Menstrual disorders in a Paediatric and Adolescent R I G I N A L Gynaecology Clinic: patient presentations and **longitudinal outcomes**

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Objective To study the presentations, diagnoses, and outcomes in

adolescents with menstrual disorders.

Design Prospective cohort study.

Paediatric and Adolescent Gynaecology Clinic, Hong Kong. Setting

A total of 577 adolescents aged 14 to 19 years. **Participants**

Main outcome measures The presentations and diagnoses of adolescents with menstrual

disorders were reviewed and their menstrual outcomes determined by a telephone survey.

In all, 47% presented with menorrhagia, prolonged menstruation, and short menstrual cycles; 27% had secondary amenorrhoea, 12% had dysmenorrhoea, 11% had oligomenorrhoea, and 3% had primary amenorrhoea. Significant diagnoses included congenital genital tract anomalies, premature ovarian failure, anorexia nervosa, and polycystic ovarian syndrome. Polycystic ovarian syndrome was diagnosed in 16% of the cohort. In all, 24% of these 577 patients had abnormal menstrual cycles 4 years later. Direct logistic regression analysis indicated a cycle length of more than 35 days at presentation (adjusted odds ratio=2.8; 95% confidence interval, 1.8-4.5), previous diagnosis of polycystic ovarian syndrome (adjusted odds ratio=2.0; 95% confidence interval, 1.1-3.4), and current body mass index of 23 kg/m² or higher (adjusted odds ratio=1.8; 95% confidence interval, 1.0-3.0) were risk factors for persistently long menstrual cycle exceeding 35 days. Adolescents who were screened out with a definitive diagnosis after initial assessment were at low risk of persistently long menstrual cycles at follow-up (adjusted odds ratio=0.3; 95% confidence interval, 0.1-0.8).

Conclusions

Adolescent menstrual disorders should not be ignored. Long cycle, diagnosis of polycystic ovarian syndrome at first consultation, and a current body mass index of 23 kg/m² or higher were statistically associated with persistent problems.

Key words

Adolescent: Amenorrhea: Menstruation disturbances; Polycystic ovary syndrome

Hong Kong Med J 2011;17:391-7

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New knowledge added by this study

- Up to 16% of Hong Kong adolescent girls presented with menstrual disorders suffered from polycystic ovarian syndrome (PCOS) in our study.
- Long cycle lengths at first consultation, diagnosis of PCOS at first consultation, and body mass index of ≥23 kg/m² at follow-up were associated with persistently long menstrual cycle length (>35 days). Adolescents who were screened out for a definitive diagnosis after initial assessment were at low risk of persistently long menstrual cycles at follow-up.

Implications for clinical practice or policy

- Those adolescents with oligomenorrhoea or amenorrhoea after 2 years following menarche should be investigated.
- Adolescent girls who fulfil diagnosis of PCOS should have long-term follow-up.
- Oligomenorrhoeic adolescents who are screened out for a definitive diagnosis after initial assessment should be managed conservatively.

Introduction

Menstrual disorders such as menorrhagia, dysmenorrhoea, and abnormal menstrual cycle length are common in adolescents. The majority of such disorders are usually self-

兒童及青少年婦科門診部對月經失調患者的症狀 及結果的縱向研究

目的 探討月經失調患者的症狀、診斷及結果。

設計 前瞻性隊列研究。

安排 香港一所兒童及青少年婦科門診部。

參與者 年齡由14至19歲共577位年青女性。

主要結果測量 回顧求診者的症狀及診斷,以及利用電話訪問得知的 治療結果。

> 結果 求診者中,47%出現月經過多、經期延長及月經週期 過短的情況。27%有繼發性閉經,12%有經痛,11% 月經過少,3%有原發性閉經。重要的診斷包括先天 性生殖器官異常、卵巢早衰、神經性厭食症和多囊卵 巢綜合症;其中多囊卵巢綜合症佔求診者16%。577 位月經失調患者中,24%於四年後出現月經週期異常 的情況。邏輯迴歸分析顯示以下三項是持續性月經週 期過長(即超過35天)的風險因素:求診時有超過 35天的月經週期情況(調整比數比=2.8;95%置信區 間:1.8-4.5)、曾有多囊卵巢綜合症的病史(調整 比數比=2.0;95%置信區間:1.1-3.4)以及身體質量 指數為23 kg/m²或以上(調整比數比=1.8;95%置信區 間:1.0-3.0)。至於那些首次求診時並未發現任何病 因的患者,她們在隨訪期內的持續性月經週期過長的 風險屬於低(調整比數比=0.3;95%置信區間:0.1-0.8) 。

