Use of progestogens and the risk of intracranial meningioma: national case-control study

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ABSTRACT

OBJECTIVE

To assess the risk of intracranial meningioma associated with the use of selected progestogens.

DESIGN

National case-control study.

SETTING

French National Health Data System (ie, *Système National des Données de Santé*).

PARTICIPANTS

Of 108 366 women overall, 18 061 women living in France who had intracranial surgery for meningioma between 1 January 2009 and 31 December 2018 (restricted inclusion periods for intrauterine systems) were deemed to be in the case group. Each case was matched to five controls for year of birth and area of residence (90 305 controls).

MAIN OUTCOME MEASURES

Selected progestogens were used: progesterone, hydroxyprogesterone, dydrogesterone, medrogestone, medroxyprogesterone acetate, promegestone, dienogest, and intrauterine levonorgestrel. For each progestogen, use was defined by at least one dispensation within the year before the index date (within three years for 13.5 mg levonorgestrel intrauterine systems and five years for 52 mg). Conditional logistic regression was used to calculate odds ratio for each progestogen meningioma association.

RESULTS

Mean age was 57.6 years (standard deviation 12.8). Analyses showed excess risk of meningioma with use of medrogestone (42 exposed cases/18 061 cases (0.2%) *v* 79 exposed controls/90 305 controls (0.1%), odds ratio 3.49 (95% confidence interval 2.38 to 5.10)), medroxyprogesterone acetate (injectable, 9/18 061 (0.05%) *v* 11/90 305 (0.01%), 5.55 (2.27 to 13.56)), and promegestone (83/18 061 (0.5%) *v* 225/90 305 (0.2 %), 2.39 (1.85 to 3.09)). This excess risk was driven by prolonged use (≥one year). Results showed no excess risk of intracranial meningioma for progesterone, dydrogesterone, or levonorgestrel intrauterine systems. No conclusions could be drawn concerning dienogest or hydroxyprogesterone because of the small number of individuals who received these drugs. A highly increased risk of meningioma was observed for cyproterone acetate (891/18 061 (4.9%) *v* 256/90 305 (0.3%), odds ratio 19.21 (95% confidence interval 16.61 to 22.22)), nomegestrol acetate (925/18 061 (5.1%) *v* 1121/90 305 (1.2%), 4.93 (4.50 to 5.41)), and chlormadinone acetate (628/18 061 (3.5%) *v* 946/90 305 (1.0%), 3.87 (3.48 to 4.30)), which were used as positive controls for use.

CONCLUSIONS

Prolonged use of medrogestone, medroxyprogesterone acetate, and promegestone was found to increase the risk of intracranial meningioma. The increased risk associated with the use of injectable medroxyprogesterone acetate, a widely used contraceptive, and the safety of levonorgestrel intrauterine systems are important new findings.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Known risk factors for intracranial meningioma include age, female sex, neurofibromatosis type 2, exposure to ionising radiation, and use of high dose progestogens: nomegestrol, chlormadinone, and cyproterone acetate

Many other progestogens are widely used for multiple indications for which the risk of meningioma associated with their use has not been estimated individually

WHAT THIS STUDY ADDS

Prolonged use of medrogestone (5 mg, oral), medroxyprogesterone acetate (150 mg, injectable), and promegestone (0.125/0.5 mg, oral) was found to be associated with an excess risk of intracranial meningioma

In countries for which the use of medroxyprogesterone acetate for birth control is frequent (74 million users worldwide), the number of attributable meningiomas may be potentially high

The results for oral, intravaginal, and percutaneous progesterone, as well as dydrogesterone and levonorgestrel intrauterine systems, are reassuring, supporting the absence of excess meningioma risk

Introduction

Meningiomas account for 40% of primary tumours of the central nervous system.[1 2] The incidence of meningioma in the United States is 9.5 per 100 000 person years.[2] Meningiomas are mostly slow growing, histologically benign tumours but can nevertheless compress adjacent brain tissue and thus patients may require surgical decompression.[3] The incidence of meningiomas increases with age, rising sharply after the age of 65 years. Conversely, meningiomas are rare before the age of 35. Other recognised risk factors for meningioma are being female, intracranial exposure to ionising radiation, neurofibromatosis type 2[2], and, as shown only recently, prolonged use (≥one year) to high doses of three potent progestogens: cyproterone acetate,[4 5] chlormadinone acetate,[4] and nomegestrol acetate.[4]

The link between female sexual hormones, in particular progesterone, and intracranial meningioma is biologically plausible.[6] Progesterone receptors are present in more than 60% of meningiomas[7] and the volume of these tumours has been observed to increase during pregnancy and to decrease post partum.[8] However, previous pregnancy does not appear to be an unequivocal risk factor for meningioma.[9] Studies have also shown a link, albeit a weak one, between breast cancer and meningiomas.[10]

No significant association between exogenous female hormones and risk of meningioma has been shown to date for hormonal contraceptives (either combined or progestogen only pills).[11 12] Additionally, data for hormone replacement treatment for menopause are contradictory. Several studies have shown a slight excess risk of meningioma associated with the use of hormone replacement treatment for menopause,[11 13] whereas others have reported no deleterious effects of these molecules.[14] By contrast, the excess risk of meningioma observed with the use of high doses of cyproterone acetate among cis women, men, and trans women has been shown to be very high[5 15 16] and somewhat lower, but still substantial, for chlormadinone acetate and nomegestrol acetate.[4] Discontinuation of each of these three progestogens generally leads to a reduction in meningioma volume,[17 18] which avoids the need for surgery and its associated risk of complications for most patients.

Whether progestogens other than these three oral progestogens at high doses have a similar effect depending on their route of administration is still unknown. Our study aimed to assess the real-life risk of intracranial meningioma associated with the use of progestogens from an extensive list (progesterone, hydroxyprogesterone, dydrogesterone, medrogestone, medroxyprogesterone acetate, promegestone, dienogest, and levonorgestrel intrauterine systems) with different routes of administration (oral, percutaneous, intravaginal, intramuscular, and intrauterine). Although some of the progestogens studied are used in France (promegestone) or in only a few countries (medrogestone), others are widely used worldwide in various doses and for various indications (progesterone, levonorgestrel, hydroxyprogesterone, medroxyprogesterone) (supplementary table A). Certain progestogens may also be risky at some doses when used over a long period of time, but not at lower doses or when used for a short period of time. Our secondary objectives were to describe the characteristics of the women who were in the cases group (age, grade, and anatomical location of the meningiomas) and to approximate the number of surgically treated meningiomas attributable to the use of the concerned progestogens.

