Oral contraceptives with progestogens desogestrel or levonorgestrel and risk of intracranial meningioma: national case-control study

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Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2025;389:e083981
http://dx.doi.org/10.1136/bmj-2024-083981

Accepted: 28 April 2025

ABSTRACT

OBJECTIVE

To assess the risk of intracranial meningioma associated with oral contraceptives containing desogestrel, levonorgestrel, or levonorgestrel combined with oestrogen.

DESIGN

Case-control study.

SETTING

French national health data system (Système National des Données de Santé).

PARTICIPANTS

8391 women living in France who required surgery for intracranial meningioma in 2020-23. Each patient was matched to 10 women without intracranial meningioma (controls) on year of birth and area of residence.

MAIN OUTCOME MEASURE

Risk of intracranial meningioma associated with oral contraceptives containing desogestrel 75µg, levonorgestrel 30µg, or levonorgestrel 50-150 µg combined with oestrogen, and duration of use: short term use was defined by one or more dispensations within the year before the index date only, and prolonged use was defined by continuous use of one year or more (up to seven or more years of continuous use). Conditional logistic regression was used to calculate odds ratios.

RESULTS

92 301 women, mean age 59.7 years (standard deviation 12.9 years), were included. Among 8391women who had undergone surgery for intracranial meningioma, 287 (3.4%) used desogestrel 75µg (*v* 2769/83 910 (3.3%) controls), 17 (0.2%) used levonorgestrel 30 µg (*v* 140 (0.2%)), and 157 (1.9%) used levonorgestrel combined with oestrogen (*v* 1933 (2.3%)). In analyses of desogestrel according to duration of use, the odds ratio for risk of intracranial meningioma for short term use was 1.02 (95% confidence interval 0.77 to 1.34) and for prolonged use was 1.32 (1.14 to 1.53). Risk was driven by more than five continuous years of use: odds ratio 1.51 (1.17 to 1.94) for five to seven years and 2.09 (1.51 to 2.90) for ≥7 years. Excess risk was greater in women with meningiomas located in the middle or anterior part of the skull base (1.90 (1.47 to 2.46) and 1.50 (1.17 to 1.93), respectively) and in those who had previously used a progestogen of known associated increased risk (3.30 (2.64 to 4.11)). Results showed no excess risk of intracranial meningioma for levonorgestrel (alone or combined with oestrogen) regardless of duration of use. The estimated number needed to harm with desogestrel was 67 300 women for one intracranial meningioma requiring surgery. Risk was no longer observed one year after discontinuation of desogestrel.

CONCLUSIONS

The results showed a small increased risk of intracranial meningioma in women who had used desogestrel 75 µg for more than five continuous years, but no risk in users of levonorgestrel (alone or combined with oestrogen).

WHAT IS ALREADY KNOWN ON THIS TOPIC

Intracranial meningiomas are typically non-cancerous tumours that might require surgery

The main risk factors for meningiomas are older age, female sex, and prolonged continuous use of six progestogens, including the progestogen only contraceptive medroxyprogesterone acetate

Previous studies on progestogen based oral contraceptives with or without oestrogen have not shown any risk of meningiomas

WHAT THIS STUDY ADDS

Use of the progestogen desogestrel at a dose of 75 µg for more than five continuous years is associated with a small increased risk of intracranial meningioma requiring surgery

Users of levonorgestrel alone or combined with oestrogen showed no risk of meningioma, regardless of treatment duration

While awaiting clinical studies, the preferred approach for intracranial meningiomas associated with desogestrel use would appear to be stopping the progestogen, surgical abstention, and neurological monitoring

Introduction

In addition to female sex, ageing,[1] intracranial irradiation, and, to a lesser extent, obesity and black race,[2 3] prolonged use of several progestogens has been gradually recognised as a risk factor for intracranial meningiomas, including, in descending order of risk: cyproterone acetate ≥25 mg (odds ratio 19.2),[4-8] medroxyprogesterone acetate 150 mg/mL (5.6),[8 9] nomegestrol acetate 3.75-5 mg (4.9),[10 11] chlormadinone acetate 5-10 mg (3.9),[12] medrogestone 5 mg (3.5),[8] and promegestone 0.5 mg (2.4).[8] Although most intracranial meningiomas are non-cancerous, they can cause various important neurological symptoms depending on location, often require surgery or radiation treatment, and can have a serious impact on quality of life. Intracranial meningiomas associated with high dose progestogens are preferentially located in the anterior and middle of the skull base and may decrease in volume after discontinuation of drug use, potentially avoiding surgery.[13 14] Identifying the

determinants of progestogen related meningiomas is therefore essential to prevent their development and avoid risky surgery.

Other possible progestogens related to risk need to be identified, especially if women use them continuously over long periods, such as in oral contraceptives. Indeed, the female to male ratio for meningioma exceeds 3:1 for ages 35-44 years, compared with 2:1 for all ages combined.[1] This finding suggests a role for endogenous and exogenous hormones for women aged 35-44 years, whether used for contraception or, for example, the treatment of endometriosis or premenopausal symptoms.

Desogestrel and levonorgestrel are synthetic progestogens used as oral contraceptives for women and derived from testosterone, unlike other progestogens already known to be associated with a risk of meningioma that are derived from 17-hydroxyprogesterone and 19-norprogesterone. Desogestrel and levonorgestrel are widely used in Europe, either alone or combined with oestrogen. European studies report a national prevalence of use in women of 9% to more than 10%, depending on the country.[15-17] These studies did not, however, report prevalence of use according to type of progestogen (ie, desogestrel or levonorgestrel). Sales data show that desogestrel accounts for 90% of progestogen only pills sold in France and the UK.[18] Between 2018 and 2023, sales of desogestrel increased in France, Germany, Italy, and Spain (as much as 43% in France), whereas they remained stable in the UK. Conversely, sales of levonorgestrel combined with oestrogen in these five countries have been decreasing, although this drug combination is still widely used in these countries. In the US and Canada, desogestrel is not marketed as a progestogen only pill, but it is available as a combined oral contraceptive.[19] Levonorgestrel is only marketed in the US for emergency contraception, and, as in the rest of the world, it is widely used as an oral contraceptive in combination with ethinylestradiol.[20]

To date, only one intramuscular contraceptive—medroxyprogesterone acetate 150 mg/mL—has been shown to increase the risk of meningioma.[8 9] Overall, observational studies and meta-analyses (2013 and 2021) have not shown a particular risk of meningioma associated with use of oral contraceptives.[21-24] Studies, however, lack information on oral contraceptive use by subtype of progestogen. In addition, risk has not been measured for continuous, current, and long term use of progestogens.

We assessed the real life risk of intracranial meningioma associated with use of oral contraceptives containing desogestrel or levonorgestrel (alone or combined). Our secondary objectives were to describe the characteristics of those women who required surgery for intracranial meningioma (age, severity of meningioma, and anatomical location of meningioma) and to estimate the number needed to harm (NNH) for one intracranial meningioma requiring surgery.

Methods

Study design and data source

We performed a case-control study using data from the French national health data system SNDS (Système National des Données de Santé). The SNDS database contains information on all health related reimbursements for more than 99% of people residing in France and is linked to the central national French hospital discharge database.[25 26] Hospitals and health-care institutions record detailed information on each patient's care, including diagnoses, treatments, surgeries, and procedures. These data are captured through specific coding systems, such as the ICD-10 (international classification of diseases, 10th revision) for diagnoses and the CCAM (common classification for medical acts) for surgical and medical procedures. The entered data are standardised and then sent to the French hospital discharge database. SNDS is a powerful tool for pharmacoepidemiology and is used in numerous studies on drug utilisation and risk.[6 8 27-30]

Given the analysis of multiple drug use in our study and the left censored characteristics of the data (desogestrel reimbursement starting in 2014), in line with our previous studies, we opted for a case-control rather than a cohort study design. This design ensured the inclusion of long term users of the progestogens of interest.

Definition of cases and selection of controls

We considered women of all ages to be eligible for participation in this study if they resided in France and had undergone surgery for intracranial meningioma between 1 January 2020 and 31 December 2023. For each case, we considered the start date of the corresponding hospital admission as the index date. The year 2020 was chosen as the start date to ensure that at least five years of data were collected for desogestrel, as this drug has been reimbursed only since 2014.

We excluded women with a pregnancy that began in the three years before the index date (ie, pregnancies that resulted in childbirth or medical termination after 22 weeks' gestation). Pregnancy is a unique condition that influences exposure to progestogens with high endogenous exposure (ie, the placental production of progesterone) and rare exogenous exposure (no contraceptive intake and rare other use of hormonal treatment during this period), the likelihood of a meningioma increasing in size, and the likelihood of hospital admission for surgery for intracranial meningioma (potentially with a lower surgical rate depending on symptoms, maternal and fetal health, and characteristics of the tumour).[31 32] To avoid recurrent meningiomas, we also excluded women with a history of hospital admission for meningioma during 2018-19.

Surgery for intracranial meningioma was defined by a meningeal tumour with ICD-10 codes D32, D42, or C70 as the main diagnosis of the hospital admission for surgery (see supplementary file, supplement 1)

doi: 10.1136/bmj-2024-083981 | BMJ 2025;389:e083981 | the bmj

during the same hospital stay. This identification algorithm has already been used successfully in our previous studies.[8-12]

We matched each woman requiring surgery for intracranial meningioma (cases) with 10 women without intracranial meningioma (controls) for year of birth and French geographical area (département) of residence (n=101). Matching was based on the risk set sampling approach—that is, controls could become cases in the future.[33] To ensure the traceability of controls and cases in SNDS, we selected only women with at least one healthcare related reimbursement in the calendar year before the index date and in the two to three calendar years preceding the index date. The same condition applied to cases.