> 結論 年青女性月經失調的情況不可忽視。以下三方面在統計學上與持續性月經失調的問題顯著相關:月經週期過長、曾有多囊卵巢綜合症的病史,以及身體質量指數達23 kg/m²或以上。

limiting as most are due to the immaturity of the hypothalamic-pituitary axis, but some are attributable to significant pathology such as premature ovarian failure and polycystic ovarian syndrome (PCOS). These conditions may have considerable physical and psychological consequences. It has also been suggested that those with persistent anovulatory menstrual patterns have an increased risk for endometrial carcinoma. In a small number of cases, other significant pathology, such as genital tract abnormality, may also be discovered.

In some school surveys, the prevalence of various menstrual disorders such as abnormal cycle length, dysmenorrhoea, and menorrhagia has been reported to be 11.3-37.2%, 18%, and 69-90%, respectively.³⁻⁵ These studies, however, did not provide information on the underlying causes. Others have reported underlying causes of menstrual disorders in adolescent girls, but the study population was not representative due to sampling of patients presenting with secondary amenorrhoea or oligomenorrhoea only, and included a significant

proportion of subjects with eating disorders.⁶ Although most adolescents had normal menstrual cycle 2 years after menarche, two thirds of those whose oligomenorrhoea persisted for more than 2 years still had oligomenorrhoea 10 years later,^{2,7} though the causes of their menstrual disorders were remained unknown. In this study, we aimed to identify the causes of the menstrual disorders and eventual menstrual outcomes of such adolescents, as information on this subject is limited.

At presentation, a clinician has to identify those who are at substantial risk of persistent problems and require long-term management, but at present how such information is to be obtained is not adequately defined. A longitudinal observational study of a population-based cohort was the best approach to shedding light on this topic, but studies to pursue these questions have been relatively uncommon.^{3,5,8}

An accredited, specialised Paediatric and Adolescent Gynaecology Clinic (PAGC) was set up in our institute to cater for adolescents with gynaecological problems. The PAGC is a tertiary centre that receives referrals mainly from other departments (61%) of three different hospitals in the same cluster (Department of Paediatrics and Adolescent Medicine, and the Accident and Emergency Department); whereas 31% of referrals were from the public screening centres, with the remaining 8% from general practitioners.

Evaluation and investigation of adolescents presenting with menstrual abnormalities was conducted in a standardised manner. We performed a telephone questionnaire survey to investigate the outcomes of adolescents who presented to the PAGC for menstrual disorders. In this cohort of adolescents aged 14 to 19 years, we also investigated risk factors for persistently abnormal menstruation.

Methods

Since the establishment of the PAGC, it has been managed by a dedicated team of specialist gynaecologists with rotating resident trainees in attendance. Patient assessment and management was according to an evidence-based protocol that was consistent with established practice. Information on the presenting menstrual symptoms, age of menarche, menstrual cycle patterns and cycle length, medical and social history, and physical examination findings was routinely obtained at the first consultation. Menorrhagia was defined as the subjective complaint of heavy menstrual flow. Short menstrual cycle was defined as a mean cycle length of less than 21 days, while a normal menstrual cycle was defined as 21 to 35 days. Oligomenorrhoea or those with long cycle lengths was defined as a mean cycle length of more than 35 days in the past 6 months, irrespective of the

amount of flow. 1,3,8,9 Primary amenorrhoea was defined as absence of menarche by the age of 16 years in the presence of normal secondary sexual characteristics, or by the age of 14 years in the absence of secondary sexual characteristics. Secondary amenorrhoea was defined as amenorrhoea for more than 3 months in those who had had previous menstrual periods. For those with dysmenorrhoea as the presenting complaint, dysmenorrhoea as the chief complaint was recognised as having this problem, even though they might have another menstrual disorder.

