OBSTETRICS

Effects of cocaine use during pregnancy on low birthweight and preterm birth: systematic review and metaanalyses

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OBJECTIVE: To review systematically maternal antenatal cocaine exposure and adverse perinatal outcomes.

STUDY DESIGN: Medline, Embase, CINAHL and secondary references in relevant studies were searched. English language studies of antenatal cocaine exposure and pregnancy outcomes published from 1966 to July 2009 were included. Metaanalyses were performed using the random effects model.

RESULTS: Thirty-one studies were included. Cocaine use during pregnancy was associated with significantly higher odds of preterm birth (odds ratio [OR], 3.38; 95% confidence interval [CI], 2.72–4.21), low birthweight (OR, 3.66; 95% CI, 2.90–4.63), and small for gestational age infants (OR, 3.23; 95% CI, 2.43–4.30), as well as shorter gestational age at delivery (−1.47 week; 95% CI, −1.97 to −0.98 week) and reduced birthweight (−492 g; 95% CI, −562 to −421 g).

CONCLUSION: Prenatal cocaine exposure is significantly associated with preterm birth, low birthweight, and small for gestational age infants.

Key words: birthweight, cocaine, gestational age, pregnancy, prematurity

Cite this article as: Gouin K, Murphy K, Shah PS, et al. Effects of cocaine use during pregnancy on low birthweight and preterm birth: systematic review and metaanalyses. Am J Obstet Gynecol 2011;204:x-ex-x-ex.

Birthweight (BW) and gestational age (GA) at birth are important determinants of perinatal, neonatal, childhood, and adult health.[1] Factors thought to be associated with low birthweight (LBW) and preterm birth (PTB) include, but are not limited to maternal, paternal, fetal, societal, environmental, life style-related, infectious, nutritional, genetic, and psychosocial factors. An association between maternal antenatal use of cocaine and adverse pregnancy outcome has been suggested. The high prevalence of cocaine use during pregnancy has become a major health concern. Approximately 15-17% of regular users of cocaine are women of childbearing age.[2] Cocaine is a central nervous system stimulant. Because of its sympathomimetic-driven vasoconstrictive effects, it can lead to hypertension in the mother and fetus, which may result in placental infarcts or hemorrhages at any time in gestation.[3] Because of its high water content, lipid solubility, low molecular weight, and low ionization at physiologic pH, cocaine is believed to cross the placental barrier by simple diffusion.[4] Exposure to cocaine has been reported to be associated with a shorter gestation, premature birth, abruptio placenta, and other adverse maternal and neonatal outcomes.[3]

Reports of fetal cocaine effects have been controversial, as the interpretation of results is hampered by the fact that cocaine use is commonly accompanied by other confounding maternal lifestyle factors. Some of these confounding factors include cigarette smoking, other drug use (heroin, cannabis, methadone, alcohol, and others), lower socioeconomic status, and lack of adequate prenatal care, all of which may combine to contribute to poor pregnancy outcome. Therefore, we believe that a thorough and current review of the literature will help elucidate and quantify the effects of maternal antenatal cocaine use on perinatal outcomes thereby providing up-to-date information. Our objective was to review systematically the effect of cocaine consumption during pregnancy on various neonatal outcomes (LBW, PTB, and small-for-gestational age [SGA] neonates).

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Presented as a poster at the Annual Meeting of Canadian Pediatric Society, Vancouver, Canada, June 22-26, 2010.

Received July 2, 2010; revised Sept. 22, 2010; accepted Nov. 2, 2010.

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This study was supported by funding from the Canadian Institute of Health Research (CIHR) Knowledge Synthesis/Translation Grant no. KRS 86242. CIHR played no role in analyses, writing of the report, interpretation of data, or decision to submit the manuscript.

Members of the Knowledge Synthesis Group on determinants of LBW/preterm births are listed at the end of this full-length article.

0002-9378/$36.00 • • doi: 10.1016/j.ajog.2010.11.013

TABLE 1
Summary of included studies of cocaine exposure and pregnancy outcomes

Author	Year of study	Type of study	Setting of study	Population	Exposure assessment (when, how)	Outcomes assessed	Confounders adjusted for	Results	Quality assessment (risk of bias)
Bingol et al[4]	1984-85	Prospective cohort with unmatched controls (similar for MA, SES, tobacco, ethnicity)	2 large inner city hospitals in New York City (Harlem, Bronx)	Poor inner city women at delivery	Neonate urine at birth	PTD, BW			Low
MacGregor et al[15]	1983-86	Retrospective cohort with matched controls (MA, parity, SES, tobacco, med complications)	Single center, Chicago	Pregnant women receiving care at the Perinatal Center for Chemical Dependence of Northwestern University	NS ? Maternal self-report antenatally	LBW, PTD, SGA, BW, GA			Low
Cherukuri et al[16]	1986	Retrospective cohort with matched controls (MA, parity, PNC, SES, race, ROH)	Single center Brooklyn NYC	Patient delivering at Kings County Hospital, on public assistance	Maternal self-report at delivery	LBW, PTD, SGA, BW, GA			Low
Chouteau et al[17]	1986	Retrospective cohort with unmatched controls	Single center, large teaching hospital, NYC	Pregnant at L+D who did not receive ANC	Maternal urine toxicology at admission	BW, GA			Low
Fulroth et al[18]	NS	Prospective cohort with unmatched controls	Single center, Oakland	All infants delivered at Highland General Hospital, Oakland	Maternal self-report or urine at admission and neonate urine	PTB			Moderate
Hadeed, Siegel[19]	1984-87	Prospective cohort with matched controls (MA, parity, tobacco, SES, ethnicity)	Single center, Hollywood Presbyterian Center in Los Angeles, California	Pregnant women receiving government subsidized medical care	Maternal and infant urine immediately after birth	BW, GA			Low
Little et al[20]	1987	Retrospective cohort with unmatched controls	Single center, Dallas, Texas	Mother of infant born at Parkland Memorial Hospital	Self-report (SW) and chart review	PTD, SGA, BW, GA			Low
Neerhof et al[21]	1986-88	Prospective cohort with unmatched controls	Single center, Chicago	All patients admitted to L+D (screening policy)	Maternal urine at admission and neonate urine	PTD, SGA, BW, GA			Moderate
Zuckerman et al[22]	1984-87	Prospective cohort with unmatched controls	Single center, Boston	Recruited at women's and adolescent prenatal clinic (52% Medicaid, low income)	Interview and maternal urine antenatally and PP	BW, GA			Low
Gillogley et al[23]	1987-88	Retrospective cohort with matched controls (race, discharge date)	Single center, Perinatal unit, University of California, Davis, Sacramento	Admission Ob service of UCDMC, urban, 93% Medicaid or no insurance, diverse ethnicity (routine testing)	Maternal urine at admission ± neonate urine	LBW, PTB, BW, GA	Multiple regression with smoking	−129g associated with tobacco use	Low
Calhoun, Watson[24]	1987-88	Prospective cohort with matched controls (parity, SES, MA)	Single center, L+D, Portland	Indigent, low rate of ANC, no insurance,	Maternal and infant urine at admission	PTB, SGA, BW, GA			Moderate
Cohen et al[25]	1986-87	Retrospective cohort with matched controls (MA, race, parity)	Single center, San Francisco General hospital	Toxic screen from L+D or nursery, 88% black	Maternal and/or neonatal urine at admission	LBW, PTB, BW, GA			Minimal
Kelley et al[26]	NS	Retrospective cohort with controls matched (age of infant, race, sex, SES)	Single center, pediatric well-child clinic, large urban teaching hospital, Boston	Infant 1wk-26 mo, 80% black, 96% Medicaid	Maternal self-report at delivery or neonate urine	LBW, PTB, SGA, BW, GA			Moderate

