Female gender and exogenous hormone intake as risk factors for spheno-orbital meningiomas

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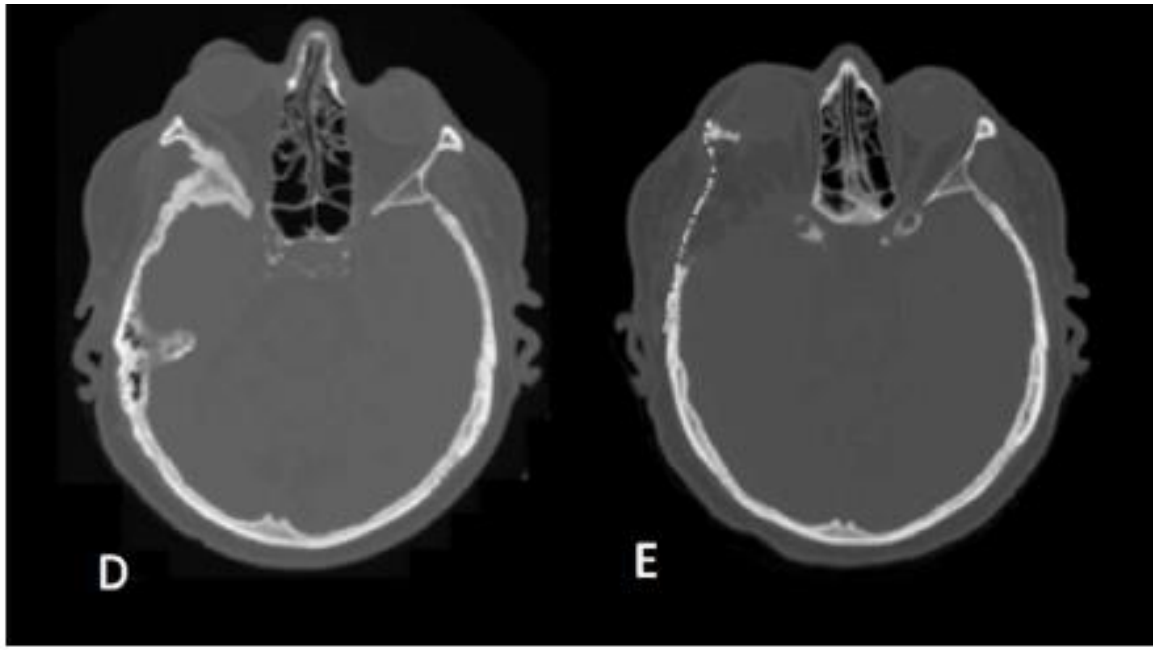
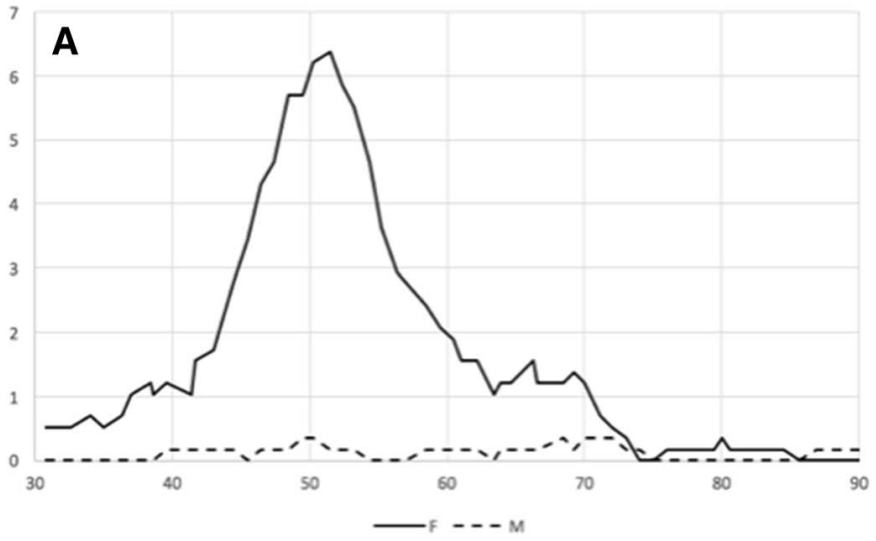
Spheno-orbital osteo-meningiomas



- Bony and meningeal tumors
- Causing proptosis & visual loss, sometimes epilepsy
- The surgical management is well described and quite consensual (Terrier et al, JNS, 2018)
- But… still 29% of recurrence (10%-56%) after a mean time of 54 months
- Definitely not perfect

Have you noticed…
that all patients with SOOM look alike ?

