HISTOPATHOLOGICAL GRADING OF MENINGIOMA IN ASSOCIATION WITH THE HORMONAL CONTRACEPTIVES' USAGE

Diansari Y[1], Anggraeni D[1], Marisdina S[1], Nindela R[1], Junaidi A[1], Sinum A[1], Aspitriani[2], and Hafy Z[3].
[1]Department of Neurology, Faculty of Medicine, Universitas Sriwijaya/Mohammad Hoesin General Hospital, Palembang, Indonesia
[2]Department of Pathology, Faculty of Medicine, Universitas Sriwijaya/Mohammad Hoesin General Hospital, Palembang, Indonesia
[3]Department of Histology, Faculty of Medicine, Universitas Sriwijaya, Palembang, Indonesia

Correspondence:
Yunni Diansari,
Department of Neurology,
Faculty of Medicine,
Universitas Sriwijaya/Mohammad Hoesin General Hospital,
Palembang, Indonesia
Email: yunnidiansari@fk.unsri.ac.id

Abstract

The high incidence of meningiomas in women indicates the role of female sex hormones in the growth of meningiomas. The use of hormonal contraceptives has been associated with an increased risk of meningiomas. Prior studies have reported an association between hormonal contraceptive use and the expression of certain hormonal receptors in meningioma tissues in which expression of progesterone and estrogen receptors have been associated with histopathological grading of meningiomas. There have been no previous studies about the association between hormonal contraceptive use and the histopathological grading of meningiomas. The aim of this study was to evaluate the association between hormonal contraceptive use and histopathological grading of meningioma. This study was an analytic cross-sectional study conducted at Mohammad Hoesin General Hospital Palembang and enrolled female meningioma patients with a history of hormonal contraceptive use from January 1st, 2018, to December 31st, 2020. Data were collected from medical records and in person or by phone interview. From 220 meningioma patients, 72 subjects were included in this study with 79.2% were low grade meningioma and 20.8% were high grade meningioma. Among the current users, 66.7% had high-grade meningioma, while 60.0% of combined hormonal contraceptives, and another 60.0% long-term users had high-grade meningioma, respectively. The status of hormonal contraceptive uses ($p = 0.038$) and the type of hormonal contraceptive ($p = 0.001$) had a significant association with the histopathological grading of meningioma and became the most significant independent variables according to multivariate logistic regression ($p = 0.034$; OR: 4.433 and $p = 0.001$; OR: 9.686) while there was no association between duration of use and histopathological grading of meningioma ($p = 0.180$). Current users and combination contraceptives (estrogen and progesterone) increased the risk of high-grade meningioma.

Keywords: Meningioma, Histopathological Grading, Hormonal Contraceptives

Introduction

Meningiomas are extra-axial central nervous system tumors originating from the arachnoid cap cells in the meningeal membranes (1). According to a review conducted by Fahlstrom et al. in 2023, meningioma stands out as the predominant nonmalignant neoplasm affecting the adult brain, constituting 38% of the total incidences of brain tumors and representing 55% of primary nonmalignant brain tumors (2). Data from the Central Brain Tumor Registry of the United States (CBTRUS) in 2013-2017 revealed that meningiomas was the most frequently reported central nervous system (CNS) tumor (38.3% of all CNS tumors) (3). The mean age at diagnosis of meningioma is 56.4 years in men and 55.9 years in women and the incidence increases with age. Meningiomas have a female predominance with a female to male ratio of 1.4-2.6:1 (4). The high incidence of meningiomas in women indicates the role of female sex hormones in the growth of meningiomas. Various studies have studied the relationship between hormonal factors and reproductive factors with the risk of meningioma. Meningiomas can grow rapidly during periods of hormonal excess, during the luteal phase of the menstrual cycle, and during pregnancy. Several studies also reported a positive correlation between breast cancer and meningiomas, in vitro proliferation of meningioma cells in culture after

exposure to estrogen, and the presence of estrogen and progesterone receptors in meningioma tissue (5).

