Supartoto et al., Int J Ophthalmic Pathol 2016, 5:3
DOI: 10.4172/2324-8599.1000183

International Journal of Ophthalmic Pathology

Research Article

A SCITECHNOL JOURNAL

Exposure to Exogenous Female Sex Hormones is Associated with Increased Risk Oforbito-Cranial Meningioma in Females: A Case-Control Study

Agus Supartoto, Indra Tri Mahayana, Reinne Natali Christine, Suhardjo, Angela Nurini Agni and Mohammad Bayu Sasongko*

Abstract

Objective: This study aimed to investigate the association of exposure to exogenous female sex hormones with orbito-cranial meningioma among females.

Methods: This was a case-control study of 115 women (40 orbitocranial meningioma cases and 75 healthy controls). All cases were confirmed by Multi-sliced head CT scan and histopathological examination following the surgical procedure. Age-matched control (±2 years) were meningioma-free, confirmed by clinical examination and head CT-scan. Detailed history of previous hormonal contraception, menstrual cycle, parity history and other demographic data were obtained by interview. The association of hormonal contraception with incident meningioma was estimated using logistic regression, adjusted for education level, age of menarche, length of menstrual cycle and number of parity.

Results: The median age of cases vs. control was 46 vs. 47 years (p=0.92). Cases had older age of menarche (13 vs. 11 years; p<0.001) and had used longer hormonal contraception (55% vs. 27% had used more than 10 years; p=0.005) compared to controls. The use of hormonal contraception containing progesterone was significantly associated with increased risk of orbito-cranial meningioma (Odds Ratio [OR] 2.47; 95% Confidence Interval [CI] 1.08-5.64; P=0.03). Exposure to hormonal contraception for more than 10 years was also significantly associated with increased risk of developing meningioma (OR 3.95, 95%CI 1.67-7.64; p= 0.002). After adjusting for education level, age of menarche, length of menstrual cycle and number of parity, only exposure to hormonal contraception for more than 10 years remained significant.

Conclusion: In this study, the use of hormonal contraception containing progesterone was associated with increased risk of developing orbitocranial meningioma in females. This finding highlights the public health importance of the use of hormonal contraception and suggests that further studies to understand its mechanisms are warranted.

Keywords

Orbitocranial meningioma; Hormonal contraception; Risk factors

***Corresponding author:** Muhammad Bayu Sasongko, MD, M Epi, Ph.D, Department of Ophthalmology, Faculty of Medicine, Universitas Gadjah Mada/ Prof. Dr. Sardjito General Hospital, Jalan Farmako Sekip Utara, Yogyakarta, Indonesia, Tel: +62 274 552850; Fax: +62 274 552850; E-mail: mb.sasongko@ugm.ac.id

Received: June 22, 2016 **Accepted:** July 28, 2016 **Published:** August 03, 2016

Introduction

Meningioma is the most common tumour of all non-malignant brain and central nervous system tumours (53.4%) with the highest incidence rate (7.86 per 100,000 population) [1]. In 2007, it is estimated that over 100,000 women in the United States had been diagnosed with intra-cerebral meningioma and approximately 9000 new cases were diagnosed in women each year [2]. Previous studies have suggested that exposure to female sex hormones may influence the development and growth of brain tumours, particularly meningioma. Consistent with this, higher female to male ratio (2-3:1) in meningioma especially during the female reproductive years, [3] and accelerated growth of the tumour during pregnancy and the luteal phase of menstruation supported this hypothesis [2-4]. Nevertheless, evidence in this regards remain less consistent.

For example, a case-control study nested within the Nurse's Health Cohort Study (NHS) showed that pre-menopausal women using exogenous hormones had more than twice the risk of developing meningioma compared to those who did not [5,6]. On the contrary, the INTERPHONE Study (Sweden, in 2000-2002) demonstrated no significant association between neither the use of oral contraceptives nor its duration and the incidence of meningioma [7]. These opposite findings may be caused by the variations in participant's characteristics or difference in data collection method (e.g. direct interview, retrieval from medical record).

In Indonesia, data from National Health Survey in 2013 showed that there were about 27 million contraceptive users and 16 million of them used exogenous contraceptive hormones intravenously(National Population and Family Planning Board, unpublished data). However, the risk of developing meningioma associated with contraceptive hormones in Indonesia is still unknown. The present study was aimed to investigate the associations of exogenous female sex hormones with the risk of orbitocranial meningioma.

