

ORIGINAL PAPER

Menstrual problems in chronic immune thrombocytopenia: A monthly challenge - a cohort study and review

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Funding information

Novartis, Grant/Award Number: Not applicable

Summary

Immune thrombocytopenia (ITP) may cause menstrual problems. This cross-sectional study assessed menstrual problems in premenopausal chronic ITP women by several questionnaires, including the pictorial bleeding assessment calendar (PBAC; score ≥ 100 indicates heavy menstrual bleeding [HMB]), and the menorrhagia multiattribute scale (MMAS). Spearman was used for assessing correlations. A literature review was performed in Pubmed. The cohort comprised 37 women (mean age 31 ± 9). A total of 29/37 (78%) had experienced clinical menstrual problems in the present or past. Of the 33 patients who returned the PBAC, 13 (39%) had a score of ≥ 100 . The median MMAS score was 79 (IQR 60–95). The PBAC scores correlated with the MMAS. Both questionnaires were unrelated to the platelet count. Patients with a levonorgestrel intrauterine device (LNG-IUD) had lower PBAC scores than patients with other or no hormonal therapy. MMAS scores were correlated with fatigue. The review identified 14 papers. HMB occurred in 6%–55% at ITP diagnosis and 17%–79% during disease. Menstrual symptoms influenced the quality of life, particularly in patients with a low platelet count. This explorative study suggested that HMB is frequent in women with chronic ITP despite management and platelet counts $>50 \times 10^9/l$. An LNG-IUD seemed to reduce blood loss significantly.

KEYWORDS

heavy menstrual bleeding, immune thrombocytopenia, menstrual problems, menstruation, quality of life

INTRODUCTION

Immune thrombocytopenia (ITP) is an autoimmune disease, in which autoantibodies attack the platelets and megakaryocytes.¹ This leads to thrombocytopenia and sometimes also platelet function defects.^{2,3} The most common clinical features include petechiae, bruises, epistaxis, and gum bleeds.⁴ A less frequently mentioned, but possibly very relevant

symptom is heavy menstrual bleeding (HMB), as ITP often affects women of reproductive age.¹

HMB is defined as menstrual periods with abnormally heavy bleeding and/or prolonged bleeding (more than 7 days).^{5,6} HMB poses a monthly challenge for women and often affects their quality of life.^{7–10} The heavy blood flow leads to impairments in several domains, including physical, social, and emotional functioning, vitality and general

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health.^{7–12} Additionally, HMB can deplete the iron stores and thus cause iron deficiency and/or anaemia, which can also significantly impair cognitive and physical performance and quality of life.^{13,14}

HMB is often associated with bleeding disorders. For example, thrombocytopenia is found in 13%–20% of adolescents with HMB.⁶ In ITP, a recent large-scale survey revealed that self-reported HMB was present in 51% of the patients at the time of diagnosis,⁴ compared to up to 30% in the normal population.^{15,16} Furthermore, HMB was rated as one of the most severe symptoms by 83% of the women who experienced it.⁴ During the course of ITP the proportion of self-reported HMB decreased to 17% at the time of survey completion.⁴ However, this survey relied on patients' own interpretation, and did not take into account the platelet count or use of hormonal and antifibrinolytic therapy.

Therapeutic options for HMB include hormonal therapy, endometrial ablation and hysterectomy.¹⁷ However, since some of these treatments impair fertility permanently, the options can be limited in ITP women.¹ In case of a future pregnancy wish, hormonal modalities, such as oral contraceptive pills (OCP) or intrauterine devices (IUD), combined with antifibrinolytic therapy may be used.^{17–20} In case of an active pregnancy wish or a wish to avoid hormonal therapy, only antifibrinolytic therapy is an option.²⁰ These management options may successfully manage HMB. However, if these options are unsuccessful and women want to preserve their fertility, it is sometimes impossible to effectively treat HMB.

In the absence of studies that objectively assess the amount of blood loss and the impact of menstruation in chronic ITP, we performed this explorative cross-sectional cohort study. We assessed the extent of menstrual problems using the pictorial bleeding assessment calendar (PBAC) and the menorrhagia multiattribute scale (MMAS) and explored which factors are related to menstrual problems. Additionally, we reviewed the available literature.

METHODS

Study population and design

This study was performed in a subset of the “PICI” study, a cross-sectional cohort study. The PICI study comprised 60 patients included between April 2019 and June 2021 at the University Medical Centre Utrecht (UMCU), who: (1) had a diagnosis of primary chronic ITP; (2) who were ≥ 16 years of age; (3) visited the outpatient clinic of our tertiary centre; and (4) gave written informed consent to participate in the study. Chronic primary ITP was defined as an ITP diagnosis of more than one year ago, a current platelet count of less than $100 \times 10^9/l$ or use of ITP-treatment, and no indication of an underlying condition. The included patients were mainly patients who were currently in care of the clinic, but we also included patients who were visiting for a second opinion or re-evaluation or were already referred back to the general

practitioner or haematologist elsewhere. The PICI study was approved by the local Medical Ethical Committee (reference number: 18–585) and was conducted in accordance with the Good Clinical Practice guidelines.

The current study was performed in a subset of the PICI study, consisting of all premenopausal women with a uterus. Furthermore, the study reopened between February and May 2022 to include extra patients who fulfilled the criteria of the subset. For this extension, patients were recruited through the social media platforms of the Dutch ITP patient association.