- In our practice 2005-2019
  - 175 > 124 patients operated for SOOM with complete data
  - 116 women (93.5%)
  - Median age 51 ± 5 for women (vs 63 ± 8 for men, p 0.02)
- 112 meningothelial grade 1 meningiomas (90.3%), including all tumors in males
- Progesterone receptors in 96.4% of females, and 50.0% of males (p < 0.001).



- In the literature : 86,4% women for SOOM vs 73,8% for all meningiomas (p=0,002)

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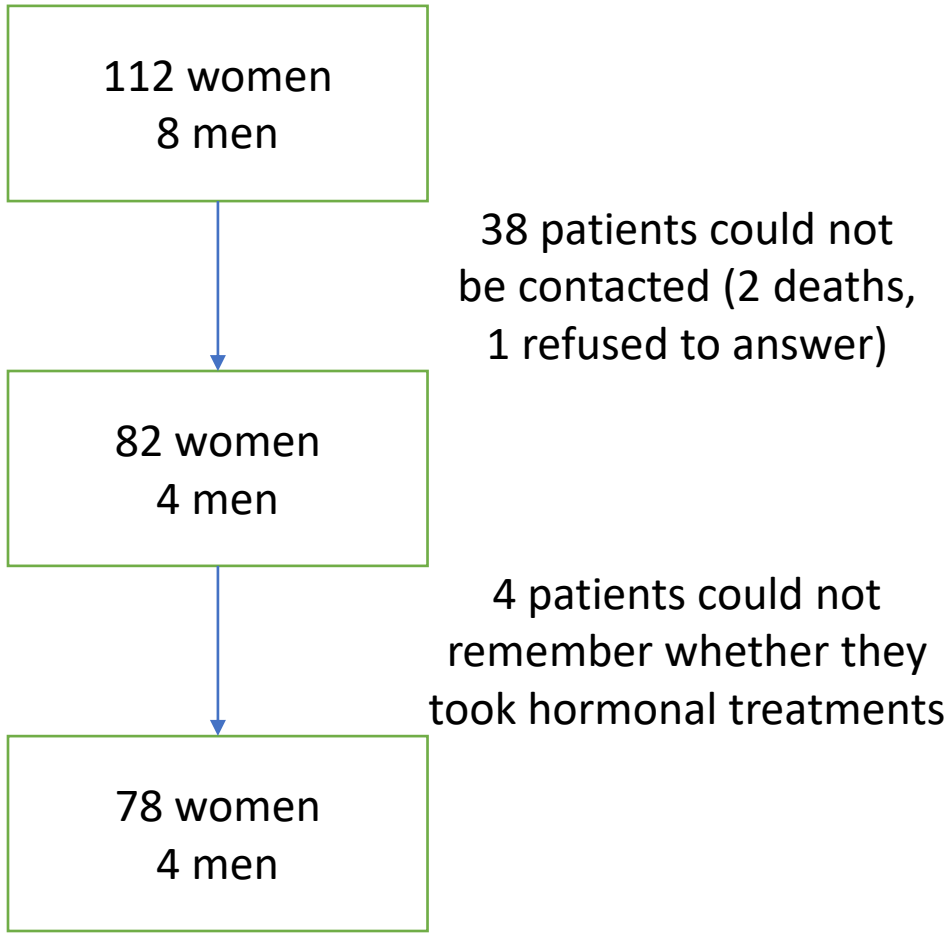
Retrospective description of the patients



- General and gynecological diseases as expected in the general population
- No cranial radiation, no neurofibromatosis
- BMI: 24.8 ± 1.8, with 16 overweight (BMI > 25, 42%) and 8 obese patients (BMI > 30, 21%)
- Gynecological status:
  - No woman was pregnant
  - 42% premenopausal
  - 12% perimenopausal
  - 46% postmenopausal

