

USING PREGNANCY RISK ASSESSMENT MONITORING SYSTEM DATA
TO INVESTIGATE PRESCRIPTION DRUG USE DURING PREGNANCY IN
HAWAI'I

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BY

EMILY K. ROBERSON

Dissertation Committee:

Eric Hurwitz, Chairperson

Robert Cooney

Alan Katz

Dongmei Li

Abby Collier

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ABSTRACT

Both legal and illicit use of prescription drugs during pregnancy is thought to be increasingly common in the state of Hawai‘i, based on trends demonstrated elsewhere in the country and throughout the world. Prescription opioids, along with antianxiety and antidepressant medications are of special concern, both for their prevalence and for the potential risks associated with using these drugs during pregnancy.

The purpose of this dissertation is to investigate prescription drug use during pregnancy in Hawai‘i, with a focus on opioids and antianxiety and antidepressant medications. The first of three studies sought to determine the prevalence of prescription opioid drug use during pregnancy in Hawai‘i, describe differences in prescription opioid drug use during pregnancy in Hawai‘i by maternal demographic characteristics, and investigate possible predictors of prescription opioid drug use during pregnancy through the use of multivariable logistic regression. The second study aimed to determine whether prescription opioid use during pregnancy was associated with poorer birth outcomes among users when compared to non-users in Hawai‘i; specifically focusing on associations between prescription opioid use during pregnancy and risk of small for gestational age, preterm, or low birth weight deliveries among women giving birth to live, singleton infants in Hawai‘i. Study three attempted to describe the under-studied topics of anxiety and depression before, during, and after pregnancy, along with related help-seeking behaviors and treatment strategies, for which there is a scarcity of information in Hawai‘i.

Findings from the three studies covered in this dissertation confirm that use of prescription opioids and antianxiety and antidepressant medications is relatively common during pregnancy in Hawai‘i. They also provide more detailed information on usage patterns, differences by demographic characteristics, and associated risk factors and birth and maternal health outcomes. All three also provide suggestions for future research avenues in order to more fully understand the complete landscape of prescription drug use during pregnancy in Hawai‘i.

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LIST OF ABBREVIATIONS

AOR	Adjusted Odds Ratio
BMI	Body Mass Index
BRFSS	Behavioral Risk Factor Surveillance System
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
FDA	United States Food and Drug Administration
FHSD	Family Health Services Division
FPL	Federal Poverty Level
HDOH	Hawai‘i Department of Health
LBW	Low Birth Weight
MCHB	Maternal Child Health Branch
NAS	Neonatal Abstinence Syndrome
NCHS	National Center for Health Statistics
NHANES	National Health and Nutrition Examination Survey
NSDUH	National Survey on Drug Use and Health
NVPU	Non-vitamin Prescription Use
PATH	Perinatal Addiction Treatment of Hawai‘i
PPA	Postpartum Anxiety
PPD	Postpartum Depression
PRAMS	Pregnancy Risk Assessment Monitoring System
PTD	Preterm Delivery
SAMHSA	Substance Abuse and Mental Health Services Administration
SGA	Small for Gestational Age
TERIS	Teratogen Information System
US	United States

CHAPTER 1.
INTRODUCTION

Prescription drug use in the United States

Recent years have seen an explosion in overall prescription drug use in the United States (Gu, Dillon, & Burt, 2010). According to the National Health and Nutrition Examination Survey (NHANES), approximately half of the population of the United States reports using at least one prescription medication in the past 30 days (National Center for Health Statistics [NCHS], 2013). This is an increase over 1988-1994 estimates of 38% (NCHS, 2013). However, a more dramatic increase has been observed in the number of Americans currently taking multiple prescription drugs. In 2007-2010, the percentage of Americans taking three or more prescriptions increased to 22% (compared with 11% in 1988-1994), and the percentage taking five or more almost tripled to 11% (compared with 4% in 1988-1994) (NCHS, 2013). Spending on prescription medication has also increased dramatically, reaching \$259 billion in 2010, and accounting for 12% of total personal health care expenditures (NCHS, 2013). Of the over 4 billion drug prescriptions written in the United States in 2011, approximately 264 million were for antidepressants, making this the most widely prescribed drug class (Koba, 2013). Prescriptions for pain killers followed close behind, with more than 131 million prescriptions written for generic Vicodin, 32 million for generic Percocet, and 29 million for generic Neurontin in the same year (Koba, 2013).

In many cases, the increase in development, availability, and use of prescription medication is positive, as appropriate use can preserve and significantly improve human health (Gu et al., 2010). However, the increased use of prescription drugs in the United States is also potentially a cause for concern. Potential concerns associated with increased population-wide usage of prescription drugs include: medication side effects (Jain & Pitchumoni, 2009), drug interactions (Hersh, Pinto, & Moore, 2007; Lindsey, Stewart, & Childress, 2012), accidental and intentional overdoses (Warner, Chen, Makuc, Anderson, & Minino, 2011), and skyrocketing healthcare expenditures on prescription

medications (Briesacher, Gurwitz, & Soumerai, 2007; R. A. Cohen, Kirzinger, & Gindi, 2013). An additional concern is the dramatic increase in prescription drug abuse in the United States, and the associated personal, medical, and societal costs associated with prescription drug abuse (Albertson, 2014; Birnbaum et al., 2011; Caplan, Epstein, Quinn, Stevens, & Stern, 2007; SAMHSA [SAMHSA], 2012). Increases in prescription medication abuse and overdoses align with increases in prescribing of specific medications (Centers for Disease Control and Prevention [CDC], 2013).

Prescription drug abuse in the United States

Prescription drug abuse has been of increasing concern in the United States for several years (Manubay, Muchow, & Sullivan, 2011; SAMHSA, 2012). Nonmedical use of prescription drugs is the second most common type of illicit drug use in the United States, after marijuana (SAMHSA, 2012), and most overdose deaths in the United States are now caused by prescription drugs (CDC, 2011). According to the 2011 National Survey on Drug Use and Health (NSDUH), more than 14 million Americans aged 12 and older used prescription-type psychotherapeutic drugs (pain relievers, tranquilizers, stimulants, and sedatives) nonmedically in the past year, and over 51 million reported lifetime nonmedical use of these drugs (SAMHSA, 2012).

The abuse of prescription (opioid) pain relievers is of particular concern (CDC, 2013; Yu, 2012). Prescription pain relievers are the most commonly misused prescription medications, with more than 11 million Americans reporting nonmedical use in 2011 alone, and more than 34 million reporting nonmedical use in their lifetimes (SAMHSA, 2012). They also account for nearly three quarters of all prescription drug overdoses in the United States (Centers for Disease Control and Prevention, 2011; C. M. Jones, Mack, & Paulozzi, 2013). There has been a greater than 300% increase in sales of opioid pain relievers in the United States since 1999 (CDC, 2011), which corresponds with dramatic increases in the number of Americans with nonmedical pain reliever dependence (SAMHSA, 2012), seeking of specialty substance abuse treatment (SAMHSA, 2012, 2013),

emergency department visits attributed to opioid pain relievers (SAMHSA, 2013), and associated mortality (Cerda et al., 2013; Paulozzi, Budnitz, & Xi, 2006). Recent attempts to quantify the societal costs of prescription opioid abuse, dependence, and misuse in the United States estimated that the total costs were approximately \$55.7 billion in 2007, with workplace costs accounting for approximately 46%, health care costs accounting for approximately 45%, and criminal justice costs accounting for approximately 9% of the total (Birnbaum et al., 2011).

Misuse and abuse of antidepressants, sedatives, and other psychiatric medications is also of great concern in the United States (Yu, 2012). Abuse of prescription benzodiazepines is widespread and growing in popularity in this country (SAMHSA, 2012). Recreational use of benzodiazepines paired with other drugs, especially opioid pain relievers, has also been extensively documented (J. D. Jones, Mogali, & Comer, 2012; Wunsch, Nakamoto, Behonick, & Massello, 2009). This polydrug abuse can be exceptionally dangerous, as the combining of benzodiazepines can increase the effects of the opioid medications in unpredictable ways (J. D. Jones et al., 2012). Benzodiazepines are present, alone or in combination with other drugs, in almost 30% prescription drug overdoses in the United States (C. M. Jones et al., 2013). While abuse of antidepressants has been documented for over 30 years (Hilliard, Barloon, Farley, Penn, & Koranek, 2013; Shenouda & Desan, 2013), the primary concerns with regard to antidepressant use are related to intentional and unintentional overdoses (CDC, 2013; McKenzie & McFarland, 2007) and polydrug use resulting in toxicity and overdose (Wunsch et al., 2009). Prescription antidepressants are present in approximately 18% prescription drug overdoses in the United States, either alone or in combination with other drugs (C. M. Jones et al., 2013). Misuse and abuse of antidepressants and benzodiazepines disproportionately affect American women (CDC, 2013; Wunsch et al., 2009).

Women and prescription drug use and abuse

Significant differences exist between men and women with regards to prescription drug use and abuse (CDC, 2013; Green, Grimes Serrano, Licari, Budman, & Butler, 2009). Women on average begin taking prescription medications at younger ages than men, and are more likely to experience adverse drug reactions due to body composition and metabolism differences (Mattison & Zajicek, 2006). Women are more likely than men to die of overdoses of psychiatric medications, or to end up in the emergency room as a result of antidepressants or benzodiazepines (CDC, 2013). And although men are still more likely than women to die of prescription painkiller overdoses, that gap is rapidly closing due to the sharp increase among women (CDC, 2013). Women are also more likely than men are to report chronic pain and be prescribed prescription painkillers (CDC, 2013).

Between 1999 and 2010, the percentage increase in deaths caused by prescription painkiller overdose among American women was greater than 400% (CDC, 2013). Approximately 9.3% of American women between the ages of 18 and 44 report using at least one prescription pain medication in the past month (NCHS, 2013). Antidepressant use is even more common among American women than prescription pain reliever use, with about 11.3% of American women between the ages of 18 and 44 using at least one antidepressant medication in the past month, and 4.7% using at least one medication for anxiety or related disorders in the past month (NCHS, 2013). In line with this, overdose deaths attributed to antidepressants and benzodiazepines also increased significantly among women in the United States between 2004 and 2010, and emergency room visits due to benzodiazepine overdoses slightly eclipsed those due to opioid overdoses in 2010 (CDC, 2013). The top three drug types involved in prescription overdose deaths among women in the United States in 2010 (the most recent data available) were opioid pain relievers, benzodiazepines, and antidepressants (CDC, 2013).

Pregnant women as a special population when discussing prescription drug use and abuse

As is the case in the general population, prescription drug use among pregnant women is very common in the United States, and has been increasing in prevalence for many years (Mitchell et al., 2011; Parisi, Spong, Zajicek, & Guttmacher, 2011). Potential explanations behind this rise include an increase in the number of prescription medications available for the treatment of chronic medical conditions (Bowen, Ray, Arbogast, Ding, & Cooper, 2008; Kulaga, Zargarzadeh, & Berard, 2009), earlier onset of chronic diseases such as diabetes (Bowen et al., 2008), and increasing maternal age during pregnancy (Bowen et al., 2008; Cooper, Hickson, & Ray, 2004). However, while women with pre-pregnancy chronic disease diagnoses are more likely to report prescription drug-exposed pregnancies than are women without chronic diseases, women without chronic diseases also report high levels of prescription drug use during pregnancy (Yang et al., 2008). An additional factor is that around half of all pregnancies in the United States are unintended (Guttmacher Institute, 2012), and therefore many in utero exposures to prescription drugs occur before the pregnancy is recognized (Desai, Babu, & Chandra, 2012; Parisi et al., 2011; van Gelder et al., 2010).

Pregnant women are considered a special population in prescription drug research due to concerns about the effects of medication exposures on the pregnancy and fetus (Adam, Polifka, & Friedman, 2011). A prescription drug is considered a teratogen if it is capable of interfering with the development of an embryo or fetus; a process which may result in to birth defects or developmental malformations (Parisi et al., 2011). Many common prescription medications have documented teratogenic or otherwise harmful effects when used during pregnancy (Malm, Martikainen, Klaukka, & Neuvonen, 2004; van Gelder et al., 2010). However, available research shows that women regularly use and are prescribed medications during pregnancy that have documented potential for fetal harm (Andrade et al., 2004; Cooper et al., 2004; Daw, Hanley, Greyson, & Morgan, 2011; Lee et al., 2006). In addition, studies have shown that American women taking prescription drugs known to cause birth defects are not significantly more

likely to be on birth control than women not on such medications, and the more prescription medications they take, the less likely they are to be adherent to oral contraceptives (Steinkellner, Chen, & Denison, 2010). This can lead to inadvertent exposures to potential teratogenic medications among women with unintended pregnancies.

Pregnant women are also considered to be a special population in addiction research for ethical and legal reasons (Lambert, Scheiner, & Campbell, 2010). According to the NSDUH, 5% of pregnant women aged 15 to 44 reported being current illicit drug users in the United States in 2010 and 2011 (SAMHSA, 2012). However, this is very likely an underestimate, as significant underreporting of illicit drug use during pregnancy is well-documented (Bessa et al., 2010; Koren, Hutson, & Gareri, 2008). Estimates generated using hospital discharge diagnosis codes projected the rate of opiate use or dependence among recently-delivered mothers at 5.63 per 1000 hospital births per year in 2009 (Patrick et al., 2012). Older research shows that nonmedical use of prescription medications is second only to marijuana among pregnant American women, with the most common medication types being pain killers and tranquilizers (SAMHSA, 2003). In addition, recent analysis of state-level data in Florida has implicated increasing prescription drug abuse among pregnant woman in that state with an observed increase in pregnancy-associated non-natural deaths (Hardt et al., 2013). In this study, 54% of pregnancy-associated non-natural deaths involved prescription drugs, with the majority being prescription opioids. Considerable co-use of opioids along with benzodiazepines was also observed (Hardt et al., 2013).

While direct and timely information about overdoses and deaths among pregnant women nation-wide due to prescription drug abuse is somewhat scarce, another indicator of a growing problem is available: a near-tripling in incidence of neonatal abstinence syndrome in the United States between 2000 and 2009 (Patrick et al., 2012). Neonatal abstinence syndrome (NAS) refers to drug withdrawal syndrome observed in newborn infants following birth (Patrick et al., 2012). Symptoms include extreme irritability, tremors, sleeping disruption,

feeding problems, seizures, diarrhea, and respiratory distress (Jansson & Velez, 2012; Patrick et al., 2012). Many different environmental and individual-level factors affect the expression and severity of NAS, however concomitant use of opioids with benzodiazepines has been shown to extend hospital stays for NAS-affected infants (Pritham, Paul, & Hayes, 2012). There is currently no professionally agreed-upon first-line treatment (Jansson & Velez, 2012), and long-term effects are not well documented (Pritham et al., 2012).

The most recent (2009) national estimates for NAS place the rate at 3.39 per 1,000 hospital births per year (Patrick et al., 2012). This translates to approximately one infant being born in the United States with NAS every hour (Koba, 2013; Patrick et al., 2012). The dramatic increase in the past decade has been widely attributed to increases in opioid pain reliever use in the United States during the same period (Jansson & Velez, 2012; H. E. Jones & Kaltenbach, 2012; Patrick et al., 2012). However, researchers have also expressed that the difficulty in identifying opiate withdrawal versus benzodiazepine withdrawal in the neonate adds an additional layer of complication, which makes further research essential (H. E. Jones & Kaltenbach, 2012; Pritham et al., 2012).

In addition to the individual costs associated with NAS in those personally afflicted, there has also been a dramatic increase in the healthcare costs associated with NAS: from around \$190 million in 2000 to \$720 million in 2009, the bulk of which is falling to Medicaid for payment (Patrick et al., 2012). This issue has received significant media attention nationally (Tanner, 2012), and states such as Florida (Hardt et al., 2013; Phoenix House, 2013) and Tennessee (Cooper et al., 2004; Dreyzehner, 2013) have designated NAS a high-priority area locally.

Knowledge gaps regarding prescription drug use during pregnancy

There are few population-based studies on perinatal prescription drug use (Daw et al., 2011). For the most part, the latest available research findings come from non-population-based data sources with limited generalizability, such as electronic medical records (Andrade et al., 2004), pharmacy dispensing records (Irvine, Flynn, Libby, Crombie, & Evans, 2010), or health insurance claims

databases (Daw, Mintzes, Law, Hanley, & Morgan, 2012). The studies included within this dissertation have substantial advantages over the currently available research articles, and are expected to significantly contribute to the body of literature on this topic.

