Review

Maternal Marijuana Use and Adverse Neonatal Outcomes

A Systematic Review and Meta-analysis

Shayna N. Conner, MD, MSCI, Victoria Bedell, MD, Kim Lipsey, MLIS, George A. Macones, MD, MSCE, Alison G. Cahill, MD, MSCI, and Methodius G. Tuuli, MD, MPH

OBJECTIVE: To estimate whether marijuana use in pregnancy increases risks for adverse neonatal outcomes and clarify if any increased risk is attributable to marijuana use itself or to confounding factors such as tobacco use.

DATA SOURCES: Two authors performed a search of the data through August 2015 utilizing PubMed, Embase, Scopus, Cochrane reviews, ClinicalTrials.gov, and Cumulative Index to Nursing and Allied Health.

METHODS OF STUDY SELECTION: We looked at observational studies that compared rates of prespecified adverse neonatal outcomes in women who used marijuana during pregnancy with women who did not.

TABULATION, INTEGRATION, AND RESULTS: Two authors independently extracted data from the selected studies. Primary outcomes were low birth weight (less than 2,500 g) and preterm delivery at less than 37 weeks of gestation. Secondary outcomes were birth weight, gestational age at delivery, small for gestational age, level II or greater nursery admission, stillbirth, spontaneous abortion, low Apgar score, placental abruption, and perinatal death. DerSimonian-Laird random-effects models were used. We assessed heterogeneity using the Q test and I^2 statistic. Stratified analyses were performed for the primary outcomes and pooled adjusted estimates were calculated. We included 31 studies that assessed the effects of maternal marijuana use on adverse neonatal outcomes. Based on pooled unadjusted data, marijuana use during pregnancy was associated with an increased risk of low birth weight (15.4% compared with 10.4%, pooled relative risk [RR] 1.43, 95% confidence interval [CI] 1.27–1.62) and preterm delivery (15.3% compared with 9.6%, pooled RR 1.32, 95% CI 1.14–1.54). However, pooled data adjusted for tobacco use and other confounding factors showed no statistically significant increased risk for low birth weight (pooled RR 1.16, 95% CI 0.98–1.37) or preterm delivery (pooled RR 1.08, 95% CI 0.82–1.43).

CONCLUSION: Maternal marijuana use during pregnancy is not an independent risk factor for adverse neonatal outcomes after adjusting for confounding factors. Thus, the association between maternal marijuana use and adverse outcomes appears attributable to concomitant tobacco use and other confounding factors.

(Obstet Gynecol 2016;0:1–11)

DOI: 10.1097/AOG.0000000000001649

Marijuana is the most common recreational drug used in pregnancy.[1] In the obstetric population, the reported prevalence ranges from 2% to 27% depending on population studied, definition of use, and method of detection.[2,3] This is likely underestimated because marijuana use is often underreported. Despite the fact that hundreds of thousands of women use marijuana in pregnancy, little is known about the effects of marijuana on neonatal outcomes.

It is biologically plausible that marijuana use during pregnancy could affect the fetus. Delta 9 tetrahydrocannabinol readily crosses the placenta and can be detected in the adult body for 30 days.[4–6] In addition, when smoked, marijuana has been shown to lead to fivefold higher serum carbon monoxide levels compared with tobacco, potentially leading to impaired maternal respiratory and gas exchange physiology and subsequent harmful effects on the fetus.[7,8]

Prior studies of varying quality and methodology investigating neonatal outcomes related to marijuana use in pregnancy have yielded conflicting results, some

From the Department of Obstetrics and Gynecology, Washington University in St. Louis, and the Washington University School of Medicine, St. Louis, Missouri.

Corresponding author: Shayna N. Conner, MD, MSCI, Department of Obstetrics and Gynecology, Washington University School of Medicine, 4911 Barnes Jewish Hospital Plaza, Campus Box 8064, St. Louis, MO 63110; e-mail: conners@wudosis.wustl.edu.

Financial Disclosure

The authors did not report any potential conflicts of interest.

ISSN: 0029-7844/16

showing increased risks for adverse neonatal outcomes whereas others show no increased risk.[9] Many are hampered by selection bias by using volunteer cohorts and classification bias by defining marijuana exposure through self-report. Additionally, previous studies do not uniformly adjust for confounding as a result of coexistent tobacco use, a vital consideration when investigating health outcomes associated with marijuana use, because marijuana is often used in combination with tobacco.

We sought to determine the effect of marijuana use during pregnancy on neonatal outcomes and clarify whether any increased risk is attributable to marijuana itself or to other confounding factors such as tobacco.

SOURCES

We performed a systematic review and meta-analysis based on a predesigned protocol registered with PROSPERO (#CRD42016036498). The protocol detailed the research question, populations, exposures, outcomes of interest, search strategies, study selection, exclusion criteria, methods of data abstraction, and statistical analysis. All methods followed the guidelines set forth by the Meta-analysis of Observational Studies in Epidemiology group.[10]

Two authors (S.N.C. and K.L.), including a medical librarian trained in systematic reviews (K.L.) conducted a systematic search of the existing biomedical literature from inception of each database through August 2015. The controlled vocabulary of each database and plain language was used in creating a search strategy including term indices for the concepts of "neonatal outcomes," "pregnancy complications", and "marijuana use." Our complete search strategy has been published on PROSPERO (#CRD42016036498). We searched the databases PubMed/MEDLINE, EMBASE, Scopus, Cochrane Library, ClinicalTrials.gov, and Cumulative Index to Nursing and Allied Health. The final search results were limited to English language and human studies using the database-supplied limit. After removing duplicate studies, two of the authors (S.N.C. and V.B.) screened the remaining publications for relevance and fulfillment of predefined inclusion and exclusion criteria.

STUDY SELECTION

We included observational studies including cohort and case–control studies that compared rates of our primary or secondary outcomes in women who used marijuana during pregnancy with women who did not use marijuana during pregnancy. We excluded studies that included marijuana users in the control group or studies that did not investigate any of our prespecified outcomes. In addition, we excluded studies for which we were unable to extract outcome data for marijuana users separately from other substance users (ie, cocaine users) and studies for which we could not extract raw data based on what was presented. We also excluded case series, case reports, abstracts, unpublished data, expert opinions, review articles, animal studies, and non-English publications. When a duplicated cohort was encountered, we included the study that provided the most data on our primary and secondary outcomes.

