Towards individualised contraceptive counselling: clinical and reproductive factors associated with self-reported hormonal contraceptive-induced adverse mood symptoms

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► Additional material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjsrh-2020-200658).

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Received 14 April 2020
Revised 30 November 2020
Accepted 9 December 2020
Published Online First 15 January 2021

To cite: Lundin C, Wikman A, Bixo M, *et al*. *BMJ Sex Reprod Health* 2021;**47**:e1.

ABSTRACT

Objective The study aim was to establish which demographic, clinical, reproductive and psychiatric factors are associated with self-reported hormonal contraceptive (HC)-induced adverse mood symptoms.

Study design We compiled baseline data from two Swedish studies: one cross-sectional study on combined oral contraceptive (COC)-induced adverse mood symptoms (n=118) and one randomised controlled trial on adverse mood symptoms on COC (n=184). Both included women eligible for COC use, aged over 18 years. All women answered a questionnaire on HC use and associated mood problems. The Mini-International Neuropsychiatric Interview (M.I.N.I.) was used to capture mood and anxiety disorders. Women who acknowledged HC-induced adverse mood symptoms, ongoing or previously (n=145), were compared with women without any such experience (n=157).

Results Compared with women without self-reported HC-induced adverse mood symptoms, women with these symptoms were younger at HC start (adjusted odds ratio (aOR) 0.83, 95% CI 0.72 to 0.95), had more often undergone induced abortion (OR 3.36, 95% CI 1.57 to 7.23), more often suffered from an ongoing minor depressive disorder (n=12 vs n=0) and had more often experienced any previous mental health problem (aOR 1.90, 95% CI 1.01 to 3.59).

Conclusions In line with previous research, this study suggests that women with previous or ongoing mental health problems and women who are younger at HC start are more likely to experience HC-induced adverse mood symptoms. Former and current mental health should be addressed at contraceptive counselling, and ongoing mental health disorders should be adequately treated.

Implications This study adds valuable knowledge for identification of women susceptible to HC-induced adverse mood symptoms. It should facilitate the assessment of whether or not a woman has an increased risk of such symptoms, and thus enable clinicians to adopt a more personalised approach to contraceptive counselling.

Key messages

- Women with self-reported hormonal contraceptive (HC)-induced adverse mood symptoms differ from their unaffected peers.
- These women more often report previous or ongoing mental health problems, are younger at HC start, and have more often had an induced abortion.
- The study adds valuable knowledge to the field of characterising women that are more likely to experience HC-induced adverse mood symptoms.

INTRODUCTION

Although the majority of users are satisfied with their hormonal contraceptive (HC), mental health side effects are today the most common reason for cessation in the Nordic countries.[1] Two Scandinavian population-based studies suggest increased risk of mental health side effects, measured as prescription of psychotropic drugs, at least among adolescents.[2 3] However, in these studies, long-acting and

non-oral HCs, such as the levonorgestrel intrauterine device (LNG-IUD) and the contraceptive patch, had the highest risk estimates, ultimately suggesting that factors not strictly dependent on hormonal levels influenced the results.

It is known that some women are more susceptible to adverse mood effects with combined oral contraceptives (COCs), where previous or ongoing mood disorders and specific personality traits seem to exert unfavourable impact.[4 5] Conversely, women with mental health conditions such as premenstrual syndrome (PMS) or premenstrual dysphoric disorder (PMDD) may benefit from COC use.[6]

Since the media tends to highlight the adverse effects of HC, users may be inclined to expect negative experiences.[7] Consequently, women who probably would not develop adverse mood symptoms might refrain from using effective contraception.

One review identified the need for additional research, specifically aimed at identifying subgroups of women susceptible to adverse mood effects,[8] and experts in the field have emphasised the need for more personalised contraceptive counselling.[9]

The purpose of the study was to establish which sociodemographic, clinical, reproductive and psychiatric factors are associated with self-reported HC-induced adverse mood symptoms.

