RESEARCH ARTICLE

Association of Hormonal Contraception with Meningioma Location in Indonesian Patients

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Abstract

Background: Meningioma is the most common primary intracranial tumor. Previous studies have shown the possible association between hormonal contraceptive use and meningioma location. Therefore, this study aimed to analyze the association between the history of hormonal contraceptive use and the location of meningioma in the Indonesian population. **Methods:** In total, 99 histologically confirmed female meningioma patients admitted to Dr. Sardjito General Hospital Yogyakarta, Indonesia, were included in this study. Data on hormonal contraception and other variables were collected from medical records. Meningioma locations were determined from brain Magnetic Resonance Imaging (MRI) or Computerized Tomography (CT) scan before surgery. **Results:** Seventy-two (72.7%) patients had a history of hormonal contraceptive use. The subjects consist of 83 (83.8%) WHO grade I and 16 (16.2%) WHO grade II and III tumors. A total of 57 (57.6%) tumors were located in the spheno-orbital region. We found a significant association between hormonal contraceptive use and meningioma location in the spheno-orbital region (Odds ratio (OR) 2.573, p=0.038). This resulted in the patients in the hormonal contraception group having more visual impairment (p=0.044). **Conclusion:** The use of hormonal contraception is associated with the location of meningioma in the spheno-orbital region.

Keywords: Meningioma- meningioma location- hormonal contraception- Indonesian population

Introduction

Meningioma is the most common primary intracranial tumor that arises from the arachnoid layer's meningothelial cells. It represents about 36% of primary intracranial tumors, with 78.9% located intracranial and 4.2% in the spine (Ostrom et al., 2018). Based on the Central Brain Tumor Registry in the US, the incidence rate of meningioma was 8.58 per 100,000 population in 2012-2016 (Goldbrunner et al., 2021). Among all the cases, about 90% of meningioma are classified as benign tumors (Fisher et al., 2021).

Several factors might correlate with meningioma incidences, such as older age, ionizing therapy, genetic susceptibility, head trauma, and the use of contraceptive therapy (Lee and Lee, 2020). Meningioma is more common in women (Wiemels et al., 2010). This might be correlated with the higher progesterone receptors in women (Baldi et al., 2018). Previous studies have already reported that progesterone, estrogen, and androgen receptors are expressed in various types of meningioma (Qi et al., 2013). About 88% of meningiomas had progesterone receptors, 40% had estrogen receptors, and 39% were positive for androgen receptors (Korhonen et al., 2006). To date, several case-control and cohort studies have shown an increased risk of meningioma in women who use hormonal contraception (Harland et al., 2018).

Meningioma could occur in some specific location influenced by their genetic profiles (van den Munckhof et al., 2012). A previous study reported that exogenous factors such as hormonal treatment also play a role in the development of meningioma in a specific location (Apra et al., 2020). The study revealed that spheno-orbital meningioma developed in women who received

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progesterone therapy, and most cases were found in the ages of fifties. The spheno-orbital locations include the greater sphenoid wing with a distinct periorbital extension (Terrier et al., 2018). The most significant symptom of spheno-orbital meningioma is a visual disturbance in 95% of cases and could happen with paresis of oculomotor nerves. The surgery is needed in most cases with symptoms, but because their location might make it challenging to do the complete resection, adjuvant radiotherapy is recommended in some cases (Terrier et al., 2018).

This study aimed to analyze the association between the history of hormonal contraceptive use and the location of meningioma in the Indonesian population.

Materials and Methods

This study collected retrospective data from medical records of all histologically confirmed meningioma patients in Dr. Sardjito General Hospital, Yogyakarta, Indonesia, from 2019 until early 2021. Because the history of hormonal contraception is the main variable in this study, only female patients were included. In addition, patients without data on hormonal contraceptive use were excluded. Due to the limited data in the medical record regarding the details of the use of hormonal contraception, data on the type of hormonal contraception and the duration of contraceptive use were not available. Therefore, we only divided patients into groups with a history of using hormonal contraception at any time during their lives and patients without such a history.