Methods

Study design and data source

This observational population based study used data derived from the French national health data system (*Système National des Données de Santé* (SNDS)). Given the analysis of multiple exposure situations (different exposure definitions and lookback periods) in our study, we opted for a case-control design rather than a cohort study, thus including long term users of the considered medications.[19]

The SNDS database contains information on all health spending reimbursements for over 99% of the population residing in France and is linked to the French hospital discharge database.[20] SNDS is currently one of the largest healthcare databases in the world and is widely used in pharmacoepidemiological studies.[4 5 21-24]

Definition of cases and selection of controls

The eligible cases in this study were women residing in France of all ages who underwent surgery for intracranial meningioma between 1 January 2009, and 31 December 2018. For each case, the start date of the corresponding admission to hospital marked the index date. Women with a pregnancy beginning in the two years before the index date were excluded from the study (pregnancies were defined as those that had resulted in childbirth or medical termination of the pregnancy after 22 weeks of amenorrhoea).

Surgery for intracranial meningioma was defined by the simultaneous combination of the following diagnoses and procedures recorded for the same hospital stay: a meningeal tumour (codes D32, D42, or C70 according to the 10th revision of the International Classification of Diseases (ICD-10)) coded as the main diagnosis of the admission to hospital and an intracranial surgery act (supplementary table B). These codes have already been used in our previous studies.[4 5]

Five women in the control group were randomly matched to each woman in the case group for the year of birth and area of residence ("*département*", a French geographical subdivision, n=101). Matching was based on the risk set sampling approach.[25] The traceability of the controls in the SNDS was ensured by selecting only women who had had at least one service reimbursed in the calendar year before the index date and the two to three calendar years preceding the index date. This criterion was also applied to the selection of cases.

For analyses relating to intrauterine systems, subsets of these cases and the matched controls were considered to ensure sufficiently long lookback periods. For the hormonal intrauterine systems containing 52 mg levonorgestrel and copper intrauterine devices, the cases and controls from the years 2011 to 2018 were retained. For the hormonal intrauterine systems containing 13.5 mg levonorgestrel, the inclusion period was restricted to 2017 to 2018 (start of commercialisation in France in 2013).

Definition of exposure

Exposure to the progestogen of interest was defined according to WHO's anatomical, therapeutic, and chemical (ATC) classification. The list included progesterone (oral and intravaginal: 100, 200 mg (ATC code G03DA04); percutaneous: 25 mg per bar (G03DA04)), dydrogesterone (10 mg, or in association with oestrogen: 5 or 10 mg (G03DB01, G03FA14, G03FB08)), hydroxyprogesterone (500 mg (G03DA03)), medrogestone (5 mg (G03DB03)), promegestone (0.125, 0.25, or 0.5 mg (G03DB07)), medroxyprogesterone acetate (injectable contraceptive, 150 mg/3 mL (G03AC06, L02AB02 partially)), dienogest (in association with oestrogen, 2 mg (G03FA15)), levonorgestrel (52 mg intrauterine systems (G02BA03); 13.5 mg intrauterine systems

(G02BA03)) (supplementary tables C and D). As drospirenone, which is a spironolactone derivative, is not reimbursed in France, we were unable to access data concerning its use. We therefore chose to study the use of spironolactone (25, 50, and 75 mg), even though its indications may be very different. The code used to identify spironolactone was C03DA01. The indications for these various progestogens in France are available in table 1.

For oral, intravaginal, percutaneous, or intramuscular progestogens, exposure was defined as at least one dispensation of the progestogen of interest in the 365 days before the index date. For intrauterine progestogens, a dispensation was sought within three years before the index date for levonorgestrel 13.5 mg (as the duration of efficacy of this intrauterine system is three years before any change or withdrawal of the device) and within five years before the index date for levonorgestrel 52 mg intrauterine systems (duration of contraceptive efficacy of five to six years according to current recommendations during the study period).

Exposure was described by three modes for each progestogen as follows: 1) exposure to the progestogen concerned, 2) exposure during the three years preceding the index date to at least one of the three high dose progestogens known to increase the risk of meningioma (ie, chlormadinone acetate, nomegestrol acetate, and cyproterone acetate), and 3) absence of exposure to the progestogen considered or to the three high dose progestogens (the reference for the analyses).

Definition of covariates

The description of sociodemographic and medical characteristics included age, area of residence, existence of neurofibromatosis type 2 (ICD-10 code Q85.1), and, for cases only, the year of surgery, anatomical site (anterior, middle, or posterior base of the skull, convexity, falx and tentorium, others; supplementary table C), and grade of severity of the meningioma (according to WHO's classification[1]: benign, malignant, or atypical, supplementary table E).

Adjuvant radiotherapy was also sought from three months before the index date to six months after (supplementary table F). Additionally, all causes mortality at two and five years after the index date was assessed in cases, as well as the use of antiepileptic drugs in the third year after the index date (supplementary table G).

Statistical analysis

Logistic regression models conditioned on matched pairs were used to estimate odds ratios and their 95% confidence intervals (CIs) for the association between exposure to the progestogens of interest and meningioma (odds ratio of exposure relative to non-exposure). Additionally, the effect of history of neurofibromatosis type 2 on the risk of meningioma was estimated, as well as the effect of chlormadinone acetate, nomegestrol acetate, and cyproterone acetate exposure, all serving as positive controls for exposure to validate our results. In parallel, exposure to a copper intrauterine device was used as a negative control for exposure (codes in supplementary table H).

The risk of meningioma associated with progestogen use was also estimated for each oral, percutaneous, intravaginal, and intramuscular progestogen according to the duration of use: short term (at least one dispensation in the year before the index date but no dispensation in the second year before the index date) and prolonged use (at least one dispensation in the year before the index date and at least one dispensation in the second year before the index date).

The population attributable fraction was approximated from the odds ratio obtained for each progestogen. The formula used was as follows: population attributable fraction=p_c (1-1/odds ratio), where p_c is the prevalence of the use of the progestogen concerned (isolated exposure) among the cases.[26] Lastly, sensitivity analyses were performed. Analyses were stratified for age (<35 years, 35-44 years, 45-54 years, 55-64 years, and ≥65 years) and for the location and grade of severity of the tumours whenever a positive association was found between exposure to the considered progestogen and meningioma surgery.

