Neurology Asia 2023; 28(1) : 1 – 11

VIEWS AND REVIEW

Estrogen and progesterone in meningioma: Bridging the gap of knowledge

Syaiful Ichwan, Fabianto Santoso, Renindra Ananda Aman, David Tandian, Ande Fachniadin, Setyo Widi Nugroho

Department of Neurosurgery Faculty of Medicine Universitas Indonesia – Dr. Cipto Mangunkusumo National General Hospital, Jakarta, Indonesia.

Abstract

Meningiomas are primary central nervous system tumor with the highest prevalence. Meningiomas have a high recurrence rate in the same location. One of the factors thought to be associated with the frequency of meningiomas is hormonal status. However, research on this subject is still controversial. This review aims to discuss the effect of sex hormones on meningiomas. Sex hormones, especially progesterone, have been shown to play a role in tumorigenesis and meningioma recurrence. Progesterone receptors also play a role in meningioma recurrence where a low number of receptors indicates a poor prognosis. However, the molecular relationship between meningiomas at low progesterone receptor expression is still unknown. Further research is still needed to determine the role of sex hormones, especially progesterone, and their receptors, in both tumorigenesis and meningioma progression. This research ensures that new science in the field of endocrinology can be utilized for both primary preventive, secondary preventive, and therapeutic strategies for meningiomas.

Keywords: Progesterone, estrogen, meningioma

INTRODUCTION

Meningioma is the primary central nervous system tumor with the highest prevalence recorded. According to the worldwide data available in epidemiology, meningioma occupies 14.3% to 19% of the entire primary intracranial neoplasms; some even state that prevalence may reach up to 30%.[1,2] Epidemiologic data of meningioma in Indonesia is not well published. Data from RSUPN Dr. Cipto Mangunkusumo, Jakarta, Indonesia, revealed that meningioma makes up 58% of primary brain tumors, followed by 24% of glioma.[3] Although the numbers are quite large, 90% of meningiomas are benign (WHO Grade I) with slow growth.[1,4] The problem with meningioma is that the recurrence rate or frequency in the same area is high, around 7 to 15%.[2,5] Studies report that patients can undergo more than three procedures due to this recurrence.[5] Studies conducted by Riemenschneider *et al*. revealed that atypical meningioma has a frequency of 40%, and anaplastic meningioma up to 80% within five years.[6]

Several studies have looked for factors that can cause frequent meningiomas. One of the factors thought to be associated with the frequency of meningiomas is hormonal status. Research on meningioma has proven a lot about the existence of hormone receptors. A study in Finland found that 88% of meningiomas have progesterone receptors (PR), and 40% have estrogen receptors (ER).[7,8] Moreover, researchers postulate that progesterone receptor amount differs by type of meningioma. An increasing number of PR means a better prognosis of meningioma. Meningiomas that have little PR or show the presence of ER correlated with a poor prognosis.[9]

However, other research shows that meningioma grows in conditions of high-level progesterone and estrogen. The growth of meningiomas usually arises in the luteal phase of the menstrual cycle or in the 2nd and 3rd trimester of pregnancy which is the highest progesterone level.[10] High body mass index (BMI) with high levels of sex hormones are also associated with meningioma incidence. Many studies have also shown that the

Address correspondence to: Dr Fabianto Santoso, Department of Neurosurgery Faculty of Medicine Universitas Indonesia – Dr. Cipto Mangunkusumo National General Hospital, Jakarta, Indonesia. Email: fabianto.santoso@ui.ac.id

Date of Submission: 22 September 2022; Date of Acceptance: 2 January 2023

https://doi.org/10.54029/2023wxj

use of hormonal contraceptives can increase the risk of meningioma.[11] Therefore, anti-progesterone as endocrine therapy in meningiomas has yielded unexpected results.[12]

With this contrasting evidence, the author would like to discuss the relationship between sex hormones, especially progesterone and estrogen, in meningioma's pathogenesis. Through this review, the author will describe the most up-to-date research and the research needed to answer these controversies.

MENINGIOMA

Meningioma is a neoplasm that develops in a slow, no infiltrative fashion, and the majority of them (90%) are benign.[1,4] Meningioma is derived from the meningothelial cells of the arachnoidal layer (arachnoid cap cells) and attaches firmly to the dura area inside.[4]

Because of it, meningiomas can grow from wherever arachnoid cells are located, including the spinal cord. Meningen coats the entire convex surface of the cerebrum, falx cerebri, and skull base. Meningiomas grow on the granulation pacciones, a type of arachnoid cell.[1,4] Meningiomas also grow ectopically, i.e., in the skull's bones or subcutaneous tissue not attached to the skull's bone. Meningiomas can also grow in multiple (8% of the entire case) and a diffuse form (meningioma en plaque).[1]

Meningioma occupies 14.3% to 19% of the entire primary intracranial neoplasms.[1] The epidemiology can be indicated by the prevalence and incidence rates. Baldi *et al*. in 2014 noted that the prevalence of meningioma reached 50.4/100,000 to 70.7/100,000.[13,14] Incidence of meningiomas in America and the whole world reached a figure of 1.28/100,000 and 70.7/10,000. The US Central Brain Tumor Registry in the United States (CTBRUS) organization states that meningioma is the most frequent primary brain tumor in America, followed by glioma.[15]

Figures reported in the study of meningioma's epidemiology cannot be separated from several factor variations, such as age and sex. The incidence increases to a peak at 45 years, with a median age of diagnosis at 65 years. A total of 3% of meningiomas are found in autopsies of patients older than 60. Older seniors reported having an increasingly high incidence. A report says that the incidence may reach up to 22.2/100,000 in patients aged between 75 and 89. Some say that 20/100,000 meningiomas are diagnosed at 55 to 75.[13] In women, meningioma occurs at a rate three times higher than men, with the difference most considerable at age 30 to 59 (the difference may reach up to 3.6 times as much).[1] Across the country, brain tumors in general and meningiomas, in particular, showed an increase in cases. However, the matter is thought to occur due to the human factors itself, such as the aging population, the improved access to healthcare and diagnostic procedures, changes in the classification of tumors, and frequently available histology results caused by the more widespread practice of neurosurgery.[13]

