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Influence of Thyroid Disorders On Pregnancy Outcomes

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INFLUENCE OF THYROID DISORDERS ON PREGNANCY OUTCOMES

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ABSTRACT

Objective: The objective of this thesis is to investigate the effects of maternal thyroid dysfunction on maternal pregnancy outcomes.

Setting and Participants: The NICHD Consecutive Pregnancy data set contains information on a total of 114,679 pregnancies from 51,086 women who delivered ≥ 20 weeks of gestation. The data come from 20 different hospitals throughout the state of Utah and were collected between the years of 2002 to 2010.

Main Outcomes: Main outcomes of interest included: breech presentation, chorioamnionitis, gestational diabetes, gestational hypertension, hemorrhage, inductions, placental abruption, placental previa, preterm birth, premature rupture of membranes (PROM), preeclampsia, and superimposed preeclampsia.

Methods: Results are presented as RRs with 95% CIs. RRs are obtained from modified Poisson regression models. Analyses are to singleton pregnancies. All results are adjusted for insurance, parity, race/ethnicity, age, smoking, and other chronic diseases.

Results: We found that hypothyroidism is significantly associated with gestational diabetes [RR: 1.28, 95% CI: 1.00-1.63], gestational hypertension [RR: 1.32, 95% CI: 1.07-

1.63], inductions [RR: 0.98, 95%CI: 0.96-0.99] and preterm birth [RR: 1.23, 95% CI: 1.08-1.41] after adjusting for confounders. Hyperthyroidism was found to be significantly associated with gestational diabetes [RR: 2.47, 95% CI: 1.28-4.76], preterm birth [RR: 2.31, 95% CI: 1.61-3.32], and preeclampsia [RR: 2.65, 95% CI: 1.44-4.87] after adjusting for confounders. Unspecified thyroid disorders were significantly associated with gestational hypertension [RR: 1.24, 95% CI: 1.01-1.53], placental abruption [RR: 1.29, 95% CI: 1.01-1.64], and preterm birth [RR: 1.20, 95% CI: 1.05-1.37] after adjusting for confounders. Adjusted results for other thyroid disorders were not significant.

Conclusions: The results of this study suggest that the presence of a thyroid disorder increases the risk of adverse outcomes during pregnancy. This supports previous findings but more research involving large racially diverse cohorts with available data on treatment is needed to further understand the complex association between thyroid disorders and pregnancy outcomes.

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LIST OF ABBREVIATIONS

CI..... Confidence Interval

GEE..... Generalized Estimating Equations

ICD-9 ..... International Classification of Diseases, Ninth Edition

NICHD .....National Institute of Child Health and Human Development

OR .....Odds Ratio

RR..... Relative Risk

SAS..... Statistical Analysis Software

TSH.....Thyroid Stimulating Hormone

US .....United States

CHAPTER 1

INTRODUCTION

1.1 BACKGROUND

Thyroid disorders are the second most common endocrine disorders affecting women during their reproductive years and can impact up to 4% of all pregnancies[1]. Of all thyroid disorders, hypothyroidism is the most prevalent, impacting approximately 2-3% of all pregnancies [2]. Hyperthyroidism is far less prevalent, impacting approximately 0.2% of all pregnancies[2]. Thyroid disorders during pregnancy have been associated with a various number of adverse outcomes among both mothers and newborns. Specifically, multiple studies have found hypothyroidism to be associated with anemia, postpartum hemorrhage, placental abruption, gestational diabetes, cardiac dysfunction, preterm birth, miscarriage and fetal death [3-6, 9-14]. Additionally, studies have found hyperthyroidism to be associated with an increased risk for hypertension during pregnancy, maternal heart failure, preterm birth, miscarriage, and stillbirth[7-9, 11-12].

1.2 HYPOTHYROIDISM

Hypothyroidism, also referred to as underactive thyroid, is a condition in which the thyroid gland does not produce a sufficient amount of thyroid hormone[15]. As a result, the body's metabolism slows down which can cause symptoms including but not limited to: fatigue, lethargy, constipation, weight gain, joint or muscle pain, irregular

menstrual periods, pale or dry skin, depression, weakness, and increased sensitivity to cold temperatures[15,16]. Hypothyroidism can be caused by numerous disorders and by conditions, some of the most common being: viral infections, autoimmune disorders, pregnancy, medications, radiation treatments, pituitary tumors, and congenital birth defects[16]. A diagnosis of hypothyroidism results from the presence of symptoms, and high levels of thyroid-stimulating hormone and low levels of thyroxine as determined by laboratory tests[15]. Hypothyroidism is generally treated with hormone replacement therapy which has shown to be effective in reducing the effects of the disease[15]. However, if left untreated, the symptoms may become more severe and can lead to difficulty in breathing, mental health problems, goiter, heart complications, and life-threatening coma[16].

1.3 HYPERTHYROIDISM

Hyperthyroidism is a condition in which the thyroid produces too much of the thyroid hormone[17]. This results in an overactive thyroid and can produce symptoms such as weight loss, chest pain, palpitations, diarrhea, nervousness, difficulty concentrating, fatigue, and increased appetite[17, 18]. Hyperthyroidism can be caused from various conditions and diseases including but not limited to: Graves' disease, consuming too much iodine, noncancerous growths of the thyroid or pituitary gland, and inflammation of the thyroid due to viral infections, medications, or pregnancy[17, 18]. Diagnosis involves the presence of symptoms in addition to blood tests indicating high levels of thyroxine and low levels of thyroid stimulating hormone[18]. Additionally, radio iodine uptake tests and thyroid scans may be used to confirm the diagnosis[18]. The main

treatment options for hyperthyroidism involve the use of antithyroid drugs, the removal of thyroid gland tissue, and radioiodine therapy[17, 18]. It is important to note that treatment of hyperthyroidism has the potential to result in hypothyroidism, which ultimately will lead to the requirement of lifetime hormone replacement therapy[18].

1.4 PURPOSE AND SPECIFIC AIMS

The purpose of this paper will be to further examine the association between thyroid disorders and adverse pregnancy outcomes. Based on previous findings, we hypothesize that thyroid disorders are associated with increased risks of adverse maternal outcomes. This study's aims and objectives is to evaluate the association of thyroid disorders on adverse pregnancy outcomes, specifically, hypothyroidism, hyperthyroidism, other thyroid disorders, and unspecified thyroid disorders.

1.5 ORGANIZATION OF THESIS

Chapter I has provided sufficient background information on both the exposure and outcomes of interest, in addition to outlining the main aims and objectives of this thesis. Chapter II will consist of a literature review covering previous findings on the influence of thyroid disorders on pregnancy outcomes and demonstrate how this thesis will address some questions. Chapter III will explain in detail the methods of research and statistical techniques used to analyze the data. The results of the analyses will be presented in Chapter IV. Chapter V will provide a summary and conclusion of the research.

CHAPTER 2

LITERATURE REVIEW

2.1 THYROID DISORDERS AND PREGNANCY

Thyroid disorders are fairly common during pregnancy and have been shown to impact up to 4% of all pregnancies[1]. Pregnancy results in a number of physiological and hormonal changes that may alter thyroid function[2]. In order to maintain normal energy and lipid metabolism, normal thyroid function is needed[9]. It is postulated that inadequate regulation of thyroid hormones may result in adverse outcomes during pregnancy [2, 3, 9]. Additionally, weight gain or lipid disturbances that are often associated with hypothyroidism may increase the risk of adverse pregnancy outcomes[9, 3].

One of the largest studies that investigated the relationship between thyroid disorders and maternal outcomes is by Männistö et al[9]. The main objective of this study was to investigate pregnancy complications (hypertensive diseases, diabetes, preterm birth, cesarean sections, inductions, and intensive care unit admissions) associated with both common and uncommon forms of thyroid disease[9]. Data from the Consortium on Safe Labor (2002–2008), a retrospective US cohort, were analyzed using multivariable logistic regression fitted by generalized estimating equations in order to obtain odds ratios (ORs) with 99% confidence intervals (99% CI)[9].

The study found primary hypothyroidism to be significantly associated with increased odds of preeclampsia [OR: 1.47; 99% CI: 1.20, 1.81], superimposed preeclampsia [OR: 2.25; 99% CI: 1.53, 3.29], gestational diabetes [OR: 1.57; 99% CI:1.33, 1.86], preterm birth [OR: 1.34 ; 99% CI: 1.17,1.53], induction [OR:1.15; 99% CI: 1.04,1.28], cesarean section [pre-labor OR: 1.31; 99% CI: 1.11,1.54; after spontaneous labor OR:1.38; 99% CI:1.14,1.66], and ICU admissions [OR: 2.08; 99% CI: 1.04, 4.15][9]. Iatrogenic hypothyroidism was significantly associated with the increased odds of placental abruption [OR: 2.89; 99% CI: 1.14, 7.36], breech presentation [OR: 2.09; 99% CI: 1.07, 4.07], and cesarean section after spontaneous labor [OR: 2.05; 99% CI: 1.01, 4.16][9]. Hyperthyroidism was significantly associated with the increased odds of placental abruption [OR: 2.89; 99% CI: 1.14, 7.36), breech presentation [OR: 2.09; 99% CI: 1.07, 4.07], and cesarean section after spontaneous labor [OR: 2.05; 99% CI: 1.01, 4.16][9]. These results indicate that thyroid diseases are associated with significant increases in morbidity during pregnancy and are consistent with previous research [3-14].

Additionally, one particular paper by Becks et al, stresses that both maternal and neonatal outcomes in pregnancy are adversely affected by multiple thyroid disorders, especially if they go undiagnosed or untreated[10]. Medici et al also found that even small subclinical variations in thyroid function have been associated with detrimental pregnancy outcomes, including low birth weight and pregnancy loss[14]. These studies support the findings by Männistö and support the association between thyroid disorders and adverse pregnancy outcomes. A summary of the findings of epidemiologic studies

on the association between thyroid disorders and pregnancy can be found in table 2.1 at the end of the chapter.

2.2 HYPOTHYROIDISM DURING PREGNANCY

Studies have shown hypothyroidism to be significantly associated with adverse pregnancy complications[3-6, 9-14,19-20]. Maraka et al conducted a systematic review and meta-analysis of results from randomized trials and cohort studies to further investigate the relationship between hypothyroidism and pregnancy outcomes[19]. They focused on the following main outcomes: pregnancy loss, preterm labor, preterm delivery, gestational hypertension, preeclampsia, eclampsia, gestational diabetes, placental complications, premature rupture of membranes, cesarean delivery, intrauterine growth restriction, low birth weight (≤2500 g), low Apgar score (≤7 at 5 min), small for gestational age, and neonatal death[19]. The pooled estimates showed that pregnancy loss [RR 2.01; 95% CI 1.66–2.44], placental abruption [RR 2.14; 95% CI 1.23–3.70], premature rupture of membranes (PROM) [RR 1.43; 95% CI 1.04–1.95], and neonatal death [RR 2.58; 95% CI 1.41–4.73] were significantly increased among women with hypothyroidism as compared to women without a thyroid condition[19]. A different meta-analysis conducted by Sheehan investigated the relationship between maternal thyroid disease and preterm birth and found similar results in regards to adverse outcomes and thyroid disorders[20]. Specifically, the results of the study indicated that overt hypothyroidism was positively associated with preterm birth with an OR of 1.19 and a 95% CI: 1.12-1.26[20].