Prior studies have reported an association between hormonal contraceptive use and the risk of meningioma. Korhonen et al. (6) reported that oral contraceptives and other hormonal contraceptives (implants and injections) can increase the risk of meningioma with odds ratios of 1.39 and 1.50. Wigertz et al. (7) reported that the risk of meningioma increased 1.5 times in women using hormonal contraceptives (implants and injections containing progesterone only), and the risk increased to 2.7 times with a long-term use (10 years or more). Wahyuhadi et al. also reported that injectable hormonal contraception for 3 months and the duration of hormonal contraceptive use >10 years increased the risk of meningioma (8). Despite numerous studies exploring the impact of hormonal contraceptives on meningioma growth, the specific role of these hormones in meningioma pathogenesis remains unclear. This study aims to fill this knowledge gap by investigating the association between hormonal contraceptive use and the histopathological grading of meningiomas, providing essential insights for future research.

There have been several studies reported the significant association, between hormonal factors and the histopathological characteristics in some female sex hormone-related neoplasms including breast and cervical cancer while there were no data reported in meningioma (9, 10). The relationship between meningiomas and sex steroids was established by the presence of sex steroid receptors on meningioma tumor cells. Some studies have consistently demonstrated a predominance of progesterone receptors (PR) in low-grade meningioma (WHO grade I) while the presence of estrogen receptor (ER) was associated with high-grade meningioma (WHO grade II and III) (11-13).

Materials and Methods

This analytical cross-sectional study includes female meningioma patients diagnosed by histopathology and having a history of hormonal contraceptive use at Dr. Mohammad Hoesin General Hospital from January 2018 to December 2020, meeting specified inclusion criteria. The minimum sample size was initially calculated with OpenEpi's 'Sample Size:X-Sectional, Cohort, & Randomized Clinical Trials' feature at 80% power and 95% confidence interval. Nonetheless, total sampling was conducted to acquire the most representable data. Total sampling was conducted based on the inclusion criteria are as follows: complete medical records, who were readily contactable, and willing to undergo in-person or phone interviews. Exclusions comprised patients with a history of death, communication or memory disorders, family history of meningioma or other malignancies, and those with a history of hormone replacement therapy. Detailed exposure histories, encompassing the status, type, and duration of hormonal contraceptive use, were meticulously obtained through structured in-person or phone interviews.

The status of hormonal contraceptives use was classified as: (i) 'current use', when the contraceptives were still being used until the diagnosed of meningioma or ended in the year before the diagnosis of meningioma; (ii) 'past use', when the most recent use was more than 1 year before the diagnosis of meningioma. The type of contraceptives was classified as: (i) 'progesterone only'; (ii) 'combination'; and the duration was classified as: (i) 'less than 10 years'; (ii) 'more than 10 years'. Progesterone only contraceptives exclusively contain progesterone and its various derivatives. Combination contraceptives contain a combination of estrogen and progesterone in various derivatives. The histopathological grading was classified as low-grade (WHO grade I) and high-grade (WHO grade II or III) meningioma.

Statistical analyses were performed with SPSS for window. Bivariate analyses using Fisher and multivariate logistic regression models were used to evaluate the association between hormonal exposure and histopathological grading of meningioma.

Results

Demographic characteristics of respondents

During the period from January 1, 2018, to December 31, 2020, there were 220 patients diagnosed with meningioma. Among them, 15 were male, leaving a total of 205 subjects for medical record retrieval. Out of these 205 subjects, only 186 had accessible medical records. From the retrieved records, it was identified that 19 individuals had died based on the medical data, and 88 patients were unreachable. Among the 79 contacted subjects, 3 individuals had communication disorders, and 4 had no history of contraception. Consequently, the final sample size comprised 72 individuals.

Table 1 shows the distribution of meningiomas patients based on histopathological grading, demographic characteristics and reproductive status. Most meningioma patients were in the age range of 35-44 years (45.8%), with an average age of 45.86 ± 7.090 years. Most of the patients had a body mass index of normoweight (43.1%). Based on their reproductive status, the majority of meningiomas patients had menarche age of 12-14 years (79.2%) and were multiparous (91.7%), with the highest age at first birth at < 20 years (55.6%) and most of them were in the premenopausal period (52.8%). Most of the subjects were low-grade meningiomas (79.2%), and the highest number were the meningothelial subtype. High-grade meningiomas were found in 15 patients (20.8%) with the frequently subtype was chordoid.

