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Full length article

Impact of family history for endometriosis, migraine, depression and early menopause on endometriosis symptoms, localization and stage: A case control study

Julian Matthias Metzler [a,*], Patrick Imesch [a], Hanna Dietrich [b], Chiara Knobel [b], Lea Portmann [b], Maria S. Neumeier [c], Gabriele Susanne Merki-Feld [b]

[a] Department of Gynecology, University Hospital Zurich, Switzerland
[b] Department of Reproductive Endocrinology, University Hospital Zurich, Switzerland
[c] Department of Neurology, University Hospital Zurich, Switzerland

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ABSTRACT

Introduction: Endometriosis is a common disabling pain condition in women of childbearing age, frequently showing familial clustering. Nevertheless, little is known about whether familial predispositions influence its severity or presentation. In this study, we investigate disease characteristics in endometriosis patients with a family history (FH) for endometriosis or the comorbidities migraine, depression and early menopause (EMP).

Materials and methods: We performed an observational case-control study enrolling women with histologically confirmed endometriosis in a tertiary center.

Based on surgical findings, patient records and phone interviews, we examined the relations between a FH for endometriosis, migraine, depression or EMP and endometriotic signs and symptoms, such as response to combined hormonal contraceptives (CHC) and analgesics, disease localization, infiltration depth, Enzian- and rASRM-scores.

Results: A positive FH for endometriosis, migraine, depression or EMP was reported by 10.2 %, 33.4 %, 32.6 % and 9.9 % of the 344 patients. A positive FH of endometriosis was associated with an increased risk for high rASRM-scores (rASRM 3 + 4: OR 2.74 (95 % CI 1.16–6.49), $p = 0.017$) and the presence of endometriomas (OR 2.70 (1.22–5.95), $p = 0.011$). A positive FH for migraine was associated with less response of endometriosis symptoms to CHC (OR 0.469 (0.27–0.82) $p = 0.025$). Depression in the family was linked to less severe rASRM-scores (rASRM 3 + 4: OR 0.63 (0.39–0.99), $p = 0.046$) and less endometriomas (OR 0.58 (0.67–0.92), $p = 0.02$), but increased the risk of both migraine (OR 1.66 (1.01–2.73), $p = 0.043$) and depression (OR 3.04 (1.89–4.89), $p < 0.001$) while showing a better response to CHC (OR 2.0 (1.15–3.48, $p < 0.001$). Patients with EMP in their family reported more current endometriosis symptoms at present (OR 3.72 (1.67–8.30), $p = 0.001$), more dysmenorrhea (OR 2.13 (1.04–4.35), $p = 0.037$), more frequent severe dysmenorrhea (OR 2.32 (1.14–4.74), $p = 0.019$) and suffered significantly more often > 5 days of non-cyclic pain (OR 3.58 (1.72–7.44), $p < 0.001$).

Conclusions: Around 30% reported a positive FH for migraine or depression. Patients with a positive FH for endometriosis, migraine, depression or EMP differ in symptoms and surgical findings when compared to controls. While a FH for endometriosis is associated with higher rASRM scores and more endometriomas, women with a FH for depression had lower rASRM scores and less endometriomas while responding better to CHC. In contrast, women with a FH for migraine showed less response to CHC.

Introduction

Endometriosis is an inflammatory and chronic disease affecting up to 10 % of women [1]. Multiple hypotheses regarding its etiology have been proposed, including retrograde menstruation, angio- or lymphogenic spread, and cell metaplasia [2–4]. Genetic studies depicted various

Abbreviations: CHC, combined hormonal contraceptives; EM, endometriosis; EMP, early menopause; FH, family history.

* Corresponding author at: University Hospital Zurich, Frauenklinikstrasse 10, 8091 Zurich, Switzerland.
E-mail address: Julian.Metzler@usz.ch (J.M. Metzler).

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candidate genes, genetic regions or incidents possibly contributing to the development of peritoneal, cystic or deep endometriosis [5–7]. Epigenetic factory may explain further hereditary aspects [3].

While expanding genetic knowledge is leading to a better understanding of the etiology, it is important to acknowledge genetic and mutual environmental aspects each account for circa 50 % of familial disease aggregation [8]. The presence of both can surpass the sum of their individual effect, as the combination of a positive family history (FH) and additional risk factors out yields the familial "baseline-risk" [9].

A positive FH has been described in 7–35 % of endometriosis patients and is associated with a 3-9x increased risk of developing the disease, highlighting the importance of obtaining a FH when counseling patients with dysmenorrhea [10–15]. Verket et al demonstrated this strong association by creating an endometriosis prediction model using anamnestic factors, with the item "family history" representing the largest risk in multivariable logistic regression [16]. The severity of the disease is also influenced by hereditary traits, with severe endometriosis being found more frequently in patients with a positive FH than without [12,17]. Vice versa, Chapron et al reported that women with deep infiltrating endometriosis had a higher rate of a positive FH than women with peritoneal or ovarian endometriosis only [18].