METHODS

Participants

Data for this study were compiled from two studies, using the same questions to assess experience of HC-induced adverse mood symptoms. Both studies included women with no contraindications for COC use, aged over 18 years, who were recruited by advertisements in newspapers and healthcare centres or on university websites, further described in online supplemental table 1. The first study was a cross-sectional study investigating COC-induced mood disturbances in women with previous or ongoing COC use.[10] It was conducted in the Department of Women's and Children's Health at Uppsala University in 2007. Of 285 women who were screened by telephone, 118 women with different mood reactions to COCs were included in the study. The second study was a randomised controlled trial (RCT) conducted in the Departments of Obstetrics and Gynaecology at seven Swedish hospitals between 2013 and 2015.[11] Of the 224 women attending the screening visit, two women were excluded due to contraindications for COC use. Of the 222 remaining women, 38 women with no previous experience of HCs were excluded, leaving a total of 184 women with different mood reactions to HCs (online supplemental figure 1)

Participants gave written informed consent prior to inclusion. Both studies were approved by the Regional Ethical Review Board in Uppsala. The RCT was registered at the European Union Drug Regulating Authorities Clinical Trials Database (EudraCT) (No. 2013-000925-30).

Table 1 Type and frequency of self-reported hormonal contraceptive-induced adverse mood symptoms.

Mood symptom	Frequency (n=145) (n (%))
Depression	121 (83.4)
Mood swings	105 (72.4)
Irritability	93 (64.1)
Decreased interest in usual activities	46 (31.7)
Anxiety	38 (26.2)
Difficulties concentrating	13 (9.0)
Sleep disturbances	11 (7.6)
Feelings of guilt	11 (7.6)
At least two symptoms	29 (20.0)
Three or more symptoms	93 (64.1)

Data are presented as n (%).
More than one response was possible from each respondent.

Self-reported HC-induced mood symptoms

Women were asked if they had experienced any previous or ongoing HC-induced adverse mood symptoms (yes/no). If so, the woman reported from a list of symptoms those she had experienced (table 1).

Variables

Demographic, reproductive and clinical variables

The women answered a study-specific questionnaire including demographic (eg, education) factors, reproductive history (eg, induced abortion), HC use (type, brand and duration of use for each HC). An open-ended question was used for clinical (ongoing or previous somatic problems) variables and height and weight were measured. Similar questionnaires were used in both substudies, but age at first HC was added in the RCT.

Psychiatric disorders

Presence of psychiatric disorders was evaluated using the Mini-International Neuropsychiatric Interview (M.I.N.I.).[12] The M.I.N.I. evaluates a number of mood disorders (major depressive disorder, dysthymia, bipolar disorder) and anxiety disorders (panic disorder, generalised anxiety disorder, obsessive–compulsive disorder, and social phobia). One subthreshold diagnosis, minor depressive disorder, was also assessed by M.I.N.I. For this diagnosis, at least one core symptom for depression and two additional depressive symptoms were acknowledged.

Daily prospective symptom ratings were used for diagnosing PMS and PMDD in the two substudies. In the cross-sectional study, we used the Cyclicity Diagnoser (CD) scale[13] while the Daily Record of Severity of Problems (DRSP) was used in the RCT.[14] Both scales have been validated for diagnosing PMS/PMDD and

the symptoms assessed by them (eg, anxiety, mood swings and irritability) are essentially the same. Any premenstrual excacerbation in symptoms was established by at least a 50% increase in symptom severity between the follicular phase and the luteal phase. While symptom ratings for at least 2 months is required, our 1-month baseline data serve as provisional PMS or PMDD diagnoses. A detailed description of how provisional diagnosis of PMS, according to International Classification of Diseases 10th Revision (ICD-10) criteria, and PMDD, according to Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5) criteria, were established has been provided previously.[10 11] Twenty-nine women did not complete the daily symptom ratings.

Personality trait scores

The Swedish Universities Scales of Personality (SSP)[15] was used in both substudies for evaluation of personality traits. The SSP comprises 91 items, covering 13 different personality traits such as adventure seeking, social desirability, and mistrust. For the purpose of the present study, the personality trait scores were summed into three personality factors: neuroticism, aggressiveness and extraversion.[15] A detailed description of SSP has been provided previously.[16]

Outcome

Women who reported adverse mood symptoms while on HC (previous or ongoing) were categorised as suffering from self-reported HC-induced adverse mood symptoms.

