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CLINICAL STUDY

# Progesterone-only contraception is associated with a shorter progression-free survival in premenopausal women with WHO Grade I meningioma

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**Abstract** The hormonally active nature of intracranial meningioma has prompted research examining the risk of tumorigenesis in patients using hormonal contraception. Studies exploring estrogen-only and estrogen/progesterone combination contraceptives have failed to demonstrate a consistent increased risk of meningioma. By contrast, the few trials examining progesterone-only contraceptives have shown higher odds ratios for risk of meningioma. With progesterone-only contraception on the rise, the risk of tumor recurrence with these specific medications warrants closer study. We sought to determine whether progesterone-only contraception increases recurrence rate and decreases progression-free survival in pre-menopausal women with surgically resected WHO Grade I meningioma. Comparative analysis of 67 pre-menopausal women taking hormone-based contraceptives (progesterone-only medication, n = 21; estrogen-only or estrogen/progesterone combination medication, n = 46) who underwent surgical resection of WHO Grade I intracranial meningioma was performed. Differences in demographics, degree of resection, adjuvant therapy and time to recurrence were compared between the two groups. Compared to patients taking combination or estrogen-only contraception, those taking progesterone-only contraception demonstrated a greater recurrence rate (33.3 vs. 19.6%) with a reduced time to recurrence (18 vs. 32 months, p = 0.038) despite a significantly shorter follow-up (p = 0.014). There were no significant demographic or treatment related differences. The results from this study suggest that exogenous progesterone-only medications may represent a specific contraceptive subgroup that should be avoided in patients with meningioma.

**Keywords** Meningioma recurrence · Progesterone · Contraception · Premenopausal women

## Introduction

The hypothesized hormonally driven relationship between sex steroids (estrogen and progesterone) and meningioma development and growth, tumor grade and recurrence has been well documented in the literature [1–3]. Both exogenous hormone sources [4–12] such as hormone replacement therapy (HRT) and sex steroid contraceptives, [4] as well as endogenous hormone sources [10] such as those found during pregnancy [13–15], breast cancer [16], uterine fibroids, [17] obesity [18] and age at menarche [10] have been inconsistently correlated with meningioma-genesis and recurrence. Conversely, a protective effect of menopause, which results in lower levels of endogenous estrogen in women, has been shown [19]. The link between meningioma and sex steroids was established via histologic studies demonstrating the presence of sex steroid receptors on meningioma tumor cells. These studies have consistently demonstrated a predominance of progesterone receptors (PRs) with fewer estrogen receptors (ERs) on WHO Grade I tumors while grades II and III commonly express far less PRs [20–22]. Therefore,

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a lower risk of tumor recurrence has been shown in PR-positive tumors in some studies [23], while others [6, 12] have shown the converse; revealing higher odds ratios (ORs) for development of intracranial meningioma in patients with higher PR expression levels.

With rare exception [6, 12, 24], the vast majority of studies examining hormone-based contraceptives and meningioma risk have included oral preparations which are most often estrogen-only or estrogen/progesterone combination therapies, leaving out progesterone-only injectable and implantable options [1, 5, 9–11, 25]. Over the last 25 years, progesterone-only contraceptives including hormone intrauterine devices (IUDs) (e.g., Mirena®, Skyla®, Liletta®), injectable options (e.g., Depo-Provera®) and implantable options (e.g., Implanon®) have been introduced to the market. Their long duration of action over the oral progesterone-only "minipill" makes them attractive options and there has been increasing use in the United States [26, 27]. Given the relative paucity of data on this subject, we sought to retrospectively compare the risk of meningioma recurrence in a series of pre-menopausal women taking progesterone-only contraception with those taking either estrogen-only or estrogen/progesterone combination therapy.