Definition of drug use

Use of oral desogestrel or levonorgestrel was defined according to the Anatomical, Therapeutic, and Chemical (ATC) classification maintained by the World Health Organization (WHO) (see supplementary file, supplement 2). The drugs of interest were desogestrel 75 µg (ATC G03AC09), levonorgestrel 30 µg (ATC G03AC03), and levonorgestrel (50 µg, 100 µg, and 150 µg) combined with oestrogen (ATC G03AA07, G03AB03).

We excluded desogestrel based combined oral contraceptives as they were only reimbursed in France from 2009 to 2013, and the data collection period was therefore less than five years. Emergency pills containing levonorgestrel were also excluded because they are used on an occasional basis.

Oral progestogen use was defined as at least one dispensation of the progestogen of interest in the 365 days before the index date. Short term use was defined as use within the past year before the index date, without dispensing in the second year before the index date. Prolonged use was defined as recent use (dispensed at least once within the first year before the index date) and continuous use in the previous years, classified by durations of 1-2 years, 2-3 years, 3-4 years, 4-5 years, ≥5 years, 5-6 years, 6-7 years, 5-7 years, and ≥7 years.

We defined drug use as use of the progestogen of interest or of any progestogens associated with a known increased risk of meningioma (cyproterone acetate ≥25 mg, nomegestrol acetate 3.75-5 mg, medroxyprogesterone acetate 150 mg/mL, chlormadinone acetate 5-10 mg, medrogestone 5 mg, and promegestone 0.5 mg) (see supplementary file, supplement 3) during the six years preceding the index date.

Previous or simultaneous use of medrogestone, promegestone, nomegestrol acetate, cyproterone acetate, chlormadinone acetate, or medroxyprogesterone acetate in the six years before was assessed in supplementary analysis. In case of use of a progestogen of interest in the year before the index date and one of the six progestogens associated with increased risk of meningioma (in the six years before or simultaneously), we searched for the date of brain magnetic resonance imaging (MRI) to get an overview of the chronology of the treatment and of the potential date of meningioma diagnosis. Apart from medroxyprogesterone acetate, we did not consider other types of contraceptives used before desogestrel or levonorgestrel.

An analysis of copper intrauterine devices was included as negative controls. These devices did not show an excess risk of meningioma in our previous study.[8] We defined use of a copper intrauterine device as reimbursement or an insertion procedure for the device, or no removal procedure in the five years of recommended use.

Definition of covariates

Personal and medical characteristics of the participants included age, département of residence, neurofibromatosis type 2 (a risk factor for meningioma, ICD-10 code Q850), endometriosis (ICD-10 codes N800 to N809 without N807), obesity, number of previous pregnancies, and, for cases only, year of surgery, single location or multiple locations of meningioma surgery, anatomical site of meningioma (anterior, middle, or posterior base of skull, convexity, falx and tentorium, other, see supplementary file, supplement 1), and severity of meningioma (graded according to the WHO classification as benign, malignant, or atypical, see supplementary file, supplement 4). In addition, we assessed all cause mortality at two years after the index date in cases and controls (for cases and controls included in the study sub period 2020-21, to receive the necessary follow-up).

Statistical analysis

Logistic regression models conditioned on matched pairs were used to estimate odds ratios and the corresponding 95% confidence intervals (CIs) for the association between desogestrel or levonorgestrel (alone or combined with oestrogen) and intracranial meningioma with adjustment for the six progestogens associated with increased risk (main analysis). Obesity and endometriosis were fully adjusted for in analyses (see supplementary analysis).

We also estimated the risk of intracranial meningioma associated with use of desogestrel, levonorgestrel, and levonorgestrel combined with oestrogen according to duration of use, stratified by age (<45 years; ≥45 years). To validate our results, the risk associated with a history of neurofibromatosis type 2, a known risk factor for meningioma, was assessed as positive controls for the progestogens of interest.

The population attributable fraction (PAF) was approximated from the odds ratio obtained for each progestogen. The formula used was: $PAF=p_c(1-1/OR)$, where p_c is the prevalence of use of the progestogen concerned among the cases.[34] We also estimated the NNH in all women who used the progestogen of interest, and in subgroups of women who used the progestogen for five or more continuous years (see supplementary file, supplement 5).

Finally, we performed sensitivity analyses stratified by age (four age groups: <35 years, 35-44 years, 45-54 years, and ≥55 years), single location or multiple locations of meningioma, intracranial location, and severity of meningioma whenever a positive association was found between use of the progestogen of interest and surgery for intracranial meningioma.

Data were analysed using SAS software version 9.4 (SAS Institute). A P value <0.05 was considered statistically significant (two tailed tests).

Patient and public involvement

In July and September 2024, a scientific committee of patient organisations (including patients who had undergone surgery for meningioma), healthcare professionals (neurosurgeon, neurologist, endocrinologist, gynaecologist, general practitioner, epidemiologist, and public health), ethicist, and sociologist analysed and discussed the methods, results, and clinical implications of the study. The study was also presented at an official scientific committee that included patient members organised by the French Safety Medicines Agency in December 2024, in the presence of three patient associations that were consulted to provide input on the communication of the study results and any future medical recommendations. These associations represented patients with meningioma after use of progestogens, patients with a diagnosis of endometriosis, and patients and users of the French healthcare system.

Results

After exclusions, a total of 92 301 women were included in the study from 2020 to 2023. Overall, 8391 women had intracranial meningioma and underwent surgery (cases), and 83 910 women had no intracranial meningioma (controls). Figure 1 shows the flow of participants through the study.

Description of cases and controls

The mean age of the women was 59.7 years (standard deviation 12.9 years) (table 1). Three quarters were older than 45 years. The distribution of social and pregnancy related variables was similar between cases and controls. Overall, 2.7% of cases (223/8391) and 1.5% of controls (1288/83 910) had a hospital diagnosis of endometriosis. Obesity was found in 7.0% of cases (587/8391) and 4.6% of controls (3898/83 910).

The annual number of surgeries for intracranial meningioma in the women was lowest in 2020 (n=1843), the first year of the covid-19 pandemic, and then stabilised for the following three years at around 2200 each year. Meningiomas requiring surgery were most frequently located at the skull base (4414/8391 (52.6%): anterior (22.3%), middle (18.3%), and posterior (12.5%), and convexity (3132/8391 (37.3%)). Most of the meningiomas were histologically non-cancerous (referred to as benign in ICD-10, 7538/8391, 89.8%), 7.7% (649/8391) were atypical, and 2.4% (204/8391) were malignant. Mortality was estimated at 3.4% two years after the index date in cases (138/4024 with a two year follow-up): 111/3572 (3.1%) for non-cancerous, 14/336 (4.2%) for atypical, and 13/116 (11.2%) for malignant meningiomas.

Use of progestogens among cases

Of the 8391 women admitted to hospital for intracranial meningioma surgery between 2020 and 2023, 287 (3.4%) used desogestrel 75 µg, 17 (0.2%) used levonorgestrel 30 µg, and 157 (1.9%) used levonorgestrel combined with oestrogen (table 2). Overall, 40.0% of women dispensed desogestrel (115/287), 47.1% dispensed levonorgestrel (8/17), and 58.6% dispensed levonorgestrel combined with oestrogen (92/157) used the drug for more than five years (see supplementary file, supplement 6).

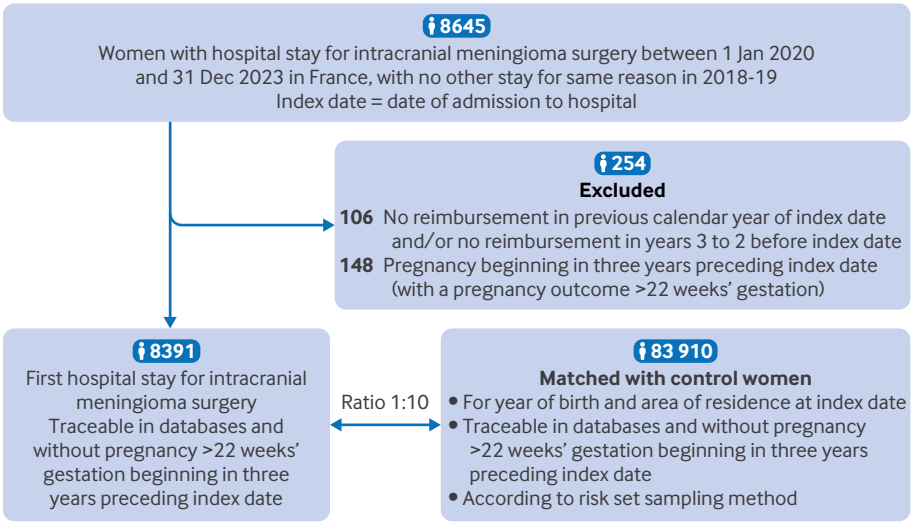

Fig 1 | Flow of participants through study

doi: 10.1136/bmj-2024-083981 | *BMJ* 2025;389:e083981 | the bmj

Table 1 | Characteristics of women with intracranial meningioma requiring surgery (cases) and women without intracranial meningioma (controls)