Women with endometriosis have an increased likelihood of suffering from comorbidities such as migraine and depression, two familial disorders that result from genetic influences, share a bi-directional association and are affected by the menstrual cycle [19–25]. Similar to endometriosis, early menopause (EMP) has been shown to be associated with early menarche and nulliparity, therefore representing a third disease to be investigated in this context [26,27]. As the impacts of these comorbidities are poorly understood, highlighting their role in the context of endometriosis might open up new opportunities to improve diagnostics and treatments in an interdisciplinary approach [28,29].

While a correlation of endometriosis, migraine and depression has been reported, to our knowledge, no studies linking a FH for these conditions have been published, and the significance of a single or combined positive FH is unclear [30].

With the present study we aimed to investigate if a positive FH for endometriosis, migraine, depression or EMP might be associated with clinical symptoms or endometriosis stage in our patients.

Materials and methods

This observational study was conducted in the Departments of Reproductive Endocrinology and Gynecology of the University Hospital Zurich. The project was authorized on 26.03.2021 by the cantonal ethics committee of Zurich, Switzerland (BASEC-Number 2021-00285) and was registered on ClinicalTrials.gov (Identifier: NCT04816357).

From a list of visits in our endometriosis clinic, we checked all patient files from January 2015 to July 2021 for women with endometriosis. Premenopausal patients aged 18–55 years who had received surgery with histologically confirmed endometriosis were included in this study. Exclusion criteria were defined as age below 18 or over 55 years as well as inability to be interviewed due to language barriers, psychiatric conditions or dementia. Furthermore, patients with scar endometriosis and sole adenomyosis, who lacked histological confirmation, were excluded. The data presented are part of a larger trial with the aim to better understand the potential impact of comorbidities on endometriosis features and course.

All patients who fulfilled the inclusion and agreed to participate were subsequently interviewed via phone by medical staff. The interviewers were familiar with the International headache society (IHS) criteria for migraine and had performed a training in 50 test interviews, where the survey was also validated [31].

In the interview, we used a standardized survey adapted from the "Women's Health Symptom Survey Questionnaire" of the World Endometriosis Research Foundation, collecting self-reported information on height and weight, medical conditions, past gynecological and obstetrical history, cycle characteristics, prior surgery, medication intake, potential migraine and depression as well as a FH for endometriosis, EMP, migraine and depression [32]. Diagnosis of the prior was self-reported but verified during the interview by asking specific questions. Data were cross-checked with medical charts to ensure consistency. Data regarding endometriosis classification and localisation (including rASRM- and Enzian- scores, histological measurements) were obtained from medical reports.

Definitions

Questions about pain were scaled from one to three (1: mild pain, 2: moderate pain, 3: severe pain). Endometriosis was classified according to the revised American Society of Reproductive Medicine (rASRM) score. For deep infiltrating endometriosis, the Enzian classification was used [33]. For depression, the definition of clinical depression was used; seeing a therapist or medication was not mandatory for the definition but documented. Migraine was defined using the International Headache Societies definition and differentiated from headache by asking questions about the typical symptoms (throbbing and pulsating pain on one side of the head, additional symptoms like photo-/phonophobia, nausea, vomiting). Women who reported migraines were queried with 30 additional questions utilizing the Migraine Disability Assessment Questionnaire (MIDAS) [34]. EMP was defined according to the American Menopause Society's criteria, characterizing early menopause as occurring between the ages of 40 to 45.

Statistics

All statistical tests were calculated in SPSS (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0). The results are reported as mean ± SD or as percentages where appropriate. $P \leq 0.05$ was considered statistically significant. The precision of the odds ratio was presented as 95 % confidence interval (CI). For chi square tests, Pearson's Chi Square was used. If >20 % of expected cell counts were below 5, significance was calculated using the Likelihood Ratio or Fisher's Exact Test, where appropriate [35].

Results

Baseline characteristics

344 endometriosis patients fulfilled the inclusion criteria and agreed to participate in the study (Fig. 1). Mean age was 36.2 ± 7.3 years. Baseline characteristics did not differ between groups except for the following criteria: patients with a positive FH for endometriosis were slightly older (39.5 vs 35.6 years); patients with a positive FH for menopause < 46 years had their first endometriosis surgery at a younger age (28.6 vs 31.1 years), and patients with a positive FH for depression had a lower weight and BMI (22.3 vs 23.4 kg/m^2, Table 1).

Cycle characteristics, endometriosis staging and symptoms

179 patients (52 %) were suffering from endometriosis-related symptoms at the time of data collection, with dysmenorrhea being the most common symptom. Regarding disease severity, 210 patients (61 %) were diagnose with a rASRM score of 3 or 4 (Table 2). Non-cyclical pain was common, occurring in 26.2 % of patients on > 5 days per month. Overall, 208 patients (60.5 %) had experienced dyspareunia in the past or present, and 155 patients (45.1 %) reported past or present dyschezia. Patient age did not correlate with the number of surgeries or endometriosis stage. With regard to current contraception, the following frequencies emerged: none/non-hormonal 79.7 %; combined hormonal contraceptives (CHC) 9.0 %, progesterone only pill (POP) 6.1 %, levonorgestrel-containing intrauterine device (LNG-IUD) 4.9 %,