We also collected data on age, symptoms, pathology results (WHO grading and histological type), and brain MRI or CT scan before surgery (meningioma location and size). Tumor dimension measurements were performed on the last imaging examination before surgery. Both contrast-enhanced CT and T1-weighted MR images were used, however in the absence of contrast administration, the measurements were still performed provided the examiner could identify the lesion border confidently. Following RECIST measurement, the longest tumor diameter in the axial plane was recorded. The second perpendicular diameter in the axial plane was also taken to allow for WHO tumor measurement compatibility. The third longest craniocaudal diameter was taken using the sagittal or coronal plane. The measurement included any component of tumors, i.e., the necrotic area, calcification, cystic component, and intraosseous part. Tumor size was determined by multiplying the two longest diameters on the imaging results.

All data were analyzed using IBM SPSS Statistics version 26. Bivariate analysis was performed to analyze the association between hormonal contraceptive use and meningioma location. We used an independent T-test or Mann-Whitney test for numeric data and Chi-Square or Fisher exact test for categorical data. Multivariate analysis using logistic regression with the backward method was then performed to identify variables independently associated with meningioma location.

Results

The demographic and clinical characteristics of the patients are shown in Table 1. Among 99 patients included in this study, 72 (72.7%) had a history of hormonal contraceptive use, while 27 (27.3%) did not. The mean age at meningioma diagnosis was 47.92±8.29 years old. There were no significant differences in age between groups with and without hormonal contraception (p=0.875). The subjects consist of 83 (83.8%) WHO grade I and 16 (16.2%) WHO grade II and III tumors. The most common histological types were meningothelial (33.3%) and transitional (24.2%). There were no statistically significant differences in WHO grading and histological type between hormonal contraception groups (p=0.129 and 0.112, respectively). We did not find a statistical difference between hormonal contraception and tumor size (p=0.974). We did not find a difference in Karnofsky Performance Scale (KPS) on admission between the two groups (p=0.517). The patients in the hormonal contraception group had significantly more visual symptoms than those without a history of hormonal contraceptive use (66.7 vs. 44.4% respectively, p=0.044).

Bivariate analysis was performed to analyze the association between various variables and meningioma location (Table 2). A total of 57 (57.6%) tumors were located in spheno-orbital, and 42 (42.4%) were distributed in other locations. There was no significant difference in age at diagnosis (p=0.779), histological type (p=0.126), and tumor size (p=0.772) between the two groups. As expected, patients with spheno-orbital meningioma had more visual symptoms than the group of tumors located in other locations (78.9% vs. 35.7%, p<0.001). In addition, patients with spheno-orbital meningioma also had less seizure (p<0.001) and fewer speech changes (p=0.039). A significant association was found between meningioma grade and location, with a higher proportion of WHO grade I meningioma in spheno-orbital tumors than meningioma in other locations (91.2 vs. 73.8%, p=0.02).

We found a significant difference in tumor location between contraception groups (p=0.038). Patients with a history of hormonal contraception had a higher proportion of meningioma in spheno-orbital locations than patients without such history. (63.9 vs. 40.7% respectively, p=0.038). Multivariate analysis was then performed to confirm this finding. Variables that could potentially affect meningioma location and with p<0.25 in bivariate analysis were included. The result of the logistic regression test using the backward method is shown in table 3. In this analysis, the only variable significantly associated with the location of meningiomas in the spheno-orbital region was the use of hormonal contraceptives (Odds ratio (OR) 2.573, p= 0.041).

Discussion

Previous studies have suggested that meningioma development is particularly influenced by female sex hormones (Bernat et al., 2015). Our study showed that around 70% of women with meningioma had a history of hormonal contraception. In line with ours, a prior

Table 1. Demographic and Clinical Characteristics of the Subjects (n=99)

