Impact of Inherited Bleeding Disorders and Iron Deficiency Anemia on Maternal Bleeding and Other Pregnancy Outcomes: A Population-based Cohort Study from Alberta, Canada

by

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ABSTRACT

Background: Inherited bleeding disorders are caused by quantitative and qualitative alterations of coagulation proteins or platelets involved in hemostasis. The most frequent inherited bleeding disorders are hemophilia, von Willebrand disease (VWD) and inherited platelet function disorder. Women with inherited bleeding disorders are at increased risk of pregnancy related bleeding, especially postpartum hemorrhage (PPH). In addition, women may develop new onset or worsening of pre-existing iron deficiency (ID) or iron deficiency anemia (IDA).

Aim: In this population based retrospective cohort study using linked administrative data we aimed to examine 1) the recent trends of PPH in women with inherited bleeding disorders compared with the general population in the province of Alberta, Canada; 2) the impact of inherited bleeding disorders and IDA on pregnancy outcomes; 3) the quality of care in relation to: a) coagulation workup in pregnant women with inherited bleeding disorders and b) rates of ID and IDA screening and correction during pregnancy.

Methods: We initially developed and validated case definitions for identifying hemophilia A , hemophilia B and VWD from administrative data using a combination of International Classification of Diseases diagnostic codes and coagulation factor levels. Subsequently, we performed two population-based retrospective cohort studies based on linked administrative data. The first study evaluated the trend of PPH in all pregnancies associated with hospitalized live births in Alberta, from 2010-2018 and examined the incidence of PPH in women with bleeding disorders compared with matched controls. Next, we examined the rates of ID and IDA detection and correction in pregnant women with or without bleeding disorders and the independent effect of IDA on pregnancy outcomes during 2014-2017. Multivariable logistic regression was used to

compute odds of pregnancy outcomes along with generalized estimating equations to account for multiple pregnancies in the same woman.

Results: Our case definitions had a sensitivity of 93.7% and specificity of 99.4% for identifying hemophilia A, a sensitivity of 90.9% and specificity of 99.8% for identifying hemophilia B and a sensitivity of 99.2% and specificity of 88.2% for identifying VWD. We identified 311,330 women with a total of 454,400 pregnancies during 2010-2018. The rate of PPH did not have any significant change from 10.13/100 deliveries (95% CI 10.10-10.16) in 2010 to 10.72/100 deliveries (95% CI 10.69-10.75) in 2018 (P for trend =0.35). We identified 93 (0.03%) women with inherited bleeding disorders with a total of 140 pregnancies. We observed increased odds of PPH (odds ratio [OR] 2.3; 95% CI 1.5-3.6), antepartum hemorrhage (OR 2.9; 95% CI 1.5-5.9) and red cell transfusion (OR 2.8; 95% CI 1.1-7.0) in women with bleeding disorders. Only 49.5% pregnancies in women with bleeding disorders had third trimester coagulation factor levels checked. Among the 207,355 pregnancies associated with hospitalized live births from 2014-2017, 36,500 (17.6%) had anemia at least once during pregnancy. Only 1 in 3 pregnancies with anemia had concurrent ferritin screening within the same trimester, and 83% of those had IDA. Inherited bleeding disorder was associated with higher odds of ID (OR 2.1 95% CI 1.02-4.5) and IDA (OR 3.5, 95% CI 1.3-9.7). ID screening was suboptimal (79.3%) even among women with bleeding disorders. Among tested, only 8% IDA from both first and third trimester achieved normalization for hemoglobin and ferritin during third trimester. Third-trimester IDA was associated with significantly higher odds of PPH and red cell transfusion compared with those without IDA. The association between third-trimester IDA and PPH disappeared in the subgroup who achieved correction of IDA.

Conclusion: We observed no significant change in the rate of PPH in Alberta between 2010-2018. Despite increased risk of pregnancy related bleeding among them, screening of coagulation factor levels and ferritin as well as correction of IDA during third trimester remained suboptimal in pregnant women with inherited bleeding disorders.

PREFACE

This thesis is an original work by Arafat Ul Alam. The research projects, of which this thesis is a part, received the following research ethics approvals from the University of Alberta Ethics Board:

Project Name "Impact of bleeding disorders and their associated quality of care on the incidence of obstetrical bleeding and adverse maternal outcomes." No. Pro00110665, June 4, 2021.

Project Name "Development of a population-based Alberta administrative database in bleeding disorders and identification of healthcare inequities through population-based cohort studies." No. Pro00077704, November 17, 2017.

A significant part of chapter 2 of this thesis has been published as: *Alam A ul, Karkhaneh M, Wu C, Sun HL. Development and validation of a case definition to identify hemophilia in administrative data. Thromb Res 2021;204:16–21.* I designed the study, performed the statistical analysis and drafted the initial manuscript and revisions. M. Karkhaneh contributed to data analysis and manuscript revision. H. Sun and C. Wu formulated the study concept, guided the study design, provided content expertise and revised all versions of the manuscript.

DEDICATION

I dedicate this work to my dear wife Shirin Akther Ruhina who supported me generously with her patience and endurance throughout my PhD program.

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CHAPTER 1

Introduction

1.1 Introduction to inherited bleeding disorders

Hemostasis is a complex process maintaining the free flow of blood within blood vessels and is regulated by a delicate balance between coagulation and fibrinolysis. In an event of vascular injury, primary hemostasis takes place and forms a platelet plug by complex interactions between platelets, collagen and von Willebrand factor (VWF) [1]. In secondary hemostasis, thrombin generation takes place through activation of the coagulation cascade which eventually converts fibrinogen to fibrin and strengthens the platelet plug. The coagulation factors are the major constituents of the coagulation system.

Inherited bleeding disorders occur due to deficiency or altered function of coagulation proteins or platelets resulting in prolonged bleeding. The most common inherited bleeding disorders are hemophilia, von Willebrand disease (VWD) and inherited platelet function disorder. The Annual Global Survey conducted by the World Federation of Hemophilia (WFH) identified a tripling in the number of people with inherited bleeding disorders (VWD, hemophilia and rare bleeding disorders) over the past 20 years, from 111,203 in 1999 to 337,641 in 2018 [2]. This increase may have resulted from increased reporting by member countries, improved diagnostics capacities, and improved life expectancy due to treatment advances. In 2020, the global reported number (from 120 countries) of people with bleeding disorders was 347,026 [3]. 61% of all these cases was reported from high and upper middle-income countries.

1.2 Hemophilia, VWD and their prevalence

Hemophilia is an X linked disorder caused by a deficiency of the coagulation factor VIII (FVIII), leading to hemophilia A, and factor IX (FIX), leading to hemophilia B [4]. Due to X linked recessive trait, hemophilia has a greater clinical impact on boys and men. However, a small proportion of women can also have significant disease [5]. Hemophilia A constitutes 80%-85% of all hemophilia cases [6]. According to the latest data from France, United Kingdom, Canada, Australia, and New Zealand, the estimated prevalence at birth (incidence) is 24.6/100,000 male babies for hemophilia A and 5.0/100,000 male babies for hemophilia B [7]. The same study

estimated the prevalence for hemophilia A at 17.1/100,000 males and for hemophilia B at 3.8/100,000 males. Using these estimates, the expected number of persons with hemophilia (PWH) globally is 815,100 [3]. In 2020 report, the annual global survey of WFH identified 165,379 persons with hemophilia A and 33,076 persons with hemophilia B [3]. In Canada, the numbers were 3223 and 701, for hemophilia A and B, respectively. Of them, 3060 (95%) and 643 (92%) were men, respectively [8]. A recent population-based study utilizing administrative database reported the prevalence at 15.7/100,000 males for hemophilia A and 2.6/100,000 males for hemophilia B for the period 2012-2019 in the province of Alberta, Canada [9]. Prevalence of hemophilia A and B in the study from Alberta is lower than the bleeding disorder registry-based prevalence estimate, which may have resulted from their stringent case definition [7].

VWD is caused by a deficiency or defective function of von Willebrand factor (VWF). During vascular injury, VWF binds to extravascular matrix proteins and capture platelets via their glycoprotein Ib receptor and form the primary hemostatic plug. In addition, it binds to Factor VIII and prevent it from premature clearance and degradation. It is the most common inherited bleeding disorder. The prevalence of VWD varies substantially based on the study population. Among patients who present to tertiary care centres with clinical symptoms the prevalence is reported to be 0.01%, whereas in symptomatic VWD in primary care clinics it is 0.1% [11,12]. VWD can affect up to 1% of the general population based on epidemiological studies [13]. Among women, VWD is relatively more prevalent than hemophilia due to its autosomal dominant inheritance. According to annual global survey (2020) of WFH , the reported number of cases of VWD globally is 87,729 with 4,709 reported from Canada [3]. 3,019 (64%) of those recorded from Canada are female [8]. VWD is subdivided into 3 types: Type 1, Type 2 and Type 3. Type 1 is characterized by partial quantitative deficiency in plasma VWF and constitutes majority (75%) of the cases. Type 2 is characterized by qualitative defects which impair one or more aspects of VWF function. Type 2 is further subdivided into four subtypes: Type 2A, 2B, 2M and 2N. Complete deficiency of VWF is defined as type 3 VWD.

1.3 Diagnosis of Hemophilia and VWD

Bleeding history and family history are key components to establish a clinical diagnosis of hemophilia. Hemophilia is suspected in an individual with easy bruising, spontaneous bleeding,

early symptoms of joint bleeds in children and excess bleeding following trauma or surgery. In PWH, a prolonged activated partial thromboplastin time (aPTT) with a normal prothrombin time (PT) is usually observed [4]. Further, FVIII or FIX activity assay is used to establish a diagnosis. Based on residual coagulant activity in blood, hemophilia is classified into three major categories: mild (5-40 IU/ml), moderate (1-5 IU/ml) and severe (<1 IU/ml) [6]. Diagnosis is usually confirmed by genetic test. In addition, women with FVIII/IX≥ 40 IU/ml with and without a bleeding phenotype are defined as symptomatic and asymptomatic hemophilia carrier, respectively [5]. Prophylaxis with coagulation factor concentrate or non-factor replacement agents is the standard of care for hemophilia with severe phenotype [4].

Typical symptoms in VWD include bruising, prolonged bleeding from superficial cuts or surgery, epistaxis, gum bleeding, gastrointestinal (GI) bleeding, postpartum and other pregnancy related bleeding and heavy menstrual bleeding. The initial laboratory evaluation includes complete blood count, aPTT and PT. VWD assays commonly include quantitative assays via VWF Antigen (VWF: Ag), functional assay via VWF ristocetin cofactor activity (VWF:RCo) or VWF glycoprotein IbM (VWF:GPIbM), and FVIII [14]. The latest international guideline recommends using a VWF level < 0.30 IU/ml regardless of bleeding, and for patients with abnormal bleeding, a VWF level <0.50 IU/ml to confirm the diagnosis of type 1 VWD [15]. Treatment options for VWD include desmopressin and replacement of VWF [14].

1.4 Disease burden, mortality and health resource utilization of Hemophilia and VWD

In PWH, recurrent joint and muscled bleeds lead to musculoskeletal damage. The prevalence of arthropathy among moderate hemophilia A has shown to be at 15%-77% [16]. 60% of adult hemophilia patients with severe phenotype develop hemarthrosis [17]. Older individuals with hemophilia are at risk for developing age-related comorbidities and malignancies. Studies showed significantly higher proportion of hypertension, hyperlipidemia and malignancies among PWH compared to control [9,18,19]. A significant proportion of PWH contracted human immunodeficiency virus (HIV) and hepatitis C virus infection in the 1980s due to contaminated plasma derived factor concentrates which made these transfusion related infections the dominant cause of death in many industrialized countries including Canada [20]. With the advent of recombinant factor concentrates and viral inactivating procedures, life expectancy of PWH has

dramatically increased [21]. However, a meta-analysis has shown that PWH still has 1.2-fold increased risk of death (standard mortality ratio [SMR] 1.2, 95% CI 1.03-1.40) compared to general population during the post 2000 era, which reflects the period following the widespread adoption of highly active anti retroviral therapy for HIV [22]. Despite advanced care, hemorrhage remains the leading cause of death in the contemporary era. Data from Alberta has shown higher risk of death (SMR 2.5; 95% CI 1.5-3.9) for hemophilia A and comparable risk of death for hemophilia B (SMR 1.1; 95% CI 0.2-3.7) to the general population during 2012-2019 [9]. Being a chronic condition, hemophilia is associated with substantial healthcare resource utilization including higher emergency department visits, hospitalizations and longer length of stay compared to general population [23,24]. Recent data from Alberta also demonstrated increased acute care utilization in PWH compared to age- and sex-matched population control [9].

Although not very common, arthropathy still occurs in 2-30% of the patients of VWD depending on severity (mostly found in type 3 VWD) and is associated with reduction in FVIII levels [25]. A US retrospective study demonstrated 2.5 times higher rate of GI bleeding in VWD patients compared to control [26]. Women with VWD are more likely to manifest bleeding symptoms compared to men as they experience reproductive tract bleeding during their lifetime due to menstruation and pregnancy. Based on a review study, the prevalence of menorrhagia among women with VWD ranges from 32-100% [27]. On the other hand, the prevalence of VWD in women with menorrhagia is 5-24% [28]. Menorrhagia is associated with anemia, fatigue, lifestyle disruptions and reduced quality of life in women [29–32]. Additionally, a Canadian study demonstrated higher morbidity burden and low health related quality of life (associated with menorrhagia) in female with VWD compared to general population [33]. Contemporary US data demonstrated higher health care utilization in VWD patients [34]. VWD with major bleeding and major surgery are associated with higher healthcare related cost[35,36]. However, in contrast to hemophilia, there is paucity of data about mortality in VWD patients.

1.5 Impact of inherited bleeding disorders on pregnancy

Excessive bleeding and physiologic changes during pregnancy are additional hemostatic challenges which place women at even higher risk of complications from bleeding disorders. Excessive bleeding after delivery is known as postpartum hemorrhage (PPH). PPH occurring

within the first 24 hours after delivery of placenta is defined as primary PPH and those occurring after 24 hours of delivery and within 6 weeks is defined as secondary PPH [36]. According to WHO systematic analysis, globally 480,000 (19.7%) maternal deaths were attributable to PPH during 2003-2009, making it the leading cause of maternal mortality [38]. It is the primary cause of maternal mortality in both low-income and developed countries [38,39]. Growing incidence of PPH have been reported from several industrialized countries in recent time [37,40,41]. PPH can lead to serious maternal morbidity such as adult respiratory distress syndrome, coagulopathy, and shock. Canadian population-based studies indicate increasing rates of PPH from 1991 to 2010 with a 29.8% increase from 2003 to 2010 in the province of Alberta [37,42]. A concurrent increase in the rates of severe PPH as measured by PPH with blood transfusion, hysterectomy and other procedures to control bleeding has been reported from Canada during 2003-2010, accompanied by a significant increase of PPH with blood transfusion in Alberta [37]. It remains unclear if this increasing trend in PPH has stabilized or continued to rise or declined beyond 2010.

Inherited bleeding disorders contribute to the risk of PPH. Although pregnancy is associated with a rise in VWF and factor VIII, they do not rise to a similar extent in women with bleeding disorders due to the underlying genetic mutations [43]. Furthermore, in type 2 VWD, the functional defect persists throughout pregnancy irrespective of VWF level. In women with type 3 VWD, factor level remains unchanged during pregnancy [43]. FVIII and VWF level fall rapidly after delivery and remain lower in pregnancies affected by VWD than pregnancies without, predisposing women to delayed PPH. A systematic review assessing pregnancy outcomes in type 3 VWD patients reported significantly higher rates of primary and secondary PPH among them compared to the reported prevalence in general population (48% vs 2.6% and 56% vs 1%, respectively) [44]. The reported prevalence of primary and secondary PPH in type 2B VWD is 45% and 46%, respectively [45]. Among carriers of hemophilia primary and secondary PPH have been reported as 10-22% and 3-11%, respectively with a greater risk for carriers of hemophilia B as the rise in FIX levels during pregnancy is not as high as FVIII levels [46–48]. U.S. population-based studies reported that in addition to higher risk of PPH, women with VWD also had a significantly higher risk of antepartum hemorrhage, transfusion requirements, caesarean section, hypertensive disorders in pregnancy and longer length of stay [49,50]. The ideal hemostatic target during delivery to prevent PPH in women with inherited bleeding disorders is still not clear [51]. According to a prospective

study from U.S.A, in women with VWD, VWF did not rise to the levels of women without VWD despite treatment and women with severe VWD still had increased blood loss at delivery [52]. Furthermore, a review study demonstrated similar incidence of PPH in women with VWD who received prophylactic treatment vs who did not [53]. A recent US retrospective study concluded even with higher dose (80 IU/Kg), neither recombinant VWF nor plasma derived VWF is sufficient to prevent PPH in women with VWD [54].

1.6 Bleeding disorders and its marker (iron deficiency anemia) are often not recognized which results in preventable major bleeding events

Women with longstanding menorrhagia often do not receive a hematology referral or workup for an underlying bleeding disorder. In a US population-based study, only one third of pregnant women with VWD had third trimester VWF testing and occurrence of PPH was significantly lower among those tested [55]. In a survey of 451 US obstetricians and gynaecologists, only 39% of respondents reported that they would consider a bleeding disorder as a possible cause of menorrhagia in women of reproductive age [56]. On the other hand, a British survey found that only 2% of obstetricians and gynecologists would arrange VWD testing for an adult woman with unexplained menorrhagia [57]. In an Irish cohort study of patients with low VWF levels, self-reporting symptoms of menorrhagia to a healthcare provider did not lead to expedited diagnosis [58]. A Canadian qualitative study among women with inherited bleeding disorders identified dismissal of symptoms by health care providers [59]. Moreover, sexism exists in the diagnosis of bleeding disorders which is evidenced by delayed diagnoses in women with hemophilia compared to their male counterpart and under representation of women with hemophilia in annual global survey of WFH [60,61].

Iron deficiency (ID) or iron deficiency anemia (IDA) is highly prevalent in women with inherited bleeding disorders. In an Irish cohort of women with VWD, 45.8% and 21.7% women developed ID and IDA, respectively [58]. Given the high prevalence, IDA may serve as an objective marker for an undiagnosed bleeding disorder. The risk of anemia increases during pregnancy due to increased iron demand for maternal red blood cell (RBC) mass expansion and for fetal development. The estimated prevalence of anemia in pregnancy in Europe and North America is 15% [62]. High prevalence of anemia in pregnancy has been reported from contemporary Canadian

studies [63,64]. Canadian studies revealed that ID is underrecognized in pregnancy despite its high prevalence [63,65]. In the general population, IDA in pregnancy is associated with preterm delivery, low birthweight, low 5-minute Apgar score, post-partum depression, perinatal transfusion, PPH, poorer cognitive development, and IDA among children [64,66–69].

1.7 Use of administrative data for population health research

Rarity of inherited bleeding disorders blocks the feasibility of clinical trials among these patients which makes the utilization of administrative database a reasonable alternative in this respect. Administrative databases contain de-identified records for nearly all contacts with the provincial health care system and cover the entire population of a province [70]. It may include claims for reimbursement, records of health services, diagnoses, medical procedures, and prescriptions. It documents individualised, anonymous, and linkable data prospectively. Some of the major data sets are Ambulatory care database (includes all ambulatory clinic visits and emergency visits) , Inpatient Discharge Abstract Database, physician claims database, laboratory database. Administrative data includes routinely collected data and is not meant for research purposes. The diagnoses are coded according to International Classification of Diseases (ICD) codes. Use of administrative data are increasingly being recognised in population health research [71]. Some of the benefits of using administrative database are: population coverage, large sample size, less expensive, longer time span and up to date data. Due to low prevalence of inherited bleeding disorders (or any other rare disease), identification of affected individuals for primary research studies is very time consuming and extensive, particularly in the settings or countries where well established bleeding disorder registries do not exist. Administrative database provides a better platform in this regard. Moreover, it is not subject to recall bias by the study participants. One of its major disadvantages is misclassification bias due to coding error. Although Canada has established bleeding disorder registry which includes patients from all provinces, utilization of administrative database in the research of inherited bleeding disorders still carries significance due to the following facts: 1) not all bleeding disorders (specially the mild cases) are followed by bleeding disorders clinics and registered in the Canadian Bleeding Disorder registry, 2) administrative data allows us to compare health outcomes and health resource utilization (such as hospitalization, length of stay, emergency department visit) with age- and sex-matched population

controls, 3) some data elements (e.g., surgical data, detailed laboratory data, etc.) are not routinely captured in most registries.

1.8 Study rationale and objectives

1.8.1 Study rationale

In Alberta, Canada, population-based administrative database research in the arena of bleeding disorders is nonexistent. Existing Canadian studies have mostly focused on very disease-specific areas of inherited bleeding disorders [72,73]. There is an urgent need for broader population-based and health outcomes research in this population. Because of the rarity of the disease and availability of data elements not routinely collected in national patient registries, administrative database can be very useful in assessing the burden of disease, healthcare utilization and outcomes in persons with inherited bleeding disorders. However, the accuracy of administrative data depends on the validity of the ICD coding, which can be affected by human factors such as misdiagnosis and misclassification by the coders. Validation of case definition of bleeding disorders by evaluating the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) is therefore critical prior to performing research using administrative databases.

Currently, to best of our knowledge, only three studies (all reported from the province of Ontario) investigated the impact of bleeding disorders on pregnancy outcomes in Canada [74–76]. Only one of them utilized population level data and others are single centre-based studies. Given the increasing rates of PPH from 1991 to 2010, it is of high importance to obtain up to date Albertan trends. Therefore, characterizing the continuing trends of PPH and its subtypes beyond 2010 in the province of Alberta and identifying the incidence of maternal (including PPH) and neonatal adverse events in women with inherited bleeding disorders compared to those without is of utmost importance. In addition, there is paucity of studies from Canada on the prevalence of ID/IDA in pregnant women with inherited bleeding disorders compared with the pregnant population without bleeding disorders. Furthermore, no Canadian study evaluated the rates of repletion of known ID or IDA during pregnancy. Identifying the prevalence of IDA and examining the quality of care in iron repletion during pregnancy will determine actionable areas for intervention and is of high importance for public health quality improvement.

