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► **To cite this version:**

Caroline Apra, Paul Roblot, Abdu Alkhayri, Caroline Le Guérinel, Marc Polivka, et al.. Female gender and exogenous progesterone exposition as risk factors for spheno-orbital meningiomas. *Journal of Neuro-Oncology*, 2020, 149 (1), pp.95-101. 10.1007/s11060-020-03576-8 . hal-03270880

HAL Id: hal-03270880

<https://hal.sorbonne-universite.fr/hal-03270880v1>

Submitted on 25 Jun 2021

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Female gender and exogenous progesterone exposition as risk factors for sphenoorbital meningiomas

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Key words : sphenoorbital meningioma, skull base meningioma, progestin, cyproterone acetate, nomegestrol acetate, osteomeningioma

Abstract word count: 250

Manuscript word count : 2,060

Tables : 2

Figures : 1

Abstract:

Objective: The great heterogeneity of meningiomas is challenging and we need to distinguish relevant subgroups. Spheno-orbital osteomeningiomas (SOOM) constitute a clinically specific entity, with slow-growing benign osteo-meningiomatous tumors, which recur after surgery in one fourth of cases. Neurosurgical daily practice, supported by the literature, shows that the vast majority of patients with SOOM are women, and we explored whether their epidemiological and hormonal profiles suggest a progesterone influence.

Methods: We retrospectively documented all radiologically and histologically confirmed cases of SOOM operated in 2005-2019 in our institution. We completed the clinical and hormone history by systematic telephone interviews.

Results: In the literature, SOOM occur significantly more often in women than other meningiomas (749/847, 86.4% versus 73.8%, $p=0.002$). Among 175 cases, we included 124 patients, 93.5% were women, younger than men (51 ± 5 versus 63 ± 8 , $p=0.02$). Women' meningiomas showed more progesterone receptors (96.4% versus 50%, $p<0.001$). Exogenous hormonal intake, reliable in 82 cases, concerned 83.3% (64/78) of women, with frequent progesterone intake: 13 oestroprogestogenic treatment only, with old-generation progesterone analogs, 41 progesterone analogs (cyproterone acetate, nomegestrol acetate, chlormadinone, promegestone, etonogestrel, levonogestrel), 7 substitutive hormonal therapy for menopause, 3 others. Duration of treatment was 2-40 years, median 10 years.

Conclusions: SOOM develop preferentially in women in their fifties, who often received progesterone analogs, and show progesterone receptors. Progesterone analogs are incriminated in skull base meningiomas, and this is the first report on the prevalence of exogenous hormone therapy specifically in SOOM. Whether SOOM reduce after treatment discontinuation, in particular the osteoma part, needs to be explored. Anti-progesterone treatments may represent an avenue for future research in SOOM.

Introduction

Meningiomas, the most frequent primitive intracranial tumors, form a heterogeneous group, with growing evidence that anatomical and molecular subgroups must be identified in order to unveil the mechanisms underlying their genesis and clinical evolution¹. It has been shown that some types of meningiomas develop in specific locations and that the genetic profile of tumors located in the skull base is quite different from the profile of convexity meningiomas². Exogenous factors, such as hormone treatment, that is being increasingly described in meningiomas development, seems to be incriminated in some locations specifically, in particular in the skull base³⁻⁵.

We believe that a precise description of some clinically relevant subgroups of tumors is necessary and we chose to focus on the spheno-orbital meningiomas because clinical practice shows that almost all patients are middle-aged women, and the literature confirms this impression, as described in this study. Spheno-orbital meningiomas form 2-9% of all meningiomas and can be segregated into a separate entity since they are mostly formed of osteomeningiomas, with grade 1 meningothelial lesions⁶. Spheno-orbital meningiomas are revealed by proptosis in 95% of cases, associated with visual impairment and oculomotor paresis. When treatment is indicated, surgery is compulsory, with good functional results, but complete resection is not feasible and many cases recur, needing adjuvant radiotherapy or repeated surgery in one fourth of patients⁶. Therefore, there is a high demand for alternative therapeutic strategies in this subgroup of meningiomas. We provide retrospective monocentric epidemiological data about spheno-orbital meningiomas, with one of the largest series of surgical spheno-orbital meningiomas published until now, and we particularly questioned the frequency of exogenous hormone intake, which has never been reported specifically in this subgroup. We do not detail the surgical strategy or results, which have been largely described in the literature already, including by our team, and are quite consensual now^{6,7}.