Methods

Study design and population

This was a case-control study of 115 females with orbito-cranial meningioma and healthy controls. We recruited 40 consecutive cases presenting at 3 major tertiary hospitals in Yogyakarta area between 2010- 2014. Cases were defined as females with confirmed orbito-cranial meningioma by histopathological examination following the surgical procedures, either craniotomy or orbitotomy. A total of 75 age-matched (± 2 years old difference), healthy females were recruited as controls. Each of control underwent careful clinical examination by experienced doctor and head CT-Scan to ensure the absence of intracranial tumours. In addition, controls were chosen from females with similar socio-demographic background to cases.

Assessment of reproductive factors and exposure to hormonal contraception

All of participants underwent detailed interview either face-to-face or telephone interview. Patients' characteristics including education level, socio-economic status, occupation, history of marriage, reproductive factors (e.g. age of menarche, number of

parity), and choice of contraception type were obtained using standardized questionnaire. Parity was defined as the number of times a patient has given birth to a fetus with a gestational age of 24 weeks or more (stillborn was also included). Hormonal contraception was divided into progesterone-contained and combined progesterone plus estrogen. This information was obtained from direct questions to the participants about the brand, and then double-checked from the health-care facilities from which the participants received the contraception, if available. Exposure to hormonal contraception and the duration of exposure were interviewed very carefully, using calendar method with major life events as guidance to ensure the accuracy of the information thus minimize the recall bias. Few examples of the questions were "when was your first child born?", "how many weeks/months after he/she was born you started using hormonal contraception?" We repeated the interview twice for exposure to hormonal contraception in cases or control to ascertain that such information was consistent.

Statistical analyses

Age, age of menarche, number of parity were analysed as continuous variables. Length of exposure to hormonal contraception and length of menstrual cycle were treated as categorical variables to reduce the possibility of inaccurate information. The length of exposure to hormonal contraception was categorized into 5 years interval (<5 years, 5-10 years, etc.) and 10 years interval group (<10 years vs. ≥ years). The length of menstrual cycle was grouped into <28 days, 28 days, >28 days and irregular cycle.

Participants' characteristics between cases and control were compared using t-test if continuous or chi-square test if categorical. The association between exposure to exogenous hormones and orbito-cranial meningioma was analysed using logistic regression, adjusted for education level, socio-economic status, age of menarche, length of menstrual cycle, and number of parity.

Results

Table 1 shows the majority of participants' characteristics, reproductive factors, and history of contraception use was similar between cases and controls. Compared to controls, generally cases had mostly lower education level, older age of menarche 13 vs. 11 years; P<0.001) and longer exposure to hormonal contraception (P=0.005).

Table 2 demonstrates the associations of the use of hormonal contraception, progesterone-contained contraception and length of exposure to exogenous hormones. In the unadjusted model, the use of hormonal contraception was not significantly associated with developing meningioma (OR 1.38; P=053). In contrast, the use of progesterone-contained contraception (OR 2.47; P=0.03) and exposure to hormonal contraception of longer than 10 years were significantly associated with increased risk of meningioma (OR 3.95; P=0.002) (Table 2). However, after adjusting for education level, age of menarche, length of menstrual cycle and number of parity, only long exposure to hormonal contraception remained associated with increased risk of meningioma (OR 3.85; P=0.02) (Table 2).

Figures 1 and 2 show that older age of menarche and longer duration of exposure to hormonal contraception were significantly associated with increasing risk of developing orbito-cranial meningioma (P for trend <0.001 and 0.001 respectively).

Discussion

In the present study, we demonstrated that longer duration of hormonal contraception use, but not the mere use of the hormones, were associated with increased risk of meningioma in females, independent of other reproductive factors. Furthermore, we also showed that older age of menarche was also independently associated with higher risk of meningioma.

The relationships between exposure to exogenous hormones and orbito-cranial meningioma have been widely investigated [6,8-16]. However, previous studies demonstrated equivocal conclusion regarding whether the use of exogenous hormones was associated or not associated with increased risk of meningioma. For example, two recent studies by Claus and associates and Korhonen and colleagues suggested that the use of exogenous hormonal therapy was positively associated with intra-cranial meningioma among women [10,13]. On the other hand, there was a study by Custer et al. [9] showing no significant associations between hormonal contraception use and meningioma [9]. Table 3 summarizes previous studies investigating the use of hormonal contraception with risk of meningioma among females. It is shown in Table 3 that most of studies conducted before year 2000 found no significant associations between the use of hormonal contraception and meningioma, while the majority of studies after year 2000 concluded that the use of exogenous hormonal contraception was associated with increased risk of meningioma. Furthermore, our finding that longer duration of hormonal contraception was associated with higher risk of developing meningioma was in line with Michaud et al. [2] which found that women with history of usage of hormonal contraception more than 15 years had significantly increased risk of orbito-cranial meningioma [2].

