ORIGINAL ARTICLE:

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

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ABSTRACT

Objective: To identify the effect of hormonal contraceptive exposure to the occurrence of meningioma.
Materials and Methods: This study, conducted in 2016, was a case-control study by collecting a group of cases comprising all patients diagnosed histopathologically with meningioma in 2012-2013 and treated in dr. Soetomo Hospital, Surabaya, Indonesia. Medical record data were analyzed and compared to control group of patients diagnosed with non-meningioma who underwent contrast head ct scan and direct interviews. We obtained 101 cases and 101 controls. Data were analyzed using univariate logistic regression test.
Results: Based on the history of hormonal contraceptive use, patients who had history of hormonal contraceptive use had 12.31 times higher risk (p=0.000). In this study, those who had contraceptive injections for one month and used contraceptive pills had a meningioma risk lower than those who used injectables 3 months. Patients who used hormonal contraception more than 10 years had an increased risk for meningioma as much as 18.216 times (p=0.000). Histopathologically, we found a non-significant association between history of hormonal contraceptive use and the distribution of histopathology, but based on descriptive data showed it was found that the most histopatological meningioma was of the transitional type in cases group.
Conclusion: There is a significant association between hormonal contraceptive use, the type of injectable hormonal contraception for 3 months, the duration of hormonal contraceptive use >10 years, and no significant association between meningioma grade and the history of hormonal contraception exposure.

Keywords: meningioma; hormonal contraception

ABSTRAK

Tujuan: Untuk mengidentifikasi efek paparan kontrasepsi hormonal terhadap terjadinya meningioma.
Bahan dan Metode: Penelitian yang dilakukan pada tahun 2016 ini merupakan penelitian kontrol kasus pada sejumlah dengan diagnosis histopatologi meningioma antara 2012-2013 di RSUD Dr. Soetomo, Surabaya, Indonesia. Data rekam medis dianalisis dan dibandingkan dengan kelompok kontrol yang didiagnosis non-meningioma yang menjalani sken kepala dan wawancara. Diperoleh 101 kasus dan 101 kontrol. Data dianalisis mengguna-kan uji regresi logistik univariat.
Hasil: Berdasarkan riwayat penggunaan kontrasepsi hormonal, pasien yang memiliki riwayat penggunaan kontrasepsi hormonal memiliki risiko 12,31 kali lebih tinggi (p=0,000). Dalam penelitian ini, pengguna KB suntik satu bulan dan pengguna pil KB berisiko meningioma lebih rendah daripada pengguna KB suntik 3 bulan. Pasien pengguna kontrasepsi hormonal lebih dari 10 tahun berpeningkatan risiko meningioma sebanyak 18,216 kali (p=0,000). Secara histopatologi, ditemukan hubungan tidak signifikan antara riwayat penggunaan kontrasepsi hormonal dan distribusi histopatologi, tetapi data deskriptif menunjukkan bahwa histopatologi meningioma terbanyak adalah tipe transisional pada kelompok kasus.
Simpulan: Terdapat hubungan signifikan antara penggunaan kontrasepsi hormonal, jenis KB hormonal suntik selama 3 bulan, lama penggunaan kontrasepsi hormonal >10 tahun, dan tidak terdapat hubungan signifikan antara derajat meningioma dan riwayat paparan kontrasepsi hormonal.

Kata kunci: Meningioma; kontrasepsi hormonal

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INTRODUCTION

Meningioma is a tumor that comes from arachnoid cells (Arachnoid cap cells) which is part of the dura mater and transforming into a slow growing neoplasm cell. The highest incidence occurs in decades 5 to 6 and female patients suffer twice as likely as males. Meningiomas are mostly benign tumors, only 10% have malignant transformation.[1-3] Harvey Cushing wrote that meningioma is a benign neoplasm derived from the dura mater or meninges.[4] Meningioma is the most commonly diagnosed primary benign brain tumor. In the United States since 2002-2006, meningioma frequency reaches 33.8% of all primary tumors in the brain and central nervous system.[5] The location of the meningioma is in the intracranial cavity, the most common is in the head's convexity.[6] In dr. Soetomo Hospital, Surabaya, Indonesia, the number of operated meningioma patients since 2010 to 2011 was as many as 138 cases with 122 female patients.

Females are two to three times more likely to suffer from meningioma than males with a ratio of 2-3: 1. Growth and development of meningioma become faster during pregnancy and lutheal phase during menstruation. This phenomenon is associated with a hormonal (endogenous and exogenous) pathway which remains a hypothesis, ie the influence of female sex hormones on the growth and development of meningioma.[5,7]

Some researchers have described the effects of exogenous hormone use, such as hormonal contraception and or hormone replacement therapy, on an increased risk of meningioma.[3,5,8] Based on an epidemiological study in Stockholm, Sweden, it was reported that women who took non-oral hormonal contraceptives had a 2.7-times increased risk of meningioma compared with those who did not use hormonal contraceptives.[7] In contrast to the results of the epidemiological study in Sweden, epidemiological studies from National Cancer Institute's Surveillance in Washington found no significant association between oral contraceptive use and the risk of meningioma occurrence, where females taking oral contraceptives had a risk of 1.5 times than that of those who did not use oral contraceptives.[9]