1.8.2 Study Objectives:

1. To examine the temporal trends of the incidence of PPH from 2010 to 2018 in the province of Alberta, Canada stratified between patients with and without inherited bleeding disorders.
2. To examine the incidence of maternal and neonatal adverse events in women with inherited bleeding disorders compared to those without and to explore the rates coagulation factor assay among pregnant women with inherited bleeding disorders.
3. To identify the prevalence of ID and IDA in pregnancy stratified by the presence of inherited bleeding disorders and to assess the quality of care in the screening and correction of ID and/or IDA.
4. To examine the association between first trimester and third-trimester IDA on maternal and neonatal outcomes, and to explore whether corrected IDA mitigated the adverse impact of IDA on pregnancy outcomes.
5. To assess the accuracy of different diagnostic algorithms in identifying patients with inherited bleeding disorders (hemophilia A, hemophilia B, VWD, inherited platelet function disorder) from administrative database against medical chart review.

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CHAPTER 2

Development and validation of case definitions to identify hemophilia and von Willebrand disease in administrative data

2.1 Abstract

Background: Administrative data is useful in population-based studies of inherited bleeding disorders. Most studies used the International Classification of Diseases (ICD) diagnostic codes to identify inherited bleeding disorders from administrative data, but the coding accuracy is unclear. **Aim:** We validated the accuracy of a case definition using a combination of ICD diagnostic codes and coagulation factor level for identifying hemophilia, von Willebrand disease (VWD), and platelet function disorders (PFD) in administrative data, compared with the diagnostic accuracy of using ICD codes alone. **Methods:** This is a retrospective population-based study of all residents of Alberta, Canada, who underwent testing for coagulation factor VIII (FVIII) or factor IX (FIX) activity between 2009 and 2017 using linked administrative data. For VWD and PFD, the baseline population was people with a record of at least one ICD diagnostic code for the disease during the same period. Our predefined case definition was a combination of the relevant ICD codes and FVIII or FIX activity <0.40 IU/ml (for hemophilia A or hemophilia B), ICD code and von Willebrand factor (VWF) antigen or activity <0.50 IU/ml (for VWD), and ICD code and abnormal platelet aggregometry (for PFD). Medical charts of 2114 randomly selected patients tested for FVIII and 528 patients tested for FIX were reviewed to identify physician diagnoses of hemophilia. For the validation of VWD, randomly selected patients with ICD code alone for VWD (n=150), ICD+VWF<0.50 IU/ml (n=150) and ICD codes of other inherited bleeding disorders (n=150) were included for chart review. Similar method was applied for PFD. A physician diagnosis of the bleeding disorder in chart review was used as the reference standard. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for our case definitions (ICD code and low factor levels) and for case identification through ICD code alone. **Results:** With our algorithm, 72 (3.4%) patients tested for FVIII and 21 (4.0%) tested for FIX met the combined ICD code and laboratory criteria for hemophilia A and hemophilia B, respectively, whereas 63 (3.0%) and 22 (4.2%) had confirmed hemophilia A and hemophilia B upon chart review. Our algorithm had a sensitivity of 93.7%, specificity of 99.4%, PPV of 81.9% and NPV of 99.8% for identifying hemophilia A, and a sensitivity of 90.9%, specificity of 99.8%, PPV of

95.2% and NPV of 99.6% for identifying hemophilia B. The diagnostic accuracy of our combined ICD and laboratory criteria algorithm for VWD was: sensitivity 99.2%, specificity 88.2%, PPV 86.7% and NPV 99.3%. In contrast, using ICD code alone was associated with markedly lower specificity and lower PPV (41.1% for hemophilia A, 66.7% for hemophilia B, 8.7% for VWD). Validation of PFD was not formally performed due to incomplete platelet aggregometry data, and very low PPV of 10% using ICD code alone. **Conclusion:** This study showed that using a case definition of ICD codes and coagulation factor activities can identify hemophilia and VWD in administrative data with very high accuracy and can be used for future research.

2.2 Introduction:

Inherited bleeding disorders occur due to deficiency or altered function of coagulation proteins or platelets resulting in prolonged bleeding. The most common inherited bleeding disorders are hemophilia, von Willebrand disease (VWD), platelet function disorder and hemophilia. Hemophilia is an X-linked bleeding disorder caused by the deficiency of coagulation factor VIII (hemophilia A) or factor IX (hemophilia B). Globally, hemophilia A and hemophilia B are estimated to affect 1 in 5000 and 1 in 30000 live male births, respectively [1]. VWD is caused by deficient or defective von Willebrand factor (VWF). It is the most common bleeding disorder, affecting up to 1% of the population [2]. In the year 2020, Canadian Hemophilia Registry recorded 3,213 patients with hemophilia A, 697 patients with hemophilia B, and 4653 patients with VWD [3]. The standard and routine collection of health data, an administrative database, is used for epidemiological research of large populations with relatively low costs. It can be very useful in the surveillance, healthcare utilization and outcomes studies in hemophilia and VWD because of the rarity of the diseases. However, the accuracy of administrative databases depends on the validity of the International Classification of Diseases (ICD) coding, which can be affected by human factors such as misdiagnosis, misclassification by the coders, and erroneous or incomplete documentation in discharge summaries or billing claims [4]. A recent U.S. study demonstrated a low accuracy of ICD codes in identifying hemophilia A and hemophilia B [5]. Validation of a case definition to identify inherited bleeding disorders in administrative data is therefore critical prior to performing research using administrative databases. The aim of this study was to evaluate the accuracy of using a combination of ICD diagnostic codes and coagulation factor level for identifying hemophilia , VWD and platelet function disorder in administrative data, using chart

review as the reference standard. An exploratory objective of this study was to examine the patterns and indications of factor VIII and factor IX testing in our province.

2.3 Methods

2.3.1 Study population

This is a retrospective population-based validation study using linked administrative data in the province of Alberta, Canada. Alberta has a population of 4.4 million [6]. For the validation of factor VIII (FVIII) and factor IX (FIX), our baseline population was people of all ages who were tested for FVIII and FIX activity in the province of Alberta between 2009-2017. FVIII testing was predominantly performed using one-stage clot-based assays, although chromogenic FVIII assays were also used in selected cases. Due to the very low prevalence of hemophilia in the general male population, we felt that conducting chart reviews in a population with available coagulation factor levels is more pragmatic than in a primary care population. A sample from this population was randomly chosen for chart review. We performed a different method for the validation of VWD. For this purpose, the baseline population was people with a record of at least one ICD diagnostic code for VWD in Alberta during the same period. A random sample from this population was chosen as study participants. To these, we added a random sample of patients with ICD codes of inherited bleeding disorders other than VWD (which includes hemophilia, platelet function disorders and hereditary deficiencies of other coagulation factors) to generate false negative (FN) and true negative cells (TN) of the 2x2 table of VWD validation. We performed similar method for platelet function disorder; where we considered those with a record of at least one ICD code for this disorder as baseline population and those with ICD codes of other inherited bleeding disorders to generate FN and TN cells of the 2x2 table. All randomizations were performed by random case selection command in SPSS program. This study is approved by the institutional research ethics board (Pro00077704).

2.3.2 Health administrative data source

The source of our data was DIMR (Analytics, Data Integration, Measurement & Reporting). It collects and reports health data within Alberta Health Services. It links the (1) ambulatory care database, (2) Discharge Abstract Database, (3) Physician Claims Database (4), Alberta Blue Cross

database, (5) Pharmaceutical Information Network, (6) Population Registry Database, (7) Medical Laboratory database and (8) Vital Statistics. This database documents individualised, anonymous and linkable data prospectively. The database contains detailed information on all hospital admissions and outpatient visits including patient demographics, the reasons for admission, discharge diagnoses (in ICD-10-CA or ICD-9-CA), diagnostic and procedure codes, payment sources, and detailed description of all charges billed.

2.3.3 Diagnostic algorithm

We compared the accuracy between two diagnostic algorithms for identifying inherited bleeding disorders from the linked administrative databases. For hemophilia A, we developed an algorithm using a combination of (1) ICD diagnostic codes (ICD-9-CA 286.0, ICD-10-CA D66) from either the Discharge Abstract Database, ambulatory care reporting system, or claims database and (2) at least one coagulation factor VIII activity <0.40 IU/ml [7]. Similarly, we used an algorithm of ICD diagnostic codes (ICD-9-CA 286.1, ICD-10-CA D67) and at least one coagulation factor IX activity <0.40 IU/ml to identify hemophilia B. For VWD, we used an algorithm of ICD diagnostic codes (ICD-9-CA 286.4, ICD-10-CA D68) and at least one VWF antigen/activity <0.50 IU/ml. Laboratory assays included VWF Antigen (VWF: Ag), VWF ristocetin cofactor activity (VWF:RCo), and VWF Glycoprotein 1bM (VWF:GPIbM). For platelet function disorder, our algorithm comprised of ICD diagnostic code (ICD-9-CA 287.1, ICD-10-CA D691) and at least one abnormal platelet aggregation study result. We compared the accuracy of these algorithms to case identification using ICD codes alone.

2.3.4 Chart review (gold standard)

Provincial healthcare numbers were encrypted in the administrative database and linked to unique identifiers. For a list of randomly selected patients, we were provided with the healthcare numbers to conduct chart reviews in electronic health records. A trained abstractor with a medical background used a data collection tool to abstract information from the medical record comprised of emergency visits, hospital admissions, selected consultation reports, laboratory and radiology reports, transfusion records and outpatient prescriptions. Patients were considered to have hemophilia or VWD or platelet function disorder if they were diagnosed by a physician with clear supportive clinical and laboratory evidence. Prior to 2021 guidelines, a person with VWF level <0.30 IU/ml was considered as having VWD and persons with VWF levels between 0.30-0.50

IU/ml without clinically significant bleeding history or family history were typically classified as "low VWF" [8,9]. The chart reviewer was blinded to the ICD coding. Unclear cases were reviewed and decided by a second reviewer who is a bleeding disorders specialist. Indeterminate and missing cases were re-classified as negative during calculation of diagnostic accuracy.

2.3.5 Exploring indications for hemostasis testing

As initial chart reviews for FVIII and FIX signaled inappropriate factor testing, we decided to examine the pattern of hemostasis test as an exploratory objective of this study. The indications for sending FVIII and/or FIX levels were identified from clinic notes, as well as on the coagulation laboratory requisition.

2.3.6 Sample size and statistical analysis

A total of 11,053 patients were tested for FVIII activity and 1522 patients were tested for FIX activity from 2009-2017. We estimated the sample size of chart reviews needed to identify hemophilia A and hemophilia B cases with a 75% sensitivity and 85% specificity, based on the prevalence of low FVIII (<0.40 IU/ml) of 4.2% and low FIX (<0.40 IU/ml) of 9.5% in this population [10]. For VWD validation, we aimed for a sample size of 300 for testing each algorithm which is generally considered as a sufficient sample size to evaluate sensitivity and specificity of diagnostic or screening tests [11]. Of these 300, 150 had ICD code for VWD (or ICD+VWF<0.50IU/ml, based on the algorithm tested) and the other 150 had ICD code for other inherited bleeding disorders (to generate FN and TN cells of 2x2 table). Hence, the total number of included patients for VWD validation was 150 (ICD alone) +150 (ICD+VWF<0.50 IU/ml) +150 (ICD for other inherited bleeding disorders) =450. Descriptive statistics were used to characterize the study population. We calculated sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of our diagnostic algorithms (ICD + low factor VIII/IX/VWF vs ICD alone) with corresponding 95% confidence intervals (CIs) against chart review diagnosis as the gold standard. We also calculated c-statistic form the area under the Receiver Operating Characteristics (ROC) curve. Subgroup analyses were performed to compare the diagnostic accuracy between male and female sex and adult vs pediatric population. In addition, we used Standards for Reporting of Diagnostic Accuracy Studies (STARD) diagram to show the flow of

patients for hemophilia validation [12]. All analyses were carried out with SPSS version 23 (IBM Corp. Released 2015 Armonk, NY) and SAS Institute Inc. 2013. SAS® 9.4 (Cary, NC: SAS Institute Inc).

2.4 Results

We randomly sampled 2114 (19%) patients from those tested for factor VIII and 528 (35%) patients from those tested for factor IX for chart review. The mean age of the total population for FVIII and FIX validation was 38 years and 1773 (67%) were women (Table 2.1). Figure 2.1 reflects the flow of the participants for factor VIII and factor IX according to STARD diagram. On the other hand, the mean age of the total population for VWF validation was 27.5 years and 206 (68.7%) were women (Table 2). Among those who underwent FVIII testing, 63 (2.9%) patients had a confirmed diagnosis of hemophilia A according to chart review, whereas 72 (3.4%) fulfilled the case definition of ICD code and FVIII <0.40 IU/ml. Of the confirmed hemophilia cases, 25 (40%), 5 (8%), and 33 (52%) have severe, moderate, and mild hemophilia A. Other pertinent diagnoses included VWD in 80 (3.8%), hemophilia A carrier with FVIII>0.40 IU/ml in 11 (0.5%), acquired hemophilia A in 6 (0.3%), and another bleeding disorder in 120 (5.7%). Among the 14 false positive cases identified by the administrative data case definition for hemophilia A, 7 (50%) had VWD, 2 (14.3%) had acquired hemophilia, 3 (21.4%) had undefined bleeding disorder, 1 (7%) had acquired von Willebrand syndrome and 1 (7%) had low von Willebrand factor levels. Common indications for coagulation FVIII testing include: one or more bleeding symptoms (excluding isolated bruising) in 824 (39%), easy bruising alone in 115 (5%), prolonged PTT in 99 (5%), arterial or venous thrombosis in 91 (4%), VWD screening in myeloproliferative neoplasm in 36 (2%) and family history in 24 (1%). There were no clearly documented indications of coagulation testing in most other cases.

Among the 528 patients who underwent FIX testing, 22 (4.2%) had a confirmed diagnosis of hemophilia B on chart review, while 21 (4.0%) met the combined ICD code and laboratory criteria. The severity of confirmed hemophilia B cases included: severe in 9 (41%), moderate in 5 (23%), and mild in 8 (36%). Other relevant diagnoses include congenital or acquired hemophilia A in 28 (5%), hemophilia B carrier with FIX>0.40 IU/ml in 5 (0.9%), and another bleeding disorder in 55 (10%). Common indications for coagulation FIX testing include: prolonged PTT in 179 (34%),

one or more bleeding symptoms in 155 (29%), coagulopathy from hepatic dysfunction or vitamin K deficiency in 32 (6%), arterial or venous thrombosis in 19 (4%), easy bruising alone in 6 and family history in 5 (1% each).

Among those with ICD code alone for VWD, only 13 (8.7%) had confirmed diagnosis of the disease on chart review. In contrast, among those with ICD code coupled with low VWF level, 130 (86.7%) had confirmed diagnosis of VWD on chart review. Other relevant diagnoses among the false positive cases in this group included: 4 (2.7%) undefined bleeding disorder, 2 (1.3%) unexplained menorrhagia. The remaining 14 false positive cases did not have any diagnosis of inherited bleeding disorders or other relevant conditions.

The database for platelet aggregation study was incomplete. Therefore, we were unable to test our ICD code plus laboratory algorithm for platelet function disorder. We performed a chart review of 50 persons with ICD code alone and it showed a PPV of only 10%. Coding errors associated with the ICD code for platelet function disorders were highly prevalent, with heterogenous clinician diagnoses upon chart review, ranging from immune thrombocytopenia to myelodysplastic syndrome. Hence, we elected not to perform the rest of the formal analyses to validate platelet function disorder due to incomplete data and coding errors.

Tables 2.3, 2.4 and 2.5 summarize the performance of the administrative case definitions for identifying hemophilia A, hemophilia B and VWD respectively. For identifying patients of hemophilia A from administrative database the diagnostic accuracy of our combined ICD and laboratory criteria algorithm were: sensitivity 93.7% (95% CI: 84.5-98.2), specificity 99.4% (95% CI: 98.9-99.6), PPV 81.9% (95% CI: 72.5-88.7) and NPV 99.8 (95% CI: 99.5 -99.9). Adding laboratory criteria to ICD alone resulted in a marked increase of PPV from 41.1% to 81.9% and improved specificity from 95.8% to 99.4%. For identifying patients of hemophilia B the diagnostic statistics of our algorithm were: sensitivity 90.9% (95% CI: 74.5-98.4), specificity 99.8% (95% CI: 99.1-100), PPV 95.2% (95% CI: 80.7-99.7) and NPV 99.6% (95% CI: 98.8 -99.9). The sensitivity, specificity and NPV are similar between 2 diagnostic algorithms for hemophilia B, although the PPV of using ICD code alone is markedly lower compared with ICD code plus laboratory criteria (66.7% vs 95.2%). The diagnostic accuracy of our combined ICD and laboratory

criteria algorithm for VWD were: sensitivity 99.2% (95% CI: 95.8-99.9), specificity 88.2% (95% CI: 82.3-92.6), PPV 86.7% (95% CI: 81.2-90.8) and NPV 99.3% (95% CI: 95.5 -99.9). In contrast, the specificity (52.1%) and PPV (8.7%) were significantly lower for ICD code alone. Our algorithm showed excellent discriminant properties for identifying hemophilia A (c-statistic 0.96), hemophilia B (c-statistic 0.95) and VWD (c-statistic 0.94). In subgroup analyses, sensitivity and PPV were much lower in women than men for hemophilia A (Table 2.3). The diagnostic accuracy for women is underpowered and hence unreliable, as there were only 8 female hemophilia patients on chart review. However, we found similar diagnostic accuracy between pediatric and adult populations for both types of hemophilia, and similar diagnostic accuracy in men and women with hemophilia B and VWD (Tables 2.4-2.5).

2.5 Discussion

Validation of administrative case definitions for identifying bleeding disorders is imperative prior to conducting research studies using administrative data. Our study is the first validation study evaluating the diagnostic accuracy of identifying hemophilia using administrative data in Canada, a country with a universal public healthcare system. And to the best of our knowledge, this study is novel in assessing the diagnostic accuracy of identifying VWD from administrative database. We demonstrated that a simple algorithm combining ICD diagnostic codes with low coagulation factor activities is associated with excellent sensitivity, specificity, PPV and NPV for identifying hemophilia A, hemophilia B and VWD against chart review.

While there is an increasing number of population-based administrative database studies in hemophilia [13–15] , the validity of identifying hemophilia cases using administrative data has not been evaluated until very recently. A U.S. study in 2017 revealed a high false positive rate of ICD-9-CM coding of hemophilia A and hemophilia B in electronic health records, although the study used only surrogates to ascertain cases of probable hemophilia without chart review [5]. This calls into question results of administrative database related hemophilia research if only a hemophilia diagnostic code is used to identify patients. Another recent U.S. validation study demonstrated excellent sensitivity and specificity in their algorithm for identifying patients with hemophilia A from administrative claims database [16]. However, this involved a complicated algorithm using machine learning and predictive modelling which decreases its applicability in other centers.

Similarly, while several population-based administrative database studies exist in VWD from North America, none of them validated any algorithm to identify this condition [17,18].

In our study, the PPV associated with ICD codes alone is markedly poor in both hemophilia A (41.1%), hemophilia B (66.7%), and VWD (8.7%) highlighting the importance of using additional criteria to improve the diagnostic accuracy in identifying hemophilia and VWD in administrative data. The addition of laboratory criteria to ICD code alone resulted in an increase in PPVs and specificities for both hemophilia and VWD. Prioritization of specificity and PPV is important in outcomes research in rare diseases, to ensure a homogenous population without many false positives.

The PPV for hemophilia B was higher than hemophilia A. This is possibly caused by relatively higher prevalence of hemophilia B (4.2%) than hemophilia A (2.9%) in our study cohort. Another explanation is that VWD patients with low FVIII activity may be miscoded as hemophilia A on ICD codes, contributing to more false positives. In fact, of patients who underwent FVIII testing, a confirmed diagnosis of VWD is more prevalent than hemophilia A in our sample. Exclusion of low von Willebrand factors in addition to ICD codes and low FVIII activities may potentially improve our PPV. This was not explored as our PPV was >80%, and our aim was to create a relatively simple diagnostic algorithm.

The lower sensitivity of our case definition in women with hemophilia can be explained by a few reasons, largely related to the higher number of false negatives. Hemophilia carriers may not have received appropriate ICD codes resulting in increased proportion of false negative cases. This could reflect clinicians' lack of awareness on the relevance of female carriers, and the current ICD codes for carriers. About a quarter (23%) of the false positive cases for hemophilia A were VWD patients who have been misclassified likely due to concomitant reduction in FVIII level which also explains the identification of relatively higher proportion of hemophilia cases by the algorithm than by chart review.

Many countries including Canada have established hemophilia and VWD registries, with which we can collect patient-specific information with greater accuracy than administrative database research. However, our approach in identifying inherited bleeding disorders cases using

administrative data allows us to compare them with age- and sex-matched population controls in our jurisdiction to assess health outcomes and healthcare resource utilization. These types of study have been done in the U.S. using ICD codes, for instance, to assess the incidence of hepatocellular carcinoma, and to estimate mortality and healthcare utilization in hemophilia patients [19,20]. However, the validity of the studies is unclear as the ICD codes were not validated. Furthermore, there is no Canadian administrative data evaluating health outcomes in hemophilia or VWD patients compared to controls except one recent study from Alberta [21]. In addition, not all patients with hemophilia or VWD are actively followed by the hemophilia treatment centers and registered in the national registry. Case identification using multiple methods (including administrative data) has been shown to identify higher incidence and prevalence of hemophilia in Indiana compared to national estimates [19].

While there are studies evaluating inappropriate coagulation testing such as for a hypercoagulable workup [22], there is scarce data on inappropriate hemostasis testing. Our population-based study observed inappropriate hemostasis evaluation in 6% of all FIX tests in the context of coagulopathy from hepatic dysfunction or vitamin K deficiency, and 4% of FIX tests in the context of "hypercoagulable" workup for arterial or venous thromboses. Prolonged PTT was the indication in 34% of FIX tests, which is likely inappropriate although the study did not specifically assess the sequencing of prolonged PTT evaluation. However, as we collected data retrospectively from clinic notes and lab requisition, the findings are prone to misclassification bias. An interpretive hemostasis testing service has been proposed as a way to improve the testing efficiency, reduce unnecessary tests and shorten the time to diagnosis [23].

