Original Research

The association between gestational age at delivery and neonatal abstinence syndrome: A systematic review and meta-analysis

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Abstract

Objectives: Some evidence suggests that infants born at later gestational age (GA) are at higher risk of developing neonatal abstinence syndrome (NAS). This systematic review estimated the association between GA at delivery and development of NAS in infants born to women on opioid agonist therapy (OAT). **Methods:** MEDLINE/PubMed, Scopus, Embase, CINAHL, and the Cochrane Central Register of Controlled Trials were searched from January 2000 to April 2023. Studies reporting data on the association between GA and NAS among pregnant women being treated with OAT were eligible for inclusion. Random effects meta-analysis was used to estimate the mean difference in GA between infants affected by NAS and unaffected infants; odds ratio (OR) for the association between preterm birth and NAS; and OR for the association between gestational week and NAS. **Results:** Of 966 records identified, 38 studies were eligible for this review. The pooled mean difference in GA between infants affected by NAS and unaffected infants was 0.62 weeks (95% CI: 0.08–1.16, I^2=90.7%). The odds of developing NAS were estimated to increase by 3% per gestational week (OR 1.03, 95% CI: 0.997-1.06, I^2=84.2%). The OR for the association between preterm birth and developing NAS was estimated to be 0.87 (95% CI: 0.63-1.21, I^2=85.7%). **Conclusions:** The data included in this review demonstrate that higher GA is unlikely to be associated with an increased risk of NAS, although poor study quality and significant study heterogeneity were observed.

Introduction

Opioid use disorder is an important public health issue, and its prevalence in pregnant women is rising[1,2]. Opioid agonist therapy (OAT) with agents such as methadone or buprenorphine is the treatment of choice for opioid use disorder during pregnancy[3-5], reducing fetal exposure to repeated cycles of withdrawal, increasing adherence to prenatal care, and improving neonatal outcomes[6,7]. However, prenatal exposure to OAT can cause neonatal abstinence syndrome (NAS), which is characterized by central nervous system hyperirritability, autonomic dysregulation and gastrointestinal tract disturbance, as well as increased length of hospital stay and admission to the neonatal intensive care unit[8-10]. The incidence of NAS in Canada tripled between 2003 and 2014[11]. Similarly, in the United States the incidence of NAS increased from 3.4 to 5.8 cases per 1,000 live births between 2009 and 2012[12].

The relationship between gestational age (GA) at delivery and NAS is unclear, and may be influenced by maternal and fetal physiology, as well as by duration of opioid agonist treatment, the type of assessment tool, and concurrent prescribed and illicit substance use and other confounding factors. Cohort and randomized studies have found that later GA at delivery is associated with an increased risk of developing NAS, increased severity of NAS, or both[13-16], while other studies found no relationship[17-19]. Given the increasing prevalence of opioid use disorder and NAS, characterization of risk factors for NAS, such as GA at delivery, is important in the clinical management of the newborn. Information regarding the role of GA in the development of NAS may help guide obstetrical and neonatal management, such as ensuring adequate pregnancy dating and normal neonatal adaptation to extrauterine life, although clinical decision making is challenged by conflicting data.

The objective of this systematic review and meta-analysis was to estimate the association between GA at delivery and development of NAS in women receiving OAT, and explore potential sources of bias and heterogeneity in the published literature. We hypothesized that infants born to mothers using OAT in pregnancy delivering at earlier GA would be less likely to develop NAS.

Methods

The protocol for this systematic review was registered

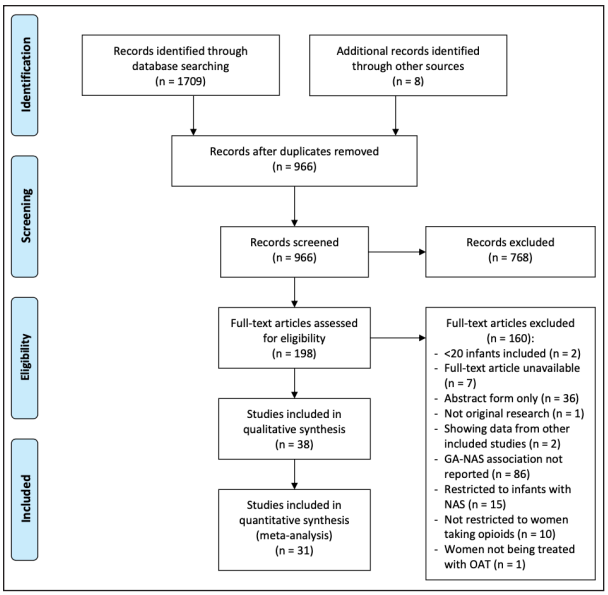

Figure 1. Systematic review of the literature evaluating the relationship between gestational age at delivery and risk of neonatal abstinence syndrome.

in PROSPERO (CRD42019118562). The systematic review and meta-analysis were reported following the PRISMA guidelines[20].