Study procedures

The study procedures comprised blood withdrawal and the completion of several questionnaires in a single visit. One questionnaire, the pictorial bleeding assessment calendar (PBAC), was to be completed at home during one subsequent month and then sent back. Additionally, data were extracted from the electronic patient files.

Menstrual bleeding assessment

Heavy menstrual bleeding

We have assessed and described the presence of menstrual bleeding in three different ways:

(1) First, menstrual blood loss was quantified using the PBAC; a validated semi-objective chart that calculates a total score based on the number of pads and/or tampons that were used in a month.²¹ In this study, lightly stained pads or tampons were scored with one, moderately stained pads or tampons with five, and soaked pads or tampons with 10 points. Days on which clots were present were scored with five additional points. HMB was considered present if the score was ≥ 100 .^{21,22} Patients who used a vaginal cup were asked to use pads and tampons for the duration of the PBAC to obtain reliable estimates.

(2) The presence of clinical menstrual problems at any point during the patient's course of disease was based on a description of ≥ 1 clinical criterion for HMB or a note by the treating physician in the patient's electronic file. The clinical criteria were: a cycle of ≥ 7 days, the need to change pads and/or tampons at least every 2 h or at night, clots, iron deficiency, and menstruation complaints leading to decreased social participation.

(3) The HMB item of the ITP-bleeding assessment tool (ITP-BAT, explained further below) has a score ranging from zero to four: zero indicates no problems, one indicates “doubling of the number of pads/tampons in the last cycle compared to pre-ITP or a phase of the disease with normal platelet count”, two indicates either “changing pads more frequently than every two hours or clot and flooding” or “requiring combined treatment with antifibrinolytics and hormonal therapy or gynaecological investigation”, three

indicates “acute menorrhagia requiring hospital admission or endometrial ablation”, and four indicates “red blood cell transfusion or haemoglobin drop of >20 g/l.”²³

Impact of menstrual problems

The impact of menstrual problems on the quality of life was assessed by the MMAS.^{24–26} It comprises six items assessing practical difficulties of the menstruation, and the impact on social life, mental health, physical health, work-life, and family life. A total score is calculated by the weighted response scores, which ranges from 0 to 100; zero indicates the most severe impact, and 100 indicates no impact.²⁷

Other measurements

We collected the demographics (including age and sex) and ITP specifics (duration of disease, current treatment, number of previous treatments, history of splenectomy) from the patient’s file. Laboratory tests included a complete blood count and ferritin levels.

Patients reported whether they currently used contraceptive treatment (OCP or IUD). We recorded the type of IUD but not the exact regimen of the OCP. The patients also reported whether they used antifibrinolytics. The antifibrinolytics were prescribed by the physician with a standard dose of 3 times a day 1,000–1,500 mg as long as needed based on the amount of blood loss, but we did not confirm the used dose and frequency with the patients.

Fatigue was measured with the extensively validated Checklist Individual Strength fatigue severity subscale (CIS8).^{28–32} We used the complete PICI cohort to validate the CIS in ITP patients.³³ The score ranges from 8 to 56 with a higher score indicating more fatigue.

The bleeding tendency was measured with the ITP-BAT.²³ This tool generates separate scores for three domains: skin (S), mucosal (M) and organ (O) bleeding. Each domain contains several items regarding specific bleeding symptoms that receive a severity score based on the worst incident in the prior 2 weeks. The severity score ranges from zero (not at all severe) to three or four (most severe) depending on the potential severity of the symptom. For each domain, the final score is based on the highest scored item within that domain.

Statistical analysis

The characteristics of the study population and the presence of menstrual problems were summarized using descriptive statistics, with a mean and standard deviation for normally distributed data and a median and interquartile range for non-normally distributed data. The association between PBAC and MMAS data and continuous variables was assessed using Spearman’s correlation coefficient. The PBAC

and MMAS results were compared between subgroups using the Kruskal-Wallis test. *p*-values were corrected for multiple testing using the Bonferroni-Holm technique, which is similar to the Bonferroni correction, but not as conservative.^{34,35} A corrected *p*-value below 0.05 was considered statistically significant.

Literature review

We searched Pubmed up to 11 April 2022 for research regarding HMB and the impact of menstruation in ITP patients, at diagnosis or throughout the course of the disease. We combined key terms for ITP and (heavy) menstruation. Specific search terms were added for ITP-specific questionnaires that include items regarding menstruation, namely the ITP-PAQ, the I-WISH and the ITP-BAT. Only articles with the full text available in English were included. We excluded review articles, therapeutic studies, case reports/series, and studies that assessed fertility or follicle and ovarian bleeding rather than menstrual problems. Data from the included articles were extracted using a standardized data extraction form. For the critical appraisal, the Joanna Briggs Institute (JBI) tool that was appropriate for the respective type of study was used, with emphasis on whether the remission state of the ITP was reported and whether the menstrual problems were assessed objectively.³⁶

RESULTS

This study included 39 premenopausal women with a uterus, of whom 37 were included in the final analyses (Table 1). One woman was excluded from the analyses because she had no vaginal bleeding at the time of the study due to pregnancy. One other woman was excluded retrospectively because the ITP was found to be secondary to an underlying disease.

