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Editorial

The Role of Hormone Receptor Expression and Hormonal Therapy (Estrogen and Progesterone) in the Management and Prognosis of Meningiomas in Females: A Systematic Review

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Abstract

Meningioma is the primary central nervous system tumour with the highest recorded prevalence. Research on meningiomas has shown an association with hormone receptor expression, but the underlying pathophysiologic mechanisms remain unclear. This systematic review presents the available information on the role of progesterone and estrogen in meningioma's pathogenesis, prognosis, and treatment. The study used the Preferred Reporting Items for Systemic Review and MetaAnalysis (PRISMA) 2020 guidelines. The authors searched and downloaded relevant published articles from the following databases; PubMed, PubMed Central (PMC), MEDLINE, the Cochrane Library, and Google Scholar. The downloaded articles were screened using set eligibility criteria and appropriate quality appraisal tools and subsequently relevant data was extracted using standardized questionnaires. Based on the papers reviewed, progesterone receptor expression in meningioma is associated with significantly more favourable prognostic factors and treatment outcomes while a negative correlation exists between overall survival and the presence of estrogen receptors. In conclusion, analysing hormone receptor expression in meningioma appears necessary for targeted hormonal and endocrine therapy. A suitable reference population must also be defined in future extensive prospective multi-centre and multi-national clinical studies.

Keywords: Meningioma, Hormone receptor, Estrogen receptor, Progesterone receptor, Hormonal therapy, Receptor expression.

Introduction

Meningioma is the most common primary intracranial neoplasm, with a prevalence rate of 14.3% to 19% (Ichwan et al., 2023). About 70% to 80% of all meningiomas are benign tumours (WHO grade 1), while 20% to 30% are atypical or borderline (WHO grade 2), and 1% to 2% are malignant WHO grade 3 tumours (Ji et al., 2015). The incidence of meningiomas in the United States of America and the world has reached 1.28/100,000 and 70.7/10,000, respectively (Ichwan et al., 2023). According to the Central Brain Tumor Registry in the United States (CTBRUS), meningioma is America's most frequent primary brain tumour (Ichwan et al., 2023).

There is already an established relationship between meningiomas and sex hormones, and arguments for such an association include female predominance, tumour growth during pregnancy, regression after delivery, a positive association with uterine fibroids, use of oral contraceptives, endometriosis and breast cancer (Bernat et al., 2015). Meningiomas tend to occur more frequently in females than males after puberty, with a relative risk (RR) of 2.5 and the highest incidence in middle-aged adults between 35 to 55 years (Girardelli et al., 2022).

Research on meningioma has shown an association with hormone receptor expression (Ichwan et al., 2023). A study in Finland found that 88% of meningiomas express progesterone receptors, while 40% express oestrogen receptors (Ichwan et al., 2023). Meningiomas usually grow in the luteal phase of the menstrual cycle and the second and third trimesters of pregnancy, probably because of the high progesterone levels during this period (Hortobagyi et al., 2017). A high body mass index with increased levels of sex hormones has also been associated with increased meningioma incidence (Hortobagyi et al., 2017).

Based on the histological and immunohistochemical analysis of progesterone receptors in meningiomas, anti-progesterone therapy has been proposed to treat unresectable meningioma. (Ghirardelli et al., 2022). Trials of anti-progesterone as an endocrine therapy in meningiomas have, however, yielded contrasting results, and there still needs to be consensus guidelines on the role of hormone receptor modulation in the management and prognosis of meningiomas. In addition, the underlying pathophysiologic mechanisms of action of endogenous and exogenous sex hormones on meningiomas largely remain unclear.

Through this systematic review, the authors aim to present the available information on the role of sex

hormones, especially progesterone and estrogen, in meningioma's pathogenesis, prognosis, and treatment. The authors also aim to explore the controversies surrounding hormones and meningiomas and provide a template for international consensus on the hormonal therapy and prognosis of meningiomas.

Materials and Methods

This systemic review used the Preferred Reporting Items for Systemic Review and MetaAnalysis (PRISMA) 2020 guidelines (Page et al., 2021).

Search Sources and Strategy

We carried out a detailed literature search of relevant databases, including PubMed, PubMed Central (PMC), MEDLINE, the Cochrane Library, and Google Scholar. We used various combinations of keywords to search each database, including; meningioma, progesterone receptors, estrogen receptors, and hormonal therapy. We also used online filters based on our inclusion and exclusion criteria to reduce the number of papers.