Search strategy and selection criteria

A search strategy was developed in consultation with a medical librarian. Peer-reviewed literature was searched to identify articles reporting the relationship between GA and NAS using MEDLINE/PubMed, Scopus, Embase, CINAHL, and the Cochrane Central Register of Controlled Trials from January 2000 to April 2023, with publications limited to the English language. Our search strategy included one string of terms related to the exposure of interest (GA at delivery) and a second string related to the outcome of interest (NAS). The MEDLINE and Embase search strategies are included in Appendix S1. The reference lists of studies included in the review were hand searched to identify additional papers for inclusion.

Studies were eligible for inclusion if the population was women who had used opioids in pregnancy and data on the association between GA and NAS were reported (even if not designed specifically to evaluate this association). Studies using any method of assessing NAS were included, and were excluded if they: contained fewer than 20 women (to differentiate case series from true cohort studies); were a review or commentary; were not published in English; were not a full-text article; were not published in a peer-reviewed journal; or included only infants who had been diagnosed with NAS. At least two reviewers (SB and either VMA or CGW) independently screened and reviewed all titles and abstracts and performed a full-text review of identified articles for eligibility. Conflicts in the title and abstract or full-text review were resolved by consensus among the three authors.

Data extraction and assessment of risk of bias

For each eligible study, population characteristics were extracted by the first author and confirmed by a second reviewer (VMA). Characteristics included: author and year published, geographic setting, years of birth included in the study, study design, sample size, type and rates of OAT used, maternal characteristics (age, rates of illicit opioid and other substance use, and infectious disease status), whether the study excluded infants below a certain GA, NAS assessment method, NAS outcome definition (e.g., pharmacologically treated NAS or NAS diagnosis), Caesarean delivery rate, and breastfeeding rate. The quantitative data on the association between GA and NAS (frequencies of GA by NAS, mean (SD) GA by NAS status, and effect estimates) were extracted by two reviewers (CGW and SB) with conflicts resolved by consensus.

Risk of bias was independently assessed using a modified Newcastle-Ottawa Quality Assessment Scale for Cohort Studies[21] by two reviewers (SB and either VMA or CGW) and all conflicts were resolved by consensus among the group of three reviewers. Risk of bias was assessed across four domains: sample selection, ascertainment of exposure, comparability, and outcome measurement. Three potential stars could be allotted for sample selection, one for exposure, two for comparability, and two for outcome. The modified risk of bias scale is attached in Appendix S2.

Data synthesis and statistical analyses

Three effect measures for the association between GA and NAS were extracted or derived from data presented in the publications: mean difference in GA between infants affected by NAS and unaffected infants; odds ratio (OR) for the association between gestational week and NAS; and OR for the association between preterm birth (<37 weeks) and NAS. For studies that presented ORs for multiple categories of GA in relation to NAS, the OR per week of GA was estimated using weighted least squares regression[22]. One paper included in the meta-analysis reported an OR for GA but not its scale; based on other information provided in the report, we determined that the OR referred to GA per week[23]. Overall pooled effect estimates were derived using a random effects model[24]. Statistical heterogeneity was quantified with the I^2 statistic, the percentage of variation among studies that is due to heterogeneity rather than chance[25]. Pre-specified subgroup analyses were

undertaken by the GA range included (infants born <34 weeks vs not), NAS definition (pharmacologically treated only vs all NAS), proportion of mothers taking methadone (100% using methadone, 33%-88% using methadone, and 0% using methadone), and rate of Caesarean delivery (<30% vs ≥30%). Analyses were performed using the *meta* package of Stata 16 (StataCorp LLC 2019). Recommended guidelines for reporting systematic reviews (PRISMA)[20] and meta-analyses of observational studies (MOOSE)[26] were followed.

Results

Study characteristics and quality

In total, 966 titles and abstracts were screened and 198 were deemed eligible for full-text review (Figure 1). One hundred and sixty papers were excluded following full-text review; therefore 38 articles were included in the systematic review[13-19,23,27-56]. The reasons for exclusion were as follows: the association between GA and NAS was not reported (n = 86); full-text article unavailable (n = 7), majority in abstract form only (n = 36); restricted to infants with NAS (n = 15); population not restricted to women taking opioids (n = 10); less than 20 infants included (n = 2); not original research (n = 1); or women not being treated with OAT (n = 1). Two articles[57,58] reported data that were reported in other included articles; results from the articles presenting more complete data that could be used in the meta-analysis from each study were included[13,15].

