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Effect of hormonal contraceptive exposure in meningioma patient on hormonal receptor and proliferative index expression in meningioma

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ABSTRACT

Background and Objectives. Hormonal contraceptive remains one of the most common birth control medications among females in the general population The use of hormonal contraceptive is believed as one of risk factor of meningioma. Research on meningioma has proven a lot about the existence of hormone receptors. Our study was designed to clarify whether the expression of hormonal receptors and proliferative index were influenced by exposure of hormonal contraceptive.

Materials and Methods. This cross-sectional study was conducted in Mohammad Hoesin General Hospital, Palembang, Indonesia, from 2018 to 2023. The inclusion criteria included meningioma patient with history exposure of hormonal contraceptive. Patient data collection was obtained from medical records and detailed interview (reproductive status and history of hormonal contraceptive used). Data regarding patient's characteristic, histology type and WHO grades tumor were extracted from the patient's clinical files The immunohistochemistry studies were performed to evaluate the Progesterone Receptor expression, Estrogen Receptor expression and Ki-67 index.

Results. The total 51 patients were reviewed in our study. Mean of age 46.88 ± 9.62 years. According to the histopathological classification, 84.3% had WHO grade I, 13.7% had Grade II and 2% had Grade III. 98% subjects had PR positive with strong staining. Only 3.9% patients with strong staining in ER expression. For proliferative index, most patients were in range ≤4%. There was no significant difference among type, duration and status of contraceptive hormonal used with expression of hormonal receptor and Ki-67 index.

Conclusions. Our findings suggested that exposure to hormonal contraceptive did not influence the expression of PR, ER and Ki-67. But we discover that there is a trend higher of PR expression in patients with history of progesterone only contained hormonal contraceptive.

Keywords: hormonal receptor, hormonal contraceptive, proliferative index

Abbreviations:

CTBRUS	: Central Brain Tumor Registry in the United States
ER	: estrogen receptors
IGF	: insulin like growth factor
NF-2	: neurofibromatosis 2
PR	: progesterone receptor

INTRODUCTION

Meningioma is known as a slow growing tumor. Globally, epidemiological data indicate that meningiomas account for 14.3% to 19% of all primary intracranial neoplasms, with some reports suggesting that their prevalence may reach as high as 30% [1,2,3,4]. The Central Brain Tumor Registry of the United States (CBTRUS) identifies meningioma as the predominant primary brain tumor in the United States, with glioma ranking as the second most common [5]. Epidemiological data on meningioma in Indonesia remains largely underreported. However, data from our institution indicates that meningioma accounts for 77.1% of primary brain tumors, followed by glioma at 13.1% [6]. The majority of meningioma cases occur in adults and the elderly, with a significantly higher prevalence among women, comprising approximately two-thirds of all cases [2,3].

Several risk factors for meningioma have been established, including age, female sex, cranial irradiation, genetic and hormonal factor. Epidemiological and pathological evidence highlights a pronounced female predominance in meningioma incidence, underscoring the potential involvement of sex hormones in the tumor's pathogenesis and progression [3,4,7]. Numerous studies have explored the association between hormonal and reproductive factors and the risk of meningioma. This connection is supported by several observations, including the higher prevalence of meningioma in women, tumor growth during pregnancy and regression postpartum, links to breast cancer, and the presence of hormonal receptors in approximately two-thirds of meningioma cases [3,4,7,8,9].

Research on meningioma has proven a lot about the existence of hormonal receptor. Molecular and immunohistochemical studies have shown progesterone receptor (PR) and estrogen

receptors (ER) are expressed in meningioma with various degrees [7,8,10]. The proliferation of human meningioma cell lines has been documented following exposure to estrogen and progesterone [3]. The use of hormonal contraceptives is considered a potential factor linking exogenous hormones to the development of meningiomas. This hypothesis arises from the presence of progesterone and estrogen receptors in meningioma cells, which, when activated by their respective hormones, may stimulate cell proliferation [8].