In PubMed, the following strategy was developed to search relevant literature in PubMed's MeSH database: (((“Meningioma/drug therapy"[Mesh] OR (“Meningioma/therapy"[Mesh]) AND (hormonal therapy [Mesh]))) OR (progesterone receptor [Mesh]) AND (oestrogen receptor [Mesh]).

Table 1: shows the databases used and the number of papers downloaded from each database (after applying online filters).

Keywords/search strategy used	Database	Number of results
(((“Meningioma/drug therapy"[Mesh] OR (“Meningioma/therapy"[Mesh]) AND (hormonal therapy [Mesh]))) OR (progesterone receptor [Mesh])) AND (oestrogen receptor [Mesh]).	PubMed MeSH database	80
Meningioma AND hormonal therapy OR progesterone receptor OR oestrogen receptor AND females	PubMed	120
Meningioma AND hormonal expression OR progesterone or oestrogen AND females	Medline	99
Meningioma AND hormone therapy or progesterone receptor expression OR progesterone receptor AND females	PMC	150
Meningioma and hormonal therapy and females	Cochrane library	58
	Google Scholar	77
Total number of tables identified		584
Number of papers after removing duplicates		356

Inclusion and Exclusion Criteria

We selected published peer-reviewed articles that used only human participants. We only included research papers written in the English language. Articles were excluded if the full text of the papers could not be retrieved. Grey literature and proposal papers were not included. We selected papers with different study designs, including observational studies, cross-sectional studies, randomized controlled clinical trials, narrative reviews, systematic reviews, and case reports. We included papers published in or after 2014. We excluded published papers on meningioma that did not focus on the management and prognostic indices of progesterone and estrogen receptor expression.

Selection Process

We transferred all the articles downloaded from all the databases searched to Microsoft Excel and removed all duplicates. The titles and abstracts of the remaining articles were screened and independently assessed by the first three authors. If there is any disagreement about whether to include or exclude any article, the concerns were discussed among all the other authors and finalized by mutual consensus. We further screened the shortlisted articles by evaluating the complete text; only relevant articles were assessed for eligibility. Inclusion and exclusion criteria were applied, and only articles that satisfied the set criteria were finally selected for quality appraisal.

Quality Assessment of the Studies

The selected articles were checked for quality by all authors using the relevant appraisal tools. Clinical trials were assessed for quality using the Jadad scale; observational studies were assessed for quality using the Newcastle-Ottawa tool; cross-sectional studies and case reports were assessed using the JBI checklist; and systematic reviews were evaluated using the Assessment of Multiple Systematic Reviews (AMSTAR) tool. The Scale for the Assessment of Narrative Review Articles (SANRA) was used for narrative reviews. Only articles that passed the quality appraisal checks were included in the systematic review.

Data Collection Process

We extracted the primary set outcomes and other relevant data from all 12 articles that passed the eligibility and quality appraisal checks. All authors jointly extracted the data and observed outcomes using data extraction questionnaires.

Results

Study Identification and Selection

We identified 584 relevant articles using all databases. In total, 228 duplicate articles were excluded before screening them in detail. After screening these articles by reviewing titles and abstracts and retrieving full texts, 74 articles were selected for eligibility and quality appraisal, and finally, 12 articles were included in the systematic review. The selection process of the studies is shown in Figure 1 in the PRISMA flowchart (Girardelli et al., 2022).

Figure 1: PRISMA flowchart showing the process of article selection. PRISMA: Preferred Reporting Items for Systemic Review and Meta-Analysis

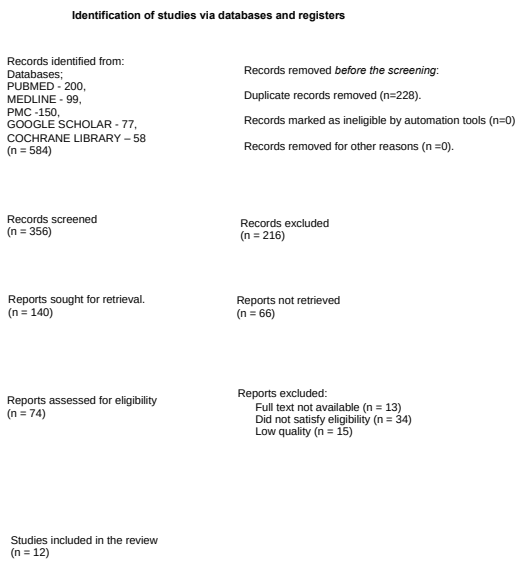

Table 2: showing the final 12 papers included in the review and tools used for quality appraisal.

