OPINION

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MENINGIOMA AND LEVONORGESTREL MORNING-AFTER PILL

Meningiomas are typically benign tumors that arise from arachnoid cells, with the majority being intracranial [1] and predominantly affecting women. These tumors are associated with certain conditions, such as neurofibromatosis and the exposure to ionizing radiation.

Since the mid-20th century, a growing body of research has suggested a potential link between the development of meningiomas and female sex hormones, particularly progestogens [2,3], prompting exploration of new therapeutic approaches [4]. In 1931, Fischer described a woman whose vision deteriorated during her first pregnancy, recovering only after delivery [2]. This pattern recurred in a subsequent pregnancy, pointing towards a hormonal influence on meningiomas. In 2008, Froehlich and his team were the first to report in the literature a possible relationship between multiple meningiomas and the use of cyproterone acetate, a potent progestogen [5]. This finding laid the groundwork for further research, and by 2010, the scientific community began to hypothesize an etiologic role for both endogenous and exogenous hormones in the development of meningiomas [6]. Today, numerous studies have confirmed the presence of progesterone receptors in meningiomas, although conclusions regarding other hormone receptors remain less definitive [7]. The functionality of these progesterone receptors is complex [8,9], potentially explaining the inconsistent outcomes of antiprogestin treatments, such as the Phase III randomized trial of the antiprogestin agent mifepristone, which failed to show efficacy in treating unresectable meningiomas [10].

Historically, certain progestins, such as nomegestrol acetate and chlormadinone acetate, have been referred to as "macroprogestins" due to their potent anti-gonadotropic effects, achieved through the complete inhibition of FSH and LH synthesis. This inhibition leads to significant anti-estrogenic and anti-androgenic activities. These macroprogestins are utilized across a range of indications, including the treatment of luteal insufficiency, endometrial pathologies such as endometriosis and fibroids, and benign breast diseases [11]. Despite the inconsistent effects of anti-progestogens on meningiomas, the role of macro-progestogens in increasing their occurrence and progression is now well recognized.

Considering recent recommendations concerning the risks associated with macro-progestogens, this article aims to explore the potential link between the levonorgestrel (LNG) 1.5 mg morning-after pill and the risk of meningioma development. LNG, a synthetic progestogen used as a contraceptive in women, is the enantiomer of norgestrel, which was synthesized in the early 1960s by American scientist Herschel Smith at Wyeth Pharmaceuticals [12]. At a dose of 1.5 mg, 50 times the dose found in the daily microprogestin pill, LNG exhibits potent antigonadotropic properties, aligning it more closely with macroprogestins.

How are exogenous sex hormones linked to the risk of meningioma?

Numerous studies following Froehlich's 2008 paper have investigated the relationship between exogenous sex hormones and meningioma risk. Moreover, the European Medicines Agency has issued recommendations regarding drugs containing nomegestrol and chlormadinone [13], following earlier warnings regarding cyproterone acetate [14].

Certain patterns of meningiomas, such as their location, number, and specific gene mutations, appear to be associated with progestin treatment [15-17]. First, current literature does not exclude the risk of meningiomas associated with oral contraceptives or hormone replacement therapy in female patients [18], particularly in locations indicative of exogenous sex hormone exposure [19,20]. Such locations include skull-based meningiomas [21] or spheno-orbital meningiomas (SOM) which are rare intracranial tumors originating at the sphenoid wing, extending into the orbit, and are often associated with hyperostosis of the sphenoid bone [22]. A recent study found a strong association between hormone replacement therapy in female patients and bilateral SOMs [18]. Second, the notable occurrence of multiple meningiomas in individuals treated with progestins, even without prior conditions, has been highlighted. However, this increase in detection must be considered in the context of advancements in imaging techniques, which have also challenged the traditional understanding of meningiomas as isolated tumors [23].

The exact etiology of meningiomas remains poorly understood, with insufficient evidence to draw definitive conclusions regarding the risks linked to fertility treatments. Additionally, data on hormone replacement therapy in menopausal women are

scarce and sometimes contradictory. However, the high prevalence of meningiomas in women, the presence of progesterone receptors, and their progression in relation to pregnancy or menstrual cycles suggest a role for progestogens in their development [24]. Patients treated with exogenous progesterone, estrogen, or growth hormone should be informed of the potential increased risk of developing meningiomas [25].

Progestogen panic

Concerns regarding the increased risk of meningiomas associated with cyproterone acetate have extended to several other progestogens. A strong association between prolonged exposure to potent progestogens and surgery for meningioma has been observed, with the risk increasing progressively from chlormadinone acetate to nomegestrol acetate to cyproterone acetate [26]. Since 2019, the French "Agence nationale de sécurité du médicament et des produits de santé" (ANSM) has issued warnings regarding the risk of meningioma associated with these three progestogens and has extended caution to other progestogens [27].

