Gingival Bleeding and Oral Hygiene of Women with von Willebrand Disease

by

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Dedication

To my mentor, Karen Ridley, who has inspired me to lead a career in dental hygiene education, involvement with the bleeding disorder community, and research in oral health and bleeding disorders. Thank you for believing in me!

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CHAPTER 1

INTRODUCTION

1.1 Problem Statement

Von Willebrand Disease (VWD) is the most common hereditary coagulation abnormality, presenting in an estimated 1% of the population.[1–4] Von Willebrand Disease (VWD) can also be acquired as a result of other medical conditions such as autoimmune disorders.[4] In those with VWD, there is a deficiency or dysfunction of von Willebrand Factor (VWF) depending on the type of VWD.[1–4] Von Willebrand Factor (VWF) is a plasma protein that controls platelet hemostatic function and stabilizes blood clotting with factor VIII. Those with VWD often experience issues with mucosal bleeding: frequent nosebleeds, heavy menstrual bleeding, and excessive bleeding after injury or surgical procedures, including dental extractions.[1–4]

Gingival bleeding is not considered a true symptom, but is experienced by many individuals that have VWD. Based upon current evidence, a positive relationship exists between plaque accumulation and gingival inflammation and bleeding.[5–7] Many studies have shown this relationship, using the experimental gingivitis model, giving evidence that the more supragingival plaque that exists, the more gingival bleeding and inflammation.[5–7]

Anecdotally, many people with VWD attribute gingival bleeding to the VWD condition itself since symptoms include mucosal bleeding. However, no studies have shown a

correlation between VWD and gingival bleeding when adjusting for possible confounding factors such as plaque accumulation, demographics, dental care utilization, or oral hygiene habits.

Those individuals with VWD are usually referred to a bleeding disorder treatment center to consult with a hematologist. As many VWD patients have poor oral hygiene from fear of causing gingival bleeding with plaque removal methods such as brushing the gums and flossing subgingivally,[3] some bleeding disorder treatment centers have employed dental hygienists to provide oral hygiene education. It is also hypothesized that many VWD patients do not attend preventive routine dental appointments due to fear of excess bleeding and treatment complications.[8]

1.2 Goal Statement

This cross-sectional study will generate pilot data to examine the correlation between VWD severity and gingival bleeding, assess the oral hygiene habits and dental care utilization in women with VWD, and address the effectiveness of having a dental hygienist to provide valuable oral hygiene education and instruction to patients with VWD. Ultimately, this information will give insight to the correlation between VWD and gingival bleeding while controlling for plaque score and other possible confounding variables.

1.3 Specific Aims

The aims of the study are as follows…

Specific Aim 1: To determine the relationship between von Willebrand factor (VWF) levels and gingival bleeding in adult women with von Willebrand Disease (VWD).

Null Hypothesis (H_0): In women with VWD, the amount of gingival bleeding will be no different regardless of VWF levels.

Alternative Hypothesis (H_1): In women with VWD, the amount of gingival bleeding will be higher in those women with lower VWF levels.

Specific Aim 2: To determine the oral hygiene habits and dental care utilization in those with von Willebrand Disease (VWD).

Null Hypothesis (H_0): Women with VWD who have received oral hygiene education from a dental hygienist at their bleeding disorder treatment center frequently to at every visit are as likely to have regular preventive dental appointments and better oral hygiene habits as women with VWD that have not had oral hygiene education from a dental hygienist at their bleeding disorder treatment center.

Alternative Hypothesis (H_1): Women with VWD who have received oral hygiene education from a dental hygienist at their bleeding disorder treatment center frequently to at every visit, are more likely to have regular preventive dental appointments and better oral hygiene habits than women with VWD that have not had oral hygiene education from a dental hygienist at their bleeding disorder treatment center.

Specific Aim 3: To determine the effectiveness of having a dental hygienist at bleeding disorder treatment centers to provide oral hygiene education to VWD patients.

Null hypothesis (H_0): Women with VWD who have had oral hygiene education from a dental hygienist at their bleeding disorder treatment center frequently to at every visit are as likely to have less gingival bleeding and less supragingival plaque as women with VWD that have not had oral hygiene education from a dental hygienist at their bleeding disorder treatment center.

Alternative Hypothesis (H_1): Women with VWD who have had oral hygiene education from a dental hygienist at their bleeding disorder treatment center frequently to at every visit are more likely to have less gingival bleeding and less supragingival plaque than women with VWD that have not had oral hygiene education from a dental hygienist at their bleeding disorder treatment center.

1.4 Significance

This clinical research sought to examine the correlation between VWD severity and gingival bleeding, assess the oral hygiene habits and dental care utilization in women with VWD, and address the effectiveness of having a dental hygienist to provide valuable oral hygiene education and instruction to patients with VWD. Ultimately, this information will give insight to the correlation between VWD and gingival bleeding when controlling for presence of plaque and other possible confounding variables. This will potentially improve the way oral hygiene education is delivered and stressed towards this population.

1.5 Thesis Overview

Chapter II is the Review of the Literature and will guide the reader through the history of von Willebrand Disease (VWD), explore the current evidence relating VWD to oral health, and examine the correlation between supragingival plaque and gingival health. Chapter III reviews the Methods & Materials of this study, outlining each specific aim and how the data was analyzed. Chapter IV, Results, focuses on the statistical results of this study. Chapter V, Discussion, will include a comprehensive discussion of the study and in Chapter VI, the final conclusions will be revealed.

CHAPTER 2

LITERATURE REVIEW

2.1 von Willebrand Disease

Von Willebrand Disease (VWD) is the most common hereditary coagulation abnormality, presenting in an estimated 1% of the population.[1–3] Von Willebrand Disease can be caused by a genetic mutation in the von Willebrand Factor (VWF) gene or as a result of other medical conditions such as autoimmune disorders.[4] Von Willebrand factor is an adhesive plasma protein that helps with blood clotting.[2] Normally, when bleeding occurs, platelets join together to stop the bleeding by forming a blood clot.[2] In VWD, there is an interruption in this process.[2] Depending on the type of VWD, there is either a qualitative or quantitative defect of von Willebrand Factor.[1–4] A person without VWD has levels of VWF that are between 50 and 200 IU dL^{-1}. There can also be a deficiency of factor VIII because VWF carries the factor VIII protein. There are three types of VWD.[1–4, 9]

Von Willebrand Disease detection and identification has changed throughout history.[9,10] In 1924, Erik Adolf von Willebrand identified what is now known to be VWD. He discovered VWD when a large family presented at his clinic with symptoms of severe mucosal bleeding. Clotting times were surprisingly normal, but the bleeding time lasted much longer than that of a normal individual. This showed Erik von Willebrand that this was a different bleeding disorder than hemophilia. After extensive laboratory

tests to check how the lack of the plasma factor influenced bleeding time, he was diverted by the fact that this lack of plasma factor did not affect coagulation time. Therefore, VWD was known in the 1960s as a combination of low factor VIII levels and another unknown plasma factor. Because of the lack of information available from the laboratory investigations, VWD was difficult to differentiate from other coagulation and platelet disorders.[9,10]

Throughout time and many more laboratory investigations, scientists have come to the conclusion that VWD "is a bleeding disorder now recognized to be characterized by deficiency of, or defects in, an adhesive plasma protein called von Willebrand factor (VWF)."[9]

Those with VWD have various symptoms mostly related to mucosal bleeding. Symptoms include epistaxis, gingival bleeding, menorrhagia, excessive bleeding from a cut, surgery or dental extraction, blood in the stool or urine, and easy bruising.[1,3,4] Eighty to ninety percent of women with VWD experience heavy menstrual bleeding, otherwise known as menorrhagia.[2] Therefore, they are either treated with oral contraceptives or other birth control methods.[2] Oral contraceptives are prescribed that either contain an estrogen (which reduces menstrual flow and likely increases VWF and Factor VIII levels) or progestin-only contraceptives, which also decrease bleeding.[2] Sometimes even a complete hysterectomy is recommended.[2] Though many believe that oral contraceptive use leads to increased risk for periodontal disease, at the present time there is not enough research to support this idea.[11,12]

Most people with VWD have a mild to moderate form and are only diagnosed after a significant bleeding episode or genetic testing due to family history.[2,13] Diagnostic tests

include VWF antigen, VWF ristocetin cofactor activity, Factor VIII clotting, VWF multimers, and platelet function.[1] There are different classifications of VWD: Type 1, Type 2A, Type 2B, Type 2M, Type 2N, and Type 3. Please see Table 1 for characteristics, prevalence, and bleeding propensity of each type of VWD.

2.1.1 Classifying VWD

Type 1 VWD

Type 1 VWD is described as a partial quantitative deficiency of VWF. This affects about 75% of symptomatic VWD patients and causes mild to moderate bleeding propensity. Persons with Type 1 VWD typically have VWF levels of less than 20 $IUdL^{-1}$. The genetic mutation for type 1 VWD is autosomal dominant.[1]

Other studies describe that the genetic defect associated with most people with Type 1 VWD is not consistent, and that the levels can vary depending on environmental factors such as medications, exercise, pregnancy, and inflammation. Other genes can also influence the expression of the VWF gene.[9,14]

Recent suggestions have been made that many of those with mild Type 1 VWD are actually false positives and do not have an identifiable VWF mutation. Many symptoms could overlap with normal individuals without coagulation abnormalities.[9] Some have even suggested that type 1 VWD be reserved for only those with markedly reduced levels, or a severe quantitative deficiency of VWF.[14]

Type 2 VWD

Type 2 VWD is described as a qualitative VWF defect. There are four subtypes: 2A, 2B, 2M, and 2N. Almost all of the remaining 25% of VWD patients are classified as

having Type 2 VWD. In Type 2 VWD, bleeding propensity varies, but is usually moderate. The genetic mutation for type 2 VWD depends on the subtype. Type 2A and 2M can be autosomal dominant or autosomal recessive. The types are noted with having VWF function than VWF antigen. The ratios between different laboratory values (Ristocetin Cofactor to VWF antigen and VWF:CB to VWF antigen) are also important in distinguishing these two subtypes from type 1 VWD. High molecular weight also plays an important role in distinguishing 2A from 2M.[15] Type 2B is autosomal dominant and Type 2N is autosomal recessive.[1] Type 2B is noted by an increased resemblance to a platelet known as GPIb. Type 2N is noted by a decreased binding affinity for factor VIII.[15] In other words, factor VIII levels are reduced in those with type 2N. More details about each subtype of Type 2 VWD can be found within the Table 1 on page 10.

Type 3 VWD

Type 3 VWD is usually recognized as having an absence of VWF, whether by having a complete deficiency or undetectable levels of VWF (1-9 IU $^{dL-1}$). This type is extremely rare, with a high bleeding propensity (severe bleeding). Type 3 VWD is autosomal recessive and is often misdiagnosed as hemophilia A.[1,9]

Table 1 VWD types and characteristics.[9,10,16]

VWD type	VWF level/defect	Prevalence	Bleeding propensity	Genetic mutation
1	Usually <20 IU^{dL-1} Quantitative	Common About 80% of those with VWD have type 1	Mild-moderate	Autosomal dominant
Type 2	Qualitative defect of VWF	About 20% of those with VWD have type 2	Moderate	Depends on subtype
2A	Qualitative defect: loss of high molecular weight (HMW)	Prevalence of subtypes unknown	Moderate	Autosomal dominant or autosomal recessive
2B	Qualitative defect: enhanced functional binding of VWF that leads to loss of HMW and mild thrombocytopenia	Prevalence of subtypes unknown	Moderate	Autosomal dominant
2M	Qualitative defect: VWF dysfunction not associated with loss of HMW VWF	Prevalence of subtypes unknown	Moderate	Autosomal dominant or autosomal recessive
2N	Qualitative defect: loss of VWF and Factor VIII binding	Prevalence of subtypes unknown	Moderate	Autosomal recessive
3	Complete deficiency or undetectable levels (1-9 IU^{dL-1}) Quantitative	Extremely rare 1-3:1,000,000	High/Severe	Autosomal recessive

2.2 Inflammatory diseases of the periodontium

Research has shown that periodontitis and gingivitis are among the most common diseases worldwide.[17] Gingivitis is more of a superficial inflammatory disease in that though bleeding of the gums may occur; the inflammation is not destructive towards the surrounding tissues such as the alveolar bone. Gingivitis can be reversed

with proper plaque removal. If left untreated, periodontitis can occur, which is characterized by alveolar bone loss that is irreversible. This can eventually lead to total loss of the tooth, in severe cases.[18] Much evidence has pointed to the bacteria within biofilm, or dental plaque, as the main cause of inflammatory disorders of the periodontium.[18–21,22] This assumption was gracefully demonstrated by the early studies of Löe and colleagues in the 1960s, using their experimental gingivitis model.[22]

In one study by Loe and colleagues, an attempt was made to introduce gingivitis to a group of healthy individuals by withholding oral hygiene practices. The goal of the study was to examine the changes in the bacteria within the plaque. Gingival Index and Plaque Index were used. Measurements were taken at the beginning of the study and instructions were given to avoid oral hygiene practices. Participants were evaluated at varying time intervals, where Gingival Index and Plaque Index values were taken again. When any inflammatory change was noted, the participants were instructed on oral hygiene methods. When the GI and PI values approached zero, the experiment was ended.[22]

This study found that at the end of the period where participants were not allowed to partake in oral hygiene practices, the PI value increased in mean from 0.43 to 1.67, which is significant. Every participant developed gingivitis at this phase as the mean GI value increased from 0.27 to 1.05. As soon as oral hygiene practices were allowed, the mean PI and GI dropped even below that of which it started at the beginning of the study. This study reveals that without proper oral hygiene practices, plaque buildup will increase rapidly and gingivitis will develop.[22]

Another study that demonstrated the link between gingivitis and supragingival plaque was a study published in 2013 by Eberhard and colleagues. In this study, gingivitis was introduced experimentally in a group of young, healthy volunteers by terminating oral hygiene. When allowing the bacterial plaque deposits to accumulate on the tooth by terminating oral hygiene in one section of the mouth for 21 days, the gingiva was markedly affected. Values were significantly different on day 21 when examining Gingival Index, volume of gingival sulcus fluid, and bleeding on probing. "This inflammatory process was found to be almost completely reversible by appropriate dental hygiene." This study shows the effects of supragingival plaque on the surrounding gingival tissues.[18]

This correlation between plaque and gingival health was also demonstrated in the study by Trombelli and colleagues, which was published in 2004. In this study, a split mouth design was used to keep the subject constant. This was also used to identify which subjects had different inflammatory responses to plaque deposits. This study also withdrew oral hygiene for 21 days. After 21 days, the changes in Gingival Index and bleeding were statistically significant.[5] This study also demonstrated the link between supragingival plaque and gingival health.

A study by Lang and colleagues assessed the effects of plaque removal methods such as tooth brushing, flossing, and using a wooden toothpick to improve gingival health. In this study 32 healthy dental students were assigned to four groups. Group 1 used the toothbrush to remove dental plaque twice a day, group 2 used the toothbrush every other day, group 3 used the toothbrush every three days, and group 4 used the toothbrush every four days. Each participant was instructed to use the same technique

for plaque removal and was to remove the plaque in its entirety. An examiner then checked to make sure plaque was removed by using disclosing solution. Only Groups 3 and 4 developed gingivitis during this period of only brushing every 72 and 96 hours respectively even though Group 2 had similar amounts of plaque present. This led the researchers to believe that there are other factors that determine the plaque's pathogenicity than accumulation alone. Overall, this study shows that gingivitis develops when someone does not remove plaque for over 48 hours. It is also evident that completely removing plaque every other day is more beneficial than attempting to do so numerous times a day inadequately.[23]

2.3 VWD relation to oral health

Patients with VWD require special dental treatment accommodations,[3] but because this bleeding disorder is rare, many dentists do not have experience in training patients with coagulation disorders, especially VWD.[3,8,17,24] Therefore, an extensive amount of research recommends that any dental treatment be discussed with the patient as well as the patient's hematologist.[3,17,24,8]

An article in the Journal of the Canadian Dental Association by Gupta and colleagues stresses the importance of the knowledge on treating patients with bleeding disorders.[8] The importance of reviewing a patient's medical history prior to treating the patient is stressed through dental and dental hygiene programs. Oral health care professionals are taught how systemic health relates to oral health and what medical conditions and medications warrant a modification in treatment. With that said dental professionals are also at the forefront of disease and can recognize many systemic conditions in which symptoms present intraorally. For instance, presence of petechiae,

intraoral hematomas, or excessive gingival bleeding should cause the dental professional to think of a possible underlying bleeding disorder. When a patient has a bleeding disorder, such as VWD, the patient's physician should be contacted prior to any treatment to consider any treatment modifications.[8]

When symptoms of post-extraction bleeding and gingival bleeding in those with and without VWD were compared in 2011, those with VWD had a statistically significant amount of increased gingival bleeding than those without VWD in both males and females.[13] These results are indicated in Tables 2 and 3.