Our data provide evidence that long exposure, but not only the use of the exogenous hormone, was associated with meningioma. There are little data that showed similar findings to our study. The mechanisms underpinning the relationships between long exposure to exogenous hormones and meningioma development among females has not been fully understood. There is evidence that exogenous progesterone in a long term might alter the in-vivo progesterone level and the expression of progesterone receptors which have wider influence at the genetic level on Merlin, a specific protein in the Neurofibromatosis-2 (NF-2) gene that regulates the growth of neuronal tissue, including meningeal tissue [17]. Therefore, we speculated that this in turn decelerate the function of the Merlin as tumour suppressor genes, specifically in meningeal tissue, and may stimulate overgrowth of the tissue. Further studies exploring the molecular mechanisms of this association are needed.

Strengths of our study include the use of detailed and calendar-method of interview to minimize the recall bias. We included all cases of meningioma from orbito-cranial topography, not only orbital. Both intra-cranial and orbital meningioma's are of the same origin, and thus we increased the variation of our cases. Furthermore, we also include only cases with confirmed histopathological findings of meningioma following the surgery, to eliminate the false positive bias in the cases selection. Nonetheless, limitations of this study are still apparent. First, the possibility of recall bias in this study remained present. Second, we only included relatively small sample size in this study due to our strict eligibility criteria. Yet, the significant associations between variable of interest were still present, suggesting those associations was likely strong [18-22].

Table 1: Baseline characteristics of cases and controls.

Demographic Variables	Cases (N= 40)	Controls (N = 75)	P-value
Age (years), mean ± SD	46,6 ± 6,2	46,5 ± 7,45	0,969
Education level			
Primary	55.0 (22)	16.0 (12)	<0.001
Secondary	35.0 (14)	43.3 (40)	
Tertiary	7.50 (3)	28.0 (21)	
Post-graduate	2.50 (1)	2.67 (2)	
Occupation			
Housewife/ unemployed	72.5 (29)	52.0 (39)	0.07
Employee/ Private sector	5.00 (2)	14.7 (11)	
Government employee	12.5 (5)	28.0 (21)	
Farmer/ self-employed	10.0 (4)	5.30 (4)	
Monthly income (in US$)			
<100	62.5 (25)	62.7 (47)	0.8
100 – 500	27.5 (11)	22.7 (17)	
501 – 1000	10.0 (4)	13.3 (10)	
>1000	0.0 (0)	1.30 (1)	
Marital status			
Single	5.00 (2)	0.0 (0)	0.09
Married	92.5 (37)	90.7 (68)	
Divorced	2.50 (1)	9.30 (7)	
Presenting chief complaints			
Blurred vision	17.5 (7)	29.3 (22)	<0.001
Protruded eye	45.0 (18)	1.33 (1)	
Chronic headache	37.5 (15)	13.3 (10)	
Reproductive factors			
Age of menarche			
<12 years	7.50 (3)	54.7 (41)	<0.001
12 – 15 years	77.5 (31)	41.3 (31)	
>15 years	15.0 (6)	4.00 (3)	
Median (Inter-quartile range)	13 (12-14.5)	11 (11-13)	<0.001
Length of menstrual cycle			
<28 days	0.0 (0)	10.7 (8)	0.005
28 days	87.5 (35)	57.3 (43)	
>28 days	5.00 (2)	13.3 (10)	
Irregular cycle	7.50 (3)	18.6 (14)	
Number of parity, median (IQR)	3 (2 - 4)	3 (3 - 4)	0.03
Contraception use			
Age at first contraception, mean (SD)	23.8 (1.82)	23.3 (4.32)	0.34
Exposure to hormonal contraception			
No	18.4 (7)	23.8 (15)	0.53
Yes	81.6 (31)	76.2 (48)	
Type of contraception			
Hormonal			
Monthly injection	2.60 (1)	17.4 (11)	0.06
3-monthly injection	55.2 (21)	33.3 (21)	
Implant	2.60 (1)	9.50 (6)	
Pills	21.0 (8)	15.9 (10)	
Non-hormonal			
Intra-uterine Device	18.4 (7)	23.8 (15)	
Length of exposure to exogenous hormones			
1-5 years	31.6 (12)	54.0 (34)	0.005
6-10 years	13.2 (5)	22.2 (14)	
10-15 years	21.1 (8)	15.9 (10)	
>15 years	34.2 (13)	7.94 (5)	

Note: All data are in %(N) except indicated as mean (SD)/median (IQR)

Table 2: Associations of exogenous hormonal contraception and duration of contraception with meningioma.