Author and year of publication	Type of publication	Quality appraisal tool used
Agopiantz et al. 2023	Systematic review	AMSTAR checklist
Ichwan et al. 2023	Narrative review	SANRA checklist
Hoisnard et al., 2022	Observational study	NEWCASTLE OTTAWA TOOL
Janah et al., 2022	Cross-sectional study	JBI CHECKLIST
Weill et al. 2021	Observational study	NEWCASTLE OTTAWA TOOL
Samarut et al., 2021	Observational study	JBI CHECKLIST
Butta et al., 2020	Observational study	NEWCASTLE OTTAWA TOOL
Cetin et al., 2019	Cross-sectional study.	JBI CHECKLIST
Shu et al., 2018	Observational study	NEWCASTLE OTTAWA TOOL
Jiet et al. 2016	Randomized clinical trial	JADAD SCORE
Jiet et al. 2015	Observational study	NEWCASTLE OTTAWA TOOL
Touat et al. 2014	Case report	JBI CHECKLIST

Outcomes Measured

The primary data obtained from the articles include; information on study type and design, the number of participants included in the study, if applicable, and data on the pathogenesis, prognosis, and treatment outcomes of meningiomas concerning estrogen and progesterone receptor expression levels. The secondary data obtained include epidemiology, histologic grade, and meningioma type concerning hormone receptor expression. Based on the p-value, confidence interval, or other statistical indices applicable to each study, we then decided whether there was a positive association between hormone receptor expression (or hormonal modulation), improved treatment outcomes, and a better prognosis.

Study Characteristics

We reviewed 12 research papers with a total of 507,880 participants. The 12 papers comprise one systematic review, narrative review, case report, randomized clinical trial, cross-sectional studies, and observational studies. Some studies focused on the expression of hormone receptors in meningiomas using immunohistochemical methods and related the expression level to histologic type, tumour location, tumour grade, prognosis, and clinical outcomes. In contrast, others focused on the effect of hormonal modulation on the biological behaviour of meningiomas. A few were population-based observational studies that analyzed the association between using exogenous hormones and the overall risk of developing meningioma.

Table 3: Showing the summary and characteristics of all the included studies.

Author and year of publication	Type of study and study period	Purpose of study	Number of participants	Results/conclusion	A positive association between PR/ER expression and therapy with better prognosis/ treatment outcomes.
Agopiantz et al. 2023	Systematic review. 1990 to 2022	To synthesize the epidemiologic, histopathologic and hormone receptors expression of meningiomas with a prognostic and therapeutic perspective.	N/A	Progesterone receptor expression is a favourable prognostic factor. However, there is a negative correlation between survival and the presence of oestrogen receptors.	YES
Ichwan et al. 2023	Narrative review.	To discuss the relationship between progesterone and oestrogen receptors and the pathogenesis of meningioma.	N/A	Progesterone receptors play a role in the aetiology and prognosis of meningioma.	YES
Hoisnard et al., 2022	A population-based case-control study. 2009-2018.	To determine the association between cyproterone acetate and intracranial meningioma.	25,216 cases were included (75% were women)	Progestogen exposure increased the risk of meningioma for all histologic grades and sites, especially the anterior and middle skull base: OR = 35.7 (95% CI 26.5– 48.2)	YES
Janah et al., 2022	Cross-sectional observational study. 2017-2020	to determine if progesterone is an important prognostic factor in orbital meningiomas.	44 cases of orbital meningioma	PR expression is a good prognostic factor in meningiomas. There was a statistically significant differential PR expression between WHO grades I and III (p = 0.024).	YES
Weill et al. (2021).	Observational cohort study.	To determine if the use of high-dose cyproterone acetate is a risk factor for the	253, 777 females aged 7-70 years living in France	A dose-effect relationship was observed between using cyproterone acetate and	YES