Patients & methods

All patients operated for a spheno-orbital meningioma and registered in the local database in 2005-2019 in the neurosurgery department of the Hôpital Fondation Adolphe de Rothschild, Paris, France, were reviewed. We excluded all patients without histological confirmation for a meningioma and all preoperative MRI were reviewed by a senior neurosurgeon, DC, to exclude non typical spheno-orbital locations. Histology was available in all cases and progesterone receptors status was routinely assessed

by immunochemistry and validated by a neuropathologist (MP). Estrogen receptors were not systematically analyzed. Clinical, pathological and radiological data was retrospectively harbored from the medical file and a telephone interview was systematically performed by CA or PR to complete the information and obtain consent from all the patients. We got exhaustive description of the patients' medical history and hormonal intake.

A literature review was performed by CA in Pubmed with the search terms « sphenoorbital meningiomas » and « spheno-orbital meningiomas », according to the PRISMA guidelines. We included all series published between 2010 and 2019 with histological confirmation and excluded those not detailing the sex of the patients. If one department had published several articles about their series, we chose to use only the largest one, in order to avoid including twice the same patient. We consider that there is no reason to suspect a bias of publication or surgical indication based on the sex of the patients. To obtain a comparative cohort of meningiomas, we used the largest published up-to-date meningioma series⁸. Statistical analysis was performed using Excel (Microsoft, Redmond, USA). We used Khi2 test, or exact Fisher test when the conditions of population were not fulfilled.

Results

In our local series, 175 patients were operated for a spheno-orbital meningioma during this period, 124 with complete imaging and histological data. One hundred and sixteen were women (93.5%) and median age for surgery was significantly younger for females (51 ± 5 versus 63 ± 8 , Khi2, $p=0.02$). There was a peak of incidence for women in their fifties (cf figure 1). All meningiomas were associated to an osteoma causing proptosis or loss of vision, which was the indication for surgery. In total, 90.3% of tumors were meningothelial grade 1 meningiomas (112/124), including all tumors in males, 4 were transitional, 2 atypical, the others angioblastic, psammomatous, secretory and microcystic. Progesterone receptors were found in more than 10% of cells in meningiomas in 96.4% of females, and 50.0% of males, which is significantly higher in women (exact Fisher test, $p<0.001$; IC95% [0.0065;0.3345]).

We could complete a reliable retrospective history for the patients in 82 women and 4 men, and reliable hormone history in 78 women and 4 men, the others could not be contacted after 3 phone calls ($n=38$, among which at least 2 dead patients), had doubts about taking hormones treatment ($n=4$) or refused to answer ($n=1$). Associated diseases included thyroid dysfunction, hypertension, diabetes, and others, as expected in the general population. No patient had received cranial radiotherapy or was

diagnosed with neurofibromatosis. 8.3% of patients had multiple meningiomas (7/84, 3 bilateral sphenoidal meningiomas). No woman was pregnant at the time of diagnosis or surgery, 42% were premenopausal, 12% were perimenopausal and 46% were postmenopausal. Gynecological comorbidities included uterine fibroids, breast fibroadenomas and cancers, ovarian cysts, cervical dysplasias and endometriosis in proportions similar to the general population.

Exogenous hormonal intake concerned 83.3% (65/78) of female patients, among which 25 were premenopausal, 9 perimenopausal and 31 postmenopausal: 61 patients have a relatively precise hormonal history (13 received only oestrogenic treatment, 41 received progesterone analogs, and 7 received substitutive hormonal therapy for menopause without precision), whereas 2 patients did not remember the type of contraception they took, one patient received only progesterone ointment, one patient reported *in vitro* fertilization, in addition to 2 patients with ovarian stimulations. (cf figure 1). The molecules are detailed in table 1. All documented oestrogenic pills contained old-generation progesterone analogs. Retrospective recollection of treatment duration was incomplete, and was reported between 2 and 40 years, median 10 years. Among patients with multiple meningiomas, all of them were women and received hormones (1 oestrogenic treatment, 4 progesterone analogs, 1 substitutive hormonal therapy for menopause). All patients were advised to stop exogenous hormones intake after surgery.

Repeated surgery was necessary in 21.0% of patients for recurrent symptoms (26/124, 25 women, 10 premenopausal, 6 perimenopausal and 9 postmenopausal). Among them, information about hormone intake was available in 16: 12 received exogenous progesterone (75%), 1 received oestrogenic pill (6.5%), 1 received substitutive hormonal therapy for menopause (6.5%), and 2 received no hormone (13%), but one of them had 8 pregnancies. Reliable information about the 48-year-old male patient could not be obtained retrospectively but erectile dysfunction was mentioned in his medical file, suggesting hormonal abnormality.

