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LONG-TERM EFFECTS OF ORAL CONTRACEPTIVES ON LEIOMYOMA DEVELOPMENT IN PRE-MENOPAUSAL WOMEN

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Abstract

Leiomyoma, commonly known as uterine fibroids, is a prevalent benign tumor affecting women of reproductive age. Oral contraceptives (OCs) are widely used for birth control and other gynecological conditions, but their long-term effects on leiomyoma development remain contentious. This study aims to assess the long-term effects of oral contraceptive use on the development of uterine leiomyoma in pre-menopausal women. A cross-sectional comparative study was conducted involving 100 pre-menopausal women aged 25-45 years from Allama Iqbal Hospital, Lahore. The participants were divided into two groups: those who had used OCs and those who had never used them. Data collection included medical history, BMI, blood pressure, contraceptive use, and ultrasound findings to detect leiomyoma. Statistical analysis, including logistic regression, assessed the relationship between OC use and leiomyoma incidence. The study found a significant association between higher body mass index (BMI $\geq$ 25 kg/m²) and leiomyoma incidence, with women in the case group having a higher mean BMI (25.6 ± 2.3) compared to the control group (23.4 ± 2.1) ($P < 0.05$). Additionally, hypertension was more prevalent in the case group (19.2%) than in the control group (14%) ($P < 0.05$). The case group, consisting of women diagnosed with leiomyomas, exhibited a significantly higher proportion of OC users (17.4%) compared to the control group (10.3%) ($P < 0.05$). The women currently using OCs had a significantly higher risk of developing leiomyoma (OR = 1.91, 95% CI: 1.22-2.94, $P < 0.05$) than those who had never used OCs. The study concludes that long-term oral contraceptive use is associated with a higher risk of leiomyoma development in pre-menopausal women, particularly in those with higher BMI or hypertension.

Introduction

Leiomyomas, commonly known as uterine fibroids, are the most prevalent benign tumors in women of reproductive age. These tumors originate from the smooth muscle layer of the uterus and can vary significantly in size and number. Although they are non-cancerous, leiomyomas can cause a range of symptoms, including heavy menstrual bleeding, pelvic pain, and reproductive complications (Moroni *et al*., 2015; Prakash *et al*., 2017). The etiology of leiomyomas is multifactorial, involving genetic, hormonal, and environmental influences. Among the hormonal factors, estrogen and progesterone play a crucial role in the growth and development of these fibroids. Given the hormonal dependence of leiomyomas, the potential impact of oral contraceptives (OCs), which modulate hormone levels, on leiomyoma development is of significant clinical interest (Ciarmela *et al*., 2014; Hussain *et al*., 2023). Oral contraceptives, widely used for birth control and other health benefits, contain synthetic forms of estrogen and progesterone. Their primary mechanism of action is to prevent ovulation, but they also cause changes in the endometrium and cervical mucus, making it less suitable for fertilization and implantation (Noori & Althanoon, 2022). Beyond their contraceptive purposes, OCs are often prescribed for managing menstrual disorders, acne, and endometriosis. The relationship between OCs and leiomyomas is complex and has been the subject of extensive research, yielding varied results. Understanding the long-term effects of OCs on leiomyoma development is crucial for informed clinical decision-making, particularly for women with or at risk of developing these tumors (Desai *et al*., 2024; Flake *et al*., 2003).