## Methods

After obtaining IRB approval, a retrospective chart review was performed to identify all female patients with surgically-treated intracranial meningioma at the University of Colorado and Emory University between January 1, 1990, and May 31, 2013. Eligible patients were pre-menopausal women, age $\geq 18$, taking hormone-based contraceptives prior to surgical resection of a histologically confirmed intracranial WHO Grade I meningioma. Exclusion criteria included male gender, pre-menopausal women not taking hormonal contraceptives, post-menopausal women based on menopausal status as described in the medical record, those taking HRT, and those having undergone hysterectomy and oophorectomy. Those patients missing these data in the medical record were also excluded. Therefore, hormone-based contraceptive use was determined through medical records that indicated use during the time of diagnosis, surgical resection, and postoperative follow-up.

Electronic medical records and radiographic images for all included patients were examined to identify demographic specifics, tumor location, type of contraceptive used prior to surgery, extent of resection, surgical outcomes, adjuvant therapies and follow-up data. The cohort was then split into two groups based on type of contraception used prior to surgery: (1) progesterone-only contraceptives or (2) estrogen–progesterone combination or estrogen-only contraceptives. Extent of resection was defined as biopsy (Simpson grade 5), subtotal (Simpson grade 4) or gross total (Simpson grade 1–3) as specified by the operative report. Length of follow-up was determined by the number of days between the date of surgical resection and the last follow-up appointment. Tumor recurrence was defined as radiographic evidence of new tumor growth or progression of residual tumor on follow-up magnetic resonance imaging (MRI) and time to recurrence was defined as the interval between surgical resection and the first sign of recurrence on MRI.

Statistical analyses were performed using Graph Pad (Graphpad Software Inc., La Jolla, CA) and Microsoft Excel (Microsoft Inc., Redmond, WA). Descriptive statistics were calculated for demographic data. To analyze differences between those taking progesterone-only contraception and patients taking combination or estrogen-only alternatives, Fisher's exact tests were used for categorical variables and Student's *t* test was employed for continuous variables. Kaplan–Meier survival curves evaluating time to recurrence were generated for each group and compared using log-rank analysis. A multivariate analysis was performed running a Cox Proportional Hazards model using factors found to be significant on univariate analysis.

## Results

### Patient demographics

1243 women with surgically resected intracranial meningioma were identified and, of this cohort, 67 met inclusion criteria for the study. This group was then divided by contraceptive type into two groups: progesterone-only ($n=21$) and estrogen/estrogen–progesterone combination or estrogen only ($n=46$). Patient demographics including average age at diagnosis, comorbid conditions, and tumor location are shown in Table 1. Demographic differences between each group failed to reach statistical significance, with the exception of hyperlipidemia ($p=0.002$) and skull base tumor location ($p=0.030$). While there was a greater proportion of skull base tumors in the progesterone-only cohort, there was no statistically significant difference in overall tumor location ($p=0.1489$), and there was no significant difference in extent of resection ($p=0.434$). Multivariate analysis was performed by running a Cox Proportional Hazards (PH) model using hyperlipidemia and skull base location. There was no significant association to these covariates.

### Treatment specifics and complications

Details regarding extent of resection are demonstrated in Table 2. Although there were small differences in the number of patients receiving gross-total resection versus subtotal resection or biopsy, none were statistically significant.

**Table 1** Demographics comparing the progesterone and estrogen-combination cohorts

| Demographic N (%) | Progesterone-only (N = 21) | Estrogen only or estrogen/progesterone combination (N = 46) | p Value |
|---|---|---|---|
| Mean age (years) | 42.1 | 44.8 | 0.440 |
| Comorbidities | | | |
| Hypertension (%) | 5 (23.8) | 6 (13.0) | 0.300 |
| Diabetes (%) | 2 (9.5) | 2 (4.3) | 0.584 |
| Hyperlipidemia (%) | 5 (23.8) | 0 (0) | 0.002 |
| CAD (%) | 1 (4.7) | 1 (2.2) | 0.532 |
| Smoking (%) | 1 (4.7) | 3 (6.5) | 0.954 |
| Prior MI (%) | 0 (0) | 0 (0) | 1.000 |
| Prior CVA (%) | 0 (0) | 0 (0) | 1.000 |
| Cancer (%) | 2 (9.5) | 7 (15.2) | 0.709 |
| Tumor location | | | 0.149 |
| Convexity (%) | 0 (0) | 6 (13.0) | 0.166 |
| Skull base (%) | 17 (80.9) | 23 (50.0) | 0.030 |
| Parafalcine/parasagittal (%) | 3 (14.2) | 13 (28.2) | 0.225 |
| Orbital (%) | 1 (4.7) | 3 (6.5) | 0.954 |
| Intraventricular (%) | 0 (0) | 1 (2.2) | 0.976 |

