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HORMONAL CONTRACEPTION AND THE RISK OF MENINGIOMA: A NARRATIVE REVIEW OF EVIDENCE FROM PROGESTOGEN-RELATED THERAPIES

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ABSTRACT

Background: Meningiomas are the most common benign intracranial tumors in adults and show a marked female predominance, suggesting a hormonal influence. The frequent expression of progesterone and estrogen receptors in these tumors has raised concerns that exogenous hormones, particularly those used in hormonal contraception, may contribute to their development or growth.
Aim: To summarize current knowledge about hormonal contraceptive use and the risk of meningioma.
Methodology: A narrative review was conducted using PubMed and Google Scholar between January and September 2025. The search included studies related to meningioma, hormonal contraception, and specific progestins such as cyproterone acetate, medroxyprogesterone acetate, nomegestrol acetate, chlormadinone acetate, desogestrel, and levonorgestrel.
Results: Most studies do not demonstrate a consistent association between combined estrogen–progestin oral contraceptives and meningioma risk; in contrast, prolonged or high-dose exposure to specific progestin-only agents has been associated with an increased risk. Particularly, depot medroxyprogesterone acetate, cyproterone acetate, nomegestrol acetate, and chlormadinone acetate have been linked to a significantly increased risk, often related to cumulative dose and duration of use. Regression of hormone-associated tumors following treatment withdrawal has been reported, and the excess risk appears to decrease over time after discontinuation.
Conclusions: Combined oral contraceptives are generally considered safe, whereas long-term use of potent progestins may promote meningioma growth. Contraceptive choices should be chosen based on individual risk profiles, especially for women requiring extended hormonal therapy. Further studies are needed to clarify underlying mechanisms and identify women at increased susceptibility.

KEYWORDS

Meningioma, Hormonal Contraception, Progesterone Receptors, Estrogen Receptors, Progestins, Contraceptive Safety, Tumor Regression, Public Health

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1. Introduction

Meningiomas are among the most common primary intracranial tumors in adults, accounting for 37% of all brain tumors and representing the largest proportion of benign central nervous system neoplasms [1]. Although typically slow-growing, meningiomas can lead to significant neurological symptoms depending on their size and location, sometimes necessitating surgical intervention or radiotherapy [2]. Epidemiologically, there is a marked female predominance. Overall female-to-male ratios are roughly 2:1, and as high as 3:1 during the reproductive years [3]. Incidence rises in mid-life (4th- 5th decades), coinciding with peri-menopausal hormonal changes [1]. Such observations have long suggested a potential hormonal influence in meningioma pathogenesis. Indeed, most meningiomas express progesterone receptors (PR), and a substantial subset also express estrogen receptors (ER) [4,5]. This receptor profile hints that female sex hormones might promote meningioma growth. The discovery of meningiomas often enlarging or becoming symptomatic during high-hormone states (eg. pregnancy) further supports a hormonal role [6,7]. These factors have raised concern that exogenous hormones, notably those used in contraceptive formulations could influence the development or progression of meningiomas. In recent years, emerging studies have highlighted possible risks associated with certain hormonal contraceptives, particularly with long-term or high-dose progestin use. This has brought renewed clinical attention to the potential association between hormonal contraception and meningioma development.

This review aims to summarise the current understanding of this association, focusing on biological mechanisms, key epidemiological findings, and differences related to contraceptive types and durations of use.

2. Materials and methods

This narrative review was conducted to summarize current evidence regarding the association between hormonal contraception and meningioma development. The literature search was conducted between January and September 2025 using the PubMed and Google Scholar databases. The following keywords and combinations were used: “meningioma,” “hormonal contraception”, “oral contraceptives”, “progestins”, “estrogen receptors”, “progesterone receptors”, “cyproterone acetate”, “depot medroxyprogesterone acetate”, “nomegestrol acetate”, and “chlormadinone acetate.”

3. Progesterone and estrogen hormone receptors in meningiomas

Meningiomas are well known to harbor hormone receptors, which provides a biological basis for hormone sensitivity. Progesterone receptors are especially prevalent. Studies report PR expression in the majority of meningiomas, often >80% of tumors [8]. Estrogen receptors are less consistently expressed, though a significant subset of meningiomas are ER-positive [9,10]. Meningiomas that do express ER have been associated with higher proliferative indices than their ER-negative counterparts [11]. In vitro experiments further suggest that estradiol can act as a potent mitogen for meningioma cells [12].

Progesterone’s role is more complex: while clinical observations implicate progesterone in tumor growth, some cell culture studies have not shown strong proliferative effects with progesterone exposure [8]. Nonetheless, the high PR positivity of meningiomas implies that progestins (synthetic progesterone analogues) could influence tumor behavior through PR- pathways.

