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Association of Postpartum Hormonal Contraception Use with Postpartum Depression

By

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Master of Public Health

Epidemiology

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Dr. Carol J. Hogue

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Hannah B. Mandle

B.A., University of Massachusetts, Lowell, 2013

Thesis Committee Chair: Carol J. Hogue PhD, MPH

An abstract of

A thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

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Master of Public Health in Epidemiology, 2018

Abstract

Association of Postpartum Hormonal Contraception Use with Postpartum Depression

By Hannah B. Mandle

Objective: Postpartum depression (PPD) affects 13-19% of women after childbirth. Studies suggest that hormonal changes may contribute to PPD, which poses a query for the safety of hormonal contraception use during the postpartum period. We investigate whether there is a possible association between PPD and postpartum hormonal contraceptive use.
Study Design: We analyzed cross-sectional data from the CDC's Pregnancy Risk Assessment Monitoring System Phase 7 Core Questionnaire, 2012-2015. The study was restricted to women with known live births, no missing PPD information, and those using a method of reversible contraception; a total of 61,790 women were eligible for analysis. Using SAS 9.4, we calculated crude prevalence differences (PDs) and ratios (PRs) as well as adjusted PRs and their 95% confidence intervals (CIs) for the association of hormonal contraception with PPD overall, by method-specific categories, and hormonal subcategories, stratified by history of depression (yes/no).
Results: Among women without a history of depression, 45.5% used a hormonal contraceptive method in the postpartum period and 9.25% had a positive indication of PPD. Among the 9.67% of women with a history of depression, 50.1% reported using a hormonal contraceptive during the postpartum period and 26.2% had PPD symptoms. After controlling for age, race/ethnicity, education, marital status, urban/rural residence, and parity, we found no material association between hormonal contraception and PPD relative to non-hormonal contraception. Women with a history of depression, however, had a 1.21 (95% CI: 1.21-1.21) prevalence ratio of PPD relative to women with no depression history.
Conclusions: Our study highlights the association of both sociodemographic factors and depression history with PPD. Prenatal screening for current depressive symptoms, depressive history, and socioeconomic risks, along with appropriate referral and interventions are needed to help reduce PPD.

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Manuscript

Introduction

Postpartum depression (PPD) is a mood disorder that affects roughly 13-19%(1) of women after childbirth. PPD not only affects the health and well-being of the mother[(2)], but also can result in negative behavioral(3), cognitive(4-6), and physical(7, 8) outcomes for the child. While risk factors for PPD have been identified(1), the cause is unknown.

A possible explanation for PPD could be the presence and/or absence of certain hormones. An early theory posited that the withdrawal of estrogen and progesterone experienced during childbirth could be the cause PPD(9, 10). However, all women experience this withdrawal while only a minority develop PPD. Furthermore, there is scant evidence that the levels of these hormones differ between women with and without PPD(10). In a novel study, Bloch et al. simulated pregnancy and the postpartum state by inducing hypogonadism, adding back supraphysiologic doses of estradiol and progesterone for eight weeks, and then withdrawing both steroids under double-blind conditions in two groups of women(11). Within the control group of healthy women without any history of psychiatric disorders, none of the eight women developed severe mood symptoms. In the experimental group of women with a history of PPD, five of the eight women developed severe mood symptoms during the withdrawal phase as well as during the add-back phase. The authors concluded that instead of a direct hormone withdrawal-induced cause of PPD, perhaps there is a certain group of women who are vulnerable to changes in hormone levels.

If postpartum hormone levels do adversely affect a subset of women, hormonal contraception use during the postpartum period may increase their risk of PPD. Hormonal contraception has been associated with a greater risk of first diagnosis of depression and first antidepressant drug use in previously healthy women without a prior psychiatric diagnosis(12). Furthermore, in animal models, administration of levonorgestrel, a synthetic progestin found in

certain forms of HC, has been shown to decrease cerebral cortical allopregnanolone (AP) levels as well as hippocampal AP levels(13). AP, the reduced metabolite of progesterone, is a potent positive allosteric modulator of the $GABA_A$ receptor, and AP levels were 60% lower in depressed patients compared to controls in a small study by Uzunova et al.(14) Despite the direct association of synthetic progestins with depression and antidepressant use, the Centers for Disease Control (CDC) guidelines for postpartum contraceptive use state that both combined and progestin-only hormonal methods are safe for postpartum women and can be initiated immediately postpartum(15).