Table 1 | Main indications (marked as x), in France, for the progestogens under study

Indications	Progesterone, 100/200 mg (oral and intravaginal) 25 mg (percutaneous)	Hydroxyprogesterone, 500 mg/2 mL	Medrogestone, 5 mg	Medroxyprogesterone acetate, 150 mg/3 mL	Dydrogesterone, 10 mg with oe: 1 mg oe/5 mg, 1 mg/10 mg, 2 mg/10 mg	Promegestone, 0.125 mg, 0.250 mg, 0.500 mg	Dienogest, 2 mg	Spironolactone, 25, 50, 75 mg	Levonorgestrel IUS, 52 mg, 13.5 mg
Contraception				x					x
Endometriosis			x		x				x (52 mg)
Menstrual cycle disorders	x	x	x		x	x			x (52 mg)
Amenorrhea					x				
Fibroma	x					x			
Premenopause	x					x			
Menopause	x		x		x	x	x		
Hypofertility (ART)	x	x			x				
Prevention of recurrent miscarriage*	x	x							
Hyperaldosteronism								x	

ART=assisted reproductive technology; IUS=intrauterine system; oe=oestrogen. *≤12th week of pregnancy.

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

Ethics

The present study was authorised by decree 2016–1871 on 26 December 2016.[27] As an authorised permanent user of the 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 with register reference T-2023-01-437.

Patient and public involvement

The list of progestogens of interest (supplementary table B) was drawn up in consultation with a temporary scientific advisory board comprised of representatives of the French National Agency for Medicines and Health Products Safety, patient organisations, and healthcare professionals (neurosurgery, endocrinology, gynaecology, and general medicine).

Results

Description of cases and controls

In total, 108 366 women were included in the study during the inclusion period of 2009 to 2018, consisting of 18 061 women in the case group were matched with 90 305 in the control group (fig 1).

Among them, 15 162 cases and 75 810 controls were retained for the analyses of intrauterine systems and copper intrauterine devices using 52 mg of levonorgestrel (restricted inclusion period: 2011 to 2018) (supplementary figure A) and 4048 cases and their 20 240 controls for the analysis of intrauterine systems of 13.5 mg of levonorgestrel (2017-18) (supplementary figure B). Descriptions of cases and controls for the analyses of intrauterine devices are detailed in supplementary I and J.

The mean age of all women was 57.6 years (standard deviation 12.8 years). The most highly represented age groups were 45-54 (26.7%), 55-64 (26.4%), and 65-74 (21.5%) years (table 2).

The number of cases steadily increased from 1329 in 2009 to 2069 in 2018. Meningiomas requiring surgery were most frequently located at the base of the skull (a total of 10 046/18 061 cases (55.6%); anterior skull base: 3979/18 061 (22.0%), middle: 3911/18 061 (21.7%), posterior: 2156/18 061 (11.9%)), followed by the convexity (6468/18 061 (35.8%)). Concerning tumour grade, most meningioma cases were benign (16 662/18 061, 92.3%) and 1047/18 061 (5.8%) were classified as atypical and 352/18 061 (1.9%) as malignant. Among cases, 28.8% (5202/18 061) of women used antiepileptic drugs three years after the index date of surgery. Mortality was also higher among cases than controls: 502 cases/18 061 (2.8%) died within two years (*v* 1.2% of controls) and 951/18 061 (5.3%) within five years (*v* 3.4% of controls). Mortality was higher for the cases with malignant tumours, 12.5% of whom died within two years and 20.7% within five.

The comparison of the cases and controls in the subsets used to analyse hormonal intrauterine systems is included the supplementary data (supplementary tables I and J).

Progestogens (others than intrauterine)

Exposure among cases

Among the 18 061 women admitted to hospital for meningioma surgery between 2009 and 2018, 329 (1.8%) had used oral or intravaginal progesterone, 90 (0.5%) percutaneous progesterone, zero hydroxyprogesterone, 156 (0.9%) dydrogesterone, 42 (0.2%) medrogestone, nine (<0.1%) medroxyprogesterone acetate, 83 (0.5%) promegestone, three (<0.1%) dienogest, and 264 (1.5%) spironolactone (table 3, supplementary figure C). These numbers excluded 2999 women who had been exposed to cyproterone acetate, nomegestrol acetate, or chlormadinone acetate, or a combination, within the previous three years (among these 2999 women, 68 had also been exposed to oral progesterone, 47 to

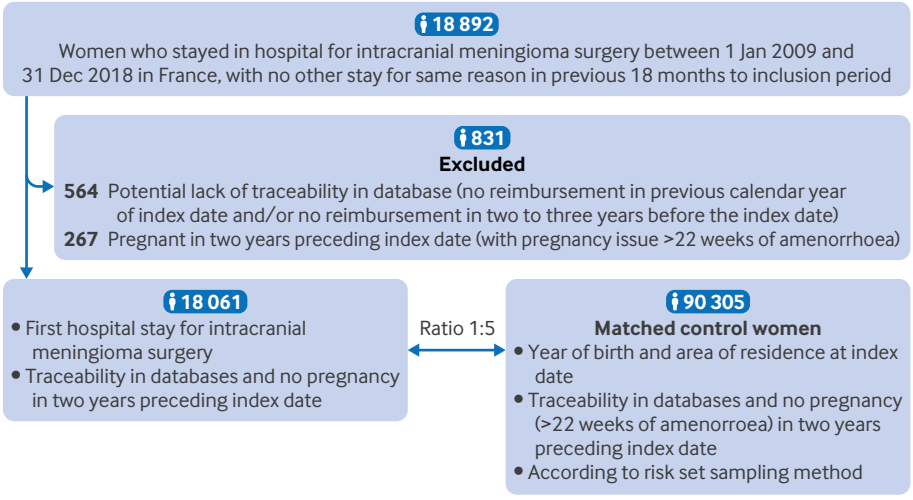

Fig 1 | Flowchart for the analyses of oral, percutaneous, intravaginal, and intramuscular progestogens. Index date is defined as the date of hospital admission

Table 2 | Description of the cases and controls (overall inclusion period 2009-18). Data are number of individuals (percentage), unless otherwise specified

