Menstrual migraine in the general population -prevalence, clinical characteristics and classification

Dissertation for the degree philosophiae doctor (PhD) at the University of Oslo

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Kjersti Grøtta Vetvik

Abbreviations

CHC	Combined Hormonal contraception
CI	Confidence Interval
DMPA	Depot Medroxyprogesterone Acetate
FSH	Follicle Stimulating Hormone
GnRH	Gonadotropin-Releasing Hormone
ICC	Intraclass Correlation
ICHD	International Classification of Headache Disorders
LH	Luteinizing Hormone
LNG-IUS	Levonorgestrel Intrauterine System
MA	Migraine with aura
MM	Menstrual Migraine
MO	Migraine without aura
NPV	Negative Predictive Value
NRS	Numeric Rating Scale
NSAIDs	Non-Steroidal Anti-inflammatory Drugs
OR	Odds Ratio
PPV	Positive Predictive Value

1. Summary

During the reproductive years, migraine is two to three times more prevalent in women compared to men. This sex difference may, at least in part, be due to the cyclic changes in female sex hormones and a subset of female migraineurs recognizes menstruation as the most important trigger of attacks. In 2004, formal diagnostic criteria for menstrual migraine were published in the appendix of the International Classification of Headache Disorders 2nd edition (ICHD II). Menstrual migraine was defined as attacks of migraine without aura occurring on the days centering on the first day of the menstrual bleeding, i.e. day -2 to +3, in at least two out of three consecutive menstrual cycles. In the revised version from 2013 (ICHD III beta), a requirement of prospective headache diaries over three menstrual cycles was added in order to confirm the diagnosis. This was based on previous studies reporting that women tend to over report menstrual migraine by self-assessment. The diagnosis is still placed in the appendix because it is considered as insufficiently validated. Most previous studies on menstrual migraine are conducted in clinic populations, and no studies have previously used the ICHD criteria in the general population. The purpose of the present study was to investigate prevalence and characteristics in menstrual migraine in the general population.

This thesis is based on four original research papers from a population-based study on menstrual migraine. The participants were recruited by questionnaires mailed to 5000 women aged 30-34 years from the general population and women with self-reported menstrual migraine were invited to a clinical interview and examination at Akershus University Hospital. Subsequently, the women were instructed to complete a headache- and menstruation diary for three consecutive menstrual cycles.

Among 308 eligible women who self-reported migraine in at least half of their menstruations by questionnaire, 237 (77%) participated in the interview. The lifetime prevalence of menstrual migraine was 17.6% among female migraineurs and 6.1%

among all women. Only one out of seven women experienced migraine exclusively in relation to menstruation.

The headache diary was returned by 123 (52%) women. A substantial agreement between menstrual migraine diagnoses given by interview versus those given by diaries was found (Kappa 0.62).

The characteristics of menstrual and non-menstrual attacks of migraine without aura were compared among the 56 women with a prospectively confirmed diary-diagnosis of menstrual migraine. In these women, menstrual attacks lasted on average nearly 11 hours longer, were significantly more often associated with severe nausea, and were on average treated with 1.4 more doses of symptomatic drugs than non-menstrual attacks. In contrast, no differences between menstrual and non-menstrual attacks were found among the 25 women who had migraine without aura but who did not fulfil the diagnostic criteria for menstrual migraine.

The clinical interview included questions about the course of migraine during use of current hormonal contraception. Women with a history of menstrual migraine who developed contraception-induced amenorrhoea were more likely to report a reduction in their total migraine frequency compared women with a history of menstrual migraine who were not amenorrhoeic.

Conclusion: Menstrual migraine occurs in about one fifth of female migraineurs in the general population and in these women, menstrual attacks are associated with more severe symptomatology than non-menstrual attacks. The diagnosis can be made by a physician's semi-structured interview and diaries should only be required in specific cases. Hormonal contraception that induces amenorrhoea might be beneficial in women with menstrual migraine.

2. Publications included

This thesis is based on the following publications, referred to in the text by their Roman numerals. All articles are reproduced with permission.

Paper I: Vetvik KG, MacGregor EA, Lundqvist AC, Russell MB.
Prevalence of menstrual migraine without aura: A population-based study. Cephalalgia. 2014 Apr; 34 (4): 280-8.

Paper II: Vetvik KG, MacGregor EA, Lundqvist C, Russell MB.
A clinical interview versus a prospective headache diary in the diagnosis of menstrual migraine without aura
Cephalalgia. 2014. Epub 2014/08/22.

Paper III: Vetvik KG, Šaltytė-Benth J, MacGregor EA, Lundqvist C, Russell MB.
Clinical characteristics of menstrual and non-menstrual attacks of migraine without aura in women with and without menstrual migraine
Submitted October 15, 2014

Paper IV: Vetvik KG, MacGregor EA, Lundqvist C, Russell MB.
Contraception-induced amenorrhoea leads to reduced migraine frequency in women with menstrual migraine without aura
J Headache Pain. 2014;15:30.

3. Introduction

3.1 Migraine

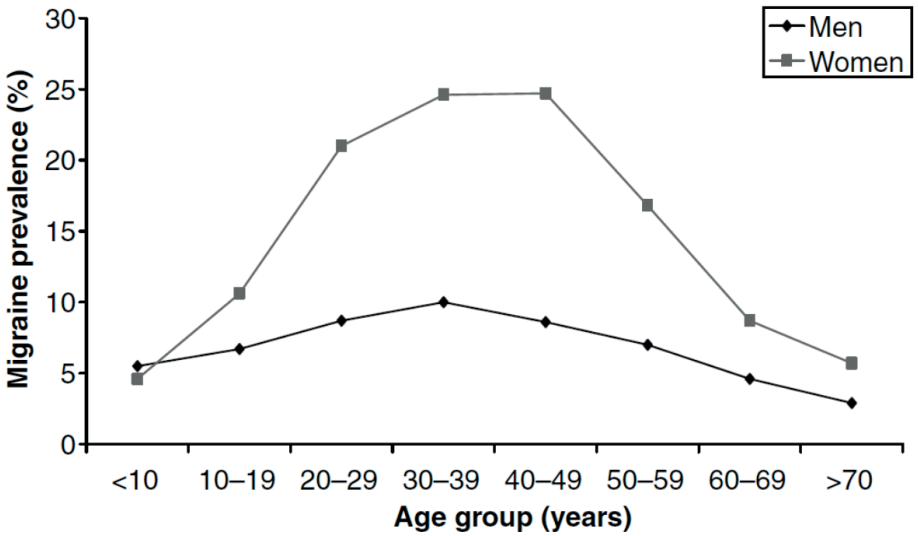
Headache is the most prevalent neurological symptom and is experienced by over 90% of the general population at some point in life [1, 2]. More than 300 different types of headaches are described in the worldwide used classification system of headache disorders; The International Classification of Headache Disorders (ICHD). The ICHD divides headaches into primary and secondary forms [3]. The primary headaches are disorders in their own right, whereas the secondary forms are typically attributed to another disorder, injury or to a substance and/or its withdrawal. The two most common presentations of primary headaches are tension-type headache and migraine with a worldwide one-year prevalence of 42% and 11%, respectively [4].

Migraine is divided into two major subtypes; migraine with and without aura [3]. The most common type, migraine without aura (MO), is characterized by recurrent attacks of unilateral throbbing headache of moderate to severe intensity, associated with nausea, vomiting, photo-, and/or phonophobia. This type of migraine is the main focus in this thesis and will be detailed later. Migraine with aura (MA) affects up to one-third of all migraineurs and is primarily characterized by the transient (5-60 minutes duration) focal neurological symptoms (i.e. visual, sensory, speech, motor or brainstem symptoms) that precede or accompany the headache [5, 6]. MA is divided into several subtypes according to the neurological symptoms, type of headache (migrainous or non-migrainous) and whether headache is present or not [3].

Although migraine is a benign disorder, it often heavily affects work and social functioning and reduces the overall quality of life [2, 7]. According to the Global Burden of Disease study from 2010, migraine is the third most prevalent disorder worldwide and the seventh-highest specific cause of years lived with disability [8]. Migraine is also the most costly neurological disorder in the European community, costing more than 27 billion Euros per year [9].

The prevalence of migraine is similar among sexes until puberty [10]. During the reproductive years, it is predominantly a female disorder with a male to female prevalence ratio 1:2-3 [4, 11]. The prevalence of migraine in women peaks during the third and forth decade followed by a gradual decline, particularly following the menopause (Figure 1). Similar figures are observed for men, but the rise and decline are more gradual.

Figure 1. *Last-year prevalence of migraine by sex and age. Reprinted with permission from* [13].



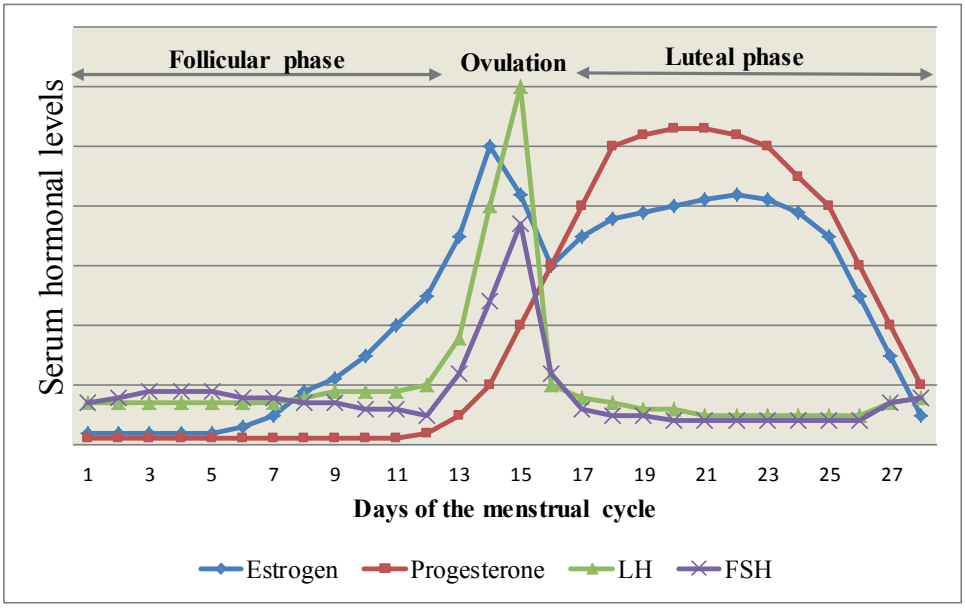
The global lifetime prevalence of migraine is 22% in women and 10% in men. These figures vary across the continents and are highest in Northern America and Europe, while they are lower in Asia and Africa [4, 12]. In Europe, the lifetime prevalence is 16-33% among women and 6-22% in men [13]. Figures from USA indicate that 43% of all women and 18% of men will experience migraine at some time during their lifetime, most before age of 35 years [14]. In addition to the higher prevalence, most studies support the finding that women experience a greater symptomatology and migraine related disability than men [15-17].