PATHOGENESIS OF MENINGIOMA

Meningioma tumorigenesis gene

Mutation or inactivation of the NF2 gene varies in WHO grade I meningioma, where 70-80% are fibroblastic and transitional meningiomas, 25% are meningothelial meningiomas, and less than 1% are secretory meningiomas. This has proved that there are cytogenetic differences in benign meningioma. In atypical and anaplastic meningioma, mutations in NF2 occur in 70% of similar fibroblastic and transitional cases. It is indicated that NF2 affects the formation of tumors, but not in malignant meningioma.[17-21]

The role of Merlin in the formation of meningiomas triggers a variety of studies to look at other proteins that are homologous in structure and have a functionality that is similar to protein 4.1. Some research postulate that the gene differentially expressed in the adenocarcinoma of the lung-1 (DAL-1), located on chromosome 18p11.3, encodes proteins 4.1B. Protein 4.1B also regulates the proliferation and apoptosis of cells. Genes and proteins suppress the growth of meningioma cells. Loss of protein 4.1B expression was detected in all WHO grades even though one group was found to be dominant at the higher grade. However, the loss of expression of protein 4.1B was found not to originate from mutations in the gene DAL-1 because only 3 of 83 meningiomas were found sporadic. The discovery suggests the possibility of other mechanisms causing the inactivation of the protein, such as changes in epigenetics that cause inactivation of DAL1/4.1B in meningioma.[6,16] Furthermore, another type of protein 4.1, namely 4.1R, is known to inhibit cell meningiomas' growth in vitro.[22] With these studies, it can be concluded that meningiomas are associated with one or more members of the 4.1 protein.

Genetics regulate not only the tumorigenesis of the oncogenes and tumor suppressor genes but

also the components that support meningioma's life. Vascular endothelial growth factor (VEGF) and its receptors, such as FLT-1 and KDR, are found in meningioma vascular systems. 23 VEGF has also been shown to play a role in the development of neovascularization and peritumor edema.[24] The relationship between meningioma staging with VEGF is not linear, which means increasingly higher stages do not cause higher VEGF expression. In recurrent meningioma, increased VEGF leads to neovascularization and the formation of feeding arteries, which precipitates peritumor edema. There is also the thought that VEGF stimulates the autocrine function of the cell tumor itself.[23] Some studies suggest that VEGF and fibroblast growth factor -2 (FGF-2) are stimulated in the presence of activated mast cells. These mast cells will also increase the permeability of the blood-brain barrier, contributing to peritumor edema. FGF also plays a role in cell proliferation and DNA synthesis in meningiomas.[25]

Proteins and genes affecting meningioma are the hypoxia-inducible factor (HIF-1), which functions like VEGF in angiogenesis, but under hypoxic conditions, plays a role in the invasion (metalloproteinase protein), anti-apoptotic behavior, and the metabolism of glucose. Like mast cells, HIF can also predict the outcome of a meningioma based on peritumor edema.[25]

Meningioma progressivity genes

The development of meningioma into a malignancy is associated with more substantial genetic instability and a more complex karyotype. Progressivity onto malignancy is associated with cumulative stages of chromosome accretion and reduction that produces a more aggressive subclone. Compared with benign meningiomas, a malignant meningioma malignant has a more complex genetical variation, with a loss at 1p, 10q, 14q, and rare loss on 6Q and 18q. Higher-grade meningioma is also associated with increased 1Q, 9q, 12q, 15Q, 17q, and 20q. Cytogenetic studies on anaplastic meningioma generate the data on the loss of chromosomes -6q, -10, -14q, and -18q, and amplification at 17q23, as depicted in Figure 1.[16] Epigenetics include the addition of CpG hypermethylation which is associated with the progression of malignant meningioma.

However, the specific genes to the majority of abnormal chromosomes have not yet been understood. In addition, there are several molecular pathways regarding proliferation, angiogenesis, and autocrine that are still opposed to tumorigenesis in general.[16]

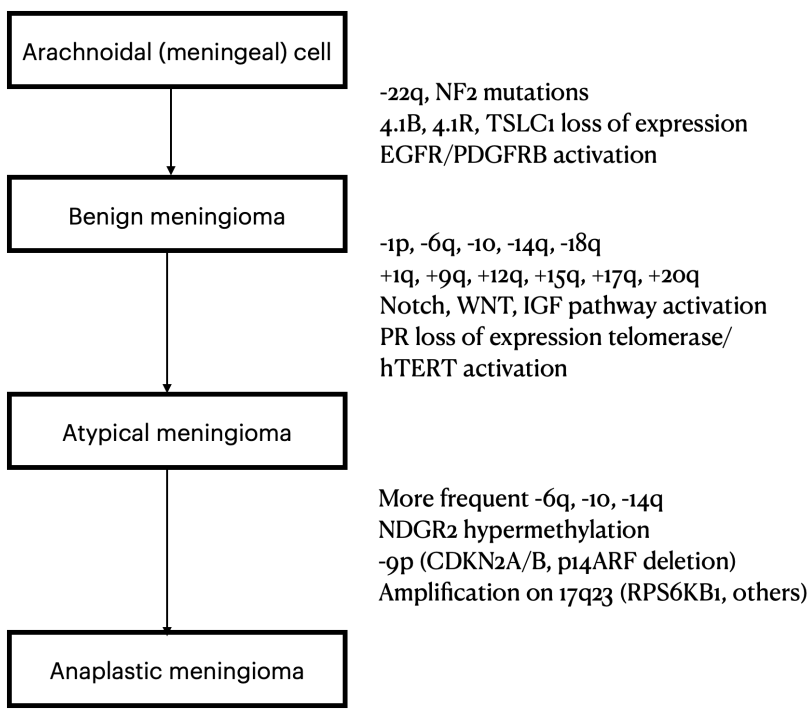

Figure 1. Tumorigenesis and progressivity gene in meningioma

Immunohistochemical staining with MIB-1 (Ki-67) antibody was consistently correlated with recurrence in meningiomas. Ki-67 is a nuclear non-histone protein expressed during a phase of proliferation in the cell cycle (G1, S, G2, M) and not expressed in resting (G0). MIB-1 staining provides an index label (labeling index/LI), which can be calculated based on dividing cells.[23] A study has proven that the MBI-1 LI <10% did not cause recurrence, and MBI-1 LI> 10% lead to the recurrence of 97% in 10 years.[26] The exact value of the MBI-1 LI cannot be concluded because of each laboratory's variation. Another marker that proves higher-grade meningioma is the proto-oncogene bcl-2, p53, P51, Fas-APO1 protein (CD95), and the protein matrix of extracellular tenascin.[23]