Other studies have also found hypothyroidism to be associated with an increased risk of adverse pregnancy complications[3-6]. Casey et al investigated this relationship between hypothyroidism and pregnancy outcomes such as hypertension, preterm birth, low birth weight, placental abruption, and fetal death[4]. Most notably the results of the study found pregnancies in women with hypothyroidism to be 3 times more likely to be complicated by placental abruption [RR: 3.0, 95% CI: 1.1-8.2] and almost 2 times as likely to experience preterm birth [RR: 1.8, 95% CI: 1.1-2.9][4]. Allan et al examined the relationship between pregnancy complications and thyroid deficiency[5]. Specifically, the study looked at vaginal bleeding, premature delivery, low birthweight, abruptio placentae, pregnancy induced hypertension, need for cesarean section, low Apgar scores, and fetal and neonatal death[5]. The results indicated that fetal death is significantly associated with thyroid-stimulating hormone (TSH) deficiency and other major adverse obstetrical outcomes [5].

Davis et al also investigated the relationship between hypothyroidism and pregnancy outcomes[3] and showed that hypothyroidism was associated with a slight insignificant increase in preeclampsia, placental abruption, anemia, postpartum hemorrhage, cardiac dysfunction, and adverse perinatal outcomes[3]. The study also emphasized the importance of proper treatment of thyroid disorders in reducing adverse pregnancy outcomes in women with thyroid disorders[3]. However, the results were not statistically significant, which was most likely a result of the limited sample size[3].

2.3 HYPERTHYROIDISM DURING PREGNANCY

Hyperthyroidism has also been found to be associated with adverse pregnancy outcomes. However, there has been far less research on hyperthyroidism compared to hypothyroidism given its lower prevalence. Previous research indicates that hyperthyroidism is associated with increased risks of adverse outcomes such as preterm birth, low birth weight, placental complications, cardiomyopathy, retinopathy of prematurity, and neonatal thyroid diseases[7-9, 11-12, 19-20].

Millar et al, examined if controlling hyperthyroidism during pregnancy reduces the risk of low birth weight and preeclampsia[7]. The results of the study showed that lack of control of hyperthyroidism significantly increases the risk of low birth weight infants [OR: 9.24, 95% CI 5.47-15.6] and severe preeclampsia [OR: 4.74, 95% CI: 1.14-19.7][7]. Davis et al also investigated the adverse effects of hyperthyroidism and its control on pregnancy outcomes[8]. The study compared pregnancy outcomes for women who were both treated and untreated for hyperthyroidism during pregnancy[8]. The results of the study showed that hyperthyroidism is associated with an increased risk of stillbirth, preterm birth, and maternal heart failure in both women who had been treated for hyperthyroidism and in those who had not received treatment[8].

2.4 GAPS IN THE LITERATURE

Previous research has indicated that thyroid disorders are associated with obstetrical, labor, and delivery complications[3-6, 9-14,19-22]. However, not all previous studies have found this to be consistently true[23-26]. While some studies did find associations between thyroid disorders and pregnancy outcomes, unlike other findings[3-

[14], the associations were not significant [23-26]. These inconsistencies in the literature may be the result of differences in populations, definition of thyroid dysfunction, and patient's baseline characteristics[27].

Additionally, there have been a limited number of large contemporary studies that have investigated the influence of thyroid disorders on adverse pregnancy outcomes. This is especially true for hyperthyroidism which has been found to affect 0.2% of all pregnancies[2]. Given the low rate of hyperthyroidism, the association between hyperthyroidism and pregnancy outcomes has not been explored in as great detail as hypothyroidism and therefore more research is needed to further understand this association.[2]

2.5 MOVING FORWARD

This paper will investigate the relationship between thyroid disorders and maternal outcomes. Based on previous findings, we hypothesize that the presence of thyroid disorders will be associated with an increased risk of pregnancy complications.

Table 2.1 Epidemiologic studies on the association between thyroid disorders and pregnancy

Author (year)	Study Population (sample size)	Study Sample Exclusion Criteria	Outcomes	Main Findings
Allan (2000)[5]	1990-1992 (n=9403)	The study was limited to women with singleton pregnancies who had undergone prenatal screening for neural tube defects and Down's syndrome.	Birth weight, gestational age, abruptio placentae, pregnancy induced hypertension, cesarean delivery, Apgar score at 5 minutes, fetal death, neonatal death	"The major adverse obstetrical outcome associated with raised TSH in the general population is an increased rate of fetal death."[5, (abstract)]
Ashoor (2011)[24]	2006 (n= 4,420)	The analysis was limited to singleton pregnancies without history of thyroid disease. Additionally, pregnancies complicated by preeclampsia were excluded.	Preterm delivery	"In pregnancies resulting in spontaneous early preterm delivery, there is no evidence of increased prevalence of antithyroid antibody positivity or maternal thyroid dysfunction at 11-13 weeks." [24 (abstract)]
Casey (2004)[4]	2000-2003 (n=16,093)	Women who had abnormally elevated serum TSH levels accompanied by abnormally low free thyroxine levels, were determined to have overt hypothyroidism and therefore excluded from the analysis.	Pregnancy Outcomes: hypertension, placental abruption, weeks gestation at delivery, cesarean delivery Infant Outcomes: birth weight, admission to intensive care, Apgar score at 5 minutes, umbilical artery blood pH, respiratory distress syndrome, necrotizing enterocolitis, intraventricular hemorrhage, major malformations, fetal death, neonatal deaths	"Pregnancies in women with subclinical hypothyroidism were 3 times more likely to be complicated by placental abruption (relative risk 3.0, 95% confidence interval 1.1–8.2). Preterm birth, defined as delivery at or before 34 weeks of gestation, was almost 2-fold higher in women with subclinical hypothyroidism (relative risk, 1.8, 95% confidence interval 1.1–2.9)."[4 (abstract)]

Chen (2014)[27]	(n=8012)	Analysis excluded women with the following conditions: overt thyroid disorder, previous or present use of thyroxin or anti-thyroid drugs, other autoimmune disease, congenital heart disease, and elevated serum transaminase or creatinine level.	Gestational hypertension (GH), gestational diabetes mellitus, placenta previa, placental abruption, prelabor rupture of membranes (PROM), premature delivery, intrauterine growth restriction (IUGR), fetal distress, low birth weight (LBW; live birth weight <= 2500 g), stillbirth, and malformation	"Compared with euthyroid status, SCH was associated with higher rates of GH (1.819% vs. 3.504%, P = 0.020; chi(2) = 7.345; odds ratio (OR), 2.243; 95% confidence interval (CI), 1.251-4.024), PROM (4.973% vs. 8.625%, P = 0.002; chi(2) = 72.102; adjusted OR, 6.014; 95% CI, 3.975-9.099), IUGR (1.008% vs. 2.965%, <0.001; chi(2) = 13.272; adjusted OR, 3.336; 95% CI, 1.745-6.377), and LBW (1.885% vs. 4.582%, P<0.001; chi(2) = 13.558; adjusted OR, 2.919; 95% CI, 1.650-5.163)."[27] (Abstract)
Cleary-Goldman (2008)[23]	1999-2002 (n= 10,990)	The analysis was limited to singleton intrauterine pregnancy without evidence of anencephaly or cystic hygroma.	Miscarriage, gestational hypertension, preeclampsia, gestational diabetes , Placenta previa, placental abruption , preterm labor, preterm premature rupture of membranes, preterm delivery, low birth weight, macrosomia, and perinatal mortality	"Subclinical hypothyroidism was not associated with adverse outcomes. In the first trimester, hypothyroxinemia was associated with preterm labor (adjusted odds ratio [aOR] 1.62; 95% confidence interval [CI] 1.00-2.62) and macrosomia (aOR 1.97; 95% CI 1.37-2.83). In the second trimester, it was associated with gestational diabetes (aOR 1.7; 95% CI 1.02-2.84). Fifteen percent (1,585 of 10,990) in the first and 14% (1,491 of 10,990) in the second trimester had antithyroid antibodies. When both antibodies were positive in either trimester, there was an increased risk for preterm premature rupture of membranes (P=.002 and P <.001, respectively)…Maternal thyroid hypofunction is not associated with a consistent pattern of adverse outcomes." [23]
Davis (1989)[8]	1974-1985 (n=60)	The analysis was limited to singleton pregnancies that were complicated by thyrotoxicosis.	Thyroxine, pulse rate, preeclampsia, gestational age, pregnancy weight gain, heart failure, thyrotoxicosis, hypothyroidism, goiter, birth weight, abortions, still births	"uncontrolled thyrotoxicosis caused significant maternal and perinatal morbidity, aggressive medical therapy seems appropriate, especially when pregnancy is advanced."[8] (abstract)