The exact mechanism for these sex differences is not fully understood, but female reproductive hormones are considered to play a significant role. The ovarian hormones estrogen and progesterone exert effects on various neurotransmitter systems which are thought to be involved in the pathophysiology of migraine; the serotonergic, noradrenergic, glutamatergic, GABAergic and opioidergic systems [18]. The activity of these systems varies with the levels of ovarian hormones [18, 19].

3.2 The menstrual cycle

The menstrual cycle represents a complex neuroendocrinologic event involving the hypothalamus, the pituitary gland, and the ovaries [20]. It can generally be divided into three main phases; the follicular phase, ovulation, and the luteal phase (Figure 2).

Figure 2 *Endocrinology of the female reproductive cycle.*



The follicular phase starts with the first day of menstruation and lasts until ovulation. During this phase, gonadotropin-releasing hormone (GnRH) from the hypothalamus stimulates the pituitary gland to secrete follicle-stimulating hormone (FSH), which in turn stimulates the development of several follicles in the ovaries.

One of these follicles becomes the dominant and ultimately ovulatory follicle during that cycle, while the others regress. The developing follicles produce estrogens which inhibit further FSH-release from the pituitary gland (negative feed back) and stimulate the release of luteinizing hormone (LH). At the time of ovulation, the mature follicle ruptures and releases the mature ovum as a response to a surge of LH. During the luteal phase, the follicle, now called corpus luteum secretes progesterone and a second rise of estrogen, which prepares the endometrium for fertilization. The high concentrations of these hormones inhibit further secretion of FSH and LH from the pituitary gland. If the ovum is not fertilized, corpus luteum rapidly degenerates 9-11 days after ovulation and the concentrations of estrogen and progesterone fall. The withdrawal of progesterone results in the menstrual bleeding.

The average duration of a menstrual cycle is 28 days, i.e. the period from the first day of one menstrual bleed to the first day of the next. Variations in menstrual cycle lengths are primarily due to changes in the follicular phase, while the luteal phase remains relatively constant (about 14 days). There is little cycle variability among women between the ages of 20 and 40 years. In comparison, significantly more variability is observed during the first 5-7 years after menarche and for the last 10 years before cessation of menses, which occurs at an average of age 51years [21, 22].

3.3 Menstrual migraine

During the normal menstrual cycle, the activity of the neurotransmitter systems which are thought to be involved in the migraine pathophysiology varies. Concomitant with the decline of estrogen and progesterone levels in the late luteal phase, inhibitory systems are at their nadir [18]. Throughout the reproductive years, menstruation is one of the most significant events related to the occurrence of migraine attacks [23, 24]. Prospective diary studies of female migraineurs consistently report a significant increased risk of MO, but not MA, during the days directly preceding and following the first day of menstruation, i.e. day -2 to +3 of the menstrual cycle (Figure 3) [25-28].

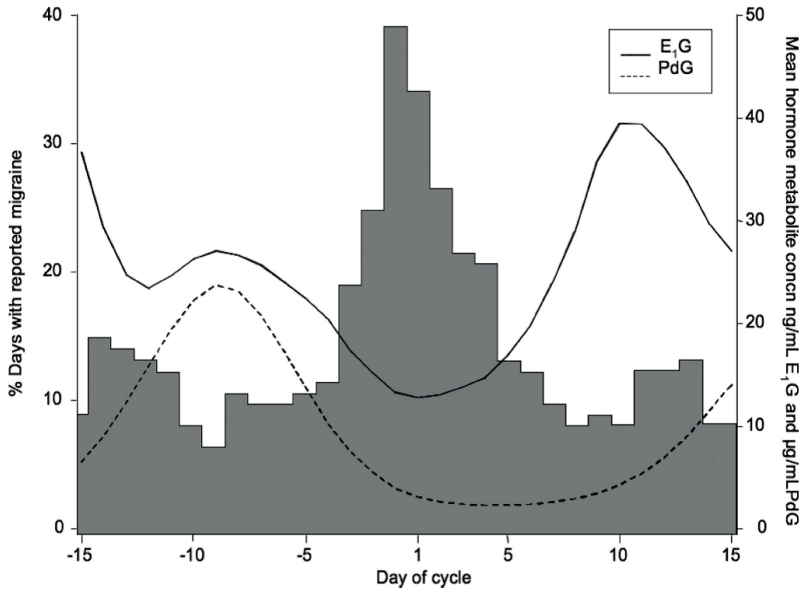


Figure 3. Incidence of migraine, urinary estrone-3-glucuronide (E1G) and pregnanediol-3-glucuronide (PdG) levels on each day of the menstrual cycle in 120 cycles from 38 women. *Reprinted from with permission from* **[28].**

Although many women report an association between ovulation and migraine, no increased risk around the expected time of ovulation has been found [25-28]. Migraine attacks occurring at menstruation are reported to be more painful, longer lasting, and more disabling than attacks at other times of the cycle [28-31], but this is not consistent across all studies [25, 32].

3.3.1 The diagnostic criteria for menstrual migraine

The above described observations contributed to the development of diagnostic criteria for pure menstrual migraine and menstrually-related migraine presented in Table 1 [3]. The main features of the criteria are i) the MO diagnosis, ii) the timing of the attacks, and iii) the frequency of attacks related to menstruation.

Women with pure menstrual migraine have MO attacks occurring exclusively during the specific five-day window, while women with menstrually-related have additional attacks outside the perimenstrual window. The requirement of occurrence in two out of three menstruations was chosen in order to ensure association between migraine and menstruation. Henceforth, the collective term menstrual migraine (MM) is used to cover both subtypes.

The criteria were first published in 2004 in the appendix of the second edition of the ICHD (ICHD II) and were primarily considered as research criteria that needed further validation [33]. In 2013, the revised beta version of the classification was published, the ICHD III beta [3]. The diagnostic criteria for MM remained in the appendix and were unchanged from those presented in ICHD II with one exception; an additional requirement of prospective headache diaries during three consecutive menstrual cycles in order to confirm the diagnosis. This was based on a combination of clinical experience and studies indicating that women tend to over report MM by self-assessment [34-36].

In the main body of ICHD III beta, another hormonal related headache is described: estrogen-withdrawal headache. This diagnosis is defined by headache or migraine developing within five days following cessation of exogenous estrogens that had been taken consistently for at least three weeks. The headache resolves spontaneously within 3 days in the absence of further estrogen [3]. Estrogen-withdrawal headache may well overlap with the criteria for MM, as evidenced by migraine during the hormone free interval of combined hormonal contraceptives [37].

Table 1. *The diagnostic criteria for migraine without aura, pure menstrual migraine and menstrually-related migraine from the International Classification of Headache Disorders 3 beta version (ICHD III beta version)*[*]

1.1 Migraine without aura (MO)

A. At least five attacks fulfilling criteria B-D
B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)
C. Headache has at least two of the following four characteristics:
   1. unilateral location
   2. pulsating quality
   3. moderate or severe pain intensity
   4. aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
D. During headache at least one of the following:
   1. nausea and/or vomiting
   2. photophobia and phonophobia
E. Not better accounted for by another ICHD-3 diagnosis

A1.1.1 Pure menstrual migraine without aura

A. Attacks, in a menstruating woman [1], fulfilling criteria for
   1.1 *Migraine without aura*
B. Attacks occur exclusively on day 1±2 (*i.e.*, days −2 to +3) [2] of menstruation in at least 2 out of 3 menstrual cycle and at no other times of the cycle

A1.1.2 Menstrually related migraine without aura

A. Attacks, in a menstruating woman, fulfilling criteria for
   1.1 *Migraine without aura*
B. Attacks occur on day 1±2 (*i.e.*, days −2 to +3) of menstruation in at least 2 out of 3 menstrual cycles and additionally at other times of the cycle.

Notes:
[1] For the purposes of ICHD-3 beta, menstruation is considered to be endometrial bleeding resulting from either the normal menstrual cycle or from the withdrawal of exogenous progestogens, as in the use of combined oral contraceptives or cyclical hormone replacement therapy.
[2] The first day of menstruation is day 1 and the preceding day is day -1; there is no day 0.

[*]The diagnostic criteria for MO are the same in the ICHD II. The diagnostic criteria for pure and menstrually related migraine are also the same, except the requirement of prospective records.

3.3.2 Pathophysiology of menstrual migraine

Even though formal diagnostic criteria for MM have only existed for 10 years, the association between menstruation and migraine is not a new discovery. In his book *De Hemicrania Menstrua* from 1660, Johannes van der Linden described a particular severe case of one-sided headache associated with nausea and vomiting which occurred monthly in proximity to the menstrual flow [38]. The patient was the Marchioness of Brandenburg.

As described above, the premenstrual phase is characterized by declining plasma levels of estrogens and progesterone (Figure 2). From 1970 to 1975 the role of ovarian hormones in the pathophysiology of MM was systematically explored in a small sample of women by the Australian neurologist Somerville [39-42]. He observed that depot-estradiol administered a few days before menstruation prevented menstrual migraine attacks, despite occurrence of menstrual bleeding. In contrast, progestins given during the same time interval only delayed menstruation, while migraine still occurred at time of the expected menstrual flow, as estrogen levels declined. These observations resulted in the estrogen-withdrawal hypothesis, which recognizes the decline in plasma estrogen levels as the trigger of menstrual migraine attacks. However, estrogen levels declines at two points in the menstrual cycle; post-ovulatory and premenstrual, but only the premenstrual decline is associated with migraine. Somerville hypothesized that several days of exposure to high levels of estrogens were necessary before withdrawal of estrogen could result in migraine [43].

The estrogen-withdrawal theory was further supported by a study demonstrating that the incidence of MO was inversely associated with urinary estrogen levels across the menstrual cycle (Figure 3) [28]. In addition, estrogen supplements during the perimenstrual period have been effective in preventing menstrual attacks [44-46], but post-dosing migraine may occur after ending the treatment [46, 47].

Increased occurrence of MO is also associated with other situations of estrogen-withdrawal, such as the days directly postpartum [48-50] and during the hormone-free interval in women using combined hormonal contraception [37, 51]. This may

additionally indicate that ovulation is not a necessary precursor of attacks to be provoked by estrogen-withdrawal, and that estrogen-withdrawal can result in MO without concomitant menstrual bleeding. Situations with stable levels of estrogens such as during pregnancy or after menopause are associated with improvement of MO [52-54]. In turn, high-estrogen states are associated with increased risk or new onset of MA [55]. This typically occurs during pregnancy when estrogen levels are 30-40 times higher than the peak during the natural menstrual cycle [56, 57] or in women starting combined hormonal contraception [31, 58] or estrogen replacement therapy [59]. Resolution of MA often occurs following a return to lower-estrogen states. One proposed pathophysiological mechanism is that the high levels of estrogens enhance susceptibility to MA by increasing cortical excitability [19].

