Nat. Volatiles & Essent. Oils, 2022; 9 (1): 1583-1592

NVEO
Natural Volatiles &
Essential Oils

Association Between Hormonal Contraception With Histopathology Grading Of Meningioma

AFadhillah Putri Rusdi

Neurosurgery Department dr. Soetomo General Hospital Surabaya, East Java Indonesia.

Abstract

Introduction: Higher histopathological meningioma have poorer survival rate and higher recurrence rate than benign histopathological meningioma. The relationship between the histopathological degree of meningioma and the use of hormonal contraception has not been widely studied.

Aim: To identify the effect of using hormonal contraception on the histopathological degree of meningioma.

Methods: This research is a cross-sectional single centre study at RSUD dr. Soetomo, Surabaya, Indonesia for meningioma patients who had surgery and histopathological examinations that were carried out between 2015-2020. Two hundred and six participant's data were analyzed statistically.

Results: There were 186 patients with a history of using hormonal contraception and 20 patients with no history of using hormonal contraception. the average use of hormonal contraception in meningioma patients is above 4 years. There was a significant difference in the duration of hormonal contraceptive use (p= 0.015) between meningioma patients with benign and non-benign histopathological grades. There was no significant difference between the history of using hormonal contraception (p= 0.084) and the type of hormonal contraception (p= 0.392) with the histopathological degree of meningioma.

Conclusion: Duration of hormonal contraceptive use has a significant effect on the histopathological degree of meningioma.

Introduction

Meningiomas are the most common benign intracranial neoplasms, accounting for 13-26% of all intracranial tumors. These tumors originate from the meningothelial cells of the arachnoid layer (1) Meningiomas are generally encapsulated and classified as benign with a limited number of genetic aberrations, but because of their intracranial location, they often have the potential to cause lethal consequences. Wiemels found that meningiomas were the most frequently diagnosed primary brain tumors in the United States from 2002-2006, with a frequency of 33.8% of all primary tumors in the central nervous system (2).

Based on the classification of the World Health Organization (WHO), the majority of meningiomas (80%) are grade I, with benign histopathology, the rest are higher grades (grade II (15% - 20%) and III (1%

- 3%)) with atypical to anaplastic histopathology and show a more aggressive development (3). Compared with WHO grade I meningiomas, higher grade meningiomas are associated with poorer survival rates and higher recurrence rates(4).

In general, the incidence of meningiomas is high in women compared to men with a ratio of 2:1 (5). Of all intracranial tumors, meningiomas responsible for 20% in men and 38% in women, the risk factors associated with this difference in incidence remain unclear, however some researcher suspected it has to do with hormonal pathways (2,6). This hypothesis is supported by the influence of female sex hormones on the growth of brain tumors, especially meningiomas, the high ratio of meningiomas in women, which is 2-3:1, gestation period and luteal phase of menstruation may affect tumor growth(7). The general prevalence of meningiomas in Indonesia ranges from 0.7%, with an incidence of 2-7 per 100,000 population(8).

Hormonal contraceptives are the most common contraceptive method used by women in Indonesia, while the use of intrauterine device (IUD) contraceptives is still relatively low. This is due to a variety of different reasons such as fear of side effects, fear of the installation process, to being banned by the husband for fear of disturbing the thread during sexual intercourse (9). Wigertz, 2006 in Stockholm, found that women who use non-oral hormonal contraception have a 2.7 times risk of developing meningioma compared to those who do not use hormonal contraception(10). The use of progestin hormonal drugs (which are also found in hormonal contraceptives) in high doses for a long time is thought to affect the occurrence of meningiomas and increase the histopathological degree of meningiomas (11,12).

This study is a single-institutional study that analyses the history, the types of hormonal contraception, and duration of use with histopathology grading of meningioma.

Method

After obtaining ethics approval, a retrospective analysis was conducted on every female menigioma patients in our institution, resulting in 452 patients. We only included patients aged 20-56 years old, had a pathological anatomy result of meningioma. We also excluded those who underwent meningioma resection more than one time, had other brain tumor other than menigioma, was using more than 1 type of hormonal contraception, were using contraception for other means than delaying pregnancy, incomplete medical record, and no available contact.Thus we were able to collect 206 data as the research sample. The extracted data were epidemiological data, histopathology grading of meningioma, history of hormonal contraception use, duration of use and type of contraception. The data were collected from medical records.

