ISSN: 3032-3134 (ONLINE)
InaJBCS | Indonesian Journal of Biomedicine and Clinical Sciences

Increasing quantitative estrogen receptor beta expression in meningioma after exogenous hormonal contraception exposure

Dhimas Hari Sakti[1,3,5]*, Muhammad Bayu Sasongko[1,3,5], Suhardjo Pawiroranu[1,3,5], Didik Setyo Heriyanto[2,4], Indra Tri Mahayana[1,3], Datu Respatika[1,3], Idhayu Anggit Widhasari[1], Prima Sugesty Nurlaila[1,3], Agus Supartoto[1,3,5]

[1]Department of Ophthalmology, Faculty of Medicine, Public Health and Nursing; Universitas Gadjah Mada, Yogyakarta, Indonesia, [2]Department of Pathology, Faculty of Medicine, Public Health and Nursing; Universitas Gadjah Mada, Yogyakarta, Indonesia, [3]Department of Ophthalmology, Dr. Sardjito General Hospital, Yogyakarta, Indonesia, [4]Department of Pathology, Dr. Sardjito General Hospital, Yogyakarta, Indonesia, [5]Dr. Yap Eye Hospital, Yogyakarta, Indonesia

https://doi.org/10.22146/inajbcs.v57i4.19604

Submitted: 2025-01-28
Accepted : 2025-09-26

ABSTRACT

Factors influencing estrogen receptor (ER) and progesterone receptor (PR) expression in meningioma are unclear. This study aimed to assess the expression of ER and PR in females with meningioma in relation to patient exogenous hormonal exposure. Cross-sectional study of females with meningioma in Yogyakarta, Indonesia, between 2010 to 2016 was conducted. Histories were obtained through interviews. Expressions of ERα, ERβ, and PR were assessed from paraffin blocks containing patients' meningioma tissue using real-time quantitative polymerase chain reaction (RT-qPCR). The study identified 28 female meningioma patients with a mean age of 45.6 ± 6.8 yr. Increased ERβ expression was found in the ≥10-yr group of hormonal contraception exposure duration (<10 yr vs ≥10 yr = 7.63 (2.3-11.31) vs 12.56 (1.87-42.22), p=0.038). Positive correlation was found between ERβ expression and the duration of hormonal contraception exposure (r=0.432; p=0.022), especially progesterone-only contraception (r=0.5; p=0.048), while no significant correlation was found between ERβ expression and duration of progesterone-estrogen contraception exposure (r=0.382; p=0.22). No significant analyses were found in ERα and PR. In conclusion, expression of ERβ in meningioma increased in accordance with exogenous hormonal exposure duration, especially progesterone. This finding suggests the importance of ERβ in meningioma and warrants further study as a potential biomarker.

ABSTRAK

Faktor-faktor yang memengaruhi ekspresi reseptor estrogen (ER) dan reseptor progesteron (PR) pada meningioma belum sepenuhnya jelas. Penelitian ini bertujuan untuk menilai ekspresi ER dan PR pada perempuan dengan meningioma yang dikaitkan dengan paparan hormon eksogen. Penelitian potong lintang ini dilakukan pada perempuan dengan meningioma di Yogyakarta, Indonesia, selama periode 2010–2016. Riwayat pasien diperoleh melalui wawancara. Ekspresi ERα, ERβ, dan PR dinilai dari blok parafin jaringan meningioma pasien menggunakan metode *real-time quantitative polymerase chain reaction* (RT-qPCR). Penelitian ini mengidentifikasi 28 pasien perempuan dengan meningioma dengan rata-rata usia 45,6 ± 6,8 tahun. Peningkatan ekspresi ERβ ditemukan pada kelompok dengan durasi paparan kontrasepsi hormonal ≥10 tahun dibandingkan dengan <10 tahun [7,63 (2,3–11,31) vs 12,56 (1,87–42,22), p=0,038]. Terdapat korelasi positif antara ekspresi ERβ dan durasi paparan kontrasepsi hormonal (r=0,432; p=0,022), khususnya kontrasepsi yang hanya mengandung progesteron (r=0,5; p=0,048), sedangkan tidak ditemukan korelasi yang signifikan antara ekspresi ERβ dan durasi paparan kontrasepsi kombinasi progesteron–estrogen (r=0,382; p=0,22). Tidak ditemukan hasil yang signifikan pada ERα dan PR. Simpulan, ekspresi ERβ pada meningioma meningkat seiring dengan lamanya paparan hormon eksogen, terutama progesteron. Temuan ini menunjukkan pentingnya peran ERβ pada meningioma dan mendukung perlunya penelitian lanjutan untuk mengeksplorasi potensinya sebagai biomarker.

Keywords:
meningioma;
estrogen receptor alpha;
estrogen receptor beta;
progesterone receptor;
polymerase chain reaction;
hormonal contraception

*corresponding author: dhimas.hari.s@ugm.ac.id

INTRODUCTION

Meningioma is the most frequent intracranial tumor, which contributes to approximately 30% of all primary brain tumors diagnosed in American adult populations.[1] The overall incidence of meningioma was 4.52 per 100,000, which remarkably shows a significant gender difference (higher in females).[2] Hormonal influences might have a crucial part in the pathophysiology. However, the underlying mechanisms remain debatable.