Table 2 Proportion of clinical bleeding history of 46 female VWD patients and 47 controls[13]

	Females with VWD (n=46)	Females without VWD (n=47)	Significance (p-value)
Prolonged bleeding post-extraction	20 (43%)	13 (28%)	Not Significant
Gingival Bleeding	21 (46%)	10 (21%)	p-value=0.011

Table 3 Proportion of clinical bleeding history of 19 male VWD patients and 16 controls[13]

	Males with VWD (n=19)	Males without VWD (n=16)	Significance (p-value)
Prolonged bleeding post-extraction	14 (88%)	4 (29%)	p-value=0.005
Gingival Bleeding	12 (63%)	4 (25%)	p-value=0.027

Research has shown that many patients with bleeding disorders have a fear of bleeding when removing plaque with brushing and flossing methods causing those with

bleeding disorders to generally have poorer oral hygiene than those without bleeding disorders.[17,21]

There has not been a significant amount of impactful research that has examined the relationship between VWD and periodontal status. [17] For instance, a study conducted in 2011 by Ziebolz and colleagues sought to determine if having a congenital bleeding disorder had some effect on oral health and bone loss. An experimental group of individuals with coagulation disorders was compared to a control group of healthy patients. An examination was performed assessing oral hygiene and DMF-T, which calculates the number of decayed teeth, missing teeth, and filled teeth. Then periodontal bone loss was assessed with a panoramic x-ray. Results of the study showed that those with bleeding disorders actually had better oral hygiene than those healthy patients. Also, though there was a statistically significant difference in periodontal bone loss, the difference is not clinically significant since the value calculates out to be less than 1mm difference.[17]

As those with VWD bleed easily and have difficulty with blood clotting, these individuals are at a higher risk when receiving extensive dental treatment.[17] In patients with bleeding disorders, there is a high risk of hematoma formation with local anesthesia injections, especially in highly vascular areas. Complications such as swelling, pain, respiratory obstruction, and even death from airway blockage can occur.[8,25]

This fatal occurrence happened to a man with hemophilia in a case study published in 1954 by Archer and Subrow. In this instance, an inferior alveolar nerve block was given to a man with hemophilia in order to restore/extract a tooth. The man was given two injections and could not get numb, so the procedure was terminated.

Two days later, the man was in the hospital with breathing difficulty. Later that evening, he was pronounced dead. From that instance, hematologists now advise patients with bleeding disorders to take their clotting factor prior to any injections in highly vascular areas.[25]

Urdaneta and colleagues conducted a study in 2008. This study, which took place at the University Hospital in Maracaibo, Venezuela, sought to examine the oral health and periodontal status of those with VWD who were treated. Forty patients were screened for this study. There was a control group of healthy individuals without bleeding disorders and a group of patients with VWD. Gingival Index (GI) and Simplified Oral Hygiene Index (SOHI) were used for this study. See Tables 4 and 5 for results of study.[3]

Table 4 Comparison of Gingival Inflammation (GI) and the Simplified Oral Hygiene Index (SOHI) in patients with von Willebrand Disease and control group.[3]

	von Willebrand	Control Group	P
GI	0.70±0.40 n=40	0.88±0.68 n=27	P=0.17
SOHI	1.7±0.80 n=40	0.76±0.55 n=27	P=0.0

Table 5 Degree of Gingival Inflammation (GI and the Simplified Oral Hygiene Index (SOHI) according to the variants of von Willebrand Disease.[3]

	Gingival Index			SOHI		
VWD	No Inflammation n=1	Slight n=30	Moderate n=9	Adequate (0.0-1.2) n=15	Acceptable (1.3-3.0) n=23	Deficient (3.1-6.0) n=2
Type 1 n=37	1 (2.5%)	29(72.5%)	7 (17.5%)	15(37.5%)	21 (52.5%)	1 (2.5%)
Type 2A n=2	0	1 (2.5%)	1 (2.5%)	0	1 (2.5%)	1 (2.5%)
Type 3 n=1	0	0	1 (2.5%)	0	1 (2.5%)	0

Preventive dentistry and education is of the utmost importance for VWD patients to avoid any extensive dental procedures.[8] Therefore, VWD patients consult with their hematologist at a bleeding disorder treatment center, where preventive oral health education may be discussed with the patients and a dental hygienist.

The most recently found study was conducted by Weickert and colleagues, and was published in 2014 in the Journal of Clinical Periodontology. In an attempt to determine if gingival bleeding was indeed a symptom of patients with type 1 von Willebrand disease, Weickert evaluated hematological reports and subject's periodontal measurements. This study found that those participants that were controls (without VWD) had more bleeding however this difference was not statistically significant. This study concluded that VWD is not associated with a more pronounced response to bacterial plaque and biofilm when looking at Gingival Bleeding Index (GBI) and Bleeding on Probing (BOP).[26] Though this study concluded that gingival bleeding is not a direct

symptom of type 1 VWD, there are limitations of the study. For instance, this study was limited to those with type 1 VWD. Scientific literature shows that many people with type 1 VWD may be considered false positives since the VWF can fluctuate to levels that would be considered normal depending on many different factors such as exercise, pregnancy, etc.[8,13]

All studies that have been reviewed have concluded that there is no evidence that those with VWD are at an increased risk for gingival bleeding or periodontal disease. With that said, the bleeding disorder does affect dental management. Preventative measures must be taken by educating the patient with VWD about risks of dental treatment and importance of adequate oral hygiene. Multidisciplinary teamwork must also be considered to be certain that those patients with VWD are treated safely and effectively.

CHAPTER 3

METHODS AND MATERIALS

3.1 Study Design

This study sought to examine the oral hygiene and gingival bleeding sites of women with von Willebrand Disease (VWD) to determine the correlation between VWD and gingival bleeding. Though a longitudinal study design may have provided more evidence about this population, plaque accumulation, and gingival bleeding over time, a cross-sectional study design was chosen due to time limitations and resources. A cross-sectional study was also chosen to provide descriptive data about this population in order to control for possible confounding variables. This study used clinical and survey components to investigate this relationship.

3.2 Source Population

The source population for this study was adult female patients with von Willebrand Disease (VWD) attending bleeding disorder treatment centers at either University of Michigan Hemophilia and Coagulation Disorders in Ann Arbor, Michigan or Michigan State University Center for Bleeding and Clotting Disorders in East Lansing, Michigan.

3.3 Participant Recruitment Strategy

Patients attending bleeding disorder treatment centers at University of Michigan Hemophilia and Coagulation Disorders in Ann Arbor or Michigan State University Center

for Bleeding and Clotting Disorders in East Lansing were identified through chart review as to their eligibility for the study. Subjects presented for their annual or biannual physical examination at the given bleeding disorder treatment center. Upon signing into the center, they were approached by the examiner and asked if they had an interest in participating in the study. The study procedures were explained in detail. If the subject was interested in participating in the study, further participant eligibility was then determined. Individuals who completed the study were compensated ten dollars cash for their time.

3.4 Eligibility Criteria

Adult women, over the age of 18 with von Willebrand Disease (VWD), were eligible to participate in the study if they had at least 12 teeth present and were capable of consenting and self-administering the survey component of the study. Subjects were excluded if they were under the age of 18, had uncontrolled diabetes, had significant psychiatric illness/social situations that would interfere with the completion of the survey, or were taking medications that cause gingival enlargement such as anti-convulsants, calcium-channel blockers (nifidipine, amolodipine, verapamil), cyclosporine, or anti-coagulants.

3.5 Data Collection

This study examined the effects of VWD on gingival bleeding when controlling for presence of plaque. The study had both a clinical and survey component to assess gingival bleeding, plaque removal, oral hygiene habits, and dental care utilization. This study did not administer any treatments or drugs to participants. Informed consent was

obtained prior to giving the questionnaire, extracting data from the patient's medical chart, and collecting clinical data.

3.5.1 Questionnaire Data Collection

Questionnaire: After obtaining a signature for consent, the survey/questionnaire portion of the study was given to the subject to fill out. This survey took about 5-10 minutes to complete and covered information regarding patient demographics, oral hygiene habits, dental care utilization, perceived frequency of gingival bleeding, and behavioral factors. The questionnaire was created based on current literature that either suggested relationships between VWD and some of the possible confounding factors or current literature that did not control for other possible confounding variables that have been shown in literature to relate to gingival bleeding.

Demographic information included which race/ethnicity the participant identified with best, age, education (less than high school, high school/some college, or college degree), and employment status (full-time, part-time, or none). Questions that covered oral hygiene habits included frequency of tooth brushing, flossing, and the use of other oral hygiene aids. Dental care utilization questions asked if there was dental insurance present, how often the participant visits the dentist (less than yearly, once a year, or more than once a year), and if the participant ever felt discriminated against due to her bleeding disorder (1 = yes, 0 = no). The questionnaire also asked how often the participant experiences gingival bleeding (less than once a month, once a month, or more than once a month). Behavioral factors assessed if the participant smokes cigarettes/cigars/pipes and drinks alcohol and how often.

Open-ended questions allowed for the participant to explain how or why she has felt discriminated against for having a bleeding disorder, why she has avoided the dentist in the past, and to explain how she was refused treatment.

The questionnaire was completed just before the oral examination was performed. Confidentiality was secured by assigning a patient identification number. Only the thesis committee has access to this information. Please see Appendix A for questionnaire.

Chart Review: VWD related data including type, von Willebrand factor (VWF) levels (mild, moderate, or severe), details of method of diagnosis, medical conditions, and medications was collected from the patient's medical record and documented on chart data sheet. See Appendix B for chart data sheet.

3.5.2 Clinical Data Collection

Oral Examinations: All oral examinations were performed at the time of the participant's appointment at one of the two bleeding disorder clinics: University of Michigan Hemophilia and Coagulation Disorders in Ann Arbor or Michigan State University Center for Bleeding and Clotting Disorders in East Lansing. A brief oral exam was performed on each patient to assess gingival bleeding and oral hygiene. Presence or absence of plaque on the mesiobuccal, buccal, distobuccal, mesiolingual, lingual, and distolingual surfaces of the six Ramfjord teeth was also recorded as 0 or 1 (0=no plaque, 1=plaque) on the Oral Examination Form (Appendix C). Carter and Barnes Gingival Bleeding Index (GBI) was used with a C-wrap floss technique to detect presence or absence of bleeding of the gingiva mesially and distally to the six Ramfjord teeth (tooth numbers 3, 9, 12, 19, 25, 28).[18] The same coding was used for bleeding (0, 1) and was also recorded on the Oral Examination Form. When one or more of the six

Ramfjord teeth was missing, the most posterior adjacent tooth was used that had a tooth in contact mesially and distally. The two examiners flossed, recorded presence or absence of plaque, and recorded presence or absence of bleeding upon flossing. Both supragingival plaque and gingival bleeding will be coded as 0-no bleeding/plaque and 1-bleeding/plaque.

3.6 Examiner training and calibration session:

Prior to enrollment of subjects, examiners completed a calibration exercise for both clinical parameters. The aims of the calibration session were to train all clinical examiners in the measurements that were taken and to determine the level of inter-examiner agreement looking at gingival bleeding and presence of supragingival plaque. One subject was recruited to participate in calibration exercises. Since there was 100% agreement between examiners on surfaces with plaque and gingival bleeding, the calibration session did not need to be repeated. The subject was made aware of the details of the study and informed consent was obtained.

3.7 Statistical Analyses

The distributions of all variables were generated and examined for outliers and the need for possible transformation prior to analysis. SPSS was the statistical software used for data analysis. All analyses will use a statistical significance at the conventional level of p=0.05.

Aim 1: To determine the relationship between gingival bleeding and VWF levels while controlling for the presence of supragingival plaque. A paired samples t- test was used to determine if presence of bleeding is dependent on plaque presence. Linear

regression was used to adjust for possible confounding variables such as VWD type/severity, oral hygiene habits, or dental utilization.

Aim 2: To determine oral hygiene habits and dental care utilization in those with VWD. Descriptive statistics were calculated for all variables. Chi-square models and linear and logistic regression to analyze the data collected from the survey/questionnaire component of the study depending on whether the variables were continuous or categorical.

Aim 3: To determine the effectiveness of having a dental hygienist at bleeding disorder clinics to provide oral hygiene education and instruction. We tested the hypothesis that receiving oral hygiene instruction from a dental hygienist at the bleeding disorder clinic is associated with less gingival bleeding and less plaque. For each outcome, linear regression was used to determine if having a dental hygienist present is associated with each outcome. Each test provided an odds-ratio and 95% confidence interval. Linear and logistic regression were used to adjust for possible confounding variables such as severity of VWD, age, race, education level, and dental utilization.

To determine the relationship between plaque and gingival bleeding, each site in the mouth had one of four possible outcomes. A site could have plaque with bleeding (YPYB), plaque with no bleeding (YPNB), no plaque with bleeding (NPYB), or no plaque with no bleeding (NPNB).

		Bleeding	
		Yes	**No**
Plaque	**Yes**	YPYB	YPNB
	No	NPYB	NPNB

3.8 Sample Size Estimation:

The study was designed to achieve at least a 45% difference in the occurrence of gingival bleeding when plaque is present, out of the twelve sites measured for this study. A power calculation was generated and it was determined that a sample size of 38 women would provide us with at least 80% power that there would be a 45% or greater incidence of gingival bleeding when plaque is present. A study by Pizzo et al was used to make this sample size calculation. In this study, the effects of hormone replacement therapy on periodontal status were looked at, where a significant difference was found in gingival bleeding between the two groups.[27]

3.9 Quality Control and Data Management:

Data was entered into Excel Spreadsheet. This document is password protective. Each subject was identified in the document with a unique patient identification number. All surveys were kept in a lockbox. Only those on the thesis committee have had access to these documents. After being entered into Excel, data was checked for errors or missing items. The data was then transferred to the statistical program, SPSS for data analysis. This program was also password protective.

3.10 Protection of Human Subjects:

IRB approval was sought at University of Michigan and Michigan State University prior to any recruitment or enrollment for the study. See Appendix D for the IRB approval letter. The source population for this study was adult female patients with VWD attending clinics at the University of Michigan Hemophilia and Coagulation Disorders in

Ann Arbor, Michigan or Michigan State University Center for Bleeding and Clotting Disorders in East Lansing, Michigan. Women in this study were above 18 years of age.

After determining patient eligibility, the informed consent form was reviewed and given to each individual to sign. See Appendix E for the Informed Consent document. The informed consent form reviewed in layman's terms, the purpose of the proposed study, benefits to the patient, time required to participate, possible risks and discomforts, name of the investigator, right of the patient to accept or refuse treatment and to withdraw at any time, and a statement of patient confidentiality.

The risk of complications was very low since the only measurements taken were with standard floss technique and using the probe supragingivally. Other data was collected with the survey and from the existing medical record.

Breach of confidentiality of personal health information was at a low risk since we used patient id numbers instead of names. A breach of confidentiality of personal health information did not occur. If this event would have occurred, the IRB would have been notified and routine procedures would have been taken to solve the incident.

Serious Adverse Event (SAE) Reporting

To the thesis committee's knowledge, an SAE did not occur. However, should any SAE occur from this point forward, which is very unlikely, the IRB will be notified as soon as possible and within 7 days from when the investigator is first informed. Protocol will still be reviewed on a weekly basis centering on potential safety issues.

CHAPTER 4

RESULTS

4.1 Patient Recruitment

A sample size of 38 adult women with VWD was desired for this study. At the University of Michigan Hemophilia and Coagulation Disorders in Ann Arbor, Michigan and Michigan State University Center for Bleeding and Clotting Disorders in East Lansing, Michigan, a total of 45 women were approached to participate in this study. Of the 45 women approached at the given bleeding disorder treatment centers, 44 agreed to participate in the study. The one individual that did not participate did not feel comfortable with the clinical portion of the exam therefore her survey and chart data was discarded.

4.2 Descriptive Statistics

Descriptive statistics for the 44 study participants are provided in Table 4. Of the 44 women that participated in this study, 20 (45.5%) women attend the University of Michigan Hemophilia and Coagulation Disorders in Ann Arbor, MI and 24 (54.5%) women attend the Michigan State University Center for Bleeding and Clotting Disorders in East Lansing, MI.

The mean age of women who participated in the study was 39.6 years (SD=16.00599). Caucasians were the largest racial/ethnic category to make up the sampled population, comprising 77.3% (n=34) of the sample that responded to this

question. Approximately 9.1% (n=4) women identified as African American, 4.5% (n=2) identified with Hispanic, and 4.5% (n=2) identified as “Other”.

Most participants, 50.0% (n=22), had an education level of High School and/or Some College, while 21 others have a college degree (47.7%). The majority of participants stated no employment, comprising 50% of the sample (n=22) yet 72.7% of participants had dental insurance (n=32). Most of the women who participated in the study did not partake in alcohol consumption, 63.4%, or tobacco use, 95.1%.

Most of the participants, 65%, stated that oral hygiene is reviewed at their bleeding disorder treatment center appointments frequently or at every visit (n=26). Only 15% of individuals stated that oral hygiene was never reviewed at these appointments (n=6). Of those surveyed, 57.5% of participants stated that a dental hygienist at their treatment center is the primary provider that reviews oral hygiene education (n=23), while 12.5% (n=5) stated that no one reviews oral hygiene education with them. Others receive oral hygiene education from a hematologist (2.5%, n=1), a dental hygienist or dentist outside of the treatment center (25%, n=10), or by another source (2.5%, n=1).