Hormonal contraceptive remains one of the most common birth control medications among females in the general population. Data from National Health Survey in 2013 showed that there were 84.5% contraceptive users whereas range of age 30-39 years was the highest group of hormonal contraceptives user in Indonesia [11]. Several previous studies demonstrated that hormonal contraceptive exposure influenced the grading of meningioma [8,10]. Whether hormonal contraceptive exposure would influence the hormonal receptor expression is still in debated. A study from Supartoto showed that exposure with progesterone contained contraceptive increased of progesterone receptor in meningioma [10]. There were a few studies have done to correlate the role of hormonal contraceptive on hormonal receptor and Ki-67 proliferative index, but varied conclusion is given regarding the correlation [9,10,12,13].

Our study aimed to investigate whether the expression profiles of hormonal receptors are influenced by exposure to hormonal contraceptives. Additionally, we examined the presence of sex hormone receptors and their correlation with cellular proliferation markers, such as Ki-67. These aspects present intriguing avenues for further research to deepen our understanding of the role of hormonal contraceptives in the pathogenesis of meningiomas.

This study was approved by Health Research Ethics Committee of Mohammad Hoesin General Hospital Palembang No.DP .04.03/D.XVIII.6.11/ETIK/89/2023

MATERIALS AND METHODS

This cross sectional study was conducted in Mohammad Hoesin General Hospital, Palembang, Indonesia, by collecting all patients whom histopathologically confirmed with meningioma from 2018 to 2023. The inclusion criteria included meningioma patient with history exposure of hormonal contraceptive. The study excluded cases with incomplete data or paraffin blocks unsuitable for immunohistochemistry analysis. Additional exclusion criteria included a history of hormone replacement therapy, a family history of malignancy, and a history of cranial irradiation. The sample size was determined retrospectively by reviewing all available records.

Patient data collection was obtained from medical records and detailed interview. All participants underwent in person or telephone interviewed for history exposure of hormonal contraceptive and reproductive status Data pertaining to the patients' demographic characteristics, histological classification, and WHO tumor grading were meticulously retrieved from the clinical records. PR, ER and Ki-67 status were recorded after reporting of the hematoxylin-eosin and immunohistochemistry-stained tissue slides, respectively. Patient's characteristics including age, history of marriage, reproductive factors (e.g. age of menarche, number of parities, menopause status, age of first birth) and history exposure of contraceptive (the status of hormonal contraceptive use, type of hormonal contraceptives and duration of use) were obtained using standardized questionnaire.

The status of hormonal contraceptive use was classified as: (1) 'current use', when the contraceptives were still being used until the diagnosed of meningioma or ended in the year before the diagnosis of meningioma; (2) 'past use', when the most recent use was more than 1 year before the diagnosis of meningioma. The type of contraceptives was classified as: (1) 'progesterone contained only' (2) 'combined progesterone plus estrogen' and the duration was classified as: (1) 'less than 5', (2) '5 to 10 years',' (3) 'more than 10 years'.

Pathological specimens (all meningioma samples) were reviewed by a neuropathologist who had no previous knowledge about these patients. The tumor was classified according to the 2016 WHO classification system. The histopathological grade of the meningioma was also divided into 2 groups: the benign group included those with grade I; the non-benign group included those with grades II and III. Immunohistochemical staining for ER, PR, and Ki-67 were performed on the subject and sample who met the criteria.

The immunohistochemistry studies were performed to evaluate the PR, ER and Ki-67 index expression. Immunohistochemistry staining was performed using Ventana BenchMark (ASSY) Gx Stainer machine. The specimens were fixed in neutral buffered 10% formalin, embedded in paraffin, and sectioned into 5 mm thickness. The expression of estrogen receptors (ER) was assessed using a monoclonal antibody (clone Sp1, Rabbit) of Ventana brand and PR were determined progesterone receptor polyclonal antibody (clone 1E2, Rabbit) of Ventana brand. Both of estrogen and progesterone antibody used breast carcinoma specimen as positive control. All slides were examined for positively stained tumor cell nuclei. Positive smears were characterized by brown staining (weak to strong intensity) on the nuclei (Figures 1,2,3).