Prevalence of HMB

The PBAC data showed that 13 (39%) of the 33 patients who returned the PBAC had a score of ≥ 100 . The median PBAC score was 88 (IQR 12–124). Concerning the ITP-BAT HMB item, 14/35 (40%; two missing values) had a score of two, indicating HMB. None of the patients recently required hospital admission for menstrual problems, although one 17-year old received intravenous immunoglobulins to raise the platelet count prior to an upcoming menstruation. Clinically, 29/37 (78%) had experienced menstrual problems now or in the past. These problems were considered controlled in 23 of them, although 8/21 (38%; two missing values) still had a PBAC score of ≥ 100 . The clinical improvement in the eight patients with a present PBAC score of ≥ 100 was due to an IUD ($n = 1$), OCP ($n = 2$), tranexamic acid ($n = 2$), IUD/OCP and tranexamic acid combined ($n = 1$), (partial) remission of the ITP ($n = 1$), and an unknown reason ($n = 1$). Similarly,

TABLE 1 Characteristics of the study population

Total	37
Mean age, years (SD)	31 (9)
Median ITP duration, years (IQR)	8 (5–14)
Current ITP treatment (%)	
None	27 (73)
Dexamethasone	1
Eltrombopag	3
Romiplostim	4
Sirolimus	1 (4)
Combined treatment ^a	1 (4)
Number of previous treatment lines (%)	
0	9 (24)
1	8 (22)
2	3 (8)
3	3 (8)
4 or more	14 (38)
ITP-BAT score	
Skin	1 (1–2)
Mucosal	1 (0–1)
Organ	1 (0–2)
Median platelet count at visit, *10 ⁹ /l (IQR)	76 (39–151)
Platelet count <50 * 10 ⁹ /l (%)	12 (32)
Median haemoglobin level, mmol/l (SD)	8.8 (8.5–9.1)
Haemoglobin <7.4 mmol/l (%)	0 (0)
Median ferritin at visit, µg/l (IQR)	33 (19–54)
Ferritin <20 µg/l (%)	10 (27)
Current use of OCP (%)	9 (24)
Combined with tranexamic acid	2/9 (22)
Current presence of LNG-IUD (%)	11 (30)
Combined with tranexamic acid	1/11 (9)
Current use of other types of hormonal contraception ^b	2 (5)
Combined with tranexamic acid	0
Current use of tranexamic acid without OCP/IUD (%)	3 (8)
Combined with IVIg	1/3 (33)

Abbreviations: ITP, immune thrombocytopenia; IVIg, intravenous immunoglobulins; IQR, interquartile range; LNG-IUD, levonorgestrel intrauterine device; *n*, number; OCP, oral contraceptive pills; SD, standard deviation; TPO-RA, thrombopoietin-receptor agonist.

^aOne patient with prednisone, eltrombopag and sirolimus.

^bOne patient with contraceptive injections and one patient with a vaginal ring (NuvaRing).

in the other 15 patients (13 with a PBAC score <100, 2 with missing PBACs) patients, improvement of clinical problems was due to an IUD (*n* = 7), OCP (*n* = 1), contraceptive injections (*n* = 1), a vaginal ring (*n* = 1), tranexamic acid (*n* = 3), (partial) remission of the ITP (*n* = 1), and an unknown reason (*n* = 1). A higher PBAC score was found in patients with current clinical menstrual problems and/or a high score on

the ITP-BAT HMB item, although the relation with clinical menstrual problems was not statistically significant (Table 2).

Impact of HMB

The median MMAS score was 79 (IQR 60–95). Only in 9/37 (24%) patients, menstruation did not at all affect daily life (MMAS score of 100). The MMAS score correlated with the PBAC score (ρ -0.55, corrected *p*-value 0.02). The group with the worst MMAS scores was the group who experienced clinical menstrual problems at the time of the study (51 [IQR 17–54]) (Table 2).

Associated factors with the amount of blood loss or impact of heavy menstrual bleeding: Explorative analyses

Hormonal therapy and antifibrinolytics

The relation between hormonal therapy and PBAC and MMAS scores are depicted in Figure 1A,B, respectively. All 11 patients with an IUD had a levonorgestrel-IUD (LNG-IUD) (Mirena in 10 patients, Kyleena in 1 patient). PBAC scores were remarkably better for patients with an LNG-IUD than for patients with OCP or without contraceptives (*p* = 0.01). MMAS scores were similar among the contraception groups (*p* = 0.32). There was no significant difference in PBAC scores between patients with and without tranexamic acid (*p* = 1.00). The MMAS scores were worse in tranexamic acid users than in non-tranexamic acid users, although not statistically significant after correction for multiple testing (56 [IQR 20–65] vs. 85 [63–100], *p* = 0.17). The median MMAS scores in patients who used tranexamic acid were the lowest after patients with current clinical menstrual problems.

Platelet count

There was no significant relationship between the PBAC and MMAS scores and the platelet count (*p* = 0.30 and *p* = 0.24 respectively; Figure 2A,B). None of the patients with a PBAC score of ≥ 100 or current clinical menstrual problems had a platelet count below $50 \times 10^9/l$.