While many drugs have well-documented harmful effects when used during pregnancy (van Gelder et al., 2010), there is unfortunately also much that is unknown about the safety and effects of specific prescription medications during pregnancy. Pregnant women are frequently excluded from clinical trials for ethical and methodological reasons, so much of the research regarding medication exposures during pregnancy relies on information extrapolated from animal studies, or on case reports and registries measuring adverse outcomes occurring in populations after the fact (Parisi et al., 2011). Recent studies conducted within the United States show that only 4% of the most commonly-reported medication exposures during the first trimester of pregnancy had a “Good to Excellent” quality and quantity of safety data available to determine teratogenic potential; the vast majority had insufficient data evidence to determine risks (Thorpe et al., 2013). Out of 172 prescription drugs approved for use by the United States Food and Drug Administration (FDA) and rated by the Teratogen Information System (TERIS) between 2000 and 2010, approximately 98% were determined to be of unknown teratogenic risk if used during pregnancy (Adam et al., 2011).

Risk classification systems regarding medication use during pregnancy exist, however there is no worldwide standard, and substantial differences exist between systems used in different countries (Addis, Sharabi, & Bonati, 2000; Law, Bozzo, Koren, & Einarson, 2010). A 2000 comparison of the pregnancy risk classification systems employed in the United States, Australia, and Sweden found that only 26% of the drugs common to all three systems were placed in the same risk category (Addis et al., 2000). The pregnancy risk classification system employed in the United States was developed and put in place by the FDA in 1979, and categorized medications into five groupings (A, B, C, D, X), with A being considered the most safe, and X being contraindicated for use during

pregnancy (Corbett, Kremzner, & Stifano, 2011). Even for drugs that have sufficient research or information on safety during pregnancy to inform an FDA rating, the system has been widely criticized for being difficult to understand and interpret for both patients and healthcare providers (Corbett et al., 2011; Doering, Boothby, & Cheek, 2002). The FDA category system has also been criticized for relying too much on data collected from animal studies (as opposed to human studies), and for an apparent readiness to categorize new medications as Category B until data exist to prove otherwise (Wong, Heller, & Murase, 2012). Another common argument against the FDA pregnancy category system is that it sometimes “misses the point” (Koren et al., 2010). A prime example of this would be oral contraceptives being categorized as Category X as a result of case reports from the 1970s (Koren et al., 2010). These drugs are some of the most common prescriptions taken in the first trimester of pregnancy due to contraception failure (women continue taking them because they do not immediately realize that they are pregnant), and subsequent research studies have not shown teratogenic effects, but they were not removed from Category X until 2008 (Koren et al., 2010). The FDA began the process of revising the pregnancy category system, and in 2007 introduced a new protocol for prescription drug labeling (Lal & Kremzner, 2007). The hope is that this new system will be less confusing than the previous FDA pregnancy category system; however it will not resolve the lack of safety information for specific medications.

The confusion and lack of knowledge that currently exists create considerable challenges and cause substantial worry for both health care providers and pregnant women (Haramburu, Miremont-Salame, & Moore, 2000; Parisi et al., 2011). While the primary concern with regards to prescription drug use during pregnancy is avoiding exposure to potential teratogens; that is not the only potential consequence of inadequate safety information. For example, medications treating chronic conditions during pregnancy might be administered at sub-therapeutic levels to reduce perceived risks to the fetus, thus causing the pregnancy to be complicated by flares of the chronic condition (Haramburu et al., 2000; Parisi et al., 2011). Patients themselves are often fearful of potentially

harming their fetuses with prescription drugs during pregnancy as well, and may become noncompliant with necessary treatment as a result (Matsui, 2012). This is of special concern with psychiatric medications, as often discontinuing medication entirely without monitoring can be very dangerous (Koren et al., 2010; Parisi et al., 2011). Additionally, at least one recent study has shown that 47% of pregnancies with documented exposure to prescription medications described as having potential for fetal harm ended in intentional termination (Kulaga et al., 2009). If the classification systems used to determine fetal risk are not reliable, this could mean that pregnancies exposed to drugs of unknown safety are being terminated unnecessarily (Adam et al., 2011).

Hawai‘i-specific data and knowledge gaps regarding prescription drug use during pregnancy

Prescription drug overdose is a leading cause of injury and death in Hawai‘i, with the majority involving opioid pain relievers (Drewes, 2012). According to the CDC, the age adjusted death rate for drug overdoses in Hawai‘i was 9.4 per 100,000 population in 2008 (CDC, 2011). The number of overdose deaths has doubled in the last decade, and there are currently more deaths due to drug overdoses in Hawai‘i than there are deaths due to motor vehicle crashes, drowning, or pedestrian accidents (Drewes, 2012). According to Hawai‘i Department of Health Injury Prevention Epidemiologist Dan Galanis, the number of nonfatal poisonings from prescription opioids in Hawai‘i has also been increasing steadily over the years, including a 115% increase between 2003 and 2009 (Galanis, 2013). Nonmedical use of prescription drugs is also increasing among Hawai‘i’s youth, with 8.6% of Hawai‘i high school students in 2009 reporting that they had used a prescription medication that they had not been prescribed by a doctor in the 30 days prior; an increase over the 6.5% reported in 2007 (Hawaii Health Data Warehouse, 2013). These trends have made prescription drug poisoning a priority area for the Hawai‘i Department of Health Office of Injury Prevention (Galanis, 2013).

Existing research on the topic shows that overall prevalence of prescription drug use during pregnancy, as well as relative frequencies of different classes and types of drugs prescribed and used, vary widely between countries, and even between regions within the same country (Daw et al., 2011; Odalovic, Vezmar Kovacevic, Ilic, Sabo, & Tasic, 2012). Additionally, it is well documented that prescription medication prescribing and drug usage practices differ significantly by geographic region within the United States (Wetmore et al., 2011; Zhang, Baicker, & Newhouse, 2010). As a result, it is important for different states and regions of the United States to have quality data on prescribing and usage practices within their own communities. As of now, there is a scarcity of information regarding prescription drug use during pregnancy in Hawai'i. However, the issue of drug abuse during pregnancy is one that receives substantial media attention in Hawai'i (Altonn, 2007, 2008), and there is at least one specialized clinic in the state that deals specifically with substance abusing pregnant women: the Honolulu Perinatal Addiction Treatment of Hawai'i (PATH) Clinic, currently housed within the Waikiki Health Center ("Waikiki Health Center Expands Services with Addition of PATH Clinic," 2011). The PATH Clinic provides services to pregnant women abusing prescription drugs as well as other illicit drugs (Wright, Schuetter, Fombonne, Stephenson, & Haning, 2012).

Another reason why it is important to research this topic in Hawai'i is that this state has a very unique population in terms of race and ethnicity. Approximately 23% of the population of Hawai'i identifies as mixed race (U. S. Census Bureau, 2010), and a far greater percentage identify as mixed ethnicity (Novotny & Daida, 2009). The multiracial and multiethnic nature of the population of Hawai'i means that generalizability of research findings from studies conducted outside the state is unclear with regards to many different topics (Kaneshiro, Geling, Gellert, & Millar, 2011; Schempf, Mendola, Hamilton, Hayes, & Makuc, 2010). The research studies put forward in this dissertation include data on racial and ethnic groups not commonly reported in the scientific literature (Kaneshiro et al., 2011; Novotny & Daida, 2009; Sorensen, Wood, & Prince, 2003).

I previously conducted research into the topic of prescription drug use before and during pregnancy in Hawai‘i (manuscript currently awaiting formal review for release). Table 1.1 provides prevalence estimates for non-vitamin prescription drug use before and during pregnancy in Hawai‘i, based on Hawai‘i Pregnancy Risk Assessment Monitoring System (PRAMS) data for the years 2009-2011. Table 1.2 uses the same dataset, and lists the types of prescription medications used before and during pregnancy in Hawai‘i, along with their respective weighted frequencies and percent prevalence. In the course of this research, I found that approximately 3.2% of women with a recent live birth reported using prescription painkillers, and 1.4% reported using prescription psychiatric medications during pregnancy (Table 1.2). These high frequencies warrant more in-depth investigation.

Table 1.1. Non-Vitamin Prescription Use (NVPU) by Maternal Characteristics, Hawai'i PRAMS, 2009-2011

Maternal characteristics	Total, n* (% of total population)	NVPU before pregnancy, n* (% reporting use)	NVPU during pregnancy, n* (% reporting use)
Total	55691 (100)	7988 (14.3)	9924 (17.8)
Age (years)			
< 20	4044 (7.3)	293 (7.3)	423 (10.5)
20-24	13160 (23.6)	1458 (11.1)	2141 (16.3)
25-29	15205 (27.3)	2351 (15.5)	2653 (17.5)
30-34	13602 (24.4)	2179 (16.0)	2613 (19.2)
35+	9681 (17.4)	1707 (17.6)	2095 (21.6)
Race/Ethnicity			
Native Hawaiian ^a	16738 (30.1)	2264 (13.5)	2604 (15.6)
White	12813 (23.0)	2951 (23.0)	3379 (26.4)
Filipino	9922 (17.8)	1238 (12.5)	1662 (16.8)
Japanese	5191 (9.3)	629 (12.1)	773 (14.9)
Other Pacific Islander ^b	4113 (7.4)	131 (3.2)	243 (5.9)
Other Asian ^c	4034 (7.2)	410 (10.2)	641 (15.9)
Other or unknown ^d	2880 (5.2)	366 (12.7)	622 (21.6)
Nativity			
Born in US	41591 (74.8)	6946 (16.7)	8396 (20.2)
Born outside US	14036 (25.2)	1042 (7.4)	1528 (10.9)
Education level			
Less than high school	4097 (7.5)	260 (6.3)	311 (7.6)
High school graduate	21743 (39.7)	2824 (13.0)	3458 (15.9)
Some college	12861 (23.5)	2021 (15.7)	2768 (21.5)
College graduate	16054 (29.3)	2817 (17.6)	3307 (20.6)
Federal Poverty Level (%)			
≤ 100%	15138 (29.3)	1663 (11.0)	1789 (11.8)
101-200%	13427 (26.0)	1790 (13.3)	2414 (18.0)
201% +	23099 (44.7)	4160 (18.0)	5120 (22.2)
Parity			
First live birth	22598 (40.6)	3211 (14.2)	4065 (18.0)
Not first live birth	33062 (59.4)	4769 (14.4)	5860 (17.7)
Pre-pregnancy chronic disease^e			
Yes	10951 (19.7)	4147 (37.9)	3993 (36.5)
No	44740 (80.3)	3842 (8.6)	5931 (13.3)
Pregnancy-related medical problem^f			
Yes	29387 (52.8)	5560 (18.9)	7339 (25.0)
No	26304 (47.2)	2429 (9.2)	2585 (9.8)

* Weighted, rounded to nearest whole number; ^a Native Hawaiian includes part Hawaiian; ^bOther Pacific Islander includes: Samoan, Guamanian, and other Pacific Islander; ^cOther Asian includes: Chinese, Korean, Vietnamese, Asian Indian, and other Asian; ^dOther or unknown includes: African American, American Indian, Puerto Rican, Cuban, Mexican, and all others; ^ePre-pregnancy chronic disease includes: diabetes, asthma, hypertension, heart problems, epilepsy, thyroid problems, depression and anxiety; ^fPregnancy-related medical problem includes: gestational diabetes, vaginal bleeding, kidney or bladder infection, severe nausea, vomiting, or dehydration, cervical cerclage, hypertension, preeclampsia, or toxemia during pregnancy, placental problems, preterm labor, or blood transfusion during pregnancy

Table 1.2. Prescription Use Before and during Pregnancy by Type, Hawai'i PRAMS, 2009-2011

Prescription type	Use before pregnancy, n* (%)	Use during pregnancy, n* (%)
Allergy	848 (1.52)	750 (1.35)
Anti-infectives^a	1077 (1.93)	2238 (4.02)
Asthma	794 (1.43)	823 (1.48)
Birth control	479 (0.86)	N/A ^b
Cardiovascular	819 (1.47)	1000 (1.80)
Diabetic	483 (0.87)	786 (1.41)
Fertility treatments	496 (0.89)	N/A
Gastrointestinal	500 (0.90)	1756 (3.15)
Other^b	649 (1.17)	726 (1.30)
Pain relievers	1567 (2.81)	1777 (3.19)
Pregnancy support	N/A	434 (0.78)
Psychiatric	1293 (2.32)	764 (1.37)
Thyroid	485 (0.87)	582 (1.04)
Unknown	211 (0.38)	368 (0.66)
Vitamins/supplements	1065 (1.91)	3861 (6.93)

*Weighted, rounded to nearest whole number; ^aAnti-infectives group includes: antibiotic, antiviral, antifungal, and antiparasitic medications; ^bOther group includes all identifiable medications not otherwise grouped; for during pregnancy time period, Other group also includes birth control

Purpose of this dissertation

This dissertation seeks to: (1) Calculate and describe prevalence estimates of opioid pain reliever use during pregnancy in Hawai‘i and investigate possible predictors of prescription opioid pain reliever use during pregnancy through the use of multivariable logistic regression, (2) investigate whether prescription opioid pain reliever use during pregnancy is associated with poorer birth outcomes among users when compared to non-users in Hawai‘i, while controlling for potential confounding factors, and (3) estimate the prevalence of depression and anxiety, along with pharmaceutical treatment and help-seeking behaviors, among a multiethnic population of women who recently delivered a live birth in the State of Hawai‘i.

Research questions

This dissertation includes several research questions that were addressed in three distinct but related studies.

Study 1: What is the prevalence of prescription opioid drug use during pregnancy in Hawai‘i? Do differences exist in prescription opioid drug use during pregnancy in Hawai‘i by maternal demographic characteristics? What are the predictors of prescription opioid pain reliever use during pregnancy as identified through the use of multivariable logistic regression?

Study 2: Is prescription opioid drug use during pregnancy associated with poorer birth outcomes among users when compared to non-users in Hawai‘i, while controlling for potential confounding factors?

Study 3: What is the prevalence of depression and anxiety, along with pharmaceutical treatment and help-seeking behaviors, among a multiethnic population of women who recently delivered a live infant in Hawai‘i?

Community buy-in

In addition to being a doctoral student in Epidemiology at the University of Hawai‘i at Mānoa, I am also the Program Coordinator for the Hawai‘i PRAMS program. As a State of Hawai‘i employee, and in my role as Hawai‘i PRAMS Program Coordinator, I have been in communication about the progress of this research project with my supervisor Danette Wong Tomiyasu, who is the Hawai‘i Department of Health, Family Health Services Division Chief, Hawai‘i Title V (Federal Maternal and Child Health Block Grant) Director, and the Principal Investigator of the Hawai‘i PRAMS grant. All research projects in this dissertation have been discussed with Ms. Tomiyasu, and have been determined to be appropriate in light of Hawai‘i Department of Health, Family Health Services Division priorities. Specifically, the issue of prescription drug use during pregnancy in Hawai‘i has been determined to fit within the Department's priority area of maternal mortality due to potential relationships between prescription medication abuse during pregnancy and maternal deaths from drug overdose, drug interactions, and accidental poisoning (Hayes et al., 2013). Additionally, prescription drug use during pregnancy is also potentially related to the Department's priority area of infant mortality, as there are concerns about use of specific drugs increasing the risk of preterm delivery and low birth weight, which are significant contributors to infant mortality in Hawai‘i (Hayes et al., 2013).

In addition to the collaboration with Ms. Tomiyasu, the Hawai‘i Department of Health Office of Injury Prevention has expressed considerable interest in the topic of prescription opioid drug use during pregnancy, and has offered their assistance and expertise related to morbidity and mortality associated with opioid abuse and overdose in Hawai‘i. They have also requested that findings from all three research projects be shared with their Office, and they have offered assistance in dissemination to the community once appropriate. All findings will also be shared with interested parties in the Hawai‘i Department of Health (HDOH), Hawai‘i PRAMS Steering Committee, Hawai‘i PRAMS

Advisory Group, Centers for Disease Control and Prevention (CDC) PRAMS Program, all other PRAMS programs, and other community stakeholders, chosen in coordination with my dissertation committee and my supervisory leadership at the HDOH and the CDC.

Human Subjects Protections

This study was reviewed and approved by the University of Hawai‘i Human Studies Program and the Hawai‘i Department of Health Institutional Review Board. Secondary analysis of Hawai‘i PRAMS data is also covered under pre-existing approvals granted by the Institutional Review Board of the Human Research Protection Office of the CDC, as well as by the State of Hawai‘i Department of Health Institutional Review Board. Documentation of these approvals is included in the Appendix.

CHAPTER 2.
STUDY 1: PRESCRIPTION OPIOID DRUG USE DURING PREGNANCY
IN HAWAI‘I

ABSTRACT

Background: In pregnancy, the use of prescription opioids is on the rise, with increases in both medical and nonmedical use observed. There are few population-based studies on prescription drug use in pregnancy in the United States, and little is known about prescription opioid use among pregnant populations in general, including Hawai‘i. The aims of this study were to (1) determine the prevalence of prescription opioid drug use during pregnancy in Hawai‘i, (2) describe differences in prescription opioid drug use during pregnancy in Hawai‘i by maternal demographic characteristics, and (3) investigate possible predictors of prescription opioid drug use during pregnancy through the use of multivariable logistic regression.