	2007 and 2014.	development of meningioma.	who started cyproterone acetate between 2007 and 2014.	the risk of developing intracranial meningioma. The incidence of meningioma in the exposed and control groups was 23.8 and 4.5 per 100 000 person-years, respectively.	
Samarut et al., 2021	Cross-sectional study 2014 to 2017.	to determine the prevalence of CPA exposure in patients with one or more intracranial meningiomas treated with surgery or radiation.	388 cases	The CPA-exposed group had an earlier onset of meningiomas compared to the control group at 48.9 years vs 61.9 years (p = 0.0005) and had more multiple meningiomas, 26.7% vs 6.1% (p = 0.0115).	YES
Butta et al., 2020	Observational study. 2016 to 2019.	To determine the epidemiological and hormonal factors involved in the development of Meningiomas	50 patients	There was a statistically significant association between histological grade and PR expression (p=0.0002)	YES
Cetin et al., 2019	Cross-sectional study. 2007 – 2028.	To examine the relationships between PR and ER expression in meningiomas and prognosis.	74 cases	There was a statistically significant difference in OS based on PR status. (p= 0.035).	YES
Shu et al., 2018	Retrospective case-control study. 2011–2016.	To investigate the link between HRT use and the pathogenesis of meningioma.	629 females	HRT is associated with an increased risk of meningioma (odds ratio [OR], 1.2; 95% confidence interval [CI], 1.0–1.4)	YES
Ji et al. 2016	Randomized clinical trial	To determine if mifepristone is effective in the treatment of unresectable meningiomas.	164 patients	The patients treated with mifepristone did not have a better treatment outcome than those who received a placebo.	NO
Ji et at. 2015	Population-based cohort study.	To determine if breast cancer patients treated with tamoxifen had a lower incidence of meningioma compared with those who did not receive tamoxifen.	227, 535 cases	The risk of meningioma is higher in women who did not receive tamoxifen, with a SIR of 1.54 (95% CI 1.30–1.81).	YES
Touat et al 2014	Case report	To demonstrate the effectiveness of the anti-progesterone agent mifepristone in the treatment of meningioma	3 cases	The treatment was well tolerated, with a long-lasting clinical and radiological response. All three patients are now stable after five to nine years of treatment.	YES

Table 3: Summary of the included studies
PR - progesterone receptor. ER – estrogen receptor. CPA - cyproterone acetate. HRT – hormone receptor therapy. OS – overall survival. SIR – standardized incidence ratio. N/A – not applicable.

The neoplastic and non-neoplastic lesions that mimic meningiomas are diverse and are listed in the table below (Ohba et al., 2019):

	Examples	**Hormone receptor status/immunohistochemistry antibody expression.**
Primary brain tumours	Solitary fibrous tumour/hemangiopericytoma	CD34, STAT6.
	Gliosarcoma	GFAP.
	Leiomyosarcomas	CD34.
	Melanocytomas	Melan A, HMB45, S100.
	Hodgkin lymphoma	Hodgkin and Reed-Sternberg cells are positive for: PAX5 (weak), CD30, CD15 (75 - 80% of cases) MUM1.
	Plasmacytomas	CD38,138. CD79a.
Non-neoplastic lesions	Inflammatory pseudotumor	Vimentin, actin.
	Plasma cell granulomas	Plasma cells: polyclonal kappa and lambda light chains. Spindle cells: vimentin, smooth muscle actin.
	Castleman disease	Hyaline vascular variant: CD21, CD23, CD35, EGFR, VCAM1 / CD106. Plasma cell variant: CD138, polytypic light chains.
	Xanthomas	-
	Rheumatoid nodules	-
	Rosai Dorfman disease	-
Infectious lesions	Tuberculomas	-
Bone hyperostosis	Paget's disease	-
	Fibrous dysplasia	-
Specific location differentials		
Cerebellopontine angle	Vestibular schwannoma	S100, Calretinin, CD 56
Pituitary region	Pituitary macroadenoma.	Adrenocorticotrophic hormone, growth hormone, prolactin.
	Craniopharyngioma	Pancytokeratin, beta catenin.
Skull base	Hypertrophic pachymeningitis.	-
	Extramedullary haematopoiesis.	-
	Chondrosarcoma.	S100
	Chordoma.	Cytokeratin, brachyury

CD - cluster of differentiation, EGFR - epithelial growth factor receptor, HMB 45– Human melanoma black 45, MUM 1– multiple myeloma 1, PAX 5- paired box family of transcription factors 5, STAT6 - Signal transducer and activator of transcription 6, VCAM – vascular cell adhesion molecule.

