HEMOGLOBINOPATHY AND PREGNANCY OUTCOMES: A HISTORICAL COHORT STUDY

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ABSTRACT

Pregnancy in women with hemoglobinopathy has been associated with an increased risk of adverse pregnancy outcomes. We conducted a historical cohort study using Discharge Abstract Database for the fiscal year 1991-1992 through 2007-2008. We estimated the frequency of pregnant women with hemoglobinopathy and examined their associations with adverse pregnancy outcomes. Women with sickle cell disease are more likely to develop pre-eclampsia and preterm labor, and to undergo cesarean delivery than women with nutritional deficiency anemia, suggesting that there are other mechanisms beyond anemia that may be responsible for an increased risk of adverse pregnancy outcomes. The data suggested a synergistic effect of hemoglobinopathy and pre-eclampsia on preterm labor and cesarean delivery. Prediction models for pre-eclampsia, preterm labor and cesarean delivery were created and internally validated for women with hemoglobinopathy, with satisfactory discrimination and calibration.

SUMMARY

To determine if women with hemoglobinopathies (sickle cell disease (SCD), sickle cell trait (SCT) and thalassemia) have an increased risk of pregnancy-related complications, we conducted a historical cohort study (N = 4,381,277) using the discharge abstract data for the period from 1991-1992 through 2007-2008 fiscal years. Logistic regression was used to compare pregnancy outcomes between women with different forms of anemia (SCD, SCT, thalassemia, and nutritional deficiency anemia (NDA)) and those with no anemia. Three measures of additive interactions, RERI (relative excess risk due to interaction), AP (attributable proportion due to interaction), and S (synergy) index, were used to test the additive interactions between hemoglobinopathies and pre-eclampsia in relation to preterm labor and cesarean delivery.

Of 4,381,277 deliveries, 419 were to women with SCD, 718 with SCT, 3803 with thalassemia, and 5782 with NDA. Women with SCD had a greater risk for both medical complications (such as infections, hemorrhagic and thromboembolic events) and pregnancy-related complications (such as pre-eclampsia, preterm labor, cesarean delivery, placenta abruption, intrauterine growth restriction, and intrauterine fetal death) during pregnancy compared with those with no anemia. The increased risk of developing these complications persisted after adjustment for demographic characteristics. Moreover, SCD appeared to have a larger effect on these medical and pregnancy-related complications compared with NDA, the most common form of anemia. All these complications except for hemorrhagic and thromboembolic events were more frequent in women with SCD than in women with NDA, suggesting that other mechanisms beyond

anemia may also play a role in these medical and pregnancy-related complications. Women with SCT were also more likely to experience pre-eclampsia, preterm labor, cesarean delivery, intrauterine growth restriction, placenta abruption, and infections compared with women with no anemia,, but to a much less extent. The risks of preterm labor, cesarean delivery, placenta abruption, infections, and hemorrhagic and thromboembolic events were increased in women with thalassemia compared with those in women with no anemia. The effect size for SCT and thalassemia was comparable to NDA. The data suggested a synergistic effect of hemoglobinopathy and pre-eclampsia on preterm labor and cesarean delivery. Prediction models for pre-eclampsia, preterm labor and cesarean delivery were created and internally validated for women with hemoglobinopathy, with satisfactory discrimination and calibration.

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1. INTRODUCTION

1.1 Inherited Hemoglobin Disorders

Inherited hemoglobin disorders, also called hemoglobinopathy, are a diverse group of autosomal recessive disorders of hemoglobin production and function. They are mainly found in areas where malaria was or remains endemic, because carriers of inherited hemoglobin disorders are resistant to malaria (1). Inherited hemoglobin disorders are the most common monogenic diseases (1, 2), and fall into two main groups - the structural hemoglobin variants that result from single amino-acid substitutions in the α or β chains, and the thalassemia that is characterized by the imbalance in the production of hemoglobin chains (3)

It has been estimated that approximately 5% of the world's population are carriers of inherited hemoglobin disorders and that over 332,000 affected conceptions or births occur annually worldwide (4). These disorders occurred most frequently in tropical regions in the past, however they are now encountered in most countries as a result of population migrations (5). According to the 2001 Canadian Census, over 3.7 million Canadians (approximately 12.5% of the populations), or one out of every four individuals in the province of Ontario, identified their ethnic origin as one known to have an increased risk of inherited hemoglobin disorders (6).

The most common structural hemoglobin variant found in the US and Canada is Hemoglobin S (HbS, also called sickle hemoglobin), which results from the substitution of a single amino-acid (valine for glutamine) on β-hemoglobin chain. Sickle-cell disorders denote all genotypes containing at least one sickle gene (HbS) and has two

main clinical syndromes: homozygous sickle cell disease (SCD, also called sickle cell anemia or hemoglobin SS disease) and sickle cell trait (SCT). Individuals who inherit two copies of HbS from their parents develop sickle cell anemia (HbSS), while people who carry one defective gene (HbS) and one normal hemoglobin gene (HbA) are carriers of the disease and are said to have sickle cell trait (7). The most common complications of sickle cell anemia result either from anemia (e.g. fatigue, shortness of breath) or from obstruction of blood flow by sickle-shaped red blood cells (e.g., pain and ischemic organ damage) (8). Virtually all the clinical and pathological manifestations seen in sickle cell disorders have been attributed to presence of sickle haemoglobin S (HbS) assisted by the other abnormal haemoglobin abetting them. Little wonder then that there is paucity of clinical manifestation when HbS co-exists with normal adult haemoglobin (HbA). This is because HbA is believed to suppress the effect of HbS clinically (9). Sickle cell trait is generally considered to be a benign carrier state with rare complications.

Thalassemia is classified based on the specific globin chain that is inadequately produced into α thalassemia and β thalassemia. Beta thalassemia has three major clinical manifestations: β thalassemia minor (also called β thalassemia trait, heterozygous state with one β thalassemia mutation), β thalassemia major (also known as Cooley's anemia, homozygous state with two β thalassemia mutations) and β thalassemia intermedia (also carry two β thalassemia mutations but has milder symptoms than β thalassemia major). Alpha thalassemia is manifested by four clinical syndromes based on the number of α thalassemia deletions: silent carrier state (deletion of one α globin gene), α thalassemia trait (deletion of two α globin genes), hemoglobin H disease (HbH, deletion of three α

globin genes), and hemoglobin Bart's hydrops fetalis (Hb Bart's, deletion of two α globin genes). There is a wide spectrum of clinical manifestations among thalassemia patients. Individuals with the mildest forms, such as α and β traits, have normal healthy lives. Those with moderate forms, such as β thalassemia intermedia and hemoglobin H disease, are anemic, but not blood transfusion dependent – except during periods of stress or illness. The most severe forms are Cooley's anemia, and Hb Bart's. Individuals with Cooley's anemia are completely transfusion-dependent for their whole lives, and those with Hb Bart's mostly die during perinatal or neonatal periods (10).

1.2 Inherited Hemoglobin Disorders and Pregnancy

With advances in hematological management, women with hemoglobinopathies enjoy an increased life expectancy and quality of life. It is increasingly common for these women to live long enough to reach childbearing age and to attempt pregnancy. Pregnancy brings about a number of physiological changes for pregnant women and their adaptation to the physiological demands of pregnancy may exacerbate the underlying diseases (i.e. hemoglobin disorders) and increase the risk of obstetric complications. Physiological changes in a normal pregnancy include increased blood volume, cardiac output, tidal volume, minute ventilatory volume, minute oxygen uptake and total pulmonary resistance. Increased blood volume lead to mild delusional anemia, but women with hemoglobin disorder may experience a significant decrease in hemoglobin level. Anemia leads to insufficient delivery of oxygen to maternal and fetal tissues. Hypoxia secondary to anemia might account for the adverse maternal and perinatal outcomes for pregnant women with inherited hemoglobin diseases. In addition,

previously asymptomatic underlying chronic cardiopulmonary complications might be evident in some women with hemoglobin disorders due to physiologic stress in pregnancy (11).

Pregnancy in women with sickle cell disease is fraught with complications that can increase the risk of maternal and perinatal mortality. Kobak and colleagues published the first report outlining the effects of sickle cell disease on pregnancy in 1941 (12). Several additional reports soon followed, based on data from the same population, noting substantial maternal morbidity and maternal and perinatal mortality associated with pregnancy in women with sickle cell disease prior to 1972 (13). Advances in SCD management and obstetric and perinatal care allow a significant improvement in the pregnancy outcome for women with sickle cell disease. Both maternal and perinatal mortality among pregnant women with sickle cell disease have been dramatically dropping since 1972 (14). Clinicians no longer counsel women with sickle cell disease to avoid pregnancy except for extreme cases. Pregnancy for these women however has been associated with an increased risk for pregnancy-related complications (15). Women with sickle cell trait usually tolerate pregnancy well with few complications.

Pregnancy is well-tolerated in women with α thalassemia trait or β thalassemia minor, and women with HbH disease or β thalassemia intermedia are able to have a successful pregnancy.

Pregnancies in women with β thalassemia major are uncommon because of a high rate of morbidity and infertility. Medical advances in hematological managements and

ovulation induction therapy have improved life expectancy and fertility significantly, which increases the possibility of pregnancy in patients with β thalassemia major.

Because of medical advances in obstetrics and neonatology, more women with hemoglobinopathies are attempting pregnancy. To date, there are only a few studies investigating the consequences of pregnancy in patients with hemoglobinopathies with the limitations of small sample size and/or unpopulation-based study design.

2. OBJECTIVES

The main objective of the study was to examine the associations of hemoglobinopathy with pregnancy outcomes. Most specially, the thesis project was to:

1) review available evidence on pregnancy outcomes in women with hemoglobinopathy (sickle cell disorders and thalassemia);

2) determine pregnancy outcomes in women with sickle cell disorders (sickle cell disease and sickle cell trait) and thalassemia;

3) assess the joint effects of hemoglobinopathy and pre-eclampsia in relation to preterm labor or cesarean delivery and

4) identify important predictors for pre-eclampsia, preterm labor and cesarean delivery among women with hemoglobinopathy.

3. LITERATURE REVIEW

3.1 Sickle Cell Disorders and Pregnancy

A literature search was conducted to identify publications that investigated the pregnancy outcomes in women with sickle cell disease and sickle cell trait. We searched PUBMED/MEDLINE and Cochrane Library for studies published in English between 1950 and 2010 by using key words relating to sickle cell disease, sickle cell trait, pregnancy (or pregnant), pregnancy outcomes, maternal and perinatal outcomes, cesarean delivery, pre-eclampsia, and preterm delivery. Other studies were identified through manual searches of references cited in both research and review articles. The titles and abstracts of these studies were reviewed to identify relevant articles.

The relevant articles found through our search were heterogeneous in study design and methods. We therefore developed a standardized scoring form to assess study quality. Quality scoring was based on six criteria: relevance of the article's study questions to the objective of this Review; rigorous and clearly described methods for selecting participants; use of a standard approach for ascertainment of sickle-cell disease and sickle cell trait among participants; inclusion of a control group; exploration of the statistical significance of study results, if appropriate; and overall impression of the study quality. Points were assigned to each quality question for a total of ten possible points per article. Articles scoring more than seven points were categorized as A quality, those scoring five to seven points were designated as B quality, and those scoring less than five points as C quality.

We extracted information from the included articles on the study years, number of participants, study design, diagnosis of sickle cell disease or sickle cell trait, controls, and

results in which we focused on the odds ratios (or relative risk) for adverse pregnancy outcomes related to sickle cell disease or sickle cell trait.

3.1.1 Sickle cell disease

A total of 145 citations were initially identified, and 96 citations remained after removal of duplicates. 18 potentially relevant articles moved forward to the quality review and data extraction phase. Eight articles met most quality criteria and included a control group, enabing us to explore the association between sickle cell disease and adverse pregnancy outcome (16-23). All of these articles received A or B score quality. These eight articles were published between 1988 and 2009 and include six retrospective studies, one cross sectional study (21) and one randomized controlled study (16). Four studies were from US, and one each from Nigeria (19), Saudi Arabia (22), and Jamaica (23). Table 1 provides more details on methodology of the eight included studies. All controls were chosen from the same hospital or same database as patients (pregnant women with SCD), and they delivered during the same period. In only two studies (19, 22) were the control groups matched with subjects in age, parity, and delivery time.

The risks for cesarean delivery in women with SCD and those with no hemoglobinopathy were reported in all eight studies (Table 2a). Three studies showed a significantly increased risk for cesarean delivery in women with SCD compared with those with no hemoglobinopathy (19, 20, 21), and in other three studies, the difference between two groups was not statistically significant (17, 22, 23). Koshy and colleagues also reported a 2-fold or more increased rate of cesarean delivery among SCD women in two studies, but no p values were reported in these studies (16, 18).

Preterm labor was investigated in seven studies (Table 2). In five studies, the risk for preterm labor was significantly increased in women with SCD compared to those with no hemoglobinopathy (17, 20-23). Koshy and colleagues reported an increased rate of preterm labor among SCD women (38% versus 17% for controls) in one study (18), but not in the other (16).

Pre-eclampsia was reported in seven studies (Table 2). Two studies have shown a significantly increased risk of pre-eclampsia in women with SCD compared with those with no hemoglobinopathy (20, 21), whereas the other three have not (17, 19, 23). The risk for pre-eclampsia in SCD women was also 4-fold higher compared with controls in the two studies by Koshy and his colleagues, but p values were not provided.

Five studies compared the risks for eclampsia between women with SCD and those with no hemoglobinopathy (Table 2) (19, 20-23). Only one study showed a significantly increased risk for eclampsia in women with SCD compared with those with no hemoglobinopathy (21).

The risk for placenta abruption was found significantly increased among SCD women in two studies (20, 21). A similar result was found in the prospective transfusion study reported by Koshy and colleagues in which women with SCD (hemoglobin genotypes SS, SC, and S*tha*) had higher rates of placenta abruption (hemoglobin genotypes SS: 3%, SC: 2%, and S*tha* 4%), compared with healthy women (0.5%) (16).

Infection and hematological complications were also investigated in some studies (Table 3). The rate of urinary tract infection among pregnant women with sickle cell disease has been reported to be increased in two studies (21, 22), but this was not noted in

a retrospective study reported by Afolabi (19). Only two studies reported pyelonephritis, and a significantly higher rate of pyelonephritis in SCD women was found in one study (21); but not in the other (17). In three studies, postpartum infections were noted to be significantly more prevalent in SCD women compared to those with no hemoglobinopathy (17, 20, 21). The rate of antepartum hemorrhage has been demonstrated to be significantly increased in SCD women in one study (21), but not in the other (23). Postpartum hemorrhage does not seem to be more common in women with SCD (19.23). In one study, the risk of postpartum hemorrhage was even reported to be significantly lower in women with SCD compared with those with no hemoglobinopathy (OR=0.5).

Table 4 shows the perinatal outcomes of pregnancies with SCD in the included studies. Most studies documented an increased incidence of fetal growth abnormalities: intrauterine growth restriction or low birth weight in women with SCD (Table 4). In three out of four studies (17, 20-22), SCD was reported to be associated with a significantly increased risk for intrauterine growth restriction (17, 21, 22), and only one study showed a non-significant difference between SCD group and controls (20). Five studies have demonstrated significantly lower mean birth weights in babies born to mothers with SCD compared with those born to mothers without hemoglobinopathy (17, 19, 20, 22, 23).

In regard to perinatal mortality, four studies documented a significantly increased incidence of stillbirth (22, 23) or perinatal death (17, 19, 22) in women with SCD compared with those without hemoglobinopathy. There was no significant difference in rates of neonatal death between these two groups (22, 23) (Table 4).

Koshy and colleagues also noted an increased risk for intrauterine growth restriction, lower birth weight, stillbirth, neonatal death, and perinatal death in women with SCD, but provided no p values in their studies (16,18) (Table 4).

Other pregnancy complications, such as retained placenta, and gestational diabetes were also reported in a few studies. Retained placenta was noted to be slightly more prevalent in the Jamaican cohort of women with HbSS (23), but not in Nigerian SCD women in another study (19). Villers and colleagues (21) reported that pregnant women with SSD were more likely to experience infections (pneumonia, pyelonephritis, postpartum infection, sepsis, systemic inflammatory response syndrome), thromboembolic events (cerebral vein thrombosis, deep venous thrombosis), Although women with SSD tended to be more likely to experience stroke and pulmonary embolus, they did not reach significance. Villers and colleagues (21) also noted that all pregnancy-related complications, with the exception of intrauterine fetal death and gestational diabetes, were significantly more common among women with SSD including hypertensive disorders of pregnancy (gestational hypertension, preeclampsia, eclampsia), antepartum bleeding, preterm labor, fetal growth restriction, asymptomatic bacteriuria, and genitourinary tract infection.

In summary, there is lack of sufficient evidence to conclude that pregnancy-related complications are more common in women with sickle cell disease when compared with unaffected women. There are only eight studies. In addition, many of the included reports were from one institution, the majority was retrospective, some had small sample sizes, inclusion of different genotypes, lengthy time periods of data acquisition, as well as vast

variability in incidence estimates of morbidity and mortality. Heterogeneity among studies from different parts of the world also limits the comparability of study results. Nevertheless, the increased tendency toward pregnancy-related complications especially in women with HbSS should not be overlooked.

Table 1. Studies of pregnancy in women with sickle cell disease (SCD)

Study	Study year	Data source	Study design	Patients	Controls	Comments
Koshy et al (16)	1978-1986	Pregnant women from six institutions in Chicago and Johns Hopkins Hospital in Baltimore	Retrospective cohort	100 women withHbSS, 66 with HbSC, 23 with HbSβ*Thal*	8981 women with normal hemoglobin (HbAA) who delivered at the same hospital and during the same period as subjects	Multicentre studies. There might be variability in management among centers.
Sun et al (17)	1980-1999	A computerised database of deliveries at Grady Memorial Hospital, Atlanta, Georgia	Retrospective cohort	69 deliveries with HbSS, 58 deliveries with HbSC	129 deliveries by African American women with HbAA who were from the same database, and delivered during same period	Small sample size
Koshy et al (18)	1986-1990	Pregnant women attending University of Illinois Hospital and Medical Center , Chicago	Retrospective cohort	39 pregnancies with HbSS, 9 with HbSC, 6 with HbSβ*Thal*	8981 women with HbAA who delivered at the same hospital and during the same period as subjects	Small sample size.
Afolabi et al (19)	1996-2000	Pregnancies delivered at Lagos university teaching hospital (Lagos, Nigeria)	Retrospective cohort	75 women with HbSS	150 women with HbAA who delivered at the same hospital and during the same period as subjects (age, parity and delivery time matched)	Confounding not controlled.

Table 1: cont'd

Study	Study year	Data source	Study design	Patients	Controls	Comments
Barfield et (20)	1998-2006	Massachusetts Pregnancy to Early Life Longitudinal (PELL) Data System	Retrospective cohort	488 women with SCD	83877 women with no hemoglobinopathy who were from the same database and delivered during the same period as subjects	Sickle- β thalassemia and other forms of thalassemia could not be distinguished using ICD-9.
Villers et. (21)	2000-2003	Nationwide Inpatient Sample (NIS) (U.S.A)	Cross section	17952 deliveries with SCD	16,756,944 deliveries without SCD who were from the same database and delivered during the same period as subjects	ICD9 codes for both sickle cell disease (282.6) and thalassemia (282.4) were used to identify the patients with sickle cell disease.
Al Jama et (22)	2000-2007	Pregnancies delivered at King fahad hospital in eastern Saudi Arabia	Retrospective cohort	145 women (255 deliveries with HbSS	500 women with HbAA who delivered at the same hospital and during the same period (age, parity and delivery time matched)	Confounding not controlled.
Surjeant et (23)	Not reported	Database of deliveries at Victoria Jubilee Hospital, (Jamaica) from 1973 to 1981	Prospective cohort	52 women (94 pregnancies) with HbSS	68 women (157 pregnancies) with HbAA who were from the same database and delivered during the same period as subjects	There might be secular and management changes over a 25-year period

Table 2. Obstetric complications for pregnancies with sickle cell disease (SCD)

	Villers[21] OR[†](95%CI) or %	Barfield[20] OR[‡] (95%CI) or %	Sun[17] RR[*] (95%CI)	Surjean[23] %		Jama[22] %		Afolab[19] %		Koshy[18] %		Koshy[16] %			
	SCD vs control	SCD vs control	HbSS vs AA	HbSS	HbAA	HbSS	HbAA	HbSS	HbAA	HbSS	HbAA	HbSS	HbSC	HbS*tha*	HbAA
Cesarean section	31% vs 25% (P<0.001)	1.3 (1.1,1.5)	36% vs 22% (P=0.11)	15.9	11.1 (P=0.31)	18.4	13.4 (P>0.05)	38.7	20.1 (P<0.05)	50	14	28	30	26	14
Preterm labor	1.4 (1.3,1.6)	1.5 (1.2,1.8)	2.8 (1.1,7.6)	44.2	14.7 (P=0.001)	12.6	5.2 (P=0.0012)	NR		38	17	26	15	22	17
Preeclampsia	1.2 (1.1-1.3)	7.5% (5.5%, 9.6%) vs 4.5% (4.3%,4.6%)	1.9 (0.7-4.2)	15.4	10.3 (P=0.27)	NR		6.7	5.6 (p>0.05)	17	4	18	9	13	4
Eclampsia	3.2 (1.8,6.0)	2.3% (1.1%, 3.3%) vs 1.8% (1.7%,1.9%)	NR	1.9	1.5 (p>0.05)	2.4	1.6 (P>0.05)	0	1.3 (p>0.05)	NR		NR			
Placenta abruption	1.6 (1.2,2.1)	1.3 (1.1,1.5)	NR	NR		NR		NR		NR		3	2	4	0.5

* RR: relative risk; reference group: HbAA

** NR: not reported

†OR: odds ratio; reference group: no hemoglobinopathy

‡OR: odds ratio; reference group: no SCD

Table 3. Infection and hemotologic complications of pregnancies with sickle cell disease (SCD)

	Villers[21] OR‡ (95% CI)	Barfield[20] OR† (95% CI)	Sun[17] RR* (95% CI)		Surjeant[23] %		Jama[22] %		Afolab[19] %	
	SCD vs control	SCD vs control	HbSS vs AA	HbSC vs AA	HbSS	HbAA	HbSS	HbAA	HbSS	HbAA
Urinary tract infection	2.3 (1.9,2.7)	NR	NR		NR		17.3 (P<0.0003)	6.8	0 (p>0.05)	1.9
Pyelonephritis	1.3 (1.0,1.8)	NR	3.1 (0.8,13)	2.2 (0.5,11)	NR		NR		NR	
Postpartum infection	1.4 (1.1,1.7)	1.5 (1.2,1.8)	9.4 (2.8,31)	4.5 (1.2,17)	NR		NR		NR	
Antepartum hemorrhage	1.7 (1.2,2.2)	NR	NR		1.9 (P=0.99)	4.4	NR		NR	
Postpartum hemorrhage	0.5 (0.3,0.6)	NR	NR		7.7 (P=0.99)	10.3	NR		1.9 p>0.05	1.3

* RR: relative risk; reference group: HbAA

** NR: not reported

† OR: odds ratio; reference group: no hemoglobinopathy

‡ OR: odds ratio; reference group: no SCD

Table 4. Perinatal outcomes of pregnancies with sickle cell disease (SCD)

	Koshy[16] %				Koshy[18] %		Afolab[19] %		Jama[22] %		Surjeant[23] %		Sun[17] RR* (95%CI		Barfield[20] OR† (95%CI)	Villers[21] OR‡ (95%CI)
	HbSS	HbSC	HbS*tha*	HbAA	HbSS	HbAA	HbSS	HbAA	HbSS	HbAA	HbSS	HbAA	HbSS	HbSC	SCD vs control	SCD vs control
Intrauterine growth restriction	15.3	5	4	9	17	9	NR		20.8 (P<0.0001)	4.6	NR		4.9 (2.7-8.9)	2.2 (1.1-4.7)	1.3 (0.9,1.8)	2.2 (1.8,2.6)
Mean birth weight (kg) ± Standard deviation	2.64	3.02	2.75	3.01	2.53	3.01	2.42 ±0.63 (P<0.05)	3.14 ±0.62	2.75 ±0.55 (P=0.0001)	3.45 ±0.58	2.5 ±0.5 (P<0.001)	3.0 ±0.6	NR	NR	NR	NR
Low birth weight (<2.5kg)	NR				NR		NR		NR		41.7 (P=0.01)	19.0	2.7 (1.7-4.3)	1.0 (0.5-2.0)	1.7 (1.1,2.6)	NR
Still birth	5.7	2	0	2	5	2	NR		4.9 (P=0.001)	0.8	7.1 (P=0.012)	0.7	NR	NR	NR	NR
Neonatal death	1.9	0	8	1	5	1	NR		2.9 (P>0.05)	1.0	1.9 (P>0.05)	1.5	NR	NR	NR	NR
Perinatal death	7.6	2	8	3	10	3	18.7 (P <0.05)	8.8	7.8 (P=0.0005)	1.8	NR		3.0 (1.0-8.9)	0.5 (0.1-3.8)	NR	NR

* RR: relative risk; reference group: HbAA ** NR: not reported

†OR: odds ratio; reference group: no hemoglobinopathy ‡OR: odds ratio; reference group: no SCD

3.1.2 Sickle cell trait

A total of 126 articles were initially identified, and 82 articles remained after removal of duplicates. Twenty-two potentially relevant articles moved forward to the quality review and data extraction phase. Ten articles met most quality criteria and included a control group (scored A or B), enabling us to explore the association between sickle cell trait and adverse pregnancy outcomes (24-33). These ten articles were published between 1977 and 2007 including six retrospective cohort studies and four prospective cohort studies. Seven studies were from US, two from London, United Kingdom (25, 31), and one from Nigeria (32). Table 5 provides more details on study methodology and diagnosis. All control groups in the included studies were from the same hospital or same database, and delivered during the same period as patient groups. Five studies chose controls matched with patients in race, age, parity, sex of offspring, delivery time, number of prenatal visits, or gestational age at entry into prenatal care.