Demographics, laboratory tests, and ITP characteristics

The correlations between PBAC and MMAS scores and demographics, laboratory tests and ITP characteristics are depicted in Table 3. The PBAC did not correlate with any of these variables, including haemoglobin and ferritin levels. Of note, none of the patients was anaemic. For the MMAS, worse scores were correlated significantly to higher levels of fatigue (CIS8).

TABLE 2 The association between the pictorial bleeding assessment calendar (PBAC) and menorrhagia multiattribute scale (MMAS) scores and other measures of HMB

		PBAC (n = 33)				Corrected p-value	MMAS (n = 37)			Corrected p-value
		N	Median	IQR	N		Median	IQR		
Score on the ITP-BAT HMB item	0	15	4	0–74	<0.01	16	98	79–100	0.08	
	1	5	39	26–81		5	74	54–84		
	2	12	183	109–247		14	60	45–78		
	Missing	1	28	-		2	-	-		
Clinical menstrual problems	Current	3	186	185–238	0.12	6	51	17–64	0.30	
	In the past	21	60	3–111		23	84	64–98		
	Never	7	28	12–88		8	90	71–100		

Abbreviations: HMB, heavy menstrual bleeding; ITP, immune thrombocytopenia; ITP-BAT, ITP-bleeding assessment tool; IQR, interquartile range; MMAS, menorrhagia multiattribute scale; PBAC, pictorial bleeding assessment calendar.

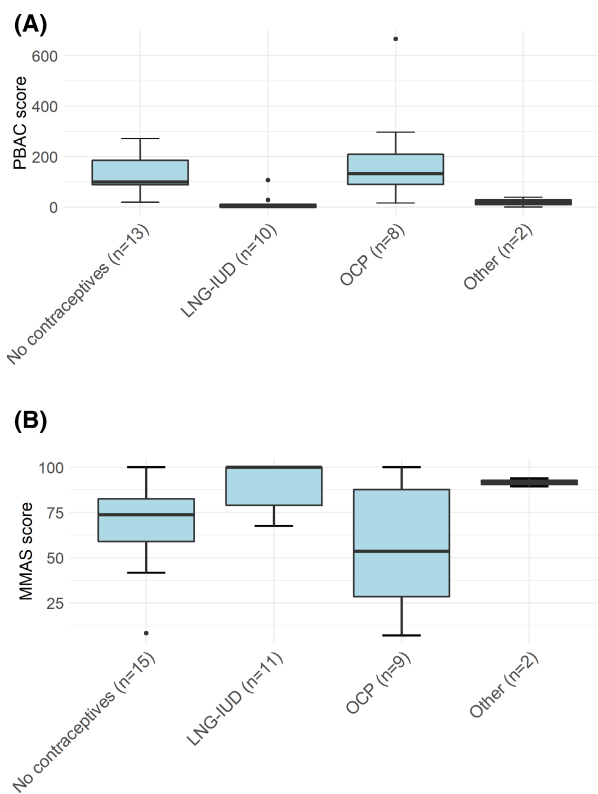


FIGURE 1 The (A) pictorial bleeding assessment calendar (PBAC) and (B) menorrhagia multiattribute scale (MMAS) scores per contraceptive group. The “other”-group includes one patient with contraceptive injections and one patient with a vaginal ring (NuvaRing). LNG-IUD, Levonorgestrel intrauterine device; OCP, Oral contraceptive pills.

Sensitivity analyses

We compared the four patients who did not return the PBAC with the 33 patients who did return the PBAC (Table S1). Both groups were more or less similar, except for a lower MMAS score in patients who did not return the PBAC (median [IQR] 57 [33–76] vs. 80 [60–100]) and a slightly longer median ITP duration (11 [7–16] vs. 8 [5–14]).

REVIEW

The search yielded 458 original articles, of which 14 were included (Figure 3). Two possibly relevant articles were excluded because the full text was unavailable. Details of the included studies including the critical appraisal can be found in Table S2. The risk of bias was low in most studies.

Prevalence of HMB

Table 4 shows the proportion of patients with HMB, as assessed by eight studies. At diagnosis, the reported prevalence ranged from 6% to 55%.^{4,37–41} None of these articles provided a clear definition of HMB. During the disease, the proportion of self-reported HMB ranged from –17% to 79%.^{4,42,43} A higher proportion was found in the Indian subset of the I-WISH study than in the complete study population (73% vs. 51% at diagnosis and 38% vs. 17% during the disease). Again, none of these studies used a clear definition of HMB. Furthermore, information on disease activity and use of (hormonal) therapy at the time of the survey was unavailable.⁴

Impact of HMB

The impact of HMB was assessed by seven studies. First, the study by Cooper et al. (mentioned above) showed that HMB was rated as one of the most severe ITP symptoms by 83% of the women with HMB at diagnosis and 62% of the women with HMB throughout the course of disease (at the time of the survey).⁴ The other six studies assessed the impact by using the ITP-Patient Assessment Questionnaire (ITP-PAQ), which contains a subscale regarding menstrual symptoms (Table 4).^{44,45} The score of this subscale ranges from 0 to 100, with higher scores reflecting a better quality of life, and the minimally important difference is 8.⁴⁵ The ITP-PAQ was developed based on the qualitative data by Mathias et al. (2008).⁴⁶ This study identified reproductive issues, including heavy menstrual bleeding