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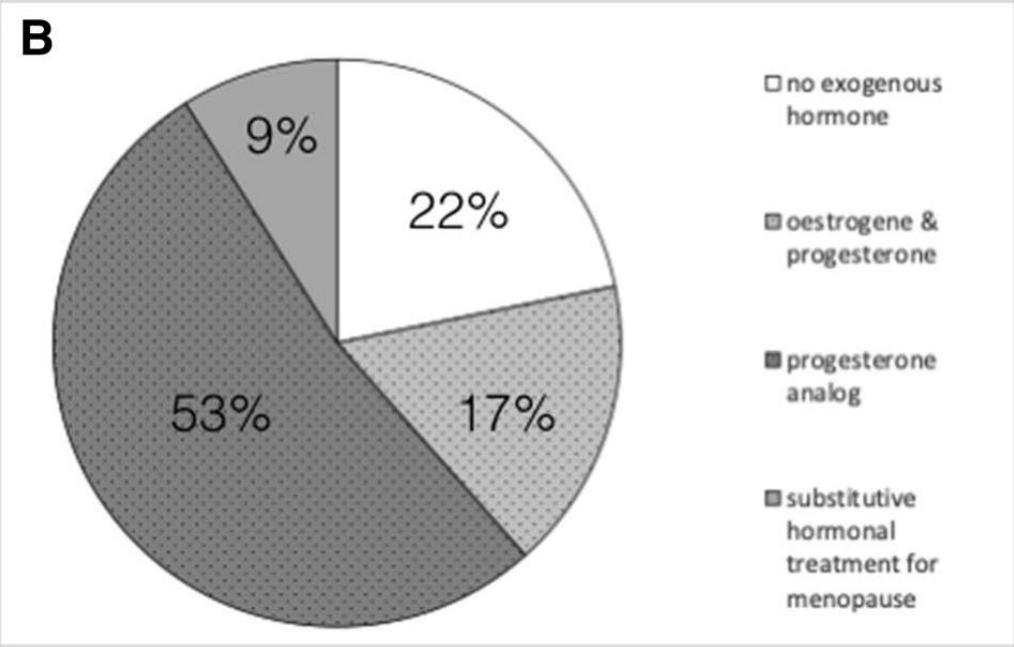
Exogenous hormone intake



2-40 years (median 10 years)

Table 1 Detailed exogenous hormone intakes in 61 women with spheno-orbital meningiomas (78.2%); 41 received progesterone therapies and 13 only oestroprogestogenic treatments, all containing old-generation progesterone

Progesterone therapies			Oestroprogestogenic therapies				
Treatment	Molecule	N. of patients	Treatment	Oestrogen	Progesterone analog	Progesterone generation	N. of patients
ANDROCUR	Cyproterone acetate 50 mg	9	ADEPAL	Ethinylestradiol 0.030–0.040 mg	Levonogestrel 0.15–0.20 mg	2	1
COLPRONE	Medrogestone 5 mg	1	DIANE 35	Ethinylestradiol 0.035 mg	Cyproterone acetate 2 mg	2	2
LUTENYL	Nomegestrol acetate 5 mg	14	GYNOPHASE	Ethinylestradiol 0.050 mg	Norethisterone acetate 1–2 mg	1	1
LUTERAN	Chlormadinone 5–10 mg	13	GYNOVLANE	Ethinylestradiol 0.050 mg	Norethisterone acetate 2 mg	1	1
SURGESTONE	Promegestone 0.5 mg	1	MINIDRIL	Ethinylestradiol 0.030 mg	Levonogestrel 0.15 mg	2	4
NEXPLANON—CONTRACEPTIVE IMPLANT	Etonogestrel	2	MINIPHASE	Ethinylestradiol 0.030–0.040 mg	Norethisterone acetate 1–2 mg	1	1
INTRAUTERINE CONTRACEPTIVE DEVICE	Levonogestrel	1	CONTRACEPTIVE OESTROGENIC PILL	–	–	–	4
		40					13

The remaining 7 received substitutive hormonal treatment for menopause, without precision. In addition, 2 received contraception pills they could not remember, 1 progesterone ointment and 1 underwent in vitro fertilization, so that 64/78 (83.3%) received exogenous hormones

