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Prevalence, burden and treatment effects of vaginal bleeding in women with (suspected) congenital platelet disorders throughout life: a cross-sectional study

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Summary

Congenital platelet disorders (CPDs) are rare bleeding disorders that are associated with mucocutaneous bleeds. However, data on vaginal bleeding in women with CPDs are scarce. A set of generic and bleeding-specific questionnaires were used to evaluate the prevalence of vaginal bleeding, its impact on quality of life (QoL) and sexual functioning and the consequences for pregnancy, miscarriage and delivery in a cohort of women who were referred for diagnostic evaluation for CPDs. A total of 78 women included in the study were either diagnosed with a CPD (n = 35) or were clinically suspected of a CPD (n = 43). Heavy menstrual bleeding (HMB) was reported by a large proportion of women, which mainly started at menarche. In all, 76% of women received any kind of HMB treatment, often leading to surgical prodecures. HMB was shown to have a high impact on QoL, which improved upon treatment. Even though women reported that vaginal bleeding affects sexuality, this topic is not frequently discussed with physicians. Heavy blood loss frequently occurred after miscarriage/delivery, often requiring treatment. Women with (suspected) CPDs frequently encounter HMB, negatively impacting daily life and sexual functioning. Together with peripartum bleeding, these data highlight the burden of vaginal bleeding in CPDs and importance of adequate treatment.

Keywords: blood coagulation disorders, inherited, uterine haemorrhage, menstruation, sexual health, quality of life.

Introduction

Congenital platelet disorders (CPDs) are rare bleeding disorders resulting in mild to severe, predominantly mucocutaneous, bleeding problems.[1] CPDs can be classified according to their quantitative or qualitative defects. Although diagnosis of some disorders can be straightforward (for instance Glanzmann thrombasthenia and Bernard–Soulier syndrome), interpretation of functional assays for other subtypes can be challenging.[2,3] Defects can involve the platelet secretion pathways (e.g. α-, δ-granule storage pool deficiencies), signal transduction receptors [e.g., thromboxane A2 (TxA2), collagen], signal transduction pathways (e.g. arachidonic acid, TxA2), and platelet adhesion receptors [e.g. glycoprotein (GP) Ia/IIa].[2] Diagnosing platelet disorders is challenging due to a lack of agreement about classification and poor standardisation of laboratory tests, availability of tests only in specialised laboratories and influence of circumstances like diet, blood drawing procedures and sample handling on test results. This probably contributes to diagnostic delays.[4,5]

Women are more likely to manifest a bleeding disorder as they experience women-specific bleeding challenges during menstruation and around childbirth. Heavy menstrual bleeding (HMB), defined as menstrual blood loss of >80 ml/menses, is more prevalent among women with bleeding disorders compared to the general population.[6] Furthermore, it has been established that bleeding disorders are more prevalent among women with HMB.[6] HMB has been associated with discomfort and pain, may lead to limitations in conducting daily activities, changes in social functioning and overall might have an adverse effect on the quality of life (QoL).[7] Women with bleeding disorders may refrain from sexual intercourse during prolonged menstrual periods, restricting their sexual QoL.[8-10] Childbirth is a significant

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challenge for haemostasis, leaving women with a CPD more prone to postpartum haemorrhage (PPH).[11] Thus, tailored counselling is required to lower the frequency and burden of these bleeding events.

Data on the prevalence of HMB and obstetric bleeding in women with CPDs, as well as their management and impact on daily life and sexual functioning, are currently lacking.[12,13] Accurate knowledge regarding the impact of bleeding disorders on QoL could help to create more awareness and tailor counselling and treatment. The present study aimed to investigate the burden of HMB and obstetric bleeding in women with a suspected or confirmed CPD who participated in a large Dutch nationwide cross-sectional study on CPDs [**T**rombocytopathy **i**n the **N**etherlands (TiN) study]. In addition, we aimed to assess the impact of their bleeding disorder on QoL in relation to HMB and sexual functioning.

Methods

Study population and design

The TiN study is a cross-sectional nationwide study that was performed in 2016 and 2017 at the Van Creveldkliniek, Utrecht, the Netherlands.[4] All patients with a suspicion of CPD and aged ≥18 years, were eligible for inclusion in the TiN study. The aim of the TiN study was to collect information on bleeding, QoL and treatment and to improve diagnostic evaluation. For the present study, TiN-Women, we selected the female participants of the TiN study and contacted them for participation.