ESTROGEN AND PROGESTERONE HORMONES

Physiology of estrogen and progesterone hormones

Steroid hormones can be formed in several organs, such as the ovaries, testes, adrenals, cerebrum, and placenta. Each organ has its own enzymes, so not every type of steroid hormone can be formed in all organs. The formation of steroid hormones or steroidogenesis starts with raw materials in 27 carbon chains of cholesterol or commonly taken from low-density lipoprotein (LDL).[27,28]

Cholesterol is then carried into ovarian cells using the steroidogenic acute regulatory protein (STAR) receptor, coded for the STAR gene. In the mitochondria, cholesterol is converted to pregnenolone with the help of the CYP11A1 enzyme. Pregnenolone is the precursor of all steroid hormones. Pregnenolone catalyzed by the enzyme 3β-hydroxysteroid dehydrogenase-Δ5,4 isomerase type 2 (HSD3B2) will become progesterone. The enzyme CYP17A1 catalyzes pregnenolone and progesterone to 17-Hydroxypregnenolone and 17-Hydroxyprogesterone. The HSD3B2 enzyme can also convert 17-Hydroxypregnenolone to 17-Hydroxyprogesterone. Progesterone can also be converted into glucocorticoids and mineralocorticoids with the help of the enzymes 21-hydroxylase and 11β-hydroxylase, but this cannot be carried out in the ovaries because these enzymes are absent. With the help of the CYP17A1 enzyme, 17-hydroxypregnenolone turns into dehydroepiandrosterone (which can turn into androstenedione via the enzyme HSD3B2), and 17-hydroxyprogesterone becomes androstenedione. This androstenedione will then turn into other androgens or other estrogens with the help of CYP19A1 or what is known as aromatase. Estrogen has a carbon chain number 18.[27-31]

PHYSIOLOGY OF ESTROGEN AND PROGESTERONE HORMONE RECEPTORS

Estrogen receptors

Estrogen receptors are divided into two groups: alpha estrogen receptors (ERα) and estrogen beta receptors (ERβ). Both types of receptors will affect whether estrogen will stimulate or inhibit an organ. The genes encoding these two receptors are on two different chromosomes, where ERα is on chromosome 6 and ERβ on chromosome 14. Morphologically, the alpha receptor has 595 amino acids with a molecular weight of 66 kDa, and beta receptors have 530 amino acids with a molecular weight of 54 kDa. This estrogen receptor has five domains with different functions, as shown in Figure 2.[32]

The A / B domain located at the N-terminal has an activation function-1 (AF-1), contributing to the estrogen receptor's transcription activation. Domain C encodes the DNA Binding Domain (DHF), which carries ER to DNA and regulates the target gene's expression. The region or domain D is a region where amino acid sequences stimulate a nucleus localization signal and facilitate post-translational modification of the ER resulting in activation of the ER signal in the cell. Finally, the E / F domain in the C-terminal consists of the

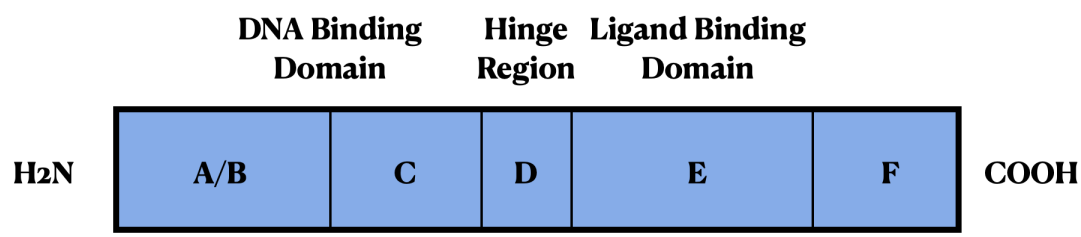

Figure 2. Domain of estrogene and progesterone receptor

ligand-binding domain (LBD), which is the site of interaction with the co-regulator and ligand-dependent activation factor-2 (AF-2). This F domain influences the action of ERα and ERβ, where the differences between ERs cause the ER's ability to control the transcription of specific genes selectively. ER will later be assisted by estrogen receptor elements (ERE) to attach to DNA. ERα receptors are found in the uterus, prostate stroma, ovarian theca cells, Leydig cells in the testes, epididymis, breast, and liver. Meanwhile, ERβ is found in the epithelium of the prostate, testes, ovarian granulosa cells, spinal cord, and brain.[32–34]

These two estrogen receptors are present in brain cells, where they have various functions. Alpha receptors have a more reproductive function, while beta receptors have a more cognitive function.[32]

Progesterone receptors

Progesterone receptors (PR) can be classified into PR-A, PR-B, and PR-C. However, PR-C is found only in endometrial tissue. PR-A receptors have fewer amino acids than PR-B, which is about 164 amino acids. In normal physiology, humans have a balanced amount of PR-A and PR-B. PR works the same way as ER because these two receptors are nuclear receptors.[30]

EFFECT OF HORMONE ESTROGEN AND PROGESTERONE AS WELL AS RECEPTORS ON NEOPLASM

Sex hormones in both men and women influence etiopathogenesis and cancer development of several organs, for example, endometrium, breast, prostate, and lung. The mechanism of hormones into cancer risk is mainly through their influence on the number and rate of mitosis of epithelial cells in related organs.