Previous studies have attempted to investigate an association of postpartum hormonal contraception with PPD. One study found no difference in Edinburgh Postnatal Depression Scale (EPDS) scores between postpartum depomedroxyprogesterone acetate (DMPA) users and non-hormonal contraception users(16). Conversely, a later study found EPDS scores to be statistically significantly higher in postpartum DMPA users than among postpartum copper intrauterine device users when measured at both one and three months postpartum(17). Lawrie et al administered norethisterone enanthate, a synthetic progestin similar to those found in contraceptives, to postpartum women within 48 hours of delivery. Relative to no administration, norethisterone was associated with significantly higher EPDS scores (10.6 vs 7.5, $p = 0.0022$) at six weeks postpartum(18). Last, a study in a military population found a subset of hormonal contraceptives (those containing etonogestrel, another synthetic progestin) to be associated with a higher risk of antidepressant use (hazard ratios 1.22-1.45, $p = 0.001$) relative to no hormonal contraceptive use(18). In summary, these published studies examined the association of only a subset of hormonal contraceptives and many used women using no contraceptive method as controls. There may be important differences between women who choose to use contraception during the postpartum period versus those who choose not to.

The purpose of this study is to investigate the association of postpartum hormonal

contraceptive use with PPD. This study includes only women who used reversible contraception during the postpartum period and is the first study, to the authors' knowledge, of associations between the various broad categories and subcategories of contraceptive methods with PPD.

Methods

This was a secondary analysis of cross-sectional data from the Centers for Disease Control (CDC) Pregnancy Risk Assessment Monitoring System (PRAMS). All data were de-identified and IRB approval was not required.

Data Collection and Study Population

The PRAMS database includes mothers randomly selected from a state's live birth certificate file. State health department personnel first contact selected women by mail 2-4 months after delivery. When there is no response to repeated mailings, personnel contact and interview women by telephone. Question topics include details about the early postpartum period as well as attitudes and feelings about the most recent pregnancy, content and source of prenatal care, maternal alcohol and tobacco consumption, physical abuse before and during pregnancy, pregnancy-related morbidity, infant health care, post-delivery contraceptive use, and mother's knowledge of pregnancy-related health issues. We used data from the Phase 7 Core Questionnaire, 2012-2015. We included only those with known live births, no missing PPD information, who used a method of reversible contraception. We excluded women who reported using more than one hormonal method or a hormonal method plus an IUD.

Study Variables

The main exposure for the present study was hormonal contraceptive use for reversible contraception. PRAMS respondents were asked "What kind of birth control are you or your husband or partner using now to keep from getting pregnant?" We excluded women indicating abstinence, tubal ligation, or vasectomy. Reversible response options included birth control pill, condoms, injection, contraceptive implant, contraceptive patch or vaginal ring, IUD, natural

family planning, withdrawal, and other, which provided a prompt to write in a method. If the "other" response mentioned one of the listed options, we reclassified it into that method. Finding a high frequency of the lactation amenorrhea method (LAM) and spermicide/diaphragm/sponge/cap in the "other" option, we created two new method categories. We classified birth control pill, injection, implant, patch and ring as hormonal. We categorized all other methods as non-hormonal. In addition to these broad categories, we also subcategorized birth control methods by method type: withdrawal/family planning (withdrawal, LAM, natural family planning), barrier (condom, spermicide/diaphragm/sponge/cap), IUD, and hormonal (birth control pill, injection, implant, patch and ring). We further parsed hormonal methods into oral (birth control pills) versus non-oral (injection, implant, patch or ring) and combined (birth control pills, patch or ring) versus progestin-only (injection, implant). Because type of IUD was not asked, we could not identify whether it was hormonal or another type.

The outcome for this study was PPD. The questionnaire contained two PPD-related questions: "since your new baby was born, how often have you felt down, depressed, or hopeless?" and "since your new baby was born, how often have you had little interest or little pleasure in doing things?" Answer options included "always," "often," "sometimes," "rarely," and "never." We used these two questions to create a dichotomized PPD indication variable (yes or no). If a woman answered "always" or "often" to at least one of the questions, we categorized her as has having a PPD indication; otherwise, if she answered both questions without "always" or "often," we classified her as having no indication.

