

EDITORIAL

WOMEN'S HEALTH

Depot Medroxyprogesterone and Meningioma Risk

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Meningiomas are the most frequent primary brain tumors and the majority are benign.¹ The annual incidence is low: 6 to 8 new cases per 100 000 with a peak in middle-aged patients.² Epidemiological data suggest an association of female sexual



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hormones with tumor incidence and growth. Meningioma is the only intracranial tumor with a clear predominance in women, with increasing incidence after puberty (from 2 to 3.5:1).³ Over 60% of meningiomas express progesterone receptors.³ In known meningioma cases, tumor size increases in periods of higher estradiol and progesterone serum levels, such as during years of childbearing potential, pregnancy, and peripartum.³ Histopathologically, there is a higher proportion of progesterone receptor expression during these periods, underscoring a plausible biological relationship of sexual hormones and meningioma evolution.³

In addition to older age, female sex, Black race, genetic disorders (mostly neurofibromatosis type 2), a family history of meningioma or a history of breast cancer, ionizing radiation, and obesity, treatment with progestogens was recently identified as a risk factor of meningioma.^{4,5} Progestogens are synthetic forms of progesterone and compounds from both main synthetic classes, progesterone-derived (cyproterone acetate, medroxyprogesterone acetate, chlormadinone acetate, medrogestone, norgestrel acetate, and promegestone) and testosterone-derived (desogestrel) have been proven to be dose-dependent risk factors of meningioma, especially after long-term use.⁶⁻⁸

A large epidemiological series, that could correlate the risk of meningioma and progestin treatments arises from the EPI-PHARE/SNDS, a French national health care data system.⁴ The first potent progestin to be incriminated in this vast series (1 300 000 person-years exposed) was cyproterone acetate. The incidence of meningiomas requiring surgery or radiotherapy, the risk of having multiple meningioma surgeries, and meningioma occurring at multiple locations was significantly higher in a dose-dependent manner, with a relative risk (RR) of 28.4 in the highest-exposed group.⁴ Later, the EPI-PHARE group released similar data regarding chlormadinone acetate (RR = 3.1)⁹ and norgestrel acetate (RR = 13).¹⁰ More recently, prolonged use of promegestone, medrogestone, and MPA were associated with increased meningioma risk, with risk ratios of 2.7, 4.1, and 5.6, respectively.⁶ A very low risk of meningioma was recently acknowledged in women taking desogestrel for more than 5 continuous years.⁸

Interestingly, progestogen-associated meningiomas are mainly located in the anterior and middle skull base, likely re-

lated to a higher prevalence of progesterone receptors¹¹ and spontaneous regression has been observed in many cases, including after delivery in pregnancy-induced meningioma or after cessation of treatment in progestogen-associated meningioma.¹² The pattern of tumor regression is fast and, in a few months, the tumor can stabilize or shrink naturally.¹³

In this issue of *JAMA Neurology*, Xiao and colleagues¹⁴ explore meningioma risk associated with depot medroxyprogesterone acetate (dMPA) and other related progestins in a large, retrospective population-based study in the US, using a national federated database. MPA is a progestogen that can be used alone or in combination with estrogens and is indicated for contraception and treatment of secondary amenorrhea, abnormal uterine bleeding, and endometrial hyperplasia prevention, and in patients with inoperable, recurrent, or metastatic endometrial carcinoma. In the US, MPA is thought to be used in one-quarter of women between 15 and 49 years.¹⁴ A previous large case-control study in the US reported increased odds of meningioma in women using injection MPA (odds ratio, 1.53; 95% CI, 1.40-1.67).¹⁵ This association was not observed for oral MPA, became stronger with longer exposure duration, and was specific to cerebral meningiomas.

In the current study,¹⁴ women without a previous diagnosis of meningioma were assigned to 7 groups based on their method of contraception, ie, dMPA, oral MPA, intrauterine devices, combined oral contraceptives, progestin only pills, subdermal implantable contraceptives, or control patients without these contraceptives. First, all groups were matched for other meningioma risk factors, including age, race, neurofibromatosis, history of pregnancy or breast cancer, body mass index (BMI), and previous exposure to radiotherapy, and experimental groups were then compared with controls. In a second, more detailed analysis, all experimental groups were matched across additional covariates and meningioma risk related to dMPA was compared with all other contraception groups.

