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Julie Smith Date

Effects of a recent pregnancy loss on maternal mental health among women with a recent live birth, PRAMS, 2012-2016

By

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Epidemiology

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By

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An abstract of
a thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
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Abstract

Effects of a recent pregnancy loss on maternal mental health among women with a recent live birth, PRAMS, 2012-2016

By Julie Smith

Background: Approximately 20% of women experienced a pregnancy loss in the United States between 1990 and 2011 (1). Much is known about the adverse association between a pregnancy loss and postpartum depression, but less is known about the experience of postpartum depression after a subsequent live birth. Using data from the Pregnancy Risk Assessment Monitoring System (PRAMS), we sought to (1) estimate the proportion of women with a recent live birth who experienced a pregnancy loss in the 12 months prior to conception and (2) determine if there are differences in self-reported postpartum depression for mothers of a recent live birth who experienced a pregnancy loss in the year before conceiving compared to those without a recent pregnancy loss.

Methods: Bivariate and multivariable associations were estimated using predicted marginals from log-binomial regression models. We controlled for confounding by marital status; maternal age, race, and education; previous number of live births; and stress. Additionally, we stratified our multivariable analyses by history of depression/anxiety and by pregnancy intention of the subsequent pregnancy. To account for the complex survey design in PRAMS, all analyses were conducted using SAS-callable SUDAAN.

Results: Among women with a recent live birth in the United States, 12.8% conceived their infant within 12 months of a pregnancy loss (SE = 0.4). For these mothers, there was a 15% increase in the prevalence of postpartum depression compared to women with a recent live birth and no recent pregnancy loss (aPR: 1.15, 95% CI: 0.98, 1.36). The effect of a previous pregnancy loss on postpartum depression was stronger for women with a history of depression or anxiety and for those who had not intended to become pregnant.

Conclusions: A substantial number of women in the United States with a recent live birth had experienced a pregnancy loss in the 12 months prior to conception. These women may be at an increased risk for postpartum depression, particularly if they have a history of depression or if the subsequent pregnancy was unintended.

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Chapter I: Background

Pregnancy Loss

Fetal mortality, or the death of a fetus that occurs prior to delivery but is not an induced termination of pregnancy, is persisting at consistent and higher than average rates in the United States (U.S.) as compared to other high-income countries (HICs) (2). Approximately 20% of women experienced a pregnancy loss in the United States between 1990 and 2011 (1). In the U.S., pregnancy losses occurring before 20 weeks gestation are classified as miscarriages, whereas those occurring at 20 weeks gestation or later are classified as stillbirths (3, 4). It can be challenging to compare stillbirth rates internationally due to differences in definitions of pregnancy loss. Among the 49 HICs around the world, the average stillbirth rate is estimated to be 3.5 per 1000 total births, where stillbirth is defined as fetal death at 28 weeks gestation or later (5). The National Vital Statistics System (NVSS) and the Centers for Disease Control and Prevention (CDC) have further subdivided fetal death during the second half of gestation into early (20-27 weeks gestation), late (28-36 weeks gestation), and term (≥37 weeks gestation) stillbirths (2, 6). In contrast, the World Health Organization (WHO) defines stillbirth by the minimum gestational age limit of 28 weeks or birthweight of 500 grams or more (7). Even with this discrepancy in the definition of a stillbirth, there exists true epidemiological variation in stillbirth rates across high-income countries (8).

If all-cause stillbirths were ranked among the top global causes of death across all age categories, they would rank fifth, ahead of diarrhea, HIV/AIDS, tuberculosis, traffic accidents, and cancer (9). Despite this prevalence, reducing fetal mortality is not included as one of the United Nations' Millennium Development Goals and tends to be less of a focus for other public health programs compared to reducing infant and maternal mortality (9, 10).

In the United States, fetal mortality rates (fetal death at ≥20 weeks gestation) declined from 6.61 to 6.05 per 1000 total births (8% decrease) between 2000 and 2006 (2). Early fetal mortality rates (20-27 weeks) decreased from 3.31 to 3.10 fetal deaths per 1000 total births (6% decrease), and late fetal mortality rates (≥28 weeks) decreased from 3.32 to 2.97 fetal deaths per 1000 total births (11% decrease) (2). From 2006 to 2012, stillbirth rates were stable – 6.05 per 1000 total births in 2006 and 2012 – with only minor fluctuations (2). Furthermore, the late-fetal mortality rate has remained essentially constant from 2014 (2.83 deaths per 1000) to 2016 (2.88 deaths per 1000) (11). Considering that the U.S. fetal mortality rates in 1990 declined from 7.49 to 6.05 per 1000 total births in 2006 (19% decrease) and that this rate stayed stable through 2012, the long-term trend of a decline has halted (12).

High quality information from fetal autopsies and placental histopathologies by skilled perinatal pathologists should be made available to parents following a stillbirth (13). Parents who are not offered an autopsy are also denied the opportunity to know the cause of the stillbirth they just experienced. In addition, when fetal autopsies and placental histopathologies are not conducted or are not offered per standard protocol, an increasing number of stillbirths go unexplained and hamper research that could ultimately reduce the burden of stillbirth (13).

The major risk factors for pregnancy loss include smoking, obesity, fetal growth restriction, pre-existing diabetes, drug use, pre-eclampsia, hypertension, poor maternal mental health, infection, and previous stillbirth (14-21). Women who are socially marginalized or disadvantaged often have at least double the risk of stillbirth compared to women who are more advantaged (13). Rates of stillbirth among women in HICs are often double for women who are disadvantaged compared to being more advantaged (22).

Examples of disadvantaged groups suffering double the risk of stillbirth are African-American women, migrants, women with low income, women with low education, and early teenagers (13). Disadvantaged women are at higher risk of experiencing stillbirth as they are less likely to receive adequate or quality prenatal care and access to prenatal care (23, 24). Differential prenatal diagnoses have also been reported due to factors such as rural-urban differences and institutionalized racism (16, 25, 26). Beyond lacking and differential prenatal care, complex social determinates disadvantage women and thereby increase their risk of stillbirth. These "causes of the causes" are poverty, experiencing discrimination, incarceration, addiction, chronic stress, inadequate education, lack of child care, unemployment, transportation restrictions, and poor living conditions (27). Other strong risk factors include intimate partner violence, mental health issues, and the consequences of stressful life events (28-30). A recent systematic review determined that care providers underestimated the risks of stillbirth due to advanced maternal age (>35 years), in-vitro fertilization, multiple gestations, and maternal obesity. On the other hand, care providers overestimated the risk of stillbirth due to pre-eclampsia, smoking, and substance misuse (31-33).

In the United States, non-Hispanic black women also have increased stillbirth rates due to a higher prevalence of spontaneous preterm birth during early gestation (34). This example underscores the importance of studying fetal deaths less than 28 weeks gestation since early gestational pregnancy losses are more common among particular racial and ethnic groups (13). Other factors often contributing to the gap in fetal mortality between white and black mothers are differences in maternal preconception health, infection, income, and access to quality health care (12).

Furthermore, the total fetal mortality rate for twins (16.08 per 1000 total births) was 2.7 times higher than for singleton births (5.85 per 1000 total births) (12). The total fetal mortality rate for triplet or greater multiple births is 4.6 times that of singleton births at rate of 27.2 per 1000 total deaths (12). Increased risk of preterm delivery, fetal growth restriction, maternal hypertension, and placenta and cord problems partially account for the increased rate of fetal mortality among non-singleton births (35).

The causes of fetal death (pregnancy loss ≥20 weeks gestation) in 2014 were: unspecified cause (29.7%); placenta, cord, and membrane complications (28.4%); maternal complications (14.2%); congenital malformations (10.2%); maternal conditions unrelated to pregnancy (7.8%); and all other causes (9.6%) (36). Results from the Stillbirth Collaborative Research Network (SCRN) study investigating the causes of death among stillborns were similar for placental, genetic, and obstetric complications. NVSS did, however, find a smaller proportion of causes attributable to medical complications or cord problems (34, 37).