We considered variables to be potential confounders based on previous evidence of their association PPD and hormonal contraception use. These variables were: age, race, ethnicity, education, history of depression, parity, and marital status.

Weighting

The PRAMS database provides information that can be generalized to a state's population of births. To be included in the multi-state data available from compiled from state-

specific surveys, CDC requires a minimum overall response rate of 55%. To increase more precise estimates from selected high-risk subpopulations such as women with low-weight births or women having certain characteristics (such as lower education), states may over-sample those subpopulations. However, high-risk groups tend to respond at lower rates, and sometimes missing records can be clustered around a certain hospital or county, resulting in bias. To compensate for such biases, CDC calculated three weights: sampling, nonresponse, and omission/noncoverage. Multiplying these weights together yields an analytic "weight" variable that can be interpreted as the number in the population that each respondent represents.

Statistical Analysis

We calculated weight-adjusted frequencies of demographic and potential confounding variables, contraception methods, and PPD. We then calculated weight-adjusted prevalence differences, prevalence ratios, and their 95% confidence intervals for the association of hormonal contraceptive use with PPD, overall and by method-specific categories, hormonal subcategories, and individual methods. Due to the high risk of PPD for those who have a history of depression, we stratified the analysis by depression history. A Log-binomial regression was used to assess whether contraceptive category was associated with PPD when controlling for confounding variables. Where there were statistically and clinically significant associations between contraceptive category and PPD, we calculated the attributable risk percent to measure the proportion of PPD in the exposed that may be accounted for by the specific contraceptive category used. All statistical analyses were conducted using SAS 9.4 statistical software (Cary, NC). A two-sided P-value ≤ 0.05 was considered statistically significant.

Results

In the PRAMS Core 7 database, 61,790 women from 33 states were eligible for this analysis. The states included 53% of all births in the U.S. in 2015(19) (Supplementary Table 1). The majority of participants were between the ages of 20-34 years, non-Hispanic white, and had

at least some college education (Table 1). Contraceptive methods, PPD, and history of depression varied across all selected characteristics.

Women without a History of Depression

Among women without a history of depression, 45.5% used a hormonal method in the postpartum period and 9.25% had a positive indication of PPD (Table 1). Table 2 presents unadjusted prevalence differences (PD) and prevalence ratios (PR) of contraceptive categories. Relative to non-hormonal, hormonal use was associated with 2.06% (95% CI: 1.99-2.13) greater PPD prevalence and a PR of 1.25 (1.24-1.26). Relative to withdrawal, each contraceptive category was statistically significantly associated with a greater prevalence of PPD. The hormonal category had the highest prevalence (PD = 3.38% [3.27-3.50], PR = 1.48 [1.46-1.51]). Among hormonal subcategories, both non-oral relative to oral and progestin-only relative to combined hormones were associated with greater PPD prevalence (Table 3).

After we controlled for age, race/ethnicity, education, marital status, urban/rural residence, and parity, we found no material association between hormonal and PPD relative to non-hormonal contraception among women without a history of depression (Table 2), nor any associations among broad contraceptive categories. We did, however, observe small associations for non-oral relative to oral and progestin-only relative to combined methods (Table 3).

Women with a History of Depression

Among the 9.69% of women with a history of depression, half reported using a hormonal form during the postpartum period and more than one-fourth (26.20%) had a positive PPD indication (Table 1). Relative to women without a history of depression, women with a depression history had an adjusted PPD indication PR of 1.21 (1.21 - 1.21). Of those with a positive PPD indication among women with a history of depression, 17.35% can be attributed to having history of depression. Within the sample of women with a depression history, relative to non-hormonal, hormonal use was associated with 69% (1.37 - 2.02) greater PPD prevalence and a PR of 1.07 (1.05 - 1.08). Similar to women without a history of depression, each contraceptive

category was statistically significantly associated with a greater prevalence of PPD relative to withdrawal and the category associated with the highest prevalence was hormonal (PD = 7.70% [7.01 - 8.40], PR = 1.04 [1.03-1.05]).