Besides the effects of ovarian steroids on neurotransmitter systems, other processes relevant to the pathophysiology of MM may occur at the same time as estrogen-withdrawal, e.g. endometrial release of prostaglandins [60, 61]. There is a threefold increase in prostaglandin levels in the endometrium from the late follicular to the luteal phase with a further increase directly before menstruation [62]. Maximum entry of prostaglandins and its metabolites into the systemic circulation occurs during the first 48 hours of menstruation. Migraine patients report delayed migraine-like attacks after injection of prostaglandin E_2 and prostaglandin I_2 [63, 64] and systemic release of prostaglandins at the start of menstruation has been proposed as a trigger of MM [65, 66]. In contrast to estrogen-withdrawal migraine which can occur in the absence of menstrual bleeding, prostaglandin levels are linked to menstruation. An association between MM and dysmenorrhoea, a condition with symptoms mediated through endometrial prostaglandin-release, has been suggested [67] and non-steroidal anti-inflammatory drugs (NSAIDs) have been effective both as perimenstrual prophylaxis and in the acute treatment of MM attacks [68, 69].

The fact that menstruation is only associated with MO in a subset of female migraineurs, might indicate that additional genetic or environmental factors play a role. To date, few studies specifically address possible genetic variations in menstrual migraineurs. In a population of 437 women, variants in two specific genes -Tumor

Necrosis Factor (TNF) and Synaptic Nuclei Expressed (SYNE1), were significantly associated with MM [70]. Other studies have shown a positive correlation between polymorphisms in estrogen and progesterone receptor genes with migraine [71, 72].

In the same way that migraine fluctuates in frequency and severity over time, the association with menstruation is similarly inconsistent [66]. Few women report a constant association between migraine and menstruation from menarche to menopause. This may indicate that the occurrence of MM is determined by more than one factor.

4. Aims of the thesis

The overall aim of this thesis was to increase the knowledge about MM in the general population. The more specific aims of the individual papers are listed below;

Paper I: To estimate the lifetime prevalence of migraine and MM in women from the general population. Secondly to describe other types of migraine related to menstruation.

Paper II: To assess the consistency between MM- diagnoses made by a semi-structured clinical interview compared with diagnoses from prospective headache- and menstruation diaries.

Paper III: To compare the clinical characteristics of menstrual and non-menstrual attacks of MO in women with and without a prospectively diary-confirmed diagnosis of MM.

Paper IV: To evaluate the consequences of contraceptive-induced amenorrhoea on migraine frequency, attack duration and pain intensity in women with a history of MM.

5. Material and methods

This population-based observational study includes a cohort of women recruited from a cross-sectional study. The data presented were collected over three stages; (1) initial screening questionnaire in 2005, (2) clinical interviews and examinations in 2011/2012, and (3) three month prospective headache- and menstruation diaries directly following the interviews.

5.1 Population and screening questionnaires

In January 2005, a random age- and gender stratified sample of 15 000 women and 15 000 men, aged 30-44 years, residing in the eastern municipalities of Akershus County, was drawn from the Central Population Registry by Statistics Norway. The sampling area consists of rural and urban areas and was chosen due to its proximity to Akershus University Hospital. The total population of the sampling area was 338 670, representing 7.4% of the Norwegian population. The sample represented 36.6% of those aged 30-44 years in the eastern municipalities of Akershus County and 2.9% of this age group in Norway. Data from statistics Norway show that the sampling area was representative of the total Norwegian population concerning age and marital status. Regarding employment, trade, hotel/restaurant, and transport sector workers were overrepresented, while industry, oil/gas and financial services were underrepresented [73].

A short screening questionnaire (appendix 1) was mailed to all people in the sample with the purpose to identify subjects for two separate studies; *"The Akershus study on chronic headache"* and the present study. While the first study included responders reporting chronic headache, the present study excluded subjects with chronic headache [73, 74].

Due to lack of resources, the present study was delayed by six years. Because of this delay, we chose to focus on the youngest group of women who were most likely to have regular menstrual cycles, i.e. the 5000 women aged 30-34 years in 2005. This

group constituted 38.6% of all women aged 30-34 years in the sampling area, and 3.0 % of all Norwegian women in this age group [75].

The questionnaire included two questions about migraine and its relation to menstruation (Question 5 and 6, appendix 1). Women with self-reported migraine in at least one out of two menstruations were included, while those reporting ≥180 headache days during the preceding year were excluded. The included women were invited to a clinical interview and examination at Akershus University Hospital in 2011/2012. The invitation letter stated, apart from ensuring confidentiality, that the objective was to study menstrual migraine. One week after mailing of the invitation letter, the women were contacted by telephone in order to make an appointment for a clinical interview. Up to five calls on different days and times of the days were made, if necessary.

5.2 Clinical interviews

The interviews took place at the Research Centre, Akershus University Hospital from September 2011 through May 2012. Women who were not able to come to the clinic were offered a telephone interview. The interview was based on predefined questions and may be termed semi-structured as the interviewer (KGV) was allowed to reword questions in order to improve communication.

Classification of headaches

Two versions of the ICHD were available during the period of this work; ICHD II and III beta version. The criteria for MO and MM are the same in both versions (except the requirement for diaries), while the sub classification of MA is slightly different. The headaches were classified according to the ICHD II by interview [33]. Pure menstrual migraine (A 1.1.1) and menstrually-related migraine (A 1.1.2) were classified according to the appendix criteria of the ICHD II [33]. If a woman experienced more than one type of headache, each separate form was diagnosed.

An extended group of menstrual migraine was additionally defined in order to explore the boundaries of the diagnostic criteria and obtain information about other types of

migraine occurring in at least one out of two menstruations. This group, named *all MM,* included;

1. MM according to the ICHD-criteria: ICHD-MM
2. Probable MM*,* including;
    a. Menstrual MA, because the migraine was MA instead of MO
    b. Probable menstrual MO/MA, because
        - the migraine diagnosis was probable MO/MA, or
        - the frequency of migraine related to menstruation was less than two out of three, but at least one out of two menstruations, or
        - the onset of MO or MA was day +4 of the cycle.

The second part of the interview encompassed questions about menstruation and menstrual symptoms, contraception, symptomatic and prophylactic treatment. The questions about contraception included type of current contraception, duration of use and whether amenorrhoea had arisen after initiating the method. Specific questions about the course of migraine in relation to current contraceptive method were included (appendix 2). Amenorrhoea was defined as the absence of menses for at least three months in women with previously normal menstruation [76, 77].

The interviews lasted 30-45 minutes and were followed by a general and neurological examination as recommended by the ICHD II. By the end of the interview, each participant was asked to complete an electronic self-administered questionnaire including demographic data. Women who were interviewed by telephone received this questionnaire by mail/email after the interview and underwent no clinical examination.

5.3 Prospective headache- and menstruation diaries

All women, irrespective of headache diagnoses, were instructed to complete a headache- and menstruation paper-pencil diary for three consecutive menstrual cycles directly following the interview. Women, who reported amenorrhoea at time of interview, were asked to complete the diary for three months. Each question in the diary was thoroughly explained to the participants. The headache diary included questions necessary for the distinction between MO, MA, and tension-type headache

(appendix 3). It additionally collected information about menstruation, sick leave, and symptomatic treatment.

When a headache occurred, the women were asked to record: time of onset and end of headache, any aura symptoms, pain quality and location, severity on Numeric Rating Scale 0-10 (NRS; 0=no pain, 10= most severe pain), aggravation by routine physical activity, medical treatment and sick leave. The associated symptoms (i.e. nausea, photo- and phonophobia) were graded 0-3; 0=no symptoms, 1=mild, 2=moderate and 3=severe.

The women were allowed to take their usual medication including migraine prophylaxis and hormonal contraception. The diaries were returned by mail in a pre-addressed envelope to the Research Centre. If a diary was not returned after three months, a single reminder was issued.

Data entry and analyses of the diaries

The diaries were reviewed by two investigators (KGV and MBR) and all data were entered into the database by one person (KGV). The diaries did not cover information about interview-diagnoses or names of the women. In order to merge diary-data with the interview-data, a five-digit identification number was placed on the front page of each diary. In cases with missing data concerning the exact timing of menstruation, the subjects were contacted by telephone to elaborate the information.

When a migraine attack lasted more than one day, it was considered as a single multiday attack, unless a pain-free interval of ≥48 hours separated the headaches. This definition was used since most of the attacks were treated with symptomatic drugs, and because migraine occurring within 48 hours is considered as a relapse in randomized controlled drug trials [78]. When an attack fulfilled all but one ICHD-criterion for MO, the attack was classified as MO if symptomatic treatment was used. Otherwise, it was classified as probable MO. Since some women reported visual disturbances ahead of their migraine attacks, not necessarily representing a migraine aura, only women

diagnosed with MA by interview were allowed to have their attacks classified as MA by diary.

A diagnosis of ICHD-MM required at least two attacks of MO with onset on day 1±2 of the menstrual cycle during three consecutive menstrual cycles. If an attack started outside the defined period (day 1±2), it was considered as a non-menstrual attack. Menstruation was defined as two or more consecutive days of uterine bleeding. In the analyses, diaries from women with oligoamenorrhoea, i.e. ≤1 menstruation recorded during three months, were excluded. In the comparison between menstrual and non-menstrual attacks, only women who recorded attacks of MO during the diary-period were included. In order to compare the same headache types inside/outside menstruation, only MO-attacks were included, while attacks of MA and tension-type headache were excluded.

5.4 Statistics

The data were analysed using the Statistical Package of Social Science (SPSS) versions 20 and 22.

5.4.1 Paper I

The crude and adjusted lifetime prevalence of migraine and menstrual migraine is presented with 95% confidence interval (CI). Since information from screening-negative women was lacking, the number of women with self-reported migraine was adjusted using figures from two Danish studies, adjusting for false positive and false negative responses. The Danish studies validated the same question ("Have you ever had migraine?") as we used to classify migraine in our questionnaires. In the first study, "true positive" migraineurs were 550 out of 590 people with self-reported migraine by questionnaire [79]. This study included a high number of subjects with self-reported migraine and few subjects without self-reported migraine. In the second study, "false negative" migraineurs were 24 out of 581 without self-reported migraine by questionnaire [80]. This study included few subjects with self-reported migraine and many without self-reported migraine.

In the prevalence of menstrual migraine, adjustments were made for women who were screening-positive, but did not participate in the interview.

5.4.2 Paper II

Demographic data and comparisons of women with and without ICHD-MM were compared with Chi_2-test for categorical variables and independent samples test for continuous variables. Estimations were two-sided and a *p*-value <0.05 was considered significant.

The interview-diagnoses of ICHD-MM were compared against the diagnoses made according to the "gold standard": the diary. The sensitivity, specificity and predictive values for the interview-diagnoses of ICHD-MM were assessed. Kappa measure of agreement was used to assess the consistency between the two different diagnostic methods, i.e. interview vs. diary. Some of the agreement may happen by chance and the Kappa measure of agreement corrects for this. Kappa has a maximum value of 1.00 when agreement is perfect while a value of 0 indicates no agreement better than chance. Negative values indicate agreement less than predicted by chance alone. Values ranging from 0.41-0.60 may be considered as moderate, 0.61-0.80 as substantial and above 0.80 as almost perfect [81].