BMI at the time of surgery was difficult to assess reliably in the retrospective cohort, but the mean BMI, in 38 women, was 24.8 ± 1.8 , with 16 overweight (BMI > 25, 42%) and 8 obese patients (BMI > 30, 21%). These figures tend to be higher than the general female population in this region, respectively 23.9% and 10.1% (Khi2; $p=0.06$ and $p=0.07$)⁹.

In the literature review, we found 83 publications between 2010 and 2019, among which 24 series of sphenoidal meningiomas, and we excluded 7 series because they lacked some relevant data¹⁰⁻¹⁶. Two teams published their series twice in this period^{6,17-19}, and we excluded the smaller one in each case. Thus, we identified 14 articles each reporting 13 to 130 patients, as detailed in table 2^{6,18,20-31}. We pooled those cases with our patients to obtain a population of 847 patients with surgical sphenoidal

orbital meningiomas. Among them, 749 were women. Statistical analysis showed that the proportion of women among patients with spheno-orbital meningiomas is significantly higher than in patients with meningiomas in general when this literature series is compared with the largest meningiomas series, that describes 81.475 female for 110.359 cases (86.4% versus 73.8%, Khi^2 , $p=0.002$)⁸. Other risk factors, such as body mass index, radiation history or hormone intake, were not described in the other series.

Discussion

Until now, spheno-orbital meningiomas had not been identified as a subgroup of meningiomas particularly prone to hormonal influence, which our study tends to suggest. Indeed, meningiomas develop more often in women than in men⁸, but spheno-orbital meningiomas develop spectacularly more often in women, with 86.4% of patients being female in our literature review and 93.5% in our series. The fact that women were significantly younger than men at the time of surgery could also be linked to the fact that spheno-orbital osteomeningiomas might grow more quickly with the female endogenous hormonal exposition. It is difficult to interpret data about pregnancies and menopause, because they are slow-growing tumors usually revealed by proptosis at a late stage, and the time of surgery may not reflect the time of development. Only 6.0% of patients in our series had multiple meningiomas, which is quite low compared to the literature (up to 38.7%⁶).

We found, by precisely questioning the patients, that the exogenous progesterone exposition seems particularly high in this group. It is challenging to define which treatment should be defined as excessive progesterone intake, since many women take, for instance, oral contraception or substitutive hormonal treatment for menopause. Therefore, we relied on already published data to focus on drugs that have been incriminated before in meningiomas development: they mainly consist of high dose progesterone treatments, especially cyproterone acetate, norgestrel acetate and chlormadinone, but any type of hormonal treatment could potentially be at risk and was included in our study^{32,33}. Levonogestrel has also been reported as inducing meningioma growth³⁴. Progesterone-only contraception is suspected, but it seems that there is no risk increase for oestrogen-only and oestrogen-progesterone contraception⁴. The association of meningiomas with some gynecological comorbidities, such as uterine fibroids, has been described but was not confirmed in our series³⁵.

The possibility that hormones dependent meningiomas develop in specific cranial areas has been suggested by a number of publications, especially in the skull base³⁻⁵, but spheno-orbital meningiomas

specifically were not reported until now: Passeri et al. reported meningiomas on the sphenoid ridge, the clivus, the clinoid and the frontal convexity that decreased after stopping nomegestrol acetate³⁶. Champagne et al. described a parasagittal meningioma that increased with both nomegestrol acetate and cyproterone acetate³⁷. Cyproterone acetate discontinuation was reported in decreasing meningiomas of various locations, preferentially the skull base, but no spheno-orbital case^{3,38}. Harland et al. documented a series of 67 female patients with grade I meningiomas and also found that, in patients who took progesterone-only contraception, there was a tendency for meningiomas located at the skull base compared to patients who took other types of contraception⁴. The anterior skull base predominance was also described by Peyre et al. in cyproterone acetate, megestrol acetate and chlormadinone acetate dependent operated meningiomas⁵. Subcutaneous Levonorgestrel implant has been reported as inducing sphenoid wing meningioma growth³⁴. Fertility treatments are also associated with multiple meningiomas in patients younger than the average³⁹. Our results show, for the first time, that spheno-orbital meningiomas seem to be a particularly relevant subgroup in analyzing exogenous hormonal intake. Contrary to the other hormonal treatments, fertility treatments were found to increase the risk of convexity meningiomas, which seems consistent with the low proportion of women with a spheno-orbital meningioma having benefited from this type of treatment (only 1 in vitro fertilization and 2 ovarian stimulations).

