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The Role of Menarcheal Age and Parity in the Development of Uterine Leiomyoma

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ABSTRACT

Uterine leiomyoma is the most prevalent benign neoplasm of the female reproductive tract during the reproductive years; however, its precise etiology remains incompletely understood. Age at menarche and parity have been proposed as potential risk factors, although previous studies have reported inconsistent findings. This study aimed to evaluate the association between age at menarche and parity with the occurrence of uterine leiomyoma. This research employed a case-control design, in which uterine leiomyoma constituted the case group and adenomyosis served as the control group, conducted at PKU Muhammadiyah Hospital Surakarta. The study included 113 participants, comprising 73 cases of uterine leiomyoma and 40 cases of adenomyosis as controls, identified through histopathological records from 2023. Data were assessed using Chi-Square and logistic regression analyses. The findings revealed that most respondents experienced menarche at a normal age and were either primiparous or multiparous. Statistical testing demonstrated a significant association between age at menarche ($p = 0.007$; OR = 1.65, 95% CI = 1.414–1.939) and the incidence of uterine leiomyoma, whereas parity was not significantly associated ($p = 0.384$; OR = 1.509, 95% CI = 0.596–3.825). Future studies are recommended to include more balanced sample group proportions and additional risk factors to obtain a more comprehensive understanding of uterine leiomyoma etiology.

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Introduction

Among benign tumors of the female reproductive system, uterine leiomyoma is the most prevalent, affecting nearly 70–80% of women at some point in their lifetime [1]. This tumor, also referred to as uterine myoma, fibromyoma, or fibroid, originates from smooth muscle cells and connective tissue of the uterus [2]. According to WHO data (2010), the global prevalence was estimated at 20–25% of women, which drastically increased to 9,643,330 cases in 2019 [3]. In the United States, the prevalence is even higher, exceeding 80% in African-American women and approximately 70% in Caucasian women[4].

In Indonesia, uterine myomas account for 2.39–11.7% of all gynecological cases and rank second after cervical cancer as a major reproductive health problem [5]. At RSUD dr. R. Goeteng Tarunadibrata Purbalingga, 38 cases of uterine myoma were reported in 2017, showing an increase compared with previous years [6]. The prevalence rises significantly in women over the age of 35, approaching 40%, particularly in Central Java, indicating a strong association with estrogenic activity [7]. Data from PKU Muhammadiyah Hospital Surakarta between 2019 and 2024 reported 129 benign uterine tumors, This cohort consisted of 65 uterine leiomyoma cases and 64 adenomyosis cases [3].

The complexity of uterine leiomyoma issues is increasingly evident with the frequent co-existence of this condition with adenomyosis. Several studies report co-existence rates reaching 15–57% [36]. Although both conditions share similar clinical manifestations, they have distinct pathophysiologies. Uterine leiomyoma develops from myometrial smooth muscle, while adenomyosis is characterized by the invasion of endometrial tissue into the myometrium [35, 36].

The exact etiology of uterine leiomyoma remains incompletely understood. Several risk factors have been identified, including genetic alterations, hormonal influences, environmental exposures, race, age, and parity [8]. Additional contributing factors are sexually transmitted infections, alcohol consumption, hypertension, chronic inflammation, exposure to estrogenic chemicals during fetal development, obesity, and early menarche [4].

Menarche age has been identified as one risk factor for uterine leiomyoma, where early menarche is corellation with increased risk through mechanisms involving genetic and environmental interactions [11,37]. Several studies in Indonesia support this relationship, such as Rudiyanti & Imron [9] who reported a significant association between menarche age and myoma incidence with p-value = 0.020. However, inconsistent evidence exists with Andriani [6] finding no association.

Previous studies have extensively examined the association between parity and the occurrence of myomas. The risk of uterine myoma has been shown to be approximately 3.5 times higher in nulliparous and primiparous women than in multiparous counterparts (p = 0.027) [9]. The protective effect of multiparity is presumed to be mediated through lactation, which suppresses estrogen levels [5]. Similarly, Andriani [6] demonstrated a significant association (p = 0.004), whereas Putu & Kurniawan [10] found no significant relationship. Age at menarche has also been reported to correlate with uterine leiomyoma [10], with Rudiyanti & Imron [9] observing a significant result (p = 0.020). However, Andriani [6] found no such association.