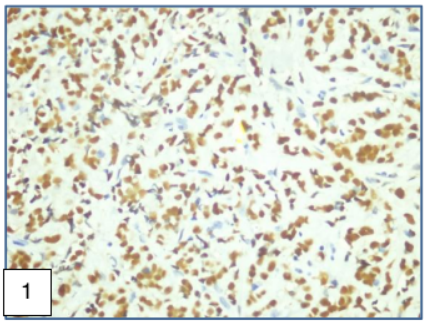

Figure 1. Immunohistochemistry stain positive of PR expression with strong intensity (400x)

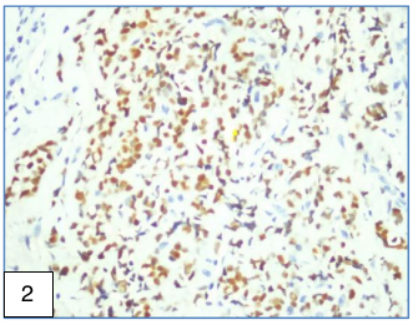

Figure 2. Immunohistochemistry stain positive of ER expression with strong intensity (400x)

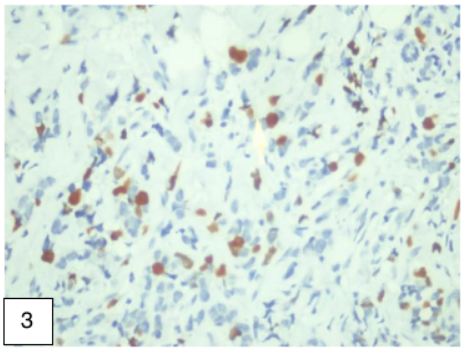

FIGURE 3. Immunohistochemistry stain of Ki-67 with high proliferative index (>11%)

Ki-67 was used to detect the proliferative index of meningioma. The expression of Ki-67 was evaluated in all specimens by using the antibody used (ready to use) Ki-67 monoclonal antibody (clone 30-9, Rabbit) Ventana brand. Tonsil tissue was used as a Ki-67 positive control in this study. For Ki-67 staining, the proliferative index was determined as the percentage of positively stained cells among 1,000 tumor cells counted within the most mitotically active regions of the tumor. The values of Ki-67 were classified into four groups: group I ≤4%, group II 4.1-7%, group III 7.1-11% and group IV >11%.

SPSS for window is used for statistical analysis. Categorical and continuous variables were summarized as percentages and mean standard deviation, respectively. The Fisher, Kolgomorov Smirnov and Kruskal Wallis test were used to determine the association between history of contraceptive used with PR, ER, and Ki-67 expression. The association was considered significant statistically when the P value < 0.05.

RESULTS

The total 51 patients between January 2018 and December 2023 were reviewed in our study. The demographic distribution, reproductive status and history exposure of hormonal contraceptive are shown in Table 1. The subjects consisted of ages ranging from 32 to 67 years with mean of age 46.88 ± 9.62 years. Mean age of menarche in our study was 13.17 ±1.07 year with the most prevalent parity was multiparous. 76.5% patients were in the reproductive age. Based on the duration, most patients (74.5%) used contraceptive more than 10 years and combined contraceptive type was less frequent than progesterone only.

Table 1. Demographic characteristic, reproductive status and history exposure of contraceptive

Characteristic	Frequency	Percentage (%)
Demography		
Age		
20-30	1	2
31-40	13	25.5
41-50	27	52.9
51-60	7	13.7
>60	3	5.9
Marital Status		
Marriage	5	100
Unmarriage		
Reproductive status		
Menarche		
≤14 year	40	78.4
>14 year	11	21.6
Parity		
nullipara	3	5.9
multiparous	48	94.1

Aged of first birth		
≤20 year	30	58.8
>20 year	21	41.2
Menopause		
Yes	12	23.5
No	39	76.5
Exposure history		
Type of contraceptive		
Progesterone only	42	82.4
Combined progesterone and estrogen	9	17.6
Duration		
<5 year	6	11.8
5-10	7	13.7
>10 year	38	74.5
Status		
Past user	33	64.7
Current user	18	35.3

According to the histopathological classification, 84.3% of meningioma patients had WHO grade 1 or benign. Following that, up to 13.7% had WHO Grade II and 2% had Grade III, for a cumulative total of 15.7% non-benign group, with the largest number (33.3%) of the meningothelial types followed by transitional (23.5%). Of 51 subjects, 98% were PR positive with strong staining while ER were absent in 41.2%. There were only 3.9% patients with strong staining in ER expression. For proliferative index, most patients were in range ≤4%. Only 3.9% patients with high proliferative index (Table 2).