Meningioma evolution in detail

- In the series, 8.3% of patients had multiple meningiomas (7/84, 3 bilateral spheno-orbital meningiomas)
  - all of them were women and received hormones (1 oestroprogestogenic treatment, 4 progesterone analogs, 1 substitutive hormonal therapy for menopause)

- 21.0% of recurrence needing surgery (26/124)
  - 25 women (10 premenopausal,6 perimenopausal and 9 postmenopausal)
  - 12/16 received exogenous progesterone (75%)
  - erectile dysfunction was mentioned in the man medical file

+++ Limits +++

- Of our study
  - Retrospective data collection (precise molecules, duration…)
  - Hormonal treatments are not « treatments »
  - Not all hormonal treatments are the same (progesterone, estrogen…)
  - Operated cases only
  - Rate of hormonal treatments in the general population ??

- For comparing the series in the literature and research
  - Extent of resection varies
  - SOOM is a vague entity, what about intra-orbital meningiomas for instance ?
  - Molecular analysis is difficult for the osseous part

Discussion

- Is hormonal treatment interruption enough to stop meningioma growth ?

➢ NO in our series

➢ In the literature : no reported case of SOOM regression

- Progesterone inhibitor mifepristone ? Controversial results, no description in SOOM (review Sharma, 2019)
- Other targeted therapy ? Molecular shift in hormone-dependent meningiomas (Peyre, 2018)

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Pending questions

- Factors for tumor regression / growth > prospective collection of data

- Confirming Is there a rationale for anti-progesterone treatment in these patients? As an adjuvant treatment ?

- How to reduce this high recurrence rate ???

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Merci !

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Molecular patterns

- Specific locations are associated with specific molecular patterns, in particular mutations in *TRAF7/AKT1* and *SMO* are found in meningiomas that develop in the anterior fossa, median middle fossa, or anterior calvarium, most of them being meningothelial or transitional meningiomas (Yuzawa et al, Br Tum Pathol, 2016 – Boetto et al, Neurooncol, 2017)
- Exogenous hormones may induce specific molecular profiles in meningiomas, with a higher frequency of *PIK3CA* and *TRAF7* mutations (Peyre at al, Ann Oncol, 2018)

Discussion

- What about progesterone inhibitor mifepristone ?
  - No univocal conclusion about the use of mifepristone in meningioma (Sharma R et al, Neurol India, 2019)
  - Ji et al, 2015: *Double-Blind Phase III Randomized Trial of the Antiprogestin Agent Mifepristone in the Treatment of Unresectable Meningioma: SWOG S9005:* 84 placebo / 80 mifepristone >> no difference in failure-free or overall survival
  - Limits: (1992-1998) very large eligibility, no information about tumor location
  - Touat et al, Acta Neurochir, long-term efficacy in meningiomatosis (female, progesterone receptors)
  - Limits: 3 case reports