**Table 2** Treatment specifics, outcomes, complications

| N (%) | Progesterone-only (N = 21) | Estrogen only or estrogen/progesterone combination (N = 46) | p Value |
|---|---|---|---|
| Extent of resection | | | |
| Gross total (Simpson I–III) | 8 (38.1) | 23 (50.0) | 0.434 |
| Sub total (Simpson IV) | 13 (61.9) | 23 (50.0) | 0.434 |
| Radiation | 5 (23.8) | 12 (26.1) | 0.964 |
| Complications | | | |
| Post-operative infections | 2 (9.5) | 4 (8.7) | 0.645 |
| Epidural empyema | 1 (4.7) | 0 (0) | 0.313 |
| Infarction | 1 (4.7) | 0 (0) | 0.313 |
| Deep venous thrombosis | 0 (0) | 1 (2.1) | 0.976 |
| Follow-up (months) | 49 | 63 | 0.014 |

Likewise, there were no significant differences in adjuvant radiation or post-operative complications between patients using progesterone-only contraception and those taking combination/estrogen-only alternatives (Table 2).

### Follow-up and recurrence

Mean follow-up time was 49 versus 63 months ($p = 0.014$) for patients using progesterone-only versus combination/estrogen-only medications, respectively. At last follow-up, recurrence was demonstrated radiographically in 33.3% of those using progesterone-only contraception versus 19.6% (combination/estrogen-only group). Median time to recurrence in those that recurred was 18 months in those taking progesterone-only contraception and 32 months for patients taking combination/estrogen-only alternatives ($p = 0.038$) (Fig. 1).

## Discussion

In our series of 67 pre-menopausal women with WHO Grade I intracranial meningioma, recurrence was more frequent and occurred earlier (18 versus 32 months, $p = 0.038$) in patients using progesterone-only contraception as compared to those using estrogen-only or estrogen/progesterone combination therapy, despite a longer follow-up in the latter group. The two groups were well matched with respect to age, comorbid conditions, tumor location, degree of resection, adjuvant treatment and complications. Confounding factors well known to affect meningioma recurrence such as degree of resection [28] were compared between the two groups and no significant difference was noted ($p = 0.286$). Likewise, histologic grade, well known to affect meningioma recurrence [29], was removed as a confounder given that only low-grade tumors (WHO I) were included in our