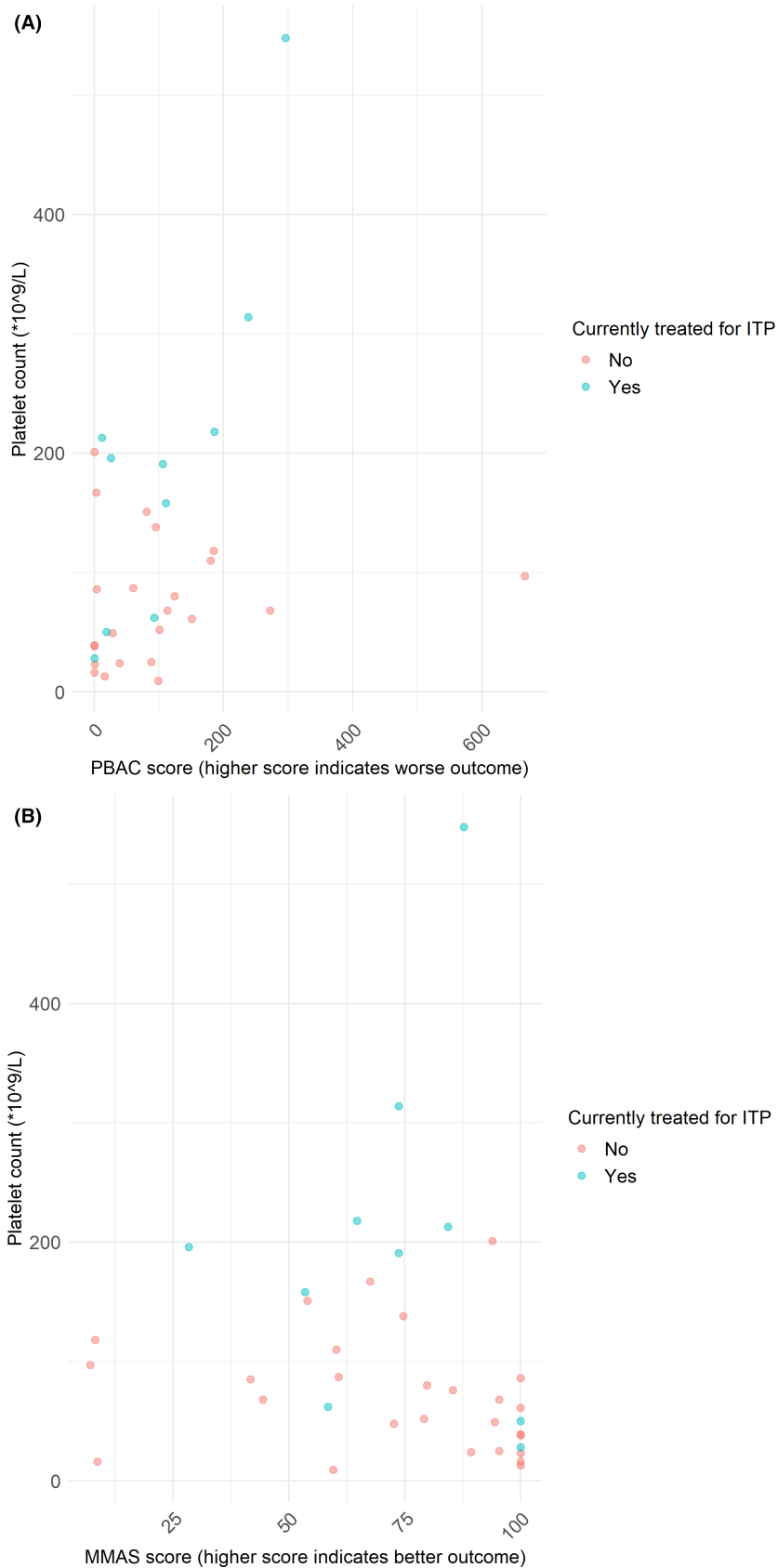
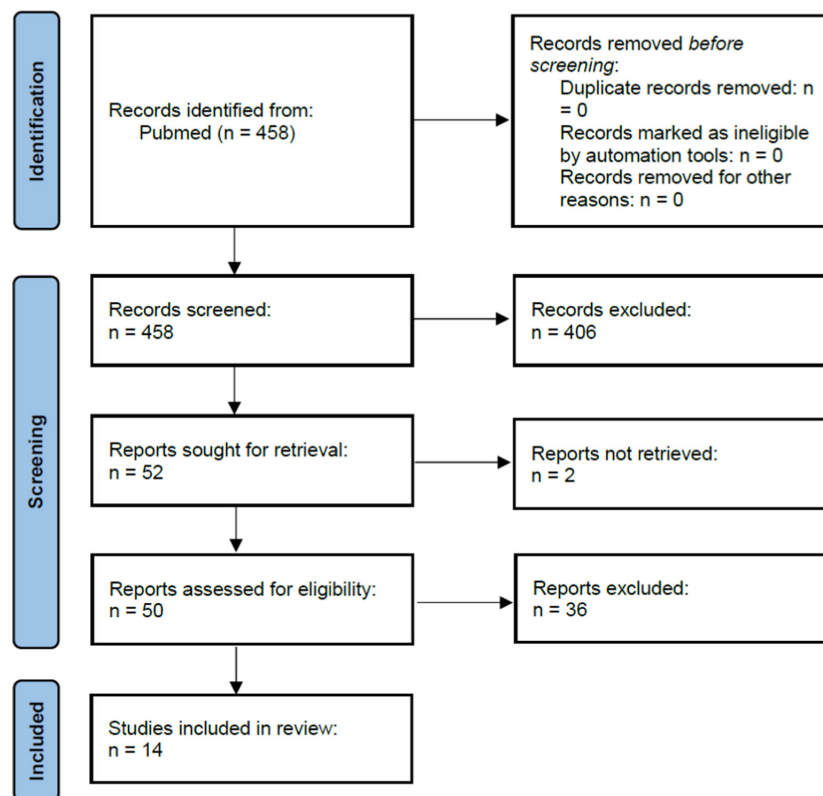