The majority, 73.8% (n=31) of the participants perceive the health of their gums to be in fair-good condition, while 23.8% (n=10) perceive them to be very good-excellent and 2.4% (n=1) in poor condition. The perception these individuals had of health of their teeth is slightly different with 76.2% (n=32) believing they were in fair-good condition, 16.7% (n=7) in very good-excellent condition, and 7.1% (n=3) in poor condition. Though 83.3% (n=35) believed the importance of oral health to be very important, 16.7% (n=5) of individuals surveyed still believe oral health is only somewhat important.

Of the women that participated, 50% (n=20) have experienced a gum bleed more than twice a month. Those that have experienced a gum bleed less than once a month make up 27.5% (n=11) of those surveyed.

When brushing, 38.1% (n=16) of those surveyed have experienced bleeding of the gums fairly often-very often, 57.1% (n=24) have experienced bleeding of the gums hardly ever-on occasion, and 4.8% (n=2) have never experience bleeding of the gums when brushing. This data is presented in Figure 5.

When flossing, 52.9% (n=18) have experienced bleeding of the gums fairly often-very often, 38.2% (n=13) have experienced bleeding with flossing hardly ever-on occasion, and only 8.8% (n=3) have never experienced bleeding with flossing. This data is presented in Figure 5.

Regarding oral hygiene habits, 74.3% (n=26) of women brush more than once a day, 20% (n=5) brush only once a day, and 5.7% (n=2) brush less than once a day. The majority of women surveyed floss 1-6 times a week, 37.1% (n=13), 34.3% (n=12) floss less than once a week, and 28.6% (n=10) floss at least once a day. This data is presented in Figures 2 and 3. The majority of women, 92.9% (n=39) use some other type of oral hygiene aid such as mouthwash, WaterPik, interdental brush, toothpick, etc.

Though 73.8% of the women surveyed have dental insurance, only 56.1% (n=23) had a dental appointment within the last six months. About 14.6% (n=6) had a dental appointment between six to twelve months ago, and for 29.3% (n=12) of women, it has been more than a year since their last appointment with a dentist.

While 40.5% (n=17) of women surveyed have avoided seeing a dentist, the most common reason for avoiding a dentist was related to not having insurance or financial reasons, which 27.6% (n=10) of women could relate to. Only 18.4% (n=8) of individuals surveyed listed reasons related to being nervous about treatment or not finding a dentist that they felt comfortable going to.

Most women, 85.7% (n=36), stated that they have never been refused treatment because of the possibility of bleeding disorder complications. However, 14.3% (n=6) of those surveyed have been refused treatment due to reasons such as “high danger of bleeding”, “refused to see because I had a blood disorder”, and “my bleeding time was 15 minutes”.

While most women stated that they had never felt any bias from any oral health care provider that they thought was due to their bleeding disorder, 8.8% (n=3) of the women stated that they had felt a bias from an oral health care provider due to high bleeding risk and the dentist not wanting to treat them. One woman even stated that it was tough at first to find a dentist who wasn’t nervous about the liability of a bleeding disorder when she was a child.

The majority, 74.42%, of the women who participated in this study had type 1 VWD. Those who had type 2 VWD comprised about 9.30%, one of which had type 2N, another who had type 2A, and two individuals whose chart did not specify the subtype. Two individuals had type 3 VWD, comprising 4.65% of the women who participated in this study.

For the purpose of analyzing this data, The variable “Severity” was broken into three categories depending on the individual’s last von Willebrand factor level reading

(1=less than or equal to 30, 2=31-60, 3=higher than 60). For those women who participated in this study, 16.3% of them had a VWF level of less than or equal to 30, 14% had a VWF level between 31 and 60, and 53.5% had a VWF level of more than 60. Data was missing on 7 individuals because lab values for VWF were not within their medical charts.

4.3 Clinical Measures

The clinical component of the study consisted of evaluating the mesial and distal surfaces on each of the six Ramfjord teeth for presence of supragingival plaque and bleeding with flossing totaling twelve sites in each mouth. On average, women had 7.34 (SD=4.46) sites of plaque and 2.41 (SD=2.55) sites of bleeding. Of the women who participated, 22.7% (n=10) had 12 sites of plaque and 36.4% (n=16) had no sites of bleeding. Please see Table 6 and 7 for a representation of the clinical data.

Data shows that on average, 44.33% (n=5.32) of the twelve sites had plaque, but no bleeding, 35.58% (n=4.27) of the twelve sites had no plaque and no bleeding, 16.25% (n=1.95) of the twelve sites had plaque with bleeding, and only 3.75% (n=0.45) of the twelve sites had no plaque with bleeding. This data is presented in Table 8.

4.4 Examining the Relationship Between Gingival Bleeding and Dental Plaque

Data was collected on twelve sites in each individual's mouth. Having four possible outcomes per site (YPYB, YPNB, NPNB, NPYB), gives us six possible combinations when analyzing the differences between possible outcomes. Since this study sought to determine if presence of gingival bleeding was more related to the

presence of plaque or having von Willebrand disease, only four of these combinations related to this study.

A paired samples t-test was used for each of these possible combinations to determine if the differences were statistically significant. See Table 9 for the paired samples t-test for each possible combination of averages.

The relationship between the surfaces with plaque and bleeding (YPYB) and no plaque with bleeding (NPYB) was explored. The average number of sites a person had with plaque and bleeding was 1.9767 (16.47%). The average number of sites a person had with no plaque, but still bleeding was 0.4186 (3.49%). The difference between the means was 1.5581, or 12.98%. This difference in means is statistically significant (p=.000).

The relationship between the surfaces with plaque and bleeding (YPYB) and plaque with no bleeding (YPNB) was also explored. The average number of sites a person had with plaque and bleeding was 1.9767 (16.47%). The average number of sites a person had with plaque and no bleeding was 5.4419 (45.35%). The difference between the means was 3.4652, or 28.88%. This difference in means is statistically significant (p=.000).

The relationship between the surfaces with plaque and no bleeding (YPNB) and no plaque with bleeding (NPYB) indicated that the average number of sites a person had with plaque and no bleeding 5.4419 (43.35%). The average number of sites a person had with no plaque, but still bleeding was 0.4186 (3.49%), therefore the difference between the means was 5.0233, or 41.86%. This difference in means is statistically significant (p=.000).

The relationship between the surfaces with no plaque and no bleeding (NPNB) and no plaque with bleeding (NPYB) was also explored. The average number of sites a person had with no plaque and no bleeding was 4.1628 (34.69%). The average number of sites a person had with no plaque, but still bleeding was 0.4186 (3.49%). The difference between the means was 3.7422, or 31.20%. This difference in means is statistically significant (p=.000).

4.5 VWF levels and gingival bleeding

Linear regression was used to determine the relationship between plaque and mean number of sites of gingival bleeding. In addition, potential confounding variables for each specific aim were examined. Each linear regression analysis, as well as the results, is described below.

The number of gingival bleeding sites was used as a dependent variable in an unadjusted linear regression analysis. Von Willebrand factor level was the independent variable and was tested with gingival bleeding for possible correlation, independent of presence of supragingival plaque. The average number of sites with bleeding for an individual with a VWF of less than 30 is 1.807. The average number of sites with bleeding for an individual with VWF level between 30 and 60 is 2.214. The average number of sites with bleeding for an individual with a VWF of greater than 60 is 2.621. The results were insignificant (p=.465).

Each paired samples t-test that was performed was also analyzed with linear regression to control for the level of von Willebrand Factor (VWF). The VWF level was divided up into three categories based on the National Heart, Lung, and Blood Institute and National Hemophilia Foundation information.

When using linear regression to determine if VWF level had an effect on the relationship between all four possible outcomes, linear regression showed that VWF level was not a contributing factor ($p>.05$).

The first test analyzed the difference of means between YPYB and NPYB. When controlling for severity, the difference between those sites that had plaque with bleeding and those that did not have plaque, but still had bleeding is no longer significant ($p=.450$). The second test analyzed the difference of means between YPYB and YPNB. When controlling for severity, the difference between those sites that had plaque with bleeding and those that did not have plaque, but still had bleeding is no longer significant ($p=.816$). The third test analyzed the difference of means between YPNB and NPYB. When controlling for severity, the difference between those sites that had plaque with bleeding and those that did not have plaque, but still had bleeding is no longer significant ($p=.532$). The fourth test analyzed the difference of means between NPNB and NPYB. When controlling for severity, the difference between those sites that had plaque with bleeding and those that did not have plaque, but still had bleeding is no longer significant ($p=.234$).

4.5.1 Socio-demographic and behavioral factors and gingival bleeding

Since there was not a significant relationship between VWF levels and mean gingival bleeding sites, other confounding variables were tested using multiple linear regression. Age seemed to have a positive effect on the amount of gingival bleeding, but this relationship was not significant. When controlling for last dental visit, the relationship between the variables was significant ($p=0.04$). This model can be found in Table 10.

When controlling for patient perception of bleeding upon flossing during at home oral hygiene, it was found to have a significant effect on the number of surfaces that had gingival bleeding when plaque was present. For those who state they bleed with flossing fairly often to very often, they would be expected to have 22.5% sites with plaque and bleeding, but for those who state they never bleed with flossing, they would be expected to have only 1.64% sites with plaque and bleeding. This difference in percentage of sites with plaque and bleeding is statistically significant (p=.024).

When controlling for last visit to the dentist, it was found that this significantly effected which surfaces had bleeding when plaque is present. For instance, if someone had been to the dentist less than 6 months ago, on average we would expect to see 11.992% of sites with bleeding and plaque. For someone who hasn't been to the dentist in over one year, we would expect about 26.46% of sites to have bleeding and plaque. This difference is statistically significant (p=.031).

Bleeding upon brushing also significantly affects the amount of gingival bleeding expected at an individual site. For instance, for an individual who states she has bleeding with brushing fairly to very often, we would expect to see about 34.47% of sites have gingival bleeding. In someone who only complains of bleeding with brushing hardly ever to on occasion, we would only expect to see gingival bleeding on 13.43% of sites. This relationship is statistically significant (p=.000)

4.5.2 Effectiveness of providing oral hygiene education for those with bleeding disorders

When examining the effectiveness of providing oral hygiene education at bleeding disorder treatment centers, both effect on plaque and gingival bleeding were

assessed as outcomes. The average number of plaque sites per person was examined while controlling for how often a provider at the bleeding disorder treatment center provides oral hygiene instruction. In those women who stated that no one ever reviews oral hygiene education with them at their treatment center, we expect to see plaque present on 10.5 out of the 12 sites measured. In those women who stated that someone reviews oral hygiene education frequently to at every visit, we would expect to see plaque present on 6.8 out of the 12 sites measured. This difference in plaque presence is statistically significant (p=0.03). This data is displayed in Figure 13.

When controlling for whom provides oral hygiene education, we expect to see 7 sites out of 12 with plaque in those who receive oral hygiene education from their dental hygienist at their treatment center. For those that receive oral hygiene education from a dental hygienist outside of their treatment center, we expect to see about 7.75 of sites out of 12 with plaque. In those that do not receive oral hygiene education at all, we expect to see an average of 10 out of 12 sites with plaque present. Though this relationship is not statistically significant, it is clinically significant. This is especially evident when examining average sites with gingival bleeding. In those who do not receive oral hygiene education, we see an average of 4.676 sites out of 12 with gingival bleeding. In those who receive oral hygiene education from a dental hygienist at their treatment center, we expect to see only 2.478 sites out of 12 with gingival bleeding. This difference is statistically significant (p=0.03).This data is displayed in Figure 14.

Chapter 5

Discussion

To the author's knowledge, this was the first study to assess the relationship between VWD, plaque accumulation, and gingival bleeding

5.1 Study Objective and Aims

The goal of this study was to examine the relationship between gingival bleeding and oral hygiene in women with von Willebrand Disease (VWD). To accomplish this goal, this study had three specific aims. Below, each aim is focused on individually. In addition, the syntheses of the research findings for each specific aim are shared.

5.2 Aim 1: Synthesis of Research Findings

Specific Aim 1 was to determine if gingival bleeding in women with VWD was related to the presence of supragingival plaque even when controlling for VWF levels. Numerous studies have shown the relationship between gingival bleeding and supragingival plaque. One study that was completed earlier this year examined the amount of gingival bleeding in those participants with VWD compared with the amount of gingival bleeding in those participants without VWD. This study determined that gingival bleeding was not considered a symptom in those with VWD considering the insignificant results.

For this particular study, severity of the bleeding disorder was controlled for in the analysis to see if there was a pattern between more bleeding sites and decreased von Willebrand Factor (VWF).The current research shows some fluctuation of VWF

throughout life in events such as hormonal contraceptive use, time during menstrual cycle, pregnancy, age, and hormonal contraceptive use. Therefore, severity was ranked according to the patient's last laboratory value of VWF. These values were also examined because even though an individual was diagnosed with a type of VWD, the severity or subtype was not always identified in the patient's chart.

The relationship between VWF level and gingival bleeding sites was first tested with linear regression. This relationship was not significant, so other confounding variables were controlled for. Age and last dental appointment seemed to have more of an effect on the amount of gingival bleeding noted on each patient. Though not a statistically significant relationship, interestingly, as age increased the amount of gingival bleeding decreased. When testing the effect on the participant's last dental visit, having a dental visit within the past six months had a protective effect on the amount of bleeding noted.

When comparing the means of the four possible outcomes to see if plaque had an effect on the amount of gingival bleeding, four analyses revealed interesting information. The first analysis was used to determine the difference in means between YPYB and NPYB. With the paired samples t-test, the difference in means was statistically significant. For a woman with VWD, it is expected that if a site in the mouth has bleeding, it is significantly more likely to have plaque. When linear regression was used to control for VWF level, the analysis showed that VWF level has no effect on this difference in means. This implies that for women with VWD, gingival bleeding is more likely caused by presence of supragingival plaque than by the level of VWF.

The second analysis was used to determine the difference in means between YPYB and YPNB. With the paired samples t-test, the difference in means was statistically significant. Therefore, for a woman with VWD, it is expected that if a site in the mouth has plaque present, it is significantly less likely to have gingival bleeding than to have gingival bleeding when a gentle C-wrap floss technique was used. When linear regression was used to control for VWF level, the analysis showed that VWF has no effect on this difference in means. Conclusions can be made that when performing a gentle C-wrap floss technique, even in those with low VWF levels, it can be performed in a manner that does not cause gingival bleeding. These findings can be shared with women with VWD in an effort to increase their awareness that flossing without causing bleeding is, in fact, possible.

The third analysis that was completed compared the difference in means between NPYB and YPNB. With the paired samples t-test, the difference in means was statistically significant. Therefore, for a woman with VWD, it is expected that significantly more sites in the mouth on average will have no bleeding even with plaque present than bleeding without plaque present. Since NPYB could potentially be indicative of VWD having an effect on gingival bleeding regardless of plaque presence, these results show that the exact opposite, which could be considered as more of a state of health (YPNB) is more likely even in someone with VWD.

The fourth analysis that was completed compared the difference in means between NPYB and NPNB. With the paired samples t-test, the difference in means was statistically significant. When testing to see if VWF level was considered a confounding variable, linear regression showed that VWF level has no effect on this difference in

means. Therefore, in a women with VWD, it is expected that those sites in the mouth that do not have plaque, a significantly lower percent will have bleeding than not bleeding, even when controlling for level of VWF. This implies, again, that VWF level has no effect on the number of sites in the mouth that have gingival bleeding. See Table 9 for each outcome relationship's paired samples t-test and linear regression results.

When assessing the relationship between presence of gingival bleeding and VWF level, data shows that the relationship is not statistically significant. Though the relationship is not statistically significant, the mean number of sites with gingival bleeding was actually higher in the group of individuals with less of a VWF deficiency. This indicates that in those with lower VWF levels, less gingival bleeding is actually expected. This is presented in Table 9.

In summary, the aforementioned analyses indicate that gingival bleeding may be more related to presence of gingival plaque than being related to and considered as a symptom of VWD. In fact, the majority of sites in the mouths of this population had plaque presence without bleeding. This study shows that there is 95% confidence that among women with VWD, the average number of sites with gingival bleeding is between 1.6032 and 3.1875 out of 12 sites measured. The fact that more sites had no bleeding even with presence of plaque indicates that women with VWD can perform gentle C-wrap technique without causing gingival bleeding. Confidently expressing this to patients with VWD can assure them that proper oral hygiene can be performed effectively without causing excessive, if any, gingival bleeding.

5.3 Aim 2: Synthesis of Research Findings

The second aim of this study was to determine the oral hygiene habits and dental care utilization in women with von Willebrand Disease (VWD). Results show that the majority of the women in this study have dental insurance and over 80% believe the importance of oral health to be very important, but for almost 30% of the women, their last visit to the dentist was over a year ago. When linear regression was used to determine if insurance had an effect on last DDS visit, this relationship was deemed to be insignificant (p=.100) With that said, when “who provides oral hygiene” was taken into consideration, there was a statistically significant relationship. For those who receive oral hygiene education from their dental hygienist whether at a bleeding disorder treatment center or at a private practice dental office, the average time since last DDS visit was significantly closer to being 6 months ago than those individuals who receive oral hygiene education from their hematologist or not at all.

Though the majority of the women surveyed stated they have never avoided seeing the dentist, 40.5% of these women stated that they have. Even though the most common reason for avoidance was related to financial issues or lack of insurance, 18.4% of these women could relate to being nervous about treatment. Some women even stated that they have been refused treatment for having a bleeding disorder and even felt a bias when interacting with an oral health care provider in the past. When controlling for noted anxiety and examining if this had an effect on last DDS visit, the relationship was not significant (p=.461).

