# SGEM Recommendation

# Use of progestins in women with incidental meningioma or after meningioma surgery

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## Background

Meningioma account for over one-third of intracranial tumors [1] with a female-to-male ratio of 2–3.5 depending on age [2]. The annual incidence rates provided by population-based registries ranges from 1.3 to 7.8/100000/year for cerebral meningioma [3, 4].While ageing is a recognized risk factor, other contributing factors include exposure to ionizing radiation, neurofibromatosis type II, family history, obesity, and various reproductive factors [5]. Meanwhile several studies demonstrate an increased risk for meningioma in women using specific types of progestins or with a history of their use [6-9]. Not all types of progestins used for progestin monotherapy (PM) seem to be associated with the same risk, others have not yet been studied sufficiently. This makes it difficult to advise patients.

Today the number of detected incidental meningioma has risen due to the widespread use of neuroimaging and will be found in approximately 0.9% to 1.0% of the general population [10]. Given the rising incidence and serious risks associated with the growth of these brain tumors, gynaecologists and GCPs should be aware that specific hormone treatments are associated with a higher risk for meningioma surgery and should be guided in the management of patients with incidental meningioma requiring contraception, hormone replacement therapy or hormone treatment for other indications. It is of paramount importance to not induce further growth of asymptomatic meningioma. In addition gynaecologists should be aware that meningioma may shrink with discontinuation of progestin use.

*The European Medical Agency (EMA) safety committee (PRAC)* has recommended measures to minimise the risk of meningioma with medicines containing nomegestrol (NOMAC), chlormadinone acetate (CMA), Cyproterone acetate (CPA) and Depot Medroxyprogesterone Acetate (DMPA). High dose CPA (≥10mg), CMA (5-10mg) or NOMAC (3.75-5mg) should be used at the lowest effective dose and for the shortest duration as possible and only if no other options are available. There is also a risk for very prolonged use of DMPA [11].

## Overview over the evidence for the risk for meningioma surgery with use of different synthetic progestins

As the incidence for symptomatic meningioma is low, only huge population-based studies can contribute to understand a potential risk increase with use of a certain progestin. Not all progestins have been investigated in adequately powered studies to allow firm conclusions regarding their impact on the risk of meningioma growth or the need for surgery. Currently, evidence is available mainly for Depot Medroxyprogesterone Acetate (DMPA), Cyproterone acetate (CPA), Chlormadinone acetate (CMA)and Nomegestrol acetate (NOMAC). In contrast, data on other widely used progestins, such as desogestrel, gestodene, drospirenone, dienogest, and levonorgestrel (LNG), remain very limited or scarce.

***Depot Medroxyprogesterone Acetate (DMPA)***

Two case-control studies including 18,061 and 117,503 cases with meningioma surgery report an increased risk for meningioma in DMPA users [9, 12]. Roland et al. found an odd ratio (OR) of 5.5 for meningioma surgery in DMPA users and a higher odd ratio of 5.6 in prolonged users. However, the meaningfulness of the results is limited by the low number of 20 DMPA users identified in this trial [12]. In contrast Griffin et al. report 2,982 cases with oral use and 813 cases with use of the DMPA injectable (table 1) [9]. In addition to the high number of affected DMPA users a strength of this study is the analysis for duration of use. The OR for meningioma was not elevated for oral users, but for users of the injectable (<1year OR 1.23; 1-2years OR 1.74; >3years OR 2.5). The higher ORs with longer duration of use support the notion of a dose-response association. *We conclude mainly based on the high quality data from the US study* [9]*, that there is high evidence for an association between risk for meningioma surgery and DMPA use. Longer duration of use is associated with a higher risk.*

***Nomegestrolacetate (NOMAC)***

NOMAC is a synthetic progestin used in combined hormonal contraceptives (CHC) at the dose of 2.5 mg/day with 1.5mg estradiol, for HRT in a sequential regime at the dose of 3.5 mg/day with 1.5 mg estradiol and as progestin-only treatment at the dose of 5 mg/day. Two recent French population-based studies and a huge cohort study substantiated the association between NOMAC exposure and an elevated risk for meningioma surgery (OR of > 4 for

current use) [7, 12]. Analyses were based on more than 18,000 patients undergoing meningioma surgery. Hoisnard et al. report age-adjusted ORs of 4.7 (current users), 1.3 (past users < 1 y) and 6.5 (prolonged users >1 y). In the cohort study with the aim to analyse the impact of different dosages (n=535,115 cases with high exposure and n= 525,664 controls with low exposure) there was a significantly lower meningioma incidence in women who were exposed to a cumulative dose of ≤ 150 mg in comparison to doses > 150mg (age-adjusted RR 2.9) [8]. The strength of this study was the option to compare the impact of very low doses (controls) with higher doses. It is of relevance to note that the risk decreased one year after NOMAC discontinuation. *We conclude based on these three studies that there is evidence for a clinical association between NOMAC use and meningioma treatment. This risk increases with cumulative exposure and duration of use and decreases after discontinuation of the progestin.*