Karakosta (2012)[6]	2007-2008 (n=1170)	The study was limited to women with singleton pregnancies.	Gestational diabetes, gestational hypertension/preeclampsia, cesarean section, preterm delivery, low birth weight, and small-for-gestational-age neonates.	"The combination of high TSH and thyroid autoimmunity in early pregnancy was associated with a 4-fold increased risk for gestational diabetes [relative risk (RR) 4.3, 95% confidence interval (CI) 2.1-8.9)] and a 3-fold increased risk for low birth weight neonates (RR 3.1,95% CI 1.2-8.0) after adjustment for several confounders. Women positive for thyroid antibodies without elevated TSH levels in early pregnancy were at high risk for spontaneous preterm delivery (RR 1.7, 95% CI 1.1-2.8), whereas the combined effect of high TSH and positive thyroid antibodies did not show an association with preterm birth." [6 (abstract)]
Karakosta (2012)[25]	2007-2008 (n=1170)	Analysis was limited to singleton pregnancies. Participants who did not provide blood samples or provided serum samples after the 18th week of gestation were excluded. Additionally, women with incomplete information on outcome variables were also excluded.	Gestational diabetes, gestational hypertension/preeclampsia, cesarean section, preterm delivery, low birth weight, and small-for-gestational-age neonates.	"The combination of high TSH and thyroid autoimmunity in early pregnancy was associated with a 4-fold increased risk for gestational diabetes [relative risk (RR) 4.3, 95% confidence interval (CI) 2.1-8.9)] and a 3-fold increased risk for low birth weight neonates (RR 3.1,95% CI 1.2-8.0) after adjustment for several confounders. Women positive for thyroid antibodies without elevated TSH levels in early pregnancy were at high risk for spontaneous preterm delivery (RR 1.7, 95% CI 1.1-2.8), whereas the combined effect of high TSH and positive thyroid antibodies did not show an association with preterm birth." [25 (abstract)]
León (2015)[22]	(n= 2170)	Analysis was limited to women with singleton pregnancies.	Birthweight, small and large for gestational age (SGA/LGA), and preterm delivery	"An inverse association of fT_4 and TSH with birthweight was found, the former remaining when restricted to euthyroid women. High fT_4 levels were also associated with an increased risk of SGA [odds ratio, 95% confidence interval (CI) 1.28 (95% CI 1.08, 1.51)]. Mean birthweight was higher in the hypothyroxinaemic group ($\beta = 109$, $P < 0.01$). Iodine intake and UIC were not associated with birth outcomes… High maternal fT_4 levels during the first half of pregnancy were related to lower birthweight and

				increased risk of SGA newborns, suggesting that maternal thyroid function may affect fetal growth, even within the normal range." [22 (abstract)]
Männistö (2013)[9]	2002-2008 (n=223,512)	The analysis was limited to singleton pregnancies. Women diagnosed with chronic hypertension were excluded from the analyses of gestational hypertension and preeclampsia. Additionally women who were diagnosed with preexisting diabetes were excluded from the analyses of gestational diabetes.	Pre-labor cesarean section, induction, spontaneous labor, route of delivery, preterm birth (<37 gestational weeks), late preterm birth (delivery between 34 and <37 weeks), early preterm birth (<34 weeks), gestational diabetes, gestational hypertension, preeclampsia, superimposed preeclampsia, placental abruption, threatened preterm birth, placenta previa, hemorrhage in late pregnancy or postpartum, chorioamnionitis, premature rupture of membranes (PROM), preterm premature rupture of membranes (PPROM) (PROM <37 weeks), breech presentation, maternal intensive care unit (ICU) admission, and maternal death.	"Primary hypothyroidism was associated with increased odds of preeclampsia (OR = 1.47, 99% CI = 1.20-1.81), superimposed preeclampsia (OR = 2.25, 99% CI = 1.53-3.29), gestational diabetes (OR = 1.57, 99% CI = 1.33-1.86), preterm birth (OR = 1.34, 99% CI = 1.17-1.53), induction (OR = 1.15, 99% CI = 1.04-1.28), cesarean section (prelabor, OR = 1.31, 99% CI = 1.11-1.54; after spontaneous labor OR = 1.38, 99% CI = 1.14-1.66), and ICU admission (OR = 2.08, 99% CI = 1.04-4.15). Iatrogenic hypothyroidism was associated with increased odds of placental abruption (OR = 2.89, 99% CI = 1.14-7.36), breech presentation (OR = 2.09, 99% CI = 1.07-4.07), and cesarean section after spontaneous labor (OR = 2.05, 99% CI = 1.01-4.16). Hyperthyroidism was associated with increased odds of preeclampsia (OR = 1.78, 99% CI = 1.08-2.94), superimposed preeclampsia (OR = 3.64, 99% CI = 1.82-7.29), preterm birth (OR = 1.81, 99% CI = 1.32-2.49), induction (OR = 1.40, 99% CI = 1.06-1.86), and ICU admission (OR = 3.70, 99% CI = 1.16-11.80)." [9 (abstract)]
Männistö (2013)[13]	2002-2008 (n=223,512)	The analysis was limited to singleton pregnancies.	Respiratory distress syndrome, intracerebral hemorrhage, seizures, oliguria, cardiomyopathy, peri- or intraventricular hemorrhage, necrotizing enterocolitis, retinopathy of prematurity, sepsis, transient tachypnea, anemia, apnea, asphyxia, infectious pneumonia, and aspiration	"Hyperthyroidism and primary hypothyroidism were associated with sepsis, respiratory distress syndrome, transient tachypnea, and apnea. Iatrogenic hypothyroidism was associated with sepsis and neonatal anemia. Hyperthyroidism was also associated with rare outcomes (prevalence, <1%) including cardiomyopathy, retinopathy of prematurity, and neonatal thyroid diseases." [13 (abstract]
Männistö (2008)[21]	1985-1986 (n = 9247)	The analysis was limited to singleton pregnancies.	Perinatal mortality, preterm delivery, absolute and gestational age-	"First-trimester antibody positivity is a risk factor for perinatal death but not thyroid hormone status as such.

			adjusted birth weight, and absolute and relative placental weight.	Thyroid dysfunction early in pregnancy seems to affect fetal and placental growth." [21(abstract)]
Männistö (2010)[26]	1985-1986 (n = 5805)	Analysis was limited to mothers with singleton pregnancies. Women with previous diagnoses diabetes, hypertension, or thyroid disease of before pregnancy were excluded from analyses of the disease in question.	preeclampsia and gestational diabetes	"Thyroid dysfunction and antibodies were not associated with pregnancy complications. Overt hypothyroidism was associated with subsequent maternal thyroid disease [hazard ratio (HR) (95% confidence interval), 17.7 (7.8-40.6)] and diabetes [6.0 (2.2-16.4)]. Subclinical hypothyroidism [3.3 (1.6-6.9)], TPO-Ab-positivity [4.2 (2.3-7.4)], and TG-Ab-positivity [3.3 (1.9-6.0)] were also associated with later thyroid disease. No association was found between thyroid dysfunction/antibodies and hypertension or overall mortality."[23 (abstract)]
Maraka (2016)[19]	(n=3995)	Cohort studies as randomized control trials were examined. Studies that lacked the required information to determine eligibility, and studies that reported on a mixed population of SCH and OH during pregnancy were excluded.	Pregnancy loss, preterm labor, preterm delivery, gestational hypertension, preeclampsia , eclampsia, gestational diabetes, placental abruption, placenta previa, premature rupture of membranes, cesarean delivery, intrauterine growth restriction, low birth weight, low Apgar score, small for gestational age, and neonatal death	"Compared with euthyroid pregnant women, pregnant women with SCH were at higher risk for pregnancy loss (relative risk [RR] 2.01 [confidence interval (CI) 1.66-2.44]), placental abruption (RR 2.14 [CI 1.23-3.70]), premature rupture of membranes (RR 1.43 [CI 1.04-1.95]), and neonatal death (RR 2.58 [CI 1.41-4.73])." [19 (abstract)]
Millar (1994)[7]	(n=181)	Analysis was limited to hyperthyroid women with singleton pregnancies.	Preeclampsia, birth weight, preterm birth	"The risk of low birth weight infants was 0.74 (95% confidence interval [CI] 0.18-3.08) among controlled women, 2.36 (95% CI 1.36-4.12) among women who were controlled during pregnancy, and 9.24 (95% CI 5.47-15.6) among women who were uncontrolled during pregnancy compared to the incidence among non-hyperthyroid mothers. The risk of severe preeclampsia was significantly higher (odds ratio 4.74, 95% CI 1.14-19.7) among

				uncontrolled women compared with those who were controlled during their pregnancies." [7] (abstract)
Sheehan (2015)[20]	(n=2,532, 704)	Analysis was limited to prospective cohort and case-control studies where the exposure of interest was maternal thyroid disease and the outcome of interest was preterm birth.	Preterm Birth	"The combined OR of preterm delivery for pregnant women with overt hypothyroidism compared with the reference group was 1.19 (95% CI, 1.12–1.26; P < .00001). There was also a significant risk of preterm birth in women with hyperthyroidism (OR, 1.24 [95%, CI 1.17–1.31]; P < .00001). Subclinical hypothyroidism and isolated hypothyroxinemia showed no significant increase in OR."[20] (abstract)
Wilson (2012)[28]	(n=24,883)	Women with evidence of overt thyroid disease were excluded from the analyses.	Hypertension and other cardiovascular-related conditions during pregnancy	"The overall incidences of hypertension in pregnancy were 6.2%, 8.5%, and 10.9% in the subclinical hyperthyroid, euthyroid, and subclinical hypothyroid groups, respectively, and were found to be significant when unadjusted (P=.016)….Women with subclinical hypothyroidism identified during pregnancy have an increased risk for severe preeclampsia when compared with euthyroid women." [28] (Abstract)

CHAPTER 3

METHODS

3.1 STUDY POPULATION

The NICHD Consecutive Pregnancy data set contains information on a total of 114,679 pregnancies from 51,086 women who delivered at least twice after 20 weeks of gestation. The data comes from 20 different hospitals throughout the state of Utah and were collected between the years of 2002 to 2010. Information was extracted by hospitals from antepartum and labor and delivery summary electronic medical records. Patient information such as demographics, past medical history, reproductive and prenatal history, pregnancy, labor and delivery outcomes, postpartum and neonatal information were available. Labor and delivery records included data on both the time and date of admission, cervical exam on admission, labor and delivery characteristics, indications for induction, and indications for cesarean. International Classification of Diseases-9 codes from maternal and newborn discharge summaries and patient medical records were used to classify the outcomes of each delivery.

3.2 EXPOSURE OF INTEREST

The exposure of interest was maternal thyroid disease and was determined using electronic medical records and International Classification of Diseases-Ninth Edition (ICD-9) codes. Thyroid disease was categorized as no thyroid disease (referent group), primary hypothyroidism, iatrogenic hypothyroidism, hyperthyroidism, other

thyroid diseases (simple or nontoxic goiter, thyroiditis, and other thyroid disorders including benign and malignant thyroid nodules), and unspecified thyroid diseases (reported in the medical record but without a discharge ICD-9 diagnostic code). A detailed classification of the exposures of interest can be found in table 3.1. Additionally, it is important to note that if there were not enough observations available within each category, they were combined to aid in the analyses. Specifically, due to a limited number of cases of iatrogenic hypothyroidism (n=28), the category was combined with primary hypothyroidism. Furthermore, once a mother was diagnosed with a thyroid disorder, all subsequent pregnancies were assumed to be affected.