The risk of pre-eclampsia was reported in four studies (Table 6). In three studies, the difference in the rate of pre-eclampsia was statistically non-significant between women with SCT and those with normal hemoglobin (24, 27, 28). Only one study (29) showed a significantly increased risk of pre-eclampsia in women with SCT compared to those with normal hemoglobin (24.7% vs 10.1% in controls, $p<0.0001$).

In regard to preterm delivery, two studies (24, 32) showed no significant difference between SCT and control groups (Table 6). In the other two studies (27, 28), sickle cell trait was found to be associated with lower odds of preterm delivery or early preterm delivery (delivery at less than 32 weeks of gestation).

Cesarean delivery was reported in three studies (Table 6). There was no statistically significant difference in the prevalence of cesarean delivery in SCT pregnancies compared with HbAA pregnancies (25, 28, 32).

A significantly increased risk of urinary tract infection was been found among African American women with SCT in a retrospective cohort study by Bryant et al. (27), but this was not showed in a prospective cohort study reported by Adeyemi et al. (30) (Table 6). Tuck and colleagues (25) reported that SCT was associated with a significantly increased risk for recurrent urinary tract infection, but not for one time urinary tract infection. Pyelonephritis was investigated in three studies, two of which showed a significantly higher rate of pyelonephritis in women with SCT compared with those with normal hemoglobin (26, 30). Another showed no significant difference between two groups (28) (Table 6). Two studies investigated asymptomatic bacteriuria, one study (26) reported a significantly increased rate in women with SCT (13%) compared with those with normal hemoglobin (9%), whereas the other (30) did not (Table 6).

In regard to fetal growth abnormalities, a significantly lower mean birth weight in women with SCT was observed in three studies (28, 29, 33), but not in the other six studies (24-27, 31, 32) (Table 7). Stillbirth was reported in four studies (24, 25, 28, 32). All these studies found no increase in the risk of stillbirth in women with SCT when compared with those with normal hemoglobin. There was no statistically significant difference between SCT and control groups in terms of intrauterine growth restriction, neonatal death, and perinatal mortality.

Other adverse pregnancy outcomes, pregnancy induced hypertension, antepartum hemorrhage, postpartum hemorrhage, and puerpyral pyrexia, were also investigated in a cohort study by Adeyemi and colleagues (32), and no statistically significant difference was observed in these adverse pregnancy outcomes between SCT patients and controls.

In summary, there have been conflicting reports on the effects of maternal sickle cell trait on pregnancy outcomes. In general, women with sickle cell trait tolerate pregnancy well with few complications. However, several adverse pregnancy outcomes have been reported to be more frequent in women with sickle cell trait including pre-eclampsia, urinary tract infection, and lower birth weight. They are not yet conclusive due to limited data and weak study design and methodology. Further studies are needed.

Table 5. Studies of pregnancies in women with sickle cell trait (SCT)

Study	Study year	Data source	Study design	Patients	Controls	Comments
Blattner et al. (24)	1972-1974	Pregnant women attending the prenatal clinic at the Bronx Municipal Hospital Center in New York	Prospective Cohort	85 women with SCT (HbAS)	85 women with HbAA. (race, age, parity, and sex of Offspring matched)	Excluding a substantially greater number of women with AS than noncarrier women who had early pregnancy loss might introduce a bias.
Tuck et al. (25)	1975-1981	Pregnant women attending Dulwich and King's College Hospitals in London	Retrospective cohort	334 pregnancies with SCT	717 pregnancies with no hemoglobinopathy (race matched)	Confounding not controlled.
Baill et. al. (26)	1979-1986	Pregnant women delivered at the Johns Hopkins Hospital in Baltimore	Retrospective cohort	914 pregnancies with SCT	914 pregnancies with HbAA (matched in race, delivery year, parity, maternal age, registration status)	The diagnosis of SCT could not be confirmed.

Table 5: Cont'd

Study	Study year	Data source	Study design	Patients	Controls	Comments
Bryant et. al (27)	1976-2001	All African-American, non- -Hispanic women delivered at the University of California at San Francisco	Retrospective cohort	326 women with SCT	4702 women with no SCT	Diagnosis of SCT could not be confirmed.
Tita et. (28)	1991-2006	Perinatal database for African American women at Jefferson County, Alabama	Retrospective cohort	3894 pregnancies with HbAS, 875 with HbAC	32724 pregnancies with HbAA	Diagnosis of SCT could not be confirmed.
Larrabee et. (29)	1994-1995	All African American women who were seen for prenatal care at the University of Texas Medical School Hermann Hospital Medicaid Clinic	Prospective cohort	162 women with SCT	1422 pregnancies with no hemoglobinopathy	Confounding not controlled.
Thurman et. (30)	1996-2003	MUSC (Medical University of South Carolina) Perinatal Information System	Retrospective cohort	455 pregnant women with SCT	448 women without SCT (matched for race, age, number of prenatal visits, and gestational age at entry into prenatal care.)	Diagnosis of SCT could not be confirmed.

Table 5: cont'd

Study	Study year	Data source	Study design	Subjects	Controls	Comments
Tan et.al (31)	2000-2005	Pregnancies delivered at St Thomas' Hospital in London	Retrospective cohort	505 pregnancies with SCT	16320 pregnancies with no hemoglobinopathy	Some potentially important confounders such as smoking were not controlled.
Adeyemi et.al (32)	2003-2005	Pregnant women who received antenatal care and delivered at Obafemi Awolowo University Teaching Hospital in Nigeria.	Prospective cohort	210 women with SCT (HbAS)	210 women with HbAA (delivery time matched)	Confounding not controlled.
Ramswa et.al (33)	Not reported	Pregnant women attending antenatal clinic at university of west indies, Trinidad	Prospective cohort	140 pregnant women with SCT	140 pregnant women with HbAA (matched for age, parity, delivery time , and ethnic origin)	Small sample size.

Table 6. Pregnancy outcomes in women with sickle cell trait (SCT)

	Tita[28] OR (95%CI)* or RR (95%CI) **		Adeyemi[32] %		Bryant[27] % or OR (95%CI)		Blattner[24] %		Larrabe[29] %		Tuck[25] %		Baill[26] %		Thurman[30] %	
	HbAS vs AA	HbAC vs AA	HbAS	HbAA	SCT	No SCT	HbAS	HbAA	SCT	HbAA	SCT	HbAA	SCT	HbAA	SCT	-no SCT
Pre-eclampsia	OR: 1.0 (0.8-1.2)	OR: 1.0 (0.6-1.3)	NR		6.4% (P=0.869)	6.7%	9 (P>0.05)	17	24.7 (P<0.0001)	10.1	NR		NR		NR	
Preterm delivery	OR: 0.8 (0.7-0.9)	OR: 0.9 (0.7-1.1)	2.4 (P=0.42)	0.7	OR : SCT vs control <32w: 0.15(0.05-0.49) <37w: 0.76(0.52-1.12)		6 (P>0.05)	8	NR		NR		NR		NR	
Cesarean delivery	RR: 1.1 (1.0-1.1)	RR: 1.1 (0.9-1.2)	35.2 (P=0.27)	38.1	NR		NR		NR		38.2 (P>0.01)	38.6	NR		NR	
Pyelonephritis	RR: 0.5 (0.1-2.2)	RR: 0.9 (0.1-6.6)	NR		NR		NR		NR		NR		2.1 (P=0.011)	1.4	2.4 (P=0.03)	0.7
Urinary tract infection (UTI）	NR		4.3 (P=1.0)	4.3	15.7% (P=0.001)	10%	NR		NR		Recurrent UTI: 6.0 (P<0.01)	3.6	NR		NR	
Asymptomatic bacteriuria	NR		NR		NR		NR		NR		NR		13 (P=0.011)	9	47.5 (P=0.63)	46.9

* OR (95% CI): odds ratio (95% confidence interval) ** RR (95% CI): relative risk (95% confidence interval) † NR: not reported

Table 7. Comparison of birthweights between babies born to mothers with sickle cell trait (SCT) and to those with normal hemoglobin

	Tita[28] RR (95%CI)*		Adeyemi[32] %		Bryant[27] %		Blattner[24] %		Larrabee[29] %		Tuck[25] %		Baill[26] %		Tan[31] %		Ramsewak[33] %	
	HbAS vs HbAA	HbAC vs HbAA	HbAS	HbAA	SCT	No SCT	HbAS	HbAA	SCT	HbAA	SCT	HbAA	SCT	HbAA	SCT	HbAA	SCT	HbAA
Low birthweight	0.9 (08-1.1)	0.8 (0.6-1.0)	17.8 (P=0.5)	15.9	NR†		NR†		NR†		NR†		NR†		NR†		NR†	
Mean birthweight(g) ± standard deviation	NR†		NR†		3158 ±613 (P=0.387)	3120 ±745	3310 ±580 (P>0.1)	3200 ±520	3082 ±591 (P<0.0001)	3369 ±573	3202 (P=NS**)	3191	3113 ±640 (P=NS**)	3062 ±638	3212 ±671 (P=0.713)	3200 ±660	3165 ±65.6 (P<0.05)	3445 ±32.9

* RR (95% CI): relative risk (95% confidence interval)

** NS = not significant

† NR = not reported

3.2 Thalassemia and Pregnancy

To date, there have been only few reports of small scale studies and case reports concerning pregnancy outcomes among women with thalassemia syndrome. Pregnancy is well-tolerated in individuals who have α thalassemia trait. Anemia is not present or is mild. Pregnancy outcome is equivalent to the general population. However, if both of the parents are carriers of the α0-thalassemia (--/αα), the fetus has a 25% of chance to be affected with Hb Bart's disease in which fetal hydrops occurs that leads to stillbirth or neonatal death. Moreover, pregnant women with Hb Bart's fetus have been associated with a higher risk of obstetric complications, including pre-eclampsia, polyhydramnios and retention of the placenta (34). Women with HbH disease can have a successful pregnancy. However, pregnancy-induced physiological changes exacerbate the chronic anemia in these women. Increased risks of pre-eclampsia, prematurity and low birth weight have been demonstrated as well as the new onset of congestive heart failure (35, 36).

Patients with β-thalassemia major tend to suffer from failure of pubertal growth and severely delayed sexual development (37). Pregnancy in β-thalassemia major was rare until the mid-1960s when the first therapeutic interventions were introduced (38). The pediatric and hematological management of patients with β-thalassemia major has improved significantly with the introduction of hypertransfusions and iron chelation therapy in the late 1970s (39). Several small studies and case series have reported favorable maternal and fetal outcomes in patients with β-thalassemia major/intermedia, but the rate of gestational and other complications was high (39-52). These included a

high demand for ovulation induction because of hypogonadism, as well as intrauterine fetal-growth retardation and preterm labor, due to low hemoglobin levels during gestation, which leads to fetal hypoxia. Furthermore, hypersplenic crises during gestation, as well as a high occurrence of cephalopelvic disproportion, increase the rate of cesarean delivery (50).

Although fertility is compromised in patients with transfusion-dependent thalassemia major, pregnancy is possible in the majority of patients with β-thalassaemia intermedia. This is particularly true with the availability of assisted reproductive techniques and as medical advances continue to increase the life expectancy of these patients who can now reach adulthood and attain reproductive capacity. There are handful reports of pregnant women with β-thalassaemia or β-thalassaemia intermedia. In a prospective cohort study of nine pregnancies in women with β-thalassemia intermedia, Nassar and colleagues reported that intrautrine growth restriction complicated more than half of the pregnancies with β-thalassemia intermedia. Transfusions are needed in most cases, even in non-transfusion-dependent patients. Postpartum splenectomy might be necessary in some patients (53). Two studies, on the other hand, that included a total of nine pregnancies for patients with thalassemia intermediate did not report evidence of an increased risk for ante-, intra-, or postpartum complications [47, 48].

Generally, β-thalassemia minor is well-tolerated in pregnancy. A few studies including small numbers of patients suggested a favorable outcome (43, 54, 55). Fertility in general among these patients is not impaired, and no menstrual abnormalities exist (43). Likewise, the incidence of premature and low birth weight was found to be comparable to

the general population (54). Recently, Sheiner and colleagues conducted a population based study comparing pregnancies with and without β-thalassemia minor, and found that oligohydramnios (OR: 2.1; 95% CI:1.2%, 3.7%), and intrauterine growth restriction (IUGR; OR 2.4; 95% CI 1.4%, 4.2%), were significantly associated with β-thalassemia minor, whereas no significant differences were noted between the groups regarding perinatal outcomes such as birth weight, low Apgar scores, congenital malformations, or perinatal mortality (55).

3.3 Definitions of Pre-eclampsia and Preterm Labor and Their Risk Factors

There were no universally accepted diagnostic criteria for pre-eclampsia before 2000 (56). Since 2000, consensus and recommendation were reached after considerable debates regarding the definition of pre-eclampsia among international working groups (57, 58, 59). Pre-eclampsia is usually diagnosed in the presence of new onset of both hypertension and proteinuria after 20 weeks' gestation (57, 58, 59). Hypertension is defined as a systolic blood pressure of at least 140 mm Hg or a diastolic blood pressure of at least 90 mm Hg on at least two occasions and at least 4-6 h apart after the 20^{th} week of gestation in women known to be normotensive beforehand (57,58, 60). Blood-pressure recordings to establish the diagnosis should be no more than 7 days apart (57, 60, 61). Proteinuria is defined as excretion of 300 mg or more of protein every 24h. If 24h urine samples are not available, proteinuria is defined as a protein concentration of 300 mg/L or more (≥ 1+ on dipstick) in at least two random urine samples taken at least 4-6 h apart (57,60). In the absence of proteinuria, pre-eclampsia should be considered when

hypertension is associated with persistent cerebral symptoms, epigastric or right upper-quadrant pain with nausea or vomiting, or with thrombocytopenia and abnormal liver enzymes.

A number of risk factors have been identified for the risk of pre-eclampsia (62) (Table 8).

Table 8. Risk factors for pre-eclampsia

- Limited sperm exposure
- Primipatermity
- Pregnancies after donor insemination, oocyte donation embryo donation
- Protective effect of partner change in the case of previous pre-eclamptic pregnancy
- Maternal or pregnancy-related risk factors
- Extremes of maternal age
- Multifetal gestation
- Pre-eclampsia in a previous pregnancy
- Chronic hypertension or renal disease
- Rheumatic disease
- Maternal low birthweight
- Obesity and insulin resistance
- Pregestational diabetes mellitus
- Maternal infections
- Pre-existing thrombophillia
- Maternal susceptibility genes
- Family history of pre-eclampsia
- Smoking (reduced risk)
- Hydropic degeneration of placenta

A preterm delivery, as defined by the World Health Organization, is one that occurs at less than 37 and more than 20 weeks' gestational age. In the United States, the preterm delivery rate is approximately 11%, whereas one in 12 babies (8%) born in Canadian hospitals was born preterm (63). This condition is the leading cause of neonatal morbidity and mortality. (64, 65). Preterm labor is usually defined as regular contractions accompanied by cervical change occurring at less than 37 weeks' gestation (64). Preterm labor likely represents a syndrome rather than a diagnosis because the causes are varied. Approximately 20% of preterm deliveries are iatrogenic and are performed for maternal or fetal indications, including intrauterine growth restriction, preeclampsia, placenta previa, and nonreassuring fetal testing (66). Of the remaining cases of preterm birth, around 30% occur in the setting of preterm premature rupture of the membranes, 20% to 25% result from intra-amniotic infection, and the remaining 25% to 30% are caused by spontaneous (unexplained) preterm labor (65). Various etiologic risk factors for premature delivery are listed in Table 9 (64-73).

Table 9. Risk factors for preterm delivery

- African American race
- Age <18 or >40 years
- Low socioeconomic status
- Stressful lifestyle
- Low maternal weight
- Smoking
- Drug use (heroin and cocaine)
- Previous preterm birth
- Anemia (hemoglobin <11 and S-ferritin 12–15 mg/L)
- Abnormal uterine anatomy
- Placenta previa
- Placenta abruption
- Polyhydramnion
- Multiple gestation
- Premature rupture of membranes
- Cervix insufficiency
- Fetal anomalies (including intrauterine growth restriction)
- Infections (urinary tract infections, genital infection, pneumonia)
- Gestational or preexisting diabetes
- Pregnancy induced or preexisting hypertension
- Preeclampsia

4. RESEARCH DESIGN AND METHODS

4.1 Data Source

Our analysis was based on data from the Discharge Abstract Database (DAD) for the study period of fiscal year 1991/1992 through 2007/2008. Discharge Abstract Database, collected by the Canadian Institute for Health Information (CIHI), contains information on most acute care hospital separations (discharges, deaths, sign-outs, transfers) across Canada, excluding only Quebec and some parts of Manitoba. Data on same day surgery, chronic care, and rehabilitation are not included in DAD. Over 4.2 million records are submitted to the DAD annually, with each record capturing a standard clinical, demographic and administrative data on an episode-specific basis. Inpatient records in the DAD represent 75% of all inpatient discharges in Canada. Each record contains information for one patient separation (discharge), and a separate record is created for a readmission. The DAD is based on the April-to-March fiscal year (April 1 to March 31). (74).

Information included in the DAD is what can be derived from a typical discharge abstract, with safeguards to protect the privacy of individual patients, physicians, and hospitals. These data include sex, age at and date of admission, home postal code, province where patients were admitted to hospitals, date and status at discharge, principal diagnosis, up to 15 secondary diagnoses (coded according to the International Classification of Disease, Ninth Revision, Clinical Modification [ICD-9 CM] or the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Canada [ICD-10 CA]), and up to 10 diagnostic, therapeutic and surgical procedures (coded according to the Canadian Classification of Diagnostic, Therapeutic,

and Surgical Procedures or the Canadian Classification of Health Interventions). All corresponding ICD-10 CA codes used were mapped from the appropriate ICD-9 CM codes. Discharge Abstract Database has been previously validated and widely used in research and perinatal health surveillance. (75, 76, 77)

4.2 Study Population

Records were identified in the DAD by ICD-9 (1991-2000) or ICD-10 codes (since 2000) for all delivery-related discharges from acute care hospitals during the period from 1991/1992 to 2007/2008. Pregnant women who were admitted to acute care hospitals for delivery in all eight provinces and territories (all provinces and territories in Canada except Quebec and Manitoba) were included in the study. Pregnant women from the provinces of Quebec and Manitoba were excluded in this analysis due to the incomplete information available from the DAD for these two provinces. The total number of deliveries included in the study was 4,381,277. These deliveries represented approximately 98% of all deliveries occurring in the study provinces and territories during the period of investigation, as 98% to 99% of deliveries in Canada occur in hospital (77, 78, 79).

4.3 Ethics Approval

The data used for this study is a denominalized version prepared under strict confidentiality guidelines by the Canadian Institute for Health Information (CIHI), and accessible at the Public Health Agency of Canada (PHAC). Individual consent was not

obtained from the patients whose data are contained in the database, and approval from an ethics review board is not required by either CIHI or PHAC (76, 77).

4.4 Statistical Analysis

4.4.1 Comparison of pregnancy outcomes among women with different types of anemia and no anemia

4.4.1.1 Independent and dependent variables

Using information available on delivery-related hospital discharge records from DAD, pregnant women were classified into five categories: sickle cell disease, sickle cell trait, thalassemia, nutritional deficiency anemia, or no anemia. Sickle cell disease cases were identified using ICD9CM codes 282.6 or ICD10CA codes D570, D571, D572, D578; sickle cell trait cases were defined by ICD9 codes 282.5 or ICD10 codes D573; the ICD9 code 282.4 and ICD10 codes D56 were used to identify thalassemia; the codes for nutritional deficiency anemia included ICD9 codes 280, 281, and ICD10 codes D50, D51, D52, D53. Women without any type of anemia (nutritional deficiency anemia (ICD9 codes 280 and 281; ICD10 codes D50-D53); hemolytic anemia (ICD9 codes 282 and 283; ICD10 codes D55-D59); aplastic anemia (ICD9 codes 284; ICD10 D60-D61); and other anemia (ICD9 codes 285, ICD10 codes D62-D64)) were used as a reference group.

Covariates included several sociodemographic characteristics available from DAD: maternal age at delivery (categorized into six groups: <20, 20-24, 25-29, 30-34, 35-39, ≥40 years); year of delivery (categorized into six groups (periods): 1991-1993, 1994-1996, 1997-1999, 2000-2002, 2003-2005, 2006-2007); province of delivery (categorized into four groups: Atlantic (New- foundland, Prince Edward Island, Nova

Scotia, and New Brunswick), Ontario, West (British Columbia, Alberta, and Saskatchewan), and others (Yukon, Nunavut and Northwest territories); multiple gestation, grand multiparity （≥5 previous viable pregnancies; and elderly primigravida (first pregnancy at ≥35 years of age). Multiple gestation, grand multiparity and elderly primigravida were coded as dichotomous variables (condition present or absent).

Chronic medical conditions were also characterized using information on DAD. Individuals with cardiorespiratory disease were those who had either lung disease (chronic airway obstruction, acute and chronic respiratory failure, and nonspecific lung disease) or heart disease (ischemic heart disease, atherosclerotic conditions, myocardial degeneration, and heart failure) or both. Chronic and end-stage renal disease and unspecified renal diseases in pregnancy were grouped together under renal disease. Women with smoking were those who had history of tobacco use and tobacco use disorders. Substance abuse includes independent abuse of all drugs except tobacco. Overweight and obesity were grouped together under obesity.

Main outcome measures included pre-eclampsia, preterm labor, and cesarean delivery. Descriptive information was also provided for intrauterine growth restriction, intrauterine fetal death, malpresentation, plancenta abruption, infection of amniotic cavity, prolonged pregnancy, antepartum hemorrhage, postpartum hemorrhage, major puerperal infection, gestational diabetes, venous thrombo-embolism (deep vein thromboembolism and pulmonary embolism), pneumonia, genitourinary tract infection, sepsis, medical induced labor, and surgical induced labor.

4.4.1.2 Descriptive analysis

Bivariate analyses were conducted to compare selected demographic and chronic medical conditions between women with each type of anemia and those with no anemia. The percentages of pregnant women with different types of anemia by selected demographic and chronic medical conditions were calculated. Chi square test was used for significance test and differences in selected demographic and chronic medical conditions were examined between each group of anemia and the group of no anemia.

4.4.1.3 Comparison of pregnancy outcomes

Logistic regression models were used to examine the associations of types of anemia with pregnancy outcomes, such as pre-eclampsia, preterm labor and cesarean delivery. Odds ratios (crude and adjusted) with 95% confidence intervals were computed before and after adjustment for maternal age, period, region, multiple gestation, grand multiparity and eldly primigravida. These variables were chosen as covariates because they were documented to be associated with maternal, perinatal, and delivery outcomes in previous studies. We used odds ratio as an association measure because of model convenience. Important outcomes of this study were not common. Data were analyzed with SAS software. Significance level was set at ≤ 0.05 for all analyses.

4.4.1.4 Assessment of interactions

Interaction in epidemiology refers to the extent to which the joint effect of two risk factors on disease differs from the independent effects of each of the factors (94, 95). Additive model was frequently used to estimate the "synergistic" effects of two risk factors. Logistic regression model used in this study is a multiplicative model, and could not be directly used to test additive interactions. Three measures of additive interactions:

RERI, the relative excess risk due to interaction; AP, the attributable proportion due to interaction; and S, the synergy index, were used in this study to assess the additive interactions between hemoglobinopathy and preeclampsia in relation to preterm labor or cesarean delivery (80). These measures are defined as follows:

$RERI = RR_{11} - RR_{10} - RR_{01} + 1;$

$AP = RERI/RR_{11};$

$S = (R_{11} - 1)/ [(RR_{10} - 1) + (RR_{01} - 1)]$

RR_{10} is the relative risk for hemoglobinopathy in the absence of preeclampsia; RR_{01} is the relative risk for preeclampsia in the absence of hemoglobinopathy; and RR_{11} is the relative risk when both of hemoglobinopathy and preeclampsia are present. The reference group are those who were unexposed to both hemoglobinopathy and preeclampsia, i.e., $RR_{00} = 1$. If there is no additive interaction, RERI and AP are equal to 0 and S is equal to 1. Since the outcomes were not common, we used ORs to substitute RRs to calculate the three interaction measures. Logistic regression analysis was used to calculate the ORs after adjustment for covariates. The 95% CIs for RERI, AP and S were estimated using the approach described by Andersson et al (81).

4.4.2. Development and validation of logistic regression models for pre-eclampsia, preterm labor, and cesarean delivery including hemoglobinopathy as a predictor.

4.4.2.1 Lists of risk factors/predictors

A set of risk factors (variables) previously identified as being associated with pre-eclampsia, preterm labor and cesarean delivery, along with other potential risk factors identified from the literature were examined for their possible association with pre-eclampsia, preterm labor and cesarean delivery. Variables that were significantly associated with pre-eclampsia, preterm labor and cesarean delivery ($p \leq 0.05$) were chosen as potential risk factors in the development of prediction models for above three conditions. Maternal age, province and year of delivery were coded as categorical variables (see Section 4.3.1), while all other risk factors were dichotomous variables

4.4.2.2 Descriptive analyses

We examined the age distributions of pre-eclampsia, preterm labor and cesarean delivery. The temporal trends in the occurrence of these three conditions were also assessed.

4.4.2.3 Logistic regression analyses

Logistic regression

Logistic regression is based on the principle of regressing a dichotomous dependent variable on a set of independent covariates (risk factors). In the present study, we used logistic regression models to examine the relations between the binary outcome (pre-eclampsia, preterm labor and cesarean delivery) and the risk factor hemoglobinopathy (sickle cell disease, sickle cell trait or thalassemia), as well as other

risk factors. We also used logistic regression models to identify explanatory risk indicators for pre-eclampsia, preterm labor and cesarean delivery, and to predict the probabilities of pre-eclampsia, preterm labor and cesarean delivery for women with hemoglobinopathy. Backward selection method, based on the likelihood ratio statistic ($p<0.05$), was used to identify important risk factors except sickle cell disease, sickle cell trait and thalassemia that were included in the models regardless of their p values. Following selection of the variables for the model, interactions between these variables were evaluated by adding an interaction term (the product of the two variables involved) into the model. The interaction term was then assessed for its contribution to the model by using the likelihood ratio test. Decisions on inclusion of interaction terms were based on model statistics, as well as clinical considerations. Interactions with a p-value ≤ 0.05 were deemed statistically significant and were entered into the model.