The key strength of this research is that our cohort represents the vast majority of our provincial population, given Canada's universal healthcare system. This offers a potentially more robust dataset compared to insurance-based administrative databases. Another strength of this study was using an uncomplicated method to improve the diagnostic accuracy in administrative data by linkage with laboratory data. Our study period spans 8 years, which reduces the risk of misclassification related to delayed diagnosis and loss to follow-ups.

There are some potential limitations to this study. First, our test results might have been affected by the relatively higher prevalence of hemophilia and VWD in our validation cohort. Second, the

reported prevalence of hemophilia and VWD, coding practices and healthcare system vary significantly across countries. Therefore, our diagnostic algorithm should be used cautiously in other jurisdictions due to limited generalizability. Moreover, for our algorithm a single low factor VIII or IX (<0.40 IU/ml) or VWF<0.50 IU/ml along with the ICD codes satisfied a positive diagnosis in the administrative data, which may lead to misclassification, due to preanalytical variables from suboptimal sample processing or shipping [24]. We did not explore the diagnostic accuracy of low factor levels alone. Despite these limitations, our case definition appeared to have high diagnostic accuracy.

2.6 Conclusion:

We have demonstrated that ICD diagnostic codes in combination with a low coagulation factor level provide a highly sensitive and specific method to identify cases of hemophilia and VWD in administrative data in a public healthcare system. This study is an essential first step before administrative data can be used by investigators to conduct health services and health outcomes research in hemophilia. Our algorithm may help guide the development and validation of administrative case definitions for hemophilia and VWD in other jurisdictions.

Table 2.1: Characteristics of patients included in the validation study of Factor VIII and Factor IX

Characteristics	**Factor VIII (N=2114)**	**Factor IX (N=528)**	**All (N=2642)**
Males, n (%)	611 (29)	258 (49)	869 (33)
Females, n (%)	1503 (71)	270 (51)	1773 (67)
Age, mean (sd [a])	39 (21)	38 (26)	39(22)
Adults (≥18 years), n(%)	1749 (83)	374 (71)	2123 (80)
Pediatric (<18 years), n (%)	365 (17)	154 (29)	519 (20)
Hemophilia identified by chart review, n (%)	63 (2.9)	22 (4.2)	84 (3.2)
Hemophilia identified by ICD [b] + factor<0.40 IU/ml, n (%)	72 (3.4)	21 (4.0)	93 (3.5)
Hemophilia identified by ICD alone, n (%)	146 (6.9)	30 (5.7)	176 (6.7)

a: standard deviation; b: International Classification of Diseases

Table 2.2: Characteristics of patients included in the validation study of von Willebrand factor (VWF)

Characteristics	**ICD [b] for VWD (N=150)**	**ICD+VWF<0. 50 IU/ml (N=150)**	**ICD for inherited bleeding disorders other than VWD (N=150)**
Males, n (%)	47 (31.3)	47 (31.3)	76 (50.7)
Females, n (%)	103 (68.7)	103 (68.7)	74 (49.3)
Age, mean (sd [a])	27.9 (19.5)	27.1 (17.4)	39.2 (23.2)
Adults (≥18 years), n(%)	101 (67.3)	98 (65.3)	115 (76.7)
Pediatric (<18 years), n (%)	49 (32.7)	52 (34.7)	35 (23.3)
VWD identified by chart review, n (%)	13 (8.7)	130 (86.7)	1 (0.67)

a: standard deviation; b: International Classification of Diseases

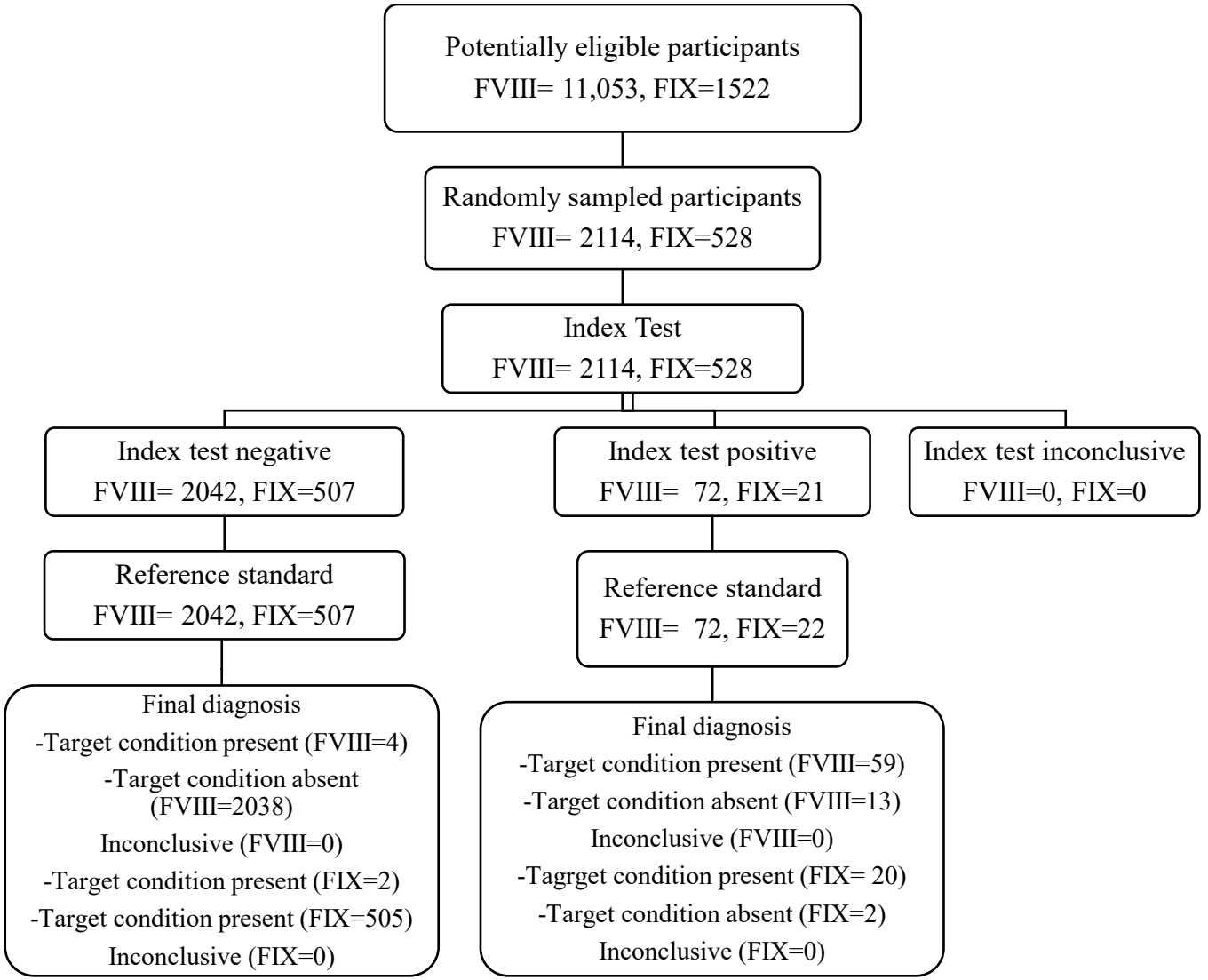

Figure 2.1: STARD diagram to report flow of participants for factors VIII and IX throughout the study

Table 2.3: Diagnostic accuracy of ICD code alone vs ICD code + coagulation Factor VIII <0.40 IU/ml

	Sensitivity (95% CI)	Specificity (95% CI)	PPV [b] (95% CI)	NPV [c] (95% CI [d])	C statistic
ICD [a] code alone					
-All	95.2 (86.7- 99.0)	95.8 (94.9-96.6)	41.1 (36.0-46.4)	99.9 (99.5-100)	0.960
-Male	98.2 (92.1-99.9)	93.4 (90.9-95.3)	59.3 (51.6-66.6)	99.8 (98.7-100)	0.957
-Female	75.0 (40.9-95.3)	96.7 (95.7-97.5)	10.9 (4.5-20.9)	99.9 (99.6-100)	0.859
-Adult	95.7 (87.2-99.3)	95.9 (94.9-96.8)	39.5 (33.9-45.3)	99.9 (99.6-100)	0.958
-Pediatric	93.8 (75.3-99.6)	95.1 (92.5-97.1)	46.9 (30.3-63.9)	99.7 (98.7-100)	0.944
ICD code + FVIII [e] <0.40 IU/ml					
-All	93.7 (84.5-98.2)	99.4 (98.9-99.6)	81.9 (72.5-88.7)	99.8 (99.5 -99.9)	0.964
-Male	98.2 (90.3-99.9)	99.1 (97.9-99.7)	91.5 (81.9-96.3)	99.8 (98.8-99.9)	0.985
-Female	62.5 (29.0-89.0)	99.5 (99.0-99.8)	38.5(15.9-65.2)	99.8 (99.5-99.9)	0.810
-Adult	93.5 (84.0-98.3)	99.4 (98.9-99.7)	81.5 (70.3-89.1)	99.8 (99.5-100)	0.964
-Pediatric	93.8 (75.3-99.6)	99.1 (97.8-99.8)	83.3 (62.3-95.6)	99.7 (98.7-100)	0.964

a: International Classification of Diseases, b: positive predictive value; c: negative predictive value; d: confidence interval; e: factor VIII

Table 2.3: Diagnostic accuracy of ICD code alone vs ICD code + coagulation Factor IX <0.40 IU/ml

	Sensitivity (95% CI)	Specificity (95% CI)	PPV [b] (95% CI)	NPV [c] (95% CI [d])	C statistic
ICD [a] code alone					
-All	90.9 (74.5- 98.4)	98.0 (96.6-99.0)	66.7 (48.9-81.7)	99.6 (98.8-99.9)	0.945
-Male	93.3 (73.8-99.6)	98.8 (96.8-99.7)	82.4 (60.8-95.3)	99.6 (98.2-100)	0.960
-Female	85.7 (50.6-99.1)	97.3 (94.9-98.8)	46.2 (21.6-72.1)	99.6 (98.3-100)	0.915
-Adult	93.3 (73.8-99.6)	97.5 (95.5-98.8)	60.9 (40.6-78.9)	99.7 (98.8-100)	0.954
-Pediatric	85.7 (50.6-99.1)	99.3 (97.0-100)	85.7 (50.6-99.1)	99.3 (97.0-100)	0.925
ICD code + FIX [e] <0.40 IU/ml					
-All	90.9 (74.5-98.4)	99.8 (99.1-100)	95.2 (80.7-99.7)	99.6 (98.8 -99.9)	0.954
-Male	93.3 (66.0-99.7)	100 (98.1-100)	100 (73.2-100)	99.6 (97.4-99.9)	0.967
-Female	85.7 (50.6-99.1)	99.6 (98.3-100)	85.7 (50.6-99.1)	99.6 (98.3-100)	0.927
-Adult	93.3 (66.0-99.7)	100 (98.7-100)	100 (73.2-100)	99.7 (98.2-99.9)	0.967
-Pediatric	85.7 (50.6-99.1)	99.3 (97.0-100)	85.7 (50.6-99.1)	99.3 (97.0-100)	0.925

a: International Classification of Diseases, b: positive predictive value; c: negative predictive value; d: confidence interval; e: factor IX

Table 2.4: Diagnostic accuracy of ICD code alone vs ICD code + VWF<0.50 IU/ml

	Sensitivity (95% CI)	Specificity (95% CI)	PPV [b] (95% CI)	NPV [c] (95% CI [d])	C statistic
ICD [a] code alone					
-All	92.9 (66.1- 99.8)	52.1 (46.1-58.0)	8.7 (7.3-10.3)	99.3 (95.7-99.9)	0.540
-Male	75.0 (19.4-99.4)	77.2 (70.6-82.9)	6.4 (3.5-11.3)	99.3 (96.5-99.9)	0.529
-Female	90.9 (58.7-99.8)	61.6 (55.1-67.7)	9.7 (7.8-12.1)	99.3 (95.8-99.9)	0.545
ICD code + VWF [e] <0.50 IU/ml					
-All	99.2 (95.8-99.9)	88.2 (82.3-92.6)	86.7 (81.2-90.8)	99.3 (95.5 -99.9)	0.937
-Male	97.4 (86.2-99.9)	94.9 (90.2-97.8)	82.2 (70.2-90.1)	99.3 (95.6-99.9)	0.908
-Female	98.9 (94.2-99.9)	92.6 (87.3-96.1)	88.6 (81.8-93.0)	99.3 (95.5-99.9)	0.940

a: International Classification of Diseases, b: positive predictive value; c: negative predictive value; d: confidence interval; e: von Willebrand factor

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CHAPTER 3

Impact of Inherited Bleeding Disorders on Maternal Bleeding and Other Pregnancy Outcomes: A Population-based Cohort Study

3.1 Abstract

Background: Increasing rate of postpartum hemorrhage (PPH) has been observed between 2003 and 2010 in Canada. Inherited bleeding disorders contribute to the risk of PPH and other maternal bleeding. **Aim**: To identify the current trend in PPH in the last decade, assess the impact of bleeding disorders on pregnancy outcomes and evaluate the coagulation workup in pregnant women with bleeding disorders. **Methods**: We conducted a retrospective population-based cohort study using the Alberta Pregnancy Birth Cohort (created by linked administrative database and described previously) from 2010 to 2018. PPH was defined as a blood loss of ≥500 ml following vaginal delivery or ≥1000 ml following Caesarean section, or as diagnosed by a healthcare provider. Inherited bleeding disorders (von Willebrand disease, hemophilia A, and hemophilia B) were identified by previously validated algorithm and matched with control by maternal age, parity and sociodemographic variables . All other diagnoses and procedures were identified by International Classification of Diseases (ICD)-10 codes and Canadian Classification of Interventions (CCI) codes, respectively. Temporal trend of the incidence of PPH was assessed by the Mann Kendall test. Logistic regression analyses were used to compute odds of pregnancy outcomes in women with bleeding disorders compared to matched controls. **Results**: We identified 311,330 women with a total of 454,400 pregnancies with live births. The rate of PPH did not change significantly from 10.13 (95% CI 10.10-10.16) in 2010 to 10.72 (95% CI 10.69-10.75) in 2018 (P for trend =0.35). Ninety-three (0.03%) women with inherited bleeding disorders had a total of 140 pregnancies. Women with bleeding disorders were significantly more likely to experience PPH (odds ratio [OR] 2.3; 95% CI 1.5-3.6), antepartum hemorrhage (OR 2.9; 95% CI 1.5-5.9) and red cell transfusion (OR 2.8; 95% CI 1.1-7.0). There was no significant difference in neonatal outcomes. Only 49.5% pregnancies with bleeding disorders had third trimester coagulation factor levels checked. Of them, 81% and 36% had factor levels ≥0.50 IU/ml and ≥1.0 IU/ml, respectively. Higher odds of PPH and antepartum hemorrhage were observed even with factor levels ≥0.50 IU/ml in third trimester. **Conclusion**: Despite a rise in the rate of PPH between 2003-2010 in Alberta, we observed no significant change in the rate of PPH between 2010-2018.

Women with inherited bleeding disorders are at an increased risk of bleeding events during pregnancy and delivery. Further work is needed to optimize coagulation workup and replacement therapy in pregnancy and peripartum period.

3.2 Introduction:

Postpartum hemorrhage (PPH) is the primary cause of nearly one quarter of all maternal deaths worldwide and the leading cause of maternal mortality in both low-income and developed countries [1,2]. Growing incidence of PPH have been reported from several industrialized countries including Australia, Canada, Ireland, and the United States during 1990s and 2000s [3–6]. PPH can lead to serious maternal morbidity such as adult respiratory distress syndrome, coagulopathy, and shock [7]. Canadian population-based studies indicate increasing rates of PPH from 1991 to 2010 across Canada accompanied by 29.8% increase from 7.5% in 2003 to 9.8% in 2010 in the province of Alberta [4,8]. But it remains unclear what is the trend of PPH in the past decade. While PPH events are sudden, unpredictable, and catastrophic on many occasions, there are also known risk factors, such as inherited bleeding disorders, history of PPH and anemia in pregnancy [9]. The most common inherited bleeding disorders include: von Willebrand disease (VWD), inherited platelet function disorders and hemophilia. In addition to higher risk of PPH, women with inherited bleeding disorders are also at increased risk of antepartum hemorrhage and other maternal and neonatal adverse events [10]. Furthermore, inherited bleeding disorders can be underdiagnosed prior to pregnancy and manifest as severe PPH as the first symptom [11]. Current literature on PPH in inherited bleeding disorders are mostly based on retrospective studies [12,13]. There are scarce population-based cohort studies comparing the risk of PPH and other pregnancy outcomes in women with bleeding disorders compared with population controls. Additionally, no population-based study in Canada evaluated whether women with inherited bleeding disorders receive adequate coagulation workup and management during their pregnancy. Given the increasing rates of PPH from 1991 to 2010, it is of high importance to obtain up-to-date trends. Therefore, we aimed to characterize the current trends of PPH beyond 2010 in the province of Alberta using a linked administrative database. A further aim was to identify the incidence of maternal and neonatal adverse events in women with inherited bleeding disorders compared to the general population. Finally, we aimed to characterize the quality of care in this patient population in relation to their hematology workup during pregnancy.

3.3 Methods:

3.3.1 Study design and data source

This is a retrospective population-based cohort study using linked de-identified administrative health databases in the province of Alberta, Canada. The data source is Alberta Pregnancy Birth Cohort which has been described previously in other studies [14,15]. It contains maternal and newborn data from all hospital-based live births between January 1, 2002, and March 31, 2019, in the province of Alberta. The Alberta Pregnancy Birth Cohort is developed by linking the following databases: Discharge Abstract Database (DAD), Ambulatory care database, Practitioner Payments Databases, Alberta Health Care Insurance Population registry, Stakeholder registry, Vital Statistics database, Laboratory database. The DAD includes information on patient characteristics, medical history, and details of all diagnostic and procedural codes assigned to patients who have been discharged from an inpatient bed. It contains 1- 25 diagnostic and 1-20 procedure codes of the International Classification of Diseases, Tenth revision, Canada (ICD-10-CA). The ambulatory care database contains 1-10 diagnostic and 1-10 procedure codes of ICD-10-CA and includes both emergency department visits and ambulatory clinic visits. The Practitioner Payments Database includes fee-for-service claims by physicians and other providers for insured health services. Vital statistics birth registry contains characteristics of all live births including year of birth, birth order, location of birth, birthweight, gestational ages at birth, parity and unique identifiers for both mothers and newborns. Vital statistics death registry contains date of death of the mothers and newborns. Population registry file records the address dissemination areas of the study population. Dissemination area is the smallest standard geographic area for which all census data are disseminated and has a corresponding Pampalon deprivation index [16]. Stakeholder registry file records country of previous residence of the mothers. Institutional research ethics board approval was obtained for this study (Pro00110665).

3.3.2 Study population

The population consisted of all women with hospital deliveries associated with live births in Alberta from January 1, 2010 to December 31, 2018. The study population was subdivided into two groups: 1) pregnancies in women with inherited bleeding disorders, 2) pregnancies in women without inherited bleeding disorders. This study primarily focused on the most common inherited

bleeding disorders including VWD, hemophilia and platelet function disorders. These cases were identified by the combination of ICD diagnostic codes and relevant laboratory tests. We extracted ICD codes from Ambulatory care database and DAD that were available from 2002 to 2018. To identify VWD cases, we used a validated algorithm comprised of ICD codes for VWD (ICD-9-CA 286.4 or ICD-10-CA D68) and at least one von Willebrand factor (VWF) antigen or activity <0.50 IU/ml against chart review as gold standard. The validation cohorts (provided by Data Integration, Measurement & Reporting of Alberta Health Services) for VWD and hemophilia were independent of the Alberta pregnancy birth cohort. For VWD, the baseline population was all residents of Alberta who had at least one ICD code for VWD or other inherited bleeding disorders (hemophilia, platelet function disorders, and hereditary deficiencies of other coagulation factors) . The test statistics for this algorithm for women were sensitivity 98.9% , specificity 92.6% and positive predictive value (PPV) 88.6%. Using ICD code alone provided poor specificity (61.6%) and PPV (8.7%). Hemophilia cases were identified by a previously established algorithm using a combination of ICD codes (ICD-9-CA 286.0 or ICD-10-CA D66 for hemophilia A, ICD-9-CA 286.1 or ICD-10-CA D67 for hemophilia B) and at least one coagulation factor VIII/IX activity <0.40 IU/ml [17]. The baseline population was all residents of Alberta who underwent testing for factor VIII or factor IX. The accuracy of this algorithm has been validated against chart audit in Alberta with sensitivity of 62.5%, specificity of 99.5% and PPV of 38.5% for identifying women with hemophilia A, and a sensitivity of 85.7%, specificity of 99.6% and PPV of 85.7% for identifying women with hemophilia B [17]. Using ICD code alone provided lower PPVs (10.9% for hemophilia A and 46.2% for hemophilia B) [17]. Validation of platelet function disorder yielded poor PPV (10%) using ICD code alone and validation could not be performed for ICD code plus laboratory component (platelet aggregation study) as laboratory database was incomplete. Hence, platelet function disorder was excluded. The control group comprised of pregnant women having no ICD codes for any inherited bleeding disorders during the entire study period. Cases were matched in 1:10 ratio to the controls by maternal age, parity, country of maternal birth, residence (urban/rural) and socioeconomic quintiles. The maternal age at delivery was the index date of matching. For a woman with inherited bleeding disorder identified by our algorithm, we included all her available pregnancies during the study period. The Pampalon material deprivation index, derived from census data (based on dissemination area), was used as a surrogate of socioeconomic status [18]. This index has quintiles (groups of 20%), from the least

deprived (Quintile 1) to the most deprived (Quintile 5). We defined rural or urban status based on the second digit of the patient's home address postal code [19]. Mother's previous country of residence was used as a surrogate to identify the geographic region of maternal birth, classified as Europe and North America, Asia, Africa, Central and South America. Within the bleeding cohort identified by our case definition, if someone had an ICD code for the bleeding disorder prior to conception, it was defined as "pregnancy with pre-existing diagnosis of bleeding disorder".