Variable	Total	Hormonal contraception		p-value
		No	Yes	
Number of patients, n (%)	99 (100)	27 (27.3)	72 (72.7)	
Mean age, years (SD)	47.92 (8.29)	48.52 (9.18)	46.38 (6.86)	0.875*
WHO grade, n (%)				
Grade I	83 (83.8)	20 (74.1)	63 (87.5)	0.129**
Others	16(16.2)	7 (25.9)	9 (12.5)	
Histological type, n (%)				
Meningothelial	33 (33.3)	9 (33.3)	24 (33.3)	0.112**
Transitional	24 (24.2)	9 (33.3)	15 (20.8)	
Fibroblastic	11 (11.1)	0 (0)	11 (15.3)	
Microcystic	10 (10.1)	1 (3.7)	9 (12.5)	
Atypical	13 (13.1)	5 (18.5)	8 (11.1)	
Other	8 (8.1)	3 (11.1)	5 (6.9)	
Size in cm², mean (SD)	28.68 (19.06)	27.66 (16.27)	29.07 (20.16)	0.974*
Symptoms, n (%)				
Headache	82 (82.8)	24 (88.8)	58 (80.6)	0.388**
Visual impairment	60 (60.6)	12 (44.4)	48 (66.7)	0.044
Seizure	21 (21.2)	8 (29.6)	13 (18.1)	0.21
Unconsciousness	8 (8.1)	2 (7.4)	6 (8.3)	1**
Personality change	6 (6.1)	2 (7.4)	4 (5.6)	0.663**
Speech changes	15 (15.2)	6 (22.2)	9 (12.5)	0.344**
Cognitive changes	6 (6.1)	2 (7.4)	4 (5.6)	0.663**
Gait abnormality	2 (2)	0 (0)	2 (2.6)	1**
Hemiparesis	18 (18.2)	8 (29.6)	10 (13.9)	0.084**
Nausea/vomiting	6 (6.1)	2 (7.4)	4 (5.6)	0.663**
KPS on admission, mean (SD)	72.61 (20.37)	77.14 (17.36)	69.81 (22.71)	0.517*

*, Mann-Whitney test; **, Fisher Exact test; ***, Independent t-test, other tests use chi square test

case-control study in Sweden found an elevated risk of meningioma with the use of hormonal contraception (Wigertz et al., 2006). The most used hormonal contraception in the study were injections containing high-dose progesterone. These findings are in line with a clinical study in Paris, France, which found that spheno-orbital meningiomas develop preferentially in women with hormonal therapy in age around fifties (Apra et al., 2020). One of the largest cohort studies in France also revealed that meningioma risk was much higher in women treated with cyproterone acetate (CPA), a progesterone synthesis, with a cumulative dose of more than 60 g. However, after one year of discontinuation of treatment, the risk of meningioma noticeably decreased (Weill et al., 2021). Another cohort study in French showed a different distribution of ages in women who took CPA compared to the non-CPA population. The women who took CPA had a median age at meningioma surgery 14 years lower than the non-CPA group (Champeaux-Depond et al., 2021). Meanwhile, in our study, there was a slight mean age difference between the population with hormonal contraception (46.38±6.86 years old) and non-hormonal contraception (48.52±9.18 years old). However, the difference was not statistically significant.

Previous studies have shown the possible association between hormonal contraception use and meningioma location, especially in the skull base (Peyre et al., 2018). Apra (2020) found that spheno-orbital meningiomas develop more often in women with hormonal contraception therapy. The study by Champeaux-Depond (2021) showed that the meningiomas induced by hormonal contraception were preferentially located on the anterior and middle skull base. Similarly, Peyre (2018) reported anterior skull-based predominance in meningioma patients who took hormonal contraception. In this study, we found spheno-orbital meningioma in 57 (57.6%) cases. Statistically, we found a significant association between hormonal contraceptive use and the location of meningioma in the spheno-orbital region in bivariate analysis (p=0.038). Multivariate analysis confirmed this association, showing that patients with a history of hormonal contraceptive use were two and a half times more likely to develop a meningioma in the spheno-orbital region than patients without a history of hormonal contraceptive use (p=0.041). However, the underlying mechanism is not clearly understood. This is probably related to the higher level of progesterone receptor (PR) of the meninges in the region. Previous studies have shown that medial skull base meningiomas have significantly higher cases with high PR expression (Apra et al.,2020; Maiuri et al., 2021). However, there is