As the primary outcome, dMPA was associated with an increased RR of 2.43 (95% CI, 1.77-3.33) for a meningioma diagnosis compared with the control population, with a number needed to harm of 1152 patients. Importantly, this risk was limited to a start age of dMPA exposure older than 31 years and an exposure duration of longer than 4 years. Oral MPA was also associated with a significantly increased risk of meningioma compared with controls (RR, 1.18; 95% CI, 1.10-1.27) with a number needed to harm of 3020 patients. Depot MPA showed a significantly increased meningioma risk compared with all other contraceptive methods investigated, including oral MPA.

There was no significantly increased risk for the nonmedroxyprogesterone acetate contraception groups.¹⁴

These findings enrich our understanding of the association between sex hormones and meningioma risk, as most previous studies are based on European populations.^{4,6,10} Divergent study populations likely account for differences in reported sex hormone-associated meningioma risk to date; in particular, there is a higher proportion of Black individuals in the US at 14.4%,¹⁶ compared with only 3.2%¹⁷ of Black individuals in the French population. Obesity in the US is as frequent as 40%,¹⁸ compared with 20%¹⁹ in France. Also, the contraceptive regimen and evaluated progestogens differed between populations.

A clear strength of the current study¹⁴ is the very large population evaluated. The authors chose an elegant statistical design using propensity score matching, which allows focus on the contribution of one risk factor, while controlling for several confounders. As they controlled for race and BMI, their findings have translational value for other populations, such as European populations. Inversely, a limitation of this study design is that interactions between progestogens and other risk factors are not assessed. The authors report that the increased meningioma risk of dMPA was confined to a longer treatment exposure (more than 4 years) and older age at starting dMPA (older than 31 years), indicating a cumulative meningioma risk of age and treatment exposure. Future studies should focus on investigating interactions of progestin exposure (duration, time, and dose) with other known meningioma risk factors. This will, first, further our understanding of underlying biological mechanisms of meningioma occurrence in women and, thus, help to develop potentially non-surgical treatment strategies. Second, it will allow clinicians more individualized counseling and treatment decisions in meningioma risk populations, as currently, the high numbers needed to harm for dMPA and oral MPA reported here indicate an overall low clinical significance that does not justify a modification of the MPA treatment indications. Thus, women using this contraception should not discard it, but discuss with a health care professional if they are concerned about the me-

ningioma risk. Interestingly, Xiao et al¹⁴ found no association between levonorgestrel and meningioma. The same results have been recently found by Roland et al⁹ in France. These combined results might allow for the opening of new fields of clinical research: in women with known meningioma, is levonorgestrel a safe option?

In France, where most epidemiological information comes from, still 10% of meningioma are associated with progestogens,⁶ and in the current study in a US population,¹⁴ among those who used dMPA compared with controls and developed meningiomas, 59% of cases may be attributable to dMPA; thus, being aware that MPA will slightly increase the risk of meningioma is important in women who have a medical or familial history of meningioma or breast cancer. In these populations, alternative treatment or contraceptive methods should be considered where possible, carefully weighing against the indications of dMPA in individual patients, such as treatment for menstrual disorders or endometriosis, and for contraception in particular in vulnerable groups, such as people with learning disabilities and psychiatric illness, and risks associated with discontinuing or changing treatment.

As progestogen-associated meningiomas have a propensity to locate in the anterior and middle skull base,¹¹ typical clinical presentations in progestin-exposed patients, such as neuro-ophthalmological symptoms, should prompt an imaging work up.⁵ Stopping the hormonal treatment will probably preclude the need for surgery in many progestin-meningioma cases, though further MPA-specific data are needed. Some patients undergo operations with significant surgical risk that may be avoided if a conservative treatment was tried first. This article underlines the need for a conservative trial period before surgery. Therefore, there is urgent need for a comprehensive review of the whole medical and, in particular, gynecological history in every woman presenting with meningioma. Overall, this large study demonstrates that the dMPA-associated meningioma risk remains very low but provides health care professionals with data to counsel women taking these medications that meningioma may be a risk to consider.

ARTICLE INFORMATION

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