Table 2. Histopathology and Immunohistochemistry Staining Characteristic

Characteristic	**Frequency**	**Percentage**
Histology type		
Metaplastic	7	13.7
Meningothelial	17	33.3
Choroid	4	7.8
Fibrous	3	5.9
Microcytic	1	2.0
Psamamatous	1	2.0

Atypical	3	5.9
Rhabdoid	1	2.0
Enplaque	1	2.0
Angiomatous	1	2.0
Transitional	12	23.5
Histology Grade		
WHO grade I	43	84.3
WHO grade II	7	13.7
WHO grade III	1	2.0
Estrogen Receptor		
Absent	21	41.2
Weak	18	35.3
Moderate	10	19.6
Strong	2	3.9
Progesterone Receptor		
Absent	1	2.0
Weak	0	0
Moderate	0	0
Strong	50	98.0
Ki -67		
<4%	37	72.5
4.1-7%	8	15.7
7.1-11%	4	7.8
> 11%	2	3.9

Table 3. Association between Hormonal Receptor Expression and Proliferation Index with Grading of Meningioma

Immunohistochemistry Staining	**Benign (WHO grade I)**	**Non-benign (WHO grade II and III)**	**P**
Progesterone Receptor			
Absent	0 (0)	1 (12.5)	
Weak	0 (0)	0 (0)	0.157*
Moderate	0 (0)	0 (0)	

Strong	43 (100)	7 (87.5)	
Estrogen Receptor			
Absent	17 (39.5)	4 (50)	
Weak	16 (37.2)	2 (25)	1.00**
Moderate	8 (18.6)	2 (25)	
Strong	2 (4.7)	0 (0)	
Ki-67			
0-4%	32 (74.5)	5 (62.5)	
4.1-7%	6 (13.9)	2 (25)	1.00**
7.1-11%	4 (9.3)	0 (0)	
>11%	1 (2.3)	1 (12.5)	

*Kolmogorov Smirnov, ** Fisher

Table 4. Association between Exposure History of Contraceptive Hormonal with Expression Hormonal Receptor and Proliferative index

Characteristic	**Progesterone Receptor**				**P**
	Absent	**Weak**	**Moderate**	**Strong**	
Type of contraceptive					
Progesterone only	1 (2.4)	0 (0)	0 (0)	41 (97.6)	
Combined	0 (0)	0 (0)	0 (0)	9 (100)	1.00*
Duration					
<5 year	0 (0)	0 (0)	0 (0)	6 (100)	
5-10year	0 (0)	0 (0)	0 (0)	7 (100)	0.843**
>10 year	1 (2.6)	0 (0)	0 (0)	37 (97.4)	
Status					
Past user	1(3.0)	0(0)	0(0)	32 (97.0)	1.00*
Current user	0(0)	0(0)	0(0)	18(100)	
	Estrogen Receptor				
	Absent	Weak	Moderate	Strong	
Type of contraceptive					
Progesterone only	18 (42.9)	15 (35.7)	8 (19)	1 (2.4)	
Combined	3 (33.3)	3 (33.3)	2 (22.2)	1 (11.1)	1.00***

Duration					
<5 year	2 (33.3)	3 (50)	1 (16.7)	0 (0)	0.492**
5-10year	1 (14.3)	4 (57.1)	2 (28.6)	0 (0)	
>10 year	18 (47.4)	11 (28.9)	7 (18.4)	2 (5.3)	
Status					
Past user	12 (36.4)	15 (45.5)	4 (12.1)	2 (6.1)	0.952***
Current user	9 (50.0)	3 (16.7)	6 (33.3)	0 (0)	
	Ki-67				
	0-4%	4.1-7%	7.1-11%	>11%	
Type of contraceptive					
Progesterone only	32 (76.2)	7 (16.7)	2 (4.8)	1 (2.4)	0.689***
Combined	5 (55.6)	1 (11.1)	2 (22.2)	1 (11.1)	
Duration					
<5 year	3 (50.0)	2 (33.3)	0 (0)	1 (16.7)	0.133**
5-10year	7 (100)	0 (0)	0 (0)	0 (0)	
>10 year	27 (71.1)	6 (15.8)	4 (10.5)	1 (2.6)	
Status					
Past user	23 (69.7)	6 (18.2)	3 (9.1)	1 (3.0)	1.00***
Current user	14 (77.8)	2 (11.1)	1 (5.6)	1 (5.6)	