Table 4: shows the differential diagnosis of dural based lesions and their hormone receptor status.

Discussion

Epidemiology

The data on incidence and prevalence across the reviewed studies show that meningioma is the most common intracranial neoplasm, with a preponderance of cases in adults and the female population, according to Shu (2019). Meningioma accounts for about one in four brain tumours in adults, and incidence studies conducted in the Nordic countries in population-based registries have demonstrated an increasing incidence over time, especially among women (Shu et al., 2019). Butta, in 2020 found that the proportion of meningioma in females was significantly higher than that of males ($Z= 5.65$; $p<0.001$); and that females develop meningiomas at a younger age with a mean age of 44.42±13.79 years and age range of 8-72 years. Ichwan et al. 2023 reported a similar finding that meningiomas occur three times higher in women than men, with the difference most considerable at ages 30 to 59. Agopiantz (2023) reported that meningioma is the only cerebral tumour that has a female predominance, with a female-to-male ratio of 2:1.7. It was noted that this ratio varies from one physiologic state to another, with the incidence of meningiomas said to increase after puberty, bringing the male-to-female ratio to 3:1 in women of childbearing age (Agopiantz et al.,2023).

Classification and tumour grading

Out of the 12 studies reviewed, only two stratified their cases into WHO histological grades and both studies reported that most were benign WHO grade I tumours. Buta et al. (2020) reported that 43 of the 50 analyzed cases were WHO-grade I meningiomas ($Z=10.75$; $p<0.0001$), while Janah et al. (2022), in their review of 44 orbital meningiomas, found that 59.1% of patients (26) had WHO Grade I tumours. This finding also correlates with what Ichwan et al. (2023) and Agopiantz et al. (2023) reported in their studies.

Role of Progesterone and Estrogen in the Pathogenesis of Meningioma

Gender, Tumour Localization, Tumour Type, Tumour Grade and Hormonal Content

Almost all the studies reviewed reported that meningiomas expressed progesterone receptors. Agopiantz et al. (2023) reported in their systematic review that 78.5% of meningiomas that developed in females expressed progesterone receptors (95% CI: 73–84) as compared to 65.1% of meningiomas in males (95% CI: 57–73.2). The study also noted that the expression of progesterone receptors in meningiomas tends to decrease with age. In the postmenopausal state, it was reported that 78.2% of meningiomas that developed in a pre-menopausal context expressed progesterone receptors (95% CI: 61.9–94.5) as compared to 68.4% of meningiomas that developed in a postmenopausal context, 95% CI: 62.6–74.2 (Agopiantz et al., 2023).

Generally, it was reported that lower-grade meningiomas expressed higher progesterone receptors. Janah (2022) found decreased mRNA PR expression in higher-grade orbital meningiomas; a statistically different PR expression was observed between WHO grade I and III groups ($p = 0.024$). This finding is also in line with what was reported by Agopiantz et al. (2023) that 76.8% of grade 1 meningiomas expressed progesterone receptors compared to 61.2% of WHO grade 2 and 17.3% of WHO grade 3 meningiomas while lower expression of oestrogen receptors was found in 8.7%, 1.6% and 6.8% of WHO grades 1, 2, and 3 meningiomas, respectively. This finding was also corroborated by Cetin et al. (2020), who found a statistically significant negative correlation between PR staining intensity and tumour grade ($p< 0.022$). The presence of oestrogen receptor expression was associated with a worse prognosis or worse outcome by Ichwan et al. (2023) and Buta et al. (2020), while Cetin (2020) found no statistically significant correlation between ER expression and tumour grade and prognosis.

According to Agopiantz et al. (2023), out of all the histologic subtypes of meningioma, meningothelial meningiomas expressed progesterone receptors the most (81.1%) (95% CI: 75.5–86.7) followed by transitional meningiomas (75.8%). This is also similar to what was found in the study by Buta et al. (2020), who reported a statistically significant association between histological subtypes of WHO and PR expression of the patients ($p<0.0001$) and that of all the subtypes that were positive for PR, meningothelial meningioma was the most common (38%), followed by transitional meningioma (28%).