The physical examination performed at the first visit included: measurement of body weight, height, and calculation of the body mass index (BMI). Hirsutism and acne scores were assessed for amenorrhoeic or oligomenorrhoeic adolescents, using the Ferriman and Gallwey system.¹⁰ Appropriate investigations were performed depending on the presenting complaints. For menorrhagia or persistent irregular short menstrual cycle lengths, a complete blood picture, coagulation profile, and thyroid function test were performed. Hormonal profile (oestradiol, luteinising hormone, follicle-stimulating hormone, and testosterone), thyroid function, and prolactin levels were tested for on day 2 of the menstrual cycle in those with oligomenorrhoea, and at first consultation in amenorrhoeic adolescents. To assess whether there were features of polycystic ovaries or other possible gynaecological abnormalities, transvaginal or transabdominal ultrasound was performed as appropriate on day 2 of the menstrual cycle for those with oligomenorrhoea, and on the day of consultation for amenorrhoeic adolescents. Ultrasound scans were also used to assess patients presenting with moderate-to-severe dysmenorrhoea.

Polycystic ovarian syndrome was diagnosed according to the Rotterdam consensus, and

anorexia nervosa was diagnosed after assessment by a psychiatrist. Those adolescents with a history of weight loss over a short period of time but not fulfilling the criteria for anorexia nervosa or where no other cause was found were classified as having eating disorders not-otherwise-specified. A diagnosis of stress was made if no other cause for menstrual abnormality was identified and the patient expressed she was experiencing excessive stress in her daily life.

For this study, we reviewed the cohort of adolescents who presented to the PAGC with menstrual disorders from January 2003 to December 2006. The information on the presenting symptoms, menstrual patterns, investigation results, and final diagnosis was retrieved from the medical records. These patients were contacted by phone throughout October 2008 to September 2009, and a standardised questionnaire was administered to assess their current menstrual status, including: cycle length, menstrual flow, dysmenorrhoea, current use of hormonal contraception, and body weight and height. This contact was made at least 3 years after their first consultation to minimise the effect of female reproductive system immaturity on the menstrual pattern.^{7,11} Those aged less than 14 years and persons known to have cognitive or developmental disabilities were excluded from the study. Verbal consent was obtained from all eligible adolescents at the time of the telephone survey.

Statistical analyses were performed using the Statistical Package for the Social Sciences (Windows version 16; SPSS Inc, Chicago [IL], US). The Chi squared test (χ^2 test) was used for categorical data and Student's t test for continuous variables. Direct stepwise logistic regression was performed to assess the impact of a putative factor affecting the current long menstrual cycle lengths. The model contained

TABLE 1. The differential diagnosis of amenorrhoeic and oligomenorrhoeic adolescents

Diagnosis*	No. (%)			
	Primary amenorrhoea group (n=30)	Secondary amenorrhoea group (n=187)	Oligomenorrhoea group (n=74)	
No cause identified	8 (27)	57 (31)	39 (53)	
MRKH	7 (23)	-	-	
POF [†]	4 (13)	=	-	
PCOS	7 (23)	77 (41)	27 (37)	
Anorexia nervosa	1 (3)	11 (6)	-	
Excessive exercise	1 (3)	2 (1)	-	
Stress	-	17 (9)	3 (4)	
Weight loss	-	8 (4)	2 (3)	
Other causes [‡]	-	2 (1)	-	
Did not complete investigations	2 (7)	13 (7)	3 (4)	

^{*} MRKH denotes Mayer-Rokitansky-Kuster-Hauser syndrome, POF premature ovarian failure, and PCOS polycystic ovarian syndrome

[†] One was idiopathic, 1 was Swyer syndrome, and 2 were Turner syndrome

[†] One was androgen-secreting ovarian tumour and 1 was Prader-Willi syndrome (excessive obesity)

seven independent variables (presenting cycle length of more than 35 days, diagnosis of PCOS at presentation, current BMI, age at menarche, postmenarche duration in years, current age at follow-up, and no cause found at initial presentation). The significance level was set at 0.05.

Ethics approval was obtained from the local institution (CRE-2007.279).