The Medical Ethical Committee of the University Medical Centre Utrecht confirmed that ethical approval was not required for this study (Reference number: 19-138) and all participants provided written informed consent.

The 36-item short-form health survey (SF-36) and International Society on Thrombosis and Haemostasis-Bleeding Assessment Tool (ISTH-BAT)

A selection of the data that were completed as part of the original TiN study were re-used in the TiN-Women study: the ISTH-BAT to assess bleeding tendency, the data from the questionnaires that comprised treatment history and social activities, and the SF-36 for QoL.[14,15]

Women-specific bleeding questionnaires

An online survey was sent by e-mail in May 2019 containing questionnaires and general questions on the prevalence and impact of three themes: (i) HMB, (ii) sexual functioning and (iii) pregnancy, miscarriages and delivery. Participants were also asked to report information on the treatment of bleeding events. Open questions at the end of the survey allowed for additional, personal remarks.

Subjective (self-reported) HMB was assessed and defined as the need to change pads/tampons more frequently than every 2 h or experiencing bleeding for >7 days.[16] The self-reported incidence in the study population was compared to the self-reported HMB prevalence in the literature.[17] Semi-objective HMB was assessed through a pictorial blood assessment chart (PBAC).[18] A paper version of the PBAC was provided to women who were still menstruating at the time of the study to quantify menstrual blood loss during two consecutive menstrual periods, while continuing any previous HMB treatment. HMB was defined as a PBAC score of >100 or menstrual cup measurement >80 ml of blood loss.[10,18]

The survey included the Menorrhagia Multi-Attribute Scale (MMAS) and the Revised Female Sexual Distress Scale (FSDS-R).[19,20] The MMAS contained a 5-point Likert scale specific to women with HMB to assess woman's perception of the consequences of HMB on six domains: family life, physical health, work routine, psychological well-being, practical problems and social life.[19] Women who had undergone HMB treatment completed this questionnaire twice to obtain a utility score before and after treatment. The FSDS-R questionnaire was used to measure sexually-related distress in women: it assesses 13 feelings or problems to determine how often each problem has caused distress in the previous 30 days. A higher scores indicates a higher level of distress, with sexual distress being defined as a FSDS-R total score of >11.[21]

A self-developed questionnaire was used to collect information on bleeding events and treatment during pregnancy, delivery and/or miscarriages.

Statistical analysis

Prior to analysis, data were checked for plausibility and completeness. The answers to open-ended questions were reviewed. In case the patient mentioned having received treatment for bleeding during pregnancy, the electronic health record was reviewed in an attempt to verify this treatment.

Continuous variables were summarised by mean ± standard deviation (SD) or as median and interquartile range (IQR) depending on their distribution. Categorical variables are displayed by frequencies and percentages. To score the SF-36, scales are standardised with a scoring algorithm to obtain a score ranging from 0 to 100, as previously described.[15] Higher scores imply a better health status, and a mean score of 50 has been expressed as a normative value for all scales.[22] The scores of women with a (suspected) CPD were compared with SF-36 and FSDS-R scores for women in the general Dutch population.[23,24] The overall score of the MMAS was normalised to obtain a utility score on a 100-point scale (0 worst affected–100 unaffected).[19] The PBAC scores or menstrual cup measurements of two consecutive menstruations were averaged to obtain a final score for further analyses. A sensitivity analysis between responders and

non-responders to the questionnaires was conducted to assess the robustness of the findings.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS®) version 21.0 (IBM Corp., Armonk, NY, USA). Participants were able to decide per questionnaire whether they wanted to share information on that topic; thus the total number of participant per questionnaire differs. The chi-square test was used to compare categorical variables between groups. Parametric tests included the Mann–Whitney *U*-test and the Wilcoxon signed-rank test for non-paired and paired data, respectively. *A priori*, we determined to statistically test each domain of all questionnaires because in the TiN study QoL was diminished both in the physical and mental domains. A two-sided $P < 0{\cdot}05$ was considered statistically significant.

Results are presented per topic for the entire study population. Subgroup analyses (confirmed *versus* suspected CPD) are provided in Table SII and in case of significant differences, the results are mentioned in the narrative.