Characteristics	Case group (n=18 061)	Control group (n=90 305)
Age (years):		
Mean age (SD)	57.6 (12.8)	57.6 (12.8)
≤19	50 (0.3)	250 (0.3)
20-34	537 (3.0)	2685 (3.0)
35-44	2181 (12.1)	10 905 (12.1)
45-54	4830 (26.7)	24 150 (26.7)
55-64	4760 (26.4)	23 800 (26.4)
65-74	3883 (21.5)	19 415 (21.5)
75-84	1646 (9.1)	8230 (9.1)
≥85	174 (1.0)	870 (1.0)
Area of residence*:		
Paris Ile-de-France	3186 (17.6)	15 930 (17.6)
Northeast	3477 (19.3)	17 385 (19.3)
Northwest	3595 (19.9)	17 975 (19.9)
Southeast	4044 (22.4)	20 220 (22.4)
Southwest	3423 (19.0)	17 115 (19.0)
Overseas	336 (1.9)	1680 (1.9)
Year of surgery:		
2009-11	4610 (25.5)	N/A
2012-15	7395 (40.9)	N/A
2016-18	6056 (33.5)	N/A
Anatomical location of the meningioma†:		
Anterior skull base	3979 (22.0)	N/A
Middle skull base	3911 (21.7)	N/A
Posterior skull base	2156 (11.9)	N/A
Convexity	6468 (35.8)	N/A
Falx and tentorium	1963 (10.9)	N/A
Other locations	261 (1.4)	N/A
Severity of the meningioma:		
Benign	16 662 (92.3)	N/A
Atypical	1047 (5.8)	N/A
Malignant	352 (1.9)	N/A
Adjuvant radiotherapy:		
All	798 (4.4)	N/A
Benign	655/16 662 (3.9)	N/A
Atypical	58/1047 (5.5)	N/A
Malignant	85/352 (24.1)	N/A
Use of antiepileptics, three years after the index date:		
All	5202 (28.8)	5359 (5.9)
Benign	4744/16 662 (28.5)	N/A
Atypical	323/1047 (30.9)	N/A
Malignant	135/352 (38.4)	N/A
All causes mortality, two years after:		
All	502 (2.8)	1123 (1.2)
Benign	419/16 662 (2.5)	N/A
Atypical	39/1047 (3.7)	N/A
Malignant	44/352 (12.5)	N/A
All causes mortality, five years after‡:		
All	951 (5.3)	2730 (3.4)
Benign	806/16 662 (4.8)	N/A
Atypical	72/1047 (6.9)	N/A
Malignant	73/352 (20.7)	N/A

N/A=not applicable; SD=standard deviation.
*Northeast: Grand Est, Bourgogne Franche-Comté, Hauts-de-France. Paris area (Ile-de-France): Paris city and France area. Northwest: Bretagne, Centre Val de Loire, Normandie, Pays de la Loire. Southeast: Auvergne-Rhône-Alpes, Provence-Alpes-Côte d'Azur, Corse. Southwest: Nouvelle-Aquitaine, Occitanie. French overseas area: Guadeloupe, Martinique, French Guiana, and Reunion Island.
†Tumours may occur at multiple sites in the same individual.
‡Restricted inclusion period: 2009-17.

percutaneous progesterone, 0 to hydroxyprogesterone, 43 to dydrogesterone, 10 to medrogestone, 0 to medroxyprogesterone acetate, 17 to promegestone, 1 to dienogest, and 56 to spironolactone). The median cumulative doses of progestogens for cases and exposed controls are shown in supplementary table K.

Effect on meningioma risk

No significant association with an increased risk of intracranial meningioma surgery was noted with exposure to oral or intravaginal progesterone (odds ratio of 0.88 (95% CI 0.78 to 0.99)) or percutaneous progesterone (1.11 (0.89 to 1.40)), dydrogesterone

Table 3 | Associations between use of oral, percutaneous, intravaginal, and intramuscular progestogen and risk of surgically treated intracranial meningioma. Data are number of individuals (percentage), unless otherwise specified

Progesterone	Case group (n=18 061)	Control group (n=90 305)	Odds ratio* (95% confidence interval)
Progesterone (oral and intravaginal):			
Current use	329 (1.8)	2149 (2.4)	0.88 (0.78 to 0.99)
Short term use	69 (0.4)	480 (0.5)	0.90 (0.70 to 1.16)
Prolonged use	260 (1.4)	1669 (1.8)	0.88 (0.77 to 1.00)
Progesterone (percutaneous):			
Current use	90 (0.5)	503 (0.6)	1.11 (0.89 to 1.40)
Short term use	72 (0.4)	415 (0.5)	1.07 (0.83 to 1.38)
Prolonged use	18 (0.1)	88 (0.1)	1.30 (0.78 to 2.17)
Hydroxyprogesterone:			
Current use	0 (0.00)	3 (0.00)	N/A
Short term use	0 (0.00)	3 (0.00)	N/A
Prolonged use	0 (0.00)	0 (0.00)	N/A
Dydrogesterone:			
Current use	156 (0.9)	990 (1.1)	0.96 (0.81 to 1.14)
Short term use	68 (0.4)	415 (0.5)	1.05 (0.81 to 1.37)
Prolonged use	88 (0.5)	575 (0.6)	0.89 (0.71 to.12)
Medrogestone:			
Current use	42 (0.2)	79 (0.1)	3.49 (2.38 to 5.10)
Short term use	2 (0.0)	16 (0.02)	N/A
Prolonged use	40 (0.2)	63 (0.1)	4.08 (2.72 to 6.10)
Medroxyprogesterone acetate:			
Current use	9 (0.05)	11 (0.01)	5.55 (2.27 to 13.56)
Short term use	1 (0.01)	1 (0.00)	N/A
Prolonged use	8 (0.04)	10 (0.01)	5.62 (2.19 to 14.42)
Promegestone:			
Current use	83 (0.5)	225 (0.2)	2.39 (1.85 to 3.09)
Short term use	17 (0.1)	73 (0.1)	1.62 (0.95 to 2.76)
Prolonged use	66 (0.4)	152 (0.2)	2.74 (2.04 to 3.67)
Dienogest:			
Current use	3 (0.02)	11 (0.01)	N/A
Short term use	2 (0.01)	3 (0.00)	N/A
Prolonged use	1 (0.01)	8 (0.01)	N/A
Spironolactone:			
Current use	264 (1.5)	1473 (1.6)	0.95 (0.84 to 1.09)
Short term use	67 (0.4)	381 (0.42)	0.94 (0.73 to 1.22)
Prolonged use	197 (1.1)	1092 (1.2)	0.96 (0.82 to 1.12)
Chlormadinone acetate:			
Current use	628 (3.5)	946 (1.0)	3.87 (3.48 to 4.30)
Short term use	101 (0.6)	392 (0.4)	1.50 (1.20 to 1.87)
Prolonged use	527 (2.9)	554 (0.6)	5.55 (4.90 to 6.28)
Nomegestrol acetate:			
Current use	925 (5.1)	1121 (1.2)	4.93 (4.50 to 5.41)
Short term use	106 (0.6)	471 (0.5)	1.34 (1.08 to 1.66)
Prolonged use	819 (4.5)	650 (0.7)	7.54 (6.76 to 8.41)
Cyproterone acetate:			
Current use	891 (4.9)	256 (0.3)	19.21 (16.61 to 22.22)
Short term use	25 (0.1)	58 (0.1)	2.28 (1.42 to 3.65)
Prolonged use	866 (4.8)	198 (0.2)	24.54 (20.85 to 28.88)
Levonorgestrel 52 mg IUS†	566/15 162 (3.7)	3888/75 810 (5.1)	0.94 (0.86 to 1.04)
Levonorgestrel 13.5 mg IUS †	10/4048 (0.2)	48/20 240 (0.2)	1.39 (0.70 to 2.77)
Copper intrauterine device†	452/15 162 (3.0)	2642/75 810 (3.5)	1.13 (1.01 to 1.25)