Perhaps the most compelling evidence of hormonal influence comes from clinical contexts of extreme endogenous hormone fluctuation. During pregnancy- when circulating estrogen and progesterone reach markedly elevated levels, dormant meningiomas in some cases have been observed to undergo rapid growth, sometimes becoming symptomatic or requiring intervention [13]. Case series have documented multiple instances of pregnancy-associated meningiomas that enlarge during gestation and then partially regress postpartum. These “pregnancy-provoked” tumors often show extensive vascularization and edema, suggesting that hormones may increase tumor blood flow and water content in addition to any direct proliferative effect [7,14].

4. Epidemiological evidence about hormonal contraceptives and meningioma risk

4.1 Combined estrogen-progestin oral contraceptives

Combined oral contraceptives (OC), containing an estrogen (usually ethinyl estradiol) plus a progestin such as levonorgestrel or desogestrel, are widely used. Overall, most epidemiological studies have not found a consistent significant increase in meningioma risk with combined pill use [15]. A large prospective European cohort found that women who currently use oral contraceptives have a higher risk of developing meningioma. Specifically, their risk was approximately 3.6 times greater compared to women who have never used them (HR =3.6, 95% CI 1.75–7.46). However, the authors noted the possibility of diagnostic bias and urged caution [16]. Other studies have shown weaker associations, a population-based case-control study observed an OR of 1.8 (95% CI 1.1-2.9) for current OC use in premenopausal women [17]. In contrast, some datasets have even suggested no risk or a slight protective effect of Combined OC [18]. Thus, evidence regarding combined estrogen-progestin pills remains mixed, with no definitive causal link established. The emerging consensus is that typical low-dose of combined Ocs, especially those containing levonorgestrel do not markedly increase meningioma incidence, though very long duration use merits further study.

4.2 Progestin - only contraceptives

Progestin-only oral contraceptives, “mini-pills” such as desogestrel 75 µg daily, do not contain estrogen. Recent evidence showed that long-term use of desogestrel-based mini-pills may indeed elevate meningioma risk. Women who used desogestrel 75 µg continuously for more than five years had a small but measurable increase in risk of intracranial meningioma [19]. This finding suggests that the specific type of progestin matters, as the same study found no similar association between meningioma risk and levonorgestrel-only formulations, such as the levonorgestrel intrauterine device (IUD) or older mini-pills. This shows that desogestrel, a third-generation progestin, may carry a higher risk profile for meningioma compared to levonorgestrel [19].

Progestin-only implants, such as the etonogestrel subdermal implant, have not been as extensively studied in relation to meningioma risk. To date, no large epidemiological studies have reported on implants specifically, and the available data are mostly case reports. One notable case from 1994 described a young woman who developed a rapidly progressing sphenoid wing meningioma shortly after placement of a

subcutaneous progesterone implant, with tumor regression noted upon removal of the implant [20]. While only anecdotal, this report shows a link between a high localized dose of progestin and accelerated meningioma growth. Overall, more research is needed on modern implantable progestin contraceptives. Currently there is insufficient evidence to conclude whether they increase meningioma risk, but biologically it remains a concern given the progesterone receptor-mediated growth effects.

4.3 Injectable progestogen contraceptives

Injectable long-acting progestogens, most notably depot medroxyprogesterone acetate (DMPA, Depo-Provera), are administered as 150 mg intramuscular injections every three months. Because they deliver sustained high systemic levels of progestin, these agents represent a potential risk factor for hormone-sensitive tumors [21]. A large cohort study using national health data was the first to quantify this risk. Women who used DMPA continuously for at least one year had a 5.6-fold higher risk of developing an intracranial meningioma requiring surgery. This statistically significant association raised global concern, particularly given that DMPA is used by an estimated 74 million women worldwide. Importantly, no excess risk was observed in women with less than one year of use, suggesting that duration of exposure is the critical factor [22].

Taken together, the evidence showed that both long-term and recent use of high-dose injectable medroxyprogesterone acetate are associated with an increased risk of meningioma. In response, regulatory authorities and manufacturers have updated Depo-Provera product information to include warnings about this risk. Although the relative risk associated with DMPA is notable, the absolute risk remains low. Nevertheless, in women with known risk factors or requiring prolonged use, careful risk–benefit assessment and consideration of alternative contraceptives may be warranted.

4.4 High-dose therapeutic progestogens and other hormonal agents

Apart from contraceptives, several high-dose progestogen therapies have been linked to meningiomas. These agents are not routinely used for birth control, but they are relevant to this discussion as they highlight the mechanism of progesterone-driven tumorigenesis. Cyproterone acetate (CPA) is one such drug. A synthetic progestin with anti-androgen properties, prescribed in high doses (50-100 mg) for conditions like severe hirsutism, androgen-dependent disorders, and as part of transgender hormone therapy [23]. Women with a CPA exposure exceeding 60 g, equivalent to approximately five years of daily 50 mg therapy, had an adjusted HR of about 21.7 for developing meningioma, representing a striking 20-fold increase in risk. Even more moderate exposure (≥3 g cumulative) was linked to a sixfold higher risk (HR around 6.6). Importantly, this risk declined after discontinuation of CPA. One year after stopping treatment, the excess risk decreased substantially (HR around 1.8). These findings led European regulators to formally acknowledge CPA's causal role in meningioma development, resulting in restrictions and the introduction of mandatory MRI monitoring for long-term users [23].