Statistical analyses

Clinical and demographic variables in the study population were examined by bivariate logistic regression with HC-induced adverse mood as a dependent variable. Independent variables for these analyses were either dichotomised, categorised or entered as continuous variables. The number of variables added in the prediction models were based on the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) Initiative Statement.[17] Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each predictor variable. Categorised predictors included age (<20, 20–24, 25–29 and >30 years) and body mass index (BMI) (<18.5, 18.5–24.99, 25.0–29.99 and ≥30.0 kg/m^2). Parity was dichotomised as nulliparous or parous. The variables smoking, previous induced abortion, repeated induced abortion, use of levonorgestrel-containing pills, use of anti-androgenic pills, previously tested more than two different combined hormonal contraceptives (CHCs), migraine, dysmenorrhoea or endometriosis, and ongoing or previous psychiatric disorders were dichotomised as yes/no. Educational years, age at first hormonal contraceptive use, and the personality factor scores were entered as continuous variables.

Variables in the multiple logistic regression analysis were chosen based on factors previously known to increase either the risk of adverse mood effects of HCs[6 8] or the risk of depression in women.[18 19] Previous induced abortions and use of several types of HCs were not considered in the model as these variables may be regarded as outcomes of HC-induced adverse mood. In order not to lose power in the multiple logistic regression model, data for participants where no information on PMDD were available was imputed. Thus, women lacking information about PMDD diagnosis (n=29) were categorised as not suffering from PMDD. As information on age at HC start was only available for 183 women, that is, the women participating in the RCT (except one woman where these data were missing), this variable was entered in a second model.

The SPSS statistical package (IBM, Armonk, NY, USA) was used for the analyses. P values <0.05 were considered statistically significant.

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of the research.

RESULTS

Of the 118 women included in the cross-sectional study, 61 women reported adverse mood symptoms from current or previous COC use. Of the 184 women from the RCT, 84 women acknowledged a history of self-reported HC-induced adverse mood symptoms. In all, 145 (48%) women acknowledged HC-induced adverse mood symptoms (online supplemental figure 1).

Compared with women with no self-reported HC-induced adverse mood symptoms, women with self-reported HC-induced adverse mood symptoms were younger when they started using HC and had more often used more than two different HCs, including CHCs with anti-androgenic progestins (table 2). Women with previous HC-induced adverse mood symptoms had more often undergone an induced abortion compared with the remaining women (OR 3.36, 95% CI 1.57 to 7.23) (table 2).

No differences regarding age, parity, BMI, educational years, smoking, somatic indication for HC use or duration of HC use were evident (table 2).

Among the self-reported HC-induced adverse mood symptoms, depression, mood swings and irritability were the most common (table 1).

Compared with women with no self-reported HC-induced adverse mood symptoms, women with self-reported HC-induced adverse mood symptoms more often suffered from an ongoing minor depressive disorder (n=12 vs n=0) (table 1) and more often had a history of any mental health problem (adjusted

Table 2 Demographic, reproductive and clinical variables among women with and without self-reported hormonal contraceptive-induced adverse mood symptoms

