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Endometriosis Awareness Promotion Project (EAPP) Collaboration Group

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Patterns of menstrual cycle, menstrual pain and medication usage in young women of high-income and middle-income countries

Endometriosis Awareness Promotion Project (EAPP) Collaboration Group*

Correspondence address:

Khaleque N Khan, MD, PhD

Department of Obstetrics and Gynecology

The Clinical and Translational Research Center

Graduate School of Medical Science

Kyoto Prefectural University of Medicine

465 Kajii-cho, Kamigyo-ku, Kyoto 602-8566, Japan

Tel: +81-75-251 5560

Fax: +81-75-212 1265

Email: nemokhan@koto.kpu-m.ac.jp

<http://orchid.org/0000-0002-9493-3340>

ABSTRACT

Research question: Do patterns of menstrual cycle, menstrual pain and the use of medication for menstrual pain differ in young women of high-income (HICs) and middle-income countries (MICs)?

Design: A multinational and multicenter cross-sectional study using pen-and-paper questionnaires survey among women was conducted between 2016 and 2021 to assess the patterns of menstrual cycle, menstrual pain and the use of medication for menstrual pain. We evaluated different parameters among these women, to identify high risk factors for causing severe menstrual pain, who were enrolled from two HICs (n=1550) and nine MICs) (n=7139).

Results: Among a total of 9114 young women, 4920 female medical students (HICs, n=696 and MICs, n=4224) and 3769 female nursing students (HICs, n=854 and MICs, n=2915) were finally recruited for this study. Comparing to HICs, significantly higher proportion of medical ($p<0.001$) and nursing ($p<0.001$) students of MICs complained of cyclic (83.9% and 86.8%, respectively) and acyclic pain (33.8% and 31.9%, respectively). Multivariate regression analysis revealed that slender women and early

onset of menarche were independent risk factors associated with severe cyclic pain among women of HICs, and family history of menstrual pain was a risk factor for severe cyclic pain among women of HICs or MICs.

Conclusions: We observed differential patterns of menstrual cycle, menstrual pain and use of medication for pain among young women of HICs and MICs. A proper educational plan may be necessary to these women and health-care providers to understand the consequence of intractable cyclic/acyclic pain to facilitate early detection and timely management of menstrual pain and its negative consequences such as endometriosis.

Key words: menstrual cycle, menstrual pain, medication, young women, high-income countries, middle-income countries

INTRODUCTION

Menstrual symptoms among women of reproductive age impose a heavy burden on afflicted women and their families that is often underestimated and inadequately investigated. The patterns of menstrual cycle and of menstrual pain vary greatly depending on individual woman, level of education, nutritional status, exposure to stress, and cultural background of each country (Sharp et al. 2022). The prevalence of menstrual pain, manifesting mainly as dysmenorrhea, is reported to range from 25% among all women to as high as 90% among adolescents (Zondervan et al. 2020; Osuga et al. 2005). Menstrual pain is the most common gynecological complaint in women of reproductive age. Among adolescent girls with dysmenorrhea, less than 15% of them seek medical help even though their symptoms interfere with their daily life. More than one-third of them, however, do nothing about their condition (Wong et al. 2010). A large survey-based research study of 4,000 Japanese women of reproductive age revealed that only 12% of surveyed women sought medical help for their menstrual pain and most of the women taking the survey felt that it was natural to experience pain during menstruation (Taketani. 2000; Tanaka et al. 2014). This perception may account

for the low consultation rate for menstrual problems in Japan, and as a result they may suffer from its consequences of inaction, such as endometriosis.

In many countries, adolescent girls, young women, the general public as well as many front-line healthcare providers are unaware of the fact that distressing and life-altering menstrual pain is anything but normal, leading to a normalization and stigmatization of symptoms and significant diagnostic delay (Zondervan et al. 2020). Young women, who could benefit from timely medical management of their symptoms, are not always provided with options for interventions due to poor or limited knowledge and awareness of menstrual pain and its consequence such as endometriosis among primary health care providers. Our knowledge is still insufficient on the basic concept of menstrual pain and its consequences among young women in Japan and other Asian countries. Therefore, raising the awareness of menstrual pain and of endometriosis, the two often neglected conditions, is important among young women in low- and middle-income countries as well as high-income country. In view of this, we recently demonstrated a rudimentary knowledge of menstrual pain and endometriosis among young women and the effect of a targeted educational program on improving this

knowledge were found in young women of high-income (HICs) and middle-income countries (MICs) (Khan et al. 2022). This educational program may be useful to raise the awareness and motivate these women to seek early medical intervention in order to reduce or eliminate unnecessary delay in treating patients.

Endometriosis is one of the consequences or a hidden cause of constant cyclic and acyclic pain in women, especially those who are resistant to medical treatment (Janssen et al. 2013). According to the recent ESHRE guideline, endometriosis can be diagnosed only with the presence of endometriosis-related pain (The members of the Endometriosis Guideline Core Group et al., 2022). Endometriosis affects roughly 10% (190 million) of reproductive age women and girls globally (Zondervan et al. 2020). Similar to menstrual pain, endometriosis has significant social, public health, and economic implications. It can negatively impact on the quality of life due to severe pain, fatigue, depression, anxiety, and infertility. Menstrual pain and endometriosis-associated pain cause considerable absenteeism in work or schooling (Culley et al. 2013). In these situations, addressing menstrual pain in young women can reduce work/school absenteeism and increase an individual's ability to improve school performance or work

productivity. A range of factors, such as short menstrual cycle, early onset of menarche, chronic cyclic and acyclic pain, family history of endometriosis and/or dysmenorrhea in first blood-related individual, and resistance to over-the-counter medication, have been considered as possible determinants to identify high-risk individuals who are susceptible to develop endometriosis (Janssen et al. 2013; Culley et al. 2013). It is conceivable that social infrastructure, cultural/ethnic background, religious belief and influence of internet/mass media in individual country may affect the patterns of menstrual cycle, self-identification of menstrual pain, and decision to take proper medication for menstrual pain in young women of HICs and low-/middle-income countries (LMICs). However, data on these issues in young women of HIC and/or MIC are scanty, if any.

Based on the significance and necessity of these unresolved issues facing young women in HICs and MICs, some potential scientific questions can be raised to form the core of our current research plan: (1) Would analysis of menstrual pain and medication for menstrual pain help us to identify high-risk individuals for early detection and timely management of endometriosis? (2) Would analysis of the pattern

of menstrual cycle and background profiles of young women in HICs and MICs give us some clue to identify high-risk individuals who are susceptible to endometriosis? In order to address these issues, we conducted a self-reported and questionnaire-based study of female medical and nursing students during the period of 2016-2021 with the following purposes: (1) Analysis of the demographic profiles, patterns of menstrual cycle, cyclic and acyclic pain, medication for menstrual pain of young women who were enrolled from HICs and MICs, in order to understand the difference, if any, in menstrual cycle, menstrual pain and medication usage to control their pain between HICs and MICs which might be helpful to identify high-risk individuals and prompt them to see a gynecologist for early diagnosis and management, (2) Based on the recent report that slim women (under weight or normal weight) are more susceptible to developing endometriosis than overweight or obese women (Hediger et al. 2005; Shah et al. 2013; Farland et al. 2017) and that suffering from dysmenorrhea and/or chronic pelvic pain could be an indirect parameter of endometriosis (Fauconnier and Chapron, 2005; Bloski and Pierson, 2008), we analyzed the relationship between body mass index (BMI) and visual analogue scale (VAS) scores (0-10) in these young women, (3) We

performed multiple logistic regression analysis with different confounding variables to identify high-risk factors in association with severe cyclic/acyclic pain.