Two authors (S.N.C. and V.B.) independently evaluated each study. Data abstracted included characteristics of the study, identification of potential sources of bias and other quality measures, and rates of the outcomes. Rates of the outcomes were further extracted for studies specifying amount of marijuana

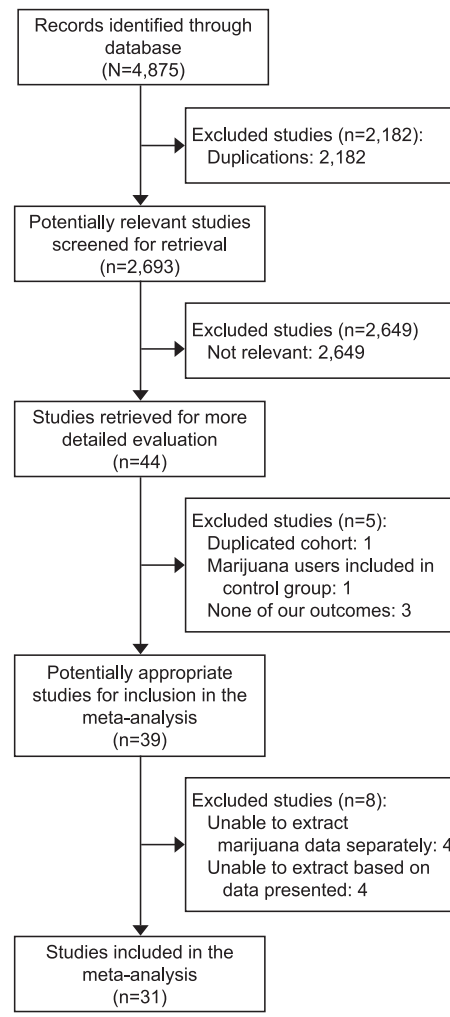

Fig. 1. Flow diagram of studies in the meta-analysis.
Conner. Marijuana and Neonatal Outcomes. Obstet Gynecol 2016.

Table 1. Characteristics of Included Studies

Study	Year	Country	Study Design	Defined MJ Use	Outcomes	MJ	Unexposed
Bada et al[15]	2005	United States	Retrospective cohort	Self-report, meconium	SGA, LBW, PTD	811	7,826
Bailey et al[16]	2012	United States	Prospective cohort	Self-report, urine, meconium	Birth weight	39	121
Bailey et al[17]	2007	United States	Retrospective cohort	Self-report	LBW	9	213
Budde et al[18]	2007	Australia	Retrospective case–control	Self-report	Abruption	17	133
Conner et al[19]	2015	United States	Retrospective cohort	Self-report, urine	LBW, NICU, low Apgar	680	7,458
Day et al[20]	1991	United States	Prospective cohort	Self-report	Birth weight, GA delivery	103	210
El Marroun et al[21]	2009	Netherlands	Prospective cohort	Self-report	Birth weight, GA delivery	214	5,540
Fergusson et al[22]	2002	United Kingdom	Prospective cohort	Self-report	Birth weight, NICU, PTD, perinatal death	309	11,769
Fried et al[23]	1984	Canada	Prospective cohort	Self-report	Birth weight, GA delivery	84	499
Gibson et al[24]	1983	Australia	Retrospective cohort	Self-report	PTD	392	6,909
Gray et al[25]	2010	United States	Prospective cohort	Self-report, meconium, oral fluid	Birth weight, PTD, GA delivery	41	45
Greenland et al[26]	1982	United States	Prospective cohort	Self-report, urine, serum, umbilical cord	LBW, PTD, low Apgar score	35	36
Hatch et al[27]	1986	United States	Prospective cohort	Self-report	Birth weight, SGA, LBW, PTD, GA delivery	357	3,490
Hayatbakhsh et al[28]	2012	Australia	Retrospective cohort	Self-report	Birth weight, SGA, NICU, GA delivery	647	24,227
Hayes et al[29]	1988	Jamaica	Prospective cohort	Self-report	Birth weight, PTD, GA delivery	30	25
Hingson et al[30]	1982	United States	Retrospective cohort	Self-report	Low Apgar score	235	1,442
Kline et al[31]	1991	United States	Retrospective case–control	Self-report	SAB	240	2,762
Linn et al[32]	1983	United States	Retrospective cohort	Self-report	LBW, NICU, PTD, stillbirth, low Apgar score, abruption	1,246	11,178
Mark et al[33]	2015	United States	Retrospective cohort	Self-report, urine	Birth weight, LBW, NICU, PTD, low Apgar score, GA delivery	51	119
Ortigosa et al[34]	2012	Spain	Retrospective cohort	Meconium	Birth weight, GA delivery, abruption	38	63
Ostrea et al[35]	1997	United States	Prospective cohort	Meconium	LBW, PTD, low Apgar score, perinatal death	157	1,658
Saurel-Cubizolles et al[36]	2014	France	Retrospective cohort	Self-report	Birth weight, SGA, PTD	156	13,348
Shiono et al[37]	1995	United States	Prospective cohort	Self-report, serum	LBW, PTD	822	6,648
Thompson et al[38]	1994	New Zealand	Retrospective case–control	Self-report	SGA	95	1,410
Van Gelder et al[39]	2010	United States	Retrospective cohort	Self-report	LBW, PTD	185	5,343
Varner et al[40]	2014	United States	Retrospective case–control	Umbilical cord	Stillbirth	34	1,434
Visscher et al[41]	2003	United States	Retrospective cohort	Self-report	LBW	49	717
Wilcox et al[42]	1990	United States	Prospective cohort	Self-report	SAB	22	149

(*continued*)

Table 1. Characteristics of Included Studies (*continued*)

Study	Year	Country	Study Design	Defined MJ Use	Outcomes	MJ	Unexposed
Williams et al[43]	1991	United States	Retrospective case–control	Self-report	Abruption	134	1,266
Witter et al[44]	1990	United States	Retrospective cohort	Self-report	Birth weight, LBW, PTD, abruption, perinatal death	417	7,933
Zuckerman et al[45]	1989	United States	Prospective cohort	Urine	Birth weight, GA delivery	202	895

MJ, marijuana; SGA, small for gestational age; LBW, low birth weight; PTD, preterm delivery; NICU, neonatal intensive care unit; GA, gestational age; SAB, spontaneous abortion.

use and if marijuana users or participants in a control group were stratified by use of tobacco.

The primary outcomes were low birth weight (less than 2,500 g) and preterm delivery at less than 37 weeks of gestation. These were selected because they are the most commonly evaluated outcomes in the literature and the most biologically plausible. Secondary outcome measures included birth weight, gestational age at delivery, small for gestational age (SGA; less than the 10th percentile), level II or greater nursery admission, stillbirth, spontaneous abortion, low Apgar score, placental abruption, and perinatal death.