Results

From January 2003 to December 2006, 1014 adolescents attended the PAGC and 860 (85%) were postmenarche. Among the 701 (69%) patients attending the clinic for menstrual disorders, 47% (n=330) presented with menorrhagia, prolonged flow or irregular short menstrual cycles; of these 330 patients, eight (2%) were diagnosed with idiopathic thrombocytopenic purpura, two had hyperthyroidism, and one had endometrial hyperplasia. The remaining 97% were diagnosed with dysfunctional uterine bleeding. Primary and secondary amenorrhoea were the presenting symptoms in 31% (n=217), followed by

11% (n=80) who had dysmenorrhoea and 11% (n=74) with oligomenorrhoea. The diagnoses of patients with amenorrhoea and oligomenorrhoea are shown in Table 1. Those presenting with dysmenorrhoea were all diagnosed with primary dysmenorrhoea based on a history, physical examination, and pelvic ultrasound. The presenting cycle length was short, normal, and long in 3% (n=2), 71% (n=49), and 26% (n=18) of these patients, respectively.

In the 701 adolescents presenting for menstrual disorders, 124 (18%) did not participate or were excluded from the study—18 (3%) because of mental incompetence or they were younger than 14 years or the necessary investigations were not available; another 11 (2%) who were expected to be persistently amenorrhoeic because of premature ovarian failure or congenital genital tract anomalies (with absent uterus) were also excluded; contact was not possible in 40 (6%) of the patients, and 55 (8%) refused to participate in the study. Therefore, 82% (n=577) completed the study. The mean age (standard deviation) of these participants at their first consultation was 15.2 (1.8) years. The study was conducted 4.3 (1.2) years after

TABLE 2. Comparison of characteristics at first consultation in the study group and non-study group (not assessed in the follow-up study)

Characteristic	Study group (n=577)*	Non-study group (n=124)*	P value
Age (years)	15.2 ± 1.8	15.4 ± 1.8	0.58
Age of menarche (years)	11.8 ± 1.3	11.9 ± 1.3	0.46
Body mass index (kg/m²)	21.1 ± 4.4	21.1 ± 5.4	0.24
Presenting symptoms			0.02
Menorrhagia/short cycle	260 (45)	70 (56)	
Amenorrhoea	179 (31)	38 (31)	
Oligomenorrhoea	69 (12)	5 (4)	
Dysmenorrhoea	69 (12)	11 (9)	
Cycle length at first consultation			0.37
Primary amenorrhoea	12 (2)	7 (6)	
<21 Days	26 (5)	4 (3)	
21-35 Days	261 (45)	58 (47)	
>35 Days	278 (48)	55 (44)	

^{*} Data were shown as mean ± standard deviation, or No. (%)

TABLE 3. The relation between cycle length at first consultation and current menstrual cycle length

Presenting cycle length	Current menstrual cycle length (n=563)*, No. (%)			
_	Short cycle	Normal cycle	Long cycle	
Primary amenorrhoea (n=12)	2 (17)	7 (58)	3 (25)	
Short cycle (n=26)	0	23 (88)	3 (12)	
Normal cycle (n=254)	1 (0.4)	218 (86)	35 (14)	
Long cycle (n=271)	2 (1)	176 (65)	93 (34)	

^{* 14} Subjects (7 had normal cycle and 7 had long cycle at presentation) who were currently on oral contraceptive pills for contraception were excluded from the analysis

their first consultation and the mean interval postmenarche was 6.3 (2.1) years.

There was no significant difference between the study group and the non-study group (those who were excluded, as they were not contacted or refused to enter the study), except that more patients had presented with menorrhagia or short cycle length and fewer had oligomenorrhoea (Table 2).

Of the 577 adolescents in the study group, at their first consultation, 48% (n=278) had menstrual cycles of >35 days, 45% (n=261) had normal cycle lengths, while 5% (n=26) had cycle lengths of <21 days and 2% (n=12) had primary amenorrhoea. At the time of the follow-up study, 73% (n=424) had normal cycle lengths, 23% (n=134) had long cycle lengths, 1% (n=5) had short cycle lengths, and 2% (n=14) reported using oral contraceptive pills for contraception. The relation between the cycle length at first consultation and the current menstrual cycle is shown in Table 3.

Among the 18 adolescents diagnosed with stress as the cause of their secondary amenorrhoea or oligomenorrhoea and completed the study, seven (39%) reported persistently long cycles. Of those with a previous secondary amenorrhoea or oligomenorrhoea due to eating disorders not-otherwise-specified who completed the study, two (20%) reported persistently long cycles despite attaining normal BMIs. In all, 9% of those with no cause identified for their amenorrhoea or oligomenorrhoea continued having long cycles (χ^2 test, P=0.02) as compared to those with an identified cause at first consultation. Of the 111 adolescents diagnosed with PCOS initially, 101 completed the follow-up telephone survey. Among them, 42 reported persistently long cycle length as compared to 92 in those without PCOS (χ^2 test, P<0.001). Besides, 6% had a current BMI of 23 to <25 kg/m² and 13% had current BMI of ≥25 kg/m²; a current BMI of ≥23 kg/m² was associated with persistently long cycle lengths as compared to those with a normal BMI (χ^2 test, P<0.01).