These conflicting findings highlight a research gap, namely the inconsistency in evidence regarding the influence of menarcheal age and parity on uterine leiomyoma. Addressing this gap is important given the rising prevalence of uterine leiomyomas, while their risk determinants remain under debate. Therefore, this study was designed to reassess the impact of age at menarche and parity on the occurrence of uterine leiomyoma.

This research is limited to the analysis of two risk factors, namely age at menarche and parity, while other variables such as genetic predisposition, obesity, and hypertension are not analyzed in depth. Despite the limitations, the findings are projected to advance medical science, particularly in gynecology, by providing additional empirical evidence regarding the risk factors of uterine leiomyoma. Furthermore, the results may assist healthcare practitioners in formulating preventive and therapeutic strategies for uterine myomas.

Broadly, this research seeks to investigate how age at menarche and parity relate to the occurrence of uterine leiomyoma. More specifically, the aims are: (a) to determine the association between menarcheal age and the incidence of uterine leiomyoma, and (b) to evaluate the impact of parity on the likelihood of developing uterine leiomyoma.

Material and Methods

This research adopted a case–control observational analytic design, in which uterine leiomyoma cases were compared with adenomyosis cases serving as the control group. The selection of adenomyosis as the control group was based on practical and pathological considerations. The gold standard for diagnosing all uterine tumors, including leiomyoma, is histopathological examination. However, obtaining histopathological specimens from the uteri of healthy women is neither ethical nor feasible. Therefore, the case and control groups were selected from the most prevalent conditions diagnosed via hysterectomy and recorded in the anatomical pathology laboratory. Uterine leiomyoma is a true benign neoplasm originating

from myometrial smooth muscle cells, while adenomyosis is a common, benign gynecological disorder characterized by the invasion of endometrial tissue into the uterine myometrium. Using adenomyosis as a control allows for a comparison between two distinct, yet frequently diagnosed, uterine pathologies within the same clinical and diagnostic setting.

Data collection and analysis were performed within the Department of Anatomical Pathology, PKU Muhammadiyah Hospital Surakarta, and the Anatomical Pathology Laboratory of the Faculty of Medicine, Universitas Muhammadiyah Surakarta.

The study population consisted of histopathological medical records of uterine tumors from 2023. Samples were purposively selected based on diagnoses of Uterine Leiomyoma (cases) and Adenomyosis (control) from 2023 records. Data collection was conducted in July-August 2025, where researchers reviewed and extracted data from the identified histopathological records. The minimum required sample size was calculated to be 85 subjects [9].

Participants were included if they had a histopathological diagnosis of uterine leiomyoma for the case group or adenomyosis for the control group, were between 25 and 50 years of age, and had complete identity data available. Exclusion criteria included: other uterine tumors, age <25 or > 50 years, history of precocious puberty, incomplete medical records, diagnosis with malignancy, or obesity (BMI ≥30kg/m^2).

The variables examined comprised age at menarche and parity as independents, with uterine leiomyoma occurrence as the dependent outcome. For analytical purposes, age at menarche was categorized into early onset (<11 years) and normal onset (≥11 years) [11]. Parity was classified into nulliparous and primiparous/multiparous [12].

The research instrument used was the anatomical pathology medical record. Data analysis included bivariate analysis using the Chi-square test to assess associations between variables, and multivariate analysis using logistic regression to identify independent risk factors, with statistical significance set at $p < 0.05$. This study received ethical approval from the Research Ethics Committee of Universitas Muhammadiyah Surakarta under ethical clearance No. 07/KEPK/RS.PKU/IX/2025.

Results and Discussions

The objective of this study was to evaluate the effect of menarcheal age and parity on uterine leiomyoma incidence in Surakarta. Data collection was conducted during July–August 2025, where researchers reviewed histopathological records from 2023 at the Department of Anatomical Pathology, PKU Muhammadiyah Hospital Surakarta, and the Anatomical Pathology Laboratory, Faculty of Medicine, Universitas Muhammadiyah Surakarta. A total of 113 subjects

were identified through anatomical pathology records from 2023. The cohort was divided into a case group of 73 uterine leiomyoma patients and a control group of 40 adenomyosis patients.