MATERIALS AND METHODS

Participants. This was a multinational and multicenter cross-sectional collaborative study of medical and nursing students conducted during the period of September 2016 and December 2021. Before initiation of this self-reported pen-and-paper questionnaire survey, the principal investigator (PI, KNK) of the study visited and/or E-mail contacted different medical and nursing schools in two HICs (Japan and Lithuania) and 9 MICs (Kazakhstan, Sri Lanka, Vietnam, Indonesia, Turkey, Thailand, Iran, Taiwan, Bangladesh) for discussion with the concerned medical and nursing personnel on study design. The definition of HIC and MIC was based on the criteria of New World Bank Classification (July 1, 2022) by Gross National Income (GNI) per capita in USD (Hamadeh et al. 2022). GNI per capita is the dollar value of a country's final income in a year divided by its population using Atlas methodology (<http://data.worldbank.org/indicator/NY.GNP.PCAP.CD/countries>). According to this classification of World Bank, MICs are nations that have a per capita GNI between

\$1,046 and \$12,695 and of >\$12,695 for HICs (www.blogs.worldbank.org).

Our proposed endometriosis awareness promotion project (EAPP) has two parts, Part I and Part II. The Part I of EAPP study was designed to evaluate the fundamental concept of menstrual pain and endometriosis among young women and the effect of education on its improvement after group discussion and lecture and is recently published (Khan et al. 2022). The current Part II of our EAPP study was designed to identify high-risk individuals who are susceptible to developing endometriosis based on their particular pattern, if any, of menstrual cycle, menstrual pain, medication usage for menstrual pain and demographic profiles of medical and nursing students in HICs and MICs. After proper explanation of the purpose, methodology and the impact of the study, the research coordinators of each university and/or institution collected survey data from medical or nursing students. All incomplete survey data were excluded. A letter of information was sent to the Principal/Dean/Director of respective participating institution and/or hospital explaining the purpose and nature of the study. Confidentiality was ensured and emphasized. All these academic institutions obtained either Ethics Committee approval for this study from respective Institutional Review

Board (IRB) or respective Institutional approval with the reference of IRB approval letter of Kyoto Prefectural University of Medicine (IRB approval No. ERB-C-648-4).

Questionnaire survey. The study was conducted using self-reported pen-and-paper method based on original and structured questionnaires. All questions written in English were translated into Japanese and native language of each participating country. After clarification of the purpose to each category of students, all paper questionnaires were distributed to groups of students in the classroom before starting lecture by the attending lecturer. They were given adequate time to complete the questionnaires which were collected from each student in the same sitting.

The questionnaires of our EAPP part II study for medical and nursing students had four sections: (1) Demographic profiles of students (age, BMI, age at menarche, age at cyclic/acyclic pain, family history of cyclic/acyclic pain, and vaginal discharge, if any). BMI was defined to be the weight in kilogram divided by the square of the height in meters and was categorized into four groups: underweight as $\text{BMI} \leq 18.5 \text{ kg/m}^2$, normal weight, $18.5\text{-}24.9 \text{ kg/m}^2$, overweight, $25\text{-}29.9 \text{ kg/m}^2$, and obese, $\geq 30 \text{ kg/m}^2$ as described elsewhere (Di Angelantonio et al. 2016). (2) Pattern of menstrual cycle

(length, regularity, duration of bleeding per cycle), (3) Pattern of menstrual pain (cyclic/acyclic pain, type of pain symptoms, multiplicity of pain, severity of cyclic/acyclic pain, school absenteeism due to cyclic pain). The degree of severity in menstrual pain was measured by the visual analog scale (VAS) to self-measure the pain severity from a scale of 0-10. A VAS score of <7 was considered as mild, moderate or no pain and of ≥ 7 as severe pain. (4) Pattern of medication usage for menstrual pain (medication received or not, if yes, type of medication, duration of medication, usefulness of medication received). All these paper questionnaires were validated before by an initial trial of female college students in Japan (Akira S, 2013).

Statistical analysis. After completion of four sections of questionnaire survey, all data in excel files from each institution were sent to the PI (KNK) of Kyoto Prefectural University of Medicine (KPUM), Kyoto in Japan. The PI of KPUM reviewed and summarized all data in excel files and tabulated them in word files with the help of one of the co-authors of KPUM (KO). All survey data were double-checked and was excluded if there was any duplicated data or missing data (KO and HO). Continuous variables of all questionnaire survey data were compared between groups

using Wilcoxon rank sum test and categorical variables were compared using Chi-squared test or Fisher's exact test. Any correlation between groups was analyzed by Spearman's rank correlation coefficient. Multivariate logistic regression analysis was used to identify independent significant risk factors for the severity of cyclic/acyclic pain and to estimate the odds ratios (ORs) and their 95% confidence intervals (CIs) for each of the selected factors. All reported p values were 2-sided. A value of $p < 0.05$ was considered statistically significant. All data analyses were conducted using SAS software version 9.4 (SAS Institute Inc. Cary, NC, USA).

RESULTS

A total of 9114 young women were initially recruited from all HICs and MICs for EAPP survey during the period between June 2016 and December 2021. After careful double check and scrutiny of all data, a proportion of medical students (HIC, $n=33$ and MIC, $n=157$) and nursing students (HIC, $n=235$) was excluded from data analysis due to duplicated and/or missing data. Finally, 4920 female medical students (HICs, $n=696$ and MICs, $n=4224$) and 3769 female nursing students (HICs, $n=854$ and MICs, $n=2915$), who completed the response of all four sections of the questionnaire

survey, were included for data analysis. A flow chart describing individual number of medical and nursing students from each of HIC and MIC is shown in Figure 1. A detail university, institution, and/or hospital-based information on the number of medical and nursing students from each of HIC and MIC are shown in Suppl. Table 1.

Demographic profiles of medical and nursing students of HICs and MICs

The detail demographic profiles of enrolled medical and nursing students are shown in Table 1. The median age of the medical students of HICs was significantly higher than that of MICs ($P < 0.001$) and the age of the nursing students of HICs was found to be significantly lower comparing to that of MICs ($P < 0.001$). Regarding age at menarche, the onset of menarche was significantly earlier among medical and nursing students of HICs ($P < 0.001$ for both) than those of MICs. The majority of medical and nursing students from both HICs and MICs started their first menstruation at the age of 12-14 years.

Family history (F/H) of cyclic and acyclic pain among the first blood-related family members has been considered as one of the high-risk factors in young women who are susceptible to developing endometriosis (Janssen et al. 2013; Culley et al.

2013). In the analysis of our data, we found that there was no difference in the proportion of F/H of cyclic and acyclic pain among medical students between HICs and MICs. However, comparing to MICs, a significantly higher proportion of nursing students of HICs responded that they had a F/H of cyclic pain (60.1% vs. 52.7%, $P=0.001$) and acyclic pain (49.7% vs. 37.9%, $P=0.004$) (Table 1).