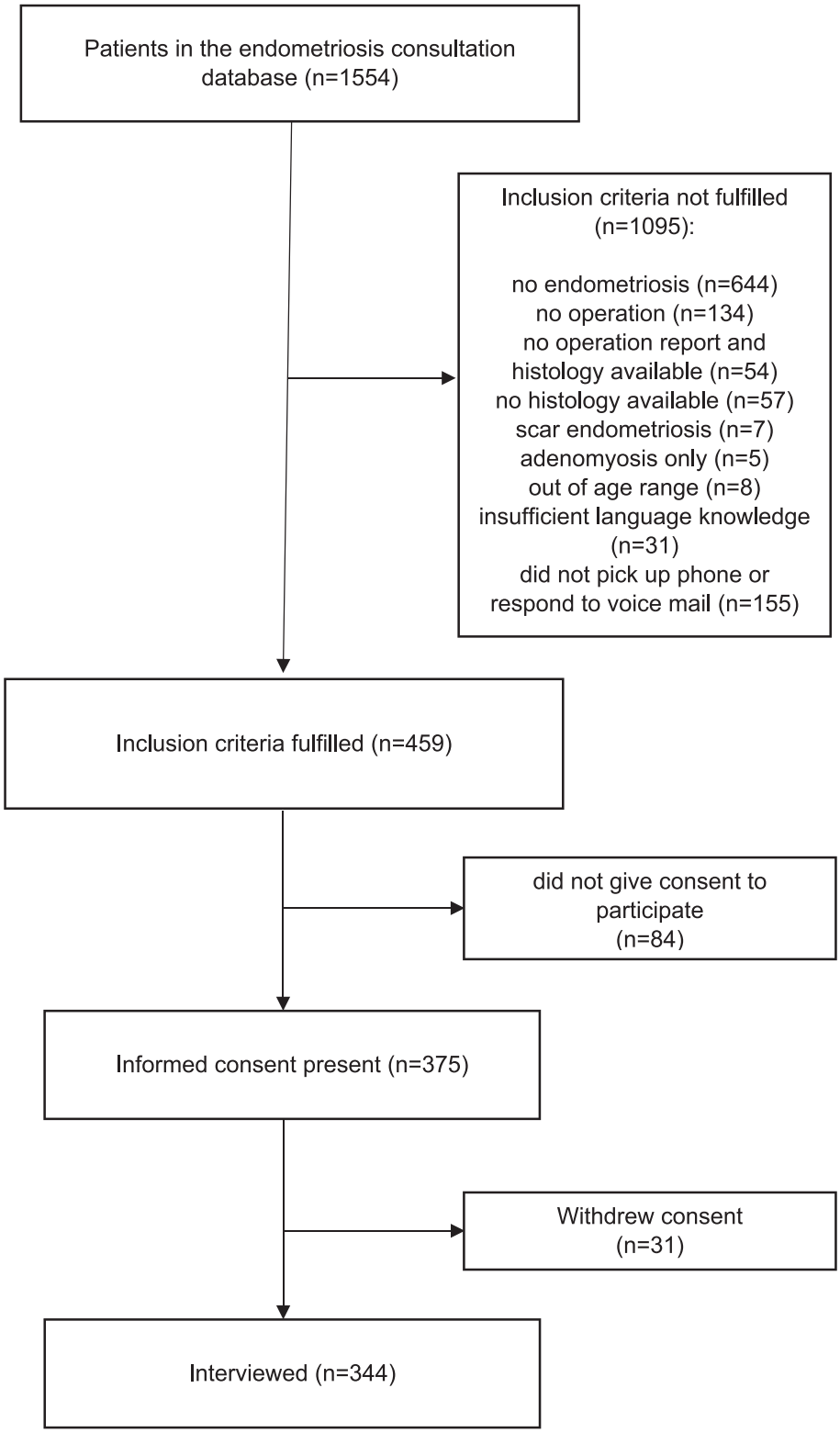

Fig. 1. Study cohort, inclusion and exclusion criteria.

progestin implant 0.3 %.

Family history

In our cohort, 35 (10.2 %) had a positive FH for endometriosis (first degree relative (FDR): 4.9 %; no information available 5.5 %). About a third (33.4 %; n = 115) of all women had a positive FH for migraine (FDR: 23.8 %, n = 82).

A positive FH for depression was reported by 32.6 % of our participants and 25.3 % (n = 87) reported that a FDR was affected.

10.8 % of patients (n = 37) reported a positive FH for EMP (FDR: 9.9 %, n = 34).

The frequency of more than one FH varied. A family history of migraine and depression was reported in 40 patients (11.6 %),

Table 1
Baseline Characteristics of cohort. BMI: Body mass index; EM: Endometriosis; MG: Migraine; EMP: Early Menopause; n: Number; SD: Standard deviation.