Characteristics	Cases (n=8391)	Controls (n=83 910)
Mean (SD) age (years)	59.7 (12.9)	59.7 (12.9)
Median (IQR) age (years)	60.0 (50.0-70.0)	60.0 (50.0-70.0)
Age group (years):		
≤19	18 (0.2)	180 (0.2)
20-34	173 (2.1)	1730 (2.1)
35-44	860 (10.2)	8600 (10.2)
45-54	2014 (24.0)	20 140 (24.0)
≥55	5326 (63.5)	53 260 (63.5)
Geographical area*:		
Ile-de-france	1532 (18.3)	15 320 (18.3)
North east	1604 (19.1)	16 040 (19.1)
North west	1662 (19.8)	16 620 (19.8)
South east	2192 (26.1)	21 920 (26.1)
South west	1187 (14.1)	11 870 (14.1)
Overseas areas	214 (2.6)	2140 (2.6)
C2S	802 (9.6)	8353 (9.9)
Social deprivation index:		
1 (least deprived)	1722 (20.5)	17 298 (20.6)
2	1697 (20.2)	16 193 (19.3)
3	1629 (19.4)	16 120 (19.2)
4	1582 (18.9)	15 993 (19.1)
5 (most deprived)	1430 (17.0)	15 085 (18.0)
Missing	331 (3.9)	3221 (3.8)
Endometriosis	223 (2.7)	1288 (1.5)
Obesity	587 (7.0)	3898 (4.6)
No of pregnancies ≤22 gestational weeks:		
1	367 (4.4)	4234 (5.0)
2	80 (1.0)	869 (1.0)
3	22 (0.3)	239 (0.3)
4	7 (0.1)	65 (0.1)
≥5	5 (0.0)	53 (0.1)
No of pregnancies >22 gestational weeks:		
1	786 (9.4)	8040 (9.6)
2	473 (5.6)	4778 (5.7)
3	92 (1.1)	1193 (1.4)
4	19 (0.2)	214 (0.3)
≥5	5 (0.0)	43 (0.0)
Year of meningioma surgery:		
2020	1843 (22.0)	NA
2021	2181 (26.0)	NA
2022	2186 (26.1)	NA
2023	2181 (26.0)	NA
Location of meningioma in skull†:		
Anterior base	1867 (22.3)	NA
Middle base	1535 (18.3)	NA
Posterior base	1052 (12.5)	NA
Convexity	3132 (37.3)	NA
Falx and tentorium	732 (8.7)	NA
Other	73 (0.9)	NA
Multiple locations‡	363 (4.3)	NA
Tumour severity:		
Non-cancerous	7538 (89.8)	NA
Atypical	649 (7.7)	NA
Malignant	204 (2.4)	NA
Mortality 2 years after index date§:		
All grade	138/4024 (3.4)	634 (0.8)
Non-cancerous	111/3572 (3.1)	NA
Atypical	14/336 (4.2)	NA
Malignant	13/116 (11.2)	NA

C2S=Complémentaire Santé Solidaire (health insurance for those with low incomes); IQR=interquartile range; NA=not applicable; SD=standard deviation.
*North east: Grand Est, Bourgogne Franche-Comté, and Hauts-de-France; Ile-de-France: Paris city and Ile-de-France area; north west: Bretagne, Centre Val de Loire, Normandie, and Pays de la Loire; south east: Auvergne-Rhône-Alpes, Provence-Alpes-Côte d'Azur, and Corse; south west: Nouvelle-Aquitaine and Occitanie; French overseas areas: Guadeloupe, Martinique, French Guiana, Reunion Island.
†For multiple locations during the same hospital stay, only the main location is presented. The main location was decided: if an anterior/medial or posterior resection was associated with a decompression procedure or under the tent of the cerebellum/falsa, the location of the resection took precedence. If different base skull locations were recorded (anterior, middle, or posterior resection), frequency of the single locations took precedence (ie, anterior first followed by middle and then posterior—for example, if anterior and middle, anterior was assigned). If a procedure concerned the convexity, this location took precedence over all others (whether or not the dural venous sinus was involved gives an indirect indication of complete or incomplete resection, respectively).
‡Tumours could occur at multiple sites during a hospital stay.
§Restricted inclusion period: 2020-21.

Table 2 | Association between duration of use of progestogen based oral contraceptives and risk of intracranial meningioma requiring surgery (cases). Controls were women without intracranial meningioma

Duration of use	Cases (n=8391)	Controls (n=83 910)	Odds ratio* (95% CI)
Desogestrel 75 µg			
Current	287 (3.4)	2769 (3.3)	1.25 (1.10 to 1.42)
Short term (<1 year)	57 (0.7)	665 (0.8)	1.02 (0.77 to 1.34)
Prolonged use:			
≥1 year	230 (2.7)	2104 (2.5)	1.32 (1.14 to 1.53)
Previous continuous use (years):			
1-2	24 (0.3)	424 (0.5)	0.67 (0.44 to 1.01)
2-3	31 (0.4)	307 (0.4)	1.23 (0.85 to 1.78)
3-4	30 (0.3)	264 (0.3)	1.36 (0.93 to 1.99)
4-5	30 (0.3)	287 (0.3)	1.28 (0.88 to 1.88)
≥5	115 (1.4)	822 (1.0)	1.70 (1.39 to 2.08)
5-6	33 (0.4)	330 (0.4)	1.22 (0.85 to 1.76)
6-7	38 (0.4)	242 (0.3)	1.93 (1.36 to 2.73)
5-7	71 (0.8)	572 (0.7)	1.51 (1.17 to 1.94)
≥7	44 (0.5)	250 (0.3)	2.09 (1.51 to 2.90)
Levonorgestrel 30 µg			
Current	17 (0.2)	140 (0.2)	1.44 (0.87 to 2.40)
Short term <1 year	5 (0.1)	35 (0.0)	NA
Prolonged use:			
≥1 year	12 (0.1)	105 (0.1)	1.37 (0.75 to 2.50)
Previous continuous use (years):			
1-2	0 (0.0)	14 (0.0)	NA
2-3	3 (0.0)	10 (0.0)	NA
3-4	0 (0)	9 (0.0)	NA
4-5	1 (0.0)	2 (0.0)	NA
≥5	8 (0.1)	70 (0.1)	1.40 (0.67 to 2.91)
5-6	1 (0.0)	9 (0.0)	NA
6-7	1 (0.0)	5 (0.0)	NA
5-7	2 (0.0)	14 (0.0)	NA
≥7	6 (0.1)	56 (0.1)	1.29 (0.55 to 3.01)
Levonorgestrel+oestrogen			
Current	157 (1.9)	1933 (2.3)	0.92 (0.77 to 1.09)
Short term <1 year	14 (0.2)	332 (0.4)	0.47 (0.27 to 0.81)
Prolonged use:			
≥1 year	143 (1.7)	1601 (1.9)	1.01 (0.85 to 1.22)
Previous continuous use (years):			
1-2	15 (0.2)	202 (0.2)	0.82 (0.48 to 1.40)
2-3	14 (0.2)	135 (0.2)	1.16 (0.67 to 2.03)
3-4	14 (0.2)	147 (0.2)	1.11 (0.63 to 1.93)
4-5	8 (0.1)	91 (0.1)	1.04 (0.50 to 2.15)
≥5	92 (1.1)	1026 (1.2)	1.04 (0.83 to 1.29)
5-6	7 (0.1)	97 (0.1)	0.81 (0.37 to 1.76)
6-7	7 (0.1)	110 (0.1)	0.73 (0.34 to 1.58)
5-7	14 (0.2)	207 (0.2)	0.76 (0.44 to 1.32)
≥7	78 (0.9)	819 (1.0)	1.11 (0.87 to 1.40)
Positive control			
Neurofibromatosis type 2	30 (0.4)	16 (0.0)	18.75 (10.22 to 34.39)
Negative control†			
Copper intrauterine devices	279 (3.3)	2870 (3.4)	1.15 (1.00 to 1.31)

CI=confidence interval; NA=not applicable.
Current use: at least one dispensing of the progestogen of interest in the year before the index date and no use of chlormadinone acetate, nomegestrol acetate, cyproterone acetate, medrogestone, promegestone, or medroxyprogesterone acetate in the six years before the index date. Short term use: recent use, with no dispensing in the second year before the index date (use in the year before the index date and no use in the second year before the index date). Prolonged use: recent use, with at least one dispensing in the second year before the index date (use in the year before the index date and in the second year before the index date).
*Data for small numbers of cases (<6) are not shown.
†Use five years before, with no withdrawal coded in SNDS (French national health data system).

Use of high risk progestogens before desogestrel or levonorgestrel

In the women who underwent surgery for intracranial meningioma, 1037/8391 (12.3%) had used at least one of the six progestogens associated with increased risk of meningioma in the previous six years. Among these 1037 women, 114 had used desogestrel the year before the index date (and 421 controls), six had used levonorgestrel (17 controls), and 14 had used levonorgestrel combined with oestrogen (119 controls). We studied the 114 women who used desogestrel and had previously or simultaneously in the past six years used one of the six progestogens associated with increased risk of meningioma. Based

doi: 10.1136/bmj-2024-083981 | *BMJ* 2025;389:e083981 | the bmj

on MRI records, we found that 105 out of the 114 women had used desogestrel before the MRI (ie, date of probable diagnosis of meningioma). Supplementary file, supplement 7 describes the remaining 105 women who underwent surgery for intracranial meningioma and had used desogestrel and one of the six progestogens associated with increased risk of meningioma. Nearly 45% (47/105) of these women had used nomegestrol acetate before desogestrel, and 42% (44/105) had used chlormadinone acetate.

Risk of intracranial meningioma

Current use of desogestrel 75 µg was associated with an excess risk of intracranial meningioma (odds ratio 1.25 (95% CI 1.10 to 1.42)). Analyses for short term and prolonged use of desogestrel showed a risk of meningioma of 1.02 (0.77 to 1.34) and 1.32 (1.14 to 1.53), respectively. The risk was significant after five years of use, with a subsequent increase according to duration of desogestrel use: 1.70 (1.39 to 2.08) for more than five years, 1.51 (1.17 to 1.94) for five to seven years, and 2.09 (1.51 to 2.90) for seven years or more (table 2). Conversely, current use of levonorgestrel, alone or combined with oestrogen, was not significantly associated with an increased risk of intracranial meningioma (1.44 (0.87 to 2.40) and 0.92 (0.77 to 1.09), respectively). The results did not show an increased risk of meningioma regardless of duration of use, alone or combined with oestrogen.

Full adjustment for obesity and endometriosis did not change the risk observed for desogestrel (1.25 (1.10 to 1.42)) and levonorgestrel. Obesity and endometriosis were associated with increased risk of meningioma: 1.50 (1.37 to 1.64) and 1.35 (1.16 to 1.57), respectively (see supplementary file, supplement 8).