Patterns of menstrual cycle among medical and nursing students of HICs and MICs

We grouped the length of menstrual cycle as short, normal, and prolonged menstrual cycle among the medical and nursing students of HICs and MICs (Table 2). The results showed significant differences between HICs and MICs for both medical and nursing students ($P=0.002$ and $P<0.001$, respectively). We found that a considerable proportion of medical students of MICs complained of short menstrual cycle (<24 days, 4.8% vs. 2.8%) as compared with those from HICs. The proportions of medical and nursing students with prolonged menstrual cycle (>32 days) were significantly higher for those from HICs than that of those from MICs (Table 2).

Excessive and/or prolonged blood loss during menstrual cycle among young

women is one of the high-risk factors for the development of endometriosis (Missmer et al. 2004). We found that the proportion of medical and nursing students of HICs with excessive blood loss (for ≥ 5 days per cycle) was significantly higher as compared with those from MICs (64.8% vs. 37.1% for medical students and 65.2% vs. 45.2% for nursing students) (Table 2).

Patterns of menstrual pain among medical and nursing students of HICs and MICs

The proportion of students complaining of cyclic and acyclic pain was significantly higher among medical (83.9% vs. 70.3%, $p < 0.001$) and nursing students (86.8% vs. 70.0%, $p < 0.001$) of MICs as compared with those in HICs (Table 3). Both medical and nursing students from HICs and MICs complained of variable patterns of menstrual pain symptoms and are shown in Figure 2. We found that abdominal pain and pelvic/back pain was the most common type of pain symptoms among these students living in both HICs and MICs. A variable proportion of students living in HICs and MICs reported dysuria (pain at urination), dyschezia (pain at defecation), and other digestive and non-digestive symptoms during menstruation (Table 3).

Considering the severity of pain, our analysis showed that both medical and nursing students of HICs more frequently and significantly complained of severe cyclic and acyclic pain (VAS score ≥ 7) as compared with those in MICs ($P < 0.001$ for each) (Table 3). A graphic representation of the patterns of menstrual pain and severity of cyclic/acyclic pain among medical and nursing students living in HICs and MICs is shown in Figure 3.

In response to the question, “how many days did you refrain from going to school due to cyclic pain”, we found that school absence due to cyclic pain was significantly more frequent among both medical and nursing students in MICs comparing to those in HICs (26.6% vs. 13.3%, $P < 0.001$ for medical students and 16.7% vs. 11.2%, $P = 0.001$ for nursing students) (Table 3).

Correlation between BMI and VAS scores of menstrual pain among medical and nursing students of HICs and MICs.

We did not find any significant relationship between BMI and VAS scores of abdominal pain and/or pelvic/back pain during menstruation in either of medical or nursing students who were enrolled from HICs and MICs (Suppl. Fig. 1).

Patterns of medication for menstrual pain among medical and nursing students of HICs and MICs

The pattern of medication for menstrual pain differs among young women depending on health care access, health insurance system, family structure, social/cultural background, and religious belief of each country. Our analysis revealed that medication usage due to menstrual pain was more frequent in medical students of MICs than those of HICs (67.8% vs. 62.4%, $P < 0.001$) and in nursing students of HICs than those of MICs (54.7% vs. 38.7%, $P < 0.001$) (Table 4). The non-steroidal anti-inflammatory drug (NSAID) was the most commonly used medication among these students of HICs and MICs. The use of anti-spasmodic drug such as hyoscine butyl bromide (buscopan) by these students was less common in HICs than in MICs. There was no significant difference in the use of hormonal medication (combined E2-P4 pill or progestin compound) among these students between HICs and MICs. The duration of NSAID intake was significantly longer (≥ 6 cycles) among medical and nursing students of HICs comparing to that among students of MICs. The duration in the use of hormonal medication among medical students of HICs was significantly longer than for

those in MICs (46.2% vs. 21.0%, $P=0.001$) (Table 4).

In response to the question “was your medication useful to control your menstrual pain?” most students of HICs and MICs responded that either NSAID or hormonal medication was useful to control their menstrual pain. These were more significantly useful for medical and nursing students of MICs than for those of HICs.

Risk factors associated with the severity of cyclic and acyclic pain.

To identify risk factors, if any, for the severity of cyclic and acyclic pain (VAS score ≥ 7), we selected several confounding factors such as age, BMI, age at menarche, F/H of cyclic pain, F/H of acyclic pain, length of menstrual cycle, duration of blood loss/cycle, usefulness of medication, and vaginal discharge. The results of multiple regression analysis are shown in Suppl. Table 2 and the detail explanation of identified risk factors in cyclic and acyclic pain is summarized in the supplementary text.

Collectively, multiple regression analysis revealed that the younger age of the women was an independent protective factor for the occurrence of cyclic pain in HICs (OR=0.87, 95% CI=0.79 to 0.96, $P=0.007$) and MICs (OR=0.93, 95% CI=0.90 to 0.96, $P<0.001$). Slender women with low BMI (OR=0.74, 95% CI=0.56 to 0.97, $P=0.03$) and

early onset of menarche (OR=0.64, 95% CI=0.43 to 0.96, P=0.030) were independent risk factors associated with severe cyclic pain among women of HICs and family history of menstrual pain was a risk factor for severe cyclic pain among women of HICs (P=0.011) and MICs (P<0.001).

DISCUSSION

In an attempt to identify high-risk individuals who are susceptible to suffer from severe cyclic and acyclic pain, we conducted a multinational cross-sectional questionnaire-based study among young women during the period of 2016-2021. We observed differential patterns of demographic profile, menstrual cycle, menstrual pain and use of medication for pain among young women of HICs and MICs. These differences might be due to local environment, knowledge gap on menstrual health hygiene and its management, differential exposure to stress/frustration, diverse basic concept on menstrual pain and early medication attention, different health care access and parents way of thinking on free discussion and medical care, religious taboo and social infrastructure between HICs and MICs. Multiple regression analysis revealed that slender women and early onset of menarche were independent risk factors associated

with severe cyclic pain among women of HICs and family history of menstrual pain was involved in suffering from severe cyclic pain among women of HICs or MICs. In fact, persistence of intractable cyclic and acyclic pain has been reported as high-risk factors leading to the development of endometriosis (Janssen et al. 2013; Culley et al. 2013).

We found that a considerable proportion of medical students of MICs complained of short menstrual cycle comparing with those from HICs. The proportions of medical and nursing students with prolonged menstrual cycle were significantly higher for those who were enrolled from HICs than that of those from MICs. Numerous epidemiological studies have indicated that nulliparous women and women with shorter menstrual cycle and heavy menstrual bleeding are at increased risk of developing endometriosis (Vigano et al., 2004; Eskenazi and Warner, 1997; Missmer and Cramer, 2003) and are consistent with young women of MICs in this study. Another meta-analysis suggests that menstrual cycle length of ≤ 27 days is associated with increased risk of endometriosis while cycle length of ≥ 29 days decreases the risk of endometriosis (Wei et al., 2016). Collectively, increased number and/or frequency of

menstruations with excessive blood loss may expose these young women to more retrograde flow of menstrual blood and consequently may elevate the risk of developing endometriosis. We need to inform these issues to increase the awareness among the local health care providers as well as among the young women of both HICs and MICs.