Table 3.1 Classification of Thyroid Disorder as Classified in the International Classification of Diseases, Ninth Edition (ICD-9) [9, 28]

Thyroid Disorder	ICD-9 Code	Definition
Primary Hypothyroidism	244	Acquired Hypothyroidism
	244.8	Other specified acquired hypothyroidism
	244.9	Unspecified hypothyroidism
	244.0	Postsurgical hypothyroidism
Iatrogenic Hypothyroidism	244.1	Other post ablative hypothyroidism
	244.2	Iodine hypothyroidism
	244.3	Other iatrogenic hypothyroidism
	243	Congenital hypothyroidism
Hyperthyroidism	242-242.9	Thyrotoxicosis with or without goiter
Other Thyroid Diseases	240-240.9	Simple and unspecified goiter
	241-241.9	Nontoxic nodular goiter
	245-245.9	Thyroiditis
	246-246.9	Other disorders of thyroid

	193	Malignant neoplasm of thyroid gland
	226	Benign neoplasm of thyroid glands

3.3 OUTCOMES OF INTEREST

Outcomes of interest were also classified using electronic medical records and International Classification of Diseases-9 (ICD-9) codes. Key outcomes of interest included: breech presentation, gestational diabetes, gestational hypertension, hemorrhage, inductions, placental abruption, preterm birth, PROM, preeclampsia, and superimposed preeclampsia. The ICD-9 codes and definitions of these outcomes are listed in Table 3.2.

Table 3.2 Classification of Outcomes of Interest [9,28]

Outcome	ICD-9 Code	Source of Data	Defined
Breech Presentation	652.2	ICD9 and EMR	Breech presentation without mention of version
Gestational diabetes	648.8	ICD9 and EMR	Other current conditions in the mothers classifiable elsewhere complicating pregnancy, childbirth, or the puerperium – Abnormal glucose tolerance
Gestational hypertension	642.3	ICD9 and EMR	Transient hypertension of pregnancy
Hemorrhage in Late Pregnancy or Post-Partum	666-666.3	ICD9 and EMR	Postpartum hemorrhage
Placental Abruption	641.2	ICD9 and EMR	Premature separation of placenta
Preeclampsia	642.4 (mild) 642.5 (severe)	ICD9 and EMR	Mild or unspecified pre-eclampsia Severe pre-eclampsia

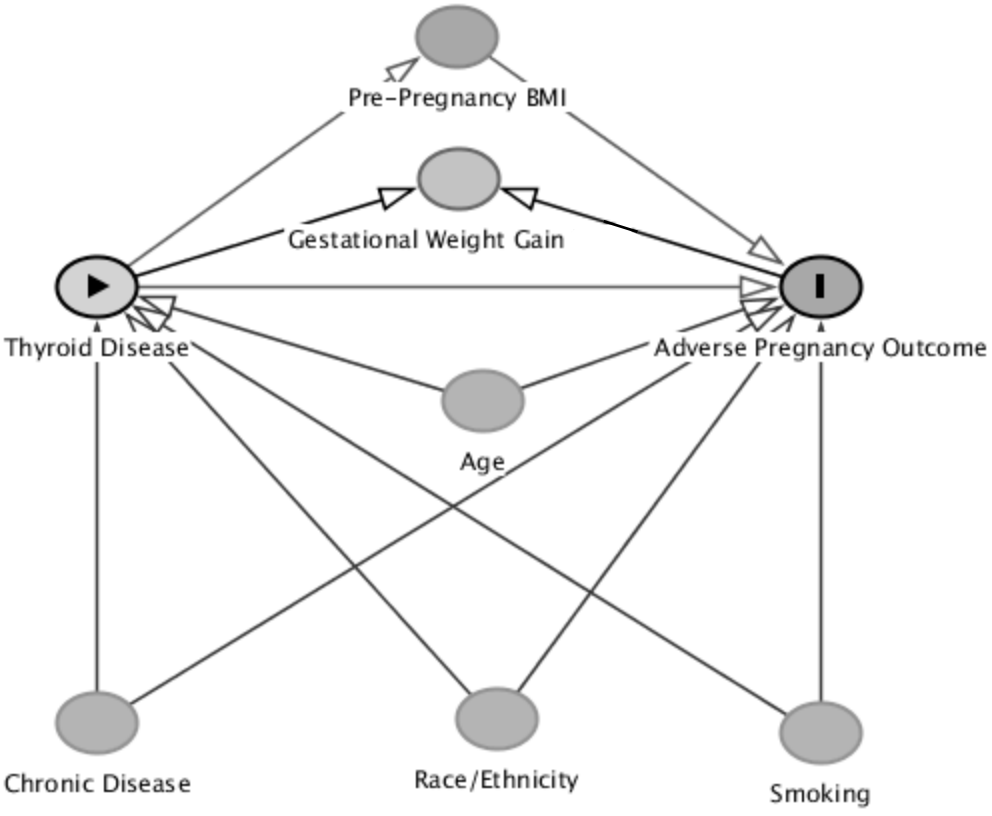
Premature Rupture of Membranes	658.1	ICD9 and EMR	Premature rupture of membranes
Preterm Birth	644.2	ICD9 and EMR	<37 Weeks Gestation
Superimposed Preeclampsia	642.7	ICD9 and EMR	Pre-eclampsia or eclampsia superimposed on pre-existing hypertension

3.4 POTENTIAL CONFOUNDERS

Covariates included in the model for thyroid disorders and adverse maternal outcomes are as follows: maternal age, race/ethnicity, smoking status, hospital of birth, parity, insurance status, and other chronic diseases (diabetes, chronic hypertension, heart disease, renal disease, depression, seizure disorder, and asthma). Despite the knowledge that gestational weight gain is often associated with several of the proposed outcomes of interest, it will not be adjusted for in the analyses[29]. This is due to the fact that thyroid diseases are known to cause weight gain or loss, therefore making it a collider in the exposure disease pathway[9, 29]. Thus, adjusting for gestational weight gain would potentially introduce bias into the results[9,29]. Additionally, we are only interested in estimating the total effect of the exposure, so no adjustment for gestational weight gain will be made. In regards to pre-pregnancy BMI, it will be regarded as a mediator in the relationship between thyroid disease and pregnancy outcomes. This is due to the fact that thyroid disorders can cause weight loss and gain which influences BMI and in turn influences pregnancy outcomes. Therefore, given its position as a mediator in the disease-exposure relationship, adjusting for it has the potential to introduce over-

adjustment bias. These relationships are illustrated in the directed acyclic graph (DAG) below.

Figure 3.1 Directed Acyclic Graph[46]



3.5 ANALYSIS

The analysis was limited to singleton pregnancies (n=113,288). Multivariate Poisson regression with generalized estimating equations was used as the primary method of analysis[30]. For all analyses, the no thyroid disease category served as the comparison group. Results are presented as RRs with their 95% CIs. Estimates of the exposure-outcome relationship were obtained, after adjusting for insurance, parity, race and ethnicity, age, smoking, and other chronic diseases. For the analyses of gestational hypertension and preeclampsia, women with chronic hypertension were excluded

(n=1,103). For the analyses of gestational diabetes, women with preexisting diabetes were excluded (n=1,819). Results from SAS outputs of multivariate Poisson regression with generalized estimating equations can be found in Appendix A. Additionally, a sensitivity analysis restricting the sample to women with their first delivery only was conducted using Poisson regression with generalized estimating equations (n= 50628). Statistical significance was set at the 5% level. Statistical analyses were carried out using Statistical Analysis Software (SAS) 9.4.

CHAPTER 4

RESULTS

4.1 STUDY POPULATION

Hypothyroidism complicated 2.25% of pregnancies, hyperthyroidism complicated 0.14% of pregnancies, other thyroid disorders complicated .27% of pregnancies, and unspecified thyroid disorders impacted 2.21% of pregnancies. The prevalence of thyroid disorders was fairly consistent amongst hospitals and across the years. A total of 878 (.86%) women who did not have a thyroid disorder in the first pregnancy developed a thyroid disorder by the time of the second pregnancy (data not shown). Table 4.1 provides demographic information for the study population by thyroid disease status.

Compared to women without a thyroid disorder, women with hypothyroidism were significantly more likely to be older, have higher BMIs, be married, have private insurance, be White, and suffer from the following chronic diseases: diabetes, hypertension, heart disease, and depression. Compared to women without a thyroid disorder, women with hyperthyroidism were significantly more likely to be older in age, be multiparous, be married, and to not suffer from renal disease. Compared to women without a thyroid disorder, women with other thyroid disorders were significantly more

likely to be older in age, have higher BMIs, be married, have private insurance, be White, and suffer from the following chronic diseases: diabetes and depression.

Compared to women without a thyroid disorder, women with unspecified thyroid disorders were significantly more likely to be older in age, have higher BMIs, have private insurance, be White, smoke, and suffer from the following chronic diseases: diabetes, hypertension, asthma, heart disease, renal disease, and depression.

Outcomes of interest included breech presentation (n=2,259), gestational diabetes (n=2,096), gestational hypertension (n=3,367), hemorrhage (n=2,909), inductions (n=43,794), placental abruption (n= 2,205), preterm birth (n=9,773), PROM (n=1953), preeclampsia (n=2,813), and superimposed preeclampsia (n=220).

4.2 HYPOTHYROIDISM

Unadjusted and adjusted results are presented in Tables 4.2 and 4.3, respectively. In the crude model, hypothyroidism was significantly associated with gestational diabetes [RR: 1.65, 95% CI: 1.30-2.08], preterm birth [RR: 1.27, 95% CI: 1.11-1.45], spontaneous preterm birth [RR: 1.31, 95% CI: 1.81-3.79], and superimposed preeclampsia [RR: 4.00, 95% CI: 2.40-6.67] (Table 4.2). After adjusting for insurance, parity, race/ethnicity, age, smoking, and other chronic diseases, hypothyroidism was significantly associated with gestational diabetes [RR: 1.28, 95% CI: 1.00-1.63], gestational hypertension [RR: 1.32, 95% CI: 1.07-1.63], inductions [RR: 0.98, 95% CI: 0.96-0.99], preterm birth [RR: 1.23, 95% CI: 1.08-1.41], and spontaneous preterm birth [RR:1.25, 95% CI: 1.09-1.43] (Table 4.3). The association for superimposed preeclampsia

was no longer significant. The adjusted results for breech presentation, hemorrhage, placental abruption, PROM, and preeclampsia were not statistically significant.

4.3 HYPERTHRYOIDISM

In the crude model, hyperthyroidism was found to be significantly associated with gestational diabetes [RR: 2.93, 95% CI: 1.49-5.79], preterm birth [RR: 2.38, 95% CI: 1.66-3.41], spontaneous preterm birth [RR: 2.62, 95% CI: 1.81-3.79], and preeclampsia [RR: 2.52, 95% CI 1.37-4.63]. After adjusting for insurance, parity, race/ethnicity, age, smoking, and other chronic diseases, hyperthyroidism was found to be significantly associated with gestational diabetes [RR: 2.47, 95% CI: 1.28-4.76], preterm birth [RR: 2.31, 95% CI: 1.61-3.32], spontaneous preterm birth [RR: 2.43, 95% CI: 1.68-3.53] and preeclampsia [RR: 2.65, 95% CI: 1.44-4.87]. The adjusted results for breech presentation, gestational hypertension, hemorrhage, inductions, placental abruption, PROM, and superimposed preeclampsia were not statistically significant.