Data analysis was carried out using a statistical computer using SPSS IBM 25 software. Data analysis of the degree of histopathology and contraceptive history was carried out using the Chi-square method, if the data did not fulfil Chi-square requirements, Fischer's analysis was conducted, with significance of $p<0.05$. The analysis of histopathological degrees and types of hormonal contraception was using the Chi-square method. If the data did not meet the requirements for Chi-square, then followed by Fisher's analysis, with a significance value of $p<0.05$. The data analysis of the histopathological degree variables and the duration of the use of hormonal contraception variables was first tested for normality of the data with Kolmogorov-Smirnov. If the data is normally distributed, then the data analysis is continued by using the unpaired t-test comparison (independent t-test). If the data are not normally

distributed, then the analysis is continued by using the Mann-Whitney comparison test, with a significance value of $p < 0.05$.

Results

Patient Demographics

From all of the 206 patient's data, we analyzed its demographics. In this study, the number of meningioma patients who underwent surgery in the period 2015 to 2020. The highest number of meningioma patients occurred in 2015 with 105 cases, while the lowest was in 2020 with 24 cases as shown in table 1.

Year of Surgery	n	%
2015	105	23,23
2016	87	19,24
2017	73	16.15
2018	82	18,14
2019	81	17,92
2020	24	5,31
Total	452	100

Table 1. Distribution table of meningioma patient's which underwent surgery from 2015 to December 2020

The results of the examination of the characteristics of the use of hormonal contraceptives consisting of from the history of contraception, type of contraception, and duration of contraception in patients undergoing meningioma surgery in the period 2015 to 2020 as shown in table 2. The number of patients who did not have a previous history of using hormonal contraception was lower than those who had a history of hormonal contraception use, which amounted to 20 patients out of 206 patients. The most common type of contraception used by patients was the 3-month injection contraceptive with a percentage of 36.0% of patients. The median duration of contraceptive use in these patients was 4 years.

No.	$\mu \pm SD$	n	%
1	**History of Hormonal Contraception**	206	100
	Yes	186	90.3
	No	20	9.7
2	**Type of Hormonal Contraception**	186	100
	Pills	60	32,3
	1-month injection	59	31,7
	3-month injection	67	36,0

3	**Duration of Hormonal contraception (year)**	4,48 ± 2,990	186	100

Table 2. Characteristic of hormonal contraceptives use in patients who underwent meningioma resection

History of hormonal contraceptives and meningioma grading

Meningioma grading in this study was divided into two according to WHO, namely benign grade (grade I) and n0n-benign grade (grade II and III). In this study, the comparative test used was Fisher's comparative test as shown in table 3. There was no significant difference (p= 0.084) between patients who had a history of hormonal contraception and those who did not have a history of hormonal contraception on the grade of meningioma.

		Grade		p-value
		Benign	**Non-Benign**	
History of Hormonal Contraceptives	**Yes**	160	26	0,084
	No	20	0	
	Total	180	26	

Table 3. Difference in history of hormonal contraceptives with meningioma grading

Hormonal contraceptives types and meningioma grading

In this study, the comparative test performed was the chi-square test, there was no significant difference in proportion (p= 0.392) between the types of hormonal contraceptives for grading meningioma, as shown in Figure 1.