Using the log-binomial model and covariates, we found an overall association of hormonal contraception and PPD relative to non-hormonal to be effectively null (Table 2). Among women with a history of depression, however, IUD was slightly associated with PPD relative to withdrawal with a PR of 1.04 (1.03-1.05). Notably, only 3.85% of PPD cases among women with a history of depression who used IUD can be attributed to the IUD. Hormonal subcategory associations were also greater for women with a history of depression: oral vs. non-oral PR = 1.06 (1.05-1.06) and progestin-only vs. combined PR = 1.08 (1.08-1.09) (Table 3.). The percent of PPD cases attributable to oral and progestin-only hormonal contraception were 5.67% and 7.41%, respectively.

Discussion

After controlling for known risk factors of PPD, we found no association between postpartum hormonal contraception use and PPD indication relative to non-hormonal contraception. This is an important finding, as it both allays concern about the potential impact of these effective contraceptive methods on women's postpartum health and highlights the association of socio-demographic and mental health factors on their postpartum mental health.

By way of hormonal subcategories, women without a history of depression had statistically significant, albeit small, associations for non-oral relative to oral and progestin-only relative to combined hormonal methods and PPD. These associations were even greater among women with a history of depression. The proportions of PPD that may be accounted for by these specific forms of hormonal contraception, however, were very small (less than 10%). These findings could indicate a small group of hormonally-sensitive women, as previously theorized by

Bloch et al(11), or could be an artifact of our inability to account for all socio-demographic factors that are associated with both PPD(1) and hormonal contraceptive use(20).

Women who use hormonal contraception were younger, less educated, not married, and black; they also had a higher PPD prevalence. This is not a new finding(1), but its importance in identifying a group of women who may need more careful prenatal screening and postpartum follow up is substantial. Of particular concern is women who had a history of depression. Consistent with previous literature(1, 21), we found having a history of depression to be statistically significantly associated with a greater prevalence of postpartum depression symptoms. More than one-fourth of women with a history of depression had a positive indication of PPD and close to one-fifth of the PPD cases in this group was attributable to recurrent depression.

This highlights the need to screen and refer prenatally for both depression history and current depressive symptoms. Prenatal identification and referral may be effective in alleviating the impact of both prenatal depression on pregnancy outcomes and the onset of postpartum depression. In a systematic review of depression screening among pregnant and postpartum women, O'Connor et al. found 6 trials which showed 18-59% relative reductions in the risk of depression at 3-5 months after participating in screening programs compared to usual care(22). Furthermore, a meta-analysis of cognitive-behavioral therapy administered to women with screen-detected depression showed a 34% increased likelihood of remission(22). It has also been previously reported that white and African American pregnant women who scored a 10 or above on the EPDS have more confidence in psychosocial treatments versus pharmaceutical treatments(23).

Only 44% of OB/GYNs surveyed in 2003 reported screening for depression(24). The majority of respondents indicated that depression screening is effective but perceived it as difficult to carry out in everyday practice(24). The EPDS is a common, brief, and reliable

measure for identifying women at risk for PPD(25), and can be incorporated into electronic medical record histories(26). Women whose EPDS score is $\geq$ 12 should be further evaluated and referred, as necessary, for mental health care(25). Alternatively, the U.S. Preventive Service Task Force, an agency which recommends regular depression screening for all adults, notes that "simple screening questions may perform as well as more complex instruments"(27). A woman's psychological history, for example, can be easily ascertained during regular prenatal visits.

The vast majority of women do obtain prenatal care and 89-92% have reported utilizing postpartum care in various parts of the U.S.(28) However, the prevalence of women who attend their postpartum visit is associated with many of the same factors we found to be associated with PPD indication such as marital status, age, race, and education(28), suggesting women who are already at a higher risk of PPD may be even less likely to seek postpartum care. In a study of 51 women at risk for depression only 30 (59%) accepted a mental health referral, 22 (41%) contacted a mental health provider, and 16 (31%) saw a provider(29). Therefore, it is important for both prenatal care providers and pregnant women to understand their possible risk of PPD and seek appropriate care.