Meningioma and Pregnancy

According to Agopiantz et al. (2023), all the cases (100%) of meningiomas that developed in pregnant and postpartum patients expressed progesterone receptors, while estrogen receptors were expressed in only 20%.

Meningioma and Exogenous Hormone Therapy

The papers in this systematic review confirmed an association between using exogenous hormones and an increased risk of meningiomas.

A solid dose-effect relationship was observed between using cyproterone acetate and the risk of developing intracranial meningiomas in a large population-based study (Weil et al., 2021). The study included 253,777 females aged between 7-70 in France who started cyproterone acetate between 2007 and 2014. In the study, sixty-nine patients with meningiomas in the exposed group and twenty in the control group were treated by surgery or radiotherapy. The incidence of meningioma in the exposed and control groups was 23.8 and 4.5 per 100 000 person-years, respectively (crude relative risk 5.2, 95% confidence interval 3.2 to 8.6; adjusted hazard ratio 6.6, 95% confidence interval 4.0 to 11.1) and after discontinuing cyproterone acetate for one year, the risk of meningioma in the exposed

group was found to be 1.8-fold higher (1.0 to 3.2) than in the control group.

In a similar sizeable population-based case-control study in France by Hoisnard et al. (2022), they studied the association between surgical intervention for intracranial meningiomas and exposure to three potent progestogens: cyproterone acetate (CPA) (≥25 mg/day), nomegestrol acetate (NOMAC) (3.75– 5 mg/day) and chlormadinone acetate (CMA) (2– 10 mg/day). A statistically significant association was identified between the prolonged use of CPA (OR = 22.7, 95% CI 19.5– 26.4), NOMAC (OR = 6.5, 95% CI 5.8– 7.2) and CMA (OR = 4.7, 95% CI 4.5– 5.3) and the increased incidence of intracranial meningioma. It was also reported that progestogen exposure increased the risk of meningioma for all histological grades and anatomical sites, particularly for the anterior and middle skull base (Hoisnard et al., 2022).

Findings from another large multi-centre hospital-based case-control study in China by Shu et al. in 2014 also confirmed the relationship between exogenous hormones and increased risk of meningiomas. The study observed that prior use of hormone replacement therapy (HRT) is associated with an increased risk of meningioma (odds ratio [OR], 1.2; 95% confidence interval [CI], 1.0–1.4) and the association was found to be more prominent among women having multiple HRT and longer-term exposure (OR, 1.3; 95% CI, 1.1–1.6). This positive association between HRT and increased meningioma risk was also found to be more among those who received combination therapy of estrogens and progestogens (OR,1.3;95% CI,1.1–1.7) compared to those with only monotherapy. (Shu et al., 2014).

This finding was also corroborated by another large landmark cohort study in Sweden that included all women diagnosed with breast cancer (227,535 women) between 1961 and 2010 (Ji Y et al., 2015). In the study, women diagnosed with breast cancer after 1987 were defined as tamoxifen-exposed, while those diagnosed before or during 1987 were defined as not exposed to tamoxifen. Of these women, 223 were reported to have developed meningiomas after using Standardized Incidence Ratios (SIRs) to calculate the risk. For those without tamoxifen exposure, the risk of meningioma was significantly increased, with a SIR of 1.54 (95% confidence interval 1.30–1.81), while the risk was not increased in those with tamoxifen exposure (SIR=1.06, 95% confidence interval 0.84–1.32). It was also noted that the increased risk of meningioma in women without tamoxifen exposure persisted during ten years of follow-up (Ji Y et al., 2015).

The positive association between meningioma development and hormone exposure was confirmed by another cohort study using three hundred eighty-eight patients with intracranial meningioma treated with surgery and radiotherapy. It was found that 3.9% of the patients had a history of prior or current use of cyproterone acetate (CPA), while 16.2% were taking other forms of hormonal treatment (Samarut et al., 2021). Compared with the group without hormonal exposure, the CPA-exposed group had a significantly earlier onset of meningiomas at 48.9 years vs 61.9 years (p = 0.0005) and had more multiple meningiomas, 26.7% vs 6.1% (p = 0.0115) (Samarut et al., 2021).