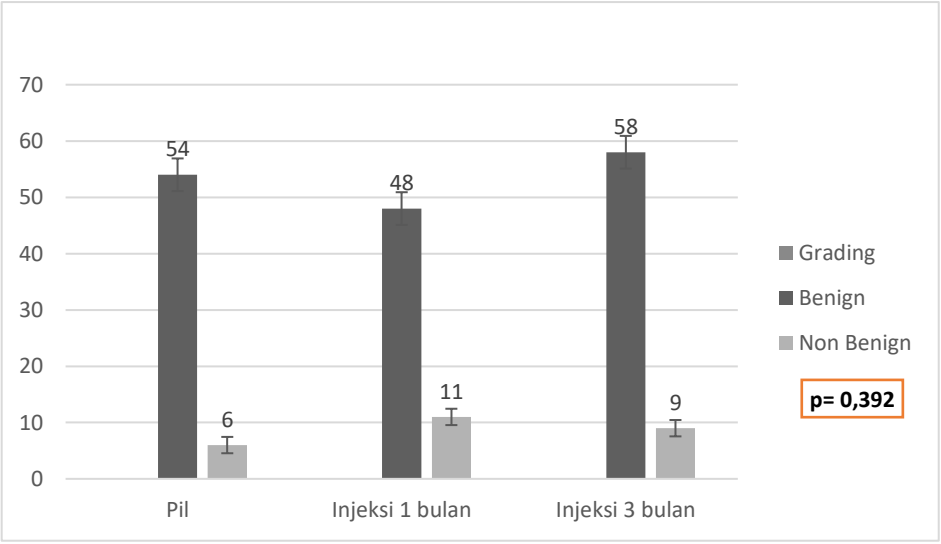

Figure 1. Diagram of chi-square comparation test of hormonal contraception types and meningioma grading.

Hormonal contraceptives duration and meningioma grading

In this study, a normality test of contraceptive duration data on meningioma grading was carried out with Kolmogorov-Smirnov data, it was found that the data were not normally distributed (p = 0.166 for non-benign data, and p = 0.000 for benign data) as shown also from figure 2.

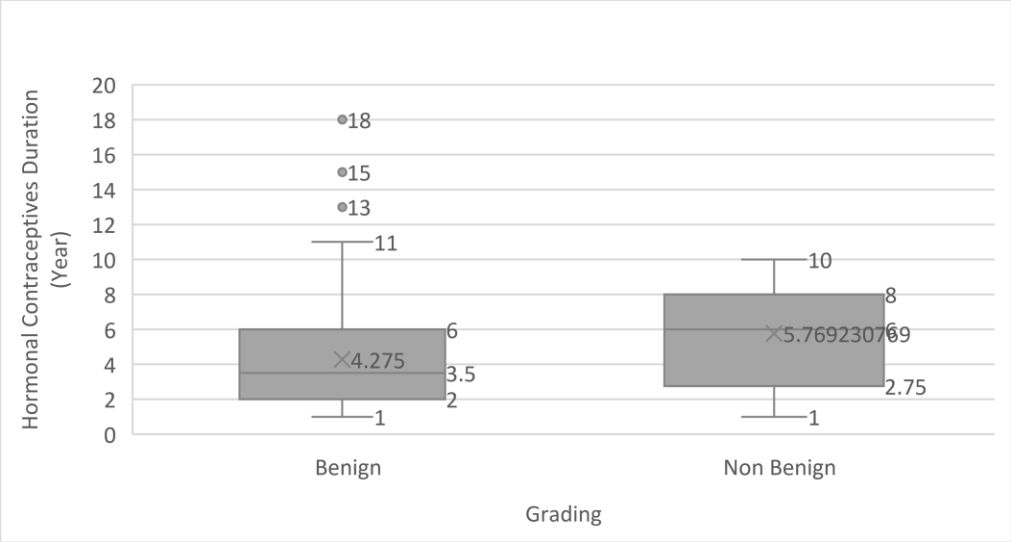

Figure 2. Box plot distribution of hormonal contraceptives duration to meningioma grading

Thus, the comparative test performed is the Mann-Whitney test. There was a significant difference in the duration of hormonal contraceptive use (p= 0.015) between meningioma patients with benign and non-benign grades as shown in table 4.

	Median (Minimum-Maximum)	**p-value**
Benign	3,50 (1 – 18,00)	**0,015***
Non-Benign	6,00 (1 – 10,00)	

Table 4. Difference of duration and its meningioma grading

Discussion

Meningiomas are the most common primary central nervous system tumors. Most (80%) are benign and slow growing. However, although most are benign with low morbidity, higher grade meningiomas (20%) are associated with higher morbidity and mortality rates (Louis et al., 2016). In this study, the number of patients undergoing meningioma surgery in the 2015-2020 period ranged from 70-100 patients per year,

but this number decreased in 2020 to 24 patients only, this could be due to the COVID-19 pandemic condition(13).

