ORIGINAL ARTICLE:

Risk of meningioma associated with exposure of hormonal contraception. A case control study

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ABSTRACT

Objective: To determine the effect of hormonal contraceptive exposure on the development of meningioma.
Materials and Methods: This case–control study, conducted in 2016, included all patients diagnosed histopathologically with meningioma between 2012 and 2013 and treated at Dr. Soetomo General Hospital, Surabaya, Indonesia. Medical record data from these patients were collected and compared with a control group consisting of non-meningioma patients who underwent contrast-enhanced head CT scans and direct interviews. A total of 101 cases and 101 controls were analyzed. Data were evaluated using univariate logistic regression analysis.
Results: Patients with a history of hormonal contraceptive use had a 12.31-fold higher risk of developing meningioma (p = 0.000). In this study, women using monthly injectable contraceptives or oral contraceptive pills demonstrated a lower risk of meningioma compared to those using three-month injectable contraceptives. Participants who had used hormonal contraception for more than 10 years had an 18.216-fold increased risk of developing meningioma (p = 0.000). Histopathological analysis revealed no significant association between hormonal contraceptive history and meningioma subtype distribution; however, descriptive data indicated that the transitional type was the most frequent histopathological subtype among the case group.
Conclusion: There is a significant association between hormonal contraceptive use and the occurrence of meningioma, particularly with the use of three-month injectable hormonal contraception and long-term use exceeding 10 years. No significant association was observed between meningioma histopathological grade and a history of hormonal contraceptive exposure.

Keywords: meningioma; hormonal contraception

ABSTRAK

Tujuan: Menilai pengaruh paparan kontrasepsi hormonal terhadap kejadian meningioma.
Bahan dan Metode: Penelitian ini merupakan studi kasus-kontrol yang dilakukan pada tahun 2016 dengan melibatkan seluruh pasien yang terdiagnosis meningioma secara histopatologis pada periode 2012–2013 dan dirawat di RSUD Dr. Soetomo, Surabaya, Indonesia. Data diperoleh dari rekam medis pasien dan dibandingkan dengan kelompok kontrol yang terdiri atas pasien non-meningioma yang menjalani pemeriksaan CT scan kepala dengan kontras serta wawancara langsung. Sebanyak 101 kasus dan 101 kontrol dianalisis. Analisis data dilakukan menggunakan uji regresi logistik univariat.
Hasil: Pasien dengan riwayat penggunaan kontrasepsi hormonal memiliki risiko 12,31 kali lebih tinggi untuk mengalami meningioma dibandingkan dengan yang tidak menggunakan kontrasepsi hormonal (p = 0,000). Pada penelitian ini, pengguna kontrasepsi suntik satu bulan dan pil kontrasepsi memiliki risiko meningioma yang lebih rendah dibandingkan dengan pengguna kontrasepsi suntik tiga bulan. Pasien yang menggunakan kontrasepsi hormonal selama lebih dari 10 tahun menunjukkan peningkatan risiko meningioma sebesar 18,216 kali (p = 0,000). Secara histopatologis, tidak ditemukan hubungan yang bermakna antara riwayat penggunaan kontrasepsi hormonal dan distribusi tipe histopatologi meningioma; namun, data deskriptif menunjukkan bahwa tipe histopatologi yang paling banyak ditemukan pada kelompok kasus adalah tipe transisional.
Simpulan: Terdapat hubungan yang bermakna antara penggunaan kontrasepsi hormonal dengan kejadian meningioma, khususnya pada penggunaan kontrasepsi hormonal suntik tiga bulan dan penggunaan jangka panjang lebih dari 10 tahun. Tidak ditemukan hubungan yang signifikan antara derajat histopatologi meningioma dan riwayat paparan kontrasepsi hormonal.

Kata kunci: Meningioma; kontrasepsi hormonal

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INTRODUCTION

Meningioma is a tumor originating from arachnoid cells (arachnoid cap cells), which are part of the dura mater, and transform into a slow-growing neoplastic lesion. The highest incidence occurs in the fifth and sixth decades of life, with female patients being affected twice as often as males. Most meningiomas are benign tumors, with only about 10% undergoing malignant transformation.[1-3] Harvey Cushing described meningioma as a benign neoplasm arising from the dura mater or meninges.[4] Meningioma represents the most frequently diagnosed primary benign brain tumor. In the United States, between 2002 and 2006, meningiomas accounted for 33.8% of all primary brain and central nervous system tumors.[5] Intracranially, the most common location is along the convexity of the brain.[6] At Dr. Soetomo Hospital in Surabaya, Indonesia, from 2010 to 2011, a total of 138 patients underwent surgery for meningioma, with 122 of them being female.