IUS=intrauterine system; N/A=note available. Current use=at least one dispensation in the year before the index date and absence of exposure to chlormadinone, nomegestrol, and cyproterone acetate in the three years before the index date (see supplementary table P and supplementary table Q for the results of all the used modes of exposure). In the analyses of chlormadinone acetate and nomegestrol, absence of exposure was tested only for cyproterone acetate; in the analyses of cyproterone acetate and neurofibromatosis type 2, no absence of exposure was tested. Short term use=current use, without dispensation in the second year before the index date.
Prolonged use=current use, with at least one dispensation in the second year before the index date
*Odds ratios involving fewer than six people who were exposed in the cases group are not shown.
†Restricted inclusion periods (2011-18 for copper and 52 mg levonorgestrel intrauterine systems, 2017-18 for 13.5 mg levonorgestrel intrauterine systems).

(0.96 (0.81 to 1.14)), or spironolactone (0.95 (0.84 to 1.09)) (table 3, supplementary figure C). Exposure to dienogest was rare, with only 14 women who were exposed (3/18 061 among cases and 11/90 305 among controls) and, consequently, the estimated odds ratio had a very large confidence interval (1.48 (0.41 to 5.35)). Additionally, we could not assess the odds ratio concerning hydroxyprogesterone because no exposed cases were found (fig 2).

By contrast, an excess risk of meningioma was associated with the use of medrogestone (3.49 (2.38 to 5.10)), medroxyprogesterone acetate (5.55 (2.27 to

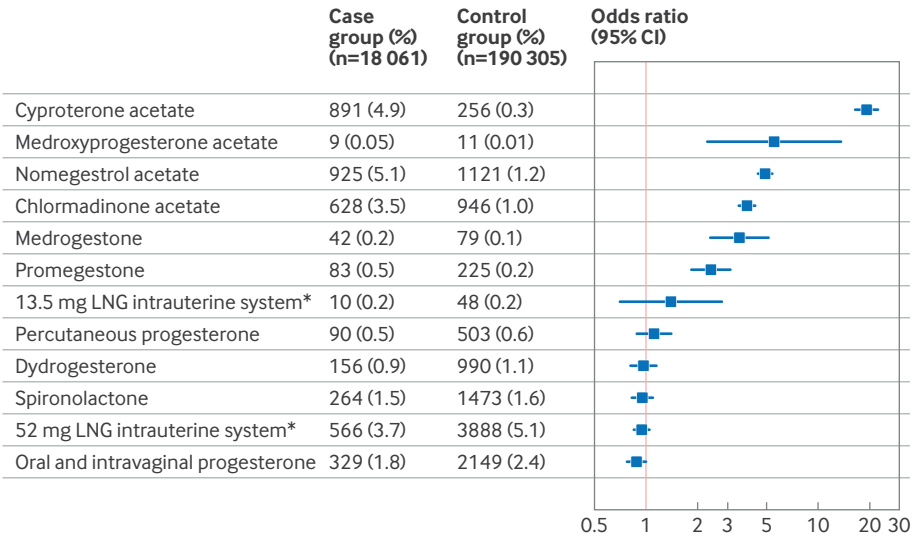

Fig 2 | Associations between various progestogens and risk of intracranial meningioma requiring surgery (case control design, 2009-18). Odds ratio in logarithmic scale. CI=confidential interval; LNG=levonorgestrel; SNDS= French National Health data System (*Système National des Données de Santé*). *LNG had different denominators due to restricted inclusion periods (10/4048 cases, 48/20 240 controls; 566/15 162 cases, 3888/75 810 controls)

13.56)), and promegestone (2.39 (1.85 to 3.09)). As expected, an excess risk of meningioma for women with positive control exposure neurofibromatosis type 2 (18.93 (10.50 to 34.11)), as well as those exposed to chlormadinone acetate (3.87 (3.48 to 4.30)), nomegestrol acetate (4.93 (4.50 to 5.41)), and cyproterone acetate (19.21 (16.61 to 22.22)) was also noted (fig 2).

The duration of exposure to medrogestone, medroxyprogesterone acetate, promegestone, chlormadinone, nomegestrol, and cyproterone acetate for exposed cases and controls is presented in supplementary table L. The results show that three quarters of the women in the cases group who had been exposed for more than a year had been exposed for more than three years. As for medrogestone, medroxyprogesterone acetate, and promegestone, the excess risk associated with prolonged use was higher than that measured for short term and prolonged exposure combined. Specifically, prolonged use of promegestone had an odds ratio of 2.74 (2.04 to 3.67) (versus 2.39 for all durations of exposure) and short term use an odds ratio of 1.62 (0.95 to 2.76). For prolonged use of medrogestone, the odds ratio was 4.08 (2.72 to 6.10) (versus 3.49 for all durations of exposure combined), and for medroxyprogesterone acetate, the odds ratio was 5.62 (2.19 to 14.42). No significant association was reported for either short or prolonged periods of use for any of the other progestogens studied.

Meningiomas before age 45 years were rare in cases of exposure to medrogestone (n=3/42), medroxyprogesterone acetate (n=3/9), or promegestone (n=10/83), and only one (medroxyprogesterone) was observed before the age of 35.