Gouin. Cocaine use during pregnancy on low birthweight and preterm birth. Am J Obstet Gynecol 2011. *(continued)*

TABLE 1
Summary of included studies of cocaine exposure and pregnancy outcomes *(continued)*

Author	Year of study	Type of study	Setting of study	Population	Exposure assessment (when, how)	Outcomes assessed	Confounders adjusted for	Results	Quality assessment (risk of bias)
McCalla et al[27]	1988-89	Cross-sectional cohort with unmatched controls	Single center, municipal hospital, NYC	Inner-city	Maternal urine at admission ± neonate urine	LBW, GA	Regression analysis for: PNC, MA, parity, tobacco, ROH	For smoking, −125.0g ($P = .04$) for BW and −0.37 wks ($P = .18$) for GA	Low
Richardson, Day[28]	1983-86	Prospective cohort with unmatched controls	Single center, Magee-Womens Hospital, interview each trimester	Young, single, low income women attending public prenatal clinic	Maternal self-report antenatally	BW, GA, LBW, SGA			Moderate
Spence et al[29]	NS	Prospective cohort with unmatched controls	Single center, Hahnemann University Hospital, Philadelphia	Consecutive admission in L+D, routine screen	Maternal urine at delivery	PTB, BW			Low
Bateman, et al[30]	1985-86	Prospective cohort with unmatched controls	Single center, Harlem Hospital, NYC	Innercity	Maternal self-report or infant urine	LBW, PTB, BW, GA	GA, MA, gravidity, race, sex, PNC, syphilis, tobacco, ROH, marijuana, PCP, opiates	Regression coefficient −121g ($P < .005$)	Low
Forman et al[31]	1990-91	Prospective cohort with unmatched controls	3 centers, Toronto	Mother-infant pairs in 3 nurseries, 69% white	Neonate urine and hairs	BW	Tobacco - LBW BW	LBW: 50% of smokers vs 8% of nonsmokers 2899 ± 750g (C+T) 3423 ± 612g (C only) 3414 ± 564 (No exp)	Low
Rosengren et al[32]	1990	Prospective cohort with unmatched controls	2 urban centers, Hartford, Connecticut	Consecutive newborns, urban and suburban population	Neonate meconium	LBW, PTB, BW			Moderate
Eyler et al[33]	1987-88	Retrospective cohort with matched controls (race, MA, parity, GA at PNC, ROH, tobacco)	Single center, regional hospital (referral center), Florida	Women using rural county public health unit (min access rehab), Medicaid, low income	Maternal history or urine or neonate urine	LBW, PTB, GA, BW			Low
Kliegman et al[34]	1990-91	Prospective cohort with unmatched controls	Single center, large urban university-based maternity hospital, Cleveland	Anonymous screen, unselected population	Maternal urine at delivery or postpartum	LBW, PTD	Race, MA, ROH, marijuana, tobacco, PNC, primiparous, history of PTB	Multivariate logistic models adjusted OR, 9.90 (0.53-1.84)	Low
Neuspiel et al[35]	1992	Retrospective cohort with unmatched controls	Single center, public hospital, Bronx, NYC	NS	Maternal urine at admission and neonate cord blood	BW, GA	Cotinine, smoking history	−204g ($P = .15$)	Moderate
Singer et al[36]	NS	Retrospective cohort with matched controls (race, SES)	NS	AA, low SES, public assistance	Maternal urine and self-report antenatally	LBW, BW, GA			Low
Miller et al[37]	1990	Retrospective cohort with matched controls (race, age, parity, month of delivery)	Single center, New Orleans	Large urban center, innercity, indigent population	Maternal urine at delivery	BW, GA, PTB, SGA	Tobacco PNC	BW/Tobacco + :2759 ± 462 (45) for cocaine vs 2824 ± 876 (75) for controls BW/Tobacco –:3051 ± 602 (17) for cocaine vs 3078 ± 853 (167) for controls GA/Tobacco+: 38.4 ± 2.5 (45) for cocaine vs 37.6 ± 4.4 (75) for controls GA/Tobacco-: 39.0 ± 1.6 (16) for cocaine vs 38.4 ± 4.3 (164) for controls	Minimal

Gouin. Cocaine use during pregnancy on low birthweight and preterm birth. Am J Obstet Gynecol 2011. *(continued)*

TABLE 1
Summary of included studies of cocaine exposure and pregnancy outcomes *(continued)*