Table 1 shows the characteristics of the 38 included studies. Six studies considered populations from Europe, 26 studies from the United States, five from Australia, and one from New Zealand. One study represented secondary cohort analyses of the MOTHER trial, a randomized controlled trial comparing the efficacy of methadone and buprenorphine in the United States, Canada and Europe[15]. Thirty-six studies were cohort studies and two were case-control studies. The assessment tool used to evaluate NAS varied among studies, with most using a modified Finnegan Neonatal Abstinence Score. The NAS outcome was usually defined as requiring pharmacologic treatment, but in some studies was based on criteria with the Finnegan scale (e.g., at least two successive scores ≥8) or on administrative codes (e.g., International Statistical Classification of Diseases, ICD). The incidence of pharmacologically treated NAS was reported in 34 papers including 6946 infants, and varied from 13% to 95%.

The risk of bias assessment indicated that most studies performed well for sample selection and exposure measurement but poorly for comparability, while quality of outcome measurement was variable. Comparability was poor because only three studies controlled for potential confounders of the relationship between GA and NAS[15,27,28]; most studies were not specifically designed to evaluate this relationship. Additionally, six studies controlled for OAT dose, a potential mediator of the relationship between GA and NAS, biasing the estimate of the association[27]. Eleven studies scored the maximum of two scores in the outcome measurement category, but the remaining 27 studies did not comment on the method of assessing NAS and/or for how many days infants were evaluated.

Association between GA and NAS

Of the 38 studies included in this review, four included only qualitative results (i.e., whether a statistically significant association was observed, but neither an effect measure nor the numbers from which an effect estimate could be calculated); all reported no significant relationship between GA at delivery and initiation of treatment for NAS[29-32]. Three additional studies reported data on the relationship between GA and NAS that could not be converted to the effect estimates considered for the meta-analyses. The first study found no difference in the median GA between infants treated for NAS and infants not treated[52]; the second found no significant association between GA and measures of NAS severity[53]; and the third found that the percentage of newborns treated for NAS was not significantly different between early term and full/late term cohorts[54].

Results from the meta-analysis are shown in Table 2 and the forest plots in Figure 2. Pooled across 15 studies, the mean GA in infants with NAS was 0.62 weeks higher than in infants without (95% CI: 0.08 – 1.16). The odds of developing NAS were estimated to increase by 3% per gestational week at delivery using data from nine studies (OR 1.03, 95% CI: 0.997 – 1.06). The pooled OR for the association between preterm birth and NAS from 17 studies was estimated to be 0.87 (95% CI: 0.63 – 1.21). Because the effect estimates varied markedly among the studies, as can be seen in the forest plots and quantified with I^2 ranging from 84.2% to 90.7%, the pooled estimates should be interpreted with caution.

Pre-specified subgroup analyses examined the impact of excluding infants with GA<34 weeks, NAS outcome definition, rates of maternal methadone use, and Caesarean birth rates (Table 2). Some between-group differences were significant; for example, results in the subgroup of studies that used an outcome definition of NAS requiring treatment tended to suggest that NAS increases with GA, but studies that used an outcome definition not specifically stating that pharmacologic treatment was used showed pooled effect estimates that were null or estimated an inverse association be-

Table 1. Characteristics of included studies

First Author, Year	Number of Infants	Location	Study Period	OAT Type (%)	Other Opioids (%)	NAS Assessment; NAS Outcome Definition	Gestational Age (Weeks)	Confounding*
O'Brien, 2002	21	Sydney, Australia Single hospital	1999-2000	Methadone: 85.7	47.6	Finnegan scale; NAS requiring treatment	38 (mean) 36-41 (range)	Not controlled
Kuschel, 2004	25	Auckland, NZ Single hospital	1999-2001	Methadone: 100	5	Modified Finnegan scale; NAS requiring treatment	38 (median) 35-41 (range)	Not controlled
O'Brien, 2004	40	Sydney, Australia Single hospital	2000-2002	Methadone: 87.5	52.5	Modified Finnegan scale; NAS requiring treatment	38.4 (mean) 35-42 (range)	Not controlled
Scully, 2004	114	Dublin, Ireland Single hospital	1999-2000	Methadone: 75	Not reported	NAS assessment tool not reported; NAS diagnosis	38.5 (mean) 17-43 (range)	Not controlled
Burns, 2007	2941	New South Wales Australia state data	1992-2002	Methadone: 100	Not reported	Assessment scale not reported; NAS diagnosis	Not reported	Not controlled
Ebner, 2007	53	Vienna, Austria Single hospital	Not reported	Methadone: 41.5 Buprenorphine: 26.4 Slow-release oral morphine: 32.1	None	Modified Finnegan scale; NAS requiring treatment	38.6 (mean) 34-42 (range)	Not controlled
Jansson, 2007	50	Baltimore, US Single hospital	2002-2004	Methadone: 100	Not reported	Modified Finnegan scale, NAS requiring treatment	39.6 (mean) 1.3 (SD) 37 (minimum)	Not controlled
Dryden, 2009	444	Glasgow, UK Single hospital	2004-2006	Methadone: 100	Heroin: 51.1	Modified Lipitz Tool; NAS requiring treatment	38 (median), 37-40 (IQR)	Not controlled
Velez, 2009	77	Baltimore, US Single hospital	2002-2007	Methadone: 100	Not reported	Modified Finnegan scale; NAS requiring treatment	39.6 (mean) 1.2 (SD) 36.6-41.1 (range)	Not controlled
Holbrook, 2010	308	Philadelphia, US Single hospital	2005-2009	Methadone: 100	15	Modified Finnegan scale; NAS requiring treatment	37.7 (mean) 2.8 (SD)	Not controlled
Jansson, 2010	64	Baltimore, US Single hospital	2006-2008	Methadone: 100	Not reported	Modified Finnegan scale; NAS requiring treatment	39.2 (mean) 1.2 (SD) 37 (minimum)	Not controlled
Liu, 2010	232	Sydney, Australia Two hospitals	2000-2006	Methadone: 100	Not reported	Finnegan scale; NAS requiring treatment	37.9 (mean)	MD not controlled; OR adjusted for mode of delivery, maternal methadone dose
Seligman, 2010	388	Philadelphia, US Single hospital	1996-2006	Methadone: 100	23	Finnegan scale; NAS requiring treatment	37.7 (mean) 2.2 (SD)	Adjusted for tobacco, opiate abuse, cocaine use, benzodiazepine use at delivery
Cleary, 2011	618	Dublin, Ireland Single hospital	2000-2007	Methadone: 100	31.1	Modified Finnegan scale; NAS diagnosis	Not reported	Adjusted for methadone dose at delivery