***Cyproterone-acetate (CPA)***

Cyproterone acetate is available for different indications in various dosages ranging from 1-100 mg daily. Good quality population-based case-control studies from the French National Health System confirm an association between CPA use and meningioma. The studies differ in the definition of drug exposure and include more than 18,000 cases with meningioma surgery each [7, 12]. ORs for meningioma surgery with current CPA exposure were 18.3 and 19.3. Hoisnard et al. report an even higher OR of 22.7 for prolonged use defined as use over at least 3 years [7]. A strong and dose dependent association was also reported in a huge pharmaco-epidemiological cohort study [13]. The incidence of surgically or radiologically treated meningioma was significantly higher in individuals with use of the high cumulative dose of > 3gr CPA (Hazard rate 23.8/100000 person years vs 4.5/100000 person-years), representing a crude relative risk of 5.2 (95% confidence interval 3.2 to 8.6). The risk was lower one year after discontinuation. Age at start was strongly associated with a higher risk of meningioma treatment (HR 10.4 for age 25-34 years vs 45-54 years). Furthermore co-prescription of estrogens was also associated with risk of meningioma HR 1.6 (CI 1.1-2.4) [13]. *Based on the two French observational studies we conclude that there is high evidence for an association between high dose CPA use and risk of meningioma. In addition, the study from Weill et al. demonstrates that the association is dose-dependent and increases with age. A significant association was also found when CPA was used in combination with an estrogen. The risk was lower already one year after discontinuation.*

***Chlormadinone-acetate (CMA)***

CMA is used at a daily dose of 2 mg in CHC and at higher doses (5mg or 10mg) as progestin therapy for various gynaecological indications. Two huge observational studies reported elevated ORs (3.3 and 3.7) for meningioma surgery among CMA users. Both also found a higher risk with increasing age and longer duration of use [7, 12]. A large-scale observational trial in France aimed to understand better the impact of dose [6]. The incidence of meningioma reached nearly 47 cases per 100,000 person-years in the group with the highest cumulative exposure (>8.64 g), corresponding to an adjusted relative risk (aRR) of 6.9 compared to controls. No significant increase in risk was observed for cumulative doses below 1.44 gram. It is important to emphasize that these findings pertain exclusively to higher-dose CMA formulations and do not include the evaluation of COC regimens containing 2 mg CMA [6]. *Based on the two French observational studies, there is evidence of an association between high-dose CMA use and the risk of meningioma. A dose-dependent effect has also been demonstrated.*

**Less investigated Progestins: Desogestrel , Levonorgestrel, Dienogest**

**Desogestrel**

Only one study addresses the risk of meningioma associated with short (< 1 year) and long-term (>1 year) use of desogestrel as a monosubstance [14]. The case-control study included 8,391 women who had undergone meningioma surgery. Only 287 cases were desogestrel users, of which 114 had used other progestins in the past. No increased risk of meningioma surgery was observed among the 58 desogestrel users who had not used other progestins within the previous 12 months or one to two years before diagnosis. The OR was 2.4 if desogestrel was used during the year preceding the index date and a higher-risk progestin (CMA, NOMAC, or CPA) between two and five years before the index date. For long-term users (> 5 years; n=115) the risk was also increased (OR 1.7). Younger users had a significantly higher risk with continuous use for more than 5 years (OR 1.7). *We conclude that, also the data indicate an increased risk for longterm users of desogestrel, the small number of desogestrel users in the database limits statistical power and warrants caution in interpreting the findings*. *Further research is needed.*

**Levonorgestrel (LNG) alone (or in combination with estrogen)**

One study identified 17 meningioma cases using the progestin-only pill with LNG 30 µg [14]. For this small number of cases no risk increase was found. More cases (n=157) had used the pill containing ethinylestradiol (EE) plus different dosages of LNG, which is recommended as pill for newstarters in Switzerland. No increased risk for meningioma surgery was found here. However in subanalysis testing for longer duration of use (≥ 7 years) there was a significant association in women aged ≥ 45 years (OR 1.6, 95% CI:1.2-2.2). *For EE/LNG we conclude that there may be an increased risk for meningioma surgery, significant however only in long-term users aged ≥ 45 years. The low number of cases in the LNG-only group does not allow a conclusion. Additional data is required.*