Author	Year of study	Type of study	Setting of study	Population	Exposure assessment (when, how)	Outcomes assessed	Confounders adjusted for	Results	Quality assessment (risk of bias)
Shiono et al[38]	1984-89	Prospective cohort with unmatched controls	Multicenter (7 centers) university-based prenatal clinics in US (Oklahoma, Louisiana, Texas, Tulane, Washington, Harlem)	Multiethnic, from Vaginal Infections and Prematurity study	Maternal serum or self-report antenatally or at delivery	LBW, PTB	Frequency use Blood concentration Tobacco ROH Marijuana	Logistic regression for smoking LBW OR, 1.1 (0.6-2.2) PTB OR, 1.5 (0.9-2.6)	Low
Kistin et al[39]	1988	Retrospective cohort with unmatched controls	Multicenter (12 centers) Univ Illinois hospital perinatal network	Patient delivering in a hospital of the network	Self-report or maternal or neonate urine at delivery	LBW, PTB, SGA	Race Age Gravidity		Low
Sprauve et al[40]	1992	Retrospective cohort with unmatched controls	Single center, Atlanta	Innercity, indigent, routine voluntary urine drug screening	Maternal urine at any time during pregnancy or within 1 wk of delivery	LBW, PTD, SGA	ROH, tobacco, weight, age, PNC, PTB	LBW: 1.59 (1.03-2.43) PTB: 0.88 (0.63-1.22) SGA: 1.7 (1.24-2.32)	Low
Richardson et al[41]	1988-93	Prospective cohort with unmatched contols	Single center, PNC clinic Magee-Women's hospital, Pittsburgh	Innercity, low income	Maternal self-report antenatally and PP	PTB, LBW, SGA	PNC		Low
Bandstra et al[42]	1990-93	Retro and prospective cohort with unmatched controls	Single center, Miami prenatal cocaine study	AA, innercity, low SES	Maternal self-report and urine, infant urine and meconium	LBW, BW, GA	Tobacco	BW −0.006 (−0.012-0.000) $P = .038$ GA 0.008 (0.002-0.014) $P = .10$	Moderate
Ogunyemi, Hernandez-Loera[43]	1991-2000	Retrospective cohort with matched controls	Single center, Los Angeles	All deliveries at this institution	Maternal toxicology screen PP	BW, GA, PTB, SGA	Tobacco	PTB coefficient regression 0.045(0.06) (−0.08 to −0.17)	Moderate
Bada et al[44]	NS	Retrospective cohort with unmatched controls	Multicenter (4 centers) Providence, Miami, Memphis, Detroit	Database Maternal Lifestyle Study	Maternal self-report or neonate meconium	LBW, PTB, SGA	Tobacco	LBW 5.57 (3.06-7.91) PTB 3.66 (0.87-6.53) SGA 13.79 (10.08-17.33)	Low

AA, African American; *ANC,* antenatal care; *BW,* birthweight; *exp,* exposure; *GA,* gestational age; *L+D,* labor and delivery suites; *LBW,* low birthweight; *MA,* maternal age; *NS,* not specified; *Ob,* obstetrics; *PNC,* prenatal care; *PP,* postpartum; *PTB,* preterm birth; *PTD,* preterm delivery; *ROH,* alcohol; *SES,* socioeconomic status; *SGA,* small for gestational age; *UCDMC,* University of California Davis Medical Center.

Gouin. Cocaine use during pregnancy on low birthweight and preterm birth. Am J Obstet Gynecol 2011.

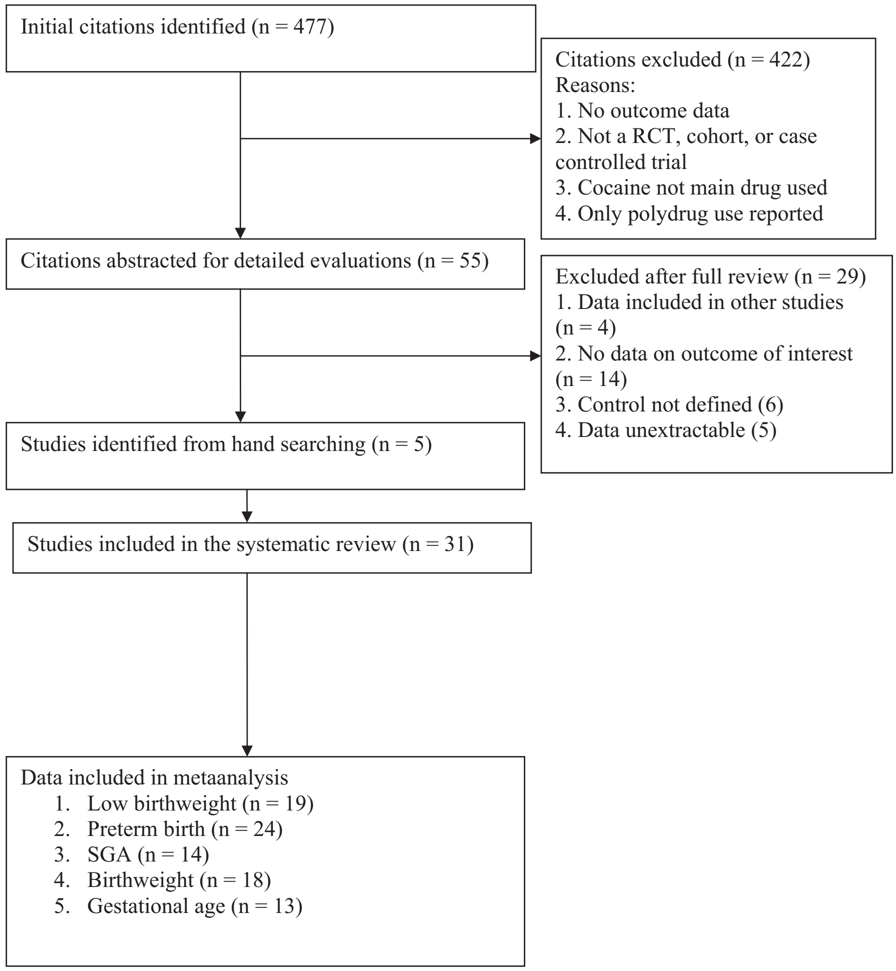
MATERIALS AND METHODS

The Meta-analysis of Observational Studies in Epidemiology (MOOSE) criteria were followed for this systematic review.[5] The methods of review by our group have been described previously.[6] The medical literature published between 1966 through July 2009 was searched in Medline, Embase, CINAHL databases, and bibliographies of identified articles for papers reporting on gestational cocaine exposure and pregnancy outcome. A search strategy using a combination of "pregnancy," "cocaine," "preterm birth," "premature," "intrauterine growth restriction," "low birthweight," "small-for-gestational age," "birthweight," "gestational age," "outcome," "complications," "intervention," and "cessation" keywords (MeSH) was used. Retrieved articles were hand searched for additional references. Non-English papers, comments, letters, editorials, and reviews were excluded. However, references of excluded publications were searched.