Finally, the risk of intracranial meningioma was increased in women with neurofibromatosis type 2, used as positive controls (30/8391 (0.36%) cases *v* 16/83 910 (0.02%), odds ratio 18.75 (10.22 to 34.39)), and no increased risk in women using copper intrauterine devices (279/8391 (3.3%) *v* 2870/83 910 (3.4%), odds ratio 1.15 (1.00 to 1.31)), used as negative controls.

Additional analyses

For past use of progestogens, the excess risk of meningioma associated with use of desogestrel 75 µg in the second year before the index date but not the first year before the index date (ie, discontinuation for more than a year) disappeared (0.83 (0.63 to 1.09)) (see supplementary file, supplement 9).

For current users of desogestrel younger than 45 years, the risk of intracranial meningioma was not significant (0.99 (0.80 to 1.23)) regardless of duration of use, but we found similar risk in women younger and older than 45 years according to duration of use (continuous use ≥5 years: <45 years 1.70 (1.18 to 2.45) *v* ≥45 years 1.70 (1.34 to 2.16); continuous use ≥7 years <45 years 2.10 (1.12 to 3.93) *v* ≥45 years 2.09 (1.43 to 3.06)) (see supplementary file, supplement 10). For levonorgestrel 30 µg, stratified analyses lacked statistical power. Lastly, risk of intracranial meningioma was observed when stratifying women older than 45 years by use of levonorgestrel combined with oestrogen: 1.37 (1.06 to 1.76) for current use, 1.49 (1.11 to 2.01) for continuous use ≥5 years, and 1.62 (1.19 to 2.20) for continuous use ≥7 years.

The risk of intracranial meningioma associated with desogestrel use (regardless of duration) increased more in women who had previously used at least one of the six progestogens known to be associated with increased risk of meningioma, regardless of use for one to six years before the index date (n=105, odds ratio 3.30 (2.64 to 4.11)) or for two to six years before the index date (n=64, 2.47 (1.88 to 3.25)) (see supplementary file, supplement 9).

In sensitivity analysis, desogestrel use was associated with an increased risk of multiple meningioma locations (odds ratio 1.89 (1.13 to 3.16)) (table 3). The risk of intracranial meningioma associated with desogestrel use was also greater in women with a meningioma located in the anterior of the skull base (1.50 (1.17 to 1.93)) or middle (1.90 (1.47 to 2.46) (medial third with involvement of the spheno-orbital angle 2.44 (1.79 to 3.33)) and in women aged 45 to 54 years (1.42 (1.20 to 1.69)) (see supplementary file, supplement 11).

Table 3 | Additional analyses for association between use of progestogen based oral contraceptives and number of locations for intracranial meningioma in women requiring surgery (cases) and women without intracranial meningioma (controls)

	One location			≥2 locations		
Duration of use	Cases (n=8028)	Controls (n=80 280)	Odds ratio (95% CI)	Cases (n=363)	Controls (n=3630)	Odds ratio (95% CI)*
Desogestrel 75 µg						
Current	267 (3.32)	2628 (3.27)	1.22 (1.06 to 1.39)	20 (5.50)	141 (3.88)	1.89 (1.13 to 3.16)
Short term <1 year	55 (0.68)	636 (0.79)	1.02 (0.77 to 1.35)	2 (0.55)	29 (0.79)	NA
Prolonged ≥1 year	212 (2.64)	1992 (2.48)	1.28 (1.10 to 1.49)	18 (4.95)	112 (3.08)	2.14 (1.24 to 3.67)
Levonorgestrel 30 µg						
Current	17 (0.21)	133 (0.16)	1.51 (0.91 to 2.51)	0 (0.0)	7 (0.19)	NA
Short term <1 year	14 (0.17)	127 (0.15)	1.30 (0.75 to 2.27)	0 (0.0)	7 (0.19)	NA
Prolonged ≥1 year	3 (0.03)	6 (0.0)	NA	0 (0.0)	0 (0.0)	NA
Levonorgestrel+oestrogen						
Current	146 (1.81)	1841 (2.29)	0.89 (0.75 to 1.07)	11 (3.03)	92 (2.53)	1.58 (0.79 to 3.13)
Short term <1 year	12 (0.14)	317 (0.39)	0.42 (0.23 to 0.76)	2 (0.55)	15 (0.41)	NA
Prolonged ≥1 year	134 (1.66)	1524 (1.89)	0.99 (0.82 to 1.19)	9 (2.47)	77 (2.12)	1.57 (0.74 to 3.33)

CI=confidence interval; NA=not applicable.
*Data for small numbers of cases (<6) are not shown.

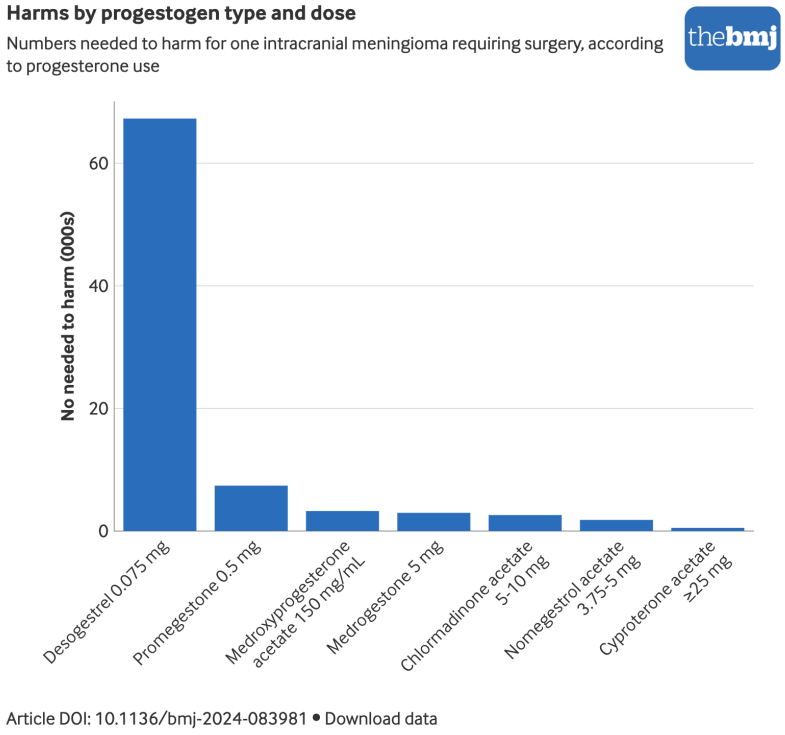

Fig 2 | Numbers needed to harm for one intracranial meningioma requiring surgery, by progestogen use. An interactive version of this graphic is available at https://public.flourish.studio/visualisation/23176824/

Finally, according to our analyses, 0.7% of meningioma cases were attributable to desogestrel use. Specifically, out of 287 surgeries for intracranial meningioma between 2020 and 2023, 59 were attributable to prolonged use of desogestrel. We estimated that 67 287 women who used desogestrel 75 µg would be necessary to observe one attributable case of intracranial meningioma requiring surgery (for any duration of use, versus 518 women for cyproterone acetate for instance) (fig 2). For use of more than five years, we estimated that 17 331 users would be needed to observe one woman with meningioma requiring surgery (versus 40 for cyproterone acetate) (fig 3). Using incidences of meningioma (see supplementary file, supplement 12), we also estimated absolute risks of meningioma associated with desogestrel use (see supplementary file, supplement 13).

Discussion

In this national case-control study on use of progestogen based oral contraceptives and risk of intracranial meningioma, we found an increased risk associated with use of desogestrel 75 µg for more than five continuous years. An increased risk was not observed for shorter durations or when desogestrel had been discontinued for more than one year, but it was if other progestogens of known associated increased risk of meningioma had been used in the six years before desogestrel. The risk resulted in more attributable cases in women older than 45 years. Notably, the risk of intracranial meningioma was observed to be increased with use of one of the progestogens of known associated increased risk of meningioma before the index date and before desogestrel use, even if the high risk progestogen was discontinued for more than one year before the index date.

Meningiomas associated with desogestrel use were histologically non-cancerous in most of the women and seem preferentially to occur in multiple locations or in the anterior or middle skull base. These characteristics are in favour of a causal association.

The magnitude of meningioma risk associated with desogestrel use is, however, much lower than that found for prolonged use of medrogestone, promegestone, cyproterone acetate, chlormadinone acetate, nomegestrol acetate, and medroxyprogesterone acetate. We estimated that 67 000 women would need to use desogestrel 75 µg for one woman to require surgery for intracranial meningioma, and 17 000 women if current use was for more than five years. The results concerning levonorgestrel, alone or combined with oestrogen, and regardless of duration of use are reassuring.

Benefit-risk balance with desogestrel

Unlike previous studies, this study found a risk of meningioma associated with use of a progestogen belonging to the gonanes group, derived from testosterone, and not from the 17-hydroxyprogesterone and 19-norprogesterone groups.[6 8 35] The risk associated with desogestrel use was, however, much lower than that associated with the progestogens of known increased risk of meningioma in previous studies.[8] Systematic magnetic resonance imaging during prolonged use of cyproterone acetate or nomegestrol acetate is justified but does not seem cost effective for an oral contraceptive pill such as desogestrel that is widely used and associated with low risk. It would seem more appropriate to consider the use of desogestrel in older women (ie, >45 years) and particularly in those past menopause (ageing being a predominant risk factor for meningioma) and those who have already used a progestogen of known increased risk of meningioma for a long duration.