Assessing the fit of the model

Goodness of fit is usually evaluated in two steps. The first step is to generate global measures to assess how well a model fits the whole set of observations; the second step is to evaluate individual observations to see whether any of them are problematic for the regression model. Some global measures of goodness of fit include R^2 measures for logistic regression; sensitivity; specificity; overall correct classification; c statistic, and Hosmer-Lemeshow goodness of fit test. The second part of evaluating goodness of fit is focused on looking for outliers and influence points.

The R^2 measures for logistic regression give the proportion of variation in a dependent variable that is explained by a set of predictors (82). However, logistic regression R^2 does

not have such intuitive explanation, and the values tend to be close to 0 even for models that fit well.

Because there is an upper bound for the basic logistic regression R^2, a rescaled R^2 is usually presented to show the fraction of the upper bound that is attained.

Sensitivity, specificity, and overall correct classification of the model were obtained from the classification table in the SAS logistic regression printout. The sensitivity of a model was the proportion of patients observed to have experienced pre-eclampsia (or preterm labor, cesarean delivery) that the model correctly predicted pre-eclampsia (or preterm labor, cesarean delivery). The reported sensitivity, specificity, and overal correct classification of the model were based on a cutoff or decision threshold. A plot of the cut-off probability (above which pre-eclampsia, preterm labor, or cesarean delivery are predicted) against the sensitivity and specificity was used to illustrate the trade-off between the sensitivity and specificity of the model at different cut-off probabilities.

Model discrimination is the ability to correctly classify those with and without the outcome of interest based on predicted risk. The discriminating (predictive) ability of the model was assessed by the area under the receiver operating characteristic (ROC) curve, which is also referred to as the c statistic (82). The c statistic represents the probability of correctly ranking a randomly selected pair of patients with and without cesarean delivery (or preeclampsia, preterm labor). In other words, it is the probability that a patient with cesarean delivery (or preeclampsia, preterm labor) has a higher predicted probability than a patient without cesarean delivery (or preeclampsia, preterm labor). The c statistic ranges from 0 to 1 with 1 indicating a perfect prediction and 0.5 indicating a chance

prediction. It has been suggested that c statistic of 0.7-0.8 could be considered acceptable and that of 0.8-0.9 excellent.

Calibration describes the accuracy of a prediction model, especially, the extent of agreement between predicted and observed outcomes (82). A calibration plot of the percent (proportion) of patients with cesarean delivery, pre-eclampsia or preterm labor against the deciles of predicted probability was used to illustrate how well the model described (fit) the observed data. In brief, sas was used to generate deciles of predicted probability. The ascending values of the estimated predicted probabilities were divided into 10 groups, partitioned at the deciles values. The mean predicted percent (i.e. mean expected proportion) of each decile was estimated. In addition, the observed proportion of patients within each decile was calculated. Observed and mean predicted percent were plotted to generate a calibration curve. Calibration curves were plotted for the whole study population, as well as women with different types of hemoglobinopathy for the assessment of model fitness among them.

The Hosmer-Lemeshow goodness of fit test (82) was used to quantitatively evaluate how well the model described the observed data. This test is based on the null hypothesis that the model is a reasonable fit of the observed data. SAS was used to generate the Hosmer-Lemeshow goodness of fit test statistic. This test statistic follows a chi-square distribution with eight degree of freedom, and a p-value greater than 0.05 indicated that the model had a reasonable fit.

The prediction error rate and its reliability were also examined for the assessment of model fitness. The reliability of the prediction error rate observed in the model-building

data set is examined by applying the chosen prediction rule to a validation data set. If the new prediction error rate is about the same as that for the model-building data set, then the latter gives a reliable indication of the predictive ability of the fitted logistic regression model and the chosen prediction rule. If the new data lead to a considerably higher prediction error rate, then the fitted logistic regression model and the chosen prediction rule do not predict new observations as well as originally indicated. We calculated the prediction error rates in women with sickle cell disease, sickle cell trait, thalassemia, and no anemia by applying the fitted logistic regression model and the chosen prediction rule to each of the groups. The prediction error rates obtained from the four groups were compared to that from the model-building data set (whole population) to see whether the fitted logistic regression model predict the four groups as well as it did to the whole population (all pregnant women).

Regression diagnostics

Regression diagnostics were used to examine how well a model described the observed data and the impact of individual covariate patterns in the model (i.e. identifying excessively influential observations, manifested by poorly fitting estimates) (82). A listing of the values of the following variables was created in the SAS: predicted probability, residual, studentized residual, leverage value, and cbar. These measures were investigated in order to identify individual patients who did not fit the model well (outliers) and whose data might have had a strong influence on the coefficient estimates (influential cases). This gave an indication of how well the model fit the observed data and how sensitive the model was to individual patients' data. Studentized residual was

first plotted against predicted probability, and then was plotted against leverage value with the size of plotted circle proportional to cbar.

All specific covariate patterns (i.e. cases) identified as outliers or influential cases were examined for individual covariate values. Changes in the estimates of parameters, R^2, goodness-of-fit measures, and area under ROC when these influential covariate patterns were deleted and the model refit were also investigated.

Residual analysis

The residual is the difference between the observed (in this case "0" or "1") and predicted probability of cesarean delivery (or preeclampsia, preterm labor) based on the model. The deviance residual was used to identify patients who appeared to be outliers according to their residuals. The deviance residual for a particular case is the change in the model deviance (-2 times the difference between log likelihoods of a reduced model and the saturated model (contains as many parameters as there are data points)) when the case is excluded (82). As a rule of thumb, 99% of the data should be within ±3 standard deviations (SD) from the mean of the residuals (83). This rule is based on the approximate normality of the residuals.

Leverage plots

Leverage was used to identify patients who might have had a covariate pattern (a single set of values for the covariates in the model) that was unusual relative to the rest of the patients (82). The leverage value is defined as the relative influence of each observation on the model's fit, and the larger the value of this statistic, the more the observation influences that estimate of the regression coefficients.

Influence of individual cases

The effects of residual analysis and leverage are combined to generate a measure that expresses the influence of each patient on the estimated coefficients (82). C and cbar are confidence interval displacement diagnostics that provide scalar measures of the influence of individual observations on the estimated coefficient. These diagnostics are based on the same idea as the Cook distance in linear regression theory. In this analysis, cbar was used to identify influential cases (i.e. to identify those covariate patterns that were poorly fit and those that had a great deal of influence on the values of the estimated coefficients). Hosmer and Lemeshow (82) suggest that the "influence diagnostic must be larger than 1.0" for an individual covariate pattern to have an effect on the estimated coefficients. Large values for CBAR identified cases that were examined further.

5. RESULTS

5.1 Pregnancy Outcomes in Women with Sickle Cell disease, Sickle Cell Trait, Thalassemia, and Nutritional Deficiency Anemia

5.1.1 Demographic and clinical characteristics of the study population

During the period from 1991 to 2007, there were 4,381,277 deliveries included in the analysis. Of these, 419 were to women with sickle cell disease (SCD), 718 with sickle cell trait (SCT), 3,803 with thalassemia, 5,782 with nutritional deficiency anemia (NDA), and 4,199,799 were to women without anemia.

There were increasing trends in proportions of deliveries to women with SCD, SCT and thalassemia during the 17-year period. The frequency of SCD increased dramatically from 2.5 per 100,000 deliveries in 1991 to 6.4 per 100,000 deliveries in 2007, while only a slight increase was observed in the frequencies of SCT (from 11.2 per 100,000 to 17.4 per 100,000), and thalassemia (from 67.7 per 100,000 to 79.4 per 100,000) over the same period.

The age distribution was similar for women with different types of anemia (SCD, SCT, thalassemia, NDA) and no anemia. Of those deliveries in women with SCD, 76.4% were in women aged 20-34, while only 7.64% and 3.34% were in those aged <20 and >40 respectively.

Most of the deliveries in women with SCD were observed in Ontario (89.26%), while only 0.48% of such deliveries were in Atlantic regions (Table 10). A similar distribution was found for the SCT group, in which 88.3%, 10.58% and 0.84 % of deliveries occur in Ontario, the west and Atlantic regions respectively. However, the regional pattern for

thalassemia and NDA groups appeared to be very much different from the SCD and SCT groups. Deliveries in women with thalassemia and NDA were more frequent in the west than in Ontario.

The proportions of multiple gestation and elderly primigravida were higher among women with SCD compared with those with no anemia. More women were elderly primigravida in SCT group than in the non-anemia group. A higher percentage of grand multiparity was observed in women with thalassemia compared with women with no anemia (Table 10).

Figure 1.Temporal trends of deliveries in women with hemoglobinopathy, Canada, 1991/1992-2007/2008

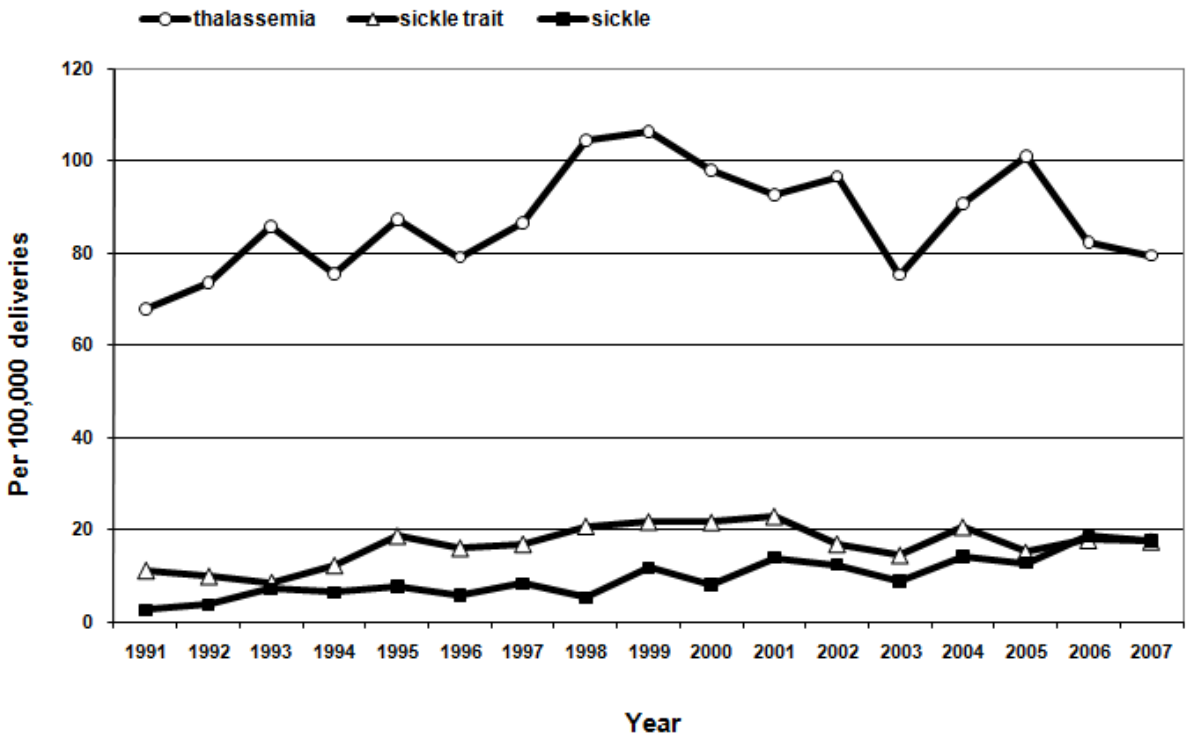


Table 10. Maternal delivery characteristics by anemia status: Canada excluding Quebec and Manitoba, 1991/1992 –2007/2008

Characteristic	Sickle cell disease (N=419)		Sickle cell trait (N=718)		Thalassemia (N=3803)		NDA** (N=5782)		No anemia (N=4199799)
	No. (%)	P value*	No. (%)	P value*	No. (%)	P value*	No. (%)	P value*	No. (%)
Age (years)									
<20	32 (7.64)	0.0032	58 (8.08)	0.0011	60 (1.58)	<0.0001	680 (11.76)	<0.0001	232235 (5.53)
20-24	96 (22.91)		144 (20.06)		424 (11.15)		1436 (24.84)		736892 (17.55)
25-29	119 (28.40)		206 (28.69)		1090 (28.66)		1639 (28.35)		1311775 (31.23)
30-34	105 (25.06)		188 (26.18)		1382 (36.34)		1342 (23.21)		1280475 (30.49)
35-39	53 (12.65)		99 (13.79)		715 (18.80)		577 (9.98)		545149 (12.98)
≥40	14 (3.34)		23 (3.20)		132 (3.47)		108 (1.87)		93273 (2.22)
Period									
1991-1993	36 (8.59)	<0.0001	81 (11.28)	<0.0001	617 (16.22)	<0.0001	1178 (20.37)	<0.0001	776272 (18.48)
1994-1996	53 (12.65)		126 (17.55)		649 (17.07)		1015 (17.55)		763878 (18.19)

Table10: cont'd

1997-1999	63 (15.04)		149 (20.75)		747 (19.64)		856 (14.80)		722015 (17.19)
2000-2002	83 (19.81)		149 (20.75)		697 (18.33)		1461 (25.27)		694102 (16.53)
2003-2005	89 (21.24)		124 (17.27)		666 (17.51)		821 (14.20)		727071 (17.31)
2006-2007	95 (22.67)		89 (12.40)		427 (11.23)		451 (7.80)		516461 (12.30)
Region									
Atlantic	2 (0.48)	<0.0001	6 (0.84)	<0.0001	59 (1.55)	<0.0001	387 (6.69)	<0.0001	358809 (8.54)
Ontario	374 (89.26)		634 (88.30)		1330 (34.97)		1955 (33.81)		2312167 (55.05)
West	41 (9.79)		76 (10.58)		2411 (63.40)		3392 (58.66)		1506135 (35.86)
others	2 (0.48)		2 (0.28)		3 (0.08)		48 (0.83)		22688 (0.54)
Multiple gestation	10 (2.39)	0.0126	12 (1.67)	0.1508	68 (1.79)	<0.0001	130 (2.25)	<0.0001	46602 (1.11)
Grand multiparity†	1 (0.24)	0.9249	5 (0.70)	0.0230	12 (0.32)	0.5205	64 (1.11)	<0.0001	11013 (0.26)
Elderly primigravida‡	10 (2.39)	0.0018	9 (1.25)	0.3631	126 (3.31)	<0.0001	61 (1.05)	0.3142	38974 (0.93)

* Compared with those with no anemia. ** NDA = nutritional deficiency anemia

† Having had ⩾ 5 previous viable pregnancies. ‡ First pregnancy at ⩾ 35 years of age.

5.1.2 Chronic medical conditions in women with sickle cell disease, sickle cell trait, thalassemia, and nutritional deficiency anemia

Table 11 shows maternal chronic medical conditions by anemia status. Women with hemoglobinopathy had more chronic medical conditions than those with no anemia. Pre-existing hypertension, pre-existing diabetes, cardiorespiratory disease, renal disease, and connective tissue disease were reported more often among women with SCD than among women with no anemia. The frequencies of all these chronic medical conditions except pre-existing diabetes were also higher among women with SCT and NDA compared to women with no anemia. Reporting of pre-existing hypertension, cardiorespiratory disease and connective tissue disease were higher in women with thalassemia than in women with no anemia.

Women with thalassemia and NDA were more likely to smoke compared to women with no anemia. Obesity was more common among women with SCT and NDA than among women with no anemia. No difference in the frequencies of smoking and obesity was found between SCD and non-anemia groups. The frequency of substance abuse was higher among women with SCD, SCT, and NDA than among women with no anemia.

Table 11. Maternal chronic medical conditions by anemia status: Canada excluding Quebec and Manitoba 1991/1992 – 2007/2008

Characteristic	Sickle cell disease (N=419)		Sickle cell trait (N=718)		Thalassemia (N=3803)		NDA** (N=5782)		No anemia (N=4199799)
	No. (%)	P value*	No. (%)	P value*	No (%)	P value*	No. (%)	P value*	No. (%)
Pre-existing hypertension	7 (1.67)	0.0003	13 (1.81)	<0.0001	35 (0.92)	<0.0001	39 (0.67)	0.0161	19320 (0.46)
Pre-existing diabetes	6 (1.43)	0.0079	7 (0.97)	0.0793	20 (0.53)	0.8826	36 (0.62)	0.2245	21371 (0.51)
Cardiorespiratory disease	7 (1.67)	<0.0001	2 (0.28)	<0.0001	4 (0.11)	0.0006	18 (0.31)	<0.0001	926 (0.02)
Renal disease	1 (0.24)	<0.0001	1 (0.14)	0.0002	1 (0.03)	0.2525	5 (0.09)	<0.0001	371 (0.01)
Connective tissue diseases	2 (0.48)	0.0009	5 (0.70)	<0.0001	14 (0.37)	<0.0001	10 (0.17)	0.0013	2735 (0.07)
Previous cesarean section	54 (12.89)	0.1406	95 (13.23)	0.0259	463 (12.17)	0.0026	730 (12.63)	<0.0001	447924 (10.67)
Obesity	3 (0.72)	0.5599	8 (1.11)	0.0240	28 (0.74)	0.0536	73 (1.26)	<0.0001	21528 (0.51)
Smoking	1 (0.24)	0.4403	2 (0.28)	0.3901	8 (0.21)	0.0102	77 (1.33)	<0.0001	21259 (0.51)
Substance abuse	12 (2.86)	<0.0001	9 (1.25)	0.0232	27 (0.71)	0.3768	150 (2.59)	<0.0001	25169 (0.60)

* Compared with those with no anemia. ** NDA = nutritional deficiency anemia

5.1.3 Pregnancy outcomes in women with sickle cell disease, sickle cell trait, thalassemia and nutritional deficiency anemia

Table 12 shows frequency of pregnancy outcomes by anemia status. Crude and adjusted odds ratios for pregnancy outcomes related to different kinds of anemia are presented in Table 16 (in appendix I) and Table 13 respectively. Women with hemoglobinopathy were at an increased risk for adverse pregnancy outcomes.

Pre-eclampsia was diagnosed in 9.6% of women with SCD, 6.6% of women with SCT, 4.3% of women with thalassemia, 6.3% of women with NDA, and 3.8% of women with no anemia (Table 12). As shown in Table 10, after adjustment for covariates, the odds of pre-eclampsia was 140% higher among women with SCD, 80% higher among women with SCT, and 70% higher among women with NDA compared to those with no anemia, but the odds ratio was not statistically significant for the thalassemia group.

Preterm labor occurred in 16% of SCD pregnancies, 11% of SCT pregnancies, 8% of thalassemia, and 8% of NDA pregnancies (Table 12). Preterm labor was associated with SCD (OR = 3.2, 95% CI = 2.5, 4.2), SCT (OR = 2.1, 95% CI = 1.7, 2.7), thalassemia (OR = 1.4, 95% CI = 1.2, 1.6), and NDA (OR = 1.4, 95% CI = 1.3, 1.6) compared with no anemia after adjustment for covariates (Table 13).

Forty-two percent of women with SCD and over one-fourth of women with SCT, thalassemia and NDA had a cesarean delivery (Table 12). Cesarean delivery rate was 160% higher among SCD women, 50% higher among SCT and NDA women, and 30% higher among thalassemia women than among women with no anemia after adjustment for covariates (Table 13).

The following adverse pregnancy outcomes were associated with an increased likelihood of occurrence in all women with four different kinds of anemia when compared to women with no anemia: intrauterine growth restriction (IUGR) (OR = 3.5, 95% CI = 2.4, 5.1 for SCD; OR = 1.5, 95% CI = 1.0, 2.3 for SCT; and OR =2.3, 95% CI = 2.0, 2.7 for thalassemia; OR = 1.2 95% CI = 1.0, 1.3 for NDA); placenta abruption (OR = 2.5, 95% CI = 1.6, 3.8 for SCD; OR = 2.2, 95% CI = 1.4, 3.5 for SCT; OR = 1.6, 95% CI = 1.3, 2.0 for thalassemia; and OR = 2.5, 95% CI = 2.1, 2.9 for NDA); infection of amniotic cavity (OR = 3.7, 95% CI = 2.3, 6.1 for SCD; OR = 2.1, 95% CI = 1.3, 3.5 for SCT; OR = 2.3, 95% CI = 1.9, 2.8 for thalassemia; and OR = 1.6, 95% CI = 1.3, 1.9 for NDA) (Table 13).

Intrauterine fetal death (IUFD) was significantly associated with SCD or thalassemia (OR = 4.0, 95% CI = 2.0, 8.0 for SCD; and OR = 1.7, 95% CI = 1.2, 2.4 for thalassemia). Women with SCD or NDA were at an increased risk for medical induced labor (OR = 1.5, 95% CI = 1.2, 1.9 for SCD, and OR = 1.2, 95% CI = 1.1, 1.3 for NDA) (Table 13).

Malpresentation, gestational diabetes, and surgical induced labor were not associated with any types of anemia that were studied, and a decreased risk for prolonged pregnancy was observed in women with SCD (OR = 0.4, 95% CI = 0.3, 0.7), or thalassemia (OR= 0.7, 95% CI = 0.6, 0.8) (Table 13).

As shown in Table 13, infection and hematological complications were more frequent among women with different types of anemia compared to those without anemia. Compared to the reference group (women without anemia), women in the four study groups (SCD, SCT, thalassemia, or NDA) were at an increased risk for pneumonia (OR =

154.9, 95% CI = 94.6, 253.7 for SCD; OR = 14.5, 95% CI = 4.7, 45.1 for SCT; OR = 9.2, 95% CI = 5.1, 16.7 for thalassemia, OR = 11.4, 95% CI = 7.5, 17.4 for NDA); genitourinary tract infection (GTI) (OR = 2.8, 95% CI = 1.7, 4.6 for SCD; OR = 3.3, 95% CI = 2.4, 4.6 for SCT; OR = 1.1, 95% CI = 1.0, 1.4 for thalassemia, OR = 2.5, 95% CI = 2.2, 2.9 for NDA); sepsis (OR = 8.1, 95% CI = 4.0, 16.4 for SCD; OR = 5.3, 95% CI = 2.8, 9.9 for SCT; OR = 3.4, 95% CI = 2.4, 4.8 for thalassemia, OR = 4.8, 95% CI = 3.9, 6.0 for NDA); and puerperal infection (OR = 8.1, 95% CI = 4.7, 14.2 for SCD; OR = 5.6, 95% CI = 3.5, 9.1 for SCT; OR = 2.9, 95% CI = 2.2, 4.0 for thalassemia, OR = 4.2, 95% CI = 3.5, 5.1 for NDA) during hospitalizations for childbirth.

All anemic women included in the study except those with SCT were at an increased risk for antepartum hemorrhage (OR = 2.0, 95% CI = 1.4, 3.0 for SCD; OR = 2.0, 95% CI = 1.7, 2.2 for thalassemia, OR = 3.0, 95% CI = 2.7, 3.3 for NDA); and postpartum hemorrhage (OR = 1.9, 95% CI = 1.3, 2.8 for SCD; OR = 2.1, 95% CI = 1.9, 2.3 for thalassemia; OR = 4.3, 95% CI = 4.0, 4.6 for NDA).Venous thrombo-embolism (VTE) was significantly more likely to be present among women with SCD (OR = 19.0, 95% CI = 8.5, 42.7) and NDA (OR = 4.7, 95% CI = 2.9, 7.4).

Table 12. Frequencies of pregnancy outcomes by anemia status: Canada excluding Quebec and Manitoba, 1991/1992 – 2007/2008

	Sickle cell disease (N=419)	Sickle cell trait (N=718)	Thalassemia (N=3803)	NDA[‡] (N=5782)	No anemia (N=4199799)
Pre-eclampsia	40 (9.55)[†]	47 (6.55)	163 (4.29)	364 (6.30)	160872 (3.83)
Preterm labor	69 (16.47)	79 (11.00)	296 (7.78)	476 (8.23)	224602 (5.35)
Caesarean delivery	176 (42.00)	203 (28.27)	1053 (27.69)	1554(26.88)	907019 (21.60)
IUGR[‡]	30 (7.16)	23 (3.20)	220 (5.79)	179 (3.10)	94168 (2.24)
IUFD[‡]	8 (1.91)	7 (0.97)	31 (0.82)	31 (0.54)	19955 (0.48)
Placenta abruption	16 (3.92)	18 (2.51)	72 (1.89)	163 (2.82)	47125 (1.12)
amniotic cavity infection	16 (3.82)	16 (2.23)	99 (2.60)	101 (1.75)	43499 (1.04)
Malpresentation	27(6.44)	55 (7.66)	308 (8.10)	426 (7.37)	306297 (7.29)
Prolonged pregnancy	19 (4.53)	55 (7.66)	2.28 (6.00)	475 (8.22)	377225 (8.98)
Medical induced labor	102 (24.34)	128 (17.83)	702 (18.46)	1155(19.98)	716334 (17.06)
Surgical induced labor	32 (7.64)	55 (7.66)	249 (6.55)	421 (7.28)	333771 (7.95)

Table 12: cont'd

Gestational diabetes	15 (3.58)	29 (4.04)	131 (3.44)	203 (3.51)	141196 (3.36)
Antepartum bleeding	16 (3.80)	22 (3.04)	153 (4.02)	327 (5.66)	79734 (1.90)
Postpartum hemorrhage	29 (6.92)	28 (3.90)	352 (9.26)	1002(17.33)	72138 (4.10)
VTE‡	6 (1.43)	2 (0.28)	6 (0.16)	18 (0.31)	2944 (0.07)
Major puerperal infection	13 (3.10)	17 (2.37)	45 (1.18)	144 (1.97)	8291 (0.44)
Pneumonia	17 (4.06)	3 (0.42)	11 (0.29)	22 (0.38)	1274 (0.03)
GTI‡	17 (4.06)	36 (5.01)	62 (1.63)	224 (3.87)	61990 (1.48)
Sepsis	8 (1.91)	10 (1.39)	33 (0.87)	83 (1.44)	11313 (0.27)

† Data are presented as No. (%).