Hormone replacement therapy (HRT) and hormonal contraception containing estrogen, progesterone, or a combination might elevate meningioma risk.[3-5] On the contrary, another study in HRT and oral contraception (OC) found otherwise, although suggesting that hormone exposure may influence tumor biology in patients with meningioma.[6] Progesterone has been shown to increase the sensitivity of meningeal cells to mitogenic stimulus in culture medium.[7] Furthermore, several reports have shown that the use of progesterone agonists can lead to the development of meningioma, but subsequently shrank following the hormone discontinuation.[8,9] Estrogen also showed its relation to meningioma. There was a reported case of a male-to-female transsexual who developed meningioma after estradiol therapy.[10] These previous studies suggested that estrogen and progesterone, as mostly associated with exogenous hormonal exposure, might have roles in meningioma tumorigenesis.

In non-meningeal tissue, estrogen exposure is known to increase progesterone receptors (PR) and estrogen receptors (ER)[11] while progesterone exposure decreases them.[12, 13] In meningioma, PR is expressed in almost 75% of patients, while ER is only expressed by 11.3%.[14,15] However, studies using the polymerase chain reaction (PCR) test resulted in a higher percentage of ER expression (44% for ERβ and 68% for ERα).[16,17] Estrogen receptor expression in meningioma is important to study as it is correlated with a worse prognosis.[14] Factors influencing the expression of ER and PR remain unclear. However, it is conceivable that the prolonged use of exogenous estrogen and progesterone might affect their expression. ER and PR expression are measured as they might reflect estrogen and progesterone exposure in the tissue.[18] Accordingly, this study aimed to assess the relationships between exogenous estrogen-progesterone exposure and the expression of ER and PR in patients with meningioma.

MATERIAL AND METHODS

Design and subjects

Inclusion criteria of this cross-sectional study were all female patients of reproductive age who underwent tumor removal surgery for meningioma by an ocular oncologist or neurosurgeon between 2010-2016 in Yogyakarta, Indonesia, and had a history of exogenous hormonal exposure from contraception. The diagnosis was established by clinical examination and confirmed by histopathological examination. This study upheld the tenets of the Declaration of Helsinki and was approved by the Ethical Review Board of the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta. Informed consent was obtained from all study participants via telephone or in person. Patients will be excluded if they cannot estimate the duration of hormonal contraceptive use.

Clinical examination and assessment of exposure to exogenous estrogen and progesterone

All of the participants were interviewed face-to-face or by telephone

as described in our previous study.[19,20] Patients' reproductive characteristics (e.g., age of menarche, number of parities), history of breast cancer, choice of contraception type, and duration of contraception use (independent variable) were acquired using a standardized questionnaire. Participants were guided using their major life events to memorize the type and duration of contraceptive use, therefore minimizing the recall bias. Examples of the questions were "How many weeks/months after your last child was born did you start using a hormonal contraceptive? Did you take it monthly or 3-monthly?". The patients' data were then divided into either the progesterone or the progesterone-estrogen group. Early menarche was defined as ≤11 yr, normal as 12-13 yr, and late as ≥14 yr.[21,22] The menstrual cycle was defined according to a previous study.[19] Duration of hormonal exposure was divided into <10 yr and ≥10 yr, as a previous study found an increased risk of meningioma in that cutoff time.[23]

Assessment of meningioma histological type and grade

Pathological examination was conducted on meningioma tissue, then classified and graded according to the World Health Organization (WHO) (independent variable).[24]

Assessment of the levels of ER and PR

Levels of ER and PR were assessed from paraffin blocks of meningioma. Paraffin blocks were sliced 5 μm using a microtome into as many as 7 slices, then the sliced tissues were transferred to a 1.5 ml microcentrifuge tube and followed standardized protocol for real-time quantitative polymerase chain reaction (RT-qPCR). We used Geneaid (Taiwan) reagents for the purpose of RT-qPCR examination, and the results were read using the DTlite Real-Time PCR System (DNA-Technology, Russia). The target sequences for ER-α-forward were: 5'-AGA CAT GAG AGC TGC CAA CC-3' and ER-α-reverse were 5'-GCC AGG CAC ATT CTA GAA GG-3', target sequences for ER-β-forward were 5'-TCA CAT CTG TAT GCG GAA CC-3' and for ER-β-reverse were 5'-CGT AAC ACT TCC GAA GTC GG-3', target sequences for PR-forward were 5'-AGC TCA TCA AGG CAA TTG GTT T-3' and PR-reverse: 5'-ACA AGA TCA TGC AAG TTA TCA AGA AGT T-3'. The expressions of ER and PR (dependent variable) were recorded as the number of expressions compared to non-tumor tissue.

Statistical analyses

Levels of ERα, ERβ, and PR in different characteristic groups were analyzed using Independent-Samples Median tests. Spearman correlation was used to test the correlation between duration of contraceptive use and ERα, ERβ, and PR expressions.