Oral contraceptives containing only progestogen have been promoted for their extra contraceptive benefits and mainly for their reduced cardiovascular risk compared with combined oral contraceptives.[36] For these reasons, some countries recently decided to sell desogestrel based oral contraceptives over the counter.[37-39] The risk of intracranial meningioma must be weighed against the cardiovascular risk associated with use of combined oral contraceptives, especially in younger women who are at lower risk of meningioma. In young women, systematic screening for meningioma using imaging as performed in France for other progestogens associated with increased risk[40] is not medically justified and would increase the cost of this contraception considerably. Duration of use, inequalities in access to contraceptive care, and use of the progestogen in specific indications such as

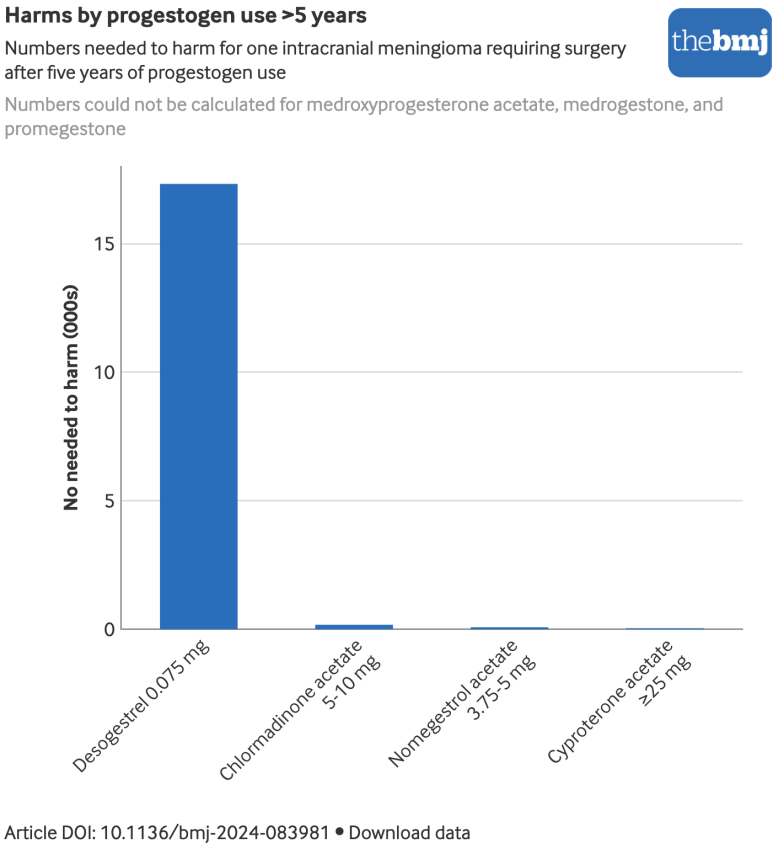

Fig 3 | Numbers needed to harm for one intracranial meningioma requiring surgery after five years of progestogen use. Numbers needed to harm could not be calculated for medroxyprogesterone acetate, medrogestone, and promegestone. An interactive version of this graphic is available at https://public.flourish.studio/visualisation/23177257/

endometriosis are also important factors to consider when prescribing progestogens. Prescribers have the difficult task of establishing a favourable benefit-risk balance on both a collective and individual scale.

Hormone induced meningiomas

The characteristics of the meningiomas in this study were similar to those we found in previous studies of progestogens and risk of meningioma (ie, mostly non-cancerous, a dose-response association, a preferential location in the skull base, and a higher risk of meningiomatis).[6 8 10-12 41] This finding leads us to believe that even a weak association between desogestrel and risk of meningioma is plausible and may correspond to the subcategory of hormone induced meningiomas. The reduction in risk on discontinuation of desogestrel is further in its favour.

The International Consortium on Meningiomas[2] describes radiation induced meningiomas (1-2% of all meningiomas) as the only meningeal tumour distinct from sporadic meningiomas.[42] Radiation induced meningiomas have their own biological and molecular characteristics,[2] with high relative growth rates,[43] justifying a chapter in the consortium's document and numerous studies over the past 20 years.[2] Although progestogen related meningiomas are not mentioned, we believe that they are probably distinct from sporadic meningiomas. In 2007, the first report of a link between cyproterone acetate and meningiomas already suggested that those meningiomas might correspond to a specific histopathological group.[41] Our previous work and that of international teams have gradually drawn up a profile of meningiomas associated with prolonged use of progestogens.

Firstly, there is a potent cumulative dose-response association between current use of certain progestogens and intracranial meningioma, although the risk is not proportional to duration of use (no risk for <1 year of use; intermediate risk for 1-5 years; greatly increased risk >5 years),[6 8 10 11] with a regression of meningioma risk to baseline after one year without use (except for cyproterone acetate when the previous cumulated dose was particularly high[6]).

Secondly, studies by other teams with clinical and radiological data have also observed a stabilisation or reduction in meningioma size when progestogen treatment is stopped[13 44-48]; a preferred location in the anterior or middle of the skull base[6 8 10 11 41 48] such as meningiomas occurring during pregnancy[47] or those expressing progesterone receptors[49] (with high Simpson scores—difficult incomplete resections and frequent recurrences); the majority of non-cancerous tumours (WHO grade 1); and an increased likelihood of meningiomatosis.[13 41 50 51]

Lastly, as with sporadic and radiation induced meningiomas, hormone induced meningiomas may have a specific histology. In histological and molecular in vitro studies these meningiomas showed a higher expression of progesterone receptors and a lower expression of oestrogen receptors, a low rate of NF2 mutations[51] (a strong marker of sporadic meningiomas[52]), a high rate of PIK3CA mutation (involved in cancer of the breast, endometrium, and colon[53]), and a lower rate of TRAF7 mutation.[54]

By analogy with previous progestogens of known associated increased risk, the findings of our study suggest that desogestrel should be discontinued if an intracranial meningioma is identified[13 14 44-56] and patients monitored clinically and radiologically rather than undergoing immediate surgery. Recommendations published in 2024 based on collaboration between neurosurgery, endocrinology, and gynaecology societies also favour such a strategy.[3]

Many questions about the pathogenesis of hormone induced meningiomas remain unanswered, and further clinical, molecular, and radiological studies are needed to better describe this unique tumour and its management. No international recommendations exist for the follow-up of women with progestogen related meningiomas according to drug type and duration of use.[46] Unlike sporadic meningiomas, hormonal induced meningiomas seem to have higher growth rates,[57] but we lacked data on growth measurements and on comparisons between surgical rates according to type of meningioma.[58] It seems that the growth rates of meningiomas differ according to their location.[14 59]

Finally, the sequelae and long term clinical conditions (eg, neurological disorders, epilepsy, or depression) after surgery for hormone induced meningiomas are poorly documented, although being located typically in the skull base—a characteristic of hormone induced meningiomas—is associated with a low health related quality of life.[2 60] Even surveillance imaging after cessation of progestogen treatment may be related to substantial anxiety and a negative impact on quality of life.[60]

Importance of age

The average age of desogestrel users in our study period increased from 34.3 years in 2020 to 34.9 years in 2023 (SNDS data). Age is a key determinant in meningioma risk.[1] We found a greater excess risk of meningioma associated with use of desogestrel in women aged ≥45 years (odds ratio 1.42 (95% CI 1.20 to 1.69)). However, analyses stratified on age suggested an excess risk in women younger than 45 years, with a dose-effect association. Although the odds ratios were similar between the groups of women younger than 45 years and older than 45 years (see supplementary file, supplement 10), the absolute risk of meningioma was not the same between age groups: from 3.1 per 100 000 in women aged 20-44 years to 11.0 per 100 000 in women aged 45-54 years (see supplementary file, supplement 12[1]). The number of women with meningiomas resulting from these risks was much lower in those younger than 45 years than older (see supplementary file, supplement 14). This must be considered in public health prevention measures for progestogen based oral contraceptives mostly used by young women.

Furthermore, the causality criteria for meningiomas related to levonorgestrel combined with oestrogen were not met. The dose-effect association was not as clear cut, and we did not find the same excess risks for locations characteristic of hormone induced meningiomas, nor increased risks for meningiomas in multiple locations. If there was a risk from use of levonorgestrel combined with oestrogen, it would be extremely low, especially in young women. Given this finding, it would seem pointless to change usual contraceptive use in young women but rather to focus on oral contraceptives in women older than 45 years to reduce their risk of intracranial meningioma.

Strengths and limitations of this study

This study compared the risk of meningioma between desogestrel and levonorgestrel based oral contraceptives. It was conducted on a national scale in all women resident in France, regardless of age. By using real life data, we avoided selection bias by including all women with a first meningioma operated on in the 2020-23 inclusion period, and by considering all dispensations for the progestogens of interest. The use of SNDS, with virtually comprehensive data on drug reimbursements since 2006, helped to avoid recall bias. History of use of medrogestone, promegestone, nomegestrol acetate, cyproterone acetate, chlormadinone acetate, or medroxyprogesterone acetate in the six years before was accounted for in a separate modality for previous or simultaneous use of at least one of the six progestogens. In this way, confounding bias was minimised.

We used three approaches that have shown validity and reliability. Firstly, to improve the reliability of risk estimates and since pregnancy influences both drug use and risk, we excluded women who were pregnant in the three years before the index date.[3 31 32] Secondly, we used a case-control design, with time accounted for in both the drawing of controls from the general population, which is dynamic (risk set sampling), and the analysis, enabling odds ratios to be interpreted as incidence rate ratios.[6 8] Lastly, we included both positive and negative controls to support the associations. In addition, the level of obesity related to risk of meningioma (odds ratio 1.50) was similar to that generally reported.[61-64]

In this study, as in previous studies of other progestogens, only hospital admission for meningioma surgery was used as the event of interest. Meningiomas may also be treated exclusively with radiotherapy (rarely) or simply monitored.[65] Using hospital admission with meningioma surgery ensured the specificity of the event studied and thus limited classification bias, despite potentially leading to an underestimation of the total number of meningiomas associated with progestogen use.

Several factors were in favour of causality of desogestrel: a dose-response association, preferential localisation in the anterior and middle of the skull base that are specific to hormone induced meningiomas, and an excess risk of multiple meningiomas. Levonorgestrel, however, showed no clear dose-effect association and no excess risk for localisation in the skull base.