Even though the selected causes of fetal death were the same by race and Hispanic origin, the rankings of these reported causes of fetal death did differ by selected maternal characteristics (36). Among non-Hispanic white and non-Hispanic black mothers, stillbirths were attributed mostly to unspecified causes, but stillbirth for Hispanic mothers was attributed mostly to placenta, cord, and membrane complications. Unspecified cause of fetal death also ranked first for single births, but maternal complications ranked first for cause of fetal death among multiple births. Unspecified causes ranked first for those with the highest (≥4,000 grams) and lowest birthweights (<1500 grams). Placenta, cord, and membrane complications ranked first for birthweights ranging from 1,500 - 3,999 grams. These data are only available because the medical staff selected a specific cause or selected "unspecified cause" following a histological/placenta examination and/or fetal autopsy. Around half of

the reported stillbirths in 2014 were not investigated at time of death or never investigated, supporting justification of efforts to continue to improve fetal cause-of-death reporting in the United States.

In 2003, the United States released the 2003 U.S. Standard Report of Fetal Death with a revised cause-of-death item. This redesign was aimed at improving the quality and specificity of data collected regarding the cause or causes of fetal death (38). Furthermore, this re-design is now consistent with the WHO's *International Statistical Classification of Diseases and Related Health problems, Tenth Revisions* (ICD-10) (39). Parts 18a and 18b of the revised fetal death form ask about the initiating cause/condition of fetal death and any other significant causes or conditions, respectively (40). The initiating cause is described as the one cause "which most likely began the sequence of events resulting in the death of the fetus" (40). Different from other death report forms, this initiating cause is to be reported separately from all other causes or conditions that contributed to the fetal death. Another goal of revising the cause-of-death item was to encourage reporting of the cause(s) of fetal death by an attending physician, medical examiner, or coroner (39). However, not all fetal deaths are reported even when required and the cause of fetal death is often unknown. Of the 43 states and areas using the revised forms in 2014, 18.3% - 75.4% of reports had an unspecified cause as the initiating cause of fetal death (36). Also, histological or placental examinations only (47.7%) were reported to be the most common method of examining a fetal death compared to fetal autopsy alone (2.8%) or histological or placental examination with a fetal autopsy (8.9%) (36). Among those who did not receive a histological/placental examination or fetal autopsy, 21% had planned to have further examination, and 28.4% did not plan to have further examination.

Fetal mortality rates are key indicators of women's health and of the quality of care women receive when pregnant and during childbirth (41, 42). Of the 49 high-income countries around the world, six had third trimester stillbirth rates of ≤ 2 per 1000 total births. Had all 49 of these countries achieved stillbirth rates of ≤ 2 per 1000 total births, 19,439 stillbirths (≥28 weeks gestation) could have been avoided in just 2015 (13). Furthermore, the range of country-specific stillbirth was 1.3 to 8.8 per 1000 total births, demonstrating that reductions in stillbirths among these HICs, including the United States, is possible (13). Negative attitudes, myths, misperceptions, and stigma exacerbate trauma for grieving parents, impact progress in stillbirth prevention, and continue to persist. Further, when parents experience stillbirth, bereavement care can be lacking, and disparity in care often has devastating consequences (43). Alleviation of poverty and improved access to unbiased health care could potentially reduce fetal mortality rates in the United States.

Postpartum Depression and Anxiety:

Postpartum depression (PPD) is a common but serious mental health outcome for many women who have just given birth, and may persist months to years after delivery (43, 44). Postpartum depression, sometimes called postpartum depressive state (PDS), is a mood disorder which affects women following childbirth and is characterized by feelings of extreme sadness, anxiety, and physical and/or emotional exhaustion (45). Postpartum depression affects not only the mother, but also her infant, other children, and family members (44).

Estimates of the prevalence of postpartum depression range from 10-19% in the United States, which is similar to that of other high-income countries (44, 46). Thirteen states reported data on postpartum depression to the Pregnancy Risk Assessment Monitoring System (PRAMS) in 2004, 2008, and 2012 (47). During that time, the prevalence

of self-reported PPD declined from 14.8% in 2004 to 9.8% in 2012 (47). Statistically significant declines were observed in 8 of these states: Alaska, Colorado, Georgia, Hawaii, Minnesota, Nebraska, Utah, and Washington (47). Among the remaining five states – Maine, Maryland, Oregon, Rhode Island, and Vermont – no statistically significant changes in postpartum depression prevalence were observed (47). Based on 2012 PRAMS data, the PPD prevalence for the 27 reporting sites was 11.5%. This prevalence ranged from 8.0% in Georgia to 20.1% in Arkansas. Postpartum depression prevalence was highest for: those women who had never had a child; were aged ≤ 24 years; were of American Indian/Alaska Native or Asian/Pacific Islander race/ethnicity; had 12 years or fewer of education; were unmarried; were postpartum smokers; had three or more stressful life events in the year before delivering this child; gave birth to term, low-birthweight infants; and had infants requiring neonatal intensive care (47).

When a mother experiences postpartum depressive symptoms, she might have a reduced inclination to breastfeed or a shorter duration of breastfeeding, weaker maternal and infant bonding, and development disorders in her infant compared to women who do not experience PPD (48-50). Among infants whose mothers are affected by postpartum depression, adverse outcomes, such as delayed/impaired cognitive development and poor maternal-infant interaction, are especially relevant for children who are born socially disadvantaged (51-53). One long-term effect of postpartum depression is that it may increase a woman's risk of persistent or recurrent depression (54-58). Other outcomes for the child of a mother suffering from postpartum depression are grave and include increased risk of accidental injury, sudden infant death syndrome, and an increased risk of hospital admissions (59-61).

The exact etiology of postpartum depression is not completely understood, but clinicians and researchers know there are many heterogeneous causes stemming from various biological, physical, and emotional factors. A biological association between pregnancy and postpartum depression is generally attributed to drastic fluctuations of steroid and peptide hormones leading to a change in the hypothalamic pituitary adrenal and hypothalamic pituitary gonadal axes. In turn, alterations in these axes are associated with mood disorders such as depression, depressive symptoms, and anxiety (46).

The six months following delivery is the highest-risk time period for developing postpartum depression (44). Major risk factors for postpartum depression include: depression during pregnancy, depression, low social support, stressful life events during pregnancy, preterm birth, and having a traumatic birth experience (62). Even though the exact etiology of postpartum depression is not completely known, these risk factors have appeared in literature as strongly associated with postpartum depression and anxiety (62).

A 2009 community-based, prospective follow up study sought to better understand the predictive power for demographic, obstetric, and psychosocial risk factors of postpartum depression (63). The study population was 6,790 women who gave birth in 1994 in Denmark with a validation sub-population of 528 women. Postpartum depression was assessed using the Edinburgh Postnatal Depression Scale four months after delivery. Multivariate logistic regression identified the following risk factors: psychological distress in late pregnancy (aOR = 6.3, 95% CI [4.4-9.1]), perceived social isolation during pregnancy (aOR = 3.6, 95% CI [1.9-7.0]), high parity (aOR = 3.8, 95% CI [1.8 – 8.0]), and a history of psychiatric disorder before pregnancy (aOR = 2.1, 95% CI [1.4-3.2]). Of these identified risk factors, the psychological distress and social isolation had the largest predictive power of 0.3 meaning one in three women suffering from psychological distress in late pregnancy with perceived

social isolation will develop postpartum depression. This strong association between social isolation or lack of social support and postpartum depression was also demonstrated in a prospective study by Burgha *et al.* in their community-based study, *The Leicester 500 Project. Social support and the development of postnatal depressive symptoms, a prospective cohort survey* (64). These studies also support the belief that psychosocially disadvantaged women and socially isolated women are at high risk of developing PPD. For these women, PPD should be viewed as a continuum of depressive symptoms and not an isolated event or condition (63).