RESULTS

Demography and meningioma types

Our study found 28 female meningioma patients with a mean age of 45.6 ± 6.8 yr. Histological types of the meningioma were divided into microcystic (3/10.7%), meningothelial (10/35.7%), transitional (9/32.1%), fibrous (1/3.6%), angiomatous (1/3.6%), psammomatous (1/3.6%), and atypical (3/10.7%). With this classification, the data consisted of 25 (89%) grade I meningioma and 3 (11%) grade II meningioma (TABLE 1).

TABLE 1. Median of hormone receptor expression among different clinical characteristics

Characteristics	Numbers (%)	ERα# (range)	ERβ~ (range)	PR^ (range)
Age of menarche				
≤11 yo	1 (4)	7.46	3.25	17.15
12-13 yo	14 (50)	5.66 (2.14-13.93)	12.15 (3.48-42.22)	25.42 (2.64-97.01)
≤14 yo	13 (46)	6.96 (2.64-22.63)	10.56 (1.87-18.38)	29.86 (6.06-97.01)
	p	0.242	0.398	0.131
Menstrual cycle				
28 days	24 (86)	6.73 (2.14-22.63)	10.56 (1.87-42.22)	22.68 (2.64-97.01)
>28 days	3 (11)	6.96 (4.59-13.93)	13 (7.46-18.38)	45.25 (6.5-97.01)
Irregular	1 (4)	3.48	2.46	24.25
	p	0.513	0.506	0.472
Parity				
0	1 (4)	5.66	6.06	7.46
1	8 (29)	6.73 (2.14-22.63)	15.69 (4.29-42.22)	39.18 (6.5-97.01)
2	13 (46)	6.96 (2.64-13.93)	10.56 (1.87-42.22)	29.86 (2.64-84.45)
3	4 (14)	6.98 (4.29-12.13)	8.08 (3.25-16)	17.76 (16-27.86)
4	2 (7)	6.83 (5.66-8)	11.4 (5.66-17.15)	17.52 (13.93-21.11)
	p	0.898	0.334	0.268
Breast tumor history				
Positive	2 (7)	4.97 (4.29-5.66)	17.59 (9.19-25.99)	18.93 (8-29.86)
Negative	26 (93)	6.96 (2.14-22.63)	10.56 (1.87-42.22)	24.25 (2.64-97.01)
	p	0.481	1	1
Hormonal contraception type				
Progesterone	16 (57)	6.73 (2.64-13.93)	8.33(1.87-42.22)	19.75 (2.64-97.01)
Progesterone and estrogen	12 (43)	6.73 (2.14-22.63)	11.31 (2.46-42.22)	27.05 (6.50-84.45)
	p	1	0.445	0.704
Hormonal contraception exposure duration				
<10 yr	8 (29)	6.5 (5.66-13.93)	7.63 (2.3-11.31)	23.5 (7.46-32)
≥10 yr	20 (71)	6.96 (2.14-22.63)	12.56 (1.87-42.22)	24.25 (2.64-97.01)
	p	0.678	0.038*	1.00
Meningioma grade				
I	25 (89)	6.96 (2.14-22.63)	10.56 (1.87-42.22)	24.25 (2.64-97.01)
II	3 (11)	6.5 (5.66-8)	11.31 (2.3-17.15)	29.86 (13.93-32)
	p	1	0.583	1
Meningioma histological types				
Microcystic	3 (10.7)	5.66 (4.29-5.66)	6.06 (4.29-6.96)	18.38 (7.46-97.01)
Meningothelial	10 (35.7)	6.96 (3.48-12.13)	9.87 (1.87-42.22)	22.68 (6.06-84.45)
Transitional	9 (32.1)	6.96 (2.14-13.93)	13 (3.48-19.7)	29.86 (2.64-97.01)
Fibrous	1 (3.6)	4.59	7.46	45.25
Angiomatous	1 (3.6)	22.63	4.29	48.5
Psammomatous	1 (3.6%)	6.96	42.22	8
Atypical	3 (10.7%)	6.5 (5.66-8)	11.31 (2.3-17.15)	29.86 (13.93-32)
	p	0.355	0.267	0.653

*Statistically significant with Independent-samples median test.
Estrogen receptor-α
~ Estrogen receptor-β
^ Progesterone receptor