Table 1 shows the characteristics of the 73 leiomyoma patients. The majority (94.5%) experienced normal menarche, while only 5.5% had early menarche. Most patients (72.6%) were primi/multiparous, while 27.4% were nulliparous. A significant proportion presented with anemia (71.2%), and most had a normal body mass index (BMI) (79.5%). Geographically, 90.4% resided in urban areas.

Table 1. Characteristics of Patients with Uterine Leiomyoma (Case Group)

Variable	Leiomyoma Uteri (n=73)	Frequency (n)	Percentage (%)
Age at Menarche	Normal	69	94.5
	Early	4	5.5
Parity	Primi/Multipara	53	72.6
	Nullipara	20	27.4
Hemoglobin	Normal	21	28.8
	Abnormal (Anemia)	52	71.2
BMI	Normal	58	79.5
	Abnormal	15	20.5
Residence	Rural	7	9.6
	Urban	66	90.4

(Source: Primary data, 2023)

Table 2 presents the characteristics of the 40 adenomyosis cases. Nearly all patients (97.5%) had normal menarche. Most (80%) were primi/multiparous, while 20% were nulliparous. The majority were anemic (77.5%), 70% had normal BMI, and 82.5% lived in urban areas.

Table 2. Characteristics of Patients with Adenomyosis (Control Group)

Variable	Adenomyosis (n=40)	Frequency (n)	Percentage (%)
Age at Menarche	Normal	39	97.5
	Early	1	2.5
Parity	Primi/Multipara	32	80
	Nullipara	8	20
Hemoglobin	Normal	9	22.5
	Abnormal (Anemia)	31	77.5
BMI	Normal	28	70

Variable	Adenomyosis (n=40)	Frequency (n)	Percentage (%)
	Abnormal	12	30
Residence	Rural	7	17.5
	Urban	33	82.5

Bivariate analysis (Table 3) showed that the Chi-square test for age at menarche yielded a p-value of 0.007. This indicates that age at menarche was significantly associated with the incidence of uterine leiomyoma. In both groups, the majority had normal menarche (>11 years), namely 83.6% in leiomyoma cases and 100% in adenomyosis controls.

Table 3. Associated Between Age at Menarche and Uterine Leiomyoma

Age at Menarche	Leiomyoma (n=73) F (%)	Non-Leiomyoma (n=40) F (%)	OR	95% CI (Lower–Upper)	*p*
Normal	61 (83.6)	40 (100)			
			1.65	1.414–1.939	0.007
Early	12 (16.4)	0 (0)			

Bivariate analysis (Table 4) revealed a Chi-square p-value of 0.384, suggesting no significant association between parity and the incidence of uterine leiomyoma. Both groups showed a predominance of primiparous/multiparous women: 72.6% in leiomyoma cases and 80% in adenomyosis controls.

Table 4. Associated Between Parity and Uterine Leiomyoma

Parity	Leiomyoma (n=73) F (%)	Non-Leiomyoma (n=40) F (%)	OR	95% CI (Lower–Upper)	*p*
Primi/Multipara	53 (72.6)	32 (80)			
			1.509	0.596–3.825	0.384
Nullipara	20 (27.4)	8 (20)			

A. Influence of Leiomyoma Uteri Incidence Based on Age at Menarche

The findings of this study demonstrated that age at menarche exerted a statistically significant associated with the occurrence of uterine leiomyoma (p=0.007). Risk estimate analysis indicated that women experiencing early menarche had 1.65-fold increased odds of developing uterine leiomyoma compared to those with normal menarche timing (OR=1.65, 95% CI : 1.414-1.939). This observation is consistent with , Rudiyanti & Imron [9] who documented that early menarche significantly increased the risk of leiomyoma and

Handayani et al. [15] who reported a 2.3-fold higher risk among women experiencing menarche at ≤12 years. However, our findings contrast with Andriani [13] at RSUD dr. R. Goeteng Tarunadibrata Purbalingga and Dzakwan et al [14] at RSUD Abdul Wahab Sjahranie Samarinda, both of which reported no association between age at menarche and leiomyoma.

The significant association between early menarche and uterine leiomyoma found in this study can be explained through several molecular mechanisms. From a biological standpoint, early menarche leads to prolonged exposure to estrogen and progesterone, hormones that play key roles in leiomyoma growth [16]. At the molecular level, estrogen works through classical genomic mechanisms by activating Estrogen Response Elements (ERE), as well as through rapid non-genomic mechanisms that directly stimulate cell cycle progression via PI3K/Akt/mTOR and MAPK/ERK pathways [31].