Hormone dependent meningiomas with regression
Cases already reported

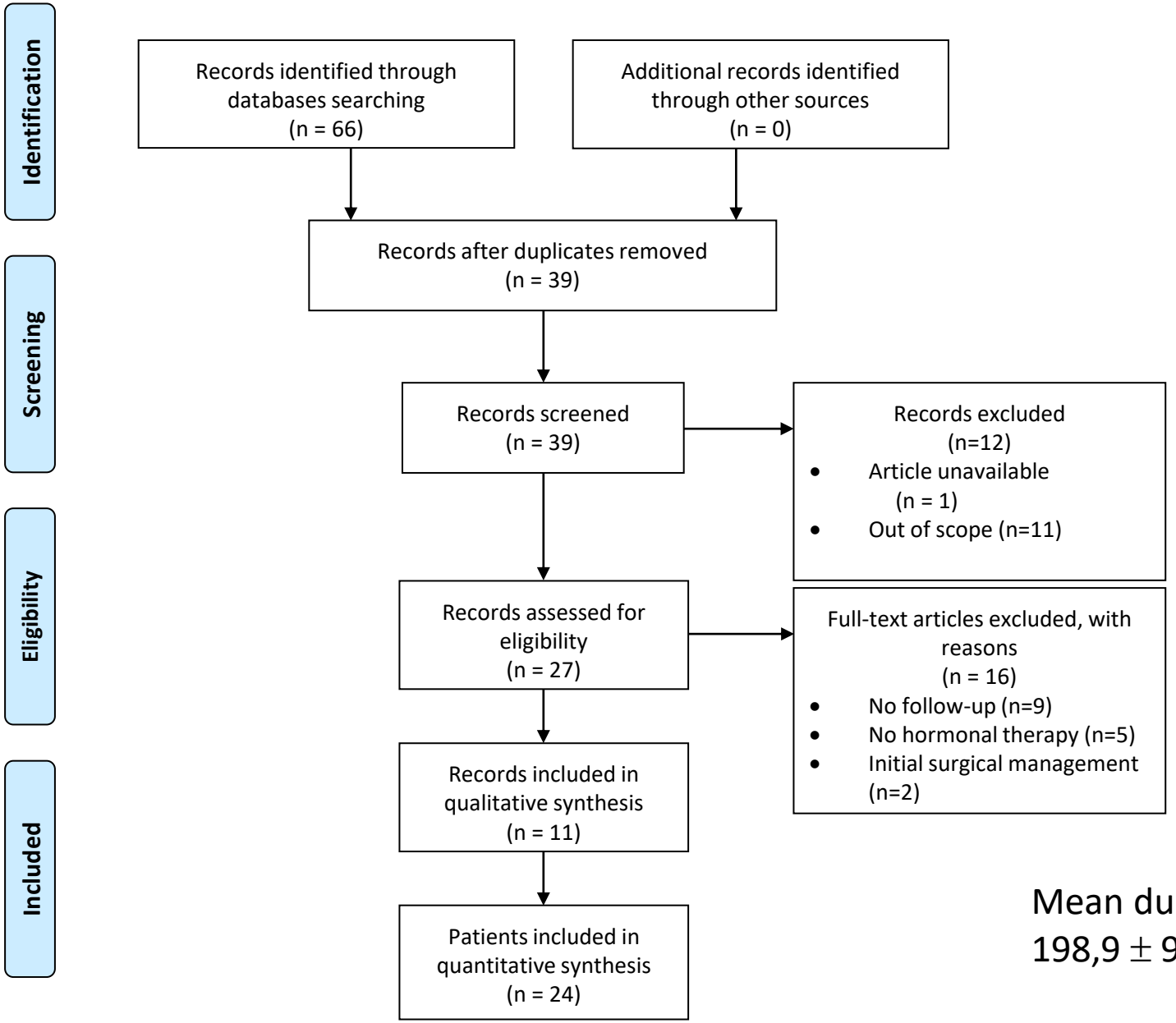

Table 1. Characteristics of all 24 patients

	Number (%) or mean
Sex	
Male	2 (8,3%)
Female	22 (91,7%)
Age (year)	51,3 ± 12,2
Number of tumors	63
Number / patient	2,6 ± 2,1
Localization	48
Skull Base	28 (58,3%)
SOOM	0
Ponto-cerebellar angle	2
Olfactory Groove	5
Convexity	20 (41,7%)
Delay before decreasing (months)	8,1 ± 7,1

Mean duration of treatment:
198,9 ± 92,6 months, 16.5 years

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In the literature

Table 2 Literature review of series of spheno-orbital meningiomas in 2010–2019

References	No. of patients	No. of women	
Honig et al. [22]	30	22	
Schick et al. [27]	77	61	
Saeed et al. [17]	90	85	
Oya et al. [26]	39	34	
Solmaz et al. [28]	13	3	
Forster et al. [19]	18	18	
Leroy et al. [24]	70	64	
Freeman et al. [20]	25	23	
Terrier et al. [6]	130	119	
Gonen et al. [21]	27	24	
Mashcke et al. [25]	31	27	
Young et al. [30]	24	22	
Kiyofuji et al. [23]	47	38	
Terpolilli et al. [29]	122	93	
Our series	124	116	
Total	867	749	86.4%*
Dolecek et al. [8]	110,359	81,475	73.8%*

The number of female patients is detailed in the third colum[illegible]. Compared to the largest series of meningiomas in general [8], spheno-orbital meningiomas develop significantly more often in women ($p = 0.002$)