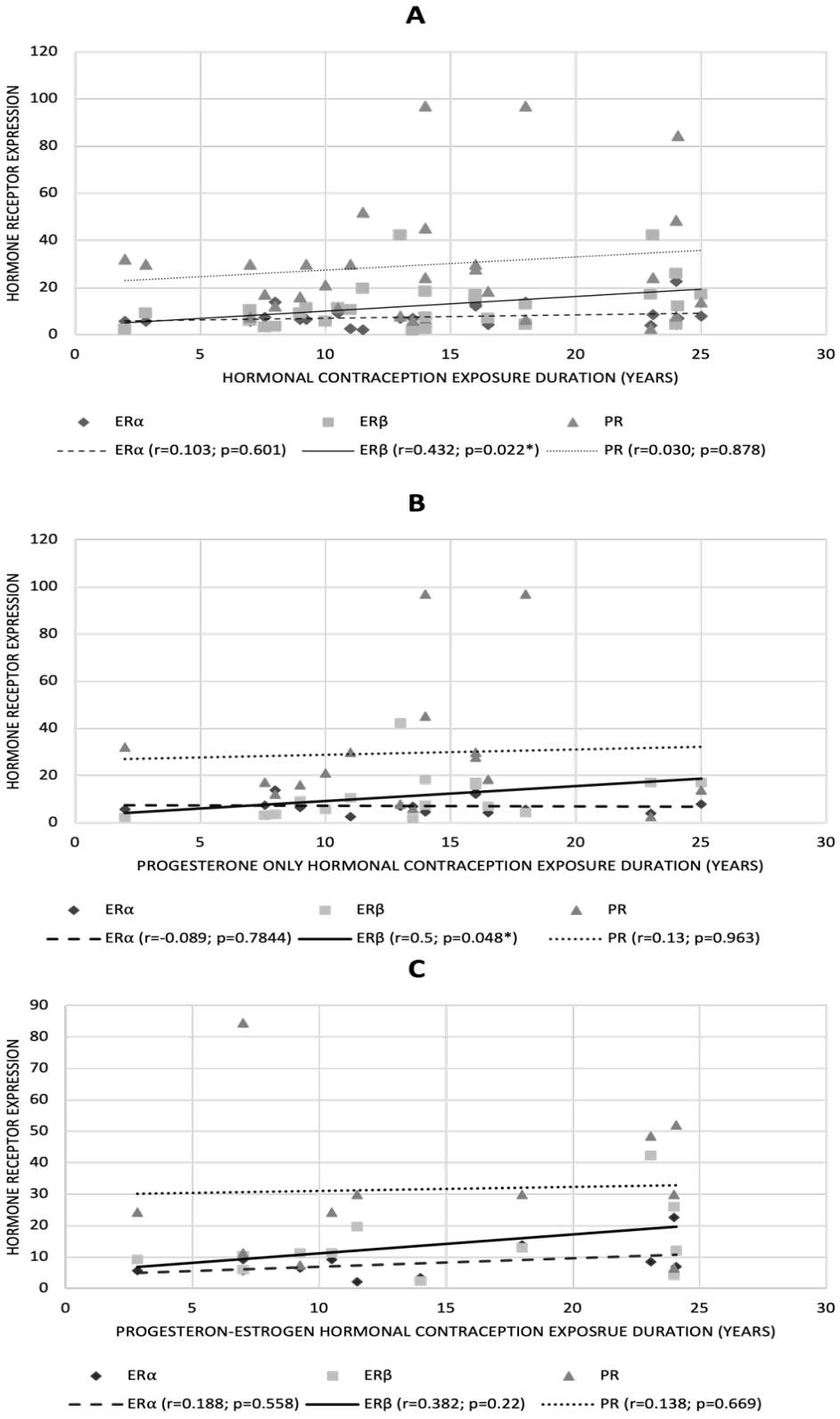

FIGURE 1. Correlation between duration of hormonal contraception exposure and hormone receptor expression. (A) All hormonal contraception (n=28). (B) Progesterone-only hormonal contraception (n=16). (C) Progesterone-estrogen hormonal contraception (n=12). *Statistically significant with the Spearman test.

Hormonal receptor expression

There were no statistically significant differences in hormonal expression between groups based on age at menarche, menstrual cycle, parity, breast tumor history, hormonal contraception type, meningioma grade, and histological types (TABLE 1). Expression of ERβ was significantly higher in the ≥10-yr group of hormonal contraception exposure duration when compared to the <10-yr group [12.56 (1.87-42.22) vs 7.63 (2.3-11.31), p=0.038]. However, expressions of ERα and PR were similar in both groups (p>0.05) (TABLE 1).

The expression of ERβ also showed significant correlation with the duration of hormonal contraception (r=0.432; p=0.022) (FIGURE 1A). On the other hand, we found no significant correlation between ERα and PR expression with the duration of hormonal contraception (p>0.05) (FIGURE 1A). Furthermore, a significant positive correlation between ERβ expression and duration of hormonal contraception use was found in the progesterone-only group (r=0.5; p=0.048) (FIGURE 1B) but not in the progesterone-estrogen combination group (r=0.382; p=0.22) (FIGURE 1C).

DISCUSSION

The present study, to our knowledge, is the first research in Indonesia to address the findings of ERα, ERβ, and PR expression in correlation to exogenous hormonal use in meningioma using RT-qPCR. RT-qPCR was often used in meningioma studies to detect gene or protein expression, but not for ER and PR expression.[25,26]

We found that the expression of ERβ, but not ERα and PR, was significantly higher in the ≥ 10-yr group of hormonal contraception exposure duration. Positive correlation was also found between ERβ expression, not Erα, and PR, and duration of hormonal contraception exposure, especially the progesterone exposure (TABLE 1 & FIGURE 1). This was contradictory to previous studies in other tissue types. Progesterone exposure was discovered to decrease ER in the hypothalamus and uterus of rats,[12,27] and specifically decrease ERβ in the hippocampus.[28] Meningioma tissue may have its own unique properties when exposed to progesterone.