Results

The original TiN study population included 159 women. A total of 102 women consented to participate in the TiN-Women study. Of those, six patients were excluded from analysis because they were diagnosed with immune thrombocytopenia (four), von Willebrand disease (one) and no confirmed CPD in addition to an ISTH-BAT of <6 (one). Another 18 women were excluded because they did not complete and return the questionnaires. As a result, 78 women were included in the analysis group (Fig 1). The analysis group consisted of women with a confirmed CPD [35 (45%)] and women of whom diagnosis was not confirmed but who were suspected of having a CPD clinically [43 (55%)].

Patient characteristics are described in Table I. The median (IQR) age of the analysis group was 44 (32–57) years. The median (IQR) ISTH-BAT score was 11 (8–14). The median (IQR) age at time of first bleeding symptoms was 11 (5–15) years. HMB was the most common presenting symptom (27%, 21/78). There were no significant differences in baseline characteristics between women with a confirmed CPD and suspected CPD. Women who completed our questionnaires received treatment for bleeding problems as often as women who did not respond (Table SI).

Menstrual bleeding

Overall, the median (IQR) age at menarche was 12 (11–13) years (Table I). At the time of the study, 25 women in the analysis group (32%) were still menstruating [10, oral contraceptives with withdrawal bleeding; nine, natural menstrual cycle; four, intrauterine device (IUD) with bleeding episodes; one, implanon and one after incomplete endometrium ablation].

The majority of the women in the analysis group, 68% (53/78), had no more menstruations at the time of study, due to the following causes: post-menopausal (20), hysterectomy (15), endometrial ablation (two), IUD without bleeding

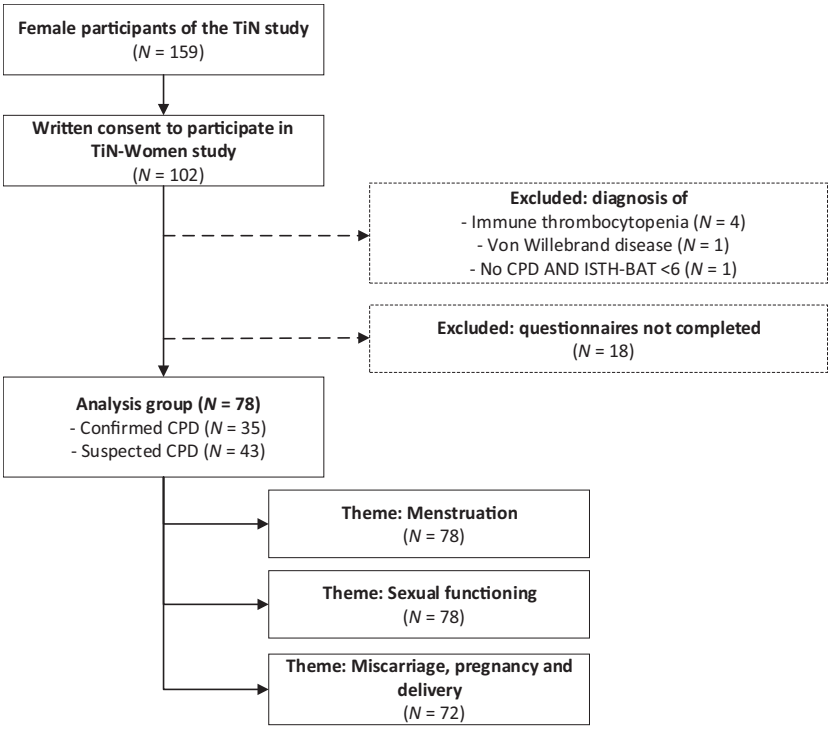

Fig 1. Study flowchart. CPD, congenital platelet disorder; ISTH-BAT, International Society on Thrombosis and Haemostasis-Bleeding Assessment Tool; TiN, **T**rombocytopathy **i**n the **N**etherlands.

Table I. Patient characteristics.