Methods: Hawai‘i Pregnancy Risk Assessment Monitoring System (PRAMS) data from 4,735 respondents were used to estimate prevalence of prescription opioid drug use during pregnancy. Data were weighted to be representative of all pregnancies resulting in live births in Hawai‘i from 2009 to 2011. Prevalence estimates, confidence intervals, measures of association, and p-values were generated using SAS-callable SUDAAN 10.0 (RTI International, Research Triangle Park, NC) to account for complex sampling.

Results: For women who delivered a live infant in Hawai‘i in 2009-2011, 1.42% reported prescription opioid use during pregnancy (95% CI: 1.04-1.93). The prevalence of prescription opioid use during pregnancy was highest among women who were White, of “other” or “unknown” race/ethnicity (which in this study includes African American, American Indian, Puerto Rican, Cuban, Mexican, and any otherwise uncategorized individuals), had a pre-pregnancy chronic disease diagnosis, and those who smoked in the three months before pregnancy. Maternal race/ethnicity and pre-pregnancy chronic disease were significant ($p < 0.01$) predictors of prescription opioid use during pregnancy using

multivariable logistic regression modeling. An association between pre-pregnancy smoking and prescription opioid use during pregnancy was also observed ($p = 0.087$).

Public Health Implications: Because prescription opioid use among the general public, including pregnant women, is increasing, there is an increased need for careful monitoring by health care providers. Understanding prescription opioid drug use patterns among pregnant women is vitally important when creating and tailoring prenatal, perinatal, and postpartum public health programs and medical care plans for potentially opioid exposed women and infants. More research is needed to determine to what degree the opioid exposures described in this study reflect occasional, chronic, recreational, and/or medically-supervised use, and to what degree predictive factors are potentially modifiable in ways that might benefit women and infants.

Keywords: Opioids, Prescription drug use, Pregnancy

BACKGROUND

Opioid use during pregnancy is a public health issue of growing concern in the United States, since the use of prescription painkillers during pregnancy is on the rise. Increases in both medical and nonmedical use have been reported observed. In recent years, dramatic increases in the incidence of neonatal abstinence syndrome (NAS), a drug withdrawal syndrome in newborn infants following birth, have been documented and widely attributed to corresponding increases in opioid use and abuse in the United States (Creanga et al., 2012; Jansson & Velez, 2012; H. E. Jones & Kaltenbach, 2012; Patrick et al., 2012). Opioid use and abuse during pregnancy has also been implicated in the increase in pregnancy-associated non-natural deaths (Hardt et al., 2013).

Due to the fact that reliable drug safety information is lacking with regards to prenatal prescription opioid exposure, use of these medications during pregnancy is generally not recommended unless the situation clearly dictates that the potential benefits outweigh the potential risks to both the woman and her fetus; for example, in a case where pain is severe to the point of being disabling, and is only controllable with opioid medication (Chou et al., 2009). If a pregnant woman is under treatment for opioid addiction however, the standard treatment currently involves maintaining the patient on a regimen of either methadone or buprenorphine in order to prevent or reduce use of drugs such as heroin, and decrease potentially harmful behaviors associated with procurement and use of illicit drugs (Stanhope, Gill, & Rose, 2013; Unger et al., 2011).

There has been very little study of prescription opioid use in pregnant women in Hawai‘i. However, prescription drug overdose is recognized as a leading cause of injury and death in Hawai‘i, with the majority of overdoses involving opioids (Drewes, 2012). Overdose deaths attributed to prescription drug abuse has doubled in the last decade, and there are currently more deaths due to drug overdose in Hawai‘i than motor vehicle crashes, drowning, or pedestrian accidents (Drewes, 2012). The number of nonfatal poisonings from prescription opioids in Hawai‘i has also been increasing steadily, including a 115% increase between 2003 and 2009 (Galanis, 2013).

The understanding of prescription opioid drug use patterns among pregnant women is essential to tailoring prenatal, perinatal, and postpartum public health programs and medical care plans for potentially opioid exposed women and infants. The aims of this study were to: (1) determine the prevalence of prescription opioid use during pregnancy using our cohort of pregnant women in Hawai‘i, (2) describe differences in prescription opioid use during pregnancy in Hawai‘i by maternal demographic characteristics, and (3) investigate possible predictors of prescription opioid use during pregnancy.

METHODS

Data Source

A secondary data analysis was conducted of Hawai‘i Pregnancy Risk Assessment Monitoring System (PRAMS) data from 2009 to 2011. The PRAMS database is a self-reported survey of recent mothers designed to collect information on maternal behaviors, attitudes, and experiences before, during, and immediately after pregnancy. The PRAMS program operates according to a standardized data collection protocol centering on a mailed questionnaire (self-administered) with telephone follow-up for non-responders. Mothers are selected for participation as part of a stratified sample drawn from the birth certificates of live births in Hawai‘i, and complete the survey 3-9 months postpartum, with the majority responding 3-4 months postpartum. The Hawai‘i PRAMS dataset includes information collected from PRAMS survey questions, as well as from selected linked birth certificate variables. Data are weighted on an annual basis according to CDC protocol to be representative of all pregnancies resulting in live births in Hawai‘i in a given year. States must achieve a minimum weighted response rate of 65% in order for survey results to be considered generalizable to all live births in the state in a given year. Hawai‘i PRAMS annual weighted response rates for the years presented in this analysis ranged from 71-73%. More detailed information on PRAMS methodology can be found at <http://www.cdc.gov/prams/Methodology.htm>.

Measures

The following question pertaining to prescription drug use during pregnancy was used for this analysis:

Did you use any of these drugs when you were pregnant? For each item, circle Y (Yes) if you used it or circle N (No) if you did not.

a. Prescription drugs

If yes, what kinds? Please tell us: _____

Write-in responses were manually reviewed in order to properly adjust for misspellings, multiple drugs listed, and other factors. In cases where initial determination was difficult, clinicians and other sources were consulted to determine which drug was being referenced. Responses were then coded into categories using SAS 9.2 “string” and “upcase” commands. Entries > 30 characters were listed in separate comment file; these responses were also manually reviewed and then coded into groups by unique ID number. The following prescription opioids (alone or in preparation) were included in this analysis: Codeine, Fentanyl, Hydrocodone, Meperidine, Methadone, Morphine, Oxycodone, and Tramadol. Prevalence estimates, confidence intervals, measures of association, and p-values were generated using SAS-callable SUDAAN 10.0 (RTI International, Research Triangle Park, NC) to account for complex sampling.

Maternal age, race/ethnicity, education, marital status, and parity were determined based on linked birth certificate variables included in the Hawai‘i PRAMS dataset. The maternal race/ethnicity variables included in the Hawai‘i PRAMS dataset were sorted into single race groups based on a standard algorithm used by the Hawai‘i Department of Health Office of Health Status and Monitoring (Sorensen et al., 2003). Federal Poverty Level (FPL) was based on maternal report of household annual income and number of dependents in the year before delivery in the Hawai‘i PRAMS survey, and was calculated according to Hawai‘i-specific threshold guidelines. Smoking status in the three months before

pregnancy and pre-pregnancy chronic disease were quantified based on maternal report in the Hawai‘i PRAMS survey. Pre-pregnancy chronic disease includes Type 1 or Type 2 diabetes (any point before pregnancy), as well as asthma, hypertension, heart problems, epilepsy, thyroid problems, depression, and anxiety (in the three months before pregnancy).

Analysis

Bivariate analyses were performed to identify potential confounders at the $p < 0.20$ (marginal significance) level. Variables were selected for the bivariate and multivariable analysis based on a review of the literature related to both prescription use during pregnancy and opioid use among pregnant and non-pregnant populations. Multivariable analyses were then performed using Hosmer and Lemeshow’s purposeful selection method to examine associations between selected maternal characteristics and prescription opioid use during pregnancy (Hosmer & Lemeshow, 2000), using $p < 0.05$ as the standard cutoff point for inclusion in the final multivariable model.

RESULTS

A total of 4,735 respondents were analyzed for this study. Maternal demographic characteristics and prescription opioid use during pregnancy are shown in Table 2.1. Of women who delivered a live infant in Hawai‘i between 2009 and 2011, 1.42% reported prescription opioid use during pregnancy (95% CI: 1.04-1.93). Prevalence of prescription opioid use during pregnancy was highest among women who were White, were of other or unknown race/ethnicity (which includes African American, American Indian, Puerto Rican, Cuban, Mexican, and any otherwise uncategorized individuals), had a pre-pregnancy chronic disease diagnosis, and among those who smoked in the three months before pregnancy. Differences by maternal race/ethnicity, pre-pregnancy chronic disease status, and pre-pregnancy smoking status were significant at the $p < 0.05$ level. No other differences were statistically significant.

The final multivariable model included the following predictive variables: maternal race/ethnicity, pre-pregnancy chronic disease, and pre-pregnancy smoking status. Maternal race/ethnicity and pre-pregnancy chronic disease were both significant predictors at the $p < 0.001$ and $p < 0.01$ levels respectively. Although smoking status before pregnancy only achieved marginal significance ($p = 0.0865$) in our analysis, this variable was retained in the model due to documented associations between smoking and opioid use (H. E. Jones et al., 2009; Log et al., 2011; Winklbaaur et al., 2009). Table 2.2 presents the resulting adjusted odds ratios (aOR) and confidence intervals (CI) showing that maternal pre-pregnancy chronic disease was associated with significantly increased odds of prescription opioid use during pregnancy when compared to no pre-pregnancy chronic disease, while Native Hawaiian or other Pacific Islander and Asian race/ethnicity were associated with significantly decreased odds of prescription opioid use during pregnancy when compared to White race/ethnicity.

Table 2.1. Prescription Opioid Use during Pregnancy by Maternal Characteristics

Maternal characteristics	Total, n* (% of total population)	Prescription opioid use during pregnancy, n* (% reporting use)
Total	55,691 (100)	790 (1.4)
Age (years)		
Less than 30	32,409 (58.2)	488 (1.5)
30 or older	23,282 (41.8)	302 (1.3)
Race/Ethnicity		
Hawaiian or other Pacific Islander^a	20,851 (37.4)	215 (1.0)
White	12,813 (23.0)	363 (2.8)
Asian^b	19,147 (34.4)	113 (0.6)
Other or unknown^c	2,880 (5.2)	100 (3.5)
Marital Status		
Married	34,081 (61.2)	573 (1.7)
Other	21,610 (38.8)	217 (1.0)
Education level		
High school graduate or less	25,840 (47.2)	404 (1.6)
Some college or more	28,915 (52.8)	381 (1.3)
Federal Poverty Level (%)		
Less than or equal to 200%	28,565 (55.3)	434 (1.5)
201% or greater	23,099 (44.7)	318 (1.4)
Parity		
First live birth	22,598 (40.6)	269 (1.2)
Not first live birth	33,062 (59.4)	522 (1.6)
Pre-pregnancy chronic disease^d		
Yes	10,951 (19.7)	323 (3.0)
No	44,740 (80.3)	467 (1.0)
Pre-pregnancy smoking		
Yes	11,443 (20.9)	268 (2.3)
No	43,360 (79.1)	518 (1.2)

* Weighted, rounded to nearest whole number, category-specific estimates may not equal overall total due to differences in missing values; ^aHawaiian or other Pacific Islander includes: Hawaiian, part Hawaiian, Samoan, Guamanian, and other Pacific Islander; ^bAsian includes: Japanese, Filipino, Chinese, Korean, Vietnamese, Asian Indian, and other Asian; ^cOther or unknown includes: African American, American Indian, Puerto Rican, Cuban, Mexican, and all others; ^dPre-pregnancy chronic disease includes: diabetes, asthma, hypertension, heart problems, epilepsy, thyroid problems, depression and anxiety

Table 2.2. Adjusted Odds Ratios (aORs) between Selected Maternal Characteristics and Prescription Opioid Use during Pregnancy

Maternal characteristics	aOR (95% CI)
Maternal race/ethnicity	
Hawaiian or other Pacific Islander^a	0.34 (0.16-0.71)**
White	Ref
Asian^b	0.22 (0.09-0.54)***
Other or unknown^c	1.16 (0.37-3.67)
Pre-pregnancy chronic disease^d	
Yes	2.48 (1.25-4.91)**
No	Ref
Pre-pregnancy smoking	
Yes	1.77 (0.92-3.41)
No	Ref

*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001

^aHawaiian or other Pacific Islander includes: Hawaiian, part Hawaiian, Samoan, Guamanian, and other Pacific Islander; ^bAsian includes: Japanese, Filipino, Chinese, Korean, Vietnamese, Asian Indian, and other Asian; ^cOther or unknown includes: African American, American Indian, Puerto Rican, Cuban, Mexican, and all others; ^dPre-pregnancy chronic disease includes: diabetes, asthma, hypertension, heart problems, epilepsy, thyroid problems, depression and anxiety

DISCUSSION

This is the first study that examines prescription opioid use during pregnancy by using maternally reported, population-based data from the PRAMS survey. This PRAMS study provides a different perspective from existing prescription drug research. There are few population-based studies on pregnancy-associated prescription drug uses in the United States (Daw et al., 2011). For the most part, the latest available research findings come from non-population-based data sources with limited generalizability, such as electronic medical records (Andrade et al., 2004), pharmacy dispensing records (Irvine et al., 2010), or health insurance claims databases (Bateman et al., 2014; Daw et al., 2012). Data from those sources do not directly address what is, arguably, the most important question in this line of research: “What drugs did pregnant women use?” Instead, they rely on proxy measures: what drugs women were prescribed, what prescriptions women filled, and what prescriptions were submitted for insurance coverage. It is well accepted that many people are prescribed medication they never fill, or fill medication that they never use, or use medication that they never submit for insurance coverage (DiMatteo, 2004; Fischer et al., 2010; Osterberg & Blaschke, 2005; Solomon & Majumdar, 2010).

Also, none of these data sources address the usage of prescription medication that is not prescribed to the individual using it. This means that any non-prescribed use of medications, such as use of medications provided by friends, family, or other means, would not be captured in those datasets. This is of concern because sharing and borrowing of prescription medication is very common among women of reproductive age (Petersen, Rasmussen, Daniel, Yazdy, & Honein, 2008), and recent research has shown that the levels of agreement between maternal report of prescription drug use during pregnancy and electronic medical data are lowest for opioid medications, compared to other prescription drug types (Sarangarm et al., 2012). Therefore, findings from studies using data sources such as such as electronic medical records, pharmacy dispensing records, or health insurance claims databases might provide biased results resulting from misclassification of exposures due to noncompliance or

medication sharing (Olesen et al., 2001; Skurtveit et al., 2013). The use of data from the Hawai‘i PRAMS survey provides advantages over findings from other data sources due to its being population-based and weighted to be representative of all pregnancies resulting in live births in Hawai‘i. It also is able to capture use of medications that might be missed in other datasets due to recreational use of drugs prescribed to other individuals, or obtained through illicit means.

Another advantage of using Hawai‘i PRAMS as a data source for these types of studies relates to the uniqueness of Hawai‘i itself. The multiethnic nature of the population of Hawai‘i means that generalizability of research findings from studies conducted outside the state is unclear with regards to many different topics (Kaneshiro et al., 2011). Nonetheless, what research that exists shows that overall prevalence of prescription drug use during pregnancy, as well as relative frequencies of different classes and types of drugs prescribed and used, vary widely between countries, and even between regions within the same country (Daw et al., 2011; Odalovic et al., 2012). Additionally, even within the US, prescribing and drug usage practices differ significantly by geographic region (Bateman et al., 2014; Wetmore et al., 2011; Zerzan et al., 2006; Zhang et al., 2010). As a result, it is important not only for different states and regions of the United States to have quality data on prescribing and usage practices within their own communities, but also to be able to disseminate research findings widely and frequently to assist all locations. Currently, there is a lack of information regarding prescription opioid use during pregnancy in Hawai‘i, as there is generally in other parts of the United States, and worldwide.