Postpartum depression is treatable with medication and therapy, even for those who are breastfeeding (44). Treatment with medication can begin as soon as a week after delivery and generally leads to depression improvement. However, a study conducted between 2005-2009 estimated that around 60% of women with depressive symptoms are clinically undiagnosed and therefore untreated (65). Of those who are clinically diagnosed with postpartum depression, half do not receive treatment or therapy (65). The American College of Obstetrics and Gynecology's recommendation is for healthcare providers to use a validated screening tool, such as the Edinburgh Postnatal Depressive Scale, to screen women for signs of depression one or more times during pregnancy and after delivery (62). Once a mother delivers a child, pediatricians are also encouraged to screen new mothers for signs of postpartum depression as they come for newborn care appointments (62, 66). In an effort to address postpartum depression, policy makers have extended Medicaid coverage for mothers, integrated therapy within primary care, and incentivized providers to screen for postpartum depressive symptoms during well-baby visits (62, 66). Women with severe postpartum depression have a 1 in 5 chance of experiencing chronic depression, and delayed treatment has the potential to exacerbate their depression (67).

Intersection of Pregnancy Loss and Postpartum Depression and Anxiety:

The associations between stillbirth and postpartum depression are more understood and researched among women and parents who have just experienced a pregnancy loss, but less is known about the effects of a recent loss on women's mental health in the postpartum period of a subsequent live birth. Studies in the United States on the effects of a previous pregnancy loss on postpartum depression are often smaller in scale than those of other countries with more robust population-based health assessments. In addition, the measurement instruments for depression and anxiety commonly vary from study to study, reducing comparability and transportability of results. Summaries of relevant studies are included here along with researchers' results and conclusions:

***The influence of prior perinatal loss on parents' psychological distress after the birth of a subsequent healthy infant* (Armstrong *et al.*, 2009)**

A small cohort study published in 2009 in the United States (n = 36 couples) studied the long-term influence of a prior prenatal loss on parents' psychological health during a subsequent childbearing experience (68). The researchers employed the Impact of Event Scale (IES), Center for Epidemiologic Studies-Depression Scale (CES-DS), Spielberger State-Trait Anxiety Inventory (STAI), and Maternal/Paternal Attitudes Questionnaire as their measurement instruments at 3 time points: during the third trimester of the pregnancy after a stillbirth, at 3 months postpartum, and at 8 months postpartum. The study concluded that levels of anxiety ($p<0.001$) and depressive symptoms ($p<0.001$) decreased significantly for these parents, but posttraumatic stress levels ($p=0.046$) remained moderately high even 8 months after a subsequent live birth (68). The depression these couples felt was significantly related to posttraumatic stress, anxiety, and concerns about their child during the third trimester (68). A limitation of this study was the lack of a comparison group, but the

researchers still recommended that parents with a history of loss should be assessed carefully during and after a subsequent pregnancy for mental distress.

***Impact of prior perinatal loss on subsequent pregnancies* (Armstrong *et al.*, 2004)**

A similarly sized cross-sectional study with 40 expectant couples who had previously experienced a pregnancy loss evaluated the influence, if any, of that previous loss on depressive symptoms, pregnancy-related anxiety, and prenatal attachment in the couples' current pregnancy and subsequent live birth (69). The measurement instruments for this study were the IES to assess influence of loss, the CES-DS to assess depressive symptoms, the Pregnancy Outcome Questionnaires to assess pregnancy-specific anxiety, and the Prenatal Attachment Inventory. Overall, mothers reported higher levels of depression, pregnancy-related anxiety, and prenatal attachment than fathers did. Eighty-eight percent of the mothers and 90% of the fathers also reported elevated stress levels related to their previous pregnancy loss (IES scores ≥19). The previous pregnancy loss' impact on psychological state during the current pregnancy was moderately correlated with both depression and pregnancy-related anxiety. However, no relationship was ascertained between the psychological distress in pregnancy after a pregnancy loss and prenatal attachment. The researchers concluded that their findings support increased awareness of parents' conflicting emotions of hope and fear during a pregnancy after having suffered a pregnancy loss.

***Perinatal loss and parental distress after the birth of a healthy infant* (Armstrong *et al.*, 2007)**

A 2-wave, 2-group comparative design study in 2007 determined whether levels of depressive symptoms and current stress related to a previous pregnancy loss following the birth of a healthy, full-term infant were different from the same levels measured during pregnancy (70). Furthermore, the researchers sought to compare any differences in

depressive symptoms during the postpartum period between parents who had a history of perinatal loss (n=38 parents) and parents who did not have a history of perinatal loss (n=36 parents). The IES, conducted over telephone, evaluated the persisting impact of a past perinatal loss. In addition, the CES-DS identified both duration and frequency of depressive symptoms for all parents in the week prior to the survey (Cronbach's alpha = 0.92). Among those parents who experienced a previous pregnancy loss, a significant overall decrease in depressive symptoms following the birth of a healthy infant was observed among the fathers but not among the mothers compared to their depressive symptoms during pregnancy. A third of these mothers also had CES-DS scores that identified them as high risk for depression. However, stress related to prior pregnancy loss significantly decreased for both mothers and fathers after delivery of their healthy infant. A positive correlation was observed between magnitude of stress related to a previous pregnancy loss and magnitude of depressive symptoms following a healthy, live birth. The researchers did not observe any significant differences in the levels of depressive symptoms when comparing the loss and non-loss groups following their recent live and healthy births. Overall, this study's findings suggest that stress and levels of depression remain high for mothers compared to fathers even after the birth of a healthy infant. These findings imply that nurses and doctors should continue to evaluate adverse mental health outcomes especially for mothers who have experienced a previous pregnancy loss, even after delivery of a healthy infant.

Anxiety, depression and relationship satisfaction in the pregnancy following stillbirth and after the birth of a live-born baby: a prospective study **(Gravensteen *et al.*, 2018)**

In 2018, the Norwegian Mother and Child Cohort Study concluded that women who have experienced stillbirth are at a significantly higher risk of suffering from both postpartum anxiety and depression during the third trimester of their current pregnancy compared to women with a previous live birth in their third trimester ($aOR_{anxiety}$= 5.47, 95%

CI [2.390-10.32], $aOR_{depression}$ = 1.91, 95% CI [1.11-3.27]) and compared to women who are pregnant for the first time and in their third trimester ($aOR_{anxiety}$ = 4.97, 95% CI [2.68-9.24], $aOR_{depression}$ = 1.91, 95% CI [1.08-3.36]) (71). Anxiety and depression were assessed with a short form version of the Hopkins Symptoms Checklist. The study population included a total of 901 pregnant women composed of 174 women who were pregnant following a stillbirth, 362 women pregnant following a live birth, and 365 previously nulliparous women. Overall, those women who were pregnant following a stillbirth had the highest prevalence of anxiety (22.5%) and depression (19.7%) during their third trimesters. For comparison, the prevalences of anxiety and depression among women with a previous live birth were 4.4% and 10.3%, respectively; and the prevalences of anxiety and depression among previously nulliparous women were 5.5% and 9.9%, respectively. The study concluded that stillbirths with a gestational age greater than 30 weeks and inter-pregnancy interval (<12 months) were associated with neither depression nor anxiety. When considering the postpartum period for women who previously had a stillbirth, both anxiety and depression significantly decreased when re-assessed at 6 months ($p<0.001$ for anxiety, $p = 0.031$ for depression). From 6 – 18 months postpartum, the prevalences of depression and anxiety were not significantly different among the three groups. However, at 36 months postpartum and among women who had a previous stillbirth, the prevalences of anxiety and depression were significantly higher compared to women with a previous live birth but not compared to previously nulliparous women. The main findings of this study were that mothers with a previous stillbirth overall had higher prevalences of both anxiety and depression in the subsequent pregnancy and in the postpartum period compared to women with previous live births or previously nulliparous women. These findings again support claims for continued

monitoring and evaluation for postpartum depression and anxiety among women who have had a stillbirth even after they deliver a live infant.

