THE EPIDEMIOLOGY OF ACUTE POISONING HOSPITAL DISCHARGES IN WOMEN OF REPRODUCTIVE AGE AND DURING PREGNANCY AND BIRTH OUTCOMES FOLLOWING ACUTE POISONING HOSPITAL DISCHARGE DURING PREGNANCY

by

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In honor of my mother,

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Poisoning is the leading cause of injury hospitalization among women of reproductive age and the third leading cause of injury hospitalization during pregnancy. The California Patient Discharge Dataset and Vital Statistics-Patient Discharge Database were utilized to identify cases of acute poisoning hospital discharges. Studies were conducted to determine the epidemiology of acute poisoning hospital discharges in women of reproductive age and during pregnancy and to investigate the effects of acute poisoning during pregnancy on birth outcomes.

Pregnancy was associated with a lower risk for acute poisoning hospital discharge (OR=0.89, p=0.0007). Acute poisoning hospital discharges were greatest among young black women, and in women with substance abuse and mental health problems, regardless of pregnancy status. Analgesic and psychiatric medications were most commonly implicated in acute poisoning hospital discharges among women of reproductive age and during pregnancy. The majority of poisonings among women of reproductive age and among pregnant women were self-inflicted.

Adverse birth outcomes associated with acute poisoning include preterm delivery (PTD), respiratory distress, cesarean delivery, and other cardiac congenital anomalies. Infants born to women delivering at their poisoning hospitalization exhibited higher rates of respiratory distress and PTD. In the later-delivery group, infants born to women with an acute poisoning during pregnancy were at a greater risk of PTD and other cardiac congenital anomalies.

Adverse birth outcomes associated with intentional acute poisoning include PTD and low birth weight (LBW). Infants born to women that were discharged for an intentional acute poisoning hospital discharge within the first nine weeks of gestation exhibited higher rates of LBW. Among women who were discharged between gestational weeks 10 and delivery, intentional acute poisoning was associated with higher rates of circulatory system congenital anomalies.

Although the etiologies of the reported adverse outcomes are speculative, it can be suggested that substance abuse or other risk-taking behaviors associated with acute poisoning may confound the relationship between poisoning and congenital anomalies.

The public health significance of this dissertation is that these results provide public health practitioners the information necessary to design programs to reduce the burden of poisonings in women and their infants.

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1.0 INTRODUCTION

1.1 OVERVIEW

Poisoning is the leading cause of injury hospitalization among all women of reproductive age and the third leading cause of injury hospitalization during pregnancy (CDC WISQARS 2001-2004; Weiss et al., 2002). Although alarming, little has been done to characterize the epidemiology and outcomes associated with poisonings during pregnancy.

This dissertation will fill in several gaps regarding the epidemiology of hospitalized poisonings in all women of reproductive age and during pregnancy. The study will also result in estimates of the effect of poisonings on birth outcomes.

1.2 SPECIFIC AIMS

Specific Aim 1. Describe the epidemiology of acute poisoning hospital discharges in women of reproductive age (ages 15-44) including: the incidence rate, risk factors, substances involved and rates of intentional, unintentional and undetermined poisonings.

Hypothesis 1. The following variables will be significantly associated with an increased risk for acute poisoning hospital discharges: age less than 20 years, African American race, Hispanic ethnicity and public insurance payer.

Specific Aim 2. Describe the epidemiology of acute poisoning hospital discharges in pregnant women including: the incidence rate, risk factors, proportions over trimesters, substances involved and rate of intentional, unintentional and undetermined poisonings.

Hypothesis 2a. The following variables will be significantly associated with an increased risk for acute poisoning hospital discharges during pregnancy: age less than 20 years, mother's years of education less than 12, African American race, Hispanic ethnicity, public insurance payer and delayed entry into prenatal care.

Hypothesis 2b. The rate of intentional acute poisoning hospital discharges will be significantly greater in the first trimester than in the second and third trimesters of pregnancy.

Specific Aim 3. Compare the rates, risk factors, substances involved, and intentional versus unintentional rates of acute poisoning hospital discharge between women of reproductive age and pregnant women.

Hypothesis 3a. The rate of acute poisoning hospital discharges in women of reproductive age will be greater than the rate of acute poisoning hospital discharges in pregnant women after controlling for age, race and insurance payer.

Hypothesis 3b. The rate of intentional acute poisoning hospital discharge will be greater in women of reproductive age than the rate of intentional acute poisoning hospital discharge during pregnancy after controlling for age, race and insurance payer.

Specific Aim 4. Describe the patterns of birth outcomes following acute poisoning hospital discharge during pregnancy.

Hypothesis 4. The rates of premature delivery, low birth weight, fetal distress, respiratory distress, congenital anomalies, and fetal death and infant death will be greater in women with an acute poisoning hospital discharge during pregnancy, than those in a non-poisoned pregnant cohort after controlling for age, parity, maternal education, race, insurance payer, and entry into prenatal care.

1.3 BACKGROUND

1.3.1 Injuries

Injuries are a major source of preventable morbidity in women. In 2005 the rate of injury related hospitalization in women of reproductive age (ages 15-44) was 337/100,000. The leading causes of injury hospitalization in women of reproductive age were poisonings (30.9%), followed by motor vehicle occupant injuries (24.3%) and falls (12%) (CDC WISQARS 2005).

Injuries during pregnancy are a major public health concern. Potentially two lives, both that of the mother and fetus, are at risk. The rate of pregnancy associated injury hospitalization in Pennsylvania in 1995 was 868 per 100,000 person years (Weiss 1999). Utilizing 1997 hospital discharge data from 19 states, Weiss et al. (2002) reported the leading causes of injury hospitalization in pregnant women as motor-vehicle occupant related injuries (27.1%), followed by falls (21.2%) and poisonings (16.4%) (Weiss et. al., 2002).

Poisoning is the leading cause of injury hospitalization among all women of reproductive age and the third leading cause of injury hospitalization during pregnancy (CDC WISQARS 2001-2004; Weiss et al., 2002). Despite these statistics there is a dearth of literature regarding the epidemiology and outcome of poisonings during pregnancy.

1.3.2 Poisonings

A poison exposure is either the intentional or unintentional ingestion of or contact with a substance that can produce toxic effects. A poisoning is a poison exposure that results in bodily harm (AAPCC, 2002).

Poisonings may be systemic or organ-specific. The source of the toxin can be a synthetic, chemical or naturally-occurring plant, animal or mineral substance (AAPCC, 2002). These toxins include: pharmaceuticals, illicit drugs, pesticides, heavy metals, gases/vapors and even common household substances (CDC, 2004).

In 2004 the Toxic Exposure Surveillance System (TESS) annual summary indicated that 2,438,644 human poison exposures were reported to United States (US) poison control centers (PCC). A male predomination is found among poison exposure victims less than 13 years of age, but the sex distribution is reversed in teenagers and adults (Watson et al., 2005).

Utilizing the National Ambulatory Medical Care Survey, 1997-2001, the number of poisoning related emergency department (ED) visits was estimated at 1,428,000, or a rate of 530 per 100,000 persons per year, representing 1.5% of all emergency room visits (McCaig et. al., 1999). Women had a significantly higher rate of poisoning-related ED visits than men (550 vs 500 per 100,000, respectively). The rate of poisoning-related ED visits was lower in whites than in blacks (520 vs 830 per 100,000, respectively) (Committee on Poison Prevention and Control, 2004).

In 2004 there were 251,987 (crude rate 85.81 per 100,000, age adjusted rate 85.39 per 100,000) poisoning related injury hospitalizations in the US. Of these 43% were classified as unintentional and 57% as violence related. Of the violence related poisoning hospitalizations greater than 99% were self-inflicted. Poisoning related hospitalizations were slightly higher in women (crude rate 88.25 per 100,000, age adjusted rate 88.00) than in men (crude rate 83.29 per 100,000, age adjusted rate 82.86 per 100,000). Using 1997-2001 National Hospital Discharge Survey data, it was observed that whites were less likely than blacks to be hospitalized for a poisoning (90 vs 110 per 100,000 respectively).

In 2004 there were 30,308 (crude rate 10.32 per 100,000, age adjusted rate 10.26 per 100,000) poisoning related deaths in the US. Of these 69% were classified as unintentional, 19% as violence related and 11% as undetermined. Of the violence related poisoning deaths greater than 98% were self-inflicted (CDC WISQARS, 2004).

A publication from 1989 reported that poisonings account for $8.5 billion of the total lifetime cost of injury, ranking as the fourth most expensive mechanism of injury. The average cost of a fatal poisoning is $372,691, ranking second only to firearm fatality. The average cost per person hospitalized for poisoning is $17,631 and $171 for those not hospitalized (Rice and MaKenzie, 1989). In 2001 a more up-to-date estimate of the economic burden of poisoning, not including costs related to alcohol deaths, was $12.6 billion (Finkelstein, 2004).

Using Centers for Disease Controls (CDC) Web-based Injury Query and Reporting System (WISQARS), the rates of poisoning-related deaths and hospitalized nonfatal poisoning related injuries per 100,000 persons, for US women of all races, ages 15-44, for the years 2001-2004 are provided in Table 1.

Table 1. Rates of poisoning related deaths and nonfatal poisoning related hospitalizations per 100,000 persons, United States females, ages 15-44, stratified by intent, 2001-2004.

	Crude	Age Adjusted
Overall poisoning deaths	**8.04**	**8.10**
Unintentional poisoning Deaths	5.11	5.15
Violence related poisoning Deaths	1.76	1.77
Homicide and legal intervention poisoning deaths	0.02	0.02
Suicide poisoning deaths	1.74	1.75
Overall poisoning related nonfatal injuries-hospitalized	**118.62**	**118.79**
Unintentional poisoning related nonfatal injuries-hospitalized	30.18	30.27
Violence related poisoning related nonfatal injuries-hospitalized	88.44	88.52
Assault related poisoning related nonfatal injuries-hospitalized	--	--
Self-harm related poisoning nonfatal injuries-hospitalized	88.06	88.13

Table 1 Source: CDC. Web-based Injury Statistics Query and Reporting System (WISQARS). U.S. Department of Health and Human Services, CDC, National Center for Injury Prevention and Control, 2001-2004 (http://www.cdc.gov/ncipc/wisqars).

During 2001-2004 the age adjusted rate of poisoning deaths in US women ages 15-44 was 8.10 per 100,000 persons. Once stratified by intent, it is clear that the rate of unintentional poisoning deaths greatly surpasses both the rates of violence and suicide poisoning deaths. The same is not true with reference to poisoning-related nonfatal injury hospitalizations. Also during 2001-2004 the overall age adjusted rate of poisoning related nonfatal injury hospitalizations in US women ages 15-44 was 118.79. The rate of self-harm poisoning related nonfatal injury hospitalization is greater than twice the rate of unintentional poisoning related nonfatal injury hospitalizations.

In 2004 there were 11,003 poisoning related deaths in US women, ages 15-44. Of these 64% were classified as unintentional, 24% as violence related and 12% as undetermined. Of the violence related poisoning deaths 98% were due to suicide. During this same year there were 79,157 poisoning related hospitalizations in US women ages 15-44. Of these 24% were classified as unintentional, and 76% were violence related. Greater than 99% of the violence related poisoning hospitalizations were self-inflicted.

The rate of poisoning related deaths per 100,000 persons, for US women of all races, ages 15-44, stratified by 5 year age groups, for the years 2001-2004 are provided in Table 2.

Table 2. Rates of poisoning related deaths per 100,000 persons, United States females, ages 15-44, stratified by age and intent, 2001-2004.

Age	Overall poisoning deaths	Unintentional poisoning deaths	Violence related poisoning deaths	Homicide and legal intervention poisoning deaths	Suicide poisoning deaths
15-19	1.96	1.22	0.51	--	0.48
20-24	4.27	2.76	0.86	--	0.83
25-29	5.66	3.58	1.25	--	1.24
30-34	7.83	4.85	1.81	--	1.79
35-39	11.71	7.53	2.42	--	2.41
40-44	15.23	9.69	3.35	--	3.33

Source: CDC. Web-based Injury Statistics Query and Reporting System (WISQARS). U.S. Department of Health and Human Services, CDC, National Center for Injury Prevention and Control, 2001-2004 (http://www.cdc.gov/ncipc/wisqars).

The rate of both intentional and unintentional poisoning death in US women increases with advancing age. The rate of poisoning related nonfatal injury hospitalizations per 100,000 persons, for United States women of all races, ages 15-44, stratified by 5 year age groups, for the years 2001-2004 are provided in Table 3.

Table 3. Rates of poisoning related nonfatal injury hospitalizations per 100,000 persons, United States women, ages 15-44, stratified by age and intent, 2001-2004.

Age	Overall poisoning related nonfatal injuries-hospitalized	Unintentional poisoning related nonfatal injuries-hospitalized	Violence related poisoning related nonfatal injuries-hospitalized	Assault related poisoning related nonfatal injuries-hospitalized	Self-harm related poisoning nonfatal injuries-Hospitalized
15-19	135.20	24.30	110.90	--	110.67
20-24	112.07	25.96	86.11	--	85.80
25-29	113.01	27.97	85.03	--	84.60
30-34	113.42	30.03	83.39	--	83.39
35-39	119.26	37.22	82.04	--	81.37
40-44	118.55	34.21	84.34	--	83.72

Source: CDC. Web-based Injury Statistics Query and Reporting System (WISQARS). U.S. Department of Health and Human Services, CDC, National Center for Injury Prevention and Control, 2001-2004 (http://www.cdc.gov/ncipc/wisqars).

The overall rate of hospitalized nonfatal poisoning related injuries is greatest among women ages 15 to 19. The rate of unintentional poisoning related injury hospitalizations is greatest among 35 to 39 year olds, while violence related poisonings were greatest among women ages 15 to 19. Assault related poisoning related injury hospitalization rates were not computed by age groups due to the small number of cases. Self harm related poisoning hospitalizations were greatest among women 15 to 19.

The specific agents involved in poisonings in women of reproductive ages have not been well delineated. 2005 TESS data revealed the most commonly reported poisonings among both men and women aged 19 and over as: analgesics, sedatives/hypnotics/antipsychotics, cleaning substances, antidepressants and bites/envenomations (Watson et al., 2005). A study of the pattern of exposures reported to Texas PCCs identified the most frequently reported exposures among women of childbearing age as analgesics, sedatives/hypnotics/antipsychotics and antidepressants (Forrester and Stanley, 2004). Since not every poison exposure is reported to a PCC, these data may be incomplete (http://www.ncspt.org/courses/course1A-self/id115.htm). The leading agents involved in self-poisoning in young adults are: paracetamol (acetaminophen), non-acetaminophen analgesics, antirheumatics and

antidepressants (Smith et. al., 1991). In pregnant women the most commonly ingested drugs used in suicide attempts were benzodiazepines (Sein Anand et al., 2005).

The rate of hospitalized poisonings in pregnant women was reported as 132 per 100,000 person years (Weiss, 1999). Poisoning ranked as the third leading cause of injury hospitalization for pregnant women (Weiss et al., 2002).

The 2004 TESS annual report indicated that of all 2,438,644 poison exposures called into PCCs, 8,431 occurred in pregnant women: 32.0% of the 8,431 occurred in the first, 37.6% in the second and 30.5% in the third trimesters, respectively (Watson et. al., 2005). Approximately 0.07% of all telephone inquiries about drug overdose at a Michigan metropolitan PCC were related to drug overdose during pregnancy (Rayburn et al., 1984). Pregnancy status, like all information reported to PCCs, is volunteered information, which clearly limits our understanding of poisoning in pregnancy.

In a population based prospective examination of the timing and outcomes following self-poisoning by pregnant women for the years 1985-1993 in Budapest, Hungary Czeizel et. al. (1999) reported a striking inverse relationship between the number of suicide attempts across postconceptional months. Sixty-one percent of all attempts occurred before the third month post conception, with a significantly lower proportion attempting suicide parallel with fetal development (Czeizel et. al., 1999). Earlier studies have also shown a decrease in suicide attempts as pregnancy progressed.

The rate of poisoning hospitalization was significantly lower in pregnant women when compared to all women of reproductive age (rate ratio 0.71, 95% CI 0.59-0.86) (Weiss, 1999). Poisoning was the third leading cause of injury hospitalization in pregnant women and the leading cause of injury hospitalization in all women of reproductive age. The difference in risk may be due to previously documented decreases in risk taking behavior in pregnant women and a lower risk of suicide during pregnancy.

1.3.3 Teratology

Very little research has been done examining the impact of non-traumatic mechanisms of injury during pregnancy, such as poisoning. Most epidemiologic studies have assessed maternal mortality after injury, but few population based studies have evaluated infant outcomes after nonfatal injuries that occurred during pregnancy (Schiff et al., 2002; El Kady et. al., 2006). Only recently have researchers begun to examine the impact of injuries in pregnant women on birth outcomes. Birth outcomes of interest include: preterm delivery, low birth weight, respiratory distress syndrome, congenital anomalies and fetal and infant death. .

Teratogens are xenobiotics (a chemical or substance that is foreign to an organism or biological system) to which the mother is exposed that induce structural and/or functional changes in offspring before or during pregnancy (Bresloe et. al., 2002). In humans the only major teratogens identified before 1950 were rubella and radiation. Nonetheless, throughout the 1950s, teratologists assumed that the human fetus was protected from chemical insults. However, in the late 1950s approximately 8,000 infants were born with severe thalidomide-induced phocomelia. The immediate result of the thalidomide disaster was heightened awareness of the human fetus's susceptibility to environmental insults, engendering a new emphasis on reproductive testing of drugs, pesticides and other chemicals. Currently, a nimiety of substances have been identified to cause malformations in humans, including: anti-epileptic drugs, anti-coagulants, alcohol, cigarettes, Accutane, methadone and Diethylstilbestrol (DES) (Ostrer, 2006). Ten percent of all fetal malformations are now believed the result of exposures to: drugs, maternal conditions or disease states, physical agents, chemicals and infections (Hogge and Prosen, 2006).

Most chemicals/drugs cross the placenta and enter fetal circulation (Hogge and Prosen, 2006). Concentration gradients and physiochemical factors such as lipid solubility, relative molecular mass and protein-binding determine the rate of placental transport. Characteristics of substances which cross the placenta include: high lipid-solubility, low molecular weight and neutral pH (Foster et al., 2001).

A maternal drug overdose may be regarded as more harmful to the fetus than a continuous therapeutic dose. In addition to dose, timing of exposure is critical (Flint et al., 2002). The time during gestation at which the fetus is exposed to a teratogen can determine fetal development and outcome.

During the first weeks of gestation from the time of conception to implantation there appears to be an 'all-or-nothing' principle. If the embryo is exposed to a teratogen at this time it is either: 1) highly toxic resulting in fetal demise or 2) innocuous causing no harmful effects (Kenner et al., 2000; Foster et al., 2001). During weeks two through ten organogenesis begins, and the germ layers appear that will lead to the development of all of the fetus' physiologic systems (Kenner et al, 2000; Hogge and Prosen, 2006).

The fetal period of development extends from week ten until birth. During this time the fetus grows in weight and length, and the organs mature. At any time during this period the most vulnerable organ system is the one that is growing most rapidly (Kenner et al, 2000; Hogge and Prosen, 2006). See Figure 1.