English language studies reporting on cocaine exposure in pregnancy and outcomes of interest: LBW (defined as BW <2500 g), PTB (defined as birth before 37 completed weeks of gestation), SGA (defined as BW <10th percentile for GA), BW in grams, and GA in weeks were reviewed. The criteria for inclusion of articles were as follows: human exposure to any amount of cocaine during any or all the trimesters of pregnancy, as evidenced by drug history, maternal or neonate urine test or neonate meconium test, and report of pregnancy outcome of interest. Prospective and retrospective cohort studies, as well as case-control studies of cocaine exposure were included. Polydrug use is common in this population and was not an exclusion criterion. We excluded studies that reported duplicate populations, exposure that was ambiguous and those that did not report on the outcomes of interest. Studies fulfilling all inclusion criteria were included for detailed review. Two reviewers (K.G. and K.M.) independently assessed eligibility, risk of bias, and extracted information using predetermined standardized data collection forms. Risk of bias for observational studies was evaluated using criteria for selection bias, exposure assessment bias, confounder adjustment, analytic bias, outcome assessment bias, and attrition bias according to our previously reported criteria[6] (Appendix 1).

The third reviewer (P.S.) acted as an arbitrator. Metaanalyses were performed using the random effects model and unadjusted odds ratio (OR) or weighted mean difference and 95% confidence interval (CI). A priori planned sensitivity and subgroup analyses were planned for recent publications vs older publications, dividing studies into 2 equal divisions based on year of publication (before or after 1991), whether objective vs self-reported use of cocaine exposure was reported in the studies, whether study was prospective or retrospective, whether studies had minimal/low risk of overall bias compared with studies with moderate risk of biases and whether matched or unmatched controls were used for analyses. Clinical heterogeneity was assessed and reported in the table of included studies (Table 1). Statistical heterogeneity was assessed using the I-squared (I^2) values.[7]

FIGURE 1
Literature search flowchart



RCT, randomized controlled trial; *SGA*, small for gestational age.

Gouin. Cocaine use during pregnancy on low birthweight and preterm birth. Am J Obstet Gynecol 2011.

RESULTS

Assessment of effects of cocaine exposure

Four hundred seventy-seven citations were identified. After review, 55 reports were retrieved for detailed evaluation. Thirty-one studies met inclusion criteria and were included in this systematic review (Figure 1). Characteristics of included studies are described in Table 1. The risk of bias and quality of the studies are reported in Appendix 2.

1. LBW: cocaine use during pregnancy was significantly associated with LBW births as compared with women who did not use cocaine during pregnancy (19 studies, 38,796 participants, unadjusted pooled OR, 3.66; 95% CI, 2.90–4.63; I^2 = 72%) (Figure 2).
2. PTB: when compared with nonusers, cocaine use during pregnancy was significantly associated with PTB before 37 weeks (24 studies, 39,860 participants, unadjusted pooled OR, 3.38; 95% CI, 2.72–4.21; I^2 = 73%) (Figure 3).
3. SGA: cocaine use during pregnancy vs no use was significantly associated with SGA (14 studies, 28,098 participants, unadjusted pooled OR, 3.23; 95% CI, 2.43–4.30; I^2 = 87%) (Figure 4).
4. GA: cocaine use during pregnancy vs no use was associated with an earlier gestational age at birth (13 studies, 4272 participants; −1.47 weeks; 95% CI, −1.97 to −0.98 weeks; I^2 = 87%) (Figure 5).
5. BW: Cocaine use during pregnancy vs no use was associated with LBW (18 studies, 6855 participants; −492g; 95% CI, −562 to −421 grams; I^2 = 71%) (Figure 6).

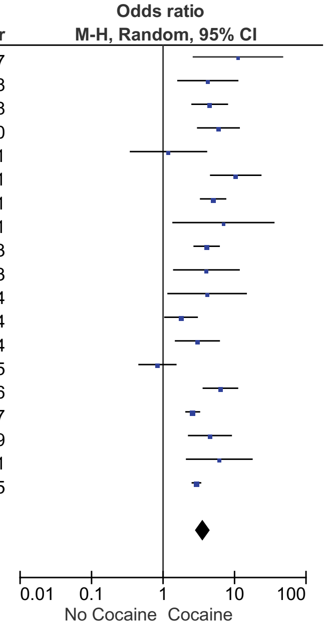
Subgroup analyses

A priori planned sensitivity and subgroup analyses were performed (Table 2). The results did not differ when earlier studies were compared with later studies whether objective or self-reported assessment of cocaine exposure were reported in the studies, whether study was prospective or retrospective, whether studies had minimal/low risk of overall bias compared with studies with moder-

FIGURE 2
Effect of antenatal cocaine exposure on LBW (<2500 g)

Study or subgroup	Cocaine Events	Cocaine Total	No cocaine Events	No cocaine Total	Weight	Odds ratio M-H, Random, 95% CI	Year
MacGregor 1987	8	24	3	70	2.1%	11.17 [2.66, 46.88]	1987
Cherukuri 1988	21	55	7	55	3.7%	4.24 [1.62, 11.08]	1988
Chouteau 1988	43	124	23	218	6.3%	4.50 [2.55, 7.95]	1988
Gillogley 1990	32	139	14	293	5.5%	5.96 [3.06, 11.61]	1990
Richardson 1991	3	34	45	600	2.7%	1.19 [0.35, 4.06]	1991
Cohen 1991	31	83	9	166	4.6%	10.40 [4.65, 23.28]	1991
McCalla 1991	52	128	118	983	7.7%	5.02 [3.36, 7.50]	1991
Kelley 1991	10	30	2	30	1.7%	7.00 [1.38, 35.48]	1991
Bateman 1993	111	361	38	387	7.7%	4.08 [2.73, 6.10]	1993
Rosengren 1993	5	21	43	600	3.3%	4.05 [1.42, 11.58]	1993
Kliegman, 1994	4	13	22	227	2.6%	4.14 [1.18, 14.56]	1994
Eyler 1994	47	168	30	168	6.7%	1.79 [1.06, 3.00]	1994
Singer 1994	33	100	14	100	5.3%	3.03 [1.50, 6.10]	1994
Shiono, 1995	12	175	591	7295	6.1%	0.84 [0.46, 1.51]	1995
Kistin 1996	18	64	756	13043	6.4%	6.36 [3.67, 11.02]	1996
Sprauve 1997	151	483	470	3158	9.2%	2.60 [2.10, 3.23]	1997
Richardson 1999	18	62	25	302	5.4%	4.53 [2.29, 8.99]	1999
Bandstra 2001	37	253	4	147	3.3%	6.12 [2.14, 17.55]	2001
Bada 2005	465	1072	1567	7565	9.7%	2.93 [2.57, 3.35]	2005
Total (95% CI)		**3389**		**35407**	**100.0%**	**3.66 [2.90, 4.63]**	
Total events	1101		3781				