The mechanism of estrogen to be a carcinogen is not known with certainty. Several studies have hypothesized how estrogen can be carcinogenetic. The electrophilic or redox-active formation of quinone is an essential mechanism in the occurrence of carcinogenesis of estrogen. O-Quinone or quinone methides, which are metabolites of estrogen, play a role in the alkalization and/or oxidative destruction of cell proteins and DNA. When o-Quinone occupies ER, the active redox effect will be high, and it is called a Trojan horse, which will attack the target DNA selectively. Meanwhile, estrogen receptors cause cell proliferation. Both of these mechanisms are hypotheses of the action of estrogen in producing cancer.[35]

Similar to estrogen, progesterone also causes carcinogenesis. Research in breast cancer suggests that progesterone promotes pre-neoplastic development by stimulating the proliferative cycle of mammary stem cells or initiating tumors from the mature breast's epithelium. When progesterone binds to PR-B in the breast, this binding signal converts paracrine to autocrine regulation of proliferation. However, some studies say that PR does not affect carcinogenesis but only as an ER work marker. These results are inconsistent across existing studies.[36]

The influence of sex hormones on cancer is mostly seen from breast cancer incidence, where there is a classification based on the presence or absence of estrogen and progesterone receptors. Furthermore, risk factors related to sex hormone levels, such as body mass index, were also increased in receptor-positive versus negative tumors. Postmenopausal women with exposure to exogenous hormones have a risk of developing tumors with positive ER.[41] In postmenopausal patients where the most widely circulating endogenous estrogen is estrone, the hazard ratio of estrone levels for breast cancer is 2.05 (CI 95% 1.24 – 3,37).[38] The study by Baglietto *et al*. (2010) added that this risk increases with age.[39] Similar results were also found in pre-menopausal patients where patients with estradiol levels in the highest quarter had a RR of 2.4 (CI 95% 1.3 – 4.5) compared to the lowest quarter for breast cancer. This association was confirmed for ER and PR positive tumor types.

In addition to breast cancer widely assessed as being related to the estrogen and progesterone hormones, ovarian carcinoma is also associated with the presence of sex hormones and their receptors.[41,42] Several studies have shown that estrogen has a role in ovarian cancer with the same genotoxic pathway as breast. Both estradiol (E2) and estrone (E4) play a role in stimulating ER to stimulate ovarian cell growth. Estradiol plays a greater role before menopause and estrone after menopause. Other studies have shown that subjects with BMI overweight or obesity have a greater risk of developing ovarian cancer.[43]

STUDY OF THE RELATIONSHIP OF ESTROGEN AND PROGESTERONE IN MINGIOMAS

Many studies discuss risk factors for meningioma, such as female sex, high BMI, radiation exposure, genetic mutations, and sex hormones. The idea of hormonal influence and risk of meningioma begins

with an increased prevalence in women compared to men. This is in line with the epidemiology of meningioma, which states the prevalence of meningiomas, especially low grade ones, in women is twice as high as that of men, three times as high in productive age, and increases in pregnancy.[44,45] Another study revealed that there are estrogen, progesterone, and androgen receptors in some meningiomas which may influence the increase in meningioma size during the luteal phase of the menstrual cycle and pregnancy, and reduction in size when estrogen agonist use is reduced.

Several studies have categorized the expression of ER and PR in 48-88% of meningiomas by differentiating them into stages according to the number of receptor expressions on meningioma cells: 0 where there is no receptor expression, 1 with less than 1% receptor expression, 2 is 1-9%, 3 is 10-49%, and stage 4, which means more than 50% are found to express receptors in the cell nucleus.[46] Finnish studies found 88% of meningiomas have progesterone receptors (PR), and 40% have estrogen receptors (ER).[7,8] Various studies have found that meningiomas with PR positive are more common in the female sex. Patients with positive PR expression have a better prognosis. Several studies have proven this. However, ER has an uncertain outcome due to the lack of findings in meningiomas with a poor prognostic tendency.[9,46,47]

Progesterone receptors regulate transcription activity by ligand-dependent co-activators and/or co-repressor proteins. Carrol et al. stated that there are three co-activators for PR in meningiomas, namely SRC-1, AIB-1, and TIF2. Different expressions for these three co-activators led to different PR responses. SRC-1 and TIF2 co-activators were associated with positive PR, whereas AIB-1 was not. However, AIB-1 will appear in PR and ER-positive tumors because it is required for the estrogen response pathway.[48]

The progesterone receptors found in meningiomas are also divided into PR-A and PR-B, but with different specifications from those found in the breast. PR-B is twice as big as PR-A. PR-A receptors are also associated with Ki67 and not with PR-B. Estrogen regulates PR-B, which is the opposite of that found in breast cancer located at PR-A. Thus, PR-A reduces ER response to ligands.[49]

Compared to ER, PR is thought to be more influential in meningiomas because it is found in a larger number. The role of progesterone and PR in meningiomas is not clear. There are some contrasting findings about this connection. Several studies have stated that PR is found more in benign meningiomas (WHO Grade I) than atypical or anaplastic meningiomas (WHO Grade II and III). This is also supported by a good prognosis and recurrence when a large number of PR are found in meningiomas.[9] This condition is also seen in pregnant patients. Some studies have shown that pregnant patients have an increased chance of developing a meningioma. Several case reports have reported a positive PR in pregnant patients. Hortobagyi *et al*. also postulated that high progesterone conditions are also thought to be associated with the occurrence of meningiomas and conditions during the luteal phase of the menstrual cycle.[10,50]

Several studies have shown that the use of exogenous hormones, such as hormone therapy, can increase the risk of meningioma.[51] The use of hormones in pre-menopausal women has a risk of up to 2.48 times the occurrence of a meningioma compared to post-menopausal women with a history of previous hormone use. However, some studies report opposite results. The cohort study using data on 1.3 million women with a mean age of 55.9 years found no association between the occurrence of meningiomas and the use of oral contraceptives. In addition, 219 cases enrolled in a case-control study at several hospitals in Chicago said that oral contraceptives had a protective effect against meningiomas with an OR of 0.2. A study using patients from the Mayo Clinic Jacksonville found that meningiomas were associated with hormone replacement therapy.[52] A study in Surabaya, Indonesia, found that oral contraceptives can increase the risk of meningioma by 18.2 times.[53] However, there is one study suggesting that the use of oral contraceptives increases the risk of meningiomas with low or no PR.