Concerning medrogestone, the most frequent locations of meningiomas in exposed cases were the base of the skull (n=21/42; 13 in the middle) and the convexity (n=19/42) (supplementary tables M, N and O). The excess risk of meningioma for the middle of the base of the skull was particularly high (odds ratio 8.30 (95% CI 3.70 to 18.63)). Additionally, the estimated excess risk among women aged 45-54 years was slightly higher than that in the main analysis (4.53 (2.73 to 7.53) *v* 3.49 (2.38 to 5.10)).

In women in the cases group who were exposed to promegestone, meningiomas were preferentially located at the front of the base of the skull (n=25/83), the convexity (n=25/83), and the middle of the base of the skull (n=22/83). The excess risk of meningioma linked to promegestone use was slightly higher in the group who were older than 65 years (odds ratio 3.21 (95% CI 1.39 to 7.43)) and for meningiomas located at the front or middle of the base of the skull (3.15 (1.95 to 5.10) and 3.03 (1.82 to 5.02), respectively).

We found no malignant grade tumours among cases exposed to medrogestone, medroxyprogesterone acetate, or promegestone (for information, the same analyses were carried out for chlormadinone acetate, nomegestrol acetate, and cyproterone acetate in supplementary table N).

Levonorgestrel intrauterine systems

Exposure among cases

In total, 566/15 162 users of hormonal levonorgestrel 52 mg were among the cases with meningioma surgery between 2011 and 2018 (3.7%) (table 3). For the intrauterine systems with 13.5 mg of levonorgestrel, 10 of 4048 users were reported among the cases from 2017 and 2018 (0.2% of

all cases). Again, women who had been exposed to cyproterone acetate, nomegestrol acetate, or cyproterone acetate, or a combination, within the previous three years were not counted (among them, 95 were exposed to the intrauterine systems of 52 mg levonorgestrel and three to intrauterine systems of 13.5 mg levonorgestrel).

Effect on meningioma risk

No excess risk of meningioma was reported with the use of hormonal intrauterine systems containing 52 mg (odds ratio 0.94 (95% CI 0.86 to 1.04)) or 13.5 mg (1.39 (0.70 to 2.77)) of levonorgestrel (fig 2).

Exposure to copper intrauterine devices, used as a negative control for exposure in this study, had an odds ratio of 1.13 (1.01 to 1.25).

Attributable cases

The population attributable fractions, which are relative to the observed overall number of surgically treated intracranial meningiomas, were 0.17% for exposure to medrogestone, 0.04% for medroxyprogesterone acetate, and 0.27% for promegestone. For comparison, they were calculated as 2.58% for chlormadinone acetate, 4.08% for nomegestrol acetate, and 4.68% for cyproterone acetate. The numbers for the attributable cases are presented in supplementary figure D.

Discussion

Principal findings

Although the risk of meningioma was already known for three progestogens, this study is the first to assess the risk associated with progestogens that are much more widely used for multiple indications, such as contraception.

This population based study shows an association between the prolonged use of medrogestone (5 mg), medroxyprogesterone acetate injection (150 mg), and promegestone (0.125, 0.25, 0.5 mg) and a risk of intracranial meningioma requiring surgery. No such risk was reported for less than one year of use of these progestogens. However, we found no excess risk of meningioma with the use of progesterone (25, 100, 200 mg; oral, intravaginal, percutaneous), dydrogesterone (10 mg, combined with oestrogen: 5, 10 mg), or spironolactone (25, 50, 75 mg), neither with short term nor prolonged use, and with the use of levonorgestrel intrauterine systems (13.5, 52 mg). A small number of women were exposed to dienogest (2 mg, in association with oestrogen) and hydroxyprogesterone (500 mg), therefore we cannot draw any conclusions concerning the association between use of these progestogens and the risk of meningioma.

No malignant meningiomas were noted for women exposed to medrogestone, medroxyprogesterone acetate, or promegestone. Moreover, the number of cases of surgically treated intracranial meningioma attributable to use of these progestogens was much lower than the number of cases attributable to the intake of chlormadinone acetate, nomegestrol acetate, and, in particular, cyproterone acetate. This finding is explained by both a lower excess risk of meningioma (for medrogestone and promegestone) and lower rates of use in France (particularly low for medroxyprogesterone acetate, with less than 5000 women exposed each quarter during the inclusion period of the study of 2009-18).

Specific considerations on meningiomas

Meningioma is a predominantly benign tumour. Between 2011 and 2015, 80.5% of the meningiomas diagnosed in the United States were grade 1, 17.7% grade 2, and 1.7% grade 3.[1] Even in the absence of malignancy, meningiomas can cause potentially disabling symptoms. In such cases, first line treatment is surgery, even for the oldest patients, entailing a risk of complications and morbidity.[28 29]

Age is an important factor both for the indication of progestogens and for considering intracranial surgery. In our study, the mean age of women in the cases group was 57.6 years. Medrogestone, medroxyprogesterone acetate, and promegestone can be used both by women of childbearing age and by premenopausal and postmenopausal women. In our study, only one user of these progestogens who had undergone meningioma surgery was younger than 35 years (medroxyprogesterone).

Postoperative complications are not uncommon for meningioma surgery. Depending on the exact location of meningiomas, the surgical risk varies but surgery may have severe neurological consequences due to the immediate proximity of highly functional cortical area and critical neurovascular structures. Cognitive function tends to improve after surgery for meningioma,[30 31] but several studies have suggested a potential for postoperative anxiety and depression and a high intake of antidepressants and sedatives in the medium term,[32 33] although other studies have reported conflicting findings for depression.[34] Seizures are also a possible short term complication of surgery,[35] leading to a need to take antiepileptic drugs in the years following the operation. In our study, almost three in 10 women (28.8% of cases) were using antiepileptic drugs three years after the operation, which was consistent with previously published findings.[36] Additionally, results showed that progestin related meningiomas tend to occur more frequently at the skull base and that surgery for lesions in this location is much more challenging. The recent evidence supporting stabilisation or regression of meningiomas after stopping chlormadinone acetate, nomegestrol acetate, and cyproterone acetate has reduced the surgical indications for these patients, thus avoiding potential complications.[17 18] A recent report showed that although the tissue portion of the meningioma most often regresses in size, the hyperostosis associated with meningiomas further increases, which may require surgical intervention, not for oncological purposes but only for decompression of the structures nerves and relief of symptoms.[37]