	Self-reported HC-induced adverse mood symptoms			
Variable	**Yes (n=145)**	**No (n=157)**	**OR (95% CI)**	**P value**
Age (years) (n (%))				
<20	9 (6.2)	7 (4.5)	1.65 (0.49 to 5.54)	0.415
20–24	58 (40.0)	74 (47.1)	1.01 (0.46 to 2.20)	0.985
25–29	64 (44.1)	58 (36.9)	1.42 (0.65 to 3.11)	0.382
>30	14 (9.7)	18 (11.5)	1	
Parous (n (%))	15 (10.3)	9 (5.7)	1.90 (0.80 to 4.48)	0.144
Induced abortion (n (%))	27 (18.6)	10 (6.4)	3.36 (1.57 to 7.23)	0.002
Repeated induced abortion, n (%)	9 (6.3)	3 (1.9)	3.40 (0.90 to 12.80)	0.071
BMI (kg/m^2) (n (%))				
<18.5	9 (6.2)	12 (7.6)	0.80 (0.33 to 1.97)	0.628
18.5–24.99	119 (82.1)	127 (80.9)	1	
25.0–29.99	14 (9.7)	16 (10.2)	0.93 (0.44 to 2.00)	0.860
>30	3 (2.1)	2 (1.3)	1.60 (0.26 to 9.75)	0.610
Smoking (n (%))	12 (8.3)	9 (5.8)	1.74 (0.73 to 4.14)	0.215
Educational years (mean±SD)	14.7±2.3	15.0±2.0	0.93 (0.84 to 1.04)	0.207
Age at start of contraceptive use* (years) (median (IQR))	16 (15–18)	17 (16–19)	0.82 (0.72 to 0.93)	0.003
Duration of HC use (months) (mean±SD)	50±43	53±38	1.00 (0.99 to 1.00)	0.530
Previous use of more than two CHCs (n (%))	36 (24.8)	9 (5.7)	5.43 (2.51 to 11.74)	<0.001
Previous use of LNG-containing pill	108 (74.5)	109 (69.4)	1.29 (0.78 to 2.30)	0.330
Previous use of anti-androgenic pill	63 (43.4)	47 (29.9)	1.80 (1.12 to 2.89)	0.015
Migraine (n (%))	6 (4.1)	11 (7.0)	0.57 (0.21 to 1.59)	0.285
Dysmenorrhoea or endometriosis (n (%))	26 (17.9)	20 (12.7)	1.50 (0.80 to 2.82)	0.212

Data are presented as n (%) or median (IQR).
Anti-androgenic pills contain either drospirenone, cyproterone acetate or desogestrel.
Statistical analyses by logistic regression.
*Information available for 183 women. Percentages are given in relation to available responses, missing values in 1.0%–2.6% of cases.
BMI, body mass index; CHC, combined hormonal contraceptive; CI, confidence interval; HC, hormonal contraceptive; IQR, interquartile range; LNG, levonorgestrel; ;OR, odds ratio; SD, standard deviation.

odds ratio (aOR) 1.90, 95% CI 1.01 to 3.59) (table 3). Presence of probable PMS and PMDD were equally common in the groups, and no difference regarding the three major personality factors was noted (table 3).

Background factors associated with self-reported HC-induced adverse mood symptoms are depicted in table 4. Having had any previous mental health problem was the only significant factor in this cohort of women (table 4). In the second model, any previous mental health problem and age at start of HC use were both significantly associated with self-reported HC-induced adverse mood symptoms. In this analysis, later start of HC use was a protective factor against adverse mood (aOR 0.83, 95% CI 0.72 to 0.95) and previous mental health problems remained a risk factor (aOR 1.90, 95% CI 1.01 to 3.59).

DISCUSSION

This study demonstrates that self-reported HC-induced adverse mood symptoms are more common in women with previous or ongoing mental health problems and in women who start taking HC at an earlier age. Furthermore, women with self-reported HC-induced adverse mood symptoms had more often had an induced abortion.

Our findings are in line with previous data suggesting that women with mental health problems more often report HC-induced adverse mood effects.[5] This also fits well with the understanding that some women with mental health problems seem more susceptible to variations in endogenous hormone levels. For instance, among treatment-seeking women with major depressive disorder (MDD), two-thirds reported premenstrual exacerbation of depressive symptoms.[20]

Conversely, a number of previous studies suggest beneficial effects of HCs on mental health conditions like PMS and PMDD, especially for certain COCs.[21] However, while CHCs have been tried for treatment of premenstrual breakthrough of MDD, results are thus far not convincing.[22]

Table 3 Ongoing and previous mental health problems and personality trait scores among women with and without self-reported hormonal contraceptive-induced adverse mood symptoms.