Table 2. Bivariate Analysis of Meningioma Location

Variable	Total	Location		p-value
		Sphenoorbital	Other	
Number of patients, n (%)	99 (100)	57 (57.6)	42 (42.4)	
Mean age, years (SD)	47.92 (8.3)	47.89 (8.5)	47.95 (8.04)	0.779*
WHO grade, n (%)				
Grade I	83 (83.8)	52 (91.2)	31 (73.8)	0.02
Others	16 (16.2)	5 (8.8)	11 (26.2)	
Histological type, n (%)				
Meningothelial	33 (33.3)	22 (38.6)	11 (26.2)	0.126**
Transitional	24 (24.2)	14 (24.6)	10 (23.8)	
Fibroblastic	11 (11.1)	8 (14)	3 (7.1)	
Microcystic	10 (10.1)	6 (10.5)	4 (9.5)	
Atypical	13 (13.1)	3 (5.3)	10 (23.8)	
Other	8 (8.1)	4 (7.1)	4 (9.5)	
Size in cm^2, mean (SD)	28.68 (19.06)	28.29 (20.04)	29.17 (18.03)	0.772*
Symptoms, n (%)				
Headache	82 (82.8)	45 (78.9)	37 (88.1)	0.233
Visual impairment	60 (60.6)	45 (78.9)	15 (35.7)	<0.001
Seizure	21 (21.2)	4 (7.1)	17 (40.5)	<0.001
Unconsciousness	8 (8.1)	3 (5.3)	5 (11.9)	0.278**
Personality change	6 (6.1)	2 (3.5)	4 (9.5)	0.397**
Speech changes	15 (15.2)	5 (8.8)	10 (23.8)	0.039
Cognitive changes	6 (6.1)	1 (1.8)	5 (11.9)	0.08**
Gait abnormality	2 (2)	1 (1.8)	1 (2.4)	1**
Hemiparesis	18 (18.2)	7 (12.3)	11 (26.2)	0.076
Nausea/vomiting	6 (6.1)	2 (3.5)	4 (9.5)	0.397**
KPS on admission, mean (SD)	72.61 (20.37)	72.45 (21.2)	72.82 (19.46)	0.819*
Hormonal contraceptive use, n(%)				
Yes	72 (100)	46 (63.9)	26 (36.1)	0.038
No	27 (100)	11 (40.7)	16 (59.3)	

*, Mann-Whitney test; **, Fisher Exact test; ***, Independent t-test, other tests use chi square

Table 3. Multivariate Analysis Using Logistic Regression for Factors Affecting Meningioma Location

Variable	Odds ratio	95 % CI	p-value
Hormonal contraceptive use	2.573	1.040-6.367	0.041

a lack of evidence associating the quantity of hormone receptors to tumor growth under treatment (Apra et al., 2020). This requires further study.

More visual impairment in patients with a history of hormonal contraception might be related to the tumor's location in this spheno-orbital region resulting in compression of the optic nerve. Indeed, our study showed that out of 72 patients with a history of hormonal contraception, 48(66.7%) of them had visual impairment (p=0.04). Almost 80% of patients with spheno-orbital meningioma had visual impairments, much higher than meningiomas in other locations (35.7%) (p<0.001). A meta-analysis study had reported that the most presenting symptoms in spheno-orbital meningioma were proptosis (84%), unilateral visual impairment (46%), and visual field deficit (31%) (Fisher et al., 2021). Therefore,

the first-line treatment is surgery due to the compression of optic nerves (Honeybul et al., 2001). In addition, spheno-orbital meningioma is also known to have a higher recurrence rate than meningiomas in other locations (Terrier et al., 2018).

The main limitation of this study is the lack of information about the duration, doses, or type of hormonal contraception used. Therefore, further study to explore the association of these variables with meningioma location in the Indonesian population is needed. Another limitation is the small number of WHO grade II and III meningiomas in our study.

In conclusion, the use of hormonal contraception is associated with meningioma in the spheno-orbital region. This, in turn, resulted in a higher number of patients with visual symptoms in the group with a history of hormonal contraception.

Author Contribution Statement

RGM and EKD formulated the presented idea and designed the study. RAH, DNFF, KRD, AR, MAS,

ASW, KD, EBS, AA, and RGM collected the samples and clinical data. NHS performed analysis on all MRI and CT scans. RGM and EKD developed the theory, performed the statistical analysis, and wrote the initial draft of the manuscript. All authors discussed the results and contributed to the final manuscript. RGM prepared the final manuscript. All projects were supervised by EKD.

Acknowledgments

Ethical approval

This study obtained ethical approval from the Institutional Review Board (IRB), Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Indonesia. Written informed consent was obtained from the patients themselves or from a family member.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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