Research on ERβ in relation to meningioma is scarce. ERβ mediates suppressive effect and inhibits proliferation in glioma, breast cancer, prostate cancer, colon, and lung; therefore, it has a potential for safer therapy development since targeting ERα has mammotrophic and uterotrophic effects.[29-31] Furthermore, ERβ expressions in overall brain cancer suggest less aggressive pathology.[32] Glioma and meningioma are often studied together with the same intervention and the same outcome.[33,34] In other studies, it was found that external hormone exposure increases meningioma risk, while it has no effect or is protective for glioma.[35,36] Nevertheless, whether the ERβ effect on meningioma is similar or reciprocal to glioma or other tumors remains elusive.

Expression of ERβ in endometriosis is increased by hypoxia-inducible factor-1α (HIF-1α)-mediated hypoxia.[37] Knockdown of HIF-1α diminished hypoxia-induced ERβ and escalated ERα.[37] Hypoxia was also known to down-regulate ERα in human breast cancer cells by an HIF-1α mediated process.[38] HIF-1α was discovered to be involved in meningioma progression via hypoxic peritumoral brain edema,[39] and it also has some role in tumor angiogenesis.[40] Conversely, overexpression of HIF-3α4 (negative regulator of HIF-1α) might suppress meningioma tumor activities.[41] Therefore, we assumed that in the event of hypoxic meningioma, ERβ might increase while ERα decreases. Since ERβ is upregulated by HIF-1α while HIF-1α itself is the sign of hypoxia and angiogenesis,

ERβ might become the biomarker of the hypoxic process or angiogenesis involved in meningioma. Especially in the event of progesterone exposure, we found a consistent significant correlation in progesterone-only exposure and ERβ expression (FIGURE 1B). This finding is in concordance with a study conducted by Kalamarides *et al.*[9] that found the cessation of progesterone in meningioma resulted in tumor shrinkage and devascularization, and with a study by Harland *et al.*[42] that found an association between progesterone-only contraception with shorter progression-free grade I meningioma.

Our study did not find any significant correlation between ERα-PR and external hormone exposure. It was in accordance with previous studies on non-meningioma cells exposed to progesterone that showed decreased ER and PR expression.[12,13] These studies described ER without dividing it into ERα and ERβ. Previous studies have also shown that a high ERβ to ERα ratio in endometrial cells was associated with suppressed PR, suggesting ERα and PR had a significant correlation.[43,44] A review of ERβ in breast cancer suggests that ERβ exhibits a repressive effect on ERα mediated transcriptional activity when coexisting with ERα.[45] It was also found that ERβ has an antiproliferative effect when exposed to ERα positive breast cancer cells, possibly by initiating the degradation of ERα.[46] The previous data suggested that our finding might be attributable to the suppression of ERα and PR by ERβ.

We found no significant difference in hormone receptor expressions based on age at menarche, menstrual cycle, and parity. Currently, to our knowledge, there are no previous studies describing differences in hormone receptors in meningioma among age at menarche, menstrual cycle, and parity. However, there are several studies describing it in other tissues. ER-PR expressions were studied in breast cancer among different ages at menarche and showed no difference.[47] On the contrary, early menarche was associated with ER-PR-positive breast cancer in another study.[48] ER-PR expressions were studied in the uterus during the actual menstrual cycle and found different expressions among layers and phases.[49] Increased parities were related to ER-PR negative breast cancer and protective against ER-PR positive breast cancer.[50,51]

We also did not find any significant difference in hormone receptor expressions among breast cancer history, meningioma grades, and histological types. One possible cause included an unbalanced number in each group. The association between breast cancer and meningioma in females has been described with ER-negative-PR-positive expression in the meningioma.[52] However, this previous study did not compare it to meningioma tissue in non-breast cancer patients. Previous studies showed PR positive and ER negative in lower-grade meningioma, while PR negative and ER positive were found in higher grades.[53,54] These previous findings may be due to the use of IHC, which had lower sensitivity than PCR.

Recall bias might become one of the limitations of this study since the patients were interviewed after several years of using the hormonal contraception. However, it was minimized using a standardized questionnaire. The second limitation is that this study lacked data on patients' age at the time of tumor removal surgery, which may add bias to the data interpretation.

CONCLUSION

In conclusion, our study demonstrated positive correlations between hormonal exposure duration, especially progesterone, and ERβ expression. These findings suggest that ERβ expression may have an important

role as a meningioma tumorigenesis biomarker, presumably reflecting hypoxia or the angiogenesis process. Further study involving multiple measurements of ERβ expression in the blood of patients with active meningioma might be needed to clarify our findings.

DECLARATION

Ethics approval and consent to participate: This study upheld the tenets of the Declaration of Helsinki and was approved by the Ethical Review Board of the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada. Informed consent was obtained from all study participants via telephone or in person.

Consent for publication: not applicable

Data availability: Data is available upon request.

Funding: This study was funded by a University Research Excellence Grant, Ministry of Higher Education and Scientific Research, Indonesia. The source of funding was not involved in the study design and analysis.