When comparing oral hygiene habits of the women that participated in this study, there is no relationship between oral hygiene habits at home and perceived gingival

bleeding with brushing, flossing, or using other oral hygiene products such as mouthwash, WaterPik, etc. However, the difference in gingival bleeding for someone who flosses at least once a day and someone that never flosses is clinically significant. Unexpectedly, the number of sites of bleeding increased the more frequently the participants stated that they floss. It is possible that the incorrect floss technique is being used at home since the majority of surfaces had plaque with no bleeding during the clinical portion of the study.

5.4 Aim 3: Synthesis of Research Findings

When examining the amount of gingival bleeding and determining confounding variables related to delivering oral hygiene instruction, linear regression was used. Two questions on the patient survey touched on providing oral hygiene education at bleeding disorder treatment centers. The first question asked, “How often does someone at your bleeding disorder treatment center discuss oral health with you?” The second question asked, “Who usually discusses the importance of oral health with you?” Both of these variables were used to assess Specific Aim 3, which analyzes the effectiveness of having a dental hygienist at bleeding disorder treatment centers to provide oral hygiene education to patients with VWD.

Results showed that there is a significant difference in both presence of plaque and gingival bleeding when controlling for the two aforementioned variables. This implies that educating patients on oral health and oral hygiene instruction can lead to patients with bleeding disorders having better oral hygiene, therefore less gingival bleeding. This relationship is statistically significant in two of the three linear regression tests that were analyzed.

5.5 Limitations and Recommendations

Though this study was used as a pilot to generate data about a small population of women with von Willebrand Disease (VWD) in hopes to gain the results and conclusions for a larger study in the future, there were many limitations to this study.

5.5.1 Limitations of Study Design

This study was a cross-sectional study, which allowed only for a snapshot in time analysis. As such, no determinations on causality can be made. Conducting a longitudinal study would have allowed for further observation as well as the correct temporal sequence in this population. However, in this study, the patients were approached at their bleeding disorder treatment centers, consented, and the study was immediately completed. Therefore, the patients were unable to prepare for the exam by perhaps brushing and/or flossing their teeth and gave a “real life” or every day view into the patients’ regular home care regimens.

The one major limitation of this study was the lack of a control group. Having a control group would have shown the relationship between those with VWD and those without VWD. The reason for not having a control group was related to funding and time constraints. Since this study was completed as a part of the Master of Science in Dental Hygiene (MSDH) program and the principal investigator was on track to graduate in two years, time was limited.

In an effort to strengthen our findings, we examined the National Health and Nutrition Examination Survey (NHANES) data on the prevalence of gingivitis in women between the ages of 17 and 51 was obtained from a study by Taichman and

colleagues.[11] This data was used as a control group to compare the prevalence of gingivitis between women with and without VWD. Gingivitis was noted as having bleeding in about 30% of the mouth. Out of the 4,169 women surveyed with the NHANES, 47.9% of them were considered to have gingivitis. Since 12 sites were measured in this study, those women who had 3 or more sites of bleeding were placed into the gingivitis category. For this study, gingivitis only presented in 44.6% of the women with VWD. When using a chi-square test to examine the difference in percentages, the Pearson's correlation (0.169) showed that there was not a statistically significant difference between the control group and experimental group. This data is presented in Table 11.

5.5.2 Limitations in Questionnaire Component

The patient questionnaire also had limitations, specifically in measuring the severity of VWD. Not all patients had labs within their chart suggesting a recent VWF level. Also, research has shown a relationship between blood type and VWF level. Data on the patient's blood type would have been helpful to be able to adequately control for severity of VWD.

5.5.3 Limitations in the Clinical Examination

Limitations also existed within the clinical component of this study. The indices used to measure plaque and gingival bleeding allowed for more consistency with measurements as well as more inter- and intra-examiner reliability since the possible outcomes for these variables were 0 or 1. Information on the amount of plaque and amount of gingival bleeding would have been helpful to accurately evaluate the relationship between the amount of gingival bleeding in this population. Also, tissue

integrity should have been taken into consideration. The gingival index would have allowed for a better description of the gingiva while the plaque index would have allowed for a more detailed description of the consistency of the dental plaque.

5.5.4 Future Study Recommendations

Due to the limitations of this study as well as the results, there are many recommendations for a future longitudinal study with a larger sample size and a true control group. Sharing the results of this current study could be used in grant writing to allow for more sponsorship for a larger, longitudinal study.

A future study may choose to collect blood samples to analyze the VWF levels and other factors that could contribute to VWD such as Factor VIII. Blood type could also be analyzed to control for its effect on VWF levels, as proposed in current research. Labs could also be taken on the control group as well since VWF levels could fluctuate depending on menstrual cycle, pregnancy, oral contraceptive use, and age. A longitudinal study would allow data to be taken on patient's VWF variability over time and how gingival bleeding is affected throughout the course of time and different life events.

When collecting data on presence of plaque and gingival bleeding, presence of plaque could be measured by the SOHI index or the plaque index, and gingival bleeding could be measured by bleeding on probing, perhaps, or with the gingival index. Also, if pocket measurements were taken on all participants, the measurements between those with and without VWD could be compared as well.

Chapter 6

Conclusions

This research study was conducted to examine the relationship between von Willebrand Disease (VWD) and gingival bleeding. Anecdotally, many people with bleeding disorders are afraid to perform adequate plaque removal along the gum line due to possibly causing bleeding of the gums. All studies that have been conducted previously have shown that plaque levels and gingival bleeding levels are not significantly different from the control group of people without VWD. Due to the high number of people with bleeding disorders that experience gingival bleeding, this study sought to assess if the gingival bleeding was related to presence of plaque even while controlling for possible confounding variables such as severity of VWD, oral hygiene habits, dental care utilization, and previous oral hygiene education delivery.

This study found that in women with VWD, when gingival bleeding is noted, it is more related to the presence of plaque than the level of VWF in the body. Also, having a dental hygienist present at bleeding disorder clinics leads to a decrease in the amount of plaque and gingival bleeding. This study also showed that women with VWD reported that they have been refused dental treatment and have felt bias from oral health care providers. Because of this access to dental care issue, it is important to have dental hygienists present at bleeding disorder treatment centers in order to educate patients with bleeding disorders and to increase awareness in other oral health care providers

about treating patients with bleeding disorders. Finally, having a dental hygienist present at bleeding disorder treatment centers can essentially help to bridge the gap between oral health and overall health.

Though this study has provided much information about gingival bleeding and oral hygiene in women with VWD, future studies should be conducted using a larger sample size, a control group, and longitudinal design. Specifically, future studies should analyze the difference between those with and without VWD and assess the relationship between gingival bleeding and VWF levels over time in order to provide more evidence-based information to those with VWD about the relationship between their bleeding disorder and gingival bleeding.

The results of this study can help oral health care providers to provide their patients with VWD evidence-based knowledge about plaque removal methods in order to prevent against gingival bleeding as well as the need for more extensive dental work which could indeed lead to treatment complications. Due to the evidence that women with VWD have been refused treatment and felt bias from an oral health care provider just shows how important it is to have a dental hygienist present at these bleeding disorder treatment centers in order to educate patients with bleeding disorders as well as other oral health care providers about treating patients with bleeding disorders. Having a dental hygienist present at bleeding disorder treatment centers can essentially help to bridge the gap between oral health and overall health.

TABLES

Table 1 Abbreviations

VWD	von Willebrand Disease
VWF	von Willebrand Factor
GBI	Gingival bleeding index

Table 2 Possible outcomes for gingival bleeding index

Code	Description
0	No gingival bleeding
1	Gingival bleeding

Table 3 Possible outcomes for plaque presence

Code	Description
0	No plaque present
1	Plaque present

Table 4 Descriptive statistics of sample

	Percent
Age	
18-30	40.9
31-50	31.8
51-70	27.3
Race	
Caucasian	77.3
African American	9.1
Asian	-
Hispanic	4.5
Other	4.5
Refused	4.5
Education	
Less than high school	-
HS and/or some college	50.0
College Degree	47.7
Refused	2.3
Employment	
None	50.0
Part Time	9.1
Full Time	38.6
Refused	2.3
Dental Insurance	
Yes	72.7
No	25.0
Refused	2.3
Alcohol Use	
Yes	61.9
No	36.4
Refused	4.5
Tobacco Use	
Yes	4.5
No	90.9
Refused	4.5
BLEEDING DISORDER TREATMENT CENTER	
University of Michigan	45.5
Michigan State University	54.5

Table 5 Possible complications interfering with access to care for women with von Willebrand disease (VWD)

Question	Percentages	Responses
Have you ever avoided seeing a dentist?	Yes – 38.6 Financial – 55.6 Anxiety – 44.4 No – 59.1 Refused – 2.3	No insurance Anxiety, fear, afraid, pain I was told I bleed a lot Dislike the dentist “It’s not fun finding someone you trust” “Not feeling comfortable with their knowledge of my bleeding disorder”
Has an oral health care provider ever refused you of treatment because of the possibility of bleeding disorder complications?	Yes – 13.6 No – 84.1 Refused – 2.3	“because of high danger of bleeding” “I have been sent away many times just for a basic cleaning” “It was tough at first to find a dentist who wasn’t nervous about liability of a BD when I was a kid” “Refuse to see because I had a blood disorder” “My bleeding time was 15 min”
Have you ever felt any bias from any oral health care provider that you thought was due to your bleeding disorder?	Yes – 9.1 No – 79.5 Refused – 11.4	“High bleeding risk” “not willing to treat me” It was tough at first to find a dentist who wasn’t nervous about the liability of a BD when I was a kid” “complains about all the blood”

Table 6 Frequency table with number of sites with plaque

Number of sites with plaque	Frequency	Percent
0	5	11.4
1	1	2.3
2	5	11.4
3	1	2.3
4	3	6.8
5	1	2.3
6	1	2.3
7	2	4.5
8	0	0
9	4	9.1
10	5	11.4
11	6	13.6
12	10	22.7

Out of the 12 sites measured per person

Table 7 Frequency table with number of sites with bleeding

Number of sites with bleeding	Frequency	Percent
0	16	36.4
1	5	11.4
2	3	6.8
3	6	13.6
4	4	9.1
5	6	13.6
6	1	2.3
7	1	2.3
8	1	2.3
9	0	0
10	1	2.3
11	0	0
12	0	0

Out of the 12 sites measured per person

Table 8 Average number of sites (out of 12 sites measured) and standard deviations for each possible clinical outcome (Y=Yes, N=No, P=Plaque, B=Bleeding)

	Mean	SD
YPYB	**1.95**	**2.27**
YPNB	**5.32**	**4.36**
NPYB	**0.45**	**0.76**
NPNB	**4.27**	**4.31**

Table 9 Difference in means between possible outcome pairs as well as significance for paired samples t-test and when using linear regression to control for VWF level

	Difference in means	P-value when comparing means	P-value when controlling for VWF level
YPYB v YPNB	3.47	< 0.01	0.82
YPYB v NPYB	1.56	< 0.01	0.45
YPNB v NPYB	5.02	< 0.01	0.53
NPNB v NPYB	3.74	< 0.01	0.23
YPYB v NPNB	3.47	< 0.01	0.22
YPNB v NPNB	1.28	0.41	0.33

Table 10 Multiple Linear Regression Model for Bleeding in Women with VWD. Gingival bleeding was the dependent variable.

Mean Number of Sites with Bleeding*				
Independent Variables	Coefficient Estimate	Std. Error	P-Value	95% CI
VWF level Less than 30 30-60 Greater than 60	 Ref 0.367 0.349	 Ref 1.145 0.891	 Ref 0.750 0.698	 Ref (-1.953, 2.686) (-1.457, 2.155)
Age	-0.285	0.256	0.273	(-0.804, 0.234)
Last DDS visit Less than 6 months ago More than 6 months ago	 Ref 1.707	 Ref 0.817	 Ref 0.044	 Ref (0.051, 3.363)

Data are shown as mean ± SE (95% CI)
*Out of the 12 sites measured

Table 11 Chi-square test for gingivitis in women from NHANES and women with VWD

	Gingivitis	
Study	**Yes**	**No**
NHANES	1996 (47.9%)	2173 (52.1%)
VWD	20 (55.6%)	16 (44.6%)

Cases weighted by N
Pearson's Correlation: 0.169

Figures

Figure 1

Percentage of participants within each von Willebrand Factor (VWF) level range (n=44).

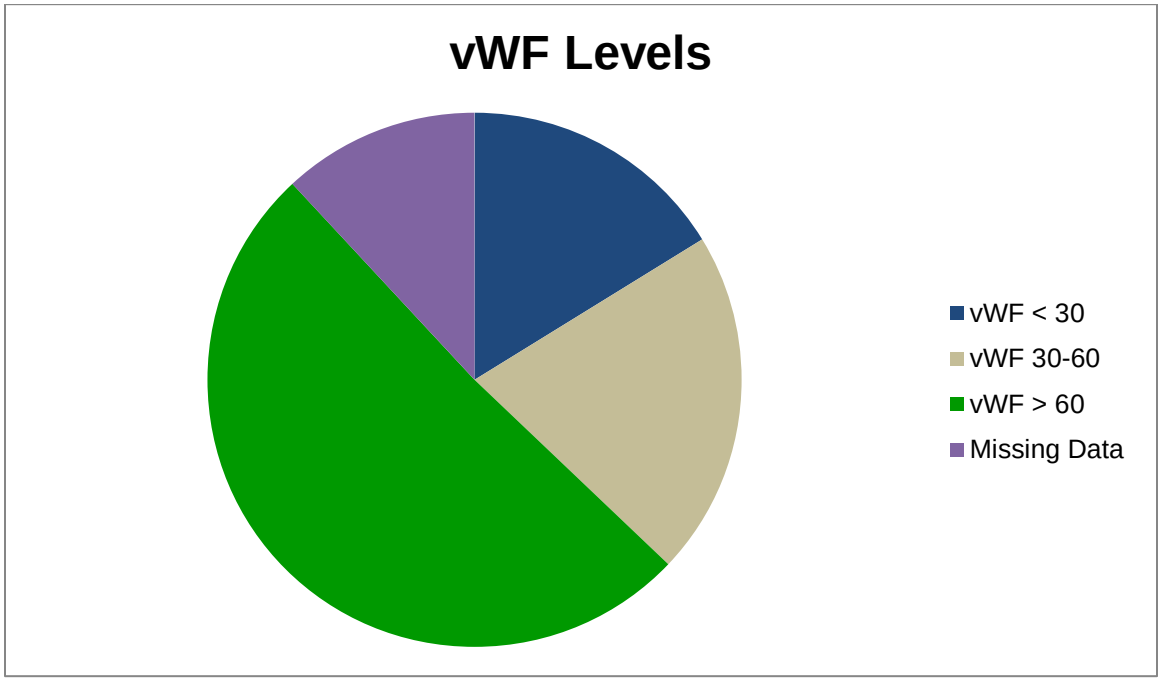


Figure 2

Percentage of participants who brush less than once a day, once a day, and more than once a day (n=44).

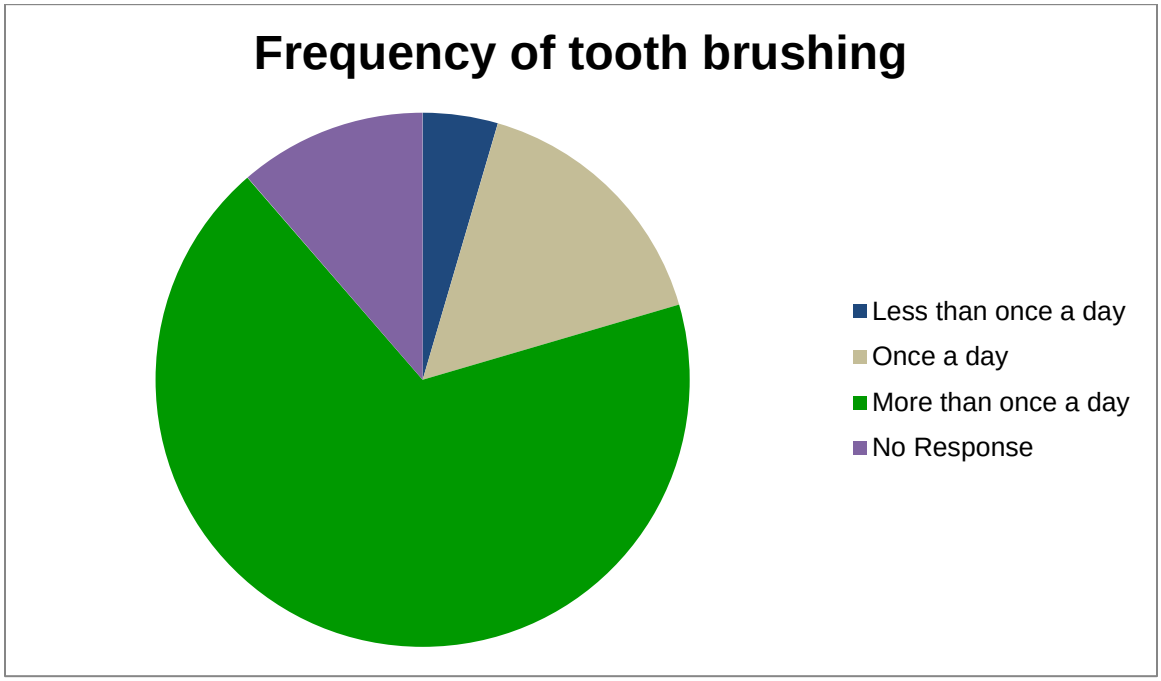


Figure 3

Percentage of participants who floss less than once a week, 1-6 times a week, and once or more a day (n=44).