3.3.3 Outcomes

Primary outcome

The primary outcome of PPH was defined by ICD-10-CA codes (O72.0 to O72.3) which identify PPH as a blood loss of ≥500 mL following vaginal delivery or ≥1000 mL following Caesarean section, or as a diagnosis noted by a health care provider. PPH occurring within the first 24 hours after delivery of placenta was defined as primary PPH. It was classified into following categories: PPH caused by retained placenta (O72.0), PPH caused by uterine atony (O72.1), and PPH caused by coagulation defects (O72.3). PPH occurring after 24 hours of delivery and within 6 weeks was defined as secondary PPH (O72.2). In a validation study the diagnostic code accuracy of PPH of the Canadian Institute for Health Information (CIHI) DAD showed excellent performance with a sensitivity of 90.2% and specificity of 98.2% [20].

Secondary outcomes

Secondary outcomes included: severe PPH, antepartum hemorrhage, obstetric hematoma, red cell transfusions, hysterectomy, maternal death, and neonatal outcomes. Severe PPH was defined as PPH with red cell transfusion, hysterectomy, or other procedures to control bleeding [4]. Other procedures to control bleeding included ligation/embolization of pelvic vessels and suturing of uterus. Mode of delivery was categorized into vaginal and caesarean section. Instrumental delivery included any delivery with forceps, vacuum extraction, both forceps and vacuum. Maternal death was defined as death of mother within 42 days of termination of pregnancy [21]. We also identified relevant neonatal outcomes including preterm birth (< 37 weeks of gestation at birth), low birth weight (< 2500 grams at birth), intracranial hemorrhage of newborns, and neonatal death (defined as deaths of newborns within 28 days of birth) [22].

The predictor variables for PPH included multiple gestation, cervical and high vaginal laceration, instrumental delivery, mode of delivery, uterine rupture, prolonged labour, labour induction, chorioamnionitis, polyhydramnios, placenta previa, abruptio placenta and hypertensive disorder in pregnancy. For the cases and controls, outcomes were collected for the overall study period regardless of when the cases of VWD and hemophilia first met the definition. All medical diagnoses were identified by ICD-10-CA codes from the DAD, while procedures were identified using the Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures (CCP) and the Canadian Classification of Interventions (CCI) codes from DAD. All diagnostic and procedure codes used in the study are listed in Supplementary Table 3.1 of the Appendices. In the validation study of CIHI DAD, the coding of selected variables: induction of labour, caesarean delivery, and blood transfusion demonstrated high performance (both sensitivity and specificity >85%) [20]. We did not include Ambulatory care database to identify outcome variables since no previous study validated perinatal information from this database.

Quality of care

As measurements of quality of care in pregnancies with inherited bleeding disorders, we calculated the proportion who underwent appropriate coagulation testing (VWF level for VWD and factor VIII level for Hemophilia A patients) in different trimesters and the proportion with coagulation factor levels ≥ 0.50 IU/ml among those tested during third trimester from 2012 to 2018 [23]. We used the period 2012-2018, due to consistent linkage of laboratory data from the year 2012. We further evaluated the maternal outcomes among pregnancies with coagulation factor levels ≥ 0.50 IU/ml during third trimester compared to 1:10 matched controls without bleeding disorders.

3.3.4 Statistical analyses

Descriptive summaries were used to report patient demographics. Continuous variables were reported as means and standard deviations (SD) or median and interquartile range (IQR); and categorical variables were reported as frequencies and percentages. Student's t test and Chi-squared test (or Fisher's exact test, as appropriate) were used to detect statistically significant differences in continuous and categorical variables, respectively. We estimated rates (per 100 deliveries) for overall PPH, different subtypes of PPH and severe PPH for each calendar year from 2010 to 2018. The temporal trends of PPH rate over yeas were evaluated by Mann Kendall test.

Univariate and multivariable logistic regression analyses were used to compute odds of maternal and neonatal outcomes among women with inherited bleeding disorders compared with those without. A variable with $p<0.20$ on univariate analysis was included in the multivariable model. To account for multiple pregnancies in the same woman during the study period, generalised estimating equations with an assumed unstructured correlation structure were used. Multiple imputation was used to impute missing data for sociodemographic variables. A 2-sided P-value of 0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 23 (IBM Corp. Released 2015 Armonk, NY) and Stata (Stata Statistical Software: Release 13; StataCorp LP, College Station, TX).

3.4 Results

3.4.1 Baseline characteristics of pregnancies from 2010-2018

Between 2010 to 2018, 311,330 women had a total of 454,400 pregnancies with live births (Table 3.1). Of all pregnancies, 93 (0.03%) women with inherited bleeding disorders had a total of 140 pregnancies. Of them, 80 women with 121 pregnancies had VWD, 11 women with 17 pregnancies had hemophilia A and 2 women with 2 pregnancies had hemophilia B. The mean age of the study cohort was 29.6 (±5.2) years. 81.3% of the pregnant women were less than 35 years of age. Primiparous women constituted 43.1% of all pregnancies. 61.5% women were born in North America or Europe and 29.7% were born in an Asian country. Our analysis did not find any significant difference for any of the sociodemographic characteristics measured between pregnancies in women with and without inherited bleeding disorders. Out of all pregnancies with inherited bleeding disorders, 60 (42.9%) were identified as "pregnancy with pre-existing diagnosis of bleeding disorder."

3.4.2 Rates and temporal trends of PPH rates over years

Between 2010 and 2018, there were a total of 47,244 events of PPH among 454,400 deliveries (10.4 per 100 deliveries, 95% CI 10.39-10.41) (Table 3.2). The rate of overall PPH did not vary significantly across years (p for trend=0.35) with a rate of 10.13/100 deliveries (95% CI 10.10-10.16) in 2010 and 10.72/100 deliveries (95% CI 10.69-10.75) in 2018 (Figure 3.1). Among

deliveries in women with inherited bleeding disorders, the overall PPH rate fluctuated from 12.50-33.33 per 100 deliveries over years (p for trend =0.08) (Figure 3.2).

Among subtypes, atonic PPH was the major constituents of PPH (39,759 of 47,244 events of PPH). The rate of atonic PPH changed from 8.47 per 100 deliveries (95% CI 8.45-8.50) in 2010 to 9.04 (95% CI 9.01-9.06) in 2018 (p for trend= 0.25) (Figure 3.3). The rate of PPH due to retained placenta remained stable around 1 per 100 deliveries: 0.97 (95% CI 9.66-9.83) in 2010 to 1.11 (95% CI 1.10-1.11) in 2018 (p for trend=0.92) (Figure 3.4). On the other hand, rate of secondary PPH decreased by 13.8%, from 0.80 per 100 deliveries (95% CI 0.79-0.80) in 2010 to 0.69 (95% CI 0.68-0.70) in 2018 (p for trend=0.02). PPH due to coagulation defect also decreased significantly by 45.5%, from 0.11 (95% CI 0.11-0.12) in 2010 to 0.06 (95% CI 0.06-0.07) in 2018 (p for trend =0.003).

Between 2010-2018, a total of 3229 cases of PPH with blood transfusion, 381 cases of PPH with hysterectomy and 922 cases of PPH with other procedures to control bleeding occurred. The rate of PPH with blood transfusion and hysterectomy showed nonsignificant increase during the study period (p for trend= 0.12 and p for trend= 0.75, respectively) (Figure 3.5). In contrast, we observed a significant increase (p for trend= 0.01) in PPH with other procedures to control bleeding by 66.7% from 0.15 (95% CI 0.14-0.15) in 2010 to 0.25 (95% CI 0.25-0.26) in 2018 accompanied by a significant increase in overall severe PPH (p for trend=0.005).

3.4.3 Maternal and neonatal outcomes of pregnancies with inherited bleeding disorders vs those without

PPH was observed in 20.7% pregnancies of women with inherited bleeding disorders compared to 10.2% pregnancies of women without bleeding disorders matched by age, parity, country of maternal birth, residence, and socioeconomic quintiles in 1:10 ratio (Table 3.3). After adjusting for established PPH risk factors, inherited bleeding disorders were associated with a significantly higher odds of PPH, with an adjusted odds ratio (aOR) of 2.3 (95% CI 1.5-3.6, p<0.001), and higher odds of severe PPH (aOR 4.7, 95% CI 1.7-12.7, p=0.003). Women with bleeding disorders had 2.1-fold increased risk of primary PPH, and 5.8-fold increased risk of secondary PPH. In addition, women with bleeding disorders also experienced higher odds of antepartum hemorrhage

(aOR 2.9, 95% CI 1.4-5.9, p=0.003) and red cell transfusions (OR 2.8, 95% CI 1.1-7.0, p=0.03). We observed a trend towards higher odds of hysterectomy (overall) in women with bleeding disorders (OR 2.9, 95% CI 0.8-10.1), albeit not statistically significant. No maternal death was observed. We observed markedly lower rates of instrumental delivery in women with bleeding disorders compared to controls (OR 0.4, 95% 0.2-0.9, p=0.04). There was no significant difference in other maternal outcomes that were measured in our analysis. Within the bleeding disorders cohort, the rate of PPH was lower in pregnancies of women with pre-existing diagnosis of bleeding disorder compared to those without (18.3% vs 22.5%), albeit not statistically significant (p=0.55). No significant difference was observed in the rates of preterm deliveries, low birth weight newborns, neonatal deaths, or intracranial hemorrhage between the groups (Table 3.4).

3.4.4 Quality of care among pregnancies with inherited bleeding disorders

Among 90 pregnancies in women with VWD during 2012-2018, VWF levels were checked in 50 (55.6%) and 45 (50.0%) pregnancies during anytime and third trimester respectively (Figure 3.6). The median VWF antigen level in third trimester was 0.78 IU/ml (IQR 0.42 IU/ml-1.00 IU/ml) and median VWF activity level in third trimester was 0.62 IU/ml (IQR 0.29 IU/ml-0.95 IU/ml). Among those tested for VWF during third trimester, 36 (80%) had a factor level of ≥ 0.50 IU/ml and 18 (40%) had a VWF level of ≥ 1.0 IU/ml. Of the 60 pregnancies with pre-existing diagnosis of bleeding disorder, only 40 (66.7%) had third trimester factor evaluation. Data on coagulation factor replacement during delivery was unavailable from administrative data. Of 17 pregnancies in women with hemophilia A during 2012-2018, factor VIII levels were checked in 8 (47.1%) pregnancies during anytime (all were performed in the third trimester) (Figure 3.7). The median factor VIII level in third trimester was 0.82 IU/ml (IQR 0.61 IU/ml-0.97 IU/ml). Among those tested for factor VIII during third trimester, 7 (87.5%) had a factor VIII level of ≥ 0.50 IU/ml and 1 (12.5%) had factor VIII level of ≥ 1.0 IU/ml.

3.4.5 Maternal outcomes of pregnancies with inherited bleeding disorders with third trimester coagulation factor levels ≥ 0.50 IU/ml

We then evaluated whether inherited bleeding disorders with third trimester VWF/FVIII levels ≥ 0.50 IU/ml were associated with higher risk of PPH compared to population controls. We matched

43 pregnancies with third trimester VWF/FVIII levels ≥ 0.50 IU/ml with 430 population controls without inherited bleeding disorder, by age, parity, socioeconomic quintiles, residence, and maternal country of birth. We observed a trend towards higher odds of PPH (OR 1.8, 95% CI 0.7-4.4) and antepartum hemorrhage in women with bleeding disorders (OR 2.1, 95% CI 0.6-7.5), although not statistically significant (Table 3.5). No severe PPH and hysterectomy occurred in the bleeding disorders cohort with third trimester levels ≥ 0.50 IU/ml. Given the small numbers, we did not examine PPH rates in pregnancies with third trimester VWF/FVIII levels ≥ 1.0 IU/ml.

3.5 Discussion:

In this large population-based cohort study, we have demonstrated that despite a rise in the rate of PPH between 2003-2010 in Alberta, there was no significant change in the rate of overall and primary PPH between 2010-2018. We also demonstrated a significant reduction in the rates of secondary PPH and PPH due to coagulation defects over this time period. Using a robust case definition based on ICD codes and laboratory criteria, we showed that inherited bleeding disorder remained an independent risk factor for adverse maternal outcomes, including PPH, antepartum hemorrhage and red cell transfusions, compared with matched population controls.

Our estimate of PPH rate (10.13 in the year 2010) is concordant with previous study where the reported rate of PPH per 100 deliveries is 9.8 during the period of 2009-2010 in the province of Alberta [4]. The changes in the trend of overall PPH rate are mostly driven by the changes in its major constituent atonic PPH; which is also reflected in our finding where the rate of atonic PPH remained stable during the study period whereas significant decreasing trends were observed in secondary PPH and PPH due to coagulation defect. PPH due to coagulation defect is a heterogenous code, which may capture women with disseminated intravascular coagulation, other acquired coagulopathies and women with inherited bleeding disorders. We do not have up to date data from other provinces to compare this observed decline. It is possible that improvement in obstetric management following initial rise in PPH across Canada has led to this decreasing trends. Our finding of nonsignificant temporal trend in overall PPH is in agreement with a recent population-based study assessing trend of severe maternal morbidity in Canada which included all hospital deliveries from 2003-2016 across Canada (excluding Quebec) [24]. This study identified a decline in severe hemorrhage (which includes both antepartum hemorrhage and PPH) in Canada

during the period 2012-2016. Absence of further increase in PPH rate in Alberta during 2010-2018 is encouraging; however further research is needed to identify underlying causes of the temporal and regional variations as they remain elusive [4,8].

We have demonstrated women with inherited bleeding disorders are at 2.3 times increased risk of PPH, and 2.9 times increased risk of antepartum hemorrhage compared to matched controls. The risk was mostly marked for severe PPH (aOR 4.7) and secondary PPH (aOR 5.8). The latter may be explained by a progressive decline of factor levels following delivery in patients with VWD and hemophilia A. We postulate that the true rate of secondary PPH may be even higher than our estimates using the DAD data, as most cases do not require hospitalizations and thus would not be captured. Equally alarming is that PPH rates remained high, regardless of whether women had pre-existing diagnosis of inherited bleeding disorders or were diagnosed after the pregnancy. PPH incidence among women with inherited bleeding disorders varies widely across studies due to difference in study design (retrospective cohort studies, population-based administrative data, interview and questionnaire), PPH definition (ICD based, objective measurement) and data source (administrative data vs medical records of patients followed by dedicated hemophilia treatment centres). Our finding is in agreement with a contemporary population-based study from Ontario, Canada which demonstrated 1.5 times higher incidence of PPH as well as higher incidence of antepartum hemorrhage among women with inherited bleeding disorders (identified using ICD codes alone) compared to those without during 2014-2019 [25]. However, the absolute incidence rates per 100 deliveries (7.29 in cases and 4.92 in controls) in that study are lower than our estimates. This can be explained by the lower baseline PPH rate in Ontario than that of Alberta (3.8 vs 9.8 per 100 deliveries during 2009-2010), as well as differences in case definitions of bleeding disorders [4]. Given the low PPV of identifying bleeding disorders using ICD codes alone, we elected to use a more stringent case definition to identify VWD and hemophilia from administrative data. This may have led to contamination, where some individuals with mild bleeding disorders may have been included in the population controls. A retrospective chart review of patients from two high risk pregnancy units in Toronto, Ontario (identified through medical records from 2009 to 2018 by using ICD codes) found an incidence of primary and secondary PPH of 5% and 6%, respectively, in women with VWD, nearly similar to rates for general population [26]. However, the study used a threshold of >1000 ml estimated blood loss within 24 hours (or

mention in medical record) for the definition of primary PPH. In addition, the median third trimester VWF antigen (1.38 IU/ml) and VWF activity (1.23 IU/ml) were much higher than our cohort. The lower rate of PPH in their study may result from their higher threshold but may also be indicative of better outcomes of this patient population in tertiary specialised centres compared to overall healthcare system. A large US population-based study using administrative data (for the period 2000-2003) reported 1.5 folds increased risk of PPH and 10 times higher risk of antepartum hemorrhage among pregnancies in VWD patients [10]. The reported rates of PPH tend to be higher and largely vary in studies that were based on retrospective survey or chart reviews on known patients with inherited bleeding disorders from hemophilia treatment centres, ranging from 31-59% in VWD and 10-22% in hemophilia in some studies [12,13,27,28]. On the other hand, population-based studies cover a wide range of patients including those from small and medium sized hospitals, and those with or without specialty follow-up, and reflect real world practice outcomes. We observed higher proportion of overall hysterectomy among cases, although not statistically significant. This finding confirms prior report and can be attributable to higher rate of menorrhagia in these patients [28,29]. Early identification and multidisciplinary management are essential to prevent hysterectomy and preserve fertility among these women. In contrast to previous studies, we did not find any significant differences in any of the neonatal outcomes, although it may be due to small number of adverse events [27,30,31].

Our study not only demonstrated a higher rate of maternal bleeding in inherited bleeding disorders, but also highlighted gaps in current practice. Existing guidelines recommend third trimester measurement of relevant factors (VWF, factor VIII) for women with inherited bleeding disorders in preparation of safe delivery [23,32]. In contrast to clinical practice guidelines, only 47-50% of women with hemophilia A and VWD underwent third trimester FVIII and VWF testing, respectively. Suboptimal third-trimester testing was observed even in the subgroup with pre-existing diagnosis of bleeding disorders. Potential explanations for low rates of third-trimester factor levels may include: patients not followed by hemophilia treatment centre, or history of adequate factor increment from prior pregnancies. Although the majority of the pregnancies in VWD patients that underwent third-trimester testing showed VWF levels ≥0.50 IU/ml, only 40% reached the level of ≥1.0 IU/ml. VWF and FVIII levels are expected to increase through normal physiological process during pregnancies with levels reaching > 0.50 IU/ml in the third trimester

and gradually return to baseline in 1-2 weeks postpartum period [30]. Ideally each woman should have a preconception diagnosis of her bleeding disorder and receive appropriate recommendation related to delivery. We have determined that a diagnosis of inherited bleeding disorder was unknown before conception in 57% of the bleeding disorders cohort. In a Dutch study, bleeding disorders remained underdiagnosed prior to pregnancy and manifested as severe PPH as the first symptom in 23% participants [11]. We observed higher rate of PPH among pregnancies in women without pre-existing diagnosis of bleeding disorders, although not significant. Delayed diagnosis leads to suboptimal haemostatic evaluation during pregnancy which eventually results in preventable major bleeding events. However, we were unable to determine the quality and intensity of factor replacement or other hemostatic therapy due to constraints of database.

We showed that, even with coagulation factor levels ≥ 0.50 IU/ml during third trimester, women with inherited bleeding disorders may bleed more during postpartum and antepartum period (ORs 1.8 and 2.1), although the difference was not statistically significant. This finding raises the concern about the optimal threshold of coagulation factor levels for safe delivery. In Canadian guideline a factor level of ≥ 0.50 IU/ml is considered adequate to allow delivery in women with VWD [23]. Existing data demonstrate that PPH may still occur with third-trimester levels ≥ 0.50 IU/ml or those receiving factor replacement to normalize factor levels, as physiologic levels of VWF/ FVIII levels exceed 1.00 IU/ml at time of delivery in women without bleeding disorders [32, 34, 35]. This has led to recommendations to target higher factor levels to further reduce PPH risk [34]. In a recent (2018-2019) international survey (including participants from Canada) among healthcare providers, 80% respondents aimed for plasma VWF or FVIII level of 0.50 IU/ml and 19% aimed for a level of ≥ 1.00 IU/ml at delivery to prevent PPH, pointing towards the ongoing controversy around it [35]. A prospective study from USA with participants from obstetrics clinics showed VWD patients (with mean VWF antigen level 0.63 IU/ml and mean VWF activity level 0.34 IU/ml during third trimester) that were treated prior to delivery still had significantly higher postpartum blood loss compared to non VWD controls [36]. A Dutch study involving 154 women from hemophilia treatment centres reported higher incidence of PPH (OR 2.7, 95% CI 1.2–6.3) among women who were treated with factor replacement due to their low third trimester VWF levels (<0.50 IU/ml) [37]. They indicated perhaps these women did not reach the target level of 1.00 IU/ml and advocated for a higher target level of 1.50-2.00 IU/ml. Findings from our study as

evidenced by low proportion of pregnancies with third trimester factor level ≥ 1.0 IU/ml and increased bleeding tendency despite third trimester factor levels ≥ 0.50 IU/ml also add to the current uncertainty of optimal dose and duration of peripartum management of women with inherited bleeding disorders. However, in our analysis, women with third trimester factor levels ≥ 0.50 IU/ml did not experience any event of severe PPH which reinforces the importance and effectiveness of appropriate peripartum management to prevent PPH and/or severe PPH among them.

To our knowledge, this is the first population-based study in Canada describing hemostasis testing and obstetric outcomes in women with inherited bleeding disorders compared with matched population controls. Besides, this is the first study from Alberta evaluating multiple maternal and neonatal outcomes among this population. One of the strengths of our study is the large sample size spanning over 9 years which gives a good representation of the Alberta population. Moreover, no previous population-based study used validated algorithm to identify inherited bleeding disorders from administrative data. There are several limitations to this study. First, case identification using administrative data is subject to coding errors and misclassification. Second, the use of our stringent case definition comprising of ICD code and laboratory data may have missed cases of mild bleeding phenotype which did not have any healthcare encounter during the study period. Furthermore, our case definitions precluded the identification of symptomatic hemophilia carriers (with baseline FVIII/FIX levels >0.40 IU/ml), platelet function disorders, and rare factor deficiencies. Third, there was no practical way to distinguish different subtypes of VWD due to database constraint. Fourth, we were unable to examine the use of prophylactic factor replacement from administrative data.