Conflicts of Interest

The authors declare that they have no conflict of interest.

ACKNOWLEDGEMENTS

The authors want to thank the ophthalmology clinic nurse and pathology laboratory assistant for their help with this study.

REFERENCES

1. Wiemels J, Wrensch M, Claus EB. Epidemiology and etiology of meningioma. J Neurooncol 2010; 99(3):307-14. https://doi.org/10.1007/s11060-010-0386-3
2. Barnholtz-Sloan JS, Kruchko C. Meningiomas causes and risk factors. Neurosurg Focus 2007; 23(4):e2. https://doi.org/10.3171/FOC-07/10/E2
3. Qi ZY, Shao C, Huang YL, Hui GZ, Zhou YX, Wang Z. Reproductive and exogenous hormone factors in relation to risk of meningioma in women: A meta-analysis. PLoS One 2013; 8(12):e83261. https://doi.org/10.1371/journal.pone.0083261
4. Wigertz A, Lonn S, Mathiesen T, Ahlbom A, Hall P, Feychting M, *et al*. Risk of brain tumors associated with exposure to exogenous female sex hormones. Am J Epid 2006; 164(7):629-36. https://doi.org/10.1093/aje/kwj254
5. Shu X, Jiang Y, Wen T, Lu S, Yao L, Meng F. Association of hormone replacement therapy with increased risk of meningioma in women: A hospital-based multicenter study with propensity score matching. Asia Pac J Clin Oncol 2019; 15(5):e147-e53. https://doi.org/10.1111/ajco.13138
6. Custer B, Longstreth WTJr, 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; 6:152. https://doi.org/10.1186/1471-2407-6-152
7. Koper JW, Foekens JA, Braakman R, Lamberts SWJ. Effects of progesterone on the response to epidermal growth factor and other growth factors in cultured human meningioma cells. Cancer Res 1990; 50(9):2604-7.
8. Shimizu J, Matsumoto M, Yamazaki E, Yasue M. Spontaneous regression of an asymptomatic meningioma associated with discontinuation of progesterone agonist administration. Neurol Med Chir 2008; 48(5):227-30. https://doi.org/10.2176/nmc.48.227

9. Kalamarides M, Peyre M. Dramatic shrinkage with reduced vascularization of large meningiomas after cessation of progestin treatment. World Neurosurg 2017; 101:814 e7- e10. https://doi.org/10.1016/j.wneu.2017.03.013
10. Deipolyi AR, Han SJ, Parsa AT. Development of a symptomatic intracranial meningioma in a male-to-female transsexual after initiation of hormone therapy. J Clin Neurosci 2010; 17(10):1324-6. https://doi.org/10.1016/j.jocn.2010.01.036
11. Ing NH, Tornesi MB. Estradiol up-regulates estrogen receptor and progesterone receptor gene expression in specific ovine uterine cells. Biol Reprod 1997; 56(5):1205-15. https://doi.org/10.1095/biolreprod56.5.1205
12. Brown TJ, MacLusky NJ. Progesterone modulation of estrogen receptors in microdissected regions of the rat hypothalamus. Mol Cell Neurosc 1994; 5(3):283-90. https://doi.org/10.1006/mcne.1994.1033
13. Read LD, Snider CE, Miller JS, Greene GL, Katzeneilenbogen BS. Ligand-modulated regulation of progesterone receptor messenger ribonucleic acid and protein in human breast cancer cell lines. Mol Endocrinol 1988; 2(3):263-71. https://doi.org/10.1210/mend-2-3-263
14. Agopiantz M, Carnot M, Denis C, Martin E, Gauchotte G. Hormone receptor expression in meningiomas: A systematic review. Cancers (Basel) 2023; 15(3):980. https://doi.org/10.3390/cancers15030980
15. Leaes CGS, Meurer RT, Coutinho LB, Ferreira NP, Pereira-Lima JFS, da Costa Oliveira M. Immunohistochemical expression of aromatase and estrogen, androgen and progesterone receptors in normal and neoplastic human meningeal cells. Neuropathology 2010; 30(1):44-9. https://doi.org/10.1111/j.1440-1789.2009.01047.x
16. Carroll RS, Zhang J, Black PM. Expression of estrogen receptors alpha and beta in human meningiomas. J Neurooncol 1999; 42(2):109-16. https://doi.org/10.1023/a:1006158514866
17. Speirs V, Boyle-Walsh E, Fraser WD. Constitutive co-expression of estrogen and progesterone receptor mRNA in human meningiomas by RT-PCR and response of in-vitro cell cultures to steroid hormones. Int J Cancer 1997; 72(5):714-9. https://doi.org/10.1002/(sici)1097-0215(19970904)72:5<714::aid-ijc2>3.0.co;2-v
18. Chen P, Li B, Ou-Yang L. Role of estrogen receptors in health and disease. Front Endocrinol (Lausanne) 2022; 13:839005. https://doi.org/10.3389/fendo.2022.839005
19. 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. Front Oncol 2019; 8:651. https://doi.org/10.3389/fonc.2018.00651
20. Supartoto A, Mahayana IT, Heriyanto DS, Sasongko MB, Respatika HD, Sakti DH, *et al*. Neurofibromatosis type 2 gene mutation and progesterone receptor messenger RNA expression in the pathogenesis of sporadic orbitocranial meningioma. Int J Ophthalmol 2019; 12(4):571-6. https://doi.org/10.18240/ijo.2019.04.07
21. Rudra CL, Williams MA. BMI as a modifying factor in the relations between age at menarche, menstrual cycle characteristics, and risk of preeclampsia. Gynecol Endocrinol 2005; 21(4):200-5. https://doi.org/10.1080/09513590500168431