The exposure was marijuana use during pregnancy of any amount, duration, or frequency. Use was defined through self-report, objective measure alone, or a combination of self-report and objective measure depending on the individual study. Marijuana users who also used other substances were included in the exposed group. Further stratification of the exposed group was performed according to amount of marijuana used, low, moderate, and high, which corresponded to use less than weekly, weekly or stated moderate, and daily or stated heavy, respectively. Additional stratification of the exposed group was performed with respect to concomitant exposure to tobacco where the raw data could be extracted. The unexposed group was defined as women who did not use marijuana during pregnancy as defined by the individual studies.

Sources of bias in meta-analyses are often the result of differences in design, analysis, and reporting among studies.[11,12] Rather than using quality scoring systems, which may be poorly discriminatory, we assessed study quality based on six factors we deemed most likely to threaten study validity: 1) objective definition of marijuana use, 2) quantity of marijuana use investigated, 3) study excluded other substance users, 4) the study stated that they made some adjustment for tobacco use, 5) risk for selection bias, and 6) the study excluded multiple gestations or fetal anomalies. Studies that defined marijuana using an objective format, using meconium, umbilical cord, urine, oral fluid, or serum, were considered to have used objective criteria for definition. Conversely, studies that used patient self-report in any form were considered to not use objective criteria for definition. When studies used self-report or an objective measure to define exposure, these studies were classified as not using an objective definition of marijuana use. To qualify favorably for criteria 4, the study must have specified either in methods or results that they adjusted for tobacco use either in the form of adjusted or stratified analyses; however, not all studies that stated that adjustment was performed included the results or raw numbers in their manuscript. Studies that relied on any form of a volunteer cohort were determined to have a high risk of selection bias. Overall quality was determined to be higher if at least three of the six criteria were assessed as favorable.

Data were analyzed using Stata 12.0 with METAN software package. Raw data were abstracted from each study and combined using the DerSimonian-Laird random-effects model. Pooled relative risks (RRs) or standard mean difference and the 95% confidence intervals (CIs) were calculated for each of the primary and secondary outcomes if two or more studies reported the specific outcome. For the secondary outcomes that included case–control studies, pooled odds ratios (ORs) were used. Pooled adjusted estimates and 95% CIs were also calculated for all outcomes in which two or more studies specified adjusted estimates and 95% CIs. Results were plotted graphically as forest plots.

Statistical heterogeneity was assessed using Cochran's Q and Higgin's I^2 tests.[13] To account for the low statistical power of tests of heterogeneity, we considered statically significant heterogeneity as Cochran's Q test with a $P<.1$ or $I^2>30\%$. We explored sources of heterogeneity using stratified analyses for amount of marijuana used during pregnancy for each of the primary outcomes and stratification by concomitant marijuana and tobacco use for outcomes in which two or more studies gave raw

data stratifying by tobacco use. We assessed publication bias graphically using funnel plots and statistically using the Harbord test for categorical outcomes or Egger test for continuous outcomes.[12,14]

RESULTS

The flow diagram of study identification for the meta-analysis is shown in Figure 1. After exclusions for duplications, 2,693 potentially relevant publications were identified. After excluding studies deemed to be not relevant to the study topic through review of titles and abstracts, 44 studies were retrieved for a more detailed evaluation. Studies were further eliminated for use of a duplicated cohort, marijuana users included in the control group, none of our prespecified outcomes investigated, inability to extract marijuana data separately from other drug users, or inability to extract raw numbers based on the data presented. After all exclusions, 31 publications were included in the meta-analysis.[15–45]

Among the 31 included studies, publication dates ranged from 1982 to 2015 and 21 of 31 (68%) were performed in the United States. In all, 13 were retrospective cohort, 13 were prospective cohort, and five were case–control studies. Together, the studies included 7,851 patients who used marijuana during pregnancy (exposed) and 124,867 patients who did not use marijuana during pregnancy (unexposed). The majority of included studies used maternal self-report to define marijuana use during pregnancy. Detailed characteristics of the included studies, providing each study's year of publication, country, study design, how marijuana was defined, outcomes of interest investigated, and numbers of exposed and unexposed patients are listed in Table 1. Methodologic quality of each included study is shown in Table 2.

Table 2. Quality Assessment of Included Studies

Study	Objectively Defined MJ Use	Investigated Quantity of Use	Excluded Other Drugs	Stated Adjusted for Tobacco	Selection Bias Risk	Excluded Multiple or Anomalies	Overall Study Quality
Bada et al[15] (2005)	Partly	No	No	Yes	High	Yes	Lower
Bailey et al[16] (2012)	Yes	No	No	Yes	High	Yes	Higher
Bailey et al[16] (2007)	No	No	No	Yes	Low	No	Lower
Budde et al[17] (2007)	No	No	No	Yes	Low	Yes	Higher
Conner et al[18] (2015)	Partly	No	No	Yes	Low	Yes	Higher
Day et al[19] (1991)	No	Yes	No	Yes	High	Yes	Higher
El Marroun et al[20] (2009)	No	Yes	No	Yes	High	No	Lower
Fergusson et al[21] (2002)	No	Yes	No	Yes	High	Yes	Higher
Fried et al[22] (1984)	No	Yes	No	Yes	High	Yes	Higher
Gibson et al[23] (1983)	No	Yes	No	Yes	High	Yes	Higher
Gray et al[24] (2010)	Yes	Yes	Yes	Yes	High	Yes	Higher
Greenland et al[26] (1982)	Yes	Yes	Yes	Yes	High	No	Higher
Hatch et al[27] (1986)	No	Yes	No	Yes	High	Yes	Higher
Hayatbakhsh et al[28] (2012)	No	No	No	Yes	Low	No	Lower
Hayes et al[29] (1988)	No	Yes	No	Yes	High	No	Lower
Hingson et al[30] (1982)	No	Yes	Yes	Yes	High	No	Higher
Kline et al[31] (1991)	No	Yes	Yes	Yes	High	No	Higher
Linn et al[32] (1983)	No	Yes	Yes	Yes	Low	Yes	Higher
Mark et al[33] (2015)	Partly	No	No	Yes	Low	Yes	Higher
Ortigosa et al[34] (2012)	Yes	No	No	No	High	Yes	Lower
Ostrea et al[35] (1997)	Yes	No	Yes	No	Low	No	Higher
Saurel-Cubizolles et al[36] (2014)	No	Yes	No	Yes	Low	No	Higher
Shiono et al[37] (1995)	Partly	Yes	No	Yes	High	Yes	Higher
Thompson et al[38] (1994)	No	No	No	Yes	High	No	Lower
Van Gelder et al[39] (2010)	No	Yes	No	Yes	High	Yes	Higher
Varner et al[40] (2014)	Yes	No	No	Yes	High	No	Lower
Visscher et al[41] (2003)	No	No	No	Yes	High	No	Lower
Wilcox et al[42] (1990)	No	No	No	No	High	No	Lower
Williams et al[43] (1991)	No	Yes	No	Yes	High	No	Lower
Witter et al[44] (1990)	No	No	Yes	No	Low	No	Lower
Zuckerman et al[45] (1989)	Yes	No	No	Yes	High	No	Lower

MJ, marijuana.