Factors	Model 1		Model 2*	
	Odds Ratio (95%CI)	P-value	OR (95% CI)	P-value
Exposure to hormonal contraception (Yes vs. No)	1.38 (0.50-3.78)	0.53	2,37 (0.69-8.16)	0.17
Hormonal content (Progesterone only vs. Combined progesterone+estrogen)	2.47 (1.08-5.64)	0.03	2.15 (0.75-6.22)	0.16
Duration (≤ 10 vs. >10 years)	3,95 (1,67-7,64)	0.002	3.85 (1.19-12.5)	0.02
Note: *Adjusted for for education level, age of menarche, length of menstrual cycle and number of parity.				

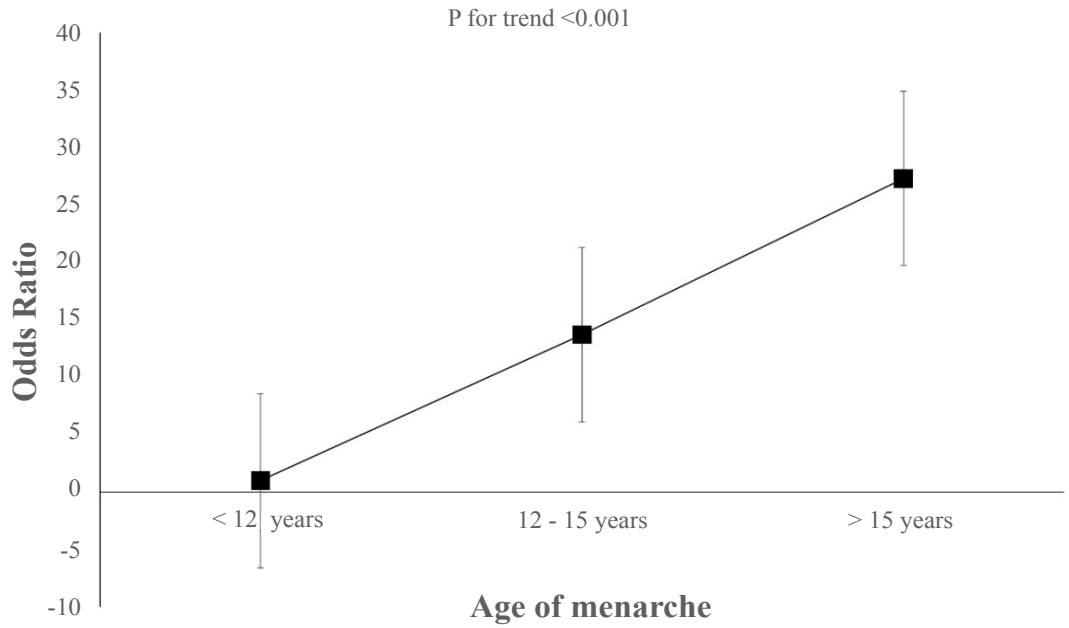

Figure 1: Association of age of menarche with risk of meningioma.