***Stillbirth as risk factor for depression and anxiety in the subsequent pregnancy: cohort study* (Hughes *et al.,* 1999)**

A British cohort study in 1999 of 60 pregnant women who experienced a previous stillbirth and 60 matched controls aimed to assess the relevance of time since loss on depression and anxiety in the current pregnancy (43). The measurement instruments were the well-tested Edinburgh Postnatal Depression Scale (EPDS), the Beck Depression Inventory (BDI), and the Spielberger State-Trait Anxiety Scale (STAI). Assessments were conducted during the third trimester of the subsequent pregnancy and at 6 weeks, 6 months, and 12 months postpartum. The researchers found that depression was significantly higher in the third trimester among women who experienced a previous stillbirth compared to the those who had not experienced a previous stillbirth ($p=0.004$). State anxiety was also significantly higher for the index group during the third trimester ($p=0.003$).

At the 12-month postpartum assessment, 19% of the women with a previous stillbirth scored high for depression compared to 8% of the reference group ($p=0.39$) with the majority of the depression in the index group being among mothers who conceived within a year of their stillbirth (28% vs 11%, $p=0.18$). One of the important findings of this study was that depression during the third trimester among mothers who had experienced a stillbirth highly predicted depression 1 year after delivery of a live infant ($p\leq0.0005$).

The main finding of this study was that the inter-pregnancy interval does play a significant role in depression and anxiety for the mothers who previously had a stillbirth. Women who conceived within a year of that stillbirth had more symptoms than controls at all assessment points, and they showed significantly higher state anxiety in the third trimester compared to those who conceived after 12 months ($p=0.02$). In addition, at the 12-month

assessment, the women who conceived within 12 months of a stillbirth had significantly higher state and trait anxiety (p=0.02) and significantly higher depression scores (p=0.01) compared to women who waited a year to conceive again. The researchers posited that women likely need at least a year to recover at least partially from the grief of a stillbirth and conceiving sooner than a year both interrupts and postpones their bereavement process. The researchers also hypothesized that a difference in basal state anxiety between women who conceived sooner than later could be related to the increased state anxiety in the third trimester.

***The association of stillbirth with depressive symptoms 6-36 months post-delivery* (Hogue *et al.*, 2015)**

A Stillbirth Collaborative Research Network (SCRN) population-based case-control study was conducted from 2006-2008 (72). In this study, the 275 cases were women who had a stillbirth, and the 522 controls were women who delivered a healthy infant. Postpartum depression was assessed 6-36 months after stillbirth or delivery using the Edinburgh Postnatal Depression Scale (Cronbach's α=0.80, good internal consistency). Before controlling for history of depression and other confounders, current postpartum depression among the cases was nearly twice as likely than among the controls (cOR=1.9, 95% CI [1.2, 3.0]). After controlling for history of depression and other confounders, the odds ratio decreased from 1.9 to 1.4 but was no longer significant (aOR=1.4, 95% CI [0.8, 2.3]). However, after controlling for confounders, those women who experienced a stillbirth but had no previous history of depression demonstrated a significant and increased risk of postpartum depression compared to controls with no history of depression (aOR=2.0, 95% CI [1.0, 3.8]).

Previous prenatal loss as a predictor of perinatal depression and anxiety **(Blackmore *et al.,* 2011)**

A large longitudinal study examining the degree to which symptoms of depression and anxiety associated with a previous loss persist in a subsequent successful pregnancy was published in 2011 and based on the Avon Longitudinal Study of Parents and Children cohort in West England (73). This cohort study assessed depression and anxiety outcomes by self-report using the EPDS to evaluate depression and Crown-Crisp Experiential Index to evaluate anxiety. The surveys were administered at multiple time points: 18 and 32 weeks gestation; and 8 weeks, 8 months, 21 months, and 33 months postpartum.

Women were eligible if they delivered between 1 April 1991 and 31 December 1992. Wilcoxon Rank testing found that there were no differences in the depression and anxiety scores for those who experienced stillbirth versus, thus all known pregnancy losses were considered together. The study sample was then categorized as follows: women with 0 losses (n=10,250), women with 1 loss (n=2158), women with 2 losses (n=515), women with 3 losses (n=131), and women with ≥4 losses (n=79). The study concluded that the number of previous pregnancy losses significantly predicted symptoms of both depression (β=0.18, SE = 0.07, $p<0.01$) and anxiety (β=0.14, SE = 0.05, $p<0.01$) in a subsequent pregnancy even after adjusting for confounding. Furthermore, this study supports others' findings that postpartum depression and anxiety associated with a previous pregnancy loss are not resolved with the birth of a live infant and that the previous loss actually is a risk factor for depression and anxiety nearly three years after the index loss.

Rates and precipitating factors for postpartum depression following screening in consecutive births **(Nelson *et al.,* 2015)**

A study aimed at measuring the recurrence of postpartum depression following implementation of universal postpartum depression screening at the University of Texas

Southwestern Medical Center analyzed risk factors potentially involved in the development of depressive symptoms following consecutive births (74). Beginning in June 2008, universal screening for postpartum depressive symptoms began at this facility. Through March 2010, 17,613 women were screened after an index delivery using the Edinburgh Postnatal Depression Scale. Of those women, 3842 (22%) returned for a subsequent delivery and completed a second EPDS evaluation. Eight percent of the women who screened positive after their index delivery also screened positive following the delivery of their next infant. Ninety-seven percent of those women who screened negative for postpartum depression after their index delivery also screened negative in their subsequent birth. The researchers found that a prior negative EPDS screening significantly reduced the risk of having a subsequent positive EPDS score ($p<0.01$). However, of the 3631 women who screened negative initially for PPD and returning for a consecutive delivery, stillbirth ($p=0.01$) and neonatal malformations ($p=0.02$) were significantly associated with an increased risk of PPD for the subsequent birth. This finding is important as further evidence that experiencing a stillbirth is a strong risk factor for postpartum depression even after a subsequent birth. Therefore, the authors concluded that if a woman has a stillbirth, she is likely to experience postpartum depression, and this depression is a precipitating factor for continued depressive symptoms following a subsequent birth.

Statement of Need

A large-scale and generalizable study assessing the associations between a previous pregnancy loss and its effects on women's mental health following a subsequent live birth is needed in the United States. Similar studies exist in other nations but are lacking in this country. Results from the analyses of such a study in the United States would help augment the current body of research and literature on stillbirth and its adverse effects on maternal

mental health even after the index postpartum period. Furthermore, estimating the proportion of women in the United States who experience a pregnancy loss and then deliver a live infant within a year and their mental health outcomes could better inform clinicians on how to council women following a pregnancy loss. Building on the existing research in this field will potentially improve the quality of life and the health of mothers and their children in the United States.

Chapter II: Manuscript

Effects of a recent pregnancy loss on maternal mental health among women with a recent live birth, PRAMS, 2012-2016

By Julie Smith

Abstract:

Background: Approximately 20% of women experienced a pregnancy loss in the United States between 1990 and 2011 (1). Much is known about the adverse association between a pregnancy loss and postpartum depression, but less is known about the experience of postpartum depression after a subsequent live birth. Using data from the Pregnancy Risk Assessment Monitoring System (PRAMS), we sought to (1) estimate the proportion of women with a recent live birth who experienced a pregnancy loss in the 12 months prior to conception and (2) determine if there are differences in self-reported postpartum depression for mothers of a recent live birth who experienced a pregnancy loss in the year before conceiving compared to those without a recent pregnancy loss.

Methods: Bivariate and multivariable associations were estimated using predicted marginals from log-binomial regression models. We controlled for confounding by marital status; maternal age, race, and education; previous number of live births; and stress. Additionally, we stratified our multivariable analyses by history of depression/anxiety and by pregnancy intention of the subsequent pregnancy. To account for the complex survey design in PRAMS, all analyses were conducted using SAS-callable SUDAAN.