Several epidemiological studies have investigated the association between OC use and the risk of developing leiomyomas. Some studies suggest that OC use may confer a protective effect against leiomyoma development, potentially due to regulating hormonal fluctuations and suppressing ovulation (Renke *et al*., 2024; Sparic *et al*., 2016). The constant, low-dose hormonal environment created by OCs might inhibit the cyclical peaks of estrogen and progesterone that can stimulate leiomyoma growth. Conversely, other studies have reported no significant association or increased risk, indicating that the relationship may be influenced by factors such as the type of OC, duration of use, dosage, and individual patient characteristics (Yang *et al*., 2021). The heterogeneity of study results underscores the need for a nuanced understanding of how different formulations and regimens of OCs impact leiomyoma development. For instance, combined OCs containing both estrogen and progesterone may have other effects compared to progestin-only pills (Allen, 2023). Additionally, the duration of OC use appears to be a critical factor, with long-term use potentially having different implications than short-term use. Furthermore, genetic predispositions, lifestyle factors, and other health conditions can modulate the effects of OCs on leiomyoma risk (Aksoy & Bornaun, 2024; Papaikonomou, 2021).

Biological mechanisms underlying the interaction between OCs and leiomyomas involve the modulation of hormone receptors and local growth factors within the uterine tissue. Estrogen and progesterone receptors are abundantly expressed in leiomyoma cells, and the activity of these receptors is influenced by exogenous hormone intake (Otify & Critchley, 2020). OCs may alter the expression of these receptors and affect the production of growth factors that drive cell proliferation and extracellular matrix formation in leiomyomas. Understanding these molecular pathways is essential for developing targeted therapeutic strategies and personalized medicine approaches.

Methodology

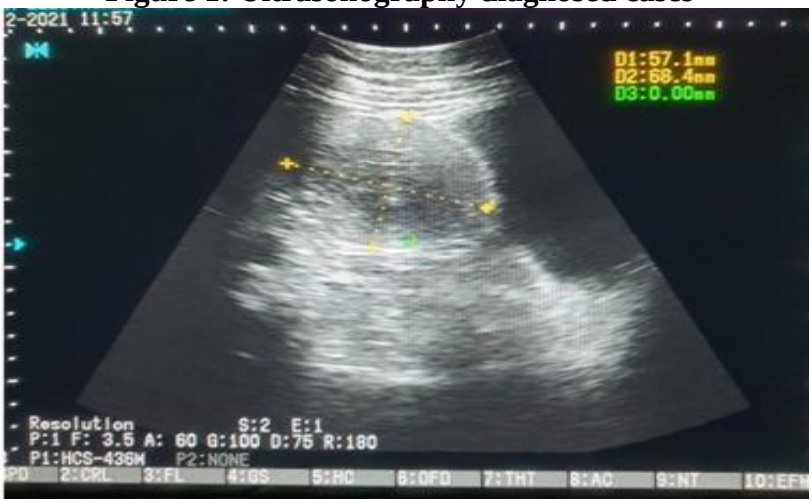
A cross-sectional, comparative study was conducted at Allama Iqbal Hospital, Lahore, to investigate the long-term effects of oral contraceptive use on uterine leiomyoma development. The study involved 100 pre-menopausal women aged 25 to 45 years, with a sample size divided into two groups: 50 women who had used oral contraceptives for at least one year and 50 women who had never used oral contraceptives. Participants were recruited from the gynaecology outpatient department of Allama Iqbal Hospital. The inclusion criteria were pre-menopausal women aged 25 to 45 years who were either currently using or had previously used oral contraceptives for more than one year. Women with prior surgical interventions for leiomyoma, such as myomectomy or hysterectomy, and those with known malignancies were excluded from the study.

Data was collected using a structured questionnaire and patient records. The variables included:

- **Demographic information** (age, education, socioeconomic status)
- **Reproductive history** (parity, history of abortions, and duration of oral contraceptive use)
- **Medical history** (BMI, history of hypertension, and genital tract infections)
- **Clinical findings** (ultrasound-confirmed diagnosis of leiomyoma)

The study also included a detailed ultrasound examination to identify leiomyomas' presence, number, and size. Participants were divided into a case group (women diagnosed with leiomyomas) and a control group (women without leiomyomas). All procedures were conducted by trained gynaecologists, and written informed consent was obtained from all participants.