4.4 OTHER THYROID DISORDERS

In the crude model, other thyroid disorders were found to be significantly associated with gestational diabetes [RR: 1.95, 95% CI: 1.15-3.32]. After adjusting for insurance, parity, race/ethnicity, age, smoking, and other chronic diseases, other thyroid disorders were not found to be significantly associated with any of the outcomes of interest.

4.5 UNSPECIFIED THYROID DISORDERS

In the crude model, unspecified thyroid disorders were found to be associated with breech presentation [RR: 1.30, 95% CI: 1.01-1.67], gestational hypertension [RR: 1.26, 95% CI: 1.02-1.55], inductions [RR: 1.02, 95% CI: 1.00-1.03], placental abruption [RR: 1.30, 95% CI: 1.01-1.64], preterm birth [RR: 1.19, 95% CI: 1.04-1.36], spontaneous preterm birth [RR:1.33, 95% CI: 1.16-1.53], and superimposed preeclampsia [RR: 2.20, 95% CI: 1.04-3.91]. After adjusting for insurance, parity, race/ethnicity, age, smoking, and other chronic diseases, unspecified thyroid disorders were found to be significantly associated with gestational hypertension [RR: 1.24, 95% CI: 1.01-1.53], placental abruption [RR: 1.29, 95% CI: 1.01-1.64], preterm birth [RR: 1.20, 95% CI: 1.05-1.37], and spontaneous preterm birth [RR:1.30, 95% CI: 1.14-1.50]. Results for breech presentation, gestational diabetes, hemorrhage, inductions, preterm birth, PROM, preeclampsia, and superimposed preeclampsia were not statistically significant.

4.6 SENSITIVITY ANALYSIS

In the sensitivity analysis restricted to the first delivery, the results remained generally similar in regards to the direction of the association, although there was a loss of significance due to smaller sample sizes and a diminished statistical power. The associations between hypothyroidism and gestational diabetes [RR: 1.05; 95%CI: 0.61-1.79], gestational hypertension [RR:1.07; 95%CI: 0.75-1.54], and preterm birth [RR:1.14, 95%CI: 0.89-1.45] became null. The associations between hyperthyroidism and both preterm birth [RR:1.64; 95%CI: 0.55-4.87] and preeclampsia [RR:1.71; 95%CI: 0.83-3.52] became null. For the associations between unspecified thyroid disease and both

gestational hypertension [RR:1.01; 95%CI: 0.99-1.02]and placental abruption [RR:1.01; 95%CI: 0.99-1.02] became null. Results from the sensitivity analysis are displayed in Table 4.4.

Table 4.1 Demographic Data by Thyroid Disease Status

	No Thyroid Disease n= 107578	Hypothyroidism n= 2511	P Value	Hyperthyroidism n= 150	P Value	Other n= 317	P Value	Unspecified n= 2732	P Value
Pregnancy Number, no. (%) [a]									
1	48690 (45.26)	668 (26.60)	<.0001	48 (32.00)	0.0010	83 (26.18)	<.0001	1139 (41.69)	<.0001
2	47374 (44.04)	1413 (56.27)		78 (52.00)		186 (58.68)		1278 (46.78)	
3	10243 (9.52)	375 (3.42)		21 (14.00)		41 (12.93)		277 (10.14)	
≥4	1271 (1.18)	55 (2.19)		3 (2.00)		7 (2.21)		38 (1.39)	
Mean Maternal Age, y (SD)	26.95 (4.72)	29.64 (4.67)	<.0001	28.72 (5.05)	0.0002	29.68 (4.37)	<.0001	28.73 (4.67)	<.0001
Parity									
Nulliparous	26588 (24.72)	316 (12.58)	<.0001	23 (15.33)	0.0002	45 (14.20)	<.0001	513 (18.78)	<.0001
Multiparous	80990 (75.28)	2195 (87.42)		127 (84.67)		272 (85.80)		2219 (81.22)	
Pre-pregnancy BMI [b], **no. (%)**									
Underweight	8046 (7.48)	99 (3.94)	<.0001	7 (4.67)	0.3942	23 (7.26)	0.0005	178 (6.52)	<.0001
Normal Weight	60723 (56.45)	1148 (45.72)		77 (51.33)		134 (42.27)		1322 (48.39)	
Overweight	23001 (21.38)	618 (24.61)		25 (16.67)		74 (23.34)		578 (21.16)	

Obese	15808 (14.69)	646 (25.73)		41 (27.34)		86 (27.13)		654 (23.94)	
Marital Status [c], no. (%)									
Married	106309 (98.82)	2477 (98.65)	<.0001	148 (98.67)	<.0001	314 (99.05)	<.0001	2693 (98.57)	<.0001
Unmarried	1269 (1.18)	34 (1.35)		2 (1.33)		3 (0.95)		39 (1.43)	
Insurance Status									
Private	78987 (73.42)	2037 (8.1.12)	<.0001	116 (77.33)	0.3314	265 (83.60)	<.0001	2239 (81.95)	<.0001
Public	28591 (26.58)	474 (18.88)		34 (22.67)		52 (16.40)		493 (18.05)	
Race Ethnicity, no. (%)									
Non-Hispanic White	92501 (85.99)	2364 (94.23)	<.0001	135 (90.00)	0.3447	301 (94.95)	<.0001	2569 (94.03)	<.0001
Hispanic	11563 (10.75)	113 (4.33)		5 (3.33)		11 (3.47)		121 (4.33)	
Asian/Pacific Islander	2310 (2.14)	19 (0.74)		8 (5.33)		4 (1.26)		22 (0.81)	
Black	479 (0.45)	7 (0.28)		0 (0.00)		0 (0.00)		7 (0.26)	
Other	725 (0.67)	8 (0.31)		2 (1.33)		1 (0.32)		13 (0.48)	
Maternal Chronic Disease, no. (%)									
Diabetes	1597 (1.48)	110 (4.28)	<.0001	4 (2.67)	0.3742	13 (4.10)	0.0308	95 (3.48)	<.0001
Hypertension	986 (0.92)	67 (2.67)	<.0001	1 (0.66)	0.6953	7 (2.16)	0.1228	42 (1.51)	0.0333

Asthma	6719 (6.25)	188 (7.49)	0.0582	15 (10.00)	0.2173	24 (7.57)	0.3744	211 (7.72)	0.0179
Heart Disease	922 (0.86)	63 (2.51)	<.0001	1 (0.67)	0.7753	5 (1.58)	0.3043	47 (1.72)	0.0050
Renal Disease	348 (0.32)	15 (0.60)	0.1156	0 (0.00)	<.0001	0 (0.00)	<.0001	23 (0.84)	0.0063
Gastrointestinal Disease	1269 (1.18)	34 (1.35)	0.5190	2 (1.33)	0.8694	3 (0.95)	0.6687	39 (1.43)	0.3136
Depression	8255 (7.67)	392 (15.61)	<.0001	20 (13.33)	0.0630	48 (15.14)	0.0003	279 (10.21)	<.0001
Smoking[d], no. (%)	3040 (2.83)	58 (2.31)	0.1690	8 (5.33)	0.3013	8 (2.52)	0.7296	49 (1.79)	0.0008

P values were obtained from binary regression using generalized estimating equations to account for correlated data with no thyroid disease as comparison group.

[a] All women contributed a minimum of 2 pregnancies to the data set.

[b] Maternal BMI is categorized as underweight if BMI is <18.5 kg/m^2, normal weight if BMI is 18.5 to 24.9 kg/m^2, overweight if BMI is 25.0 to 29.9 kg/m^2, obese if BMI is ≥30.0

[c] Marital Status frequency missing=14

[d] Smoking frequency missing=132

Table 4.2 Unadjusted Relative Risks of Adverse Pregnancy Outcomes among Women with Thyroid Diseases in the NICHD Consecutive Pregnancies Data Set

	Hypothyroidism n= 2511	Hyperthyroidism n= 150	Other n= 317	Unspecified n= 2732
Breech Presentation	1.28 (0.99-1.65)	0.31 (0.04-2.34)	1.26 (0.57-2.35)	1.30 (1.01-1.67)*
Gestational Diabetes [a]	1.65 (1.30-2.08)*	2.93 (1.49-5.79)*	1.95 (1.15-3.32)*	1.10 (0.84-1.45)
Gestational Hypertension [b]	1.23 (0.99-1.52)	1.43 (0.62-3.27)	1.24 (0.70-2.20)	1.26 (1.02-1.55)*
Hemorrhage	1.01 (0.79-1.31)	1.25 (0.52-3.01)	0.99 (0.50-1.94)	0.72 (0.54-0.95)
Inductions	1.00 (0.98-1.01)	1.02 (0.96-1.08)	1.02 (0.98-1.06)	1.02 (1.00-1.03)*
Placental Abruption	1.14 (0.86-1.52)	1.04 (0.34-3.17)	1.50 (0.79-2.83)	1.30 (1.01-1.64)*
Preterm Birth	1.27 (1.11-1.45)*	2.38 (1.66-3.41)*	0.94 (0.63-1.40)	1.19 (1.04-1.36)*
Medically Indicated	1.12 (0.82-1.52)	1.84 (0.74-4.57)	0.17 (0.02-1.71)	0.86 (0.61-1.19)
Spontaneous	1.31 (1.14-1.50)*	2.62 (1.81-3.79)*	1.20 (0.81-1.77)	1.33 (1.16-1.53)*
PROM	1.01 (0.75-1.35)	0.80 (0.21-3.03)	0.55 (0.19-1.65)	1.12 (0.85-1.47)
Preeclampsia [b]	0.91 (0.68-1.21)	2.52 (1.37-4.63)*	0.75 (0.31-1.81)	0.98 (0.76-1.26)
Superimposed Preeclampsia	4.00 (2.40-6.67)*	3.85 (0.62-24.04)	2.07 (0.38-11.17)	2.02 (1.04-3.91)*

All numbers are RRs with 95% CIs. RRs are obtained from multivariate Poisson regression with generalized estimating equations. Analysis was limited to singleton pregnancies. No thyroid disease (n=108875) served as the reference group.