‡ NDA = nutritional deficiency anemia; IUGR = intrauterine growth restriction; IUFD = intrauterine fetal death; PROM = premature rupture of membranes; VTE = Venous Thrombo-Embolism; GTI = Genitourinary Tract Infection

Table 13. Adjusted[†] odds ratios and 95% confidence intervals for pregnancy outcomes related to different types of anemia: Canada excluding Quebec and Manitoba, 1991/1992 – 2007/2008

Characteristic	Sickle cell disease (N=419)	Sickle cell trait (N=718)	Thalassemia (N=3803)	NDA[‡] (N=5782)
Pre-eclampsia	2.4 (1.8-3.4)	1.8 (1.3-2.4)	1.1 (0.9-1.3)	1.7 (1.5-1.9)
Preterm labor	3.2 (2.5-4.2)	2.1 (1.7-2.7)	1.4 (1.2-1.6)	1.4 (1.3-1.6)
Cesarean delivery	2.6 (2.1-3.2)	1.5 (1.3-1.7)	1.3 (1.2-1.4)	1.5 (1.4-1.5)
IUGR[‡]	3.5 (2.4-5.1)	1.5 (1.0-2.3)	2.3 (2.0-2.7)	1.2 (1.0-1.3)
IUFD[‡]	4.0 (2.0-8.0)	2.0 (0.9-4.2)	1.7 (1.2-2.4)	1.1 (0.8-1.5)
Placenta abruption	3.5 (2.6-4.8)	2.2 (1.4-3.5)	1.6 (1.3-2.0)	2.5 (2.1-2.9)
Infection of amniotic cavity	3.7 (2.3-6.1)	2.1 (1.3-3.5)	2.3 (1.9-2.8)	1.6 (1.3-1.9)
Malpresentation	0.9 (0.6-1.3)	1.0 (0.8-1.4)	1.0 (0.9-1.1)	1.0 (0.9-1.3)
Prolonged pregnancy	0.4 (0.3-0.7)	0.8 (0.6-1.1)	0.7 (0.6-0.8)	0.9 (0.8-1.0)
Medical Induced Labor	1.5 (1.2-1.9)	1.1 (0.9-1.3)	1.1 (0.9-1.2)	1.2 (1.1-1.3)
Surgical Induced Labor	0.8 (0.6-1.2)	0.8 (0.6-1.1)	0.9 (0.8-1.1)	1.0 (0.9-1.1)

Table 13: Con'd

Gestational diabetes	1.2 (0.7-2.1)	1.2 (0.9-2.1)	1.1 (0.9-1.4)	1.1 (0.9-1.2)
Antepartum/intrapartum hemorrhage	2.0 (1.4-3.0)	1.6 (0.9-2.8)	2.0 (1.7-2.2)	3.0 (2.7-3.3)
Postpartum hemorrhage	1.9 (1.3-2.8)	1.1 (0.7-1.6)	2.1 (1.9-2.3)	4.3 (4.0-4.6)
VTE‡	19.0 (8.5-42.7)	3.8 (0.9-15.1)	2.2 (1.0-4.8)	4.7 (3.0-7.4)
Major puerperal infection	8.1 (4.7-14.2)	5.6 (3.5-9.1)	2.9 (2.2-4.0)	4.2 (3.5-5.1)
Pneumonia	154.9 (94.6-253.7)	14.5 (4.7-45.1)	9.2 (5.1-16.7)	11.4 (7.5-17.4)
GTI‡	2.8 (1.7-4.6)	3.3 (2.4-4.6)	1.1 (1.0-1.4)	2.5 (2.2-2.9)
Sepsis	8.1 (4.0-16.4)	5.3 (2.8-9.9)	3.4 (2.4-4.8)	4.8 (3.9-6.0)

† Models adjusted for age, birth year, province, multiple gestation, grand multiparity, elderly primigravida.

‡ NDA = nutritional deficiency anemia; IUGR = intrauterine growth restriction;
IUFD = intrauterine fetal death; PROM = premature rupture of membranes;
VTE = Venous Thrombo-Embolism; GTI =Genitourinary Tract Infection

5.1.4 Assessment of potential biological interactions

5.1.4.1 Additive interactions between pre-eclampsia and hemoglobinopathy relation to preterm labor

Additive interactions between preeclampsia and different kinds of anemia in relation to preterm labor were investigated and shown in Tables 14-17 and in figures 2-5.

The four bars in Figure 2 displays from left to right the risk (defined as 1) in reference group (women without anemia or preeclampsia), the odds ratio for women with sickle cell disease (SCD), the odds ratio for women with preeclampsia, and the odds ratio for women with both SCD and preeclampsia. The three measures of additive interactions, RERI, AP and S, were 15.5 (95%CI: 2.9, 28.0), 0.8 (0.6-0.9), and 5.5 (95%CI: 2.7-11.1) respectively, suggesting that there was an additive interaction between sickle cell disease and preeclampsia in relation to preterm labor (Table 14). The odds ratio for preterm labor was 2.5 among women with sickle cell disease, and 2.9 among women with preeclampsia; but it increased dramatically to 19.9 when a SCD woman developed preeclampsia during pregnancy (Table 14), which was much more than the simple algebra addition of the two risks for SCD and preeclampsia.

Table 15 shows the three measures of additive interaction between sickle cell trait (SCT) and preeclampsia in relation to preterm labor: RERI (7.5, 95% CI: 0.8-14.2), AP (0.7, 95% CI: 0.5-0.9), and S (3.7, 95%CI: 1.9-7.3). All these three measures indicated that there was an additive interaction between SCT and preeclampsia in relation to preterm labor. The odds ratio for preterm labor was only 1.8 among women with SCT, but increased to 11.3 among women with both SCT and preeclampsia, suggesting that

compared to women without anemia and preeclampsia, women with SCT were only 1.8 times more likely to have preterm labor, but they would be 11.3 times more likely to have preterm labor if they developed preeclampsia during pregnancy (Table 15).

As shown in Table 16, all the three measures of additive interaction, RERI (3.0, 95% CI: 0.8-5.3), AP (0.5, 95% CI: 0.3-0.7), and S (2.4, 95% CI: 1.5-3.6), indicate a possible additive interaction between thalassemia and preeclampsia in relation to preterm labor. The odds ratio for preterm labor was 1.3 among women with thalassemia, and 6.2 among women with both thalassemia and preeclampsia.

The three measures of additive interaction presented in Table 17, RERI, AP, and S were 0.7 (95% CI: -0.4-11.8), 0.2 (95% CI: -0.06-0.4), and 1.3 (95% CI: 0.9-1.9) respectively, suggesting that there is no significant additive interaction between NDA and preeclampsia in relation to preterm labor.

Table 14. Additive interaction between sickle cell disease (SCD) and preeclampsia in relation to preterm labor

Exposure	OR*	95% Confidence Interval	
SCD	2.5	1.8	3.5
Preeclampsia	2.9	2.9	3.0
SCD & Preeclampsia	19.9	10.6	37.3

Measure	Point estimate	95% Confidence Interval	
RERI**	15.5	2.9	28.0
AP†	0.8	0.6	0.9
S‡	5.5	2.7	11.1

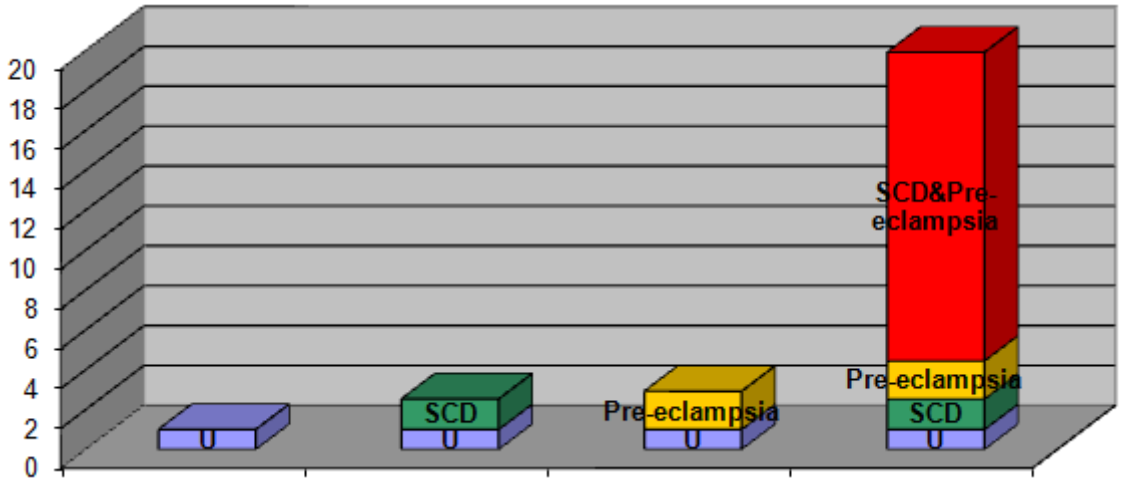
* OR = odds ratio; model adjusted for age, birth year, province, multiple gestation, grand multiparity and elderly primigravida; reference group: those who are unexposed to either anemia or preeclampsia

** RERI = relative excess risk due to interaction

† AP = attributable proportion due to interaction

‡ S = synergy index

Figure 2. Odds ratio for preterm labor among women who were exposed to sickle cell disease (SCD), preeclampsia or both.



* U is the reference category: those who were unexposed to either anemia or preeclampsia

Table 15. Additive interaction between sickle cell trait (SCT) and preeclampsia in relation to preterm labor

Exposure	OR*	95% Confidence Interval	
SCT	1.8	1.4	2.4
Preeclampsia	2.9	2.9	3.0
SCT & preeclampsia	11.3	6.2	20.4

Measure	Point estimate	95% Confidence Interval	
RERI**	7.5	0.8	14.2
AP†	0.7	0.5	0.9
S‡	3.7	1.9	7.3

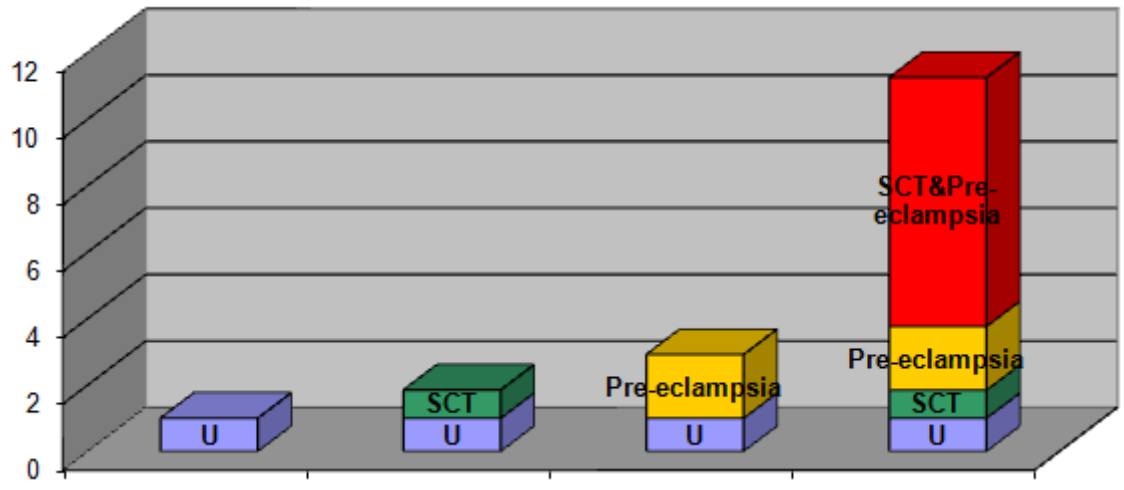
* OR = odds ratio; model adjusted for age, birth year, province, multiple gestation, grand multiparity and elderly primigravida; reference group: those who are unexposed to either anemia or preeclampsia

** RERI = relative excess risk due to interaction

† AP = attributable proportion due to interaction

‡ S = synergy index

Figure 3. Odds ratio for preterm labor among women who were exposed to sickle cell trait (SCT), preeclampsia or both.



* U is the reference category: those who were unexposed to either anemia or preeclampsia

Table 16. Additive interaction between thalassemia and preeclampsia in relation to preterm labor

Exposure	OR*	95% Confidence Interval	
Thalassemia	1.3	1.2	1.5
Preeclampsia	2.9	2.9	3.0
Thalassemia & Preeclampsia	6.2	4.3	8.9

Measure	Point estimate	95% Confidence Interval	
RERI**	3.0	0.8	5.3
AP†	0.5	0.3	0.7
S‡	2.4	1.5	3.6

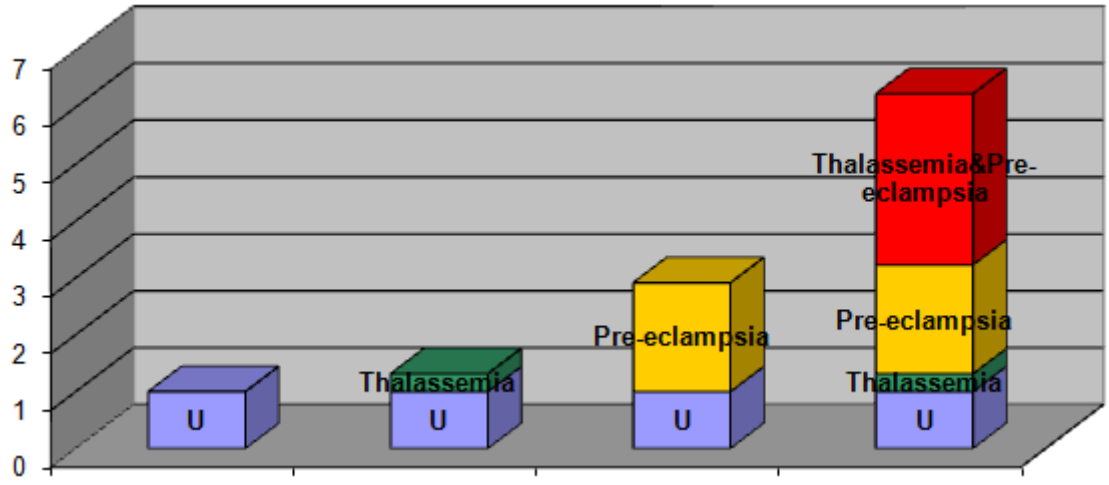
* OR = odds ratio; model adjusted for age, birth year, province, multiple gestation, grand multiparity and elderly primigravida; reference group: those who are unexposed to either anemia or preeclampsia

** RERI = relative excess risk due to interaction

† AP = attributable proportion due to interaction

‡ S = synergy index

Figure 4. Odds ratio for preterm labor among women who were exposed to thalassemia, pre-eclampsia or both.



* U is the reference category: those who were unexposed to either anemia or preeclampsia

Table 17. Additive interaction between nutritional deficiency anemia (NDA) and preeclampsia in relation to preterm labor

Exposure	OR*	95% Confidence Interval	
NDA	1.4	1.3	1.5
Preeclampsia	2.9	2.9	3.0
NDA & preeclampsia	4.0	3.0	5.2

Measure	Point estimate	95% Confidence Interval	
RERI**	0.7	-0.4	1.8
AP†	0.2	-0.06	0.4
S‡	1.3	0.9	1.9

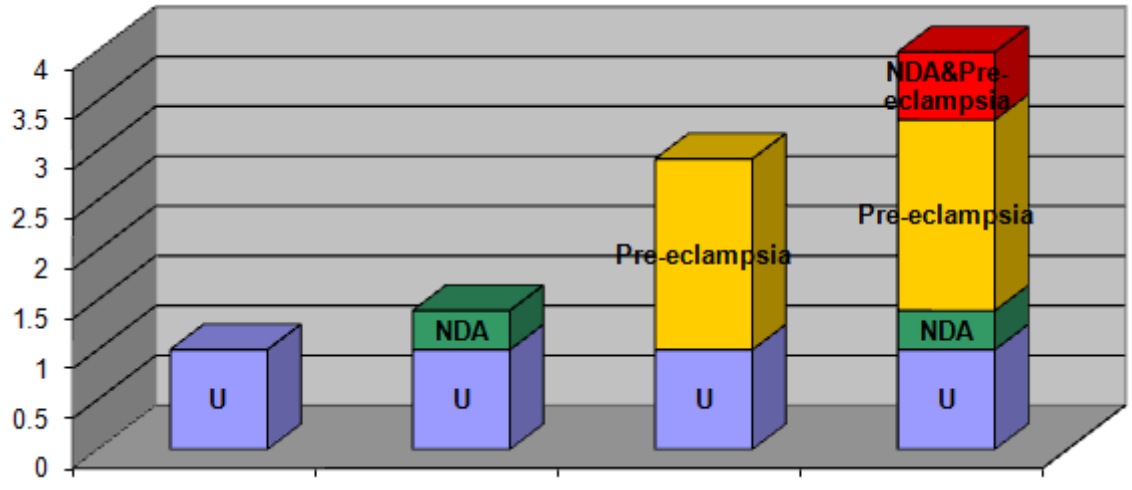
* OR = odds ratio; model adjusted for age, birth year, province, multiple gestation, grand multiparity and elderly primigravida; reference group: those who are unexposed to either anemia or preeclampsia

** RERI = relative excess risk due to interaction

† AP = attributable proportion due to interaction

‡ S = synergy index

Figure 5. Odds ratio for preterm labor among women who were exposed to nutritional deficiency anemia (NDA), preeclampsia or both.



* U is the reference category: those who were unexposed to either anemia or preeclampsia

5.1.4.2 Additive interactions between pre-eclampsia and hemoglobinopathy in relation to cesarean delivery

Additive interactions between preeclampsia and different kinds of anemia in relation to cesarean delivery were also investigated and shown in Table 18-21 and in Figure 3-6.

As shown in Table 18, the three measures of additive interaction, RERI, AP and S, were 10.4 (95%CI: 0.4-21.2), 0.8 (95%CI: 0.6-1.0), and 5.3 (95%CI: 2.2-12.6) respectively, indicating there was a significant additive interaction between SCD and preeclampsia in relation to cesarean delivery. The odds ratio for cesarean delivery was 2.3 among women with SCD, and 2.1 among women with preeclampsia. But this risk increased dramatically from 2.3 to 13.8 when a woman with SCD developed preeclampsia during pregnancy.

The additive interaction also occurred between SCT and preeclampsia in relation to cesarean delivery. RERI, AP, and S were 3.9 (95%CI: 0.05-7.8), 0.6 (95%CI: 0.4-0.8) and 3.6 (95%CI: 1.7-7.6) respectively (Table 19). Compared to women without preeclampsia or anemia, women with SCT were 1.4 times more likely to have cesarean delivery (OR = 1.8), whereas for women with both SCT and preeclampsia, it was 6.4 times (OR = 11.3).

There was an additive interaction between thalassemia and preeclampsia in relation to cesarean delivery (RERI: 0.5, 95%CI: 0.03-1.4; AP: 0.2, 95%CI: 0.1-0.4; and S: 1.3, 95%CI: 0.8-2.2) (Table 20). The odds ratio was only 1.3 for women with thalassemia, but was 2.9 if a woman had both thalassemia and preeclampsia during pregnancy.

The three measures, RERI (-0.03, 95% CI: -0.6, 0.5), AP (-0.01, 95% CI: -0.2, 0.2), and S (1.0, 95% CI: 0.7-1.4) are presented in Table 21, suggesting that there was no significant additive interaction between NDA and preeclampsia in relation to cesarean delivery.

Table 18. Additive interaction between sickle cell disease (SCD) and preeclampsia in relation to cesarean delivery

Exposure	OR*	95% Confidence Interval	
SCD	2.3	1.8	2.8
Preeclampsia	2.1	2.1	2.2
SCD & preeclampsia	13.8	6.3	30.2

Measure	Point estimate	95% Confidence Interval	
RERI**	10.4	0.4	21.2
AP†	0.8	0.6	1.0
S‡	5.3	2.2	12.6

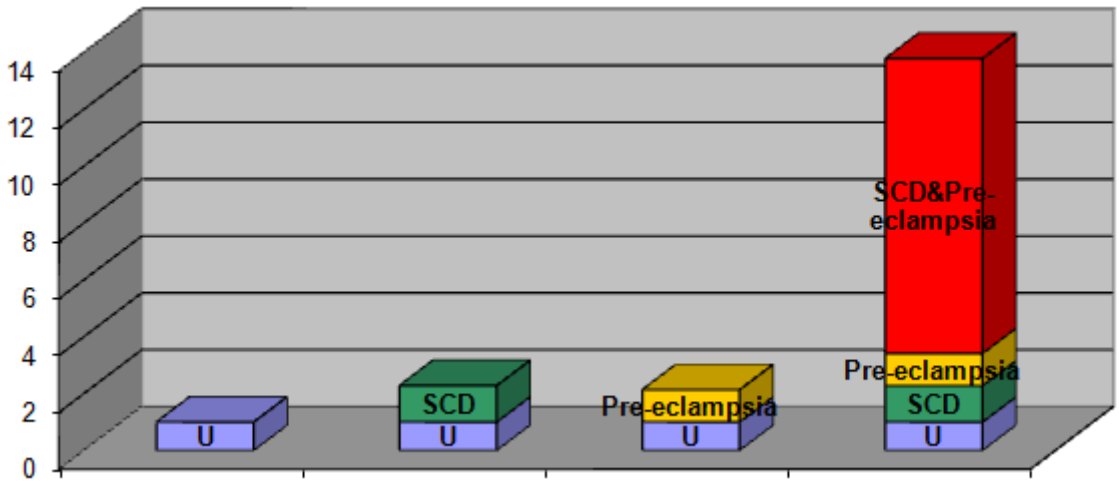
* OR = odds ratio; model adjusted for age, birth year, province, multiple gestation, grand multiparity and elderly primigravida; reference group: those who are unexposed to either anemia or preeclampsia

** RERI = relative excess risk due to interaction

† AP = attributable proportion due to interaction

‡ S = synergy index

Figure 6. Odds ratio for cesarean delivery among women who were exposed to sickle cell disease (SCD), preeclampsia or both.



* U is the reference category: those who were unexposed to either anemia or preeclampsia

Table 19. Additive interaction between sickle cell trait (SCT) and preeclampsia in relation to cesarean delivery

Exposure	OR*	95% Confidence Interval	
SCT	1.4	1.1	1.6
Preeclampsia	2.1	2.1	2.2
SCT & preeclampsia	6.4	3.5	11.7

Measure	Point estimate	95% Confidence Interval	
RERI**	3.9	0.05	7.8
AP†	0.6	0.4	0.8
S‡	3.6	1.7	7.6

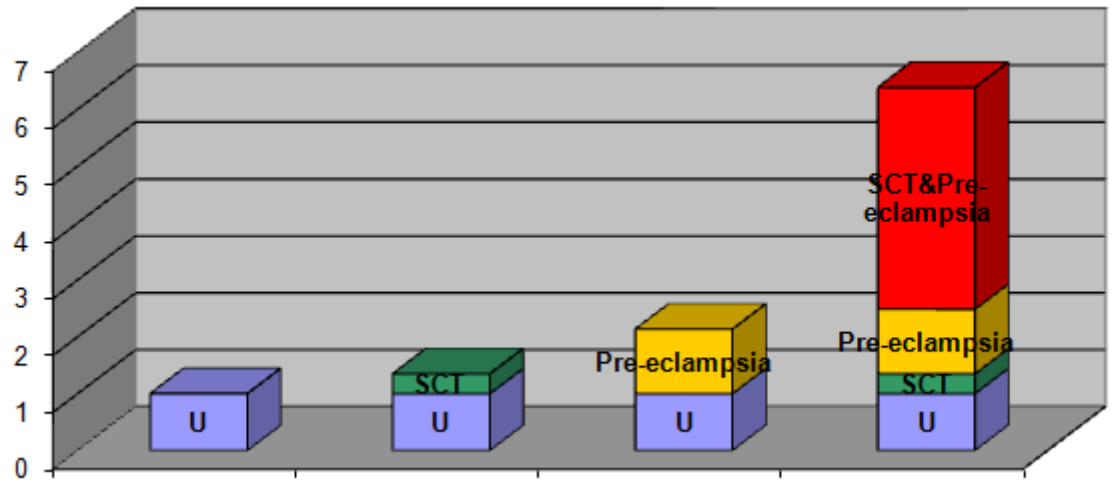
* OR = odds ratio; model adjusted for age, birth year, province, multiple gestation, grand multiparity and elderly primigravida; reference group: those who are unexposed to either anemia or preeclampsia

** RERI = relative excess risk due to interaction

† AP = attributable proportion due to interaction

‡ S = synergy index

Figure 7. Odds ratio for cesarean delivery among women who were exposed to sickle cell trait (SCT), preeclampsia or both.