Figure 1: Ultrasonography diagnosed cases



Statistical Analysis

Data analysis was performed using SPSS version 25. Descriptive statistics were used to summarize demographic data and clinical variables. Chi-square tests were employed to compare categorical variables between the case and control groups. A logistic regression model was used to assess the relationship between oral contraceptive use and the risk of leiomyoma, adjusting for potential confounders such as BMI, parity, and hypertension.

Results

The demographic and clinical characteristics of the participants are summarized in Table 1. There was no significant difference in age between the control group (35.4 ± 4.2 years) and the case group (36.7 ± 4.8 years). The mean BMI was significantly higher in the case group (25.6 ± 2.3) compared to the control group (23.4 ± 2.1), with 38.2% of women in the case group having a BMI ≥ 25 kg/m², compared to 26.6% in the control group ($P < 0.05$). There were no significant differences between the groups in terms of pregnancy (1.6 ± 0.8 vs. 1.8 ± 0.9, $P > 0.05$), parity (0.5 ± 0.2 vs. 0.6 ± 0.2, $P > 0.05$), or abortion number (1.2 ± 0.6 vs. 1.1 ± 0.5, $P > 0.05$). Genital tract infection rates were similar between the case (31.8%) and control groups (31.4%) ($P > 0.05$). However, oral contraceptive use was significantly higher in the case group (17.4%) compared to the control group (10.3%) ($P < 0.05$). The use of other contraceptive methods was not significantly different between the two groups, with 80.5% of the control group and 73.1% of the case group using methods other than oral contraceptives ($P > 0.05$). These findings suggest that higher BMI and oral contraceptive use are associated with an increased risk of leiomyoma development.

Table 1: General Information Comparison between Case and Control Groups

Variable	Control Group (mean ± SD, %)	Case Group (mean ± SD, %)	*p-value*
Age	35.4±4.2	36.7±4.8	
BMI	23.4 ± 2.1, 26.6%	25.6 ± 2.3, 38.2%	<0.05
Pregnancy	1.6 ± 0.8, 29.5%	1.8 ± 0.9, 30.3%	>0.05
Parity	0.5 ± 0.2, 87.4%	0.6 ± 0.2, 88.8%	>0.05
Abortion number	1.2 ± 0.6, 37.5%	1.1 ± 0.5, 38.6%	>0.05
Genital tract infection	0.3 ± 0.1, 31.4%	0.4 ± 0.1, 31.8%	>0.05
Oral contraceptive use	0.4 ± 0.1, 10.3%	0.5 ± 0.2, 17.4%	<0.05
Other contraceptive method	60.3 ± 2.5, 80.5%	57.4 ± 2.8, 73.1%	>0.05

Relationship Between Oral Contraceptives and Uterine Leiomyoma Incidence

The comparison of oral contraceptive use between the case and control groups is presented in Table 2. Women who were currently using oral contraceptives had a significantly higher risk of developing leiomyomas compared to those who never used oral contraceptives (OR = 1.91, 95% CI: 1.22-2.94, $P < 0.05$). The proportion of oral contraceptive users in the case group (17.4%) was notably higher than in the control group (10.3%).

Table 2: Relationship Between Oral Contraceptives and the Incidence of Uterine Leiomyomas

Oral Contraceptive Use	Control Group (%)	Case Group (%)	OR (95% CI)	P-value
Never used	47.5%	48%	1.00	>0.05
Once used	42.2%	34.6%	1.32 (0.95-1.86)	<0.05
Currently used	10.3%	17.4%	1.91 (1.22-2.94)	<0.05

Logistic regression analysis was conducted to assess the influence of several factors, including BMI, hypertension, and oral contraceptive use, on the risk of developing uterine leiomyomas Table 3). The analysis revealed that both higher BMI (≥25 kg/m²) and current oral contraceptive use were significant risk factors for leiomyoma development. The odds of developing leiomyomas were 1.45 times higher in women with a BMI ≥ 25 kg/m² compared to those with a BMI < 25 kg/m² (OR = 1.452, 95% CI: 1.205-6.61, $P < 0.05$). Women using oral contraceptives had a 1.85-fold increased risk of developing leiomyomas (OR = 1.845, 95% CI: 1.106-2.783, $P < 0.05$).