Although meningioma is considered a clinically and epidemiologically hormone-fed cancer in endogenous or exogenous hormone use, it is unclear whether these factors increase the incidence of meningioma. In general, meningioma incidence is high in females compared to males with a ratio of 2-3:1.[4] The presence of a deletion of the Type-2 Neurofibromatosis gene (NF2), ionizing radiation, and head trauma is associated with an increased risk of meningioma. On the other hand, sex hormones to date have not definitely influen-ced the incidence of meningioma risk.[9-11] The purpose of this study was to analyze the association between hormonal contraception and the incidence of meningi-oma.

MATERIALS AND METHODS

This study was a case-control observational study, with case study subjects consisting of all meningioma patients at Dr. Soetomo Hospital from January 2012 to December 2013 who had undergone surgery, met the inclusion criteria, and were registered in the medical record of Dr. Soetomo Hospital. The control group was non-meningioma patients who had undergone contrast head CT-scan of meeting inclusion criteria females aged 20-65) and direct interviews were possible.

The data collected included the use of hormonal contraceptives, the type of hormonal contraceptive used, and the duration of hormonal contraceptive use. The causal relationship between risk factors and effect was obtained indirectly by calculating the relative risk that in the case-control study was expressed as odds ratio.[12] The study was conducted in 2016.

RESULTS AND DISCUSSION

Data collected from medical records Dr. Soetomo Hospital from January 2012 to December 2013 showed 165 cases of meningioma. Based on the inclusion criteria we obtained 101 cases of meningioma.

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 samples had age variation from 20 to 65 years with mean 43.64 years and median 43.00 years. Most cases (73.26%) of meningioma occurred in the age group 40-59 years.

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 meningioma cases have a history of contraceptive use.

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

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

Table 3 shows that 98.95% of people with meningioma had a history of hormonal contraceptive use and only 1.04% of the meningioma patients 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 of 95 meningioma patients who used hormonal contraceptives, 88.42% used injectable hormonal contraceptives for 3 months.

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 shows that 63.15% of meningioma patients use hormonal contraceptives for >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 shows that 97% of meningioma patients had a WHO grade 1 histopathologic distribution, mostly the transitional type of 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 have a WHO grade 1 histopathologic distribution, with the highest number being the transitional type of 71.57%, meningothelial 12.63% and 7.36% fibroblastic, while the atypical type is only 3.15% (WHO grade 2).

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

By age, age category of 40-59 years had a risk of developing meningioma 1,997 times higher than age category 20-39 years (p=0.03). In higher age category, that is 60-79 years, the risk of suffering from meningioma of 0.894 times, but the statistical results showed no significance (p=0.870).

Based on the history of hormonal contraceptive use, patients who had hormonal contraceptive use had a risk of 12.31 times higher (p=0.000). When not using contraceptives, the risk of meningioma was 0.583 when compared with those with hormonal use, but the results were not significant (p = 0.638).

This type of contraception has an effect on the onset of meningioma. In this study, 1 month of injectable contraception, pill and contraceptive use had a lower rate of meningioma risk than 3 months of injectable contraceptive use with risk values of 0.042, 0.032, and 0.071, respectively ($p<0.05$). This suggests that 3-month injectable contraception has the highest risk rate compared to others.

Duration of a contraceptive use also affects the risk of meningioma. Patients who use contraceptives with a duration of more than 10 years experienced an increased risk of meningioma as much as 18,216 times ($p = 0.000$). On the use of less than 10 years, the rate fell to 5.86 times ($p = 0.001$).

Table 9. Association between hormonal contraceptive use and meningioma grade

History of contraceptive type	*Grading* WHO (persentage)		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 malignancy grading of meningioma between types of hormonal contraceptives in case group ($p = 1,000$, Eta 0.065). Patients with meningioma from January 2012 to December 2013 who had fulfilled the inclusion criteria consisted of 101 patients. Age of meningioma patients varied from 20 to 65 years with mean 43.64 years and median 43.00 years. Most meningioma cases (73.26%) occurred in the age group 40-49 years. This is inconsistent with previous reports and literatures suggesting that the incidence of meningioma is progressively increasing with age, especially decades 5 and 6.[1,3,5,13] Distinct distributions of research data obtained in the literatures are likely due to the effect of oncogen or substances exposure that promote the onset of earlier meningiomas as well as different genetic profiles. This is stimulating for further studies.