Only a few studies have examined the effects of endogenous sex hormones against meningioma. Research so far has measured endogenous hormones only from their physical characteristics.[54] Rhein-Neckar-Odenwald from 1987 to 1988 conducted a case-control study which found that menopause reduces the risk of experiencing meningioma with RR 0.58 (CI95% 0.18-1.90).[55] Another study assessed the indirect relationship of BMI and reported that obese patients have a 2.5 times greater risk of developing meningiomas than those who are not.[11]

With the discovery of progesterone receptors in meningiomas, not only prognostic studies were conducted, but also therapeutic studies.

Several studies have tried to use anti-progesterone for meningiomas, such as those used in breast cancer. The most common drug used is hormone therapy; mifepristone (RU486). Mifepristone acts by inhibiting progesterone receptor transcription during high progestin conditions. However, the success rate of hormone therapy is still unclear.[12] Several studies of association PR or ER in meningioma were resumed in Table 1.

DISCUSSION

Based on several studies disclosed in the previous section, the role of sex hormones estrogen and progesterone are still not fully understood in meningiomas. Most receptors found in meningiomas are the progesterone receptors (PR), while the estrogen receptors are found in a minimal amount (<10%). The number of PR was also inversely related to WHO staging and prognosis and recurrence. The more PR found in meningiomas, the better the degree, prognosis, and recurrence are. This raises a new question about the role of progesterone and its receptors in the pathogenesis of meningiomas.

Another fact states that breast cancer incidence is also associated with meningiomas, which has led to research on estrogen and progesterone receptors in meningiomas.[58] This fact underlies

Table 1: Several studies of association PR/ER in meningioma

Author	Results/ Conclusion	The Association of PR/ER in Meningioma
Hsu *et al*. (1997)[46]	The presence of PRs, even in a small number of tumor cells, is a favorable prognostic factor for meningiomas.	Yes
Pravdenkova *et al*. (2006)[9]	The expression of the PR alone in meningiomas signals a favorable outcome	Yes
Korhonen *et al*. (2006)[8]	he PR positivity was equally common among men and women (91.5% and 87.1%)	No
Hatiboglu *et al*. (2008)[50]	The epidemiological and clinical studies on pregnant women suggest that sex steroid hormones and growth factors play roles in the development of the meningiomas	Yes
Blitshteyn *et al*. (2008)[51]	The study provides evidence of a positive association between HRT use and diagnosis of meningioma, and therefore, HRT use may be a risk factor for meningioma (OR 2.2 (95% CI, 1.9 to 2.6))	Yes
Custer *et al*. (2006)[56]	This study found little evidence of associations between meningioma and exogenous hormone exposures in women but did suggest that some hormonal exposures may influence tumor biology in those women who develop meningioma.	No
Claus *et al*. (2007)[52]	There is no statistical evidence of an increased risk of meningioma among users of oral contraceptives.	No
Supartoto *et al*. (2018)[57]	The longer the exposure to exogenous progesterone injection, the lower the expression of PR.	Yes

that progesterone and estrogen have a role in meningioma and breast cancer, although their role is opposite to meningioma in terms of prognosis. This is supported by several studies stating that meningiomas are also found during pregnancy and the luteal phase of the menstrual cycle. These two times are the times when the progesterone level in the blood rises.

Epidemiologic studies have proven that primary meningiomas are WHO grade I meningiomas, the meningiomas with the highest PR number. On the other hand, a study conducted by Iskandar MM showed that recurrence in meningiomas was associated with a lower number of PR and a higher WHO grade.[59] Furthermore, recurrences were not related to the use of hormonal contraceptives, as only 16% of hormonal birth control users had recurrences. However, Supartoto proved that the longer the exposure to exogenous progesterone, the lower the expression of progesterone receptors in the blood. This low PR expression is associated with tumorigenesis and recurrence of meningiomas.[57]

For therapeutic implications, because this tumor shows a relationship with hormonal receptors, especially progesterone, the use of hormonal therapy can increase the risk of meningioma. A study by Andersen et al showed that the use of hormonal replacement therapy led to an increased risk of meningioma.[60] Therefore, one of the ideas postulated was endocrine therapy in the treatment of meningioma. Although there have been several studies on the use of endocrine therapy in the management of meningioma, these studies were not conclusive.[60] Studies using mifepristone and tamoxifen as anti-progesterone and anti-estrogen agents also did not show satisfactory results.[62]

Most of the studies using anti-estrogen and anti-progesterone hormonal therapy for meningioma were done about 10 to 20 years ago. Rather than demonstrating a therapeutic effect on tumors, several studies have reported significant side effects.[63] A study by Oura *et al*. reported regression of meningioma after administration of an antiestrogenic agent called mepitiostane.[63] Fourteen years after the study was published, regression of meningioma after administration of mepitiostane was also reported in three cases by Miyai *et al*.[65] A meta-analysis discussing the therapeutic effect of mifepristone, an oral progesterone antagonist agent, on meningioma concluded that there is still no clear evidence in recommending this agent for the management of meningioma, although it may be used in cases of diffuse meningiomatosis.[66] However, mifepristone is used to treat progesterone-receptor-positive meningioma at a dose of 200 mg daily. Possible side effects of this therapy are hypothyroidism and endometrial hyperplasia, requiring extensive monitoring.[67]

Therefore, the authors postulate that progesterone's role in meningiomas is tumorigenesis, a conclusion drawn from the tendency of meningiomas to be benign rather than malignant. The usual recurrences in WHO grades II and III are not associated with progesterone. On the other hand, WHO grade II-III meningiomas do not have many progesterone receptors. The authors hypothesize that progesterone and PR only affect tumor formation, which tends to be benign. The formation and progression of a higher meningioma are also influenced by factors and genetics other than hormonal.

Based on the discussion above, there is a gap of knowledge illustrated in the Figure 3. Several questions remain unanswered:

- How is the PR expression in normal meningen?
- Does the use of hormonal contraception affect the incidence of meningioma?
- Will prolonged use of progesterone affect PR expression and meningioma pathophysiology?
- Does the use of high levels of progesterone in the body affect PR expression and the pathophysiology of meningioma?