3.6 Conclusion

In this large population-based study we have found that rate of PPH remained stable in Alberta between 2010 to 2018. Our study provides evidence that, women with inherited bleeding disorders are at increased risk of PPH and antepartum hemorrhage during pregnancy, although not for neonatal outcomes. Hemostasis workup during third trimester of pregnancy remains suboptimal in this population, even among those with pre-existing diagnosis of inherited bleeding disorders. Further study is required to identify factors associated with delayed diagnosis and inadequate

hemostasis workup to help ensure early identification and management of underlying bleeding disorders. We demonstrated a trend towards higher incidence of PPH among women with third trimester factor levels ≥ 0.50 IU/ml compared with population controls. Future prospective studies (PRIDES study NCT NL6770; VIP study NCT 04146376) are ongoing to identify the optimal hemostatic target during pregnancy and delivery.

Table 3.2: Baseline characteristics of pregnancies associated with hospitalized live births in Alberta from 2010-2018 (N=454,400)

Variable	Pregnancies in women with inherited bleeding disorders N (%)	Pregnancies in women without inherited bleeding disorders N (%)	P[a] value
Total	140	454,260	
Mean age in years (±SD [b])	29.6 (5.2)	29.7 (5.3)	0.82
Age groups (in years)			
<20	2 (1.4)	13845 (3.0)	0.82
20-24	19 (13.6)	62265 (13.7)	
25-34	93 (66.4)	293068 (64.5)	
≥35	26 (18.6)	85082 (18.7)	
Parity			0.39
Primiparous	55 (39.3)	195914 (43.1)	
Multiparous	85 (60.7)	258346 (56.9)	
Geographic region of maternal birth			0.29
Europe/North America	96 (68.6)	279607 (61.9)	
Asia	33 (23.6)	134890 (29.9)	
Africa	7 (5.0)	27857 (6.2)	
Central/South America	4 (2.9)	9449 (2.1)	
Residence			
Urban	105 (75.0)	355765 (78.7)	0.30
Rural	35 (25.0)	96038 (21.3)	
Socioeconomic quintiles [c]			
1	38 (27.1)	87357 (19.3)	0.08
2	22 (15.7)	85394 (18.9)	
3	28 (20.0)	86678 (19.2)	
4	30 (21.4)	89967 (19.9)	
5	22 (15.7)	102407 (22.7)	
Pregnancy characteristics			
Multiple gestation	3 (2.1)	8121 (1.8)	0.74
Uterine rupture	1 (0.7)	614 (0.1)	0.17
Prolonged labour	9 (6.4)	25964 (5.7)	0.72
Labour induction	46 (32.9)	137279 (30.2)	0.50
Chorioamnionitis	0 (0.0)	6037 (1.3)	0.27
Hypertensive disorder in pregnancy	3 (2.1)	27594 (6.1)	0.05
Cervical laceration	0 (0.0)	905 (0.2)	0.99
High vaginal laceration	1 (0.7)	1429 (0.3)	0.36
Polyhydramnios	5 (3.6)	3373 (0.7)	0.004
Premature rupture of membrane	13 (9.3)	72047 (15.9)	0.03

a: based on chi square test for categorical and student's t test for continuous variable; ; b: standard deviation; c: a: based on material deprivation index (5=most deprived, 1= least deprived)

Table 3.2: Number of different subtypes of postpartum hemorrhage (PPH) in Alberta from 2010-2018

Year	No of deliveries	All PPH	Atonic PPH	PPH due to retained placenta	PPH due to coagulation defect	Secondary PPH
2010	47,920	4856	4061	467	55	384
2011	48,187	4869	4009	541	48	353
2012	49,617	5047	4178	557	48	341
2013	50,164	5039	4190	577	52	334
2014	52,544	5235	4352	563	39	352
2015	53,646	5803	4954	556	38	351
2016	52,524	5661	4892	533	30	318
2017	50,558	5456	4673	552	27	286
2018	49,240	5278	4450	544	31	341
Total N (%)^	454,400	47,244 (10.4)	39,759 (8.7)	4890 (1.1)	368 (0.08)	3060 (0.67)

^ per 100 deliveries

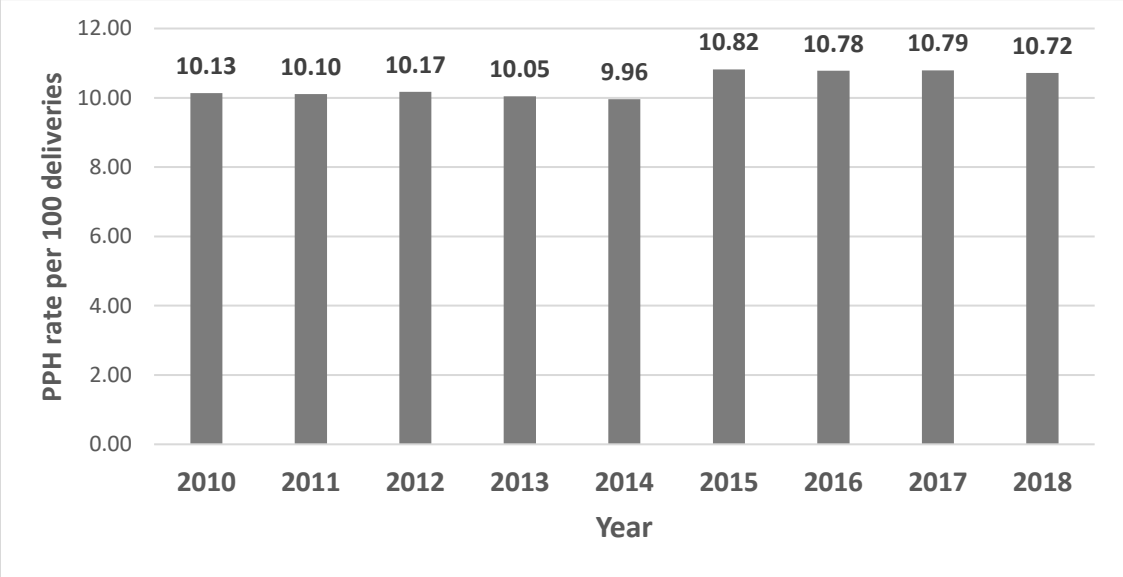

Figure 3.1: Trend of overall postpartum hemorrhage (PPH) rate per 100 deliveries from 2010-2018

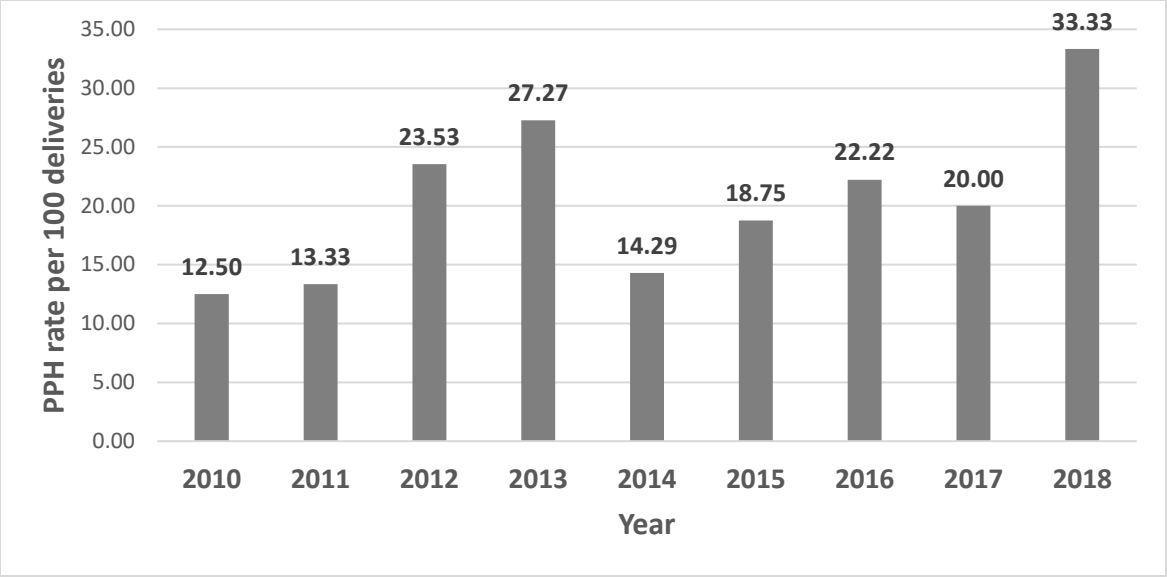

Figure 3.2: Trend of overall postpartum hemorrhage (PPH) rate per 100 deliveries in women with inherited bleeding disorders from 2010-2018

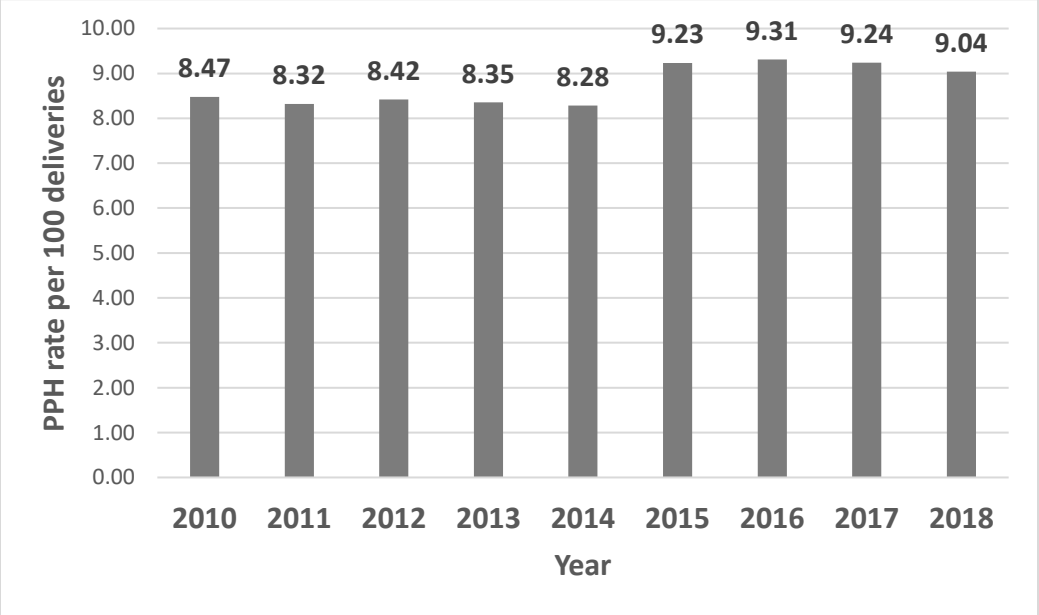

Figure 3.3: Trend of atonic postpartum hemorrhage (PPH) rate per 100 deliveries from 2010-2018

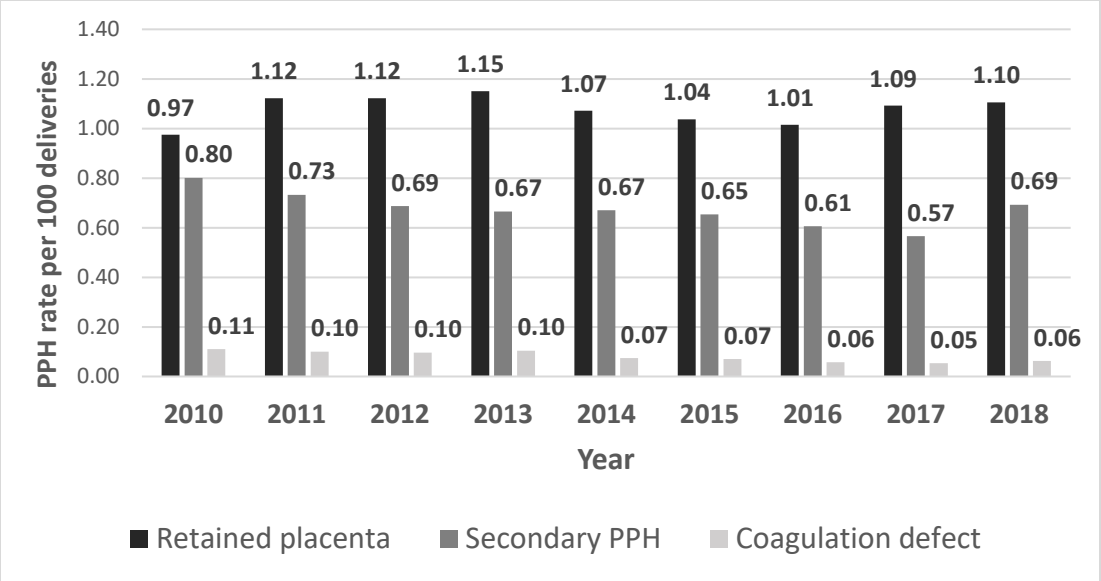

Figure 3.4: Trends of postpartum hemorrhage (PPH) rates due to retained placenta, coagulation defect and secondary PPH rate per 100 deliveries from 2010-2018

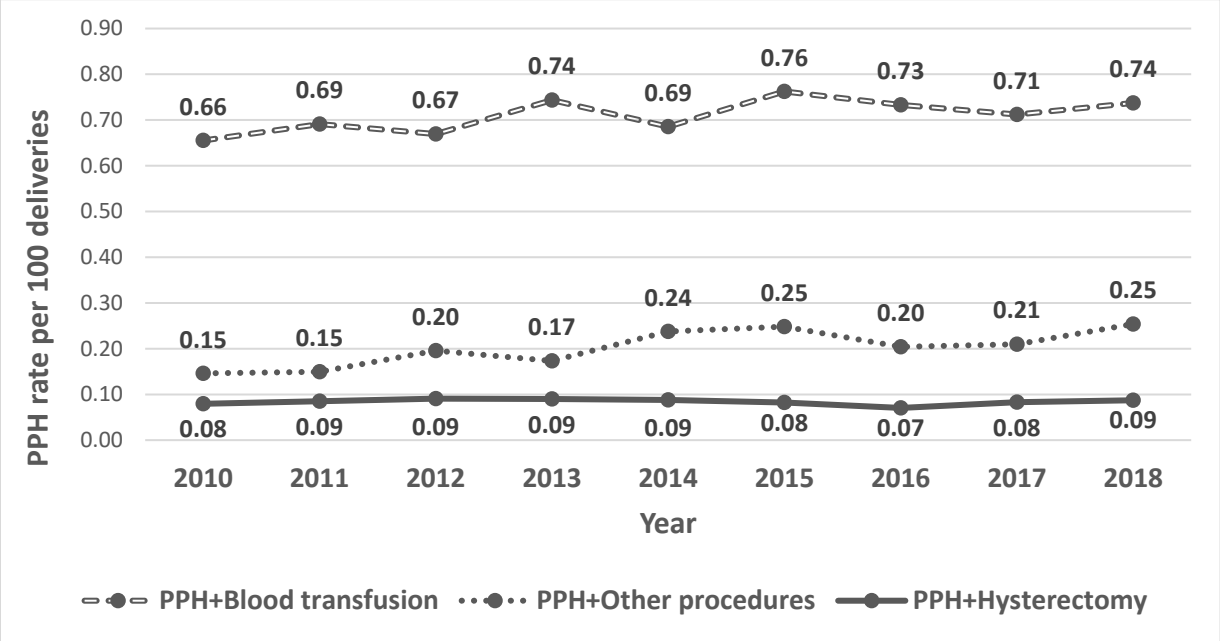

Figure 3.5: Trends of postpartum hemorrhage (PPH)+ Blood transfusion, PPH+ Other procedures , PPH+ Hysterectomy rates per 100 deliveries from 2010-2018

Table 3.3: Maternal outcomes of pregnancies with inherited bleeding disorders vs without inherited bleeding disorders during 2010-2018

	Pregnancies in women with inherited bleeding disorders N (%)	Matched pregnancies in women without inherited bleeding disorders N(%)	OR [a] (95% CI [b])	P	Adjusted OR	P
Total	140	1400				
Postpartum hemorrhage (PPH)[c]	29 (20.7)	143 (10.2)	2.3 (1.5-3.6)	<0.001	2.3 (1.5-3.6)*	<0.001
Primary PPH	27 (19.3)	138 (9.9)	2.2 (1.4-3.4)	0.001	2.1 (1.3-3.4) *	0.002
Secondary PPH	4 (2.9)	9 (0.6)	4.5 (1.4-14.9)	0.013	5.8 (1.7-20.0) *	0.01
Severe PPH	7 (5.0)	15 (1.1)	4.9 (1.9-12.1)	0.001	4.7 (1.7-12.7)*	0.003
Antepartum hemorrhage	8 (5.7)	17 (1.2)	2.9 (1.5-5.9)	0.002	2.9 (1.4-5.9)**	0.003
Mode of delivery						
Caesarean	41 (29.3)	414 (29.6)	0.9 (0.7-1.4)	0.94		
Vaginal	99 (70.7)	986 (70.4)	1.0 (0.7-1.5)	0.94		
Hysterectomy (in the year of childbirth)^	1 (1.1)	5 (0.4)	2.0 (0.2-17.3)	0.53		
Hysterectomy (overall)^	3 (3.2)	16 (1.1)	2.9 (0.8-10.1)	0.10		
Obstetric hematoma	1 (0.7)	1 (0.1)	10.1 (0.6-161.8)	0.10		
Instrumental delivery	6 (4.3)	139 (9.9)	0.41 (0.18-0.94)	0.04		
Red cell transfusion	6 (4.3)	22 (1.6)	2.8 (1.1-7.0)	0.03		
Maternal death	0 (0.0)	0 (0.0)	N/A			

*a: odds ratio; b: confidence interval; c: a pregnancy with both primary and secondary PPH was counted once; ^ no of women (93 cases and 1398 controls) was used as denominator; *adjusted for multiple gestation, cervical and high vaginal laceration, instrumental delivery, mode of delivery, uterine rupture, prolonged labour, labour induction, chorioamnionitis, polyhydramnios, placenta previa, abruptio placenta and hypertensive disorder in pregnancy*

***adjusted for multiple gestation, cervical and high vaginal laceration, history of caesarean section, polyhydramnios, premature rupture of membrane, history of uterine rupture and hypertensive disorder in pregnancy*

Table 3.4: Neonatal outcomes of pregnancies with inherited bleeding disorders vs without inherited bleeding disorders during 2010-2018

	Pregnancies in women with inherited bleeding disorders N (%)	Matched pregnancies in women without inherited bleeding disorders N(%)	OR [a] (95% CI [b])	P
Total	140	1400		
Gestational age (in weeks)				
<37	11 (7.9)	113 (8.1)	0.9 (0.5-1.9)	0.93
37-42 (reference)	129 (92.1)	1287 (91.9)	1.0	
>42	0 (0.0)	0 (0.0)	N/A	
Birth weight (in grams)				
<2500	6 (4.3)	82 (5.9)	0.7 (0.3-1.7)	0.43
2500-3999 (reference)	121 (86.4)	1174 (84.4)	1.0	
≥4000	13 (9.3)	135 (9.7)	0.9 (0.5-1.7)	0.82
Neonatal death	1 (0.7)	7 (0.5)	1.4 (0.2-11.7)	0.74
ICH [c] (in neonatal period)	0 (0.0)	7 (0.5)	0.7 (0.04-11.8)	0.78

a:odds ratio; b: confidence interval; c: intracranial hemorrhage

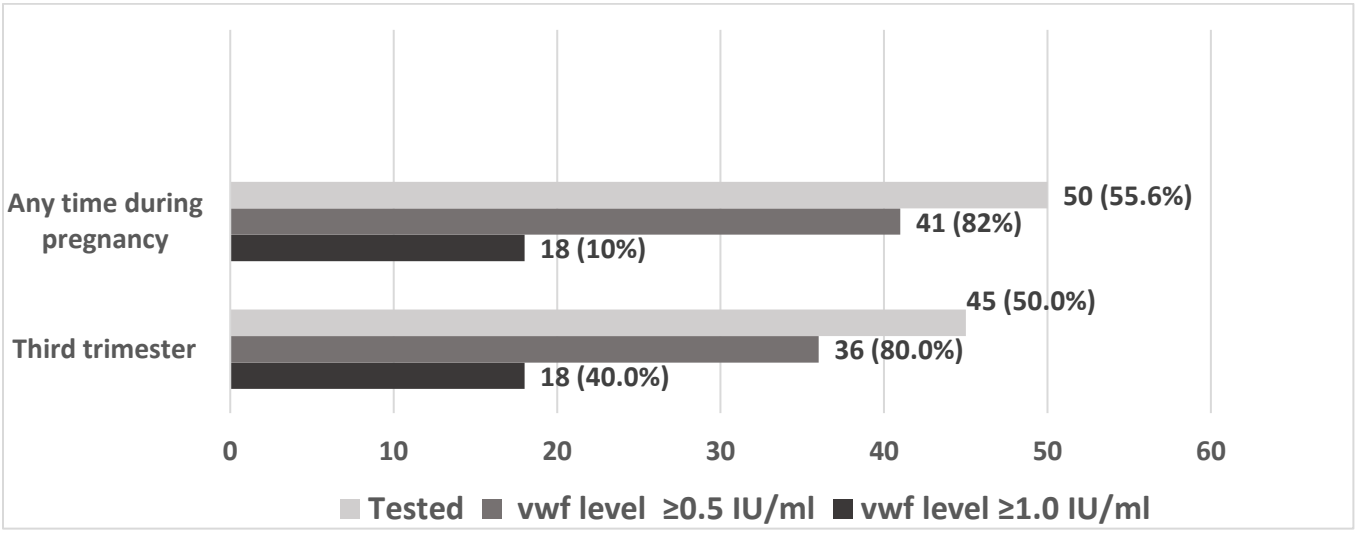

Figure 3.6: Proportion of von Willebrand factor (VWF) (VWF antigen and/or activity) testing among pregnancies with von Willebrand disease during 2012-2018 (No. of total pregnancies=90)