*Fisher, **Kruskal Wallis, *** Kolgomorov Smirnov

Table 3 show that expression of PR was strong within benign meningioma group and interestingly no subject in non-benign group revealed strong expression of ER. Among the PR positive cases, overall cases with strong staining while only one case with absent of PR expression (WHO grade III). Surprisingly, 87.5% of non-benign meningiomas had strong expression PR. We also performed Immunohistochemistry for Ki-67 Index, and majority of the benign group had Ki-67 expression <4%. There was one subject in both of benign and non-benign meningioma that expressed high proliferative index with level Ki-67 >11%. Ki-67 index only significant high in 1 of 8 subject in non-benign group. Statistical analysis revealed that there was no significant relationship between grading of meningioma with expression of hormonal receptor and proliferative index.

Both of type contraceptive hormonal (progesterone only and combined) had similar strong expression of PR (Table 4). Vice versa, expression of ER was absent 42.9% subject with progesterone only. In the combined contraceptive group, the expression of ER was dominated with absent expression. ER expression only strong in 2 subjects with >10 year in duration of contraceptive used. There was no significant relationship among type, duration and status of

contraceptive used and expression of hormonal receptor. However, quantitatively, it was found that there was an increase in the number of patients progesterone only contraception (89.1%) in cases of meningioma with a benign histopathological degree (data not shown). We also performed analysis the association between Ki-67 expression with type, duration and status of contraceptive used and the result showed no significant difference.

DISCUSSION

Sex hormones in both men and women play a crucial role in the etiopathogenesis and development of cancers in various organs, including the endometrium, breast, prostate, lung, and brain. Their contribution to cancer risk primarily involves influencing the rate and frequency of mitosis in epithelial cells within these organs [3,4]. In case of meningioma, predominance female sex is thought that hormonal factor contributes to the growth of meningioma, whether it is from the inside (endogenous hormone) or outside (exogenous hormone). The presence of hormonal receptors on meningioma tumor cells rises also the possibility the relationship between meningiomas and sex steroids. Progesterone and estrogen jointly have the potential to stimulate the proliferation of meningioma cells. This is supported by findings that meningioma cell lines exhibit increased proliferation when exposed to these hormones, providing both molecular and physiological evidence for the role of sex steroid hormones in the development and growth of meningiomas [3,10,15].

Some researchers have described that exogenous hormone used increased risk of meningioma [4,7,14,16,17,18]. Neverless, the role of estrogen and progesterone hormones are still not fully understood in meningiomas. Hormonal contraceptives containing progesterone and estrogen are widely utilized by women for birth control. Several studies have investigated the potential link between their use and the risk of meningiomas. However, the findings from these studies remain inconsistent and inconclusive to date [10,14,15,16,18,19].

There were few studies have been done till now to investigate the role of ER, PR, and Ki-67 in case of meningioma and the correlation with hormonal contraceptive exposure [10,15,19]. Based on age, our study found that the mean of age was 46.88 ± 9.62 years. The previous findings indicated that patients with meningiomas were more prevalent in the older age group while the prevalence of meningiomas rises gradually with age and the peak incidence during the sixth and seventh decades [2,5,7,9]. This variation may be attributed to earlier exposure to oncogenes or substances that could trigger the development of meningiomas. Our study found that the initial use of contraceptive hormones was more common among younger individuals. In our country, there

has been an increasing trend in the use of hormonal contraceptives among younger women, with injectable contraceptives being the most commonly used method. In contrast, in the United States, contraceptive use is predominantly seen in women aged 40-49 years, with non-hormonal methods, such as sterilization, being the most frequently used [11,20]. This suggests a heightened and earlier exposure to exogenous hormones in Indonesian women compared to Americans. The early exposure to hormonal contraceptive might alter the function of suppressor gene as merlin so leading to oncogenesis [7,16].