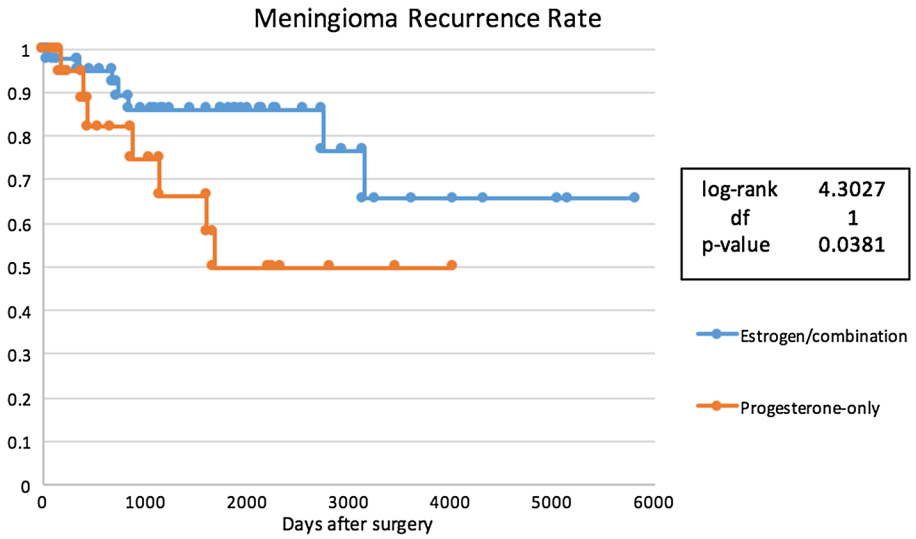


**Fig. 1** Kaplan–Meier survival curves demonstrating progression-free survival (PFS) in patients taking progesterone only versus estrogen or estrogen–progesterone combination contraceptives. Log rank analysis of each curve demonstrates a significant difference in PFS

analysis. We also performed a multivariate analysis running a Cox Proportional Hazards model using hyperlipidemia and skull base location (factors found to be significant differences between cohorts on univariate analysis). There was no significant association to these covariates. This supports the primary statistical conclusions of the paper.

## Progesterone-only contraception and meningioma risk

In contrast to the current literature examining estrogen-only and estrogen–progesterone combination contraceptives, a paucity of data exist regarding progesterone only-contraception and meningioma development or recurrence. The two largest trials examining the effect of progesterone-only contraception (long acting-implantable or injectable contraceptives and hormonal intrauterine devices), are the 2006 and 2010 retrospective cohort studies conducted in Sweden by Wigertz et al. [12] (178 patients) and in Finland by Korhonen et al. [6] (264 patients), respectively. Patient data for each trial was drawn from the international case–control INTERPHONE parent study [26], primarily designed to study the association of cell phone use on brain and salivary gland tumor development. In each trial, "ever use" of progesterone-only contraceptives resulted in an increased risk for meningioma (Wigertz OR 1.42, 95% CI 0.95–2.11 and

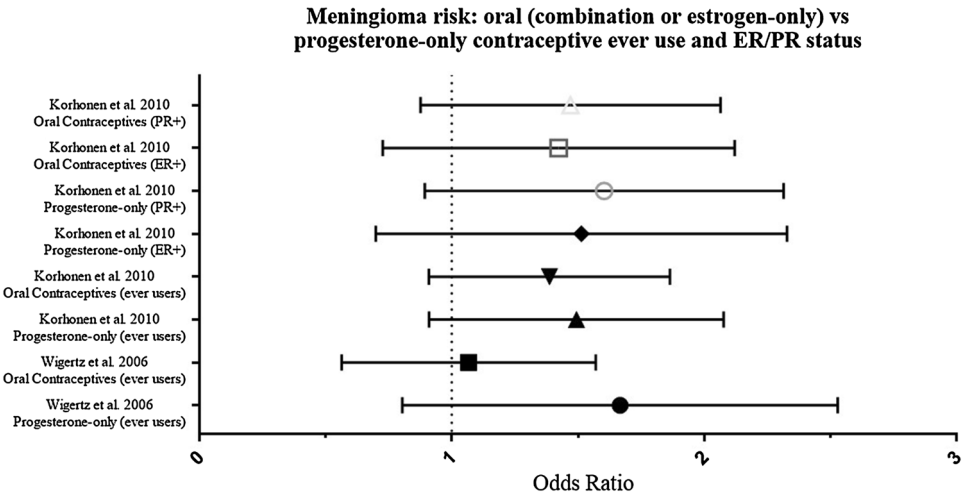


**Fig. 2** Forest plots from Wigertz et al. [12] and Korhonen et al. [6] demonstrating that "ever use" of progesterone-only contraception (injectable, implantables, IUDs) resulted in an increased risk for meningioma as compared to those taking oral combination or estrogen only alternatives (Wigertz OR 1.42, 95% CI 0.95–2.11 and Korhonen OR 1.50, 95% CI 0.9–2.60) and for patients taking progesterone-only contraception, the OR for meningioma was slightly higher in the PR-positive group as compared to the ER-positive group (1.50 CI 0.95–2.36 vs. 1.37 CI 0.78–2.39)