* U is the reference category: those who were unexposed to either anemia or preeclampsia

Table 20. Additive interaction between thalassemia and preeclampsia in relation to cesarean delivery

Exposure	OR*	95% Confidence Interval	
thalassemia	1.3	1.2	1.4
preeclampsia	2.1	2.1	2.2
Thalassemia & preeclampsia	2.9	2.1	4.0

Measure	Point estimate	95% Confidence Interval	
RERI**	0.5	0.03	1.4
AP†	0.2	0.1	0.4
S‡	1.3	0.8	2.2

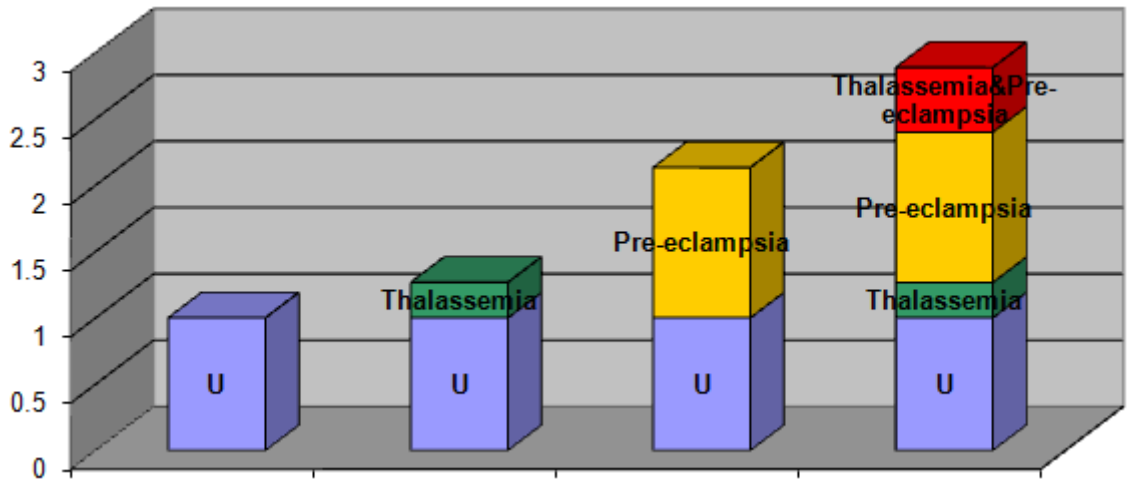
* OR = odds ratio; model adjusted for age, birth year, province, multiple gestation, grand multiparity and elderly primigravida; reference group: those who are unexposed to either anemia or preeclampsia

** RERI = relative excess risk due to interaction

† AP = attributable proportion due to interaction

‡ S = synergy index

Figure 8. Odds ratio for cesarean delivery among women who were exposed to thalassemia, preeclampsia or both.



* U is the reference category: those who were unexposed to either anemia or preeclampsia

Table 21. Additive interaction between nutritional deficiency anemia (NDA) and preeclampsia in relation to cesarean delivery

Exposure	OR*	95% Confidence Interval	
NDA	1.4	1.4	1.5
Preeclampsia	2.1	2.1	2.2
NDA & preeclampsia	2.5	2.1	3.2

Measure	Point estimate	95% Confidence Interval	
RERI**	-0.03	-0.6	0.5
AP†	-0.01	-0.2	0.2
S‡	1.0	0.7	1.4

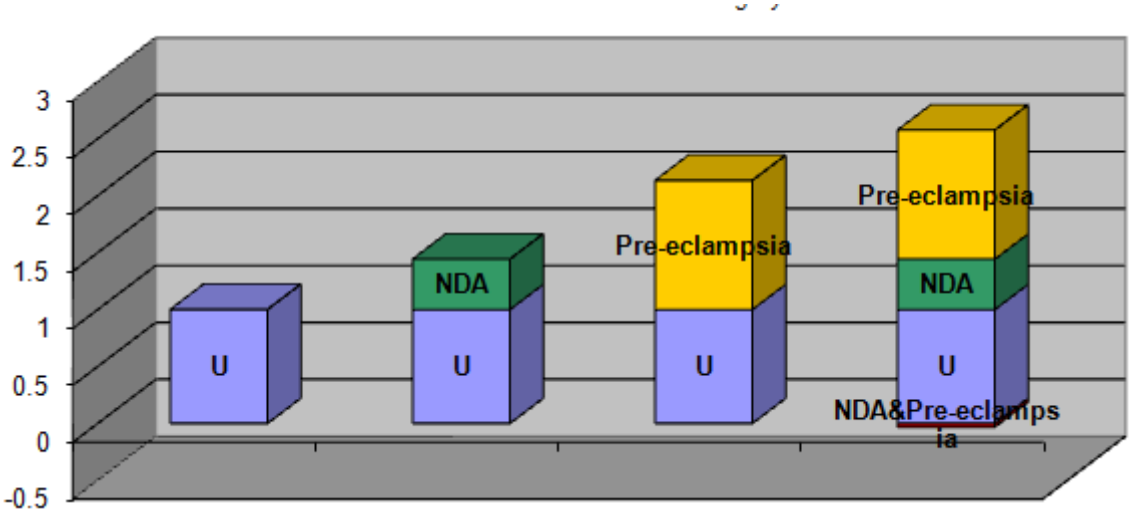
* OR = Odds ratio; model adjusted for age, birth year, province, multiple gestation, grand multiparity and elderly primigravida; reference group: those who are unexposed to either anemia or preeclampsia

** RERI = relative excess risk due to interaction

† AP = attributable proportion due to interaction

‡ S = synergy index

Figure 9. Odds ratio for cesarean delivery among women who were exposed to nutritional deficiency anemia (NDA), preeclampsia or both



* U is the reference category: those who were unexposed to either anemia or preeclampsia

5.2 Development and Validation of Logistic Regression Models for Pre-eclampsia, Preterm Labor and Cesarean Delivery, with Hemoglobinopathy as a Potential Risk Factor.

5.2.1 Descriptive analyses

The overall rate of cesarean delivery increased from 187 per 1000 deliveries in 1991 to 204 per 1000 deliveries in 1999, and then rose dramatically to 282 per 1000 delivery in 2007 (Figure 10). A similar trend was observed for the occurrence of pre-eclampsia: from 30 per 1000 delivery in 1991 to 36 per 1000 delivery in 2001, and continued to increase to 55 per 1000 delivery in 2007. The rate of preterm labor increased from 44 per 1000 delivery in 1991 to 65 per 1000 delivery in 2007.

As shown in Figure 11-13, the rate of cesarean delivery increased with advancing age, while the rate of preterm labor was higher among younger (aged 20 or less) or older (aged 40 or over) women, and the rate of pre-eclampsia increased dramatically in women aged 40 or over.

Figure 10. Rates of pre-eclampsia, preterm labor, and cesarean delivery, Canada (excluding Quebec and Manitoba), 1991/1992-2007/2008.

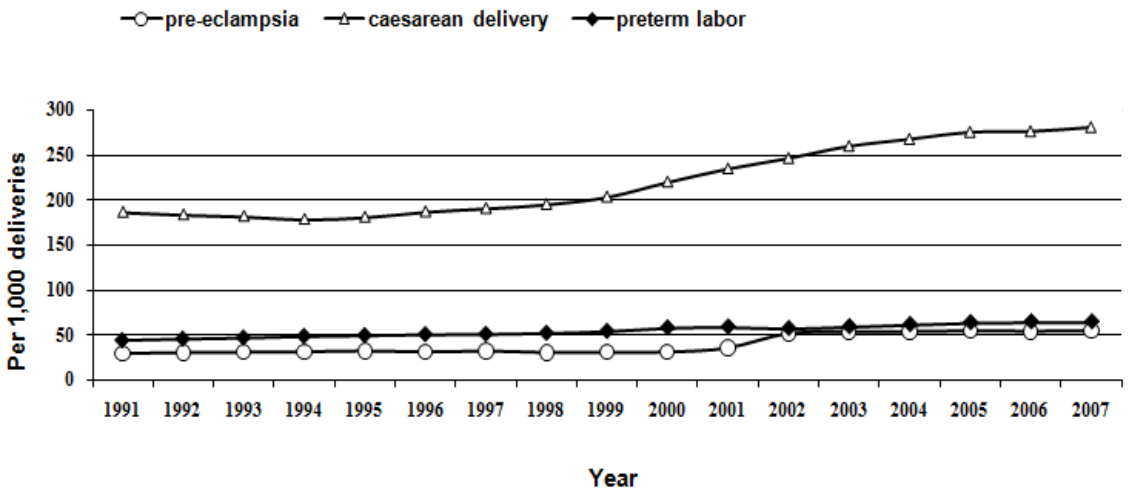


Figure 11. Cesarean delivery rates by maternal age, Canada (excluding Quebec and Manitoba), 1991/1992-2007/2008

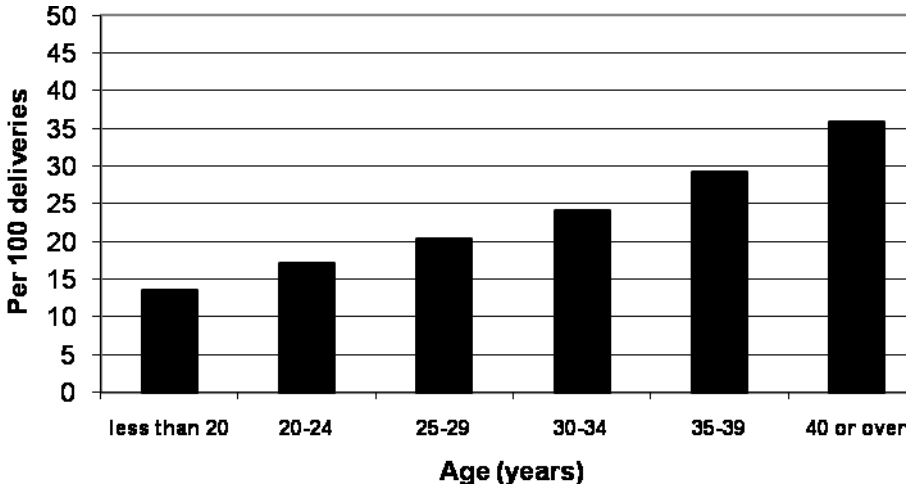


Figure 12. Preterm labor rates by maternal age, Canada (excluding Quebec and Manitoba), 1991/1992-2007/2008

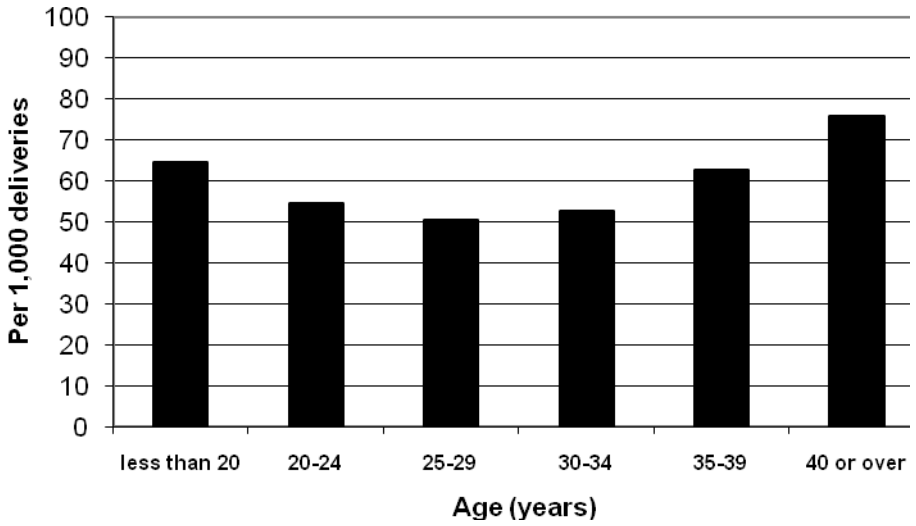
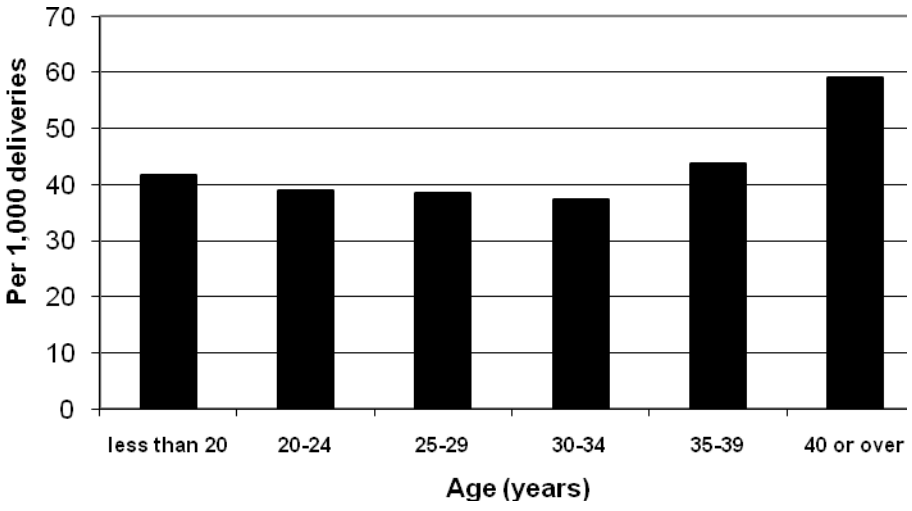


Figure 13. Preeclampsia rates by maternal age, Canada (excluding Quebec and Manitoba), 1991/1992-2007/2008



5.2.2 Selection of potential risk factors

As described in Section 5.3.2.1, a set of variables that were significantly associated with pre-eclampsia, preterm labor and cesarean delivery, were selected as their potential predictors. The crude odds ratios for these potential risk factors (ORs for age, period and region were not shown) associated with the three adverse pregnancy outcomes are presented on Tables 17-19 in Appendix II.

5.2.3 Development and validation of logistic regression models

All three multivariate logistic regression models were developed in a systematic way, as described in Sections 3.4.2.3. The results for pre-eclampsia model are described in detail as follows to illustrate the process used for all other models. The results for preterm labor and cesarean delivery models are shown in Appendix III and Appendix IV respectively.

Pre-eclampsia model (Model 1)

Twenty-three risk factors were identified following multivariate regression analyses and are shown in the order of decreasing odds ratio for this pre-eclampsia model (Table 22). Most of the risk factors had significantly positive association with pre-eclampsia. Pre-existing hypertension, cardiorespiratory disease, renal disease, pre-existing diabetes, and obesity were most strongly associated with pre-eclampsia; followed by pneumonia, multiple gestation, connective tissue disease, gestational diabetes, and elderly primigravida. Grand multiparity and smoking were associated with a decreased risk for pre-eclampsia. Thalassemia was not independently associated with pre-eclampsia.

Table 22. Parameter estimate (β), standard error (SE), odds ratio (OR) and its 95% confidence interval (CI) and p value for the pre-eclampsia model.

Parameter	β	SE	OR	95% CI	P value
Age (years)*					
<20	0.1392	0.0111	1.15	1.13-1.18	<0.0001
20-24	0.0300	0.00742	1.03	1.02-1.05	<0.0001
30-34	-0.0765	0.00645	0.93	0.92-0.94	<0.0001
35-39	-0.0293	0.00827	0.97	0.96-0.99	0.0004
⩾40	0.1789	0.0149	1.20	1.16-1.23	
Period**					
1994-1996	0.0324	0.00906	1.03	1.02-1.05	0.0003
1997-1999	0.00136	0.00925	1.00	0.98-1.02	0.8830
2000-2002	0.2286	0.00886	1.26	1.24-1.28	<0.0001
2003-2005	0.5605	0.00829	1.75	1.72-1.78	<0.0001
2006-2007	0.5609	0.00893	1.75	1.72-1.78	<0.0001
Region†					
West	0.0183	0.00540	1.02	1.01-1.03	0.0007
Atlantic	0.3975	0.00810	1.49	1.47-1.51	<0.0001
Other	-0.3461	0.0397	0.71	0.66-0.77	<0.0001

Table 22: cont'd

Sickle disease	0.6329	0.1730	1.88	1.34-2.64	0.0003
Sickle trait	0.3818	0.1558	1.47	1.08-1.99	0.0143
Thalassemia	-0.0234	0.0815	0.98	0.83-1.15	0.7736
Pre-existing hypertension	1.8292	0.0171	6.23	6.02-6.441	<0.0001
Cardiorespiratory disease	1.5783	0.0733	4.85	4.20-5.60	<0.0001
Renal disease	1.3007	0.1095	3.67	2.96-4.55	<0.0001
Pre-existing diabetes	1.2212	0.0199	3.39	3.26-3.53	<0.0001
Obesity	1.1680	0.0197	3.22	3.09-3.34	<0.0001
Pneumonia	1.1357	0.0737	3.11	2.70-3.60	<0.0001
Multiple gestation	1.1293	0.0143	3.09	3.01-3.18	<0.0001
Connective tissue diseases	0.9102	0.0599	2.49	2.21-2.79	<0.0001
Gestational diabetes	0.6721	0.0102	1.96	1.92-2.00	<0.0001

Table 22: cont'd

Elderly primigravida	0.6326	0.0190	1.88	1.81-1.95	<0.0001
Sepsis	0.6283	0.0331	1.87	1.76-2.00	<0.0001
VTE‡	0.4921	0.0650	1.64	1.44-1.86	<0.0001
NDA‡	0.4109	0.0555	1.51	1.35-1.682	<0.0001
Genitourinary Tract Infection	0.3847	0.0169	1.47	1.42-1.52	<0.0001
Substance abuse	0.2054	0.0259	1.23	1.17-1.29	<0.0001
Grand multiparity	-0.2248	0.0501	0.80	0.72-0.88	<0.0001
Smoking	-0.2413	0.0388	0.79	0.73-0.85	<0.0001
Intercept	-3.5892	0.0331			<0.0001

* reference group: 25-29;

** reference group: 1991-1993;

† reference group: Ontario

‡ NDA = nutritional deficiency anemia; VTE = Venous Thrombo-Embolism;

Some of the logistic regression statistics for pre-eclampsia model are shown in Table 23. The value of R^2 in the model was 0.23, indicating that 23% of the variation in the dependent variable (pre-eclampsia) could be explained by the predictors. Overall, 80.2% of patients were correctly classified. The sensitivity of the model was 20.4%, meaning 20.4% of patients who had pre-eclampsia were correctly classified as having pre-eclampsia, and the specificity of the model was 97.9%, indicating that 97.9% of patients who did not have pre-eclampsia were correctly predicted by the model not to have had pre-eclampsia at the cut-off probability of 0.5. C statistic, the most valid measure for predictive accuracy of a logistic regression model, was 0.72 for this model, suggesting that there was an acceptable discrimination for the pre-eclampsia prediction model. A low p-value in the Hosmer-Lemeshow goodness-of-fit test suggests a poor fit of a model. However, when a sample size is very large, the result of Hosmer-Lemeshow test should be cautiously interpreted since even a small difference between the observed and expected values becomes statistically significant

Table 23. Logistic regression statistics for pre-eclampsia model

R-square	0.14
Max-rescaled R-square	0.23
Overall correct classification	80.2
Sensitivity	20.4
Specificity	97.9
C statistic	0.72
Hosmer and Lemeshow Goodness of fit	P<0.0001

As shown in Figure 14, the ROC curve was generated from predicted probability and observed outcome. The area under ROC curve, or c statistic, was 0.72, suggesting an acceptable discrimination for the pre-eclampsia prediction model.

Figure 15 illustrates the calibration plots of predicted versus observed probability of pre-eclampsia occurrence across the deciles of predicted probability among all women (Figure 15a), and among women in different study groups (SCD, SCT, thalassemia) (Figure 15b, 15c, 15d respectively). As shown in the figure, the observed and predicted rates of pre-eclampsia did not substantially differ across the deciles of risk among all women and women with different kinds of hemoglobinopathy, and therefore the model was well calibrated. The model fitted data from all women the best, then those from women with thalassemia, and SCD, and while fitted data from SCT women the worst.

Figure 14. Area under receiver operating characteristic (ROC) curve of pre-eclampsia model

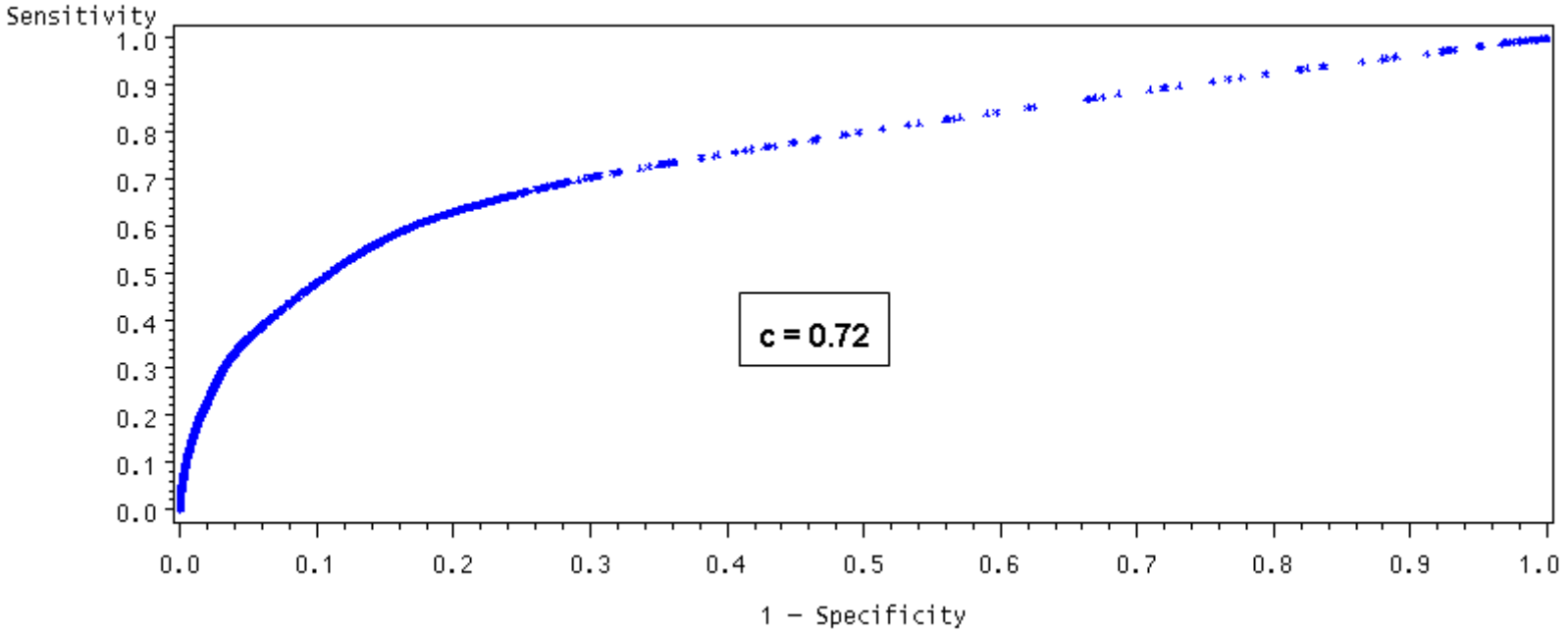
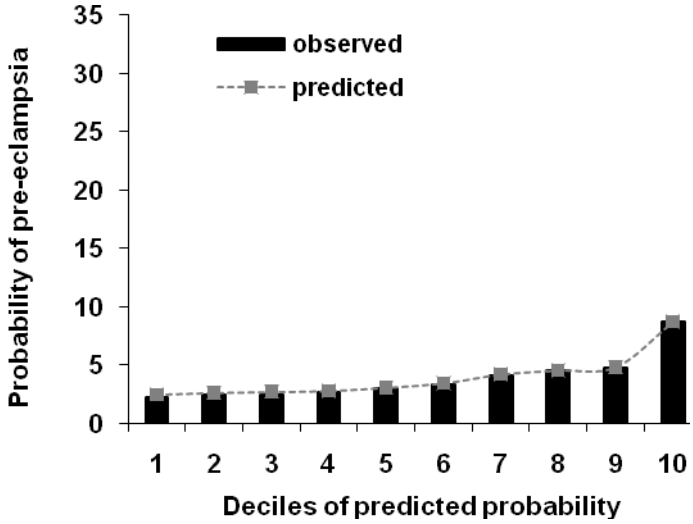
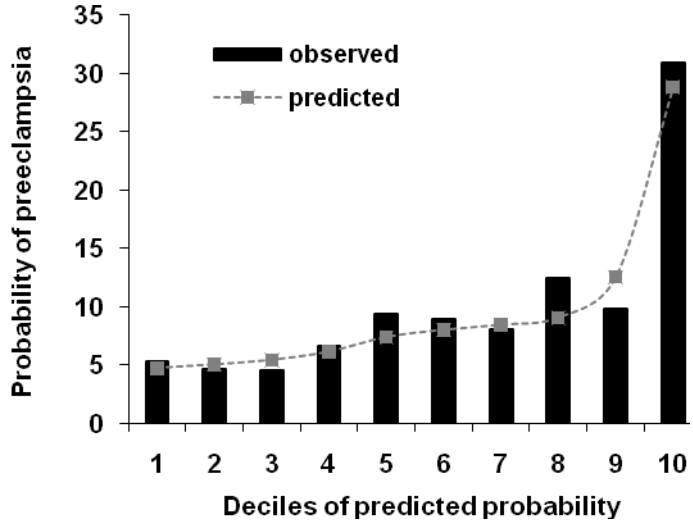


Figure 15. Predicted versus observed probability of developing pre-eclampsia for all women and women with different kinds of anemia across deciles of predicted probability

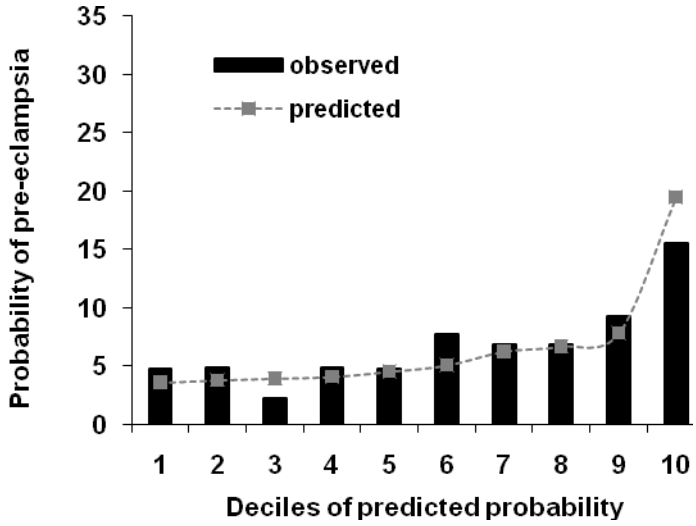
a. All women



b. Women with sickle cell disease



c. Women with sickle cell trait



d. Women with thalassemia

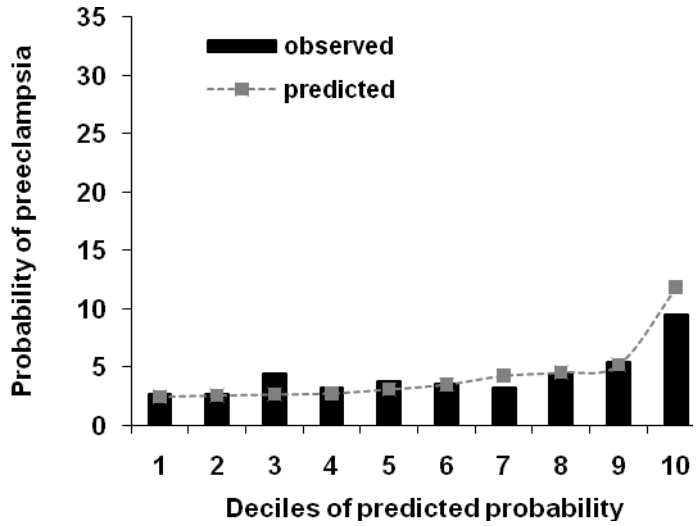


Table 24 shows the prediction error rates observed among all women, and among women with different kinds of hemoglobinopathy. The prediction error rate for the whole study population was 19.8%. The prediction error rates for women with different kinds of hemoglobinopathy were slightly higher than that for the whole population, suggesting that the predictive ability of our model is slightly lower for women with different kinds of hemoglobinopathy than for the whole population.