The duration of the use of hormonal contraception in meningoma patients in this study was more than 4 years. Custer et al., reported that use of hormonal contraception for more than five years increased the risk of meningioma, as was reported by Wigertz et al., that long-term use of hormonal contraceptives for more than 10 years increased the risk of meningioma by 18.22 times while the use of less than 10 years increased the risk of meningioma 5.86 times compared to those who did not use hormonal contraception(10,14). Supartoto et al., linking the duration and incidence of meningiomas due to the expression of progesterone receptors (PR) given exogenous progesterone causes an increase in the production of pro-inflammatory cytokines such as: IL-1β. Increased IL-1β triggers NF2 inactivation resulting in accelerated cell growth and meningioma development. In addition, the use of hormonal contraception for a long time is a risk factor for orbitocranial meningioma (WHO grade I)(15).

Different results were presented by Korhonen et al., who reported that the use of hormonal contraception did not affect the risk of meningioma(16). Yang et al., also reported that there was no significant increased risk of meningioma in women taking oral contraceptives for less than one year (RR, 0.99; 95% CI, 0.8-1.22; I^2: 0%). (CI, 0.8-1.22; I^2: 0%). Similar results were also found in the group using oral contraceptives for 1-10 years and above 10 years, with (RR, 1.16; 95% CI, 0.95-1.42; I^2: 0%) and (RR, 0.99; 95% CI, 78- 1.25; I^2: 0%), respectively. Yang also found that there was a non-linear correlation between the duration of oral contraceptive use and the risk of meningioma (Pnonlinear=0.033), but there was no significant relationship between the increased duration of oral contraceptive use and the risk of meningioma(17).

Research from Wahyuhadi et al., states that the use of hormonal contraception and the duration of its use (above 10 years) affect the risk of meningioma, but the use of hormonal contraception has no effect on the degree of meningioma(18). A study conducted by Maiuri et al., in patients using progesterone contraceptives showed an increased risk of meningioma in patients using contraception for more than 5 years and patients with PR-positive meningiomas(19,20).

There was no significant difference between the history of hormonal contraceptive use and the grading of meningioma in this study. This was also reported by Wahyuhadi et al., and Maiuri et al., about the absence of a relationship between the use of hormonal contraceptives with meningioma grade and progesterone receptors (PR) expression(18,20). A different report was submitted by Yang et al., that oral contraceptives can decrease the level of PR expression regulation which is negatively correlated with a high histopathological degree and meningioma recurrence rate(17).

Patients who use contraceptives containing only progesterone have a higher risk of meningioma recurrence and lower progression free survival (PFS) when compared to using other contraceptives that also contain estrogen(19).This study differs from the results of this study which did not find a significant difference between types of hormonal contraception on the grading of meningiomas.

There is a significant difference between the duration of hormonal contraceptive use and the histopathological degree of meningioma. Similar results were reported by a study Supartoto et al., which showed a relationship between duration of use of hormonal contraceptives and meningioma grading, the longer exposure to exogenous hormonal contraceptives in the form of progesterone correlated with lower expression of PR and neurofibromatosis type 2 (NF2) in serum(15). Mutations in NF2 and telomerase reverse transcriptase (TERT) are associated with grade II atypical meningiomas(4). The neurofibromatosis type 2 (NF2) mutation is the most common chromosomal abnormality and is found in up to 80% of meningiomas (21,22). The frequency of these abnormalities increases with the degree of histopathology of the tumor and occurs in 50% of benign meningiomas and 75-85% of atypical or anaplastic meningiomas(3). The results of this study showed a significant difference in the duration of hormonal contraceptive use between benign and non-benign meningiomas. Where, the longer the use of hormonal contraception, the higher the possibility of non-benign meningioma.

Based on a study Wigertz et al., patients who used contraception with a duration of more than 10 years experienced an 18,216-fold increased risk of meningioma ($p = 0.000$). At less than 10 years of use, the risk decreased to 5.86 times ($p = 0.001$)(10). Women with a history of long-term use of hormonal contraceptives had a higher risk of developing meningiomas, especially those with a duration of > 10 years, with an odds ratio of 2.7 (95% CI 0.9-7.5). This clearly shows that the longer the exposure to oncogenes (exogenous hormones), the higher the likelihood of developing meningiomas. Maiuri also reported that the risk of meningioma increases in users of hormonal contraception for more than 5 years(20,23).