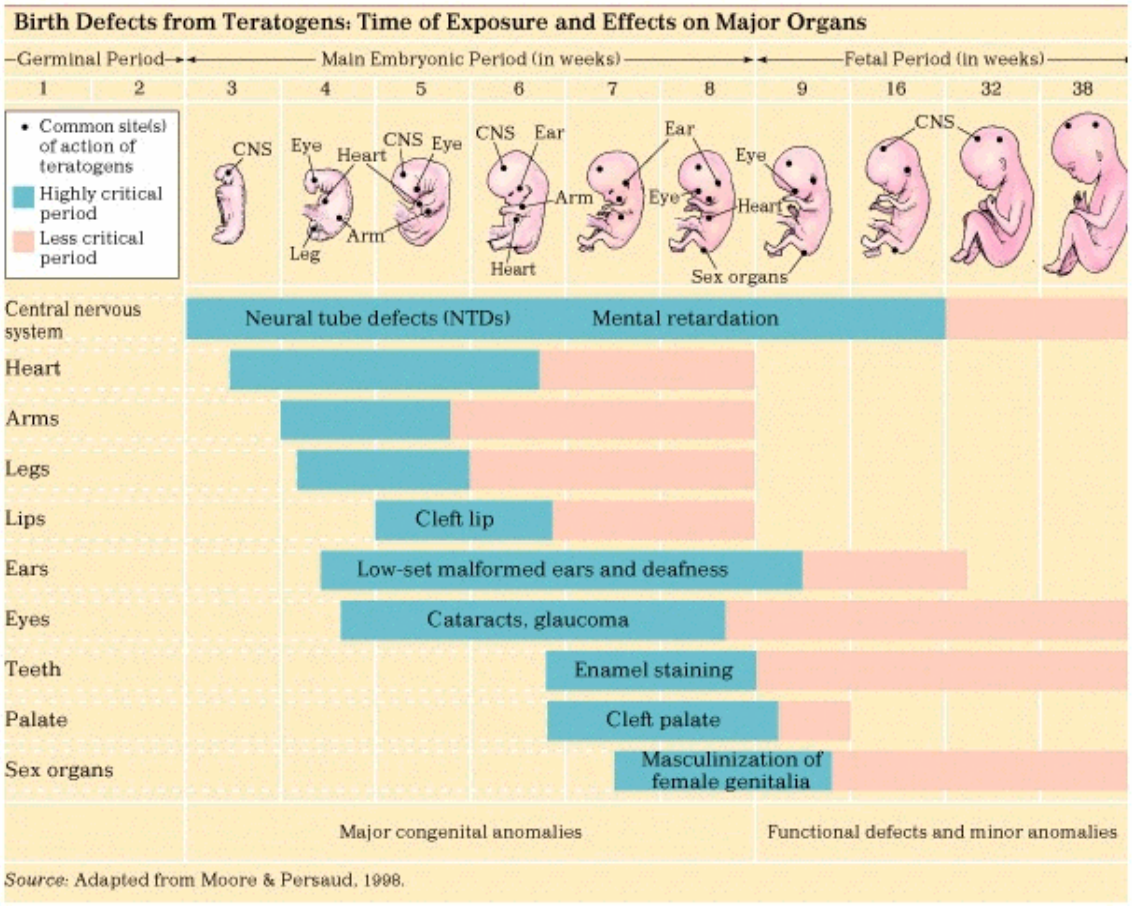

Figure 1. Time of teratogen exposure and their effects on major organs.

Source: Moore & Persaud, 1998.

Teratogenic mechanisms have mainly been studied in laboratory animals. Previously, there have been two approaches to study poisonings as reproductive hazards in humans: case studies examining exposures and epidemiological studies of self-poisoning.

Several case studies have been published regarding poisonings during pregnancy, encompassing a broad array of both legal and illicit drugs as well as environmental poisons. Reported birth outcomes range from premature delivery, low birth weight and length, and congenital anomalies, to spontaneous abortion and infant death. In some instances the exposures resulted in the aforementioned outcomes, while in others the poisonings were not associated with any apparent adverse effects.

It is difficult to make generalizations using case reports/series. Based on the cited case reports and case series the fetal toxicity of various substances was described. Toxicity varied depending on dose and apparent timing of exposure during the pregnancy. In some instances fetal toxicity was reported even despite seemingly low toxin concentrations compared with the mother. Table 4 includes a sample of case studies reported in the literature.

Table 4. Sample of case studies of poisoning during pregnancy.

Author	Title	Age/Gestation	Agent	Outcome
Zurawski and Kelly (1997)	Pregnancy outcome after maternal poisoning with brodifacoum, a long acting warfarin-like rodenticide	22 weeks	brodifacoum	aggressive vitamin k therapy to mom, healthy infant
Boye et. Al. (2001)	Management of maternal Amanita phalloides poisoning during the first trimester of pregnancy: a case report and review of the literature	22 year old, 11 weeks	amanita	no fetal damage
Brugwiler et. al. (1994)	Severe accidental magnesium poisoning in a twins pregnancy in the 32nd week of pregnancy	32 weeks, twins	magnesium	oxygen mask, ventilation calcium iv, and forced diuresis in mom prevented further sequelae for children
True and Heinze (1990)	Drug poisoning in the 39th week of pregnancy, a case report	39 weeks	nitrazepam	fetal cardiotachogram showed silent oscillation, pregnancy terminated

Table 4 continued

Gill et. al. (2002)	Acute fatty liver of pregnancy and acetaminophen toxicity leading to liver failure and postpartum liver transplantation	18 year old, 33 weeks	acetaminophen	fetal death
Palatnick and Tenenbein (1998)	Aspirin poisoning during pregnancy: increased fetal sensitivity	17 year old, 37 week	aspirin	fetal demise, autopsy diffuse petechiae in lungs heart, thymus and kidneys, salicylic acid in cord blood;
Gelbier and Ingram (1989)	Possible fetotoxic effects of mercury vapour: a case report.	31 year old, 35 week	mercury vapor	mercury vapor in excess of threshold limit, gave birth at 42 weeks to a small for dates baby with severe brain damage
Sancewicz-Pach et. al. (1999)	Suicidal paracetamol poisoning of a pregnant woman just before a delivery	21 years	paracetamol	healthy infant
Wang et. al. (1997)	Acetaminophen poisoning in late pregnancy, a case report	38 year old, 31 week	acetaminophen	c-section for fetal distress, infant died 34 hours after delivery, mom died 40 hours after admission
Malgorn et. al. (2004)	Benzodiazepine poisoning in a neonate: clinical and toxicokinetic evaluation following enterodialysis with activated charcoal	38 weeks	clorazepate dipotassium, benzodiazepine	birth 39 weeks, no spontaneous breathing, intubation, day 6 infant still on ventilator; charcoal given to infant, reduced ICU days

Table 4 continued

Belson and Morgan (2004)	Methanol toxicity in a newborn	28 year old, 30 weeks	ethanol	C section, low apgar, required aggressive resuscitation, intraventricular bleed, death, mother died; fatal neonatal methanol toxicity can result from transplacental exposure
Hoffman (2000)	Thallium poisoning during pregnancy: a case report and comprehensive literature review	1st trimester pregnant	thallium salts	fetal demise; review: 5 case 1 tri, 5 second, 8 third, range of fetal effects from sever toxicity to normal development, trend toward prematurity and lbw when exposed early gestation, thallium crosses the placenta
Fischer et. al. (2003)	Acute ethanol intoxication during pregnancy and consecutive fetal cardiac arrest: a case report	35 week gestation	ethanol	cardiac arrest of newborn, recovery
Nagahama et. al. (1993)	Severe theophylline toxicity in a pregnancy asthmatic patient	32 year old	theophylline	c-section, infant on ventilator for several days, discharge without trouble
Mazurek and Mazurek (1975)	Acute barbiturate poisoning in the 39th week of pregnancy	39 week pregnant	barbiturate	mom in coma, required c section

Table 4 continued

Olenmark et. al. (1987)	Fatal iron intoxication in late pregnancy	30 year old, 36 weeks	iron	healthy infant, mother died, supports the view that the potential lethal dose of iron is lower for adults than children
Fischer et. al. (2003)	Acute ethanol intoxication during pregnancy and consecutive fetal cardiac arrest: a case report	35 week gestation	Ethanol	cardiac arrest of newborn, recovery
Tran et. al. (1998)	Acute intentional iron overdose in pregnancy	27 year old, 37 weeks	Iron	no maternal or fetal complications
Madani et. al. (2006)	Atractylis gummifera poisoning in a pregnant woman	28 year old, 24 weeks	Atractylic gummifera (plant)	healthy infant
Sebe et. al. (2006)	Organophosphate poisoning associated with fetal death: a case study		chlorpyrifos	fetal death
Kamha et. al. (2005)	Organophosphate poisoning in pregnancy: a case report	42 year old, 26 weeks	Diazinon (pesticide)	healthy infant
Raynard, Bossard, and Carles (2003)	Paraquat poisoning at the beginning of pregnancy	10 weeks	paraquat	healthy infant
Hansen, Megerian, and Donnenfeld (1997)	Haloperidol overdose during pregnancy	34 weeks	haloperidol	healthy infant after 5 days

Several studies have shown no effect of self-poisoning on the prevalence of congenital anomalies, prematurity or low birth weight (Gunnarskog and Kallen, 1993, McEllhatton et. al. 1997). Gunnarkog and Kallen (1993) reported no increased risk of congenital anomalies in a register-based study of 424 infants exposed to chemicals *in utero*, of which 70 were exposed during the period of organogenesis. In a population-based prospective study of 559 self-poisoned pregnant women admitted to the toxicology

inpatient clinic the overall prevalence of congenital anomalies and proportion of multi-malformed babies was significantly higher in the 178 infants in the study group than comparable controls. However, after excluding eight infants with fetal alcohol syndrome, the rate of congenital anomalies in the remaining infants (9%) was not significantly different than that in the control group (6.1%). Therefore, no teratogenic effects were identified, even though in 27 cases large doses of drugs were ingested between the 3rd and 8th weeks of fetal development. Characteristics of women admitted for self-poisoning included lower education and employment levels, single marital status and tobacco and alcohol use. (Czeizel et. al., 1997).

However, in Denmark, researchers reported that among 122 women exposed to drug overdose during pregnancy (paracetamol, salicylates, benzodiazepines, and psychotropics) 44 underwent elective abortions, 17 experienced spontaneous abortion and 61 gave birth. The proportion of spontaneous abortion was nearly double that of the background population with a rate ratio of 1.7; the background population corresponds to crude figures from the surrounding population during the study period. There was no increased risk of major malformation or premature birth when compared to the background population. The authors do, however, cite lack of power to detect congenital anomalies which usually depends upon a short time-window of drug exposure (Flint et al., 2002). They concluded that a drug overdose shortly before or during pregnancy was associated with a substantially increased risk of miscarriage, but no increase in fetal birth defects among survivors.

Utilizing the California linked Vital Statistics- Patient Discharge Database, Ghandi et. al. (2006) reported that of all pregnant women attempting suicide in California, 86% attempted by ingestion of a solid or liquid- primarily a drug overdose or poisoning or poisoning with a corrosive substance. The women who attempted suicide were more likely to be: younger, (age less than 30), single, African American, less educated and Medicaid recipients compared to those not suicidal (Ghandi et al., 2006). Adverse birth outcomes associated with attempted suicide during pregnancy included neonatal and infant death, preterm delivery, and respiratory distress syndrome (Ghandi et. al., 2006).

In addition to case studies of poisonings and epidemiologic research of self-poisoning there is also a substantial degree of literature regarding the association of maternal alcohol and drug abuse during pregnancy and poor birth and developmental outcomes. Immediate adverse birth outcomes include: spontaneous abortion, premature delivery, low birth weight, small for gestational age infants and birth defects. Long term disabilities include: decreased motor development and an increased vulnerability for physical, academic, social and emotional problems (Conners et. al., 2004; Ludlow et. al., 2004).

1.3.4 Dissertation Objectives

This dissertation will fill in several gaps regarding the epidemiology of poisonings in all women of reproductive age and during pregnancy that will provide public health practitioners the information necessary to implement effective programs to reduce the burden of poisonings in women. The identification of the epidemiology of poisonings will provide a basis for prescribing preventative actions to reduce the morbidity and mortality attributed to poisonings. The study will also result in estimates of the effect of poisonings on birth outcomes. The burden that poisonings pose in offspring in terms of adverse birth outcomes only adds to the burden of poisonings in the health of women, highlighting an even greater need for knowledge and prevention.

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2.0 ARTICLE ONE: THE EPIDEMIOLOGY OF ACUTE POISONING HOSPITAL DISCHARGES IN WOMEN OF REPRODUCTIVE AGE AND DURING PREGNANCY IN CALIFORNIA, 2000-2004

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2.1 ABSTRACT

Objective: The purpose of this study was to 1) describe the epidemiology of hospitalized poisonings in women of reproductive age (aged between 15-44) including the incidence rate, risk factors, substances involved and rates of intentional versus unintentional poisonings 2) describe the epidemiology of hospitalized poisonings among pregnant women including the incidence rate, risk factors, distribution over trimesters, substances involved and rate of intentional versus unintentional poisonings and 3) compare the rates, risk factors, substances involved and intentional versus unintentional rates of hospitalized poisonings between women of reproductive age and pregnant women.

Methods: Two datasets, the Patient Discharge Dataset (PDD) and the Vital Statistics-Patient Discharge Database (VSPDD), maintained by the California Office Statewide Health Planning and Development, were utilized to identify cases of acute poisoning hospital discharges.

Results: There were 4,436,019 hospital discharges in women aged between 15 and 44, for the years 2000-2004, identified in the dataset. Of those hospital discharges, 44,393 (1%) were for an acute poisoning (rate 115.28 per 100,000 person-years). There were 2,285,540 deliveries fulfilling the study criteria in the VSPDD between 2000 and 2004. There were 833 hospital discharges for an acute poisoning during pregnancy in the database (rate 48.60/100,000 person-years). Pregnancy was associated with a lower risk of acute poisoning hospital discharge (OR=0.89, p=0.0007). Acute poisoning hospital discharges were greatest among young black women regardless of pregnancy status. Women with substance abuse or mental health problems were also at a greater risk of acute poisoning hospital discharge. Analgesic and psychiatric medications were most commonly implicated in acute poisoning hospital discharges among

women of reproductive age and during pregnancy. The majority of poisonings among women of reproductive age and among pregnant women were self-inflicted (69.6% and 61.6%, respectively).

Conclusions: Pregnancy lowers the risk of acute poisoning hospital discharge. Young black women, and women with substance abuse and mental illness, were at greatest risk of acute poisoning hospital discharge, regardless of pregnancy. Multiple interactions between a woman and her obstetrician/gynecologist or treating physician during the reproductive years and pregnancies yield education, screening and appropriate referral opportunities for high-risk women to prevent acute poisonings.

2.2 INTRODUCTION

Poisoning is the leading cause of injury hospitalization in women of reproductive age and the third leading cause of injury hospitalization during pregnancy (CDC WISQARS 2001-2004; Weiss et al., 2002). Despite the alarming nature of these observations, little research has been done to characterize the epidemiology of poisonings in women. In order to address this gap in the literature this study aims to: 1) describe the epidemiology of acute poisoning hospital discharges in women of reproductive age (aged between 15-44) including the incidence rate, risk factors, substances involved and rates of intentional versus unintentional poisonings 2) describe the epidemiology of acute poisoning hospital discharges among pregnant women including the incidence rate, risk factors, distribution over trimesters, substances involved and rate of intentional versus unintentional poisonings and 3) compare the rates, risk factors, substances involved and intentional versus unintentional rates of acute poisoning hospital discharges between women of reproductive age and pregnant women.

The results of this study may provide health practitioners the necessary information to develop effective programs to reduce poisoning morbidity and mortality in young women.

2.3 METHODS

A study was conducted to determine the epidemiology of acute poisoning hospital discharges in women of reproductive age and in pregnant women. Two datasets, the Patient Discharge Dataset (PDD) and the Vital Statistics-Patient Discharge Database (VSPDD), both maintained by the California Office Statewide Health Planning and Development, were utilized to address the aims of this study. All California licensed hospitals are mandated to semi-annually submit specific data on every discharged patient. These data

include patient demographic information, diagnostic and treatment information, disposition, total hospital charges, and payer source. The VSPDD includes data from several sources including California Patient Discharge Data, Vital Statistics Birth Certificate Data, Vital Statistics Death Certificate Data, the Vital Statistics Fetal Death File, and the Vital Statistics Birth Cohort File. It includes maternal antepartum and postpartum hospital records for the nine months prior to, and one year post-delivery. The database also includes birth records and all infant readmissions occurring during the first year of life. Linkage was successful in 98% of the cases. Detailed linkage procedures have been described previously (Herrchen et. al., 1997).

This study was approved by the University of Pittsburgh Institutional Review Board, the California Department for the Protection of Human Subjects, and the California Office of Statewide Health Planning and Development. No unique patient identifiers were included in the database.

Hospital discharges for acute poisonings were identified by the presence of the following International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis and external cause of injury codes: 960-979 (poisoning by drugs, medicinal, and biological substances), 980-989 (toxic effects of substances chiefly nonmedicinal as to source), E850-E858 (accidental poisoning by drugs, medicinal substances, and biologicals), E860.2-E869 (accidental poisoning by other solid and liquid substances, gases, and vapors), E905 (venomous animals and plants as the cause of poisoning and toxic reactions), E950-E952 (suicide and self-inflicted poisoning), E962 (assault by poisoning) and E980-E982 (poisoning, undetermined whether accidentally or purposely inflicted).

All hospital discharges for an acute poisoning were identified in women between 15 and 44 years old in the California Patient Discharge Dataset. Hospital discharges for acute poisonings in women aged between 15 and 44, that were identified in the Patient Discharge Dataset were compared to all other non-poisoning hospital discharges during the five year period 2000-2004.

Also, all hospital discharges for acute poisonings in pregnant women aged between 15 and 44 who had a pregnancy outcome consisting of a live birth or fetal death that occurred within gestational ages 20 to 42 weeks, in the linked Vital Statistics Hospital Discharge Dataset, were identified. Hospital

discharges for acute poisonings in pregnant women were compared to all other non-poisoning hospital discharges during pregnancy during the five year period 2000-2004.

To determine if pregnancy alters the risk of acute poisoning hospital discharge, the rate of acute poisoning hospital discharges in women of reproductive age was compared to the rate of acute poisoning hospital discharges during pregnancy. This comparison, rather than a pregnant verus nonpregnant group was done for several reasons. First, after subtracting out the pregnant women, there are likely still pregnant women in the sample (in the first trimester); these women would be erroneously classified as non-pregnant. Secondly, the goal is to compare pregnant to nonpregnant women and the comparison done in this study considers the three month period out of each year that a pregnant woman is not pregnant (Weiss et al., 2002).

Incidence rates were cacluated per 100,000 person years, following the methodology used by Greenblatt et al (1997). For the pregnant population, denominators were adjusted downward to account for the nine of twelve months of the year a pregnant woman is pregnant.

The demographic characteristics between those with acute poisoning hospital discharges were compared to those with non-poisoning hospital discharges. Data were summarized as means plus or minus the standard deviation or median interquartile range for continuous variables and frequencies for categorical variables. In order to determine statistical signficance, T-tests or Wilcoxon rank sum tests were computed for continuous variables and the chi-square test was computed for categorical variables. Odd ratios and 95% confidence intervals were caclulated for risk factors using logistic regression analyses.

Rates are presented as the number of acute poisoning hospital discharges per 100,000 person-years, unless otherwise noted. To compare incidence rates, group specific rate ratios and their 95% confidence intervals were calculated according to Rosner (1994). Generalized estimating equations were utilized to determine if pregnancy is a significant risk factor for poisoning when controlling for potential confounders including age, race, and insurance payer .

All analyses were calculated using SAS 8.2 software. All p-values less than 0.05 were considered statistically significant.

2.4 RESULTS

2.4.1 Acute Poisoning Hospital Discharges in Women of Reproductive Age

There were 4,436,019 hospital discharges in women aged between 15 and 44, identified in the dataset. Of those hospital discharges, 44,393 (1%) were for an acute poisoning during the study period, resulting in a rate of 115.28 hospital discharges per 100,000 person-years. Utilizing E-codes, 30,890 (69.6%) of the 44, 393 acute poisoning hospital discharges were identified as intentional, 9,526 (21.5%) as unintentional and 2,687 (6.1%) as acute poisoning hospital discharges of undetermined intent (rates 80.22, 24.74, and 6.98 per 100,000 person-years, respectively). In poisoned women with non-missing record linkage numbers (N=32,353), 2,945 (9.0%) women were discharged twice during the five year study period for an acute poisoning, 589 (1.8%) three times, and 362 (1.1%) women were discharged four or more times during the five year study period for an acute poisoning.