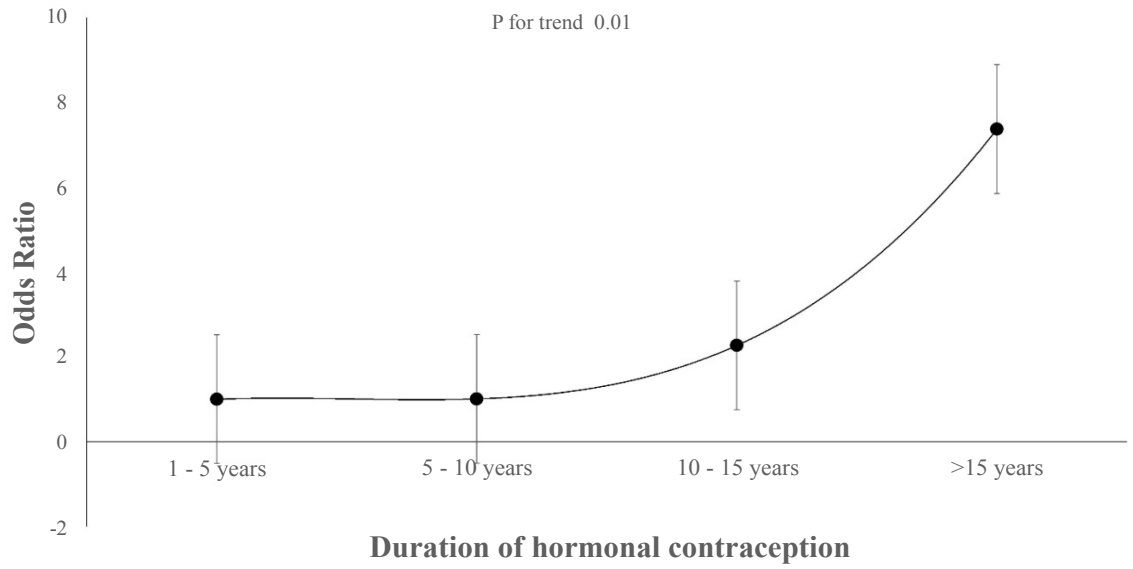

Figure 2: Association of duration of hormonal contraception use with risk of meningioma.

Table 3: Studies investigating the associations of exogenous hormones with orbito-cranial meningioma.

No	Author(s), Year	Study design	Timeframe	Location	Age	Histology Exam	No of cases	No of control	Risks	OR/ RR (95 CI)
1	Custer, Longstreth [9]	Population-based case-control	1995-1998	US (8 states)	≥18	Yes	143	286	OC	2.5 (0.50-12.6)
2	Lee, Grutsch [18]	Hospital-based case-control	1987-1992	US (3 hospitals in Chicago)	Not mentioned	Yes	219	260	OC	0.5 (0.4-0.8); current user: 0.2 (0.0-0.8)
3	Benson, Pirie [19]	Population-based cohort	1996-2005	UK	50-65	Not mentioned	390		OC	5+ years: 1.10 (0.86-1.40)
4	Michaud, Gallo [2]	Prospective cohort	1990-2006	Netherlands, Denmark, Italy, Norway, Spain, Swedia, and UK	Not mentioned	Not mentioned	194		OC	Total: 3.61 (1.75-7.46); pre-menopause: 3.7 (0.88-15.6); post-menopause: 3.54 (1.50-8.37)
5	Korhonen, Raitanen [10]	Population-based case control	2000-2002	Finland	20-69	Yes	264	505	OC	1.33 (0.94-1.89); duration of use 13-48: 2.05 (1.30-3.22)
6	Claus, Calvocoressi [13]	Population-based case control	2006-2011	US (Connecticut, Massachusetts, San Francisco, North Carolina)	29-79	Not mentioned	1127	2404	OC	current user: 1.45 (0.94-2.24)
7	Jhawar, Fuchs [7]	Prospective cohort	1976-1996	US (11 states)	30-55	Not mentioned	125		HRT	Pre-menopause: 2,48 (1,29-4,77); Post-menopause: 1.86 (1.07-3.24); Estrogen and progestin: 1.3 (0.6-2.8)
8	Blitshteyn, Crook [20]	Cross-sectional	1993-2003	US (Mayo clinic)	26-86	No	1390		HRT	2.20 (1.90-2.60); Age 26-55: 4.1 (2.7-6.4)
9	Cea-Soriano, Blenk [21]	Nested case-control	1996-2008	UK	12-89	Not mentioned	745	10000	HRT	Current use of cyproterone acetate and oestrogen combination: 1.51 (0.33-6.86); past use of LHRH agonists: 2.89 (0.30-27.64); current use of androgen analogues: 19.09 (2.81-129.74); Current use of cyproterone acetate: 6.30 (1.37-28.94)
10	Korhonen, Auvinen [22]	Prospective cohort	1994-2009	Finland	≥50	Yes	296		HRT	Estradiol therapy: 1.29 (1.15-1.44)

Conclusion

Our findings suggested that long hormonal contraception use increased the risk of developing orbito-cranialeningioma among females. However, these findings need to be interpreted cautiously as to what extend long exposure to hormonal contraception influence meningioma development. Further studies investigating the role of hormonal receptors and other biologic markers at molecular or genetic level are strongly needed to rule out the mechanisms behind these associations.

Acknowledgement

Funded by research grant from Ministry of Research, Technology and Higher Education- Government of Indonesia.

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Author Affiliation

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Department of Ophthalmology, Faculty of Medicine, Universitas Gadjah Mada/ Dr. Sardjito General Hospital, Yogyakarta, Indonesia