Based on evaluations in the six specified categories, 14 studies were classified as lower quality and 17 studies were classified as higher quality.

Based on the pooled unadjusted analysis, women using marijuana in pregnancy were at increased risk for low birth weight (12 studies: 15.4% compared with 10.4%, RR 1.43, 95% CI 1.27–1.62; Table 3; Fig. 2) and preterm delivery (14 studies: 15.3% compared with 9.6%, RR 1.32, 95% CI 1.14–1.54; Table 3; Fig. 3). There was evidence of statistical heterogeneity among studies ($P=.03$, $I^2=47.6\%$ for low birth weight, and $P<.01$, $I^2=65.7\%$ for preterm delivery). To explore the sources of heterogeneity, we stratified the analyses on amount of marijuana used and concomitant tobacco use. Stratification by amount of marijuana used eliminated the heterogeneity and showed that women using marijuana less than weekly during pregnancy were not at a significantly increased risk for low birth weight (two studies: 8.8% compared with 6.7%, RR 1.22, 95% CI 0.91–1.64) or preterm delivery (five studies: 6.8% compared with 5.7%, RR 1.09, 95% CI 0.91–1.32) compared with women who did not use marijuana. However, women who used marijuana at least weekly during pregnancy were at significantly higher risk for low birth weight (two studies: 11.2% compared with 6.7%, RR 1.90, 95% CI 1.44–2.45) and preterm delivery (five studies: 10.4% compared with 5.7%, RR 2.04, 95% CI 1.32–3.17). Similarly, stratification by coexisting tobacco use eliminated the heterogeneity and showed that women who smoked marijuana only were not at increased risk for preterm delivery (two studies: 7.1% compared with 5.7%, RR 1.25, 95% CI 0.63–2.50) compared with women who did not use either substance. Conversely, women who smoked marijuana

Table 3. Pooled Estimates for Primary Outcomes With Stratified Analyses

Outcome	Stratification	No. of Studies	MJ Exposed	MJ Unexposed	Pooled RR	95% CI	Heterogeneity: Cochran's *P*	Heterogeneity: I^2 (%)
LBW less than 2,500 g	Overall	12	15.4 (742/4,819)	10.4 (5,462/52,619)	1.43	1.27–1.62	0.03	47.6
	Stratify by amount							
	MJ low compared with no use	2	8.8 (91/1,038)	6.7 (990/14,668)	1.22	0.91–1.64	0.29	11.4
	MJ MOD compared with no use	2	11.2 (49/438)	6.7 (990/14,668)	1.90	1.44–2.45	0.52	0.0
	MJ high compared with no use	0	—	—	—	—	—	—
	Stratify by tobacco use	0	—	—	—	—	—	—
	Adjusted estimates	4	—	—	1.16	0.98–1.37	0.56	0.0
	Unadjusted estimates from same studies	4	18.7 (466/2,498)	10.4 (2,858/27,275)	1.60	1.40–1.84	0.20	35.6
PTD at less than 37 wk of gestation	Overall	14	15.3 (767/4,999)	9.6 (7,293/76,327)	1.32	1.14–1.54	<0.01	65.7
	Stratify by amount							
	MJ low compared with no use	5	6.8 (108/1,583)	5.7 (1,904/33,371)	1.09	0.91–1.32	0.89	0.0
	MJ MOD compared with no use	5	10.4 (64/616)	5.7 (1,904/33,371)	2.04	1.32–3.17	0.03	63.2
	MJ high compared with no use	2	11.9 (16/135)	7.2 (805/11,203)	1.73	1.09–2.73	0.71	0.0
	Stratify by tobacco use							
	MJ only compared with no MJ and no tobacco	2	7.1 (8/112)	5.7 (886/15,582)	1.25	0.63–2.50	0.30	6.0
	MJ and tobacco compared with no MJ and no tobacco	2	11.4 (26/228)	5.7 (886/15,582)	1.85	1.21–2.81	0.25	23.1
	Adjusted estimates	4	—	—	1.08	0.82–1.43	0.08	56.2
	Unadjusted estimates from same studies	4	23.3 (460/1,974)	11.2 (3,714/33,165)	1.47	1.12–1.94	<0.01	81.6

MJ, marijuana; RR, relative risk; CI, confidence interval; LBW, low birth weight; MOD, moderate; PTD, preterm delivery.
Data are % (n outcome/n exposed) unless otherwise specified.