There are inherent limitations in this study, primarily related to the Hawai‘i PRAMS survey itself. These limitations include that the data are self-reported, and subject to recall bias and/or reporting factors. This may have affected the study results since previous research has shown that women are more likely to recall use of some types of medications than others when retrospectively asked about medication use during pregnancy (van Gelder, van Rooij, de Walle, Roeleveld, & Bakker, 2013). However, a strength of this study is that further research has demonstrated that recall effects are modest for the time period during

which the majority of PRAMS surveys are completed (Tinker et al., 2013). Some mode bias (mail versus telephone) may also have occurred, as mothers who completed the surveys via mail were significantly more likely to report prescription drug use both before and during pregnancy than those questioned via telephone (data not shown). Despite this, approximately 81% of survey respondents completed the Hawai‘i PRAMS questionnaire by mail in 2009 – 2011, so the effects of this mode bias are expected to be minimal. Additionally, in the foundational statistical model, PRAMS nonresponse weights are calculated based on assumptions that women in a particular subgroup who responded would be predicted to have similar responses to those who did not respond. Although it is unclear how valid this assumption may be for the outcomes examined in this study, it is expected that opioid drug use would follow major other classes of drug use/abuse in pregnancy (Halbesleben & Whitman, 2013).

An added issue that bears remark with regard to survey-based studies is the limitation related to the Hawai‘i PRAMS prescription drug use questions. It is possible that respondents may have struggled with comprehension of this specific question; for example, some individuals might only have listed medications that were prescribed to them, not medications they used recreationally. It was not always possible to determine exactly which drug was being referenced (e.g. spelling errors did not allow for reliable determination of drug being used). Also, which medications were being referred to was sometimes unknown due to the fact that some answers did not specifically refer to drug name (e.g. “painkillers”), some women did not know what they took (e.g. “can’t remember”), and some women left the space blank. These factors introduce a source of error whereby use of prescription opioids may have been missed. It is expected that any effects on study findings were minimal. In this study, there were fewer than 5 (unweighted) cases where a drug listed was not able to be reliably identified due to extreme spelling errors, fewer than 10 (unweighted) cases where women did not remember or state what type of medication they used during pregnancy and did not provide additional information that could be used to make an informed determination, and fewer than 20 (unweighted) cases where the space was left

blank, without additional information provided in the comment section that could be used to identify the prescription drug type used. These individuals, along with women indicating use of other non-opioid prescription drugs, were included in the study, but were not included in the prescription opioid drug user group. Cases where a respondent indicated that they used prescription pain killers, but did not provide a drug name or other information that would indicate that the drug was an opioid, were also not included in the prescription opioid drug user group. When non-opioid medications (e.g. ibuprofen) and non-specific mentions of prescription pain reliever use were included, the prevalence estimate for prescription pain reliever use during pregnancy in our population was 3.19% (95% CI: 2.58-3.95). It is very possible that this estimate includes a number of prescription opioid drugs which have been excluded from the current study due to misclassification resulting from responses not referencing specific drug names. This study prioritized minimizing the number of true non-users of prescription opioids included in the opioid user group; a decision which is supported by existing research showing that specificity is of greater importance than sensitivity when conducting research on prescription drug use during pregnancy (Skurtveit et al., 2013).

Finally, the Hawai‘i PRAMS survey questions related to prescription drug use do not have information on dosages or frequency of use, pregnancy trimester of usage, or if the medication was prescribed to the individual taking it. This lack of detail means that these findings cannot be used to produce mechanistic or safety guidelines, but the study does demonstrate a way forward for including this information in the future to inform better safety toxicology, pre-clinical, or clinical trials.

As prescription opioid use continues to increase, there is a greater need for careful monitoring by health care providers in the entire population. This is critically important in special and vulnerable populations, which includes pregnant and reproductive-aged women. Women, on average, begin taking prescription medications at younger ages than men, and are more likely to experience adverse drug reactions due to body composition and metabolism

differences (Mattison & Zajicek, 2006). Women are also more likely than men are to report chronic pain and be prescribed opioids, and between 1999 and 2010, the percentage increase in deaths caused by prescription opioid overdose among American women was greater than 400% (CDC, 2013).

Opioid exposed pregnancies do not occur in a vacuum, but rather as part of a larger constellation of behaviors and experiences that happen before and during pregnancy. This study identified maternal pre-pregnancy chronic disease, race/ethnicity, and smoking status as factors associated with prescription opioid use during pregnancy. Further research is needed to determine to what degree the opioid exposures described in this study reflect prescription drug use that is occasional, chronic, recreational, and/or medically-supervised, and what role prescription opioid addiction is playing.

In addition, more information is needed regarding opioid drug safety during pregnancy. This study has shown that prescription opioid use during pregnancy is relatively common in Hawai'i, and previous research has shown it to be increasingly common in the United States as a whole (Bateman et al., 2014; Buchi, Suarez, & Varner, 2013; CDC, 2013; Cerda et al., 2013; Creanga et al., 2012; Epstein et al., 2013; Hardt et al., 2013). What must be determined next is not only whether this widespread use of prescription opioid drugs is safe during pregnancy, but also which factors related to use of prescription opioids during pregnancy are potentially modifiable targets for interventions aimed at reducing unnecessary risks to women and infants.

CHAPTER 3.

STUDY 2: PRESCRIPTION OPIOID DRUG USE DURING PREGNANCY AND BIRTH OUTCOMES IN HAWAI‘I

ABSTRACT

Background: Use of prescription opioids by the general public is rising, and risks specific to pregnant and reproductive-aged women are increasingly being recorded. Aside from the well-documented association between opioid pain reliever use during pregnancy and neonatal abstinence syndrome (NAS), other effects on pregnancy are not well understood. This study sought to determine whether prescription opioid use during pregnancy is associated with poorer birth outcomes among users when compared to non-users in Hawai‘i.

Methods: Hawai‘i Pregnancy Risk Assessment Monitoring System data from 4,578 respondents were used to estimate prevalence of prescription opioid pain reliever use during pregnancy. Data were weighted to be representative of all pregnancies resulting in singleton live births in Hawai‘i from 2009 to 2011. Prevalence estimates, confidence intervals, measures of association, and p-values were generated using SAS-callable SUDAAN 10.0 (RTI International, Research Triangle Park, NC) to account for complex sampling. Three separate multivariable analyses were performed to examine associations between prescription opioid use during pregnancy and small for gestational age (SGA), preterm delivery (PTD), and low birth weight (LBW), while controlling for selected confounders.

Results: Among women who had a singleton live birth in Hawai‘i between 2009 and 2011, 1.34% reported prescription opioid use during pregnancy (95% CI: 0.97-1.84). After controlling for maternal race/ethnicity, pregnancy weight gain adequacy, smoking in the last trimester of pregnancy, parity, and maternal pre-pregnancy BMI, maternal use of prescription opioids during pregnancy was associated with an increased odds of delivering a SGA infant, with an adjusted odds ratio (aOR) of 3.18 (95% CI: 1.30, 7.77; $p < 0.05$). After controlling for previous PTD, maternal pre-pregnancy chronic disease, pregnancy weight gain

adequacy, maternal race/ethnicity, pre-pregnancy BMI, and maternal stress level, maternal use of prescription opioids during pregnancy was not associated with increased odds of PTD [aOR: 0.71, (95% CI: 0.21, 2.36), $p = 0.5796$]. After controlling for previous low birth weight delivery, pregnancy weight gain adequacy, maternal race/ethnicity, maternal nativity, maternal pre-pregnancy chronic disease, and poverty level, maternal use of prescription opioids during pregnancy was associated with decreased odds of delivering a LBW infant, with an aOR of 0.17 (95% CI: 0.03, 1.01; $p = 0.0512$).

Public Health Implications: The dramatic increase in incidence over the past decade of NAS has focused attention on the issue of opioid use during pregnancy. However, more information is needed to determine what other health outcomes might be associated with prenatal opioid exposure. These findings preliminarily indicate an association between prescription opioid use in pregnancy and SGA infants. More research with a larger cohort is needed in order to confirm these associations, and potentially determine appropriate strategies to mitigate adverse health effects.

Keywords: Opioids, Prescription drug use, Birth outcomes

BACKGROUND

Use of prescription opioid drugs during pregnancy is rising, with increases in both medical and nonmedical use observed in recent years (Brennan & Rayburn, 2012; Creanga et al., 2012; Hardt et al., 2013; Rayburn & Brennan, 2011). A considerable increase in incidence over the past decade of neonatal abstinence syndrome (NAS), a drug withdrawal syndrome observed in newborn infants following birth, has been attributed to substantial increases in opioid use in the United States during the same period (Jansson & Velez, 2012; H. E. Jones & Kaltenbach, 2012; Patrick et al., 2012). Opioid use and abuse during pregnancy has also been implicated in an observed increase in pregnancy-associated non-natural deaths in some states (Hardt et al., 2013). Aside from the well-documented association between opioid use during pregnancy and NAS however, other effects on pregnancy are not well understood, although there appear to be associations between opioid use and some birth defects and poor birth outcomes (Brennan & Rayburn, 2012; Broussard et al., 2011).

Little is known about prescription opioid use among pregnant populations in general, and this is also true in Hawai‘i. However, among the general population of the state, prescription drug overdose is a leading cause of injury and death, with the majority of overdoses involving opioid drugs (Drewes, 2012). The number of overdose deaths has doubled in the past ten years, and drug overdoses kill more people in Hawai‘i than do motor vehicle crashes, drowning, or pedestrian accidents (Drewes, 2012). The number of serious nonfatal poisonings from prescription opioid drugs has also been increasing steadily in the state, including a 115% increase between 2003 and 2009 (Galanis, 2013).

This study aimed to determine whether prescription opioid use during pregnancy is associated with poorer birth outcomes among users when compared to non-users in Hawai‘i. Specifically, this project focused on examining associations between prescription opioid use during pregnancy and risk of small for gestational age, preterm delivery, or low birth weight deliveries among women giving birth to live, singleton infants in Hawai‘i.

METHODS

Data Source

A secondary data analysis was conducted of Hawai'i Pregnancy Risk Assessment Monitoring System (PRAMS) data from 2009 to 2011. PRAMS is a self-reported survey of recent mothers designed to collect information on maternal behaviors, attitudes, and experiences before, during, and immediately after pregnancy. It is a joint program between the Centers for Disease Control and Prevention (CDC) and state and local health departments. The PRAMS program operates according to a standardized data collection protocol centering on a self-administered mailed questionnaire with telephone follow-up for non-responders. Mothers are selected for participation as part of a stratified sample drawn from the birth certificates of live births in Hawai'i, and complete the survey 3-9 months postpartum, with the majority responding 3-4 months postpartum. The Hawai'i PRAMS dataset includes information collected from Hawai'i PRAMS survey questions, as well as from selected linked birth certificate variables, provided in coordination with the Hawai'i Office of Health Status and Monitoring. Data are weighted annually by CDC to be representative of all pregnancies resulting in live births in Hawai'i in a given year. Hawai'i PRAMS annual weighted response rates for the years presented in this analysis ranged from 71-73%; well above the minimum weighted response rate of 65% required by CDC in order for survey results to be considered generalizable to all live births in the state in a given year. More information on PRAMS methodology can be found at <http://www.cdc.gov/prams/Methodology.htm>.

Measures

The following question pertaining to prescription drug use during pregnancy was used for this analysis:

Did you use any of these drugs when you were pregnant? For each item, circle Y (Yes) if you used it or circle N (No) if you did not.

a. Prescription drugs

If yes, what kinds? Please tell us: _____

Write-in responses to the prescription drug question were manually reviewed in order to adjust for misspellings, multiple drugs listed, and other factors. In situations where initial determination proved difficult, clinicians and other sources were consulted to determine which drug was being referenced. Responses were coded into categories using SAS 9.2 “string” and “upcase” commands. Entries consisting of more than 30 characters were listed in separate comment file, and were also manually reviewed, then coded into groups by unique ID number. The following prescription opioids (alone or in preparation) were included in this analysis: Codeine, Fentanyl, Hydrocodone, Meperidine, Methadone, Morphine, Oxycodone, and Tramadol. SAS-callable SUDAAN 10.0 (RTI International, Research Triangle Park, NC) was used to account for complex sampling in generating prevalence estimates, confidence intervals (CI), measures of association, and p-values.

Maternal age, race/ethnicity, nativity (born within or outside the United States), education, marital status, gestational weight gain, birth weight, gestational age, and parity were determined based on linked birth certificate variables included in the Hawai‘i PRAMS dataset. The maternal race/ethnicity variables were sorted into single race groups based on a standard algorithm used by the Hawai‘i Department of Health, Office of Health Status and Monitoring prior to being included in the Hawai‘i PRAMS dataset (Sorensen et al., 2003). Low birth weight (LBW) was defined as an infant weighing less than 2,500 grams at birth, preterm delivery (PTD) was defined as a gestational age less than 37 weeks at birth, and small for gestational age (SGA) was defined as weight below the tenth percentile for gestational age, taking into account infant race and gender. Smoking status during and in the three months before pregnancy, previous history of preterm delivery, previous history of low birth weight delivery, maternal stress

level, and pre-pregnancy chronic disease were based on maternal report in the Hawai'i PRAMS survey. Maternal stress level was constructed using a question asking which, if any, of thirteen possible stressful life events the mother experienced in the twelve months before delivery. Maternal stress was grouped into low (0-2 stressors) and high (3 or more stressors) levels for this study. Pre-pregnancy chronic disease included Type 1 or Type 2 diabetes (occurring at any point before pregnancy), as well as asthma, hypertension, heart problems, epilepsy, thyroid problems, depression, and anxiety (occurring in the three months before pregnancy). Federal Poverty Level (FPL) was based on maternal report of household annual income and number of dependents in the year before delivery in the Hawai'i PRAMS survey, and was calculated according to Hawai'i-specific threshold guidelines. Adequacy of weight gained during pregnancy was determined by calculating maternal pre-pregnancy body mass index (BMI) from maternal report of height and pre-pregnancy weight in combination with gestational weight gain from the birth certificate, and using BMI-specific guidelines released in 2009 by the Institute of Medicine (Institute of Medicine, 2009). This project was limited to singleton deliveries in order to limit the known effects of multiple gestations with respect to the birth outcomes of interest.

Analysis

In order to determine whether prescription opioid pain reliever use during pregnancy was associated with poorer birth outcomes among users when compared to non-users in Hawai'i, potential confounding factors were first identified based on a review of the literature related to prescription opioid use, as well as SGA, PTD, and LBW. In addition, a previous analysis of this dataset identified predictors of opioid use during pregnancy in Hawai'i, and these findings also informed the selection of potential covariates. Bivariate analyses were performed to identify confounders using $p < 0.20$ (marginal significance) as a cut off. Three separate multivariable analyses were then performed using the purposeful selection method developed by Hosmer and Lemeshow (Hosmer & Lemeshow, 2000) to examine associations between prescription opioid use during

pregnancy and the three birth outcomes of interest, while controlling for selected confounders.

RESULTS

Data were available for 4,578 respondents with singleton live births in the years 2009 to 2011. Maternal demographic characteristics and prescription opioid use during pregnancy are shown in Table 3.1. Of women who delivered a singleton live infant in Hawai'i between 2009 and 2011, 1.34% reported using prescription opioid drugs during pregnancy (95% CI: 0.97-1.84). Prevalence of prescription opioid use during pregnancy was highest among women who were of White, or other/unknown race/ethnicity (which includes African American, American Indian, Puerto Rican, Cuban, Mexican, and any otherwise uncategorized individuals), had a pre-pregnancy chronic disease diagnosis, and those who smoked in the three months before pregnancy. Table 3.2 presents SGA, PTD, and LBW prevalence estimates by maternal demographic characteristics.

The final model examining the association between prescription opioid use during pregnancy and SGA included the following variables in addition to opioid use during pregnancy: maternal race/ethnicity, pregnancy weight gain adequacy, smoking in the last trimester of pregnancy, parity, and maternal pre-pregnancy BMI. After controlling for these covariates, maternal use of prescription opioids during pregnancy was associated with statistically significant increased odds of delivering a small for gestational age infant, with an adjusted odd ratio (aOR) of 3.18 (95% CI: 1.30, 7.77; $p < 0.05$). Table 3.3 presents the adjusted odds ratios and confidence intervals for the SGA analysis.

In examining the association between prescription opioid use during pregnancy and PTD, the final model included previous PTD, maternal pre-pregnancy chronic disease, pregnancy weight gain adequacy, maternal race/ethnicity, pre-pregnancy BMI, and maternal stress level in addition to opioid use during pregnancy. Use of prescription opioids during pregnancy was not associated with PTD after adjusting for these variables [aOR: 0.71, (95% CI: 0.21,

2.36), $p = 0.5796$]. Table 3.4 shows the adjusted odds ratios and confidence intervals for the PTD analysis.

After controlling for previous LBW delivery, pregnancy weight gain adequacy, maternal race/ethnicity, maternal nativity, maternal pre-pregnancy chronic disease, and federal poverty level, maternal use of prescription opioids during pregnancy was associated with a decreased odds of delivering a LBW infant, with an aOR of 0.17, (95% CI: 0.03, 1.01; $p = 0.0512$). Table 3.5 shows the adjusted odds ratios and confidence intervals for the LBW analysis.