Characteristic	All (100 %, n = 344)	No FH EM (84.3 %, n = 290	FH EM (10.2 %, n = 35)	p	No FH MG (64.2 %, n = 221)	FH MG (33.4 %, n = 115)	p	No FH EMP < 46 (55.5 %, n = 191)	FH EMP < 46 (10.8 %, n = 37)	p	No FH Depression (64.5 %, n = 222)	FH Depression (32.6 %, n = 112)	p
Age years mean (SD)	36.2 (7.3)	35.6 (7.2)	39.5 (7.7)	**0.0029**	35.8 (6.9)	36.5 (8.1)	0.4069	35.5 (7.5)	34.0 (6.3)	0.2553	36.4 (7.5)	35.1 (6.7)	0.1224
Height cm mean (SD)	167.4 (7.0)	167.5 (6.8)	167.9 (8.4)	0.7492	167.1 (7.2)	168.0 (6.5)	0.2622	167.2 (6.6)	168.1 (7.8)	0.4623	167.4 (7.2)	167.4 (6.6)	1.00
Weight cm mean (SD)	64.5 (11.2)	64.2 (11.0)	66.2 (10.6)	0.3085	64.1 (11.2)	64.9 (10.2)	0.5225	64.6 (10.4)	63.5 (9.5)	0.5513	65.2 (11.8)	62.6 (8.8)	**0.0402**
BMI kg/m2 mean (SD)	23.1 (4.0)	23.0 (3.8)	23.6 (4.2)	0.3837	23.1 (4.1)	23.0 (3.4)	0.8226	23.2 (3.6)	22.5 (3.1)	0.2701	23.4 (4.3)	22.3 (3.0)	**0.0158**
Age menarche mean (SD)	12.8 (1.6)	12.8 (1.6)	12.8 (1.4)	1.00	12.7 (1.5)	12.8 (1.7)	0.5803	12.7 (1.6)	12.5 (1.6)	0.4872	12.7 (1.7)	12.8 (1.4)	0.5915
Number of endometriosis operations mean (SD)	1.56 (1.0)	1.52 (0.9)	1.83 (1.3)	0.0692	1.56 (1.0)	1.51 (0.8)	0.6427	1.54 (0.9)	1.4 (1.4)	0.435	1.6 (1.0)	1.46 (0.9)	0.2128
Age at first enndometriosis surgery (SD)	31.7 (6.7)	31.3 (6.6)	33.4 (7.3)	0.0798	31.6 (6.4)	31.6 (7.3)	1.00	31.1 (6.5)	28.6 (5.6)	**0.0298**	31.7 (6.6)	31.1 (6.7)	0.4357

depression and early menopause in 16 patients (4.7 %), endometriosis and depression in 12 cases (3.5 %), endometriosis and migraine in 12 cases (3.5 %), migraine and early menopause 10 cases (2.9 %), endometriosis and early menopause in 6 cases (1.74 %). More complex combinations were found in smaller percentages, such as endometriosis, depression, and early menopause 5 cases (1.45 %), and endometriosis, depression, and migraine in 4 cases (1.16 %). See Fig. 2 for a graphical representation.

Correlations

We found several significant correlations between positive family histories and the occurrence of certain endometriosis signs and symptoms:

Associations among family histories

A positive family history for one of the diseases did not correlate with the presence of a second family history. A **positive FH for endometriosis** was not associated with a positive FH for migraine (p = 0.910), early menopause (p = 0.227), or depression (p = 0.818).

A **positive FH for migraine** was not associated with a positive FH for early menopause (p = 0.382) or depression (p = 0.533).

A **positive FH for depression** was not associated with a positive FH for menopause (p = 0.142).

Associations between family histories and symptoms (Table 2)

In our cohort, a **positive FH for endometriosis** was linked to an increased risk of high rASRM-scores (OR 2.74, p = 0.017) and the occurrence of ovarian endometriosis (OR 2.70, p = 0.011, Tables 2 and 3).

A **positive FH for migraine** was significantly associated with a personal manifestation of migraine (OR 3.18, p < 0.001), even more so when first-degree relatives (FDR) were affected (OR 3.36, p < 0.001).

In this group, less patients described a response of endometriosis symptoms to CHC (OR 4.69, p = 0.025).

Heavy bleeding > 2 days (37.4 vs 28.1 %) and dyspareunia (67.0 vs 57 %) seemed to be increased, but missed statistical significance (p = 0.08 and p = 0.077, respectively).

Migraine in first-degree relatives also correlated with currently symptomatic disease (OR 1.75, p = 0.03), and deep infiltrating endometriosis of the bladder (OR 1.77, p = 0.033).

Patients with **early menopause** in their family reported more frequently a current presence of endometriosis symptoms (OR 3.72, p = 0.001) and dysmenorrhea (OR 2.13, p = 0.037), as well as severe dysmenorrhea (p = 0.019, Table 2). Non-cyclical pain for more than 5 days occurred more often in patients with both non-FDR and FDR affected (p < 0.001). In this group, the patients had their first endometriosis surgery significantly earlier (28.6 vs 31.7 years, p = 0.007).

Patients with a **positive FH for depression** had less severe rASRM-scores (OR 0.63, p = 0.046) and endometriomas (OR 0.58, p = 0.02), both effects being aggravated when first-degree relatives were affected.