5.4.3 Paper III

Continuous demographic and clinical characteristics were presented as means and standard deviations (SDs), while frequencies and percentages were used to describe dichotomous characteristics. Independent samples test and Fischer's exact test were used to compare the characteristics between women with and without ICHD-MM.

Three continuous (pain score, duration and number of doses), three graded categorical (nausea, photo-and phonophobia) and two dichotomous (treatment and sick leave) parameters were analysed for each migraine attack, resulting in repeated measurements for each woman. Adjustments due to intra-correlation were made. Differences in menstrual and non-menstrual migraine attacks were assessed by a regression model for repeated measurements adjusting for intra-individual correlations; linear for continuous, ordinal for categorical and logistic for dichotomous

parameters. Intra-class correlation coefficient (ICC) was calculated to assess the proportion of variance occurring within-women. The regression models contained fixed effect for variables, categorizing the attacks into menstrual and non-menstrual attacks in women with and without a diagnosis of MM, with non-menstrual attacks in women with a diagnosis of MM as the reference category. A random effect for intercept, accounting for within-woman variability, was included in the model.

The results are presented as coefficients or as odds ratios (ORs) with 99% confidence intervals (CIs) for categorical and ordinal data. The coefficient from a linear model (i.e. continuous data) represents the estimated average difference between the reference and three other categories (i.e. menstrual and non-menstrual attacks in women without MM and menstrual attacks in women with MM). Ordinal and logistic regression models were used to estimate the odds for presence of a specific symptom in a certain category with respect to the reference category. The ratio of the generalized χ^2 statistic and its degrees of freedom was nearly one in the logistic models indicating no overdispersion in the data. Baseline factors differing between the groups were included into the models with significant associations one at a time to test if the associations were modified. In addition, the models were adjusted for progestin-only and combined hormonal contraception. None of the associations were affected by these adjustments.A significance level of 0.01 was chosen to partially address for multiplicity.

5.4.4 Paper IV

A Fisher's exact test with mid-p corrections was used to compare categorical data from women with and without amenorrhoea; the use of mid-p corrections are appropriate under various conditions, and always when the groups compared are of (roughly) the same size [82, 83]. Differences regarding self-reported changes of MO between the two groups (women with and without amenorrhoea) were presented as Odds Ratio (OR) with 95% confidence interval. Estimations of significance were two-sided *p*-values and significance level set to 0.05.

5.5 Ethics

The study was approved by the Regional Committee for Medical Research Ethics and the Data Protection Authorities. All participants who were invited to the clinical interview had given consent to further contact by adding their phone number to the screening questionnaire. The participants received written and verbal information about the project and inclusion was based on informed consent. The information letter stated the participant's right to withdraw from the study at any time without giving any reason. All collected data were anonymized and secured on a research server at Akershus University Hospital. No reimbursement for participation or completing diaries was given.

6. Results

6.1 Screening questionnaire, interviews and diaries

Figure 4 is a flow chart of the study. The response rate of the screening questionnaire was 73.2% (3514/4802). A total of 360 women met the inclusion criteria and were invited to participate in the clinical interview; 52 were not eligible. The participation rate of the clinical interview was 76.9% (237/308) since 71 women declined to participate due to lack of time, no interest, or acute illness. The majority were interviewed face-to-face, 63.3% (150/237). There were no significant differences between participants and non-participants in their responses to the screening questions (Table 2).

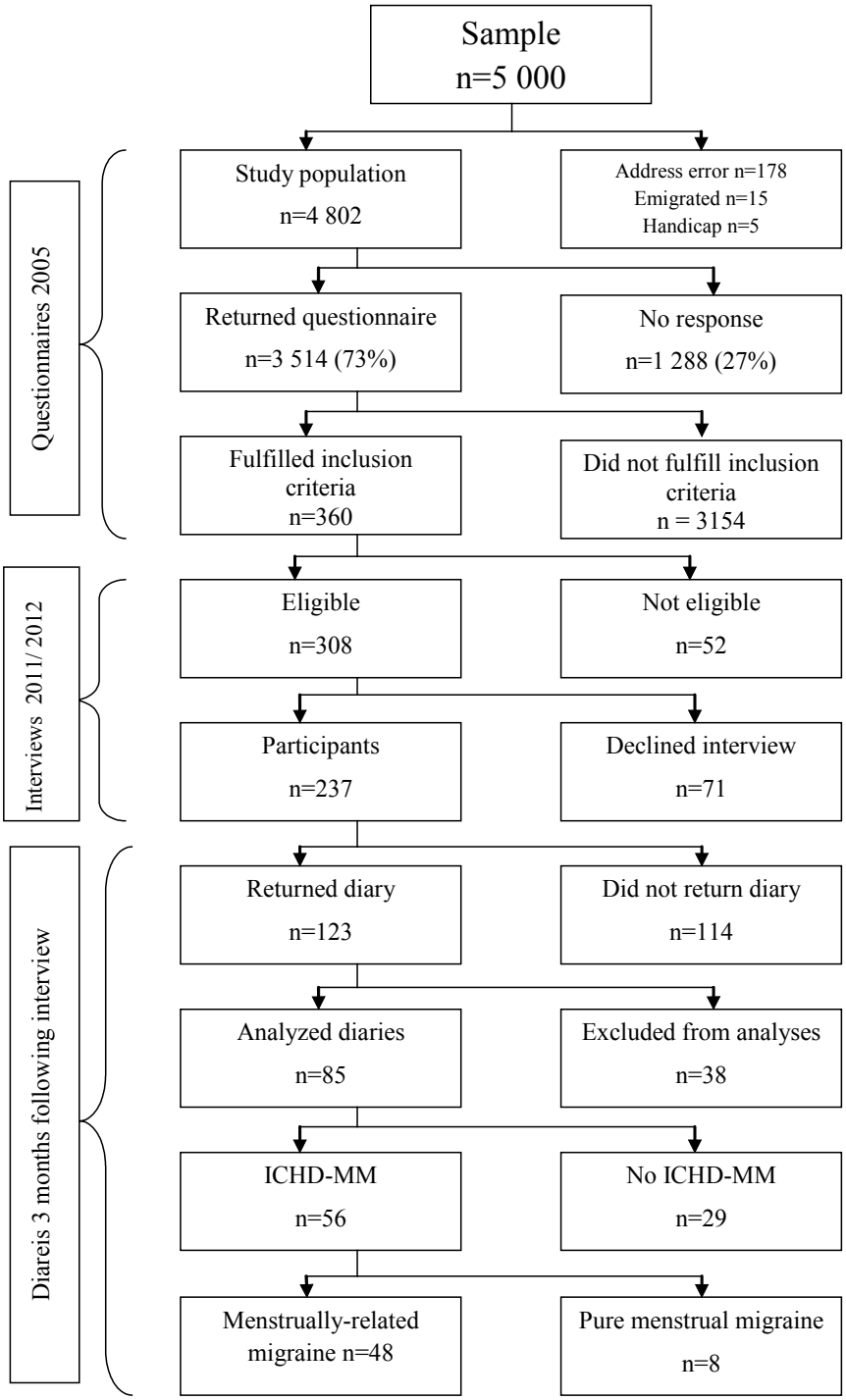
Table 2. *Questionnaire responses among participants and non-participants*

	Participants n=237 n (%)	Non-participants n=123[1] n (%)	*p*-value
Do you have migraine in relation to your menstruation? *Yes*	226 (95.4%)	119 (96.7%)	0.40
How often do you have migraine in relation to your menstruation;			
• Every time	85 (35.9)	41 (33.3)	0.73
• 2 out of 3 menstruations	88 (37.1)	44 (35.8)	
• 1 out of 2 menstruations	64 (27.0)	38 (30.9)	

[1]*Women who fulfilled the inclusion criteria, but were non-eligible or declined participation*

The self-administered questionnaire was completed by all women interviewed face-to-face, and by 59% (51/87) of the women who were interviewed by telephone.

Figure 4. *Flow chart of the study*



Among the 237 participants, 224 (94.5%) were diagnosed with migraine. Table 3 shows clinical and demographic characteristics of the participants. Data from Statistics Norway show that the participants were representative of the age-and gender matched Norwegian population regarding employment rate and marital status. Concerning profession, office jobs were overrepresented while academic professions and sales- and service were underrepresented [84].

There were no differences in the proportions of ICHD-MM diagnoses made face-to-face versus by telephone (59% vs. 61%, p=0.73), or from the first to the second half of the interview period (56% vs. 63%, p=0.34). Neurological examination did not uncover previously unknown neurological deficits in any of the participants.

The headache and menstruation diary was returned by 123 of the 237 participants (52%). There were no differences between women who returned the diary compared to those who did not concerning migraine diagnoses, migraine frequency or demographic variables [85]. However, women interviewed face-to-face were significantly more likely to return the diary compared to women who were interviewed by telephone (61.3% vs. 35.6%, p<0.001).

Table 3. *Clinical and demographic characteristics of the participants (N=237)*

Clinical characteristics	n	%
Migraine diagnosis[1]	224	94.5
Migraine without aura (MO) alone	158	70.5
Migraine with aura (MA) alone	20	8.9
Migraine with and without aura (MO and MA)	46	20.5
Menstrual migraine without aura (ICHD-MM)	141	62.9
Probable menstrual migraine (probable MM)	35	15.6
Migraine prophylaxis [1]	14	6.3
Hormonal contraception[2]	80	33.8
Combined hormonal contraception	19	23.8
Progestin-only contraception	61	76.3
Demographic characteristics	n	%
Married/living with a partner[3]	164	81.6
Have children	210	88.6
Employd[3]	170	84.6
Higher education (≥4 years college/university)[3]	108	53.7
Profession[4]		
Office and secretarial job	47	25.4
College career, health or education, engineering	35	18.9
Academic profession	33	17.8
Sales- and service	23	12.4
Management profession	11	5.9
Craftsman, fisher, farmer	8	4.3
Other	28	15.1

[1]Subtypes of migraine and migraine prophylaxis are presented as percentages of all migraineurs. [2] Subtypes of hormonal contraception is presented as percentages of all women using contraception. [3] 36 missing values. [4] 52 missing values.

6.2 Prevalence of migraine and menstrual migraine (paper I)

Of the 3514 women who returned the questionnaire, 1215 gave a positive response to the question "Have you ever had migraine?" while 2299 answered "no". The adjusted number of women with migraine was 1228, i.e. (1215x (550/590)) + (2299x (24/581)). The crude lifetime prevalence of self-reported migraine was 34.6% (1215/3514) in the population and the adjusted prevalence was 34.9% (1228/3514).

The crude and adjusted lifetime prevalence figures of the different types of migraine related to menstruation are presented in Table 4. Menstrually-related migraine was 6.5 times more common than pure menstrual migraine among the women with ICHD-MM (19 versus 122 women). An active ICHD-MM, i.e. MM occurring during the preceding year, was reported by 65.2% (92/141). Women with probable menstrual MO did not fulfil the required frequency (n=6), timing of attacks (n=4) or the definite MO-diagnosis (n=3). The women with probable menstrual MA did not fulfil attack frequency (n=5) or timing of attacks (n=3).