Table 3.1. Prescription Opioid Use during Pregnancy by Maternal Characteristics (Singleton Deliveries)

Maternal characteristics	Total, n* (% of total population)	Prescription opioid use during pregnancy, n* (% reporting use)
Total	54,662 (100)	731 (1.3)
Age (years)		
Less than 30	31,971 (58.5)	488 (1.5)
30 or older	22,691 (41.5)	302 (1.3)
Race/Ethnicity		
Hawaiian or other Pacific Islander^a	20,524 (37.5)	215 (1.0)
White	18,743 (34.3)	363 (2.8)
Asian^b	12,598 (23.0)	113 (0.6)
Other or unknown^c	2,796 (5.1)	100 (3.5)
Marital Status		
Married	33,391 (61.1)	573 (1.7)
Other	21,272 (38.9)	217 (1.0)
Education level		
High school graduate or less	25,514 (47.5)	404 (1.6)
Some college or more	28,231 (52.5)	381 (1.3)
Federal Poverty Level (%)		
Less than or equal to 200%	28,061 (55.4)	434 (1.5)
201% or greater	22,602 (44.6)	318 (1.4)
Parity		
First live birth	22,399 (41.0)	269 (1.2)
Not first live birth	32,232 (59.0)	522 (1.6)
Pre-pregnancy chronic disease^d		
Yes	10,668 (19.5)	323 (3.0)
No	43,994 (80.5)	467 (1.0)
Pre-pregnancy smoking		
Yes	11,286 (21.0)	268 (2.3)
No	42,499 (79.0)	518 (1.2)

* Weighted, rounded to nearest whole number, category-specific estimates may not equal overall total due to rounding and differences in missing values; ^aHawaiian or other Pacific Islander includes: Hawaiian, part Hawaiian, Samoan, Guamanian, and other Pacific Islander; ^bAsian includes: Japanese, Filipino, Chinese, Korean, Vietnamese, Asian Indian, and other Asian; ^cOther or unknown includes: African American, American Indian, Puerto Rican, Cuban, Mexican, and all others; ^dPre-pregnancy chronic disease includes: diabetes, asthma, hypertension, heart problems, epilepsy, thyroid problems, depression and anxiety

Table 3.2. Selected Birth Outcomes by Maternal Demographic Characteristics (Singleton Deliveries)

Maternal characteristics	Total n* (% of total population)	SGA n* (% prevalence)	Preterm n* (% prevalence)	LBW n* (% prevalence)
Total	54,662 (100)	5,065 (9.3)	4,448 (8.2)	3,577 (6.5)
Age (years)				
Less than 30	31,971 (58.5)	3,230 (10.2)	2,464 (7.7)	2,115 (6.6)
30 or older	22,691 (41.5)	1,835 (8.1)	1,985 (8.8)	1,461 (6.4)
Race/Ethnicity				
Hawaiian or other Pacific Islander^a	20,524 (37.5)	1,496 (7.3)	1,722 (8.4)	1,456 (7.1)
Asian^b	18,743 (34.3)	2,392 (12.8)	1,799 (9.6)	1,474 (7.9)
White	12,598 (23.0)	981 (7.8)	680 (5.4)	474 (3.8)
Other or unknown^c	2,796 (5.1)	197 (7.0)	248 (8.9)	173 (6.2)
Maternal nativity				
Born in the United States	40,770 (74.7)	3,651 (9.0)	3,262 (8.0)	2,742 (6.7)
Born outside the United States	13,828 (25.3)	1,414 (10.3)	1,178 (8.5)	834 (6.0)
Marital Status				
Married	33,391 (61.1)	2,795 (8.4)	2,617 (7.9)	1,861 (5.6)
Other	21,272 (38.9)	2,271 (10.7)	1,832 (8.6)	1,716 (8.1)
Education level				
High school graduate or less	25,514 (47.5)	2,473 (9.7)	2,050 (8.1)	1,768 (6.9)
Some college or more	28,231 (52.5)	2,547 (9.0)	2,308 (8.2)	1,759 (6.2)
Federal Poverty Level (%)				
Less than or equal to 200%	28,061 (55.4)	2,592 (9.3)	2,289 (8.2)	1,984 (7.1)
201% or greater	22,602 (44.6)	1,999 (8.9)	1,788 (7.9)	1,274 (5.6)
Parity				
First live birth	22,399 (41.0)	2,675 (12.0)	1,827 (8.2)	1,725 (7.7)
Not first live birth	32,232 (59.0)	2,391 (7.4)	2,622 (8.2)	1,852 (5.7)

* Weighted, rounded to nearest whole number, category-specific estimates may not equal overall total due to rounding and differences in missing values; ^aHawaiian or other Pacific Islander includes: Hawaiian, part Hawaiian, Samoan, Guamanian, and other Pacific Islander; ^bAsian includes: Japanese, Filipino, Chinese, Korean, Vietnamese, Asian Indian, and other Asian; ^cOther or unknown includes: African American, American Indian, Puerto Rican, Cuban, Mexican, and all others

Table 3.3. Adjusted Odds Ratios (aORs) between Selected Maternal Characteristics and SGA

Maternal characteristics	aOR (95% CI)
Opioid use during pregnancy	
Yes	3.18 (1.30-7.77)*
No	Ref
Maternal race/ethnicity	
Hawaiian or other Pacific Islander ^a	0.86 (0.57-1.30)
Asian ^b	1.79 (1.23-2.59)**
White	Ref
Other or unknown ^c	0.90 (0.44-1.84)
Pregnancy weight gain	
Adequate	Ref
Inadequate	1.76 (1.30-2.38)***
Smoking in last trimester	
Yes	1.87 (1.17-2.97)**
No	Ref
Parity	
First live birth	1.84 (1.38-2.45)****
Not first live birth	Ref
Pre-pregnancy BMI	
Underweight (less than 18.5)	1.39 (0.82-2.36)
Normal (18.5-24.9)	Ref
Overweight (25.0-29.9)	0.75 (0.52-1.08)
Obese (30.0 or greater)	0.60 (0.39-0.91)*

*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001

^aHawaiian or other Pacific Islander includes: Hawaiian, part Hawaiian, Samoan, Guamanian, and other Pacific Islander; ^bAsian includes: Japanese, Filipino, Chinese, Korean, Vietnamese, Asian Indian, and other Asian; ^cOther or unknown includes: African American, American Indian, Puerto Rican, Cuban, Mexican, and all others

Table 3.4. Adjusted Odds Ratios (aORs) between Selected Maternal Characteristics and PTD

Maternal characteristics	aOR (95% CI)
Opioid use during pregnancy	
Yes	0.71 (0.21-2.36)
No	Ref
Previous preterm delivery	
Yes	3.87 (2.59-5.80)****
No	Ref
Maternal race/ethnicity	
Hawaiian or other Pacific Islander ^a	1.40 (0.83-2.35)
White	Ref
Asian ^b	1.71 (1.01-2.88)*
Other or unknown ^c	1.86 (0.81-4.24)
Pre-pregnancy BMI	
Underweight (less than 18.5)	1.27 (0.45-3.62)
Normal (18.5-24.9)	Ref
Overweight (25.0-29.9)	1.23 (0.78-1.95)
Obese (30.0 or greater)	1.87 (1.16-3.02)**
Pregnancy weight gain	
Adequate	Ref
Inadequate	1.82 (1.24-2.67)**
Pre-pregnancy chronic disease^d	
Yes	1.57 (1.05-2.35)*
No	Ref
Maternal stress level	
Light (0-2 stressors)	Ref
Heavy (3 or more stressors)	0.54 (0.38-0.77)***

*p<0.05; **p<0.01; ***p<0.001; ****p<0.0001

^aHawaiian or other Pacific Islander includes: Hawaiian, part Hawaiian, Samoan, Guamanian, and other Pacific Islander; ^bAsian includes: Japanese, Filipino, Chinese, Korean, Vietnamese, Asian Indian, and other Asian; ^cOther or unknown includes: African American, American Indian, Puerto Rican, Cuban, Mexican, and all others;

^dPre-pregnancy chronic disease includes: diabetes, asthma, hypertension, heart problems, epilepsy, thyroid problems, depression and anxiety

Table 3.5. Adjusted Odds Ratios (aORs) between Selected Maternal Characteristics and LBW

Maternal characteristics	aOR (95% CI)
Opioid use during pregnancy	
Yes	0.17 (0.03-1.01) ⁺
No	Ref
Previous LBW delivery	
Yes	4.52 (3.09-6.60)****
No	Ref
Maternal race/ethnicity	
Hawaiian or other Pacific Islander ^a	1.55 (0.99-2.43) ⁺
White	Ref
Asian ^b	2.28 (1.49-3.50)***
Other or unknown ^c	1.43 (0.67-3.04)
Federal Poverty Level (%)	
Less than or equal to 200%	1.50 (1.10-2.05)*
201% or greater	Ref
Pregnancy weight gain	
Adequate	Ref
Inadequate	2.37 (1.70-3.29)****
Pre-pregnancy chronic disease^d	
Yes	1.62 (1.13-2.33)**
No	Ref
Maternal nativity	
Born in the United States	Ref
Born outside the United States	0.55 (0.38-0.80)**

⁺0.05<p<0.06; *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001

^aHawaiian or other Pacific Islander includes: Hawaiian, part Hawaiian, Samoan, Guamanian, and other Pacific Islander; ^bAsian includes: Japanese, Filipino, Chinese, Korean, Vietnamese, Asian Indian, and other Asian; ^cOther or unknown includes: African American, American Indian, Puerto Rican, Cuban, Mexican, and all others;

^dPre-pregnancy chronic disease includes: diabetes, asthma, hypertension, heart problems, epilepsy, thyroid problems, depression and anxiety

DISCUSSION

As previously described, despite a well-documented association between opioid use during pregnancy and NAS, other prescription opioid effects on pregnancy are not well understood. All three birth outcomes examined in this project; SGA, PTD, and LBW, are also known to be multifactorial (Goldenberg, Culhane, Iams, & Romero, 2008; McCowan & Horgan, 2009; Valero De Bernabe et al., 2004). This complexity is reflected in the differences in associations observed between prescription opioid use and the three different birth outcomes examined.

Research addressing prescription opioid use in pregnancy and birth outcomes has been incomplete and often conflicting in terms of findings. Previous studies have shown increased risk of all three of the birth outcomes examined in this study (SGA, PTD, LBW) associated with opioid use during pregnancy (Almario, Seligman, Dysart, Berghella, & Baxter, 2009; Hulse, Milne, English, & Holman, 1997; Lam, To, Duthie, & Ma, 1992; Quesada et al., 2012). Yet other studies have found no associations (Bada et al., 2005; Liu, Sithampanathan, Jones, Cook, & Nanan, 2010; Patel et al., 2013; Schempf & Strobino, 2008; Zuckerman et al., 1989). Part of the problem is that research of this type often focuses on individuals with known drug addiction, often enrolled in addiction treatment programs (Hulse et al., 1997; Lam et al., 1992; Liu et al., 2010; Unger et al., 2011). These individuals are often subject to a number of other exposures and adverse circumstances that would not necessarily affect occasional prescription opioid users or those on prescription opioid drug therapy as part of a medically-supervised pain treatment program (Hulse et al., 1997; Lam et al., 1992; Liu et al., 2010; Schempf, 2007). Since the 1990s, prescribing of opioid drugs to the general population (including pregnant and reproductive-age women) has become much more common (Bateman et al., 2014; CDC, 2013). Therefore, it would be expected that a large number, if not the majority, of prescription opioid exposures in pregnancy occur as the result of women taking prescribed medication, often in short courses, under the supervision of a healthcare professional; not as the result of heavy use associated with long term

opioid addiction (Bateman et al., 2014; Flood & Raja, 2014). An additional factor is that the specific opioid drugs studied most frequently are methadone and buprenorphine (Kakko, Heilig, & Sarman, 2008; Patel et al., 2013; Stanhope et al., 2013; Unger et al., 2011). These drugs are important for in addiction-related pregnancy research as they are the medications of choice for treating opioid addicts throughout pregnancy (Kakko et al., 2008; Stanhope et al., 2013), however they are not the most commonly used prescription opioid drugs used in the wider pregnant population (Bateman et al., 2014). As might be expected, different opioid drugs have been documented to have different specific modes of action and effects (Kakko et al., 2008; Patel et al., 2013; Stanhope et al., 2013), so this could cause difficulty in interpretation of findings. In light of all of these dynamics, assuming that associations between opioid use and birth outcomes as observed among individuals in drug abuse treatment programs would hold true for the total population of prescription opioid users does not seem appropriate. There is also a heavy reliance on small case studies or case series reports in research concerning opioid addiction during pregnancy that provide useful information, but lack wider generalizability (Kakko et al., 2008; Lam et al., 1992; Patel et al., 2013; Schempf, 2007; Unger et al., 2011).

The findings of past research studies indicating increased risk of poor birth outcomes associated with prescription opioid use during pregnancy have been called into question for the reasons described above, with some researchers arguing that observed effects are the result of other factors associated with illicit drug abuse instead of the opioids themselves (Schempf, 2007). A prime example of this would be the strong association between smoking and prescription opioid abuse (H. E. Jones et al., 2009; Log et al., 2011; Winklbaaur et al., 2009), as smoking during pregnancy is a well-documented independent risk factor for adverse birth outcomes (Horta, Victora, Menezes, Halpern, & Barros, 1997; McCowan & Horgan, 2009; Winklbaaur et al., 2009). Inadequate nutritional status during pregnancy (Schempf & Strobino, 2008; Tomedi, Bogen, Hanusa, Wisner, & Bodnar, 2012), use of other illicit, prescription, or legal recreational drugs (Handal, Engeland, Ronning, Skurtveit, & Furu, 2011; Patel et al., 2013;

Schempf, 2007; Schempf & Strobino, 2008), and other factors known to frequently co-occur with drug addiction have also been cited as potential sources of confounding in these studies (Schempf, 2007). While some studies have employed different methods in attempts to control for smoking and/or poly substance use (Kakko et al., 2008; Schempf & Strobino, 2008; Winklbaaur et al., 2009), the fact still exists that drug addicts differ from the general population in many ways, and not all of these factors can be fully addressed through non-population based research (Schempf, 2007).

The use of data from the Hawai'i PRAMS survey provides advantages over findings from other data sources due to its being population-based and weighted to be representative of all pregnancies resulting in live births in Hawai'i. This survey also relies on maternal report of use, which has advantages over other research using proxy measures for medication use, such as data from electronic medical records, pharmacy dispensing records, or health insurance claims databases. Data from those sources do not directly address what drugs women used, but instead rely on proxy measures such as what were women prescribed, what prescriptions they filled, and what prescriptions were submitted for insurance coverage. Yet, many people are prescribed medication that they never fill, or fill medication that they never use, or use medication that they never submit for insurance coverage (DiMatteo, 2004; Fischer et al., 2010; Osterberg & Blaschke, 2005; Solomon & Majumdar, 2010). Additionally, none of these data sources address the usage of prescription medication that is not prescribed to the woman herself. This is problematic due to the fact that sharing and borrowing of prescription medication is very common among American women of reproductive age (Petersen et al., 2008). Research has also shown that the levels of agreement between electronic medical data and maternal report of prescription drug use during pregnancy are lowest for prescription opioid medications, compared to other drug types (Sarangarm et al., 2012). Consequently, findings from studies relying on electronic medical records, pharmacy dispensing records, or health insurance claims databases might result in biased findings due to misclassification of exposures (Olesen et al., 2001).

In addition, there is a lack of information regarding prescription opioid use among pregnant populations in Hawai‘i, despite a growing awareness of increasing fatalities and injuries in the general population that have been attributed to use and abuse of these medications. As prescription medication prescribing and drug usage practices differ significantly by geographic region within the United States (Bateman et al., 2014; Wetmore et al., 2011; Zerzan et al., 2006; Zhang et al., 2010), an added advantage of using Hawai‘i PRAMS as a data source for this study is that it provides local data for use by Hawai‘i healthcare providers, researchers, and program staff members to better understand the local landscape with regards to prescription opioid use during pregnancy and associated birth outcomes. The multiethnic nature of the population of Hawai‘i also means that generalizability of research findings from studies conducted outside the state is unclear with regards to many different topics (Kaneshiro et al., 2011; Novotny & Daida, 2009; Sorensen et al., 2003).