Table 24. Overall prediction error rates of the pre-eclampsia model in the whole population and in women with different kinds of hemoglobinopathy

Groups of women	Prediction error rate %
Whole population	19.8
Sickle cell disease	22.1
Sickle cell trait	22.9
Thalassemia	21.4

Cutoff probability = 0.5.

Possible interactions among the indicators were investigated, and when each of the interactions was individually entered into the model with all the indicators, none appeared to enhance the fit of the model.

Regression diagnostic analyses were performed to identify patients whose observed outcome deviated from the predicted outcome. Deviance residual, leverage and cbar were analyzed to identify problematic cases that were either outliers or influential observations.

Outliers are observations with extremely large residuals. Checking for outliers was done by plotting deviance residuals against predicted probability of outcome: pre-eclampsia. As shown in Figure 16, the residuals in the logistic regression residual plot fall on two curves, one for each outcome level. The higher curve was for women who had pre-eclampsia, and the lower curve was for women who did not. Most of the residuals in the plot were within ± 3 standard deviations. There were some subjects who did not have pre-eclampsia despite having a very high predicted probability in the model. The mismatch between the observed outcomes of no pre-eclampsia and high predicted probabilities of pre-eclampsia in the regression model for these subjects creates large residuals, these were the points in the lower right region of the figure. A number of these subjects have residual values < -3 and might be considered outliers. As mentioned earlier, for a large data set as ours, we should expect some values of residuals beyond the limits of ±3. As a rule of thumb, for a large data set, 99% of the data should be within ±3 standard deviations (SD) from the mean of the residuals (83). In this residual plot, no more than 1% of the residuals exceed the absolute value of 3. Excluding the cases with residuals < -3 from the dataset resulted in very similar values in coefficients, -2LL, and c statistic as in the original model. Therefore, these cases were not excluded from the dataset although their residuals were less than -3.

Leverage values were used for detecting the observations that had the large impact on the predicted probabilities. Cbar, the logistic regression version of Cook's distance, provides a measure of how much the model estimates change when each point is removed. Figure 17 shows deviance residue versus leverage for the pre-eclampsia model.

The size of the plotted circle is proportional to the influence of an observation (cbar). No women had large leverage values, and no extreme values in cbar (extremely big circles) were observed. Therefore, no influential observations were found in the dataset.

Figure 16. Deviance residual versus predicted probability for the pre-eclampsia model

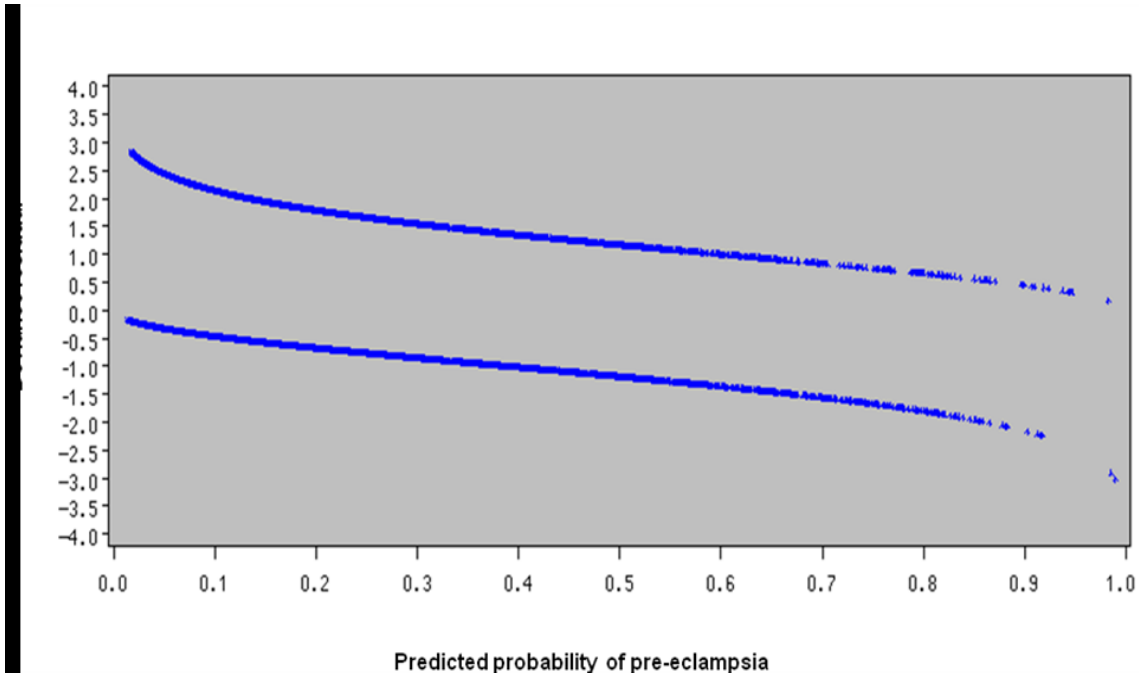
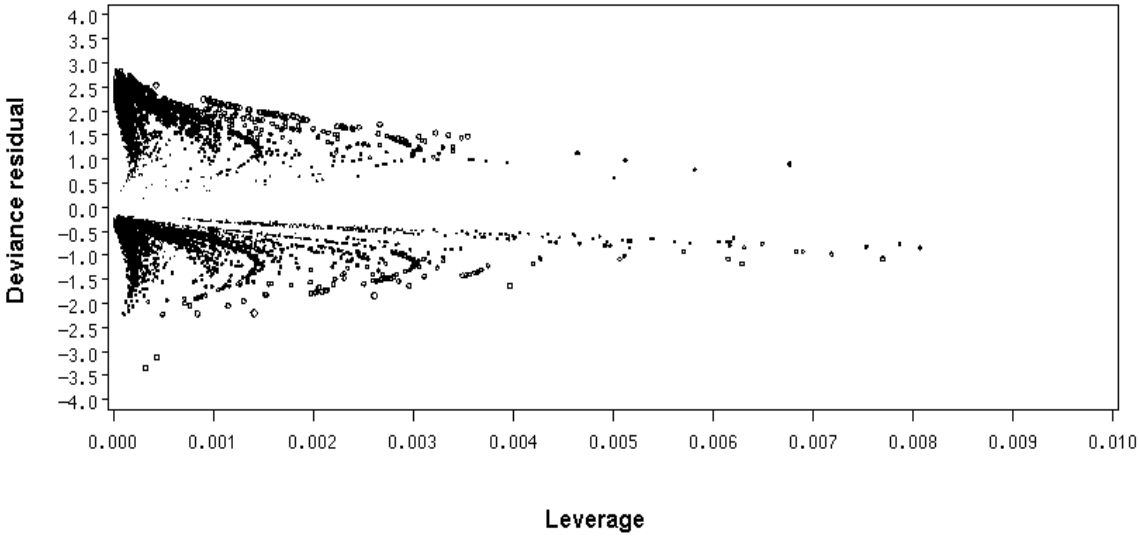


Figure 17. Deviance residue versus leverage for the pre-eclampsia model. The size of the plotted circle is proportional to the influence of an observation (cbar).



6. DISCUSSION

6.1 Summary of Findings

Women with SCD were at an increased risk for both medical complications (such as infections, hemorrhagic and thromboembolic events) and pregnancy-related complications (such as pre-eclampsia, preterm labor, cesarean delivery, placenta abruption, intrauterine growth restriction, and intrauterine fetal death) during pregnancy compared with those with no anemia. The increased risk of developing these pregnancy complications persisted after adjustment for demographic characteristics. Moreover, SCD appeared to have a more severe effect on pregnant women compared with NDA, the most common form of anemia. All these complications except hemorrhagic and thromboembolic events were more frequent in women with SCD than in women with NDA, suggesting that other mechanisms besides anemia may also play a role in these pregnancy-related complications. Some predisposing factors, such as increased metabolic demands, hypercoaguable state and vascular stasis associated with pregnancy might be responsible for these complications (15, 84, 85).

It was found that pre-eclampsia was more prevalent in women with SCD compared with those with no anemia, similar to findings from other studies (16, 18, 20, 21). Also, our study showed that there was an increased risk of preterm labor in women with SCD, which is consistent with previous observations (16-18, 20, 21). The mechanisms for pre-eclampsia and preterm labor among women with SCD remain unclear.

In this study, women with SCD were more likely to have cesarean delivery than those with no anemia. Cesarean deliveries are likely undertaken because of fetal compromise. For pregnant women with SCD, an increase in the incidence of fetal distress (86), closer

fetal monitoring and a lower threshold to tolerate non-reassuring fetal heart rate patterns may contribute to this trend.

Our study found that SCD was associated with an increased risk for intrauterine growth restriction. This finding was consistent with those from previous studies (16-18, 21, 22). The pathological basis for an increased risk of intrauterine growth restriction in women with SCD remains unknown. Chronic maternal anemia during gestation might lead to fetal hypoxia, predisposing the fetus to intrauterine growth restriction (55). Compromised placental blood flow due to vaso-oclusion on the maternal side of the placenta is likely to lead to placental infarction and an insufficient placental function unable to supply the nutritional needs and metabolic exchange of the growing fetus (87).

An increased risk for intrauterine fetal death was observed for SCD women in our study. However, a previous study by Villers (21) found no significant change in the risk for intrauterine fetal death in SCD women. We believe that the incidence of intrauterine fetal death in SCD women reported by Villers et al might be underestimated, perhaps resulted from the misclassification of thalassemia cases into SCD in their study. In Villers' study, SCD and thalassemia were grouped together under the "SCD group".

Thromboembolic events have been found to be associated with maternal death from SCD. Our study confirms that women with SCD are more likely to experience venous thrombo-embolism. Noteworthy, compared with women with no anemia, only a slight increase of risk for antepartum and postpartum hemorrhage was observed in SCD women. This might be attributed to small fetal size and hypercoagulability in women with SCD.

Our study also supports the findings from previous studies that infections, such as

pneumonia, urinary tract infection, sepsis, and postpartum infection, are more prevalent in women with SCD. Added to this, our study demonstrated an increased risk of amniotic cavity infection in SCD women.

In this study, women with SCT were also found to be more likely to experience pre-eclampsia, preterm labor, cesarean delivery, intrauterine growth restriction, placenta abruption, and infections compared with women with no anemia,, although to a much less extent than women with SCD. With an exception of preterm labor, the incidence of the studied complications in women with SCT was similar to that in women with NDA. Preterm labor was more frequent in women with SCT than in women with NDA. As mentioned in Section 1.1.1, all the clinical and pathological manifestations seen in sickle cell disorders have been attributed to presence of sickle hemoglobin S (HbS) assisted by the other abnormal hemoglobin abetting them. Little wonder then that there is paucity of clinical manifestation when HbS co-exists with normal adult hemoglobin (HbA). This is because HbA is believed to suppress the effect of HbS clinically (9). This may explain the much lower incidence of pregnancy-related complications seen in women with SCT. Most previous studies found no increase in the risks for pregnancy-related complications in women with SCT (24, 28, 32). There is an important difference between these studies and our current one. Our study is population based and we made a comparison between women with SCT and women with no anemia, whereas other studies compared women with SCT with those with no hemoglobinopathy.

Data in this study showed that risks of preterm labor, cesarean delivery, placenta abruption, hemorrhagic and thromboembolic events, and infection increased in women

with thalassemia, and to a similar extent to women with NDA. The incidences of intrauterine growth restriction and intrauterine fetal death were more frequent in women with thalassemia than in women with NDA. The literature concerning thalassemia and pregnancy outcomes is limited. A population based study by Sheiner et al reported an increased risk of intrauterine growth restriction in women with thalassemia minor (55). The nature of our database limits a further classification of thalassemia although the severity and symptoms vary greatly among different forms of thalassemia. Before 2004, ICD9 codes for thalassemia (282.4) lacked specificity. All forms of thalassemia were grouped together. Sheiner et al (55) showed that no significant association was found between hemoglobin levels and intrauterine growth restriction among thalassemic women, a different mechanism other than anemia might be responsible for intrauterine growth restriction in women with thalassemia. Like SCD, the incidence of antepartum and postpartum hemorrhage was lower in women with thalassemia than in those with NDA. Small fetal size and hypercoagulability in thalassemia women might explain this.

In this study, we observed an additive interaction occurs between hemoglobinopathy and pre-eclampsia in relation to preterm labor and cesarean delivery. Women with hemoglobinopathy would be far more likely to have preterm labor or cesarean delivery if they developed pre-eclampsia during pregnancy. Compared to women without anemia or preeclampsia, women with SCD were only 2.5 times more likely to have preterm labor, but they would be about 20 times more likely to have preterm labor if they developed preeclampsia during pregnancy. Women with SCD were 2.3 times more likely to have cesarean delivery, whereas for women with both SCD and pre-eclampsia, it was 13.8

times. To our knowledge, there have been no publications concerning the additive interaction between hemoglobinopathy and pre-eclampsia in relation to preterm labor and cesarean delivery.

In this study, risk prediction models for pre-eclampsia, preterm labor, and cesarean delivery were derived and internally validated. Twenty-three risk factors were identified to be associated with pre-eclampsia. Pre-existing hypertension, cardiorespiratory disease, renal disease, pre-existing diabetes, and obesity were found to be the five top predictors that were most strongly associated with pre-eclampsia. The discrimination of the three models was either excellent (cesarean delivery model) or acceptable (pre-eclampsia model and preterm labor model), evidenced by c statistic (0.72 for pre-eclampsia, 0.76 for preterm labor, and 0.88 for cesarean delivery model). The calibration of the model was good, with an agreement between predicted and observed rates of pre-eclampsia (or preterm labor, cesarean delivery) in most risk deciles in calibration plot. The pre-eclampsia model fitted data from all women the best, followed by those from women with thalassemia, and SCD, and fitted data from SCT women the worst.

6.2 Strengths of the Study

This is the largest study up to date on pregnancy with hemoglobinopathy and provides a nationwide assessment of pregnancy complications associated with hemoglobinopathy in Canada. The main strength of this study lies in the nature of the DAD database used in this study: population-based database, large sample size, and detailed information on medical and obstetric conditions. The DAD is a large national database containing

information on most acute care hospital separations across Canada. Inpatient records in DAD represent 75% of all hospitalizations in Canada. Our large sample size allows for analysis of uncommon diseases such as sickle cell disorders and thalassemia that would be otherwise hard to assess. Moreover, large sample size permits ample power to detect associations and results could be generalizable to the population.

The data that was used in the study contain principal diagnosis and up to 15 secondary diagnoses. Many studies have demonstrated that medical conditions are underreported when discharge abstract forms only allow for the coding of a small number of diagnosis (five diagnoses in Medicare data) (88, 89, 90). Medical conditions are much better reported when the diagnosis fields are extended to 9 or more (91). The data used in the present study likely provided more complete comorbidity profiles for hemoglobinopathy patients than the data with only a small number of coding fields, thus allowing us to detect more pregnancy complications associated with hemoglobinopathy.

Pregnancy with hemoglobinopathy is associated with an increased incidence of medical- and pregnancy-related complications. The mechanisms remain unclear. Anemia is the most common complication in hemoglobinopathy patients. Comparison of pregnancy complications was conducted between women with hemoglobinopathy and those with NDA (the most common form of anemia) to test whether anemia is responsible for the increased risk for pregnancy complications in hemoglobinopathy patients. To our knowledge, this is the first study to compare the pregnancy complication between hemoglobinopathy and NDA.

This study showed that there was an additive interaction between hemoglobinopathy and pre-eclampsia in relation to preterm labor and cesarean delivery. This finding is interesting as there are no published studies concerning these associations

6.3 Limitations of the Study

This study is inherited with numerous limitations. Women with sickle- β thalassemia are usually included with the SCD group because they have similar clinical manifestations during pregnancy (92). However, sickle- β thalassemia in ICD-9 codes was included in the group of thalassemia. Prior to 2004, ICD-9 codes lacked specificity to distinguish between sickle- β thalassemia (282.41, 282,42); and other types of thalassemias (282.49). Therefore, instead of being included with the SCD group, women with sickle- β thalassemia were included as part of the thalassemia group in this study for the study period from 1991/1992 to 2001/2002. Moreover, as mentioned in Section 1.1.2, the clinical courses and pregnancy outcomes vary greatly among different forms of thalassemia. In this study, all forms of thalassemia were grouped together due to the lack of specificity of ICD9 codes for thalassemia.

Due to the nature of administrative data, certain variables which may be associated with the exposures or outcomes were not available and could not be taken into account. The database is lack of some important factors that might confound the association between hemoglobinopathy and pregnancy outcomes, such as ethnicity, maternal education, parity, plurality, adequacy of prenatal care, and infant gender. The DAD did not link mothers with their babies, and the information on APGAR scores, birth weight,

newborn intensive care unit admission, or congenital abnormalities was not available for this analysis. Therefore, we are unable to comment on adverse infant outcomes, such as low birth weight and small for gestational age.

We were not able to link sequential hospital admissions for the same woman because of a lack of personal identifiers. Undoubtedly, some women might have more than one admission during their pregnancy. Some medical complications that occur during pregnancy (i.e. infections and thromboembolic events) might not be recorded at the time of hospitalization for childbirth. Similarly, some women might have more than one pregnancy, and these pregnancies are correlated. However, women with hemoglobinopathy, especially sickle cell disease, were unlikely to have more than one pregnancy due to their infertility and high risk of morbidity and mortality during pregnancy.

Sickle cell disease and thalassemia might be misdiagnosed and underdiagnosed. No general screening of sickle cell disease and thalassemia was performed in Canada, and there is no uniform testing for sickle cell disease and thalassemia. However, because sickle cell disease and thalassemia are serious and life-long conditions, it is less likely to be underdiagnosed for pregnant women.

Administrative databases are always open to questions regarding accuracy of coding. The data used in this study were not validated by chart review and are subject to the quality of administrative record data. However, DAD, the database used in this study, has been widely used for perinatal surveillance and research (77, 78). In this study we are not able to test the accuracy of pre-eclampsia coding. However, a previous study has found

that ICD-9 codes for pre-eclampsia has a sensitivity of 89% (95% confidence interval 78% to 94%) and a specificity of 67% (79% to 94%) for patients with true pre-eclampsia (93).

In this study, some lifestyle variables were underestimated due to the nature of administrative data. For example, the prevalences of smoking (0.51%) and obesity (0.51%) were found to be very low in the study population. Based on the data from Statistics Canada, the prevalences of smoking and obesity among Canadian women in 2008 were 17.7% and 16% respectively.

Several important risk factors of pre-eclampsia, such as parity, previous pre-eclampsia, family history of pre-eclampsia, and maternal low birth weight, are unavailable in our database, which may have an impact on the prediction performance of pre-eclampsia model developed from this study. Limited by the size of patients with hemoglobinopathy, the prediction models of pre-eclampsia, preterm labor and cesarean delivery were not validated in a separate dataset.

6.4 Impact of Study Findings

Despite advances in hematology, obstetrics and neonatal care bring about a remarkable improvement in the survival and pregnancy outcomes for women with hemoglobinopathy, our study shows that SCD remains an important risk factor for pregnancy- and delivery-related complications in Canada. Due to the existence of interaction between hemoglobinopathy and pre-eclampsia in relation to preterm labor and cesarean delivery, women with hemoglobinopathy would have a much higher risk for preterm labor and cesarean delivery if they developed pre-eclampsia during pregnancy.

These findings warrant close monitoring of all patients with SCD throughout pregnancy. Adequate prenatal care should be available at an institution prepared to manage SCD complications and high-risk pregnancies. SCD patients contemplating pregnancy should be informed of the serious complications which may occur to them as well as to the children, both before and after birth. Moreover, preconception counseling and care, as well as education and prevention of high-risk behaviors (e.g., smoking) are also important for SCD women contemplating pregnancy.

Understanding the adverse medical conditions, events and pregnancy-related complications that pregnant women with hemoglobinopathy experience is important to improve maternal and child health for this group of people in this country.

6.5 Future Work

This study has provided valuable information on the associations between hemoglobinopathy and pregnancy-related complications. However, these results prompted questions to arise. As mentioned in Section 5.3, due to the nature of the database, sequential hospital admissions for the same woman cannot be linked together; some important factors that might confound the association between hemoglobinopathy and pregnancy outcomes were not available; and the database did not include data about infants. Longitudinally linked data could provide more information and are useful for assessing factors associated with adverse health outcomes among women with specific medical conditions, such as SCD (20). Ideally, future studies will use longitudinally linked data to explore the association between hemoglobinopathy and adverse pregnancy

outcomes. In this study, we showed that there might be other mechanisms besides anemia responsible for the association between hemoglobinopathy and adverse pregnancy outcomes. Further research is needed to test this hypothesis and have a better understanding of biologic mechanisms.

6.6 Conclusions

Advances in hematology, obstetrics and neonatal care bring about a remarkable improvement in the survival and pregnancy outcomes for women with hemoglobinopathy, SCD remains an important risk factor for adverse pregnancy outcomes in Canada.

Women with SCD are more likely to have adverse pregnancy outcomes than those with NDA, suggesting that there might be other mechanisms besides anemia that are responsible for the association between SCD and adverse pregnancy outcomes.

Due to the existence of interaction between hemoglobinopathy and pre-eclampsia in relation to preterm labor and cesarean delivery, women with hemoglobinopathy could have a very high risk of preterm labor and cesarean delivery if they developed pre-eclampsia during pregnancy.

SCD patients contemplating pregnancy should be informed of the serious complications which occur to them as well as to the children, both before and after birth. Close monitoring and prenatal care should be provided to all patients with SCD throughout pregnancy.

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APPENDIX A. Unadjusted odds ratios for pregnancy-related complications related to different types anemia

Table 25. Unadjusted odds ratios[†] and 95% confidence intervals for pregnancy-related complications related to different types of anemia: canada excluding Quebec and Manitoba, 1991/1992 – 2007/2008.

Characteristic	Sickle disease (N=419)	Sickle trait (N=718)	Thalassemia (N=3803)	NDA[‡] (N=5782)
Pre-eclampsia	2.7 (1.9-3.7)	1.8 (1.3-2.4)	1.1 (2.0-1.3)	1.7 (1.5-1.9)
Cesarean delivery	2.6 (2.2-3.2)	1.4 (1.2-1.7)	1.4 (1.3-1.5)	1.3 (1.3-1.4)
Preterm labor	3.5 (2.7-4.5)	2.2 (1.7-2.8)	1.5 (1.3-1.7)	1.6 (1.5-1.7)
IUGR[‡]	3.4 (2.3-4.9)	1.4 (1.0-2.2)	2.7 (2.3-3.1)	1.4 (1.2-1.6)
IUFD[‡]	4.1 (2.0-8.2)	2.1 (1.0-4.3)	1.7 (1.2-2.5)	1.1 (0.8-1.6)
Placenta abruption	2.6 (1.6-3.9)	2.3 (1.4-3.6)	1.7 (1.4-2.2)	2.6 (2.2-3.0)
Infection of amniotic cavity	3.8 (2.3-6.3)	2.2 (1.3-3.6)	2.6 (2.1-3.1)	1.7 (1.4-2.1)
Malpresentation	0.9 (0.5-1.3)	1.1 (0.8-1.4)	1.1 (1.0-1.3)	1.0 (0.9-1.4)
Prolonged pregnancy	0.5 (0.3-0.8)	0.8 (0.6-1.1)	0.7 (0.6-0.7)	0.9 (0.8-1.0)
Medical Induced Labor	1.6 (1.3-2.0)	1.1 (0.9-1.3)	1.1 (1.0-1.2)	1.2 (1.1-1.3)

Table 25: Con'd

Surgical Induced Labor	1.0 (0.7-1.4)	1.0 (0.7-1.3)	0.8 (0.7-0.9)	0.9 (0.8-1.0)
Gestational Diabetes	1.1 (0.6-1.8)	1.2 (0.9-2.2)	1.0 (0.9 -2.0)	1.1 (0.9-1.2)
Antepartum hemorrhage	1.5 (1.1-2.7)	1.0 (0.9-1.1)	2.2 (1.8-2.6)	3.1 (2.8-3.5)
Postpartum hemorrhage	1.7 (1.2-2.5)	1.0 (0.7-1.4)	2.4 (2.1-2.7)	4.9 (4.6-5.3)
VTE‡	20.7 (9.24-46.40)	4.0 (1.0-16.0)	2.5 (1.0-5.0)	4.5 (2.80-7.08)
Pneumonia	139.4 (8.5-227.1)	13.8 (4.4-43.0)	9.6 (5.3-17.3)	12.6 (8.25-19.20)
GTI‡	2.8 (1.7-4.6)	3.5 (2.5-4.9)	1.1 (0.9-1.4)	2.7 (2.4-3.1)
Sepsis	7.2 (3.6-14.5)	5.2 (2.8-9.8)	3.2 (2.3-4.6)	5.4 (4.3-6.7)
Major puerperal infection	7.2 (4.2-12.7)	5.5 (3.4-9.0)	2.7 (2.0-3.7)	4.6 (3.8-5.5)

† Reference group: those without anemia

‡ NDA = nutritional deficiency anemia; IUGR = intrauterine growth restriction; IUFD = intrauterine fetal death; PROM = premature rupture of membranes; VTE = Venous Thrombo-Embolism; GTI =Genitourinary Tract Infection

APPENDIX B The initial Lists of risk factors associated with pre-eclampsia, preterm labor and cesarean delivery.