Table 1: Demographic, reproductive status and histopathological grading distribution of patients with meningioma

Characteristics	No. of cases	Percentage (%)
Age (years)		
18-34	2	2.8
35-44	33	45.8
45-54	29	40.3
55-64	8	11.1
Body mass index (kg/m²)		
Underweight (< 18.5)	4	5.6
Normoweight (18.5-24.9)	31	43.1
Overweight (25-29.9)	27	37.5
Obese (≥ 30)	10	13.9
Age of menarche (years)		
< 12	1	1.4
12-14	57	79.2
> 14	14	19.4
Parity		
Primipara	1	1.4
Multipara	66	91.7
Grandemultipara	5	6.9
Age at first birth (years)		
< 20	40	55.6
20-30	31	43.1
> 30	1	1.4
Menopausal status		
Premenopause	38	52.8
Perimenopause	20	27.8
Postmenopause	14	19.4
Meningioma grading		
Low-grade	57	79.2
High-grade	15	20.8

Table 2 shows no significant demographic differences were found between low-grade and high-grade meningioma groups.

The characteristics of hormonal contraceptives use is summarized in Table 3. It shows that 56.9% of meningioma patients were past users. The most common types of contraception were progesterone only (76.4%) and the majority of the patients (75%) had a relatively long duration of use for more than 10 years.

Table 2: Bivariate analyses of the association between demographic, reproductive status and histopathological grading of meningioma

Variables	Classification	Histopathological grading of meningioma		p value
		High-grade n (%)	Low-grade n (%)	
Age (years)	18-34	1 (1.8)	1 (6.7)	0.251*
	35-44	29 (50.9)	4 (26.7)	
	45-54	22 (38.6)	7 (46.7)	
	55-64	5 (8.8)	3 (20.0)	
Body mass index (kg/m2)	Underweight (< 18.5)	2 (3.5)	2 (13.3)	0.532*
	Normoweight (18.5-24.9)	25 (43.9)	6 (40)	
	Overweight (25-29.9)	22 (38.6)	5 (33.3)	
	Obese (≥ 30)	8 (14.0)	2 (13.3)	
Age of menarche (years)	< 14 ≥ 14	10 (66.7) 5 (33.3)	30 (52.6) 27 (47.4)	0.496*
Age of first birth (years)	< 20 ≥ 20	5 (33.3) 10 (66.7)	23 (40.4) 34 (59.6)	0.843*
Parity	≥ 3 < 3	6 (40.0) 9 (60.0)	12 (21.1) 45 (78.9)	0.180**
Menopausal status	Premenopausal Postmenopausal	8 (53.3) 7 (46.7)	30 (52.6) 27 (47.4)	1.000*

*Chi-Square, **Fisher

Table 3: Hormonal contraceptives exposure characteristics of patients with meningioma

Characteristics	No. of cases	Percentage (%)
Status of hormonal contraceptives use		
Past use	41	56.9
Current use	31	43.1
Type of contraception		
Progesterone only	54	75.0
Combination (progesteron and estrogen)	18	25.0
Duration		
< 10 years	18	25.0
10 years	54	75.0

Table 4 shows the association between hormonal contraceptives use and histopathological grading of meningioma. Among the current users, 66.7% had high-grade meningioma, while 60.0% of combined hormonal contraceptives, and another 60.0% long-term users had high-grade meningioma, respectively. Statistical analysis revealed significant association between the status of hormonal contraceptives use and type of hormonal contraceptives with histopathological grading of meningioma (p value = 0.038 and 0.001).

Table 4: Association between hormonal contraceptive use and histopathological grading

Variables	Classification	Histopathological grading of meningioma				p value
		High-grade		Low-grade		
		n	%	n	%	
Status of hormonal contraceptives use	Current use	10	66.7	21	36.8	0.038*
	Past use	5	33.3	36	63.2	
Type of hormonal contraception	Combination (Progesterone and estrogen)	9	60.0	9	15.8	0.001**
	Single (Progesterone only)	6	40.0	48	84.2	
Duration of use	≥ 10 years	9	60.0	45	78.9	0.180
	< 10 years	6	40.0	12	21.1	

*Chi-Square, **Fisher

Table 5 shows the multivariate logistic regression models. The status of hormonal contraceptives uses (95% CI, 1.116-17.601) and type of hormonal contraceptives (95% CI, 2.461-38.128) affects the risk of having high-grade meningioma (p value= 0.034 and 0.001). Current users of hormonal contraceptives experienced an increased risk of high-grade meningioma as much as 4.433 times and in patient with combination contraceptives the risk increased to 9.686 times.