Use of the studied progestogens in France and worldwide

Medrogestone is indicated in France for the treatment of menstrual cycle disorders and luteal insufficiency (eg, dysmenorrhea, functional menorrhagia or fibroid-related menorrhagia, premenstrual syndrome, and irregular cycles), endometriosis, mastodynia, and hormone replacement therapy for menopause. In the United States, medrogestone has never been approved by the US Food and Drug Administration. Outside of France, this molecule is also used in Germany, in combination with oestrogen (0.3 mg/5 mg, 0.6 mg/2 mg, 0.6 mg/5 mg).[38] The use of medrogestone increased significantly in France in 2019, notably as a result of postponements in the prescription of chlormadinone acetate, nomegestrol acetate, and cyproterone acetate, following the French and European recommendations to reduce the risk of meningioma attributable to these progestogens in 2018 and 2019.[39 40] As therapeutic alternatives have not shown an increased risk of meningioma, switching from products that notoriously increase this risk to medrogestone should be reconsidered.

Worldwide, in 2019, 3.9% of women of childbearing age were using injectable contraception (medroxyprogesterone), that is, 74 million users, but figures vary widely between world regions (from 1.8% in high income countries to 8.7% in low income countries).[41] This method of contraception is the most widely used in Indonesia (13 million women),[42] Ethiopia (4.6 million women), and South Africa (3.6 million women).[41] In the USA, medroxyprogesterone acetate is used in more than 2 million prescriptions in 2020 and more than one of five sexually active American women report having used injected medroxyprogesterone acetate (150 mg/3 mL) in their lifetime.[43 44] Injectable contraceptives are much less widely used in Europe (3.1% of women of childbearing age in the UK and 0.2% in France[41]). Our results support preliminary findings from studies of meningioma cases exposed to chronic use of medroxyprogesterone acetate or cases of high dose administration.[45-49] In particular, our results show similarities with those of a retrospective review of 25 patients diagnosed with meningioma who had a history of chronic medroxyprogesterone acetate use and were treated at the University of Pittsburgh Medical Center between 2014 and 2021 concerning the characteristics of cases exposed to medroxyprogesterone acetate (women (mean age of 46 years) with meningiomas commonly located at the base of the skull).[48] In addition, medroxyprogesterone acetate used as an injected contraceptive is known to be prescribed to specific populations, especially people with mental illnesses.[50] The protection of these vulnerable populations from additional drug risks is particularly important. Depot medroxyprogesterone acetate (150 mg) is registered for use as a form of birth control in more than 100 countries worldwide.[41] In countries that have high numbers of people using medroxyprogesterone acetate, the number of meningiomas attributable to this progestogen may be potentially high. Furthermore, medroxyprogesterone (non-acetate) is also used orally, at lower doses, in some countries other than France (notably in the US), for which no data exists on a risk of meningioma so far.

Promegestone was only available in France (not marketed in any other country) and was withdrawn from the market in 2020. This drug was indicated for the relief of premenopausal symptoms and hormone replacement therapy for menopause. With the discontinuation of its marketing, some users could have switched to medrogestone in 2020, a molecule also implicated in the risk of meningioma in our results. Clinicians therefore must remain vigilant because meningioma risk could last beyond market withdrawal and a potential switch to another progestogen.

The FDA defines a therapeutic class as "all products (...) assumed to be closely related in chemical structure, pharmacology, therapeutic activity, and adverse reactions".[51 52] Various subtypes of progestogens exist depending on the molecule from which the progestogen is derived (ie, progesterone, testosterone, and spironolactone) (supplementary table B).[53] Their chemical structures and pharmacological properties differ according to this classification, which explains why no class effect is reported for certain benefits and risks associated with their use (eg, breast cancer and cardiovascular risk).[54-57] Progestogens have distinct affinities for different target organ steroid receptors, which may vary even within a subclass, determining their activity.

Our study suggests that 17-OH-hydroprogesterone and 19-norprogesterone derivatives, both progesterone derivatives, have a class effect on meningioma risk. Four of five progestogens belonging to the 17-OH-hydroprogesterone group have shown an increase in the risk of meningioma (supplementary table R). However, the fact that we found different sizes of risk appears to be more a question of duration and cumulative dose than that of belonging to a progestogen class. We could not draw any conclusions about hydroxyprogesterone (due to a lack of power), the fifth progestogen in the subclass, but its main indication (assisted reproductive technology) corresponded to fewer women exposed and very short exposure (approximately 15 days), which could explain why this drug differs from the others. Finally, to date, at the doses considered in the study, no excess risk of meningioma associated with testosterone derivatives has been shown. However, the risk of meningioma associated with the use of these derivatives at other doses and in other regimens needs to be investigated.

Strengths and limitations

To our knowledge, this study of meningioma risk is the first to expand the list of progestogens of interest beyond chlormadinone acetate, nomegestrol acetate, and cyproterone acetate, detailing the risk associated with each progestogen, with different modes of administration. This study was conducted on a national scale for women of all ages for both the cases and their controls. The SNDS database allowed the

use of exhaustive real-world data from over a period of 12 years (2006-18; postoperative information was searched even up to 2022), thus preventing recall bias.

The exclusion of women with a pregnancy beginning in the two years preceding the index date ensured that estimates of the risks associated with progestogen use were reliable. Pregnancy is a unique state, affecting exposure to progestogens (of endogenous or exogenous origin), the likelihood of a meningioma appearing or increasing in volume,[9 58 59] and the likelihood of admission to hospital for surgery (possibly with a lower surgery rate, depending on the symptoms, maternal and foetal health, and tumour characteristics).[59]

Another potentially important confounding factor, use of chlormadinone acetate, nomegestrol acetate, or cyproterone acetate, was considered in the analyses by modelling exposure to each progestogen of interest with a separate mode of prior or simultaneous exposure to these drugs. Furthermore, the results obtained for the negative and positive control exposure, including exposure to chlormadinone acetate, nomegestrol acetate, and cyproterone acetate, support the appropriateness of the method chosen for this study.

