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Full title: Depression in Adolescents and Young Adults with Heavy Menstrual Bleeding in a Referral Clinic Setting

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Running Title: Depression and heavy menstrual bleeding

Word Count: Main Text: 1480 words, 1 Table

To the Editor:

Heavy menstrual bleeding (HMB) is a common problem reported in up to 40% of adolescent females, with a greater frequency in adolescents with bleeding disorders (BDs).[1] HMB is known to negatively affect health due to high rates of associated iron deficiency (ID) and iron deficiency anemia(IDA), both of which have been linked to decreased health related quality of life (HRQOL) in adults.[2] Adolescents with HMB also report decreased HRQOL compared to adolescents without HMB, and on par with or worse than adolescents with cystic fibrosis and juvenile arthritis.[3] Studies suggest that reduction in HMB, and treatment of ID leads to improvement in HRQOL.[1,2] While there is increasing evidence that HMB in adolescents impacts HRQOL negatively, the association with depression and anxiety, is unknown. We conducted a retrospective chart review at the University of Michigan to evaluate the impact of HMB on mental health disorders, specifically depression and anxiety, in adolescents and young adults. We further evaluated if a BD diagnosis, IDA, or ID were associated with depression and anxiety in this population and compared the prevalence of depression and anxiety to the general age matched US population.

We identified females 9-25 years old with HMB and/or a BD, including a factor deficiency, von Willebrand disease (VWD), a platelet function disorder (PFD), hypo-/dys-fibrinogenemia or immune thrombocytopenia (ITP), evaluated in the pediatric hematology or combined pediatric hematology and gynecology clinic between 2016 and 2020.   We defined HMB as bleeding lasting more than seven consecutive days, requiring changing of sanitary products more frequently than every two hours, or multiple episodes of bleeding during the month significant enough to impact daily routines (e.g. missing school, work or extracurricular activities).[1] Patients were determined to have depression and anxiety if a provider documented these diagnoses in a note in their electronic medical record (EMR), or if they had a Patient Health Questionnaire-9 score greater than ten. ID was defined as a ferritin less than 30ng/mL, and severe ID as a ferritin less than 15 ng/mL. IDA was defined as ID in addition to a hemoglobin value below the normal age-based range. Severe anemia was defined as a hemoglobin less than or equal to 9 g/dL. Adolescents were defined as patients ages 12-17 years old, and young adults were defined as patients 18-25 years old. Statistical analysis was performed using two proportion z-tests to compare proportions and t-tests to compare means. The University of Michigan Institutional Review Board approved this study.

In total 272 patients were included. HMB was present in 253 patients (93%) and 138 patients (50.7%) were diagnosed with a BD (86.2% of whom had HMB). The mean age of the patients was 16 years and 10 months. The majority of patients were Caucasian (73.5%), 9.2% were African American, and additional represented races composed 5% or less of the population. Patients were predominantly non-Hispanic (93.8%).

Represented BDs included VWD (68%), PFDs (19%), factor deficiencies (8%), and ITP (5%). The mean age of onset of menarche was 11.8 years, onset of HMB was 13 years,

and mean age at initial evaluation for HMB was 14.5 years. Twenty-four patients (9.5%) presented for initial evaluation of a BD in young adulthood.

Overall, 40.1% of patients in this study had a diagnosis of depression, 37.1% had anxiety, 50% were anemic, and 77.6% were iron deficient. The prevalence of depression and anxiety were evaluated in patients with and without IDA and ID and revealed anxiety was more prevalent in patients without ID (p=0.049), though no significant difference was seen with regards to depression. Patients with severe anemia or severe ID were not found to have higher rates of depression (p=0.73, p=0.68 respectively). Rates of depression and anxiety were similar between patients with and without a BD and are presented in table 1.

Of the patients with HMB, 43.1% had depression and 37.9% had anxiety. Among these patients with HMB, depression was diagnosed in 6 patients prior to 12 years of age, 79 patients (33%) during adolescence, and 24 (25%) patients during adulthood. Excluding the 16 (14.7%) patients who had onset of depression prior to HMB, the average time from onset of HMB to diagnosis of depression was 2.3 years. Anxiety was present in half the young adult patients versus 32% of patients ages 13 to 17 years.

Patients with HMB with and without a BD were compared, revealing no difference in age at onset of HMB (p=0.25) or at initial evaluation for HMB (p=0.26) based on the presence of a BD. However, on average those with a BD were evaluated 1.4 years earlier than those without a BD as 24 (20.2%) patients presented prior to onset of HMB due to a family history of a BD or other bleeding manifestations (p=0.006). Interestingly, those without a BD were more likely to be anemic (p=0.019) and iron deficient (p=0.024) than patients with a BD perhaps due to pre-menarchal anticipatory guidance.

Patients with a BD diagnosis with and without HMB were compared and results are presented in table 1. Those without HMB on average presented 43 months earlier than those with HMB (p<0.0001) as 36.8% without HMB presented at a young age due to a family history of a BD versus only 21% of patients with HMB.

Other factors with potential to impact depressive symptoms including sexual activity and use of hormonal medications were also evaluated. Seventy patients (25.7%) were sexually active and were more likely to be depressed than those who were abstinent (p<0.0001). Hormonal medications were prescribed to 234 (93%) patients for HMB, 45% of whom had a diagnosis of depression.