Heterogeneity: Tau² = 0.14; Chi² = 64.25, df = 18 (*P* < .00001); I² = 72%
Test for overall effect: Z = 10.84 (*P* < .00001)



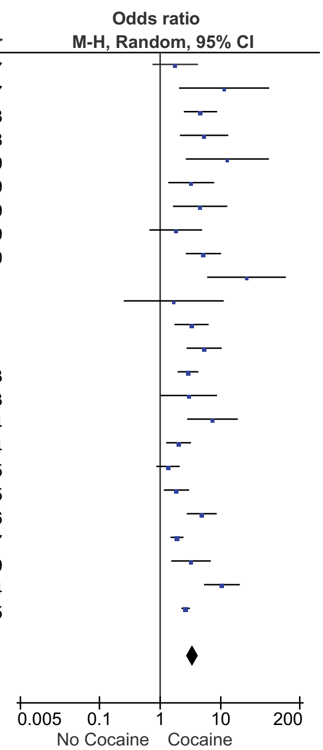
LBW, low birthweight.

Gouin. Cocaine use during pregnancy on low birthweight and preterm birth. Am J Obstet Gynecol 2011.

FIGURE 3
Effect of antenatal cocaine exposure on PTB (<37 weeks)

Study or subgroup	Cocaine Events	Cocaine Total	No cocaine Events	No cocaine Total	Weight	Odds ratio M-H, Random, 95% CI	Year
Bingol 1987	8	50	33	340	3.6%	1.77 [0.77, 4.09]	1987
MacGregor 1987	6	24	2	70	1.4%	11.33 [2.11, 60.96]	1987
Chouteau 1988	38	124	19	218	4.8%	4.63 [2.52, 8.48]	1988
Cherukuri 1988	28	55	9	55	3.4%	5.30 [2.18, 12.89]	1988
Little 1989	11	53	2	100	1.6%	12.83 [2.73, 60.43]	1989
Neerhof 1989	28	114	8	88	3.6%	3.26 [1.40, 7.56]	1989
Fulroth 1989	5	35	36	1021	2.9%	4.56 [1.67, 12.44]	1989
Hadeed 1989	13	56	8	56	3.1%	1.81 [0.69, 4.80]	1989
Gillogley 1990	32	139	16	293	4.6%	5.18 [2.73, 9.82]	1990
Calhoun 1991	34	91	2	91	1.7%	26.54 [6.14, 114.79]	1991
Kelley 1991	3	28	2	30	1.2%	1.68 [0.26, 10.89]	1991
Spence 1991	20	63	43	348	4.8%	3.30 [1.78, 6.13]	1991
Cohen 1991	35	83	20	166	4.6%	5.32 [2.81, 10.08]	1991
Bateman 1993	115	361	54	387	6.4%	2.88 [2.01, 4.14]	1993
Rosengren 1993	5	21	57	600	2.8%	2.98 [1.05, 8.43]	1993
Kliegman, 1994	11	20	46	321	3.2%	7.31 [2.87, 18.60]	1994
Eyler 1994	81	168	53	168	5.8%	2.02 [1.30, 3.15]	1994
Shiono, 1995	27	175	868	7295	6.0%	1.35 [0.89, 2.05]	1995
Miller 1995	47	138	60	276	5.8%	1.86 [1.18, 2.93]	1995
Kistin 1996	19	64	1043	13043	5.2%	4.86 [2.83, 8.34]	1996
Sprauve 1997	136	483	540	3158	7.1%	1.90 [1.53, 2.37]	1997
Richardson 1999	14	62	25	302	4.2%	3.23 [1.57, 6.66]	1999
Ogunyemi 2004	80	200	12	200	4.6%	10.44 [5.46, 19.98]	2004
Bada 2005	457	1068	1671	7559	7.5%	2.64 [2.31, 3.01]	2005
Total (95% CI)		**3675**		**36185**	**100.0%**	**3.38 [2.72, 4.21]**	
Total events	1253		4629				

Heterogeneity: Tau² = 0.16; Chi² = 84.24, df = 23 (*P* < .00001); I² = 73%
Test for overall effect: Z = 10.92 (*P* < .00001)



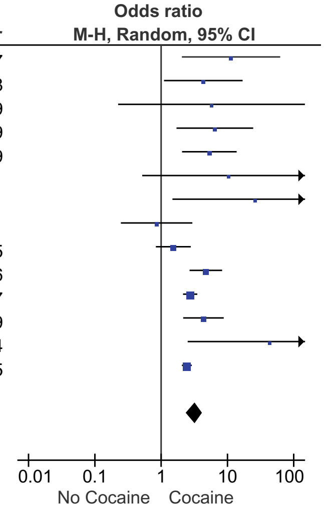
PTB, preterm birth.

Gouin. Cocaine use during pregnancy on low birthweight and preterm birth. Am J Obstet Gynecol 2011.

FIGURE 4
Effect of antenatal cocaine exposure on SGA (<10th percentile for GA)

Study or subgroup	Cocaine Events	Cocaine Total	No cocaine Events	No cocaine Total	Weight	Odds ratio M-H, Random, 95% CI	Year
MacGregor 1987	6	24	2	70	2.5%	11.33 [2.11, 60.96]	1987
Cherukuri 1988	11	55	3	55	3.8%	4.33 [1.14, 16.52]	1988
Little 1989	1	53	0	100	0.8%	5.74 [0.23, 143.44]	1989
Hadeed 1989	15	56	3	56	3.9%	6.46 [1.75, 23.83]	1989
Neerhof 1989	32	114	6	88	6.7%	5.33 [2.12, 13.44]	1989
Kelley 1991	4	30	0	30	0.9%	10.36 [0.53, 201.45]	1991
Calhoun 1991	11	91	0	91	1.0%	26.14 [1.52, 450.70]	1991
Richardson 1991	3	34	61	600	4.4%	0.86 [0.25, 2.88]	1991
Miller 1995	23	138	32	276	11.7%	1.52 [0.85, 2.72]	1995
Kistin 1996	19	64	1069	13043	12.5%	4.73 [2.76, 8.11]	1996
Sprauve 1997	140	483	410	3158	19.9%	2.74 [2.19, 3.42]	1997
Richardson 1999	18	62	26	302	9.9%	4.34 [2.20, 8.57]	1999
Ogunyemi 2004	19	200	0	200	1.0%	43.08 [2.58, 718.68]	2004
Bada 2005	297	1071	1027	7554	21.3%	2.44 [2.10, 2.83]	2005
Total (95% CI)		**2475**		**25623**	**100.0%**	**3.23 [2.43, 4.30]**	
Total events	599		2639				