Results: Among women with a recent live birth in the United States, 12.8% conceived their infant within 12 months of a pregnancy loss (SE = 0.4). For these mothers, there was a 15% increase in the prevalence of postpartum depression compared to women with a recent live birth and no recent pregnancy loss (aPR: 1.15, 95% CI: 0.98, 1.36). The effect of a previous pregnancy loss on postpartum depression was stronger for women with a history of depression or anxiety and for those who had not intended to become pregnant.

Conclusions: A substantial number of women in the United States with a recent live birth had experienced a pregnancy loss in the 12 months prior to conception. These women may be at an increased risk for postpartum depression, particularly if they have a history of depression or if the subsequent pregnancy was unintended.

Introduction:

Compared to other high-income countries (HICs), fetal mortality is persisting at consistent and higher than average rates in the United States (U.S.) (2). In the U.S., pregnancy losses occurring before 20 weeks gestation are classified as miscarriages, whereas those occurring at 20 weeks gestation or later are classified as stillbirths (3, 4). It has been

estimated that 20% of women experienced a pregnancy loss in the United States between 1990 and 2011 (1). Fetal mortality rates in the U.S. had been on the decline from 7.49 fetal deaths per 1000 total births in 1990 to 6.05 per 1000 total births in 2006 (19% decrease) (13). However, rates between 2006 and 2012 remained stable at approximately 6 fetal deaths per 1000 total births, halting the long-term trend of a decline (13).

The sense of loss and grief experienced by both mothers and fathers following a pregnancy loss is profound. In addition, depression can manifest in the postpartum period adding to one's suffering. Postpartum depression is a common but serious, adverse mental health outcome for many women who have recently given birth and even months after delivery (6). Estimates of the prevalence of postpartum depression in the United States range from 10-19%, which is similar to rates in other high-income countries (7, 8).

When a woman experiences depressive symptoms in the postpartum period, she might have a reduced inclination to breastfeed, experience weaker bonding with her infant, and have more developmental disorders in her infant compared to women who do not experience postpartum depression (48-50). Among infants whose mothers are affected by postpartum depression, adverse outcomes such as delayed/impaired cognitive development and poor maternal-infant interaction are even more likely if they are born socially disadvantaged (51-53). A long-term effect of postpartum depression on maternal mental health is the potential increase of a woman's risk of persistent or recurrent depression (54-58).

The associations between pregnancy loss and postpartum depression are better understood, but have largely been explored among women and parents who have just experienced a loss. However, less is known about the effects of a pregnancy loss on maternal mental health in the postpartum period of a subsequent live birth. Therefore, we sought to

contribute to this growing field of research using data from the United States' Pregnancy Risk Assessment and Monitoring System (PRAMS) to study the relationship between a pregnancy loss in the 12 months prior to conception and postpartum depression among women who recently delivered a healthy live born infant.

The objectives of this research were to (1) estimate the prevalence of having experienced a pregnancy loss in the 12 months prior to conception among a sample of women who had a recent live birth and (2) determine if there are differences in self-reported postpartum depression for mothers who recently had a live birth and who experienced a pregnancy loss in the year before conceiving compared to new mothers who did not experience a pregnancy loss during the year prior to conception.

Methods:

Study Setting and Design:

For this study, we analyzed Pregnancy Risk Assessment Monitoring System (PRAMS) survey data from 2012 to 2016 (Phases 7-8). Detailed background and methods for the PRAMS surveillance system have been previously described (75). Briefly, PRAMS is a population-based and on-going surveillance system which operates at the state-level and is coordinated by the Centers for Disease Control and Prevention's Division of Reproductive Health. Participating states (n=47) and sites (n=4) stratify their sample by important characteristics such as maternal age, race, infant birth weight, and geographic area. Women are sampled using their infants' birth certificates between 2 and 6 months after delivery and are invited to participate with a mailed introductory letter. Questionnaires are then delivered by mail, with telephone follow-up for non-responders. All responses are self-reported by the participant. Annually, around 1000-3000 women are sampled per state.

Participants:

All of the participants in this study gave birth to a live infant during the surveillance year and were contacted by PRAMS 2 to 6 months postpartum. In an effort to exclude women with preterm infants or infants affected by a complicated health issue, this sample was restricted to those women whose infants left the hospital within 5 days and were still alive at the time of survey.

Previous Pregnancy Loss and Postpartum Depression:

To assess the association between a pregnancy loss in the 12 months prior to conception and postpartum depression following a live birth, we identified the survey questions which best measured our exposure (previous pregnancy loss) and outcome (postpartum depression).

The question used to determine whether a woman had a pregnancy loss in the 12 months before this recent pregnancy is a standard survey question. Standard survey questions are optional and used at the discretion of each state in contrast to core survey questions which are required to be administered by participating states. The following question was asked by only 5 states and was used to determine whether a woman experienced a pregnancy loss in the 12 months prior to conception:

> "During the 12 months before you got pregnant with your new baby, did you have a miscarriage, fetal death (baby died before being born), or stillbirth?"

The two questions used to create the postpartum depression indicator variable were:

1. "Since your new baby was born, how often have you felt down, depressed, or hopeless?"
2. "Since your new baby was born, how often have you had little interest or little pleasure in doing things you usually enjoyed?"

Mothers answering "always" or "often", to either of these questions were coded as experiencing postpartum depression at the time of the survey.

Covariates of Interest:

Supplemental to a previous pregnancy loss (exposure) and postpartum depression (outcome), covariates of interest included marital status (married, other); maternal age, race, and education; previous number of live births; number of stresses experienced before pregnancy; history of depression and anxiety; and pregnancy intent. We categorized maternal race into these 6 groups to avoid small cell sizes: Asian, white, black, Native American, mixed race, and other race. Maternal age and number of live births were categorized according to the standards of the National Association for Public Health Statistics and Information Systems (NAPHSIS). PRAMS assesses stress by asking about events experienced during the 12 months prior to this most recent live birth. These events are profound and include events such as: a close family member being sick and hospitalized; separation or divorce; financial difficulty; and physical fighting and increased verbal arguments. Women were asked if they visited a health care worker to be checked for depression or anxiety in the 12 months before this recent pregnancy and were then classified as having no history of depression or having a history of depression. To ascertain the pregnancy intention for this most recent pregnancy, women were asked to think back to the time *just before* they became pregnant with their newest infant and report how they felt about becoming pregnant.

We selected these covariates to be included in our analyses following literature review and use of directed acyclic graphs (DAGs). Maternal age, maternal race, previous number of live births, history of depression/anxiety, stress, and pregnancy intent were

assessed as potential effect measure modifiers of the association between a recent pregnancy loss and postpartum depression.

A collinearity assessment was conducted to ensure covariates were not affected by problems related to correlation. Assessments of effect measure modification were then conducted for maternal age, maternal race, number of previous live births, stress, history of depression, and pregnancy intent. Using a 10% change in measure approach following log transformation, we examined potential confounding by marital status, maternal age, maternal race, maternal education, number of previous live births, stress, history of depression, and pregnancy intent.

Data Analysis:

To estimate the proportion of women with a recent live birth who experienced a pregnancy loss within the previous 12 months before becoming pregnant again, we calculated the proportion of women responding "yes" to the relevant question regardless of other maternal characteristics and experiences.

Predicted marginals, with survey weights, were used to obtain crude and adjusted prevalence ratios and confidence intervals. These prevalence ratios were used in investigating the bivariate and multivariable associations between a previous pregnancy loss and postpartum depression among women with a recent live birth.

All analyses were conducted using SAS-callable SUDAAN version 9.4 (Cary, NC). This study received a human subjects research exemption under 45 CFR 46.101(d)(4) from Emory University's Internal Review Board (IRB) (Appendix).

Results:

Inclusion and Exclusion Criteria:

We analyzed survey responses from 17,564 women representing a weighted total of 800,581 live births. These women gave birth to infants who were still alive at the time of survey, did not experience any complicated health outcomes following delivery, and were residents of: Arkansas, Tennessee, Texas, Vermont, and Wisconsin.

A collinearity assessment for the regression model containing all a priori effect modifiers and confounders did not identify an issue of collinearity. Confounding assessment and reexamination of confounders using DAGs and literature resulted in a final model adjusting for marital status, maternal age, maternal race, maternal education, number of previous live births, and stress.