CONCLUSION

Sex hormones, especially progesterone, have been shown to play a role in tumorigenesis and meningioma recurrence. Progesterone receptors also play a role in meningioma recurrence, where a low number of receptors indicates a poor prognosis. However, the molecular relationship between the occurrence of meningiomas at low progesterone receptor expression is still unknown. Further research is still needed to determine the role of sex hormones, especially progesterone, and their receptors in both tumorigenesis and meningioma progression. By knowing this role, new science in endocrinology can be utilized for primary preventive, secondary preventive, and therapeutic strategies for meningiomas.

DISCLOSURE

Financial support: None

Conflict of interest: None.

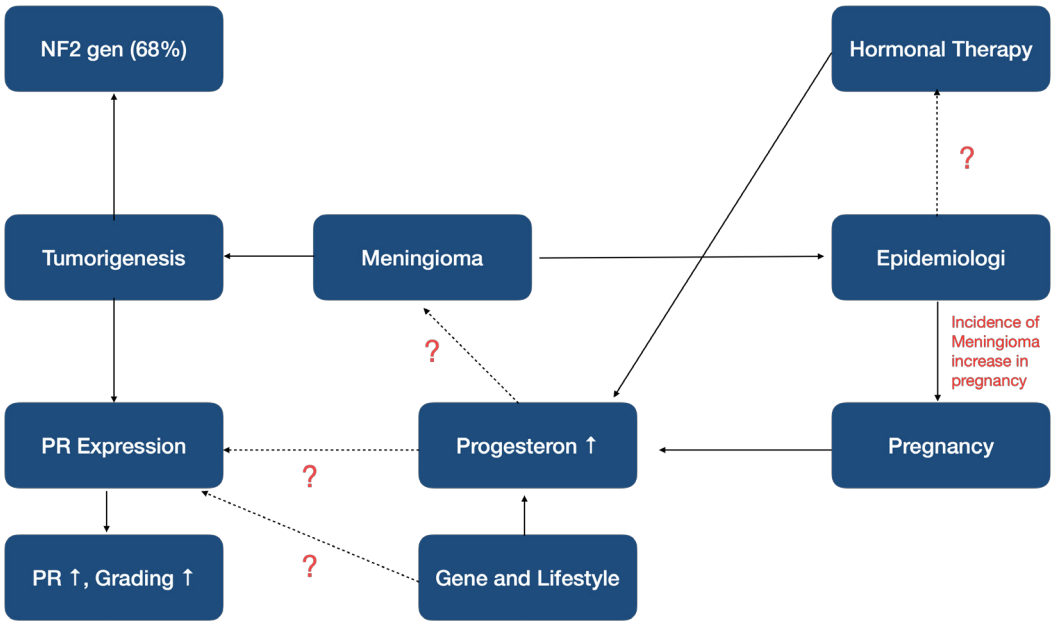

Figure 3. Gap of knowledge in progesterone receptor in meningioma

REFERENCES

1. Greenberg MS: Handbook of neurosurgery. 9th ed. New York: Thieme, 2019:707-16.
2. Yang CC, Tsai CC, Chen SJ, *et al*. Factors associated with recurrence of intracranial meningiomas after surgical resection: A retrospective single-center study. *Int J Gerontol* 2018; 12(1):57-61. doi: 10.1016/j.ijge.2017.02.002
3. Iskandar MM, Aman RA, Tjahjadi H, Safri AY, Aninditha T. The identification of factors affecting intracranial meningioma recurrence two years postoperatively. *J Phys Conf Ser* 2017; 884(1):30-3. https://doi.org/10.1088/1742-6596/884/1/012032
4. Winn H. Youmans & Winn neurological surgery. 7th Ed. 2016. 8256-64.
5. Lemée JM, Corniola M V., Meling TR. Benefits of re-do surgery for recurrent intracranial meningiomas. *Sci Rep* 2020; 10(1):1-8. doi: 10.1038/s41598-019-57254-5
6. Riemenschneider MJ, Perry A, Reifenberger G: Histological classification and molecular genetics of meningiomas. *Lancet Neurol* 2006; 5(12):1045-54. doi: 10.1016/S1474-4422(06)70625-1
7. Marosi C, Hassler M, Roessler K, *et al*. Meningioma. *Crit Rev Oncol Hematol* 2008; 67(2):153-71. doi: 10.1016/j.critrevonc.2008.01.010z
8. Korhonen K, Salminen T, Raitanen J, Auvinen A, Isola J, Haapasalo H. Female predominance in meningiomas can not be explained by differences in progesterone, estrogen, or androgen receptor expression. *J Neurooncol 2006;* 80(1):1-7. doi: 10.1007/s11060-006-9146-9
9. Pravdenkova S, Al-Mefty O, Sawyer J, Husain M. Progesterone and estrogen receptors: Opposing prognostic indicators in meningiomas. *J Neurosurg* 2006; 105(2):163-73.
10. Hortobágyi T, Bencze J, Murnyák B, Kouhsari MC, Bognár L, Marko-Varga G. Pathophysiology of meningioma growth in pregnancy. *Open Med* 2017; 12(1):195-200. doi: doi: 10.1515/med-2017-0029
11. Wahab M, Al-Azzawi F: Meningioma and hormonal influences. *Climacteric* 2003; 6(4):285-92. doi: 10.1080/cmt.6.4.285.292
12. Chargari C, Védrine L, Bauduceau O, Le Moulec S, Ceccaldi B, Magné N. Reapprasial of the role of endocrine therapy in meningioma management. *Endocr Relat Cancer* 2008; 15(4):931-41. doi: 10.1677/ERC-08-0083
13. Baldi I, Engelhardt J, Bonnet C, *et al*. Epidemiology of meningiomas. *Neurochirurgie* 2018; 64(1):5-14. doi: 10.1016/j.neuchi.2014.05.006.
14. Porter KR, McCarthy BJ, Freels S, Kim Y, Davis FG. Prevalence estimates for primary brain tumors in the United States by age, gender, behavior, and histology. *Neuro Oncol* 2010; 12(6):520-7. doi: 10.1093/neuonc/nop066
15. Duong LM, BJ M, McLendon RE, Dolecek TA, *et al*. Descriptive epidemiology of malignant and nonmalignant primary spinal cord, spinal meninges, and cauda equina tumors, United States, 2004–2007. *Cancer* 2012; 118(17):4220-7. doi: 10.1002/cncr.27390
16. Choy WC, Kim W, Nagasawa D, *et al*. The molecular genetics and tumor pathogenesis of meningiomas and the future directions of meningioma treatments. *Neurosurg Focus* 2011; 30(5):E6. doi: 10.3171/2011.2.FOCUS1116
17. Liu Y, Pang JCS, Dong S, Mao B, Poon WS, Ng HK. Aberrant CpG island hypermethylation profile is associated with atypical and anaplastic meningiomas. *Hum Pathol* 2005;36(4):416-25. doi: 10.1016/j.humpath.2005.02.006