Heterogeneity: Tau² = 0.09; Chi² = 29.40, df = 13 (*P* = .006); I² = 56%
Test for overall effect: Z = 8.09 (*P* < .00001)



GA, gestational age; *SGA*, small for gestational age.

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ate risk of bias and whether matched or unmatched controls were used for analyses. However, there was no statistical difference in the results between subgroups ($P > .05$).

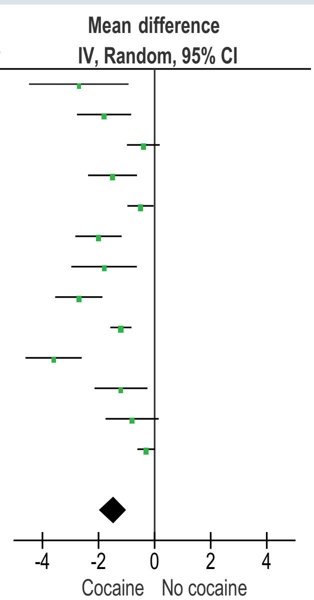
COMMENT

A discussion about the effects of cocaine use during pregnancy must be prefaced with caution given the nature of the available evidence. Four issues are of particular concern: (1) the difficulty of accurately measuring illicit substance use patterns among women throughout pregnancy; (2) the difficulty of separating the effects of cocaine use from the effects of the other confounding adverse personal and social circumstances in which substance use often takes place; (3) the common pattern of poly substance use by this population; and (4) publication bias or the apparent reviewer/editorial bias that results in preferential publication in the scientific literature of studies that show unfavorable outcomes in association with substance use.[8] We explored the heterogeneity be-

FIGURE 5
Effect of antenatal cocaine exposure on GA at delivery (weeks)

Study or subgroup	Cocaine Mean	Cocaine SD	Cocaine Total	No cocaine Mean	No cocaine SD	No cocaine Total	Weight	Mean difference IV, Random, 95% CI	Year
MacGregor 1987	36.6	4.2	24	39.3	2	70	4.5%	-2.70 [-4.44, -0.96]	1987
Cherukuri 1988	37.4	3	55	39.2	1.9	55	7.3%	-1.80 [-2.74, -0.86]	1988
Little 1989	38.9	1.4	53	39.3	2.1	100	8.7%	-0.40 [-0.96, 0.16]	1989
Neerhof 1989	37.5	3.7	114	39	2.4	88	7.6%	-1.50 [-2.34, -0.66]	1989
Zuckerman 1989	38.8	2.3	114	39.3	1.9	1010	9.1%	-0.50 [-0.94, -0.06]	1989
Cohen 1991	36.9	3.3	83	38.9	2.4	166	7.8%	-2.00 [-2.80, -1.20]	1991
Kelley 1991	37.9	2.9	30	39.7	1.3	30	6.5%	-1.80 [-2.94, -0.66]	1991
Calhoun 1991	37	3.7	91	39.7	1.4	91	7.8%	-2.70 [-3.51, -1.89]	1991
Bateman 1993	38	2.7	361	39.2	2.1	387	9.3%	-1.20 [-1.55, -0.85]	1993
Singer 1994	34.9	4.1	100	38.5	2.8	100	7.1%	-3.60 [-4.57, -2.63]	1994
Eyler 1994	36.6	5	168	37.8	3.4	168	7.4%	-1.20 [-2.11, -0.29]	1994
Miller 1995	37	4.2	138	37.8	5	276	7.4%	-0.80 [-1.72, 0.12]	1995
Bandstra 2001	39.4	1.4	253	39.7	1.4	147	9.5%	-0.30 [-0.58, -0.02]	2001
Total (95% CI)			**1584**			**2688**	**100.0%**	**-1.47 [-1.97, -0.98]**	

Heterogeneity: Tau² = 0.66; Chi² = 93.93, df = 12 (*P* < .00001); I² = 87%
Test for overall effect: Z = 5.79 (*P* < .00001)



GA, gestational age.

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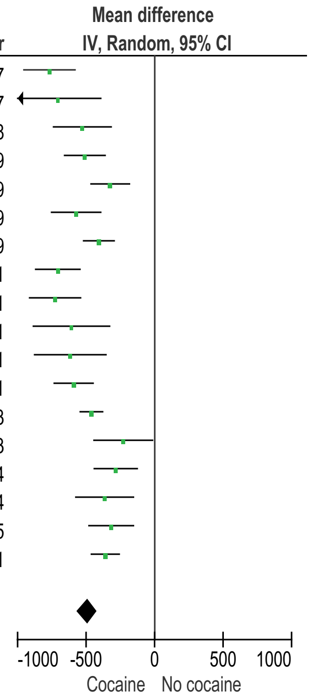
FIGURE 6
Effect of antenatal cocaine exposure on BW (grams)