First Author, Year	Number of Infants	Location	Study Period	OAT Type (%)	Other Opioids (%)	NAS Assessment; NAS Outcome Definition	Gestational Age (Weeks)	Confounding*
Kaltenbach, 2012/ Unger, 2011**	129	US, Canada, Europe Multiple clinics	2005-2008	Methadone: 55.7 Buprenorphine: 44.3	8	Modified Finnegan scale; NAS requiring treatment	38.4 (mean)	Adjusted for birthweight, tobacco use, anxiolytics, SSRIs, mode of delivery, maternal weight, OAT dose and duration
Cleary, 2012	114	Dublin, Ireland Two hospitals	2009-2010	Methadone: 100	36.4	Modified Finnegan scale; NAS requiring treatment	39.2 (median) 32.9-41.9 (range)	Adjusted for methadone dose, opiates, benzodiazepines, cocaine
Wachman, 2013	86	Massachusetts and Maine, US Four hospitals	2011-2012	Methadone: 55.7 Buprenorphine: 44.3	Not reported	Modified Finnegan scale; NAS requiring treatment	Not reported	Not controlled
Parlier, 2014	96	North Carolina, US Single hospital	2010-2012	Methadone: 61.5 Buprenorphine: 9.4 Buprenorphine/ Naloxone: 3.1	26	NAS assessment tool not reported; NAS diagnosis	Not reported	Not controlled
Liu, 2015	120	Florida, US Two hospitals	2003-2010	Methadone: 100	Not reported	Modified Finnegan scale; NAS requiring treatment	37.5 (mean) 2.5 (SD)	MD not controlled; OR per week GA adjusted for methadone dose; OR for preterm not controlled
McCarthy, 2015	62	California, US Eight hospitals	2008-2013	Methadone: 100	Not reported	Finnegan scale; NAS requiring treatment	38.2 (mean) 4.9 (SD) 23-42 (range)	Not controlled
Ruwanpathirana, 2015	909	New South Wales, Australia Multiple hospitals	2004, 2007	Methadone: 42.5 Buprenorphine: 3.6	17.5	Modified Finnegan scale; NAS requiring treatment	37.7 (mean)	Adjusted for amphetamine-type stimulant, cannabis, breastfeeding, polydrug use
Allocco, 2016	94	Boston, US Single hospital	2006-2010	Methadone: 100	41.5	Modified Finnegan scale; NAS requiring treatment	Preterm: 35 (median), 33-36 (IQR) Term: 39 (median), 38-40 (IQR)	Not controlled
Gibson, 2017	403	Cleveland, US Single hospital	2000-2014	Methadone: 57 Buprenorphine: 9	34	Modified Finnegan scale; NAS requiring treatment	38 (median) 34-41 (range)	Not controlled
Isemann, 2017	143	Cincinnati, US Single hospital	2013-2015	Methadone: 32.9 Buprenorphine: 21.7	31	Modified Finnegan scale; NAS requiring treatment	38 (median) 37, 39 (IQR) 34 (minimum)	Not controlled
Lemon, 2018**	716	Pittsburgh, US Single hospital	2013-2015	Methadone: 55.7 Buprenorphine: 43	Not reported	Finnegan scale; NAS requiring treatment	38 (mean) 2.8 (SD)	