Direct logistic regression indicated that cycle length of >35 days (adjusted odds ratio [OR]=2.8; 95%

confidence interval [CI], 1.8-4.5), diagnosis of PCOS (adjusted OR=2.0; 95% CI, 1.1-3.4) at presentation, and current BMI of \geq 23 kg/m² (adjusted OR=1.8; 95% CI, 1.0-3.0) were risk factors for persistently long menstrual cycle lengths. When no cause was found after assessment at initial presentation, the risk of persistently long menstrual cycle lengths was low at the follow-up study (adjusted OR=0.3; 95% CI, 0.1-0.8) [Table 4].

The overall current menstrual cycle length was not affected by age of menarche (χ^2 test, P=0.48). There was no statistical relationship between perceived stress and current cycle length (P=0.22) or dysmenorrhoea (P=0.78).

At the time of the survey, 40% (n=231) had dysmenorrhoea, of whom 64% (n=148), 28% (n=64), and 8% (n=19) had mild, moderate, and severe symptoms, respectively. Moreover, 55% (n=127) did not take any analgesics, 30% (n=69) occasionally took analgesics, while 10% (n=23) took them regularly, and 5% (n=12) occasionally took sick leave.

Discussion

Many studies have reported the prevalence of menstrual disorders, including abnormal menstrual cycle lengths in adolescents. However, few have reported on the outcome of those who had presented with such problems.^{4,5,8} We were able to investigate the menstrual outcome of more than 80% of the adolescents who presented for menstrual disorders to our dedicated clinic. There was no major difference in clinical characteristics between the study group and the remaining 20% of the original cohort who had presented to the clinic. The reported use of oral contraceptive pills for contraception was low (2.5%) as compared to another study.8 This was expected in our locality, where there is general reluctance to use any form of hormonal therapy. There were several limitations to our study that need to be addressed. We could not validate the information on the self-reported menstrual cycles

TABLE 4. Logistic regression predicting current cycle length of >35 days

Independent variable*	Odds ratio	95% Confidence interval for odds ratio		P value
		Lower	Upper	
Presenting cycle length >35 days	2.8	1.8	4.5	<0.01
Diagnosis of PCOS at presentation	2.0	1.1	3.4	<0.01
Current BMI ≥23 kg/m ²	1.8	1.0	3.0	0.04
Age at menarche	0.9	0.8	1.0	0.16
Post-menarche years	1.0	1.0	1.0	0.32
Current age	1.0	0.9	1.1	0.53
No cause found at initial presentation	0.3	0.1	0.8	0.03

^{*} PCOS denotes polycystic ovarian syndrome, and BMI body mass index

and BMIs obtained through the telephone survey at the time of follow-up. Nevertheless, with a decent sample size, we believe that our result was robust enough to analyse menstrual outcomes in the large group of adolescents who had presented for medical attention for menstrual problems.

The 4-year mean follow-up after their first consultation and a mean of 6.3 (2.1) post-menarche years at the time of study should have minimised the immaturity of the hypothalamic-pituitarygonadal axis as a cause of persistent menstrual disorders. The reproductive system usually requires approximately 2 years to mature before adolescents have consistently regular ovulatory cycles.7,11 The mean cycle length has been reported to become constant from the sixth post-menarche year and a normal cycle has been reported by 85 to 88% of adolescents from the second year after menarche.^{5,8} Our study design was therefore able to elucidate risk factors for abnormal menstrual cycles in adolescents, other than hypothalamic-pituitarygonadal axis immaturity.

The information on outcomes of adolescent menstrual disorders is important as a guide to providing appropriate investigation, treatment, and follow-up. Those who have short cycle lengths or dysfunctional uterine bleeding after screening for endocrine causes or bleeding disorders can be reassured, and no special follow-up is required in this group. In cross-sectional studies, the prevalence of short cycles in adolescent 3 years after menarche was 1.9 to 5.2%.^{5,8} Nearly 90% of adolescents with short cycles at presentation in our study had normal menstrual cycle lengths at the time of the follow-up.