The overall rate of acute poisoning hospital discharges in women of reproductive age was greatest among women aged between 15 and 19 (155.97/100,000 person-years). The rate of intentional acute poisoning hospital discharges was also greatest among women aged between 15 and 19 (125.43/100,000 person-years), while unintentional poisoning hospital discharges were greatest in women aged between 40 and 44 (36.32/100,000 person-years).

The diagnostic codes of the five leading substances implicated in acute poisoning hospital discharges for women of reproductive age are presented in Table 5. In addition, the five leading substances identified by E-codes, stratified by intent, are also listed. Analgesics and tranquilizers were the most common substances implicated.

The demographic characteristics of women of reproductive age with acute poisoning hospital discharges are presented in Table 6. Compared to women of other age groups, women aged between 15 and 19 had the greatest likelihood of acute poisoning hospital discharges, followed by women aged between 40 and 44. White women were more likely to be hospitalized for an acute poisoning compared to non-White women. Also, non-Hispanic women were more likely to be hospitalized for an acute poisoning compared to Hispanic women. Women with Medi-Cal insurance were less likely to be hospitalized for an acute poisoning compared to women with other types of insurance payers. The concomitant diagnoses of substance abuse and mental illness were associated with higher odds of acute poisoning hospital discharge.

2.4.2 Acute Poisoning Hospital Discharges During Pregnancy

There were 2,285,540 deliveries fulfilling the study criteria identified in the Vital Statistics-Patient Discharge Database from 2000-2004, accounting for 2,471,524 hospital discharges. A total of 833 hospital discharges for an acute poisoning during pregnancy were identified in the database (48.60/100,000 person-years). Seven hundred ninety-four (0.03% of deliveries) women accounted for the 833 hospital discharges (population-based rate 46.32/100,000 person-years); thirty-seven women were admitted two or more times during the same pregnancy for an acute poisoning.

The distribution of poisoning hospital discharges by gestational age is presented in Figure 2. Intentional poisonings peak in the first week of gestation, whereas the greatest numbers of unintentional poisonings are observed between gestational weeks 39 and 41. Of all poisoning hospital discharges during pregnancy, 35.89%, 28.34%, and 35.77% occurred in the first, second, and third trimesters, respectively. The rate of acute poisoning hospital discharges did not significantly differ across trimesters (17.50, 13.83, and 17.27 per 100,000 person-years, respectively). There were 128 (16.12%) deliveries that occurred at the time of poisoning hospitalization.

Utilizing E-codes, 513 (61.6%) of the 833 documented cases of acute poisoning hospital discharges were identified as intentional (rate 29.93/100,000 person-years). Of the remaining cases, 241 (28.9%) were classified as unintentional and 34 (4.1%) as acute poisoning hospital discharges of undetermined intent (rates 14.06 and 1.98 per 100,000 person-years, respectively).

The rate of intentional poisonings was significantly greater in the first trimester than in the second and third (13.36 versus 9.33 and 7.23 per 100,000 person-years, respectively; $p<0.05$). After subtracting out the number of intentional poisonings in the first week of gestation, the rate of intentional poisonings in the first trimester (10.91/100,000 person-years) remained significantly greater than the rate in the third trimester. However it was no longer significantly different when compared to the rate in the second trimester. The rate of unintentional poisonings was significantly greater in the third trimester in comparison to that of the first and second (7.47, 3.33, and 3.25 per 100,000 person-years, respectively; $p<0.05$).

The overall rate of acute poisoning hospital discharges during pregnancy was greatest among women aged between 15 and 19 (rate 91.88/100,000 person-years); this age group also had the highest rates of both intentional and unintentional poisoning hospital discharges (rates 66.43 and 22.97 per 100,000 person-years, respectively).

The diagnostic codes of the five leading substances implicated in acute poisoning hospital discharges during pregnancy are presented in Table 7. In addition, the five leading substances identified by E-codes, stratified by intent, are also listed. Analgesics were the most common substance implicated, irrespective of intent.

Demographic characteristics of women with an acute poisoning hospital discharge during pregnancy are shown in Table 8. This analysis determined that women aged between 15 and 25 had the greatest likelihood of acute poisoning hospital discharge during pregnancy. African American women were more likely to be hospitalized for an acute poisoning during pregnancy when compared to white women. Non-Hispanic women were more likely to be hospitalized for an acute poisoning during pregnancy when compared to Hispanic women. Women with a college education were less likely to be

hospitalized for an acute poisoning compared to women with less than a high school education. In addition, compared to women with Medi-Cal insurance, women with self-pay, indigent, and government insurance payers were more likely, and women with private insurance payers less likely, to be hospitalized with an acute poisoning. Both substance abuse and mental illness were each associated with higher odds of acute poisoning hospital discharge during pregnancy. Neither parity nor initiation of prenatal care was associated with acute poisoning hospital discharge during pregnancy.

2.4.3 Comparing Acute Poisoning Hospital Discharges In Women of Reproductive Age to Acute Poisoning Hospital Discharges During Pregnancy

Rate ratios and their associated 95% confidence intervals for acute poisoning hospital discharges during pregnancy and acute poisoning hospital discharges in women of reproductive age are shown in Table 9. The crude rates of acute poisoning hospitalization were greater in women of reproductive age than during pregnancy, irrespective of intent.

Because pregnant women are more likely to be hospitalized for a less severe injury than all women (Weiss et al., 2002), rates and their associated 95% confidence intervals for acute poisoning hospital discharges during pregnancy with a length of stay greater than or equal to two days, a proxy for poisoning severity, were calculated and compared to the rates of acute poisoning hospital discharges in women of reproductive age. The rate ratios comparing pregnant women to women of reproductive age decreased significantly overall and for both intentional and unintentional poisonings ($p<0.05$).

The rates of acute poisoning hospital discharges during pregnancy and in women of reproductive age stratified by age and race are presented in Figure 3. The rates of acute poisoning hospital discharges (both white and nonwhite) during pregnancy were lower than that of women of reproductive age. In addition, the rates of acute poisoning hospital discharges in nonwhite women were generally higher in the lower age groups than the rates of poisoning in white women.

In a multivariable model, controlling for age, race, insurance payer, and ethnicity, pregnancy remained to be significantly inversely associated with acute poisoning hospital discharges (OR=0.89, 95% CI 0.83-0.95, p=0.0007). However, the patterns in Figure 3 suggest interactions between pregnancy and both age and race. In a multivariable model controlling for race, insurance payer, and ethnicity, the interactions between pregnancy and age and pregnancy and race were statistically significant ($p<0.0001$).

2.5 DISCUSSION

This is the one of the first studies to examine the epidemiology of acute poisoning hospital discharges during pregnancy and in women of reproductive age. These data come from a very large and heterogeneous statewide population. In addition, this is one of the first papers to present population-based estimates of acute poisoning hospital discharges during pregnancy to include poisonings in the first weeks of pregnancy; most data sources are limited to recognizable pregnancies. Several gaps in the literature regarding the epidemiology of poisonings in women of reproductive age and during pregnancy are filled by this study

The rates of poisoning hospital discharges (all intents, intentional, and unintentional) in women of reproductive age documented in this study correspond well to the rates of hospitalized nonfatal poisoning related injuries reported by the Centers for Disease Control Web-based Injury Statistics Query and Reporting System (CDC WISQARS) (115.28, 80.22 and 24.74 per 100,000 person-years in contrast to 118.62, 88.44 and 30.18 per 100,000 persons, respectively). The similarity between the rates in this study and those reported by WISQARS further increases confidence in these results. CDC WISQARS provides reliable national estimates of injuries in the United States. This study went beyond the scope of WISQARS and American Association of Poison Control Centers data to report the rates of acute poisoning hospital discharges specifically among pregnant women. Very few studies have focused on acute poisoning hospital discharges during pregnancy.

Weiss (1999) studied pregnancy-associated injury in Pennsylvania and reported a rate of pregnancy-associated poisoning hospital discharges of 132 per 100,000 person-years and the rate ratio of acute poisoning hospital discharges in pregnant women compared to women of reproductive age as 0.71(95% CI 0.59-0.86). The rate and associated rate ratio reported in this study, although of the same magnitudes, are significantly lower than that reported by Weiss. Specifically, this study resulted in a rate of 48.60 acute poisoning hospital discharges per 100,000 person-years during pregnancy. A comparison of the rate of acute poisoning hospital discharges during pregnancy compared to acute poisoning hospital discharges in women of reproductive age yielded a rate ratio of 0.42(95% CI 0.38-0.45). The reasons for these differences are unclear; however, it is thought that racial and ethnic differences, which vary considerably between Pennsylvania and California, may account for at least a portion this disparity. However, the results in this study may be a more accurate reflection of the true rate of acute poisoning hospital discharges during pregnancy because the rates are based on five year data in a much larger, more heterogeneous statewide population.

In this study, the most common substances implicated in acute poisoning hospital discharge in women of reproductive age were analgesics, benzodiazepine-based tranquilizers and antidepressants. This is similar to results of a previous study examining the pattern of exposures reported to Texas Poison Control Centers (PCC) that identified the most frequently reported exposures among women of childbearing age as analgesics, sedatives/hypnotics/antipsychotics and antidepressants (Forrester and Stanley, 2004). PCC data are limited; not every poison exposure is reported to PCCs and those reported are likely of lower severity. These limitations are addressed by reporting results from a population-based dataset with specific emphasis on acute poisoning hospital discharge.

For another comparison of substances, a study that used data from the Toxic Exposure Surveillance System (TESS), showed that the most commonly reported poisonings among both men and women aged 19 and over as due to: analgesics, sedatives/hypnotics/antipsychotics, cleaning substances, antidepressants and bites/envenomations (Watson et. al., 2005). TESS data are a compilation of data from US poison centers and are therefore subject to the same limitations as PCC data. The data reported in this

study are more specific to women aged between 15 and 44; therefore, the results reported in this study provide a more accurate reflection of the substances implicated in acute poisoning hospital discharges in women of reproductive age.

Specific to pregnancy, the most common substances implicated in intentional poisoning hospital discharges during pregnancy were analgesics, antipyretics, and antirheumatics and other specified drugs and medicinal substances, followed by tranquilizers and antipsychotic agents. Similarly, ingestion of 50 different types of over-the-counter and prescription drugs consisting primarily of analgesics (mainly acetaminophen), vitamins and iron, sedatives, antibiotics, and antihistamines or decongestants were identified in a study of 111 suicide attempts by overdose during pregnancy reported to a metropolitan poison control center (Rayburn et al. 1984). This is in contrast to Sein Anand et al. 2005, who reported that the most commonly ingested drugs used in suicide attempts during pregnancy were benzodiazepines. The results in this study are more comprehensive due to the limited sample size in the Sein et al. (2005) study (N=19). However, a benefit to their design was the ability to more completely describe the factors associated with self-inflicted poisonings. The main reason for suicidal self-inflicted acute poisoning was unplanned pregnancy. This study was limited to the data collected as part of a statewide hospital administrative system and therefore such factors could not be examined.

It is of interest to note that the leading substances implicated in acute poisoning hospital discharges in women of reproductive age and among pregnant women, regardless of intent, were mainly analgesics which are widely accessible medications. Public health professionals should implement programs to inform patients on the proper use of over the counter medications. In addition, healthcare providers should alert patients to focus their attention to package labeling, specifically to active ingredients, so that they may make informed decisions on the types and dosages of over the counter medications they consume.

The 2004 the Toxic Exposure Surveillance System annual report indicated that of all 2,438,644 poison exposures called into Poison Control Centers, 8,431 occurred in pregnant women: 32.0% of the 8,431 occurred in the first, 37.6% in the second and 30.5% in the third trimesters, respectively (Watson et

al., 2005). A similar trend was revealed in this study. Although the overall rate of acute poisoning hospital discharges did not differ significantly across trimesters, the rate of intentional poisonings was significantly greater in the first trimester of pregnancy. Previous research has documented decreases in risk taking behavior in pregnant women which may serve as a possible explanation for this trend.

For example, in a population based prospective examination of the timing and outcomes following self-poisoning by pregnant women for the years 1985-1993 in Budapest, Hungary Czeizel et al. (1999) reported a striking inverse relationship between the numbers of suicide attempts across postconceptional months. Due to the high number of intentional poisonings in the first few weeks of gestation and the quick decline thereafter, it may be speculated that the rates of intentional poisonings decrease due to increasing awareness of pregnancy.

Although unsettlingly high, the proportion (62%) of intentional poisoning hospital discharges was not unexpected because poisonings are the most frequent method of self-inflicted, non-fatal injury in women (Schnitzer and Runyan, 1995). Furthermore, Ghandi et al. (2006) who also used California linked Vital Statistics-Patient Discharge Data, reported that of all pregnant women attempting suicide in California, 86% attempted by ingestion of a solid or liquid- primarily a drug overdose or poisoning with a corrosive substance. It can be argued that intentional poisonings during pregnancy pose a greater financial and health-care burden than in non-pregnant women because not only is the woman affected, but the fetus as well.

The documented decreased risk taking behavior in pregnant women is further supported because, after controlling for potential confounding factors, the risk of acute poisoning hospital discharges remained significantly lower during pregnancy compared to all women of reproductive age. Also of interest, a significant interaction between age and pregnancy persisted, such that in pregnant women, age increase was associated with decreasing rates of poisoning. A second interaction, between race and pregnancy, was also significant; exhibiting that black race was associated with a higher risk of acute poisoning hospital discharges during pregnancy. The distribution of the pregnant population, being younger and more often of minority race and the higher rates of poisoning in women of minority race,

may aid in elevating the base rate of acute poisoning hospital discharges in pregnant women. Pregnancy also had less of a protective effect in Asian women. Prevention efforts are most effective when targeted at the highest risk women; in the case of acute poisoning hospitalizations, practitioners should focus their prevention efforts on young black women, regardless of pregnancy status. Substance abuse and mental health screening, and appropriate referral opportunities, by an obstetrician/gynecologist or treating physician may have the potential to prevent acute poisonings in high-risk women.

There are other limitations to this study. Utilization of administrative data includes possible coding and reporting errors. In addition, this study may have selection bias as the dataset included hospitalized poisonings only, excluding deliveries prior to 20 weeks gestation and coroner's cases, which may lead to an underestimate of the true number of acute poisoning cases. It was not possible to calculate population-based estimates of acute poisoning hospital discharge in women of reproductive age due to a high proportion of missing record linkage numbers.

Future research in the field of acute poisonings should make an effort to distinguish poison severity. Currently, neither the Injury Severity Score System nor hospital administrative data provide indications of the dose of substance implicated in a poisoning. For a greater understanding of factors associated with acute poisonings during pregnancy, future studies should focus data collection efforts to include 1) the time the woman became aware of her pregnancy in relation to the time of the poisoning 2) the true intent of the poisoning (accidental, suicide attempt, or abortion attempt) 3) whether the pregnancy was a planned pregnancy and 4) concomitant diagnosis of mental illness or substance abuse. Furthermore, additional research should investigate the effects of acute poisoning during pregnancy on maternal and neonatal outcomes.

2.6 CONCLUSIONS

In summary, pregnancy is associated with an overall reduction in the risk for an acute poisoning hospital discharge. However, acute poisoning hospital discharges were greatest among young black women regardless of pregnancy status. Additionally, women with substance abuse or mental health problems were at a higher risk of acute poisoning hospital discharge. Analgesic and psychiatric medications were most commonly implicated in acute poisoning hospital discharges among women of reproductive age and during pregnancy. The majority of poisonings among women of reproductive age and among pregnant women were self-inflicted. Multiple interactions between a woman and her obstetrician/gynecologist or treating physician during the reproductive years and pregnancies yield education, screening and appropriate referral opportunities for high-risk women to prevent acute poisonings.

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Table 5. The five leading substances implicated in acute poisoning hospital discharges and substance specific rates in all women of reproductive age by diagnosis code and then by e-code, stratified by intent.

All (Diagnosis Code)	**Rate (per 100,000 person- years)**
Poisoning by aromatic analgesics, NEC Acetanilid; Paracetamol [acetaminophen]; Phenacetin [acetphenetidin]	22.90
Poisoning by benzodiazepine-based tranquilizers Chlordiazepoxide; Diazepam; Flurazepam; Lorazepam; Medazepam; Nitrazepam	19.89
Poisoning by antidepressants Amitriptyline; Imipramine; Monoamine Oxidase [MAO] Inhibitors	17.40
Poisoning by other opiates and related narcotics Codeine [methylmorphine]; Meperidine [pethidine]; Morphine	6.93
Toxic effect of ethyl alcohol Denatured alcohol; ethanol; grain alcohol	6.92
Intentional (E-Code)	
Suicide and self-inflicted poisoning by tranquilizers and other psychotropic agents	33.33
Suicide and self-inflicted poisoning by analgesics, antipyretics, and antirheumatics	33.18
Suicide and self-inflicted poisoning by other specified drugs and medicinal substances	23.74
Suicide and self-inflicted poisoning by other and unspecified solid and liquid substances	6.54
Suicide and self-inflicted poisoning by other sedatives and hypnotics	3.68
Unintentional (E-Code)	
Accidental poisoning by benzodiazepine-based tranquilizers Chlordiazepoxide; Diazepam; Flurazepam; Lorazepam; Medazepam; Nitrazepam	3.33
Accidental poisoning by aromatic analgesics, NEC Acetanilid; Paracetamol [acetaminophen]; Phenacetin [acetophenetidin]	3.20
Accidental poisoning by other opiates and related narcotics Codeine [methylmorphine]; Meperidine [pethidine]; Morphine; Opium (alkaloids)	3.16
Accidental poisoning by psychostimulants Amphetamine; Caffeine	2.38
Accidental Poisoning By Antidepressants Amitriptyline; Imipramine; Monoamine oxidase [MAO] inhibitors	1.80

Table 6. Demographic Characteristics of Women with Acute Poisoning Hospital Discharges and Non-Poisoning Hospital Discharges, Women of Reproductive Age, 2000-2004.

		Non-Poisoning Hospital Discharges Women 15-44	Acute Poisoning Hospital Discharges Women 15-44				
Characteristic	**Category**	**n**	**n**	**%**	**OR**	**95% CI**	**P**
Age	15-19	443560	9569	2.11	3.58	3.47-3.70	<0.0001
	20-24	821488	6452	0.78	1.3	1.26-1.35	<0.0001
	25-29	925014	5570	0.6	1	Ref	
	30-34	944500	6516	0.69	1.15	1.11-1.19	<0.0001
	35-39	716868	7588	1.05	1.76	1.70-1.82	<0.0001
	40-44	540196	8698	1.58	2.67	2.59-2.77	<0.0001
Race	White	2929533	33129	1.12	1	Ref	
	Black	377887	3768	0.99	0.88	0.85-0.91	<0.0001
	Asian	363891	2762	0.75	0.67	0.65-0.70	<0.0001
	Other	662382	4123	0.62	0.55	0.53-0.57	<0.0001
Ethnicity	Hispanic	1718981	10017	0.58	0.45	0.44-0.46	<0.0001
	Non-Hispanic	2589698	33446	1.28	1	Ref	
Insurance	Medicare/Other Government	182409	3610	1.94	2.7	2.60-2.80	<0.0001
	Medi-Cal	1684765	12361	0.73	1	Ref	
	Private	2252601	19257	0.85	1.17	1.14-1.19	<0.0001
	Indigent	150075	5818	3.73	5.28	5.12-5.45	<0.0001
	Self-pay	71215	2792	3.77	5.34	5.13-5.57	<0.0001
	Other	49651	534	1.06	1.47	1.34-1.60	<0.0001
Substance Abuse	Yes	216765	18013	7.67	13.15	12.90-13.41	<0.0001
	No	4174861	26380	0.63	1	Ref	
Mental Illness	Yes	381865	28502	6.95	18.83	18.47-19.21	<0.0001
	No	4009761	15891	0.39	1	Ref	

OR=odds ratio; CI=confidence interval

Table 7. The five leading substances implicated in acute poisoning hospital discharges during pregnancy and substance specific rates by diagnosis code and then by e-code, stratified by intent.