Table 4. *Lifetime prevalence of menstrual migraine among all women and female migraineurs*

		Among all women (N=3514)		Among migraineurs (N=1215)	
	n	Crude % (95% CI)	Adjusted[1] % (95% CI)	Crude % (95% CI)	Adjusted[1] % (95% CI)
ICHD-MM	141	4.0 (3.4-4.7)	6.1 (5.4-6.9)	11.6 (9.9-13.5)	17.6 (15.6-19.9)
Probable MM					
Menstrual MA	14	0.4 (0.2-0.7)	0.6 (0.4-0.9)	1.2 (0.7-1.9)	1.7 (1.1-2.6)
Probable menstrual MO	13	0.4 (0.2-0.6)	0.6 (0.4-0.9)	1.1 (0.6-1.8)	1.1 (0.6-1.8)
Probable menstrual MA	8	0.2 (0.1-0.5)	0.3 (0.2-0.6)	0.7 (0.3-1.3)	1.0 (0.6-1.7)
All MM	176	5.0 (4.3-5.8)	7.6 (6.8-8.5)	14.5 (12.6-16.6)	22.0 (19.7-24.4)

[1] Example of calculation of adjusted prevalence of ICHD-MM among all women: (((141/237) x123) + 141)/3514 =0.061. The number of women with ICHD-MM (141) divided by all participants (237), multiplied by the number of non-participants (123), gives the assumed number of women with ICHD-MM among non-participants (73), adding the 141 women with ICHD-MM among participants, gives the estimated number of affected women in the study population (141+73=214). Divided into all responders and multiplied by 100, gives an adjusted prevalence of 6.1%.

6.3 A clinical interview versus prospective headache diaries (paper II)

Of the 123 returned diaries, 38 were excluded due to oligo-/amenorrhoea (n=36) or incompleteness (n=2).

Among the 85 women whose diaries were analysed, 51 were diagnosed with ICHD-MM by interview, but 56 were prospectively diagnosed with ICHD-MM by diary. The sensitivity, specificity, and predictive values of the ICHD-MM diagnosis given by interview are presented in Table 5. The observed agreement rate was 82% and the chance-corrected agreement rate, Kappa, was 0.62 (95% CI 0.45-0.79).

Table 5. Sensitivity, specificity, and predictive values of the clinical diagnosis of menstrual migraine without aura (ICHD-MM)

		Diary diagnosis			
		MM	No MM	Total	
Interview	MM	46	5	51	PPV=46/51=90%
diagnosis	No MM	10	24	34	NPV=24/34=71%
	Total	56	29	85	
		Sensitivity= 46/56=82%	Specificity= 24/29=83%		

PPV: positive predictive value. NPV: Negative predictive value

Among the 10 negatively misclassified women, six were diagnosed with probable menstrual migraine by interview. In the five women positively misclassified by interview, two had MO attacks occurring in relation to their menstrual periods (≥2/3), but the attacks started earlier than required (day -5 and -4).

When the criteria were expanded to additionally include the women with probable MM (n=6; four menstrual MA and two probable menstrual MO), the Kappa value was slightly higher; 0.64 (95% CI 0.47-0.83) with equal positive and negative misclassification.

6.4 Menstrual versus non-menstrual migraine attacks (paper III)

In the comparisons of menstrual and non-menstrual MO-attacks, an additional four diaries were excluded from the analyses, because only attacks classified as tension-type headache were recorded. Thus, 81 diaries were analysed from 56 women prospectively diagnosed with ICHD-MM and 25 women with MO-attacks but not ICHD-MM.

The 81 women recorded a total of 261 menstrual cycles over 7202 diary days. Overall, 470 migraine attacks were recorded, of which 35 were classified as MA and thus excluded from the analyses. Of the 435 analysed MO- attacks, missing values occurred most frequently for attack duration (6.2%, n=27), phonophobia (1.4%, n=6), photophobia (1.5%, n=5) and nausea (0.5%, n=2). Information regarding sick leave and pain intensity was missing in one attack respectively.

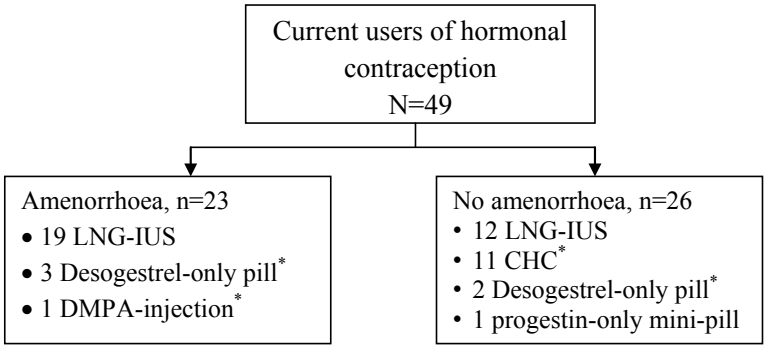
In women with ICHD-MM, the menstrual MO-attacks were significantly longer (on average 10.65 hours, 99% CI 3.17-18.12) and more frequently associated with severe nausea (OR 2.14, 99% CI 1.20-3.84) than non-menstrual MO-attacks. The menstrual attacks were treated with significantly more doses of symptomatic drugs (mean difference 1.37, 99% CI 0.50-2.24) and multiple agent treatment strategies (OR 2.10, 99% CI 1.05-4.23). A non-significant trend towards more painful attacks (on average 0.37 on an 11-point scale, 99% CI -0.08-0.81) and more occurrences of status migrainosus (OR 4.34, 99% CI 0.94; 20.09) was found, but there were no differences in sick leave.

No significant differences in characteristics or treatment between menstrual and non-menstrual MO-attacks were found among women with MO, but no MM.

6.5 Contraception-induced amenorrhoea (paper IV)

Among the 141 women with a history of ICHD-MM by interview, 49 were current users of hormonal contraception. Contraception-induced amenorrhoea was reported by 23 women. Figure 5 gives an overview over the different types of hormonal contraception used by the women.

Figure 5. *Current users of hormonal contraception*



**Expected inhibition of ovulation. LNG-IUS: Levonorgestrel intrauterine system. DMPA: Depot medroxyprogesterone acetate. CHC: combined hormonal contraception.*

A reduction in the total MO-frequency was significantly more often reported by women with amenorrhoea compared to women without amenorrhoea (OR 3.5, 95% CI 1.1; 11.4, p=0.04). No difference was found with respect to attack duration and pain intensity. Women with amenorrhoea were more likely to report that they were migraine-free during the preceding month compared to women without amenorrhoea (OR 16.1, 95% CI 1.8; 140.4, p=0.003).

An additional analysis of contraceptive methods with and without expected inhibition of ovulation was carried out. Women using expected anovulatory methods were less likely to report a reduction in migraine-frequency compared to those with preserved ovulation (OR 0.2, 95% CI 0.1; 0.9, p=0.03). Again, no differences concerning duration and pain intensity were found.

7. Discussion

7.1 Methodological considerations

This observational study includes a cohort of women recruited from a population-based cross-sectional study. The study comprises retrospective data from questionnaires and interviews as well as prospectively recorded data from diaries. Retrospective data are associated with recall bias, and selection bias may have occurred along the three stages. These issues will be discussed more specifically in relation to each stage.

7.1.1 Population and screening

Women with self-reported migraine in at least one out of two menstruations were recruited from a large population-based sample. The large sample size and high response rate (73%) to the questionnaire should provide representativeness of women aged 30-34 years in the general population. Since the screening questionnaire only included questions about headache, headache sufferers may be overrepresented among the responders. For ethical reasons we were not allowed to contact non-responders. A Danish population-based study did not find difference in headache diagnoses between responders and non-responders [79].

The questionnaire included two questions about menstrual migraine; "Do you have migraine in relation to your menstruation?" and "How often do you experience migraine in relation to your menstruation?" A review of the questionnaires identified some women who had failed to respond, or gave a negative response to the first question, but still replied to the second question. No one answering 'yes' to the first question had missing values on the second question. In order to make a broad inclusion, we chose the latter as our key question for inclusion. In addition, we included women who reported migraine in 1/2 menstruations instead of 2/3 to further increase ascertainment.

Due to our screening method, some women with MM in the original population have probably not been identified. We did not interview screening-negative women. No studies have evaluated MM diagnoses in women who report that they do not have

MM. However, previous studies have shown that women tend to over report MM by self-assessment [35, 36]. Interviews of responders with migraine who did not report MM may have given additional data and contributed to more precise prevalence estimates of MM in our study. Some women may not know that their headache was a migraine. However, the question: "Have you ever had migraine?" has previously been validated with a high chance corrected agreement rate (kappa 0.87) and it identifies about 80% of migraineurs [80]. Our population encompassed all women who had answered 'yes' to that question, but additionally some who had answered 'no' to the migraine question, but 'yes' to the menstrual migraine questions in order to make a broad inclusion. Women with onset of MM after screening and before interview could not be identified by our study design. As a consequence of this, our lifetime prevalence figures are only valid for women aged 30-34 years and should be considered as a minimum of the true prevalence for this group.

The six years delay between screening and interview has probably increased the influence of recall bias and may have led to an underestimation of the prevalence estimates in paper I. It may also have contributed to a lower participation rate. This delay did probably not influence the results of paper II and III, since these papers only include data collected in close temporal relation from interviews and prospective headache diaries. Regarding paper IV, the six years delay provided an opportunity for a retrospective analysis of women in whom their MM had ceased due to contraception-induced amenorrhoea.

7.1.2 Clinical interviews

In the absence of biological markers for migraine, the diagnosis is based on the subjects' history and recall of specific symptoms. A clinician's interview is considered as the gold standard in terms of diagnosing specific headache disorders, especially in subjects with more than one type of headache [86]. A face-to-face interview has, in contrast to a telephone interview, the advantage that it allows participants to be examined, which is recommended by the ICHD in order to rule out secondary headaches [3, 33]. However, a face-to-face interview is time-consuming and consequently expensive compared to both telephone interviews and questionnaires.

The invitation letter stated that the purpose was to study menstrual migraine, and menstrual migraineurs may be overrepresented among the participants (participation bias). However, participants and non-participants did not differ regarding their questionnaire responses concerning menstrual migraine.

7.1.3 Prospective headache diaries

In clinical practice, patients may have difficulties recalling precisely the headache characteristics, especially if they have several types of headache. The episodic nature of the disease constitutes a bias towards the most severe or recent headache attack [87]. Moreover, difficulties are related to the headache syndromes themselves, because clinical features may change from one attack to the next. In menstrual migraine both the timing of attacks in relation to the first day of menstruation, and the frequency related to menstruation, represent additional challenges. The most precise descriptions of migraine characteristics and the timing of migraine in relation to menstruation are thus likely to be obtained from prospective headache- and menstruation diaries which are less influenced by recall bias than a clinical interview.