For persons presenting with oligomenorrhoea and amenorrhoea after approximately 2 years following menarche, investigation should not be delayed. Some may be suffering from premature ovarian failure and require long-term hormonal replacement therapy. Eating disorders should be looked for and if present, multidisciplinary management should be started. A large proportion of the adolescents in our study fulfilled the diagnosis of PCOS, which was also consistent with other case series.¹²

In our clinic, treatment of persons diagnosed with PCOS was individualised and depended on the presenting symptoms. If they presented with oligomenorrhoea or secondary amenorrhoea, hormonal treatment was offered for a period of 4 to 6 months. The treatment could be progesterone for withdrawal bleeding or oral contraceptive pills if there were concomitant symptoms of acne, hirsutism or dysmenorrhoea. The menstrual pattern was observed for the next 3 to 4 months. If they had persistent oligomenorrhoea or secondary amenorrhoea, a further course of hormonal

treatment was given. In the current study, their menstrual patterns were only assessed during the observation period, while they were not on any hormonal treatment. No other non-hormonal medical treatment (eg tranexamic or mefenamic acid) at the time of follow-up was expected to affect outcome. Further studies are therefore required to investigate whether diet control or exercise can impact on menstrual outcomes. Optimal treatment for this group of adolescents is still awaited.

A high proportion of adolescents who had PCOS at the time of presentation had persistently long menstrual cycle lengths several years later. One limitation of our study was that we did not investigate patients with persistently long menstrual cycle lengths. Wiksten-Almströmer et al⁶ found that 59% of their adolescents who had persistent menstrual disturbances fulfilled the criteria for PCOS. Women suffering from this condition have a high risk of developing long-term complications, including: cardiovascular disease, type II diabetes mellitus, metabolic syndrome, and reproductive health problems.13-15 Adolescents with PCOS should be offered early management as they usually respond well to treatment. Improvement in their cycle profiles usually ensues after 1 year of treatment, and such adolescents should be provided with long-term follow-up. 16-18 Our finding indicates that PCOS may develop during adolescence,19 and future research on appropriate treatment should also include this patient group.

Reassuringly, the majority of those with no cause identified for amenorrhoea or oligomenorrhoea later had normal cycles. Oligomenorrhoeic adolescents in this category should be managed conservatively, whilst those with persistent menstrual abnormality should be investigated again. Two years of persistent abnormality constitutes reasonable grounds for repeated investigation. It has been shown that adolescents often lack adequate knowledge of menstruation.^{5,20} If they are managed conservatively, this should include education on menstruation, and in particular how to calculate the menstrual cycle length. Documentation of their menstrual period has been recommended and health care provider may help to identify those who have persistently abnormal menstrual cycles.

The aetiology of the oligomenorrhoea and amenorrhoea vary depending on study centres and populations. For example, a much higher proportion of eating disorders may prevail in some centres,⁶ in which case it should develop its own protocol for managing adolescents. Education of primary health care providers may also enhance understanding on specific disease entities within each population.

Among those with long menstrual cycle in the follow-up study, 6.2% and 13.3% had BMIs of 23 to

<25 and ≥25 kg/m², respectively. Body mass index of ≥23 kg/m² was associated with persistently long cycles, even though BMI between 23 and <25 kg/m² is not regarded as overweight.²¹ Notably, BMI is an independent risk factor for persistent menstrual problems. It is uncertain whether a BMI of ≥23 kg/m² may have implications on the long-term reproductive outcome in adolescents, for which further research is needed.

they had secondary amenorrhoea, dysmenorrhoea, oligomenorrhoea, and primary amenorrhoea. In 16%, the diagnosis was PCOS. In all, 24% had persistent short or long cycles at follow-up. Long cycle lengths at first consultation, diagnosis of PCOS at first consultation, and BMI of ≥23 kg/m² at follow-up are associated with persistently long menstrual cycle lengths. Long-term follow-up and management is necessary for this group. The remainder should be reassured.

Conclusions

The majority of adolescents with menstrual disorders in our study had menorrhagia, short cycles or prolonged menstruation. Less frequently

Acknowledgements

The authors wish to thank Miss Albe WL Pang for assisting the data collection and data entry.

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