A study conducted by Harland et al., stated that there was a positive correlation between the risk of meningioma and the use of oral contraceptives for more than 5 years, however, there was no increase in risk with increasing duration of contraceptive use(19).

However, two other studies (Johnson et al., 2011; Korhonen et al., 2010) showed the opposite result, namely that there was a protective effect of using oral hormonal contraceptives for more than 10 years(16,24). In the study group, there were several durations of contraceptive use, namely estrogen alone or combined estrogen-progesterone in which there was an increased risk of meningioma at the duration of use between 1 to 4 years(16).

In the variable type of hormonal contraception, there was no significant difference in the histopathological degree of meningioma. These results are similar to a meta-analysis study conducted by Yang et al., involving a total of 2,138,608 subjects the results that use of oral contraceptives does not increase the risk of glioma or meningioma. In contrast, over time the use of long-term oral contraceptives can significantly reduce the risk of glioma, and the "tipping point" is 7.5 years. However, the results of the qualitative analysis showed that the use of oral contraceptives did not increase the risk of meningioma, and similar results were also reported in the dose-response analysis(17).

In the study Wahyuhadi et al., the use of injectable contraceptives, the pill and 1 month of contraception had a lower risk of meningioma than the use of 3-month injectable contraceptives with risk values of 0.042, 0.032, and 0.071, respectively ($p<0, 05$). This shows that the 3-month injectable contraceptive has the highest risk level compared to the others. However, there was no significant

difference in the degree of malignancy of meningiomas between types of hormonal contraception in each group (p = 1000, Eta 0.065)(18).

Limitations

This study still has not analysed the mechanism of the relationship between the variables studied at the biomolecular level so that it is hoped that in future studies an analysis of the mechanism of the relationship between variables at the molecular level will be carried out. Then there is no data regarding the type of hormonal contraceptive pill used by the patient, so it is hoped that in future research can be investigated further about the type of contraceptive pill used and added the combined hormonal contraceptive method as an alternative solution in preventing meningioma. In addition, there is no clear data regarding the duration of use of hormonal family planning with the occurrence of meningioma, namely whether the subject using hormonal family planning years later experienced a meningioma, or there was discontinuation of the use of hormonal family planning and a meningioma occurred so that there is a possibility that meningioma is not the result of the effects of hormonal family planning. .

Conclusion

Meningioma grading in patients who had a history of hormonal contraceptives had no significant difference in those who do not. Different forms of hormonal contraceptives had no significant difference in meningioma grading. However, duration of hormonal contraceptives use had a significant difference in meningioma grading. Further research needs to be done by adding research variables including oncogenesis factors such as the expression of progesterone receptor (PR), estrogen receptor (ER), NF2, and PIK3CA. Further research on the combined hormonal contraceptive method as an alternative solution in the prevention of meningiomas is also important.

References:

1. DeMonte F, McDermott MW, Al-Mefty O. Al-Mefty's Meningiomas. 2nd ed. New York: Thieme; 2011.

2. Wiemels J, Wrensch M, Claus EB. Epidemiology and etiology of meningioma. Journal of Neuro-Oncology. 2010;99(3):307–14.

3. Lee YS, Lee YS. Molecular characteristics of meningiomas. Journal of Pathology and Translational Medicine. 2020;54(1):45–63.

4. Roux A, Tauziede-Espariat A, Zanello M, Gareton A, Malaize H, Benzakoun J, et al. Symptomatic progestin-associated atypical grade II meningioma. A first case report. Neurochirurgie. 2020;66(3).

5. Choy WC, Kim W, Nagasawa D, Stramotas S, Yew D, Gopen Q, et al. The molecular genetics and tumor pathogenesis of meningiomas and the future directions of meningioma treatments. Neurosurgical Focus. 2011;30(5).

6. Claus EB, Morrison L. Epidemiology of Meningiomas. In: Al-Mefty's Meningioma. 2nd ed. New York: Thieme; 2011. p. 35–9.