As with any observational study, this study has limitations. Firstly, SNDS does not provide information on the use of non-reimbursed drugs, including third generation pills containing desogestrel (2% of combined oral contraceptive users in France, sales data)[66] and one brand of desogestrel (Cerazette; Organon, France), 1% of progestogen only pill users). This incomplete detection of drug use might bias the associations towards the null. We nonetheless had access to practically all contraception used in France, as 86% of combined oral contraceptives (second generation—all levonorgestrel based combined oral contraceptives), 93% of progestogen only pills (desogestrel without Cerazette and levonorgestrel), all contraceptive implants, and intrauterine devices are reimbursed and hence available in SNDS.

The risk of intracranial meningioma we have highlighted concerns pills containing a lower dose of desogestrel than that contained in combined pills (75 µg alone versus 150 µg when associated with ethinylestradiol). However, the cumulative dose associated with risk of meningioma also depends on duration of use: it is possible that the risk in users of desogestrel based combined pills appears after a

shorter duration of use (even if use is discontinuous). Moreover, desogestrel is a pro-drug rapidly metabolised into 3-keto-desogestrel (or etonogestrel), an active substance of a widely used contraceptive implant (Nexplanon; Organon, France). Caution is therefore needed when extrapolating possible risks to these contraceptives. Furthermore, as regards hormonal treatments for menopause, we adjusted for treatments that had already shown an association with risk of meningioma in our previous study (medrogestone, promegestone, nomegestrol acetate, chlormadinone acetate) in the six years before. Nevertheless, we did not have access to some non-reimbursed continuous oestrogen-progestogen treatments that could be associated with meningioma, as shown by a nationwide Danish study.[67] It seems unlikely, however, that desogestrel taken after age 50 years is concomitant with post-menopausal treatment.

Secondly, SNDS does not provide information on clinics and indications for which desogestrel and levonorgestrel have been prescribed. Even though most women who use these products will do so for contraception, desogestrel is also recommended, for example, for the treatment of endometriosis. This makes it impossible to assess the benefit:risk ratio of prescriptions, which could be favourable in the absence of an effective alternative, if the progestogens are used at the minimum effective dose and for the shortest duration. Moreover, without access to clinical data we do not know whether conservative treatment for intracranial meningioma had been considered before surgery.

Thirdly, we were unable to account for all confounding factors. The two main risk factors identified for meningiomas, apart from age and female sex, are genetic predisposition, notably attributed to inherited mutations of the neurofibromatosis type 2 gene, and medical or environmental exposure to high doses of ionising radiation. Of all the possible medical reasons for exposure to intracranial radiation, radiotherapy for brain cancer (particularly during childhood) is probably the most important. However, these two risk factors account for only 1-2% of all meningiomas.[2] Our data did not provide information on previous exposure to intracerebral radiation, and we were therefore unable to take this factor into account in our study, but we considered it highly unlikely that irradiation would be responsible for an important miscalculation of the impact of progestogens. Finally, although intracerebral irradiation in childhood is an important risk factor for the development of meningiomas in adulthood, having undergone cerebral radiotherapy or having a malignant brain tumour in childhood (around 250 girls each year in France) remains rare in the general population.[68-70] Moreover, specific and updated studies on meningiomas occurring after cancer in a patient's lifetime would be advantageous. We were unable to determine risk according to ethnicity as SNDS does not record information on race. Some American studies have shown a higher incidence of meningioma in black people, although according to the International Consortium on Meningiomas, "these racial and ethnic differences remain unknown and the limitations of reporting based on population-based epidemiological data need to be considered, particularly for comparisons between different countries and/or continents."[2]

Fourthly, it is possible that errors occurred in the measurement of drug use. Women may have been prescribed contraceptives but not actually taken them. However, the long duration of use, the multiple dispensations for each woman we observed, and the existence of a small co-payment make this hypothesis unlikely and would support the null hypothesis. Fifthly, we did not perform multiple tests, as this work is based on a strong a priori hypothesis derived from our previous work. However, some associations could be due to chance. Finally, our study lacked power in the analyses on users of levonorgestrel alone owing to a lower number of women. We could hypothesise that oestrogens may reduce the risk of meningioma in association with progestogens, given our results for levonorgestrel combined with. Ideally, we should also have studied desogestrel combined with an oestrogen, but information was not available in SNDS (and this drug combination is little used in France). Countries that have access to these data should provide answers, especially as desogestrel is available in higher doses in combination pills. However, in our previous studies, exogenous oestrogens did not seem to play a role in the risk of meningioma, this risk being associated with progestogens alone.[6 8 10 11]

Clinical implications and perspectives

The association between sex hormones of endogenous or exogenous origin and neurological pathophysiology in women is a particularly important subject and one receiving increasing attention.[67 71-75] In this context, contraception is a treatment in its own way, with specific prescription characteristics not found in other treatments. Firstly, it is not used to treat disease, and women in good or poor health can use contraception for at least 30 years—that is, for long periods, with possible changes between the hormonal molecular constituents of the contraceptive, and discontinuation of use or a continuity with hormone treatments for perimenopause. Furthermore, contraceptive pills are increasingly prescribed for long periods without restrictions or dispensed over the counter in many countries, making it difficult to provide information and identify risks associated with prolonged use.[39]

Yet, the fact that cumulative doses and treatment durations are so important in our current and previous work on risk of meningioma suggests that health professionals need to change the paradigm of one treatment, one risk. Clinicians must consider the whole trajectory of factors for women who have used different hormone treatments over the years, including number of pregnancies, infertility treatment, and familial risk. In addition, the dose equivalence of each progestogen should be established to determine a general cumulative dose as close as possible to that

for each progestogen actually received.[76] To assess the overall risk of meningioma, the use of different progestogens must also be taken into account over the course of a woman's lifetime, as hormonal related risks evolve with age rather than as isolated independent treatments.

The risk of meningioma associated with prolonged use of desogestrel remains low compared with that of other progestogens. If a meningioma is discovered in women using desogestrel, immediate discontinuation of the progestogen and clinical and radiological monitoring with neurosurgical advice should be recommended. A more general review of the use of desogestrel as a progestogen only contraception beyond age 45 years with possible off-label use of desogestrel would also be in order. As fertility declines with age, prescribing desogestrel for menopause related symptoms should be avoided. Above all, it is advisable to prevent women older than 40 years who are using desogestrel from switching to combined oral contraception, which would present a thromboembolic risk at this age. Furthermore, discontinuing contraception in general should also be avoided, to lower the risk of unwanted pregnancies. In addition, it would not be desirable to switch between progestogens for which the risk of meningioma is higher than that of desogestrel 75 µg or as yet unknown (dienogest, drospirenone). The lifelong risk of intracranial meningioma should be assessed when using progestogens continuously, accounting for discontinuation periods and switches between different progestogens that have been associated with meningioma risk, whether for premenopausal treatment (eg, contraception, endometriosis) or postmenopausal treatment (hormone replacement therapy).

Other countries using more desogestrel based combined oral contraceptives (and that have access to data on use of these contraceptives) should consider assessing the risk of meningioma associated with use, as a function of cumulative dose, as was done in the US for medroxyprogesterone acetate after our 2023 case-control study.[8 9] The European Medicines Agency could play a leading role in encouraging member countries to carry out this type of study in Europe. In addition, the use of desogestrel 75 µg in women older than 45 years should be avoided and replaced by an alternative contraceptive option or levonorgestrel treatment.

Conclusions

Our results show an absence of meningioma risk in levonorgestrel users (alone or in combined form). Monitoring for meningioma should focus on women who have used desogestrel 75 µg for more than five continuous years, in whom we found a small risk of meningioma. As with the other progestogens, risk increased with duration of use and after use of a progestogen of known associated increased risk. The risk in desogestrel users was low (number needed to harm was 67 300 women using the oral contraceptive for one intracranial meningioma requiring surgery) compared with that observed for the six progestogens known to be associated with increased risk of meningioma (eg, 518 women using high dose cyproterone acetate for one woman requiring surgery for intracranial meningioma).

The many countries where other combined or progestogen only oral contraceptives are used should consider assessing the potential risk of meningioma associated with progestogens, depending on cumulative dose. Future research is also needed on risk of meningioma in women with long term continuous use of different progestogens of known associated increased risk of meningioma.

We thank all members of the scientific study committee.

Contributors: AW, NR, and EK conceived and planned the study. NR and AW drafted the manuscript. EK managed the data. EK, NR, and AW did the statistical analyses. PD, LD, and SF proofread and edited earlier versions of the manuscript. AW and MZ ensured project and study management. All authors approved the final manuscript. AW is the guarantor. The corresponding author attests that all listed authors meet the authorship criteria and that no others meeting the criteria have been omitted.

Funding: This research was funded by the French National Health Insurance Fund (CNAM, Caisse nationale de l'Assurance Maladie) and the French National Agency for Medicines and Health Products Safety (ANSM) through the Health Product Epidemiology Scientific Interest Group EPI-PHARE. The funders had no role in considering the study design or in the collection, analysis, interpretation of data, writing of the report, or decision to submit the article for publication.

Competing interests: All authors have completed the ICMJE uniform disclosure form at https://www.icmje.org/disclosure-of-interest/ and declare: support from French National Health Insurance Fund (CNAM, Caisse nationale de l'Assurance Maladie) and the Health Product Epidemiology Scientific Interest Group EPI-PHARE for the submitted work; NR and AW are employees of CNAM, and EK and MZ are employees of ANSM; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, and no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: The present study was authorised by decree 2016-1871 on 26 December 2016 from Système national des données de santé (SNDS). As a permanent user of SNDS, the author's team was exempt from approval from the institutional review board. This work was declared, before implementation, on the register of studies of the EPI-PHARE Scientific Interest Group requiring use of SNDS (register reference: T-2024-01-493).

Data sharing: Under the terms of the SNDS data use agreement, the complete study data cannot be shared with other investigators (https://www.snds.gouv.fr). However, the authors try to share publication related data as much as possible: algorithms and other additional information are provided in the supplemental data; aggregated data can be supplied upon request by contacting the lead author at alain.weill@assurance-maladie.fr.