	Self-reported HC-induced adverse mood symptoms			
Parameter	**Yes (n=145)**	**No (n=157)**	**OR (95% CI)**	**P value**
Ongoing mental health problems (n (%))				
Any premenstrual disorder	28 (20.6)	22 (15.8)	1.38 (0.74 to 2.55)	0.307
Premenstrual syndrome	17 (13.6)	16 (12.0)	1.15 (0.55 to 2.39)	0.706
Premenstrual dysphoric disorder	11 (8.1)	6 (4.3)	1.95 (0.70 to 5.43)	0.201
Any mood disorder	15 (10.3)	7 (4.5)	2.47 (0.98 to 6.25)	0.056
Minor depressive disorder	12 (8.3)	0	NC	<0.000
Major depressive disorder	3 (2.1)	3 (1.9)	NC	1.000
Bipolar disorder	0	4 (2.5)	NC	0.124
Any anxiety syndrome	15 (10.3)	13 (8.3)	1.28 (0.59 to 2.79)	0.537
Panic disorder	2 (1.4)	1 (0.6)	NC	0.609
Generalised anxiety disorder	7 (4.8)	3 (1.9)	NC	0.204
Obsessive–compulsive disorder	1 (0.7)	3 (1.9)	NC	0.624
Social phobia	7 (4.8)	7 (4.5)	NC	0.879
Previous mental health problems (n (%))				
Any previous mental health problem*	79 (54.5)	58 (36.9)	2.04 (1.29 to 3.24)	0.002
Minor depressive disorder	25 (17.2)	16 (10.2)	1.84 (0.94 to 3.60)	0.077
Major depressive disorder	49 (33.8)	41 (26.1)	1.44 (0.88 to 2.37)	0.146
Panic disorder	18 (12.4)	16 (10.2)	1.25 (0.62 to 2.55)	0.542
Personality trait scores (mean±SD)				
Neuroticism factor	290±39	285±40	1.00 (0.99 to 1.01)	0.285
Adventure-seeking factor	55±19	54±20	1.00 (0.99 to 1.01)	0.682
Aggressiveness factor	96±27	94±27	1.00 (0.99 to 1.01)	0.684

Data are presented as n (%) or mean±SD.
Percentages are given in relation to available responses, missing values in 8.9%–9.3 % in terms of premenstrual disorders.
Statistics are by logistic regression or, in the case of small numbers, Fisher's exact test.
*Previous mental health problems as assessed by the Mini-International Neuropsychiatric Interview (M.I.N.I.) interview.
CI, confidence interval; HC, hormonal contraceptive; NC, not calculated; OR, odds ratio; SD, standard deviation.

The mechanisms behind the increased reporting of HC-induced adverse mood symptoms in women with previous or ongoing mental disorders is unknown. It has been hypothesised that major depressive episodes may lead to permanent residual psychosocial and cognitive impairments often referred to as the 'scar

Table 4 Multivariable logistic regression analyses on independent variables associated with self-reported hormonal contraceptive-induced adverse mood symptoms

	Model 1* (n=297)		Model 2† (n=179)	
Variable	**aOR (95% CI)**	**P value**	**aOR (95% CI)**	**P value**
Parity	0.52 (0.21 to 1.27)	0.151	0.54 (0.18 to 1.61)	0.266
Smoking	1.48 (0.60 to 3.63)	0.399	2.67 (0.77 to 9.24)	0.122
Educational years	0.93 (0.83 to 1. 04)	0.193	0.98 (0.85 to 1.13)	0.786
Dysmenorrhoea or endometriosis	1.28 (0.66 to 2.47)	0.470	0.70 (0.28 to 1.76)	0.450
Premenstrual dysphoric disorder	1.85 (0.64 to 5.32)	0.255	1.21 (0.37 to 3.97)	0.751
Any previous mental health problem	1.97 (1.23 to 3.18)	0.005	1.90 (1.01 to 3.59)	0.047
Any ongoing mood disorder	2.26 (0.86 to 5.86)	0.092	0.45 (0.17 to 1.77)	0.253
Age at first HC use			0.83 (0.72 to 0.95)	0.009

*Model 1 included parity, smoking, educational years, dysmenorrhoea or endometriosis, premenstrual dysphoric disorder, any previous mental health problem, any ongoing mood disorder.
†Model 2 included all variables of Model 1, but also age at first HC use. This variable was only available for 179 women.
aOR, adjusted odds ratio; CI, confidence interval; HC, hormonal contraceptive.