The limits of our retrospective study are the lack of precision about the treatments duration, doses and even the molecule the patients received, especially because hormonal therapies are often not considered as medication by the patients themselves, or by their surgeon. Bias of recall have been evaluated in the literature before, and it is established that recall of treatment use is relatively reliable, for both oral contraception and hormone replacement therapy, but that the patients have great difficulty remembering the name of the drug and the dates of use³³. To improve the quality of recall in future studies, interviews should be based on drug lists or photo prompts. In addition, we were not able to contact all patients, and only part of the cohort could be analyzed. These limits should however not impact the sex ratio or overestimate the prevalence of exogenous hormones intake in the population.

As compared to other published cases, our series focuses on surgically treated and histologically confirmed spheno-orbital meningiomas, and therefore cannot answer a central therapeutic question: how often do spheno-orbital meningiomas regress after stopping hormonal therapy? We need to know more about the natural history of spheno-orbital meningiomas, for instance in patients who do not have visual impairment. The fact that no spontaneous regression of spheno-orbital meningiomas has been described before in patients taking progesterone analogs yet may be due either to the scarcity of reported cases compared to the clinical experience of each neurosurgeon, or to the fact that an

osteoma is associated and symptomatic in most cases, and might not regress as often as the meningeal part of the tumor. The results in our series about this question are incomplete and inconclusive: although the 3 patients with bilateral sphenoidal osteomeningiomas did not need contralateral surgery, 21% of operated patients needed ipsilateral reintervention despite having stopped hormonal treatment, even in 9 post-menopausal women. Thus, we observe that, once the sphenoidal meningioma has developed, stopping the treatment will not systematically lead to tumor regression.

Although meningiomas hormonal dependency is now well established, the mechanisms underlying this risk factor are not understood yet. Factors include endogenous and exogenous hormonal sources: sex, age, overweight, treatments. On the histological point of view, progesterone receptors are present in about 70% of the meningiomas, a property that has been described for many years now⁴⁰. There is conflicting evidence about the correlation between the sex of the patient and the presence of progesterone or estrogen receptors^{41,42}. However, it seems that progesterone receptors are more expressed in progestin-dependent meningiomas, although they are not found in all cases⁵. There is no evidence linking the quantity of hormone receptors to tumor growth under treatment, and, conversely, progesterone receptors are regularly found in patients who never took hormonal treatments. In our series, sphenoidal meningiomas in women had significantly more progesterone receptors than the rare cases found in men (96.4% versus 50%), which seems to confirm the role of endogenous or exogenous progesterone on the tumor's growth. The exact type and proportion of receptors need to be described more thoroughly in those cases.

In general, progesterone receptor expression is a good prognostic sign, particularly when considered with a low mitotic index and a low grade⁴³, but this is apparently not the case in sphenoidal meningiomas, with a high rate of symptomatic recurrences in grade 1 meningothelial tumors. Unfortunately, most histological studies do not detail the localization of meningiomas enough to identify sphenoidal meningiomas specifically, and we suspect sphenoidal meningiomas were systematically excluded from some studies, since complete resection of the osteoma and the en plaque part cannot be achieved⁴⁴. The progesterone inhibitor mifepristone has been proposed to treat recurrent or unresectable meningiomas with a good efficacy *in vitro*, but it had contradictory results *in vivo*, with minimal or temporary efficacy in some cases, which could mean that we still lack criteria to predict which patients will benefit from it⁴⁵⁻⁴⁷. This type of treatment may represent an avenue for future research in sphenoidal meningiomas specifically. In addition, a particular molecular profile for sphenoidal meningiomas has not been described yet, but there is evidence that specific locations are associated with specific molecular patterns, in particular mutations in *TRAF7/AKT1* and *SMO* are found in meningiomas that develop in the anterior fossa, median middle fossa, or anterior calvarium, most of them being meningothelial or transitional meningiomas^{2,48}. There is also evidence

that exogenous hormones may induce specific molecular profiles in meningiomas, with a higher frequency of *PIK3CA* and *TRAF7* mutations⁵.

Conclusion

Spheno-orbital meningiomas are a homogeneous subgroup of meningiomas, with an important osseous part, nearly all being grade I tumors with progesterone receptors, that typically develop in women in their fifties, a large proportion of which have received high-dose progesterone in their lifetime. Our study is the first report on the prevalence of exogenous hormone therapy specifically in spheno-orbital meningiomas. Systematic recollection of hormonal history at the time of diagnosis is necessary and additional epidemiological or histological data may help understand specific molecular patterns found in these tumors. Progesterone inhibitors may represent an avenue for future research in this specific type of osteomeningiomas, to complete the surgical management in frequent recurrent cases.