Study or subgroup	No cocaine Mean	No cocaine SD	No cocaine Total	Cocaine Mean	Cocaine SD	Cocaine Total	Weight	Mean difference IV, Random, 95% CI	Year
Bingol 1987	2,464	590	42	3,232	475	307	5.3%	-768.00 [-954.18, -581.82]	1987
MacGregor 1987	2,677	706	24	3,382	551	70	3.2%	-705.00 [-1015.55, -394.45]	1987
Cherukuri 1988	2,528	619	55	3,056	500	55	4.8%	-528.00 [-738.29, -317.71]	1988
Hadeed 1989	2,795	448	56	3,305	345	56	6.2%	-510.00 [-658.10, -361.90]	1989
Little 1989	2,970	415	53	3,295	433	100	6.4%	-325.00 [-465.30, -184.70]	1989
Neerhof 1989	2,644	685	114	3,217	612	88	5.5%	-573.00 [-752.34, -393.66]	1989
Zuckerman 1989	2,847	572	114	3,254	617	1010	7.0%	-407.00 [-518.68, -295.32]	1989
Cohen 1991	2,556	642	83	3,263	558	166	5.9%	-707.00 [-869.12, -544.88]	1991
Calhoun 1991	2,613	757	91	3,340	494	91	5.4%	-727.00 [-912.72, -541.28]	1991
Spence 1991	2,520	1,077	63	3,127	777	348	3.7%	-607.00 [-885.19, -328.81]	1991
Kelley 1991	2,652	540	30	3,268	487	30	3.9%	-616.00 [-876.21, -355.79]	1991
McCalla 1991	2,560	778	128	3,151	699	983	6.3%	-591.00 [-732.69, -449.31]	1991
Bateman 1993	2,713	569	361	3,174	573	387	7.6%	-461.00 [-542.88, -379.12]	1993
Forman 1993	3,162	645	37	3,391	573	563	4.8%	-229.00 [-442.15, -15.85]	1993
Eyler 1994	2,704	742	168	2,988	721	168	6.0%	-284.00 [-440.45, -127.55]	1994
Singer 1994	2,624	769	100	2,989	750	100	4.8%	-365.00 [-575.54, -154.46]	1994
Miller 1995	2,626	721	138	2,943	926	276	5.9%	-317.00 [-479.50, -154.50]	1995
Bandstra 2001	2,971	474	253	3,331	514	147	7.2%	-360.00 [-461.57, -258.43]	2001
Total (95% CI)			**1910**			**4945**	**100.0%**	**-491.52 [-562.18, -420.85]**	

Heterogeneity: Tau² = 15296.60; Chi² = 58.96, df = 17 (*P* < .00001); I² = 71%
Test for overall effect: Z = 13.63 (*P* < .00001)



BW, birthweight.

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tween studies by assessing clinical and statistical heterogeneities and performing subgroup analyses.

Another limitation includes the inaccuracy in determining GA. Women who use cocaine often lack prenatal care; precise dating by last menstrual period or early dating ultrasound were unavailable for several studies. Some studies used the Dubowitz score[9] to determine GA. Inaccuracies in dating can account for inaccurate reporting of PTB and SGA. How-

TABLE 2
Sensitivity/subgroup analysis

Variable	Group	PTB n studies/participants	PTB OR (95% CI)	LBW n studies/participants	LBW OR (95% CI)
Year of study	≤1991	13/3791	4.29 (3.11–5.92)	8/3032	5.23 (3.72–7.34)
	>1991	11/36069	2.93 (2.28–3.76)	11/35764	3.02 (2.32–3.93)
Method of exposure assessment	Self-report	11/32123	2.97 (2.25–3.93)	12/32160	3.21 (2.29–4.48)
	Objective	13/7737	3.80 (2.59–5.57)	7/6636	4.62 (3.09–6.89)
Type of cohort	Retrospective	13/28711	3.69 (2.75–4.95)	12/14501	3.97 (3.05–5.17)
	Prospective	11/11149	3.09 (2.13–4.48)	7/24295	3.28 (1.96–5.47)
Quality assessment (risk of bias)	Minimal/low	18/37341	2.99 (2.42–3.70)	15/37081	3.66 (2.85–4.70)
	Moderate	6/2519	5.44 (2.73–10.85)	4/1715	3.71 (1.72–7.99)
Type of controls	Matched	10/2387	4.35 (2.59–7.30)	7/1481	4.72 (2.67–8.34)
	Unmatched	14/37473	2.94 (2.34–3.69)	12/37315	3.37 (2.59–4.39)

CI, confidence interval; *LBW*, low birthweight; *OR*, odds ratio; *PTB*, preterm birth.

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ever, despite this limitation, BW and LBW reports are unaffected by GA and remain significantly lower in cocaine-using mothers. Consistency in the results between studies and the strength of association between cocaine use and PTB suggests that the possibility of false-positive results is less likely.

The concomitant use of tobacco was one of the major confounding factors in this metaanalysis. In 1997, Hulse et al[10] conducted a metaanalysis using studies that had adjusted for tobacco exposure and suggested that, despite tobacco use, maternal cocaine use independently contributes to LBW, and that the effect is greater with heavier use. In this metaanalysis, we have included several additional studies that have focused on neonatal outcomes and have provided subgroup analyses to strengthen the association.

There are other environmental factors that could not be taken into account in these studies. The possible interaction of social factors with the pathophysiologic effects of cocaine could lead to an overestimation of its impact. These factors are difficult to study, quantify, and control. Therefore, the authors rely on the available cohort or case-controlled studies.

This review summarizes adverse neonatal outcomes related to cocaine exposure during pregnancy. Several investigators have explored interventions to stop or reduce cocaine consumption in pregnancy to improve perinatal outcomes. Interventions are diverse, the spectrum including standard prenatal care[11] to residential rehabilitation programs.[12] Overall, there appears to be a trend toward improvement of perinatal outcomes with interventions focused on reducing maternal cocaine exposure. Racine et al[13] published results indicating an improvement in BW and decrease in LBW with 4 or more prenatal care visits. Comfort et al[14] compared inpatient residential versus outpatient substance abuse treatment program. The perinatal outcomes following both of these interventions were similar.[14] Limited research suggests that interventions to decrease cocaine exposure during pregnancy may be effective. However, future studies are needed to compare the different types of interventions and to determine the best strategies to help pregnant women who are cocaine dependent and to reduce or prevent cocaine addiction.

Conclusions

Maternal prenatal cocaine consumption is significantly associated with PTB, LBW, and SGA births. Cocaine use during pregnancy is a preventable contributor to adverse perinatal outcomes. Therefore, it is important to provide interventions and support to pregnant women who are cocaine dependent. Future studies controlling for confounders and impact of intervention are needed.

Contributors

All authors participated in writing the original grant application, and were members of the steering committee. P.S. was the principal investigator and led the Knowledge synthesis team. K.G. and K.M. were principal investigators on this project, and collected articles, assessed for inclusion and quality, retrieved data, performed metaanalyses. K.G. wrote the first draft and K.M. and P.S. critically reviewed and revised the manuscript. Joseph Beyene was the team statistician and contributed to the planning and supervision of data analyses.