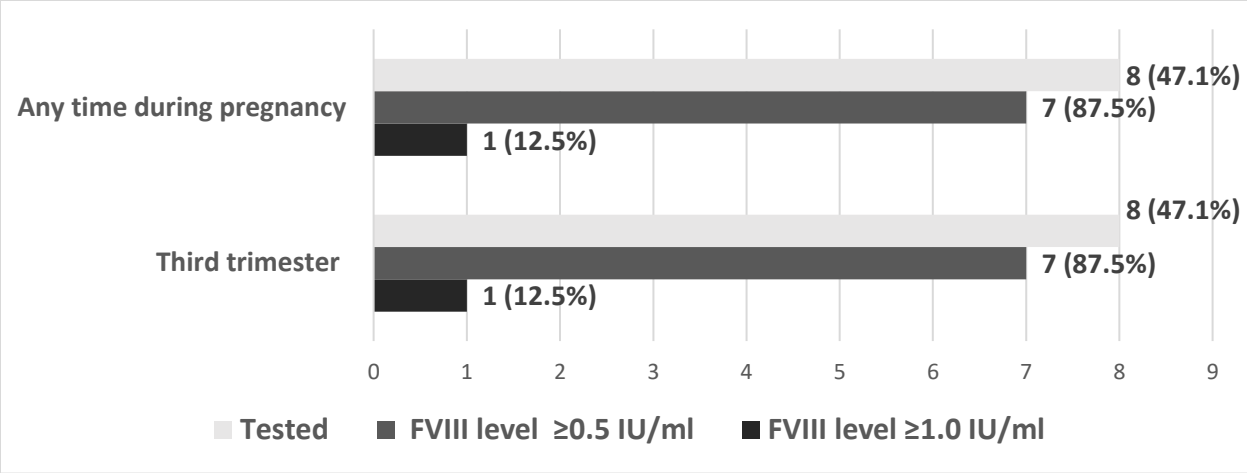

Figure 3.7: Proportion of factor VIII testing frequency among pregnancies with Hemophilia A during 2012-2018 (No. of pregnancies=17)

Table 3.5: Maternal outcomes of pregnancies with inherited bleeding disorders with third trimester coagulation factor levels ≥0.50 IU/ml vs pregnancies without inherited bleeding disorders during 2012-2018

	Pregnancies in women with inherited bleeding disorders N (%)	Matched pregnancies in women without inherited bleeding disorders N(%)	OR [a] (95% CI [b])	P
Total	43	430		
Postpartum hemorrhage (PPH)[c]	7 (16.3)	41 (9.5)	1.8 (0.7-4.4)	0.17
Primary PPH	7 (16.3)	38 (8.8)	2.0 (0.8-4.8)	0.12
Secondary PPH	1 (2.3)	4 (0.9)	2.5 (0.3-23.2)	0.41
Severe PPH	0 (0.0)	2 (0.5)	0.3 (0.01-7.8)	0.47
Antepartum hemorrhage	3 (7.0)	15 (3.5)	2.1 (0.6-7.5)	0.26
Mode of delivery				
Caesarean	11 (25.6)	143 (33.3)	0.7 (0.3-1.4)	0.31
Vaginal	32 (74.4)	287 (66.7)	1.5 (0.7-2.9)	0.31
Hysterectomy (in the year of childbirth)[^^]	0 (0.0)	2 (0.5)	0.3 (0.01-7.8)	0.47
Hysterectomy (overall)[^^]	0 (0.0)	7 (1.6)	0.8 (0.04-14.0)	0.85
Obstetric hematoma	0 (0.0)	1 (0.2)	0.3 (0.01-7.8)	0.47
Instrumental delivery	1 (2.3)	44 (10.2)	0.21 (0.03-1.6)	0.13
Red cell transfusion	1 (2.3)	7 (1.6)	1.4 (0.2-11.9)	0.74
Maternal death	0 (0)	0 (0)	N/A	

a: odds ratio; b: confidence interval; c: a pregnancy with both primary and secondary PPH was counted once; ^^no of women (38 cases and 430 controls) was used as denominator

3.7 References

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CHAPTER 4

Iron deficiency is under-investigated and highly prevalent in pregnancy and associated with adverse pregnancy outcomes

4.1 Abstract

Background: Iron deficiency anemia (IDA) is highly prevalent among pregnant women worldwide and women with inherited bleeding disorders are at increased risk of iron deficiency (ID) and IDA during pregnancy. **Aim**: 1) To describe the frequency of ID and IDA in pregnancy with or without inherited bleeding disorders, 2) to assess the quality of care in the identification and correction of IDA in pregnancy and 3) to examine the impact of first- and third-trimester IDA on adverse pregnancy outcomes. **Methods**: This is a retrospective population-based cohort study using the Alberta Pregnancy Birth Cohort. We included all hospitalized pregnancies associated with live births between January 1, 2014 and December 31, 2017. Anemia was defined as hemoglobin <110 g/l in the first and third trimesters and <105 g/l in the second trimester. ID was defined as ferritin <30 mcg/l in any trimester. IDA was defined as at least one record of concurrent anemia and low ferritin within the same trimester. Corrected IDA was defined as normalized hemoglobin (≥ 110 g/l) and ferritin (≥ 30 mcg/l) in third trimester. Inherited bleeding disorders were identified by validated algorithms. Logistic regression was used to identify risk factors of IDA and assess the association between first- and third-trimester IDA and pregnancy outcomes. **Results**: Among the 207,355 pregnancies with available hemoglobin results, 36,500 (17.6%) had anemia at least once during pregnancy. Only 1 in 3 pregnancies with anemia had a concurrent ferritin test and over 80% of them demonstrated ID. Ferritin screening occurred at least once in only 59.6% of our overall cohort and in 79.3% of the bleeding disorders cohort. Rate of ID was significantly higher in the bleeding disorders cohort (76.1% vs 60.8%, OR 2.1, 95% CI 1.02-4.5). Young maternal age, multiparity, lower socioeconomic status, presence of bleeding disorders and mothers from African and Asian countries were identified as significant predictors of IDA. First trimester and third trimester IDA were associated with increased risk of adverse neonatal and maternal outcomes, respectively. Among tested, only 43 (8.2%) from first trimester and 96 (8.5%) from third trimester IDA were corrected in third trimester. **Conclusion**: Screening and correction of ID and IDA remained suboptimal among pregnant women, despite their high prevalence.

Revised guidelines on ID screening in pregnancy may promote better IDA identification and management as well as optimize pregnancy outcomes.

4.2 Introduction

Anemia in pregnancy remains an important public health concern in both developed and developing countries. Globally, the estimated prevalence of anemia in pregnancy is 36% with high variability across regions, ranging from 15% in Europe and North America to 48% in South Asia, and 52% in West and central Africa [1]. The risk of anemia increases during pregnancy due to increased iron demand for maternal red blood cell (RBC) mass expansion and for fetal development. Recent evidence suggests 37% of anemia in women with reproductive age is due to iron deficiency (ID) [2]. Anemia during pregnancy is associated with a number of adverse neonatal and maternal outcomes including preterm birth, low birth weight, stillbirth, small for gestational age, caesarean delivery, postpartum hemorrhage (PPH), RBC transfusion and long-term effects on mental and psychomotor development in the children [3–6]. Women with inherited bleeding disorders are at increased risk of anemia during pregnancy due to pre-pregnancy iron deficit resulting from high menstrual bleeding as well as other blood loss during pregnancy, i.e., antepartum hemorrhage [7,8]. A large proportion (32-100%) of women with von Willebrand disease (VWD) suffers from menorrhagia [9]. Menorrhagia with consequent iron deficiency anemia (IDA) is often the first manifestation that prompts workup for an underlying bleeding disorder. Although IDA in pregnancy is simple to diagnose and treat, it often remains undiagnosed and untreated even in developed countries. A study from Ontario, Canada revealed that 40% of pregnant women never underwent screening for ID [10]. The existing Canadian guidelines recommend routine ID screening only in high-risk pregnancies [11]. We hypothesize that due to existing guidelines, rate of ID screening is low even in women with inherited bleeding disorders. To-date, no study in Canada has examined the rates of ID screening and correction in inherited bleeding disorders compared with the general population. Anemia in pregnancy has differential impact on maternal and neonatal outcomes in different trimesters (early or late trimester). Therefore, timing of detection and correction of IDA is crucial in preventing adverse pregnancy outcomes. There is still paucity of data regarding the impact of corrected IDA on pregnancy outcomes. The primary aim of this population-based study using administrative data was to determine the burden of ID and IDA among pregnant women in Alberta, Canada, stratified by the

presence of inherited bleeding disorders (VWD, Hemophilia). A further aim was to assess the quality of care pertaining to the identification and correction of ID and IDA in these women in different trimesters. Finally, we examined the association between first- and third-trimester IDA and adverse pregnancy outcomes and explored if the adverse outcomes could be avoided by correction of IDA.

4.3 Methods:

4.3.1 Study design and data source

We performed a population-based retrospective cohort study by linking de-identified administrative health databases in the province of Alberta, Canada. The data source is the Alberta Pregnancy Birth Cohort which has been described previously in other studies [12,13]. Alberta is a province in western Canada with an estimated population about 4.4 million in 2021 [14]. Due to the publicly funded healthcare system, healthcare encounters by all residents of Alberta are recorded in the provincial administrative database systems. The Alberta Pregnancy Birth Cohort contains maternal and newborn data from all hospital-based live births between January 1, 2002, and March 31, 2019, in the province of Alberta. It is comprised of the following databases: Discharge Abstract Database (DAD), Ambulatory Care Database, Practitioner Payments Databases, Alberta Health Care Insurance Population registry, Stakeholder registry, Vital Statistics database, Laboratory database. The DAD includes all admissions to inpatient facilities with most responsible diagnosis, up to 25 other diagnoses or comorbidities, and up to 20 procedures in International Classification of Diseases, Tenth Revision, Canada (ICD-10-CA) codes. The Ambulatory Care Database tracks all visits to hospital-based physicians' offices and the emergency department and contains up to 10 diagnostic conditions and 10 procedures using ICD-10-CA codes. Vital Statistics birth registry contains characteristics of all live births including year of birth, birth order, location of birth, birthweight, gestational ages at birth, parity, maternal age, and unique identifiers for both mothers and newborns. Vital Statistics death registry provides mortality data. Laboratory database includes test names, dates and results, patient age and ordering provider speciality. Population registry file includes address dissemination areas which are the smallest standard geographic areas for which all census data are disseminated and have corresponding Pampalon deprivation index [15]. Stakeholder registry file records country of previous residence

of the mothers. The University of Alberta Health Research Ethics Board approved this study (Pro00110665).

4.3.2 Study population

The study population consisted of hospital deliveries with live births in Alberta as documented by Vital statistics birth registry. Based on the availability of consistent laboratory data and to capture the rate of anemia or ID from first trimester until postpartum period , we restricted our study population for the livebirths that occurred between January 1, 2014 to December 31, 2017. Records of live births from Vital Statistics birth registry were linked with Laboratory database and DAD using the unique scrambled identifier. We estimated the date of conception based on date of delivery and gestational age at birth. To identify VWD cases, we used an algorithm comprised of ICD codes for VWD (ICD-9-CA 286.4 or ICD-10-CA D68) and at least one von Willebrand factor (VWF) antigen or activity <0.50 IU/ml which has previously been validated with 98.9% sensitivity and 92.6% specificity for women. Hemophilia cases were identified by a previously established algorithm using a combination of ICD codes (ICD-9-CA 286.0 or ICD-10-CA D66 for hemophilia A, ICD-9-CA 286.1 or ICD-10-CA D67 for hemophilia B) and at least one coagulation factor VIII or factor IX activity <0.40 IU/ml (with 62.5% sensitivity and 99.5% specificity for identifying women with hemophilia A, and with 85.7% sensitivity and 99.6% specificity for identifying women with hemophilia B) [16]. We extracted ICD codes for VWD and hemophilia from Ambulatory care database and DAD that were available from 2002 to 2018. The laboratory data for VWF, factor VIII and factor IX were available from June 2012. The Pampalon material deprivation index, derived from census data, was used as a surrogate of socioeconomic status [17]. It is reported in quintiles, with the first quintile being least deprived, and fifth quintile being most deprived. We defined rural or urban status based on the second digit of the patient's home address postal code [18]. Mother's previous country of residence was used to identify geographic region of maternal birth and classified as Europe and North America, Central and South America, Asia, Africa.

4.3.3 Study outcomes

The primary outcomes were proportion of hemoglobin and ferritin tests during different trimesters and the prevalence of anemia, ID and IDA during pregnancy. Hemoglobin and ferritin tests ordered

for the study population were retrieved from laboratory database. Anemia was defined according to the latest guideline of World Health Organization (WHO) as hemoglobin concentration <110 g/l in first and third trimesters and <105g/l in second trimester [19]. ID was defined as serum ferritin level < 30mcg/l in any trimester [20]. IDA was defined as at least one record of concurrent anemia and low ferritin within the same trimester. Pregnancy with normal hemoglobin and normal ferritin level was defined as the comparator group "no IDA". The secondary outcomes included preterm birth, low birth weight, fetal distress, neonatal death, caesarean delivery, red cell transfusion, PPH, maternal death and late maternal death. Preterm birth was defined as gestational age <37 weeks at birth. A birth weight of <2500 grams was defined as low birth weight. PPH was defined by ICD-10-CA codes (O72.0 to O72.3) which identify PPH as a blood loss of ≥500 mL following vaginal delivery or ≥1000 mL following Caesarean section, or as a diagnosis noted by a health care provider. Data on preterm birth and low birth weight were extracted from Vital Statistics birth registry. All other medical diagnoses were identified by ICD-10-CA codes from the DAD, while procedures were identified using the Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures (CCP) and the Canadian Classification of Interventions (CCI) codes from the DAD. In a validation study the diagnostic code accuracy of PPH, caesarean delivery, and blood transfusion of the Canadian Institute for Health Information (CIHI) DAD demonstrated high performance (both sensitivity and specificity >85%) [21]. All diagnostic and procedure codes used in the study are listed in Supplementary Table 4.1 of the Appendices. Death of a mother within 42 days of delivery was defined as maternal death and death of mother more than 42 days but less than 365 days of delivery was defined as late maternal death [22]. Neonatal death was defined as death of newborn within 28 days of birth [23].

Quality of care

As measurements of quality of care in pregnancies with IDA, we calculated the proportion of first trimester and third trimester IDA who underwent repeat testing in third trimester for hemoglobin, ferritin, and both. Among tested, we further identified the proportion of pregnancies that had normal hemoglobin and ferritin level in third trimester. "Corrected IDA" was defined as normalized hemoglobin (≥ 110 g/l) and ferritin (≥ 30 mcg/l) in third trimester.

4.3.4 Statistical analyses

Descriptive summaries were used to report patient demographics. Continuous variables were reported as means and standard deviations (SD), and categorical variables were reported as frequencies and percentages. We estimated the prevalence of anemia, ID and IDA in pregnancy stratified by the presence of inherited bleeding disorders. In addition, we calculated the prevalence of anemia and ID per trimesters for the overall cohort. Univariate and multivariable logistic regression analyses were used to compute odds of pregnancy outcomes among pregnancies with "IDA" vs no "IDA" groups. Univariate logistic regression was used to compute odds of pregnancy outcomes among "corrected IDA" vs "no IDA" groups. In multivariable analyses, we adjusted for maternal age, parity, country of maternal birth, socioeconomic quintiles, and residence for all the outcome variables listed above. In addition, based on their established relevance to the outcome variables, risk factors from the following list were included for adjusted analyses: pregnancy induced hypertension, multiple pregnancy, placenta previa, abruptio placenta, prolonged labour, antepartum hemorrhage, inherited bleeding disorders, uterine rupture, caesarean section, and hysterectomy. A variable with $p<0.20$ on univariate analysis was included in the multivariable model. To account for multiple pregnancies in the same woman during the study period, generalised estimating equations with an assumed unstructured correlation matrix were used. Multiple imputation was used to impute missing data for sociodemographic variables. A 2-sided P-value of 0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 23 (IBM Corp. Released 2015 Armonk, NY) and SAS Institute Inc. 2013. SAS® 9.4 (Cary, NC: SAS Institute Inc).

4.4 Results:

4.4.1 Frequency of hemoglobin and ferritin testing and prevalence of anemia, ID and IDA

Between January 1, 2014 to December 31, 2017, 177,848 women had a total of 209,661 pregnancies with live births (Figure 4.1). Of them, 50 women with inherited bleeding disorders had a total of 58 pregnancies. Of all pregnancies, 207,355 (98.9%) had hemoglobin checked anytime during pregnancy. 14 (24.1%) pregnancies in women with bleeding disorders developed anemia, compared to 36,486 (17.6%) pregnancies in women without bleeding disorders (Odds Ratio [OR] 1.5, 95% CI 0.75-2.8). Only 12,803 (35.1%) pregnancies with anemia had a concurrent

ferritin test. Of these, 10,662 (83.3%) demonstrated ID. Ferritin screening occurred for at least once in 46 (79.3%) and 124,884 (59.6%) pregnancies in women with and without bleeding disorders, respectively (Figure 4.1). Of them, 35 (76.1%) and 75,395 (60.8%) showed ID, respectively (OR 2.1, 95% CI 1.02-4.5). Frequencies of hemoglobin and ferritin test by trimesters in all pregnancies are shown in Figure 4.2 and Figure 4.3. Proportion of hemoglobin test and corresponding prevalence of anemia were more frequent in third trimester than other two trimesters (Figure 4.2). The prevalence of ID rose steadily across the three trimesters, reaching a peak of 82.3% in third trimester. However, the rates of ferritin testing were markedly lower in the second and third trimester (24.1% and 21.2%, respectively) compared with first trimester (41.6%) (Figure 4.3).

4.4.2 Baseline characteristics of IDA vs no IDA

We identified 10,662 pregnancies with IDA and 42,880 pregnancies with no IDA (Table 4.1). 23.1% of the pregnant women were more than 35 years of age. Multiparous women comprised of 52.7% of all pregnancies. Compared to women without IDA, those with IDA were significantly younger (OR 0.9 for age >35, 95% CI 0.8-0.9), more likely to be multiparous (OR 1.6, 95% CI 1.6-1.7), born from an Asian (OR 1.1 95% CI 1.1-1.2) or African country (OR 1.8, 95% CI 1.7-1.9), live in a rural area (OR 1.5, 95% CI 1.4-1.6), of low socioeconomic status (OR 2.2, 95% CI 2.1-2.4 in quintile 5 vs quintile 1), and have inherited bleeding disorders diagnosis (OR 3.5, 95% CI 1.3-9.7).

4.4.3 Pregnancy outcomes in first and third trimester IDA vs no IDA

Preterm birth was reported in 141 (11.1%) pregnancies with first trimester IDA with 1.3 times increased risk in this group compared to pregnancies with no IDA (adjusted OR [aOR] 1.3, 95% CI 1.1-1.6) (Table 4.2). IDA in first trimester was identified as a significant predictor of low birth weight (aOR 1.4, 95% CI 1.2-1.7). Pregnancies with first trimester IDA were more likely to receive red cell transfusion and undergoing Caesarean section than pregnancies with no IDA (aOR 4.4, 95% CI: 3.3-5.9 and aOR 1.4, 95% CI: 1.2-1.6, respectively).

On the other hand, IDA in third trimester was significantly associated with a lower risk of preterm birth (aOR 0.9, 95% CI 0.8-0.9) and low birth weight (aOR 0.7, 95% CI 0.6-0.8) and neonatal death (aOR 0.3, 95% CI 0.1-0.6) (Table 4.3). 13.8% pregnancies in third trimester IDA group developed PPH compared to 8.6% in no IDA group with aOR 1.8 (95% CI 1.7-1.9). Rates of red cell transfusion was also significantly higher in third trimester IDA vs no IDA with aOR 3.5 (95% CI 2.9-4.0). Women with third trimester IDA had 3-fold increased risk of late maternal death (aOR 3.1, 95% CI 1.1-8.9).

4.4.4 Repeat test and correction among first and third trimester IDA and pregnancy outcomes in corrected IDA

Among first trimester IDA, 93.3% and 41.1% were retested for hemoglobin and ferritin, respectively in third trimester (Figure 4.4). Of those with repeat test, only 56.9% and 14.3% had normal hemoglobin and ferritin levels, respectively. On the other hand, 58.3% and 16.7% IDA from third trimester had a repeat test during third trimester for hemoglobin and ferritin, respectively (Figure 4.5). Of them, 67.9% achieved normalization of hemoglobin, and 13.0% achieved normalization of ferritin. Among those tested for both hemoglobin and ferritin, 43 (8.2%) IDA from first trimester and 96 (8.5%) IDA from third trimester were corrected during third trimester.

No significant association was found between preterm birth, low birth weight and corrected first trimester IDA (Table 4.4). However, corrected first trimester IDA was still associated with higher risk of Caesarean delivery (OR: 2.0, 95% CI 1.1-3.6) and red cell transfusion (OR: 5.0, 95% CI 1.2-20.8). In contrast, except for red cell transfusion (OR 3.3, 95% CI 1.0-10.5), we did not observe any increased risk in any other outcomes measured in corrected third trimester IDA vs no IDA (Table 4.5). Corrected third trimester IDA showed a lower risk of late (>42 days from delivery) maternal death (OR 0.04, 95% CI 0.002-0.7).

4.5 Discussion

In this large population-based cohort study, we identified a substandard rate of screening and correction of IDA in pregnancy and demonstrated adverse pregnancy outcomes in uncorrected IDA. We have also shown that, despite existing literatures support a high prevalence of ID and

anemia in the bleeding disorders population, ferritin screening is still suboptimal in this high-risk population.