Characteristic	Analysis group (N = 78)*	Confirmed CPD (N = 35)	Suspected CPD (N = 43)	*P*
Age, years, median (IQR)	44 (31–57)	42 (30–54)	46 (33–60)	0·39†
Age at menarche, years, median (IQR)	12 (11–13)	12 (11–14)	12 (11–13)	0·73†
BMI, kg/m^2, median (IQR)	25 (23–29)	25 (22–28)	26 (23–30)	0·30†
Diagnosis, *n* (%)	NA		NA	
ADP pathway defect		8 (22·8)		
TxA2 pathway defect		8 (22·8)		
Glanzmann thrombastenia		6 (17·1)		
Bernard–Soulier syndrome		1 (2·9)		
Dense granule deficiency		4 (11·4)		
Isolated thrombocytopenia		7 (20·0)		
Complex abnormalities		1 (2·9)		
Bleeding score (ISTH-BAT), median (IQR)	11 (8–14)	9 (5–16)	11 (10–14)	0·20†
Age at time first bleeding symptoms, years, median (IQR)	11 (6–16)	8 (3–25)	11 (8–14)	0·33†
First symptom, *n* (%)				
Nose bleeding	13 (18·8)	7 (25·9)	6 (15·0)	
Heavy menstrual bleeding	24 (34·8)	9 (33·3)	15 (37·5)	
After tonsillectomy	18 (26·1)	7 (25·9)	11 (27·5)	
Other	12 (17·4)	5 (18·5)	7 (17·5)	
Unknown	2 (2·9)	1 (3·7)	1 (2·5)	
Treatment bleeding, *n* (%)	55 (71·4)	24 (68·6)	31 (73·8)	0·26†
Tranexamic acid	40 (51·9)	22 (62·9)	18 (42·9)	
DDAVP	27 (35·5)	14 (40·0)	13 (31·7)	
NovoSeven	10 (13·0)	6 (17·1)	4 (9·5)	
Blood transfusion	35 (45·5)	13 (37·1)	22 (52·4)	
Platelets transfusion	29 (38·2)	14 (40·0)	15 (36·6)	

BMI, body mass index; CPD, congenital platelet disorder; DDAVP, 1-deamino-8-D-arginine vasopressin; ISTH-BAT, International Society on Thrombosis and Haemostasis-Bleeding Assessment Tool; IQR, interquartile range; NA, not applicable; TxA2, thromboxane A2.
*N = 68–78 depending on questionnaire responding rate.
†Mann–Whitney *U*-test.
††Chi-square test.

episodes (nine), continuous use of oral contraceptives (three), IUD combined with oral contraceptives (one) or pregnancy/lactation at the time of the survey (three).

> 'It is very unpleasant to be confronted with excessive blood loss, my puberty was characterised by months of hospital stays...' – Woman with suspected CPD

Heavy menstrual bleeding – self-reported. In our analysis group, self-reported prevalence of HMB was much higher than the general population (87% vs. 30% respectively).[17] Most of the women (68/78; 87%) self-reported HMB at any time in their life. Nearly all of them had to change pads/tampons more frequently than every 2 h (64/68 women; 94%) and experienced bleeding for >7 days (52/68 women; 76%). HMB started at the onset of menarche in 75% (51/68) of the women.

Heavy menstrual bleeding – PBAC score and menstrual cup measurement. In addition to the subjective, self-reported prevalence of HMB, PBAC and menstruation cup measurement were used to objectively quantify blood loss during menstruation. In all, 11 of the 25 women who were still menstruating completed the PBAC (10) or menstruation cup assessment (one), during 22 menstruations in total. The median (range) PBAC score was 59 (21–699) and median menstrual cup measurement was 89 ml; these results are indicative for (ongoing) HMB in three of the 11 women despite eight receiving HMB treatment. Women with ongoing HMB had a natural menstrual cycle (two) or treatment with oral contraceptives (one). Of the eight women without HMB currently, seven received hormonal treatment (three, IUD; and four oral contraceptives) and one had a natural cycle. No further analyses were made due to limited amount of available data.

Heavy menstrual bleeding – treatment. Of the women that reported HMB, 76% (52/68) reported to have received medical treatment for HMB. Hormonal treatment (e.g. oral contraceptives, hormonal IUD, injection, implanon) was prescribed most often in 85% (44/52) of treatment strategies. Haemostatic therapy [i.e. tranexamic acid, 1-deamino-8-D-arginine vasopressin (DDAVP), platelet transfusions,

Table II. The 36-item short-form health survey (SF-36) domain scores.