Therapeutic interventions for patients with depression were evaluated and 63.3% of patients were treated with an antidepressant, 46.8% of whom received concurrent therapy. In addition, 22% of patients were in therapy alone, and 14.7% did not receive any treatment for their depression.

Our study found a higher prevalence of depression in adolescents (33%) and young adults (25%) with HMB than in the adolescent female population in the US (20% in

adolescent females, 13.3% in young adults), unrelated to the presence of an underlying BD.[4]

The prevalence of anxiety in our population of patients ages 13 to 17 years old (32%), was similar to the US population (38%), but the percentage of young adults with HMB and anxiety (50%) was twice that of the general adult population (23.4%).[4]

While this study suggests that HMB is associated with depression in adolescents and depression and anxiety in young adults, the etiology of these mood disorders is likely multifactorial. Our results do not suggest that patients with a BD, ID or IDA are more likely to be depressed. This is somewhat contradictory to prior studies which have shown a correlation between IDA and decreased HRQOL, which has been associated with depressive symptoms.[2] Meanwhile anxiety was more prevalent in patients without ID. As only 27 patients in this study were not ID, a larger cohort of patients without ID is needed to validate these findings.

One potential confounding variable in this study was the large proportion of girls treated with hormonal medication. The impact of hormonal medication on mood has been studied extensively and results are contradictory. One study has shown that women taking oral contraceptives for reasons other than contraception, like most of the patients in our study, are more likely to have depression, suggesting the reason for initiation may have more of an impact on mood than the medication itself.[5] Due to our high hormonal treatment rates, we were not able to evaluate if use was associated with depression.

Sexual activity was noted to be associated with depression in this study. While this could confound our data, it is important to note that only 25.7% of patients were sexually active which is far below the US national average where 51.4% of females 15-17 years old, and 91.8% of females 20-24 years report being sexually active.[6]

A significantly higher percentage of our adolescent patients with HMB received treatment for their depression (85.3%) compared to the US population (39.9%).[4] One explanation for this discrepancy is that patients with HMB have higher rates of severe depression requiring therapeutic intervention. Alternatively, patients with HMB, particularly those in our study with access to healthcare, may be more frequently evaluated for depression by health care professionals, increasing opportunities for diagnosis and treatment.

Limitations of our study include that it was retrospective and therefore reliant on provider documentation. In addition, our cohort of women with BDs without HMB was small, and a larger cohort is necessary to further validate our findings in this group.

In conclusion this study demonstrates that mental health screening is imperative in adolescents and young adults with HMB given the high prevalence of depression and anxiety. From our study it is unclear whether the treatment of HMB with hormonal medications could increase or potentially decrease rates of depression. Further

longitudinal studies are needed to determine the association between hormonal medications and depression in patients with HMB.

Conflicts of Interests

The authors have no conflicts of interest to disclose.

Author Contributions

All authors designed the study and wrote the manuscript. MM performed the data collection and analysis. All authors approved the final version of the manuscript for submission.

Funding Information

Data Availability Statement

Author elects to not share data.

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Table 1. Comparison of patients by bleeding disorder diagnosis and HMB

			BD			BD			
		Total	HMB	No HMB	p-value	Yes	No	p-value	Ongoing BD Evaluation
Total N (%)		272	119 (43.8)	19 (7.0)		138 (50.7)	77 (28.3)		57 (21.0)
Depression N (%)	Yes	109 (40.1)	58 (48.7)	0 (0)	0.00006	58 (42)	28 (36.4)	0.42	23 (40.4)
	No	163 (59.9)	61 (51.2)	19 (100)		80 (58)	49 (63.6)		34 (59.6)
Anxiety N (%)	Yes	101 (37.1)	53 (44.5)	5 (26.3)	0.14	58 (42)	24 (31.2)	0.12	19 (33.3)
	No	171 (62.9)	66 (55.5)	14 (73.7)		80 (58)	53 (68.8)		38 (66.7)
Depression, Anxiety or Both N (%)	Yes	135 (49.6)	69 (58)	5 (26.3)	0.01	74 (53.6)	35 (45.5)	0.25	26 (45.6)
	No	137 (50.4)	50 (42)	14 (73.7)		64 (46.4)	42 (54.5)		31 (54.4)
Iron Deficiency N (%)	Yes	211 (77.6)	87 (73.1)	7 (36.8)	0.002	94 (68.1)	72 (93.5)	0.004	45 (78.9)
	No	27 (9.9)	12 (10.1)	6 (31.6)		18 (13.0)	2 (2.6)		7 (12.3)
	Unknown	34 (12.5)	20 (16.8)	6 (31.6)		26 (18.8)	3 (3.9)		5 (8.8)
Anemia N (%)	Yes	136 (50)	54 (45.4)	1 (5.3)	0.001	55 (39.9)	49 (63.6)	0.02	32 (56.1)
	No	131 (48.2)	62 (52.1)	16 (84.2)		78 (56.6)	28 (36.4)		25 (43.9)
	Unknown	5 (1.8)	3 (2.5)	2 (10.5)		5 (3.6)	0 (0)		0 (0)