Discussion

Our study found that status of hormonal contraceptives use affected the histopathological grading of meningioma. Previously reported studies have shown that the risk of meningioma increased in patients with oral contraceptives who were current users (14, 15). However, there have been no studies evaluate the status of hormonal contraceptives use and histopathological grading of meningioma. A case report in Canada reported fast-growing high-grade meningioma (atypical meningioma) in a 36-year-old woman undergoing fertility treatments using clomiphene citrate (selective estrogen receptor modulators that increase the circulating levels of estradiol) and exogenous progesterone (16). Another case report from Japan reported a previously health 29-year-old woman suffered from rhabdoid meningioma (WHO grade III) who was undergoing clomiphene citrate therapy (17). Those cases suggested that high-grade meningioma might grow rapidly in patients who were under the influence of high hormone levels. However, in this study, the high proportion of current users in high-grade meningioma group might be due to most patients in this group being in the third and fourth decades which is the fertile period, and the peak of contraceptives use.

Table 5: Multivariate logistic regression models of the association between hormonal contraceptives use and histopathological grading of meningioma.

	B	S.E	Wald	df	sig	Exp(β)	CI (95%) exp(B)	
							Lower	*Upper*
Step 1								
Duration of use	0.772	0.797	0.940	1	0.332	2.165	0.454	10.324
Status of hormonal contraceptives use	1.607	0.729	4.861	1	0.027	4.989	1.195	20.824
Type of hormonal contraception	2.076	0.724	8.226	1	0.004	7.971	1.930	32.928
Constant	-3.122	0.710	19.355	1	0.000	0.044		
Step 2								
Status of hormonal contraceptives use	1.489	0.704	4.480	1	0.034	4.433	1.116	17.601
Type of hormonal contraception	2.271	0.699	10.549	1	0.001	9.686	2.461	38.128
Constant	-2.925	0.665	19.318	1	0.000	0.054		

B: Beta
S.E: Standard Error
CI: Confidence Interval

There was a significant association between type of contraceptives and histopathological grading of meningioma. In the low-grade meningioma group, the majority of patients were single hormonal contraceptive users. Meanwhile, in the high-grade meningioma group, most patients were combined hormonal contraceptive users. Single hormonal contraceptives only contain a progesterone component, while combined contraceptives contain estrogen and progesterone. This probably reflects the influence of estrogen in higher grade meningiomas. Several studies have reported a predominance of progesterone receptors (PR) in WHO grade I meningiomas, whereas estrogen receptor (ER) expression has been associated with high grade meningiomas (7, 11, 12). PR-positive status occurs more frequent in benign meningiomas than in malignant tumors (18-20). Meanwhile, estrogen receptors were more common in atypical and malignant meningiomas in the study conducted by Hsu et al. (21). Hua et al. also found that grade III meningiomas expressed more estrogen receptors and had been associated with a poorer prognosis (13). ER-expressing meningiomas have been associated with a high proliferative index. Estrogen that binds to ER will activate its receptor and increase cell proliferation by stimulating RNA synthesis in target cells (22). Estradiol has been reported as a potent agent in increasing meningioma cell proliferation in vitro (23). Estrogen can interact with IGF (insulin like growth factor) which can also stimulate tumor growth and prevent cell apoptosis (24). Thus, the presence of estrogen can lead to higher cell growth. High-grade meningiomas are characterized by high mitotic activity. Unfortunately, in this study, immunohistochemical examination was not performed to prove the presence of ER expression in high grade meningiomas which could describe the activity of these hormones in meningioma tissue.

We found no significant association between duration of hormonal contraceptives use and histopathological grading of meningioma. Either high-grade or low- grade group had a long-term use for more than 10 years. This finding is consistent with Wahyuhadi et al. in 2018 which the duration of contraceptives had no association with meningioma grading (8). In contrary, several studies reported that there was a positive correlation between grade and duration of hormonal exposure in some hormone-related neoplasms including breast and cervical cancer (9, 10). The lack of a significant association between the duration of hormonal contraceptive use and meningioma grade may stem from the de novo origin of these tumors, independent of hormonal influences. Meningioma development involves complex genetic and molecular factors, with individual variability and the influence of other environmental triggers contributing to the nuanced relationship. Disparities in hormonal levels, receptor expression, and a potential latency period for manifestation further complicate the understanding of how hormonal contraceptives may impact meningioma grade. Investigating these factors provides valuable insights into the intricate dynamics between hormonal contraceptive use and meningioma development. Further exploration into the intricate molecular mechanisms governing meningioma pathogenesis is essential for a comprehensive understanding of these complex relationships.