Legend:

Table 1: Detailed exogenous hormone intakes in 61 women with spheno-orbital meningiomas (78.2%); 41 received progesterone therapies and 13 only oestroprogestogenic treatments, all containing old-generation progesterone. The remaining 7 received substitutive hormonal treatment for menopause, without precision. In addition, 2 received contraception pills they could not remember, 1 progesterone ointment and 1 underwent in vitro fertilization, so that 64/78 (83.3%) received exogenous hormones.

Table 2: Literature review of series of spheno-orbital meningiomas in 2010-2019. The number of female patients is detailed in the third column. Compared to the largest series of meningiomas in general (Dolecek et al., 20128), spheno-orbital meningiomas develop significantly more often in women ($p=0.002$).

Figure 1: Description of patients with operated sphenoidal meningiomas A: Age repartition of patients with a sphenoidal meningioma, solid line: women, dotted line: men, with a 5 years mean. Age of surgery is significantly lower in females, and there is a peak of incidence in women around 51-52 years (51 ± 5 versus 63 ± 8 , $p=0.02$). B: Repartition of exogenous hormone intake in 78 women with sphenoidal meningiomas ; 41 received progesterone therapies ; 13 received only oestrogenic treatments ; 7 received substitutive hormonal treatment for menopause.

Disclosure: the authors declare no conflict of interest. The authors declare no funding.

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Table 1: Literature review of series of sphenoidal meningiomas in 2010-2019. The number of female patients is detailed in the third column. Compared to the largest series of meningiomas in general (Dolecek et al., 2012⁸), sphenoidal meningiomas develop significantly more often in women (p=0.002).

Reference	N. of patients	N. of women
Honig et al., 2010 ²²	30	22
Schick et al., 2010 ²⁷	77	61
Saeed et al., 2011 ¹⁷	90	85
Oya et al., 2012 ²⁶	39	34
Solmaz et al., 2014 ²⁸	13	3
Forster et al., 2014 ¹⁹	18	18
Leroy et al., 2016 ²⁴	70	64
Freeman et al., 2017 ²⁰	25	23
Terrier et al., 2018 ⁶	130	119
Gonen et al., 2018 ²¹	27	24
Mashcke et al., 2019 ²⁵	31	27
Young et al., 2019 ³⁰	24	22
Kiyofuji et al., 2019 ²³	47	38
Terpolilli et al., 2019 ²⁹	122	93
Our series	124	116
TOTAL	867	749

86.4% *

Dolecek et al., 2012 ⁸	110,359	81,475
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73.8% *

Table 2: detailed exogenous hormone intakes in 61/78 women with speno-orbital meningiomas (78.2%) ; 40 received progesterone therapies (51.3%) and 13 only oestroprogestogenic treatments, all containing old-generation progesterone. The remaining 8 received substitutive hormone treatment for menopause, without precision.

Progesterone therapies			Oestroprogestogenic therapies				
Treatment	Molecule	N. of patients	Treatment	Oestrogen	Progesterone analog	Progesterone generation	N. of patients
<i>ANDROCUR</i>	Cyproterone acetate 50mg	9	<i>ADEPAL</i>	Ethinylestradiol 0.030-0.040mg	Levonogestrel 0.15-0.20mg	2	1
<i>COLPRONE</i>	Medrogestone 5mg	1	<i>DIANE 35</i>	Ethinylestradiol 0.035mg	Cyproterone acetate 2mg	2	2
<i>LUTENYL</i>	Nomegestrol acetate 5mg	14	<i>GYNOPHASE</i>	Ethinylestradiol 0.050mg	Norethisterone acetate 1-2mg	1	1
<i>LUTERAN</i>	Chlormadinone 5-10mg	13	<i>GYNOVLANE</i>	Ethinylestradiol 0.050mg	Norethisterone acetate 2mg	1	1
<i>SURGESTONE</i>	Promegestone 0.5mg	1	<i>MINIDRIL</i>	Ethinylestradiol 0.030mg	Levonogestrel 0.15mg	2	4
NEXPLANON – CONTRACEPTIVE IMPLANT	Etonogestrel	2	<i>MINIPHASE</i>	Ethinylestradiol 0.030-0.040mg	Norethisterone acetate 1-2mg	1	1
INTRAUTERINE CONTRACEPTIVE DEVICE	Levonogestrel	1	CONTRACEPTIVE OESTROGENIC PILL	-	-	-	4
		40					13