FIGURE 2 The (A) pictorial bleeding assessment calendar (PBAC) and (B) menorrhagia multiattribute scale (MMAS) scores in relation to the platelet count. [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 3 The association between the pictorial bleeding assessment calendar (PBAC) and menorrhagia multiattribute scale (MMAS) scores and other factors

	PBAC			MMAS		
	Correlation coefficient/ median	IQR	Corrected <i>p</i> -value	Correlation coefficient/ median	IQR	Corrected <i>p</i> -value
Age	-0.18	-	1.00	-0.29	-	0.80
CIS8	-0.33	-	0.67	-0.64	-	<0.01
Haemoglobin level	-0.41	-	0.27	0.11	-	1.00
Ferritin level	-0.09	-	1.00	0.17	-	1.00
ITP duration	-0.03	-	1.00	0.14	-	1.00
Current treatment for ITP						
Yes	100	21–167	1.00	74	60–87	1.00
No	81	4–119		80	60–98	

Abbreviations: CIS8, Checklist Individual Strength fatigue severity subscale; HMB, heavy menstrual bleeding; ITP, immune thrombocytopenia; IQR, interquartile range; MMAS, menorrhagia multiattribute scale; OCP, oral contraceptive pills; PBAC, pictorial bleeding assessment calendar.

**FIGURE 3** PRISMA flowchart of study selection. [Colour figure can be viewed at wileyonlinelibrary.com]

and hysterectomy because of bleeding, as a relevant concept in ITP-related quality of life. Since the ITP-PAQ is an ITP-specific questionnaire, the data cannot be interpreted in the context of other populations.

Associated factors with the amount of blood loss or impact of heavy menstrual bleeding

No studies assessed which factors were correlated with the amount of blood loss or the presence of HMB in ITP.

However, several studies assessed ITP-specific factors related to the impact of the menstruation measured with the ITP-PAQ subscale. None of the studies provided information on the use of OCP, IUD or antifibrinolytics.

Platelet count

The platelet count seemed to relevantly impact patients' quality of life concerning menstrual symptoms (Table 4).^{44–48} Snyder et al. and Mathias et al. (2009)

TABLE 4 Heavy menstrual bleeding in immune thrombocytopenia patients: results of the review

Prevalence of heavy menstrual bleeding				
Study	Timing of assessment	Definition/method of assessment	Number of patients	Proportion of patients with HMB
Supe et al. 2009 ³⁸	At diagnosis	NR ^a	22	55%
Farid et al. 2012 ³⁹	At diagnosis	NR ^a	70	6%
Andres et al. 2012 ⁴⁰	At diagnosis	NR ^a	156	18%
Hassan et al. 2017 ⁴¹	At diagnosis	NR ^a	6	33%
Aronis et al. 2004 ³⁷	At diagnosis and/or during disease	Severe menorrhagia at menarche necessitating blood transfusions	20	25%
Cooper et al. 2021 ⁴	At diagnosis	I-WISH questionnaire	957	51% (at diagnosis)
	During disease			17% (during disease)
Chakrabarti et al. 2022, ^{42,b}	At diagnosis	I-WISH questionnaire	26	73% (at diagnosis)
	During disease			38% (during disease)
Khair et al. 2022 ⁴³	During disease	NR	58	79% "heavy periods" 57% "prolonged periods"
Menstrual symptoms as measured by the ITP-PAQ				
Study	Timing of assessment	Groups	Number of patients	Mean score of menstrual symptoms subscale (SD) ^c
Snyder et al. 2008 ⁴⁷	During disease ITP patients recruited from the PDSA	Per splenectomy status		
		Splenectomized	171	55 (7)
		Non-splenectomized	302	52 (6)
				NS
		Per platelet count (*10⁹/l)		
		<10	8	47 (NR)
		10–29	23	55 (NR)
		30–49	54	61 (NR)
		50–99	98	64 (NR)
		100–149	72	68 (NR)
>150	218	71 (NR)		
		NS		
George et al. 2009 ⁴⁸	During disease ^d At baseline of a clinical trial	Per splenectomy status		
		Splenectomized	38	55 (36)
		Non-splenectomized	43	66 (33)
		NS		
Mathias et al. 2009 ⁴⁵	During disease ^d At baseline of a clinical trial		81	61 (34)
		After treatment		
	at week 24 of two romiplostim trials (romiplostim <i>n</i> = 55, placebo <i>n</i> = 26)	Per response status^e		53
		Response	NR ^f	86 (24)
No response	NR ^f	61 (35)		
			Sign.	
Mathias et al. 2007 ⁴⁴	After treatment at week 24 of a romiplostim trial with extended use	Per durable platelet response^g		
		Durable platelet response	7	71 (39.3)
		No durable platelet response	6	77 (43.5)
			NS	

Abbreviations: HMB, heavy menstrual bleeding; NR, not reported; NS, not significant; PDSA, platelet disorder support association; sign., significant.