First Author, Year	Number of Infants	Location	Study Period	OAT Type (%)	Other Opioids (%)	NAS Assessment; NAS Outcome Definition	Gestational Age (Weeks)	Confounding*
Nguyen, 2018	26	West Virginia, US Single hospital	2016-2017	Buprneorphine/ Naloxone: 100	12	NAS assessment scale not reported; NAS requiring treatment	37.4 (mean) 3.1 (SD)	Not controlled
Bakhireva, 2019	42	Albuquerque, US Multiple prenatal clinics	2013-2013	Methadone: 40.5 Buprenorphine: 54.5 Methadone + buprenorphine: 4.2	54.8	Assessment scale not reported; NAS requiring treatment	38.7 (mean)	Not controlled
Oji-Mmuo, 2019	202	Pennsylvania, US Single hospital	2011-2016	Methadone: 47 Buprenorphine: 16	35	Modified Finnegan scale; NAS requiring treatment	39 (median) 38.0-39.6 (IQR) 37-42 (range)	Not controlled
Parikh, 2019	651	Baltimore, US Single hospital	2008-2017	Methadone: 53	Not reported	Modified Finnegan scale; NAS requiring treatment	38.1 (mean) 35-42 (range)	Race, methadone use, benzodiazepine use
Mullins, 2020	193	North Carolina, US Single centre	2014-2018	Buprenorphine: 56 Buprenorphine/ naloxone: 44	Not reported	Modified Finnegan scale; NAS requiring treatment	25 (minimum)	OAT type, prescriber, dose; year; hepatitis C
Rodriguez, 2020	25	Massachusetts, US Single institution	2015-2018	Methadone: 20 Buprenorphine: 56	Not reported	Modified Finnegan scale; NAS requiring treatment	Not reported	Not controlled
Scott, 2020	204	US Midwest Single institution	2011-2017	Methadone: 24 Buprenorphine: 21	48	Modified Finnegan scale; NAS requiring treatment	37.2 (mean) 28-41 (range)	Not controlled
Towers, 2020	230	Knoxville, US Single clinic	2017-2018	Methadone or buprenorphine: 47 (Naltrexone: 53)	Not reported	Finnegan scale; NAS requiring treatment	38.0 (mean) 27.6-41.2 (range)	Not controlled
Leyenaar, 2021	7207	Texas, US Medicaid insured	2010-2014	Methadone: 13.2	Not reported	ICD-9-CM code 779.5 (drug withdrawal syndrome in newborn)	37.5 (mean) 22-43 (range)	Not controlled
Pourcyrous, 2021	150	Memphis, US Single hospital	2013-2017	Methadone: 24 Buprenorphine: 21	74	Modified Finnegan scale: NAS requiring treatment	39 (mean) 1 (SD) 37 (minimum)	Not controlled
Townsel, 2021	49	Connecticut, US Single institution	2007-2017	Not reported	Not reported	Finnegan scale; "severe NOWS"	37.0 (mean) 2.6 (SD) 34 (minimum)	Not controlled
Amiri, 2022	166	Buffalo, US Single hospital	2014-2020	Not reported	Not reported	Modified Finnegan scale: NAS requiring treatment	37.8 (mean) 1.1 (SD) 32 (minimum)	Not controlled
Rana, 2022	30	Memphis, US Single centre	2017-2019	Methadone: 17 Buprenorphine: 30	Not reported	Modified Finnegan scale: NAS requiring treatment	38.3 (mean) 1 (SD) 36 (minimum)	Not controlled

IQR, inter-quartile range; MD, mean difference; NAS, neonatal abstinence syndrome; OAT, opioid agonist therapy; OR, odds ratio.
*With respect to the data available to estimate the gestational age – NAS associations included in this systematic review.
**The two papers were based on the same population. Data from only the more complete report were included.

Table 2: Pooled estimates for the association between gestational age at delivery and neonatal abstinence syndrome from the meta-analyses.