Additional analyses were performed to evaluate association between histopathological grading and endogenous hormonal factors or reproductive status including age at menarche, age at first birth, parity, menopausal status, and meningioma grading but we found no statistical significance. To date, no studies have reported that relationship.

The significant association between hormonal contraceptive use and the type of contraceptives with meningioma histopathological grading highlights the clinical importance of considering contraceptive history in meningioma cases. This suggests the need for healthcare providers to assess and document contraceptive history in individuals diagnosed with meningioma. Future research should explore the underlying molecular pathways linking specific contraceptives to meningioma histopathology, potentially leading to tailored therapeutic approaches and improved risk stratification for better patient outcomes.

This study has some limitations such as the possibility of recall bias because the history of contraceptives use was explored based on self-reported by interview. To mitigate these biases, efforts were made to reinforce participants' recall accuracy through detailed questioning and cross-referencing information with medical records wherever possible. Additionally, the study recognizes the importance of future research incorporating prospective designs and objective measures to provide a more robust assessment of hormonal contraceptive history. Furthermore, the investigation did not encompass an evaluation of potential variations in the effects of single progesterone or estrogen-progesterone combinations, which could have been elucidated through the examination of PR and ER expression via immunohistochemistry.

Exogenous hormones, including ER and PR, are pivotal mediators in meningiomas. The expression of ER and PR in these tumors suggests their susceptibility to hormonal influences. Interactions between exogenous hormones and these receptors significantly impact tumor behavior, with ongoing research exploring specific effects on growth. Notably, a study by Maiuri et al. found a significant correlation between increased PR expression and a higher incidence of 5-year recurrence (25).

A comprehensive understanding of the interplay between exogenous hormones and meningiomas holds promise for targeted therapeutic interventions and refined risk stratification. Ichwan et al. (26) identified three knowledge gaps: the expression of PR in normal meninges, the impact of hormonal contraception on meningioma incidence, and the effects of prolonged progesterone use on PR expression and meningioma pathophysiology. Addressing these gaps are crucial for advancing personalized patient management, considering factors like hormonal contraceptive history and the unique receptor profiles of individual tumors (13, 18-21).

Conclusion

In summary, the status of hormonal contraceptives uses, and the type of hormonal contraceptives had a significant association with histopathological grading of meningioma. Current users and combination contraceptives (estrogen and progesterone) increased the risk of high-grade meningioma.

Acknowledgement

None declared

Competing interests

The authors declared that they have no competing interest.

Ethical Clearance

We obtained approval from the by Health Research Ethics Committee of Mohammad Hoesin General Hospital Palembang., registered under No64/KepkRSMH/2021.

Financial support

This study was funded by Grant from Ministry of Education, Culture, Research and Technology, Government of Indonesia.