Of 101 meningiomas, 95 (95.04%) of patients had a history of hormonal contraceptive use. Of 95 patients with meningioma who used hormonal contraceptives, 88.42% of them use injectable hormonal contraceptives for 3 months. This data were similar to the description data of oral hormonal contraceptive use in meningioma patients in Sweden in 2000-2002. According to the Interphone study the use of oral hormonal contraceptives in patients with meningioma was 75.28%.[7]

Of 95 meningiomas patients with a history of hormonal contraceptive use, 63.15% of whom used the contraceptive for >10 years. This suggests that exogenous hormonal influences cannot be denied or significant in the oncogenesis of meningioma. This is in accordance with some of the results of studies and the existing literatures.[3,5,8]

Of 101 meningioma patients, 97% of patients had a WHO grade 1 histopathology distribution, with the largest number (68.3%) of the transitional types. Of 95 meningiomas with a history of hormonal contraceptive use, 96.84% had WHO grade 1 histopathologic distributions, with the largest number (71.57%) of transitional type followed by meningothelial (12.63%) and fibroblastic (7.36%) types.

This is in accordance with the literature that mentions the three most common types of meningioma subtypes, the meningothelial, transitional, and fibroblastic types. Transitional meningiomas themselves are histopathologically a mixture of meningothelial and fibroblastic and are not associated with hormonal use, either exogenous or endogenous.[4,10,14] The mechanism of meningioma oncogenesis is likely to be driven by hormones, but the progression of neoplasm cells is not associated with hormones. This needs further studies.

Based on the history of hormonal contraceptive use, patients who had a hormonal contraceptive use had a 12.31 times higher risk than those who did not use contraception. This is in line with Wigertz's (2006) study which states that long-term use of hormonal contraceptives (hormonal IUDs, injectable contraceptives, implant contraceptives) with use of more than 10 years has an increased risk of meningioma of 2.7 times.[7] The risk of meningioma in women with a history of oral contraceptives use has been shown to increase.[8,15]

Laboratory evidence suggests that meningioma has estrogen receptors (ER) and progesterone (PR) receptors. The expression of these receptors also determines the prognostic factor. Positive PR indicates a low proliferation of tumor cells compared to positive ER. Existence of the association between exogenous hormone use, eg, hormonal contraception, with meningioma incidence is clearly proven in vitro or with clinical studies, in which progesterone agonist plays a role in the development of meningioma.[10,16] Contraceptive preparations that contain progesterone only, may be pills (especially minipil), injectable depo, IUDs (intrauterine contraceptives) or implants.

This type of contraception also has an effect on the onset of meningioma. In this study, 1 month of injectable contraception, pill and contraceptive use had a lower rate of meningioma risk than 3 months injectable contraception. This suggests that 3 months inject-

able contraception had the greatest risk rate compared to others. No studies have specified that 3 months injectable contraception has a higher risk than other types of contraception. However, the Swedish Interphone study by Wigertz in 2006 suggested that non-oral hormonal contraceptives such as implants, injections, and hormonal IUDs, increased the risk of meningioma 1.5 (95% degree of confidence, 0.9, 2.6).[7,17]

The content of 3-month injectable contraception, or commonly called Depo-Medroxyprogesterone Acetate (DMPA), is a contraceptive that contain only progestin. There are 2 formulations of 150 mg/ml for intramuscular injection and 104 mg/0.65 ml subcutaneous injection. The 1-month injection contraception contains a combination of progestin and synthetic estrogens. Progestin prevents pregnancy through several mechanisms, which inhibits gonadotropin secretion that inhibits follicular maturation and ovulation and inhibits ovarian function, causing hypoestrogen status, so that endometrial proliferation is inhibited and implantation process is impaired. In addition, progestin also acts by changing the consistency of the cervical mucosa and decreasing tubal motility.[18]

Since sex hormone receptors have been found in meningiomas, further studies have revealed that the attachment to ER is less common than PR and AR. PR itself was successfully identified in the arachnoid granulation cytosol. High positive PR becomes a marker of better prognosis of meningioma than the presence of a low positive PR or a positive ER. This is associated with an increased karyotype abnormality, high involvement of chromosomes 14 and 22 in tumors, and an increase in tumor aggressiveness, progression, and recurrence.[10,14]

The duration of contraception use also affects the risk of meningioma incidence. Patients using contraceptives with a duration of more than 10 years will experience an increased risk of meningioma events as much as 18.216 times. In less than 10 years of use, the figure drops to 5.86. This is consistent with the Wigertz study that women with a history of long-acting hormonal contraceptives have a higher risk of developing meningioma, especially with a duration of> 10 years, with an odds ratio of 2.7 (95% CI 0.9-7.5).[5,7,8] This clearly shows that the longer the exposure of oncogenes (exogenous hormones), the higher the likelihood of neoplasm of meningioma.

Based on the grading, there was no significant correlation between history of hormonal contraception use and meningioma grading. However, descriptively, the widest histopathologically distributed type in patients with a history of hormonal contraceptive use is of the transitional type. This is because WHO meningioma grade I with transitional type mostly express PR (X> 25%) and few express E, also the expression of PRB> PRA was found.[19]

CONCLUSION

The use of hormonal contraceptives and the duration of their use (over 10 years) had an effect on the risk of meningioma, but the use of hormonal contraceptives did not affect the grade of meningioma. Further studies are needed to assess endogenous factors, ie the progresterone and estrogen receptors, as well as genetic profiles in patients with meningioma and governments should be advised to be more selective in hormonal contraceptive use to women and to monitor and limit their long-term use.

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