Transparency: The lead author (AW) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted, and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: Throughout the study, from planning to publication, we have endeavoured to incorporate the opinion of patients with a diagnosis of meningioma, progestogen user organisations, and medical societies in general medicine, gynaecology, and neurosurgery. Likewise, efforts will be made to disseminate these results not only to the European Medicines Agency but also to international associations such as the International Brain Tumor Association, and to colleges of healthcare professionals (eg, pharmacists, as desogestrel is available over the counter in many countries) to share the information in the most relevant and educational manner. The results of this study were first presented on 18 December 2024 at a meeting organised by the French National Agency for Medicines and Health Products Safety (ANSM) to invite patient association representatives, gynaecologists, endocrinologists, neurosurgeons, and general practitioners. The study

report (in French) was than published on 19 December 2024, on the EPI-PHARE, ANSM and French National Health Insurance Fund (CNAM, Caisse nationale de l'Assurance Maladie) websites and was sent to the European Medicines Agency. The French press release is available in supplementary file, supplement 16.

Provenance and peer review: Not commissioned; externally peer reviewed.

1 Wiemels J, Wrensch M, Claus EB. Epidemiology and etiology of meningioma. *J Neurooncol* 2010;99:307-14. doi:10.1007/s11060-010-0386-3
2 Wang JZ, Landry AP, Raleigh DR, et al, International Consortium on Meningiomas (ICOM). Meningioma: International Consortium on Meningiomas consensus review on scientific advances and treatment paradigms for clinicians, researchers, and patients. *Neuro Oncol* 2024;26:1742-80. doi:10.1093/neuonc/noae082
3 Reuter G, Potorac I, de Herdt C, et al. Recommendations on the management of meningioma and sex hormone therapy: The results of a collaborative effort between neurosurgical, endocrine and gynecological societies. *Brain Spine* 2024;5:104154. doi:10.1016/j.bas.2024.104154
4 Gil M, Oliva B, Timoner J, Maciá MA, Bryant V, de Abajo FJ. Risk of meningioma among users of high doses of cyproterone acetate as compared with the general population: evidence from a population-based cohort study. *Br J Clin Pharmacol* 2011;72:965-8. doi:10.1111/j.1365-2125.2011.04031.x
5 Nota NM, Wiepjes CM, de Blok CJM, et al. The occurrence of benign brain tumours in transgender individuals during cross-sex hormone treatment. *Brain* 2018;141:2047-54. doi:10.1093/brain/awy108
6 Weill A, Nguyen P, Labidi M, et al. Use of high dose cyproterone acetate and risk of intracranial meningioma in women: cohort study. *BMJ* 2021;372:n37. doi:10.1136/bmj.n37
7 Mikkelsen AP, Greiber IK, Scheller NM, Hilden M, Lidegaard Ø. Cyproterone acetate and risk of meningioma: a nationwide cohort study. *J Neurol Neurosurg Psychiatry* 2022;93:222-3. doi:10.1136/jnnp-2021-326138
8 Roland N, Neumann A, Hoisnard L, et al. Use of progestogens and the risk of intracranial meningioma: national case-control study. *BMJ* 2024;384:e078078. doi:10.1136/bmj-2023-078078
9 Griffin RL. The Association between Medroxyprogesterone Acetate Exposure and Meningioma. *Cancers (Basel)* 2024;16:3362. doi:10.3390/cancers16193362
10 Nguyen P, Roland N, Neumann A, et al. Prolonged use of nomegestrol acetate and risk of intracranial meningioma: a population-based cohort study. *Lancet Reg Health Eur* 2024;42:100928. doi:10.1016/j.lanepe.2024.100928
11 Hoisnard L, Laanani M, Passeri T, et al. Risk of intracranial meningioma with three potent progestogens: A population-based case-control study. *Eur J Neurol* 2022;29:2801-9. doi:10.1111/ene.15423
12 Roland N, Nguyen P, Neumann A, et al. Prolonged use of chlormadinone acetate and risk of intracranial meningioma: A population-based cohort study. *Eur J Neurol* 2025;32:e16505. doi:10.1111/ene.16505
13 Bernat AL, Oyama K, Hamdi S, et al. Growth stabilization and regression of meningiomas after discontinuation of cyproterone acetate: a case series of 12 patients. *Acta Neurochir (Wien)* 2015;157:1741-6. doi:10.1007/s00701-015-2532-3
14 Voormolen EHJ, Champagne PO, Roca E, et al. Intracranial Meningiomas Decrease in Volume on Magnetic Resonance Imaging After Discontinuing Progestin. *Neurosurgery* 2021;89:308-14. doi:10.1093/neuros/nyab175
15 Hognert H, Skjeldestad FE, Gemzell-Danielsson K, et al. High birth rates despite easy access to contraception and abortion: a cross-sectional study. *Acta Obstet Gynecol Scand* 2017;96:1414-22. doi:10.1111/aogs.13232
16 Lindh I, Skjeldestad FE, Gemzell-Danielsson K, et al. Contraceptive use in the Nordic countries. *Acta Obstet Gynecol Scand* 2017;96:19-28. doi:10.1111/aogs.13055
17 Kurvits K, Laius O, Uusküla M, Laanpere M. Trends in the use of hormonal contraception in Estonia 2005-2019 and the risk of arterial and venous thromboembolism: a population-based study. *Eur J Contracept Reprod Health Care* 2021;26:413-20. doi:10.1080/13625187.2021.1931839
18 IQVIA. MIDAS®. 2024. https://www.iqvia.com/solutions/commercialization/brand-strategy-and-management/market-measurement/midas (accessed 8 December 2024)
19 ClinCalc DrugStats Database. Desogestrel; Ethinyl Estradiol - Drug Usage Statistics. 2021. https://clincalc.com/DrugStats/Drugs/DesogestrelEthinylEstradiol (accessed 2 July 2024)
20 ClinCalc DrugStats Database. Ethinyl Estradiol; Levonorgestrel - Drug Usage Statistics, ClinCalc DrugStats Database. 2021. https://clincalc.com/DrugStats/Drugs/EthinylEstradiolLevonorgestrel (accessed 2 July 2024)
21 Qi Z-Y, Shao C, Huang Y-L, Hui GZ, Zhou YX, Wang Z. Reproductive and exogenous hormone factors in relation to risk of meningioma in women: a meta-analysis. *PLoS One* 2013;8:e83261. doi:10.1371/journal.pone.0083261
22 Michaud DS, Gallo V, Schlehofer B, et al. Reproductive factors and exogenous hormone use in relation to risk of glioma and meningioma in a large European cohort study. *Cancer Epidemiol Biomarkers Prev* 2010;19:2562-9. doi:10.1158/1055-9965.EPI-10-0447
23 Yang X, Liu F, Zheng J, Cheng W, Zhao C, Di J. Relationship Between Oral Contraceptives and the Risk of Gliomas and Meningiomas: A Dose-Response Meta-Analysis and Systematic Review. *World Neurosurg* 2021;147:e148-62. doi:10.1016/j.wneu.2020.11.175
24 Hage M, Plesa O, Lemaire I, Raffin Sanson ML. Estrogen and Progesterone Therapy and Meningiomas. *Endocrinology* 2022;163:bqab259. doi:10.1210/endocr/bqab259
25 Maillard O, Bun R, Laanani M, et al. Use of the French National Health Data System (SNDS) in pharmacoepidemiology: A systematic review in its maturation phase. *Therapie* 2024;79:659-69. doi:10.1016/j.therap.2024.05.003
26 Bezin J, Duong M, Lassalle R, et al. The national healthcare system claims databases in France, SNIIRAM and EGB: Powerful tools for pharmacoepidemiology. *Pharmacoepidemiol Drug Saf* 2017;26:954-62. doi:10.1002/pds.4233
27 Billioti de Gage S, Drouin J, Desplas D, et al. Intravitreal Anti-Vascular Endothelial Growth Factor Use in France During the Coronavirus Disease 2019 Pandemic. *JAMA Ophthalmol* 2021;139:240-2. doi:10.1001/jamaophthalmol.2020.5594
28 Jourdain H, de Gage SB, Desplas D, Dray-Spira R. Real-world effectiveness of pre-exposure prophylaxis in men at high risk of HIV infection in France: a nested case-control study. *Lancet Public Health* 2022;7:e529-36. doi:10.1016/S2468-2667(22)00106-2
29 Roland N, Baricault B, Weill A, et al. Association Between Doses of Levonorgestrel Intrauterine Systems and Subsequent Use of Psychotropic Drugs in France. *JAMA* 2023;329:257-9. doi:10.1001/jama.2022.21471
30 Swital M, Drouin J, Miranda S, Bakchine S, Botton J, Dray-Spira R. Use of multiple sclerosis disease-modifying therapies during pregnancy in France: Nationwide study between 2010 and 2021. *Mult Scler* 2024;30:227-37. doi:10.1177/13524585231223395
31 Laviv Y, Ohla V, Kasper EM. Unique features of pregnancy-related meningiomas: lessons learned from 148 reported cases and theoretical implications of a prolactin modulated pathogenesis. *Neurosurg Rev* 2018;41:95-108. doi:10.1007/s10143-016-0762-3
32 Carbone L, Somma T, Iorio GG, et al. Meningioma during pregnancy: what can influence the management? A case series and review of the literature. *J Matern Fetal Neonatal Med* 2022;35:8767-77. doi:10.1080/14767058.2021.2004585
33 Mansournia MA, Hernán MA, Greenland S. Matched designs and causal diagrams. *Int J Epidemiol* 2013;42:860-9. doi:10.1093/ije/dyt083
34 Greenland S. Concepts and pitfalls in measuring and interpreting attributable fractions, prevented fractions, and causation probabilities. *Ann Epidemiol* 2015;25:155-61. doi:10.1016/j.annepidem.2014.11.005
35 AlDoheyan TA, Del Bigio MR. Regression of multiple intracranial meningiomas after cessation of long-term synthetic progesterone (megestrol) medication: case report and autopsy. *Free Neuropathol* 2024;5:27. doi:10.17879/freeneuropathology-2024-5813
36 Weill A, Dalichampt M, Raguideau F, et al. Low dose oestrogen combined oral contraception and risk of pulmonary embolism, stroke, and myocardial infarction in five million French women: cohort study. *BMJ* 2016;353:i2002. doi:10.1136/bmj.i2002.
37 No authors listed. Over-the-Counter Access to Hormonal Contraception: ACOG Committee Opinion, Number 788. *Obstet Gynecol* 2019;134:e96-105. doi:10.1097/AOG.0000000000003473
38 Brandi K, Upadhya KK, Teal SB. Over-the-Counter Oral Contraception as an Opportunity to Reduce Contraceptive Access Inequity. *JAMA* 2023;330:407-8. doi:10.1001/jama.2023.10825
39 Zuniga C, Forsberg H, Grindlay K. Experiences of progestin-only pill users in the United States and attitudes toward over-the-counter access. *Perspect Sex Reprod Health* 2023;55:104-12. doi:10.1363/psrh.12223
40 Samoyeau T, Provost C, Roux A, et al. Meningioma in patients exposed to progestin drugs: results from a real-life screening program. *J Neurooncol* 2022;160:127-36. doi:10.1007/s11060-022-04124-2