All (Diagnosis Code)	**Rate (per 100,000 person- years)**
Poisoning by aromatic analgesics, NEC Acetanilid; Paracetamol [acetaminophen]; Phenacetin [acetphenetidin]	10.79
Poising by antidepressants Amitriptyline; Imipramine; Monoamine Oxidase [MAO] Inhibitors	4.38
Poisoning by benzodiazepine-based tranquilizers Chlordiazepoxide; Diazepam; Flurazepam; Lorazepam; Medazepam; Nitrazepam	3.38
Poisoning by antirheumatics (antiphlogistics) Propionic acid derivatives Fenoproten; Fluriprofen; Ibruprofen; Ketoprofen; Naproxen; Oxaprozin	3.03
Poisoning by salicylates Acetylsalicylic acid [aspirin]; Salicylic acid salts	2.92
Intentional (E-Code)	
Suicide and self-inflicted poisoning by analgesics, antipyretics, and antirheumatics	14.41
Suicide and self-inflicted poisoning by other specified drugs and medicinal substances	9.92
Suicide and self-inflicted poisoning by tranquilizers and other psychotropic agents	7.88
Suicide and self-inflicted poisoning by other and unspecified solid and liquid substances	1.75
Suicide and self-inflicted poisoning by other sedatives and hypnotics	0.64
Unintentional (E-Code)	
Accidental poisoning by aromatic analgesics, NEC Acetanilid; Paracetamol [acetaminophen]; Phenacetin [acetophenetidin]	1.75
Venomous spiders causing poisoning and toxic reactions Black widow spider; Brown spider; Tarantula (venomous)	1.28
Accidental poisoning by anticonvulsant and anti-parkinsonism drugs Amantadine; Hydantoin derivatives; Levodopa [L-dopa]; Oxazolidine derivatives [paramethadione] [trimethadione]; Succinimides	0.99
Accidental poisoning by second-hand tobacco smoke	0.99
Accidental poisoning by psychostimulants Amphetamine; Caffeine	0.88

Table 8. Demographic Characteristics of Women with Acute Poisoning Hospital Discharges During Pregnancy and Non-Poisoning Hospital Discharges During Pregnancy, 2000-2004.

		Non-Poisoning Hospital Discharges During Pregnancy	Acute Poisoning Hospital Discharges During Pregnancy				
Characteristic	**Category**	**n**	**n**	**%**	**OR**	**95%CI**	**p**
Maternal Age	15-19	234746	148	0.06	2.44	1.95-3.04	<0.0001
	20-24	556034	222	0.04	1.54	1.26-1.89	<0.0001
	25-29	641472	166	0.03	1	Ref	
	30-34	617240	173	0.03	1.08	0.88-1.34	0.46
	35-39	339859	96	0.03	1.09	0.85-1.40	0.49
	40-44	81340	28	0.03	1.33	0.89-1.99	0.16
Race	White	1967593	624	0.03	1	Ref	
	Black	157674	104	0.07	2.08	1.69-2.56	<0.0001
	Asian	296404	79	0.03	0.98	0.75-1.30	0.91
	Other	41517	25	0.06	0.96	0.72-1.28	0.76
Ethnicity	Hispanic	1122697	330	0.04	0.77	0.67-0.89	0.0003
	Non-Hispanic	1299812	495	0.03	1	Ref	
Maternal Education	Less than High School	690821	279	0.04	1	Ref	
	Completed High School	686473	250	0.04	0.9	0.76-1.07	0.24
	Some college, no degree	475268	176	0.04	0.92	0.76-1.11	0.37
	College	573331	106	0.02	0.46	0.37-0.57	<0.0001
Insurance	Medicare/Other Government	25300	33	0.13	3.75	2.63-5.36	<0.0001
	Medi-Cal	1069770	372	0.03	1	Ref	
	Private	1304717	307	0.02	0.68	0.58-0.79	<0.0001
	Indigent	52389	77	0.15	4.23	3.31-5.40	<0.0001
	Self-pay	3535	34	0.95	27.66	19.44-39.36	<0.0001
	Other	14626	10	0.07	1.97	1.05-3.69	0.03
Parity	Nulliparous	4854	*	*	1	Ref	
	1	955581	325	0.03	0.83	0.21-3.32	0.79
	2	784331	203	0.03	0.63	0.16-2.53	0.51
	≥3	725152	303	0.04	1.01	0.25-4.08	0.98
Prenatal Care	First Trimester	2140703	680	0.03	1.01	0.33-3.15	0.98
	Second Trimester	254252	124	0.05	1.56	0.50-4.89	0.45
	Third Trimester	49617	19	0.04	1.22	0.36-4.13	0.75
	None	9569	*	*	1	Ref	
Substance Abuse	Yes	26899	237	0.87	36.13	31.06-42.02	<0.0001
	No	2443792	596	0.02	1	Ref	
Mental Illness	Yes	17521	374	2.09	114.09	99.45-130.88	<0.0001
	No	2453170	459	0.02	1	Ref	

OR=odds ratio; CI=confidence interval; *=cell frequency<5: data not reported

Table 9. Rates of acute poisoning hospital discharges during pregnancy and for women of reproductive age, stratified by intent, 2000-2004.

	Pregnant (rate per 100,000 person years)	**Women of Reproductive Age (rate per 100,000 person years)**	**Rate Ratio**	**95% CI**
All Acute Poisoning Hospital Discharges	48.60	115.28	0.42	0.38-0.45
Intentional	29.93	79.08	0.37	0.34-0.40
Unintentional	14.06	24.74	0.57	0.50-0.65
Undetermined	1.98	6.98	0.28	0.20-0.39

CI=confidence interval

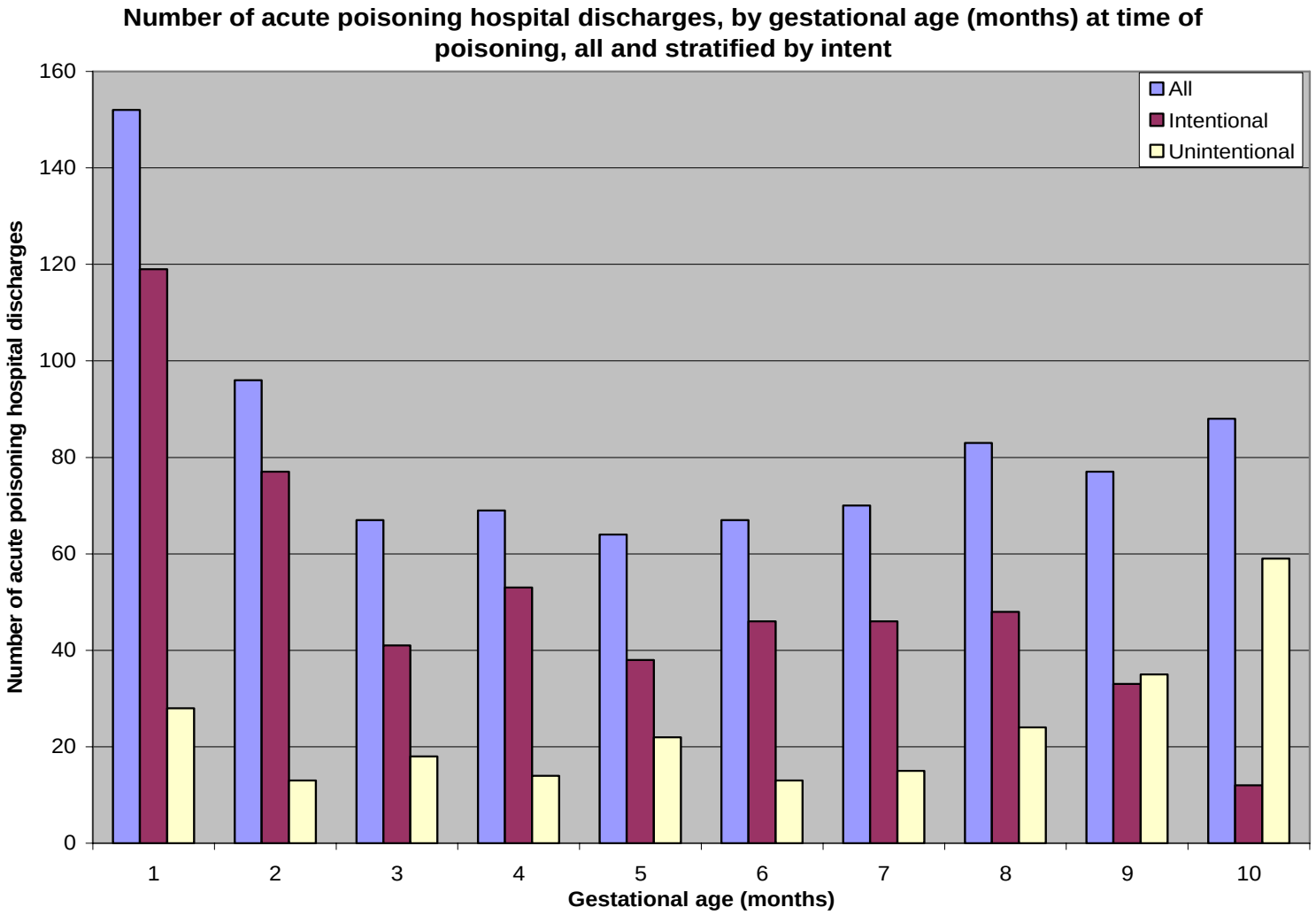

Figure 2. Number of acute poisoning hospital discharges during pregnancy by gestational age at time of poisoning; overall and stratified by intent.

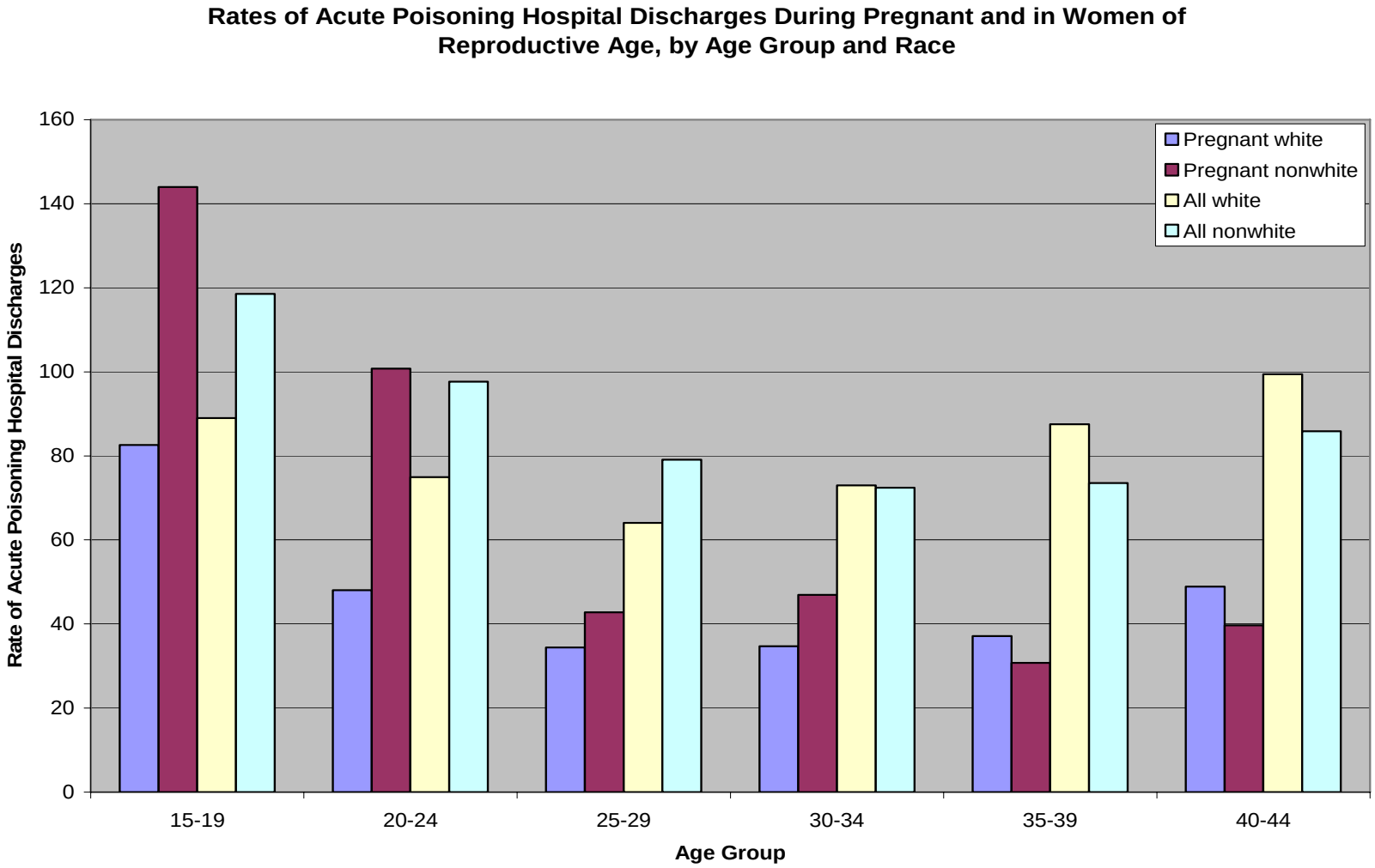

Figure 3. Rates of acute poisoning hospital discharges during pregnancy and in all women of reproductive age stratified by age group and race.

3.0 ARTICLE TWO: BIRTH OUTCOMES FOLLOWING ACUTE POISONING HOSPITAL DISCHARGE DURING PREGNANCY

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3.1 ABSTRACT

Objective: The purpose of this study was to describe the patterns of birth outcomes following acute poisoning hospital discharge during pregnancy.

Methods: The Vital Statistics-Patient Discharge Database (VSPDD), maintained by the California Office Statewide Health Planning and Development, was utilized to identify cases of acute poisoning hospital discharge. An analyses of birth outcomes following acute poisoning hospital discharge during pregnancy is presented.

Results: There were 2,216,214 deliveries fulfilling the study criteria identified in the Vital Statistics-Patient Discharge Database between 2000 and 2004. Seven hundred twenty-four women with hospital discharges for an acute poisoning during pregnancy were documented in the dataset (population-based rate 43.56/100,000 person-years); 35% occurred in the first trimester, 28% in the second trimester and 37% in the third trimester. Analgesics were the leading substances implicated in acute poisoning hospitalization during pregnancy. Young black women and women with substance abuse or mental health problems were at greatest risk of acute poisoning hospital discharge. Adverse birth outcomes associated with acute poisoning included preterm delivery, respiratory distress, cesarean delivery, and other cardiac congenital anomalies. Infants born to women in the immediate-delivery group exhibited higher rates of respiratory distress and preterm delivery. Infants born to women with an acute poisoning during pregnancy were at a greater risk of preterm delivery and other cardiac congenital anomalies.

Conclusions: Acute poisoning during pregnancy was associated with adverse birth outcomes including preterm delivery, respiratory distress, cesarean delivery, and other cardiac congenital anomalies.

Although the etiologies of the reported adverse outcomes are speculative, it can be suggested that substance abuse or other risk-taking behaviors associated with acute poisoning may confound the relationship between poisoning and congenital anomalies. Young black women and women with substance abuse or mental health problems were at greatest risk of an acute poisoning hospital discharge during pregnancy. Public health professionals should implement programs to inform patients on the proper use of over the counter medications. In addition, substance abuse and mental health screening with appropriate referral by an obstetrician/gynecologist or treating physician may prevent acute poisonings in high-risk women.

3.2 INTRODUCTION

Poisonings are the leading cause of injury hospitalization in women of reproductive age and the third leading cause of injury hospitalization during pregnancy (CDC WISQARS 2001-2004; Weiss et al., 2002). It can be argued that acute poisonings during pregnancy pose a greater financial and health-care burden than in non-pregnant women because not only is the woman affected, but the fetus as well. Further, the consequences of acute poisoning on maternal, fetal and newborn outcomes are not well documented.

The aim of this study was to describe the patterns of birth outcomes following acute poisonings during pregnancy, including: preterm delivery, low birth weight, respiratory distress, fetal distress, birth asphyxia, congenital anomalies and fetal, and neonatal and infant death.

3.3 METHODS

A study was conducted to determine the epidemiology of acute poisoning in pregnant women based on hospital discharges data. The Vital Statistics-Patient Discharge Database (VSPDD), maintained by the California Office Statewide Health Planning and Development was utilized. All California licensed hospitals are mandated to semi-annually submit specific data on every discharged patient. These data include: patient demographic information, diagnostic and treatment information, disposition, total hospital charges and payer source. The VSPDD includes data from several sources including: California Patient Discharge Data, Vital Statistics Birth Certificate Data, Vital Statistics Death Certificate Data, the Vital Statistics Fetal Death File and the Vital Statistics Birth Cohort File. It includes maternal antepartum

and postpartum hospital records for the nine months prior to, and one year post-delivery. The database also includes birth records and all infant readmissions occurring in the first year of life. Linkage was successful in 98% of the cases. Detailed linkage procedures have been described previously (Herrchen et. al., 1997).

This study was approved by the University of Pittsburgh Institutional Review Board, the California Department for the Protection of Human Subjects and the California Office of Statewide Health Planning and Development. No unique patient identifiers were included in the database.

Acute poisoning hospital discharges were identifed by the presence of the following International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis and external cause of injury codes: 960-979 (poisoning by drugs, medicinal, and biological substances), 980-989 (toxic effects of substances chiefly nonmedicinal as to source), E850-E858 (accidental poisoning by drugs, medicinal substances, and biologicals), E860.2-E869 (accidental poisoning by other solid and liquid substances, gases, and vapors), E905 (venomous animals and plants as the cause of poisoning and toxic reactions), E950-E952 (suicide and self-inflicted poisoning), E962 (assault by poisoning) and E980-E982 (poisoning, undetermined whether accidentally or purposely inflicted).

All hospital discharges for acute poisonings in pregnant women aged between 15 and 44, who had a pregnancy outcome consisting of a singleton live birth or fetal death that occurred between gestational ages 20 and 42 weeks, were identified in the linked VSPDD. Women with an acute poisoning hospital discharge during pregnancy were compared to all other women, aged between 15 and 44, who had a pregnancy outcome consisting of a singleton live birth or fetal death that occurred between gestational age 20 and 42 weeks, with non-poisoning hospital discharges during pregnancy, for the years 2000 through 2004.

Incidence rates were cacluated per 100,000 person years, following the methodology used by Greenblatt et. al. (1997). For the pregnant population, denominators were adjusted downward to account for the nine of twelve months of the year a woman is pregnant.

Data were summarized as means plus or minus the standard deviation or median interquartile range for continuous variables and frequencies for categorical variables. In order to determine statistical signficance, t-tests or Wilcoxon rank sum tests were computed for continuous variables and the chi-square test was computed for categorical variables. Odd ratios and 95% confidence intervals were caclulated for risk factors using logistic regression analyses.

Birth outcomes were identified by the presence of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes or by notation in the dataset. Preterm delivery was defined as birth at less than 37 weeks gestation. Low birth weight was defined as a birth weight less than 2,500 grams and extremely low birth weight as less than 1,500 grams. Fetal death was defined as an intrauterine death identified by a fetal death certificate. Neonatal death was defined as death within 30 days of life, and infant death was defined as death before one year of age. Cesarean delivery was defined by note on birth certificate. Respiratory distress, fetal distress, birth asphyxia and non-chromosomal congenital anomalies were determined utilizing ICD-9-CM codes as listed in Table 10.