Subgroup	No. studies	Mean difference (CI), GA, weeks, treated vs untreated		I^2	p-value*	No. studies	OR, per week GA (CI)		I^2	p-value*	No. studies	OR, preterm birth-NAS (CI)		I^2	p-value*
Overall	15	0.62	(0.08 – 1.16)	90.7	-	9	1.03	(1.00 – 1.06)	84.2	-	17	0.87	(0.63 – 1.21)	85.7	-
Exclusion based on gestational age					0.300					0.312					0.320
No	7	0.97	(-0.16 – 2.09)	95.4		6	1.05	(0.99 – 1.11)	83.7		14	0.83	(0.57 – 1.20)	88.3	
Yes	8	0.31	(-0.20 – 0.83)	63.1		3	1.15	(0.97 – 1.38)	88.3		3	1.09	(0.73 – 1.63)	0.0	
NAS definition					<0.001					0.016					0.019
All NAS	2	-0.30	(-0.43 – -0.17)	0.00		2	1.00	(0.97 – 1.03)	78.6		6	1.37	(1.08 – 1.74)	55.2	
Treated NAS	13	0.81	(0.22 – 1.39)	84.4		7	1.15	(1.03 – 1.27)	85.3		11	0.70	(0.42 – 1.16)	81.6	
Proportion treated with methadone					0.852					0.081					0.021
0%	1	0.90	(-2.42 – 4.22)	**		0	-				2	0.33	(0.19 – 0.59)	0.0	
20-88%	9	0.70	(-0.05 – 1.44)	88.6		5	1.04	(0.98 – 1.10)	82.1		5	0.80	(0.56 – 1.13)	18.5	
100%	3	1.06	(0.05 – 2.07)	70.8		3	1.27	(1.02 – 1.59)	85.9		8	0.95	(0.49 – 1.84)	89.5	
Proportion delivered by Caesarean					0.059					0.222					0.601
<30%	3	0.90	(-0.05 – 1.85)	64.8		4	1.01	(0.98 – 1.05)	61.2		6	1.04	(0.70 – 1.54)	72.3	
≥30%	5	-0.08	(-0.44 – 0.29)	60.5		5	1.13	(0.96 – 1.33)	86.4		8	0.87	(0.51 – 1.48)	60.2	

CI, 95% confidence interval; GA, gestational age; NAS, neonatal abstinence syndrome; OR, odds ratio
*P-value for differences between subgroups.
**Only one study within subgroup so heterogeneity not relevant.