41 Froelich S, Dali-Youcef N, Boyer P, et al. *Does cyproterone acetate promote multiple meningiomas?* Endocrine Abstracts, 2008: 16.
42 Heymer EJ, Hawkins MM, Winter DL, et al. Risk of subsequent gliomas and meningiomas among 69,460 5-year survivors of childhood and adolescent cancer in Europe: the PanCareSurFup study. *Br J Cancer* 2024;130:976-86. doi:10.1038/s41416-024-02577-y
43 Gillespie CS, Islim AI, Taweel BA, et al. The growth rate and clinical outcomes of radiation induced meningioma undergoing treatment or active monitoring. *J Neurooncol* 2021;153:239-49. doi:10.1007/s11060-021-03761-3
44 Cebula H, Pham TQ, Boyer P, Froelich S. Regression of meningiomas after discontinuation of cyproterone acetate in a transsexual patient. *Acta Neurochir (Wien)* 2010;152:1955-6. doi:10.1007/s00701-010-0787-2
45 Passeri T, Champagne P-O, Bernat A-L, et al. Spontaneous regression of meningiomas after interruption of nomegestrol acetate: a series of three patients. *Acta Neurochir (Wien)* 2019;161:761-5. doi:10.1007/s00701-019-03848-x
46 Malaize H, Samoyeau T, Zanello M, et al. Evolution of the neurosurgical management of progestin-associated meningiomas: a 23-year single-center experience. *J Neurooncol* 2021;152:279-88. doi:10.1007/s11060-021-03696-9
47 Agopiantz M, Carnot M, Denis C, Martin E, Gauchotte G. Hormone Receptor Expression in Meningiomas: A Systematic Review. *Cancers (Basel)* 2023;15:980. doi:10.3390/cancers15030980
48 Froelich S, Pham QT, Boyer P, et al. L'acétate de cyprotérone (Androcur) favorise-t-il la méningiomatose? *Rev Med Interne* 2007;28S:S317-89.
49 Bouillot P, Pellissier JF, Devictor B, et al. Quantitative imaging of estrogen and progesterone receptors, estrogen-regulated protein, and growth fraction: immunocytochemical assays in 52 meningiomas. Correlation with clinical and morphological data. *J Neurosurg* 1994;81:765-73. doi:10.3171/jns.1994.81.5.0765
50 Shahin MN, Bowden SG, Yaghi NK, et al. Regression of Multiple Meningiomas after Discontinuation of Chronic Hormone Therapy: A Case Report. *J Neurol Surg Rep* 2021;82:e38-42. doi:10.1055/s-0041-1735553
51 Passeri T, Giammattei L, Le Van T, et al. Atypical evolution of meningiomatosis after discontinuation of cyproterone acetate: clinical cases and histomolecular characterization. *Acta Neurochir (Wien)* 2022;164:255-63. doi:10.1007/s00701-021-05005-9
52 Williams EA, Santagata S, Wakimoto H, et al. Distinct genomic subclasses of high-grade/progressive meningiomas: NF2-associated, NF2-exclusive, and NF2-agnostic. *Acta Neuropathol Commun* 2020;8:171. doi:10.1186/s40478-020-01040-2
53 Samuels Y, Velculescu VE. Oncogenic mutations of PIK3CA in human cancers. *Cell Cycle* 2004;3:1221-4. doi:10.4161/cc.3.10.1164
54 Peyre M, Gaillard S, de Marcellus C, et al. Progestin-associated shift of meningioma mutational landscape. *Ann Oncol* 2018;29:681-6. doi:10.1093/annonc/mdx763
55 Cornu E, Pintiaux A, Reuter G, Kridelka F, Pétrossians P, Potorac I. [Meningioma under progestin treatment : what attitude to adopt?]. *Rev Med Liege* 2023;78:550-7. doi:10.1016/j.maturitas.2023.04.203
56 Lebeau J, Deprez L, Pintiaux A, Reuter G. Petroclival meningioma regression after combined oestrogen and nomegestrol acetate interruption. *BMJ Case Rep* 2025;18:e263529. doi:10.1136/bcr-2024-263529
57 Islim AI, Kolamunnage-Dona R, Mohan M, et al. A prognostic model to personalize monitoring regimes for patients with incidental asymptomatic meningiomas. *Neuro Oncol* 2020;22:278-89. doi:10.1093/neuonc/noz160
58 Sheehan J, Pikis S, Islim AI, et al. An international multicenter matched cohort analysis of incidental meningioma progression during active surveillance or after stereotactic radiosurgery: the IMPASSE study. *Neuro Oncol* 2022;24:116-24. doi:10.1093/neuonc/noab132
59 Florea SM, Passeri T, Abbritti R, et al. Opposed evolution of the osseous and soft parts of progestin-associated osteomeningioma after progestin intake discontinuation. *J Neurosurg* 2023;139:944-52. doi:10.3171/2022.12.JNS222006
60 Nassiri F, Suppiah S, Wang JZ, et al. How to live with a meningioma: experiences, symptoms, and challenges reported by patients. *Neurooncol Adv* 2020;2:vdaa086. doi:10.1093/noajnl/vdaa086
61 Michaud DS, Bové G, Gallo V, et al. Anthropometric measures, physical activity, and risk of glioma and meningioma in a large prospective cohort study. *Cancer Prev Res (Phila)* 2011;4:1385-92. doi:10.1158/1940-6207.CAPR-11-0014
62 Niedermaier T, Behrens G, Schmid D, Schlecht I, Fischer B, Leitzmann MF. Body mass index, physical activity, and risk of adult meningioma and glioma: A meta-analysis. *Neurology* 2015;85:1342-50. doi:10.1212/WNL.0000000000002020
63 Muskens IS, Wu AH, Porcel J, et al. Body mass index, comorbidities, and hormonal factors in relation to meningioma in an ethnically diverse population: the Multiethnic Cohort. *Neuro Oncol* 2019;21:498-507. doi:10.1093/neuonc/noz005
64 Khazanchi R, Nandoliya KR, Shahin MN, et al. Obesity and meningioma: a US population-based study paired with analysis of a multi-institutional cohort. *J Neurosurg* 2024;140:1558-67. doi:10.3171/2023.11.JNS23732
65 Ostrom QT, Price M, Neff C, et al. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2015-2019. *Neuro Oncol* 2022;24(Suppl 5):v1-95. doi:10.1093/neuonc/noac202
66 OpenHealth. Data France 2023. [cited 17 May 2025.] https://www.openhealth.fr/fr/company.
67 Pourhadi N, Mørch LS, Holm EA, Torp-Pedersen C, Meaidi A. Menopausal hormone therapy and dementia: nationwide, nested case-control study. *BMJ* 2023;381:e072770. doi:10.1136/bmj-2022-072770
68 Taylor AJ, Little MP, Winter DL, et al. Population-based risks of CNS tumors in survivors of childhood cancer: the British Childhood Cancer Survivor Study. *J Clin Oncol* 2010;28:5287-93. doi:10.1200/JCO.2009.27.0090
69 Braganza MZ, Kitahara CM, Berrington de González A, Inskip PD, Johnson KJ, Rajaraman P. Ionizing radiation and the risk of brain and central nervous system tumors: a systematic review. *Neuro Oncol* 2012;14:1316-24. doi:10.1093/neuonc/nos208
70 Garcia CM, Ganga A, Weil RJ, Toms SA. Cranial Irradiation for Childhood Cancers and Adult Risk of Meningioma. *Pediatr Neurosurg* 2022;57:396-406. doi:10.1159/000527565
71 Schipper HM. Neurology of sex steroids and oral contraceptives. *Neurol Clin* 1986;4:721-51. doi:10.1016/S0733-8619(18)30945-9
72 Silberstein SD. Sex hormones and headache. *Rev Neurol (Paris)* 2000;156(Suppl 4):S30-41.
73 Zacur HA. Hormonal changes throughout life in women. *Headache* 2006;46(Suppl 2):S49-54. doi:10.1111/j.1526-4610.2006.00554.x
74 Brinton RD, Yao J, Yin F, Mack WJ, Cadenas E. Perimenopause as a neurological transition state. *Nat Rev Endocrinol* 2015;11:393-405. doi:10.1038/nrendo.2015.82
75 Beltz AM. Hormonal contraceptives and behavior: Updating the potent state of the nascent science. *Horm Behav* 2024;164:105574. doi:10.1016/j.yhbeh.2024.105574
76 Schindler AE, Campagnoli C, Druckmann R, et al. Classification and pharmacology of progestins. *Maturitas* 2003;46(Suppl 1):S7-16. doi:10.1016/j.maturitas.2003.09.014

Supplementary information: Supplements 1-16