The proportion of students complaining of cyclic and acyclic pain was significantly higher among medical and nursing students of MICs as compared with those of HICs. This could be explained by the inadequate health care. Proper education is urgently needed for these young women of MICs in order to improve their knowledge about menstrual pain and its consequences such as endometriosis. Our analysis revealed that medication usage for menstrual pain was more frequent in medical students of MICs than those of HICs and in nursing students of HICs than those of MICs. The exact explanation of this differential uptake of medication between HICs and MICs is unclear at this moment.

Multiple regression analysis further revealed that the younger age was an independent protective factor for the occurrence of cyclic pain in HICs and MICs. The fact that younger age was associated with less menstrual pain could be explained by the

more frequent anovulation or irregular ovulation with hormonal fluctuation among younger women. Alternatively, for a woman at a very young age, not enough menstruations have occurred to allow the development of endometriosis and/or the onset of dysmenorrhea. Although not significant among the nursing students, we found that medical students of HICs were more slender than those of MICs. Compared with MICs, the lean physique of young women of HICs in our study may be due to more educational information on health care or personal health consciousness of these women. In our correlation analysis, we did not find any significant association between BMI and the severity of cyclic/acyclic pain among these young women living in either HICs or MICs. On the other hand, multiple regression analysis indicated that slender women of HICs with lower BMI was a significant risk factor associated with severe acyclic pelvic/back pain. These groups of women may be more susceptible to developing endometriosis. Our findings are consistent with two published reports. In one report, endometriosis was inversely associated with BMI in early life at 18 years and with current adult BMI (Shah et al., 2013). In another laparoscopy cohort study, women complaining of severe menstrual pain and diagnosed with endometriosis had a

consistently lean physique during adolescent and young adulthood (Hediger et al., 2005).

All these findings are validated in an experimental mouse model suggesting that altered metabolism mediated by the liver contributes to the clinically observed low BMI that is characteristic of women with endometriosis (Goetz et al., 2016).

Age at onset of menarche was significantly earlier among medical and nursing students of HICs and the proportion of nursing students in HICs with family history of cyclic and acyclic pain was significantly higher than those of MICs. These findings were consistent with our findings of multiple regression analysis showing that early age at menarche and F/H of cyclic/acyclic pain were significant risk factors for causing severe cyclic/acyclic pain. In fact, early menarche (≤ 12 yrs), detection of endometriosis and/or dysmenorrhea in first-degree relatives, and short menstrual cycle were considered as high-risk factors for developing endometriosis in young women (Treloar et al., 2010; Nnoaham et al., 2012; Steenberg et al., 2013; Missmer et al., 2004). Initial publication examining the hereditary aspects of endometriosis demonstrated an up to seven-fold risk of endometriosis in first-degree relatives of endometriosis (Nouri et al., 2010). Our findings are congruent with this report.

Early menarche in young women living in HICs can be explained by one of several factors such as better nutrition, stressful family environments, different life style and psychological factors, raised in urban environments (Padez C, 2003; Wronka and Pawlinska-Chmara, 2005), and consumption of more animal proteins (Berkey et al., 2000). Despite the risk of endometriosis, a recent population-based Korean study has shown a strong association between early menarche and the risk of metabolic syndrome, diabetes, breast cancer, and cardiovascular disease in adulthood (Kim and Lim, 2021). On the other hand, delayed menarche, as we found in young women of MICs, has been shown to have decreased bone mineral density resulting in osteoporosis and increased risk of fracture later in life (Fox et al. 1993). Therefore, it is necessary to educate pre-pubertal girls and their parents as well as young women of both HICs and MICs on the progression of puberty and development of the menstrual cycle and risk of early and delayed onset of menarche.

A recent systematic and meta-analysis report demonstrated that the prevalence of dysmenorrhea was high (71.1%) among school and university students, irrespective of the economic status of the country (Armour et al., 2019). Our current survey suggests

that the prevalence of cyclic and acyclic pain in university students differs between HICs and MICs. Both medical and nursing students in MICs significantly and more frequently suffer from cyclic and acyclic pain as compared with their counterpart in HICs. This may force these women of MICs to more frequent absence from school or work. Therefore, it is crucial to identify these young women in order to timely manage their intractable menstrual pain.

The main strengths of our current study are as follows: (1) The large sample size of the study that was performed among young women of HICs and MICs with organized collaboration and support of different research centers during the period of 2016-2021, (2) We performed detailed analysis of demographic profiles, and patterns of menstrual cycle, menstrual pain and medication usage for menstrual pain among all women, (3) We conducted multiple regression analysis with different confounding variables to identify independent risk factors related to the occurrence of severe cyclic/acyclic pain.

There are also some limitations in this study: (1) We could not include study population from low-income countries (LICs) due to the lack of contact and/or

academic interest and insufficient study organization in different institutions of these LICs. We need more motivational approach to these countries, (2) We included only medical and nursing students for our current study. Our ongoing school/college-based EAPP study in HICs and LMICs may improve our knowledge on these issues among adolescent girls. (3) We did not evaluate the presence of any obstructive anomaly of reproductive tract among our study population that may cause severe menstrual pain and elevate the risk of endometriosis.

In conclusion, we identified some high-risk factors in association with severe cyclic/acyclic pain with consequent possibility of developing endometriosis among young women living in HICs and MICs. Our multivariate analysis revealed these factors such as early menarche, low BMI, and family history of menstrual pain that were consistent with published reports (Janssen et al. 2013; Culley et al. 2013; Zondervan et al. 2020). While lower BMI and early onset of menarche were independent risk factors for severe cyclic pain among young women of HICs, family history of menstrual pain (mother or sister) was associated with severe menstrual pain among women of HICs or MICs. We also observed differential patterns of demographic profile, menstrual cycle,

menstrual pain and medication usage for pain among these women of HICs and MICs.

Based on the findings of our current study, we propose that a targeted educational program is important to improve the basic concept and to raise awareness of menstrual pain and its consequences among young women of HICs and LMICs. This doable approach may motivate these young women to seek early medical intervention to relieve their intractable menstrual pain and to improve their QOL. Addressing the consequence of menstrual pain such as endometriosis in the early life of young women will empower those affected by it and make them conscious to visit gynecologist without any further delay. We also need to educate parents, teachers, health-care providers and society leaders on this long-overlooked issue in HICs and LMICs. If prevention is still better than cure, we believe that our study approach and findings may be useful to prevent the cascade of disease progression from early to advanced endometriosis and to preserve fertility.

The authors' index of the EAPP collaboration group:*JAPAN**

(a) Kyoto Prefectural University of Medicine, Kyoto

Department of Obstetrics and Gynecology: Khaleque N Khan (principal investigator), Kanae Ogawa, Koichi Iwasa, Haruo Kuroboshi, Akemi Koshiba, Hiroyuki Okimura, Taisuke Mori, Jo Kitawaki; *School of Nursing:* Tomoko Matsuoka; *Department of Biostatistics:* Satoshi Teramukai, Go Horiguchi; *Department of Pathology and Applied Neurobiology:* Kyoko Itoh; *The Clinical and Translational Research Center (CTREC):* Khaleque N Khan, Teiji Sawa, Satoaki Matoba; *The Center for Quality Assurance in Research (CQAR):* Shinji Fushiki.

