia, or endocervical polyps and an increased risk of abnormal uterine bleeding.

The present study had certain limitations, including the retrospective design and the exclusion of some patients due to incomplete data. In addition, we had no data on cesarean scar defects. Therefore, we could not study the possible association between abnormal uterine bleeding and the nature of such defects. Scar defects are associated with high rates of abnormal uterine bleeding[18] and may indeed be the principal cause of such bleeding. Uterine leiomyoma may be an incidental finding in such patients. Future studies of the frequency of cesarean scar defects and associations between such defects and abnormal uterine bleeding are needed. In addition, we included only patients who required hysterectomies. Prospective population-based studies including patients who are asymptomatic or who are managed medically are required to confirm our present findings.

In conclusion, a history of cesarean section was a risk factor for abnormal uterine bleeding in patients with uterine leiomyomas. Furthermore, submucosal leiomyoma and coexisting adenomyosis increased the risk of abnormal uterine bleeding in such patients.

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