Table 3: Logistic Regression Analysis of Uterine Leiomyoma Risk Factors

Variable	β	SE	Wald X^2	OR (95% CI)	P-value
BMI (≥ 25 kg/m² vs < 25)	0.542	0.328	4.873	1.452 (1.205-6.61)	<0.05
Hypertension (Y vs N)	0.367	0.241	6.682	1.394 (1.025-1.941)	<0.05
Oral contraceptives (Y vs N)	0.614	0.272	7.033	1.845 (1.106-2.783)	<0.05

Discussion

This study aimed to investigate the long-term effects of OC use on the development of uterine leiomyomas in pre-menopausal women, focusing on women aged 25-45 years from Allama Iqbal Hospital, Lahore. The results indicated a significant association between OC use and the risk of developing uterine leiomyomas. Specifically, women who currently used oral contraceptives had a 1.91-fold increased risk of developing leiomyomas compared to women who had never used them. Other factors, such as higher BMI and hypertension, were also identified as contributing risk factors. The findings of this study align with the body of evidence suggesting that the use of oral contraceptives may be linked to an increased risk of leiomyoma development. Previous studies have yielded mixed results on this topic, with some reporting an increased risk of leiomyoma development associated with OC use, while others have suggested a protective effect (Qin *et al*., 2013; Salehi *et al*., 2023). The increased risk found in this study is consistent with a study conducted by Lin *et al*. (2021), which also reported that women who used oral contraceptives had a higher risk of developing

uterine leiomyomas, particularly with long-term use (Lin *et al*., 2021). This Lin *et al*. (2021) study found a comparable risk ratio of 1.5-1.9, depending on the duration of contraceptive use, which aligns with the odds ratio (OR = 1.91) found in our current research.

However, contrary findings exist in the literature, particularly in studies from different populations or those examining different formulations of oral contraceptives. For instance, a large cohort study by Bernardi *et al*. (2022) found no significant association between oral contraceptive use and the risk of leiomyomas in African American women. Bernardi *et al*. (2022) argued that oral contraceptives might reduce the risk of leiomyoma development by lowering the overall exposure to endogenous estrogen (Bernardi *et al*., 2022). Estrogen plays a key role in leiomyoma growth, and OCs suppress ovulation, potentially leading to decreased leiomyoma growth. It is essential to note that different formulations of oral contraceptives, varying dosages of estrogen and progestin, and the duration of use may account for the contradictory findings across studies (Alali & Churnosov, 2023; Otify & Critchley, 2020).
Another study by Harmon *et al*. (2022) suggested a protective role of oral contraceptives, with long-term users exhibiting a reduced risk of leiomyomas. Their study found that progestin-dominant oral contraceptives might decrease the risk of leiomyoma growth by opposing the proliferative effects of estrogen (Harmon *et al*., 2022). However, the population studied and the specific types of contraceptives used (especially with varying hormone levels) may account for the discrepancies between this and the present study (Le Guen *et al*., 2021). Our findings suggest that in the population of pre-menopausal women in Lahore, long-term use of oral contraceptives is associated with a heightened risk of developing uterine leiomyomas. This discrepancy from studies showing a protective effect could be attributed to several factors, including the type of contraceptives used, genetic predispositions, lifestyle factors, and cultural differences in contraceptive use and reproductive health practices in different regions (Emokpae & Brown, 2021).