For non-surgical outcomes, we observed a correlation with a personal history of both migraine (p = 0.043) and depression (p < 0.001). In contrast to patients with migraineurs in their family, which showed reduced response to CHC against endometriosis symptoms, we found a higher rate of symptom improvement for patients with depressive family members (OR 2.0, p = 0.014). Of note, no differences between groups were found for the item “dysmenorrhea responding to analgesics”. Additionally, an increased risk for current endometriosis symptoms (OR 1.85, p = 0.016) was noted in this group.

Table 3 lists significant odd‘s ratios for positive family histories, symptoms and surgical outcomes.

Discussion

In this study, we found that a positive FH of endometriosis, migraine, depression or early menopause may influence symptoms and surgical findings in endometriosis patients.

The rate of women with a positive family history for endometriosis in our study (10 %) was within the range of previously published reports (7–35 %) [10–13].

None of the family histories was associated with age at menarche or number of operations, confirming previous findings [36]. Surgical reports showed that the small group of patients with a **FH for endometriosis** had higher rASRM scores and more endometriomas, with no differences in other locations/compartments. Notably, this was not associated with more dysmenorrhea, dyschezia or dyspareunia (Table 2). rASRM scores within this group may be attributed to the presence of endometriomas, which contribute significantly to the total points in the rASRM scoring system. The limited manifestation of additional endometriosis symptoms aligns with current literature, suggesting that pain is often associated with concurrent peritoneal lesions

Table 2
Surgical and anamnestic parameters plotted by history for endometriosis, migraine, menopause < 46 years of age and depression. P-values compare the two previous columns respectively (patients with and without a certain family history). Because some participants were unable to provide information on certain family histories, the numbers typically do not add up to the total of 344. EM = Endometriosis, EMP = Menopause, USL = Uterosacral ligaments.