22. Abetew DF, Enquobahrie DA, Dishi M, Rudra CB, Miller RS, Williams MA. Age at menarche, menstrual characteristics, and risk of preeclampsia. ISRN Obstet Gynecol 2011; 2011:472083. https://doi.org/10.5402/2011/472083
23. Andersen L, Friis S, Hallas J, Ravn P, Schroder HD, Gaist D. Hormone replacement therapy increases the risk of cranial meningioma. Eur J Cancer 2013; 49(15):3303-10. https://doi.org/10.1016/j.ejca.2013.05.026
24. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, *et al*. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. Acta Neuropathol 2016; 131(6):803-20. https://doi.org/10.1007/s00401-016-1545-1
25. Spiegl-Kreinecker S, Lotsch D, Neumayer K, Kastler L, Gojo J, Pirker C, *et al*. TERT promoter mutations are associated with poor prognosis and cell immortalization in meningioma. Neuro Oncol 2018; 20(12):1584-93. https://doi.org/10.1093/neuonc/noy104
26. Ke HL, Ke RH, Li ST, Li B, Lu HT, Wang XQ. Expression of RACGAP1 in high grade meningiomas: A potential role in cancer progression. J Neurooncol 2013; 113(2):327-32. https://doi.org/10.1007/s11060-013-1121-7
27. Smanik EJ, Calderon JJ, Muldoon TG, Mahesh VB. Effect of progesterone on the activity of occupied nuclear estrogen receptor in vitro. Mol Cell Endocrinol 1989; 64(1):111-7. https://doi.org/10.1016/0303-7207(89)90071-3
28. Aguirre C, Jayaraman A, Pike C, Baudry M. Progesterone inhibits estrogen-mediated neuroprotection against excitotoxicity by down-regulating estrogen receptor-beta. J Neurochem 2010; 115(5):1277-87. https://doi.org/10.1111/j.1471-4159.2010.07038.x
29. Nilsson S, Gustafsson JA. Estrogen receptors: therapies targeted to receptor subtypes. Clin Pharmacol Ther 2011; 89(1):44-55. https://doi.org/10.1038/clpt.2010.226
30. Zhou M, Sareddy GR, Li M, Liu J, Luo Y, Venkata PP, *et al*. Estrogen receptor beta enhances chemotherapy response of GBM cells by down regulating DNA damage response pathways. Sci Rep 2019; 9(1):6124. https://doi.org/10.1038/s41598-019-42313-8
31. Warner M, Gustafsson JA. The role of estrogen receptor beta (ERbeta) in malignant diseases--a new potential target for antiproliferative drugs in prevention and treatment of cancer. Biochem Biophys Res Commun 2010; 396(1):63-6. https://doi.org/10.1016/j.bbrc.2010.02.144
32. Gallo D, Stefano ID, Prisco MG, Scambia G, Ferrandina G. Estrogen receptor beta in cancer an attractive target for therapy. Curr Pharm Des 2012; 18(19):2734-57. https://doi.org/10.2174/138161212800626139
33. Benson VS, Pirie K, Green J, Casabonne D, Beral V, Million Women Study C. Lifestyle factors and primary glioma and meningioma tumours in the million women study cohort. Br J Cancer 2008; 99(1):185-90. https://doi.org/10.1038/sj.bjc.6604445
34. Schüz J, Böhler E, Berg G, Schlehofer B, Hettinger I, Schlaefer K, *et al*. Cellular phones, cordless phones, and the risks of glioma and meningioma (Interphone Study Group, Germany). Am J Epid 2006; 163(6):512-20. https://doi.org/10.1093/aje/kwj068
35. Michaud DS, Gallo V, Schlehofer B, Tjonneland 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 Epidemiol Biomarkers Prev 2010; 19(10):2562-9. https://doi.org/10.1158/1055-9965.EPI-10-0447
36. Cowppli-Bony A, Bouvier G, Rue M,