hypothesis', whereas others have proposed that these women may have had certain characteristics from the outset that made them vulnerable to depression, that is, the 'vulnerability hypothesis'.[23 24] Such scars, or vulnerabilities, may also be manifested by disruption of the hypothalamus-pituitary-adrenal (HPA) axis as higher cortisol awakening response and lower evening cortisol in patients who have recovered from depression have been detected.[25 26] Activation and inhibition of the HPA axis is central to the response and adaption to stress, and previous studies suggest an association between chronic stress and development of affective disorders.[27]

Potentially, similar scars or vulnerabilities exist in the hypothalamus-pituitary-gonadal (HPG) axis. Approximately 5% of women of childbearing age suffer from PMDD and about 10% develop depression postpartum, both periods in which changes in sex hormone levels are evident.[6 28] Ovarian hormones and their metabolites exert several effects in the central nervous system, and receptors are expressed in, for example, the amygdala and prefrontal cortices, which are areas of the brain involved in emotional and cognitive regulation.[29] Estrogen, among other routes of action, decreases monoamine oxidase and thereby acts as a positive modulator of serotonergic transmission.[30] Progesterone may enhance or counteract the estradiol-induced effects on serotonergic neurotransmission, and has multiple actions mediated via classic and membrane-bound receptors.[31 32] In all, evidence suggests that ovarian hormones affect emotional and cognitive control.

Alternatively, the mechanism in these susceptible women could be that HCs influence the HPA axis. Elevated stress responsivity, measured as higher salivary cortisol response and increased heart rate during a social stress test, was reported in women using a LNG-IUD compared with women using CHC and naturally-cycling women.[33] In contrast, a blunted response to the same stress test, measured as salivary free cortisol levels, was shown in women on CHC compared with naturally cycling women.[34] Whether this reflects an hyporeactive HPA axis in CHC-using women, or if it corresponds to the CHC-induced increase of corticosteroid-binding globulin, remains unclear.

Women who reported HC-induced adverse mood symptoms started HC at a younger age. This is similar with previous studies that found the strongest associations between HC use and need for antidepressant treatment in the youngest cohorts.[2 3] Whether younger women are more vulnerable regarding exogenous steroid hormones exposure, or if there is something that distinguishes women who are young when they start HC compared with their older peers, calls for more research. One interpretation might be that girls in need of contraception at a younger age are subject to a more vulnerable life situation. Low socioeconomic status and smoking are two factors associated with young age at coitarche.[35] Alternatively, these young women might suffer from medical conditions and may have started HCs not primarily for contraceptive reasons. Medical conditions commonly treated with HC, such as acne, are independent risk factors for depressive symptoms.[36] Thus, the results should be interpreted with a possible confounding by indication in mind.

Women who reported previous HC-induced adverse mood symptoms had more often undergone induced abortion compared with women with no previous HC-induced adverse mood symptoms. Women who discontinue HC due to mental health problems often turn to less effective contraceptive methods, rendering them susceptible to unplanned pregnancies.

Since mental health problems are associated with HC-induced adverse mood effects, our study elucidates the need for careful contraceptive counselling to certain subsets of women in order to limit cessation or inconsistent use.

Our study is strengthened by the detailed phenotyping of the participants. The major limitation is the cross-sectional design, from which we are unable to draw any causality conclusions.

The concept of HC-induced adverse mood symptoms is based on self-report, which also opens up for problems with causality assessments. What women perceive as being associated with their HC use may in fact be triggered by other causes.

Finally, the results should be interpreted bearing a potential selection bias in mind as women with more severely impaired mental health might not have had the capacity to sign up for recruitment.

CONCLUSIONS

Our study suggests that women with previous or ongoing mental health problems and women who are younger at HC start are more susceptible to experiencing HC-induced adverse mood symptoms. A careful assessment of the HC-seeking woman should be carried out during contraceptive counselling, and their former and current mental health should be evaluated.

Correction notice This article has been corrected since it first published. The provenance and peer review statement has been included.

Contributors Study conception, planning, design and conduct: CL, ISP. Data interpretation: CL, AW, ISP. Statistical analysis: CL, ISP. Drafting of the manuscript: CL, ISP. Critical revision of the manuscript: CL, AW, MB, KGD, ISP.