The major concern about the use of diaries is the low compliance rate, as demonstrated in our (52%) and previous studies [25, 26]. Recording diaries is time consuming and patients tend to be less compliant in maintaining them over long periods of time [88]. For the purpose of this study, we used a diagnostic diary with series of multiple questions in order to distinguish between headache types (appendix 3). The three months period and the rather comprehensive design of the diary might have been too demanding for some women, resulting in the modest compliance rate. However, since we wanted to categorize each attack, multiple questions were inevitable, and the ICHD requires a long period (i.e. three months) in order to establish the diagnosis of MM. Frequent reminders, a closer monitoring during the diary-period, a compensation for filling in the diary, and/or a re-visit after three months, could possibly have increased the return rate. Despite the extensive questions, only two diaries were incomplete and not eligible for analysis. The thorough explanation in advance may have contributed to this.

Even though the participants were aware that the objective was to study menstrual migraine, no differences were found between women who returned the diary and those who did not regarding clinical ICHD-MM diagnosis, migraine frequency, or amenorrhoea [85]. The only difference detected was type of interview; women who were interviewed face-to -face were significantly more likely to return the diary compared to those interviewed by telephone. This may indicate that 1) women who invested more time in order to come to the hospital for a face-to-face interview were more motivated and interested in participation and/or that 2) the personal contact with the interviewer increased the motivation and engagement.

A paper-pencil diary is easy to use and a low-cost low-threshold method, but is also connected with the possibility of backfilling entries [88]. In turn, electronic diaries may be associated with technical challenges and possible selection bias [89]. During the past years, an increasing proportion of the Western population own a smartphone and a variety of headache diary applications (Apps) are available free of charge. This portable and fast-access method might represent a better means to achieve higher compliance rates. During the period when the diaries in our study were recorded, only 60% of all Norwegians owned a smartphone, as compared to >80% today [90]. A disadvantage may again be selection bias towards inclusion of subjects with higher socioeconomic status.

7.2 Discussion of the results

7.2.1 Prevalence of migraine and menstrual migraine

The lifetime prevalence of migraine and menstrual migraine were defined as the proportion of women who fulfilled the criteria of migraine or menstrual migraine at any time during their lives. This is equivalent to the lifetime risk. The lifetime prevalence of migraine includes both those with an active disease and those who are into remission. Conversely, the one-year prevalence and the point prevalence are functions of incidence (i.e. new cases) and remission (ceased cases) during a specific period and are generally lower than the lifetime prevalence. The lifetime prevalence may be more influenced by recall bias, especially when the participants are older and their migraine went into remission several years ago. Another drawback is that lifetime prevalence does not give a clear indication of those actually having an active disease.

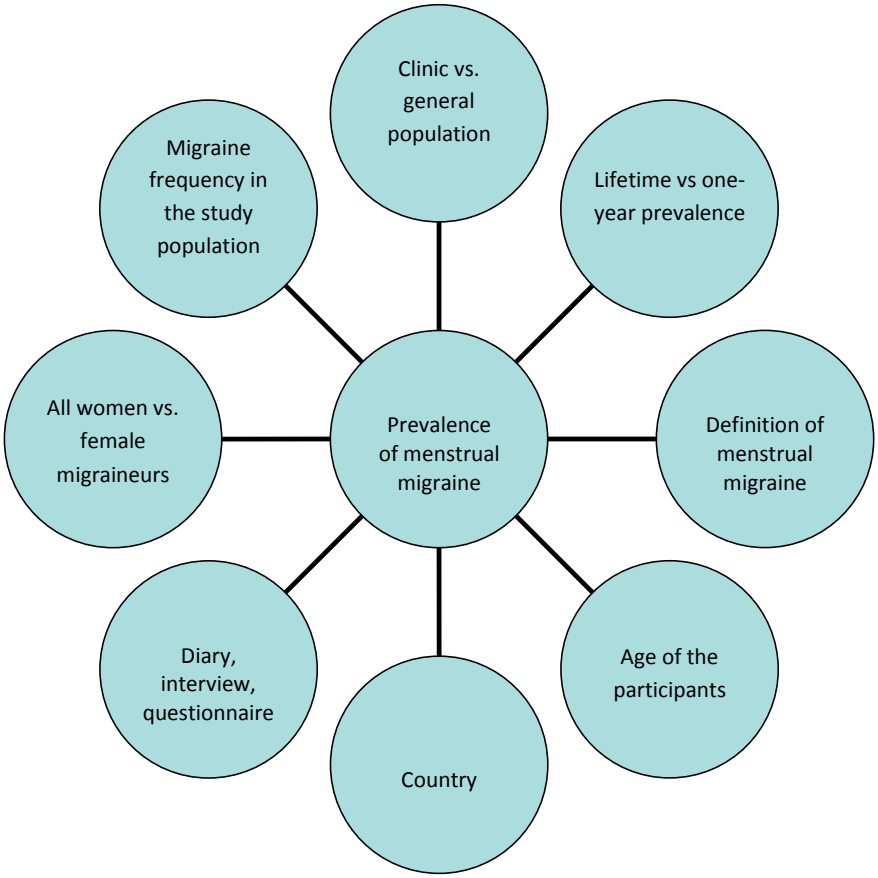
Our 34.9% lifetime prevalence of migraine among women in their 30s is comparable to figures from the Netherlands, Germany, Canada, USA and South America [14, 91-94], but is higher than other studies from Europe and Asia [79, 95, 96].

Prevalence of menstrual migraine

We chose to present lifetime prevalence figures of MM based on interview-diagnoses instead of the diary-diagnoses due to the modest compliance rate of the diaries. We also present prevalence figures for the total female population and for women with migraine, since one or both are presented in previous studies.

A review of the literature revealed great variations in prevalence figures of MM, ranging from 4% to 70%. This can be explained by differences in the study populations, assessment, and varying definitions of MM. Figure 6 illustrates some factors contributing to the differences.

Figure 6. *Influences on the prevalence figures of menstrual migraine*

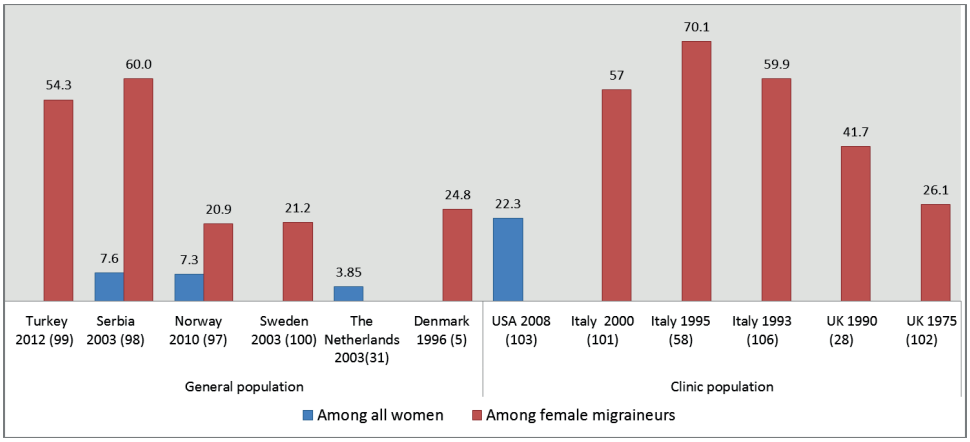


Prevalence figures from at least five different populations are presented in the literature: all women in the general population [30, 97, 98], female migraineurs in the general population [5, 97-100], female migraineurs attending to headache clinics [27, 31, 58, 101, 102] and women in an obstetrics and gynecology setting [103]. In addition, some present prevalence figures confined to women with MO or MA, while others refer to all women with migraine.

The prevalence of MM is naturally higher among female migraineurs than among all women. The definition of MM requires a minimum frequency of migraine; at least two attacks during three months, which is above the average frequency reported by

migraineurs from the general population [104]. MM is thus more likely to occur in a headache clinic population, as shown in Figure 7. Two studies from the general population stand out, probably due to looser definitions of MM, this will be discussed below [98, 99].

Figure 7. *Prevalence of menstrual migraine in different study populations*



Our 17.6% lifetime prevalence of ICHD-MM among all female migraineurs aged 30-34 years is slightly lower than lifetime prevalences from Swedish (21.2%) and Danish (24.8%) population-based studies [5, 100]. These prevalence-figures are confined to women with MO. A simplified adjustment assuming that 2/3 of all female migraineurs have MO, indicates that 26% of women with MO have ICHD-MM in our population. The two Scandinavian studies did also include older populations, i.e. women ≥40 years old. We have previously published prevalence figures based on the questionnaire responses from all women aged 30-44 years in our original population [97]. The lifetime prevalence of self-reported MM increased slightly with age, from 19.8% in female migraineurs aged 30-34 to 21.7% among those aged 40-44 years [97].

However, differences in study populations alone can probably not explain the disparities. Due to the lack of uniform criteria until 2004, different definitions of MM

have been used; including various definitions of the perimenstrual period and the required frequency of migraine related to menstruation. The perimenstrual period has been defined as all days occurring between day -3 until 3 days after menstruation [58], from day -3 to +5 [99], from day -3 to +3 [105] or from day -2 to +2 [30]. Similarly, has the required frequency of concurrency between migraine and menstruation been defined as "attacks mostly occurring during menstruation"[101], "aggravation of migraine during menstruation"[98], attacks occurring regularly just before or after menstruation [102] – or a definition is lacking [30, 99]. The highest prevalence figures are found in studies which either define an extended perimenstrual period or in studies not considering the frequency of migraine related to menstruation; 57-79% [58, 98, 99, 101].

Even though most researchers after 2004 have used the same criteria, they may have been differently interpreted; as the current criteria do not clearly state that the attacks have to *start* on day 1±2. If only migraine days occurring during the five perimenstrual days are counted, without considering time of onset of the attacks, most women with chronic migraine will naturally fulfil the criteria for MM.

Previous studies have used different methods in the assessment. A subjective assessment by the patients themselves, rather than careful interviews or prospective diaries, may lead to an overestimation of MM [35, 36], but there is no consistency in the previous prevalences indicating that one method leads to higher figures than the other. This is probably explained by some of the above-mentioned issues.

Prevalence calculation is about numerators, denominators, and time. What we enumerate (i.e. women with MM) has differed due to different definitions of MM and time frame (i.e. life-time vs. one-year). The denominators differ because different populations have been studied. By presenting the lifetime prevalence of ICHD-MM, we have shown the percentage of female migraineurs who are at risk of experiencing menstrual migraine until age 30-34 years. Even though our study was not perfectly designed for prevalence estimations (due to the six years delay), no other studies have presented prevalence figures for MM in the general population based on the ICHD criteria.

Menstrual migraine among all women in the general population

We found a 6.1% prevalence of ICHD-MM and 7.6% prevalence of *all menstrual migraine* among all women in our population. The prevalence among all women from the general population has been calculated in two previous studies [30, 98] (Figure 7). The Dutch questionnaire-based study of regularly menstruating women aged 13-55 reported a prevalence of 3.9% [30], probably representing last-year prevalence. If we consider that about two thirds (92/141) of all women with ICHD-MM in our study had MM during the preceding year, the Dutch results are similar to our figures.