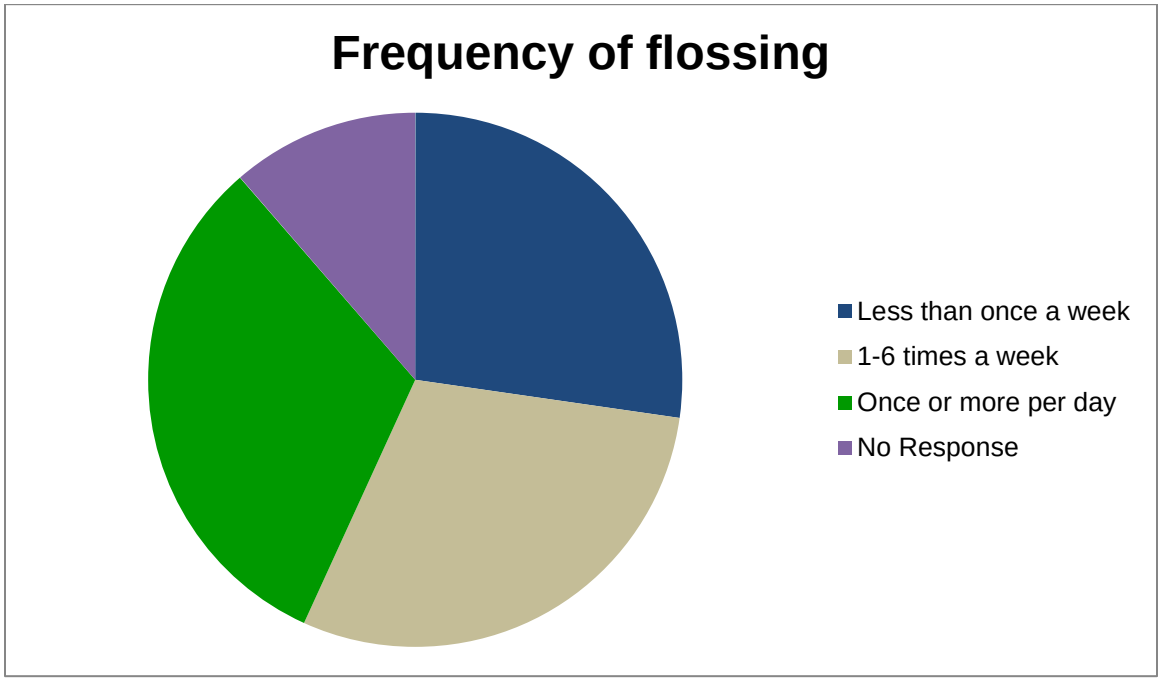


Figure 4

Percentage of women, stratified by VWF level, perceived gingival health (n=44). This relationship is not significant (p=0.331).

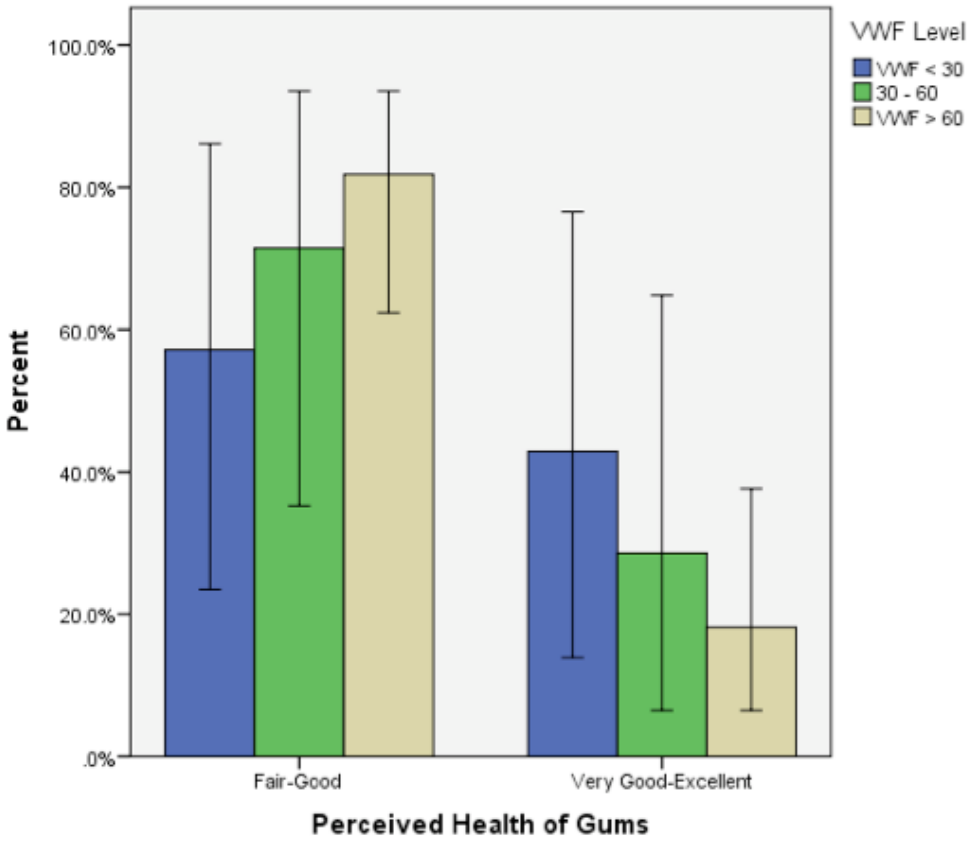
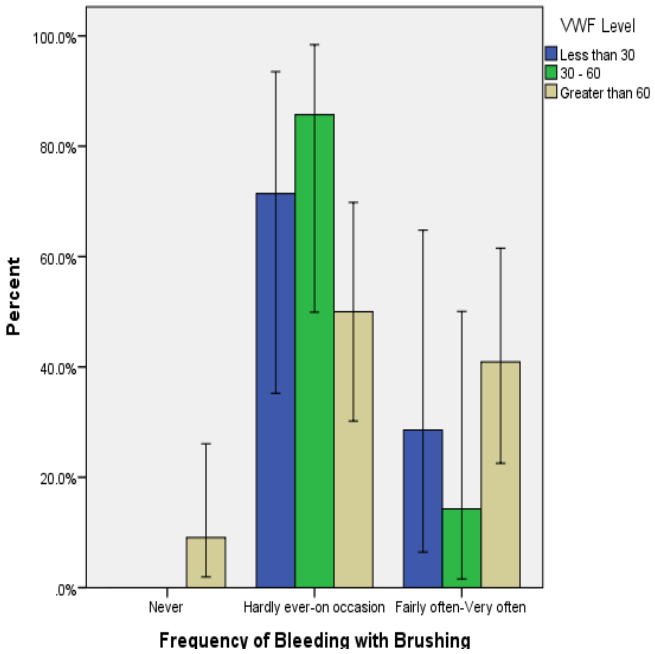


Figure 5

Percentage of women, stratified by VWF level, and frequency of gingival bleeding with tooth brushing and flossing (n=44). Neither relationship was significant (p>0.05).



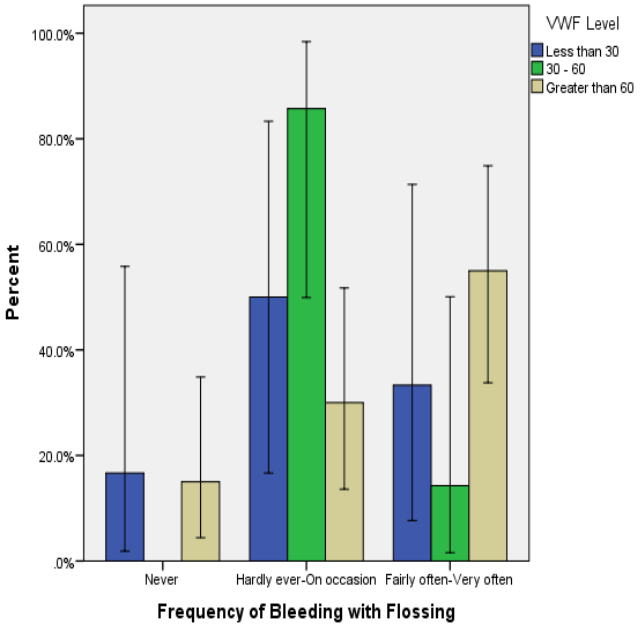


Figure 6

Percentage of participants and date of last dental visit (n=44).

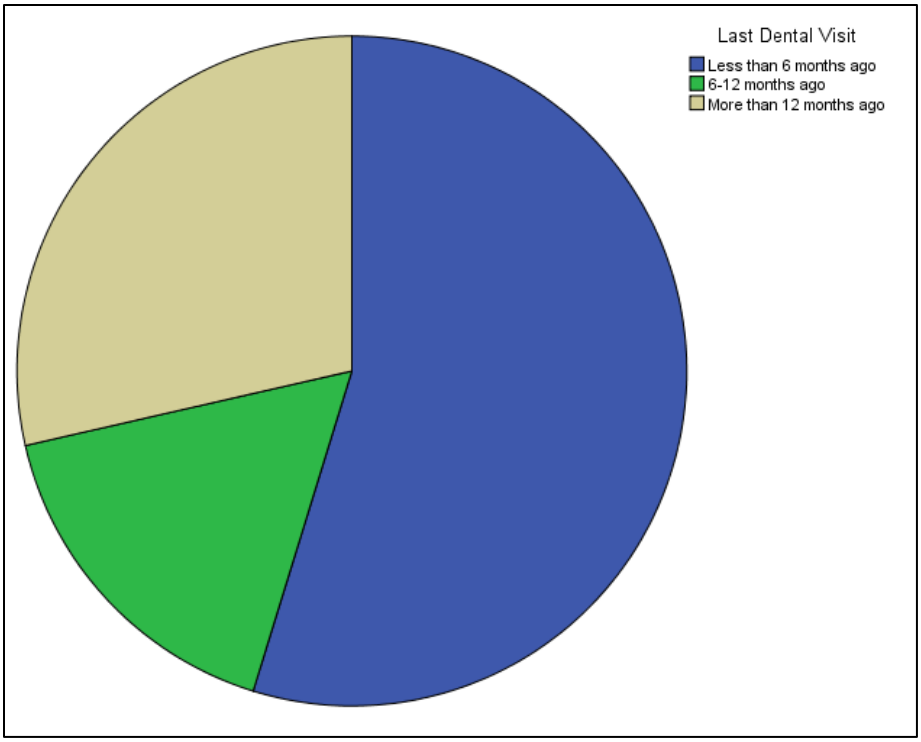


Figure 7

Percentage of those who stated that they have avoided seeing the dentist and likely reasons for avoidance (n=44).

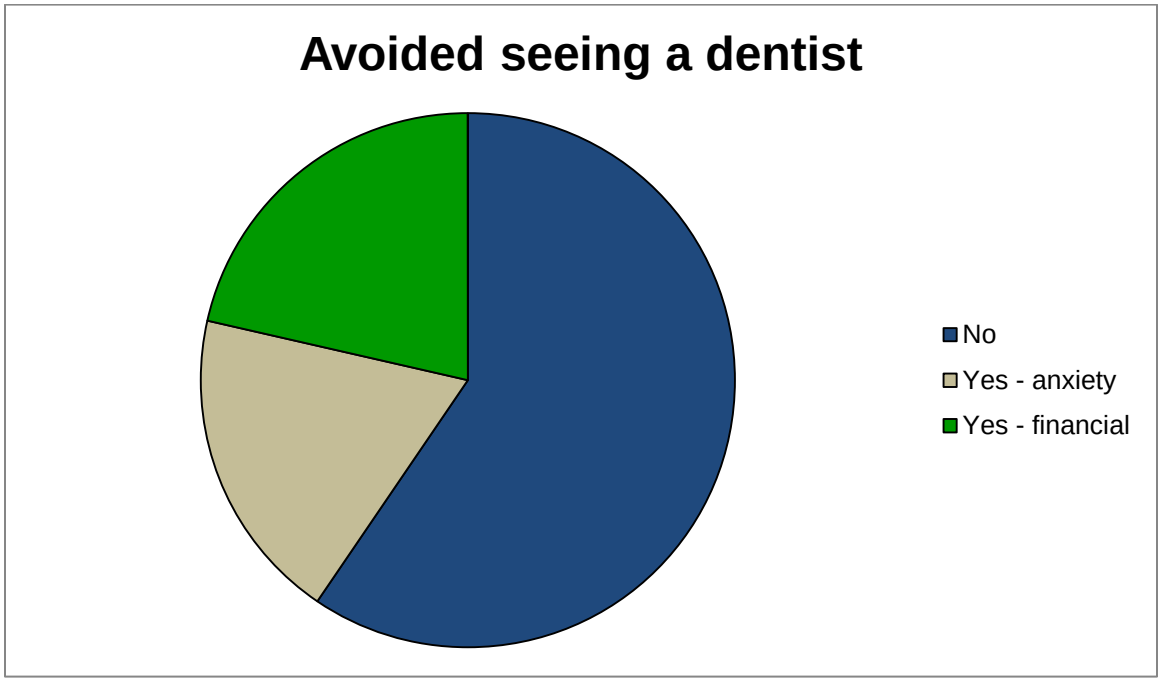


Figure 8

Average number of sites (out of the 12 measured sites) with plaque, stratified by VWF level.

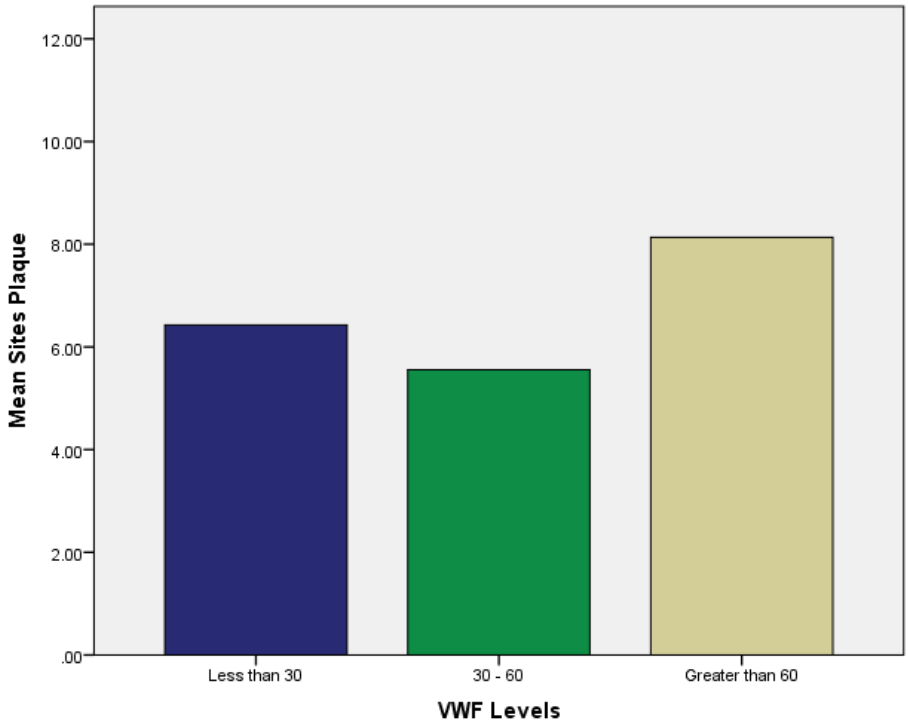


Figure 9

Average number of sites (out of the 12 sites measured) with gingival bleeding, stratified by VWF level.

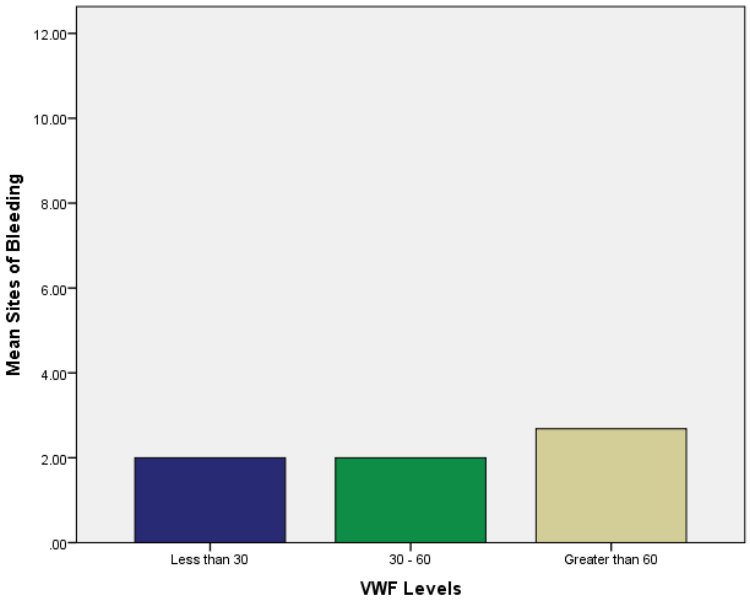

12.00
10.00
8.00
6.00
4.00
2.00
.00
Mean Sites of Bleeding
Less than 30
30 - 60
Greater than 60
VWF Levels

Figure 10

Each site had four possible outcomes (YPYB, YPNB, NPYB, and NPNB). The average number of sites (out of the 12 sites measured) for each possible outcomes was paired with other possible outcomes to determine the difference in means.