Females are two to three times more likely to develop meningioma than males, with a ratio of 2–3:1. The growth and progression of meningioma tend to accelerate during pregnancy and the luteal phase of the menstrual cycle. This phenomenon has been hypothesized to involve hormonal pathways (both endogenous and exogenous), particularly the influence of female sex hormones on the growth and development of meningioma.[5,7]

Several studies have reported the effects of exogenous hormone exposure, such as hormonal contraceptives and hormone replacement therapy, on an increased risk of meningioma.[3,5,8] An epidemiological study conducted in Stockholm, Sweden, revealed that women using non-oral hormonal contraceptives had a 2.7-fold higher risk of developing meningioma compared with non-users.[7] In contrast, an epidemiological study from the National Cancer Institute's Surveillance Program in Washington found no significant association between oral contraceptive use and meningioma risk, with oral contraceptive users exhibiting only a 1.5-fold higher risk than non-users.[9]

Although meningioma is considered a clinically and epidemiologically hormone-dependent neoplasm influenced by endogenous and exogenous hormonal factors, it remains unclear whether these factors directly increase its incidence. Overall, the incidence of meningioma is consistently higher in females than in males, with a ratio of 2–3:1.4 Deletion of the Type-2 Neurofibromatosis gene (NF2), exposure to ionizing radiation, and head trauma have been associated with an elevated risk of meningioma. Conversely, the role of sex hormones in influencing meningioma risk remains inconclusive.[9-11] The aim of this study was to analyze the association between hormonal contraceptive use and the incidence of meningioma.

MATERIALS AND METHODS

This research employed a case–control observational design. The case group consisted of all patients diagnosed with meningioma at Dr. Soetomo General Hospital between January 2012 and December 2013 who had undergone surgical intervention, fulfilled the inclusion criteria, and were registered in the hospital's medical record database. The control group comprised non-meningioma patients who had undergone contrast-enhanced head CT scans, met the inclusion criteria (female subjects aged 20–65 years), and were available for direct interviews.

The collected data included information on hormonal contraceptive use, the type of hormonal contraceptive employed, and the duration of hormonal contraceptive utilization. The causal relationship between risk factors and outcomes was determined indirectly by calculating the relative risk, which in a case–control study is expressed as an odds ratio.[12] The study was conducted in 2016.

RESULTS AND DISCUSSION

Data obtained from the medical records of Dr. Soetomo General Hospital from January 2012 to December 2013 revealed 165 cases of meningioma. Based on the inclusion criteria, 101 meningioma cases were included in this study.

Table 1. Age distribution of patients with meningioma

Age (years)	N	%
20-39	23	22.77
40-59	74	73.26
60-79	4	3.96
Total	101	100

The subjects ranged in age from 20 to 65 years, with a mean age of 43.64 years and a median of 43.00 years. The majority of meningioma cases (73.26%) occurred in the 40–59-year age group.

Table 2. Distribution of history of contraceptive use in patients with meningioma

Contraceptive	N	%
Yes	96	95.04
No	5	4.95
Total	101	100

Table 2 shows that 95.04% of patients with meningioma had a history of contraceptive use.

Table 3. Distribution of the history of contraceptive use in patients with meningioma

Contraceptive types	N	%
Hormonal	95	98.95
Non Hormonal	1	1.04
Total	96	100

Table 3 demonstrates that 98.95% of patients with meningioma reported a history of hormonal contraceptive use, while only 1.04% used non-hormonal contraceptives.

Table 4. Distribution of history of the use of hormonal contraceptive type in patients with meningioma

Contraceptive hormones	N	%
Injectable 3 months	84	88.42
Injectable 1 month	1	1.05
Pills	4	4.21
Combination	6	6.31
Total	95	100

Table 4 shows that among 95 meningioma patients who used hormonal contraceptives, 88.42% utilized three-month injectable hormonal contraceptives.

Table 5. Distribution of duration of hormonal contraceptive use of meningioma patients

Duration	N	%
< 10 years	35	36.84
≥ 10 years	60	63.15
Total	95	100

Table 5 indicates that 63.15% of meningioma patients had used hormonal contraceptives for more than 10 years.

Table 6. Histopathological distribution of meningioma patients

No	Histopathology	N	%
1	WHO grade I		
	Angiomatous	2	2.0
	Fibroblastic	10	9.9
	Meningothelial	13	12.8
	Microcystic	3	3
	Psammomatous	1	1
	Transitional	69	68.3
2	WHO grade 2		
	Atypical	3	3.0
	Total	101	100

Table 6 reveals that 97% of meningioma patients had WHO grade 1 histopathologic features, with the transitional type being the most prevalent (68.3%).