(b) Saiseikai Nagasaki Hospital, Nagasaki

Department of Gynecology: Akira Fujishita

(c) Nagasaki University School of Medicine

Department of Molecular and Diagnostic Pathology: Masahiro Nakashima

(d) Doshisha Women's College of Liberal Arts, Kyoto

Nursing School: Emiko Manabe, Mie Izumi

(e) Faculty of Medicine, Oita University, Oita

Department of Obstetrics and Gynecology: Kaei Nasu, Kentaro Kai, Yoko Aoyagi

(f) Tokyo Medical and Dental University, Tokyo

Department of Women's Health: Masakazu Terauchi, Yuki Iwahara

(g) Faculty of Medicine, Ryukyu University, Naha, Okinawa

Department of Obstetrics and Gynecology: Yoichi Aoki, Keiko Mearu

(h) Faculty of Medicine, Tottori University, Tottori

Department of Obstetrics and Gynecology: Tasuku Harada, Fuminori Taniguchi

(i) Hyogo College of Medicine, University of Hyogo, Nishinomiya, Hyogo

Department of Obstetrics and Gynecology: Atsushi Fukui, Ayano Yamaya, Yu Wakimoto, Hiroaki Shibahara

LITUANIA

Medical Faculty of Vilnius University, Vilnius

Department of Obstetrics and Gynecology: Diana Ramasauskaite, Mindaugas Silkunas, Migle Cerniauskaite

KAZAKHSTAN

Kazakh National Medical University, Almaty

Department of Obstetrics and Gynecology: Issenona Saule Shaikenovna, Kabyl Bakyt Khan, Zhambylov Nurbolat

CHINA

Fudan University, Shanghai

Shanghai Obstetrics and Gynecology Hospital: Sun-Wei Guo

SRI LANKA

Faculty of Medicine, University of Colombo

Department of Obstetrics and Gynecology: Hemantha Senanayake

VIETNAM

(a) Hanoi Obstetrics and Gynecology Hospital, Hanoi

ThuHa Nguyen Thi, Dat Tuan, Nguyen Duy Anh

(b) Hue University of Medicine and Pharmacy, Hue city

Department of Obstetrics and Gynecology: Minh Tam Le, Dac Nguyen Nguyen, Quoc Huy Vu Nguyen

INDONESIA

Faculty of Medicine, University of Indonesia, Jakarta

Department of Obstetrics and Gynecology: Andon Hestiantoro, Achmad Kemal, Raden Muharam

TURKEY

(a) Faculty of Medicine, Acibadem Mehmet Ali Aydinlar University, Istanbul

Department of Obstetrics and Gynecology: Hale Goksever Celik

(b) Faculty of Medicine, Bezmialem Vakif University, Istanbul

Department of Obstetrics and Gynecology: Engin Oral,

(c) Florence Nightingale Faculty of Nursing, Istanbul University Cerrahpasa, Istanbul

Women Health and Diseases Nursing Department: Nevin H. Sahin,

(d) Basaksehir Cam and Sakura City Hospital, Istanbul: Buket Tugba Caliskan,

(e) Zeynep Kamil Women and Children Diseases Research and Training Hospital, Istanbul, *Department of Obstetrics and Gynecology:* Miray Nilufer Cimsit Kemahli

(f) Van Özalp State Hospital, Istanbul

Department of Obstetrics and Gynecology: Ecem Atak Mutlu

THAILAND

(a) Faculty of Medicine, Mahidol University, Bangkok

Department of Obstetrics and Gynecology, Ramathibodi Hospital: Sangchai Preutthipan,

Areepan Sophonsritsuk

(b) Faculty of Science, Mahidol University, Bangkok

Department of Anatomy: Morakot Sroyraya

(c) Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Bangkok

Department of Basic Medical Science: Veerawat Sansri

(d) Faculty of Science, Mahidol University, Bangkok

Molecular Medicine Program, Multidisciplinary Unit: Panlekha Rungruang

IRAN

(a) Iran University of Medical Science, Tehran

Endometriosis Research Center: Abolfazl Mehdizadehkashi, Shahla Chaichian, *Leila

Allahqoli, Kobra Tahermanesh, Maryam Matloobi

**Current affiliation:* Ministry of Health and Medical Education (MOHME), Tehran

Department of Radiology: Reza Saadat

(b) Faculty of Medicine, Shiraz University, Shiraz

Department of Obstetrics and Gynecology: Saeed Alborzi, Tahereh Poordast

TAIWAN

(a) College of Medicine, National Cheng Kung University, Tainan

Department of Obstetrics and Gynecology: Meng-Hsing Wu

Department of Physiology: Shaw-Jenq Tsai

(b) Taichung Veterans General Hospital, Taichung

Department of Obstetrics, Gynecology and Women's Health: Ming-Jer Chen

BANGLADESH

(a) Obstetrical and Gynecological Society of Bangladesh (OGSB) Hospital and Institute of Reproductive and Child Health (IRCH), Dhaka

Department of Obstetrics and Gynecology: Sameena Chowdhury, A.T.M. Iqbal Anwar

(b) Anwar Khan Modern Medical College Hospital, Dhaka

Department of Obstetrics and Gynecology: Sharmin Abbasi

(c) Bangabandhu Sheikh Mujib Medical University, Dhaka

Department of Obstetrics and Gynecology: Saleha Begum Chowdhury

(d) Bangladesh University of Health Sciences, Center for Injury Prevention and Research, Dhaka, *Department of Epidemiology:* AKM Fazlur Rahman

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FIGURE LEGENDS

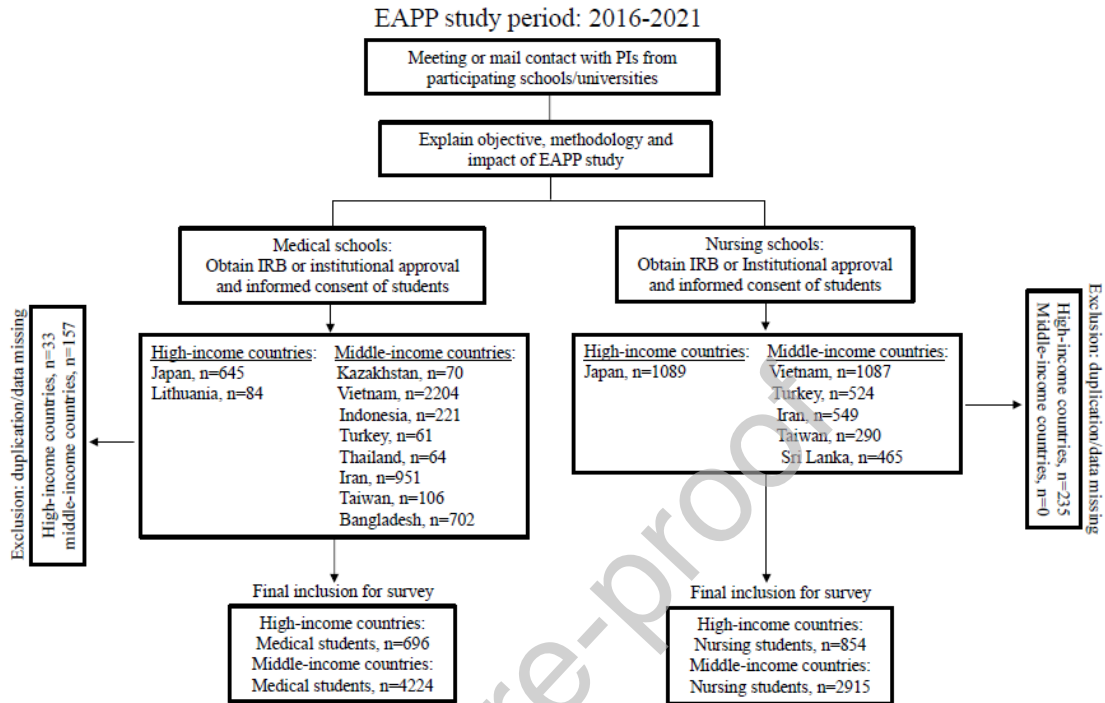


Figure 1. A flow chart of the study population who participated in this questionnaire-based cross-sectional survey study in high-income and middle-income countries during the period of 2016 to 2021. EAPP, endometriosis awareness promotion project, PI, principle investigator, IRB, institutional review board.