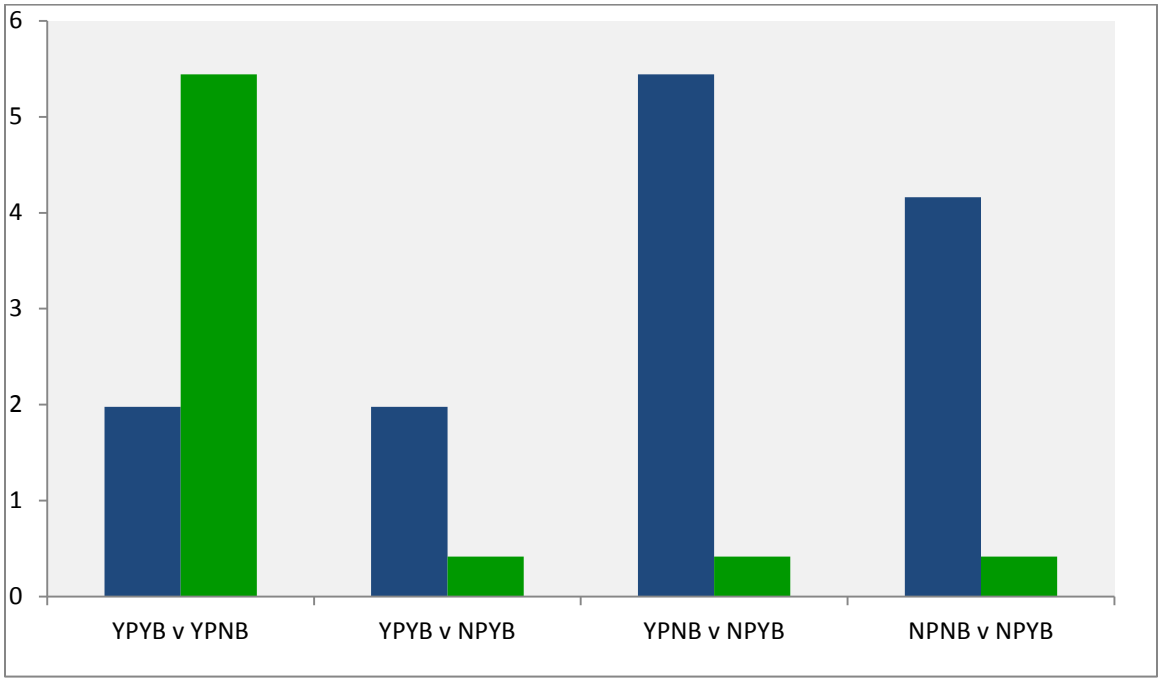
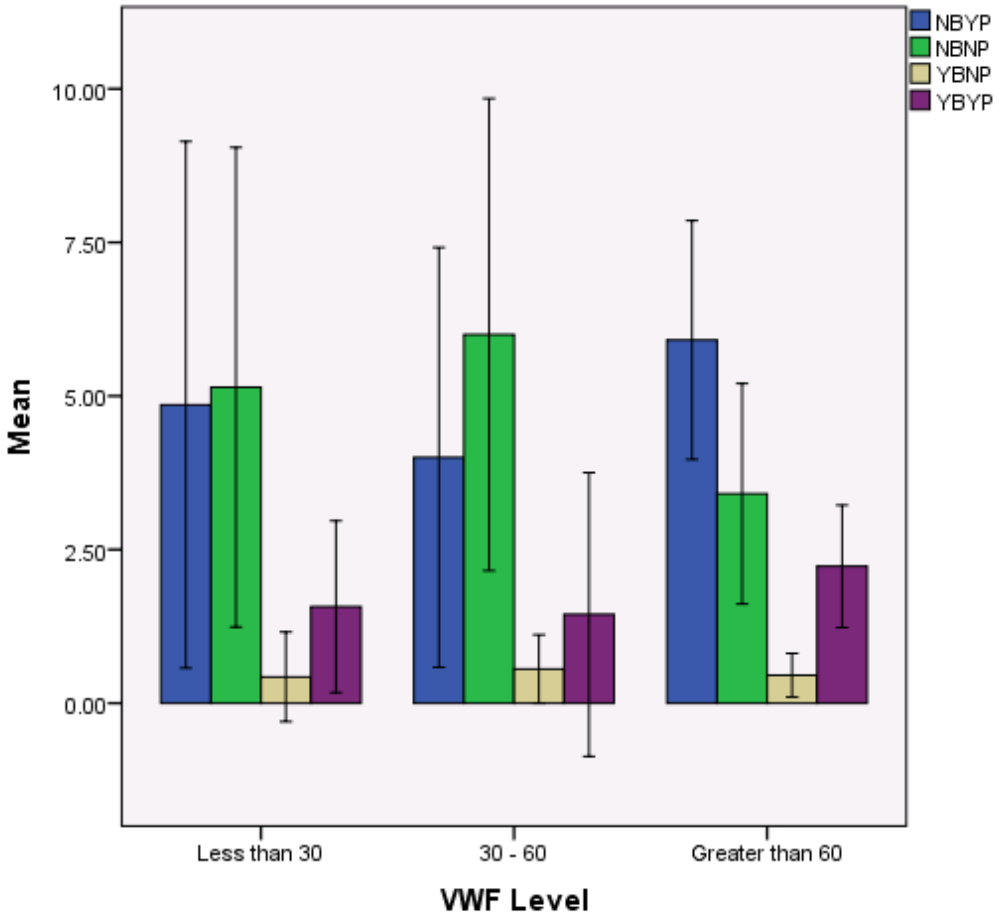


Figure 11

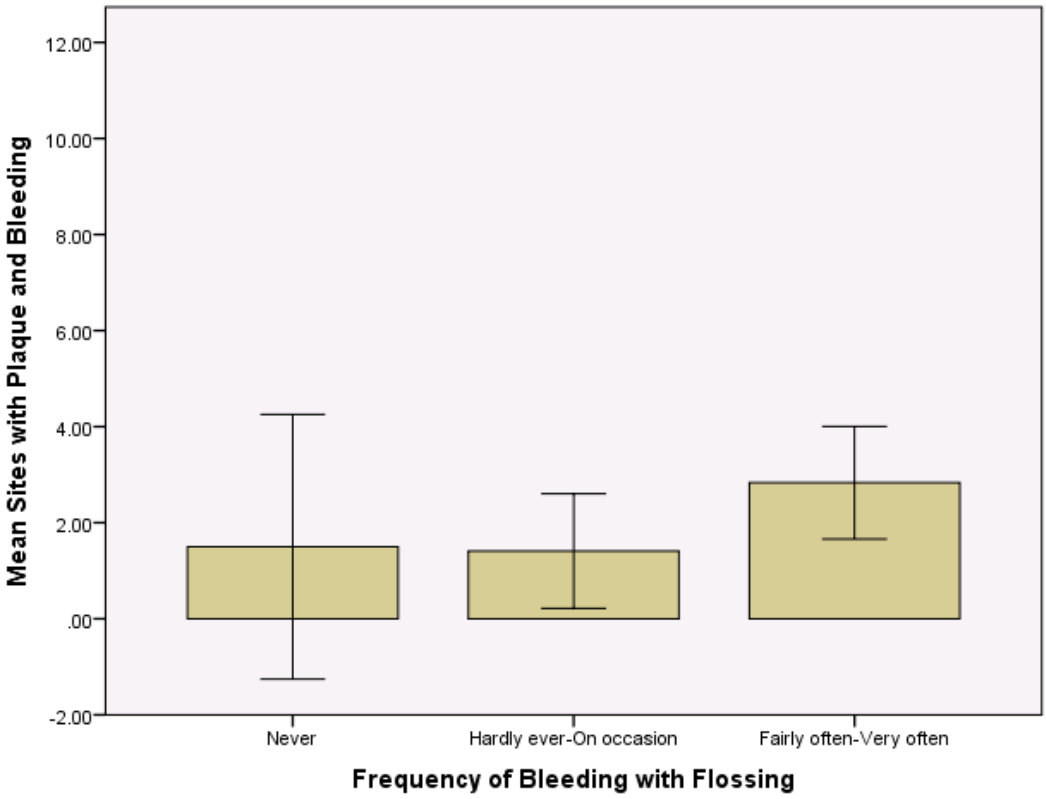
Average number of sites (out of 12) for each possible outcome when considering VWF level. When using ANOVA to determine the correlation between VWF levels and outcomes, none of the relationships were significant (p>0.05)



Error bars represent 95% CI

Figure 12

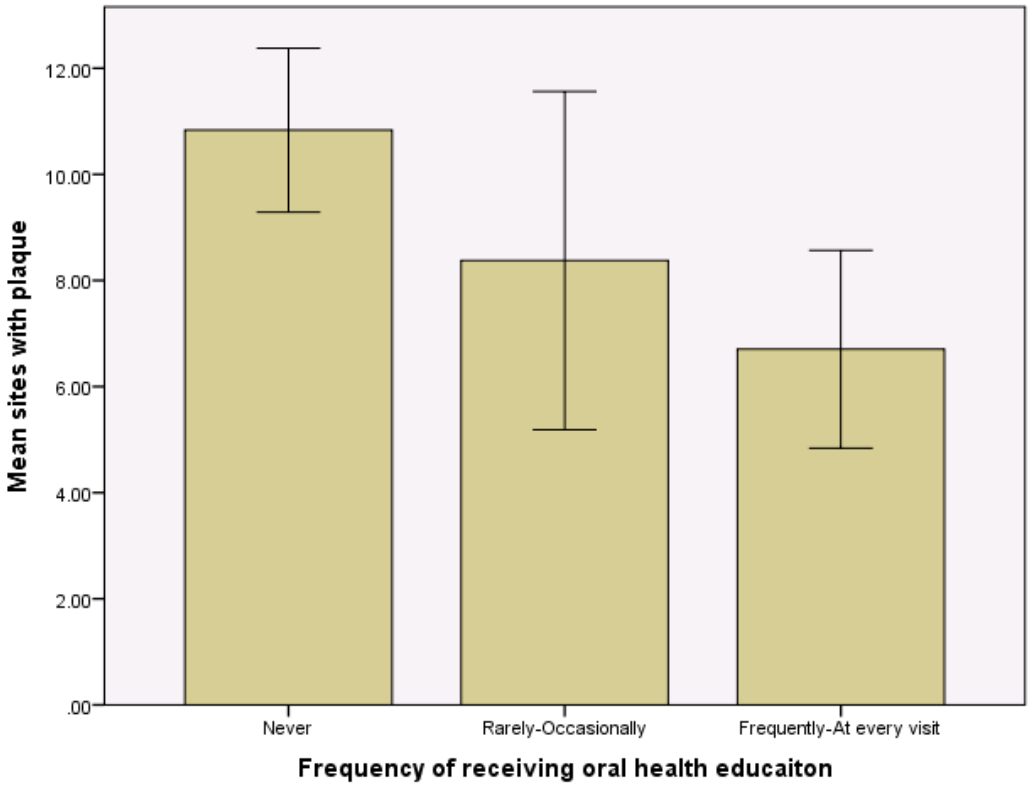
Number of sites with plaque and bleeding depending on patient perception of bleeding upon flossing (p>0.05)



Error bars represent 95% CI

Figure 13

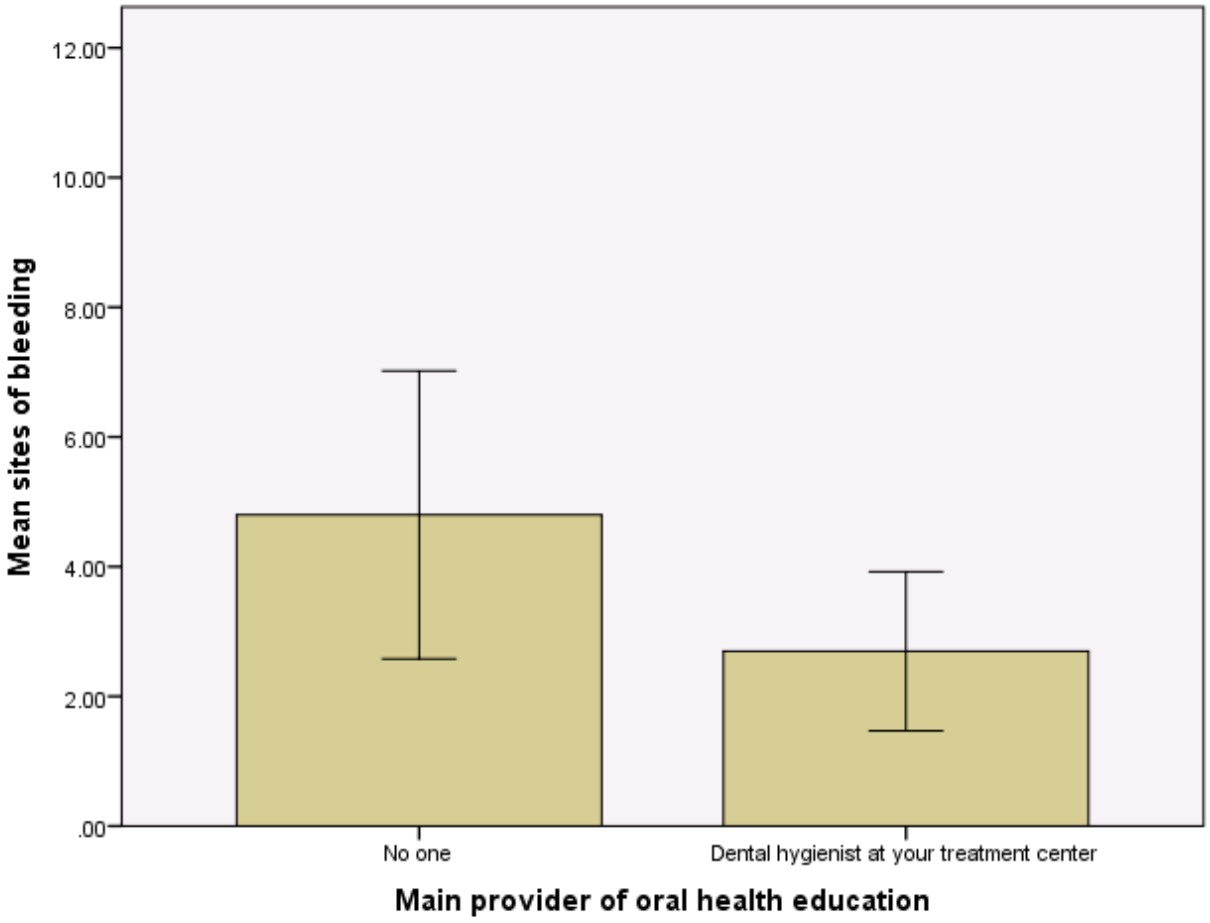
Percentage of sites with plaque present depending on how frequently oral health education is reviewed at the bleeding disorder treatment center (p=0.031)



Error bars represent 95% CI

Figure 14

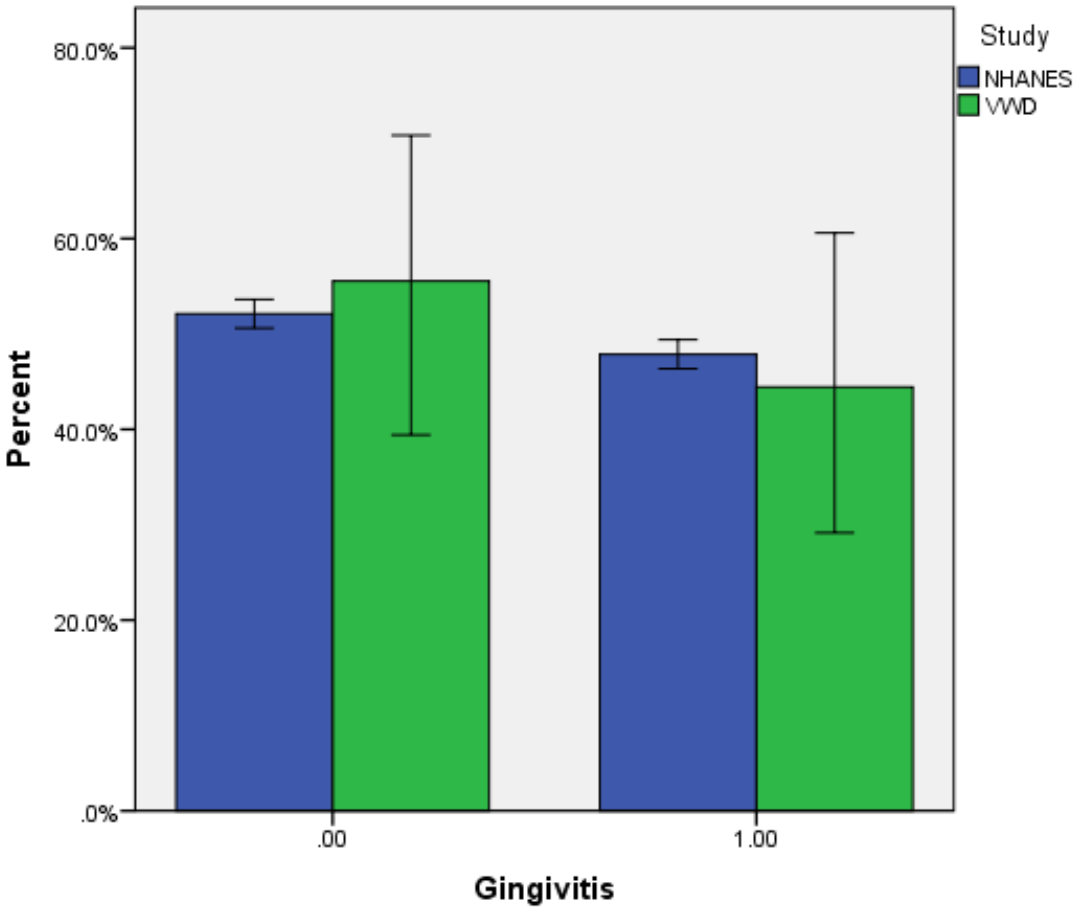
Average number of sites (out of the 12 sites measured) with bleeding upon flossing when considering whether oral health education is delivered to patients with VWD (p=0.033)



Error bars represent 95% CI

Figure 15

There was not a statistically significant difference between gingivitis occurring in the women with VWD when compared to the women who participated in the NHANES study (Pearson correlation= 0.169).