Parameter	All, % (n = 344)	No FH EM % (n = 290)	FH EM, % (n = 35)	p	No FH Migraine % (n = 221)	FH Migraine % (n = 115)	p	No FH EMP % (n = 191)	FH EMP % (n = 37)	p	No FH Depression % (n = 222)	FH Depression % (n = 112)	p
1st Endom. surgery < 20y	4.9 (17)	5.5 (16)	2.9 (1)	0.471	3.6 (8)	7.8 (9)	0.095	5.2 (10)	8.1 (3)	0.448	4.1 (9)	7.1 (8)	0.225
1st Endom. surgery < 29y	37.5 (129)	39.0 (113)	31.4 (11)	0.386	38.0 (84)	38.3 (44)	0.964	41.9 (80)	56.8 (21)	0.096	39.6 (88)	35.7 (40)	0.486
rASRM 3 + 4	61 (210)	59.3 (172)	80.0 (28)	**0.017**	60.06 (134)	60.0 (69)	0.91	57.1 (109)	64.9 (24)	0.379	64.9 (144)	53.6 (60)	**0.046**
Infiltration >=1 cm	40.1 (138)	39.0 (113)	51.4 (18)	0.156	40.3 (89)	39.1 (45)	0.839	35.1 (67)	45.9 (17)	0.21	40.5 (90)	42.0 (47)	0.803
Infiltration >=3 cm	18.6 (64)	17.9 (52)	25.7 (9)	0.265	19.5 (43)	18.3 (21)	0.791	17.3 (33)	21.6 (8)	0.529	21.2 (47)	15.2 (17)	0.189
Enzian A (Recto-Vaginal)	46.5 (160)	46.9 (136)	51.4 (18)	0.612	45.2 (100)	48.7 (56)	0.548	45.5 (87)	62.2 (23)	0.064	43.7 (97)	52.7 (59)	0.12
Enzian B (USL, Pelvic sidewall)	70.9 (244)	72.1 (209)	65.7 (23)	0.432	72.4 (160)	69.6 (80)	0.585	71.2 (136)	75.7 (28)	0.58	70.7 (157)	71.4 (80)	0.893
Enzian C (Rectum)	11.6 (40)	11.7 (34)	17.1 (6)	0.41	13.1 (29)	8.7 (10)	0.229	8.4 (16)	16.2 (6)	0.139	10.4 (23)	15.2 (17)	0.2
Enzian FB (Bladder)	28.2 (97)	27.2 (799)	34.3 (12)	0.381	26.2 (58)	33.0 (38)	0.191	29.8 (57)	35.1 (13)	0.523	27.5 (61)	30.4 (34)	0.582
Enzian FI (Intestinal)	7.8 (27)	7.2 (21)	17.1 (6)	0.071	6.8 (15)	9.6 (11)	0.366	7.3 (14)	10.8 (4)	0.504	8.1 (18)	8.0 (9)	0.982
Enzian FO (Extragenital)	5.2 (18)	6.2 (18)	0.0 (0)	0.236	5.4 (12)	5.2 (6)	0.935	5.2 (10)	8.1 (3)	0.448	5.9 (13)	4.5 (5)	0.595
Endometrioma(s) present	53.8 (185)	51.7 (150)	74.3 (26)	**0.011**	53.8 (119)	53.0 (61)	0.889	52.9 (101)	54.1 (20)	0.896	59.0 (131)	45.5 (51)	**0.02**
Heavy bleeding	57.8 (199)	57.2 (166)	60.0 (21)	0.755	57.0 (126)	59.1 (68)	0.709	60.2 (115)	64.9 (24)	0.595	58.1 (129)	57.1 (64)	0.866
Heavy bleeding > 2 days	31.4 (108)	30.6 (89)	31.4 (11)	0.929	28.1 (62)	37.4 (43)	0.08	32.5 (62)	35.1 (13)	0.751	31.1 (69)	31.3 (35)	0.975
Current presence of any EM symptom	52 (179)	53.1 (154)	40.0 (14)	0.143	49.3 (109)	56.5 (65)	0.21	45.5 (87)	75.7 (28)	**0.001**	48.6 (108)	58.9 (66)	0.076
Current presence of dysmenorrhea	44.5 (153)	46.2 (134)	31.4 (11)	0.097	45.2 (100)	44.3 (51)	0.875	40.8 (78)	59.5 (22)	**0.037**	42.8 (95)	50.0 (56)	0.212
Dysmenorrhea score 2–3	40.4 (139)	42.4 (123)	25.7 (9)	0.057	42.1 (93)	39.1 (45)	0.602	36.1 (69)	56.8 (21)	**0.019**	38.7 (86)	45.5 (51)	0.233
Dyspareunia	60.5 (208)	62.1 (180)	51.4 (18)	0.223	57.0 (126)	67.0 (77)	0.077	62.8 (120)	70.3 (26)	0.388	57.7 (128)	66.1 (74)	0.138
Severe dyspareunia (score 2 + 3)	44.2 (152)	45.2 (131)	40.0 (14)	0.561	41.6 (92)	48.7 (56)	0.216	45.5 (87)	54.1 (20)	0.343	45.5 (101)	43.8 (49)	0.762
Dyschezia	45.1 (155)	46.9 (136)	42.9 (15)	0.895	42.5 (94)	47.8 (55)	0.126	47.1 (90)	59.0.5 (22)	0.169	45.0 (100)	44.6 (50)	0.944
Dysuria	17.4 (60)	17.6 (51)	17.1 (6)	0.948	15.8 (35)	20.9 (24)	0.25	17.8 (34)	16.2 (6)	0.817	17.1 (38)	18.8 (21)	0.712
>5 Days of acyclic pain	26.2 (90)	25.2 (73)	37.1 (13)	0.129	29.0 (64)	22.6 (26)	0.212	20.9 (40)	48.6 (18)	**<0.001**	24.3 (54)	31.3 (35)	0.177
Endometriosis responding to CHC	38.4 (132)	40.3 (117)	34.3 (12)	0.489	43.0 (95)	30.4 (35)	**0.025**	41.4 (79)	48.6 (18)	0.412	32.0 (71)	51.8 (58)	**<0.001**
Dysmenorrhea responding to analgesics	70.1 (241)	71.0 (206)	65.7 (23)	0.515	70.1 (155)	71.3 (82)	0.824	70.2 (134)	73.0 (27)	0.731	69.4 (154)	73.2 (82)	0.466
Personal history of migraine	27.3 (94)	27.2 (79)	31.4 (11)	0.601	19.5 (43)	43.5 (50)	**<0.001**	27.7 (53)	29.7 (11)	0.806	24.3 (54)	34.8 (39)	**0.043**
Personal history of depression	34.9 (120)	35.5 (103)	31.4 (11)	0.632	32.1 (71)	40.0 (46)	0.151	35.1 (67)	45.9 (17)	0.21	26.1 (58)	51.8 (58)	**<0.001**
Extrauterine pregnancy	0.6 (2)	0.7 (2)	0.0 (0)	0.622	0.5 (1)	0.9 (1)	0.637	0.5 (1)	2.7 (1)	0.299	0.5 (1)	0.9 (1)	1
Ever pregnant	39.8 (133)	40.0 (116)	40.0 (14)	1	39.4 (87)	40.9 (47)	0.789	42.4 (81)	48.6 (18)	0.483	37.4 (83)	44.6 (50)	0.201

rather than the presence of endometriomas per se [37].

These findings are in line with those from Campo et al, who investigated risk factors for endometrioma recurrence after laparoscopic surgery [38]. Of all factors, a positive FH for endometriosis was the only variable independently associated with endometrioma recurrence (recurrence rate of 40 % vs 14.8 % in controls, OR 3.2). Other disease characteristics, like dysmenorrhea, infertility, adhesions or peritoneal implants did not differ. The author's explanation "of a genetic basis both to endometriosis and to its clinical behavior" seems likely, as earlier studies demonstrated a link e between the "aggressiveness" (manifestation) of the disease and a positive FH [12,18].On the other hand, data on the correlation between clinical stage and FH is inconsistent [39]. Potentially this is related to the fact that not only genetic factors, but also shared and non-shared environmental factors contribute to the complex etiology of disease phenotype [8].