18. Ragel BT, Jensen RL. Molecular genetics of meningiomas. *Neurosurg Focus* 2005; 19(5):1-8. doi: 10.3171/foc.2005.19.5.10
19. Gusella JF, Ramesh V, MacCollin M, Jacoby LB. Merlin: The neurofibromatosis 2 tumor suppressor. *Biochim Biophys Acta - Rev Cancer* 1999; 1423(2): M29-32 doi: 10.1016/s0304-419x(99)00005-0.
20. Morrison H, Sherman LS, Legg J, *et al.* The NF2 tumor suppressor gene product, merlin, mediates contact inhibition of growth through interactions with CD44. *Genes Dev* 2001; 15(8):968-80. doi: 10.1101/gad.189601
21. Ragel BT, Jensen RL. Aberrant signaling pathways in meningiomas. *J Neurooncol* 2010; 99(3):315-24. doi: 10.1007/s11060-010-0381-8
22. Robb VA, Li W, Gascard P, Perry A, Mohandas N, Gutmann DH. Identification of a third Protein 4.1 tumor suppressor, Protein 4.1R, in meningioma pathogenesis. *Neurobiol Dis* 2003; 13(3):191-202. doi: 10.1016/s0969-9961(03)00071-8
23. Ragel B, Jensen RL. Pathophysiology of meningiomas. *Semin Neurosurg* 2003; 14(3):169-85.
24. Schmid S, Aboul-Enein F, Pfisterer W, Birkner T, Stadek C, Knosp E. Vascular endothelial growth factor: The major factor for tumor neovascularization and edema formation in meningioma patients. *Neurosurgery* 2010; 67(6):1703-8. doi: 10.1227/NEU.0b013e3181fb801b
25. 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. doi: 10.1007/s11060-013-1208-1
26. Ho DMT, Hsu CY, Ting LT, Chiang H. Histopathology and MIB-1 labeling index predicted recurrence of meningiomas: A proposal of diagnostic criteria for patients with atypical meningioma. *Cancer* 2002; 94(5):1538-47. doi: 10.1002/cncr.10351
27. Samavat H, Kurzer MS. Estrogen metabolism and breast cancer. *Cancer Lett 2015;* 356(200):231-43. doi: 10.1016/j.canlet.2014.04.018
28. Sumit Bhateja AB. Carcinogenesis and sex hormones: A review. *Endocrinol Metab Syndr* 2015; 04(01):1-4. doi: 10.4172/2161-1017.1000156
29. Trabert B, Sherman ME, Kannan N, Stanczyk FZ: Progesterone and breast cancer. *Endocr Rev* 2020; 41(2):320-44. doi: 10.1210/endrev/bnz001
30. Taraborrelli S. Physiology, production and action of progesterone. *Acta Obstet Gynecol Scand* 2015; 94:8-16. doi: 10.1111/aogs.12771
31. Reed BG, Carr BR. The normal menstrual cycle and the control of ovulation. Available at: https://www.ncbi.nlm.nih.gov/books/NBK279054/ 42
32. Lee HR, Kim TH, Choi KC. Functions and physiological roles of two types of estrogen receptors, ERα and ERβ, identified by estrogen receptor knockout mouse. *Lab Anim Res* 2012; 28(2):71. doi: 10.5625/lar.2012.28.2.71
33. Nilsson S, Mäkelä S, Treuter E, *et al*. Mechanisms of estrogen action. *Physiol Rev* 2001; 81(4):1535-65. doi: 10.1152/physrev.2001.81.4.1535
34. Hewitt SC, Korach KS. Estrogen receptors: New directions in the new millennium. *Endocr Rev* 2018; 39(5):664-75. doi: 10.1210/er.2018-00087
35. Bolton JL, Thatcher GRJ. Potential mechanisms of estrogen quinone carcinogenesis. *Chem Res Toxicol* 2008; 21(1):93-101. doi: 10.1021/tx700191p
36. Joshi PA, Goodwin PJ, Khokha R. Progesterone exposure and breast cancer risk: Understanding the biological roots. *JAMA Oncol* 2015; 1(3):283-6. doi: 10.1001/jamaoncol.2015.0512
37. Williams C, Lin CY. Oestrogen receptors in breast cancer: Basic mechanisms and clinical implications. *Ecancermedicalscience* 2013; 7(1):1-12. doi: 10.3332/ecancer.2013.370
38. Sieri S, Krogh V, Bolelli G, *et al*. Sex hormone levels, breast cancer risk, and cancer receptor status in postmenopausal women: The ORDET cohort. *Cancer Epidemiol Biomarkers Prev* 2009; 18(1):169-76. doi: 10.1158/1055-9965.EPI-08-0808
39. Baglietto L, Severi G, English DR, *et al*. Circulating steroid hormone levels and risk of breast cancer for postmenopausal women. *Cancer Epidemiol Biomarkers Prev* 2010; 19(2):492-502. doi: 10.1158/1055-9965.EPI-09-0532
40. Eliassen AH, Missmer SA, Tworoger SS, *et al*. Endogenous steroid hormone concentrations and risk of breast cancer among premenopausal women. *J Natl Cancer Inst* 2006; 98(19):1406-15. doi: 10.1093/jnci/djj376
41. Daniell H. Progesterone action in breast, uterine, and ovarian cancers. *Caroline* 2012; 76:211-20.
42. Ho SM. Estrogen, progesterone and epithelial ovarian cancer. *Reprod Biol Endocrinol* 2003; 1:1-8. doi: 10.1186/1477-7827-1-73
43. Colditz GA, Rosner BA, Chen WY, Holmes MD, Hankinson SE. Risk factors for breast cancer according to estrogen and progesterone receptor status. *J Natl Cancer Inst* 2004; 96(3):218-28. doi: 10.1093/jnci/djh025
44. Madhunapantula SR V., Mosca P, Robertson GP. Steroid hormones drive cancer development. *Cancer Biol Ther* 2010; 10(8):765-6. doi: 10.4161/cbt.10.8.13531
45. Du Z, Santagata S. Uncovering the links between systemic hormones and oncogenic signaling in the pathogenesis of meningioma. *Ann Oncol* 2018; 29(3):537-40. doi: 10.1093/annonc/mdy010
46. Hsu DW, Efird JT, Hedley-Whyte ET. Progesterone and estrogen receptors in meningiomas: Prognostic considerations. *J Neurosurg* 1997; 86(1):113-20. doi: 10.3171/jns.1997.86.1.0113
47. Bao SD. Estrogen and progesterone receptors in meningiomas. *Chinese J Clin Oncol* 1994; 21(3):216-8.
48. Carroll RS, Glowacka D, Dashner K, Black PM. Progesterone receptor expression in meningiomas. *Cancer Res* 1993; 53:1312-6.
49. Mukherjee S, Ghosh SN, Chatterjee U, Chatterjee S. Detection of progesterone receptor and the correlation with Ki-67 labeling index in meningiomas. *Neurol India* 2011; 59(6):817-22. doi: 10.4103/0028-3886.91357
50. Hatiboglu MA, Cosar M, Iplikcioglu AC, Ozcan D. Sex steroid and epidermal growth factor profile