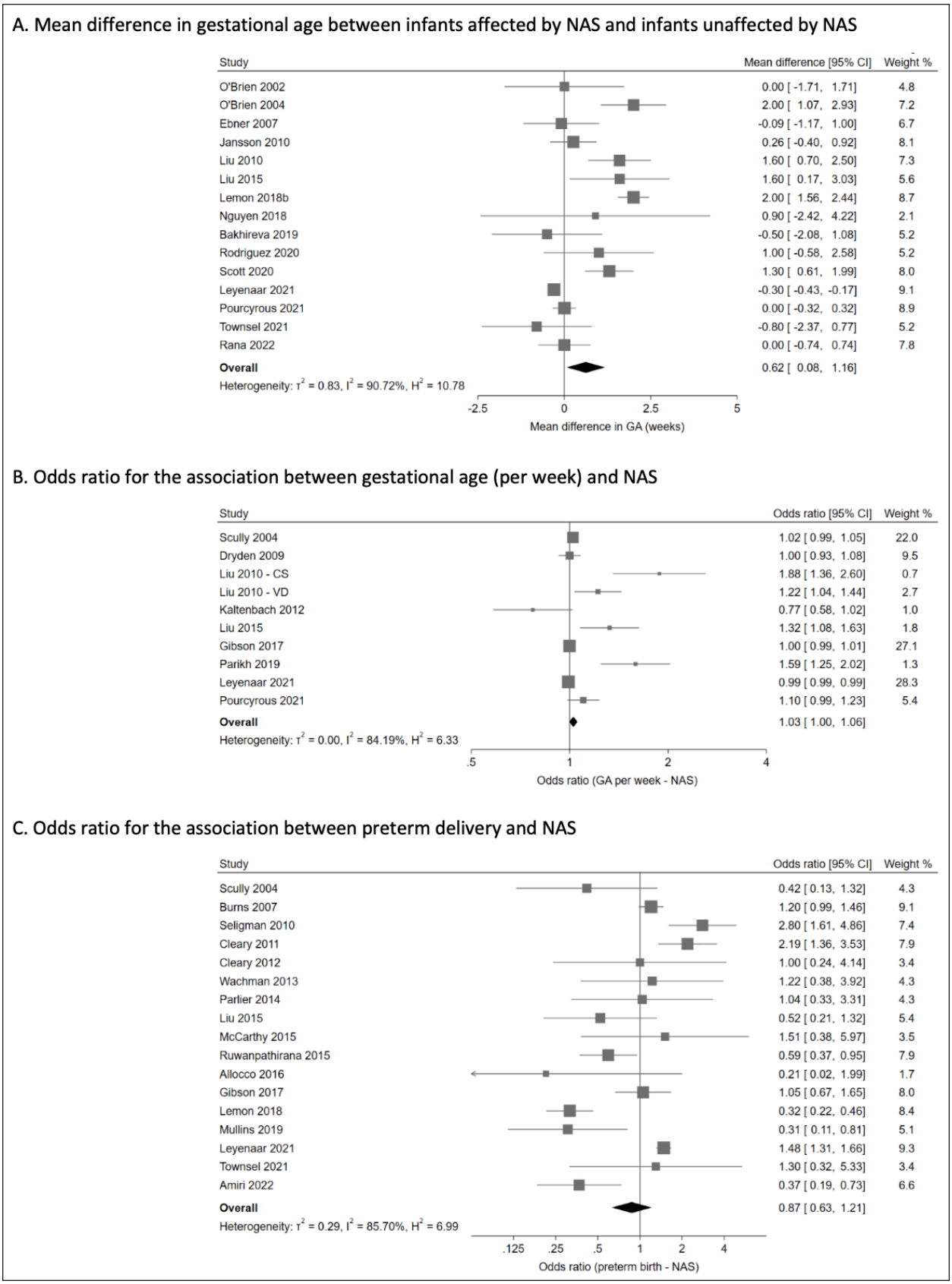

Figure 2. Forest plots for the association between gestational age and the development of NAS. CI, confidence interval; GA, gestational age; NAS, neonatal abstinence syndrome.

tween GA and NAS. In general, a high amount of heterogeneity persisted among the studies within each of the subgroups.

Discussion

The results of this systematic review and meta-analysis do not demonstrate a strong and consistent relationship between GA at delivery and development of NAS. While infants with NAS were born, on average, 0.67 weeks later than infants without NAS, the odds of developing NAS were only estimated to increase 3% per week GA. In addition, the OR for the association between preterm birth and NAS failed to show an association (OR 0.87, 95% CI: 0.63-1.21); however, dichotomizing GA into preterm versus term increases the probability of a type II error (missing a true association)[59]. All meta-analyses demonstrated significant heterogeneity among studies, which should be taken into account when interpreting these pooled estimates. Heterogeneity remained high in subgroup analyses suggesting that these factors do not explain the high heterogeneity observed in the overall association.

Two potential biological and clinical explanations could explain an apparent relationship between GA and an increased risk of NAS. The first is that as pregnancy progresses, increasing doses of OAT are often required to prevent withdrawal symptoms[3]. Pregnancy alters methadone pharmacokinetics, with higher observed clearance later in gestation[60-62]. However, a systematic review and meta-analysis found no clear relationship between maternal methadone dose and the incidence and duration of NAS[63]; increased dose requirements likely do not explain the relationship between GA and NAS. A second explanation relates to changes in placental physiology that occur throughout pregnancy. The syncytiotrophoblast (in direct contact with maternal blood) thins throughout gestation, while its surface area increases[64] and diffusion distance decreases[65]; these changes to placental physiology impact the transport of methadone across the placenta. One study found that both the amount of methadone in fetal circulation and the fetal transfer rate of methadone was significantly lower in preterm compared to term placentas[66].

Strengths and limitations

This review included a large body of evidence spanning two decades and we were able to combine evidence across multiple studies to generate overall effect estimates. Furthermore, this study followed the recommended guidelines for reporting systematic reviews (PRISMA)[20] and meta-analyses of observational studies (MOOSE)[26].

However, this study had some limitations. We restricted studies to those published in English and, to increase the quality of the data included, reported in full-text and published in a peer-reviewed journal; these restrictions may have resulted in some data being excluded. The Newcastle-Ottawa Scale used to assess risk of bias of included studies has some limitations, such as potential over-emphasis on the community representativeness of the exposed cohort and lack of definition regarding important confounders[67]. We modified the Newcastle-Ottawa Scale to better evaluate the studies included in our review and to exclude items where no variability would be possible in this context (e.g., demonstration that NAS was not present at the start of the study), but these changes may have decreased the validity of the tool.

The most significant limitation affecting the validity of the pooled estimates derived in the meta-analysis is the high risk of bias in most of the studies included. Our risk of bias assessment showed that most of the included studies did not account for important confounders. Most studies were not specifically designed to evaluate the relationship between GA at delivery and NAS. Although these studies presented enough data to extract or derive effect estimates, only nine studies adjusted for covariates, of which six presented results adjusted for OAT dose that was a potential mediator. Additionally, a majority of studies either did not provide specific details on the NAS assessment tool used or for how long infants were monitored. In some of the included studies, it was noted that there was a policy of admitting all infants to a neonatal intensive care unit for monitoring or that observation by trained health care providers was conducted on the postnatal wards. While it can be assumed that a validated assessment instrument was used at an acceptable frequency in these settings, it would not be applied in a blinded fashion (i.e., GA would be known). Finally, the sensitivity of the Finnegan and modified Finnegan instruments may be inversely correlated with GA, which could induce a positive bias in the GA-NAS association.

Conclusion

A clear understanding of the relationship between GA and NAS is needed to help guide obstetrical management of women receiving OAT. While the data included in this review do not demonstrate a strong and consistent relationship between GA and NAS, this conclusion is weakened by poor study quality and significant study heterogeneity. Further high-quality research designed to specifically address this question is needed to guide recommendations for optimal management.