The limitations of this project include relatively small unweighted numbers of women who used prescription opioids during pregnancy and experienced the birth outcomes of interest. This limited the complexity of the analyses that were possible. Additional limitations related to the Hawai‘i PRAMS survey itself include that the data are self-reported, and consequently subject to bias due to recall or reporting factors. This could impact the results of this study, as previous investigations have shown that women are more likely to recall use of some types of medications than others when retrospectively asked about medication use during pregnancy (van Gelder et al., 2013). Other studies however have shown that these effects are modest for the time period during which the majority of PRAMS surveys are completed (Tinker et al., 2013). There may also be some effects due to mode bias (mail versus telephone), as respondents who completed the surveys via mail were significantly more likely to report prescription drug use both before and during pregnancy when compared with phone respondents (data not shown). The effects of this mode bias are expected to be minimal though, as approximately 81% of survey respondents completed the Hawai‘i PRAMS questionnaire by mail in the years included in this

analysis. Additionally, PRAMS nonresponse weights are calculated based on assumptions that women in a particular subgroup who responded would be predicted to have similar responses to those who did not respond. It is unclear how valid this assumption may be for the outcomes examined in this study (Halbesleben & Whitman, 2013).

Limitations also exist related to the Hawai'i PRAMS prescription drug use questions. There may have been issues with comprehension of this specific question; for example, some individuals might only list medications that were prescribed to them, not medications they used recreationally. Occasionally, it is not possible to determine exactly which drug was being referenced; for instance, if there were spelling errors that did not allow for reliable determination of which drug was being used. Which medications were being referred to was also sometimes unknown due to the fact that some answers did not specifically refer to drug name (e.g. "painkillers"), some respondents did not know what they took (e.g. "can't remember"), and some respondents indicated that they had used prescription drugs during pregnancy, but then left the space provided for drug names blank. These factors may have resulted in some use of prescription opioids to have been missed. These effects are expected to be minimal however. In this study, there were fewer than 5 (unweighted) cases in total where a drug listed was not able to be reliably identified due to spelling errors, fewer than 10 (unweighted) cases in total where women did not remember or state what type of medication they used during pregnancy and did not provide additional information that could be used to make an informed determination, and fewer than 20 (unweighted) cases in total where the space was left blank, without additional information provided in the comment section that could be used to identify the prescription drug type(s) used. These cases were included in the study along with women indicating use of other non-opioid prescription drugs, but were not included in the prescription opioid drug user group. Cases where respondents indicated that they used prescription pain killers, but did not provide drug names or other information that would indicate that the drugs were opioids, were also included in the study, but not included in the prescription opioid drug

user group. The prevalence estimate for prescription pain reliever use during pregnancy in our population was 3.19% (95% CI: 2.58-3.95) when non-opioid pain medications (e.g. ibuprofen) and non-specific mentions of prescription pain reliever use were included. It is very possible that this estimate contains a number of prescription opioid drugs which have been excluded from the current study due to misclassification as a result of responses not referencing specific drug names. This study prioritized minimizing the number of true non-opioid users included in the opioid user group. This decision is supported by existing research showing that specificity is of greater importance than sensitivity when conducting research on prescription drug use during pregnancy where the overall prevalence of exposure is low (Skurtveit et al., 2013).

As use of prescription opioids by pregnant and reproductive-age women, in addition to the general public, continues to increase, risks specific to pregnant and reproductive-aged women require special attention. The dramatic increase in incidence of NAS in recent years has begun to bring awareness to the issue of prescription opioid use during pregnancy, but more research is needed to determine what other health outcomes might be associated with prenatal opioid exposure. This study indicated that prescription opioid use during pregnancy was associated with significantly increased odds of SGA when compared to non-opioid users, even when controlling for other SGA risk factors. More research is needed to confirm that these findings reflect a true increased risk associated with prescription opioid use during pregnancy. The lack of an association between prescription opioid use and PTD, and the decreased odds of LBW associated with prescription opioid use also require further investigation; preferably with larger sample sizes, and more detailed information on medication dosage, frequency, trimester of exposure, and reasons for use. As different opioid drugs are known to have different specific modes of action and effects, research investigating individual drugs and/or drug combinations would also be incredibly useful.

Without information on frequency, dosage, or whether the individuals in this study were using medication prescribed as part of a treatment regimen overseen by a healthcare provider, it is not possible to determine whether the

opioid use captured in this study reflects occasional use, chronic use, or addiction-related drug abuse. Each of these situations could potentially be addressed differently in the context of a planned or unplanned pregnancy. It is likely that the users of prescription opioids in our population include a spectrum of usage patterns with different causes, effects, and public health implications.

What is known is that, at minimum, hundreds of pregnancies in Hawai'i and thousands of pregnancies in the rest of the country are exposed to prescription opioid drugs every year (Bateman et al., 2014; Epstein et al., 2013; SAMHSA, 2012). What is not known is exactly what effects these drugs are having on women and their fetuses. Existing research findings regarding safety of opioids during pregnancy provide an incomplete and often contradictory picture, and too often rely on non-representative data sources and small case series reports (Hulse et al., 1997; Schempf, 2007). This is no longer acceptable in light of the increasingly widespread usage of these drugs on a population-wide scale. Recent trends indicate that prescription opioid use among pregnant and non-pregnant populations is continuing to increase (CDC, 2013; Epstein et al., 2013). It is imperative that drug safety research catch up with the pace of use of these drugs in order to better inform healthcare providers and their patients going forward.

CHAPTER 4.
STUDY 3: DEPRESSION AND ANXIETY AROUND THE TIME OF
PREGNANCY IN HAWAI‘I

ABSTRACT

Background: Depression and anxiety are common among pregnant and postpartum women, as well as among women of reproductive age in general. When these conditions and other psychiatric disorders occur around the time of pregnancy, they have been associated with poor birth outcomes, decreased maternal health, and continued ill effects throughout infancy and childhood. However, pregnant and postpartum women require special considerations for treatment of psychiatric conditions, which can make medical decisions complicated for healthcare providers. This study sought to describe the prevalence of depression and anxiety, along with pharmaceutical treatment and help-seeking behaviors, among a multiethnic population of women who recently delivered a live infant in the State of Hawai‘i.

Methods: Hawai‘i Pregnancy Risk Assessment Monitoring System (PRAMS) data from 4,735 respondents were used to estimate prevalence of several indicators related to anxiety and depression before, during, and after pregnancy among women with recent live births. Data were weighted to be representative of all pregnancies resulting in live births in Hawai‘i from 2009 to 2011. Prevalence estimates, confidence intervals, and p-values were generated using SAS-callable SUDAAN 10.0 (RTI International, Research Triangle Park, NC).

Results: Of women who delivered a live infant in Hawai‘i between 2009 and 2011, 7.3% reported that they had visited a health care worker to be checked or treated for depression or anxiety in the year before their most recent pregnancy (95% CI: 6.4-8.3). Approximately 4.9% reported that they had depression in the three months before pregnancy (95% CI: 4.2-5.7) and 5.9% reported that they had anxiety in the same time period (95% CI: 5.1-6.8). The total prevalence of antianxiety and antidepressant prescription use was 2.3% in the month before pregnancy (95% CI: 1.8-2.9) and 1.4% during pregnancy (95% CI: 1.0-1.9). An

estimated 9.1% (95% CI: 8.1-10.2) of Hawai'i women with a recent live birth screened positive for postpartum depression (PPD), and 6.9% reported asking a doctor, nurse, or other health care worker for help for anxiety since their new baby was born (95% CI: 6.0-7.9). Women who reported pre-pregnancy depression were significantly more likely to screen positive for PPD than women who did not report depression in the three months before pregnancy ($p < 0.0001$), although among women who reported having depression pre-pregnancy, women who took antidepressant or anti-anxiety medication during pregnancy were not significantly more likely to screen positive for PPD than were those who did not take these types of medications during pregnancy ($p = 0.4029$). Of women who reported having anxiety pre-pregnancy, women who took antidepressant or anti-anxiety medication during pregnancy were significantly more likely to seek help for anxiety in the postpartum period than were those who did not take these types of medications during pregnancy ($p < 0.05$). Additionally, women who reported pre-pregnancy anxiety were more likely overall to report seeking help for anxiety postpartum than women who did not have anxiety in the three months before pregnancy ($p < 0.0001$).

Public Health Implications: Mental health conditions including depression and anxiety are common among pregnant and postpartum populations, and pose treatment challenges for health care providers. More research is needed to fully describe the burden of anxiety and depression around the time of pregnancy, and better inform health care providers and mental health professionals, along with their patients, of potential risks and benefits of different treatment options.

Keywords: Depression, Anxiety, Pregnancy, Psychiatric medication

BACKGROUND

Depression and anxiety are common among pregnant and postpartum women, as well as among women of reproductive age in general (Farr, Dietz, O'Hara, Burley, & Ko, 2014; Ko, Farr, Dietz, & Robbins, 2012; O'Hara & McCabe, 2013; Ross & McLean, 2006; Vesga-Lopez et al., 2008). When these conditions and other psychiatric disorders occur around the time of pregnancy, they have been associated with poor birth outcomes, decreased maternal health, and continued ill effects throughout infancy and childhood (Alder, Fink, Bitzer, Hosli, & Holzgreve, 2007; Dunkel Schetter & Tanner, 2012; Grigoriadis et al., 2013; O'Hara & McCabe, 2013). Treatments available for depression and anxiety include counseling or therapy, behavioral interventions, and prescription medications (Diket & Nolan, 1997; Ko et al., 2012). However, pregnant and postpartum women require special considerations for treatment of psychiatric conditions, which can make medical decisions complicated for healthcare providers (Chaudron, 2013; Diket & Nolan, 1997; McGrath, Buist, & Norman, 1999).

There is much that is not known about the safety and effects of specific psychiatric medications, particularly in pregnancy. Pregnant women are frequently excluded from clinical trials for ethical and methodological reasons, so much of the research regarding medication exposures during pregnancy relies on information extrapolated from animal studies, or on case reports and registries measuring adverse outcomes occurring in populations after the fact (Parisi et al., 2011). Recent studies conducted within the United States show that only 4% of the most commonly-reported medication used during the first trimester of pregnancy had a "Good to Excellent" quality and quantity of safety data available to determine teratogenic potential; the vast majority had insufficient data evidence to determine risks (Thorpe et al., 2013).

Although the primary concern with prescription drug use during pregnancy is avoiding birth defects, that is not the only, or even the most pressing issue regarding the treatment of psychiatric conditions during pregnancy. Healthcare providers treating women with psychiatric conditions must be

concerned with the potential dangers of continuing treatment that has unknown safety throughout pregnancy, and this must be balanced with the dangers of discontinuing treatment (Chaudron, 2013). As has been shown with medications treating other chronic diseases during pregnancy, some providers choose to administer medications at lower levels during pregnancy in an attempt to reduce perceived risks to the fetus (Haramburu et al., 2000; Parisi et al., 2011). However, this risks falling below therapeutic thresholds, and could cause the pregnancy to be complicated by the underlying chronic condition (Haramburu et al., 2000; Parisi et al., 2011). This is problematic with chronic psychiatric conditions, as maternal depression and anxiety have both been independently associated with harmful maternal behaviors during pregnancy as well as poor birth outcomes (Berle et al., 2005; Chaudron, 2013; Martini, Knappe, Beesdo-Baum, Lieb, & Wittchen, 2010; Newport et al., 2012). Patients themselves are also often fearful of potentially harming their fetuses with prescription drugs during pregnancy, and may become noncompliant with necessary treatment as a result (Matsui, 2012). Both of these scenarios are of special concern with regards to psychiatric medications, as reducing or discontinuing medication can cause a relapse of serious psychiatric symptoms, including self-harm behaviors (L. S. Cohen et al., 2006; Koren et al., 2010; Parisi et al., 2011).

Anxiety and depression before, during, and after pregnancy, along with related help-seeking behaviors and treatment strategies, are not well-described for the state of Hawai'i. One previous analysis of Hawai'i PRAMS data from 2004 to 2007 indicated that symptomology consistent with postpartum depression (PPD) was relatively common, with approximately 14.5% reporting PPD symptoms and 30.1% reporting possible PPD symptoms (Hayes, Ta, Hurwitz, Mitchell-Box, & Fuddy, 2010). However, pre-pregnancy anxiety or depression, mental health help-seeking behavior, and use of psychiatric medications before or during pregnancy were not addressed (Hayes et al., 2010). An additional study using 2008 data from the Hawai'i Behavioral Risk Factor Surveillance System (BRFSS) found that Pacific Islander adults had higher rates of severe depression when compared with other race groups in the state (Aczon-Armstrong, Inouye, &

Reyes-Salvail, 2013), but did not examine anxiety, help-seeking behavior, or psychiatric medication use, and did not discuss pregnant women. Hawai'i also has a very unique population in terms of race and ethnicity, with approximately 23% of the population identifying as mixed race (U. S. Census Bureau, 2010), and a far greater percentage identifying as mixed ethnicity (Novotny & Daida, 2009). The multiracial and multiethnic nature of the population of Hawai'i means that generalizability of research findings from studies conducted outside the state is unclear with regards to many different topics (Kaneshiro et al., 2011; Schempf et al., 2010). This study includes data on racial and ethnic groups not commonly reported in the scientific literature (Kaneshiro et al., 2011; Novotny & Daida, 2009; Sorensen et al., 2003) as it sought to describe the prevalence of depression and anxiety, along with pharmaceutical treatment and help seeking behaviors, among a multiethnic population of women who recently delivered a live infant in the State of Hawai'i.

METHODS

Data Source

A secondary data analysis was performed of Hawai'i Pregnancy Risk Assessment Monitoring System (PRAMS) data from 2009 to 2011. PRAMS is a survey of women with recent live births designed to collect information on behaviors, attitudes, and experiences before, during, and immediately after pregnancy. PRAMS operates according to a standardized data collection protocol involving a mailed self-administered survey with follow-up by telephone for mail non-responders. Individuals are selected for participation as part of a stratified sample drawn from certificates of live births in Hawai'i. Respondents complete the survey 3-9 months postpartum, with most responding 3-4 months postpartum. In addition to information collected from PRAMS survey questions, the Hawai'i PRAMS dataset includes selected linked birth certificate variables. Data are weighted annually according to Centers for Disease Control and Prevention (CDC) protocol to be representative of all pregnancies resulting in live births in Hawai'i in a given year. PRAMS programs must achieve a minimum weighted

response rate of 65% for survey results to be considered generalizable to all live births in the participation area in a given year. Annual weighted response rates for Hawai'i PRAMS in the years 2009-2011 ranged from 71-73%. More comprehensive information on PRAMS methodology can be found at <http://www.cdc.gov/prams/Methodology.htm>.

Measures

The following questions were used for this analysis:

At any time during the 12 months before you got pregnant with your new baby, did you do any of the following things? For each item, circle Y (Yes) if you did it or circle N (No) if you did not.

- f. I visited a health care worker to be checked or treated for depression or anxiety

During the 3 months before you got pregnant with your new baby, did you have any of the following health problems? For each item, circle Y (Yes) if you had the problem or circle N (No) if you did not.

- g. Depression
- h. Anxiety

During any of your prenatal care visits, did a doctor, nurse, or other health care worker talk with you about any of the things listed below? Please count only discussions, not reading materials or videos. For each item, circle Y (Yes) if someone talked with you about it or circle N (No) if no one talked with you about it.

- k. What to do if I feel depressed during my pregnancy or after my baby is born

Below is a list of feelings and experiences that women sometimes have after childbirth. Read each item and determine how well it describes your

feelings and experiences. Then, write on the line the number of the choice that best describes how often you have felt or experienced things this way since your new baby was born. Use the scale when answering:

1 Never 2 Rarely 3 Sometimes 4 Often 5 Always

- a. I felt down, depressed, or sad
- b. I felt hopeless
- c. I felt slowed down

Since your baby was born, have you asked for help for anxiety from a doctor, nurse, or other health care worker?

No

Yes

Did you use any of these drugs in the month before you got pregnant? For each item, circle Y (Yes) if you used it or circle N (No) if you did not.

- a. Prescription drugs

If yes, what kinds? Please tell us: _____

Did you use any of these drugs when you were pregnant? For each item, circle Y (Yes) if you used it or circle N (No) if you did not.

- a. Prescription drugs

If yes, what kinds? Please tell us: _____

Write-in responses to the prescription drug questions were manually reviewed to correct for misspellings, multiple drugs listed, and other factors. When initial determination was difficult, clinicians and other resources were consulted to determine which drug was being referenced. Responses were coded into category groups using SAS 9.2 “string” and “upcase” commands. Medications with possible indications in multiple groups were cross-checked with maternal and/or birth certificate report of diagnoses to determine most likely group for categorization. For example, drugs such as Lamotrigine that could be prescribed

for psychiatric or non-psychiatric conditions were cross-checked with maternal report of medical conditions to determine the most likely categorization, and then were individually coded by unique ID number. Entries of more than 30 characters were listed in separate comment file, which was also manually reviewed, with responses coded into groupings by unique ID number. The following prescription drugs (alone or in combination) were reported as used either before or during pregnancy in our dataset and were included in this analysis: Alprazolam, Amitriptyline, Aripiprazole, Bupropion, Buspirone, Citalopram, Clozapine, Clonazepam, Diazepam, Desvenlafaxine, Duloxetine, Escitalopram, Fluoxetine, Fluvoxamine, Lamotrigine, Lorazepam, Nortriptyline, Paroxetine, Quetiapine, Sertraline, Trazodone, and Venlafaxine. Entries that did not specifically list drug names, but instead included a reference to non-specific antidepressant or anxiety medication were also included. Prevalence estimates, confidence intervals (CI), and p-values were produced using SAS-callable SUDAAN 10.0 (RTI International, Research Triangle Park, NC) to account for complex sampling.