**Indicates significant results.*

[a] *Women with preexisting diabetes were excluded from the analyses of gestational diabetes.*

[b] *Women with chronic hypertension were excluded from the analyses of gestational hypertension and preeclampsia.*

Table 4.3 Relative Risks of Adverse Pregnancy Outcomes among Women with Thyroid Diseases in the NICHD Consecutive Pregnancies Data Set

	Hypothyroidism (n= 668)	Hyperthyroidism (n= 48)	Other (n= 83)	Unspecified (n= 1139)
Breech Presentation	1.24 (0.96-1.59)	0.32 (0.5-2.15)	1.12 (0.56-2.26)	1.25 (0.97-1.61)
Gestational Diabetes [a]	1.28 (1.00-1.63)*	2.47 (1.28-4.76)*	1.62 (0.94-2.78)	1.00 (0.76-1.31)
Gestational Hypertension [b]	1.32 (1.07-1.63)*	1.58 (0.71-3.49)	1.27 (0.72-2.26)	1.24 (1.01-1.53)*
Hemorrhage	1.07 (0.83-1.38)	1.31 (0.55-3.11)	1.06 (0.54-2.09)	0.76 (0.58-1.01)
Inductions	0.98 (0.96-0.99)*	1.01 (0.95-1.07)	1.00 (0.97-1.04)	1.00 (0.99-1.02)
Placental Abruption	1.10 (0.82-1.46)	1.00 (0.33-2.99)	1.46 (0.77-2.77)	1.29 (1.01-1.64)*
Preterm Birth	1.23 (1.08-1.41)*	2.31 (1.61-3.32)*	0.94 (0.62-1.41)	1.20 (1.05-1.37)*
Medically Indicated	1.03 (0.75-1.41)	1.85 (0.74-4.59)	0.17 (0.02-1.80)	0.86 (0.62-1.19
Spontaneous	1.25 (1.09-1.43)*	2.43 (1.68-3.53)*	1.17 (0.78-1.75)	1.30 (1.14-1.50)*
PROM	1.09 (0.81-1.46)	0.80 (0.22-2.98)	0.59 (0.19-1.78)	1.18 (0.90-1.56)
Preeclampsia [b]	1.02 (0.77-1.34)	2.65 (1.44-4.87)*	0.81 (0.34-1.91)	1.01 (0.79-1.30)
Superimposed Preeclampsia	1.68 (0.98-2.88)	4.31 (0.90-20.69)	1.42 (0.21-9.71)	1.19 (0.59-2.38)

All numbers are RRs with 95% CIs. RRs are obtained from multivariate Poisson regression with generalized estimating equations. All results are adjusted for insurance, parity, race/ethnicity, age, smoking, and other chronic diseases. Analysis was limited to singleton pregnancies. No thyroid disease (n=108875) served as the reference group.

**Indicates significant results.*

[a] *Women with preexisting diabetes were excluded from the analyses of gestational diabetes.*

[b] *Women with chronic hypertension were excluded from the analyses of gestational hypertension and preeclampsia.*

Table 4.4 Relative Risks of Adverse Pregnancy Outcomes from Sensitivity Analysis Restricted to First Delivery

	Hypothyroidism (n= 2511)	Hyperthyroidism (n= 150)	Other (n= 314)	Unspecified (n= 2732)
Breech Presentation	1.01 (0.99-1.03)	0.98 (0.97-1.00)	1.01 (0.97-1.05)	1.01 (0.99-1.02)
Gestational Diabetes [a]	1.05 (0.61-1.79)	4.50 (1.83-11.04)*	2.11 (0.68-6.56)	1.20 (0.80-1.80)
Gestational Hypertension [b]	1.07 (0.75-1.54)	1.64 (0.55-4.87)	1.43 (0.61-3.32)	1.27 (0.61-3.32)
Hemorrhage	0.89 (0.55-1.45)	1.48 (0.39-5.63)	1.33 (0.43-4.05)	0.88 (0.60-1.30)
Inductions	0.96 (0.93-0.99) *	1.04 (0.94-1.15)	0.90 (0.84-0.97) *	1.00 (0.98-1.02)
Placental Abruption	1.00 (0.99-1.02)	0.98 (0.97-1.00)	1.01 (0.97-1.04)	1.01 (0.99-1.02)
Preterm Birth	1.14 (0.89-1.45)	1.71 (0.83-3.52)	0.96 (0.43-2.08)	1.18 (0.98-1.43)
Medically Indicated	1.01 (0.98-1.04)	1.09 (0.94-1.25)	0.98 (0.92-1.03)	1.01 (0.99-1.03)
Spontaneous	1.17 (0.86-1.60)	1.66 (0.62-4.41)	1.30 (0.55-1.11)	1.32 (1.05-1.66) *
PROM	1.03 (0.61-1.74)	0.89 (0.13-6.09)	0.58 (0.08-4.05)	1.22 (0.83-1.79)
Preeclampsia [b]	0.83 (0.52-1.29)	2.24 (0.88-5.70)	1.69 (0.73-3.93)	0.89 (0.63-1.26)
Superimposed Preeclampsia	1.01 (0.99-1.02)	1.00 (0.99-1.01)	1.00 (0.99-1.01)	0.99 (0.99-1.00)

All numbers are RRs with 95% CIs. RRs are obtained from multivariate Poisson regression with generalized estimating equations. All results are adjusted for insurance, parity, race/ethnicity, age, smoking, and other chronic diseases. Analysis was restricted to the first delivery and limited to singleton pregnancies. No thyroid disease (n=108875) served as the reference group.

**Indicates significant results.*

[a] *Women with preexisting diabetes were excluded from the analyses of gestational diabetes.*

[b] *Women with chronic hypertension were excluded from the analyses of gestational hypertension and preeclampsia.*

CHAPTER 5

DISCUSSION

5.1 SUMMARY OF RESULTS

In summary, the results suggest that the presence of a thyroid disorder increases the risk of adverse outcomes during pregnancy. This is consistent with the majority of previous findings[-6, 9-14,19-20]. Hypothyroidism, hyperthyroidism, and unspecified thyroid disorders were found to be associated with various adverse pregnancy outcomes. No significant findings were found for other thyroid disorders.

5.2 HYPOTHYROIDISM

In the adjusted model, hypothyroidism was found to be associated with gestational diabetes, gestational hypertension, inductions, and preterm birth, which is consistent with the literature[2,4,9,20,23,27,28]. Specifically, in regards to preterm birth, it would appear hypothyroidism is positively associated with an increased risk of spontaneous preterm birth. Most of the literature has failed to specifically investigate the influence of thyroid disorders on induced and spontaneous preterm birth, but the literature does suggest that hyperthyroidism is positively associated with preterm birth in general [20]. Männistö et al found hypothyroidism to be significantly associated with gestational diabetes, inductions, and preterm birth, in addition to other various adverse pregnancy outcomes[9]. Additionally, Clearly-Goldman found a significant association

between hypothyroidism and both preterm birth and gestational diabetes[23]. Findings in the literature also indicate that hypothyroidism is associated with an increased risk of gestational hypertension[27,28]. Specifically, Chen et al found hypothyroidism to be associated with higher rates of gestational hypertension compared to women without a thyroid condition[27]. This supports the results from this analysis.

Research indicates that thyroid hormones influence various aspects of pregnancy and fetal growth[2]. Pregnancy results in a number of physiological and hormonal changes that may alter thyroid function[2]. In order to maintain normal energy and lipid metabolism, normal thyroid function is needed[9]. Additionally, weight gain or lipid disturbances that are often associated with hypothyroidism may increase the risk of adverse pregnancy outcomes[9,37]. Barber et al suggests that thyroid hormones play a key role in placentation and regulation of early pregnancy, offering a potential explanation for the association between hypothyroidism and gestational hypertension and preterm birth[38]. Additionally, thyroid hormones regulate cardiovascular activities and blood pressure, and long-term thyroid hormone disorder can result in cardiovascular dysfunction[27]. This offers more insight into the association between hypothyroidism and gestational hypertension. In regards to gestational diabetes, changes in weight and energy metabolism may offer a potential explanation for the association between hypothyroidism and gestational diabetes[9].

5.3 HYPERTHYROIDISM

In the adjusted model, hyperthyroidism was found to be associated with gestational diabetes, preterm birth, and preeclampsia. Specifically, in regards to preterm birth, it appears that after categorizing the outcome into spontaneous and induced preterm birth, it appears that spontaneous preterm birth drives this association. Most of the literature has failed to investigate these categories of preterm birth, but the literature does suggest that hyperthyroidism is positively associated with preterm birth [6, 9, 20, 25]. Specifically, Männistö et al found hyperthyroidism to be associated with almost double the odds of having a preterm delivery compared to individuals without a thyroid disorder[9]. Previous research has postulated that this association is directly related to the presence of thyroid antibodies[20]. More specifically, positive thyroid peroxidase antibodies have been linked to preterm delivery, however further research is required to identify the biological mechanism[20].

Additionally, studies within the literature support the findings on gestational diabetes [6, 25]. Furthermore, the observed association between hyperthyroidism and preeclampsia is supported by the literature[7, 9]. Both Männistö et al and Millar et al found a significant association between hyperthyroidism and preeclampsia[7,9]. Millar et al further investigated this association and found the association between preeclampsia and hyperthyroidism to be stronger amongst women not properly treating their condition[7]. Given that previous research has indicated that the proper management of hyperthyroidism significantly reduces the risk of these adverse pregnancy outcomes,

this suggests that the abundance of thyroid hormone during pregnancy may be the underlying cause of many of these adverse outcomes[9,39].

5.4 OTHER THYROID DISORDERS

Other thyroid disorders were not found to be significantly associated with any of the adverse pregnancy outcomes looked at in this study. Männistö et al examined the relationship between other thyroid disorders and pregnancy outcomes and also reported null findings[9]. However, the Männistö study results did find a significant association between other thyroid disorders and PROM [RR:2.02; 95% CI: 1.23–3.30][9]. Potential explanations for the null results will be discussed later in the chapter.

5.5 UNSPECIFIED THYROID DISORDERS

Unspecified thyroid disorders were found to be associated with gestational hypertension, placental abruption, and preterm birth, which is consistent with previous research[6, 9,19, 20, 23, 25,27,28]. Using a similar definition of unspecified thyroid disorders, Männistö et al found unspecified thyroid disorders to be associated with placental abruption and preterm birth[9]. The literature also suggests that gestational hypertension is associated with thyroid disorders[27, 28]. Again, this is likely attributable to the influence of thyroid hormones on various aspects of pregnancy and fetal growth[2]. Due to the fact that this group only had their thyroid disease status noted in their medical records and did not have specific diagnoses included in their discharge summaries, it is possible that the individuals in this group may have had milder disease or disease that was not complicated during pregnancy[9].

5.6 DIFFERENCES IN THE LITERATURE

While the majority of studies within the literature found associations between thyroid disorders and adverse pregnancy outcomes to exist, not all studies found this to be true[23-26]. Additionally, this study failed to find significant results with various adverse outcomes such as breech presentation, hemorrhage, PROM, and superimposed preeclampsia, all of which have been previously found to have an association with thyroid disorders. These differences can be attributed to variation in the study populations, inconsistent definitions of thyroid dysfunction and outcomes of interest, differences in inclusion criteria, small sample sizes, and differences in patient's baseline characteristics.