Funding The Swedish Research Council (K2013-99X-22269-01-3) and the Family Planning Foundation supported this study.

Disclaimer No support was obtained from any pharmaceutical company. The funding source was not involved in the design of the study, the collection, analysis and interpretation of data, in the writing of the report or the decision to submit the article for publication.

Competing interests MB serves occasionally as medical advisor for Asarina Pharma. KGD reports honorarium for lectures from MSD/Merck, Bayer AG, Gedeon Richter, Exeltis, Azanta, HRA-Pharma, Mithra and Exelgyn, and her clinic has participated in clinical trials conducted by Exeltis, Mithra, Bayer, MSD,

Removaid and Myovant. Over the past 5 years, ISP has served occasionally on advisory boards or acted as an invited speaker at scientific meetings for MSD, Bayer Health Care, Gedeon Richter, Peptonics, Shire/Takeda and Lundbeck A/S.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement As far as is practicable, data will be available upon reasonable request from the corresponding author.

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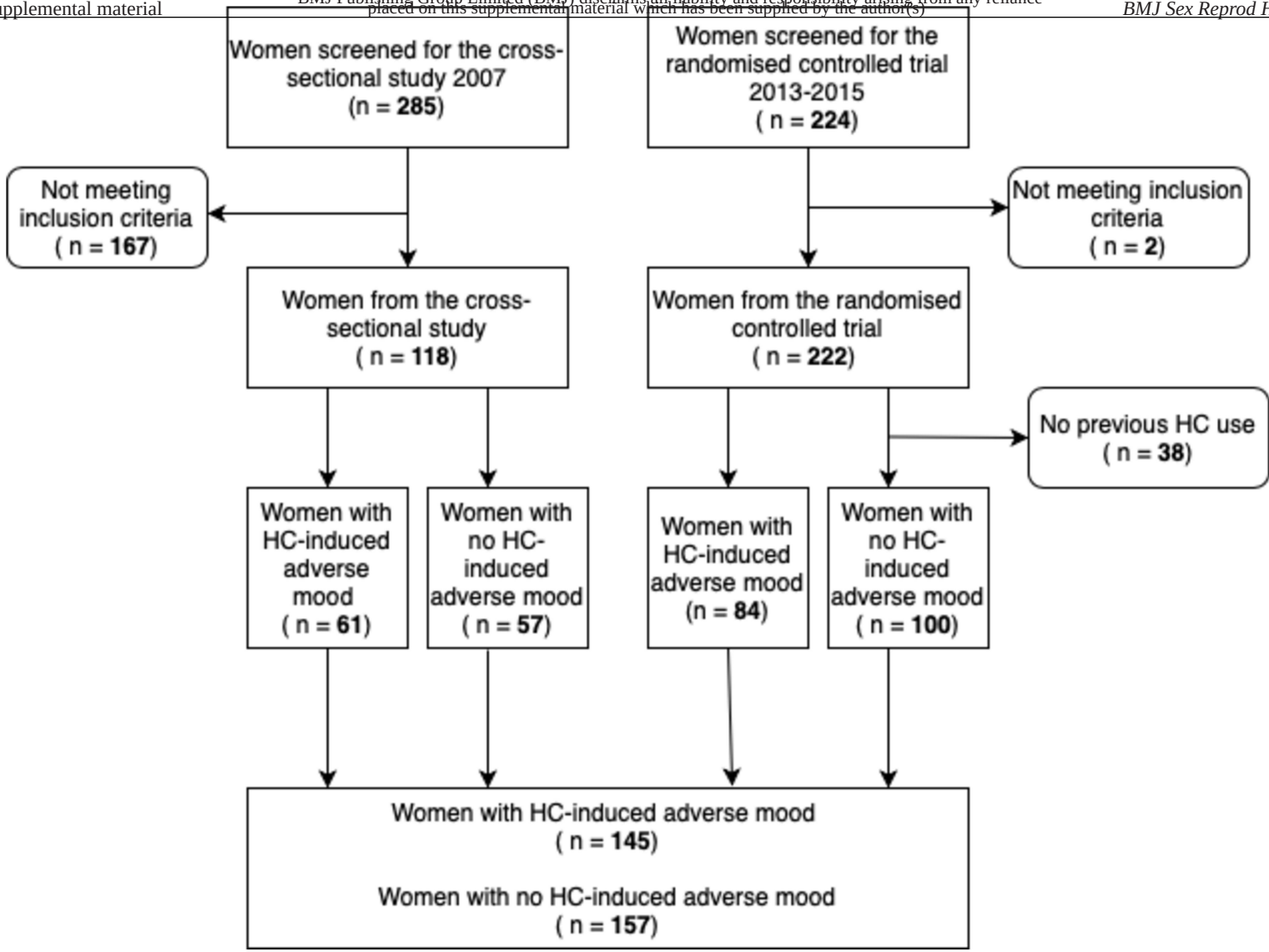
Women screened for the cross-sectional study 2007 (n = 285)
Women screened for the randomised controlled trial 2013-2015 (n = 224)
Not meeting inclusion criteria (n = 167)
Not meeting inclusion criteria (n = 2)
Women from the cross-sectional study (n = 118)
Women from the randomised controlled trial (n = 222)
No previous HC use (n = 38)
Women with HC-induced adverse mood (n = 61)
Women with no HC-induced adverse mood (n = 57)
Women with HC-induced adverse mood (n = 84)
Women with no HC-induced adverse mood (n = 100)
Women with HC-induced adverse mood (n = 145)
Women with no HC-induced adverse mood (n = 157)