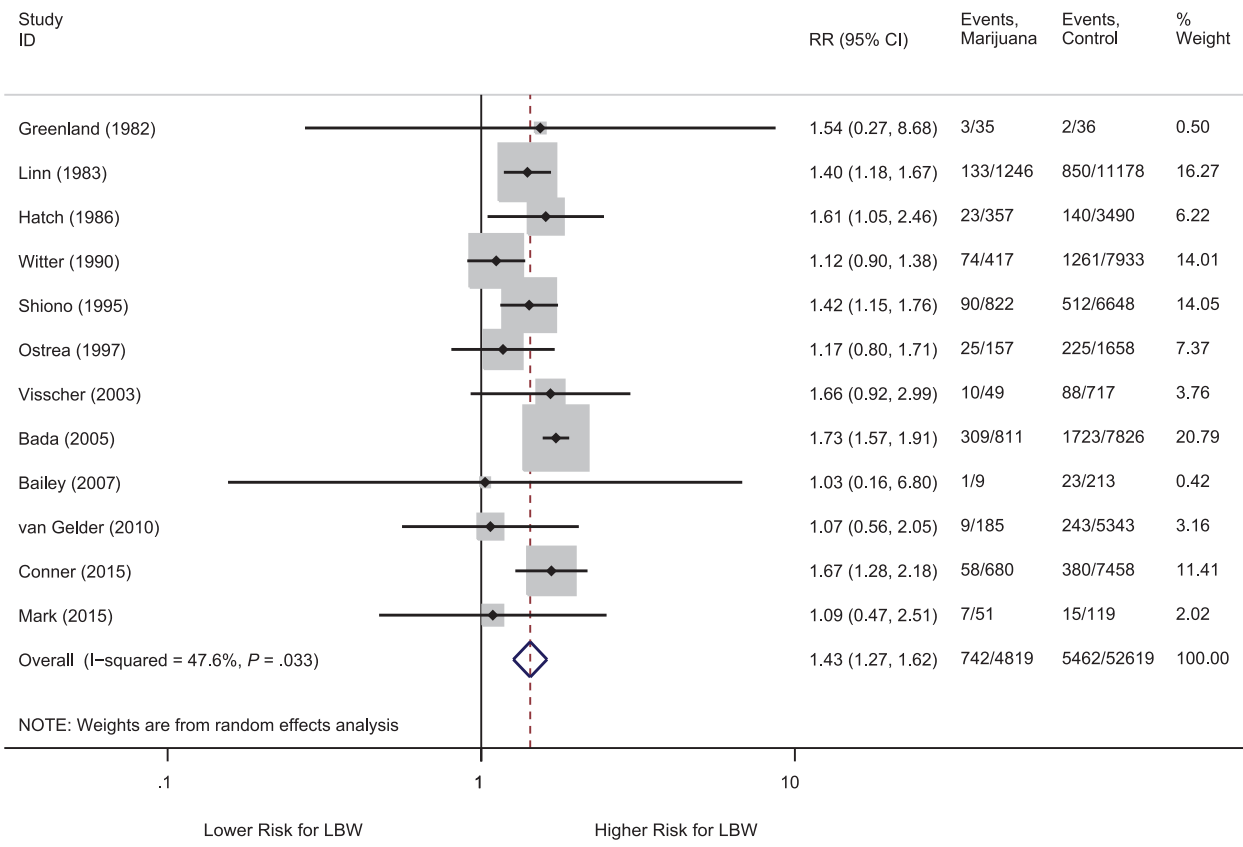

Fig. 2. Forest plot marijuana use and low birth weight (LBW, less than 2,500 g). RR, relative risk; CI, confidence interval. *Conner. Marijuana and Neonatal Outcomes. Obstet Gynecol 2016.*

and tobacco were at increased risk for preterm delivery compared with women who did not use either substance (two studies: 11.4% compared with 5.7%, RR 1.85, 95% CI 1.21–2.81).

To further explore the role of confounding factors in the relationship between marijuana use in pregnancy and adverse neonatal outcomes, we pooled the adjusted estimates from the individual studies adjusting for confounders. The studies that performed these analyses universally adjusted for tobacco use, four of seven adjusted for other drug use, and they all varied in selected socioeconomic and demographic factors that were assessed as potential confounders.[15,19,28,36–39] The pooled adjusted estimates showed that women who used marijuana in pregnancy were not at increased risk for low birth weight (four studies: adjusted OR 1.16, 95% CI 0.98–1.37; Fig. 4A) or preterm delivery (four studies: adjusted OR 1.08, 95% CI 0.82–1.43; Fig. 4B) after adjusting for confounding factors. The pooled unadjusted estimates from the same studies providing adjusted estimates are shown in Appendix 1A and B, available online at http://links.lww.com/AOG/A865. There was no evidence of publication bias for either low birth weight (Harbord's P=.24; Appendix 2A, available online at http://links.lww.com/AOG/A865) or preterm delivery (Harbord's P=.67; Appendix 2B, available online at http://links.lww.com/AOG/A865).

Pooled analysis of the secondary outcomes is illustrated in Table 4. Whereas women using marijuana were at increased risk for having neonates who were SGA based on the unadjusted estimates (five studies; OR 1.96, 95% CI 1.57–2.45), pooled adjusted estimates showed no increased risk for SGA in women using marijuana after adjusting for confounding factors (four studies: Adjusted OR 1.59, 95% CI 0.87–2.31). Similarly, women using marijuana in pregnancy were at increased risk for placental abruption based on pooled unadjusted estimates (five studies: OR 1.60, 95% CI 1.29–2.02) but not pooled adjusted estimates (two studies: adjusted OR 1.35, 95% CI 0.28–2.42). Women who used marijuana during pregnancy were at increased risk for lower mean birth weight, stillbirth, and low Apgar score based on pooled unadjusted estimates, but adjusted estimates were not able to be pooled for