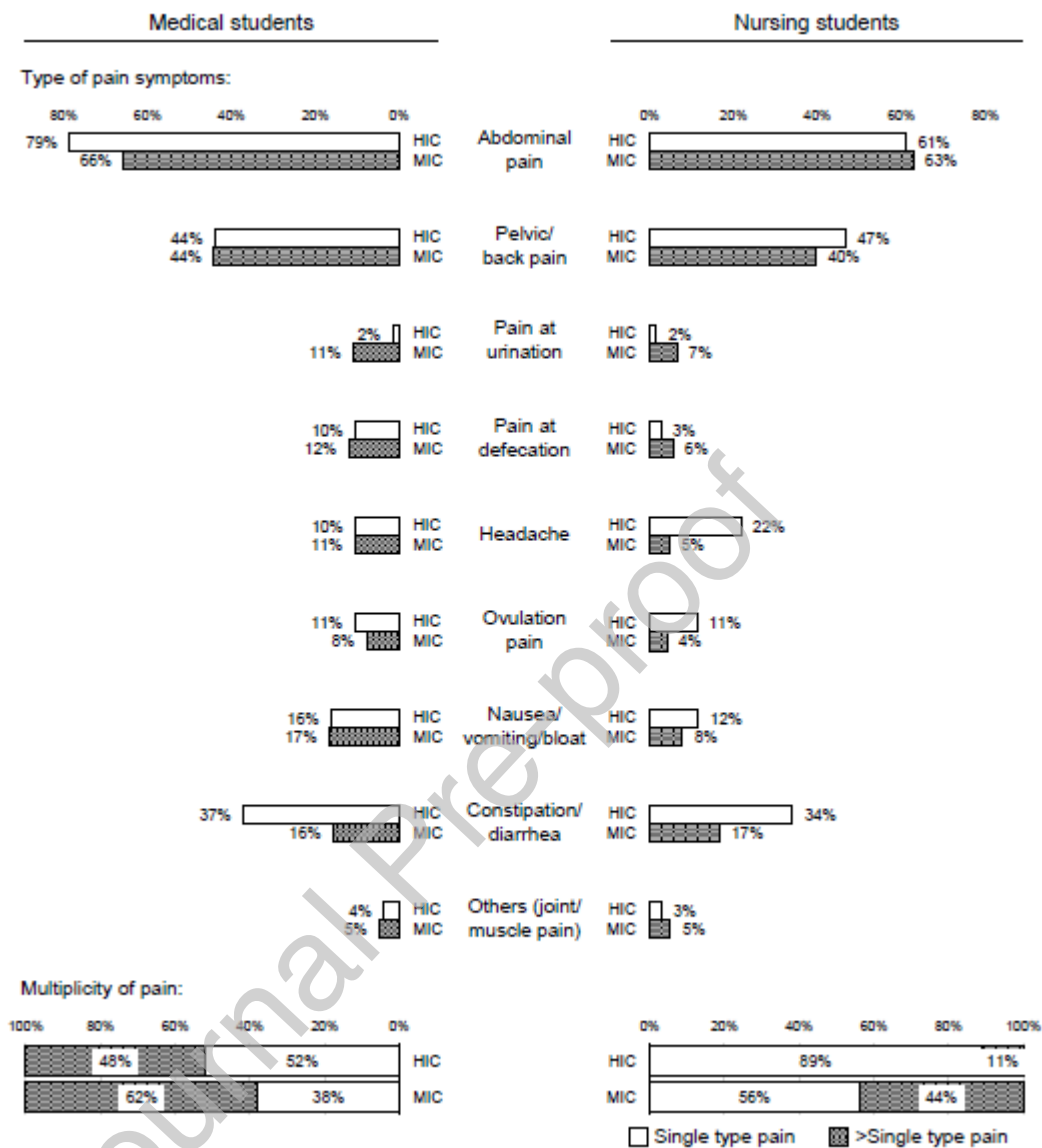


Figure 2. Shows a graphic representation of the different types of gynecologic or non-gynecologic pain symptoms, multiplicity of pain and their prevalence (%) among medical students (left panel) and nursing students (right panel) who were recruited from high-income (HICs, white bar) and middle-income countries (MICs, hatched bar).