Maternal age, race/ethnicity, education level, marital status, and parity were determined based on linked birth certificate variables included in the Hawai'i PRAMS dataset. The maternal race/ethnicity variables included in the Hawai'i PRAMS dataset were sorted into single race/ethnic groups based on a standard algorithm used by the Hawai'i Department of Health Office of Health Status and Monitoring (Sorensen et al., 2003). Federal Poverty Level (FPL) was based on maternal report in the Hawai'i PRAMS survey of annual household income and number of dependents in the year before delivery, and was calculated according to year-specific Hawai'i-specific threshold guidelines. Postpartum depression was assessed using the Hawai'i PRAMS question asking about feelings and experiences that women sometimes have after childbirth, along with three subparts where respondents use a Likert scale. Based on question analysis and testing conducted by the CDC in coordination with the University of Iowa, CDC recommends using a cut off of greater than or equal to 10 as an indication of postpartum depressive symptoms. This cut off point is calculated by adding parts a, b & c of the depression question together (depressed, hopeless, and slowed

down). This provides a sensitivity of 57%, a specificity of 87% (O'Hara et al., 2012).

RESULTS

Data for 4,735 respondents were used in this study. Maternal demographic characteristics and selected maternal mental health indicators before and during pregnancy are shown in Table 4.1. Pre-pregnancy depression prevalence estimates differed significantly by maternal race/ethnicity ($p < 0.0001$) and FPL ($p < 0.05$). Differences in prevalence of pre-pregnancy anxiety by maternal race/ethnicity were also statistically significant ($p < 0.0001$). PPD estimates differed significantly by FPL ($p < 0.01$), and differences in PPD by maternal age were borderline statistically significant ($p = 0.0544$). Prevalence of postpartum seeking help for anxiety differed significantly for the following demographic variables: FPL ($p < 0.01$), maternal race/ethnicity ($p < 0.05$), and maternal education level ($p < 0.05$).

Among women who delivered a live infant in Hawai'i between the beginning of 2009 and end of 2011, 7.3% reported that they had visited a health care worker to be checked or treated for depression or anxiety in the year before their most recent pregnancy (95% CI: 6.4-8.3). Of the women who reported visiting a healthcare worker to be checked or treated for depression or anxiety in the year before pregnancy, 58.6% reported that they had depression or anxiety in the three months before they became pregnant (95% CI: 52.0-65.0). Overall, 4.9% of women with recent live births in Hawai'i reported that they had depression in the three months before pregnancy (95% CI: 4.2-5.7), and 5.9% reported that they had anxiety in the same time period (95% CI: 5.1-6.8). There was significant overlap between the two groups; 7.6% reported suffering from anxiety, depression, or both in the three months before pregnancy (95% CI: 6.7-8.6). Among women who attended prenatal care, 66.8% reported that a doctor, nurse, or other health care worker talked with them about what to do if they feel depressed during or after pregnancy (95% CI: 65.0-68.5). This prevalence was only slightly higher for women who reported pre-pregnancy depression, with

73.0% (95% CI: 65.4-68.3) reporting discussion of this topic during prenatal care, compared to 66.5% (95% CI: 64.7-79.4) of women who did not report suffering from depression pre-pregnancy ($p = 0.0977$).

The total prevalence of antianxiety and antidepressant prescription use was 2.3% in the month before pregnancy (95% CI: 1.8-2.9) and 1.4% during pregnancy (95% CI: 1.0-1.9). Among women who indicated that they had depression in the three months before pregnancy, 27.8% reported that they took either antidepressant or antianxiety medication in the month before pregnancy (95% CI: 21.2-35.7), and 18.7% reported that they took either type of medication during pregnancy (95% CI: 13.0-26.0). Of women who indicated that they had anxiety in the three months before pregnancy, 23.5% reported that they took either antidepressant or antianxiety medication in the month before pregnancy (95% CI: 17.8-30.3), and 11.4% reported that they took either type of medication during pregnancy (95% CI: 7.4-17.0). Of women with depression, anxiety, or both in the three months before pregnancy, 25.4% reported that they took antidepressant or antianxiety medication in the month before pregnancy (95% CI: 20.1-31.5), and 13.8% reported that they took these medications during pregnancy (95% CI: 9.8-19.0). Among women who reported taking antidepressant and/or antianxiety medication in the month before pregnancy, 52.2% also reported taking these types of medications during pregnancy (95% CI: 40.3-63.8).

Overall, 9.1% (95% CI: 8.1-10.2) of Hawai'i women with a recent live birth screened positive for postpartum depression (PPD) using the PRAMS survey screen, and 6.9% reported asking a doctor, nurse, or other health care worker for help for anxiety since their new baby was born (95% CI: 6.0-7.9). Among women who reported having depression pre-pregnancy, women who took antidepressant or antianxiety medication during pregnancy were not significantly more likely to screen positive for PPD at the time of the Hawai'i PRAMS survey 3-9 months postpartum than were those who did not take these types of medications during pregnancy (51.2% vs. 42.2%; $p = 0.4029$). Women who reported pre-pregnancy depression were however significantly more likely to screen positive for PPD than women who did not report depression in the three

months before pregnancy (43.8% vs. 7.2%; $p < 0.0001$). These findings are summarized in Table 4.2. There was no statistically significant difference in PPD prevalence between women who did and did not discuss depression during or after pregnancy with a health care worker during prenatal care (8.8% vs. 9.8%; $p = 0.3880$).

Of women who reported having anxiety pre-pregnancy, women who took antidepressant or anti-anxiety medication during pregnancy were significantly more likely to seek help for anxiety in the postpartum period than were those who did not take these types of medications during pregnancy (57.4% vs. 28.0%; $p < 0.05$). Additionally, women who reported pre-pregnancy anxiety were significantly more likely overall to report seeking help for anxiety postpartum than women who did not have anxiety in the three months before pregnancy (31.4% vs. 5.3%; $p < 0.0001$). These findings are summarized in Table 4.3.

Table 4.1. Selected Mental Health Indicators by Maternal Characteristics

Maternal characteristics	Total n* (% of total population)	Pre-pregnancy Depression n* (% prevalence)	Pre-pregnancy Anxiety n* (% prevalence)	Postpartum Depression n* (% prevalence)	Postpartum Sought Help for Anxiety n* (% prevalence)
Total	55,691 (100)	2,694 (4.9)	3,223 (5.9)	5,048 (9.1)	3,704 (6.9)
Age (years)					
Less than 20	4,044 (7.3)	216 (5.4)	183 (4.6)	298 (7.4)	299 (7.5)
20-24 years old	13,160 (23.6)	759 (5.8)	837 (6.4)	1,265 (9.6)	995 (7.8)
25-29 years old	15,205 (27.3)	780 (5.2)	905 (6.0)	1,660 (10.9)	935 (6.3)
30-34 years old	13,602 (24.4)	570 (4.2)	787 (5.9)	1,219 (9.0)	815 (6.1)
35 or older	9,681 (17.4)	369 (3.9)	511 (5.4)	606 (6.3)	660 (7.2)
Race/Ethnicity					
Hawaiian	16,738 (30.1)	918 (5.5)	1,057 (6.4)	1,776 (10.6)	970 (6.0)
White	12,813 (23.0)	853 (6.8)	1,158 (9.2)	1,232 (9.6)	818 (6.5)
Filipina	9,922 (17.8)	226 (2.3)	252 (2.6)	829 (8.4)	653 (6.9)
Japanese	5,191 (9.3)	159 (3.1)	202 (3.9)	430 (8.3)	243 (4.8)
Other Pacific Islander^a	4,113 (7.4)	#	#	189 (4.6)	498 (12.6)
Other Asian^b	4,034 (7.2)	152 (3.8)	168 (4.2)	295 (7.3)	260 (6.6)
Other or unknown^c	2,880 (5.2)	364 (12.9)	345 (12.1)	297 (10.3)	263 (9.5)
Marital Status					
Married	34,081 (61.2)	1,522 (4.5)	2,018 (6.0)	2,909 (8.5)	2,052 (6.2)
Other	21,610 (38.8)	1,172 (5.5)	1,206 (5.6)	2,140 (9.9)	1,651 (7.9)
Education level					
Less than high school	4,097 (7.5)	204 (5.0)	214 (5.3)	258 (6.3)	413 (10.7)
High school graduate	21,743 (39.7)	1,160 (5.4)	1,433 (6.7)	2,058 (9.5)	1,568 (7.4)
Some college or more	28,915 (52.8)	1,310 (4.6)	1,555 (5.5)	2,634 (9.1)	1,626 (5.8)
Federal Poverty Level (%)					
Less than or equal to 100%	15,138 (29.3)	939 (6.3)	886 (5.9)	1,780 (11.8)	1,364 (9.3)
101 – 200%	13,427 (26.0)	638 (4.8)	675 (5.1)	1,174 (8.7)	763 (5.9)
201% or greater	23,099 (44.7)	859 (3.8)	1,324 (5.8)	1,731 (7.5)	1,224 (5.4)
Parity					
First live birth	22,598 (40.6)	979 (4.4)	1,122 (5.0)	2,191 (9.7)	1,574 (7.2)
Not first live birth	33,062 (59.4)	1,714 (5.2)	2,101 (6.4)	2,857 (8.6)	2,123 (6.6)

*Weighted, rounded to nearest whole number, category-specific estimates may not equal overall total due to rounding and differences in missing values;

[#]Number too small to report; ^aOther Pacific Islander includes: Samoan, Guamanian, and other Pacific Islander; ^bOther Asian includes: Chinese, Korean,

Vietnamese, Asian Indian, and other Asian; ^cOther or unknown includes: African American, American Indian, Puerto Rican, Cuban, Mexican, and all others

Table 4.2. Postpartum Depression (PPD) Prevalence, by Pre-Pregnancy Depression and Pregnancy Treatment Status

Pre-pregnancy Depression and Pregnancy Treatment Status	PPD N*	PPD % prevalence (95% CI)	P-value
Total	5,048	9.1 (8.1-10.2)	
No pre-pregnancy depression reported	3,771	7.2 (6.3-8.3)	
Pre-pregnancy depression reported	1,181	43.8 (36.1-51.9)	p < 0.0001
Medication^a used during pregnancy	257	51.2 (32.6-69.4)	
No medication^a used during pregnancy	924	42.2 (33.8-51.1)	p = 0.4029

*Weighted, rounded to nearest whole number, category-specific estimates may not equal overall total due to rounding and differences in missing values; ^aMedication includes the following drugs, alone or in combination: Alprazolam, Amitriptyline, Aripiprazole, Bupropion, Buspirone, Citalopram, Clozapine, Clonazepam, Diazepam, Desvenlafaxine, Duloxetine, Escitalopram, Fluoxetine, Fluvoxamine, Lamotrigine, Lorazepam, Nortriptyline, Paroxetine, Quetiapine, Sertraline, Trazodone, and Venlafaxine.

Table 4.3. Postpartum Anxiety (PPA) Help-Seeking Prevalence, by Pre-Pregnancy Anxiety and Pregnancy Treatment Status

Pre-pregnancy Anxiety and Pregnancy Treatment Status	PPA help seeking N*	PPA help seeking % prevalence (95% CI)	P-value
Total	3,704	6.9 (6.0-7.9)	
No pre-pregnancy anxiety reported	2,675	5.3 (4.5-6.3)	
Pre-pregnancy anxiety reported	995	31.4 (24.9-38.7)	p < 0.0001
Medication^a used during pregnancy	210	57.4 (35.7-76.6)	
No medication^a used during pregnancy	785	28.0 (21.4-35.6)	p = 0.0108

*Weighted, rounded to nearest whole number, category-specific estimates may not equal overall total due to rounding and differences in missing values; ^aMedication includes the following drugs, alone or in combination: Alprazolam, Amitriptyline, Aripiprazole, Bupropion, Buspirone, Citalopram, Clozapine, Clonazepam, Diazepam, Desvenlafaxine, Duloxetine, Escitalopram, Fluoxetine, Fluvoxamine, Lamotrigine, Lorazepam, Nortriptyline, Paroxetine, Quetiapine, Sertraline, Trazodone, and Venlafaxine.

DISCUSSION

The findings presented in this study illustrate the complexity of the mental health issues surrounding pregnancy in Hawai‘i. Both depression and anxiety are common among recently-pregnant women in Hawai‘i, and there is significant overlap between the two conditions. However, there are also differences in both conditions by demographic factors, and these differences do not necessarily track in exactly the same way. For example, racial and ethnic differences related to pre-pregnancy anxiety, pre-pregnancy depression, and post-partum anxiety help-seeking behaviors were all statistically significant in our population, while differences in PPD were not ($p = 0.1425$). This may be related to the fact that PPD in this study was measured through use of a validated screening tool, whereas the other indicators were based on maternal report of the condition/behavior. If so, this may imply that observed differences in pre-pregnancy anxiety, pre-pregnancy depression, and post-partum anxiety help-seeking reflect differences or bias related to reporting, possibly including social desirability factors. In either case however, the other Pacific Islander group (which includes Samoan, Guamanian, and other non-Hawaiian Pacific Islanders) is especially interesting for the fact that so few women reported pre-pregnancy anxiety that the numbers were not reportable (fewer than 5 unweighted cases), however the estimates for post-partum help-seeking for anxiety were higher than any other race/ethnic group at 12.6% (95% CI: 8.4-18.5). More in-depth research is needed on this group to fully understand if these numbers are reflecting unmet need, differences related to reporting or something else entirely.

This study was the first to examine use of psychiatric medication through analysis of the Hawai‘i PRAMS dataset. While the prevalence estimates for anxiety and depression medication use before and during pregnancy in Hawai‘i are novel on their own, the additional inclusion of other mental health indicators helps to provide a more detailed picture of the larger setting in which use of these medications is taking place. The finding that approximately one in four Hawai‘i women with depression, anxiety, or both before pregnancy also reported that they took antidepressant or anti-anxiety medication before pregnancy shows that

psychiatric medication use is relatively common among women with pre-depression or anxiety in Hawai'i. However, this study also showed that almost half of women who used these drugs before pregnancy discontinued when they became pregnant. Discontinuation rates during pregnancy in this population are likely to be even higher than 50% if one assumes that some of these women had unintended pregnancies, of which approximately half of all pregnancies are (Gutmacher Institute, 2012), that resulted in inadvertent drug exposures early in pregnancy, with later cessation of medication use once the pregnancy was discovered. Although the Hawai'i PRAMS survey does not collect information on psychiatric treatment plans or medical oversight of medication use, this is important information for health care providers in light of concerns about psychiatric medications noncompliance during pregnancy (L. S. Cohen et al., 2006; Koren et al., 2010; Matsui, 2012; Parisi et al., 2011). More investigation is needed to determine if the anxiety and/or depression medication cessation in pregnancy observed in this study reflects medically-supervised changes in treatment plans, prescription medication noncompliance, or perhaps occasional and/or recreational use of psychiatric medication that may or may not be prescribed to the individual using it.

The examination of PPD and postpartum anxiety help-seeking behavior in light of pre-pregnancy anxiety and depression and prescription drug use during pregnancy attempted to take a preliminary look at post-partum mental health outcomes while controlling for confounding by indication. Although our sample size prevented more complex analysis of the issue as part of this study, the initial results as reported in tables 4.2 and 4.3 are intriguing. The increased risk of PPD associated with pre-pregnancy depression was expected and is in line with previous research (Chaudron, 2013; O'Hara & McCabe, 2013). The lack of a significant difference in PPD estimates among previously-depressed women who did or did not use antidepressant or antianxiety medication during pregnancy was more interesting. While the first impression might be that taking psychiatric medication during pregnancy does not affect PPD risk, it could also be postulated that women with more severe depression were more likely to be treated with

psychiatric medication than were women with mild depression, in effect “bringing them down” to the risk level of the women with milder depression. A similar phenomenon could be used to explain the opposite results related to anxiety that were presented in Table 4.3; that perhaps women with more severe anxiety were more likely to be on medication during pregnancy and also more likely to seek help for their anxiety following delivery (illness severity being the confounding factor). However, it is important to remember that the Hawai‘i PRAMS survey question addressing PPD is a validated PPD screen, whereas the postpartum anxiety question does not screen for anxiety itself, but rather asks if the respondent has asked for help for anxiety from a doctor, nurse, or other health care worker since her new baby was born. Additionally, it is also possible that women who used prescription anxiety medication during pregnancy might interpret following up with a mental health professional in order to refill or modify their prescription medication as “asking for help for anxiety from a doctor, nurse, or other health care worker.” In that way, question interpretation alone could be partially or entirely responsible for the results presented in Table 4.3.