5.7 STRENGTHS AND LIMITATIONS

One particular strength of this study is the large sample size. This allowed us to examine less common outcomes and exposures. Additionally, a strength of this study lies in its ability to distinguish between spontaneous and induced preterm birth. Previous studies have failed to break preterm birth down into these categories and investigate these specific relationships[20]. Given the knowledge that thyroid disorders are associated with adverse maternal outcomes, many of which are indications for induction, we would expect to see an increased risk of induced preterm birth. However, no significant results were found for induced preterm birth. Thyroid disorders (hypothyroidism, hyperthyroidism, unspecified thyroid disorders) increased the risk of spontaneous preterm delivery. It has been suggested that antithyroid antibodies and

hypothyroxinemia may be associated with this increased risk of spontaneous preterm delivery[40].

However, despite the strengths of this study, there are some key limitations that need to be noted. Given the limited racial and ethnic diversity in the data, the findings might not be generalizable. However, the homogeneous nature of the study population can be seen as potentially beneficial reducing the possibility of residual confounding. Additionally, it is important to note that information on treatment of thyroid disorders during pregnancy was not available. As a result, we were unable to explore whether inadequate treatment was the cause of adverse pregnancy outcomes or if adverse pregnancy outcomes were a result of increased risk caused by the presence of a thyroid disease itself. Given the fact that data on treatment wasn't collected or adjusted for in the model, there was a potential for residual confounding.

5.8 FUTURE STUDIES

Previous research has indicated that race and ethnicity may be an important modifying factor between the association of thyroid disorders and adverse pregnancy outcomes[9, 31]. This study contained a sample of women that was not racially and ethnically diverse, and therefore did not allow the influence of race on the association between thyroid disorders and adverse pregnancy outcomes to be studied. Throughout the literature, other studies have also had limited diversity and have failed to investigate this association as well. This is a notable limitation given the knowledge that racial and

ethnic disparities have been documented throughout multiple aspects of both health and health care[41-45].

As previously mentioned, this study lacked detailed information of treatment of individuals suffering from thyroid disorders. This is also true for other studies throughout the literature. It is understood that uncontrolled thyroid disease poses a significant threat to both the mother and fetus, however, the optimal treatment method is still unknown[23]. Some researchers hypothesize that specific treatment methods may pose additional risks during pregnancy[23]. As such, more research is needed to understand the influence of specific treatments of different thyroid disorders and how these may impact pregnancy outcomes.

5.9 CONCLUSIONS

The results of this study suggest that the presence of a thyroid disorder increases the risk of adverse outcomes during pregnancy. Specifically, this is true for hypothyroidism, hyperthyroidism, and unspecified thyroid diseases. This supports previous findings but more research involving large racially diverse cohorts with available data on treatment is still needed to further understand the complex association between thyroid disorders and pregnancy outcomes.

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APPENDIX A – FULL TABLES FROM SAS OUTPUT OF MULTIVARIATE POISSON REGRESSION WITH GENERALIZED ESTIMATING EQUATIONS

Table A.1 Breech Presentation

Analysis Of GEE Parameter Estimates							
Empirical Standard Error Estimates							
Parameter		**Estimate**	**Standard Error**	**95% Confidence Limits**		**Z**	**Pr > |Z|**
Intercept		-4.5849	0.1390	-4.8573	-4.3124	-32.99	<.0001
thyroid2	Hypo	0.2128	0.1275	-0.0372	0.4627	1.67	0.0952
thyroid2	Hyper	-1.1524	0.9774	-3.0680	0.7632	-1.18	0.2384
thyroid2	Other	0.1138	0.3573	-0.5865	0.8141	0.32	0.7501
thyroid2	Unspec	0.2251	0.1280	-0.0259	0.4760	1.76	0.0788
Momage		0.0415	0.0053	0.0311	0.0519	7.81	<.0001
Race	hisp	0.0151	0.0760	-0.1338	0.1640	0.20	0.8424
Race	other	-0.0645	0.1240	-0.3076	0.1786	-0.52	0.6029
smoking	2	0.3131	0.1187	0.0804	0.5459	2.64	0.0084
parity2	1	-0.7318	0.0488	-0.8275	-0.6360	-14.98	<.0001
Insurance	2	0.0460	0.0550	-0.0617	0.1537	0.84	0.4027
Diabetes	2	0.4441	0.1381	0.1733	0.7148	3.21	0.0013
ChronicHBP	2	0.4249	0.1739	0.0840	0.7658	2.44	0.0146
Hxheartdis	2	0.4242	0.1767	0.0778	0.7706	2.40	0.0164
Hxrenaldis	2	-0.3754	0.4151	-1.1890	0.4382	-0.90	0.3658
Hxdepression	2	0.0320	0.0806	-0.1260	0.1900	0.40	0.6913
Hxasthma	2	0.0401	0.0846	-0.1257	0.2059	0.47	0.635

Table A.2 Gestational Diabetes Mellitus

Analysis Of GEE Parameter Estimates							
Empirical Standard Error Estimates							
Parameter		**Estimate**	**Standard Error**	**95% Confidence Limits**		**Z**	**Pr > |Z|**
Intercept		-7.2565	0.1351	-7.5214	-6.9916	-53.69	<.0001
thyroid2	Hypo	0.2440	0.1239	0.0013	0.4868	1.97	0.0488
thyroid2	Hyper	0.9152	0.3330	0.2625	1.5679	2.75	0.0060
thyroid2	Other	0.4831	0.2770	-0.0597	1.0260	1.74	0.0811
thyroid2	Unspec	-0.0021	0.1398	-0.2761	0.2719	-0.01	0.9881
Momage		0.1098	0.0047	0.1006	0.1190	23.51	<.0001
race	hisp	0.9572	0.0650	0.8298	1.0846	14.73	<.0001
race	other	0.9145	0.0964	0.7256	1.1034	9.49	<.0001
smoking	2	0.3172	0.1304	0.0617	0.5727	2.43	0.0150
parity2	1	-0.1394	0.0557	-0.2486	-0.0303	-2.50	0.0123
Insurance	2	0.1526	0.0550	0.0448	0.2605	2.77	0.0055
ChronicHBP	2	1.0551	0.1237	0.8126	1.2975	8.53	<.0001
Hxheartdis	2	-0.0799	0.2389	-0.5481	0.3883	-0.33	0.7379
Hxrenaldis	2	-0.9619	0.5662	-2.0717	0.1478	-1.70	0.0893
Hxdepression	2	0.2983	0.0692	0.1628	0.4339	4.31	<.0001
Hxasthma	2	0.3506	0.0850	0.1841	0.5172	4.13	<.0001

Table A.3 Gestational Hypertension

Analysis Of GEE Parameter Estimates							
Empirical Standard Error Estimates							
Parameter		**Estimate**	**Standard Error**	**95% Confidence Limits**		**Z**	**Pr > |Z|**
Intercept		-3.2414	0.1127	-3.4622	-3.0206	-28.77	<.0001
thyroid2	Hypo	0.2781	0.1083	0.0658	0.4903	2.57	0.0102
thyroid2	Hyper	0.4532	0.4054	-0.3414	1.2479	1.12	0.2636
thyroid2	Other	0.2402	0.2930	-0.3342	0.8145	0.82	0.4124
thyroid2	Unspec	0.2179	0.1053	0.0115	0.4243	2.07	0.0385
Momage		0.0159	0.0044	0.0074	0.0244	3.65	0.0003
race	hisp	-0.4039	0.0743	-0.5496	-0.2582	-5.43	<.0001
race	other	-0.3671	0.1249	-0.6118	-0.1224	-2.94	0.0033
smoking	2	-0.3494	0.1301	-0.6044	-0.0943	-2.68	0.0073
parity2	1	-1.0436	0.0376	-1.1173	-0.9699	-27.74	<.0001
Insurance	2	-0.0618	0.0462	-0.1524	0.0289	-1.34	0.1817
Diabetes	2	0.6279	0.1138	0.4048	0.8510	5.52	<.0001
Hxheartdis	2	0.0629	0.1818	-0.2934	0.4192	0.35	0.7294
Hxrenaldis	2	0.6822	0.2000	0.2902	1.0742	3.41	0.0006
Hxdepression	2	0.2068	0.0642	0.0809	0.3327	3.22	0.0013
Hxasthma	2	0.2724	0.0641	0.1468	0.3980	4.25	<.0001

Table A.4 Hemorrhage

Analysis Of GEE Parameter Estimates							
Empirical Standard Error Estimates							
Parameter		**Estimate**	**Standard Error**	**95% Confidence Limits**		**Z**	**Pr > |Z|**
Intercept		-3.5219	0.1152	-3.7476	-3.2961	-30.58	<.0001
thyroid2	Hypo	0.0662	0.1282	-0.1851	0.3176	0.52	0.6056
thyroid2	Hyper	0.2719	0.4429	-0.5963	1.1401	0.61	0.5393
thyroid2	Other	0.0584	0.3464	-0.6205	0.7372	0.17	0.8662
thyroid2	Unspec	-0.2699	0.1424	-0.5490	0.0093	-1.89	0.0581
Momage		-0.0013	0.0045	-0.0101	0.0074	-0.29	0.7688
race	hisp	0.5379	0.0564	0.4273	0.6485	9.53	<.0001
race	other	0.5784	0.0861	0.4098	0.7471	6.72	<.0001
smoking	2	-0.0051	0.1156	-0.2316	0.2215	-0.04	0.9649
parity2	1	-0.3846	0.0434	-0.4697	-0.2996	-8.86	<.0001
Insurance	2	0.0828	0.0463	-0.0079	0.1735	1.79	0.0735
Diabetes	2	0.3175	0.1298	0.0632	0.5718	2.45	0.0144
ChronicHBP	2	0.6512	0.1405	0.3759	0.9265	4.64	<.0001
Hxheartdis	2	0.1857	0.1806	-0.1683	0.5397	1.03	0.3039
Hxrenaldis	2	0.3630	0.2808	-0.1874	0.9134	1.29	0.1961
Hxdepression	2	0.3167	0.0639	0.1914	0.4421	4.95	<.0001
Hxasthma	2	0.1604	0.0713	0.0206	0.3001	2.25	0.0245