SF-36 domain, median (IQR)	General population (N = 761)	Analysis group (N =75–77)	P*
Physical functioning	90 (75–100)	85 (65–95)	0·38
Role-physical	100 (50–100)	75 (25–100)	0·02
(Bodily) pain	74 (62–88)	62 (51–84)	0·03
General health	72 (57–87)	59 (40–72)	0·00
Vitality	68 (50–80)	60 (40–85)	0·02
Social functioning	88 (75–100)	75 (63–100)	0·00
Role-emotional	100 (67–100)	100 (100–100)	0·16
Mental health	76 (64-88)	80 (68–88)	0·48

IQR, interquartile range; SF, short form.
Data of women of the general Dutch population.[23]
*Mann–Whitney *U*-test.

Table III. The 36-item short-form health survey (SF-36) domain scores.

SF-36 domain, median (IQR)	Self-reported HMB (N = 66)	No self-reported HMB (N = 10)	P*
Physical functioning	85 (65–95)	95 (90–100)	0·06
Role-physical	75 (25–100)	100 (100–100)	0·04
(Bodily) pain	62 (51–84)	84 (62–100)	0·11
General health	57 (40–72)	70 (52–87)	0·11
Vitality	60 (45–70)	68 (55–80)	0·34
Social functioning	75 (63–88)	94 (75–100)	0·03
Role-emotional	100 (67–100)	100 (100–100)	0·07
Mental health	76 (68–88)	84 (80–88)	0·19

HMB, heavy menstrual bleeding; IQR, interquartile range; SF, short form.
*Mann–Whitney *U*-test.

NovoSeven] was reported by 56% (29/52) of women treated (Table II). All women with HMB were treated with tranexamic acid (100% 29/29). Additionally, in 54% (28/52) of women, iron was administered at least once in their life.

Surgical interventions were reported in 18 women who received medical treatment for HMB (35%, 18/52). Six women underwent endometrium ablation (one ADP pathway defect, one TxA2 pathway defect, two complex abnormalities and two uterine balloon tamponade). In all, 10 women (one Glanzmann thrombasthenia, one ADP pathway defect, one isolated thrombocytopenia, one TxA2 pathway defect, one complex abnormalities and five suspected CPD) underwent hysterectomy, of whom four had previously been unsatisfactorily treated with endometrium ablation or had undergone curettage. Furthermore, one woman underwent curettage (Glanzmann thrombastenia) and one woman (Glanzmann thrombastenia) underwent laparoscopic surgery for blood clots in the abdominal cavity.

Daily functioning

Menorrhagia-specific QoL. All 78 women in the analysis group completed the menorrhagia-specific QoL MMAS questionnaire. The median (IQR) overall MMAS score during natural/untreated menstrual cycle was 56 (38–74). Women who were treated for HMB (52) reported siqnificantly lower QoL before their treatment, compared to the 26 untreated women, at a mean (IQR) of 51 (34–69) *versus* 73 (43–84) (P = 0·009).

After treatment, 21 women had no menstruations anymore and therefore no MMAS score was obtained. In the remaining 31 women, the score improved from a median (IQR) of 54 (33–66) pre-treatment to 63 (47–88) post-treatment (P = 0·005). Analysis of the MMAS domains demonstrated that 44% (15/34) of women initially had severe practical problems in daily life due to HMB. This decreased to 9% (three of 34) after HMB treatment. Severe problems experienced at work (18%, six of 34) and in social functioning (6%, two of 34) completely resolved with treatment.

General QoL. Compared to the scores of women in the general Dutch population, women with a confirmed or suspected CPD tended to report poorer scores on the SF-36 in the domains of physical role (i.e. limitations in the type or amount of regular daily activities due to physical health problems), (bodily) pain, general health (i.e. perception of general health status), vitality (i.e. energy levels and fatigue) and social functioning (i.e. limitations in social activities) (Table II).[23]

Women with self-reported HMB appeared to have lower SF-36 scores in all domains compared to women without self-reported HMB, especially in the domains of physical role and social functioning (Table III).

Sexual functioning

Bleeding tendency and HMB. Our self-developed questionnaire to investigate the impact of bleeding tendency on sexuality was returned by 75 women in the analysis group. Some women did not complete one or more questions related to themes that were either not applicable for them or they felt uncomfortable to talk about. Missing data were removed from the analysis. This explains the changing denominator throughout this section. Sexuality and bleeding tendency were discussed during outpatient evaluations in 21% of the consultations: this topic was initiated by doctors in 5% (four of 75) and by women themselves in 16% (12/75) of the study population. Discussing this topic would be appreciated by 21% (16/75) of women, whereas 41% (31/75) were unsure about this and 37% (43/75) were not interested. Menstruations negatively impacted sexual activity in 59% (41/69) of women: 32 women reported this was due to long or heavy menstruations, eight expressed feelings of insecurity and some women indicated feeling unclean. Two women described that intercourse caused heavy bleeding. Four

women (15%, 4/27) used tranexamic acid to prevent bleeding during intercourse.