^aNo other definition of HMB is present in the article than "menorrhagia."

^bIndian subset from the I-WISH study.

^cRange: 0–100 (higher scores reflect better quality of life); minimally important difference: 8.⁴⁵

^dBoth studies have the same study population.

^eResponse status was defined as platelet count more or less than $50 \times 10^9/l$ at week 24.

^fThe number of women per response group was not reported, only the total number of men and women combined.

^gDurable platelet response was defined as a platelet count of $>50 \times 10^9$ cells/l and a doubling of baseline values on more than six occasions during weeks 17–24.

showed higher ITP-PAQ scores in patients with higher platelet counts.^{45,47} Although Mathias et al. (2007) found no significant difference between patients with a platelet count of more or less than $50 \times 10^9/l$, this was only in a small sample of patients.⁴⁴ Lastly, Mathias et al. (2007) reported a mean score of 3.8 (standard deviation 1.0) for the individual item “Thinking about your last period, how bothered were you by: heavier bleeding than before having ITP?”⁴⁹ This item ranges from one (most bothered) to five (not bothered) and was asked in patients with “active” disease (as judged by a clinician).

Other factors

No significant differences in menstrual symptom scores on the ITP-PAQ were found between splenectomised and non-splenectomised ITP patients.^{47,48}

DISCUSSION

In our explorative study, 39% of the women with chronic ITP experienced HMB and 78% had experienced clinical menstrual problems now or in the past. The use of an LNG-IUD seemed associated with less blood loss. Furthermore, a higher impact of menstrual problems on patients' daily life correlated with higher levels of fatigue. Both HMB and a high impact of the menstruation seemed to occur despite the use of tranexamic acid or OCP and despite normal platelet counts. Our review showed that menstrual symptoms impact the quality of life in ITP and showed a particularly high prevalence of HMB at the time of ITP diagnosis.

The study is the first to prospectively assess the extent of menstrual problems in chronic ITP with (semi-)objective assessment methods. Furthermore, it is the first to explore the correlation of menstrual problems with other factors in ITP patients. The most important weaknesses of the study are the small sample size, the lack of a control group, and the missing data in the PBAC and the ITP-BAT HMB item. However, as an explorative study, it does highlight this underestimated problem. Furthermore, the reliability of the PBAC has been questioned.⁵⁰ However, a systematic review found the reliability of the PBAC to be reasonably high, despite some low values for sensitivity, specificity and discriminatory power (sensitivity 86%–99% and specificity 7.5%–89% for diagnosing >80 ml blood loss with a cut-off of 100 points).²² Furthermore, the PBAC is practical and more reliable than self-rapportage.^{22,51} Another weakness of our study is that, although the MMAS has previously been validated,^{25,52} there are no normative data available to place the outcomes of our study in context. The last weakness is that, due to the explorative design of the study, the information on the dose and frequency of antifibrinolytic therapy and oral contraceptives is incomplete.

Prevalence of HMB

Our study suggests a prevalence of HMB (PBAC ≥ 100 or ITP-BAT HMB score of ≥ 2) of 39% in patients with chronic ITP. This proportion seems higher than the 30% reported for the general population, although a direct comparison should confirm this.^{15,16} At diagnosis, a high prevalence of HMB has been previously reported.^{4,37–41} Our study suggests, however, that the proportion remains high despite management of ITP in a specialized centre. Of note, the prevalence of HMB throughout the course of disease was found to vary largely in different studies be much lower (17%–79%).^{4,42,43} These studies all relied on self-rapportage, which is known to be unreliable.²² For example, in one study, only 27% of patients with a PBAC score of ≥ 100 reported having HMB through self-assessment.⁵³ Furthermore, the disease activity and the use of hormonal therapy, antifibrinolytic agents, or an IUD were not considered in any of these studies. Based on our data, awareness of HMB in ITP patients may be warranted even in later phases of the ITP and when platelet counts are $>50 \times 10^9/l$.

Impact of the menstruation

We found a median MMAS score of 79 (IQR 60–95). For comparison: at the start of clinical trials for HMB treatments, MMAS scores were much lower (range 35–58)^{54–59} than in our ITP cohort. After treatment for HMB, trial patients had a score of 80–100,^{54–57,60} indicating that there is room for improvement for at least half of our ITP patients. The impact of the menstruation seemed related to the amount of blood loss, which is in line with the positive effects of HMB treatment on women's quality of life.^{7–12} Furthermore, the correlation between MMAS scores and fatigue as well as our review showed that menstrual problems impact the quality of life, which is in line with previous research.^{7–12} Of note, an overview of the current standards for women with ITP reported that moderate menorrhagia may be present with a platelet count $<20\text{--}30 \times 10^9/l$, but is “easily manageable.”⁶¹ This advice seems not in line with the findings of our study. We suggest, therefore, that ITP patients may experience a negative impact of their menstruation on their quality of life and may be related to the frequently reported symptom of fatigue.⁴

Associated factors with menstrual problems

ITP patients with an LNG-IUD in our study experienced little blood loss. These results are in line with a recent Cochrane review, showing that an LNG-IUD improves the amount of blood loss compared to other medical therapies for HMB.⁶² Furthermore, this review shows that an LNG-IUD possibly improves the MMAS scores (mean difference 13, 95% CI: 10–17),⁶² which was not confirmed in our small study. Overall, larger, preferably prospective studies are needed to

confirm the advantages of IUD in chronic ITP patients, but an LNG-IUD seems effective in improving blood loss and possibly also the quality of life.