Table 7. Histopathological distribution of meningioma patients with a history of hormonal contraceptive use

No	Histopathology	N	%
1	WHO grade I		
	Angiomatous	1	1.05
	Fibroblastic	7	7.36
	Meningothelial	12	12.63
	Microcystic	3	3.15
	Psammomatous	1	1.05
	Transitional	68	71.57
2	WHO grade 2		
	Atypical	3	3.15
	Total	95	100

Table 7 shows that 96.84% of meningioma patients exhibited WHO grade 1 histopathologic distribution, with the transitional subtype accounting for the largest proportion (71.57%), followed by meningothelial (12.63%) and fibroblastic (7.36%) types, while the atypical type (WHO grade 2) represented only 3.15%.

Table 8. Logistic regression and odds ratio of meningioma based on age, history of hormonal contraception, history of hormonal contraceptive type, and duration of hormonal contraceptive use.

Variables	Meningioma	Control	OR (CI 95%)	p
Age				
20-39	23	36		
40-59	74	58	1.997	0.030
60-79	4	7	0.894	0.870
Hormonal contraceptive history				
Hormonal	95	54	12.315	0.000
Non Hormonal	1	12	0.583	0.638
No contraceptive	5	35		
History of contraceptive types				
Injectable 3 mths	84	14		
Injectable 1 mth	1	4	0.042	0.006
Pills	4	21	0.032	0.000
Combination	6	14	0.071	0.000
Contraceptive duration				
No contraceptive	5	35		
<10 years	36	43	5.86	0.001
>10 years	60	23	18.216	0.000

Based on age, individuals aged 40–59 years had a 1.997-fold higher risk of developing meningioma compared to those aged 20–39 years (p = 0.03). In the older age group (60–79 years), the risk was 0.894 times higher; however, this difference was not statistically significant (p = 0.870).

According to the history of hormonal contraceptive use, patients with a history of hormonal contraceptive use had a 12.31-fold higher risk of developing meningioma

(p = 0.000). In contrast, those without contraceptive use had a relative risk of 0.583 compared with users of hormonal contraception, but this difference was not statistically significant (p = 0.638).

The type of contraception also influenced the occurrence of meningioma. In this study, users of one-month injectable contraceptives and oral contraceptive pills had a lower risk of developing meningioma compared with users of three-month injectable contra-ceptives, with risk values of 0.042, 0.032, and 0.071, respectively (p < 0.05). These findings suggest that three-month injectable contraception carries the highest risk compared with other forms.

The duration of contraceptive use likewise affected the risk of meningioma. Patients who had used contraceptives for more than 10 years experienced an 18.216-fold increase in meningioma risk (p = 0.000), whereas those with less than 10 years of use demonstrated a 5.86-fold increase (p = 0.001).

Table 9. Association between hormonal contraceptive use and meningioma grade.

History of contraceptive type	WHO grading (percentage)		p
	WHO grade I	WHO grade II	
Injectable 3 month	81 (96.4%)	3 (3.6%)	1.000
Injectable 1 month	1 (100%)	0 (0.0%)	
Pills	4 (100%)	0 (0.0%)	
Combination	6 (100%)	0 (0.0%)	

There was no significant difference in meningioma malignancy grading among the various types of hormonal contraceptives in the case group (p = 1.000, Eta = 0.065). Patients diagnosed with meningioma from January 2012 to December 2013 who met the inclusion criteria consisted of 101 individuals. The ages of meningioma patients ranged from 20 to 65 years, with a mean of 43.64 years and a median of 43.00 years. The majority of meningioma cases (73.26%) occurred in the 40–49-year age group. This finding is inconsistent with previous reports and literature indicating that the incidence of meningioma increases progressively with age, particularly during the fifth and sixth decades of life.[1,3,5,13] The differing distribution of research data reported in the literature is likely influenced by oncogenic factors or exposure to certain substances that may promote earlier onset of meningioma, as well as by genetic variability. These findings warrant further investigation.

Of the 101 meningioma patients, 95 (95.04%) had a history of hormonal contraceptive use. Among the 95 patients with meningioma who used hormonal contraceptives, 88.42% used three-month injectable hormonal contraceptives. These findings are consistent with data from studies in Sweden conducted between 2000 and 2002, which described the prevalence of oral hormonal contraceptive use among meningioma patients. According to the Interphone study, the proportion of meningioma patients using oral hormonal contraceptives was 75.28%.[7]

Among the 95 meningioma patients with a history of hormonal contraceptive use, 63.15% had used these contraceptives for more than 10 years. This finding suggests that exogenous hormonal influence may play a significant role in meningioma oncogenesis. This observation aligns with the results of several previous studies and existing literature.[3,5,8]

Of the 101 meningioma patients, 97% demonstrated WHO grade 1 histopathologic features, with the transitional subtype being the most frequent (68.3%). Among the 95 meningioma patients with a history of hormonal contraceptive use, 96.84% exhibited WHO grade 1 histopathologic distribution, with the transitional type predominating (71.57%), followed by meningothelial (12.63%) and fibroblastic (7.36%) subtypes.