Odds ratios and 95% confidence intervals were calculated to determine if acute poisoning hospital discharge was associated with birth outcome. Reported odds ratios are adjusted for age, race, ethnicity, maternal education, and insurance payer.

Further analyses based on timing of delivery was performed with subsets of the study group. Specifically, women who delivered at time of poisoning (immediate-delivery) and those who were discharged for an acute poisoning and delivered at a later hospitalization (later-delivery) were further assessed.

All analyses were calculated using SAS 8.2 software. All p-values less than 0.05 were considered statistically significant.

3.4 RESULTS

There were 2,216,214 deliveries fulfilling the study criteria identified in the Vital Statistics-Patient Discharge Database between 2000 and 2004. Seven hundred twenty four women with hospital discharges for an acute poisoning during pregnancy were identified in the dataset (population-based rate 43.56/100,000 person-years). Among poisonings with a valid E-code, 434 (63.5%) were intentional, 222 (32.5%) unintentional and 27 (4.0%) were of undetermined intent.

The distribution of acute poisoning hospital discharges by gestational age is presented in Figure 4. Of all acute poisoning hospital discharges during pregnancy, 35% occurred in the first trimester, 28% in the second trimester and 37% in the third trimester. The rate of acute poisoning hospital discharges differed significantly between the second and third trimesters (rates 15.22, 12.21, and 16.21 per 100,000 person-years, respectively).

There were 126 (17.40%) deliveries that occurred at the time of poisoning hospitalization. Delivery occurred on the same day as the poisoning hospitalization in 63% of these cases and 92% within 48 hours. The median gestational age of deliveries occurring at the time of poisoning hospitalization was 272 days (IQR (261-281). Of the remaining 598 cases, the mean time from poisoning hospital discharge to delivery was 165 days (IQR 86-235). The median gestational age at delivery of infants who were exposed to a poisoning in utero but were not delivered at the time of poisoning hospitalization was 275 days (IQR (266-283).

The diagnostic codes of the five leading substances implicated in acute poisoning hospital discharges during pregnancy are presented in Table 11. In addition, the five leading substances identified by E-codes and stratified by intent are also listed. Analgesics were the leading substances implicated in acute poisonings during pregnancy.

Demographic characteristics of women with an acute poisoning hospital discharge during pregnancy are shown in Table 12. This analysis determined that compared to women of other age groups, pregnant women aged between 15 and 24 were most likely to be hospitalized for an acute poisoning. African American women were more likely to be hospitalized for an acute poisoning hospital discharge during pregnancy when compared to Caucasian women. In addition, non-Hispanic women were more likely to be hospitalized for an acute poisoning hospital discharge when compared to Caucasian and Hispanic women. Women with less than a high school education had the greatest odds of acute poisoning hospitalization during pregnancy when compared to women with additional schooling. In addition, pregnant women with private insurance were least likely to be hospitalized for an acute poisoning when compared to women with other insurance payers. Neither parity nor initiation of prenatal care was associated with acute poisoning hospital discharge during pregnancy. The presence of concomitant substance abuse and mental illness were each associated with higher odds of acute poisoning hospitalization during pregnancy.

The influence of acute poisoning hospital discharge on birth outcome is presented in Table 13. Compared to birth outcomes in women with non-poisoning hospital discharges, birth outcomes in women with an acute poisoning showed higher rates of respiratory distress, low birth weight, preterm delivery, cesarean delivery, and cardiac congenital anomalies. This held true after controlling for age, race, ethnicity, insurance payer and maternal education. Once gestational age was incorporated into the multivariable model, respiratory distress, cesarean delivery and cardiac congenital anomalies remained statistically significant (OR=1.77, 95%CI (1.03-3.04), p=0.04; OR=1.20, 95%CI (1.01-1.42), p=0.04; OR=2.40, 95%CI (1.14-5.06), p=0.02, respectively). Low birth weight was no longer significantly associated with acute poisoning after controlling for gestational age. When substance abuse was incorporated into the model including age, race, ethnicity, insurance payer, and maternal education, preterm delivery was the only adverse outcomes associated with acute poisoning hospitalization (OR=2.19, 95% CI (1.05-4.61), p=0.04).

Infants born to women in the immediate-delivery group demonstrated higher rates of low birth weight, extremely low birth weight, respiratory distress, cesarean delivery and preterm delivery in multivariable models controlling for age, race, ethnicity, insurance payer and maternal education ($p<0.05$) (see Table 14). After incorporating gestational age to the model, low birth weight and extremely low birth weight no longer remained significantly associated with acute poisoning hospitalization. However, respiratory distress and cesarean delivery remained significantly associated with acute poisoning hospital discharge at time of delivery (OR=3.20, 95%CI 1.28-7.98, p=0.01 and OR=1.96, 95%CI 1.35-2.85, p=0.0004, respectively). When substance abuse was introduced to the multivariable model, preterm delivery remained significantly associated with acute poisoning hospital discharge (OR=1.92, 95%CI 1.22-3.01, p=0.005). When substance abuse was introduced to the model including age, race, ethnicity, insurance payer, maternal education, and gestational age acute poisoning hospital discharge at time of delivery remained significantly associated with respiratory distress and cesarean delivery (OR=3.00, 95%CI 1.20-7.47, p=0.02 and OR=1.93, 95%CI 1.33-2.81, p=0.0006, respectively).

Acute poisoning hospital discharge and delivery at a later date was associated with preterm delivery and cardiac congenital anomalies in a multivariable model controlling for age, race, ethnicity, insurance payer and maternal education ($p<0.05$). Once gestational age was added to the multivariable model, cardiac congenital anomalies remained significantly associated with acute poisoning (OR=2.58, 95%CI 1.15-5.76, p=0.02). After substance abuse was added to the model including age, race, ethnicity, insurance payer, and maternal education, acute poisoning with delivery at a later date was associated with preterm delivery (OR=1.92, 95% CI, 1.22-3.01, p=0.005).

3.5 DISCUSSION

This is the one of the first population based studies to examine birth outcomes following acute poisoning hospital discharge during pregnancy. The data are derived from a very large, heterogeneous

statewide population. A limited number of population-based studies of self-poisoning during pregnancy exist, and the majority of previous reports are only case studies and series. Acute poisonings of all intents were included in this analysis. Poisonings occurring in the first weeks of pregnancy were included; most data sources are limited to recognizable pregnancies and thus do not include poisonings in the first few weeks of gestation.

This analysis revealed that women with an acute poisoning hospital discharge during pregnancy were at a greater risk of preterm delivery, respiratory distress, cesarean delivery, and other cardiac congenital anomalies. Observations of significant associations of acute poisonings with adverse birth outcomes have been paradoxically both supported and contradicted in the literature. Czeizel et. al. (1988) and Czeizel (1984) reported no association of drug toxicity with any of the following: mean birth weight, low birth weight, spontaneous abortion, major or minor congenital anomalies, infant mortality or specific childhood diseases. However, self-poisoning during pregnancy was reported to be significantly associated with lower mean birth weight, low birth weight and intrauterine growth restriction in other published reports (Czeizel et. al., 1988; Lendvay and Czeizel, 1992; Czeizel, 1996). In addition, a recent analysis utilizing hospital discharge data from California reported that suicide during pregnancy was associated with neonatal and infant death, preterm delivery and respiratory distress syndrome (Ghandi et. al., 2006). The data are inconclusive and outcomes are likely to vary based on severity, type and timing of poisoning, as well as potential confounders such as: substance abuse, stress, illnesses, medication use and other risk-taking behaviors. Larger, more powerful studies should examine birth outcomes following acute poisonings focusing on the aforementioned variables.

Offspring of women in the immediate-delivery group exhibited higher rates of respiratory distress and preterm delivery. In this group, the majority of deliveries occurred on the same day of poisoning hospitalization. These infants also had significantly lower gestational age at delivery than infant born to women who delivered later. These observations suggest that poisoning may have initiated a cascade of events leading to delivery. The risk of respiratory distress was five times greater in neonates born to women with an acute poisoning. It is possible that certain substances implicated in poisonings may illicit

respiratory distress. However, the events preceding delivery and the extent to which the acute poisoning actually influenced the course of delivery are unknown. In addition, information regarding the use of interventions to prolong or hasten delivery is unknown. Future research should more closely examine the events preceding delivery in association with acute poisonings.

Infants born to women with an acute poisoning hospital discharge during pregnancy with delivery at a later date exhibited higher rates of preterm delivery and cardiac congenital anomalies. Although these women were more likely to delivery prematurely, they did not deliver until later. The women whose infants suffered cardiac congenital anomalies were discharged for poisonings during different periods of their pregnancy and varied substances were implicated in the poisonings (Table 6). The observed association between acute poisoning in the weeks following the development of the heart with the prevalence of respective congenital anomalies suggests the presence of other confounding variables, particularly substance abuse.

Although the etiologies of the reported adverse outcomes are speculative, it can be suggested that substance abuse, stress, or other risk-taking behaviors associated with acute poisoning may confound the relationship between poisoning and congenital anomalies. It is difficult to quantify these factors from the existing data. Future research should focus data collection on potential confounders specifically substance abuse, mental illness, stress, medical, social, and behavioral risk factors that would influence birth outcomes, especially during the time of organogenesis.

The immediate-delivery group may not provide health care providers sufficient time to intervene; therefore, efforts to improve outcomes should focus on prevention. Public health professionals should implement programs to inform patients on the proper use of over-the-counter medications. In addition, healthcare providers should inform patients about potentially deleterious, active ingredients in over-the-counter medications. Substance abuse and mental health screening with appropriate referral by an obstetrician/gynecologist or treating physician may help prevent acute poisonings in high-risk women. In addition education and screening should be implemented following delivery to women who suffered an

overdose to prevent future poisonings and to improve the health and well-being of both the infant and mother.

There are several limitations to this study. It utilizes administrative data which may include possible coding and reporting errors. In addition, this study may have selection bias as the dataset included hospitalized poisonings only and excluded deliveries prior to 20 weeks gestation and coroner's cases, which may lead to an underestimate of the true number of acute poisoning cases.

Future research in the field of intentional acute poisoning should make an effort to distinguish poison severity. Currently, neither the Injury Severity Score System nor hospital administrative data provides indications of the dose of substance implicated in a poisoning. Birth outcomes are likely to differ based on the severity of the poisoning. Additionally, birth outcomes are likely to differ based on the agent implicated in the poisoning. Future studies with sufficient power to examine the effects of specific agents on birth outcomes should be planned.

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Table 10. ICD-9-CM code definitions for birth outcomes.

Birth Outcomes	**ICD-9-CM Code(s)**
Birth Asphyxia	7685,7686, 7687, 7689
Fetal distress	6563, 7682, 7683, 7684
Respiratory distress	769
Non-chromosomal anomalies	
Anancephalus and similar anomalies	740
Bulbus cordis anomalies and anomalies of cardiac septal closure	745
Certain congenital musculoskeletal deformities	754
Cleft palate and cleft lip	749
Congenital anomalies of genital organs	752
Congenital anomalies of the ear, face, and neck	744
Congenital anomalies of the eye	743
Congenital anomalies of the integument	757
Congenital anomalies of the respiratory system	748
Congenital anomalies of the urinary system	753
Other congenital anomalies of limbs	756
Other congenital anomalies of nervous system	742
Other congenital anomalies of the circulatory system	747
Other congenital anomalies of the digestive system	751
Other congenital anomalies of the heart	746
Other congenital anomalies of upper alimentary tract	750
Other congenital musculoskeletal anomalies	756
Spina bifida	741

Table 11. Substances implicated in acute poisoning hospitalizations during pregnancy and substance specific population-based rates by diagnosis code and by E-code, stratified by intent.

All (Diagnosis Code)	**Rate (per 100,000 person- years)**
Poisoning by aromatic analgesics, NEC Acetanilid; Paracetamol [acetaminophen]; Phenacetin [acetphenetidin]	9.99
Poising by antidepressants Amitriptyline; Imipramine; Monoamine Oxidase [MAO] Inhibitors	3.61
Poisoning by benzodiazepine-based tranquilizers Chlordiazepoxide; Diazepam; Flurazepam; Lorazepam; Medazepam; Nitrazepam	2.83
Poisoning by salicylates Acetylsalicylic acid [aspirin]; Salicylic acid salts	2.59
Poisoning by antirheumatics (antiphlogistics) Propionic acid derivatives Fenoproten; Fluriprofen; Ibruprofen; Ketoprofen; Naproxen; Oxaprozin	
Intentional (E-Code)	
Suicide and self-inflicted poisoning by analgesics, antipyretics, and antirheumatics	12.93
Suicide and self-inflicted poisoning by other specified drugs and medicinal substances	8.84
Suicide and self-inflicted poisoning by tranquilizers and other psychotropic agents	6.32
Suicide and self-inflicted poisoning by other and unspecified solid and liquid substances	1.38
Suicide and self-inflicted poisoning by other sedatives and hypnotics	0.54
Unintentional (E-Code)	
Accidental poisoning by aromatic analgesics, NEC Acetanilid; Paracetamol [acetaminophen]; Phenacetin [acetophenetidin]	1.68
Venomous spiders causing poisoning and toxic reactions Black widow spider; Brown spider; Tarantula (venomous)	1.08
Accidental poisoning by second-hand tobacco smoke	1.02
Accidental poisoning by anticonvulsant and anti-parkinsonism drugs Amantadine; Hydantoin derivatives; Levodopa [L-dopa]; Oxazolidine derivatives [paramethadione] [trimethadione]; Succinimides	0.90
Accidental poisoning by other opiates and related narcotics Codeine [methylmorphine]; Meperidine [pethidine]; Morphine; Opium (alkaloids)	0.78

Table 12. Demographic Characteristics of Women with Acute Poisoning Hospital Discharge During Pregnancy and Non-Poisoning Hospital Discharge During Pregnancy, 2000-2004.

		Non-Poisoning Hospital Discharge During Pregnancy Control N=2,215,490	Poisoning Hospital Discharge During Pregnancy N=724				
Characteristic	**Category**	**n**	**n**	**%**	**OR**	**95%CI**	**P**
Maternal Age	15-19	211458	142	0.07	2.6	2.06-3.27	<0.0001
	20-24	499769	204	0.04	1.58	1.28-1.95	<0.0001
	25-29	579672	150	0.03	1	Ref	
	30-34	554635	140	0.03	0.98	0.78-1.23	0.83
	35-39	299906	65	0.02	0.84	0.63-1.12	0.23
	40-44	70050	23	0.03	1.27	0.82-1.97	0.29
Race	White	1769223	543	0.03	1	Ref	
	Black	130531	85	0.07	2.12	1.69-2.67	<0.0001
	Asian	272143	71	0.03	0.98	0.73-1.31	0.87
	Other	36644	24	0.07	1.03	0.77-1.39	0.84
Ethnicity	Hispanic	1021208	311	0.03	0.87	0.75-1.00	0.05
	Non-Hispanic	1150066	405	0.04	1	Ref	
Maternal Education	Less than High School	627022	267	0.04	1	Ref	
	Completed High School	612110	208	0.03	0.8	0.67-0.96	0.01
	Some college, no degree	421636	137	0.03	0.76	0.62-0.94	0.01
	College	514835	92	0.02	0.42	0.33-0.53	<0.0001
Insurance	Medicare/Other Government	21440	29	0.14	3.89	2.66-5.69	<0.0001
	Medi-Cal	958375	333	0.03	1	Ref	
	Private	1170391	262	0.02	0.64	0.55-0.76	<0.0001
	Indigent	48737	65	0.13	3.84	2.94-5.01	<0.0001
	Self-pay	3072	28	0.90	26.23	17.81-38.64	<0.0001
	Other	13151	7	0.05	1.53	0.73-3.24	0.26
Parity	Nulliparous	3980	*	*	1	Ref	
	1	872506	300	0.03	0.68	0.17-2.75	0.59
	2	704959	180	0.03	0.51	0.13-2.05	0.34
	≥3	633402	242	0.04	0.76	0.19-3.06	0.7
Prenatal Care	First Trimester	1914651	597	0.03	0.91	0.29-2.83	0.87
	Second Trimester	231225	100	0.04	1.26	0.40-3.99	0.7
	Third Trimester	45965	17	0.04	1.08	0.32-3.70	0.9
	None	8768	*	*	1	Ref	
Substance Abuse	Yes	23714	222	0.93	40.87	34.88-47.89	<0.0001
	No	2191776	502	0.02	1	Ref	
Mental Illness	Yes	14304	336	2.30	133.26	115.05-154.36	<0.0001
	No	2201186	388	0.02	1	Ref	

OR=odds ratio; CI=confidence interval; *=cell frequency<5: data not reported

Table 13. Birth outcomes following acute poisoning hospital discharge during pregnancy and non-poisoning hospital discharge during pregnancy.

Birth Outcome	Non-Poisoning Hospital Discharge N=2,215,490		Acute Poisoning Hospital Discharge N=724				
	n	%	n	%	AOR	95%CI	p
Preterm Delivery	225820	10.19	108	14.92	1.5	1.22-1.85	0.0002
Cesarean Delivery	565030	25.5	202	27.9	1.22	1.03-1.45	0.02
Low Birth Weight	118062	5.33	60	8.29	1.54	1.18-2.02	0.002
Extremely Low Birth Weight	23833	1.08	12	1.66	1.35	0.72-2.52	0.35
Birth Asphyxia	3569	0.16	*	*	0.92	0.13-6.53	0.93
Respiratory Distress	27172	1.23	18	2.49	1.89	1.15-3.11	0.01
Fetal Distress	10523	0.47	6	0.83	1.53	0.63-3.69	0.34
Fetal Death	9304	0.42	5	0.69	1.42	0.53-3.78	0.49
Neonatal Death	6066	0.27	*	*	0.53	0.08-3.73	0.53
Infant Death	3119	0.14	*	*	2.67	0.86-8.29	0.09
Anancephalus and similar anomalies	107	0	0	0			
Bulbus cordis anomalies and anomalies of cardiac septal closure	22001	0.99	9	1.24	1.19	0.59-2.38	0.63
Certain congenital musculoskeletal deformities	9658	0.44	*	*	0.34	0.05-2.42	0.28
Cleft palate and cleft lip	3826	0.17	*	*	0.83	0.12-5.93	0.86
Congenital anomalies of genital organs	16797	0.76	*	*	0.19	0.03-1.37	0.1
Congenital anomalies of the ear, face, and neck	5689	0.26	*	*	1.14	0.28-4.56	0.86
Congenital anomalies of the eye	2849	0.13	0	0			
Congenital anomalies of the integument	46535	2.1	19	2.62	1.3	0.82-2.05	0.26
Congenital anomalies of the respiratory system	5842	0.26	*	*	1.10	0.28-4.41	0.89
Congenital anomalies of the urinary system	8582	0.39	*	*	0.39	0.06-2.76	0.35
Other congenital anomalies of limbs	9880	0.45	*	*	1.27	0.47-3.38	0.64
Other congenital anomalies of nervous system	4466	0.2	*	*	1.42	0.36-5.68	0.62
Other congenital anomalies of the circulatory system	30944	1.4	15	2.07	1.36	0.79-2.36	0.27
Other congenital anomalies of the digestive system	5202	0.23	*	*	1.22	0.31-4.90	0.78
Other congenital anomalies of the heart	9042	0.41	7	0.97	2.54	1.21-5.34	0.01

Table 13 continued

Other congenital anomalies of upper alimentary tract	7951	0.36	*	*	1.62	0.60-4.32	0.34
Other congenital musculoskeletal anomalies	7754	0.35	*	*	0.81	0.20-3.25	0.77
Spina bifida	685	0.03	0	0			
Congenital anomalies of any type	155220	7.01	53	7.32	1.06	0.80-1.41	0.69

AOR=Adjusted odds ratio; odds ratio adjusted for age, race, ethnicity, maternal education, insurance payer; CI=confidence interval; *=cell frequency<5: data not reported

Table 14. Birth outcomes following acute poisoning hospital discharge during pregnancy and non-poisoning hospital discharge during pregnancy, stratified by time of poisoning.