In addition, earlier onset of menstruation increases the frequency of menstrual cycles, which may induce repetitive inflammatory responses and ischemic-reperfusion injury eithin the uterine tissue. This process generates Reactive Oxygen Species (ROS), leading to oxidative stress and DNA damage. Local hypoxia activates Hypoxia Inducible Factor-1α (HIF-1α), which triggers transcription of pro-angiogenic genes like VEGF and pro-fibrotic genes such as TGF-β [32]. Additionally, aromatase activity in adipose tissue enhances the conversion of androgens into estrogens, further accelerating leiomyoma growth [18].

The molecular pathology of leiomyoma involves monoclonal transformation of mesenchymal stem cells from the myometrium, often initiated by somatic mutations in the MED12 gene. Mutations in MED12 occur in approximately 70-80% of sporadic leiomyomas and disrupt the function of the mediator complex that interacts with estrogen. This disruption ultimately activates the WNT/β-catenin signalling pathway, promoting uncontrolled cell proliferation and inhibiting apoptosis [33, 34].

Furthermore, early menarche increases the total number of menstrual cycles, leading to cumulative exposure to these molecular mechanisms. The recurrent inflammatory microenvironment, combined with prolonged hormonal stimulation, creates favorable conditions for the initiation and progression of uterine leiomyoma.

B. Influence of Leiomyoma Uteri Incidence Based on Parity

The analysis also revealed no significant association between parity and leiomyoma incidence (p=0.384), with the majority of respondents in both groups categorized as primi/multiparous. This result aligns with Putu & Kurniawan [10]at RSUD Wangaya Denpasar, who similarly reported no meaningful association between parity and

leiomyoma. In contrast, Rudiyanti & Imron [9], Dzakwan et al.[14], Nufra & Azimar [28], and Nadila et al. [29] confirmed that nulliparity confers a higher risk compared to multiparity.

From a physiological perspective, multiparity may exert a protective effect through several mechanisms. During pregnancy, estriol is the predominant estrogen, which is weaker than estradiol, thus reducing proliferative stimulation of myometrial tissue. Postpartum, lactation suppresses estrogen production, while myometrial remodeling through apoptosis and differentiation decreases the likelihood of leiomyoma development [20]. Conversely, in nulliparous women, estradiol secretion from the ovaries predominates, providing stronger proliferative stimulation to the myometrium [29].

The absence of significant findings in this study may also be explained by the relatively homogeneous respondent characteristics and exclusion criteria that minimized other risk factors, such as obesity or coexisting uterine tumors. Moreover, evidence indicates that leiomyoma risk is influenced by a multifactorial interplay of metabolic and inflammatory factors. For instance, Fauzan Farma & Kurniati [3] highlighted BMI and neutrophil-to-lymphocyte ratio (NLR) as predictors, while Duan et al. [30] emphasized the multifactorial etiology of leiomyoma, encompassing genetic, hormonal, metabolic, and inflammatory interactions. Therefore, although this study did not identify significant associations for menarche age and parity, uterine leiomyoma etiology should still be understood as a product of complex, multifactorial risk interactions.

Conclusion

The present study found a significant association between age at menarche and the occurrence of uterine leiomyoma, but no significant association was observed between parity and uterine leiomyoma. These findings suggest that reproductive factors may exert differing influences on the risk developing uterine leiomyoma.

The retrospective case–control design, although efficient, limited the ability to control for all potential confounding variables and relied heavily on the completeness and accuracy of medical record documentation. In addition, the generalizability of the results should be interpreted with caution, as the study population was derived from a single healthcare center. Other potential risk factors, including family history, environmental exposures, and more detailed hormonal profiles, could not be assessed within the scope of this study.

The significant association observed between menarcheal age and uterine leiomyoma underscores the importance of preventive strategies initiated early in life. Future research should focus on identifying modifiable determinants of menarcheal timing, such as nutritional

status, physical activity, and environmental exposures during childhood, to better inform early prevention efforts for uterine leiomyoma.

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Conflict of Interest

The authors confirm that there are no conflicts of interest that could have influenced the study's result or interpretations. The research was conducted with full adherence to scientific integrity and ethical standards at every stage, from planning to reporting.

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