A second paper reports on a Serbian questionnaire-study of female students aged 18-28 years [98]. The prevalence reported was 7.6%, but the definition of MM was less specific; i.e. "migraine aggravated during menstruation" and might be more comparable to our *all MM* group, where we found a prevalence of 7.6%.

Prevalence of the subtypes; pure and menstrually-related migraine

Only 19 out of 141 women with MM had pure menstrual migraine. The lower figures of pure menstrual migraine as compared to menstrually related migraine are consistent with all previous studies from clinic and the general populations, except one study from the obstetrics and gynecology population [103]. The prevalence of pure menstrual migraine varies less across studies, probably due to the more uniform definition restricted to include women with exclusively menstrual attacks.

The variations in prevalence figures of MM are thus mainly caused by variations in the proportion of women with menstrually-related migraine. This is primarily caused by the different definitions of menstrual migraine described above.

Extended criteria MM –why include this group?

The diagnostic criteria for MM are placed in the appendix of the ICHD II and III beta. The primary purpose of the appendix is to present research criteria for novel entities that have not been sufficiently validated by research so far [3, 33]. In order to explore the boundaries of menstrual migraine, we expanded the criteria to include probable MM, i.e. women fulfilling all, but one ICHD appendix criteria for MM, in addition to probable menstrual MA (violates two criteria). One fifth of all women had probable MM. "Probable-diagnoses" are given for all primary headaches in the ICHD and people may fulfil the definite diagnoses at some time and at other times the probable diagnoses. In clinical management, the probable-diagnoses provide a basis for treatment pending later diagnostic confirmation [86]. Comparisons of our interview- and diary- diagnoses may indicate that this could be relevant for the diagnosis of MM as well.

Six women reported MO in ≥1/2, but <2/3 menstruations by interview and four stated that their migraine attacks started regularly on day +4 of the menstrual cycle. It is well known that inter- and intra-individual variations in the levels of ovarian hormones between the menstrual cycles occur and that each menstrual cycle is not a reproducible hormonal event [106-108]. In certain individuals this may cause an earlier or later trigger (e.g. estrogen-withdrawal), leading to attacks just outside the five-day window. In others, the hormonal fluctuations may not exceed the threshold for triggering a migraine attack in each cycle. Likewise, the levels of prostaglandins in the menstrual fluid tend to fluctuate at different times during different cycles [62]. In clinical practice, these women may be treated in the same way as menstrual migraineurs but for the purpose of research, inclusion of such "outliers" may result in a less homogenous group and thus dilute results.

Only menstrual attacks of MO are considered in the diagnosis of MM, while no requirement for the non-menstrual migraine type is given. Separate analyses of MO and MA consistently report that MO is more likely than MA to be associated with menstruation. The previous prevalence figures for menstrual MA among women with MA are 4% -37% [5, 58, 100, 101]. We found a prevalence of 1.7% of menstrual MA

among all migraineurs. If we assume that 1/3 of all migraineurs have MA, the prevalence of menstrual MA would be about 5% in women with MA in our study.

In contrast to this, a diary-study of women with frequent MA attacks found a significantly increased risk of MA on day +1-+3 of menstruation compared to other times of the cycle (OR 2.41; 95% CI 1.62-3.59) [109]. This study only described the timing of attacks related to menstruation but not the frequency. Menstruation was also reported to be a significant trigger of MA-attacks in a questionnaire study [110].

Among the 14 women diagnosed with menstrual MA by interview in our study, only four returned a diary. All recorded MA-attacks on day 1±2 in 2/3 menstruations in their diaries. In 3/4 cases, their menstrual attacks represented ≥50% of all migraine attacks (unpublished data), compared to the average 47% of women with ICHD-MM, indicating that a chance occurrence is less likely. Until further evidence is available it could be worth including menstrual MA into the appendix of the ICHD in order to explore potential underlying pathophysiological mechanisms. In turn, it is absolutely necessary to analyse menstrual MO and MA separately.

7.2.2 A clinical interview diagnosis of menstrual migraine

The diagnosis of MM differs from most other conditions in the ICHD by virtue of the temporal relationship with a specific event: menstruation. Besides a precise headache diagnosis, the attacks have to be correctly timed and occur in a specific frequency in relation to menstruation. Three previous clinic studies have demonstrated this challenge, as MM was over reported in 19%, 62%, and 89% of women by self-assessment [34-36]. As a consequence of this, the *recommendation* of three months prospective records in the ICHD II was changed to a *requirement* in the ICHD III beta version. MM has thus its special position in the ICHD III beta as the only headache diagnosis requiring a diary before establishment. This has some practical implications since the diagnosis cannot be made during the first visit and women who are non-compliant in recording diaries can never be diagnosed.

In contrast to the previous studies, we found a substantial agreement between diagnoses of ICHD-MM made by interview versus diary (Kappa 0.62). The diagnosis was confirmed in 90% (46/51) of all women diagnosed with ICHD-MM by interview. This is in line with one previous study [111]. Unlike the previous studies, we additionally evaluated women without an ICHD-MM diagnosis from interview, and found a tendency towards under reporting.

The interviews were however imprecise in the discrimination between pure and menstrually related migraine. Eight women were diagnosed with pure menstrual migraine by interview and seven by diary; in only three cases did it represent the same woman. The three months period might have been too short to detect non-menstrual attacks in women misclassified as menstrually-related migraine by interview.

A clinical interview, based on the ICHD-criteria, is though valid for the diagnosis of MM. Headache diaries should not be mandatory in order to diagnose MM, but might be necessary in order to distinguish between the subtypes of MM, monitor treatment and to exclude a chance association.

7.2.3 Menstrual versus non-menstrual attacks of migraine without aura

Menstrual attacks of MO were significantly longer, more often associated with severe nausea and required a higher number of symptomatic drugs compared to non-menstrual MO attacks in women prospectively diagnosed with ICHD-MM. These findings are in line with previous studies conducted on menstrual migraineurs from clinic populations [28-31, 112], but have never been demonstrated in the general population using diaries (Table 6). Studies conducted on all female migraineurs, report divergent findings concerning possible differences [24, 25, 32, 113, 114]. These studies include all women with migraine, instead of restricting the sample to women with MM, and are probably likely to include women who coincidentally happened to experience a migraine during one of the menstrual periods studied.

The longer duration and more resistance to acute therapy of menstrual attacks as compared to non-menstrual attacks are consistently reported across the previous studies of menstrual migraineurs [24, 29-31, 112]. The menstrual attacks in our study were treated with a significantly greater number of symptomatic drugs and lasted on average nearly 11 hours longer than non-menstrual attacks. Both findings may be explained by a prolonged trigger or indicate higher resistance to treatment. The significantly higher number of triptan doses per menstrual attack can be the result of lower effectiveness of the first dose or higher relapse rate. All, but one previous study comparing treatment efficacy between menstrual and non-menstrual attacks in women diagnosed with MM have been performed in selected clinic populations, where patients might be more resistant to treatment [115]. Our results may indicate that menstrual attacks are more resistant to treatment also in the general population.

Whether menstrual and non-menstrual attacks differ with respect to pain intensity and associated symptoms is not clearly demonstrated, as the results differ across the studies of menstrual migraineurs (Table 6). We did not find a significant difference in pain scores. These findings might have been influenced by the higher consumption of symptomatic drugs during the menstrual attacks. The occurrence of more severe nausea is in line with one of the previous studies [28], while two others reported no difference [29, 31]. Nausea can be related to the side-effects of the higher number of

symptomatic drugs or due to systemic prostaglandin-release around the first day of menstruation.

We were not able to detect significant differences between menstrual and non-menstrual attacks in women who did not fulfil the diagnostic criteria for MM. Bearing in mind that the group of women without MM was small we cannot exclude the possibility that these analyses were underpowered. The lack of difference could though indicate that women with MM represent a subset of female migraineurs with a distinct "drive" of their attacks.

Table 6. *Characteristics of menstrual versus non-menstrual migraine attacks*

Author, year	Country, population	Design	Pain intensity	Associated symptoms	Duration	Disability	Treatment
Women with menstrual migraine							
MacGregor, 2010 [112]	USA Clinic	153 women with self-reported MM, 1 month diary, post-hoc analyses	No difference	NR	Longer	Greater impairment	More likely to relapse
Pinkerman, 2010 [29]	USA Clinic	107 women, diary-confirmed MM-diagnosis	More painful	No difference	Longer	More disabling	Higher number of doses, lower 2h pain free-responses, more relapses
MacGregor, 2006 [28]	UK Clinic	38 women, diary-confirmed MM-diagnosis, 3 cycles	More severe	More nausea and vomiting	NR	NR	NR
Granella, 2004 [31]	Italy Clinic	64 women, 2 months diaries	No difference	No difference	Longer	More disabling	Lower 2h pain free responses, more relapses
Couturier, 2003 [30]	The Netherlands General	32 women with self-reported MM in a questionnaire	More painful	NR	Longer	More disabling	More resistant to treatment
Women with migraine							
Diamond, 2008 [113]	USA Clinic	190 women, diary, pooled analysis of all reporting ≥1 menstruation from a RCT	Similar pretreatment pain intensity	No difference	NR	Similar pretreatment disability	No difference in 2h pain response or sustained pain free
Dowson, 2005 [114]	USA Clinic	30 women, 2 months diaries	NR	NR	NR	More work-related disability	NR
MacGregor, 2004 [25]	UK Clinic	155 women, ≥2 cycles diary	More painful	More nausea and vomiting	NR	NR	NR
Silberstein, 2002 [32]	USA Clinic	95 women, RCT, diaries	Similar pretreatment severity	NR	NR	NR	No difference
Stewart, 2000 [25]	USA General	81 women, 98 days diary	Slightly more painful	No difference	No difference	No difference	NR

NR: not reported

7.2.4 Contraception-induced amenorrhoea

Ever since the estrogen-withdrawal theory was launched in the 70ies, the theory has hardly been challenged and little attention have been directed towards other potential pathophysiological mechanisms, e.g. the role of the menstrual bleeding as such.

Among menstrual migraineurs in our population using hormonal contraception, achievement of amenorrhoea was associated with a self-reported reduction in migraine frequency. According to the estrogen-withdrawal hypothesis, one would expect that the improvement in amenorrhoeic women was caused by hormonal contraception that suppresses the hypothalamus-pituitary-ovary axis, consequently reducing the hormonal fluctuations. However, the majority of women with amenorrhoea in our study used the LNG-IUS (19/23), a method that mainly exerts its effects locally within the endometrial cavity with strong suppression of growth and induction of endometrial insensitivity to ovarian estradiol. Only about 15% of LNG-IUS users develop anovulation and the incidence is similar in women with and without amenorrhoea [116]. The plasma levels of estrogens and progesterone are also similar in LNG-IUS users with and without amenorrhoea, indicating that the absence of menstrual bleeding is not a predictor of ovarian function but a result of the local endometrial changes [117].