In 2024, a large-scale pharmaco-epidemiological study was conducted in France involving 18,061 women aged 45 to 74 who underwent surgery for meningioma between 2009 and 2018, matched with 90,305 control women [28]. This study confirmed an increased risk of meningioma associated with the use of medroxyprogesterone acetate, médrogestone, and promegestone when used for more than one year. The authors further noted that their study might have underestimated the risk associated with all macro-progestogens, as it only considered hospital admissions for symptomatic meningiomas requiring surgery and did not account for the occurrence of non-operated meningiomas. This underestimation is particularly relevant because, after the discontinuation of progestin treatment, a conservative approach, often involving monitoring rather than surgery, is commonly recommended. In rare cases, meningiomas may also be treated with radiotherapy.

Conversely, some experts argue that the so-called "progestogen panic" may be overstated. Meningioma remains a rare tumor, benign in over 90% of cases, and its malignancy does not appear to increase in individuals with a history of hormone treatment. Furthermore, meningiomas are ten times less common than breast cancer and frequently occur in the absence of any progestogen treatment [29].

Macro-progestogen risk, state of play

The ANSM has identified increased risks of surgical meningioma associated with the use of certain macro-progestogens for over one year [30]. The relative risk multipliers are as follows:

- Promegestone: x2.7
- Medrogestone: x4.1
- Chlormadinone: x5.5
- Medroxyprogesterone: x5.6
- Nomegestrol: x7.5
- Cyproterone: x24.5

According to the latest BMJ study of Roland *et al*. [28], LNG intrauterine devices (IUD) are considered safe across all dosages. The study specifies that a 52 mg LNG IUD, designed for five years of use, releases approximately 0.020 mg of LNG per day. For a three-year period, the IUD contains 13.5 mg of LNG, releasing about 0.012 mg per day, with the dosage decreasing over time post-implantation [31]. Additionally, there is an LNG IUD containing 19.5 mg for five years, which delivers an average LNG daily dose of 0.01 mg. In comparison, the daily microprogestin pill contains 0.03 mg of LNG.

Despite the BMJ study's favorable conclusions regarding LNG IUDs, subcutaneous LNG implant has been reported as inducing sphenoid wing meningioma growth [21]. One case study involved a patient who experienced visual disturbances four weeks after LNG implant placement, later found to have a sphenoid wing meningioma [32]. The LNG present in older contraceptive implants has now been swapped for etonogestrel. Another case reported the unexpected development of a pulmonary meningioma in a person with a LNG IUD [33]. Although the literature regarding the association between LNG and meningiomas is limited, it does not entirely dismiss the potential correlation. Evidence suggests that women who used long-acting hormonal contraceptives, such as subdermal implants, injections, or hormonal IUDs, had an increased risk of meningioma [34].

EudraVigilance has recorded several cases of meningiomas associated with other macro-progestogens, including cyproterone acetate, nomegestrol, and chlormadinone acetate, particularly in connection with LNG implants [35]. It should be noted that the BMJ study focused on meningiomas requiring surgical intervention and did not account for non-surgical cases that could be managed conservatively by discontinuing macro-progestogen therapy.

What is beyond doubt is the well-established class effect linking progestogens to meningiomas, as evidenced by numerous recent recommendations from the ANSM [36]. However, it is important to note that these findings pertain specifically to macro-progestogens. According to the ANSM, contraceptive microdoses are not currently implicated in these risks.

What about the macro progestin LNG 1.5?

LNG 1.5 mg is notably absent from French health recommendations, despite being fifty times the dosage of the daily LNG pill. This discrepancy raises important questions about the growing popularity of the Plan B morning-after pill as a preferred contraceptive method. In France, the use of daily oral contraception has steadily declined over the past decade, with its popularity dropping from 45% in 2010 to 37% today, according to a Santé Publique France study [37]. This trend is often attributed to increasing hormonophobia. Paradoxically, HRA Pharma reports that 2.2 million morning-after pills are sold each year in France, with two-thirds of these being LNG 1.5 mg. In many countries, LNG 1.5 mg is available over the counter, which may contribute to the perception that it is a harmless option.

When asked about the risks associated with Plan B, the US Planned Parenthood chatbot provides reassuring information, stating that side effects are generally mild and temporary, with no reports of serious problems among the millions of users [38]. Despite the fact that many aspects of its use are being discussed, such as timing, price, patient weight, and interactions with other medications, this response does not address the implications for the patient of taking 1.5 mg of LNG on the potential long-term risks of meningioma development. This omission is noteworthy, especially given the trend in contraception towards lower estrogen doses in daily pills aimed to reduce risks.

Additionally, a review of the US Food and Drug Administration (FDA) website's Drug-Specific Information section reveals the Plan B dosage but lacks any mention of the risks associated with macro-progestogens or meningioma.