Subsequently, two other potent progestogens widely prescribed in Europe nomegestrol acetate and chlormadinone acetate were commonly used in high doses for menopausal hormone therapy or gynecologic conditions. In 2021, studies demonstrated that prolonged use of these agents was associated with a significantly increased risk of meningioma, although the magnitude of risk was lower than that observed with CPA. Reported relative risks were approximately three- to fourfold higher compared with non-use. In response, the European Medicines Agency (EMA) issued updated safety recommendations in 2022, advising that both the dose and duration of nomegestrol and chlormadinone therapy be minimized [24,25]. Notably, these high-dose progestogens are rarely used in the United States or United Kingdom, which may explain why standard contraceptive pills in those regions have not been linked to meningioma risk. Nevertheless, evidence from CPA, nomegestrol, and chlormadinone supports the concept of a class effect, whereby chronic exposure to potent progestogenic stimulation can precipitate meningioma development in susceptible individuals.

5. Gaps and future directions

Despite significant advances in our understanding, several important questions about hormones and meningiomas remain unanswered. First, the mechanistic basis for why certain progestins are more meningiomagenic than others is not fully known. Is it purely a function of dose and PR binding affinity, or do specific agents trigger unique molecular pathways in meningioma cells? For example, desogestrel's slight risk vs. levonorgestrel's apparent safety might reflect differences in metabolism or cross-talk with estrogen receptors. Studies examining meningioma tissue from hormone-exposed patients, such as those exposed to

CPA and it has begun to reveal distinct gene expression profiles [26]. Unfortunately, more work is needed to understand how exogenous hormones influence tumor biology at the molecular level.

The association is clear for tumor promotion/progression, but it is less clear whether exogenous hormones play a role in the initial formation of meningiomas. Meningiomas often have defined driver mutations (in NF2 or other genes) as the primary event, and hormones might act more as growth accelerators of an existing microscopic tumor. Long-term prospective studies could help determine if hormone use truly increases incidence or mainly shifts the timing of diagnosis by enlarging preclinical lesions.

Another gap lies in identifying which patients are most at risk. Most women on birth control will never get a meningioma, so there may be genetic or environmental cofactors that predispose a subset of hormone users to tumor development. It would be valuable to study whether women who develop meningiomas on hormonal therapy have particular genetic polymorphisms (for hormone receptors, metabolism enzymes, etc.) or preexisting tumor suppressor mutations. Such knowledge could eventually lead to personalized risk assessment.

More data are needed on other contraceptive methods, such as implants and newer oral progestins, and on post-therapy outcomes. The current studies have focused on surgery-requiring meningiomas. It is unknown if milder cases are also more frequent with hormone use or if those never come to clinical attention. Future research may involve cohorts of long-term contraceptive users to detect even asymptomatic meningiomas. Moreover, while we have evidence that tumors regress after stopping hormones, the long-term fate of these regressed tumors is not well described. Do they remain dormant or could they regrow years later independent of hormones? Follow-up of cases like the CPA series,beyond the one year reported, would suffice.

Further research in public health and contraceptive safety policy is needed to guide future recommendations and population-based interventions. With millions of women exposed to various hormonal regimens. It will be important to monitor meningioma incidence at the population level as contraceptive prescribing practices evolve. The benefit–risk balance of contraceptives should be continually reassessed as new data emerge. This includes not only medical aspects but also patient perspectives. Some women, for example, might feel anxious about any cancer risk and opt for non-hormonal methods, whereas others may prioritize contraceptive effectiveness over a very remote risk. Clear communication and updated clinical guidelines are be needed.

6. Conclusions

Long-term or high-dose use of some progestin-based hormonal therapies can increase the risk of developing meningiomas, while standard combined oral contraceptives appear generally safe. The risk depends on the type of hormone and the duration of use, and it tends to decrease after treatment is stopped. When choosing contraception, it is essential to consider each woman's individual situation and discuss possible alternatives if long-term hormonal therapy is planned. More research is needed to understand why certain hormones carry higher risks and to ensure safer contraceptive options in the future.

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Conceptualization, K.M., and E.S.; methodology, K.M., and E.S.; check, L.S., J.B., D.G., M.C., R.S., and M.A.; formal analysis, E.S., J.B., and L.S.; investigation, K.M.; resources, K.M., and E.S.; writing - rough preparation, K.M., E.S., and L.S.; writing - review and editing, J.B., M.A., M.C., R.S., D.G., and M.A.; visualization, L.S.; supervision, J.B.,L.S., M.C.,R.S., D.G., and M.A.; project administration, L.S., K.M., and E.S.

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