The small group of patients with a **FH for EMP** did not differ very much concerning surgical findings. The affected women reported significantly more often current endometriosis symptoms, severe

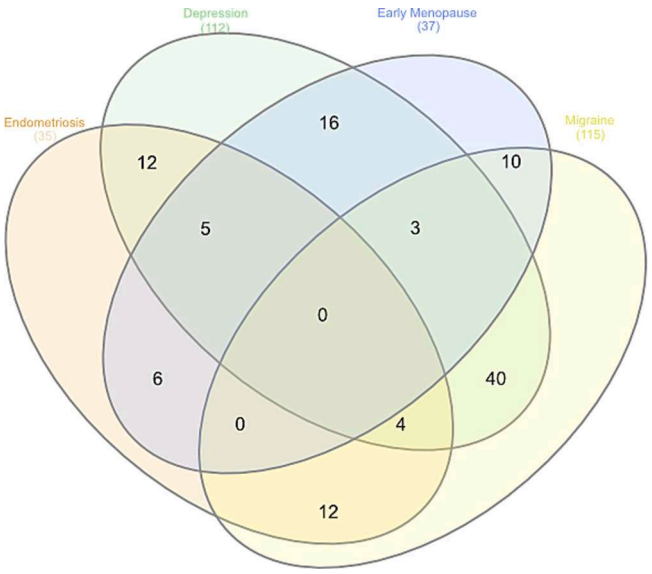

Fig. 2. Venn Diagram illustrating the intersection of various family histories.

dysmenorrhea and more days of non-cyclic pain.

EMP and premature ovarian insufficiency (POI) have a wide range of etiologies including genetic, autoimmune, environmental and idiopathic causes, making causal linkage difficult. Up to 30 % of women with POI have a family history for EMP [40]. On the other hand, endometriosis can result in POI due to ovarian tissue damage by endometrioma surgery. A recently published study revealed a 50 % greater risk for early natural menopause for women with laparoscopically confirmed endometriosis, particularly for nulliparous women and those who never used oral contraceptives [41]. Paracrine factors may play a role; for example, low levels of inhibin B increases the likelihood of POI [42], and are also associated with infertility in women with endometriosis [43]. Moreover, the prenatal hormonal environment, measured through the surrogate marker "anogenital distance", was linked to both POI and certain endometriosis characteristics [44,45]. Lastly, bi-directional associations between dysmenorrhea and depression as well as depression and early menopause have been described [46]. FH for EMP in our study was not associated with a higher number of operations or less pregnancies. EMP however is not POI and will allow the majority of women to experience some pregnancies. It is however interesting that those women tend to experience more pain and the high frequency of non-cyclic pain is remarkable.

FH for migraine was positive in around a third of our cohort, and strongly associated with the presence of migraine in the patient herself. Treatment of endometriosis symptoms with CHC was less successful in these women, while endometriosis symptoms did not. In contrast, participants with a FH for depression responded well to CHC and the percentage of currently symptomatic women was lower. These differences hormonal treatment response might be due to changes like central sensitization occurring in individuals with chronic pain [47].

While we could not demonstrate different pain scores for women with a sole family history for migraine, it is reasonable to assume that migraineurs and asymptomatic subjects with a positive FH may share certain traits making them less responsive to CHC. In addition, CHC are prescribed more cautiously in this group and are contraindicated in many cases, making data interpretation difficult. Conjointly, estrogen withdrawal migraine triggered by a placebo week in conventional CHC-regimes should be considered [48]. The fact that migraineurs had significantly more surgery in our population (despite having less severe rASRM scores) is consistent with insufficient medical symptom control.

A **FH for depression** correlated with both personal history of depression and for migraine, supporting a bidirectional comorbidity [24,49]. Women with FH for depression had lower rASRM scores and less endometrioma, but tended to report more symptoms at present and more dysmenorrhea. This is in line with the knowledge that depression and chronic pain may aggravate symptom severity; endometriosis patients with depression or psychiatric conditions have a high prevalence of pain symptoms [50]. It is assumed that the occurrence and development of pain and depression are associated with some identical neuroplasticity changes [51]. For treating endometriosis-associated pain, it is helpful to know that the majority of these women responded very well to CHC.

Strengths of our study include the large number of included individuals as well as the fact that all patients were surgically explored, resulting in a histologically proven diagnosis and solid documentation of the disease extent. The interviews were conducted by health care professionals, which allowed for clarifications and focused follow-up questions. The interview questions had previously been validated in test interviews. Besides endometriosis, we were able to collect data for additional frequently occurring conditions, allowing for broad insights and comparisons of endometriosis patient's disease characteristics with regards to their familial profile. Collecting family medical history data, particularly when it's provided by a third party and not the affected patient themselves, raises ethical concerns related to consent, accuracy, and privacy. Maintaining the accuracy of this second-hand information and safeguarding the privacy of both the patient and their family members is essential to address these ethical considerations. In our study, we upheld all required ethical standards by anonymizing and encrypting all data, ensuring stringent data protection in compliance with the Swiss Human Medicine Act. Regarding confounders, it is worth highlighting that in our study, nearly 80 % of the patients did not use hormonal contraception, while approximately 10 % employed amenorrhea-inducing preparations. This distribution is expected to enhance the reliability and generalizability of our findings.