In the study, Agopiantz et al. (2023) also reported a positive association between the use of exogenous hormones and subsequent increased risk of meningioma. They found that 89% of meningiomas that developed under hormonal treatment expressed progesterone receptors (95%CI:78.7–99.3) as compared to 71% of meningiomas that developed without any form of hormonal treatment or exposure, 95% CI: 66.3–75.7 (Agopiantz et al., 2023).
However, some studies have reported conflicting results. According to one of the papers in the narrative review by Ichwan (2023), a cohort study that used 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, while another paper using 219 females enrolled in a case-control study at several hospitals in Chicago found that oral contraceptives had a protective effect against meningiomas. However, another study in Surabaya, Indonesia, found that oral contraceptives can increase the risk of meningioma by 18.2 times (Ichwan et al., 2023).

Role of Progesterone and Estrogen Treatment of Meningioma

Despite the existential evidence about the association between progesterone receptors in particular and the growth of meningiomas, attempts at treatment of meningiomas using antiprogestin or progesterone receptor blockers have yielded conflicting results.

In a case report, Toutat et al. (2014) described three women who had multiple benign WHO grade I meningiomas that were treated successfully with mifepristone (RU 486), a synthetic competitive inhibitor of the progesterone receptor. Mifepristone causes irreversible inhibition of the transcriptional activity of the progesterone receptor by altering its conformation and causing DNA modification signalling through promoter interference at concentrations much lower than progesterone. The treatment was said to have been successful and resulted in long-lasting clinical and radiological responses five to nine years post-treatment. However, such isolated cases like this do not provide enough convincing evidence about the success of hormonal therapy in the definitive treatment of meningioma, especially in high-grade meningioma or surgically unresectable cases (Toutat et al., 2014).

A Double-Blind Phase III randomized trial of the antiprogestin agent mifepristone in the treatment of unresectable meningioma failed to demonstrate mifepristone's efficacy in treating meningioma. (Ji, Y et al., 2015). The study enrolled 164 eligible patients, out of which 80 were randomly assigned to mifepristone and 84 to placebo (Ji, Y et al., 2015). Only twenty-four

patients (30%) could complete two years of mifepristone without disease progression, adverse effects, or other reasons for discontinuation. In comparison, twenty-eight patients (33%) in the placebo arm completed the 2-year study. It was reported that the overall survival (OS) was not significantly better in the mifepristone treatment arm as compared to the placebo treatment group (estimated mifepristone to placebo HR, 1.05; 95% CI, 0.69 to1.59; two-sided P=.84).

Notably, the patient's tumour hormone receptor status was only considered in this trial after treatment commenced. Thus, some patients, particularly those with aggressive tumours, lacked progesterone receptors. The two-year follow-up period was too short to evaluate the effect of mifepristone. Finally, standard radiological evaluation may not be appropriate for these slow-growing tumours, which ideally require a volumetric measure of the growth rate before and after treatment, an essential factor that was considered by Toutat et al. in the evaluation of their cases (Toutat et al., 2014).

In one of the papers reviewed by Ichwan et al. (2023), a meta-analysis discussing the therapeutic effect of mifepristone on meningioma concluded that there is still no clear enough evidence to recommend this agent for managing meningioma. Another study recommended that mifepristone can treat progesterone-receptor-positive meningiomas at a daily dose of 200 mg (Karena et al., 2022).

Conclusion

This systematic review has provided an overview of the current knowledge about the expression and role of estrogen and progesterone hormone receptors in the pathogenesis, management and prognosis of meningioma in females. Based on the papers reviewed, progesterone receptors are associated with significantly more favourable prognostic factors and better treatment outcomes. At the same time, a negative correlation exists between overall survival and the presence of estrogen receptors. Therefore, we believe the data concerning progesterone receptor expression in meningiomas are currently the strongest. In contrast, information on estrogen receptor expression is still patchy and requires further study. Analyzing hormone receptor expression in meningiomas appears necessary for targeted hormonal and endocrine therapy. A suitable reference population must also be defined in future more extensive prospective multi-centre and multi-national clinical studies.

Limitation

This systematic review had some limitations; not enough information was obtained about estrogen receptor expression in meningiomas (as most of the studies had information mainly on progesterone receptors); most of the studies also did not provide enough information on the correlation between hormone receptor expression, precise tumour location, histologic subtype and WHO grades.

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Conflict of Interests

The authors declare no conflict of interest whatsoever.

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