Supplementary table 1. Demographic, reproductive and clinical variables among women from the two included sub-studies.
Data presented as n (%) or median (interquartile range).

	Substudy 1[a] (n = 118)	**Substudy 2[b] (n = 184)**	**p**
Age			0.001
< 20 years, n (%)	1 (0.8)	15 (8.2)	
20-24 years, n (%)	50 (42.4)	82 (44.6)	
25-29 years, n (%)	60 (50.8)	62 (33.7)	
>30 years, n (%)	7 (5.9)	25 (13.6)	
Parous, n (%)	6 (5.1)	18 (9.8)	0.141
Induced abortion, n (%)	10 (8.5)	27 (14.7)	0.109
Repeated induced abortion, n (%)	3 (2.5)	9 (4.9)	0.378
BMI			0.906
<18.5 kg/m^2, n (%)	9 (7.6)	12 (6.5)	
18.5 – 24.99 kg/m^2, n (%)	97 (82.2)	149 (81)	
25.0 – 29.99 kg/m^2, n (%)	10 (8.5)	20 (10.9)	
>30 kg/m^2, n (%)	2 (1.7)	3 (1.6)	
Smoking, n (%)	9 (7.6)	14 (7.8)	0.962
Educational years, mean ± SD	14.94 ± 2.1	14.81 ± 2.2	0.604
Age of start of contraceptive use, median (IQR)	-	16 (15 -18)	
Duration of HC use, months, mean ± SD	40 ± 35	55 ± 41	0.008
Previous use of more than 2 CHCs, n (%)	20 (16.9)	25 (13.6)	0.423
Previous use of LNG-containing pill, n (%)	96 (81.4)	121 (65.8)	0.003
Previous use of anti-androgenic pill, n (%)	51 (43.2)	59 (32.1)	0.049
Migraine, n (%)	12 (10.2)	5 (2.7)	0.006
Dysmenorrhea or endometriosis, n (%)	21 (17.8)	25 (13.6)	0.321

[a] = the cross-sectional study, carried out in 2007. [b] = the randomised controlled trial, carried out in 2013-2015.
Percentages given in relation to available responses, missing values in 1.0 – 2.6% of cases. BMI = Body Mass Index; CHC = Combined hormonal contraceptive; CI = confidence interval; HC = hormonal contraceptive; IQR = interquartile range; LNG = levonorgestrel; SD = standard deviation.
Anti-androgenic pills contain either drospirenone, cyproterone acetate or desogestrel.
P-values according to chi-square test or, in case of less then five values, Fisher's Exact test.