Table A.5 Inductions

Analysis Of GEE Parameter Estimates							
Empirical Standard Error Estimates							
Parameter		**Estimate**	**Standard Error**	**95% Confidence Limits**		**Z**	**Pr > |Z|**
Intercept		0.2878	0.0070	0.2740	0.3015	41.04	<.0001
thyroid2	Hypo	-0.0237	0.0076	-0.0386	-0.0087	-3.11	0.0019
thyroid2	Hyper	0.0062	0.0302	-0.0530	0.0654	0.21	0.8375
thyroid2	Other	0.0021	0.0191	-0.0353	0.0396	0.11	0.9107
thyroid2	Unspec	0.0025	0.0072	-0.0115	0.0166	0.35	0.7243
Momage		0.0020	0.0003	0.0015	0.0025	7.39	<.0001
race	hisp	-0.1054	0.0040	-0.1131	-0.0976	-26.55	<.0001
race	other	-0.0825	0.0065	-0.0951	-0.0699	-12.79	<.0001
smoking	2	-0.0401	0.0069	-0.0536	-0.0267	-5.85	<.0001
parity2	1	0.0048	0.0026	-0.0003	0.0099	1.85	0.0649
Insurance	2	-0.0228	0.0028	-0.0283	-0.0174	-8.23	<.0001
Diabetes	2	0.0102	0.0091	-0.0077	0.0281	1.12	0.2631
ChronicHBP	2	0.0927	0.0105	0.0722	0.1131	8.87	<.0001
Hxheartdis	2	-0.0168	0.0116	-0.0395	0.0060	-1.44	0.1487
Hxrenaldis	2	0.0176	0.0178	-0.0173	0.0525	0.99	0.3218
Hxdepression	2	0.0014	0.0040	-0.0064	0.0092	0.36	0.7192
Hxasthma	2	0.0047	0.0047	-0.0045	0.0138	1.00	0.3169

Table A.6 Placental Abruption

Analysis Of GEE Parameter Estimates							
Empirical Standard Error Estimates							
Parameter		**Estimate**	**Standard Error**	**95% Confidence Limits**		**Z**	**Pr > |Z|**
Intercept		-4.3307	0.1405	-4.7061	-4.1552	-31.53	<.0001
thyroid2	Hypo	0.0920	0.1458	-0.1938	0.3779	0.63	0.5280
thyroid2	Hyper	0.0007	0.5590	-1.0950	1.0963	0.00	0.9990
thyroid2	Other	0.3812	0.3264	-0.2585	1.0210	1.17	0.2429
thyroid2	Unspec	0.2514	0.1227	0.0109	0.4918	2.05	0.0404
Momage		0.0084	0.0053	-0.0020	0.0188	1.58	0.1147
race	hisp	0.0588	0.0721	-0.0825	0.2000	0.82	0.4149
race	other	0.0240	0.1184	-0.2081	0.2561	0.20	0.8394
smoking	2	0.6473	0.0946	0.4620	0.8326	6.85	<.0001
parity2	1	0.1454	0.0565	0.0348	0.2561	2.58	0.0100
Insurance	2	0.2600	0.0526	0.1568	0.3631	4.94	<.0001
Diabetes	2	0.2307	0.1487	-0.0607	0.5221	1.55	0.1208
ChronicHBP	2	0.0393	0.2000	-0.3526	0.4313	0.20	0.8441
Hxheartdis	2	0.3375	0.1960	-0.0467	0.7217	1.72	0.0851
Hxrenaldis	2	0.4513	0.2859	-0.1091	1.0118	1.58	0.1145
Hxdepression	2	0.1489	0.0725	0.0069	0.2909	2.05	0.0399
Hxasthma	2	0.0808	0.0827	-0.0812	0.2428	0.98	0.3284

Table A7 Preterm Birth

Analysis Of GEE Parameter Estimates							
Empirical Standard Error Estimates							
Parameter		**Estimate**	**Standard Error**	**95% Confidence Limits**		**Z**	**Pr > |Z|**
Intercept		-2.3647	0.0762	-2.5142	-2.2153	-31.01	<.0001
thyroid2	Hypo	0.2093	0.0674	0.0771	0.3415	3.10	0.0019
thyroid2	Hyper	0.8366	0.1852	0.4735	1.1996	4.52	<.0001
thyroid2	Other	-0.0665	0.2092	-0.4765	0.3435	-0.32	0.7505
thyroid2	Unspec	0.1831	0.0676	0.0505	0.3157	2.71	0.0068
Momage		-0.0127	0.0030	-0.0185	-0.0069	-4.30	<.0001
race	hisp	0.0263	0.0392	-0.0505	0.1031	0.67	0.5020
race	other	0.2341	0.0566	0.1231	0.3451	4.13	<.0001
smoking	2	0.6919	0.0467	0.6004	0.7834	14.82	<.0001
parity2	1	-0.0438	0.0253	-0.0934	0.0058	-1.73	0.0832
Insurance	2	0.1548	0.0271	0.1016	0.2080	5.70	<.0001
Diabetes	2	0.7239	0.0613	0.6039	0.8440	11.82	<.0001
ChronicHBP	2	0.6116	0.0806	0.4536	0.7695	7.59	<.0001
Hxheartdis	2	0.3785	0.0923	0.1977	0.5594	4.10	<.0001
Hxrenaldis	2	0.5283	0.1261	0.2811	0.7755	4.19	<.0001
Hxdepression	2	0.2544	0.0351	0.1857	0.3232	7.25	<.0001
Hxasthma	2	0.1496	0.0416	0.0681	0.2312	3.60	0.0003

Table A.8 PROM

Analysis Of GEE Parameter Estimates							
Empirical Standard Error Estimates							
Parameter		**Estimate**	**Standard Error**	**95% Confidence Limits**		**Z**	**Pr > |Z|**
Intercept		-3.7294	0.1488	-4.0210	-3.4378	-25.06	<.0001
thyroid2	Hypo	0.0863	0.1512	-0.2102	0.3827	0.57	0.5684
thyroid2	Hyper	-0.2234	0.6698	-1.5363	1.0894	-0.33	0.7387
thyroid2	Other	-0.5323	0.5648	-1.6394	0.5747	-0.94	0.3460
thyroid2	Unspec	0.1682	0.1412	-0.1085	0.4449	1.19	0.2336
Momage		-0.0016	0.0059	-0.0131	0.0099	-0.27	0.7878
race	hisp	0.0765	0.0774	-0.0751	0.2282	0.99	0.3225
race	other	0.2026	0.1173	-0.0273	0.4325	1.73	0.0841
smoking	2	0.7847	0.0993	0.5901	0.9793	7.90	<.0001
parity2	1	-0.6227	0.0536	-0.7277	-0.5176	-11.62	<.0001
Insurance	2	0.1571	0.0571	0.0453	0.2689	2.75	0.0059
Diabetes	2	0.5150	0.1537	0.2138	0.8163	3.35	0.0008
ChronicHBP	2	-0.0275	0.2214	-0.4613	0.4064	-0.12	0.9013
Hxheartdis	2	0.3179	0.2047	-0.0833	0.7191	1.55	0.1204
Hxrenaldis	2	-0.4260	0.4561	-1.3199	0.4679	-0.93	0.3502
Hxdepression	2	0.2325	0.0788	0.0780	0.3870	2.95	0.0032
Hxasthma	2	0.1971	0.0838	0.0329	0.3613	2.35	0.0186

Table A.9 Preeclampsia

Analysis Of GEE Parameter Estimates							
Empirical Standard Error Estimates							
Parameter		**Estimate**	**Standard Error**	**95% Confidence Limits**		**Z**	**Pr > |Z|**
Intercept		-3.4589	0.1249	-3.7037	-3.2141	-27.69	<.0001
thyroid2	Hypo	0.0156	0.1417	-0.2622	0.2934	0.11	0.9125
thyroid2	Hyper	0.9783	0.3100	0.3708	1.5859	3.16	0.0016
thyroid2	Other	-0.2155	0.4406	-1.0790	0.6480	-0.49	0.6247
thyroid2	Unspec	0.0141	0.1276	-0.2361	0.2642	0.11	0.9123
Momage		0.0143	0.0049	0.0048	0.0238	2.95	0.0032
race	hisp	-0.0118	0.0698	-0.1487	0.1250	-0.17	0.8652
race	other	0.2733	0.1004	0.0765	0.4701	2.72	0.0065
smoking	2	0.0907	0.1141	-0.1329	0.3142	0.79	0.4267
parity2	1	-1.1228	0.0418	-1.2047	-1.0410	-26.89	<.0001
Insurance	2	0.1195	0.0479	0.0257	0.2134	2.50	0.0125
Diabetes	2	0.9535	0.1068	0.7442	1.1628	8.93	<.0001
Hxheartdis	2	0.4014	0.1770	0.0545	0.7482	2.27	0.0233
Hxrenaldis	2	0.9626	0.2029	0.5650	1.3603	4.74	<.0001
Hxdepression	2	0.3424	0.0687	0.2079	0.4770	4.99	<.0001
Hxasthma	2	0.1883	0.0734	0.0444	0.3323	2.56	0.0103

Table A.10 Superimposed Preeclampsia

Analysis Of GEE Parameter Estimates							
Empirical Standard Error Estimates							
Parameter		**Estimate**	**Standard Error**	**95% Confidence Limits**		**Z**	**Pr > |Z|**
Intercept		-8.8285	0.3908	-9.5944	-8.0627	-22.59	<.0001
thyroid2	Hypo	0.5182	0.2759	-0.0226	1.0590	1.88	0.0604
thyroid2	Hyper	1.4585	0.8010	-0.1114	3.0285	1.82	0.0686
thyroid2	Other	0.3472	0.9827	-1.5788	2.2732	0.35	0.7239
thyroid2	Unspec	0.1737	0.3545	-0.5212	0.8686	0.49	0.6242
Momage		0.0802	0.0149	0.0510	0.1094	5.39	<.0001
race	hisp	0.6890	0.2274	0.2432	1.1347	3.03	0.0025
race	other	0.0535	0.3619	-0.6557	0.7628	0.15	0.8824
smoking	2	0.5684	0.3269	-0.0723	1.2091	1.74	0.0821
parity2	1	-0.5976	0.1848	-0.9598	-0.2354	-3.23	0.0012
Insurance	2	0.1598	0.1792	-0.1914	0.5109	0.89	0.3726
Diabetes	2	0.7310	0.2429	0.2549	1.2072	3.01	0.0026
Hxheartdis	2	-0.6098	0.6026	-1.7909	0.5713	-1.01	0.3116
Hxrenaldis	2	1.7754	0.3632	1.0635	2.4873	4.89	<.0001
ChronicHBP	2	3.5258	0.2155	3.1034	3.9482	16.36	<.0001
Hxdepression	2	0.5070	0.1951	0.1247	0.8893	2.60	0.0093
Hxasthma	2	0.6514	0.2056	0.2485	1.0543	3.17	0.0015