Identification

Screening

Eligibility

Included

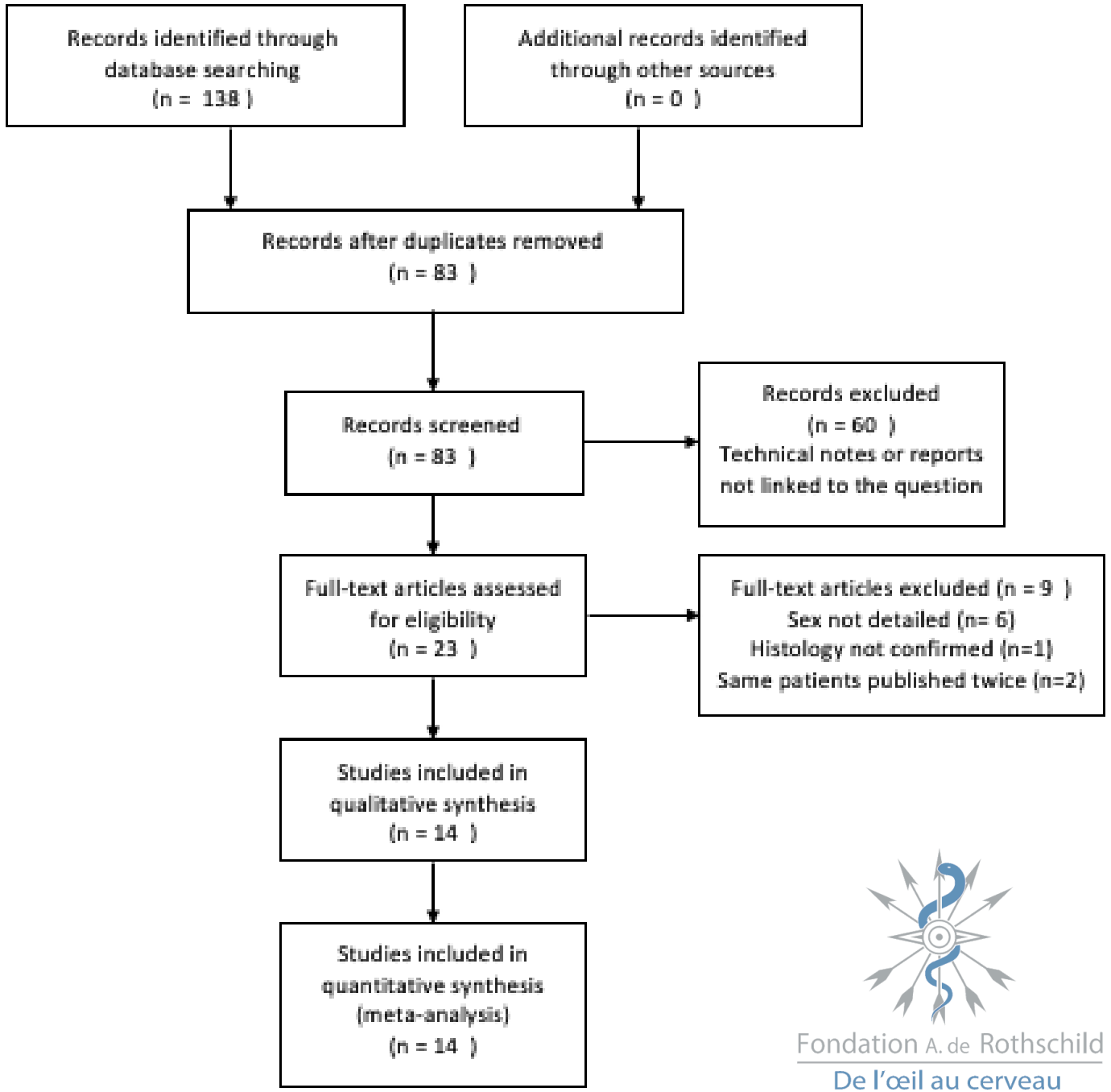

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Table 2. Hormonal treatments before diagnosis

Treatment	Patients	Mean duration of treatment (months)	Mean Dose (mg/day)
Cyproterone	17	192 ± 79	48,4 ± 17
Nomegestrol	3	300 ± 103	5 ± 0
Chlormadinone	1	Inconnu	Inconnu
Cyproterone/Chlormadinone	1	254	Inconnu
Medroxyprogesterone	1	60	500
Megestrol	1	84	160

Mean duration of treatment: 198,9 ± 92,6 months, 16.5 years