Strengths of this study include the large sample size across the U.S. and the analytic weight variables that allowed adjustment for non-response and non-coverage in producing population-based estimates. However, these estimates assume that respondents represent non-respondents; survey results could be biased if there is an association between having PPD and answering the survey. Also, given the timing and cross-sectional design of the study, we cannot differentiate whether women initiated hormonal contraceptive methods before or after onset of PPD and therefore cannot assess causality. The PPD indicator variable was calculated from depression-related questions; clinical diagnoses of PPD were not provided, which may have resulted in outcome misclassification and biased our results. Another limitation was the restricted list of contraceptive methods women had to choose from on the questionnaire. Mainly, women were not able to differentiate between combined and progestin-only oral contraceptive pills or

copper and progestin IUD. Furthermore, we were unable to distinguish the type of synthetic progestins or estrogens in the contraceptives.

In summary, our analysis did not support an association between types of postpartum contraceptive methods and PPD, which suggests that hormonal methods do not increase risk of postpartum depression. Previous research that reported an association may not have accounted for the numerous sociodemographic differences among women who choose different contraceptive methods. However, the results highlight sociodemographic factors and depression history associated with postpartum depression. More emphasis on prenatal screening and early interventions is needed to provide the best mental health care for women and their children.

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Table 1. Demographic characteristics of eligible subjects in the PRAMS* Core 7 database

	Unweighted N	Weighted[a] % using HC*	Weighted[a] % with PPD*	Weighted[a] % with a History of Depression
All Women	61,790	45.94	10.89	9.69
Age, years				
≤19	5,011	62.71	18.2	13.74
20-24	14,875	55.25	15.13	11.60
25-29	18,644	45.12	9.56	9.43
30-34	16,072	39.69	8.35	7.95
35-39	5,993	34.87	7.73	8.43
≥40	1,195	34.15	8.15	7.52
Race/Ethnicity				
Non-hispanic white	32,415	45.06	9.75	11.49
Non-hispanic black	8,892	61.12	15.64	7.15
Hispanic	9,342	43.91	9.51	5.59
Other/unknown	11,141	35.69	14.58	7.25
Education, years				
≤11	8,546	51.95	15.82	13.11
12	15,270	54.56	14.36	11.32
13-15	17,574	47.33	11.54	11.15
≥ 16	20,400	37.34	6.47	6.33
Marital Status				
Married	36,544	38.90	8.18	7.39
Other	25,246	57.18	15.20	13.34
Urban vs. Rural				
Urban	23,673	43.28	9.93	8.28
Rural	13,147	50.27	11.31	10.93
Unknown	24,970	46.87	11.7	10.61
Parity				
0	28,633	49.57	11.34	10.20
1	19,450	43.87	10.04	8.95
2	8,488	41.90	10.77	9.23
3+	5,219	40.70	12.08	10.62
History of Depression				
No	55,351	45.5	9.25	-
Yes	6,439	50.09	26.20	-

*Abbreviations: PRAMS = Pregnancy Risk Assessment Monitoring System; HC = hormonal contraception; PPD = postpartum depresion.

[a]Weights calculated by multiplying sampling, nonresponse, and noncoverage factors. Weights represent the number of women like herself in the population that each respondent represents

Table 2. Associations of Contraceptive Categories with Postpartum Depression by History of Depression in the PRAMS* Core 7 Database

	N	% with PPD*	Weighted[a] % with PPD *	Weighted[a], Unadjusted PD* (95% CI*)	Weighted[a], Unadjusted PR* (95% CI)	Weighted[a], Adjusted[b] PR (95% CI)
No History of Depression						
Non-Hormonal	29,490	9.65	8.31	Ref		
Hormonal	25,861	11.38	10.37	2.06% (1.99 - 2.13)	1.25 (1.24 - 1.26)	1.01 (1.01-1.01)
Withdrawal, Rhythm/FAM, LAM*	4,633	8.89	7.00	Ref		
Barrier	14,888	9.44	8.26	1.27% (1.15 - 1.40)	1.18 (1.16 - 1.20)	1.00 (1.00 - 1.01)
IUD*	9,969	10.31	9.14	2.16% (2.02 - 2.29)	1.31 (1.29 - 1.33)	1.01 (1.00 - 1.01)
Hormonal	25,861	11.38	10.37	3.38% (3.27 - 3.50)	1.48 (1.46 -1.51)	1.01 (1.01 - 1.01)
History of Depression						
Non-Hormonal	3,131	27.15	25.35	Ref		
Hormonal	3,308	30.00	27.04	1.69% (1.37 - 2.02)	1.07 (1.05 - 1.08)	1.01 (1.01 - 1.01)
Withdrawal, Rhythm/FAM, LAM	403	23.33	22.09	Ref		
Barrier	1,328	24.70	22.00	-0.11% (-0.78 - 0.57)	1.00 (0.97 - 1.03)	0.96 (0.96 - 0.97)
IUD	1,400	30.57	29.80	7.70% (7.01 - 8.40)	1.35 (1.31 - 1.39)	1.04 (1.03 - 1.05)
Hormonal	3,308	30.00	27.04	4.95% (4.32 - 5.58)	1.22 (1.19 - 1.26)	1.01 (1.00 - 1.02)