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Appendix S1

Embase and Medline search strategies for the systematic search of the literature related to gestational age at delivery and neonatal abstinence syndrome

Embase Search Strategy

['neonatal abstinence syndrome'/exp OR 'neonatal abstinence syndrome':ti,ab OR nas:ti,ab OR 'neonatal opioid withdrawal':ti,ab OR 'neonatal withdrawal':ti,ab OR 'neonatal opiate withdrawal':ti,ab] AND ['gestational age'/exp OR 'gestational age':ti,ab OR 'prematurity'/exp OR 'postmaturity'/exp OR 'prolonged pregnancy'/exp OR 'term birth'/exp OR ((birth OR pregnancy OR gestational OR infant OR baby) NEAR/2 term):ti,ab) OR ((prematu* OR preterm OR postmatu* OR postterm OR 'post-term') NEAR/2 (birth OR pregnancy OR infant OR baby):ti,ab) OR 'prolonged pregnancy':ti,ab]

Medline Search Strategy

((((((((((((((("gestational age"[MeSH Terms]) OR "gestational age"[Title/Abstract]) OR "premature birth"[MeSH Terms]) OR "infant, premature"[MeSH Terms]) OR "term birth"[MeSH Terms]) OR "infant, postmature"[MeSH Terms]) OR "pregnancy, prolonged"[MeSH Terms]) OR (prematur* [Title/Abstract] AND (birth[Title/Abstract] OR infant[Title/Abstract] OR baby) AND Title/Abstract)) OR (preterm[Title/Abstract] AND (birth[Title/Abstract] OR infant[Title/Abstract] OR baby) AND Title/Abstract)) OR (term[Title/Abstract] AND (birth[Title/Abstract] OR pregnancy[Title/Abstract] OR infant[Title/Abstract] OR baby) AND Title/Abstract)) OR "gestational term"[Title/Abstract]) OR (postmatur*[Title/Abstract] AND (birth[Title/Abstract] OR pregnancy[Title/Abstract] OR infant[Title/Abstract] OR baby) AND Title/Abstract)) OR (postterm[Title/Abstract] AND (birth[Title/Abstract] OR pregnancy[Title/Abstract] OR infant[Title/Abstract] OR baby) AND Title/Abstract)) OR ("post¬term"[Title/Abstract] AND (birth[Title/Abstract] OR pregnancy[Title/Abstract] OR infant[Title/Abstract] OR baby) AND Title/Abstract)) OR "prolonged pregnancy"[Title/Abstract])) AND (((((((("neonatal abstinence syndrome"[MeSH Terms]) OR "neonatal abstinence syndrome"[Title/Abstract]) OR NAS[Title/Abstract]) OR "neonatal opioid withdrawal" [Title/Abstract]) OR "neonatal withdrawal"[Title/Abstract]) OR "neonatal opiate withdrawal" [Title/Abstract])))

Appendix S2

Modified Newcastle-Ottawa Quality Assessment Scale for Cohort Studies used to assess risk of bias

Selection
S1) Representativeness of the exposed cohort A - truly representative* B - somewhat representative* C - selected group of users D - no description of derivation of cohort
S2) Selection of non-exposed cohort A - drawn from same community as exposed* B - drawn from a different sources C - no description
S3) Bias due to missing data A - no or only small # participants with missing data* B - adjustment techniques used that likely correct for the presence of selection biases* C - due to missing data, <90% of participants included in final analysis D - no statement
Total Selection Stars
Exposure
E1) Ascertainment of exposure A - secure record* B - structured interview* C - written self-report D - no description
Total Exposure Stars
Comparability
C1) Comparability of cohorts on basis of design/analysis A - study controls for tobacco, SSRIs, benzodiazepine, cannabis* B - study controls for OAT dose and/or duration, birthweight, maternal weight, mode of delivery, breast feeding, Hepatitis C infection, other substances (such as opiates, cocaine)*
C2) Study does not inappropriately control for potential mediators A - no inappropriate control for mediators* B - inappropriate control for mediators
Total Comparability Stars
Outcome
O1) Assessment of outcome (validated instrument used at an acceptable frequency) A - yes* B - no
O2) Was follow-up long enough? A - yes* B - no
Total Outcome Stars

Modified from: Wells G, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2013. Available at: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

The following modifications were performed:

- Item S3 (original NOS): "Ascertainment of exposure" was separated out to be included under "Exposure" because it has nothing to do with selection.
- Item S3 (modified NOS): "Bias due to missing data" was listed in the original NOS as item O3 "Adequacy of follow-up of cohorts". It has been included here under "Selection" because loss to follow-up bias is a form of selection bias.

- Item S4 (original NOS): "Demonstration that outcome of interest was not present at start of study" was omitted because it would have yielded a "yes" for all eligible studies based on the nature of the topic only, not by design.
- Item C1: Factors that were controlled for in eligible articles were considered because of their effect on risk of NAS.
- Item O1: Using a validated instrument at an acceptable frequency was most relevant for assessing validity of the outcome assessment.