This study identified a significant association between higher BMI and the development of uterine leiomyomas, with women in the case group having a higher mean BMI (25.6 ± 2.3) than the control group (23.4 ± 2.1). This finding is consistent with multiple previous studies that have established a clear link between obesity and an increased risk of leiomyoma formation (Strzałkowska *et al*., 2021). Obesity is a well-documented risk factor for uterine leiomyomas due to its association with increased estrogen production. Adipose tissue is known to convert androgens to estrogens via the enzyme aromatase, thereby increasing circulating estrogen levels (Larraín & Prado, 2024). Since leiomyomas are estrogen-sensitive tumors, this elevated estrogen environment in obese women is likely to contribute to leiomyoma growth and development. A meta-analysis by Jenabi *et al*. (2022) confirmed that women with higher BMI have a significantly increased risk of leiomyomas compared to women with lower BMI (Jenabi *et al*., 2022). Similarly, a study by Salcedo *et al*. (2022) found that for every 1 kg/m² increase in BMI, the risk of developing leiomyomas increased by 7% (Salcedo *et al*., 2022). Therefore, the higher incidence of leiomyomas in women with higher BMI in our study corroborates the existing literature and highlights the importance of managing obesity in reproductive health. In our study, hypertension was also identified as a significant risk factor for leiomyoma development. The prevalence of hypertension was higher in the case group (19.2%) compared to the control group (14%), which aligns with previous research findings. The association between hypertension and leiomyoma development has been explored in several studies, with most supporting a positive correlation.

For instance, a study by Kirschen *et al*. (2021) found that women with hypertension had a higher risk of developing leiomyomas compared to normotensive women. The proposed mechanism for this association is that hypertension may cause vascular changes in the uterus, promoting leiomyoma growth (Kirschen *et al*., 2021). Chronic hypertension is associated with increased arterial stiffness, endothelial dysfunction, and reduced uterine blood flow, which may create hypoxic conditions that stimulate the growth of leiomyomas (Zhang *et al*., 2020). Additionally, hypertension is often associated with obesity, which, as discussed earlier, increases estrogen levels, further promoting

leiomyoma development. The co-occurrence of hypertension and obesity in many women may have a synergistic effect on the risk of leiomyoma development, compounding the impact of each factor (Gannon, 2023). Our study's findings suggest that managing hypertension and obesity could play a crucial role in reducing the risk of leiomyomas in women of reproductive age. In contrast to the significant findings related to BMI, hypertension, and oral contraceptive use, our study did not find any statistically significant differences in pregnancy history, parity, or abortion number between the case and control groups. This is consistent with some previous studies but differs from others that have found associations between these reproductive factors and leiomyoma development (Cook *et al*., 2010; Walker *et al*., 2001). A study by Styer and Rueda (2016) reported that women with higher parity (the number of pregnancies carried to a viable gestational age) were at a reduced risk of developing leiomyomas. It has been suggested that pregnancy and childbirth lessen the risk of leiomyomas by altering the hormonal milieu and inducing uterine changes that make leiomyoma development less likely (Styer & Rueda, 2016). However, our study's lack of association between parity and leiomyomas suggests that other factors, such as contraceptive use and metabolic factors, may play a more dominant role in leiomyoma development in our population. Similarly, while some studies have suggested a link between abortion history and leiomyoma risk, our study found no significant differences in abortion numbers between the two groups (Jiang *et al*., 2021; Song *et al*., 2017). It is possible that any effects of abortion on leiomyoma risk are confounded by other reproductive health factors or that abortion history may not play as significant a role in leiomyoma development as previously thought.

Conclusion

This study concludes that the use of OCs is significantly associated with an increased risk of uterine leiomyoma development in pre-menopausal women, with current OC users showing nearly double the risk compared to non-users. Additionally, higher BMI and hypertension were identified as significant risk factors, reinforcing the importance of metabolic and cardiovascular health in leiomyoma formation. While previous studies offer mixed findings on the relationship between OCs and leiomyomas, this research highlights the need for careful consideration of individual risk factors when prescribing OCs, particularly in women with obesity or hypertension. Future studies should further explore the role of different contraceptive formulations and durations of use, while public health strategies aimed at managing obesity and hypertension may help reduce the incidence of leiomyomas in women of reproductive age.

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