Due to the bleeding tendency, sexual activity was marginally disrupted in 33% (22/67), while 6% (four of 67) reported to be severely restricted in sexual activity. One woman reported that sexual intercourse was impossible considering her bleeding tendency. HMB (25%, 17/67), fatigue (15%, 10/67), pain (10%, seven of 67) and postcoital bleeding (6%, four of 67), were reported as main reasons for restricted sexual activity.

During menstruation, 22% (15/69) of women reported to have sexual intercourse, in which additional protection against blood loss in the form of towels was used by 53% (eight of 15). Blood loss other than menstrual bleeding during sexual intercourse was experienced occasionally in 21% (15/71) of the women, while 3% (two of 71) to 4% (three of 71) of women experienced this frequently to always, respectively.

> 'Very, very, very glad that this can finally be discussed! ... Please talk about this more often!' – Woman with confirmed CPD

Sexual distress. The FSDS-R to measure sexual-related distress level was was completed by the 72 women in the analysis group. The six remaining women did not feel comfortable to return a questionnaire about this topic. Sexual distress was reported by 34 of the 72 women. The median (IQR) FSDS-R score was 10·5 (2·0–22·8). A large proportion of women reported feeling sexually inadequate (17%) or guilty about sexual difficulties (15%) (Fig 2).

To test whether the sexual-related distress within the analysis group was related to the bleeding tendency, we compared the FSDS-R results with the results from the sexual functioning quetionnaires. The FSDS-R score was higher in women reporting limitations in sexual activity due to their bleeding tendency (27 women), compared to women without self-reported limitations (40), with a median (IQR) FSDS-R score of 20 (8–26) *versus* 6 (1–14) ($P = 0{\cdot}002$).

Pregnancy and delivery

Miscarriages were reported by 23 women, of which 18 women reported to have experienced heavy blood loss due to miscarriage. In all, 12 women reported having received treatment for blood loss caused by miscarriage (four, iron tablets; two, hormonal treatment; three, tranexamic acid; one, desmopressin; two, clotting factors; nine, curettage; three, platelets transfusion; two, blood transfusion). Three of these women reported an emergency hospital visit and treatment.

Of the analysis group, a total of 138 live infants (117 vaginal deliveries, 21 caesarean sections) were born to 58 women. Women with a confirmed CPD more often delivered via caesarean section than women suspected of a CPD (24% vs. 11%, $P = 0{\cdot}04$). Bleeding problems were reported by 81% (47/58) of the women in one or more deliveries. These bleeding problems were reported to require treatment in at least 62% (29/47) of women (eight with unknown treatment are reported here as having no treatment received). Tranexamic acid and iron treatment were most often prescribed, followed by blood and platelet transfusion.

> 'Heavy bleeding after delivery. I didn't know about my bleeding tendency at that time, I thought it was normal to lose so much blood after giving birth.' – Woman with a suspected CPD

Discussion

In the present study, we evaluated the prevalence and burden of vaginal bleeding in a cohort of women with confirmed or suspected CPD. The self-reported prevalence of HMB was particularly high (87%) compared to a self-reported prevalence of HMB in the general population of ~30%.[17] Bleeding tendency equally impacted QoL in women with a confirmed CPD and suspected CPD, underlining the importance of efficient treatment, independent of a confirmed diagnosis.