The use of the Hawai‘i PRAMS dataset has advantages when compared to findings using other datasets due to its being population-based and weighted to be representative of all pregnancies resulting in live birth in the State of Hawai‘i. Hawai‘i PRAMS relies on maternal report of prescription medication, which has benefits over other research relying on proxy measures for medication use, such as data from electronic medical records, pharmacy dispensing records, or health insurance claims databases. Findings from studies using data sources such as such as electronic medical records, pharmacy dispensing records, or health insurance claims databases might provide biased results resulting from misclassification of exposures due to noncompliance or medication sharing (Olesen et al., 2001; Skurtveit et al., 2013). This is of special concern for psychiatric medications, as it has been previously illustrated that women may become noncompliant with regards to prescribed medications out of concern for the effect of the drugs on their fetus (Matsui, 2012).

There are some limitations related to the Hawai‘i PRAMS survey itself, including the fact that the data are self-reported, and consequently subject to bias due to recall or reporting factors, including in some manners which have been previously discussed here. This could impact the findings of this study, as research has shown that women are more likely to recall use of some types of medications than others when retrospectively asked about medication use during pregnancy (van Gelder et al., 2013). These effects are expected to be modest for the time period during which the majority of PRAMS surveys are completed based on previous research however (Tinker et al., 2013). There may also be some effects as a result of mode bias (i.e. mail versus telephone survey completion), as mothers who completed the surveys via mail were significantly more likely to report prescription drug use both before and during pregnancy (data not shown). Nevertheless, the vast majority (81%) of survey respondents completed the Hawai‘i PRAMS questionnaire by mail between 2009 and 2011, so the effects of mode bias are expected to be minimal. Also, PRAMS nonresponse weights are generated based on assumptions that women in a particular subgroup who responded would be expected to have similar responses to those who did not respond, but is unclear how valid this assumption is for the outcomes examined here (Halbesleben & Whitman, 2013).

There are also limitations intrinsic to the Hawai‘i PRAMS prescription drug use questions in particular. For example, there may have been issues with comprehension of this specific question. This comprehension issue could manifest in some individuals only reporting use of medications that were prescribed to them, not medications they used recreationally. Also, which medications were being referred to was sometimes unknown. This was due to the fact that some answers did not specifically refer to drug name (e.g. “antidepressants”), some women did not know what they took (e.g. “something for anxiety”), some women did not remember what kind of medication they used at all (e.g. “can’t remember”), sometimes it was not possible to determine exactly which drug was being referenced for other reasons (e.g. spelling errors that made determination of drug type impossible), and some respondents indicated that they

had used prescription drugs during pregnancy, but then left the space provided for drug names blank. These factors may have resulted in some use of prescription anxiety or depression medication to have been missed. The impacts of these factors are however expected to be minimal. In the study described here, there were fewer than 5 (unweighted) cases in which a drug listed was not able to be reliably identified due to spelling errors, fewer than 10 (unweighted) cases in which women did not remember or state what type of medication they used during pregnancy and did not provide additional information that could be used to make an informed determination, and fewer than 20 (unweighted) cases in which the space was left blank, without additional information provided in the comment section that could be used to identify the prescription drug type(s) used. These cases were included in the study along with women indicating use of other non-anxiety or antidepressant drugs, but were not included in the prescription anxiety or antidepressant drug user group. It is possible that true use of prescription drugs used for anxiety or depression were missed in some of these cases, however, this study prioritized minimizing the number of true non-users included in the anxiety or antidepressant drug user group.

For this project specifically, relatively small unweighted numbers of women who used prescription antidepressants or anxiety medications during pregnancy and reported the other outcomes of interest limited the complexity of the analyses that were possible. Also, small numbers issues when looking at specific drugs, in combination with the frequency of multiple drugs being listed for single individuals, necessitated grouping prescription different antidepressants or anxiety medications (with different mechanisms of action and potential side effects) together. For these reasons related to small numbers and polypharmacy, as well as current trends in treatment and prescribing practices making exact determinations of reasons for specific drugs' use difficult, antidepressants and anxiety medications were combined into a single group.

The Hawai'i PRAMS survey questions related to prescription drug use did not include information related to prescription dosages, frequency of use, pregnancy trimester of usage, or whether or not the medication was prescribed to

the individual taking it. This lack of detail precludes usage of these findings to create or modify mechanistic or safety guidelines, but does not limit its use in encouraging future research projects that would investigate these matters.

Mental health conditions including depression and anxiety are very common among pregnant and postpartum populations, and pose many treatment challenges for health care providers (Diket & Nolan, 1997; Dunkel Schetter & Tanner, 2012). This study reflects a preliminary step in an attempt to more fully describe the mental health landscape as it relates to pregnancy in Hawai‘i. More research is needed to fully describe the burden of anxiety and depression around the time of pregnancy, associated risk factors, and the risks and benefits of different treatment strategies. This information is crucial for mental health providers, public health workers, and women who are pregnant or may become pregnant. Yet at the same time, the available research is severely lacking, both within and outside the state of Hawai‘i. More study is sorely needed in order to better inform providers, patients, and researchers moving forward.

CHAPTER 5.

CONCLUSION

Prescription drug use during pregnancy is common in the state of Hawai‘i, in line with national and international trends. Information on drug safety during pregnancy for many of the most common prescription medications is lacking however. This dissertation focused on prescription opioids and medications used to treat anxiety and depression; drugs of special concern due to their prevalence and potential risks associated with their use. The findings covered in the three research studies all underscore the complexity of the landscape within which women and their healthcare providers are operating.

The first two studies both centered on prescription opioid use, with study one seeking to determine the prevalence of prescription opioid drug use during pregnancy in Hawai‘i, describe differences by maternal demographic characteristics, and examine possible predictors of prescription opioid drug use during pregnancy. Study two on the other hand attempted to determine whether prescription opioid use during pregnancy was associated with poorer birth outcomes among users when compared to non-users in Hawai‘i. Both emphasized the intricacy of the environmental and behavioral milieus in which opioid exposed pregnancies occur.

The first study identified maternal pre-pregnancy chronic disease, race/ethnicity, and smoking status as factors significantly associated with prescription opioid use during pregnancy. These findings were not surprising, and generally fell in line with what little research exists on the topic. The findings of the second study, addressing prescription opioid use during pregnancy and selected birth outcomes, were less straightforward. This study showed that prescription opioid use during pregnancy was associated with increased odds of SGA when compared to non-opioid users, even when controlling for other SGA risk factors. At the same time, it demonstrated that there was not a significant association between prescription opioid use during pregnancy and PTD, and that there were decreased odds of LBW associated with prescription opioid use during

pregnancy. Previous research on prescription opioid use during pregnancy has produced wildly inconsistent findings with respect to these birth outcomes. This is most likely a result of focusing on opioid drug addicts in treatment programs as study subjects paired with inconsistent study designs, small sample sizes, and inadequate controlling for confounding factors. The research findings presented in study two provide a more population-based perspective, which confirmed that hundreds of pregnancies in Hawai‘i are exposed to prescription opioids every year, and underscored the need for more comprehensive research into associated birth outcomes in the future, ideally with larger sample sizes, and more detailed medication information.

Study three was a departure from the topic of opioid use during pregnancy, but stayed within the theme of examining common and potentially problematic prescription drug exposures during pregnancy. The initial focus was to center on the examination of PPD and postpartum anxiety help-seeking behavior in light of pre-pregnancy anxiety and depression and prescription drug use during pregnancy. This was to be a first attempt at addressing the effects of prescription psychiatric drug use on postpartum mental health outcomes, while controlling for potential confounding by indication. Once the project began however, it was clear that there were several other understudied variables related to anxiety and depression included in the Hawai‘i PRAMS dataset that might be useful to examine in order to get a more complete and descriptive picture of the mental health landscape before, during, and immediately following pregnancy in Hawai‘i. At the same time, sample size limitations prevented more complex analysis related to the confounding by indication issue, so it was decided to take a more holistic perspective, while at the same time presenting some intriguing findings that could hopefully inspire future research into the topic.

Study three also illustrated the issue of the risk-benefit analysis inherent in discussions of prescription drug use during pregnancy. As described previously, there are potential risks associated with both the use of prescription anxiety and/or depression medication during pregnancy, as well as with the discontinuation of these medications during pregnancy. The tragedy is that such difficult

calculations as these are being undertaken by healthcare professionals and pregnant women without a sufficient research base to inform these decisions. Study three reported a great deal of information that has not been available elsewhere to this point, but more than anything it is a call to action for more research into anxiety and depression around the time of pregnancy, along with its associated risk factors, and the risks and benefits of treatment strategies involving prescription psychiatric medications.

The findings from the three studies covered in this dissertation confirm that prescription opioid drugs, as well as prescription medications treating anxiety and depression, are frequently used during pregnancy in Hawai‘i. These studies also provide detailed information on local usage patterns, differences by relevant demographic characteristics, and associated risk factors and birth and maternal health outcomes. But more importantly, all three studies serve to highlight the dearth of information that currently exists with regards to prescription drug use during pregnancy. While the findings presented in this dissertation are expected to significantly contribute to the existing research on prescription drug use during pregnancy, both within and outside the state of Hawai‘i, it is hoped that they will also inspire future researchers to pick up where this dissertation leaves off, so that they may also make meaningful contributions to a body of literature that is currently falling short of meeting the needs of pregnant women and their healthcare providers.

APPENDIX.
HUMAN SUBJECTS PROTECTIONS DOCUMENTATION

**Memorandum**

Date March 8, 2013

From Felecia Peterson
IRB-G Administrator, Human Research Protection Office

Subject IRB Approval of Continuation #13 of CDC Protocol #2233, "Pregnancy Risk Assessment Monitoring System (PRAMS)" (Expedited)

To Leslie Harrison, MPH
NCCDPHP/DRH

CDC's IRB-G has reviewed and approved your request to continue protocol #2233 for the maximum allowable period of one year and it will expire on 3/11/2014. The protocol was reviewed in accordance with the expedited review process outlined in 45 CFR 46.110(b)(1), category 7. Active research; contact with subjects continuing.

If other institutions involved in this protocol are being awarded CDC funds through the CDC Procurement and Grants Office (PGO), you are required to send a copy of this IRB approval to the CDC PGO award specialist handling the award. You are also required to verify with the award specialist that the awardees has provided PGO with the required documentation and has approval to begin or continue research involving human subjects as described in this protocol.

As a reminder, the IRB must review and approve all human subjects' research protocols at intervals appropriate to the degree of risk, but not less than once per year. There is no grace period beyond one year from the last IRB approval date. It is ultimately your responsibility to submit your research protocol for continuation review and approval by the IRB along with available IRB approvals from all collaborators. Please keep this approval in your protocol file as proof of IRB approval and as a reminder of the expiration date. **To avoid lapses in approval of your research and the possible suspension of subject enrollment and/or termination of the protocol, please submit your continuation request along with all completed supporting documentation at least six weeks before the protocol's expiration date of 3/11/2014.**

Any problems of a serious nature must be brought to the immediate attention of the CDC IRB, and any proposed changes to the protocol should be submitted as an amendment to the protocol for CDC IRB approval before they are implemented.

If you have any questions, please contact your National Center Human Subjects Contact or the CDC Human Research Protection Office (404) 639-7570 or e-mail: huma@cdc.gov.

cc:

Joan Redmond-Leonard
Shanna Cox

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Centers for Disease Control
and Prevention (CDC)

Carolyn Leighton



Memorandum

Date March 3, 2014

From Felecia Peterson
IRB-G Administrator, Human Research Protection Office

Subject IRB Approval of Continuation #14 of CDC Protocol #2233, "Pregnancy Risk Assessment Monitoring System (PRAMS)" (Expedited)

To Leslie Harrison, MPH
NCCDPHP/DRH

CDC's IRB-G has reviewed and approved your request to continue protocol #2233 for the maximum allowable period of one year and it will expire on **3/11/2015**. The protocol was reviewed in accordance with the expedited review process outlined in 45 CFR 46.110(b)(1), category 7. Active research; contact with subjects continuing.

If other institutions involved in this protocol are being awarded CDC funds through the CDC Procurement and Grants Office (PGO), you are required to send a copy of this IRB approval to the CDC PGO award specialist handling the award. You are also required to verify with the award specialist that the awardees has provided PGO with the required documentation and has approval to begin or continue research involving human subjects as described in this protocol.

As a reminder, the IRB must review and approve all human subjects' research protocols at intervals appropriate to the degree of risk, but not less than once per year. There is no grace period beyond one year from the last IRB approval date. It is ultimately your responsibility to submit your research protocol for continuation review and approval by the IRB along with available IRB approvals from all collaborators. Please keep this approval in your protocol file as proof of IRB approval and as a reminder of the expiration date. **To avoid lapses in approval of your research and the possible suspension of subject enrollment and/or termination of the protocol, please submit your continuation request along with all completed supporting documentation at least six weeks before the protocol's expiration date of 3/11/2015.**

Any problems of a serious nature must be brought to the immediate attention of the CDC IRB, and any proposed changes to the protocol should be submitted as an amendment to the protocol for CDC IRB approval before they are implemented.

If you have any questions, please contact your National Center Human Subjects Contact or the CDC Human Research Protection Office (404) 639-4961 or e-mail: huma@cdc.gov.

cc:
Joan Redmond-Leonard

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Centers for Disease Control
and Prevention (CDC)

Carolyn Leighton

NEIL ABERCROMBIE
GOVERNOR OF HAWAII



LORETTA J. FUDDY, A.C.S.W., M.P.H.

DIRECTOR OF HEALTH

STATE OF HAWAII
DEPARTMENT OF HEALTH


P.O. Box 3378

HONOLULU, HAWAII 96801-3378

October 15, 2103

In reply, please refer to:
File:

TO: Terri Byers
Chief, MCHB

FROM: Catherine A. Sorensen, Dr. PH 
Chair, DOH Institutional Review Board

RE: Approval of PRAMS Continuation

The Department of Health's Institutional Review Board has reviewed your continuation application for: *PRAMS* under expedited review. Your application qualifies for expedited review under 45 CFR 46.110 and 21 CFR 56.110, category 7 of the DHHS list of expedited review categories.

Your project with sample distribution modifications is approved for continuation through October 31, 2014. Your research is subject to Department of Health review for any scholarly or scientific papers resulting from this work. This committee must review any articles prepared for scientific publication prior to publication.

If you have any questions, please contact Betty Wood at 586-4530.

c:  Emily Roberson



UNIVERSITY
of HAWAII[°]
MĀNOA

Office of Research Compliance
Human Studies Program

November 1, 2013

TO: Emily Roberson
Principal Investigator
Public Health Sciences

FROM: Denise A. Lin-DeShetler, MPH, MA
Director

A handwritten signature in black ink, appearing to read "Denise A. Lin-DeShetler".

SUBJECT: CHS #21607- "Prescription Drug Use During Pregnancy in Hawaii"

This letter is your record of the Human Studies Program approval of this study as exempt.

On November 1, 2013, the University of Hawai'i (UH) Human Studies Program approved this study as exempt from federal regulations pertaining to the protection of human research participants. The authority for the exemption applicable to your study is documented in the Code of Federal Regulations at 45CFR 46.101(b)(Exempt Category 4).

Exempt studies are subject to the ethical principles articulated in The Belmont Report, found at <http://www.hawaii.edu/irb/html/manual/appendices/A/belmont.html>.

Exempt studies do not require regular continuing review by the Human Studies Program. However, if you propose to modify your study, you must receive approval from the Human Studies Program prior to implementing any changes. You can submit your proposed changes via email at uhirb@hawaii.edu. (The subject line should read: Exempt Study Modification.) The Human Studies Program may review the exempt status at that time and request an application for approval as non-exempt research.

In order to protect the confidentiality of research participants, we encourage you to destroy private information which can be linked to the identities of individuals as soon as it is reasonable to do so. Signed consent forms, as applicable to your study, should be maintained for at least the duration of your project.

This approval does not expire. However, please notify the Human Studies Program when your study is complete. Upon notification, we will close our files pertaining to your study.

If you have any questions relating to the protection of human research participants, please contact the Human Studies Program at 956-5007 or uhirb@hawaii.edu. We wish you success in carrying out your research project.

1960 East-West Road
Biomedical Sciences Building B104
Honolulu, Hawai'i 96822
Telephone: (808) 956-5007
Fax: (808) 956-8683

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