Several shortcomings and/or biases may be considered. In this cross-

Table 3
Significant Odd's ratios for positive family histories and certain symptoms/findings. CHC: Combined hormonal contraceptives; EMP: Early menopause; FH: Family history.

Family History	Symptoms/Findings	OR	95 % CI
FH Endometriosis	rASRM 3 + 4	2.74	1.16–6.49
FH Endometriosis	Endometrioma	2.7	1.22–5.95
FH Migraine	Personal history of migraine	3.18	1.94–5.23
FH Migraine	Endometriosis symptoms responding to CHC	0.469	0.27–0.82
FH EMP	Current presence of any endometriosis symptom symptoms	3.72	1.67–8.30
FH EMP	Current presence of dysmenorrhea	2.13	1.04–4.35
FH EMP	Dysmenorrhea score 2–3	2.32	1.14–4.74
FH EMP	>5 Days of acyclic pain	3.58	1.72–7.44
FH Depression	Endometriosis symptoms responding to COC	2	1.15–3.48
FH Depression	Personal history of depression	3.04	1.89–4.89
FH Depression	Personal history of migraine	1.66	1.01–2.73
FH Depression	rASRM 3 + 4	0.63	0.39–0.99
FH Depression	Endometrioma	0.58	0.37–0.92

sectional study, it is important to note that causation cannot be determined due to its observational design, and further research is needed to explore causal relationships. While we consider the sample size of 344 individuals reasonable within the study's specific context, the single-center nature of the research introduces potential limitations. The findings may not be readily generalizable to a broader population or more diverse patient groups, given the inherent biases and characteristics associated with a single-center study design. A multicenter study with access to family members' health records would enhance generalizability by including a more diverse patient population, improve the study's external validity and lead to more robust and widely applicable findings. Some predictor variables are subjective or prone to misclassification. Recall bias is a notable concern when patients are required to remember family medical history and past symptoms. We tried to minimize this with interviews involving highly specific questioning, and there was an opportunity to address open-ended questions in a follow-up phone call. Part of the personal medical information (such as the response to a treatment) are strongly subjective and could be inaccurate when being recalled years after the event. We didn't have access to the medical records of the affected family members, and not all details about the own FH may be known to the patient. While the occurrence of depression, migraine and even endometriosis may be apparent, early menopause is possibly more obscure and less of a talk-topic and therefore could be present more frequently than reported. Other circumstances as the historically lower diagnosis rates of conditions like endometriosis could lead to underreporting, potentially affecting the accuracy of our findings.

This study has clinical implications, as it underscores the importance of physicians routinely gathering family history, which plays a pivotal role in risk assessment and guiding personalized treatment decisions. This proactive approach not only facilitates early diagnosis and attentive patient follow-up but also enables the development of tailored treatment plans, ultimately enhancing patient care and improving outcomes for individuals living with endometriosis.

In future research, a primary focus should be to thoroughly explore the fundamental mechanisms and causal relationships that underlie the identified associations. This effort is critical for advancing our understanding of how family histories influence endometriosis characteristics and responses to treatment. Achieving this goal necessitates the conduct of both foundational (genetic & molecular) investigations as well as prospective observational and interventional studies.

Conclusions

Endometriosis features differ between patients with a positive FH for endometriosis, migraine, depression, or early menopause compared to those with an unremarkable FH. The presence of these familial conditions leads to variations in rASRM scores, ovarian involvement, symptoms, and responses to combined oral contraceptives among groups. These findings underscore the influence of hereditary or shared environmental factors on endometriosis symptoms and severity. Future research should explore the underlying mechanisms and causal links behind these associations to better understand how family histories impact endometriosis characteristics and treatment responses. Physicians should routinely inquire about family history for early diagnosis, more precise risk assessment, tailored treatment decisions and improved monitoring, ultimately enhancing patient outcomes.

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Key message

Familial predispositions may influence the severity or presentation of endometriosis. In this observational study, we can show that endometriosis patients with a family history for endometriosis migraine, depression and early menopause differ in symptoms and surgical findings when compared to controls.

CRediT authorship contribution statement

Julian Matthias Metzler: Conceptualization, Writing – original draft, Writing – review & editing, Project administration. **Patrick Imesch:** Supervision, Validation, Writing – review & editing. **Hanna Dietrich:** Data curation, Writing – review & editing. **Chiara Knobel:** Data curation, Writing – review & editing. **Lea Portmann:** Data curation, Writing – review & editing. **Maria S. Neumeier:** Writing – review & editing. **Gabriele Susanne Merki-Feld:** Conceptualization, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Trial registration number: NCT04816357, https://clinicaltrials.gov/ct2/show/NCT04816357 (first submitted Mar 22, 2021; first patient enrollment: Mar 25, 2021).

Details of Ethics Approval

The project was authorized on 26th of March 2021 by the cantonal ethics committee of canton Zurich, Switzerland (BASEC-Number 2021-00285). The patients who agreed to participate in this study received an email with information about the project's details and about their rights, especially that they could leave the project at any time. They were also informed about the safety and the encoding of their data. If the women were still interested in participating, they could give consent by answering this email or orally during the prearranged telephone call.

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