Although there is a general agreement that the majority of meningiomas contain the PR and are lack of the ER, the biological function of these hormonal receptor and their molecular basis are still unknown [8]. The histopathological distribution of meningioma patients in this study were in line with other studies whereas the majority of patients suffered from meningioma grade 1 [5,7,22,23]. PR have been found to be highly expressed in meningiomas. This was also reflected in the present study while majority (98%) of the cases were PR positive. In this study, we found that 86% cases that PR positive were benign meningioma while 12.5% cases of non-benign meningioma absent of PR. There were 48.8% subjects had ER, but only 3.9% with strong expression of ER. Interestingly, strong ER expression was found in of benign group. Non-benign group expressed 50% of ER expression.

However, several previous studies have reported varying findings. The prevalence of progesterone receptor (PR) and estrogen receptor (ER) expression in meningioma patients has been shown to be influenced by various clinicopathologic factors, particularly tumor grade, as classified by the WHO. This could lead to inconsistent expression of hormone receptors across different tumor grades, and even within the same grade and among different individuals. For example, Agopiantz et al reported 76.8% of grade 1 meningiomas expressed PR compared to 61.2% of grade II and 17.3% of grade III meningiomas. ER were found in 8.7%, 1.6% and 6.8% of grade I, II, and III meningiomas, respectively [4]. Study by Deghan et al showed that, the level of expression also varied from zero to 80% in grade one meningioma [7]. A study by Shanthi et al, found that none of the patients had ER-positive [21]. However, in the study by Mukhopadhyay et al, 3.66% of grade 1 meningiomas and all grade 2 cases were positive for ER [22]. The variation in the expression of PR and ER across studies may stem from several factors, including differences in methodological approaches, tumor biology, and the genetic constitution of the individuals included in the respective studies. However, the difference in the PR and ER expression regarding the WHO grades of the meningioma patients in our study was not significant. Similar finding has also reported by Portet et al. [8].

This present study reviewed about the detailed history exposure of hormonal contraceptive and the expression of hormonal receptor. Of 50 subjects with positively PR, 90.57% used progesterone only contained hormonal contraceptive. Our study also found that in benign group with strong expression of PR, all of the subjects had history of progesterone only contained hormonal contraceptive, without significance difference in duration and status of contraceptive used. Noneless, statistical analysis revealed no significant difference on expression hormonal receptor within female with history exposure of hormonal contraceptive in this study.

The similar results were described by several studies whereas duration, type and status of contraceptive hormonal used not correlated with PR expression [2,14,16]. This finding was not in line with study by Portet et al, they reported that meningiomas developed on cyproterone acetate (progestin agonist) were the most PR with 97% positivity [8]. Study by Supartoto showed that the longer exposure to exogenous progesterone injection, the lower the expression of PR [10]. Agopiantz et al found that 89% of meningiomas that developed under hormonal treatment expressed progesterone receptors as compared to 71% of meningiomas that developed without any form of hormonal treatment or exposure. This study also shown 6% of meningiomas developed under hormonal treatment expressed estrogen vs 11% of meningiomas developed without any hormonal treatment [4].

The discrepancies in the results of these studies could be attributed to variations in the characteristics of the study subjects, differences in data collection methods (e.g., direct interviews, retrieval from medical records), the techniques used for hormonal receptor analysis, or genetic factors. Tumor biology has been reported to be influenced by genetic composition, which is often determined by an individual's race and geographic location, further contributing to the variability in findings [23].

The precise mechanisms linking prolonged exposure to exogenous hormones and the development of meningiomas in females remain inadequately elucidated. Interestingly, meningiomas do not exhibit enlargement during the proliferative phase of the menstrual cycle, when estrogen levels are elevated. In contrast, these tumors have been observed to grow during the second and third trimesters of pregnancy, as well as during the luteal phase of the menstrual cycle, when circulating progestins are elevated. This suggests that progesterone may play a role in the growth of meningiomas [3,17]. There is evidence suggesting that long-term exposure to exogenous progesterone may alter in vivo progesterone levels and modulate the expression of progesterone receptors, potentially exerting a broader impact at the genetic level. Specifically, this alteration may influence the Merlin protein, encoded by the Neurofibromatosis 2 (NF-2) gene, which plays a critical role in regulating the growth of neuronal and meningeal tissues. Such changes could impair

the tumor-suppressor function of Merlin, particularly within meningeal tissue, thereby promoting tissue overgrowth. Additionally, estrogens have been implicated in promoting genomic instability in cells. Estrogens also interact with insulin-like growth factor (IGF), which not only stimulates tumor growth but also inhibits apoptosis, further contributing to tumor progression [17,24].