*Abbreviations: PRAMS = Pregnancy Risk Assessment Monitoring System; PD = prevalence difference; RR= prevalence ratio; PPD = postpartum depression; CI = confidence interval; FAM = fertility awareness method; LAM = lactation amenorrhea method; IUD = intrauterine device.

[a]Weights calculated by multiplying sampling, nonresponse, and noncoverage factors. Weights represent the number of women like herself in the population that each respondent represents

[b]Log-binomial model adjusting for age, race/ethnicity, education, marital status, parity, and urban/rural residence

Table 3. Associations of Hormonal Contraceptive Sub-Categories with Postpartum Depression by History of Depression in the PRAMS* Core 7 Database

	N	% with PPD*	Weighted[a] % with PPD	Weighted[a], Unadjusted PD* (95% CI*)	Weighted[a], Unadjusted PR* (95% CI)	Weighted[a], Adjusted[b] PR (95% CI)
No History of Depression						
Oral	15,764	9.06	8.32	Ref		
Non-Oral	10,097	15.00	14.36	6.04% (5.91 - 6.16)	1.73 (1.71 - 1.74)	1.04 (1.04 - 1.04)
Combined	16,957	9.35	8.67	Ref		
Progestin-Only	8,904	15.23	14.50	5.84% (5.70 - 5.97)	1.67 (1.66 - 1.69)	1.03 (1.03 - 1.04)
History of Depression						
Oral	1,670	26.00	24.12	Ref		
Non-Oral	1,638	34.07	31.12	7.00% (6.52 - 7.48)	1.29 (1.27 - 1.31)	1.06 (1.05 - 1.06)
Combined	1,837	26.24	23.74	Ref		
Progestin-Only	1,471	34.67	32.62	8.87% (8.38 - 9.37)	1.37 (1.35 - 1.40)	1.08 (1.08 - 1.09)

*Abbreviations: PRAMS = Pregnancy Risk Assessment Monitoring System; PD = prevalence difference; PR = prevalence ratio; PPD = postpartum depression; CI = Confidence Interval.

[a]Weights calculated by multiplying sampling, nonresponse, and noncoverage factors. Weights represent the number of women like herself in the population that each respondent represents

[b]Log-binomial model adjusting for age, race/ethnicity, education, marital status, parity, and urban/rural residence

Supplementary Table 1. Birth Percentages by State in the PRAMS* and The United States Populations, 2015

State	Prams Percent	U.S. Percent
Alabama	0.93	1.5
Alaska	3.12	0.28
Arkansas	1.73	0.98
Colorado	3.08	1.67
Connectict	1.34	0.9
Delaware	3.09	0.28
Georgia	0.77	3.3
Hawaii	2.86	0.46
Illinois	4.01	3.97
Iowa	2.41	0.99
Maine	2.6	0.32
Maryland	3.48	1.85
Massacusetts	4.5	1.8
Michigan	3.98	2.85
Minnesota	2.5	1.76
Missori	3.33	1.89
Nebraska	4.42	0.67
New Hampshire	1.33	0.31
New Jersey	2.95	2.59
New Mexico	4.18	0.65
New York	5.93	5.96
Ohio	1.68	3.5
Oklahoma	5.46	1.34
Oregan	2.42	1.15
Pennsylvania	2.93	3.55
Rhode Island	3.41	0.28
Tennessee	2.28	2.05
Utah	4.8	1.28
Vermont	3.2	0.15
Washington	1.12	2.24
West Virginia	3.62	0.5
Wisconsin	4.64	1.69
Wyoming	1.9	0.2
Total	100.00	52.89

*Abbreviations: PRAMS = Pregnancy Risk Assessment Monitoring System