Loiseau H, Vital A, Lebailly P, *et al*. Brain tumors and hormonal factors: Review of the epidemiological literature. Cancer Causes Control 2011; 22(5):697-714. https://doi.org/10.1007/s10552-011-9742-7
37. Wu M-H, Lu C-W, Chang F-M, Tsai S-J. Estrogen receptor expression affected by hypoxia inducible factor-1a in stromal cells from patients with endometriosis. Taiwan J Obstet Gynecol 2012; 51(1):50-4. https://doi.org/10.1016/j.tjog.2012.01.010
38. Cho J, Kim D, Lee S, Lee Y. Cobalt chloride-induced estrogen receptor alpha down-regulation involves hypoxia-inducible factor-1alpha in MCF-7 human breast cancer cells. Mol Endocrinol 2005; 19(5):1191-9. https://doi.org/10.1210/me.2004-0162
39. Reszec J, Hermanowicz A, Rutkowski R, Bernaczyk P, Mariak Z, Chyczewski L. Evaluation of mast cells and hypoxia inducible factor-1 expression in meningiomas of various grades in correlation with peritumoral brain edema. J Neurooncol 2013; 115(1):119-25. https://doi.org/10.1007/s11060-013-1208-1
40. Pugh CW, Ratcliffe PJ. Regulation of angiogenesis by hypoxia role of the HIF system. Nat Med 2003; 9(6):677-84. https://doi.org/10.1038/nm0603-677
41. Ando H, Natsume A, Iwami K, Ohka F, Kuchimaru T, Kizaka-Kondoh S, *et al*. A hypoxia-inducible factor (HIF)-3alpha splicing variant, HIF-3alpha4 impairs angiogenesis in hypervascular malignant meningiomas with epigenetically silenced HIF-3alpha4. Biochem Biophys Res Commun 2013; 433(1):139-44. https://doi.org/10.1016/j.bbrc.2013.02.044
42. 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. J Neurooncol 2018; 136(2):327-33. https://doi.org/10.1007/s11060-017-2656-9
43. Xue Q, Lin Z, Cheng YH, Huang CC, Marsh E, Yin P, *et al*. Promoter methylation regulates estrogen receptor 2 in human endometrium and endometriosis. Biol Reprod 2007; 77(4):681-7. https://doi.org/10.1095/biolreprod.107.061804
44. Bulun SE, Monsavais D, Pavone ME, Dyson M, Xue Q, Attar E, *et al*. Role of estrogen receptor-beta in endometriosis. Semin Reprod Med 2012; 30(1):39-45. https://doi.org/10.1055/s-0031-1299596
45. Haldosen LA, Zhao C, Dahlman-Wright K. Estrogen receptor beta in breast cancer. Mol Cell Endocrinol 2014; 382(1):665-72. https://doi.org/10.1016/j.mce.2013.08.005
46. Zhao C, Matthews J, Tujague M, Wan J, Strom A, Toresson G, *et al*. Estrogen receptor beta2 negatively regulates the transactivation of estrogen receptor alpha in human breast cancer cells. Cancer Res 2007; 67(8):3955-62. https://doi.org/10.1158/0008-5472.CAN-06-3505
47. Zhou X-L, Fan W, Yang G, Yu M-X. The clinical significance of PR, ER, NF-B, and TNF-alpha in breast cancer. Dis Markers 2014; 2014:494581. https://doi.org/10.1155/2014/494581
48. Ritte R, Lukanova A, Tjonneland A, Olsen A, Overvad K, Mesrine S, *et al*. Height, age at menarche and risk of hormone receptor-positive and -negative breast cancer: A cohort study. Int J Cancer 2013; 132(11):2619-29. https://doi.org/10.1002/ijc.27913
49. Englund K, Blanck A, Gustavsson I, Lundkvist U, Sjöblom P, Norgren A, *et al*. Sex steroid receptors in human myometrium and fibroids: changes during the menstrual cycle and gonadotropin-releasing hormone treatment. J Clin Endocrinol Metab

1998; 83(11):4092-6. https://doi.org/10.1210/jcem.83.11.5287
50. Palmer JR, Boggs DA, Wise LA, Ambrosone CB, Adams-Campbell LL, Rosenberg L. Parity and lactation in relation to estrogen receptor negative breast cancer in African American women. Cancer Epidemiol Biomarkers Prev 2011; 20(9):1883-91. https://doi.org/10.1158/1055-9965.EPI-11-0465
51. Lord SJ, Bernstein L, Johnson KA, Malone KE, McDonald JA, Marchbanks PA, *et al*. Breast cancer risk and hormone receptor status in older women by parity, age of first birth, and breastfeeding: A case-control study. Cancer Epidemiol Biomarkers Prev 2008; 17(7):1723-30. https://doi.org/10.1158/1055-9965.EPI-07-2824
52. Kubo M, Fukutomi T, Akashi-Tanaka S, Hasegawa T. Association of breast cancer with meningioma: report of a case and review of the literature. Jpn J Clin Oncol 2001; 31(10):510-3. https://doi.org/10.1093/jjco/hye109
53. Mukhopadhyay M, Das C, Kumari M, Sen A, Mukhopadhyay B, Mukhopadhyay B. Spectrum of meningioma with special reference to prognostic utility of ER,PR and Ki67 expression. J Lab Physicians 2017; 9(4):308-13. https://doi.org/10.4103/JLP.JLP_158_16
54. Hua L, Zhu H, Li J, Tang H, Kuang D, Wang Y, *et al*. Prognostic value of estrogen receptor in WHO Grade III meningioma: A long-term follow-up study from a single institution. J Neurosurg 2018; 128(6):1698-706. https://doi.org/10.3171/2017.2.JNS162566