APPENDICES

Appendix A
Participant Questionnaire

Oral Hygiene Education and Oral Health of Women with von Willebrand Disease

Date: _____ Initials: _____ Patient ID: _____

Thank you very much for filling out this questionnaire. All of your answers are strictly confidential. Your name will not appear on any of the materials containing data. Please be honest and try to answer all of the questions below.

1. How old are you?
    a. I am _____years old.
2. What is your ethnic/racial background?
    a. Caucasian
    b. African American
    c. Asian
    d. Hispanic
    e. Other _____
3. What is your highest level of education completed?
    a. Less than high school
    b. High school
    c. Some college
    d. Associates Degree
    e. Bachelor's Degree
    f. Master's Degree
    g. PhD
4. What is your employment status?
    a. Full-Time
    b. Part-Time
    c. None
5. Do you have dental coverage?
    a. Yes
    b. No
6. Do you drink alcohol?
    a. Yes
    b. No
7. If yes, how many drinks do you have per week? _____
8. Do you smoke cigarettes/cigars/pipe?

a. Yes
b. No

9. If yes, how much do you smoke per day? _____

10. Which bleeding disorder treatment center do you visit?
    a. University of Michigan Hemophilia and Coagulation Disorders in Ann Arbor, MI
    b. Michigan State University Center for Bleeding and Clotting Disorders in East Lansing, MI
    c. Henry Ford Hospital Hemophilia and Thrombosis Treatment Center in Detroit, MI
11. How often do you visit your treatment center?
    a. Less than once a year
    b. Once a year
    c. More than once a year
12. How often does someone at your treatment center discuss oral health with you?
    a. Never
    b. Rarely
    c. Occasionally
    d. Frequently
    e. At every visit
13. Who usually discusses the importance of oral health with you?
    a. Hematologist
    b. Dental hygienist at your treatment center
    c. Dental hygienist or dentist outside your treatment center
    d. Other
    e. No one
14. How would you describe the health of your gums?
    a. Poor
    b. Fair
    c. Good
    d. Very Good
    e. Excellent

15. How would you describe the health of your teeth?

a. Poor
b. Fair
c. Good
d. Very Good
e. Excellent

16. How important is your oral health to you?
    a. Not at all important
    b. Somewhat important
    c. Very important
17. How often do you experience a gum bleed?
    a. Less than once a month
    b. 1-2 times a month
    c. 3-4 times a month
    d. More than 4 times a month
18. How often do your gums bleed when brushing?
    a. Never
    b. Hardly ever
    c. On occasion
    d. Fairly often
    e. Very often
19. How often do your gums bleed when flossing?
    a. Never
    b. Hardly ever
    c. On occasion
    d. Fairly often
    e. Very often
20. How often do you experience pain in your mouth?
    a. Never
    b. Hardly ever
    c. On occasion
    d. Fairly often
    e. Very often

21. How often do you brush your teeth?

a. Less than once a day
b. Once a day
c. Twice a day
d. More than twice a day

22. How often do you floss?
    a. Less than once a week
    b. 1-3 times a week
    c. 4-6 times a week
    d. Once a day
    e. More than once a day
23. Which of the following products, if any, do you use to maintain oral health? (Select all that apply).
    a. Mouthwash
    b. WaterPik
    c. Interdental brush
    d. Toothpick
    e. Stimudent
    f. Other _____
24. When was the last time you visited a dentist?
    a. 0-3 months ago
    b. 3-6 months ago
    c. 6-12 months ago
    d. Over 12 months ago
25. Have you ever avoided seeing a dentist?
    a. Yes
    b. No
26. If yes, what was the reason for not maintaining regular visits?

27. Has an oral health care provider ever refused you of treatment because of the possibility of bleeding disorder complications?
    a. Yes
    b. No
28. If yes, please explain.

29. Have you ever felt any bias from any oral health care provider that you thought was due to your bleeding disorder?
    a. Yes
    b. No
30. If yes, please explain.

31. Are you pre-menopausal?
    a. Yes
    b. No
32. If yes, when was your last menstrual period? _____

33. Are you taking oral contraceptives (birth control pills) or another method such as an IUD to control menstrual bleeding?
    a. Yes
    b. No
34. If yes, please explain.

Thank you very much for answering all of the questions presented above. If you have any questions regarding this questionnaire, please contact
Stefanie Marx by phone: (586) 804-2610 or by email: stefmarx@umich.edu

Appendix B
Chart Data Sheet
Patient ID: _____ Date of Data Extraction: _____ Patient DOB: _____

1. **Diagnosis Information**
    - **a.** Type of Von Willebrand Disease:
    - **b.** Last Von Willebrand factor levels/Date:
    - **c.** Date of VWD Diagnosis:
    - **d.** Treatment:

2. **Medical History**
    - **a.** Other medical conditions:
    - **b.** Medications:

Appendix C
Oral Examination Form
Patient ID: _____ Date of Examination: _____ Patient DOB: _____

Plaque Accumulation (0=No Plaque, 1=Plaque Present)

	Distobuccal	Buccal	Mesiobuccal	Distolingual	Lingual	Mesiolingual
3						
9						
12						
19						
25						
28						

Gingival Bleeding Index (0=No Bleeding, 1=Bleeding)

	Distal	Mesial
3		
9		
12		
19		
25		
28		

Visible oral manifestations:

APPENDIX D

Medical School Institutional Review Board (IRBMED) • 2800 Plymouth Road, Building 520, Room 3214, Ann Arbor, MI 48109-2800 • phone (734) 763 4768 • fax (734) 763 9603 • irbmed@umich.edu

To: Stefanie Marx

From:

Michael	Geisser
Alan	Sugar

Cc:

Stefanie	Marx
Karen	Ridley
Jill	Bashutski
Linda	Taichman

Subject:Initial Study Approval for [HUM00077611]

SUBMISSION INFORMATION:
Study Title: Gingival Bleeding and Oral Hygiene of Women with von Willebrand Disease
Full Study Title (if applicable):
Study eResearch ID: HUM00077611
Date of this Notification from IRB:10/7/2013
Review:Expedited
Initial IRB Approval Date: 9/30/2013
Current IRB Approval Period:**9/30/2013 - 9/29/2014**
Expiration Date: Approval for this expires at **11:59 p.m. on 9/29/2014**
UM Federalwide Assurance (FWA): FWA00004969 (For the current FWA expiration date, please

visit the UM HRPP Webpage)
OHRP IRB Registration Number(s): IRB00001999

Approved Risk Level(s):

Name	Risk Level
HUM00077611	No more than minimal risk

NOTICE OF IRB APPROVAL AND CONDITIONS:
The IRBMED has reviewed and approved the study referenced above. The IRB determined that the proposed research conforms with applicable guidelines, State and federal regulations, and the University of Michigan's Federalwide Assurance (FWA) with the Department of Health and Human Services (HHS). You must conduct this study in accordance with the description and information provided in the approved application and associated documents.

APPROVAL PERIOD AND EXPIRATION:
The approval period for this study is listed above. Please note the expiration date. If the approval lapses, you may not conduct work on this study until appropriate approval has been re-established, except as necessary to eliminate apparent immediate hazards to research subjects. Should the latter occur, you must notify the IRB Office as soon as possible.

IMPORTANT REMINDERS AND ADDITIONAL INFORMATION FOR INVESTIGATORS

APPROVED STUDY DOCUMENTS:
You must use any date-stamped versions of recruitment materials and informed consent documents available in the eResearch workspace (referenced above). Date-stamped materials are available in the "Currently Approved Documents" section on the "Documents" tab.

RENEWAL/TERMINATION:
At least two months prior to the expiration date, you should submit a continuing review application either to renew or terminate the study. Failure to allow sufficient time for IRB review may result in a lapse of approval that may also affect any funding associated with the study.

AMENDMENTS:
All proposed changes to the study (e.g., personnel, procedures, or documents), must be approved in advance by the IRB through the amendment process, except as necessary to eliminate apparent immediate hazards to research subjects. Should the latter occur, you must notify the IRB Office as soon as possible.

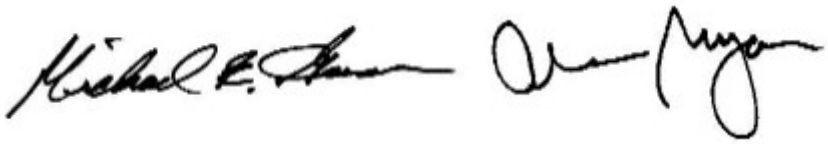
AEs/ORIOs:
You must inform the IRB of all unanticipated events, adverse events (AEs), and other reportable information and occurrences (ORIOs). These include but are not limited to events and/or information that may have physical, psychological, social, legal, or economic impact on the research subjects or other.

Investigators and research staff are responsible for reporting information concerning the approved research to the IRB in a timely fashion, understanding and adhering to the reporting guidance (http://www.med.umich.edu/irbmed/ae_orio/index.htm), and not implementing any changes to the research without IRB approval of the change via an amendment submission. When changes are necessary to eliminate apparent immediate hazards to the subject, implement the change and report via an ORIO and/or amendment submission within 7 days after the action is

taken. This includes all information with the potential to impact the risk or benefit assessments of the research.

SUBMITTING VIA eRESEARCH:
You can access the online forms for continuing review, amendments, and AEs/ORIOs in the eResearch workspace for this approved study (referenced above).

MORE INFORMATION:
You can find additional information about UM's Human Research Protection Program (HRPP) in the Operations Manual and other documents available at: www.research.umich.edu/hrpp.



Michael Geisser
Co-chair, IRBMED

Alan Sugar
Co-chair, IRBMED

Appendix E
Informed Consent Document 1

Study ID: HUM00077611 IRB: IRBMED Date Approved: 9/30/2013 Expiration Date: 9/29/2014

UNIVERSITY OF MICHIGAN
CONSENT TO BE PART OF A RESEARCH STUDY

INFORMATION ABOUT THIS FORM

You may be eligible to take part in a research study. This form gives you important information about the study. It describes the purpose of the study, and the risks and possible benefits of participating in the study.

Please take time to review this information carefully. After you have finished, you should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others (for example, your friends, family, or other doctors) about your participation in this study. If you decide to take part in the study, you will be asked to sign this form. Before you sign this form, be sure you understand what the study is about, including the risks and possible benefits to you.

1. GENERAL INFORMATION ABOUT THIS STUDY AND THE RESEARCHERS

1.1 Study title: Gingival Bleeding and Oral Hygiene of Women with von Willebrand Disease

1.2 Names, degrees, and affiliations of the researchers conducting the study:

Principal Investigator:	Stefanie Marx RDH, BSDH	Periodontics and Oral Medicine
Chair:	Susan Taichman RDH, MS, MPH, PhD	Periodontics and Oral Medicine
Committee Members:	Jill Bashutski DDS, MS	Periodontics and Oral Medicine
	Karen Ridley RDH, MS	Periodontics and Oral Medicine

2. PURPOSE OF THIS STUDY

2.1 Study purpose:

The purpose of the study is to determine the relationship between von Willebrand Disease, the most common hereditary coagulation disorder, and one of the most common symptoms of the disease, bleeding of the gums. Many people attribute gum (gingival) bleeds to the von Willbrand Disease itself however there is no current research that shows vWD directly causing gingival bleeding. Those with bleeding disorders often fear brushing and flossing due to causing gingival bleeding. Dental plaque is often left along the gumline, which is most likely the cause of the increased gingival bleeding that is often seen in the von Willebrand Disease population.

3. INFORMATION ABOUT STUDY PARTICIPANTS (SUBJECTS)

Taking part in this study is completely voluntary. You do not have to participate if you don't want to. You may also leave the study at any time. If you leave the study before it is finished, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled.

3.1 Who can take part in this study?

If you are an adult woman with von Willebrand Disease and at least 12 teeth present, you may be eligible for this study.

3.2 How many people (subjects) are expected to take part in this study?

66 subjects are expected to be enrolled for this study. Approximately 22 subjects will be enrolled from UM.

4. INFORMATION ABOUT STUDY PARTICIPATION

4.1 What will happen to me in this study?

You will be given this informed consent to read and sign. You will receive a brief dental exam to check for any abnormalities. Only a mirror with a light on it and gauze will be used. Next, 6 teeth will be checked for presence of plaque. A blunt instrument will slide across your tooth without touching your gums to check for the plaque. Next,

the same 6 teeth will be flossed using the same technique that you should use at home. Any areas of bleeding of the gums will be recorded. This exam process should take 3-5 minutes to complete. Next, you will complete a survey. The survey should take you another 3-5 minutes to complete.

4.2 How much of my time will be needed to take part in this study?
This study overall should take 15 minutes in addition to your already scheduled appointment with the hematologist. Some of the time will be while you are waiting for your doctor to start your appointment.

4.3 When will my participation in the study be over?
Study participation will end after your visit today.

5. INFORMATION ABOUT RISKS AND BENEFITS

5.1 What risks will I face by taking part in the study? What will the researchers do to protect me against these risks?
The known or expected risks are:

There is minimal risk associated with this study. Risks associated with plaque detection and flossing are not higher than if you were to floss on your own.

The researchers will try to minimize these risks by:

Having a registered dental hygienist complete the examination.

As with any research study, there may be additional risks that are unknown or unexpected.

5.2 What happens if I get hurt, become sick, or have other problems as a result of this research?
The researchers have taken steps to minimize the risks of this study. Even so, you may still have problems or side effects, even when the researchers are careful to avoid them. Please tell the researchers listed in Section 10 about any injuries, side effects, or other problems that you have during this study. You should also tell your regular doctors.

5.3 If I take part in this study, can I also participate in other studies?
Being in more than one research study at the same time, or even at different times, may increase the risks to you. It may also affect the results of the studies. You should not take part in more than one study without approval from the researchers involved in each study.

5.4 How could I benefit if I take part in this study? How could others benefit?
You may not receive any personal benefits from being in this study.

5.5 Will the researchers tell me if they learn of new information that could change my willingness to stay in this study?
Yes, the researchers will tell you if they learn of important new information that may change your willingness to stay in this study. If new information is provided to you after you have joined the study, it is possible that you may be asked to sign a new consent form that includes the new information.

6. OTHER OPTIONS

6.1 If I decide not to take part in this study, what other options do I have?
Participation in this study is completely voluntary and there is no penalty for not participating.

7. ENDING THE STUDY

7.1 If I want to stop participating in the study, what should I do?
You are free to leave the study at any time. If you leave the study before it is finished, there will be no penalty to you. You will not lose any benefits to which you may otherwise be entitled. If you choose to tell the researchers

why you are leaving the study, your reasons for leaving may be kept as part of the study record. If you decide to leave the study before it is finished, please tell one of the persons listed in Section 10 "Contact Information" (below).

7.2 Could there be any harm to me if I decide to leave the study before it is finished?
There is no harm in leaving the study before it is finished.
7.3 Could the researchers take me out of the study even if I want to continue to participate?
Yes. There are many reasons why the researchers may need to end your participation in the study. Some examples are:

- ✓ The researcher believes that it is not in your best interest to stay in the study.
- ✓ You become ineligible to participate.
- ✓ Your condition changes and you need treatment that is not allowed while you are taking part in the study.
- ✓ You do not follow instructions from the researchers.
- ✓ The study is suspended or canceled.

8. FINANCIAL INFORMATION

8.1 Who will pay for the costs of the study? Will I or my health plan be billed for any costs of the study?
The study will pay for research-related items or services that are provided only because you are in the study. If you are not sure what these are, see Section 4.1 above or ask the researchers for a list. If you get a bill you think is wrong, call the researchers' number listed in section 10.1.

You or your health plan will pay for all the things you would have paid for even if you were not in the study, like:

- Health care given during the study as part of your regular care
- Items or services needed to give you study drugs or devices
- Monitoring for side effects or other problems
- Deductibles or co-pays for these items or services.