Korhonen OR 1.50, 95% CI 0.9–2.60) (Fig. 2). However, subset analysis differed in each study. In the 2006 study by Wigertz et al. [12] duration of contraceptive use was studied and a protective effect was noted in patients taking any contraceptive for <5 years [11]. By contrast, an increased risk for meningioma was found in those taking progesterone-only contraception 5–10 years (OR 2.5, 95% CI 1.0–6.3) and greater than 10 years (OR 2.7, 95% CI 0.9–7.5). The Finnish 2010 study by Korhonen et al. [6] examined the effect of ER/PR status in the progesterone-only contraception group (Fig. 2). The OR for meningioma was slightly higher in the PR-positive group as compared to the ER-positive group (1.50 CI 0.95–2.36 vs.1.37 CI 0.78–2.39). To our knowledge, the only other published work examining the effect of progesterone-only contraception on meningioma risk is a case report by Piper and colleagues [23] in which clinical progression of a sphenoid wing meningioma following placement of Norplant, a subcutaneous implant containing the progesterone agonist, levonorgestrel, is noted. Our study represents the first to demonstrate a higher risk of meningioma recurrence and a shorter progression-free survival in patients taking progesterone-only contraception when compared with oral estrogen-containing alternatives. The significant difference in follow-up times for the two groups in our study is likely related to the clinical timing of progesterone-only contraception's popularity. This is a more recent phenomenon, resulting in a shorter follow-up time. Also, the group with the shorter follow-up also has the higher rate of recurrence. This makes time of follow-up highly unlikely to confound the conclusions of the study, supporting the conclusion that progesterone-only contraception increases recurrence in WHO Grade I meningioma.

## Estrogen-only or estrogen–progesterone contraceptives and meningioma risk

To date, study results pertaining to meningioma risk in patients taking estrogen-only or combined estrogen/progesterone oral contraceptive medications have demonstrated mixed results [1, 5, 8–11, 23] (Fig. 3). Subset analysis examining ER/PR status [1, 6], past versus current use [1, 5, 7, 10] and duration of use has been performed [1, 6, 9–11, 23].

## ER/PR status

Studies examining the effect of ER/PR status have not consistently demonstrated the anticipated effect on tumor growth between ER-positive tumors and estrogen-containing contraceptives. In the previously mentioned trial by Korhonen et al. [6] the authors also analyzed patients taking oral estrogen based contraceptives (combination/estrogen-only) by ER/PR status. In this group, the OR for meningioma was nearly identical for patients with ER-positive versus PR-positive tumors (OR 1.31, 95% CI 0.79–2.17 vs. OR 1.39, 95% CI 0.92–2.10 respectively) (Fig. 2) despite the preponderance of estrogen contained in oral contraceptives. By contrast, a 2006 case–control study of 143 patients with intracranial meningioma matched with 286 controls demonstrated that oral contraceptive use was associated with increased risk of meningioma in those with lower (0–25%) rather than higher (25–100%) PR expression [1]. These results may be explained by the relative paucity of progesterone within oral contraceptives, the fact that PR positivity has been correlated with less aggressive tumor biology [2] and lower recurrence rate [27, 30], or the fact that hormone receptors on meningioma may be surface binding proteins with no real receptor signaling mechanism at all.