We found no beneficial effect of OCP, nor tranexamic acid on menstrual problems. This is contradictory to the literature, which shows benefit of both OCP and tranexamic acid on menstrual blood loss.^{63–65} This is likely because of confounding by indication: patients with worse menstrual problems were probably more likely to use OCP. Of note, the efficacy of OCP and tranexamic acid on menstrual blood loss has never been assessed specifically in ITP patients. Furthermore, the use and regime of OCP were not assessed in this study. Longitudinal research is needed to assess the benefit of OCP, including specific regimes, and tranexamic acid in ITP patients with heavy menstrual bleeding. However, our research suggests that ITP patients experience menstrual problems despite the current standard of care.

The effect of platelet count on menstrual problems was contradictory between our cohort, where we found no association, and our review, where we found a larger impact on quality of life in patients with low platelet counts. In our study, the vast majority (68%) had platelet counts of $>50 \times 10^9/l$ and management for HMB was often already initiated, which could be the reason why platelet counts were unrelated to PBAC/MMAS scores. In this scenario, platelet function defects may be causing the menstrual problems. Although more research is necessary to further explore this subject, our results do suggest that menstrual problems can be present despite almost normal platelet counts.

We found no association between the amount of blood loss and haemoglobin or ferritin levels, despite the association found in previous studies.^{53,66} Iron deficiency and anaemia were previously found to be associated with a decreased quality of life.^{13,14,67–70} In our study, however, no patients were anaemic and 73% had normal iron levels, probably due to frequent monitoring. In conclusion, our study suggests that in chronic ITP an increased impact of HMB might exist despite the prevention of anaemia and iron deficiency.

Clinical implications

This study should raise awareness of menstrual problems in patients with chronic ITP. Even despite the use of tranexamic acid or OCP, normal haemoglobin and ferritin levels, and normal platelet counts, our study suggests that patients may still experience HMB and a negative impact of their menstruation on their quality of life. It is important to realize that embarrassment or not knowing what is normal may prevent a patient to raise the topic herself. It is, therefore, the responsibility of the clinician to discuss any menstrual problems and counsel patients about possible treatment options. An LNG-IUD should be considered in case of HMB without an active pregnancy wish, considering the effectiveness

we found in our study. The PBAC and/or MMAS may aid in the identification and discussion of menstrual problems and assessing the effect of treatment. Any counselling and intervening should focus primarily on increasing a woman's quality of life.¹⁷ Particular attention should be given to counselling regarding a pregnancy wish, as this might lead to patients' quitting effective hormonal treatment. Close collaboration between haematologists and gynaecologists is encouraged to provide patients with the best care.

Unanswered questions and future research

Further research should address why menstrual problems in chronic ITP patients seem to exist despite management. For example, defects in platelet function or the presence of gynaecological abnormalities in ITP patients may be relevant. Furthermore, effective management strategies and the role of menstrual problems in the patient's quality of life should be the subject of study. Because randomized trials are likely unfeasible, we suggest the use of prospective observational studies to assess the effectiveness of interventions in ITP patients, and qualitative research to inform clinicians on the patient's appreciation of current management, identify areas with room for improvement, and explore the role of menstrual problems in fatigue and health-related quality of life as a whole.

CONCLUSION

This explorative study suggests that women with ITP of child-bearing age seem prone to menstrual problems, including HMB and a high impact of the menstruation on quality of life. The use of an LNG-IUD seems associated with less blood loss, but the effect on the impact of menstruation is not evident in this study. Clinicians should be aware that menstrual problems may exist even in the case of (sub) normal platelet counts, normal haemoglobin and ferritin levels, and the use of OCP or antifibrinolytics. A close collaboration between haematologists and gynaecologists is encouraged to improve counselling and management, focusing on interventions to increase a woman's quality of life, while taking into account an active or passive pregnancy wish.

CONFLICT OF INTEREST

R.E.G. Schutgens received a grant from Novartis. The other authors have no potential conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

The research was designed and performed by Wobke E.M. van Dijk, Karin P.M. van Galen, and Roger E.G. Schutgens. The analyses and literature review were performed by Wobke E.M. van Dijk. Wobke E.M. van Dijk wrote the manuscript, which was critically revised by Marieke Punt, Jeanette van Leeuwen, A. Titia Lely, and Roger E.G. Schutgens.

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SUPPORTING INFORMATION

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How to cite this article: van Dijk WEM, Punt MC, van Galen KPM, van Leeuwen J, Lely AT, Schutgens REG. Menstrual problems in chronic immune thrombocytopenia: A monthly challenge - a cohort study and review. *Br J Haematol*. 2022;198:753–764. <https://doi.org/10.1111/bjh.18291>