These findings are consistent with the literature, which identifies meningothelial, transitional, and fibroblastic meningiomas as the three most common histopathologic subtypes. The transitional subtype, histologically characterized as a mixture of meningothelial and fibroblastic components, has not been associated with hormonal exposure, either exogenous or endogenous.[4,10,14] The oncogenic mechanism of meningioma development is likely hormone-driven; however, the progression of neoplastic cells appears unrelated to hormonal factors. Further studies are necessary to elucidate this mechanism.

Based on the history of hormonal contraceptive use, patients who had used hormonal contraceptives demonstrated a 12.31-fold higher risk of developing meningioma compared to those who had never used contraception. This finding is consistent with the study by Wigertz (2006), which reported that long-term use of hormonal contraceptives (including hormonal intrauterine devices, injectable contraceptives, and implants) for more than 10 years was associated with a 2.7-fold increased risk of meningioma.[7] The risk of meningioma has also been shown to rise among women with a history of oral contraceptive use.[8,15]

Laboratory evidence has demonstrated that meningiomas express estrogen receptors (ER) and progesterone receptors (PR), the expression of which may influence prognostic outcomes. Positive PR expression indicates a lower rate of tumor cell proliferation compared to

positive ER expression. The relationship between exogenous hormone use, such as hormonal contraception, and meningioma incidence has been clearly demonstrated in both in vitro and clinical studies, wherein progesterone agonists play a role in meningioma development.[10,16] Hormonal contraceptive preparations containing only progesterone include pills (particularly the minipill), depot injections, intrauterine devices (IUDs), and implants.

This study also demonstrated that the type of contraception influences meningioma onset. Patients who used one-month injectable contraceptives, oral pills, or other hormonal contraceptives had a lower meningioma risk compared to those using three-month injectable contraceptives. This indicates that three-month injectable contraception carries the highest relative risk among the different types studied. Although no previous studies have explicitly stated that three-month injectable contraceptives confer a greater risk than other types, the Swedish Interphone study by Wigertz (2006) reported that non-oral hormonal contraceptives—including implants, injections, and hormonal IUDs—increased the risk of meningioma by 1.5 times (95% confidence interval, 0.9–2.6).[7,17]

The three-month injectable contraceptive, commonly known as Depo-Medroxyprogesterone Acetate (DMPA), contains only progestin and is available in two formulations: 150 mg/mL for intramuscular injection and 104 mg/0.65 mL for subcutaneous injection. In contrast, the one-month injectable contraceptive combines progestin with synthetic estrogens. Progestin prevents pregnancy through several mechanisms, including inhibition of gonadotropin secretion, which suppresses follicular maturation and ovulation, and inhibition of ovarian function, resulting in a hypoestrogenic state that reduces endometrial proliferation and interferes with implantation. Additionally, progestin alters the consistency of cervical mucus and reduces tubal motility.[18]

Since sex hormone receptors have been identified in meningiomas, subsequent studies have shown that attachment to ER is less common than to PR and androgen receptors (AR). PR has been successfully identified in the cytosol of arachnoid granulations. A high PR-positive status serves as a marker of a more favorable meningioma prognosis compared to low PR positivity or ER positivity. This difference is associated with an increased frequency of karyotypic abnormalities, particularly involving chromosomes 14 and 22, as well as higher tumor aggressiveness, progression, and recurrence rates.[10,14]

The duration of contraceptive use also influences meningioma risk. Patients who used contraceptives for more than 10 years had an 18.216-fold increased risk of developing meningioma, while those with less than 10 years of use had a 5.86-fold increase. These results are consistent with Wigertz's findings, which indicated that women with a history of long-term hormonal contraceptive use had a higher risk of developing meningioma, especially with durations exceeding 10 years, with an odds ratio of 2.7 (95% CI 0.9–7.5).[5,7,8] This clearly indicates that prolonged exposure to exogenous hormones (oncogenic stimuli) increases the likelihood of meningioma neoplasia.

With respect to tumor grading, there was no significant correlation between the history of hormonal contraceptive use and meningioma grade. However, descriptively, the most frequent histopathologic subtype observed among patients with a history of hormonal contraceptive use was the transitional type. This finding may be attributed to the fact that WHO grade I transitional meningiomas predominantly express PR (>25%), with minimal ER expression, and a higher ratio of PRB to PRA expression was also identified.[19]

CONCLUSION

The use of hormonal contraceptives and the duration of their use (exceeding 10 years) influenced the risk of developing meningioma; however, hormonal contraceptive use did not affect the histopathological grade of the tumor. Further investigations are warranted to evaluate endogenous factors, such as progesterone and estrogen receptor expression, as well as the genetic profiles of patients with meningioma. Moreover, governmental authorities should be encouraged to adopt more stringent measures in the selection of hormonal contraceptive use among women and to implement monitoring and restrictions on their long-term administration.

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