Ki-67 is a nuclear non-histone protein expressed during active phases of the cell cycle, including G1, S, G2, and M phases, but it is absent in resting cells (G0 phase). Its expression serves as a marker of cell proliferation, indicating ongoing cell division [7,22]. As marker of proliferation cell, it reflects a number of mitoses, while the value of Ki-67 is in line with histology grading of meningioma based on several studies [22,23,25]. The issue about Ki-67, grading of meningioma and hormonal receptor has been established for a long time. Benign tumors were typically associated with a low proliferative index, high PR positivity, and ER negativity. Meningiomas that exhibited a higher proliferative index and PR negativity were more likely to be classified as Grade II or Grade III. Some literatures said that benign meningioma with high PR expression usually had low proliferative index. However, whether hormonal contraceptive exposure is correlated with proliferative index has not been established.

Our study found that majority benign group meningioma had Ki-67 below 4%. Interestingly 62.5% of non-benign group had Ki-67 less than 4%. This result is consistent with the results of previous study [7,25]. Study by Shahane revealed 85.33% subjects Ki-67 index below 4% which were largely grade I, 13.33% were having Ki-67 in the range of 5-10% which were mainly grade II, only 1 patient had Ki-67 Li of 14% which was grade III tumor [9]. Different result was found in study by Telugu et al that revealed the mean of Ki-67 in different grades of meningioma (grade one 3.1%, grade two 7% and grade three 14.2%) [23]. Other study showed that all grade one meningioma cases had Ki-67 expression less than 4% [7]. This present series showed no significant difference mean value of Ki-67 between benign group (1.39 ± 0.76) and non-benign group (1.63 ± 1.06). The previous studies have shown contradictory results [7,12,13,22,23].

To our knowledge, there was no study investigated correlation between proliferative index and history exposure of hormonal contraceptive. This present study found that majority (72.45%) subjects with Ki-67 below 4% had history of progesterone only contraceptive. The higher rate of Ki-67>7% was found in 7.2% patients had history of progesterone only and 33.3% combined contraceptive. We also revealed that benign meningioma subjects who had low proliferative index, mostly used progesterone only contraceptive. However, statistical analysis showed no significant difference between type, duration and status of contraceptive hormonal used with expression of proliferative index.

The strengths of our study include the use of comprehensive interviews to minimize recall bias. However, several limitations are evident. First, the study included a relatively small sample size due to the application of strict eligibility criteria. Second, the majority of our patients used hormonal contraceptives containing only progesterone. This uneven distribution of subjects across the variables may introduce bias into the study findings.

CONCLUSION

Our findings suggest that exposure to hormonal contraceptive do not influence the expression of PR, ER and Ki-67. But we discover that there is a trend higher of PR expression in patients with history of progesterone only contained hormonal contraceptive. Also, our study reveal that Ki-67 is not significantly different in different grades of meningioma. Further study to investigate the impact of contraceptive hormonal to other biologic markers at molecular or genetic level are strongly needed to clear out the mechanisms.

CONFLICT OF INTEREST

I undersign and certificate that I have / do not have any financial or personal relationships that might bias the content of this work

AUTHOR'S CONTRIBUTIONS

Conceptualization, Y.D., A., D.A.; methodology, Y.D. and R.S.; software, R.S.; validation, Y.D.; formal analysis, Y.D. and R.S.; investigation, D.A. and A.J.; resources, Y.D., D.A., and A.; data curation, Y.D. and D.A.; writing—original draft preparation, Y.D. and R.S.; writing—review and editing, Y.D. and R.S.; visualization, A. and Y.D.; supervision, Y.D. and A.; project administration, Y.D. and A.J.; funding acquisition, Y.D. and A.J. All authors have read and agreed to the published version of the manuscript.

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None declared

Ethical Clearance

This study was approved by Health Research Ethics Committee of Mohammad Hoesin General Hospital Palembang, register under No .04.03/D.XVIII.6.11/ETIK/89/2023

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