If you do not have a health plan, or if you think your health plan may not cover these costs during the study, please talk to the researchers listed in Section 10 below or call your health plan's medical reviewer.

By signing this form, you do not give up your right to seek payment if you are harmed as a result of being in this study.

8.2 Will I be paid or given anything for taking part in this study?
You will receive a $10 stipend after completing this study.
8.3 Who could profit or financially benefit from the study results?
No person or organization has a financial interest in the outcome of the study.

9. CONFIDENTIALITY OF SUBJECT RECORDS AND AUTHORIZATION TO RELEASE YOUR PROTECTED HEALTH INFORMATION

The information below describes how your privacy and the confidentiality of your research records will be protected in this study.

9.1 How will the researchers protect my privacy?
Research information will be stored in a locked cabinet to protect your privacy. This information will not be part of your regular medical record.
9.2 What information about me could be seen by the researchers or by other people? Why? Who might see it?
Signing this form gives the researchers your permission to obtain, use, and share information about you for this study, and is required in order for you to take part in the study. Information about you may be obtained from any hospital, doctor, and other health care provider involved in your care, including:

- Hospital/doctor's office records, including test results (X-rays, blood tests, urine tests, etc.)
- All records relating to your condition, the treatment you have received, and your response to the treatment
- Billing information

There are many reasons why information about you may be used or seen by the researchers or others during or after this study. Examples include:

- The researchers may need the information to make sure you can take part in the study.
- The researchers may need the information to check your test results or look for side effects.
- University, Food and Drug Administration (FDA), and/or other government officials may need the information to make sure that the study is done in a safe and proper manner.
- Study sponsors or funders, or safety monitors or committees, may need the information to:
    - Make sure the study is done safely and properly
    - Learn more about side effects
    - Analyze the results of the study
- Insurance companies or other organizations may need the information in order to pay your medical bills or other costs of your participation in the study.
- The researchers may need to use the information to create a databank of information about your condition or its treatment.
- Information about your study participation may be included in your regular UMHS medical record.
- If you receive any payments for taking part in this study, the University of Michigan accounting department may need your name, address, social security number, payment amount, and related information for tax reporting purposes.
- Federal or State law may require the study team to give information to government agencies. For example, to prevent harm to you or others, or for public health reasons.

The results of this study could be published in an article, but would not include any information that would let others know who you are.

9.3 What happens to information about me after the study is over or if I cancel my permission?

As a rule, the researchers will not continue to use or disclose information about you, but will keep it secure until it is destroyed. Sometimes, it may be necessary for information about you to continue to be used or disclosed, even after you have canceled your permission or the study is over.

Examples of reasons for this include:

- To avoid losing study results that have already included your information
- To provide limited information for research, education, or other activities (This information would not include your name, social security number, or anything else that could let others know who you are.)
- To help University and government officials make sure that the study was conducted properly

As long as your information is kept within the University of Michigan Health System, it is protected by the Health System's privacy policies. For more information about these policies, ask for a copy of the University of Michigan "Notice of Privacy Practices". This information is also available on the web at http://www.uofmhealth.org/patient+and+visitor+guide/hipaa. Note that once your information has been shared with others as described under Question 9.2, it may no longer be protected by the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA).

9.4 When does my permission expire?
Your permission expires at the end of the study, unless you cancel it sooner. You may cancel your permission at any time by writing to the researchers listed in Section 10 "Contact Information" (below).

10. CONTACT INFORMATION

10.1 Who can I contact about this study?
Please contact the researchers listed below to:

- Obtain more information about the study
- Ask a question about the study procedures or treatments
- Talk about study-related costs to you or your health plan
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished
- Express a concern about the study

Principal Investigator: Stefanie Marx, RDH, BSDH
Mailing Address: 1011 N. University Avenue, Ann Arbor, MI 48109
Telephone: (586) 804-2610

You may also express a concern about a study by contacting the Institutional Review Board listed below.

University of Michigan Medical School Institutional Review Board (IRBMED)
2800 Plymouth Road
Building 520, Room 3214
Ann Arbor, MI 48109-2800
Telephone: 734-763-4768 (For International Studies: US Country Code: 001)
Fax: 734-763-1234
e-mail: irbmed@umich.edu

If you are concerned about a possible violation of your privacy or concerned about a study you may contact the University of Michigan Health System Compliance Help Line at 1-866-990-0111.

When you call or write about a concern, please provide as much information as possible, including the name of the researcher, the IRBMED number (at the top of this form), and details about the problem. This will help University officials to look into your concern. When reporting a concern, you do not have to give your name unless you want to.

11. RECORD OF INFORMATION PROVIDED

11.1 What documents will be given to me?
Your signature in the next section means that you have received copies of all of the following documents:

- This "Consent to be Part of a Research Study" document. (*Note: In addition to the copy you receive, copies of this document will be stored in a separate confidential research file and may be entered into your regular University of Michigan medical record.)*
- Other (specify):_____

12. SIGNATURES

Consent/Assent to Participate in the Research Study

I understand the information printed on this form. I have discussed this study, its risks and potential benefits, and my other choices with _____. My questions so far have been answered. I understand that if I have more questions or concerns about the study or my participation as a research subject, I may contact one of the people listed in Section 10 (above). I understand that I will receive a copy of this form at the time I sign it and later upon request. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Date of Birth (mm/dd/yy): _____

ID Number: _____

Principal Investigator or Designee

I have provided this participant and/or his/her legally authorized representative(s) with information about this study that I believe to be accurate and complete. The participant and/or his/her legally authorized representative(s) indicated that he or she understands the nature of the study, including risks and benefits of participating.

Legal Name: _____

Title: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Appendix F
Informed Consent Document 2

Study ID: HUM00077611 IRB: IRBMED Date Approved: 8/14/2014 Expiration Date: 8/13/2015

UNIVERSITY OF MICHIGAN
CONSENT TO BE PART OF A RESEARCH STUDY

INFORMATION ABOUT THIS FORM

You may be eligible to take part in a research study. This form gives you important information about the study. It describes the purpose of the study, and the risks and possible benefits of participating in the study.

Please take time to review this information carefully. After you have finished, you should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others (for example, your friends, family, or other doctors) about your participation in this study. If you decide to take part in the study, you will be asked to sign this form. Before you sign this form, be sure you understand what the study is about, including the risks and possible benefits to you.

1. GENERAL INFORMATION ABOUT THIS STUDY AND THE RESEARCHERS

1.1 Study title: Gingival Bleeding and Oral Hygiene of Women with von Willebrand Disease

1.2 Names, degrees, and affiliations of the researchers conducting the study:

Principal Investigator:	Stefanie Marx RDH, BSDH	Periodontics and Oral Medicine
Chair:	Susan Taichman RDH, MS, MPH, PhD	Periodontics and Oral Medicine
Committee Members:	Jill Bashutski DDS, MS	Periodontics and Oral Medicine
	Karen Ridley RDH, MS	Periodontics and Oral Medicine

2. PURPOSE OF THIS STUDY

2.1 Study purpose:
The purpose of the study is to determine the relationship between von Willebrand Disease, the most common hereditary coagulation disorder, and one of the most common symptoms of the disease, bleeding of the gums. Many people attribute gum (gingival) bleeds to the von Willbrand Disease itself however there is no current research that shows vWD directly causing gingival bleeding. Those with bleeding disorders often fear brushing and flossing due to causing gingival bleeding. Dental plaque is often left along the gumline, which is most likely the cause of the increased gingival bleeding that is often seen in the von Willebrand Disease population.

3. INFORMATION ABOUT STUDY PARTICIPANTS (SUBJECTS)

Taking part in this study is completely voluntary. You do not have to participate if you don't want to. You may also leave the study at any time. If you leave the study before it is finished, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled.

3.1 Who can take part in this study?
If you are an adult woman with von Willebrand Disease and at least 12 teeth present, you may be eligible for this study.

3.2 How many people (subjects) are expected to take part in this study?
66 subjects are expected to be enrolled for this study. Approximately 22 subjects will be enrolled from UM.

4. INFORMATION ABOUT STUDY PARTICIPATION

4.1 What will happen to me in this study?
You will be given this informed consent to read and sign. You will receive a brief dental exam to check for any abnormalities. Only a mirror with a light on it and gauze will be used. Next, 6 teeth will be checked for presence of plaque. A blunt instrument will slide across your tooth without touching your gums to check for the plaque. Next,

the same 6 teeth will be flossed using the same technique that you should use at home. Any areas of bleeding of the gums will be recorded. This exam process should take 3-5 minutes to complete. Next, you will complete a survey. The survey should take you another 3-5 minutes to complete.

4.2 How much of my time will be needed to take part in this study?
This study overall should take 15 minutes in addition to your already scheduled appointment with the hematologist. Some of the time will be while you are waiting for your doctor to start your appointment.

4.3 When will my participation in the study be over?
Study participation will end after your visit today.

5. INFORMATION ABOUT RISKS AND BENEFITS

5.1 What risks will I face by taking part in the study? What will the researchers do to protect me against these risks?
The known or expected risks are:

There is minimal risk associated with this study. Risks associated with plaque detection and flossing are not higher than if you were to floss on your own.

The researchers will try to minimize these risks by:

Having a registered dental hygienist complete the examination.

As with any research study, there may be additional risks that are unknown or unexpected.

5.2 What happens if I get hurt, become sick, or have other problems as a result of this research?
The researchers have taken steps to minimize the risks of this study. Even so, you may still have problems or side effects, even when the researchers are careful to avoid them. Please tell the researchers listed in Section 10 about any injuries, side effects, or other problems that you have during this study. You should also tell your regular doctors.

5.3 If I take part in this study, can I also participate in other studies?
Being in more than one research study at the same time, or even at different times, may increase the risks to you. It may also affect the results of the studies. You should not take part in more than one study without approval from the researchers involved in each study.

5.4 How could I benefit if I take part in this study? How could others benefit?
You may not receive any personal benefits from being in this study.

5.5 Will the researchers tell me if they learn of new information that could change my willingness to stay in this study?
Yes, the researchers will tell you if they learn of important new information that may change your willingness to stay in this study. If new information is provided to you after you have joined the study, it is possible that you may be asked to sign a new consent form that includes the new information.

6. OTHER OPTIONS

6.1 If I decide not to take part in this study, what other options do I have?
Participation in this study is completely voluntary and there is no penalty for not participating.

7. ENDING THE STUDY

7.1 If I want to stop participating in the study, what should I do?
You are free to leave the study at any time. If you leave the study before it is finished, there will be no penalty to you. You will not lose any benefits to which you may otherwise be entitled. If you choose to tell the researchers

why you are leaving the study, your reasons for leaving may be kept as part of the study record. If you decide to leave the study before it is finished, please tell one of the persons listed in Section 10 "Contact Information" (below).

7.2 Could there be any harm to me if I decide to leave the study before it is finished?
There is no harm in leaving the study before it is finished.
7.3 Could the researchers take me out of the study even if I want to continue to participate?
Yes. There are many reasons why the researchers may need to end your participation in the study. Some examples are:

- ✓ The researcher believes that it is not in your best interest to stay in the study.
- ✓ You become ineligible to participate.
- ✓ Your condition changes and you need treatment that is not allowed while you are taking part in the study.
- ✓ You do not follow instructions from the researchers.
- ✓ The study is suspended or canceled.

8. FINANCIAL INFORMATION

8.1 Who will pay for the costs of the study? Will I or my health plan be billed for any costs of the study?
The study will pay for research-related items or services that are provided only because you are in the study. If you are not sure what these are, see Section 4.1 above or ask the researchers for a list. If you get a bill you think is wrong, call the researchers' number listed in section 10.1.

You or your health plan will pay for all the things you would have paid for even if you were not in the study, like:

- Health care given during the study as part of your regular care
- Items or services needed to give you study drugs or devices
- Monitoring for side effects or other problems
- Deductibles or co-pays for these items or services.

If you do not have a health plan, or if you think your health plan may not cover these costs during the study, please talk to the researchers listed in Section 10 below or call your health plan's medical reviewer.

By signing this form, you do not give up your right to seek payment if you are harmed as a result of being in this study.

8.2 Will I be paid or given anything for taking part in this study?
You will receive a $10 stipend after completing this study.
8.3 Who could profit or financially benefit from the study results?
No person or organization has a financial interest in the outcome of the study.

9. CONFIDENTIALITY OF SUBJECT RECORDS AND AUTHORIZATION TO RELEASE YOUR PROTECTED HEALTH INFORMATION

The information below describes how your privacy and the confidentiality of your research records will be protected in this study.

9.1 How will the researchers protect my privacy?
Research information will be stored in a locked cabinet to protect your privacy. This information will not be part of your regular medical record.
9.2 What information about me could be seen by the researchers or by other people? Why? Who might see it?
Signing this form gives the researchers your permission to obtain, use, and share information about you for this study, and is required in order for you to take part in the study. Information about you may be obtained from any hospital, doctor, and other health care provider involved in your care, including:

- Hospital/doctor's office records, including test results (X-rays, blood tests, urine tests, etc.)
- All records relating to your condition, the treatment you have received, and your response to the treatment
- Billing information

There are many reasons why information about you may be used or seen by the researchers or others during or after this study. Examples include:

- The researchers may need the information to make sure you can take part in the study.
- The researchers may need the information to check your test results or look for side effects.
- University, Food and Drug Administration (FDA), and/or other government officials may need the information to make sure that the study is done in a safe and proper manner.
- Study sponsors or funders, or safety monitors or committees, may need the information to:
    - Make sure the study is done safely and properly
    - Learn more about side effects
    - Analyze the results of the study
- Insurance companies or other organizations may need the information in order to pay your medical bills or other costs of your participation in the study.
- The researchers may need to use the information to create a databank of information about your condition or its treatment.
- Information about your study participation may be included in your regular UMHS medical record.
- If you receive any payments for taking part in this study, the University of Michigan accounting department may need your name, address, social security number, payment amount, and related information for tax reporting purposes.
- Federal or State law may require the study team to give information to government agencies. For example, to prevent harm to you or others, or for public health reasons.

The results of this study could be published in an article, but would not include any information that would let others know who you are.

9.3 What happens to information about me after the study is over or if I cancel my permission?

As a rule, the researchers will not continue to use or disclose information about you, but will keep it secure until it is destroyed. Sometimes, it may be necessary for information about you to continue to be used or disclosed, even after you have canceled your permission or the study is over.

Examples of reasons for this include:

- To avoid losing study results that have already included your information
- To provide limited information for research, education, or other activities (This information would not include your name, social security number, or anything else that could let others know who you are.)
- To help University and government officials make sure that the study was conducted properly

As long as your information is kept within the University of Michigan Health System, it is protected by the Health System's privacy policies. For more information about these policies, ask for a copy of the University of Michigan "Notice of Privacy Practices". This information is also available on the web at http://www.uofmhealth.org/patient+and+visitor+guide/hipaa. Note that once your information has been shared with others as described under Question 9.2, it may no longer be protected by the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA).

9.4 When does my permission expire?
Your permission expires at the end of the study, unless you cancel it sooner. You may cancel your permission at any time by writing to the researchers listed in Section 10 "Contact Information" (below).

10. CONTACT INFORMATION

10.1 Who can I contact about this study?
Please contact the researchers listed below to:

- Obtain more information about the study
- Ask a question about the study procedures or treatments
- Talk about study-related costs to you or your health plan
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished
- Express a concern about the study

Principal Investigator: Stefanie Marx, RDH, BSDH
Mailing Address: 1011 N. University Avenue, Ann Arbor, MI 48109
Telephone: (586) 804-2610

You may also express a concern about a study by contacting the Institutional Review Board listed below.
University of Michigan Medical School Institutional Review Board (IRBMED)
2800 Plymouth Road
Building 520, Room 3214
Ann Arbor, MI 48109-2800
Telephone: 734-763-4768 (For International Studies: US Country Code: 001)
Fax: 734-763-1234
e-mail: irbmed@umich.edu

If you are concerned about a possible violation of your privacy or concerned about a study you may contact the University of Michigan Health System Compliance Help Line at 1-866-990-0111.

When you call or write about a concern, please provide as much information as possible, including the name of the researcher, the IRBMED number (at the top of this form), and details about the problem. This will help University officials to look into your concern. When reporting a concern, you do not have to give your name unless you want to.

11. RECORD OF INFORMATION PROVIDED

11.1 What documents will be given to me?
Your signature in the next section means that you have received copies of all of the following documents:

- This "Consent to be Part of a Research Study" document. (*Note: In addition to the copy you receive, copies of this document will be stored in a separate confidential research file and may be entered into your regular University of Michigan medical record.)*
- Other (specify):_____

12. SIGNATURES

Consent/Assent to Participate in the Research Study

I understand the information printed on this form. I have discussed this study, its risks and potential benefits, and my other choices with _____. My questions so far have been answered. I understand that if I have more questions or concerns about the study or my participation as a research subject, I may contact one of the people listed in Section 10 (above). I understand that I will receive a copy of this form at the time I sign it and later upon request. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Date of Birth (mm/dd/yy): _____

ID Number: _____

Principal Investigator or Designee

I have provided this participant and/or his/her legally authorized representative(s) with information about this study that I believe to be accurate and complete. The participant and/or his/her legally authorized representative(s) indicated that he or she understands the nature of the study, including risks and benefits of participating.

Legal Name: _____

Title: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

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BIBLIOGRAPHY

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