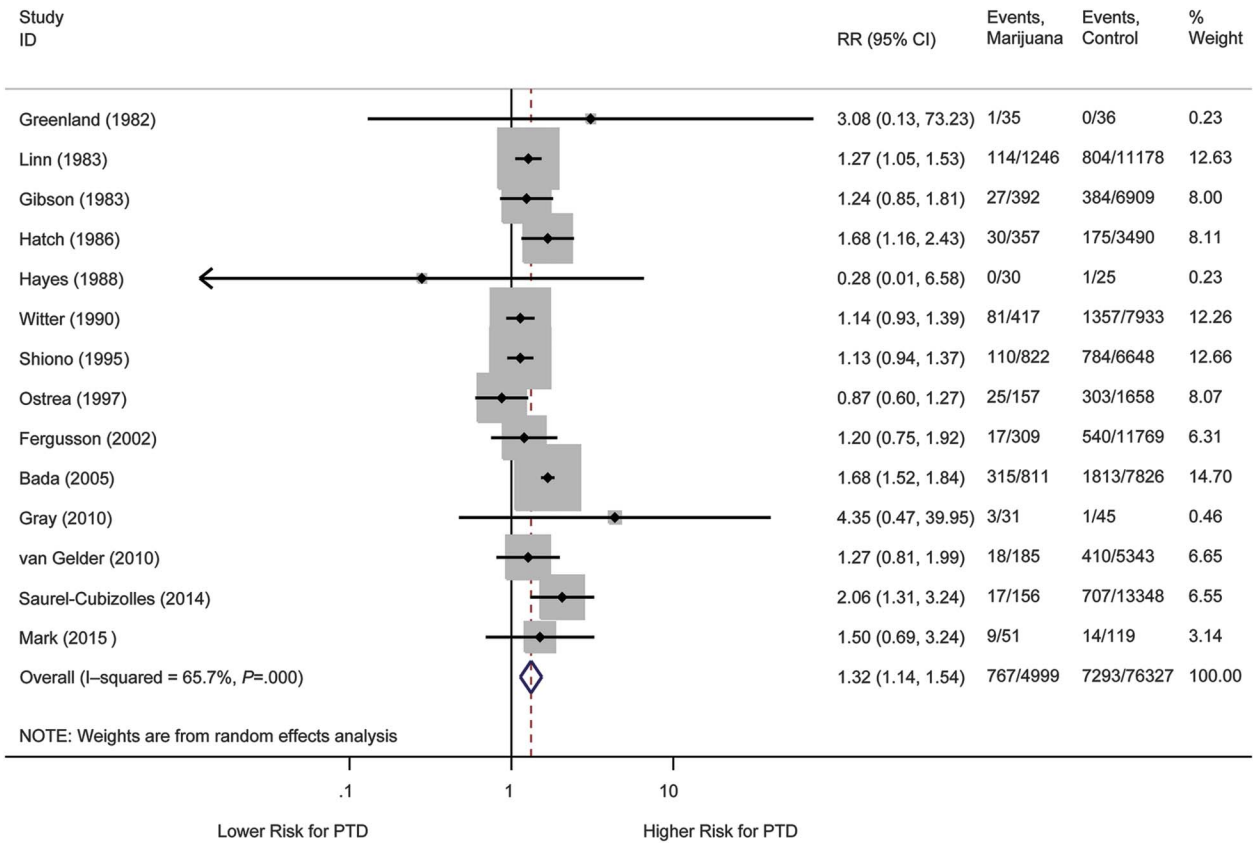

Fig. 3. Forest plot marijuana use and preterm delivery (PTD) at less than 37 weeks of gestation. RR, relative risk; CI, confidence interval.

Conner. Marijuana and Neonatal Outcomes. Obstet Gynecol 2016.

these secondary outcomes. Women using marijuana in pregnancy were not at increased risk for level II or greater nursery admission or spontaneous abortion, and there was no difference in gestational age at delivery. There was significant heterogeneity for the outcomes of birth weight, gestational age at delivery, SGA, and level II or greater nursery admission. There was no evidence of publication bias for any of the secondary outcomes.

DISCUSSION

We found that maternal marijuana use during pregnancy is not an independent risk factor for low birth weight or preterm delivery after adjusting for factors such as tobacco use. There also does not appear to be an increased risk for other adverse neonatal outcomes such as SGA and placental abruption once we account for other influencing factors. Our results indicate that increasing frequency of marijuana use during pregnancy may play a role in risk for adverse neonatal outcomes. However, women who use marijuana more frequently are also more likely to use higher amounts of tobacco and other drugs, which we could not account for in our study, likely confounding these results. These data suggest that the association between maternal marijuana use and adverse pregnancy outcomes may be attributable to concomitant tobacco use and other confounding factors and not marijuana alone.

Our study offers several important advances over the previous meta-analyses on this subject.[46,47] Since the first meta-analysis by English et al[46] in 1997, which included only studies that adjusted for tobacco use and found results congruent with ours that marijuana use during pregnancy did not lead to an increased risk for low birth weight, more than 20 years of data have accrued. Perhaps the greatest strength of our study was our ability to adjust for tobacco and other confounding factors through using adjusted estimates and stratification, which was not able to be performed in the most recent meta-analysis by Gunn et al.[47] Additionally, we were able to evaluate effects relating to amount of marijuana use, which was not performed in the most recent

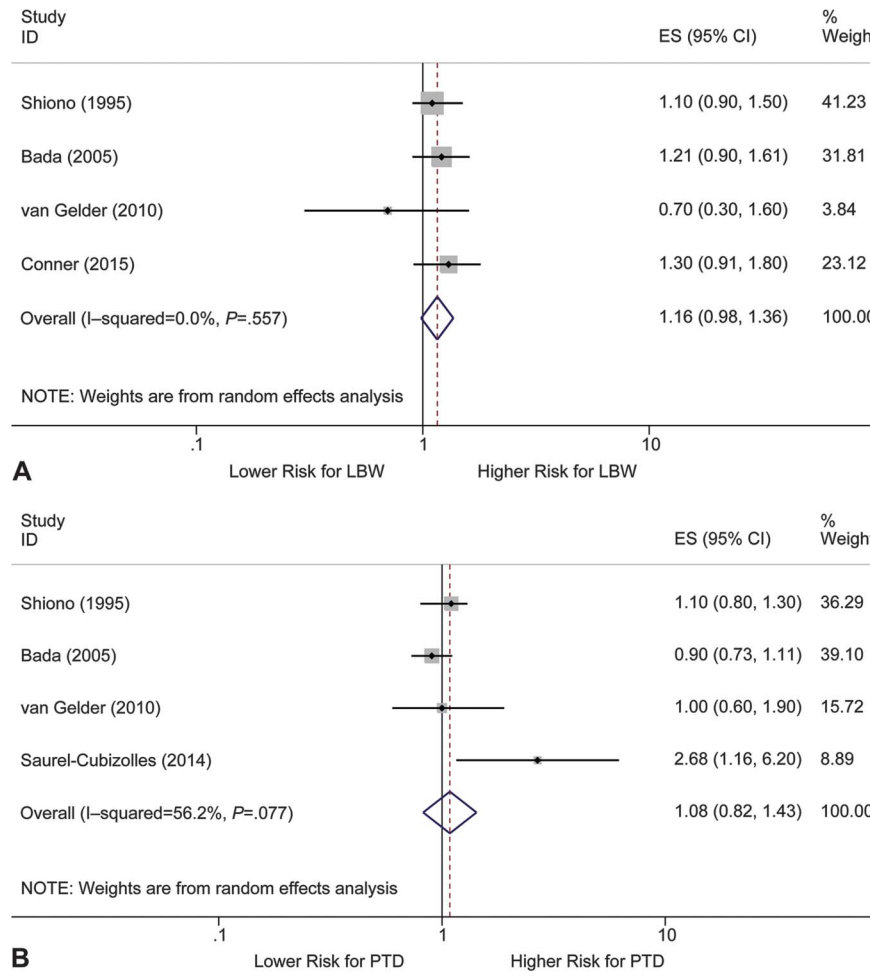

Fig. 4. Forest plot adjusted estimates for marijuana use. **A**. Low birth weight. **B**. Preterm delivery. ES, effect size; CI, confidence interval; PTD, preterm delivery.

Conner. Marijuana and Neonatal Outcomes. Obstet Gynecol 2016.

meta-analysis. We conducted an extensive review of the available literature by two reviewers including six databases with the aid of a Master of Library and Information Science–credentialed librarian yielding a transparent and reproducible search strategy. Moreover, our study adhered to a rigorous design with a prespecified, published protocol.