Table 26. Unadjusted odds ratios for risk factors associated with pre-eclampsia

	Pre-eclampsia No. (%) (N=173234)	No pre-eclampsia No. (%) (N=4208043)	Unadjusted odds ratio (95% CI)
Sickle disease	40 (0.02)	379 (0.01)	2.56 (1.85-3.55)
Sickle trait	47 (0.03)	671 (0.02)	1.70 (1.27-2.29)
Thalassemia	163 (0.09)	3640 (0.09)	1.09 (0.93-1.27)
Renal disease	161 (0.09)	325 (0.01)	12.04 (9.97-14.55)
Cardiorespiratory disease	300 (0.17)	881 (0.02)	8.28 (7.27-9.44)
Pre-existing hypertension	5191 (3.00)	15660 (0.37)	8.27 (8.01-8.54)
Pneumonia	252 (0.15)	1367 (0.03)	4.48 (3.92-5.13)
Pre-existing diabetes	3362 (1.94)	19390 (0.46)	4.28 (4.12-4.44)
Obesity	3446 (1.99)	20315 (0.48)	4.18 (4.03-4.34)
Multiple gestation	5932 (3.42)	45596 (1.08)	3.24 (3.15-3.33)

Table 26: cont'd

Connective tissue diseases	347 (0.20)	2718 (0.06)	3.11 (2.78-3.47)
Elderly primigravida	3587 (2.07)	38830 (0.92)	2.27 (2.19-2.35)
VTE†	287 (0.17)	3094 (0.07)	2.26 (2.00-2.55)
Gestational diabetes	12055 (6.96)	137810 (3.27)	2.21 (2.17-2.25)
Sepsis	1063 (0.61)	12511 (0.30)	2.07 (1.94-2.20)
Nutritional deficiency anemia	364 (0.21)	5418 (0.13)	1.63 (1.47-1.82)
Substance abuse	1687 (0.97)	26057 (0.62)	1.58 (1.50-1.66)
Genitourinary Tract Infection	3967 (2.29)	63835 (1.52)	1.52 (1.47-1.57)
Grand multiparity	429 (0.25)	11571 (0.27)	0.90 (0.82-0.99)
Smoking	707 (0.41)	21817 (0.52)	0.79 (0.73-0.85)

† NDA = nutritional deficiency anemia; VTE = Venous Thrombo-Embolism;

Table 27. Unadjusted odds ratios for risk factors associated with preterm labor

	Preterm labor No. (%) (N=239847)	No preterm labor No. (%) (N=4141430)	Unadjusted odds ratio (95% CI)
Sickle disease	69 (0.03)	350 (0.01)	3.40 (2.63 -4.41)
Sickle trait	79 (0.03)	639 (0.02)	2.14 (1.69-2.70)
Thalassemia	296 (0.12)	3507 (0.08)	1.46 (1.29-1.64)
Multiple gestation	22656 (9.45)	28872 (0.70)	14.86 (14.59-15.13)
Placenta abruption	119109 (7.97)	34017 (0.82)	10.45 (10.26-10.65)
Renal disease	182 (0.08)	304 (0.01)	10.34 (8.61-12.43)
Cervix incompetence	7441 (3.10)	13739 (0.33)	9.62 (9.35-9.90)
Antipartum hemorrhage	29380 (12.25)	62520 (1.51)	9.11 (8.98-9.24)
Amniotic cavity infection	14176 (5.91)	34095 (0.82)	7.57 (7.42-7.72)
Placenta previa	6585 (2.75)	15975 (0.39)	7.29 (7.08-7.50)
Cardiorespiratory disease	341 (0.14)	840 (0.02)	7.02 (6.19-7.96)
Pneumonia	453 (0.19)	1166 (0.03)	6.72 (6.03-7.49)
Connective tissue diseases	589 (0.25)	2476 (0.06)	4.12 (3.76-4.50)
IUGR[†]	18227 (7.60)	81505 (1.97)	4.10 (4.03-4.17)
PROM[†]	58034 (24.20)	312135 (7.54)	3.92 (3.88-3.96)
Pre-existing diabetes	4049 (1.69)	18703 (0.45)	3.79 (3.66-3.92)

Table 27: cont'd

Pre-existing hypertension	3506 (1.46)	17345 (0.42)	3.53 (3.40-3.66)
Oligohydramnios	9651 (4.02)	49975 (1.21)	3.43 (3.36-3.51)
Substance abuse	4473 (1.86)	23271 (0.56)	3.36 (3.26-3.47)
Polyhydramnios	3244 (1.35)	16981 (0.41)	3.33 (3.21-3.46)
Pre-eclampsia	25351 (10.57)	147883 (3.57)	3.19 (3.15-3.24)
Sepsis	2032 (0.85)	11542 (0.28)	3.06 (2.92-3.21)
Malpresentation	43486 (18.13)	282872 (6.83)	3.02 (2.99-3.05)
VTE†	485 (0.20)	2896 (0.07)	2.90 (2.63-3.19)
Genitourinary tract infection	7518 (3.13)	60284 (1.46)	2.19 (2.14-2.24)
Elderly primigravida	3576 (1.49)	38841 (0.94)	1.60 (1.54-1.65)
Gestational diabetes	12280 (5.12)	137585 (3.32)	1.57 (1.54-1.60)
NDA†	476 (0.20)	5306 (0.13)	1.55 (1.41-1.70)
Grand multiparity	904 (0.38)	11096 (0.27)	1.41 (1.32-1.51)
Obesity	1553 (0.65)	22208 (0.54)	1.21 (1.15-1.27)
Previous cesarean delivery	24772 (10.33)	446906 (10.79)	0.95 (0.94-0.97)

† NDA = nutritional deficiency anemia; IUGR = intrauterine growth restriction; PROM = premature rupture of membranes; VTE = Venous Thrombo-Embolism;

Table 28. Unadjusted odds ratios for risk factors associated with cesarean delivery

	Caesarean delivery No. (%) (N=965072)	No caesarean delivery No. (%) (N=3416205)	Unadjusted odds ratio (95% CI)
Sickle disease	176 (0.02)	243 (0.01)	2.56 (2.11-3.11)
Sickle trait	203 (0.02)	515 (0.02)	1.40 (1.19-1.64)
Thalassemia	1053 (0.11)	2750 (0.08))	1.36 (1.26-1.46)
fetopelvic disproportion	108755 (11.27)	4323 (0.13)	100.24 (97.23-103.34)
Placenta previa	19611 (2.03)	2949 (0.09)	24.01 (23.09-24.96)
Previous cesarean section	347027 (35.96)	124651 (3.65)	14.83 (14.72-14.93)
Malpresentation	208607) (21.62)	117751 (3.45)	7.72 (7.67-7.78)
Pneumonia	954 (0.10)	665 (0.02)	5.08 (4.60-5.61)
Cardiorespiratory disease	694 (0.07)	487 (0.01)	5.05 (4.50-5.67)
Sepsis	7702 (0.80)	5872 (0.17)	4.67 (4.52-4.83)
Multiple gestation	26684 (2.76)	24844 (0.73)	3.88 (3.81-3.95)
Pre-existing diabetes	11187 (1.16)	11565 (0.34)	3.45 (3.36-3.54)
Amniotic cavity infection	23485 (2.43)	24786 (0.73)	3.41 (3.35-3.47)
Renal disease	231 (0.02)	255 (0.01)	3.21 (2.68-3.83)
Antipartum hemorrhage	42919 (4.45)	48981 (1.43)	3.20 (3.16-3.24)
Polyhydramnios	9537 (0.99)	10688 (0.31)	3.18 (3.09-3.27)
Obesity	10832 (1.12)	12929 (0.38)	2.99 (2.91-3.07)

Table 28: cont'd

VTE†	1499 (0.16)	1882 (0.06)	2.82 (2.64-3.02)
Elderly primigravida	17716 (1.84)	24701 (0.72)	2.57 (2.52-2.62)
Pre-existing hypertension	8972 (0.93)	11879 (0.35)	2.56 (2.11-3.11)
Placenta abruption	22083 (2.29)	31043 (0.91)	2.55 (2.51-2.60)
Oligohydramnios	24673 (2.56)	24673 (2.56)	2.54 (2.50-2.58)
Pre-eclampsia	66964 (6.94)	106270 (3.11)	2.32 (2.30-2.36)
Fetal distress	174866 (18.12)	354170 (10.37)	1.91 (1.90-1.93)
Connective tissue diseases	1068 (0.11)	1997 (0.06)	1.89 (1.76-2.04)
IUGR†	34245 (3.55)	65487 (1.92)	1.88 (1.86-1.91)
Gestational diabetes	50310 (5.21)	99555 (2.91)	1.83 (1.81-1.85)
Preterm labor	75927 (7.87)	163920 (4.80)	1.69 (1.68-1.71)
Genitourinary Tract Infection	19987 (2.07)	47815 (1.40)	1.49 (1.47-1.51)
NDA†	1554 (0.16)	4228 (0.12)	1.30 (1.23-1.38)
Substance abuse	7376 (0.76)	20368 (0.60)	1.28 (1.25-1.32)
Prolonged pregnancy	89177 (9.24)	307012 (8.99)	1.03 (1.02-1.04)
PROM†	73724 (7.64)	296445 (8.68)	0.87 (0.86-0.88)
Smoking	4216 (0.44)	18308 (0.54)	0.81 (0.79-0.84)
Grand multiparity	2104 (0.22)	9896 (0.29)	0.75 (0.72-0.79)

† NDA = nutritional deficiency anemia; IUGR = intrauterine growth restriction; PROM = premature rupture of membranes; VTE = Venous Thrombo-Embolism;

APPENDIX C. Preterm labor model (Model 2)

The results of multivariate regression analyses are shown in Table 29, in the decreasing order of odds ratio. Some of the logistic regression statistics for preterm labor are presented in Table 30. C statistic was 0.76 for this model, suggesting an acceptable discrimination. Figure 18 demonstrates the ROC curve of the preterm labor model and Figure 19 illustrates the calibration plots of predicted versus observed probability of having preterm labor across the deciles of predicted probability among all women and women with different kinds of hemoglobinopathy. It seems that the model was well calibrated and fitted data from all women the best, followed by those from women with thalassemia, and sickle cell trait, and fitted SCD women data the worst. As shown in Table 31, the predictive ability of the model is slightly lower for women with different types of hemoglobinopathy than for the whole study population. Possible interactions among the indicators were investigated, and none appeared to enhance the fit of the model.

Regression diagnostic analyses were performed, and as identified in the pre-eclampsia, the scatter plot of deviance residual versus predicted probability indicated that most of the residuals (>99%) in the plot were within ± 3 standard deviations (Figure 20). Excluding the cases with residuals < -3 from the dataset resulted in very similar values in coefficients, -2LL, and c statistic as in the original model. Therefore, these cases were not excluded from the dataset although their residuals were less than -3. No large leverage values, and no extreme values in cbar (extremely big circles) were observed (Figure 21), and therefore, no influential observations were found in the dataset.

Table 29. Parameter estimate (β), standard error (SE), odds ratio (OR), 95% confidence interval (CI) and p value for the preterm labor model.

parameter	β	SE	OR	95% CI	P value
Age (years)*					
<20	0.3829	0.00967	1.47	1.44-1.50	<0.0001
20-24	0.1378	0.00678	1.15	1.13-1.16	<0.0001
30-34	-0.0285	0.00592	0.97	0.96-0.98	<0.0001
35-39	0.0550	0.00751	1.06	1.04-1.07	<0.0001
>=40	0.1243	0.0142	1.13	1.10-1.16	<0.0001
Period**					
1994-1996	0.0701	0.00787	1.07	1.06-1.09	<0.0001
1997-1999	0.1259	0.00791	1.13	1.12-1.15	<0.0001
2000-2002	0.1755	0.00782	1.19	1.17-1.21	<0.0001
2003-2005	0.1981	0.00772	1.22	1.20-1.24	<0.0001
2006-2007	0.2476	0.00833	1.28	1.26-1.30	<0.0001
Region***					
West	-0.0735	0.00483	0.93	0.92-0.94	<0.0001
Atlantic	-0.2730	0.00904	0.76	0.75-0.78	<0.0001
Other	-0.3205	0.0345	0.73	0.68-0.78	<0.0001

Table 29: cont'd

Sickle disease	0.7944	0.1480	2.21	1.66-2.96	<0.0001
Sickle trait	0.4157	0.1382	1.52	1.16-1.99	0.0026
Thalassemia	0.0382	0.0679	1.04	0.91-1.19	0.5733
Multiple gestation	2.3089	0.0105	10.06	9.86-10.27	<0.0001
Cervix incompetence	1.8919	0.0173	6.63	6.41-6.86	<0.0001
Infection of amniotic cavity	1.5788	0.0119	4.85	4.74-4.96	<0.0001
Antepartum hemorrhage	1.4694	0.0160	4.35	4.21-4.49	<0.0001
PROM[†]	1.4585	0.00564	4.30	4.25-4.35	<0.0001
Renal disease	1.3579	0.1102	3.89	3.13-4.83	<0.0001
Pneumonia	1.2686	0.0665	3.56	3.12-4.05	<0.0001
Pre-existing diabetes	1.1918	0.0195	3.29	3.17-3.42	<0.0001
Cardiorespiratory disease	1.1642	0.1094	3.20	2.59-3.97	<0.0001

Table 30: cont'd

Placenta previa	1.1070	0.0202	3.03	2.91-3.15	<0.0001
Connective tissue diseases	1.0544	0.0523	2.87	2.59-3.18	<0.0001
Pre-eclampsia	1.0480	0.00802	2.85	2.81-2.90	<0.0001
IUGR[†]	1.00009	0.0100	2.72	2.67-2.78	<0.0001
Polyhydramnios	0.9504	0.0219	2.59	2.48-2.70	<0.0001
Substance abuse	0.9039	0.0187	2.47	2.38-2.56	<0.0001
Placenta abruption	0.8341	0.0186	2.30	2.22-2.39	<0.0001
Pre-existing hypertension	0.8210	0.0214	2.27	2.18-2.37	<0.0001
Oligohydramnios	0.7527	0.0134	2.12	2.07-2.18	<0.0001
Malpresentation	0.7116	0.00662	2.04	2.01-2.06	<0.0001
Genitourinary Tract Infection	0.5723	0.0140	1.77	1.72-1.82	<0.0001
VTE[†]	0.5623	0.0582	1.76	1.57-1.97	<0.0001

Table 29: cont'd

Sepsis	0.4653	0.0289	1.59	1.51-1.69	<0.0001
Smoking	0.3384	0.0256	1.40	1.33-1.48	<0.0001
Gestational diabetes	0.2953	0.0107	1.34	1.32-1.37	<0.0001
Previous abortion	0.2209	0.0212	1.25	1.20-1.30	<0.0001
Grand multiparity	0.1595	0.0386	1.17	1.09-1.27	<0.0001
Obesity	-0.4322	0.0295	0.65	0.61-0.69	<0.0001
Intercept	-3.7324	0.00716			<0.0001

* Reference group: 25-29

** Reference group: 1991-1993

† Reference group: Ontario

‡ NDA = nutritional deficiency anemia; IUGR = intrauterine growth restriction;
PROM = premature rupture of membranes; VTE = Venous Thrombo-Embolism;

Table 30. Logistic regression statistics for preterm labor model

Statistics	
R-square	0.06
Max-rescaled R-square	0.18
Overall correct classification	84.6
Sensitivity	28.7
Specificity	96.2
C statistic	0.76
Hosmer-Lemeshow Goodness of fit	P<0.0001

Table 31. Overall prediction error rate of the preterm labor model in the whole study population and in women with different types of anemia

Groups of women	Prediction error rate %
Whole study population	15.4
Sickle cell disease	18.3
Sickle cell trait	18.8
Thalassemia	17.4

Cutoff probability = 0.5.

Figure 18. Area under receiver operating characteristic (ROC) curve of preterm labor model

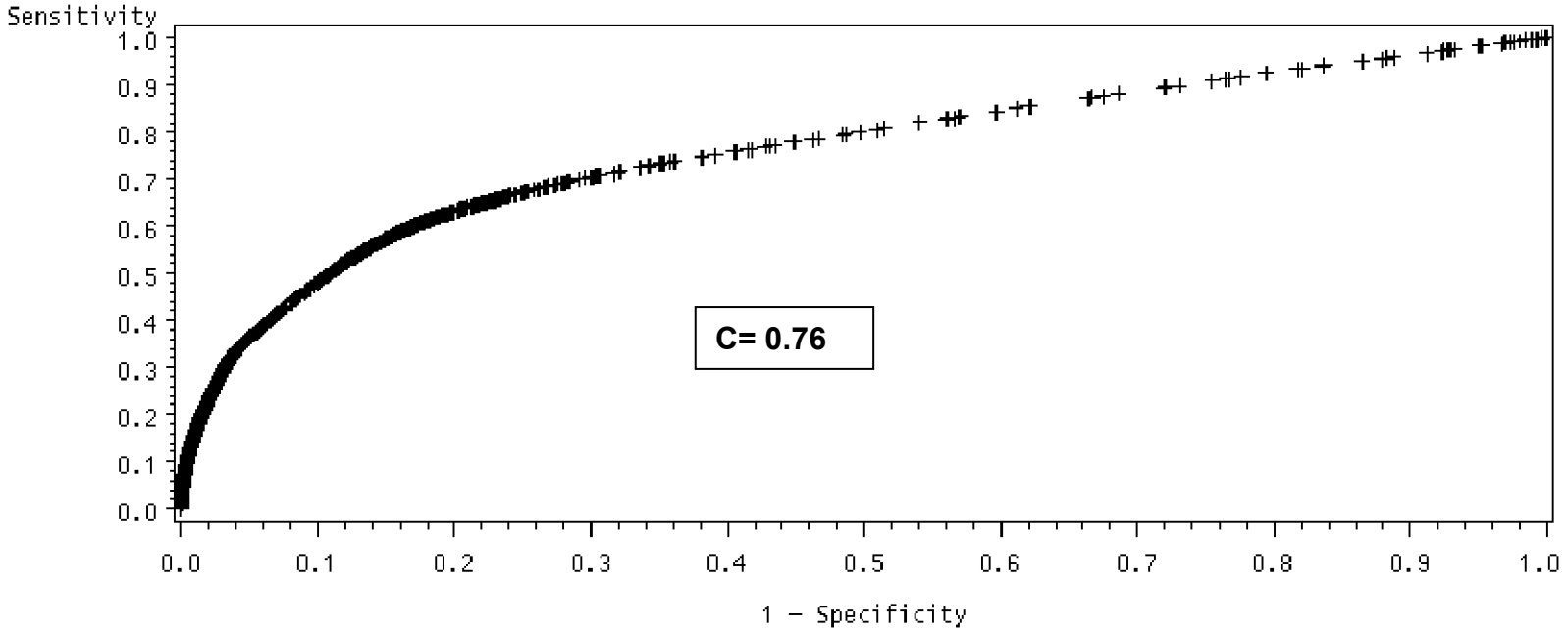
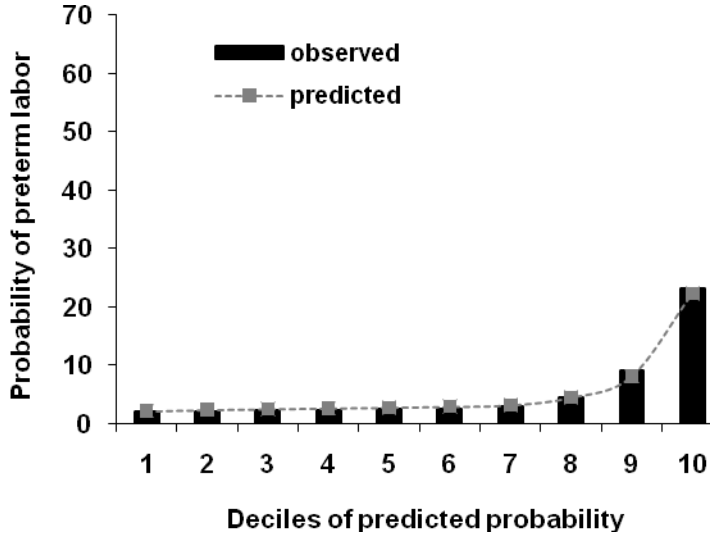
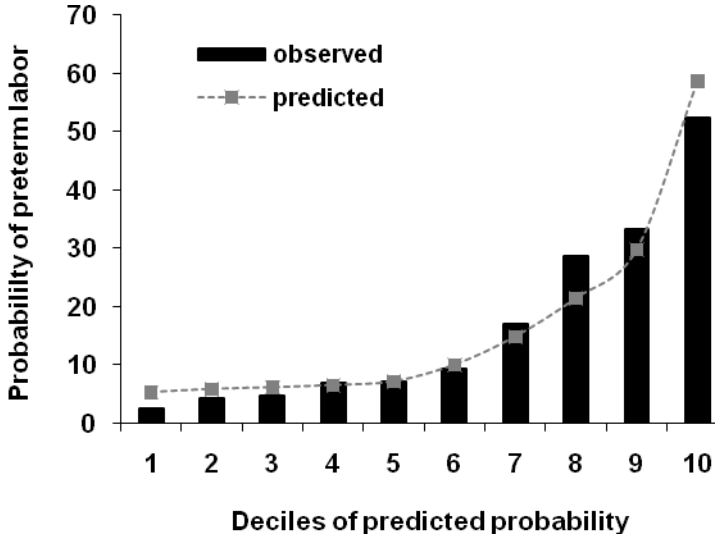


Figure 19. Predicted versus observed probability of having preterm labor for all women and women with different kinds of anemia across deciles of predicted probability

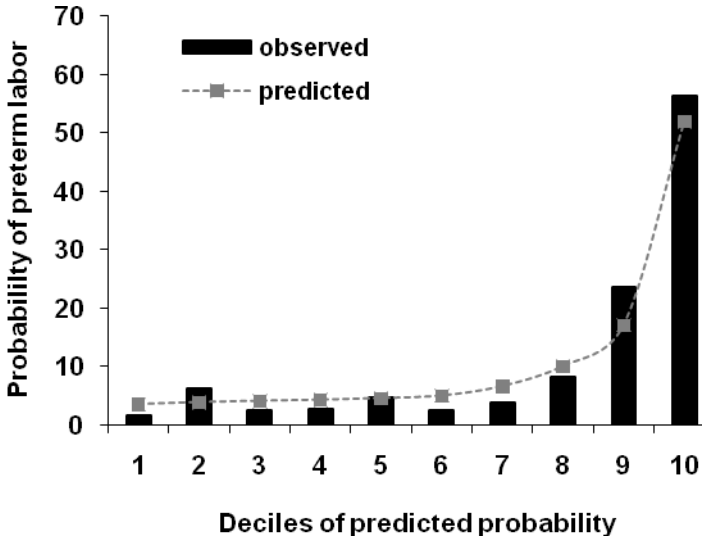
a. All women



b. Women with sickle cell disease



c. Women with sickle cell trait



d. Women with thalassemia

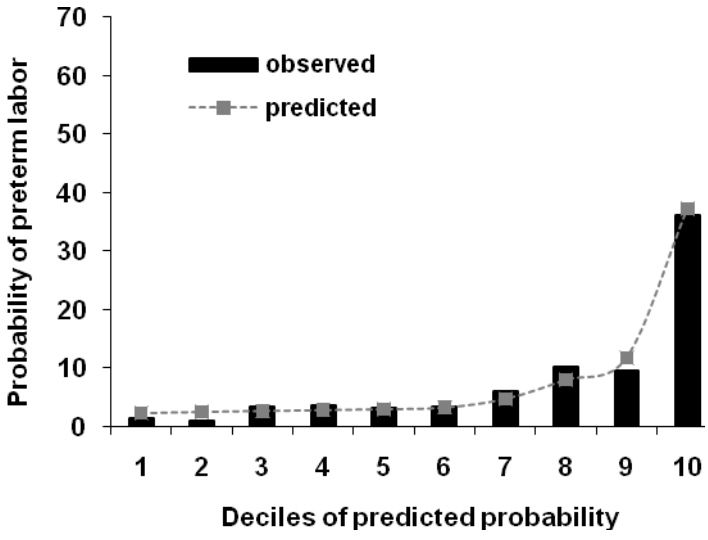


Figure 20. Deviance residual versus predicted probability for the preterm labor model

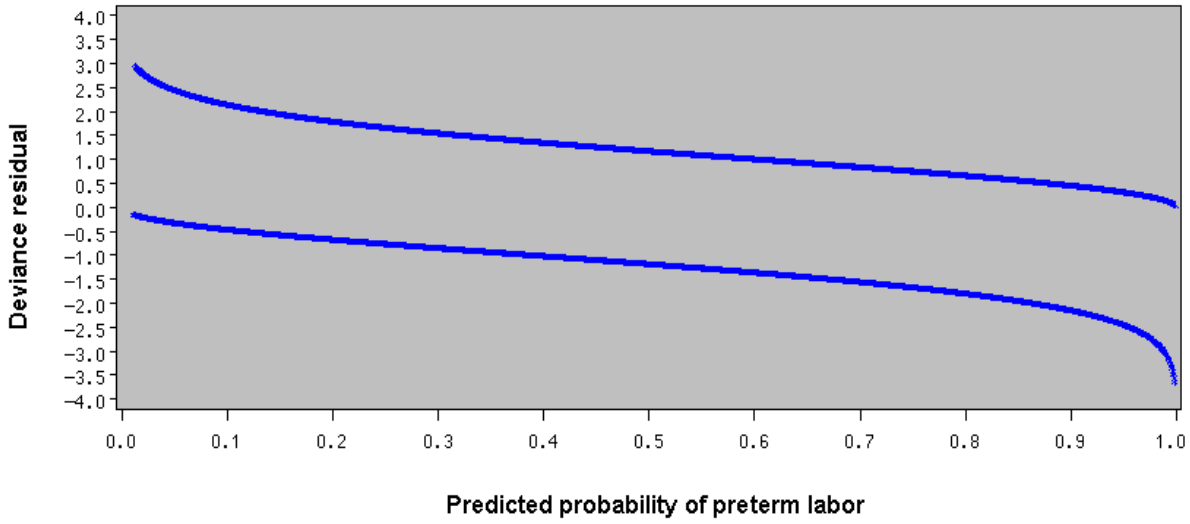
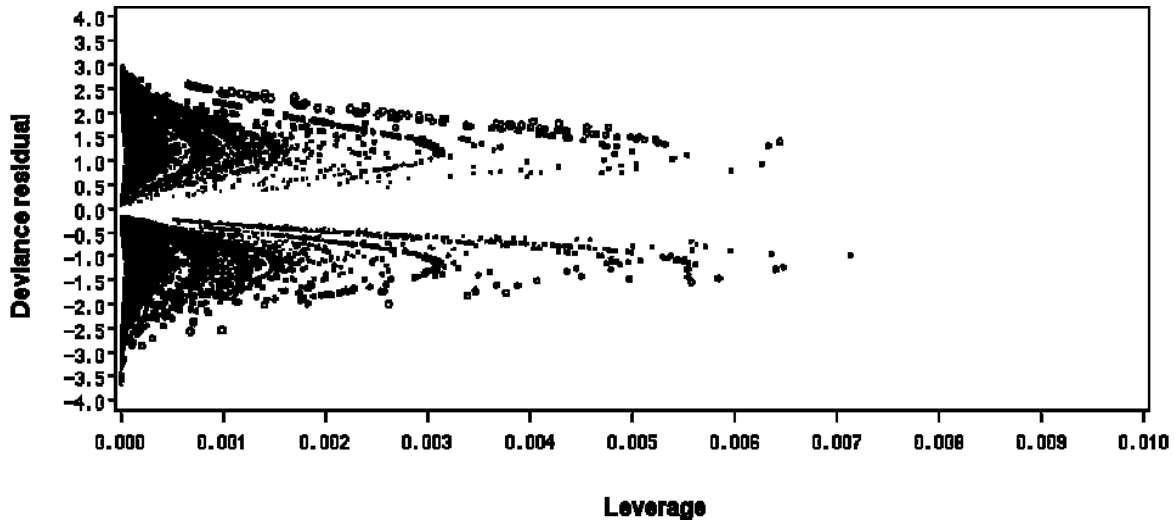


Figure 21. Deviance residue versus leverage for the preterm labor model. The size of the plotted circle is proportional to the influence of an observation (cbar).