However, this study also had several limitations. As a result of the scarcity of historical data in the SNDS (which began in 2006, and did not have information for some reimbursement schemes during the first few years), we have only three years of lookback period for the oldest meningioma cases (2009-06), and 12 years for the most recent. The SNDS does not provide information on non-reimbursed drugs, which obliged us to study dienogest in association with oestrogen rather than dienogest alone. Further studies will therefore be necessary. Similarly, we were unable to study other progestogens, such as norgestimate, gestodene, and norethisterone, contained in non-reimbursed products (supplementary table B). Conversely, desogestrel is available and reimbursed in France. Its dosage is much lower and, thus, we chose not to study the drug. Further study to assess a dose-response association in the event of prolonged use would be needed. The progestogen implants (etonogestrel) are also rarely used in France, and concern young women, for whom the risk of meningioma is probably very low.[60 61] We have also not studied the risk associated with the use of hormonal intrauterine systems containing 19.5 mg levonorgestrel because its marketing in France was too recent (2018). However, any excess risk associated with the use of the levonorgestrel 19.5 mg intrauterine systems is unlikely because this dose of levonorgestrel is lower than that of the levonorgestrel 52 mg intrauterine systems, for which we observed no risk.

Moreover, the SNDS does not provide information on all the clinical details and medical indications for which progestogens are prescribed. These missing data mean assessing the risk-benefit ratio of prescriptions is not possible, which could be favourable in the absence of an effective alternative, for example, in the case of relief of endometriosis symptoms. We only have some indirect idea of the indication, depending on the age of the user, and the molecule used (progesterone is not indicated for endometriosis, for example, and dydrogesterone is indicated for endometriosis but is rarely used in this indication). Nevertheless, a risk-benefit assessment was not the aim of our study and will require further studies using other sources of data for product efficacy. Furthermore, no evidence suggests that an increase in meningioma risk depends on the medical indication for the progestogen prescription. In the study of Weill and colleagues in 2021, the excess risk of meningioma associated with the use of cyproterone acetate was equivalent for men and women, who, nevertheless, use cyproterone acetate for radically different indications.[5]

In this study, only admission to hospital for meningioma surgery was used as the outcome of interest. However, meningiomas can also be treated with radiotherapy (in rare cases) or simply monitored. Therefore, this study is highly likely to have underestimated the prevalence of meningiomas attributable to the use of progestogens by limiting itself solely to symptomatic tumours that require surgery. However, using admission to hospital for surgery as the outcome ensured diagnostic specificity and thus limited classification bias. The SNDS does not specify the histological characteristics of the meningiomas or the isolated or multiple nature of the tumour, both of which are important criteria in determining severity and the choice of appropriate treatment. Nevertheless, for the cases selected for this study, WHO's severity grade of the meningioma is coded via the main diagnosis, which is entered according to the ICD-10 code at the end of the hospital stay after a reading of the pathology report. As such, we had indirect information about the histology of the tumours.

Our study has several confounding factors. The two main risk factors identified for meningioma, in addition to age (which was considered in this study) and being female (only women were included in this study), are genetic predisposition, attributed, in particular, to hereditary mutations of the neurofibromatosis type 2 gene, and medical or environmental exposure to high doses of ionising radiation. Radiotherapy for brain cancer (especially during childhood) is probably the most important of the possible medical reasons for intracranial radiation exposure, but only a small proportion of individuals in the general population had cerebral radiotherapy or a malignant brain tumour during childhood.

The progestogens investigated in our study that did not result in an increase to risk of meningioma should be considered under the specific conditions of use in France. These results may not be generalised to the use of these progestogens for other indications, increased doses, or increased duration of use. Similarly, the use of one or more of these progestogens might increase the meningioma risk, when the patient had previously received another type of progestogen.

Prescribers need to be aware of previous progestogen use of any kind and any changes in type of progestogen prescribed that may have occurred and should consider the cumulative dose of progestogens for each patient.

The list of progestogens we studied is wide ranging, covering a variety of indications (summarised in table 1) for women of all ages (childbearing, premenopausal, and menopausal). As in hormone replacement therapy for menopause, progestogens can be easily substituted for each other, and thus progesterone appears to be the safest alternative. For endometriosis, however, therapeutic alternatives are much more limited, and each indication must be discussed on the basis of the personal benefit to risk ratio. If a high risk progestogen is to be continued, clinical and radiological monitoring and compliance with recommendations are essential.

Finally, we did not estimate the effect of concomitant oestrogen use on the risk of meningioma. In a previous report, having a concomitant oestrogen prescription was weakly but significantly associated with meningioma risk, with an age adjusted hazard ratio of 1.6 (95% CI 1.1 to 2.4) for use of cyproterone acetate. In our previous studies, the simultaneous prescription of oestrogen with chlormadinone acetate (hazard ratio 0.8 (0.5 to 1.3)) and nomegestrol acetate (1.0 (0.7 to 1.7)) was not significantly associated with a risk of meningioma.[28 62] In addition, in these two studies, which were cohort studies of women initiating treatment with the progestogen considered, the proportion of women with a simultaneous prescription of oestrogen at the initiation of progestogen treatment was relatively low (6.8%, and 5.0%, respectively per study).

Conclusions

Prolonged use of medrogestone, medroxyprogesterone acetate, and promegestone was found to be associated with an increased risk of meningioma. Future studies should further clarify the association between the duration of use and risk for the progestogens studied, and extend the discussion of meningioma risk to dienogest and hydroxyprogesterone. Finally, no excess risk of meningioma was associated with the use of progesterone, dydrogesterone, or spironolactone, or the hormonal intrauterine systems used worldwide, regardless of the dose of levonorgestrel they contained.

Further studies are also needed to assess the meningioma risk with the use of medroxyprogesterone acetate, which, in this study, was considered at a dose of 150 mg and corresponded to a second line injectable contraceptive that is rarely used in France. Studies from countries with a broader use of this product, which, furthermore, is often administered to vulnerable populations, are urgently needed to gain a better understanding of its dose-response association.

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Ethical approval: The present study was authorised by decree 2016–1871 on December 26, 2016.[27] As a permanent user of the 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 the SNDS (register reference: EP-0437).

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 corresponding author at noemie.roland@assurance-maladie.fr.

Transparency: The lead author 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: The results were presented for the first time on 12 June 2023, at a meeting organised by the French National Agency for Medicines and Health Products Safety to invited patient association representatives, gynecologists, endocrinologists, neurosurgeons, and general practitioners. The report on this study (in French) was than published on 26 June 2023, on the EPI-PHARE, ANSM (Agence nationale de sécurité du médicament et des produits de santé), and Cnam (Caisse nationale de l'assurance maladie)) websites and was sent to the European Medicine Agency.

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