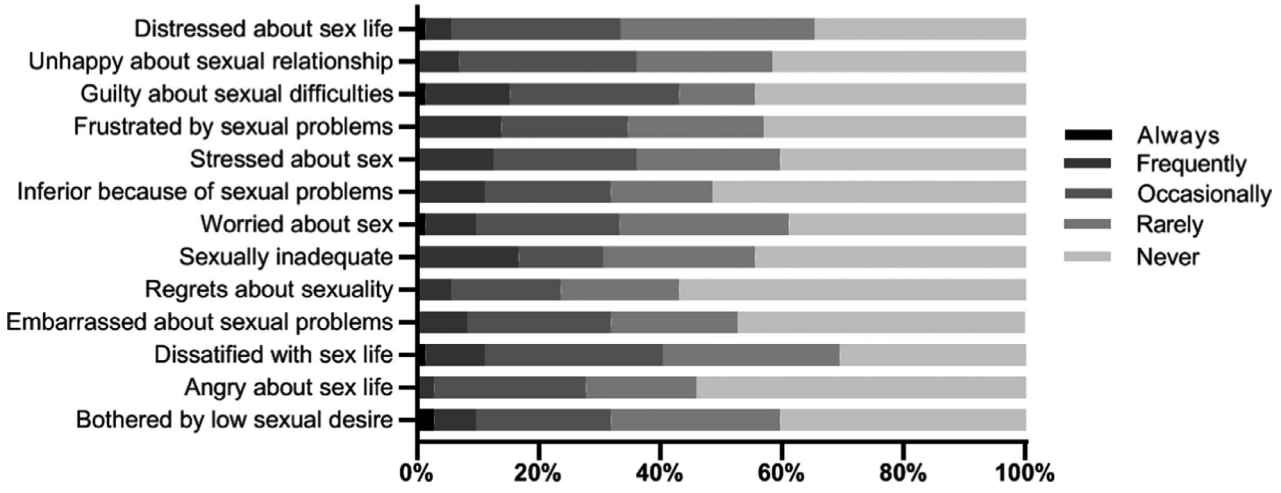

Fig 2. Sexual functioning in the total cohort ($N = 72$).

Previous studies in women with von Willebrand disease, haemophilia carriers and women with other factor deficiencies have shown similar results: up to 90% of women with bleeding disorders experience HMB.[25] The burden of having a CPD or suspected CPD is demonstrated by lower scores in several domains of general QoL questionnaires compared to the general population and is similar between women with a CPD or suspected CPD.[26] The reported HMB by these women severely impacted daily life, as women with self-reported HMB had lower scores in the domains of general health, physical role and social functioning ($P = 0{\cdot}00$, $0{\cdot}04$ and $0{\cdot}03$ respectively). This is consistent with previous findings in the general population, where women with HMB have significantly lower QoL than women with normal menstrual bleeding in all dimensions of the SF-36.[17] Using the menorrhagia-specific MMAS questionnaire, we could further show that QoL was scored much higher after adequate treatment for HMB. A large proportion of women (35%) only reached satisfactory treatment results after surgical intervention, although this is not an option for women of reproductive age that want to keep the option of having a(nother) child open.

Results of our present study demonstrate that HMB has a negative impact on sexual activity and causes sexual distress in the majority of women with a CPD or unknown bleeding tendency. Women also mentioned that doctors should address this topic more often in the consultation room. Discussing the possible implications of bleeding tendency on sexual health may not only support women in feeling recognised in their disease, but it may also allow to discuss possible solutions. According to our present data, topics that should be discussed in the consultation room include impact and treatment options of HMB, postcoital bleeding and contact bleeding, including practical tips. The behaviour of partners as a possible (unconscious) contributing factor on distress was not specifically investigated in the present study, but multiple women mentioned the importance of their partner's attitude in the free-text fields of the questionnaires. A survey amongst 301 Dutch men aged 18–45 years of the general population who had been in a relationship for ≥6 months, reported that 31% of the men questioned did not want to see menstrual blood loss at all. Key motives these men raised were the possible negative effect of this on the couple's sex life, social life and relationship quality.[27] This emphasises the need to discuss the effects of vaginal bleeding on (sexual) health in the consultation room.[28]

About half of the women in our present study reported excessive peripartum bleeding, requiring platelet and/or blood transfusion in ~15% of deliveries. This is comparable to the self-reported incidence of excessive peripartum blood loss in women with von Willebrand disease (51%) or women with different kinds of CPDs (ranging from 37 to 63%), and is much higher than the 19% reported in the general population.[12,13,29] Guidelines from the United Kingdom Haemophilia Centre Doctor's Organisation (UKHCDO) and Royal College of Obstetricians and Gynaecologists (RCOG) on the management of inherited bleeding disorders in pregnancy advise pre-pregnancy counselling by a multidisciplinary specialist team with expertise in caring for patients with platelet function disorders.[30] More progress should be made in the identification of obstetric problems in these women and defining optimal obstetric management.[30]

We believe that the TiN-Women study is representative for all women with a (suspected) CPD, as the TiN study cohort consisted of a large cohort of patients from all around the Netherlands and included both patients with a confirmed and suspected CPD that is representative of clinical practise. However, selection bias is to be considered due to the possible under representation of mild CPD cases, as those patients are more likely to stay undiagnosed. In addition, a suspected CPD was often suspected in cases with an increased ISTH-BAT score of which HMB and PPH are components, potentially increasing the HMB incidence. Furthermore, we cannot rule out that the bleeding tendency is not caused by another, not yet identified bleeding disorder that is not related to platelet function.