Reports evaluating the effect of hormonal contraception in relation to MM are limited and have mostly focused on prevention of estrogen withdrawal. Combined hormonal contraception (CHC) is usually given in a 21/7 regimen, i.e. 21 days with active hormones (estrogens and a progestin) followed by a seven days hormone-free interval, which is associated with withdrawal bleeds. Alternative dosing regimens, such as extended cycle with active hormones for 84-168 days followed by a 4-7 days hormone-free interval, or continuously use of active hormones without a hormone-free interval, have been studied. Such dosing regimens eliminated MM in 91% of women with very frequent migraine and reduced headache scores in another study [118, 119]. This effect was explained through stabilization of estrogen levels in one of the studies [118]. Another strategy, CHC with a shortened hormone-free interval of four, instead

of seven days, was associated with a significant reduction in attack duration and pain intensity –but not frequency, of menstrual migraine attacks [120]. This was explained by a shorter period of hypoestrogenism. Neither of the studies provides exact information about changes in bleeding pattern. While extended regimens of CHC are associated with reduction/absence of withdrawal bleeds during the period of active hormones, the shortened hormone free interval reduces the duration and/or quantity of bleeding, but not the incidence of withdrawal bleeds [121, 122]. Continuous use induces amenorrhoea in 80% to 100% of women [123]. The hormonal manipulations may thus not be the only explanation of the positive outcomes in these studies; a change in menstrual bleeding may also play a role. This is supported by one study reporting changes in bleeding patterns in menstrual migraineurs using a combined contraceptive pill administered with a very short hormone-free interval (two days). This administration resulted in a significant reduction in bleeding days and significant reduction in the frequency, intensity and duration of migraine attacks in women with menstrually-related migraine [124].

If the bleeding as such plays a role, systemic prostaglandin-release during the first 48 hours of menstruation may be a potential mechanism, as intravenous infusion of prostaglandins is known to trigger migraine attacks in subjects with migraine [62-64, 125, 126]. It could be hypothesized that the observed benefit of contraception-induced amenorrhoea in women with ICHD-MM was a result of reduced prostaglandin synthesis and subsequently diminished release from endometrium. Since the systemic release of prostaglandins coincides with the falling levels of estrogens, both mechanisms may be responsible for triggering menstrual migraine attacks. Elimination of at least one of the pathways/mechanism, may lead to improvement.

Categorizing the diverse types of contraception into two groups based on the effect on withdrawal bleeds/menstruation may seem overly simplistic due to the different mechanisms of action in the diverse types. However, the aim of this retrospective analysis was to explore the effect of amenorrhoea per se and our study did not include enough cases to describe each type of contraception separately. The majority of

amenorrhoeic women used the LNG-IUS and no former studies have evaluated the effect of the LNG-IUS on menstrual migraine.

The low number of women using hormonal contraception and the retrospective design represent obvious limitations of these analyses. Paper IV is first and foremost meant to be hypothesis-generating and only future prospective studies evaluating the effect of amenorrhoea using different strategies to achieve amenorrhoea -with and without inhibition of ovulation, can provide more robust answers.

8. Conclusion and the future

About one fifth of all female migraineurs have migraine occurring during the perimenstrual period in at least 50% of their cycles and the majority of these women fulfil the ICHD criteria for MM. The lifetime prevalence of ICHD-MM was 17.6% among female migraineurs and 6.1% among all women aged 30-34 years in this general population. A thorough clinical interview is valid for the diagnosis of MM, but cannot replace a diary for the diagnosis of the subtypes of MM; pure and menstrually related migraine. Menstrual migraine attacks are associated with more severe symptomatology, but only in women who fulfil the diagnostic criteria for MM. Women with a history of ICHD-MM reported improvement of their total frequency of MO after initiating progestin-only contraception leading to amenorrhoea. While estrogen-withdrawal has been promoted as the main trigger for menstrual attacks, this research suggests that an alternative pathophysiology associated specifically with menstrual bleeding may play a role as a trigger of menstrual attacks.

8.1 The diagnostic criteria of menstrual migraine

This study raised some questions about the diagnostic criteria for MM. The wording in the ICHD-criteria: "... attacks occur on day 1±2 of the menstrual cycle..." opens for misinterpretation. MM may be diagnosed if one day in a multiday-attack occurs within this time period, even if the attack started earlier than day -2. The wording "…attacks starting on day 1±2 of the menstrual cycle..." is less ambiguous.

The criteria allows for inclusion of women in whom the association between migraine and menstruation is weak, since no upper limit of non-menstrual attacks is defined. This contradicts the aim of the criteria: to identify women with an association between migraine and menstruation that is greater than by chance [127]. Inclusion of such cases is likely to dilute research results and additional methods for exclusion of chance occurrence among women who otherwise fulfil the ICHD-criteria would improve the diagnostic criteria. One proposed algorithm is that the number of non-menstrual migraine days must be no more than double the number of menstrual migraine days

[127]. A statistical approach for association has also recently been published [128]. Calculations from this paper indicate that an observational period of three consecutive menstrual cycles is too short to determine whether an association is present and that a minimum of four perimenstrual periods are needed. This method is awaiting clinical validation.

As previously shown and discussed, a small subgroup of women with MA experienced regularly MA-attacks in relation to menstruation. Whether these women share the same pathophysiological mechanisms as women with ICHD-MM is unknown. Inclusion of this group into the appendix of the ICHD III could facilitate research on this group.

MM affects more women than most other headache disorders recognized by the ICHD. Women with MM may have different pathophysiology of their menstrual attacks concerning the differences in symptomatology and greater resistance to treatment. We have shown that this is also true in the general population. Women with MM can be offered different treatment strategies than other female migraineurs. The present thesis, combined with previous studies, suggest that MM should be defined as a subtype of MO in the ICHD III.

8.2 Future questions

Many questions remain unanswered. The role of the menstrual bleeding as such needs further exploration. Prospective studies of MM in relation to different types of hormonal contraception with and without inhibition of ovulation may represent models in order to study this. Another question is why only a subset of female migraineurs develops MM and why not all menstrual migraineurs report a constant association between migraine and menstruation from menarche to menopause. Genetic and experimental studies, together with epidemiological studies, might provide some answers. The crucial point is that we all study the same group, which is only possible if the diagnostic criteria are used and interpreted in the same way.

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10. Errata

Page/line	Original text	Revised text
18/2	Presented in table 2	Presented in table 1
21/20	"….prostaglandins have been proposed as a trigger migraine of MM".	"….prostaglandins have been proposed as a trigger of MM".
33/10	(Table 3)	(Table 2)
35/1	Table 4	Table 3
37/8	Presented in Table 5	Presented in Table 4
38/7	Presented in Table 6	Presented in Table 5
43/20	(Appendix 2)	(Appendix 3)
49/1 + 13	7.2.3 and 7.2.4	Removed from the text
50/1	7.2.5	Removed from the text
53/7 + 26	(Table 7)	(Table 6)
55	Table 7	Table 6
73/question 1		Added the variable "1 day"
73/question 6	In 1 out of two menstruations	In 1 out of 2 menstruations

11. Appendix

11.1 Appendix 1: The screening questionnaire

1	How many days did you experience headache during the preceding *month*?	☐ 0 days ☐ 1 day ☐ 2-6 days ☐ 7-14 days ☐ 15 days or more
2	How many days did you experience headache during the preceding *year*?	☐ 0 days ☐ 1-11 days ☐ 12-30 days ☐ 31-84 days ☐ 85-179 days ☐ 180 days or more
3	Have you ever had migraine?	☐ Yes ☐ No
4	Have you had migraine during the preceding year?	☐ Yes ☐ No
5	Do you have migraine in relation to your menstruation?	☐ Yes ☐ No
6	How often do you have migraine in relation to your menstruation?	☐ Every time ☐ In 2 out of 3 menstruations ☐ In 1 out of 2 menstruations ☐ Seldom

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11.2 Appendix 2: Questions from the semi-structured interview

	Yes	No
1. Do you use contraception?	☐	☐

2. Type	Amenorrhoea Yes	No
a. Combined oral contraceptive pill (monophasic)	☐	☐
b. Combined oral contraceptive pill (multiphasic)	☐	☐
c. Transdermal patch	☐	☐
d. Combined contraceptive vaginal ring	☐	☐
e. Etonorgestrel implant	☐	☐
f. Progestin-only pill	☐	☐
g. Levonorgestrel intrauterine system	☐	☐
h. DMPA-injection	☐	☐
i. Copper intrauterine device	☐	☐

3. Did your migraine without aura change after initiation of current contraceptive method regarding

	Less	Unchanged	More
Frequency	☐	☐	☐
	Better	**Unchanged**	**Worse**
Pain intensity	☐	☐	☐
	Shorter	**Unchanged**	**Longer**
Attack duration	☐	☐	☐

4. Duration of current contraceptive treatment (months) ☐☐☐

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11.3 Appendix 3: The headache- and menstruation diary

ID number	Date:	/	/	/	/	/	/
When did the headache start?	Indicate nearest hour:						
Before headache started, was there	vision:	☐	☐	☐	☐	☐	☐
there any disturbance of:	numbness/tingling in your skin:	☐	☐	☐	☐	☐	☐
	other disturbances:	☐	☐	☐	☐	☐	☐
Is the headache	right sided:	☐	☐	☐	☐	☐	☐
	left sided:	☐	☐	☐	☐	☐	☐
	on both sides:	☐	☐	☐	☐	☐	☐
Is the headache	Pulsating/throbbing:	☐	☐	☐	☐	☐	☐
	tightening/pressuring:	☐	☐	☐	☐	☐	☐
How intense is the headache on a scale from 0-10 (0=no pain, 10=worst imaginable pain)		☐☐	☐☐	☐☐	☐☐	☐☐	☐☐
Does the headache change by routine physical activity?	aggravation:	☐	☐	☐	☐	☐	☐
	unchanged:	☐	☐	☐	☐	☐	☐
	improved:	☐	☐	☐	☐	☐	☐
Do you suffer from nausea during headache?	no:	☐	☐	☐	☐	☐	☐
	mild:	☐	☐	☐	☐	☐	☐
	moderate:	☐	☐	☐	☐	☐	☐
	severe:	☐	☐	☐	☐	☐	☐
Are you bothered by light during headache?	no:	☐	☐	☐	☐	☐	☐
	mild:	☐	☐	☐	☐	☐	☐
	moderate:	☐	☐	☐	☐	☐	☐
	severe:	☐	☐	☐	☐	☐	☐
Are you bothered by sounds during headache?	no:	☐	☐	☐	☐	☐	☐
	mild:	☐	☐	☐	☐	☐	☐
	moderate:	☐	☐	☐	☐	☐	☐
	severe:	☐	☐	☐	☐	☐	☐
When did the headache end?	Indicate nearest hour:						
Menstruation (x)		☐	☐	☐	☐	☐	☐
Spotting (x)		☐	☐	☐	☐	☐	☐
Sick leave	yes:	☐	☐	☐	☐	☐	☐
	no:	☐	☐	☐	☐	☐	☐
Did you take any medication? Please record name, dose and time taken							

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