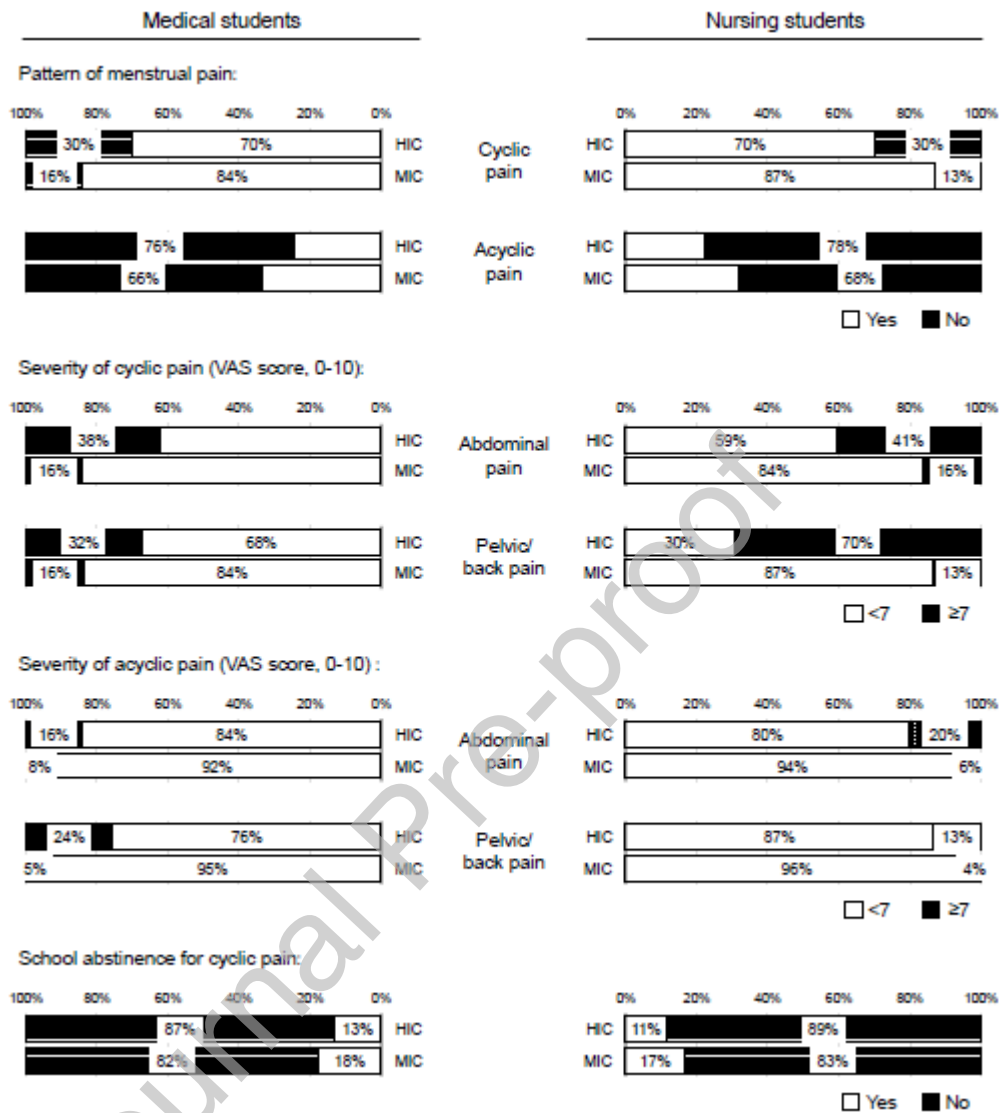


Figure 3. Shows a graphic representation of the pattern of menstrual pain, severity of cyclic/acyclic pain (VAS score, <7 vs. ≥ 7) and pattern of school absence for cyclic pain among medical students (left panel) and nursing students (right panel) who were recruited from high-income (HICs, white bar) and middle-income countries (MICs, hatched bar).

KEY MESSAGE

Differential patterns of demographic profile, menstrual cycle, menstrual pain and medication usage for pain were observed among young women of high- and middle-income countries. Multiple regression analysis revealed that slender women and early onset of menarche were independent risk factors associated with severe cyclic pain among women of HICs, while family history of menstrual pain was associated with severe cyclic pain among women of HICs or MICs. A proper educational plan may be necessary for these women and health-care providers so that they can understand the consequence of intractable cyclic/acyclic pain in order to facilitate early detection and timely management of menstrual pain and its negative consequences such as endometriosis.

Author's biography:



Khaleque N Khan, MD, PhD, is an Associate Professor and Project Coordinator of the Kyoto Prefectural University of Medicine in Kyoto, Japan. His main research interest is to investigate the pathogenesis and physiopathology of endometriosis, adenomyosis and uterine myoma. He has published over 100 articles in peer-reviewed eminent journals.

Table 1. Demographic profiles of medical and nursing students of high-income and middle-income countries

			Medical students		
Nursing students			HIC	MIC	P value
HIC	MIC	P value	(n=696)	(n=4224)	
(n=854)	(n=2915)				
Age in years			21.6 ± 2.4	21.2 ± 2.4	
19.2 ± 1.3	21.0 ± 3.6				
Median (range)			21 (18-37)	21 (16-45)	<0.001
19 (18-38)	20 (20-24)	<0.001			
No response, n			27	11	
22	24				
Body height (cm.)			159.8 ± 6.3	158.8 ± 6.7	
157.9 ± 5.1	159.9 ± 6.6				
Median (range)			160 (143-179)	158 (120-197)	<0.001
158 (141-185)	160 (120-186)	<0.001			
No response, n			32	14	
24	13				
Body weight (kg.)			51.6 ± 7.1	52.9 ± 8.7	
50.3 ± 5.6	52.9 ± 9.7				
Median (range)			50 (37-90)	52 (35-112)	0.013
50 (37-83)	51 (32-120)	<0.001			
No response, n			78	17	
94	25				
BMI (kg/m ²)			20.2 ± 2.0	20.9 ± 3.0	
20.2 ± 2.1	20.7 ± 3.2				
Median (range)			20 (15.0-30.9)	20.4 (13.9-37.4)	<0.001
20 (14.6-35.6)	20.1 (12.1-47.2)	0.192			
Underweight, <18.5, n (%)			118 (19.1)	868 (20.7)	
134 (17.6)	766 (26.6)				

Normal weight, 18.5-24.9, n (%)	484 (78.3)	2958 (70.5)	
612 (80.5) 1841 (63.9)			
Over weight, 25-29.9, n (%)	15 (2.4)	318 (7.6)	
12 (1.6) 234 (8.1)			
Obese, ≥ 30 , n (%)	1 (0.2)	54 (1.3)	
2 (0.3) 41 (1.4)			
No response, n	78	26	
94 33			
Age at menarche (yrs.)	12.3 \pm 1.4	13.1 \pm 1.5	
12.4 \pm 1.4 13.3 \pm 1.4			
Median (range)	12 (7-17)	13 (7-20)	<0.001
12 (9-17) 13 (7-19)			<0.001
9-11 yrs. n (%)	177 (27.3)	558 (13.3)	
219 (27.0) 243 (8.4)			
12-14 yrs. n (%)	423 (65.3)	2981 (70.9)	
525 (64.7) 2133 (73.9)			
>14 yrs. n (%)	48 (7.4)	666 (15.8)	
67 (8.3) 510 (17.7)			
No response, n	48	19	
43 29			
Age at cyclic pain (yrs.)	15.5 \pm 2.9	15.3 \pm 2.6	
15.1 \pm 2.1 15.1 \pm 3.0			
Median (range)	15 (10-28)	15 (9-25)	0.120
15 (9-22) 15 (9-33)			0.002
No response, n	193	877	
209 933			
Age at acyclic pain (yrs.)	17.0 \pm 3.3	15.5 \pm 2.3	
16.0 \pm 2.3 15.0 \pm 2.2			
Median (range)	17 (10-26)	15 (9-24)	<0.001
16 (10-25) 15 (9-32)			<0.001
No response, n	564	1747	
658 1788			

F/H of cyclic pain, Yes, n (%)	270 (57.2)	1937 (54.8)	0.326
353 (60.1)	1318 (52.7)	0.001	
If Yes, mother/sister/both (n)	185/72/13	1247/406/187	0.009
NR/NR/NR	899/281/132		
No response, n		0	97
353	6		
F/H of acyclic pain, Yes, n (%)	65 (44.2)	584 (42.4)	0.674
84 (49.7)	336 (37.9)	0.004	
If Yes, mother/sister/both (n)	43/20/2	401/122/51	0.088
NR/NR/NR	224/79/18		
No response, n		0	10
84	15		
Vaginal discharge, Yes, n (%)	206 (31.0)	2474 (58.9)	<0.001
179 (22.8)	1815 (62.9)	<0.001	
If Yes, regular/irregular (n)	84/122	1003/1370	0.678
53/126	757/799	<0.001	
No response, n		0	101
0	259		

The results are expressed as mean \pm SD; Continuous variables were compared between groups using Wilcoxon rank sum test and categorical variables were compared using Chi-squared test or Fisher's exact test. HIC, high-income countries; MIC, middle-income countries; BMI, body mass index; F/H, family history, NR, no response.