of giant meningiomas associated with pregnancy. *Surg Neurol* 2008; 69(4):356-62. doi: 10.1016/j.surneu.2007.03.013
51. Blitshteyn S, Crook JE, Jaeckle KA. Is there an association between meningioma and hormone replacement therapy? *J Clin Oncol* 2008; 26(2):279-82. doi: 10.1200/JCO.2007.14.2133
52. Claus EB, Black PM, Bondy ML, *et al*. Exogenous hormone use and meningioma risk: What do we tell our patients? *Cancer* 2007; 110(3):471-6. doi: 10.1002/cncr.22783
53. Wahyuhadi J, Heryani D, Basuki H. Risk of meningioma associated with exposure of hormonal contraception. A case control study. *Maj Obstet Ginekol* 2018; 26(1):36. doi: 10.20473/mog.V26I12018.36-41
54. Jhawar BS, Fuchs CS, Colditz GA, Stampfer MJ. Sex steroid hormone exposures and risk for meningioma. *J Neurosurg* 2003; 99(5):848-53. doi: 10.3171/jns.2003.99.5.0848
55. Schlehofer B, Blettner M, Wahrendorf J. Association between brain tumors and menopausal status. *J Natl Cancer Inst* 1992;84(17): 1346-49. doi: 10.1093/jnci/84.17.1346
56. Custer B, Longstreth JT, 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; 6:1-9. doi: 10.1186/1471-2407-6-152
57. Supartoto A, Sasongko MB, Respatika D, *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 doi: 10.3389/fonc.2018.00651
58. Istianggoro H. Gambaran karakteristik dan hubungan meningioma reseptor progesteron positif dengan penggunaan kontrasepi hormonal pada perempuan dengan tumor otak meningioma di Rumah Sakit Umum Pusat Nasional Cipto Mangunkusumo Tahun 2015. Jakarta: Universitas Indonesia, 2018.
59. Iskandar MM. Faktor yang mempengaruhi risiko rekurensi pada meningioma intrakranial dua tahun pascaoperasi di RSUPN Dr. Cipto Mangunkusumo Tahun 2010-2015. Jakarta: Universitas Indonesia, 2017.
60. Andersen L, Friis S, Hallas J, Ravn P, Schrøder HD, Gaist D. Hormone replacement therapy increases the risk of cranial meningioma. *Eur J Cancer* 2013;49(15):3303-10. doi: 10.1016/j.ejca.2013.05.026
61. Chargari C, Védrine L, Bauduceau O, Le Moulec S, Ceccaldi B, Magné N. Reapprasial of the role of endocrine therapy in meningioma management. *Endocr Relat Cance*r 2008;15(4):931-41. doi: 10.1677/ERC-08-0083
62. Chargari C, Védrine L, Bauduceau O, Le Moulec S, Ceccaldi B, Magné N. Reapprasial of the role of endocrine therapy in meningioma management. *Endocr Relat Cance*r 2008;15(4):931-41. doi: 10.1677/ERC-08-0083
63. Markwalder TM, Seiler RW, Zava DT. Antiestrogenic therapy of meningiomas-a pilot study. *Surg Neurol* 1985;24(3):245-9. doi: 10.1016/0090-3019(85)90030-8
64. Oura S, Sakurai T, Yoshimura G, *et al*. Regression of a presumed meningioma with the antiestrogen agent mepitiostane. Case report. *J Neurosurg* 2000;93(1):132-5. doi: 10.3171/jns.2000.93.1.0132
65. Miyai M, Takenaka K, Hayashi K, Kato M, Uematsu K, Murai H. Effect of an oral anti-estrogen agent (mepitiostane) on the regression of intracranial meningiomas in the elderly. *Brain Nerve* 2014;66(8):995-100.
66. Cossu G, Levivier M, Daniel RT, Messerer M. The role of mifepristone in meningiomas management: A systematic review of the literature. *Biomed Res Int* 2015;2015. doi: 10.1155/2015/267831
67. Karena Z V, Shah H, Vaghela H, Chauhan K, Desai PK, Chitalwala AR. Clinical utility of mifepristone: Apprising the expanding horizons. *Cureus* 2022;14(8): e28318. doi: 10.7759/cureus.28318