Characteristics of Mothers:

Characteristics of the study population are presented in Table 1. Approximately 13% of women experienced a pregnancy loss in the year prior to the conception of the most recent pregnancy, and 15% of new mothers experienced postpartum depression at the time of survey (15.2%). Among those with postpartum depression, a lower proportion of women were married compared to those without postpartum depression (46.3% vs. 67.0%). There were no differences in the experience of postpartum depression by maternal age, maternal race, and number of previous live births. Postpartum depression was more common among women with lower education attainment (16.2% vs. 34.0%). The experience of ≥3 stressful life events was almost twice as common among women with postpartum depression than among those who did not indicate experiencing postpartum depression.

Bivariate Analyses:

There was a 12% increase in postpartum depression after delivering a live birth for those who experienced a pregnancy loss in the 12 months before conceiving versus not (cPR: 1.12, 95% CI: 0.94, 1.33) (Table 2). When compared to women aged 25-29 years, the younger age groups (≤24 years old) reported more postpartum depression while the older age groups (30-40+ years old) reported less postpartum depression. All non-white maternal race groups had an increased prevalence of postpartum depression compared to white mothers.

An association was observed between stressful life events and postpartum depression across all strata. The proportion of women experiencing postpartum depression increased 1.6 times (95% CI: 1.3, 1.9), 3.1 times (95% CI: 2.6, 3.7), and 5.1 times (95% CI: 4.2, 6.2) for women who experienced 1-2, 3-5, and ≥ 6 stressful life events (vs. none) during the year before this recent birth, respectively.

Marital status had a significant protective effect on the prevalence of postpartum depression such that being married reduced the prevalence of postpartum depression by half compared to being divorced, separated, single, or dating a partner (cPR: 0.48, 95% CI: 0.43, 0.54). Compared to having a high school degree or equivalent, having some college education/associate's degree significantly reduced the prevalence of depression by 22% (cPR: 0.78, 95% CI: 0.68, 0.91) and by 61% for those with a bachelor's degree or higher (cPR: 0.39, 95% CI: 0.33, 0.46). There was no association between the number of previous live births a woman had and experiencing postpartum depression after a live birth.

Multivariable Analysis:

After adjusting for marital status, maternal age, maternal race, maternal education, number of previous live births, and stress, the prevalence of postpartum depression was

15% higher among those mothers who experienced a pregnancy loss in the year before becoming pregnant compared to women who had not experienced a loss during this time frame (aPR: 1.15, 95% CI: 0.98, 1.36) (Table 3).

Stratified, Adjusted Prevalence Ratios from Multivariable Analysis:

The effect of a previous pregnancy loss on the prevalence of postpartum depression did not differ significantly by maternal age, maternal race, number of previous live birth, or stress (data not shown).

Multivariable analyses assessing the association between a previous pregnancy loss and postpartum depression were stratified by whether women visited a health care worker to be checked for depression or anxiety in the 12 months before this recent pregnancy and by pregnancy intent. The results of these stratified analyses suggest variation in postpartum depression outcomes by history of depression/anxiety and pregnancy intention for this recent pregnancy (Table 3.).

Among women with a history of depression or anxiety, there was an increase in prevalence of postpartum depression for women with a recent pregnancy loss compared to those without a recent loss (aPR: 1.28, 95% CI: 0.97, 1.70). Among women without a history of depression or anxiety, there did not appear to be an association between a pregnancy loss experienced in the 12 months before conceiving and postpartum depression following a subsequent live birth (aPR: 1.08, 95% CI: 0.88, 1.34).

The effect of a previous pregnancy loss on postpartum depression outcomes varied by whether the mother intended on being pregnant or not with her recent baby. Our findings suggest that having a desire to be pregnant within 12 months of a pregnancy loss reduced the likelihood of experiencing postpartum depression (aPR: 0.86, 95% CI: 0.62, 1.19). In contrast, for the mothers who did not want to be pregnant so soon or ever,

postpartum depression outcomes were higher for those with a pregnancy loss in the previous 12 months compared to mothers with no recent loss (Table 3). Being unsure of whether they wanted to be pregnant or not similarly increased postpartum depression outcomes for mothers with a recent loss (vs. no loss) (aPR: 1.5; 95% CI: 1.07, 2.13).

Discussion:

Approximately 13% of women with a recent live birth conceived within 12 months of experiencing a pregnancy loss. Our results suggest that the prevalence of postpartum depression among women who experience a pregnancy loss and conceive within 12 months of that loss is approximately 15% higher than the corresponding prevalence of postpartum depression among women who did not have a pregnancy loss in the same time frame.

This association was even stronger for women who reported a history of depression or anxiety. Pregnancy intention could either strengthen or weaken the association between a previous pregnancy loss and postpartum depression following a recent live birth. The effect of a previous pregnancy loss on postpartum depression was stronger for mothers who did not intend on becoming pregnant. On the other hand, wanting to be pregnant attenuated the association between a previous pregnancy loss and postpartum depression following a subsequent live birth.

Overall, our results are consistent with those of previous studies (43, 69, 71, 73). Large cohort studies from Norway and Great Britain similarly found that women who experienced a previous and recent pregnancy loss are at increased risk of experiencing postpartum depression after a subsequent pregnancy compared to women who had only had live births or those who were previously nulliparous (71, 73).

Differences in the association between pregnancy loss and postpartum depression in a subsequent pregnancy by history of depression were found in a cohort study from the

University of Texas' Southwestern Medical Center (74). Nelson *et al.* found that screening positive for postpartum depression was a precipitating factor for experiencing postpartum depression in the future. For women who experienced a pregnancy loss, postpartum depression was more common even after a subsequent live birth. Further, they found that a prior negative Edinburgh Postnatal Depression Score, or no evidence of a history of depression, significantly *reduced* a woman's risk of having a future positive EPDS score after a subsequent live birth.

We found that pregnancy intention plays an important role in the association between a previous pregnancy loss and postpartum depression. This finding is consistent with that of Hughes *et al.* who found that women conceiving within a year of a pregnancy loss had more depressive symptoms and higher depressive scores compared to women who waited more than a year to become pregnant after a loss (43). Hughes *et al.* also considered inter-pregnancy interval and not pregnancy intention specifically, but their results have similar implications – delaying pregnancy for a year or more after a recent pregnancy loss could likely reduce postpartum depression outcomes following a subsequent live birth. A probable explanation for these results is that women may need a full year or more to recover from the grief of a pregnancy loss, and conceiving sooner than a year may interrupt and postpone their bereavement process.

Our results suggest that women who have experienced a previous pregnancy loss should continue to be monitored by their health care providers for symptoms of postpartum depression even if she becomes pregnant again and subsequently gives birth to a live and healthy infant. Further, women who have had a recent pregnancy loss and a history of depression or anxiety should be counseled by their health care providers in treatment and supportive care options for depression during and after a future pregnancy.

Health care providers should also aim to incorporate more family planning education and recommendations into their practice when their patients experience a miscarriage or a stillbirth. The timing and delivery of family planning counseling should be appropriate and respectful of the woman's recent loss. Incorporating this practice is important as we found that the women in our study who experienced a loss and became pregnant again within 12 months had elevated levels of postpartum depression if they had not intended on being pregnant at that time, ever, or were unsure of their pregnancy intention.

This study is not without limitations. Postpartum depression was self-reported, and the questions used to assess this outcome were not validated instruments. Only five states administered the survey question ascertaining whether a mother had a pregnancy loss in the 12 months before this recent pregnancy. These states were Arkansas, Tennessee, Texas, Vermont, and Wisconsin. In addition, we only had data on women who recently had a live birth, and of those women who had a pregnancy loss, we were unable to adequately distinguish whether their losses were stillbirths or miscarriages. Further, there may selection bias such that those women with a previous pregnancy loss and postpartum depression after a subsequent live birth may have been less likely to complete the PRAMS survey compared to women experiencing less or no depression. If this is the case, we may have underestimated the relationship between a pregnancy loss within 12 months of conception and postpartum depression. These limitations could potentially reduce the external validity of our results.