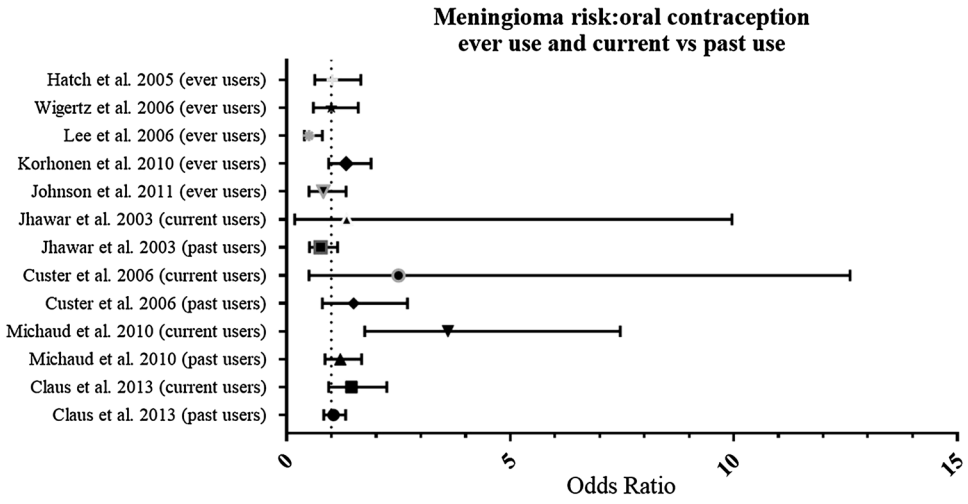


**Fig. 3** Forest plot of the largest studies to date examining the effect of "ever use" and "prior versus current use" on meningioma risk in patients with WHO I meningioma taking estrogen-only and estrogen–progesterone contraception. The graph demonstrates a mixed effect in "ever users" but consistently demonstrates an increased risk for current versus past users

### Current versus past use

Figure 3 demonstrates an analysis of the largest studies to date examining the effect of prior versus current use of estrogen-only and estrogen–progesterone contraception on meningioma risk [1, 5, 7, 10, 31]. All four studies, two prospective cohort [7, 10] and two retrospective case–control [1, 5], demonstrated an increased risk of meningioma development in patients currently using oral contraception than those having taken them in the past. It should be noted, however, that confidence intervals were relatively wide and crossed one in three [1, 5, 7] of the four studies. Examination of risk ratios in the past use group alone suggests only mild elevated risk in two studies [1, 10], no risk in one [5] and a protective effect in the fourth [7].

### Duration of use

Six studies performed subset analyses based on duration of oral contraceptive use [1, 6, 9–11, 23]. Three [1, 10, 11] demonstrated a positive correlation between meningioma risk and oral contraceptive use greater than 5 years. However, no consistent upward trend was found as time increased. The other three studies [6, 9, 23] showed the opposite result, demonstrating a protective effect of oral contraception use greater than 10 years. Within this latter group of trials, there were a few durations of estrogen-only or estrogen–progesterone contraceptive use wherein a higher risk of meningioma development was seen: between 1 and 4 years of use in the Korhonen study [6] and 5–9 years in the Hatch study [24]. Again, no consistent trends could be appreciated.

### Conclusions about exogenous hormone use and meningioma risk

When the results of these studies and the current study are taken together, the overall conclusion is that oral contraception with estrogen only or estrogen/progesterone combination medications is not consistently associated with an increased risk of meningioma. Therefore, no recommendation guidelines can be made against oral contraception in patients with or at risk for meningioma. By contrast, the results of the few studies examining progesterone only-contraception and meningioma risk have all suggested a positive correlation and deserve further examination.

### Strengths and limitations

This study represents the first comparative analysis of meningioma recurrence in a cohort of pre-menopausal women using contraception that were stratified by hormone composition: oral estrogen-only and estrogen–progesterone combination therapies versus progesterone-only alternatives. It is weakened by its retrospective nature with a relatively small number of patients. Furthermore, we did not perform ER/PR analysis of the tumor tissue given the retrospective nature of the cohort and unavailability of pathologic samples in many cases. Of course, our study included only WHO I tumors and PR receptors are present on most WHO I tumors, so one can infer that most tumors were likely PR positive [32–34].

## Conclusion

In our cohort of 67 pre-menopausal women with surgically resected meningioma, progesterone-only contraception was associated with an increased risk of recurrence and a statistically significant shorter time to recurrence when compared to estrogen-only and estrogen/progesterone combination contraception. This study supports prior data suggesting that exogenous progesterone-only medications may represent a specific contraceptive subgroup that should be avoided in patients with meningioma. Properly powered randomized-controlled trials with correlative biology of the patient tumor tissue are needed to further investigate this association before more definitive treatment recommendations can be provided.

#### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was not obtained due to the retrospective nature of this chart review.

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