Table 2. Pattern of menstrual cycle among medical and nursing students of high-income and middle-income countries

			Medical students		
<u>Nursing students</u>			HIC	MIC	P value
HIC	MIC	P value	(n=854)	(n=2915)	(n=696)
					(n=4224)
<i>Length of menstrual cycle:</i>					0.002
<0.001					
<24days, n (%)			18 (2.8)		203 (4.8)
42 (5.0)	164 (5.7)				
24-28days, n (%)			146 (22.5)		1130 (26.8)
223 (26.6)	943 (32.6)				
29-32days, n (%)			354 (54.5)		2190 (51.9)
410 (48.9)	1396 (48.2)				
>32days, n (%)			131 (20.2)		693 (16.4)
163 (19.5)	392 (13.5)				
No response, n				47	8
16	20				
<i>Regularity of menstrual cycle:</i>					0.246
0.001					
≤2days difference, n (%)			176 (27.5)		911 (24.4)
165 (19.6)	748 (26.1)				
3-4days difference, n (%)			319 (49.8)		1937 (51.9)
448 (53.2)	1407 (49.1)				
≥5days difference, n (%)			145 (22.7)		885 (23.7)
229 (27.2)	711 (24.8)				
No response, n				56	491
12	49				
<i>Duration of blood loss per cycle:</i>					<0.001
<0.001					

<3days, n (%)	7 (1.0)	183 (4.6)
7 (0.8) 99 (3.4)		
3-4days, n (%)	235 (34.2)	2305 (58.3)
284 (33.9) 1483 (51.4)		
≥5days, n (%)	445 (64.8)	1465 (37.1)
546 (65.2) 1303 (45.2)		
No response, n	9	271
17 30		

Categorical variables were compared using Chi-squared test or Fisher's exact test.
HIC/MIC, high-income/middle-income countries.

Table 3. Pattern of menstrual pain among medical and nursing students of high-income and middle-income countries

		Medical students		
Nursing students		HIC	MIC	P value
HIC	MIC	(n=696)	(n=4224)	
(n=854)	(n=2915)			
<i>Pattern of menstrual pain:</i>				
Cyclic pain, Yes, n (%)		474 (70.3)	3542 (83.9)	<0.001
597 (70.0)	2508 (86.8)			<0.001
No response, n			22	3
1	24			
Acyclic pain, Yes, n (%)		160 (24.4)	1425 (33.8)	<0.001
178 (22.1)	910 (31.9)			<0.001
No response, n			39	3
50	60			
<i>Type of pain symptoms: n (%)</i>				
Abdominal pain:		547 (78.6)	2775 (65.7)	
522 (61.1)	1832 (62.8)			
Pelvic/back pain:		306 (44.0)	1866 (44.2)	
399 (46.7)	1157 (39.7)			
Pain at urination:		11 (1.6)	467 (11.1)	
14 (1.6)	190 (6.5)			
Pain at defecation:		73 (10.5)	512 (12.1)	
23 (2.7)	163 (5.6)			
Headache:		73 (10.5)	450 (10.7)	
186 (21.8)	138 (4.7)			
Ovulation pain:		74 (10.6)	327 (7.7)	
96 (11.2)	119 (4.1)			
Nausea/vomiting/bloat:		113 (16.2)	709 (16.8)	
99 (11.6)	230 (7.9)			

Constipation/diarrhea:	259 (37.2)	667 (15.8)	
291 (34.1) 485 (16.6)			
Others (joint/muscle pain):	25 (3.6)	198 (4.7)	
24 (2.8) 146 (5.0)			
<i>Multiplicity of pain: n (%)</i>			<0.001
<0.001			
Single type pain:	326 (51.9)	1062 (37.9)	
344 (88.9) 1028 (56.1)			
>Single type pain:	302 (48.1)	1743 (62.1)	
43 (11.1) 804 (43.9)			
<i>Severity of cyclic pain (VAS score, 0-10): n (%)</i>			
Abdominal pain: <7	294 (62.0)	2978 (84.1)	<0.001
353 (59.1) 2042 (83.7)	<0.001		
≥7	180 (38.0)	564 (15.9)	
244 (40.9) 399 (16.3)			
Pelvic/back pain: <7	320 (67.5)	2817 (83.8)	<0.001
60 (30.5) 2117 (86.7)	<0.001		
≥7	154 (32.5)	544 (16.2)	
137 (69.5) 325 (13.3)			
<i>Severity of acyclic pain (VAS score, 0-10): n (%)</i>			
Abdominal pain: <7	135 (84.4)	1304 (92.4)	0.001
142 (79.8) 764 (93.9)	<0.001		
≥7	25 (15.6)	107 (7.6)	
36 (20.2) 50 (6.1)			
Pelvic/back pain, <7	121 (75.6)	1172 (95.0)	<0.001
154 (86.5) 756 (96.4)	<0.001		
≥7	39 (24.4)	62 (5.0)	
24 (13.5) 28 (3.6)			
<i>School abstinence for cyclic pain:</i>			
Yes, n (%)	63 (13.3)	921 (26.6)	<0.001
67 (11.2) 417 (16.7)	0.001		
If Yes, <2days, n (%)	58 (92.1)	802 (87.1)	0.249

61 (91.0)	380 (91.1)	0.983		
	≥2days, n (%)		5 (7.9)	119 (12.9)
6 (9.0)	37 (8.9)			
	No response, n		0	82
0	6			

Categorical variables were compared using Chi-squared test or Fisher's exact test. HIC, high-income countries; MIC, middle-income countries; VAS, visual analog scale to self-measure level of pain severity from a scale of 0-10. A VAS score of <7 means mild to moderate pain and of ≥7 means severe pain.

Journal Pre-proof

Table 4. Pattern of medication for menstrual pain among medical and nursing students of high-income and middle-income countries

			Medical students		
<u>Nursing students</u>			HIC	MIC	P value
HIC	MIC	P value	(n=696)	(n=4224)	
(n=854)	(n=2915)				
<i>Medication for pain:</i>					
Yes, n (%)			405 (62.4)	1319 (67.8)	<0.001
426 (54.7)	1128 (38.7)	<0.001			
No response, n				47	125
75	0				
<i>If YES, type of medication:</i>					
NSAID: n (%)			321 (82.3)	1025 (78.7)	0.124
351 (85.4)	898 (82.2)	0.135			
No response, n				15	17
15	35				
Anti-spasmodic: n (%)			34 (8.6)	187 (14.4)	0.003
0 (0)	73 (6.7)	<0.001			
No response, n				10	16
36	94				
Hormonal: n (%)			39 (10.1)	162 (12.4)	0.203
29 (7.3)	73 (6.7)	0.660			
No response, n				17	16
29	31				
<i>Traditional China Medicine:</i>					
n (%)			3 (0.8)	103 (7.9)	<0.001
0 (0)	68 (9.4)	<0.001			
No response, n				10	15
35	90				
<i>Duration of medication: n (%)</i>					

NSAID: <6cycle		136 (42.4)	638 (62.2)	<0.001
140 (39.9)	486 (54.1)	<0.001		
≥6 cycle		185 (57.6)	387 (37.8)	
211 (60.1)	412 (45.9)			
Hormonal: <6cycle		21 (53.8)	128 (79.0)	0.001
20 (69.0)	45 (61.6)	0.488		
≥6 cycle		18 (46.2)	34 (21.0)	
9 (31.0)	28 (38.4)			
<i>Was medication useful?</i>				
NSAID or hormonal: Yes, n (%)		193 (55.1)	992 (85.7)	<0.001
263 (72.1)	726 (78.2)	0.018		
No response, n		10	30	
15	43			

Categorical variables were compared using Chi-squared test or Fisher's exact test. HIC, high-income countries; MIC, middle-income countries; NSAID, non-steroidal anti-inflammatory drug, Hormonal medication includes either of combined estrogen-progesterone pill or progestin compound.