In our study, nearly 1 in 5 pregnancies developed anemia anytime during pregnancy. The prevalence of anemia in our cohort is higher than a recent retrospective cohort study from Ontario, Canada, which used data from outpatient private laboratories (Dynacare) between 2013-2018 and identified a prevalence of anemia (define as hemoglobin <105g/l anytime during pregnancy) of 8.3% in pregnant women [24]. Our prevalence of third-trimester anemia is comparable to population-based study from the province of British Columbia (utilizing perinatal data registry) which also demonstrated 17.3% third-trimester anemia among those with available hemoglobin values (defined as hemoglobin <110g/l) from 2004-2016 [6]. Another population-based study from Ontario looking at the similar time span (2014-2019) to ours identified anemia (defined by ICD code combined with hemoglobin test result) at delivery in only 1.8% women [8]. Higher rate of anemia in our study can be partly explained by differences in case definition or population (differences in ethnicities and comorbidities). Given the association between IDA and adverse maternal and neonatal outcomes, high prevalence of anemia is a significant concern demanding further investigation to identify underlying etiology, potential gaps in care as well as pre-pregnancy nutritional status of the Albertan population. While it is expected that every woman would receive a hemoglobin check at the first trimester, it happened in only 78% of our study cohort, indicating that 1 in every 5 patients received substandard care. We also demonstrated suboptimal screening for ID during pregnancy. Our finding is in agreement with the study from Ontario which found that only 59.4% of patients had their ferritin checked during pregnancy [24]. Using the same cut off (<30 mcg/l), this study identified 52.8% ID, congruent to our finding. The suboptimal ID screening in the contemporary Canadian studies may be a reflection of the existing Canadian guidelines which do not recommend universal ferritin test in pregnant women [11]. The American College of Obstetrics and Gynecologists also recommend routine assessment of hemoglobin, but not ferritin, during first trimester and 24 weeks gestation [25]. However, in Canada, optimization of ID screening and management has been prioritized in recent years. Contemporary Canadian studies as well as Obstetrics/gynecology practitioners have advocated for routine ferritin screening of all pregnancies [24,26–28]. Further studies with more up to date data

will help elucidate the burden of ID in pregnancy with an aim to harmonize obstetrical guidelines to recommend routine ferritin screening during pregnancy.

We demonstrated higher rates of anemia and ID in pregnant women with inherited bleeding disorders than those without. These findings contribute to the body of the evidence indicating that anemia remains a significant concern in pregnant women with inherited bleeding disorders [7,8]. Congruent to our findings, the population-based cohort study in Ontario looking at pregnancy outcomes reported higher rate of anemia on admission for delivery among women with bleeding disorders [8]. High burden of heavy menstrual bleeding and associated ID in women with inherited bleeding disorders put them at higher risk of developing ID/IDA during pregnancy [29]. We have shown that although screening rate is better than women without bleeding disorders (ferritin screening at least once: 79% vs 60%), it is still inadequate in women with bleeding disorders. In our study, even among those with known anemia during pregnancy, only 57% of pregnancies associated with bleeding disorders underwent ferritin screening. Some potential explanations to this finding are 1) we only reported ferritin testing within same trimester of anemia to define IDA, 2) not all bleeding disorders patients are followed by a bleeding disorders specialist, 3) some women had pre-pregnancy ID or IDA and may have received iron replacement without repeating ferritin. Targeted interventions in inherited bleeding disorders may include: screening for inherited bleeding disorders in women with heavy menstrual bleeding, treating heavy menstrual bleeding with tranexamic acid or hormonal therapy (prior to pregnancy planning), correcting ID before conception or in the first trimester, and ensuring monitoring of hemoglobin and ferritin throughout pregnancy. Early recognition and optimization of ID/anemia management throughout the continuum of care of these high-risk population is critical to alleviate the adverse impact of anemia during pregnancy and the postpartum period.

We have shown that women from lowest socioeconomic quintiles, rural areas and born in Asian and African countries are at higher risks of developing IDA, despite publicly funded universal healthcare system in Canada. Racial and socioeconomic disparity in the risk of developing ID has also been reported in US pregnant population [30]. Variation in ID prevalence based on mother's sociodemographic variables offer opportunities to identify gap in early and pre-pregnancy care and highlights the necessity of targeted intervention among these high-risk groups. Similar to our

findings, young maternal age has been identified as a predictor of maternal anemia in previous studies [31,32]. Pubertal growth and early menstruation lead to low iron stores in young mothers which improves with advancing age, less menstrual blood loss by contraceptive use, and iron supplementation.

In this study, the observed link between first trimester IDA and increased risk of preterm birth and low birth weight adds to the existing evidence of their association and confirms that maternal anemia plays an important role in relation to neonatal outcomes [33]. We have also showed that associations between maternal IDA and pregnancy outcomes vary by trimesters. Similar to our findings, different associations by trimesters have been observed in previous works where low hemoglobin concentration in first trimester was associated with higher risk of preterm birth and this association reversed in third trimester [34]. Altered feto-placental angiogenesis takes place during first trimester anemia which might be responsible for adverse fetal outcomes [35]. It is also plausible that, poor fetal outcomes may be associated with inadequate pre pregnancy dietary intake among mother with first trimester IDA [36]. We reported higher risk of PPH in women with third trimester IDA. Prior studies also recognized maternal anemia as a risk factor for PPH and postulated anemia reduces myometrial contractility leading to reduced oxygenation and eventually increases the risk of uterine atony [8,37,38].

Our study is novel in examining the impact of corrected IDA on pregnancy outcomes in a Canadian context. In our unadjusted logistic regression analysis, limited by small numbers of pregnancies with corrected IDA, we showed that correction of IDA may avoid downstream morbidities. This is concordant with the findings from the single centre-based study from China which involved 46,578 pregnant women [39]. A higher risk of fetal distress in the presence of first trimester anemia was eliminated by subsequent correction of this by later stage of pregnancy in that study. However, cautious interpretation is needed due to unadjusted confounding, small numbers, potential imbalances between the corrected IDA group and no IDA group, and lack of pathophysiological explanation. It is important to note that despite corrections, first-trimester and third-trimester IDA remained as significant predictors of red cell transfusions compared with pregnancies without IDA. These findings highlight the importance of timely identification and prompt management of ID, ideally pre-conception, to prevent the risk of negative fetal outcomes. Furthermore, we have

demonstrated events of PPH can be prevented by correcting IDA, which is of particular importance for women with inherited bleeding disorders who suffer from significant burden of PPH [8].

To our knowledge, this is the first population-based study in Canada describing the impact of IDA at different timepoints of pregnancy on maternal and fetal outcomes. In addition, no prior population-based study from Canada evaluated the quality of ID screening and the prevalence of ID and IDA among pregnant women with inherited bleeding disorders. There were a few limitations that may have affected the findings of our study. First, some of our pregnancy outcomes were identified by ICD code alone which is prone to misclassification bias resulting from coding error. Second, the use of our stringent case definition comprising of ICD code and laboratory data to detect VWD and hemophilia may have missed cases of mild bleeding phenotype which did not have any healthcare encounter during the study period. Third, our look back period for coagulation factor assays goes back to 2012 only which may have misclassified some women as not having inherited bleeding disorders. Fourth, we were limited in our ability to assess the adjusted association between corrected IDA and pregnancy outcomes due to the small number of events in corrected IDA group and this analysis is underpowered due to imbalance between groups. Fifth, the impact of concomitant treatment on the correction of IDA was not explored due to limitations of database. Finally, some of our results may not be generalizable to resource limited settings where the baseline nutrition status of the pregnant women may be different.

4.6 Conclusion:

In conclusion, we have demonstrated high prevalence of anemia and ID in pregnant women in Alberta. Despite this, screening, and correction of IDA remained suboptimal. Women with inherited bleeding disorders have higher rates of anemia and ID compared to general population. Racial and socioeconomic differences exist in the risk of developing IDA. All these findings provide actionable areas for interventions and underscores the necessity of updating existing guidelines to consider routine ferritin testing in pregnancy as well as more deliberate testing and management of the high-risk groups. Prevention and treatment of IDA might have the potential to improve pregnancy outcomes and therefore management of IDA pre-conception and during early pregnancy is crucial.

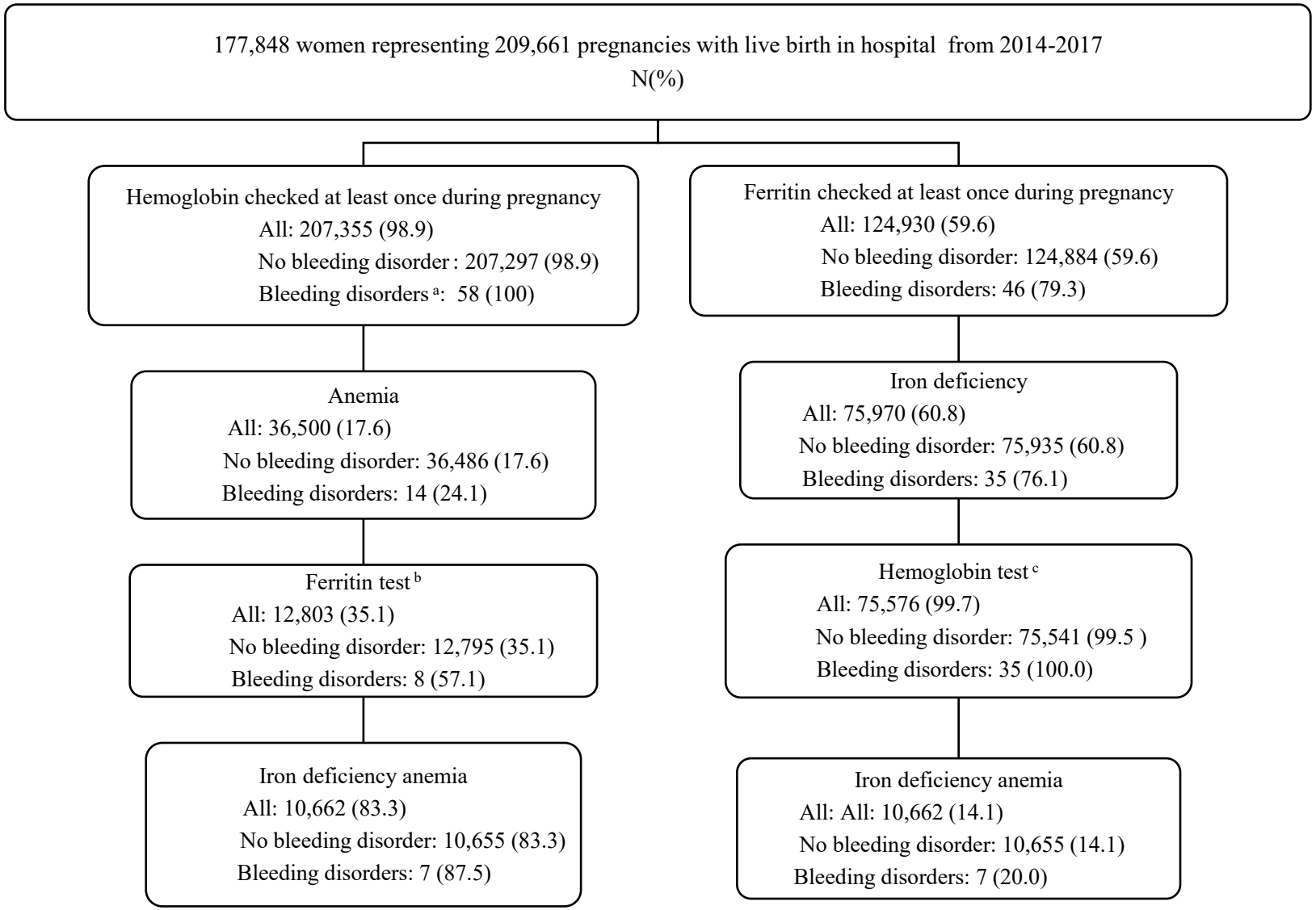

Figure 4.1: Frequency of hemoglobin and ferritin test and prevalence of iron deficiency anemia from 2014-2017

a: inherited bleeding disorders only; b: test done during the same trimester of anemia; c: test done during the same trimester of iron

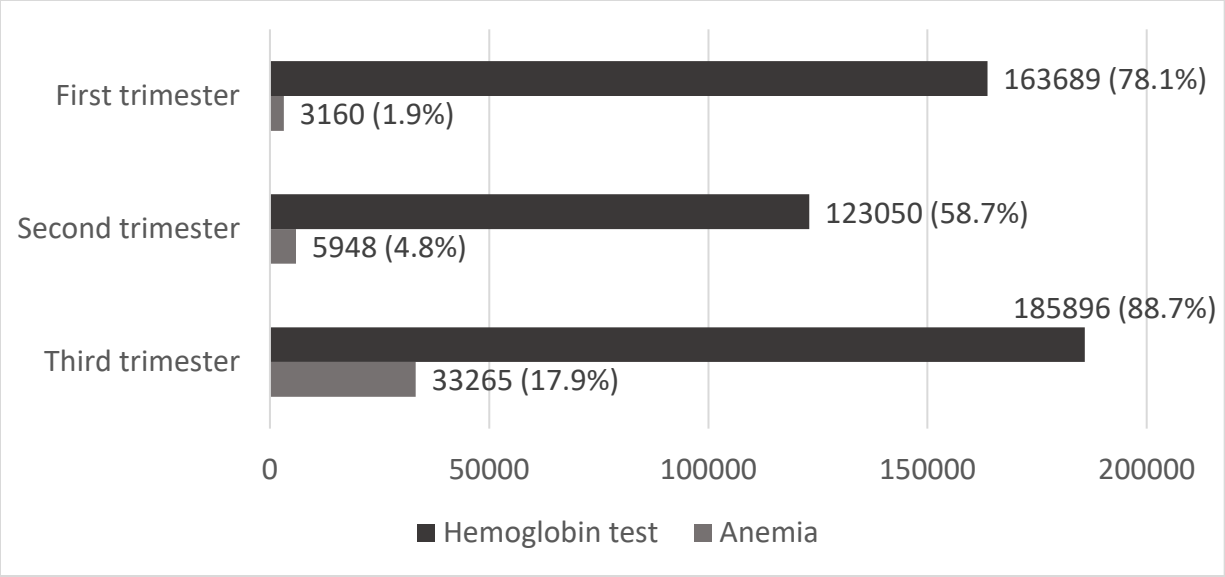

Figure 4.2: Frequency of hemoglobin test by different trimesters (n=209,661)

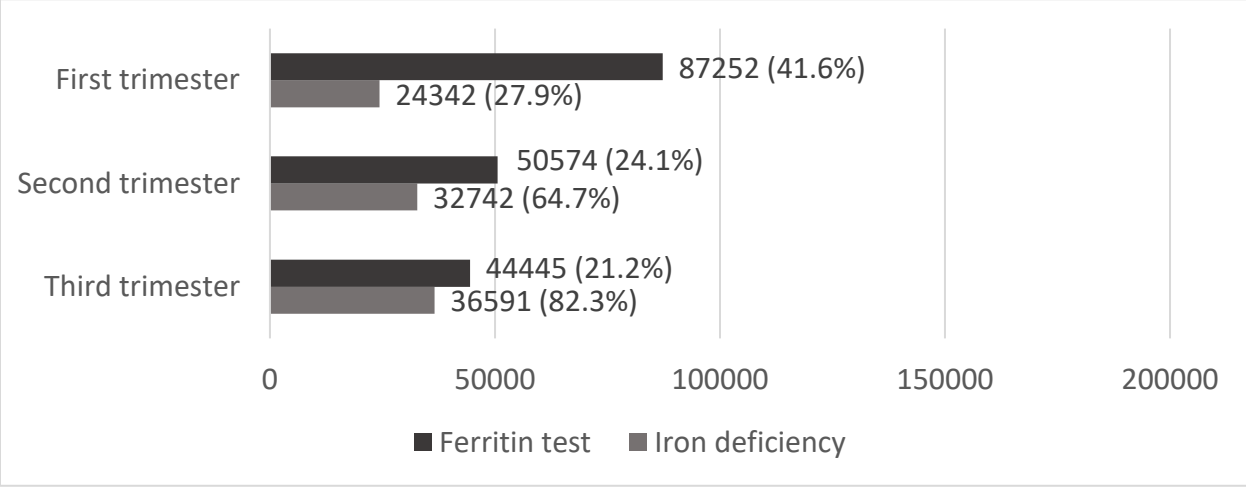

Figure 4.3: Frequency of ferritin test by different trimesters (n=209,661)

Table 4.1 :Baseline characteristics of iron deficiency anemia (IDA) vs no IDA

	IDA (N=10,662)	**No IDA (N=42,880)**	**Crude OR [a] (95% CI [b])**	**P value**
	n (%)	n (%)		
Maternal age (missing: n= 87)				
≤35 (reference)	8397 (78.9)	32824 (76.7)		
>35	2247 (21.1)	9987 (23.3)	0.9 (0.8-0.9)	<0.001
Parity				
Primiparous (reference)	4026 (37.8)	21284 (49.6)		
Multiparous	6636 (62.2)	21596 (50.4)	1.6 (1.6-1.7)	<0.001
Geographic region of maternal birth (missing: n= 25621)				
Europe & North America (reference)	2822 (46.7)	12323 (56.3)		
Asia	2337 (38.7)	7946 (36.3)	1.1 (1.1-1.2)	<0.001
Africa	810 (13.4)	1233 (5.6)	1.8 (1.7-1.9)	<0.001
Central & South America	76 (1.3)	374 (1.7)	0.9 (0.8-1.2)	0.94
Residence (missing: n= 1020)				
Urban (reference)	8436 (82.1)	36814 (87.1)		
Rural	1841 (17.9)	5431(12.9)	1.5 (1.4-1.6)	<0.001
Socioeconomic quintiles [c] (missing: n=1994)				
1 (reference)	1838 (17.9)	10244 (24.8)		
2	1573 (15.4)	8644 (20.9)	1.02 (0.9-1.1)	0.59
3	1801 (17.6)	7687 (18.6)	1.3 (1.2-1.4)	<0.001
4	1811 (17.7)	7148 (17.3)	1.4 (1.3-1.5)	<0.001
5	3221 (31.4)	7581 (18.4)	2.2 (2.1-2.4)	<0.001
Inherited bleeding disorders				
Absent (reference)	10655 (99.9)	42872 (99.9)		
Present	7 (0.1)	8 (0.02)	3.5 (1.3-9.7)	0.02

a: odds ratio, b: confidence interval; c: based on material deprivation index (5=most deprived, 1= least deprived).

Table 4.2: Pregnancy outcomes in first trimester IDA vs No IDA

	IDA N= 1276	No IDA N= 42880	OR [a]	P	aOR [b]	P
	n (%)	n (%)				
Preterm birth	141 (11.1)	3532 (8.2)	1.4 (1.2-1.7)	<0.001	1.3 (1.1-1.6)	0.01
Low birth weight	138 (10.8)	3211 (7.5)	1.5 (1.3-1.8)	<0.001	1.4 (1.2-1.7)	0.01
Fetal distress	430 (33.7)	15202 (35.5)	0.9 (0.8-1.0)	0.20	1.0 (0.9-1.1)	0.92
Neonatal death	3 (0.2)	135 (0.3)	0.7 (0.2-2.3)	0.62	0.5 (0.2-1.6)	0.26
Postpartum hemorrhage	121 (9.5)	3694 (8.6)	1.1 (0.9-1.3)	0.28	1.2 (0.9-1.4)	0.12
Caesarean delivery	420 (32.9)	11363 (26.5)	1.4 (1.2-1.5)	<0.001	1.4 (1.2-1.6)	<0.001
Red cell transfusion	57 (4.5)	413 (1.0)	4.8 (3.6-6.4)	<0.001	4.4 (3.3-5.9)	<0.001
Maternal death	0 (0.0)	1 (0.002)	0.1 (0.004-2.2)	0.14		
Late maternal death	0 (0.0)	8 (0.02)	0.5 (0.03-8.8)	0.64		

a: odds ratio; b: adjusted odds ratio (adjusted for significant sociodemographic variables and pregnancy characteristics from univariate analysis)

Table 4.3: Pregnancy outcomes in third trimester IDA vs No IDA

	IDA N= 8475	No IDA N= 42880	OR [a]	P	aOR [b]	P
	n (%)	n (%)				
Preterm birth	687 (8.1)	3532 (8.2)	0.9 (0.9-1.1)	0.72	0.9 (0.8-0.9)	0.03
Low birth weight	503 (5.9)	3211 (7.5)	0.8 (0.7-0.9)	<0.001	0.7 (0.6-0.8)	<0.001
Fetal distress	2914 (34.4)	15202 (35.5)	0.9 (0.9-1.0)	0.08	1.1 (0.9-1.1)	0.06
Neonatal death	7 (0.1)	135 (0.3)	0.3 (0.1-0.6)	0.001	0.3 (0.1-0.6)	0.002
Postpartum hemorrhage	1171 (13.8)	3694 (8.6)	1.7 (1.6-1.8)	<0.001	1.8 (1.7-1.9)	<0.001
Caesarean delivery	2206 (26.1)	11363 (26.5)	0.9 (0.9-1.0)	0.42	1.0 (0.9-1.1)	0.84
Red cell transfusion	344 (4.1)	413 (1.0)	4.4 (3.8-5.0)	<0.001	3.5 (2.9-4.0)	<0.001
Maternal death	1 (0.01)	1 (0.002)	5.1 (0.5-48.7)	0.16		
Late maternal death	6 (0.1)	8 (0.02)	3.8 (1.3-10.9)	0.01	3.1 (1.1-8.9)	0.04

a: odds ratio; b: adjusted odds ratio (adjusted for significant sociodemographic variables and pregnancy characteristics from univariate analysis)