We had a relatively high response rate to our TiN-Women questionnaires (82%). In order to determine if responders to the questionnaire might have more bleeding problems than non-responders and would therefore be more willing to participate, we compared bleeding data of the responders with the non-responders and found out that there was an equal incidence of treatment for bleeding in both groups and no significant difference in bleeding scores. We therefore do not think this biased our present results on bleeding incidence. However, the age of TIN-Women participants was older in those who responded compared to those who did not. This may have contributed to the high percentage (35%) of women that underwent surgical treatment for their HMB, as young women more often do not chose this option because this interferes with the possibility of having (more) children.

Although we were able to include a relatively large cohort of women with a good response rate, especially when taking into account that a CPD is a relatively rare bleeding disorder, we were still hampered by small subgroups in our present analysis. Therefore, we chose to present the raw data in the tables in case of small subgroups. Challenges in prospective studies in rare disorders emphasises the importance of the present cross-sectional study.

The use of data from both generic and disease-specific QoL questionnaires reduced the possibility that important information would be missed.[10] However, caution should be exercised as multiple testing throughout analyses of each theme might have resulted in false positives.

The information we asked for with our questionnaires was not only information about the current clinical situation, but also any occurrences in the past, and therefore recall bias could have influenced the present results. It has been argued that generic QoL questionnaires, such as the SF-36, have inadequate face validity for women with HMB as menstrual bleeding is not a constant, but a cyclic complaint.[17]

Nevertheless, the SF-36 has been validated in women with HMB and together with a menorrhagia-specific instrument, such as the MMAS, these instruments can be used to determine perception and effect of HMB (treatment).[31] Self-reported peripartum haemorrhage could also have been influenced by recall and perception bias, as clinical records were not available for each patient to verify self-reported PPH treatment and to gather data on obstetric PPH risk factors that could have contributed to the PPH next to the bleeding disorder.

In conclusion, results of the TiN-Women study demonstrate the burden of vaginal bleeding in women with a (suspected) CPD throughout the different stages of life. It also emphasises the need to address this topic more prominently during outpatient clinic visits. The negative impact of vaginal bleeding on the QoL of patients with a (suspected) CPD should alert physicians to discuss vaginal bleeding and sexuality with their patients and offer individualised treatment for HMB and optimal pregnancy management. Further research should focus on improving non-surgical HMB treatment, optimising physicians counselling of women on sexual functioning and optimising peripartum management.

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Authors contributions

M. C. Punt and K. P. M. van Galen designed the research study. M. C. Punt and N. D. Ruigrok performed the research. M. C. Punt, N. D. Ruigrok ran the analyses which was critically reviewed by K. W. M. Bloemenkamp, N. Uitslager, R. T. Urbanus, I. C. L. Kremer Hovinga and R. E. G. Schutgens. M. C. Punt, N. D. Ruigrok and K. P. M. van Galen drafted the first version of the manuscript, which was revised by the other authors.

Conflicts of interest

M. C. Punt, N. D. Ruigrok, R. T. Urbanus, I. C. L. Kremer Hovinga, E. Groot, K. W. M. Bloemenkamp: none, N. Uitslager: received a research grant from Sobi, speakers fee from and consultancy for Bayer, R. E. G. Schutgens: received research grants from Bayer, CSL Behring, Pfizer, NovoNordisk, Sanquin, Shire and Sobi, consultancy for Bayer, NovoNordisk and Shire and speakers fee from Freeline, Boehringer Ingelheim, Roche and Sobi. K. P. M. van Galen: received unrestricted research grants from CSL Behring and Bayer in the past and speakers fee from Takeda and Amgen.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table SI. Baseline characteristics of responders and non-responders to questionnaire.

Table SII. Overview of main study results in total cohort, women with confirmed congenital platelet defect and women with suspected congenital platelet defect.

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