Similarly, professional guidelines for US healthcare providers may recommend medroxyprogesterone for conditions like endometriosis without addressing the associated risks for meningioma. Continuous progestin use is described as safe, effective and well-tolerated by most women [39]. Options such as injectable medroxyprogesterone (Depo-Provera®) and the LNG IUD (Mirena® IUD) are highlighted as suitable long-acting progestin-only contraceptive methods, which may be useful in treating endometriosis [40].

The question remains: what are the potential risks of a macro-dose of LNG, particularly considering emerging data on meningioma and macro-progestogens? While LNG 1.5 mg has been overlooked in French health recommendations, the absence of official guidelines in the USA regarding macro-progestogens further underscores the need for a more comprehensive assessment of the potential risks of meningioma development associated with the consumption of higher macro-progestogens doses.

Macro-Progestogens and meningioma in USA: a non-event?

Most of the research investigating the relationship between exogenous progestogens and meningiomas has originated in Europe, where the link between synthetic progestogens and meningiomas is well established. This body of evidence has led to specific recommendations. For instance, the European Medicines Agency's safety committee (PRAC: Pharmacovigilance Risk Assessment Committee) has introduced measures to minimize the risk of meningioma with drugs containing nomegestrol or chlormadinone [13]. However, the situation appears markedly different across the Atlantic.

According to the public digital database DrugCentral 2023, meningiomas are reported in 7.8% of women taking nomegestrol. However, these cases represent only 0.67% of all reported meningiomas [41]. One study reported 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 [42]. To date, the US FDA has not issued any recommendations or guidelines regarding the increased risk of meningioma associated with progestogen use.

Increased risk of meningioma: due to progestogenic action or to anti-androgenic action of progestogens?

The initial observations linking meningiomas to progestin treatment primarily involved cyproterone acetate, a drug known for its potent anti-androgenic properties. Notably, this association between meningiomas and progestin use has not been observed in the United States, where cyproterone acetate is not available. This discrepancy raises the hypothesis that the development of meningiomas might be related to the anti-androgenic effects of these progestins.

To mitigate the androgenic side effects of earlier contraceptives, newer molecules with strong anti-androgenic effects have been developed. Chlormadinone acetate, cyproterone acetate, and dienogest are potent, orally active progestogens with anti-androgenic rather than partial androgenic activity [43]. They primarily function by blocking androgen receptors in target organs. Supporting this hypothesis, an American study explored the link between anti-gonadotropic treatments used in prostate cancer and the development of meningiomas in treated patients, further suggesting a potential role of anti-androgenic effects in meningioma growth [44].

Additionally, an increased expression of androgen receptors has been observed in meningiomas that develop during cyproterone acetate treatment [45]. This finding implies that androgens and their receptors might participate in the development of meningiomas within the context of cyproterone acetate therapy. However, current data remain insufficient to definitively determine the function and significance of hormone receptors in meningiomas, whether in the context of progestin treatment or otherwise [46].

Conclusions

The relationship between endogenous progestogen hormones and meningiomas has been well-documented since the 20th century, indicating that the risk of iatrogenic meningioma may be modulated by individual factors such as genetics, diet, and environmental exposures. This underscores that not all individuals undergoing progestogen treatment will develop meningioma.

Among exogenous progestogens, cyproterone acetate was clearly associated in European scientific literature with the highest risk of iatrogenic meningioma. The recent French BMJ study [28] highlights the potential for dose-dependent risks associated with newer progestogen molecules, indicating that the class effect of exogenous progestogens on meningioma development cannot be ruled out. This effect has not been reported in the American literature, likely because cyproterone acetate is not available in the United States.

LNG 1.5 mg, a macro-progestogen typically sold over the counter, can be used repeatedly, particularly by young women who may avoid consulting a doctor regarding contraception due to shyness or financial concerns. Emerging scientific papers have suggested that the risk of meningioma with LNG cannot be entirely excluded, despite its androgenic activity [47,48]. The class effect linking macro-progestogens to meningioma [21,49,50] necessitates the inclusion of LNG 1.5 mg in new European and French prescription guidelines. Current literature raises significant questions regarding the anti-androgenic action of progestin treatments and the role of androgen receptors in meningiomas that appear in the context of macro-progestogen therapy. The development of meningiomas may be linked to the anti-androgenic effects of these treatments.

The interaction between progestogens and hormone receptors, especially androgen receptors, is complex, as progestins can modify androgen action through either potentiation or inhibition [51]. Recent non-European research on the meningioma-progestogen link could potentially validate European measures restricting the use of progestins [44,47,48]. Therapeutic alternatives, such as IUDs and ulipristal acetate, are available, and it is crucial that users be informed of these options.

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