References

1. Nabors LB, Portnow J, Ahluwalia M, Baehring J, Brem H, Brem S, *et al.* National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology. Plymouth: NCCN; 2020:32-3.
2. Fahlstrom A, Dwivedi S, Drummond K. Multiple Meningioma: epidemiologi, management and outcome. Neuro-Oncology Advances. 2023; 5(S1):35-48.
3. Ostrom QT, Patil N, Truitt G, Cioffi G, Waite K, Kruchko C, *et al*. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2013-2017. 2020; 22(S1):1-96.
4. Aninditha T. Meningiomas and other meningeal tumors. In: Aninditha T, Andriani R, Malueka RG, Eds. Neurooncology textbook. 1st ed. Jakarta, Indonesia: Indonesian medical publisher. 2019.
5. Sakti DH. Correlation between exposure to hormonal contraceptives on messenger RNA expression of progesterone receptors and estrogen receptors in orbitocranial meningioma patients. Thesis. Yogyakarta: Gadjah Mada University Libraries. 2017.
6. Korhonen K, Raitanen J, Isola J, Haapasalo H, Salminen T, Auvinen A. Exogenous sex hormone use and risk of meningioma: a population-based case-control study in Finland. J Cancer Causes Control. 2010; 21:2149-56.
7. Wigertz A, Lonn S, Mathiesen T, Ahlbom A, Hall P, Feychting M. Risk of brain tumors associated with exposure to exogenous female sex hormones. Am J Epidemiol. 2006; 164(7):629-36.
8. Wahyuhadi J, Heryani D, Basuki H. Risk of meningioma associated with exposure of hormonal contraception. A case-control study. Maj Obs Gin. 2018; 26:36-41.
9. Soewoto W, Mudigdo A, Aryandono T, Dirgahayu P. Correlation between duration of estrogen exposure with grading of breast cancer. Bali Med J. 2018; 7(3):778-81.
10. Anderson NM, Bazuaye PE, Jackson MD, Smikle M, Fletcher HM. Cervical dysplasia and cancer and the use of hormonal contraceptives in Jamaican women. J Biomed Central. 2008; 8(9):1-6.
11. Harland TA, Freeman JL, Davern M, McCracken DJ, Celano EC, Lillehei K, *et al*. Progesterone-only contraception is associated with a shorter progression-free survival in premenopausal women with WHO grade I meningioma. J Neurooncol. 2018; 136:327-33.
12. Pravdenkova S, Al-Mefty O, Sawyer J, Husain M. Progesterone and estrogen receptors: opposing prognostic indicators in meningiomas. J Neurosurg. 2006; 105:163-73.
13. Hua L, Zhu H, Li J, Tang H, Kuang D, Wang Y, *et al*. Prognostic value of estrogen receptor in WHO Grade III meningioma: a long-term follow-up study from a single institution. J Neurosurg. 2018; 128:1698–1706.
14. Michaud DS, Gallo V, Schlehofer B. Reproductive factors and exogenous hormone use in relation to risk of glioma and meningioma in a large European cohort study. Cancer Epidemiol Biomark Prev. 2010; 19(10):2562–2569.
15. Claus EB, Morrison AL. Epidemiology of meningiomas. In: Al-Mefty, Eds. Al-Mefty's Meningioma. New York, United States: Thieme. 2011:36-7.
16. Patterson A, Elashaal A. Fast-growing meningioma in a woman undergoing fertility treatments. Case Rep Neurol Med. 2016; 2016:3287381.
17. Motegi H, Kobayashi H, Terasaka S, Ishii N, Ito M, Shimbo D, *et al*. Hemorrhagic onset of rhabdoid meningioma after initiating treatment for fertility. Brain Tumor Pathol. 2012; 29:240-4.
18. Gursan N, Gundogdu C, Albayrak A, Kabalar ME: Immunohistochemical detection of progesterone receptors and the correlation with Ki-67 labeling indices in paraffin-embedded sections of meningiomas. Int J Neurosci. 2002; 112:463–70.
19. Nagashima G, Aoyagi M, Wakimoto H, Tamaki M, Ohno K, Hirakawa. Immunohistochemical detection of progesterone receptors and the correlation with Ki-67 labeling indices in paraffin- embedded sections of meningiomas. J Neurosurgery. 1995; 37:478–83.
20. Roser F, Nakamura M, Bellinzona M, Rosahl SK, Ostertag H, Samii M. The prognostic value of progesterone receptor status in meningiomas. J Clin Pathol. 2004; 57:1033–7.
21. Hsu DW, Efird JT, Hedley-Whyte ET. Progesterone and estrogen receptors in meningiomas: prognostic considerations. J Neurosurg. 1997; 86:113–20.
22. Dickson RB, Stancel GM. Estrogen receptor-mediated process in normal and cancer cells. National Cancer Institute Monographs. 1999; 27:135-45.

23. Dresser L, Yuen CA, Wilmington A, Walker M, Vogel TJ, Merrell RT, *et al*. Estrogen hormone replacement therapy in incidental intracranial meningioma: a growth-rate analysis. Scientific Reports. 2020; 10:1-7.
24. Qi ZY, Shao C, Huang YL, Hui GZ, Zhou YX, Wang Z. Reproductive and exogenous hormone factors in relation to risk of meningioma in women: a meta-analysis. J Plos One. 2013; 8(12):1-10.
25. Maiuri F, Mariniello G, De Divitiis O, Esposito F, Guadagno E, Teodonno G, *et al*. Progesterone Receptor Expression in Meningiomas: Pathological and Prognostic Implications. Front Oncol. 2021; 11:611218.
26. Ichwan S, Santoso F, Aman RA, Tandian D, Fachniadin A, Nugroho SW. Estrogen and progesterone in meningioma: Bridging the gap of knowledge. Neurology Asia. 2023; 28:1–11.