Birth Outcome	Non-poisoning hospital discharge N=2,215,490		Acute poisoning at delivery N=126					Acute poisoning hospital discharge and later delivery N=598				
	n	%	N	%	AOR	95%CI	p	n	%	AOR	95%CI	p
Preterm Delivery	225820	10.19	26	20.63	2.42	1.55-3.77	<0.0001	82	13.71	1.33	1.05-1.69	0.02
Cesarean Delivery	565030	25.50	54	42.86	2.09	1.44-3.03	0.0001	148	24.75	1.07	0.88-1.30	0.48
Low Birth Weight	118062	5.33	16	12.70	2.62	1.52-4.50	0.0005	44	7.36	1.34	0.98-1.84	0.07
Extremely Low Birth Weight	23833	1.08	6	4.76	4.19	1.72-10.21	0.002	6	1	0.8	0.33-1.94	0.63
Birth Asphyxia	3569	0.16	*	*	5.3	0.74-37.94	0.1	0	0			
Respiratory Distress	27172	1.23	8	6.35	5.08	2.37-10.92	<0.0001	10	1.67	1.27	0.66-2.46	0.48
Fetal Distress	10523	0.47	*	*	3.72	0.92-14.99	0.06	*	*	1.1	0.35-3.42	0.87
Fetal Death	9304	0.42	*	*	2.17	0.30-15.53	0.44	*	*	1.27	0.41-3.96	0.68
Neonatal Death	6066	0.27	*	*	3.25	0.45-23.20	0.24	0	0			
Infant Death	3119	0.14	*	*	6.17	0.86-44.06	0.07	*	*	2.08	0.52-8.32	0.3
Anancephalus and similar anomalies	107	0.00	0	0				0	0			
Bulbus cordis anomalies and anomalies of cardiac septal closure	22001	0.99	*	*	1.74	0.43-7.04	0.44	7	1.17	1.07	0.48-2.40	0.86
Certain congenital musculoskeletal deformities	9658	0.44	0	0				*	*	0.41	0.06-2.92	0.9
Cleft palate and cleft lip	3826	0.17	0	0				*	*	1	0.14-7.13	1
Congenital anomalies of genital organs	16797	0.76	0	0				*	*	0.24	0.03-1.66	0.15
Congenital anomalies of the ear, face, and neck	5689	0.26	*	*	3.29	0.46-23.49	0.24	*	*	0.69	0.10-4.90	0.71
Congenital anomalies of the eye	2849	0.13	0	0				0	0			
Congenital anomalies of the integument	46535	2.10	*	*	1.21	0.38-3.82	0.75	16	2.68	1.32	0.80-2.17	0.28
Congenital anomalies of the respiratory system	5842	0.26	0	0				*	*	1.33	0.33-5.32	0.69
Congenital anomalies of the urinary system	8582	0.39	0	0				*	*	0.47	0.07-3.36	0.45
Other congenital anomalies of limbs	9880	0.45	*	*	3.91	0.98-15.67	0.05	*	*	0.76	0.19-3.03	0.69
Other congenital anomalies of nervous system	4466	0.20	*	*	4.33	0.61-30.98	0.14	*	*	0.85	0.12-6.01	0.87
Other congenital anomalies of the circulatory system	30944	1.40	*	*	1.22	0.30-4.93	0.78	12	2.01	1.39	0.77-2.53	0.28
Other congenital anomalies of the digestive system	5202	0.23	*	*	3.69	0.52-26.19	0.19	*	*	0.74	0.10-5.22	0.76

Table 14 continued

Other congenital anomalies of the heart	9042	0.41	*	*	2.1	0.29-15.04	0.46	6	1	2.61	1.17-5.83	0.02
Other congenital anomalies of upper alimentary tract	7951	0.36	*	*	2.42	0.34-17.23	0.38	*	*	1.46	0.47-4.53	0.52
Other congenital musculoskeletal anomalies	7754	0.35	0	0				*	*	0.97	0.24-3.88	0.96
Spina bifida	685	0.03	0	0				0	0			
Congenital anomalies of any type	155220	7.01	16	12.7	1.37	0.74-2.56	0.32	41	6.86	1.00	0.72-1.37	0.98

AOR=Adjusted odds ratio; odds ratio adjusted for age, race, ethnicity, maternal education, insurance payer; CI=confidence interval; *=cell frequency<5: data not reported

Table 15. Characteristics of acute poisoning hospital discharge resulting in other cardiac congenital anomalies.

Case number	Substance	Intent	Maternal age	Gestational age at time of poisoning	Days between poisoning and birth	Gestational age at birth
1	Salicylates and Propionic Acid Derivative	Intentional	19	69	165	234
2	Toxic Effect Gas/Vapor	Unintentional	38	274	1	275
3	Salicylates	Intentional	20	129	151	280
4	Medicinal Agent NEC	Undetermined	38	119	134	253
5	Salicylates and Propionic Acid Derivatives	Unintentional	18	98	142	240
6	Antipsychotic NEC	Intentional	25	27	228	255
7	Antidepressant	Intentional	23	155	131	286

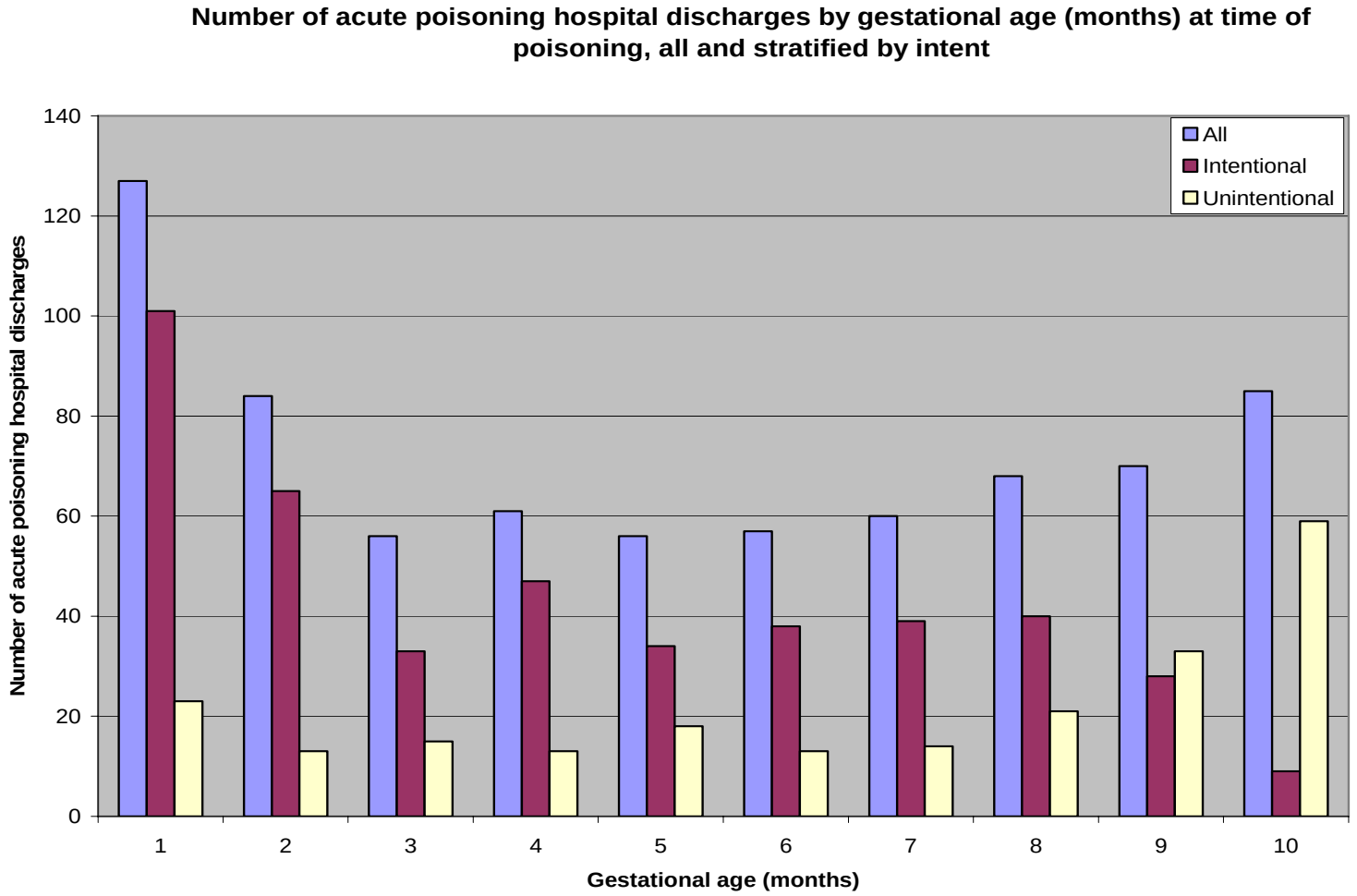

Figure 4. Number of acute poisoning hospital discharges during pregnancy by gestational age at time of poisoning; overall and stratified by intent.

4.0 ARTICLE THREE: BIRTH OUTCOMES FOLLOWING INTENTIONAL ACUTE POISONING HOSPITAL DISCHARGE DURING PREGNANCY

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4.1 ABSTRACT

Objective: The purpose of this study was to describe the patterns of birth outcomes following intentional (suicide, attempted suicide and self-inflicted injuries specified as intentional) acute poisoning hospital discharge during pregnancy

Methods: The Vital Statistics-Patient Discharge Database (VSPDD), maintained by the California Office Statewide Health Planning and Development, was utilized to identify cases of intentional acute poisoning hospital discharge. An analysis of birth outcomes following intentional acute poisoning hospital discharge during pregnancy is presented.

Results: There were 2,215,920 deliveries fulfilling the study criteria identified in the Vital Statistics-Patient Discharge Database from 2000-2004. Four hundred thirty hospital discharges for an intentional acute poisoning during pregnancy were documented (population-based rate 25.87/100,000 person-years). The rates of intentional acute poisoning hospital discharge were greatest in first weeks of gestation, and declined with increasing gestational age. Analgesics, antipyretics, and antirheumatics were the most common substances implicated in intentional poisonings. Young black women and women with substance abuse or mental health problems were at greatest risk of intentional acute poisonings. Adverse birth outcomes associated with intentional acute poisoning included preterm delivery and low birth weight. Infants born to women that were discharged for an intentional acute poisoning hospital discharge within the first nine weeks of gestation exhibited higher rates of low birth weight. In women who were discharged with an intentional acute poisoning between gestational weeks 10 and delivery, intentional acute poisoning hospital discharge was associated with greater rates of circulatory system congenital anomalies and respiratory system congenital anomalies. However, these relationships may be confounded

by factors such as substance abuse, medical, social and behavioral factors that may also influence birth outcomes.

Conclusions: Intentional acute poisoning during pregnancy was associated with adverse birth outcomes including preterm delivery, low birth weight, and congenital anomalies. Young black women and women with substance abuse and mental illness were at greatest risk of intentional acute poisoning hospital discharge. Pre-natal visits with an obstetrician or primary care physician could allow for substance abuse and mental health screening and referral opportunities for high-risk women to help prevent intentional acute poisonings during pregnancy.

4.2 INTRODUCTION

Poisonings are the most frequent method of self-inflicted, non-fatal injury in women (Schnitzer and Runyan, 1995). Of all pregnant women attempting suicide in California, 86% attempted by ingestion of a solid or liquid, primarily by drug overdose or poisoning with a corrosive substance (Ghandi et. al., 1999). Although common among non-pregnant women, intentional poisonings during pregnancy have only recently garnered attention. It is conceivable that poisonings during pregnancy pose a greater burden than in non-pregnant women due to their potential deleterious effects not only on the mother, but on the fetus as well.

The aim of this study was to describe the patterns of birth outcomes following intentional acute poisonings during pregnancy, including: preterm delivery, low birth weight, respiratory distress, fetal distress, birth asphyxia, congenital anomalies and fetal, neonatal and infant death.

4.3 METHODS

A study was conducted to determine the epidemiology of acute poisoning hospital discharge in pregnant women. The Vital Statistics-Patient Discharge Database (VSPDD), maintained by the California Office Statewide Health Planning and Development was utilized. All California licensed hospitals are mandated to semi-annually submit specific data on every discharged patient. These data include: patient demographic information, diagnostic and treatment information, disposition, total hospital charges and payer source. The VSPDD includes data from several sources including: California Patient Discharge Data, Vital Statistics Birth Certificate Data, Vital Statistics Death Certificate Data, the Vital Statistics Fetal Death File and the Vital Statistics Birth Cohort File. It includes maternal antepartum and postpartum

hospital records for the nine months prior to, and one year post-delivery. The database also includes birth records and all infant readmissions occurring in the first year of life. Linkage was successful in 98% of the cases. Detailed linkage procedures have been described previously (Herrchen et. al., 1997).

This study was approved by the University of Pittsburgh Institutional Review Board, the California Department for the Protection of Human Subjects and the California Office of Statewide Health Planning and Development. No unique patient identifiers were included in the database.

Intentional acute poisoning hospital discharges were identifed by the presence of an International Classification of Diseases, Ninth Revision, Clinical Modification External Cause of Injury Codes (ICD-9-CM E-Code) E950-E952 (suicide, attempted suicide and self-inflicted injuries specified as intentional).

All hospital discharges for intentional acute poisonings in pregnant women aged between 15 and 44, who had a pregnancy outcome consisting of a singleton live birth or fetal death that occurred between gestational ages 20 and 42 weeks, were identified in the linked VSPDD. Women with an intentional acute poisoning hospital discharge during pregnancy were compared to all other women, aged between 15 and 44, who had a pregnancy outcome consisting of a singleton live birth or fetal death that occurred between gestational age 20 and 42 weeks, with non-poisoning hospital discharges during pregnancy, for the years 2000-2004.

Incidence rates were calculated per 100,000 person years, following the methodology used by Greenblatt et. al. (1997). For the pregnant population, denominators were adjusted downward to account for the nine of twelve months of the year the woman is pregnant..

Data were summarized as means plus or minus the standard deviation or median interquartile range for continuous variables and frequencies for categorical variables. In order to determine statistical signficance, t-tests or Wilcoxon rank sum tests were computed for continuous variables and the chi-square test was computed for categorical variables. Odd ratios and 95% confidence intervals were caclulated for risk factors using logistic regression analyses.

Birth outcomes were identified by the presence of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes or by notation in the dataset. Preterm delivery was defined as birth at less than 37 weeks gestation. Low birth weight was defined as a birth weight less than 2,500 grams and extremely low birth weight as less than 1,500 grams. Fetal death was defined as an intrauterine death identified by a fetal death certificate. Neonatal death was defined as death within 30 days of life, and infant death was defined as death before one year of age. Cesarean delivery was defined by note on birth certificate. Respiratory distress, fetal distress, birth asphyxia and non-chromosomal congenital anomalies were determined utilizing ICD-9-CM codes as listed in Table 16.

Odds ratios and 95% confidence intervals were calculated to determine if intentional acute poisoning hospital discharge was associated with birth outcome. Reported odds ratios are adjusted for age, race, ethnicity, maternal education and insurance payer.

Further analyses based on timing of intentional acute poisonings hospital discharge was performed with subsets of the study group. Time of poisoning was calculated by subtracting the days between mom's admission for poisoning and delivery from gestational age in days at delivery. Specifically, women who were discharged during the first nine weeks of pregnancy and those discharged between ten weeks gestation and delivery were further assessed.

All analyses were calculated using SAS 8.2 software. All p-values less than 0.05 were considered statistically significant.

4.4 RESULTS

There were 2,215,920 deliveries fulfilling the study criteria identified in the VSPDD between 2000 and 2004. Four hundred thirty women with hospital discharges for an intentional acute poisoning during pregnancy (population-based rate 25.87/100,000 person-years) were documented. These women comprised the study group, and 2,215,490 women with non-poisoning hospital discharge comprised the

control group. Further analysis of the study group revealed that 178 (41%) of the acute intentional poisoning hospital discharges occurred within the first nine weeks of gestation.

The distribution of intentional acute poisoning hospital discharges by gestational age is presented in Figure 5. Intentional poisonings peak in the first week of gestation. Of all intentional acute poisoning hospital discharges during pregnancy, 45% occurred in the first trimester, 31% in the second and 24% in the third. The rate of acute poisoning hospital discharges in the first trimester was significantly greater than that in the second and the third ($p<0.05$); the rate of poisonings in the second trimester did not differ significantly from that in the third (11.67, 8.00, and 6.20 per 100,000 person-years, respectively).

The diagnostic codes of the five leading substances implicated in intentional acute poisoning hospital discharges during pregnancy are presented in Table 17. The leading substances implicated in intentional acute poisoning hospital discharge during pregnancy were analgesics, antipyretics, and antirheumatics, irrespective of time of the poisoning during pregnancy.

Demographic characteristics of women with an intentional acute poisoning hospital discharge during pregnancy are shown in Table 18. This analysis determined that compared to women of other age groups, women aged between 15 and 19 were more likely to suffer an intentional acute poisoning during pregnancy. African American women were more likely to be hospitalized for an intentional acute poisoning hospital discharge compared to white women. Non-high school educated women had the greatest odds of intentional acute poisoning hospitalization during pregnancy when compared to women with additional schooling. In addition, compared to women with Medi-Cal insurance, self-pay, indigent, and government insurance payers, women with private insurance payers were less likely to be hospitalized for an intentional acute poisoning during pregnancy. Women who had given birth two times were at a lower risk of intentional acute poisoning hospital discharge than women who were giving birth for the first time. Initiation of prenatal care was not associated with intentional acute poisoning hospital discharge. The presence of concomitant substance abuse and mental illness were each associated with higher odds of intentional acute poisoning hospital discharge during pregnancy.

The median gestational ages at delivery between cases and controls were not significantly different (276 days IQR(267-283) and 276 days IQR(269-283), respectively, p=0.36). In addition, the median gestational ages at delivery of women with an intentional acute poisoning between conception through nine weeks and those ten weeks until delivery were not significantly different (276 days IQR(268-284) and. 275 days IQR(266-283), respectively, p=0.31).

The influence of intentional acute poisoning on birth outcomes is outlined in Table 19. Low birth weight and preterm delivery were significantly associated with intentional acute poisoning after controlling for age, race, ethnicity, payer source and maternal education. However, once gestational age was added into the multivariable model, low birth weight no longer remained significant. When substance abuse was added to the multivariable model, no adverse birth outcomes were significantly associated with acute poisoning hospital discharge.

Infants born to women in the group that was discharged for an intentional acute poisoning within the first nine weeks of gestation exhibited higher rates of low birth weight infants (Table 20). After controlling for gestational age, low birth weight no longer remained significantly associated with intentional acute poisoning hospital discharge. In women who were discharged with an intentional acute poisoning between gestational weeks ten and delivery, intentional acute poisoning was associated with a higher rate of circulatory system congenital anomalies. These anomalies remained significantly associated with intentional acute poisoning after adjusting for gestational age. Once substance abuse was added to the multivariable models, no outcomes remained significantly associated with intentional acute poisoning hospital discharge, regardless of timing of the poisoning during pregnancy.

4.5 DISCUSSION

This is the one of the few population based studies examining birth outcomes following intentional acute poisoning hospital discharge during pregnancy. The data are derived from a very large and heterogeneous

population. In addition, this is one of the first papers to present population-based estimates of intentional acute poisoning hospital discharges during pregnancy to include poisonings in the first weeks of pregnancy; most data sources are limited to recognizable pregnancies.