**LNG IUS (Intrauterine system) and Copper-Intrauterine device (Cu-IUD)**

Altogether 566 menigioma cases used the LNG 52 mg IUS, 10 the LNG 13.5 mg IUS and 452 were Cu-IUD users in a recent population-based case control study searching for cases with meningioma surgery [12]. Women with exposure to high risk progestins within the previous 3 years were excluded. The authors did not find an elevated risk for meningioma with both hormonal IUS. However there was a slightly elevated risk for meningioma with use of a Cu-IUD (OR 1.13); Cases n=451. No analyses were performed for duration of use. Only cases with dispensation of the IUS/IUD were included. *We conclude, that at present it is unclear if there is an elevated risk for meningioma growth with use of any LNG-IUS. The results observed with the Cu-IUD may be due to chance.*

**Dienogest**

Dienogest, a commonly used progestin for contraception and endometriosis/adenomyosis treatment, was linked to only three cases in a French case-control study [12]. *No data are available for dienogest, but caution with its use in risk patients is needed.*

## Meningioma regression after discontinuation of progestin use

Case reports and two observational studies describe meningioma shrinkage, often associated with regression of clinical symptoms after discontinuation of treatment with CPA, NOMAC, CMA, or following pregnancy [15-18]. This underlines the potential significant role of these hormones in tumor development and progression. In less than 10% of the cases with longterm follow-up further growth was observed.

## Gaps of knowledge and limitations

There are no data on the percentage of incidental meningioma which will grow spontaneous and become symptomatic in later life.

It is unclear if addition of an estrogen to the progestin, like in CHC but also in hormone replacement therapy (HRT) will modify the risk for meningioma growth.

Conclusive evidence is still insufficient for the today mostly used progestins desogestrel, gestodene, dienogest and drospirenone, but also for norethisterone. This is related to the lack of sufficiently powered studies. Not all types of progestins seem to be associated with the same risk.

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## Recommendation

1. **Before prescribing a progestin**

- Obtain a detailed history for all types of meningioma
- The absolute number of meningioma and progestin-induced meningioma in young women is low. Therefore, the majority of young women can benefit from progestin therapy.
- If the history for meningioma is positive avoid use of progestins.

2. **Patients with symptomatic meningioma or after meningioma surgery/treatment**

- In women with symptomatic meningioma progestin therapy has to be stopped and should not be reinitiated after meningioma surgery or other kinds of treatment.

3. **Incidental meningioma**

- Procedures need to be discussed with the neuro-oncologist/neurosurgeon
- Discuss intervals for monitoring with MRI (Consider tumor size and location)
- Review cumulative progestin exposure in the past. Discontinuation might be reasonable
- Discuss risk and benefits also based on other risk factors for meningioma

**3.1 Incidental meningioma- recommendation for women, who stop progestin use**

- Discuss intervals for monitoring with MRI with the neuro-oncologist/neurosurgeon. A first follow-up 3-6 months after discontinuation is reasonable
- Monitor regularly for symptoms (e.g., headache, visual changes)
- Consider surgical options for bleeding or contraception if fertility is not desired; copper IUDs are alternatives.

**3.2 Incidental meningioma- recommendation for women using a progestin**

- Assess individual risk (age, family history, obesity, ionizing radiation, hormone exposure, tumor size and location)
- Continuing or starting progestins in young women may be reasonable due to the low rate of symptomatic meningioma in this group.
- Plan MRI monitoring in a time frame agreed with the neuro-oncologist/neurosurgeon. A first follow-up 3-6 months after diagnosis or start of a progestin is recommended, thereafter periodically.
- Monitor regularly for symptoms (headache, change in vision)
- Use the lowest possible progestin dose especially for CPA, CMA, NOMAC and DMPA for the shortest possible duration. (per EMA guideline)
- Qualified data on the LNG-IUS and low dosed progestins in POC or COC are still lacking
- For treatment of endometriosis/adenomyosis switching to a GnRH antagonist in combination with estradiol 1 mg/norethisterone acetate (NETA) 0.5 mg daily is one option (This combination contains the lowest NETA dose available)
- Stop progestin therapy immediately if neurological symptoms occur or the tumor enlarges.

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