This study did have certain strengths, however. Our analysis was a unique way to investigate the impact of a recent pregnancy loss particularly among women with a recent live birth. PRAMS surveys are administered by the majority of the United States to stratified samples of women with a large range of geographical and demographic characteristics. This

stratified style of sampling aided us in preserving maternal diversity even after restrictions and exclusions. Another strength is that PRAMS collects information on women's experiences before, during, and after pregnancy. This breadth of data allowed us to control for confounding by important experiences like stressful events experienced before this recent pregnancy and allowed us to stratify for important effect modifiers like history of depression and anxiety. Finally, our study had the largest sample size compared to other studies investigating the same association between a previous pregnancy loss and postpartum depression after a subsequent live birth.

Since this study supports the finding that the prevalence of postpartum depression is higher among mothers who have had a recent pregnancy loss compared to mothers who have not, being able to re-assess this association among more mothers in the United States is important. Further research to understand the mental health impact of pregnancy loss is critical and could be aided by more PRAMS states collecting information on postpartum depression, pregnancy loss, and type of pregnancy loss.

This large cross-sectional study found that there may be an increase in the prevalence of postpartum depression among new mothers in the United States if they experienced a pregnancy loss and became pregnant again within a year. Among women responding to the relevant PRAMS questions, 12.8% experienced a pregnancy loss within 12 months of becoming pregnant again, and 13.7% experienced postpartum depression following a live birth. These proportions represent a considerable number of women experiencing profound life events. For those who suffer through a pregnancy loss, a subsequent live birth might interrupt the grieving process, especially if the subsequent pregnancy was unintended or if the woman has a history of depression or anxiety. Building on the existing research in this

field will potentially improve the quality of life and the health of mothers and their children in the United States.

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Tables:

Table 1. Characteristics of PRAMS-surveyed Mothers by Postpartum Depression Status[a] Following a Live, Healthy[b] Birth, PRAMS, 2012-2016

	Women Eligible for Analysis (N = 17,546) (weighted N = 800,581)		Experienced PPD[c] (n = 2,659) (weighted n = 107,275)		No PPD (n = 14,887) (weighted n = 693,306)	
	No.[d]	%[e] (SE)	No.[d]	%[e] (SE)	No.[d]	%[e] (SE)
Pregnancy loss in the 12 months prior to this recent pregnancy						
Yes	2,208	12.8 (0.4)	347	14.0 (1.2)	1,861	12.6 (0.4)
No	15,338	87.2 (0.4)	2,312	86.0 (1.2)	13,026	87.4 (0.4)
Marital status						
Married	10,049	64.2 (0.6)	1,106	46.3 (1.6)	8,943	67.0 (0.6)
Other	7,497	35.8 (0.6)	1,553	53.7 (1.6)	5,944	33.0 (0.6)
Maternal age, years						
≤17	437	1.8 (0.2)	97	3.1 (0.6)	340	1.6 (0.2)
18-19	975	4.9 (0.3)	232	7.8 (0.9)	743	4.4 (0.3)
20-24	4,349	23.4 (0.5)	818	31.9 (1.5)	3,531	22.1 (0.5)
25-29	5,288	32.2 (0.5)	729	29.2 (1.5)	4,559	32.6 (0.6)
30-34	4,382	26.1 (0.5)	523	19.3 (1.2)	3,859	27.1 (0.6)
35-39	1,745	9.8 (0.3)	218	7.1 (0.8)	1,527	10.2 (0.4)
≥40	370	1.9 (0.2)	42	1.6 (0.4)	328	1.9 (0.2)
Maternal race						
Asian	690	3.0 (0.2)	127	4.0 (0.5)	563	2.8 (0.2)
White	10,732	77.5 (0.4)	1,365	69.5 (1.4)	9,367	78.7 (0.5)
Black	4,329	12.2 (0.4)	896	18.7 (1.2)	3,433	11.2 (0.4)
Native American	119	0.6 (0.1)	19	0.7 (0.2)	100	0.5 (0.1)
Mixed race	777	2.1 (0.1)	138	2.4 (0.4)	639	2.0 (0.1)
Other race	899	4.7 (0.2)	114	4.7 (0.7)	785	4.7 (0.3)
Maternal education						
≤ 8th grade	660	2.9 (0.2)	83	2.6 (0.5)	577	2.9 (0.2)
9th - 12th grade, no diploma	2,468	9.9 (0.3)	525	16.8 (1.2)	1,943	8.9 (0.3)
High school graduate/GED	5,149	25.5 (0.5)	967	33.5 (1.5)	4,182	24.3 (0.5)
Some college/associate's	4,882	30.1 (0.5)	746	31.0 (1.5)	4,136	30.0 (0.6)
Bachelor's/master's/doctorate	4,387	31.6 (0.5)	338	16.2 (1.1)	4,049	34.0 (0.6)
Number of previous live births						
none	6,491	38.0 (0.6)	927	37.3 (1.6)	5,564	38.1 (0.6)
1	5,279	32.0 (0.6)	783	30.8 (1.5)	4,496	32.2 (0.6)
2	3,100	17.2 (0.4)	462	17.1 (1.2)	2,638	17.2 (0.5)
3-5	2,474	11.9 (0.4)	439	13.7 (1.0)	2,035	11.7 (0.4)
≥ 6	202	0.9 (0.1)	48	1.1 (0.3)	154	0.8 (0.1)
Number of stresses in the 12 months before delivery						
none	4,744	28.9 (0.5)	395	14.5 (1.1)	4,349	31.1 (0.6)
1-2	7,079	40.7 (0.6)	866	32.3 (1.5)	6,213	42.0 (0.6)
3-5	4,489	24.4 (0.5)	950	37.6 (1.6)	3,539	22.3 (0.5)
≥ 6	1,234	6.0 (0.3)	448	15.5 (1.2)	786	4.6 (0.3)
Depression before pregnancy[f]						
Yes	3,286	17.9 (0.5)	807	29.1 (1.5)	2,479	16.2 (0.5)
No	13,423	82.1 (0.5)	1,759	70.9 (1.5)	11,664	83.8 (0.5)
Pregnancy Intent[g]						
Wanted later	4,350	23.9 (0.5)	780	29.7 (1.5)	3,570	23.1 (0.5)
Wanted sooner	2,166	13.5 (0.4)	274	10.7 (1.0)	1,892	14.0 (0.4)
Wanted at that time	6,539	41.3 (0.6)	659	27.1 (1.4)	5,880	43.5 (0.6)
Did not want to be pregnant then or ever	1,406	6.8 (0.3)	355	10.6 (1.0)	1,051	6.2 (0.3)
Unsure	2,776	14.5 (0.4)	537	21.9 (1.4)	2,239	13.3 (0.4)

[a] Postpartum depression indicated by self report to questions about mood and loss of interest since delivery

[b] Infant released from hospital in ≤ 5 days or infant not born in hospital

[c] PPD = postpartum depression

[d] Unweighted count

[e] Percent based off weighted count

[f] Unweighted n = 16,709, weighted n = 785,663; reported seeking help for depression/anxiety from a health care provider in the 12 months before recent pregnancy

[g] Unweighted n = 17,237, weighted n = 783,195; reported pregnancy intention just before becoming pregnant

Table 2. Bivariate Analysis Results: Associations Between Select Characteristics and Postpartum Depression [a] after a Recent Live and Healthy Birth[b] by Analysis Sample Characteristics, PRAMS, 2012-2016