7. Wigertz A, Lönn S, Mathiesen T, Ahlbom A, Hall P, Feychting M. Risk of Brain Tumors Associated with Exposure to Exogenous Female Sex Hormones. American Journal of Epidemiology. 2006 Oct 1;164(7):629–36.

8. Christine RN, Supartoto A, Agni AN. Hubungan Pemakaian Kontrasepsi Hormonal Terhadap Risiko Meningioma Orbitokranial Pada Wanita [PhD Thesis]. Universitas Gadjah Mada; 2015.

9. Amir F. Faktor-Faktor yang Berhubungan dengan Pemilihan Alat Kontrasepsi pada Pasangan Usia Subur (PUS) di Puskesmas Minasaupa Makassar Tahun 2017. JURNAL KESEHATAN DELIMA PELAMONIA. 2017;1(2).

10. Wigertz A, Lönn S, Hall P, Auvinen A, Christensen HC, Johansen C, et al. Reproductive factors and risk of meningioma and glioma. Cancer Epidemiology Biomarkers and Prevention. 2008;17(10):2663–70.

11. Gil M, Oliva B, Timoner J, Maciá MA, Bryant V, de Abajo FJ. Risk of meningioma among users of high doses of cyproterone acetate as compared with the general population: Evidence from a population-based cohort study. British Journal of Clinical Pharmacology. 2011;72(6):965–8.

12. Peyre M, Gaillard S, de Marcellus C, Giry M, Bielle F, Villa C, et al. Progestin-associated shift of meningioma mutational landscape. Annals of Oncology. 2018;29(3).

13. Bhangu A, Lawani I, Ng-Kamstra JS, Wang Y, Chan A, Futaba K, et al. Global guidance for surgical care during the COVID-19 pandemic. British Journal of Surgery. 2020;107(9):1097–103.

14. Custer B, Longstreth JT, Phillips LE, Koepsell TD, Van Belle G. Hormonal exposures and the risk of intracranial meningioma in women: A population-based case-control study. BMC Cancer. 2006;6.

15. Supartoto A, Sasongko MB, Respatika D, Mahayana IT, Pawiroranu S, Kusnanto H, et al. Relationships between neurofibromatosis-2, progesterone receptor expression, the use of exogenous progesterone, and risk of orbitocranial meningioma in females. Frontiers in Oncology. 2019;9(JAN).

16. 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. Cancer Causes and Control. 2010;21(12).

17. Yang X, Liu F, Zheng J, Cheng W, Zhao C, Di J. Relationship Between Oral Contraceptives and the Risk of Gliomas and Meningiomas: A Dose-Response Meta-Analysis and Systematic Review. World Neurosurgery. 2021;147.

18. Wahyuhadi J, Heryani D, Basuki H. Risk of meningioma associated with exposure of hormonal contraception. A case control study. Majalah Obstetri & Ginekologi. 2018;26(1).

19. 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. Journal of Neuro-Oncology. 2018;136(2).

20. Maiuri F, Mariniello G, Somma T, Guadagno E, Corvino S, Pagano S, et al. Meningiomas in Premenopausal Women: Role of the Hormone Related Conditions. Frontiers in Oncology. 2020;10.

21. Clark VE, Erson-Omay EZ, Serin A, Yin J, Cotney J, Özduman K, et al. Genomic analysis of non-NF2 meningiomas reveals mutations in TRAF7, KLF4, AKT1, and SMO. Science. 2013;339(6123):1077–80.

22. Karsy M, Azab MA, Abou-Al-Shaar H, Guan J, Eli I, Jensen RL, et al. Clinical potential of meningioma genomic insights: A practical review for neurosurgeons. Neurosurgical Focus. 2018;44(6):1–7.

23. Michaud DS, Gallo V, Schlehofer B, Tjønneland A, Olsen A, Overvad K, et al. Reproductive factors and exogenous hormone use in relation to risk of glioma and meningioma in a large European cohort study. Cancer Epidemiology Biomarkers and Prevention. 2010;19(10).

24. Johnson DR, Olson JE, Vierkant RA, Hammack JE, Wang AH, Folsom AR, et al. Risk factors for meningioma in postmenopausal women: Results from the Iowa Women's Health Study. Neuro-Oncology. 2011;13(9).