APPENDIX D. Cesarean delivery model (Model 3)

The results of multivariate regression analyses are shown in Table 32 in Appendix D, in the decreasing order of odds ratio. Some of the logistic regression statistics for cesarean delivery are presented in Table 33. C statistic was 0.88 for this model, suggesting an excellent discrimination. ROC curve and the calibration plots were shown in Figure 22 and Figure 23. The model was well calibrated and fitted data from all women the best, followed by those from women with thalassemia, and sickle cell trait, and fitted SCD women data the worst. As presented in Table 34, the predictive ability of the model is slightly lower for women with different types of hemoglobinopathy than for the whole study population. Possible interactions among the indicators were investigated, and none appeared to enhance the fit of the model. Most of the residuals (>99%) in the scatter plot of deviance residual versus predicted probability were within ± 3 standard deviations (Figure 24). Excluding the cases with residuals >3 or < -3 from the dataset resulted in very similar values in coefficients, -2LL, and c statistic as in the original model, suggesting that these cases would not be excluded from the dataset. There were no large leverage values and no extreme values in cbar (extremely big circles) (Figure 25) in the plot of leverage versus deviance residues, and therefore, no influential observations were observed in the dataset.

Table 32. Parameter estimate (β), standard error (SE), odds ratio (OR), 95% confidence interval (CI) and p value for the cesarean delivery model.

Parameter	β	SE	OR	95% CI	P value
Age (years)*					
<20	-0.18	0.0077	0.84	0.83-0.85	<0.0001
20-24	-0.09	0.0040	0.92	0.91-0.93	<0.0001
30-34	0.06	0.00385	1.06	1.06-1.07	<0.0001
35-39	0.14	0.00493	1.15	1.14-1.16	<0.0001
⩾40	0.39	0.00948	1.48	1.45-1.50	<0.0001
Period**					
1994-1996	-0.04	0.0055	0.96	0.95-0.97	<0.0001
1997-1999	0.19	0.00552	1.21	1.20-1.22	<0.0001
2000-2002	0.53	0.00534	1.70	1.68-1.72	<0.0001
2003-2005	0.77	0.00516	2.16	2.13-2.18	<0.0001
2006-2007	0.83	0.00554	2.30	2.27-2.32	<0.0001
Region***					
West	-0.05	0.00327	0.95	0.94-0.95	<0.0001
Atlantic	0.33	0.00538	1.39	1.38-1.41	<0.0001
other	-0.39	0.0232	0.68	0.65-0.71	<0.0001

Table 32: cont'd

Sickle disease	0.79	0.1282	2.21	1.72-2.84	<0.0001
Sickle trait	0.11	0.1123	1.12	0.90-1.39	0.3292
Thalassemia	0.11	0.0490	1.12	1.02-1.23	0.0221
Fetopelvic disproportion	5.59	0.0159	267.26	259.07-275.72	<0.0001
Placenta previa	3.67	0.0230	39.32	37.59-41.14	<0.0001
Previous casserean delivery	3.37	0.00418	29.01	28.78-29.25	<0.0001
Malpresentation	2.73	0.00460	15.40	15.26-15.54	<0.0001
Sepsis	1.49	0.0228	4.42	4.23-4.62	<0.0001
Pneumonia	1.32	0.0654	3.73	3.28-4.25	<0.0001
Cardiorespiratory disease	1.22	0.0750	3.38	2.91-3.91	<0.0001
Infection of amniotic cavity,	1.14	0.0118	3.13	3.06-3.21	<0.0001
Pre-existing diabetes	1.10	0.0174	3.01	2.91-3.11	<0.0001
Fetal distress	1.07	0.00408	2.92	2.90-2.95	<0.0001

Table 32: cont'd

Pre-eclampsia	1.02	0.00641	2.77	2.73-2.80	<0.0001
Polyhydramnios	0.98	0.0186	2.66	2.56-2.76	<0.0001
Elderly primigravida	0.89	0.0128	2.43	2.37-2.49	<0.0001
VTE‡	0.88	0.0460	2.42	2.21-2.65	<0.0001
Obesity	0.79	0.0176	2.21	2.13-2.28	<0.0001
Oligohydramnios	0.73	0.0108	2.07	2.03-2.12	<0.0001
Multiple gestation	0.64	0.0118	1.89	1.85-1.94	<0.0001
Pre-existing hypertension	0.64	0.0184	1.89	1.83-1.96	<0.0001
Placenta abruption	0.61	0.0196	1.84	1.77-1.91	<0.0001
IUGR‡	0.60	0.00887	1.83	1.80-1.86	<0.0001
Renal disease	0.49	0.1176	1.63	1.30-2.06	<0.0001
Antepartum hemorrhage	0.46	0.0164	1.59	1.54-1.64	<0.0001
Connective tissue diseases	0.41	0.0497	1.50	1.36-1.66	<0.0001

Table 32: cont'd

Antepartum hemorrhage	0.46	0.0164	1.59	1.54-1.64	<0.0001
Connective tissue diseases	0.41	0.0497	1.50	1.36-1.66	<0.0001
Gestational diabetes	0.40	0.00752	1.49	1.47-1.52	<0.0001
Prolonged pregnancy	0.35	0.00509	1.42	1.40-1.43	<0.0001
Genitourinary Tract Infection	0.34	0.0114	1.40	1.37-1.43	<0.0001
NDA‡	0.13	0.0404	1.14	1.05-1.23	0.0016
Substance abuse	0.06	0.0175	1.06	1.02-1.09	0.0014
Preterm labor	0.03	0.00653	1.03	1.01-1.04	<0.0001
PROM‡	-0.05	0.00556	0.95	0.94-0.96	<0.0001
Smoking	-0.22	0.0223	0.81	0.77-0.84	<0.0001
Grand multiparity	-0.89	0.0320	0.41	0.39-0.44	<0.0001
Intercept	-3.10	0.00505			<0.0001

* Reference group: 25-29 ** Reference group: 1991-1993

† Reference group: Ontario

‡ NDA = nutritional deficiency anemia; IUGR = intrauterine growth restriction;

PROM = premature rupture of membranes; VTE = Venous Thrombo-Embolism;

Table 33. Logistic regression statistics for cesarean delivery model

Statistics	
R-square	0.32
Max-rescaled R-square	0.49
Overall correct classification	86.7
sensitivity	60.4
Specificity	94.1
C statistic	0.88
Hosmer and Lemeshow Goodness of fit	P<0.0001

Table 34. Overall prediction error rate of the cesarean delivery model in the whole study population and in women with different kinds of hemoglobinopathy.

Groups of women	Prediction error rate (%)
Whole population	13.3
Sickle cell disease	18.6
Sickle cell trait	17.4
Thalassemia	16.0

Cutoff probability = 0.5.

Figure 22. Area under receiver operating characteristic (ROC) curve of cesarean delivery model

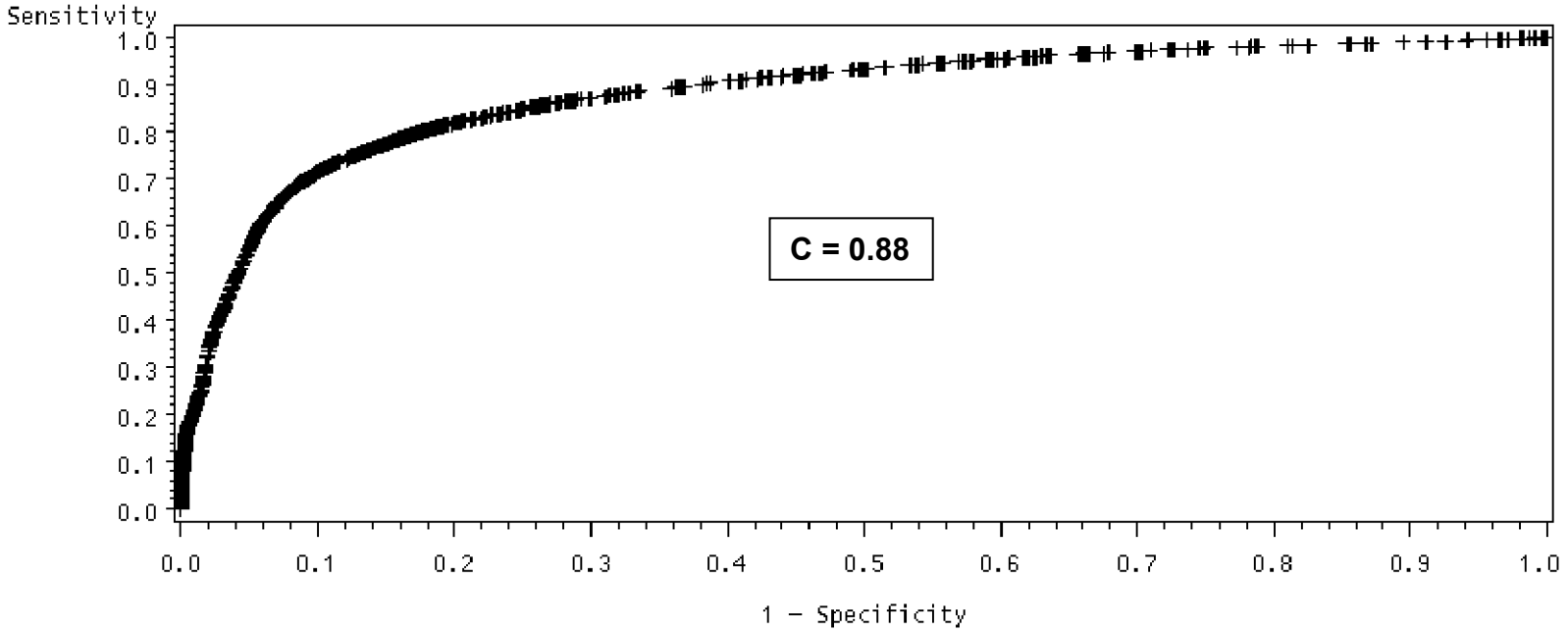
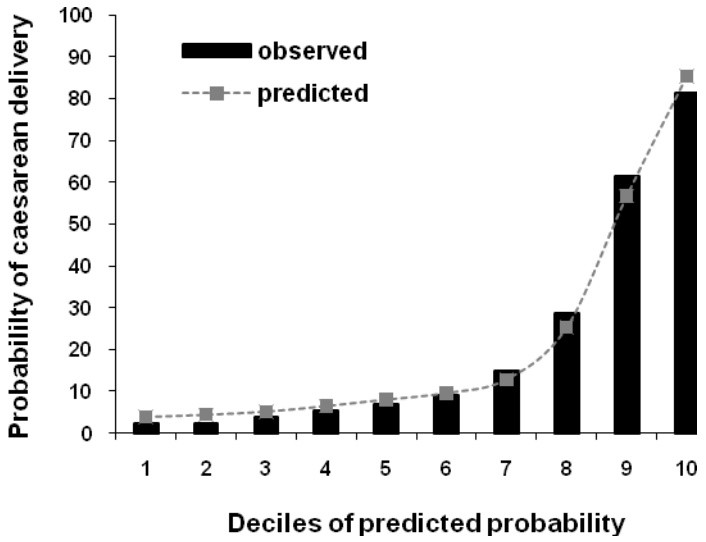
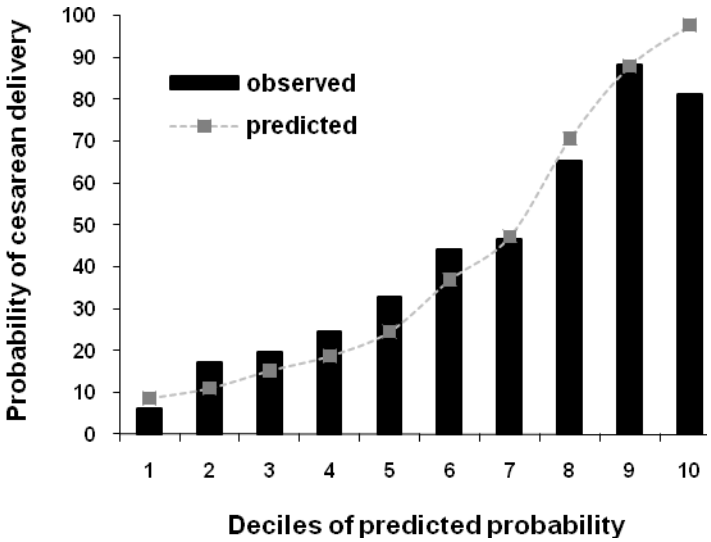


Figure 23. Predicted versus observed probability of having caesarean delivery for all women and women with different kinds of anemia across deciles of predicted probability

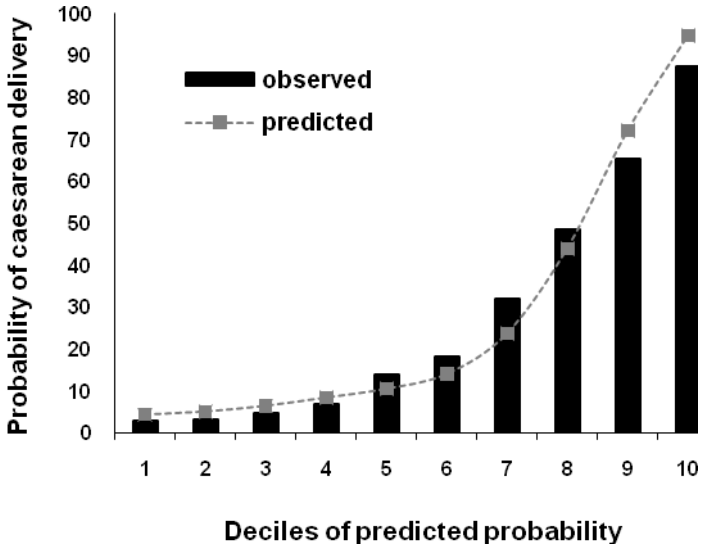
a. All women



b. Women with sickle cell disease



c. **Women with sickle cell trait**



d. **Women with thalassemia**

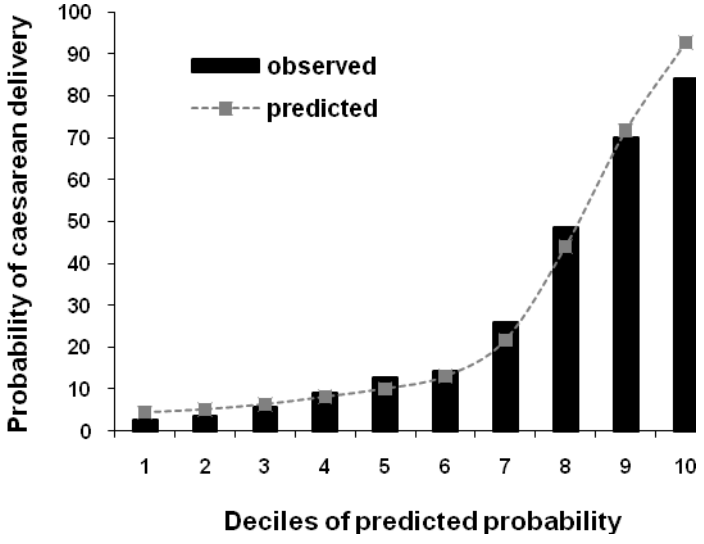


Figure 24. Deviance residual versus predicted probability for the cesarean delivery model

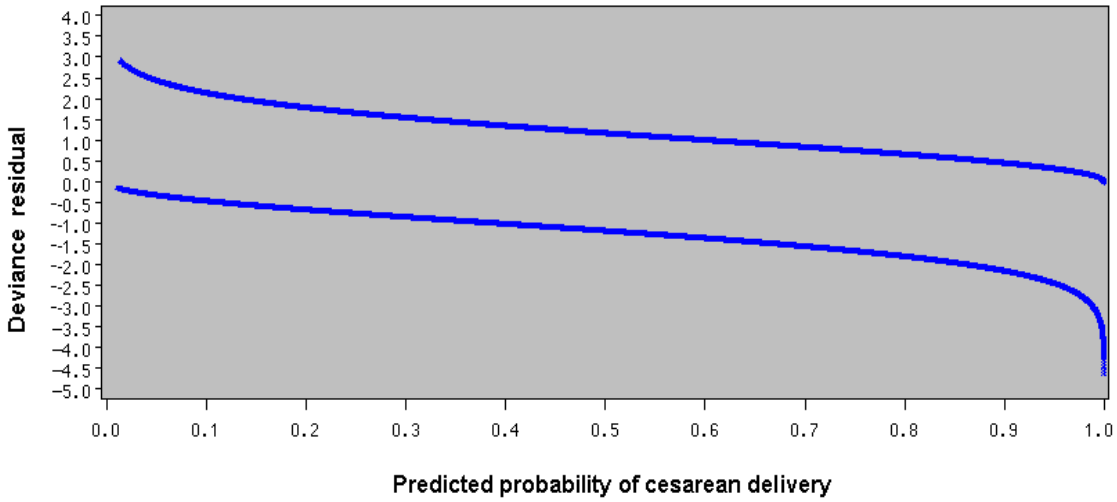
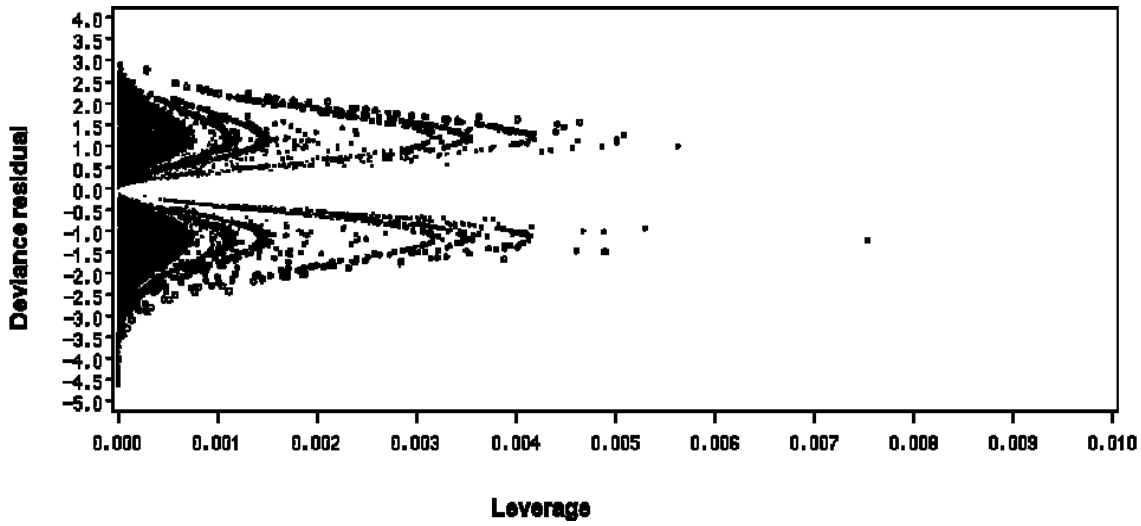


Figure 25. Deviance residue versus leverage for the cesarean delivery model. The size of the plotted circle is proportional to the influence of an observation (cbar).



APPENDIX E. List of ICD9 and ICD10 codes used in the study

Medical conditions	ICD-9 codes	ICD-10 codes
Sickle cell disease	282.6	D570, D571, D572, D578
Sickle cell trait	282.5	D573
Thalassemia	282.4	D560, D561, D562, D563, D568, D569
Nutritional deficiency anemia	280, 281	D50-D53
Anemia	280-285, 648.2	D50-D64, O990
Multiple gestation	651	O30
Grand multiparity	659.4	Z354
Elderly primigravida	659.5	Z355
Pre-existing hypertension	401-405, 642.0, 642.1, 642.2	I10-I15, O10
Pre-existing diabetes	250, 648.0	E10-E14, O24.0-O24.3
Cardiorespiratory disease	414,428,429,496,5188	I23, I25, I411, I418, I46.1, I46.9, I50, I51, I97.0, I97.1, I97.8, J44.0, J44.9, J96, J98.4
Renal disease	585, 646.2	N18, O121
Connective tissue diseases	710, 714, 725	M05, M06, M32-M34, M35.0, M35.1, M35.3, M35.8, M35.9, M36.0
Obesity	278.0	E66
Smoking	305.1, V15.82, 649.0	F17, Z72.0, Z71.6
Substance abuse	305.0, 305.2-305.7, 648.3	F10.0, F10.1, F11.0, F11.1, F12.0, F12.1, F13.0, F13.1, F14.0, F14.1, F15.0, F15.1, F16.0, F16.1, O993

Appendix E: cont'd

Pre-eclampsia	642.4, 642.5, 642.7	O11, O13, O14
Preterm labor	644	O47, O60
Cesarean delivery	CCP codes: 860-862, 868-869	CCI codes: 5MD60
Intrauterine growth restriction	656.5	O36.5
Intrauterine fetal death	656.4	O36.4
Placenta Previa	641.0, 641.1	O44
Placenta abruption	641.2	O45
Oligohydramnios	658.0	O41.0
Polyhydramnios	657	O40
Infection of amniotic cavity	658.4	O411
Premature rupture of membranes	658.1	O42
Malpresentation	652	O32
fetopelvic disproportion	653.4	O33.4, O33.9
Cervix incompetence	654.5, 654.6	O34.3, O34.4
Fetal distress	656.3	O36.3, O68
Prolonged pregnancy	645	O48
Antepartum hemorrhage	640, 641.1, 641.3 641.8, 641.9	O20, O44.1, O46, O67
Postpartum hemorrhage	666	O72
Venous thrombo-embolism	451.1, 451.2, 415.1, 671.3, 671.4, 673	I80.1-I80.3, I26, O22.3, O87.1, O88

Appendix E: cont'd

Major puerperal infection	670, 672	O85, O86.4, O86.8
Pneumonia	480-483, 486, 487.0	J10.0, J11.0, J12-J16, J18
Genitourinary tract infection	646.6	O23, O86.0-O86.3
Sepsis	038, 659.3, 670	A40, A41, O75.3, O85
Gestational diabetes	648.8	O244 (2001-2005), O248 (2006-2007)
Previous cesarean section	654.2	O34.2, O75.7
Medical induced labor	CCP codes: 855	CCI codes: 5AC30ALI2, 5AC30CAI2, 5AC30GUI2, 5AC30HAI2, 5AC30YAI2, 5AC30YBI2, 5AC30ZZI2, 5AC30CKI2, 5AC30CKA2
Surgical induced labor	CCP codes: 850.1, 851	5AC30AP, 5AC30AN, 5AC30CK, 5AC30CKBD, 5AC30CKW6
Delivery-related discharges	CCP codes: any one diagnosis code of 641 to 676 and with a fifth digit of "1" or "2"; 650 or v27 Deliveries in which an abortive procedure was provided are excluded: any one procedure code of 78.52, 86.3, 86.4, 87.0, 87.1, or 87.2.	CCI codes: any one diagnosis code of O10 to O16, O21 to O29, O30 to O37, O40 to O46, O48, O60 to O69, O70 to O75, O85 to O89, O90 to O92, O95, O99 with sixth digit of "1" or 2"; or Z37 Deliveries in which an abortive procedure was provided are excluded: any one procedure code of 5.CA.88, 5.CA.89 or 5.CA.93