Although our study has many strengths, the potential limitations must be considered as well. Inherent to performing a meta-analysis, the quality of our findings is dependent on the quality of the primary studies included. Because we were restricted to the data available in the literature, we were unable to perform stratification for all the secondary outcomes. Similarly, the number of studies that allowed for extraction of marijuana users separately from women who also used tobacco was small, limiting our stratification abilities for the outcome of low birth weight. Although we were able to stratify by concomitant tobacco use for the outcome of preterm delivery, we were severely underpowered to detect a difference resulting in a risk for type II error. To have 80% power to detect a 25% increased risk for preterm delivery in patients using marijuana only, more than 2,000 patients would be needed. We were also underpowered with respect to the secondary outcomes of spontaneous abortion and perinatal death. Another limitation to our study was the limited number of studies that offered adjusted estimates. Although we performed an extensive search of the literature, we excluded non-English studies and studies in which the raw data could not be extracted, possibly introducing some selection bias to our study. Additionally, the number of women using other drugs in each individual study was not always specified. Therefore, it is possible that some women in the unexposed group used drugs other than marijuana, which could potentially bias the results toward the null. However, this is unlikely to significantly bias the results, because women who use marijuana also use other drugs at a significantly

Table 4. Pooled Unadjusted and Adjusted Estimates for Secondary Outcomes

Outcome	No. of Studies	MJ Exposed	MJ Unexposed	Pooled RR (*OR)/ Mean Difference	95% CI	Heterogeneity		Publication Bias Harbord's *P* or Egger test *P*
						Cochran's *P*	I^2 (%)	
Birth weight (g)	8	—	—	−167	−245 to −90	<.01	99.4	.46
Adjusted	N/A	—	—	—	—	—	—	—
GA delivery (wk)	6	—	—	−0.1	−0.5 to 0.3	<.01	91.4	.25
Adjusted	N/A	—	—	—	—	—	—	—
SGA	5	20.2 (418/2,066)	10.0 (5,005/50,235)	2.19*	1.70–2.81	<.01	73.0	.63
Adjusted	4	—	—	1.59	0.87–2.31	<.01	83.9	—
NICU	5	15.9 (467/2,933)	11.9 (6,498/54,751)	1.41	0.99–2.0	<.01	89.9	.80
Adjusted	N/A	—	—	—	—	—	—	
Stillbirth	2	2.0 (26/1,280)	3.7 (469/12,612)	1.74*	1.03–2.93	.28	15.9	—
Adjusted	N/A	—	—	—	—	—	—	
SAB	2	31.7 (83/262)	30.0 (920/3,074)	1.10*	0.84–1.44	0.94	0.0	—
Adjusted	N/A	—	—	—	—	—	—	—
Low Apgar score	6	5.9 (143/2,404)	4.6 (1,009/21,891)	1.26	1.07–1.49	.78	0.0	.05
Adjusted	N/A	—	—	—	—	—	—	—
Abruption	5	3.3 (62/1,852)	1.8 (376/20,573)	1.78*	1.32–2.40	.77	0.0	.94
Adjusted	2	—	—	1.35	0.28–2.42	.68	0.0	—
Perinatal death	3	1.4 (12/883)	1.2 (260/21,360)	1.09	0.62–1.91	.43	0.0	.47
Adjusted	N/A	—	—	—	—	—	—	—

RR, relative risk; OR, odds ratio; CI, confidence interval; N/A, not applicable; GA, gestational age; SGA, small for gestational age; NICU, neonatal intensive care unit; SAB, spontaneous abortion.
Data are % (n outcome/n exposed) unless otherwise specified.

higher rate than nonusers. Additionally, in the analysis utilizing the adjusted estimates, a majority of the studies adjusted for concomitant use of other drugs.[15,19,28,37] Lastly, although our results reflect a large number of clinically relevant neonatal outcomes, it is important to note that we did not investigate long-term neurodevelopmental outcomes after exposure to marijuana in utero, and further study is warranted in this regard.

In conclusion, the results of this systematic review and meta-analysis suggest that the increased risk for adverse neonatal outcomes reported in women using marijuana in pregnancy is likely the result of coexisting use of tobacco and other cofounding factors and not attributable to marijuana use itself. Although these data do not imply that marijuana use during pregnancy should be encouraged or condoned, the lack of a significant association with adverse neonatal outcomes suggests that attention should be focused on aiding pregnant women with cessation of substances known to have adverse effects on the pregnancy such as tobacco.

REFERENCES

1. Martin CE, Longinaker N, Mark K, Chisolm MS, Terplan M. Recent trends in treatment admission for marijuana use during pregnancy. J Addict Med 2015;9:99–104.
2. Schauberger CW, Newbury EJ, Colburn JM, Al-Hamadani M. Prevalence of illicit drug use in pregnant women in a Wisconsin private practice setting. Am J Obstet Gynecol 2014;211:255.e1–4.
3. Warner TD, Roussos-Ross D, Behnke M. It's not your mother's marijuana: effects on maternal-fetal health and the developing child. Clin Perinatol 2014;41:877–94.
4. Hill M, Reed K. Pregnancy, breast-feeding, and marijuana: a review article. Obstet Gynecol Surv 2013;68:710–8.
5. Behnke M, Smith VC; Committee on Substance Abuse; Committee on Fetus and Newborn. Prenatal substance abuse: short-and long-term effects on the exposed fetus. Pediatrics 2013;131:e1009–24.
6. Bailey JR, Cunny HC, Paule MG, Slikker W Jr. Fetal disposition of Δ9-tetrahydrocannabinol (THC) during late pregnancy in the rhesus monkey. Toxicol Appl Pharmacol 1987;90:315–21.
7. Frank DA, Bauchner H, Parker S, Huber AM, Kyei-Aboagye K, Cabral H, et al. Neonatal body proportionality and body composition after in utero exposure to cocaine and marijuana. J Pediatr 1990;117:622–6.
8. Wu TC, Tashkin DP, Djahen B, Rose JE. Pulmonary hazards of smoking marijuana as compared with tobacco. N Engl J Med 1988;318:347–51.