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ACKNOWLEDGMENTS

We would sincerely like to thank Ms Elizabeth Uleryk, Chief Librarian at the Hospital for Sick Children, Toronto, for her contribution in developing the search strategies and running the search on a periodic basis.

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APPENDIX 1

Risk of bias assessment for observational studies

Bias	None	Low	Moderate	High	Can't tell
Selection	• Consecutive unselected population • Sample selected from general population rather than a select group • Rationale for case and control selection explained • Follow up or assessment time explained	• Sample selected from large population but selection criteria not defined • A select group of population (based on race, ethnicity, residence, etc) studied	• Sample selection ambiguous but sample may be representative • Eligibility criteria not explained • Rationale for case and controls not explained • Follow up or assessment time not explained	• Sample selection ambiguous and sample likely not representative • A very select population studied making it difficult to generalize findings	•
Exposure assessment	• Direct questioning (interview) or completion of survey by mother regarding her BW or GA	• Assessment of exposure from global dataset (National register, Vital statistics)	• Extrapolating data from population exposure sample (with some assumptions) and not direct assessment at any time	• Indirect method of assessment (obtaining data from others and not from mother or father)	•
Outcome assessment	• Assessment from hospital record, birth certificate or from direct question to mother regarding BW of infant	• Assessment from administrative database (national register, vital statistics) • Direct question to mother regarding gestational age	• Assessment from "open-ended' questions (was your infant early? or premature? or small? or before due date)	• Assessment from nonvalidated sources or generic estimate from overall population	•
Confounding factor	• Controlled for common confounders	• Only certain confounders adjusted	• Not controlled for confounders		
Analytical	• Analyses appropriate for the type of sample • Analytical method accounted for sampling strategy in cross-sectional study • Sample size calculation performed and adequate sample studied	• Analyses not accounting for common statistical adjustment (eg, multiple analyses) when appropriate • Sample size calculation not performed, but all available eligible patients studied • Sample size calculated and reasons for not meeting sample size given	• Sample size estimation unclear or only subsample of eligible patients studied	• Analyses inappropriate for the type of sample/study	•
Attrition	• 0-10% attrition and reasons for loss of follow-up explained • All subjects from initiation of study to the final outcome assessment were accounted for	• 0-10% attrition and reasons for loss of follow-up not explained • 11-20% attrition, reasons for loss of follow-up explained	• 11-20% attrition but reasons for loss of follow-up not explained • >20% attrition but reasons for loss of follow-up explained • All subjects from initiation of study to final outcome assessment not accounted for	• >20% attrition, reasons for loss of follow-up not explained	•

BW, birthweight; *GA*, gestational age.

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APPENDIX 2
Studies quality assessment (risk of bias) of included studies of cocaine exposure

Author	Type of study	Selection bias	Exposure assessment bias	Outcome assessment bias	Confounding factor bias	Analytical bias	Attrition bias	Overall assessment bias
Bingol et al[4]	Prospective cohort with unmatched controls	Low	None	None	Low	Low	Low	Low
MacGregor et al[15]	Cohort with matched controls	Low	None	None	Low	Low	None	Low
Cherukuri et al[16]	Retrospective cohort with matched controls	Low	None	None	Moderate	Low	None	Low
Chouteau et al[17]	Retrospective cohort with unmatched controls	Low	None	None	Moderate	Low	None	Low
Fulroth et al[18]	Cohort with unmatched controls	Moderate	None	None	Moderate	Low	None	Moderate
Hadeed, Siegel[19]	Retrospective cohort with matched controls	Low	Low	None	Low	Low	None	Low
Little et al[20]	Retrospective cohort with unmatched controls	Low	None	None	Low	Low	None	Low
Neerhof et al[21]	Prospective cohort with unmatched controls	Moderate	None	None	Moderate	Low	None	Moderate
Zuckerman et al[22]	Prospective cohort with unmatched controls	Low	Low	None	Low	Low	Low	Low
Gillogley et al[23]	Retrospective cohort with matched controls	Low	None	None	Low	Low	Moderate	Low
Calhoun, Watson[24]	Prospective cohort with matched controls	Moderate	Low	None	Low	Low	None	Moderate
Cohen et al[25]	Retrospective cohort with matched controls	Low	None	None	Low	Low	None	Minimal
Kelley et al[26]	Retrospective cohort with matched controls	Low	None	None	Moderate	Low	ns	Moderate
McCalla et al[27]	Cross-sectional cohort with unmatched controls	Low	None	None	Low	Low	Moderate	Low
Richardson and Day[28]	Prospective cohort with unmatched controls	Low	None	None	Low	Low	Moderate	Moderate
Spence et al[29]	Prospective cohort with unmatched controls	Low	None	None	Moderate	Low	Low	Low
Bateman et al[30]	Prospective cohort with unmatched controls	Low	None	None	None	Low	ns	Low
Forman et al[31]	Prospective cohort with unmatched controls	Low	None	None	Low	Low	None	Low
Rosengren et al[32]	Prospective cohort with unmatched controls	Low	None	None	Moderate	Low	None	Moderate
Eyler et al[33]	Retrospective cohort with matched controls	Low	Low	None	None	Low	ns	Low
Kliegman et al[34]	Cohort with unmatched controls	Low	None	None	None	Low	ns	Low
Neuspiel et al[35]	Retrospective cohort with unmatched controls	Low	None	None	Low	Low	Moderate	Moderate
Singer et al[36]	Retrospective cohort with matched controls	Low	None	none	Low	Low	ns	Low
Miller et al[37]	Retrospective cohort with matched controls	None	None	None	None	Low	Low	Minimal
Shiono et al[38]	Prospective cohort with unmatched controls	Low	None	None	Low	Low	Low	Low
Kistin et al[39]	Retrospective cohort with unmatched controls	Low	None	None	Low	Low	None	Low
Sprauve et al[40]	Retrospective cohort with unmatched controls	Low	None	None	None	Low	Low	Low
Richardson et al[41]	Prospective cohort with unmatched controls	Low	None	None	Low	Low	Low	Low
Bandstra et al[42]	Retrospective and prospective cohort with unmatched controls	Low	Low	None	None	Low	Moderate	Moderate
Ogunyemi, Hernandez-Loera[43]	Retrospective cohort with matched controls	Moderate	Low	None	Low	Low	Low	Moderate
Bada et al[44]	Retrospective cohort with unmatched controls	Low	None	None	None	Low	Low	Low

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