	Women Eligible for Analysis (n = 17,546) (weighted n = 800,581)	
	cPR[c]	**95% CI**
Pregnancy loss in the 12 months prior to this recent pregnancy		
Yes	1.12	(0.94, 1.33)
No	*ref*	*ref*
Marital status		
Married	0.48	(0.43, 0.54)
Other	*ref*	*ref*
Maternal age, years		
≤17	1.85	(1.32, 2.60)
18-19	1.77	(1.40, 2.24)
20-24	1.50	(1.29, 1.75)
25-29	*ref*	*ref*
30-34	0.81	(0.69, 0.97)
35-39	0.80	(0.64, 1.01)
≥40	0.95	(0.59, 1.54)
Maternal race		
Asian	1.50	(1.16, 1.93)
White	*ref*	*ref*
Black	1.71	(1.47, 1.98)
Native American	1.47	(0.84, 2.58)
Mixed race	1.27	(0.94, 1.71)
Other race	1.11	(0.85, 1.46)
Maternal education		
≤ 8th grade	0.69	(0.48 ,1.00)
9th - 12th grade, no diploma	1.29	(1.09, 1.53)
High school graduate/GED	*ref*	*ref*
Some college/associate's	0.78	(0.68, 0.91)
Bachelor's/master's/doctorate	0.39	(0.33, 0.46)
Number of previous live births		
None	*ref*	*ref*
1	0.98	(0.85, 1.13)
2	1.01	(0.85, 1.20)
3-5	1.17	(0.98, 1.39)
≥ 6	1.30	(0.79, 2.14)
Number of stresses in the 12 months before delivery		
None	*ref*	*ref*
1-2	1.58	(1.31, 1.90)
3-5	3.08	(2.57, 3.68)
≥ 6	5.13	(4.20, 6.28)

[a] Postpartum depression indicated by self report to questions about mood and loss of interest in activities since delivery

[b] Infant released from hospital in ≤ 5 days or infant not born in hospital

[c] Crude prevalence ratio

Table 3. Multivariable Analysis Results: Prevalence of Postpartum Depression[a] after a Recent Live and Healthy Birth[b] Overall and by History of Depression/Anxiety and Pregnancy Intent, PRAMS, 2012-2016

	Overall[c]		Depression/Anxiety Before this Pregnancy[d]		Pregnancy Intent Just Before this Pregnancy[e]				
			Yes	No	Wanted to be Pregnant Later	Wanted to be Pregnant Sooner	Wanted to be Pregnant Then	Did not Want to be Pregnant Then or Ever	Was Unsure of What She Wanted
	aPR[f]	95% CI	aPR[g] and 95% CI		aPR[h] and 95% CI				
Pregnancy loss in the 12 months prior to this recent pregnancy									
Yes	1.15	(0.98, 1.36)	1.28 (0.97, 1.70)	1.08 (0.88, 1.34)	1.42 (0.96, 2.09)	1.06 (0.72, 1.56)	0.86 (0.62, 1.19)	1.37 (0.76, 2.48)	1.51 (1.07, 2.13)
No	*ref*		*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*

[a] Postpartum depression indicated by self report to questions about mood and loss of interest in activities since delivery

[b] Infant released from hospital in ≤ 5 days or infant not born in hospital

[c] Unweighted n = 17,546, weighted n = 800,581

[d] Unweighted n = 16,709, weighted n = 785,663; reported seeking help for depression/anxiety from a health care provider in the 12 months before recent pregnancy: "yes" (n=3,286), "no" (n=13,423)

[e] Unweighted n = 17,237, weighted n = 783,195; reported pregnancy intention just before becoming pregnant: "wanted to be pregnant later" (n=4350), "wanted to be pregnant sooner" (n=2166),"wanted to be pregnant then" (n=6539), "did not want to be pregnant then or ever" (n=1406), "unsure" (n=2776)

[f] Prevalence ratio adjusted for marital status, maternal age, maternal race, maternal education, number of previous live births, and stress

[g] Prevalence ratio adjusted for depression before this pregnancy, marital status, maternal age, maternal race, maternal education, number of previous live births, and stress

[h] Prevalence ratio adjusted for pregnancy intent, marital status, maternal age, maternal race, maternal education, number of previous live births, and stress

Chapter III: Summary, Public Health Implications, Possible Future Directions

Of the women who had a recent live birth in the United States between 2012 and 2016, we estimated that around 13% became pregnant with their new infants within just a year of experiencing a pregnancy loss. This substantial subset of women experienced a 15% increase in prevalence of postpartum depression compared to their counterparts who did not experience a pregnancy loss in the 12 months before their recent pregnancies. That 15% increase in postpartum depression prevalence grows to 28% for the mothers with a loss who also reported depression or anxiety in the year before the intervening pregnancy. Since these women experienced their pregnancy losses in the same time period as their reported depression, we might be able to assume that their depression is related to their loss. Ascertaining a history of depression during prenatal care should be done regularly by health care providers because of the impact that depression could have on future postpartum depression and chronic depression. Early identification of these higher risk women could allow providers the time to develop treatment plans for depression and anxiety with their patients or time to refer patients to appropriate perinatal psychiatrists.

Another important finding with implications for maternal mental health is that unintended pregnancies in the same year as a pregnancy loss further increase the prevalence of postpartum depression for mothers with recent losses. We additionally observed a decrease in the prevalence of postpartum depression among those mothers who wanted to be pregnant soon after a loss. Taken together, these findings imply that women experiencing a pregnancy loss in the United States might not be receiving adequate family planning recommendations or contraceptive options from their providers. It is understandable that presenting family planning options to women while they are grieving a loss is a delicate matter. However, strong and well-coordinated guidelines on family planning aimed at

preventing unintended pregnancy tailored to women who have recently experienced a loss do not exist. Further research is needed on this topic, but providers should consider promoting a delay in conceiving too soon after a pregnancy loss on account of other known benefits such as uninterrupted time for bereavement and time to regain physical strength and health.

All of these suggested interventions for future care should be client-centered, timely, efficient, accessible, and equitable to all demographics if they are to be sustainable and if they are to impact the maximum number of target women.

Further study is needed to determine whether this association is different depending on the length of gestation of the pregnancy loss (i.e., whether the loss was a miscarriage or a stillbirth). Additionally, further study is needed to explore whether this relationship persists when the subsequent pregnancy occurs more than 12 months after a pregnancy loss. Quantitative research will require enhanced response to PRAMS questions regarding previous pregnancy loss, type of loss, and the timing of the loss. The results of this future research could inform more evidence-based interventions which might improve maternal mental health outcomes. As an indirect result, these interventions would also reduce adverse emotional and physical health outcomes for the infants and young children of mothers affected by postpartum depression.

Appendix:

EMORY UNIVERSITY | Institutional Review Board

Date: March 5, 2019

Julie Smith
Principal Investigator
*SPH: Epidemiology

RE: **Exemption of Human Subjects Research**
IRB00109338
Investigating the effects of a previous pregnancy loss followed by a live birth on maternal mental health in the United States

Dear Principal Investigator:

Thank you for submitting an application to the Emory IRB for the above-referenced project. Based on the information you have provided, we have determined on **February 28, 2019** that although it is human subjects research, it is exempt from further IRB review and approval.

This determination is good indefinitely unless substantive revisions to the study design (e.g., population or type of data to be obtained) occur which alter our analysis. Please consult the Emory IRB for clarification in case of such a change. Exempt projects do not require continuing renewal applications.

This project meets the criteria for exemption under 45 CFR 46.101(d)(4). Specifically, you will conducting a secondary data analysis of PRAMS data..

- Protocol:
  - Thesis Proposal

Please note that the Belmont Report principles apply to this research: respect for persons, beneficence, and justice. You should use the informed consent materials reviewed by the IRB unless a waiver of consent was granted. Similarly, if HIPAA applies to this project, you should use the HIPAA patient authorization and revocation materials reviewed by the IRB unless a waiver was granted. CITI certification is required of all personnel conducting this research.

Unanticipated problems involving risk to subjects or others or violations of the HIPAA Privacy Rule must be reported promptly to the Emory IRB and the sponsoring agency (if any).

In future correspondence about this matter, please refer to the study ID shown above. Thank you.

Sincerely,

Maria-Gracia Beltran, BA
Research Protocol Analyst
This letter has been digitally signed