9. Metz TD, Stickrath EH. Marijuana use in pregnancy and lactation: a review of the evidence. Am J Obstet Gynecol 2015;213:761–78.
10. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283:2008–12.
11. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions. Version 5.1.0. London (UK): The Cochrane Collaboration; 2011.
12. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
13. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–58.
14. Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. Stat Med 2006;25:3443–57.
15. Bada HS, Das A, Bauer CR, Shankaran S, Lester BM, Gard CC, et al. Low birthweight and preterm births: etiologic fraction attributable to prenatal drug exposure. J Perinatol 2005;25:631–7.
16. Bailey BA, McCook JG, Hodge A, McGrady L. Infant birth outcomes among substance using women: why quitting smoking during pregnancy is just as important as quitting illicit drug use. Matern Child Health J 2012;16:414–22.
17. Bailey BA, Byrom AR. Factors predicting birth weight in a low-risk sample: the role of modifiable pregnancy health behaviors. Matern Child Health J 2007;11:173–9.
18. Budde MP, De Lange TE, Dekker GA, Chan A, Nguyen AM. Risk factors for placental abruption in a socio-economically disadvantaged region. J Matern Fetal Neonatal Med 2007;20:687–93.
19. Conner SN, Carter EB, Tuuli MG, Macones GA, Cahill AG. Maternal marijuana use and neonatal morbidity. Am J Obstet Gynecol 2015;213:422.e1–4.
20. Day N, Sambamoorthi U, Taylor P, Richardson G, Robles N, Jhon Y, et al. Prenatal marijuana use and neonatal outcome. Neurotoxicol Teratol 1991;13:329–34.
21. El Marroun H, Tiemeier H, Steegers EA, Jaddoe VW, Hofman A, Verhulst FC, et al. Intrauterine cannabis exposure affects fetal growth trajectories: the Generation R Study. J Am Acad Child Adolesc Psychiatry 2009;48:1173–81.
22. Fergusson DM, Horwood LJ, Northstone K; ALSPAC Study Team, Avon Longitudinal Study of Pregnancy and Childhood. Maternal use of cannabis and pregnancy outcome. BJOG 2002;109:21–7.
23. Fried PA, Watkinson B, Willan A. Marijuana use during pregnancy and decreased length of gestation. Am J Obstet Gynecol 1984;150:23–7.
24. Gibson GT, Baghurst PA, Colley DP. Maternal alcohol, tobacco, and cannabis consumption and the outcome of pregnancy. Aust N Z J Obstet Gynaecol 1983;23:15–9.
25. Gray TR, Eiden RD, Leonard KE, Connors GJ, Shisler S, Huestis MA. Identifying prenatal cannabis exposure and effects of concurrent tobacco exposure on neonatal growth. Clin Chem 2010;56:1442–50.
26. Greenland S, Staisch KJ, Brown N, Gross SJ. The effects of marijuana use during pregnancy. I. A preliminary epidemiologic study. Am J Obstet Gynecol 1982;143:408–13.
27. Hatch EE, Bracken MB. Effect of marijuana use in pregnancy on fetal growth. Am J Epidemiol 1986;124:986–93.
28. Hayatbakhsh MR, Flenady VJ, Gibbons KS, Kingsbury AM, Hurrion E, Mamun AA, et al. Birth outcomes associated with cannabis use before and during pregnancy. Pediatr Res 2012;71:215–9.
29. Hayes JS, Dreher MC, Nugent JK. Newborn outcomes with maternal marihuana use in Jamaican women. Pediatr Nurs 1988;14:107–10.
30. Hingson R, Gould JB, Morelock S, Kayne H, Heeren T, Alpert JJ, et al. Maternal cigarette smoking, psychoactive substance use, and infant Apgar scores. Am J Obstet Gynecol 1982;144:959–66.
31. Kline J, Hutzler M, Levin B, Stein Z, Susser M, Warburton D. Marijuana and spontaneous abortion of known karyotype. Paediatr Perinat Epidemiol 1991;5:320–32.
32. Linn S, Schoenbaum SC, Monson RR, Rosner R, Stubblefield PC, Ryan KJ. The association of marijuana use with outcome of pregnancy. Am J Public Health 1983;73:1161–4.
33. Mark K, Desai A, Terplan M. Marijuana use and pregnancy: prevalence, associated characteristics, and birth outcomes. Arch Womens Ment Health 2016;19:105–11.
34. Ortigosa S, Friguls B, Joya X, Martinez S, Mariñoso ML, Alameda F, et al. Feto-placental morphological effects of prenatal exposure to drugs of abuse. Reprod Toxicol 2012;34:73–9.
35. Ostrea EM Jr, Ostrea AR, Simpson PM. Mortality within the first 2 years in infants exposed to cocaine, opiate, or cannabinoid during gestation. Pediatrics 1997;100:79–83.
36. Saurel-Cubizolles MJ, Prunet C, Blondel B. Cannabis use during pregnancy in France in 2010. BJOG 2014;121:971–7.
37. Shiono PH, Klebanoff MA, Nugent RP, Cotch MF, Wilkins DG, Rollins DE, et al. The impact of cocaine and marijuana use on low birth weight and preterm birth: a multicenter study. Am J Obstet Gynecol 1995;172:19–27.
38. Thompson JM, Wright SP, Mitchell EA, Clements MS, Becroft DM, Scragg RK. Risk factors for small gestational age infants: a New Zealand study. New Zealand Cot Death Study Group. N Z Med J 1994;107:71–3.
39. van Gelder MM, Reefhuis J, Caton AR, Werler MM, Druschel CM, Roeleveld N; National Birth Defects Prevention Study. Characteristics of pregnant illicit drug users and associations between cannabis use and perinatal outcome in a population-based study. Drug Alcohol Depend 2010:109:243–7.
40. Varner MW, Silver RM, Rowland Hogue CJ, Willinger M, Parker CB, Thorsten VR, et al. Association between stillbirth and illicit drug use and smoking during pregnancy. Obstet Gynecol 2014;123:113–25.
41. Visscher WA, Feder M, Burns AM, Brady TM, Bray RM. The impact of smoking and other substance use by urban women on the birth weight of their infants. Subst Use Misuse 2003;38:1063–93.
42. Wilcox AJ, Weinberg CR, Baird DD. Risk factors for early pregnancy loss. Epidemiology 1990;1:382–5.
43. Williams MA, Lieberman E, Mittendorf R, Monson RR, Schoenbaum SC. Risk factors for abruptio placentae. Am J Epidemiol 1991;134:965–72.
44. Witter FR, Niebyl JR. Marijuana use in pregnancy and pregnancy outcome. Am J Perinatol 1990;7:36–8.
45. Zuckerman B, Frank DA, Hingson R, Amaro H, Levenson SM, Kayne H, et al. Effects of maternal marijuana and cocaine use on fetal growth. N Engl J Med 1989;320:762–8.
46. English DR, Hulse GK, Milne E, Holman CDJ, Bower CI. Maternal cannabis use and birth weight: a meta-analysis. Addiction 1997;92:1553–60.
47. Gunn JK, Rosales CB, Center KE, et al. Prenatal exposure to cannabis and maternal and child health outcomes: a systematic review and meta-analysis. BMJ Open 2016;6:e009986.