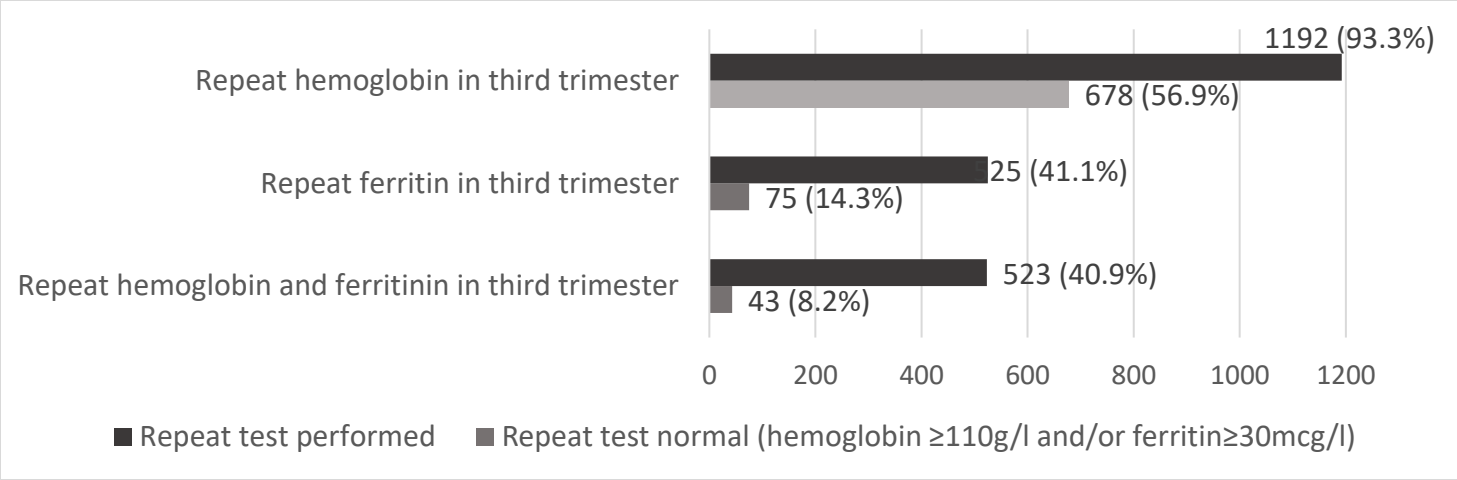

Figure 4.4: Repeat testing of hemoglobin and ferritin among first trimester IDA (n=1278)

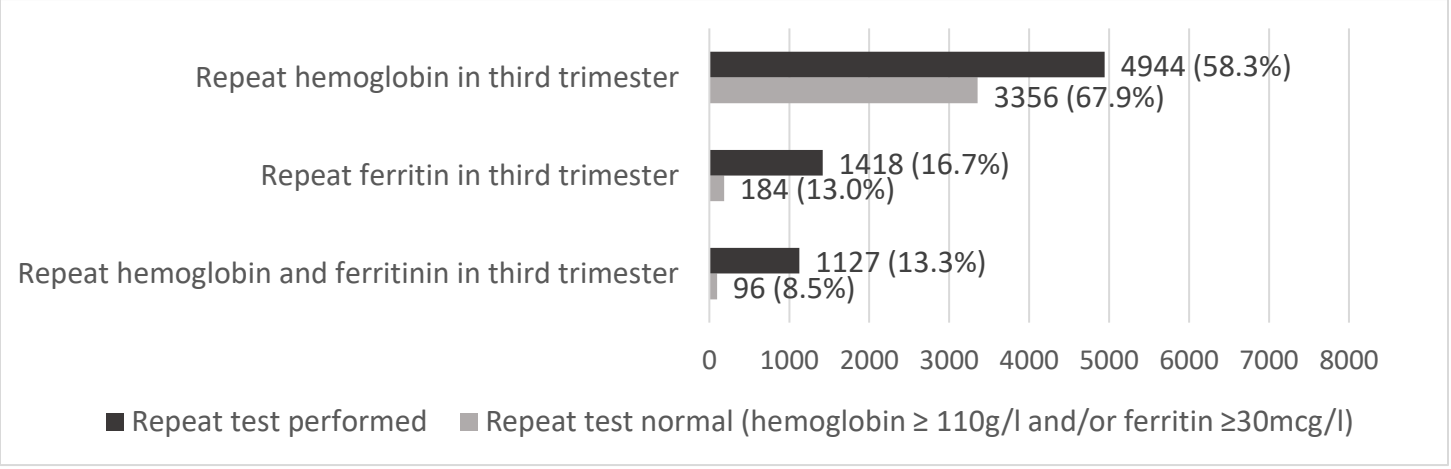

Figure 4.5: Repeat testing of hemoglobin and ferritin among third trimester IDA (n=8475)

Table 4.4: Pregnancy outcomes in corrected IDA from first trimester vs No IDA

	Corrected IDA N= 43	**No IDA N= 42880**	**OR [a]**	**P**
	n (%)	n (%)		
Preterm birth	3 (7.0)	3532 (8.2)	0.8 (0.3-2.7)	0.76
Low birth weight	3 (7.0)	3211 (7.5)	0.9 (0.3-2.9)	0.90
Fetal distress	14 (32.6)	15202 (35.5)	0.9 (0.5-1.7)	0.69
Neonatal death	0(0.0)	135 (0.3)	0.3 (0.02-4.7)	0.99
Postpartum hemorrhage	5 (11.6)	3694 (8.6)	1.4 (0.5-3.5)	0.48
Caesarean delivery	18 (41.9)	11363 (26.5)	2.0 (1.1-3.6)	0.03
Red cell transfusion	2 (4.7)	413 (1.0)	5.0 (1.2-20.8)	0.03
Maternal death	0 (0.0)	1 (0.002)	N/A	
Late maternal death	0 (0.0)	8 (0.02)	N/A	

a: odds ratio

Table 4.5: Pregnancy outcomes in corrected IDA from third trimester vs No IDA

	Corrected IDA N= 96	**No IDA N= 42880**	**OR [a]**	**P**
	n (%)	n (%)		
Preterm birth	8 (8.3)	3532 (8.2)	1.0 (0.5-2.1)	0.97
Low birth weight	6 (6.3)	3211 (7.5)	0.8 (0.4-1.9)	0.65
Fetal distress	41 (42.7)	15202 (35.5)	1.4 (0.9-2.1)	0.14
Neonatal death	0 (0.0)	135 (0.3)	0.6 (0.04-10.0)	0.99
Postpartum hemorrhage	10 (10.4)	3694 (8.6)	1.2 (0.6-2.4)	0.53
Caesarean delivery	32 (33.3)	11363 (26.5)	1.4 (0.9-2.1)	0.13
Red cell transfusion	3 (3.1)	413 (1.0)	3.3 (1.0-10.5)	0.04
Maternal death	0 (0.0)	1 (0.002)	N/A	
Late maternal death	0 (0.0)	8 (0.02)	0.04 (0.002-0.7)	0.03

a: odds ratio

4.7 References

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CHAPTER 5

Discussion and conclusion

5.1 Overview:

In this research, three different studies have been presented that focused on inherited bleeding disorders during pregnancy among the population of Alberta, Canada. The primary objectives were to examine contemporary trends in postpartum hemorrhage (PPH) , to assess the risk of adverse pregnancy outcomes in inherited bleeding disorders and iron deficiency anemia (IDA), to explore the quality of care in these subgroups in relation to their hematology workup and to validate case definitions to identify patients with inherited bleeding disorders from administrative database. The following discussion summarizes the results and implications of these studies and provides future research directions.

5.2 Findings and implications of the validation study (Chapter 2)

A case definition with high sensitivity, specificity, and predictive values is essential to accurately identify cases of inherited bleeding disorder from linked administrative database. Therefore, in the second chapter of this thesis, we validated the case definitions of hemophilia and von Willebrand disease (VWD) that would accurately identify these patients and minimize misclassification bias that could potentially render all subsequent analysis invalid. The case definitions with relevant ICD codes and low coagulation factor levels (factor VIII or factor IX or von Willebrand factor) showed high sensitivity, specificity, PPV and NPV for women with VWD and Hemophilia B along with moderate sensitivity, high specificity and NPV, but poor PPV for women with Hemophilia A. In contrast, we demonstrated that using ICD codes alone was associated with reduced specificity and PPV, especially for VWD. We were unable to identify an accurate case definition for identifying inherited platelet function disorders from administrative data and found frequent miscoding in those with ICD codes. Results of the validation study highlighted the importance of validation of case definitions prior to using administrative data in epidemiological studies. Applying these case definitions, we selected 93 women with inherited bleeding disorders with a total of 140 pregnancies from our study cohort for the period 2010-2018. Our case definitions are simple and can be easily applied in other provinces of Canada as well as other jurisdictions which will eventually contribute to health outcomes research in this population. Given the rarity of the

disease, utilization of administrative database is a powerful way to conduct population-based research among patients with inherited bleeding disorders and validation of case definition is the important first step in doing so.

5.3 Findings and implications of the study examining the impact of inherited bleeding disorders on maternal and neonatal outcomes (Chapter 3)

We have demonstrated that despite a rise in the rate of PPH between 2003-2010 in Alberta and across Canada, there was no significant change in the rate of overall PPH in Alberta between 2010-2018, which is a welcome development. However, the rate of severe PPH showed significant increase over the years. While the rates of severe PPH requiring blood transfusions or hysterectomy remained stable, the rate of severe PPH requiring other procedures to control bleeding increased significantly over time. It is plausible that there has been a shift in the mean maternal age towards older age groups over the years, giving rise to this observation. However, examining the predictors of PPH was beyond the scope of our study. In addition, the PPH rate in women with inherited bleeding disorders showed a nonsignificant increasing pattern. This is concerning and identify areas for further attention. Consistent with our findings, a population-based study from Ontario also reported nonsignificant increasing trend of PPH in the subgroup of women with bleeding disorders during 2014-2019 [1]. The incidence of PPH in Alberta is almost double the incidence in Ontario (~10.0/100 deliveries vs ~5.0/100 deliveries) during the contemporary era, which underscores the importance of examining local data [1]

In our study, women with bleeding disorders showed an increased risk of bleeding events (PPH and antepartum hemorrhage) and red cell transfusion during pregnancy but did not appear to be at increased risk of poor neonatal outcomes, although the analysis for neonatal outcomes may be under-powered. PPH and antepartum hemorrhage contribute to higher maternal morbidity, mortality and health services utilization. Higher rate of red cell transfusion leads to higher utilization of health care resources and increased risk of transfusion related complications. Therefore, identifying women at increased risk of adverse maternal outcomes is an important approach in reducing these consequences.

This study identifies areas of suboptimal care in women with bleeding disorders. First, we highlighted diagnostic delays in women with bleeding disorders, congruent with previous studies

[2,3]. In our analysis, out of all pregnancies with inherited bleeding disorders, only 42.9% had a known diagnosis (determined by ICD code) prior to conception, using a lookback period between 2002-2018. Second, one in every two pregnancies with hemophilia A or VWD did not have any coagulation factor testing during the third trimester, which is not in keeping with Canadian as well as international guidelines. Even among pregnancies with a pre-existing diagnosis of inherited bleeding disorders, only 66.7% had third trimester factor evaluation. Similar to our finding, a recent administrative database study from the USA reported that only one third of pregnant women with ICD codes of VWD received third trimester factor testing [4]. Third, while most patients who underwent third-trimester testing demonstrated an increment ≥0.50 IU/ml, only a minority achieved an increment ≥ 1.00 IU/ml. We observed a non-significant trend towards higher risk of PPH in pregnancies with third-trimester factor levels ≥ 0.50 IU/ml compared with the control population. This adds to the growing body of uncertainty about the peripartum target levels of coagulation factors in hemophilia A and VWD. A target level of ≥ 0.50 IU/ml may not be appropriate since the levels reach around 2.00-3.00 IU/ml in the normal population [5].

Our findings identified critical gaps in the early identification and peripartum management in women with bleeding disorders, and potential areas of quality improvement. First, given the high prevalence of heavy menstrual bleeding and iron-deficiency in bleeding disorders, raising awareness among women with bleeding symptoms is paramount, along with ongoing education of primary care providers and gynecologists. Early identification of inherited bleeding disorders, optimizing iron store pre-conception, and appropriate referral to a multidisciplinary bleeding disorders program may help prevent the first PPH event. Recently, initiatives such as Let's Talk Period! aimed to raise awareness among reproductive age women through an informational website, online self-administered Bleeding Assessment Tool (Self-BAT), and recommendations to seek medical attention for abnormal Self-BAT scores [6]. Second, we identified room for improvement in third-trimester coagulation factor testing. Due to the nature of our research using administrative data, we were unable to ascertain reasons for suboptimal third-trimester testing. We hypothesize this may reflect suboptimal rates of referrals to a bleeding disorders program, barriers to coagulation testing in remote areas, or practice patterns within the bleeding disorders program. Future program audits are required to identify gaps in care. Finally, our findings highlighted that higher factor levels may be needed to prevent PPH. Ongoing prospective studies (PRIDES study

NCT NL6770; VIP study NCT 04146376) will help discern the optimal hemostatic target during delivery.

5.4 Findings and implications of the study examining IDA in pregnancy (Chapter 4)

Our study found high prevalence of anemia (17.5%) and iron deficiency (60.8%) in pregnant women in Alberta. Despite this, only 35.1% pregnancies with anemia had concurrent ferritin test and 83.3% of them had IDA. There are ongoing controversies on the utility of routine iron deficiency (ID) screening in the general obstetric population. On one hand, the British guidelines and the Canada's Drug and Health Technology Agency (CADTH) recommended against routine testing on the basis of costs, interpretability of serum ferritin during pregnancy, and lack of cost-effectiveness data [7,8]. On the other hand, there are increasing proponents for routine ID screening in all pregnancies [9–12]. At the minimum, existing guidelines recommend that non-anemic women at risk of ID should be identified, and either started on iron supplementation empirically or undergo ferritin testing [8]. Among the inherited bleeding disorders subgroup, a population at high risk of ID, we showed that rates of serum ferritin testing, while higher than the control population, remained suboptimal (79.1% any time during pregnancy and only 57.1% among those with concurrent anemia). Furthermore, we showed a discordance between the timing of ID screening and prevalence of ID across the trimesters. The rate of ferritin testing was lowest during third trimester (21.2% vs 41.6% in first trimester), when the risk of developing ID is highest. This finding demands strategies to improve awareness among health care providers to optimize the rate and timing of ID screening in this high-risk group. Congruent with previous Canadian data, we demonstrated racial and social disparity in the risk of developing IDA and this data is vital to allocate resources accordingly to meet the demands of the high-risk population [13].

We report variable impact of IDA in different trimesters on pregnancy outcomes and suboptimal correction of anemia, ID and IDA during third trimester. Our finding suggests detection and correction of anemia from early trimester of pregnancy is crucial as it is associated with adverse neonatal outcomes. Third trimester IDA has shown to be associated with increased risk of PPH which holds significant concern for women with bleeding disorders. Correction of anemia/ID is critical and may avoid downstream morbidities. These observations indicate that there is room for improvement in the identification and repletion of IDA during pregnancy in the province of

Alberta to ensure better maternal and neonatal outcomes. Our findings of high prevalence of anemia in pregnancies, along with adverse impacts of IDA on neonatal outcomes, highlight the importance of routine ferritin screening in pregnancy, and call for modifications of existing clinical practice guidelines [10,14].

5.5 Strengths of the study

The Alberta pregnancy birth cohort database is a de-identified individual-level, longitudinal data, obtained from the administrative health databases for persons registered under the Alberta Health Care Insurance Plan (AHCIP). The AHCIP covers 99% of Albertan residents [15]. Thus, utilizing the Alberta Pregnancy birth cohort provides a true representation of the pregnant population in Alberta. Our study is the first validation study evaluating the diagnostic accuracy of identifying hemophilia and VWD using administrative data in Canada. The excellent diagnostic accuracy of the algorithms minimizes the misclassification bias. Utilization of administrative database allowed us to capture women outside of bleeding disorder clinics and reflect real-world practice patterns and outcomes on a population level. The retrospective cohort design with linked database provided an inexpensive and valid method to evaluate the study outcomes. Besides, some of the outcome variables have previously been validated [16]. This is the first Canadian population-based study to evaluate the rates of coagulation factor testing in women with bleeding disorders and correction of ID or IDA during pregnancy.

5.6 Limitations of the study

Like other observational studies, our study has limitations inherent to the design and data sources. First, case identification using administrative data is subject to coding errors and misclassification. Second, the use of our stringent case definition comprising of ICD code and laboratory data may have missed cases of mild bleeding phenotype which did not have any healthcare encounter during the study period. Third, we did not have consistent laboratory data prior to June 2012 and thus it is likely that some women with inherited bleeding disorder may have been misclassified. Fourth, our study was underpowered to detect the association of corrected IDA with pregnancy outcomes due to small number of events. Fifth, we ere unable to identify indigenous population since there

was no relevant information in the database. Finally, data regarding administration of coagulation factor replacement was not available in the databases.

5.7 Future research directions

This research should encourage further investigations into the realm of inherited bleeding disorders during pregnancy and beyond. First, it will be useful to explore the hematology workup among pregnant women with inherited bleeding disorders in other Canadian provinces. Second, future work should focus on identifying factors associated with underdiagnosis of bleeding disorders during pregnancy. Third, there is still knowledge gap regarding optimal peripartum management of women with bleeding disorders and further studies are required to inform practice guidelines [17,18]. Fourth, it would be valuable to assess the impact of isolated ID on maternal and neonatal outcomes. In addition, to examine the impact of corrected IDA on pregnancy outcomes, further analysis with adequate sample size is required. Fifth, applying our case definition and by harnessing administrative database, we can further assess the disease burden, mortality, and health care utilizations among persons with VWD.

5.8 Conclusion

We have demonstrated, coagulation factor and ferritin assessment are suboptimal among pregnant women with inherited bleeding disorders, despite their increased risk of obstetric bleeding, IDA, and transfusion requirements. Pregnancy is a critical period in the lives of women with inherited bleeding disorders and expedited work up will allow for prompt implementation of preventative and therapeutic strategies and decrease major bleeding events. Findings of this study identified actionable areas for interventions and will help health care providers to better understand the unperceived needs of optimal adherence to standard protocols in the diagnosis and management of these women.

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Appendices

Supplementary Table 3.1: Relevant ICD-10 diagnostic codes and Canadian Classification of Interventions (CCI) diagnosis/procedure codes.

Diagnosis/procedure code	ICD-10	CCI
Postpartum hemorrhage	0720- 0723	
Placenta previa	044	
Hypertensive disorders	010, 011, 013,014,015, 016	
Placental abruption	045	
Uterine rupture	0710, 0711	
Polyhydramnios	040	
Chorioamnionitis	0411	
High vaginal laceration	0714	
Laceration of cervix	0713	
Multiple gestation	O30801O30803O30809O30901 O30903O30909	
Prolonged labour	O63001O63003O63009O63101 O63103O63109	
Premature rupture of membranes	O42011O42013O42019O42021 O42023O42029O42091 O42093O42099O42111 O42113O42119O42121 O42123O42129O42191 O42193O42199O42203 O42209O42901O42903 O42909	
Induction of labour		5AC30ALI2; 5AC30CAI2; 5AC30GUI2; 5AC30HAI2; 5AC30YAI2; 5AC30YBI2; 5AC30ZZI2, 5AC30AP, 5AC30
Forceps		5MD53KL, 5MD53KN, 5MD53KJ, 5MD53KK, 5MD53KM, 5MD53KH, 5MD55
Vacuum		5MD54
		5.MD.50, 5.MD.51, 5.MD.52, 5.MD.56.AA, 5.MD.56NL, 5.MD.56.NM, 5.MD.56. NP, 5.MD.56. NQ, 5.MD.56. NU, 5.MD.56. NV, 5.MD.56. GH, 5.MD.56. PA, 5.MD.56. PB, 5.MD.56. PD, 5.MD.56. PE, 5.MD.56. PG, 5.MD.56. PH
Non operative vaginal delivery		5.MD.50, 5.MD.51, 5.MD.52, 5.MD.56.AA, 5.MD.56NL, 5.MD.56.NM, 5.MD.56. NP, 5.MD.56. NQ, 5.MD.56. NU, 5.MD.56. NV, 5.MD.56. GH, 5.MD.56. PA, 5.MD.56. PB,

		5.MD.56. PD, 5.MD.56. PE, 5.MD.56. PG, 5.MD.56. PH
Episiotomy		5MD50GH, 5.MD.53KS, 5MD53JE, 5MD53KL, 5MD53KN, 5MD53KJ, , 5MD53KS, 5.MD.54.KJ, 5.MD.54.KL, 5.MD.54.KN, 5.MD.54.NF, 5.MD.55.KN, 5.MD.55.KL, 5.MD.55.KJ, 5.MD.55.KR, 5.MD.56. GH, 5.MD.56. PA, 5.MD.56. PB, 5.MD.56. PD, 5.MD.56. PE, 5.MD.56. PG, 5.MD.56. PH, 5MD56PC, 5MD56PF, 5.MD.56PJ
Caesarean delivery		5.MD.60
Hysterectomy		5MD60RC, 5MD60RD, 5MD60KE, 5MD60CB, 1.RM.89.LA, 1.RM.89.CA, 1.RM.91.LA, 1.RM.91.CA, 1.RM.87.LAGX
Suturing of uterus		5.PC.91.LA
Control of postpartum hemorrhage by ligation of pelvic vessels		1KT51
Control of postpartum hemorrhage by embolization of pelvic vessels		1RM13
Antepartum hemorrhage	O46	
Perineal hematoma	O71.7	
Intra cranial hemorrhage	I601 I602 I603 I604 I605 I606 I607 I608 I609 I610 I611 I612 I613 I614 I615 I616 I618 I619 I620 I621 I629 I690 I691 I692 P100 P101 P102 P103 P108 P109 P122 P520 P521 P5220 P5221 P523 P524 P525 P526 P528	
Hemophilia A	D66	
Hemophilia B	D67	
Von Willebrand disease (VWD)	D680	

Supplementary Table 4.1: Relevant ICD-10 diagnostic codes and Canadian Classification of Interventions (CCI) diagnosis/procedure codes.

Diagnosis/procedure code	ICD-10	CCI
Postpartum hemorrhage	0720- 0723	
Placenta previa	044	
Hypertensive disorders	010, 011, 013,014,015, 016	
Placental abruption	045	
Uterine rupture	0710, 0711	
Multiple pregnancy	O30801O30803O30809O30901 O30903O30909	
Multiple gestation	O30801O30803O30809O30901 O30903O30909	
Prolonged labour	O63001O63003O63009O63101 O63103O63109	
Caesarean delivery		5.MD.60
Hysterectomy		5MD60RC, 5MD60RD, 5MD60KE, 5MD60CB, 1.RM.89.LA, 1.RM.89.CA, 1.RM.91.LA, 1.RM.91.CA, 1.RM.87.LAGX
Antepartum hemorrhage	O46	
Fetal distress	O68	
Hemophilia A	D66	
Hemophilia B	D67	
Von Willebrand disease (VWD)	D680	