The most common substances implicated in intentional poisonings in pregnant women were aromatic analgesics, antidepressants, propionic acid derivatives, benzodiazepine-based tranquilizers, and salicylates. Similarly, ingestion of 50 different types of over-the-counter and prescription drugs consisting primarily of analgesics (mainly acetaminophen), vitamins, iron, sedatives, antibiotics and antihistamines or decongestants were identified in a study of 111 suicide attempts by overdose during pregnancy reported to a metropolitan poison control center (Rayburn et. al., 1984).

In a population based prospective examination of the timing and outcomes following self-poisoning by pregnant women for the years 1985-1993 in Budapest, Hungary Czeizel et. al. (1999) reported a striking inverse relationship between the numbers of suicide attempts with increasing gestational age. The results of this study reveal a similar pattern. Due to the high number of intentional poisonings in the first few weeks of gestation and the quick decline thereafter, it may be speculated that the rates of intentional poisonings decrease due to increasing awareness of pregnancy.

It can be argued that intentional poisonings during pregnancy pose a greater financial and health-care burden than in non-pregnant women because not only is the woman affected, but the fetus as well. Infants born to women with an intentional acute poisoning hospital discharge during pregnancy exhibited higher rates of preterm birth and low birth weight. These observations have been paradoxically both supported and contradicted in the literature. Czeizel et. al. (1988) reported no association of drug toxicity with any of the following: mean birth weight, spontaneous abortion, major congenital anomalies, minor anomalies, infant mortality or specific childhood diseases. However, lower mean birth weight has been reported to be significantly associated with poisoning during pregnancy (Czeizel et. al., 1988; Lendvay and Czeizel, 1992). In addition, a recent analysis utilizing hospital discharge data from California, reported that suicide attempt during pregnancy was associated with neonatal and infant death, preterm delivery and respiratory distress syndrome (Ghandi et. al., 2006). The data are inconclusive and

outcomes are likely to vary based on severity, type and timing of poisoning, as well as potential confounders such as: substance abuse, illnesses, medication use and other risk-taking behaviors. Larger, more powerful studies should examine birth outcomes following intentional acute poisonings focusing on the aforementioned variables.

In an effort to examine the effects of self-poisoning on birth outcomes during the period of conception through organogenesis (between weeks two and nine), cases of intentional acute poisoning hospital discharge were stratified into two groups. The first group included women with an intentional acute poisoning discharge within the first nine weeks of pregnancy, and the second included women with a poisoning discharge between weeks ten and delivery. Infants born to women with an intentional acute poisoning hospital discharge within the first nine weeks of pregnancy showed higher rates of low birth weight; however, after adjusting for gestational age, no adverse birth outcomes were associated with intentional acute poisoning during the first nine weeks of pregnancy. However, in a study of 126 pregnant women self-poisoned in the first month of fetal development, 114 pregnancies ended in very early fetal loss, and 12 fetuses survived until delivery. The authors suggest that though based on small numbers, these findings are consistent with an 'all or nothing' effect of chemical poisoning very early in human gestation (Czeizel et. al., 1997). Similar results were reported among 122 Danish women exposed to drug overdose during pregnancy; the proportion of spontaneous abortion was nearly double that of the background population with a rate ratio of 1.7. However, there were no increased risks of major malformation or premature birth when compared to the background population. The authors concluded that a drug overdose shortly before or during pregnancy was associated with a substantially increased risk of miscarriage, but no increase in fetal birth defects among survivors (Flint et. al., 2002).

The 'all-or-nothing' theory asserts that adverse environmental influences within the first stages of conception either result in death or normal development. The data in this study support the "nothing" aspect of the theory, since no adverse effects of acute poisoning in early development on birth outcomes were demonstrated. However, the dataset is limited to live births or fetal deaths greater than or equal to 20 weeks gestation. Therefore, a poisoning early in development that may have resulted in an early fetal

death (prior to 20 weeks gestation) would not be captured. In addition, if intentional acute poisoning was associated with congenital anomalies, it is in this subgroup that the effect should be apparent. However, no association of intentional acute poisoning hospital discharge during organogenesis with the presence of congenital anomalies was found.

Analyses revealed an increased rate of circulatory system congenital anomalies in infants born to women with an intentional acute poisoning hospital discharge between gestational weeks 10 and delivery. Contrarily, several studies have shown no effect of self-poisoning on the prevalence of congenital anomalies (Czeizel et. al., 1984; Czeizel et. al., 1988; Gunnarskog and Kallen, 1993; Flint et. al., 2002). However, lack of statistical power is often cited as a limitation to detecting differences in the rates of congenital anomalies between cases and controls. This was not an issue in this study because there was sufficient power to detect differences in the prevalence of the majority of congenital anomalies. However it should be noted that observing an association between intentional acute poisoning in the weeks following organogenesis with the prevalence of congenital anomalies suggest the presence of other confounding variables.

After substance abuse was added into the multivariable model, acute intentional poisoning during pregnancy was no longer associated with congenital anomalies. This is consistent with an earlier population-based prospective study of 559 self-poisoned pregnant women admitted to a toxicology inpatient clinic where the overall prevalence of congenital anomalies and proportion of multi-malformed babies was significantly higher in the 178 infants in the study group than comparable controls. However, after excluding eight infants with fetal alcohol syndrome, the rate of congenital anomalies in the remaining infants (9%) was not significantly different than that in the control group (6.1%). Therefore, no teratogenic effects were identified, even though in 27 cases large doses of drugs were used between the 3rd and 8th weeks of fetal development (Czeizel et. al., 1997).

Although it can only be speculated as to the etiologies of the congenital anomalies, it can be suggested that substance abuse or other risk-taking behaviors associated with intentional acute poisoning may confound the relationship between poisoning and congenital anomalies. It is difficult to quantify

these factors; however future research should collect data on potential confounders such as substance abuse, stress, medical, social and behavioral factors that would influence birth outcomes.

There are several limitations to this study. It utilizes administrative data which may include possible coding and reporting errors. In addition, this study may have selection bias as the dataset included hospitalized poisonings only and excluded deliveries prior to 20 weeks gestation and coroner's cases, which may lead to an underestimate of the true number of intentional acute poisoning cases. In addition, excluding deliveries prior to 20 weeks gestation and coroner's cases may lead to an underestimation of the most severe outcomes of intentional acute poisoning during pregnancy - fetal death. The use of administrative data restricted knowledge of the severity of each poisoning. Serum concentrations or poisoning dose are likely recorded in the medical record, but are not abstracted to administrative datasets.

Finally, although the results are reported after adjusting for the concomitant diagnosis of substance abuse, acute poisoning may in itself be a sign of substance abuse. In essence, because they may reflect the same issue, adjustment may not be appropriate or straight-forward. Concomitant diagnoses of substance and/or mental illness may suffer from selection bias; women with intentional acute poisoning hospital discharge are more likely to be simultaneously diagnosed with substance abuse or mental illness than women discharged with other diagnoses.

Future research in the field of intentional acute poisoning should make an effort to distinguish poison severity. Currently, neither the Injury Severity Score System nor hospital administrative data provide indications of the dose of substance implicated in a poisoning. Birth outcomes are likely to differ based on the severity of the poisoning. Additionally, birth outcomes are likely to differ based on the agent implicated in the poisoning. Studies with sufficient power to examine the effects of specific agents on birth outcomes are a future avenue of research.

To further understand factors associated with intentional acute poisonings during pregnancy, future studies should focus data collection efforts to include: 1) the time the woman became aware of her pregnancy in relation to the time of the poisoning 2) the true intent of the poisoning (accidental, a gesture

for help, suicide or an abortion attempt) 3) whether the pregnancy was a planned and 4) concomitant diagnosis of mental illness or substance abuse. Additionally, the concept of an "all-or-nothing" effect of acute poisoning during pregnancy resulting in early fetal loss should be examined.

4.6 CONCLUSIONS

In conclusion, the rates of intentional acute poisoning hospital discharge were greatest in first weeks of gestation and decline with increasing gestational age. Analgesics, antipyretics, and antirheumatics were the most common substances implicated in suicide and self-inflicted poisonings. Young black women were at the greatest risk of intentional acute poisoning. In addition, women with substance abuse or mental health problems were at a higher risk of intentional acute poisoning hospital discharge. Adverse birth outcomes associated with intentional acute poisoning included: preterm delivery, low birth weight and congenital anomalies. However, these relationships may be confounded by substance abuse and other social, behavioral and medical factors. Furthermore, based upon this data, pre-natal visits with an obstetrician or primary care physician could allow for substance abuse and mental health screening and referral opportunities for high-risk women to help prevent acute poisonings. In addition, education and screening should be implemented following delivery to women who suffered an overdose to prevent future poisonings and to improve the health and well-being of both the infant and mother

4.7 LITERATURE CITED

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Table 16. ICD-9-CM code definitions for birth outcomes.

Birth Outcomes	**ICD-9-CM Code(s)**
Birth Asphyxia	7685,7686, 7687, 7689
Fetal distress	6563, 7682, 7683, 7684
Respiratory distress	769
Non-chromosomal anomalies	
Anancephalus and similar anomalies	740
Bulbus cordis anomalies and anomalies of cardiac septal closure	745
Certain congenital musculoskeletal deformities	754
Cleft palate and cleft lip	749
Congenital anomalies of genital organs	752
Congenital anomalies of the ear, face, and neck	744
Congenital anomalies of the eye	743
Congenital anomalies of the integument	757
Congenital anomalies of the respiratory system	748
Congenital anomalies of the urinary system	753
Other congenital anomalies of limbs	756
Other congenital anomalies of nervous system	742
Other congenital anomalies of the circulatory system	747
Other congenital anomalies of the digestive system	751
Other congenital anomalies of the heart	746
Other congenital anomalies of upper alimentary tract	750
Other congenital musculoskeletal anomalies	756
Spina bifida	741

Table 17. Substances implicated in intentional acute poisoning hospital discharge during pregnancy and substance specific population-based rates by E-code and by diagnosis code.

Intentional (E-code)	**Rate (per 100,000 person- years)**
Suicide and self-inflicted poisoning by analgesics, antipyretics, and antirheumatics	12.94
Suicide and self-inflicted poisoning by other specified drugs and medicinal substances	8.85
Suicide and self-inflicted poisoning by tranquilizers and other psychotropic agents	6.32
Suicide and self-inflicted poisoning by other and unspecified solid and liquid substances	1.38
Suicide and self-inflicted poisoning by other sedatives and hypnotics	0.54
Intentional (Diagnosis Code)	
Poisoning by aromatic analgesics, NEC Acetanilid; Paracetamol [acetaminophen]; Phenacetin [acetphenetidin]	8.18
Poisoning by antidepressants Amitriptyline; Imipramine; Monoamine Oxidase [MAO] Inhibitors	2.89
Poisoning by antirheumatics (antiphlogistics) Propionic acid derivatives Fenoproten; Fluriprofen; Ibruprofen; Ketoprofen; Naproxen; Oxaprozin	2.35
Poisoning by benzodiazepine-based tranquilizers Chlordiazepoxide; Diazepam; Flurazepam; Lorazepam; Medazepam; Nitrazepam	2.11
Poisoning by salicylates Acetylsalicylic acid [aspirin]; Salicylic acid salts	2.11

Table 18. Demographic characteristics of women with intentional acute poisoning hospital discharge and non-poisoning hospital discharge, during pregnancy, 2000-2004.

		Non-Poisoning Hospitalizations During Pregnancy N=2,215,490	Intentional Poisoning Hospitalizations During Pregnancy N=430				
Characteristic	**Category**	**n**	**n**	**%**	**OR**	**95%CI**	**p**
Maternal Age	15-19	211458	103	0.05	3.28	2.47-4.37	<0.0001
	20-24	499769	139	0.03	1.89	1.88-2.45	<0.0001
	25-29	579672	86	0.01	1.00	Ref	
	30-34	554635	69	0.01	0.84	0.84-1.15	0.28
	35-39	299906	20	0.01	0.45	0.45-0.73	0.001
	40-44	70050	13	0.02	1.25	0.70-2.24	0.45
Race	White	1769223	324	0.02	1.00	Ref	
	Black	130531	51	0.04	2.13	1.59-2.87	<0.0001
	Asian	272143	41	0.02	1.02	0.70-1.49	0.91
	Other	36644	14	0.04	0.92	0.61-1.38	0.68
Ethnicity	Hispanic	1021208	193	0.02	1.00	Ref	
	Non-Hispanic	1150066	234	0.02	0.93	0.77-1.13	0.46
Maternal Education	Less than High School	627022	175	0.03	1.00	Ref	
	Completed High School	612110	125	0.02	0.73	0.58-0.92	0.008
	Some college, no degree	421636	78	0.02	0.66	0.51-0.87	0.003
	College	514835	40	0.01	0.28	0.20-0.39	<0.0001
Insurance	Medicare/Other Government	21440	18	0.08	3.97	2.45-6.42	<0.0001
	Medi-Cal	958375	203	0.02	1.00	Ref	
	Private	1170391	133	0.01	0.54	0.43-0.67	<0.0001
	Indigent	48737	47	0.10	4.56	3.32-6.26	<0.0001
	Self-pay	3072	24	0.78	36.89	24.13-56.40	<0.0001
	Other	13151	5	0.04	1.80	0.74-4.36	0.20
Parity	Nulliparous	3980	0	0	--	--	--
	1	872506	192	0.02	1.00	Ref	
	2	704959	104	0.01	0.67	0.53-0.85	0.001
	≥3	633402	134	0.02	0.96	0.77-1.20	0.73
Prenatal Care	First Trimester	1914651	352	0.02	1.00	Ref	
	Second Trimester	231225	62	0.03	1.61	0.23-11.48	0.63
	Third Trimester	45965	10	0.02	2.35	0.33-16.96	0.40
	None	8768	*	*	1.91	0.24-14.90	0.54
Substance Abuse	Yes	23714	289	0.60	46.05	37.67-56.31	<0.0001
	No	2191776	143	0.01	1.00	Ref	
Mental Illness	Yes	14304	283	1.94	296.28	242.59-361.86	<0.0001
	No	2201186	147	0.01	1.00	Ref	

OR=odds ratio; CI=confidence interval; * =cell frequency<5: data not reported

Table 19. Birth outcomes following intentional acute poisoning hospital discharge and non-poisoning hospital discharge during pregnancy.

Birth Outcome	Non-Poisoning Hospital Discharge N=2,215,490		Intentional Acute Poisoning Hospital Discharge N=430				
	n	%	N	%	AOR	95%CI	p
Preterm Delivery	225820	10.19	58	13.49	1.34	1.01-1.77	0.04
Cesarean Delivery	565030	25.50	107	24.88	1.11	0.89-1.40	0.35
Low Birth Weight	118062	5.33	34	7.91	1.49	1.04-2.12	0.03
Extremely Low Birth Weight	23833	1.08	5	1.16	0.9	0.34-2.42	0.84
Birth Asphyxia	3569	0.16	0	0.00			
Respiratory Distress	27172	1.23	7	1.63	1.19	0.53-2.67	0.67
Fetal Distress	10523	0.47	*	*	1.03	0.26-4.15	0.96
Fetal Death	9304	0.42	*	*	1.19	0.30-4.77	0.81
Neonatal Death	6066	0.27	0	0			
Infant Death	3119	0.14	*	*	2.87	0.72-11.49	0.14
Anancephalus and similar anomalies	107	0.00	0	0			
Bulbus cordis anomalies and anomalies of cardiac septal closure	22001	0.99	5	1.16	1.27	0.53-3.07	0.59
Certain congenital musculoskeletal deformities	9658	0.44	0	0			
Cleft palate and cleft lip	3826	0.17	*	*	1.41	0.20-10.04	0.73
Congenital anomalies of genital organs	16797	0.76	*	*	0.33	0.05-2.33	0.27
Congenital anomalies of the ear, face, and neck	5689	0.26	0	0			
Congenital anomalies of the eye	2849	0.13	0	0			

Table 19 continued

Congenital anomalies of the integument	46535	2.10	14	3.26	1.63	0.96-2.78	0.07
Congenital anomalies of the respiratory system	5842	0.26	*	*	0.94	0.13-6.66	0.95
Congenital anomalies of the urinary system	8582	0.39	*	*	0.67	0.10-4.77	0.69
Other congenital anomalies of limbs	9880	0.45	*	*	1.06	0.26-4.25	0.94
Other congenital anomalies of nervous system	4466	0.20	0	0			
Other congenital anomalies of the circulatory system	30944	1.40	11	2.56	1.8	0.96-3.36	0.07
Other congenital anomalies of the digestive system	5202	0.23	*	*	1.03	0.15-7.35	0.97
Other congenital anomalies of the heart	9042	0.41	*	*	2.48	0.93-6.61	0.07
Other congenital anomalies of upper alimentary tract	7951	0.36	*	*	1.35	0.34-5.43	0.67
Other congenital musculoskeletal anomalies	7754	0.35	*	*	0.68	0.10-4.81	0.7
Spina bifida	685	0.03	0	0			
Congenital anomalies of any type	155220	7.01	31	7.21	1.06	0.73-1.53	0.78

AOR=adjusted odds ratio; odds ratio adjusted for age, race, ethnicity, maternal education, and insurance payer; CI=confidence interval; *=cell frequency<5: data not reported

Table 20. Birth outcomes following intentional acute poisoning hospital discharge and non-poisoning hospital discharge during pregnancy, stratified by timing of poisoning.

Birth Outcome	Non-poisoning hospital discharge N=2,215,490		Acute intentional poisoning hospital discharge after ten weeks gestation N=252					Acute intentional poisoning hospital discharge within nine weeks gestation N=178				
	n	%	n	%	AOR	95%CI	P	n	%	AOR	95%CI	P
Preterm Delivery	225820	10.19	34	13.49	1.36	0.94-1.96	0.1	24	13.48	1.31	0.84-2.03	0.24
Cesarean Delivery	565030	25.50	61	24.21	1.01	0.74-1.36	0.96	46	25.84	1.28	0.91-1.80	0.16
Low Birth Weight	118062	5.33	18	7.14	1.31	0.80-2.15	0.29	16	8.99	1.74	1.04-2.91	0.04
Extremely Low Birth Weight	23833	1.08	*	*	0.78	0.19-3.12	0.72	*	*	1.08	0.27-4.36	0.91
Birth Asphyxia	3569	0.16	0	0				0	0			
Respiratory Distress	27172	1.23	5	1.98	1.36	0.51-3.66	0.54	*	*	0.96	0.24-3.85	0.95
Fetal Distress	10523	0.47	*	*	0.89	0.13-6.33	0.91	*	*	1.24	0.17-8.82	0.83
Fetal Death	9304	0.42	*	*	1.02	0.14-7.26	0.99	*	*	1.43	0.20-10.20	0.72
Neonatal Death	6066	0.27	0	0				0	0			
Infant Death	3119	0.14	*	*	2.47	0.35-17.61	0.37	*	*	3.38	0.47-24.17	0.22
Anancephalus and similar anomalies	107	0.00	0	0				0	0			
Bulbus cordis anomalies and anomalies of cardiac septal closure	22001	0.99	0	0				*	*	1.23	0.30-4.94	0.77
Certain congenital musculoskeletal deformities	9658	0.44	0	0				0	0			
Cleft palate and cleft lip	3826	0.17	*	*	2.44	0.34-17.29	0.37	0	0			

Table 20 continued

Congenital anomalies of genital organs	16797	0.76	0	0				*	*	0.79	0.11-5.66	0.82
Congenital anomalies of the ear, face, and neck	5689	0.26	0	0				0	0			
Congenital anomalies of the eye	2849	0.13	0	0				0	0			
Congenital anomalies of the integument	46535	2.10	9	3.57	1.86	0.95-3.62	0.07	5	2.81	1.33	0.55-3.25	0.53
Congenital anomalies of the respiratory system	5842	0.26	*	*	1.61	0.23-11.42	0.63	0	0			
Congenital anomalies of the urinary system	8582	0.39	*	*	1.15	0.16-8.17	0.89	0	0			
Other congenital anomalies of limbs	9880	0.45	*	*	0.91	0.13-6.47	0.92	*	*	1.27	0.18-9.07	0.81
Other congenital anomalies of nervous system	4466	0.20	0	0				0	0			
Other congenital anomalies of the circulatory system	30944	1.40	*	*	2.17	1.02-4.59	0.04	*	*	1.29	0.41-4.03	0.66
Other congenital anomalies of the digestive system	5202	0.23	0	0				*	*	2.5	0.35-17.72	0.36
Other congenital anomalies of the heart	9042	0.41	*	*	2.11	0.52-8.48	0.29	*	*	2.97	0.74-11.97	0.13
Other congenital anomalies of upper alimentary tract	7951	0.36	0	0				*	*	3.31	0.82-13.31	0.09
Other congenital musculoskeletal anomalies	7754	0.35	*	*	1.16	0.16-8.27	0.88	0	0			
Spina bifida	685	0.03	0	0				0	0			
Congenital anomalies of any type	155220	7.01	20	7.94	1.16	0.73-1.85	0.54	11	6.18	0.91	0.50-1.68	0.77

AOR=Adjusted odds ratio; odds ratio adjusted for age, race, ethnicity, maternal education, and insurance payer; CI=confidence interval; *=cell frequency<5: data not reported

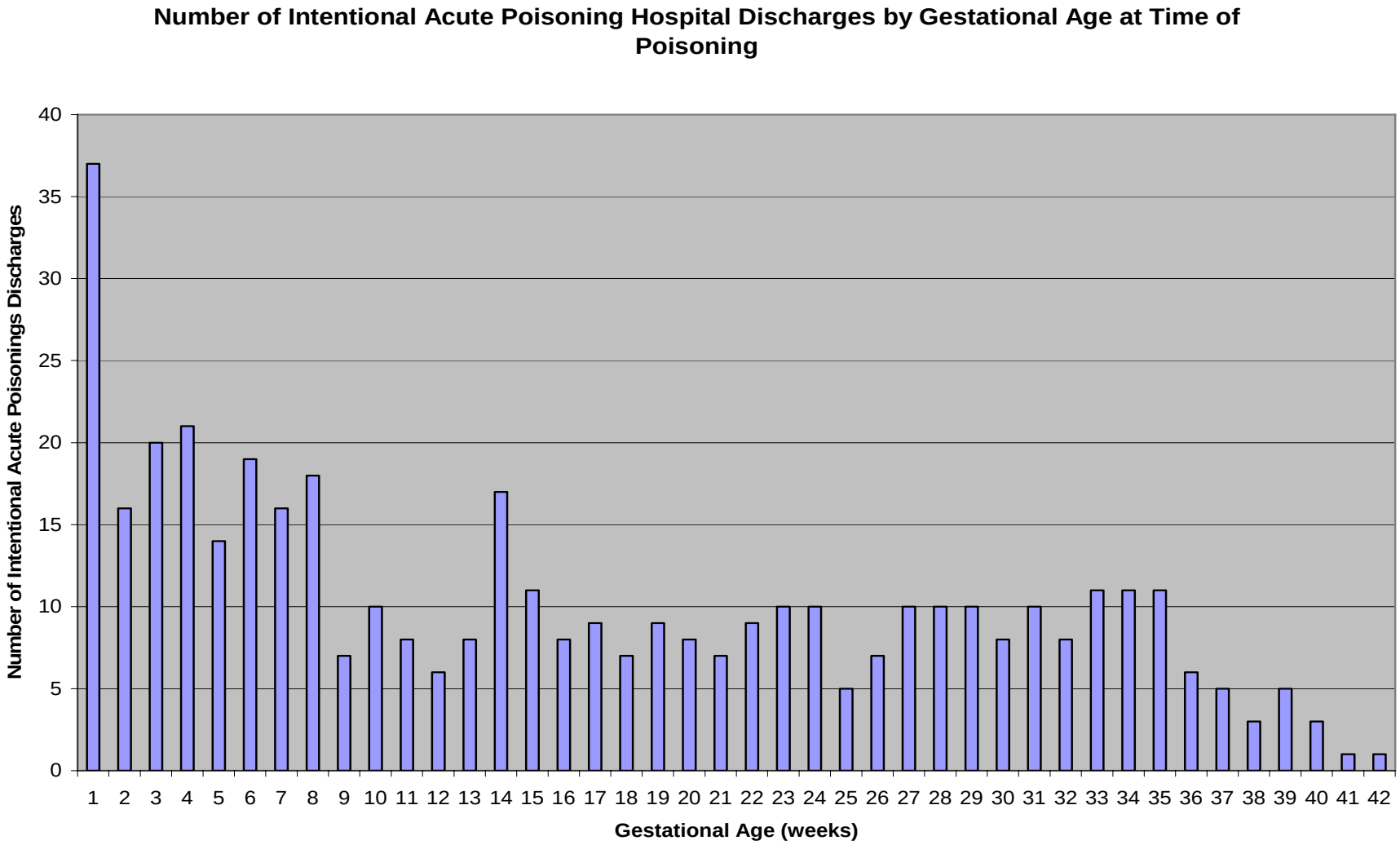

Figure 5. Number of intentional acute poisoning hospital discharges during pregnancy by gestational age at time of poisoning.

5.0 OVERALL DISCUSSION

Injuries are a major source of preventable morbidity in women. Poisoning is the leading cause of injury hospitalization among all women of reproductive age and the third leading cause of injury hospitalization during pregnancy (CDC WISQARS 2001-2004; Weiss et al., 2002). Despite these observations there is a dearth of literature regarding the epidemiology and outcome of poisonings during pregnancy.

Therefore, this dissertation sought to fill in several gaps regarding the epidemiology of poisonings in women of reproductive age and during pregnancy.

5.1 REVIEW OF SPECIFIC AIMS

5.1.1 Specific Aim 1

Specific Aim 1. Describe the epidemiology of acute poisoning hospital discharges in women of reproductive age (ages 15-44) including: the incidence rate, risk factors, substances involved and rates of intentional, unintentional and undetermined poisonings.

Hypothesis 1. The following variables will be significantly associated with an increased risk for acute poisoning hospital discharge: age less than 20 years, African American race, Hispanic ethnicity and public insurance payer.

Of 4,436,019 hospital discharges, 44,393 (1%) were for an acute poisoning during the study period, resulting in a rate of 115.28 hospital discharges per 100,000 person-years. Utilizing E-codes, 30,890 (69.6%) of the 44, 393 acute poisoning hospital discharges were identified as intentional, 9,526 (21.5%) as unintentional and 2,687 (6.1%) as acute poisoning hospital discharges of undetermined intent (rates 80.22, 24.74 and 6.98 per 100,000 person-years, respectively). The rates of poisoning hospital discharges (all intents, intentional and unintentional) in women of reproductive age documented in this study correspond well to the rates of hospitalized nonfatal poisoning related injuries reported by the Centers for Disease Control Web-based Injury Statistics Query and Reporting System (CDC WISQARS). In addition, the high proportion of poisonings identified as intentional was not surprising because poisonings are the most frequent method of self-inflicted, non-fatal injury in women.

Analgesics and tranquilizers were the most common substances implicated in acute poisoning hospital discharges in women of reproductive age. These results are similar those of previous studies examining the pattern of exposures reported to Poison Control Centers. In addition to the variables reported above, substance abuse and mental illness were associated with a higher risk of acute poisoning hospital discharge.

Hypothesis 1 was not supported. Compared to women of other age groups, women aged between 15 and 19 had the greatest likelihood of acute poisoning hospital discharges, followed by women aged between 40 and 44. Women with Medi-Cal insurance were less likely to be hospitalized for an acute poisoning compared to women with other types of insurance payers. However, white women were more likely to be hospitalized for an acute poisoning compared to non-White women. Also, non-Hispanic women were more likely to be hospitalized for an acute poisoning compared to Hispanic women. There exists a paradox in epidemiology, such that Hispanics in the United States tend to have substantially better health than the average population despite what aggregate socio-economic factors would indicate (Morales et. al., 2002).

5.1.2 Specific Aim 2

Specific Aim 2. Describe the epidemiology of acute poisoning hospital discharges in pregnant women including: the incidence rate, risk factors, proportions over trimesters, substances involved and rate of intentional, unintentional and undetermined poisonings.

Hypothesis 2a. The following variables will be significantly associated with an increased risk for acute poisoning hospital discharges during pregnancy: age less than 20 years, mother's years of education less than 12, African American race, Hispanic ethnicity, public insurance payer and delayed entry into prenatal care.

Hypothesis 2b. The rate of intentional acute poisoning hospital discharges will be significantly greater in the first trimester than in the second and third trimesters of pregnancy.

There were 2,285,540 deliveries fulfilling the study criteria identified in the Vital Statistics-Patient Discharge Database from 2000-2004, accounting for 2,471,524 hospital discharges. A total of 833 hospital discharges for an acute poisoning during pregnancy were identified in the database (48.60/100,000 person-years). Of all acute poisoning hospital discharges during pregnancy, 35.89%, 28.34% and 35.77% occurred in the first, second and third trimesters, respectively. The rate of acute poisoning hospital discharges did not significantly differ across trimesters (17.50, 13.83, and 17.27 per 100,000 person-years, respectively). Utilizing E-codes, 513 (61.6%) of the 833 documented cases of acute poisoning hospital discharges were identified as intentional (rate 29.93/100,000 person-years). Of the remaining cases, 241 (28.9%) were classified as unintentional and 34 (4.1%) as acute poisoning hospital discharges of undetermined intent (rates 14.06 and 1.98 per 100,000 person-years, respectively).

The rate of acute poisoning hospital discharges reported in this study, although of the same magnitude, is significantly lower than that reported in a 1999 study of pregnancy-associated injury in Pennsylvania. The reason for this difference is unclear; however, it is thought that racial and ethnic differences, which vary considerably between Pennsylvania and California, may account for at least a

portion this disparity. However, the results in this study may be a more accurate reflection of the true rate of acute poisoning hospital discharges during pregnancy because the rates are based on five year data in a much larger, more heterogeneous statewide population.

Similar to the results observed in women of reproductive age, analgesics were the most common substances implicated in acute poisoning hospital discharge during pregnancy. This observation extends the information in current literature.

In addition to the variables reported above, substance abuse and mental illness were associated with a higher risk of acute poisoning hospital discharge.

The results of paper one support hypothesis 2a. Risk factors for acute poisoning are similar to those for injury in general. Women aged between 15 and 25 had the greatest likelihood of acute poisoning hospital discharge during pregnancy. African American women were more likely to be hospitalized for an acute poisoning during pregnancy when compared to white women. Women with a college education were less likely to be hospitalized for an acute poisoning compared to women with less than a high school education. In addition, compared to women with Medi-Cal insurance, women with self-pay, indigent and government insurance payers were more likely, and women with private insurance payers less likely, to be hospitalized with an acute poisoning. Initiation of prenatal care was not associated with acute poisoning hospital discharge during pregnancy. However, non-Hispanic women were more likely to be hospitalized for an acute poisoning during pregnancy when compared to Hispanic women.

Hypothesis 2b was also supported. The rate of intentional poisonings was significantly greater in the first trimester than in the second and third (13.36 versus 9.33 and 7.23 per 100,000 person-years, respectively; $p<0.05$). These results correspond well to those reported in a population based prospective examination of the timing of self-poisoning by pregnant women for the years 1985-1993 in Budapest, Hungary. Czeizel et al. (1999) reported a striking inverse relationship between the numbers of suicide attempts across postconceptional months.

5.1.3 Specific Aim 3

Specific Aim 3. Compare the rates, risk factors, substances involved and intentional versus unintentional rates of acute poisoning hospital discharges between women of reproductive age and pregnant women.

Hypothesis 3a. The rate of acute poisoning hospital discharges in women of reproductive age will be greater than the rate of acute poisoning hospital discharges in pregnant women after controlling for age, race, ethnicity and insurance payer.

Hypothesis 3b. The rate of intentional acute poisoning hospital discharge will be greater in women of reproductive age than the rate of intentional acute poisoning hospital discharges during pregnancy after controlling for age, race and insurance payer.

The rates of acute poisoning hospital discharge were greater in women of reproductive age than during pregnancy, irrespective of intent. Among women of reproductive age, young white women were at the greatest risk of acute poisoning hospital discharge. However, young black women were at greatest risk of acute poisoning hospital discharge during pregnancy. These differences may persist due to significant interactions between age and pregnancy, such that in pregnant women, age increase was associated with decreasing rates of poisoning, and between race and pregnancy; exhibiting that black race was associated with a higher risk of acute poisoning hospital discharges during pregnancy. The distribution of the pregnant population, being younger and more often of minority race and the higher rates of poisoning in women of minority race, may aid in elevating the base rate of acute poisoning hospital discharges in pregnant women. The leading substances implicated in acute poisoning hospital discharges in women of reproductive age and among pregnant women, regardless of intent, were analgesics.

Hypothesis 3a was supported. In a multivariable model, controlling for age, race, insurance payer, and ethnicity, pregnancy remained to be significantly inversely associated with acute poisoning hospital discharges (OR=0.89, 95% CI 0.83-0.95, p=0.0007). This result corresponds well to the documented decrease in risk taking behaviors during pregnancy. In addition, this finding corresponds to the observed

lower risk of poisoning during pregnancy when compared to the risk in women of reproductive age reported by Weiss (1999) in a study of pregnancy-associated injury in Pennsylvania.

Hypothesis 3b was also supported. In a multivariable model, controlling for age, race, ethnicity and insurance payer, pregnancy remained to be significantly inversely associated with intentional acute poisoning hospital discharges (OR=0.77, 95%CI 0.70-0.84, p<0.0001). This was not unexpected as the risk of suicide decreases during pregnancy.

5.1.4 Specific Aim 4

Specific Aim 4. Describe the patterns of birth outcomes following acute poisoning hospital discharge during pregnancy.

> Hypothesis 4. The rates of premature delivery, low birth weight, fetal distress, respiratory distress, congenital anomalies, and fetal death and infant death will be greater in women with an acute poisoning hospital discharge during pregnancy, than those in a non-poisoned pregnant cohort after controlling for age, parity, maternal education, race, insurance payer and entry into prenatal care.

Hypothesis 4 was supported. Adverse birth outcomes associated with acute poisoning included preterm delivery, respiratory distress, cesarean delivery and cardiac congenital anomalies. Infants born to women in the immediate-delivery group exhibited higher rates of respiratory distress and preterm delivery. In the later-delivery group, infants born to women with an acute poisoning during pregnancy were at a greater risk of preterm delivery and other cardiac congenital anomalies. Adverse birth outcomes associated with intentional acute poisoning included preterm delivery and low birth weight. Infants born to women that were discharged for an intentional acute poisoning hospital discharge within the first nine weeks of gestation exhibited higher rates of low birth weight. In women who were discharged with an intentional acute poisoning between gestational weeks 10 and delivery, intentional acute poisoning

hospital discharge was associated with a greater rate of circulatory system congenital anomalies. However, these relationships may be confounded by factors such as substance abuse, stress, medical, social and behavioral factors that may also influence birth outcomes.

5.2 LIMITATIONS

There were several limitations to this study. It utilized administrative data which may include possible coding and reporting errors. It was not possible to calculate population-based estimates of acute poisoning hospital discharge in women of reproductive age due to a high proportion of missing record linkage numbers. In addition, this study may have selection bias as the dataset included hospitalized poisonings only and excluded deliveries prior to 20 weeks gestation and coroner's cases, which may have lead to an underestimate of the true number of acute poisoning cases. Excluding deliveries prior to 20 weeks gestation and coroner's cases may also have lead to an underestimation of the most severe outcomes of acute poisoning during pregnancy - fetal death. The use of administrative data restricted knowledge of the severity of each poisoning. Serum concentrations or poisoning dose are likely recorded in the medical record, but are not abstracted to administrative datasets. Although Poison Control Centers (PCC) collect information on poison severity, PCCs do not always collect data on the pregnancy status of their callers. Therefore, although limited, the utilization of hospital discharge data was more appropriate to address the aims of this study.

Finally, although the results are reported after adjusting for the concomitant diagnosis of substance abuse, acute poisoning may in itself be a sign of substance abuse. In essence, because they may reflect the same issue, adjustment may not be appropriate or straight-forward. Concomitant diagnoses of substance and/or mental illness may suffer from selection bias; women with intentional acute poisoning hospital discharge are more likely to be simultaneously diagnosed with substance abuse or mental illness than women discharged with other diagnoses.

5.3 PUBLIC HEALTH SIGNIFICANCE

Injuries are a major source of preventable morbidity in women. Similarly, injuries during pregnancy are a major public health concern. Potentially two lives, both that of the mother and fetus, are at risk. Poisoning is the leading cause of injury hospitalization among all women of reproductive age and the third leading cause of injury hospitalization during pregnancy (CDC WISQARS 2001-2004; Weiss et al., 2002).

The results of this dissertation provide public health practitioners the information necessary to implement programs to reduce the burden of poisonings in women. This dissertation describes the epidemiology of acute poisoning hospital discharge in women of reproductive age and during pregnancy. The results of the analyses included in this dissertation suggest that young black women, and women with substance abuse and mental illness, are at greatest risk of acute poisoning hospital discharge, regardless of pregnancy status. Analgesics and psychiatric medications were the substances most often implicated in acute poisonings in women of reproductive age and during pregnancy. In addition, irrespective of pregnancy, the majority of the poisonings were self-inflicted. Although the risk of acute poisoning hospital discharge is reduced during pregnancy, results indicate that several adverse birth outcomes are associated with acute poisoning during pregnancy.

There are a number of measures health professionals could implement to reduce the burden of poisonings among women and their infants. Public health professionals should implement programs to inform patients on the proper use of over-the-counter medications. In addition, healthcare providers should inform patients about potentially deleterious, active ingredients in over-the-counter medications. Substance abuse and mental health screening with appropriate referral by an obstetrician/gynecologist or treating physician may help prevent acute poisonings in high-risk women. Among pregnant women, pre-natal visits with an obstetrician or primary care physician could allow for substance abuse and mental health screening and referral opportunities for high-risk women to help prevent intentional acute poisonings during pregnancy. In addition education and screening should be implemented following

delivery to women who suffered an overdose to prevent future poisonings and to improve the health and well-being of both the infant and mother.

5.4 FUTURE RESEARCH

Future research in the field of intentional acute poisoning should make an effort to distinguish poison severity. Currently, neither the Injury Severity Score System nor hospital administrative data provides indications of the dose of substance implicated in a poisoning. Birth outcomes are likely to differ based on the severity of the poisoning. Researchers have demonstrated the validity of the Poison Severity Score, developed by the International Programme on Chemical Safety, the Commission of the European Union, and the European Association of Poison Centres and Clinical Toxicologists (Casey et al. 1998). Possible severity measures could include dosage of poison, serum concentrations or the poison severity score. Also, severity could possibly be indirectly measured using administrative data by examining concomitant diagnoses of respiratory failure, coma, delirium, liver failure, kidney failure, and shock in association with the poisoning. Additionally, birth outcomes are likely to differ based on the agent implicated in the poisoning. Future studies with sufficient power to examine the effects of specific agents on birth outcomes should be planned.

To further understand factors associated with intentional acute poisonings during pregnancy, future studies should focus data collection efforts to include: 1) the time the woman became aware of her pregnancy in relation to the time of the poisoning 2) the true intent of the poisoning (accidental, a gesture for help, suicide or an abortion attempt) and if intentional the circumstances surrounding the injury (interpersonal conflict, depression, etc.) 3) whether the pregnancy was planned and 4) concomitant diagnosis of mental illness or substance abuse. In addition, although it is difficult to quantify other potentially significant confounders such stress, and other medical, social and behavioral factors,

researchers should attempt to adjust for these factors in future analyses examining the relationship between acute poisoning and adverse birth outcomes.

5.5 LITERATURE CITED

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