Psychological Medicine

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Assessing risk of neurodevelopmental disorders after birth with oxytocin: a systematic review and meta-analysis

Nicole N. Lønfeldt[1,2], Frank C. Verhulst[1,3], Katrine Strandberg-Larsen[2], Kerstin J. Plessen[1,4] and Eli R. Lebowitz[5]

[1]Child and Adolescent Mental Health Services, Capital Region of Denmark, Copenhagen, Denmark; [2]Section for Epidemiology, Department of Public Health, University of Copenhagen, Copenhagen, Denmark; [3]Department of Child and Adolescent Psychiatry/Psychology, Erasmus University Medical Center, Rotterdam, The Netherlands; [4]Division Child Psychiatry, Department of Psychiatry, Lausanne University Hospital, Lausanne, Switzerland and [5]Yale Child Study Center, New Haven, Connecticut, USA

Review Article

Cite this article: Lønfeldt NN, Verhulst FC, Strandberg-Larsen K, Plessen KJ, Lebowitz ER (2019). Assessing risk of neurodevelopmental disorders after birth with oxytocin: a systematic review and meta-analysis. *Psychological Medicine* **49**, 881–890. https://doi.org/10.1017/S0033291718003021

Received: 7 June 2018
Revised: 19 September 2018
Accepted: 21 September 2018
First published online: 16 November 2018

Key words:
ADHD; adolescents; ASD; children; oxytocin; perinatal risk factors

Author for correspondence:
Nicole N. Lønfeldt, E-mail: nicole.nadine.loenfeldt@regionh.dk

Abstract

Experts have raised concerns that oxytocin for labor induction and augmentation may have detrimental effects on the neurodevelopment of children. To investigate whether there is the reason for concern, we reviewed and evaluated the available evidence by searching databases with no language or date restrictions up to 9 September 2018. We included English-language studies reporting results on the association between perinatal oxytocin exposure and any cognitive impairment, psychiatric symptoms or disorders in childhood. We assessed the quality of studies using the Newcastle–Ottawa Quality Assessment Scales. Independent risk estimates were pooled using random-effects meta-analyses when at least two independent datasets provided data on the same symptom or disorder. Otherwise, we provided narrative summaries. Two studies examined cognitive impairment, one examined problem behavior, three examined attention-deficit/hyperactivity disorder (ADHD) and seven focused on autism spectrum disorders (ASD). We provided narrative summaries of the studies on cognitive impairment. For ADHD, the pooled risk estimate was 1.17; 95% confidence interval (CI) 0.77–1.78, based on a pooled sample size of 5 47 278 offspring. For ASD, the pooled risk estimate was 1.10; 95% CI 1.04–1.17, based on 8 87 470 offspring. Conclusions that perinatal oxytocin increases the risks of neurodevelopmental problems are premature. Observational studies of low to high quality comprise the evidence-base, and confounding, especially by the genetic or environmental vulnerability, remains an issue. Current evidence is insufficient to justify modifying obstetric guidelines for the use of oxytocin, which state that it should only be used when clinically indicated.

Introduction

Experts have raised concerns about the potential neurodevelopmental risks of perinatal synthetic oxytocin for offspring. Many women receive synthetic oxytocin for labor induction and/or augmentation. Induction is involved in approximately 25% of all term births in developed countries (World Health Organization, 2011), and nearly 50% of induced births use synthetic oxytocin (Goffinet *et al.*, 2003). Synthetic oxytocin is also the first-choice agent for labor augmentation (World Health Organization, 2014). Estimates of augmentation are as high as 55 and 57% of births in Sweden and the USA (Declercq *et al.*, 2007; Selin, 2009). Overmedicalization of labor is a global issue, with coverage estimates for oxytocin-augmentation as high as 79% in some countries (Miller, 2016). Experts on autism spectrum disorder (ASD) proposed that synthetic oxytocin for induction and augmentation could enter fetal circulation and deactivate oxytocin receptors, increasing the risk of psychiatric disorders, such as ASD (Hollander *et al.*, 1998; Wahl, 2004). Neuroscientists stated this hypothesis more boldly, asserting that oxytocin used for induction *causes* disruption in the oxytocinergic system of infants, triggering the development of ASD in children with genetic and epigenetic vulnerabilities (Gialloreti *et al.*, 2014). Oxytocin experts within obstetrics and psychiatry have also suggested that synthetic oxytocin may increase the risk of other neurodevelopmental disorders, such as attention-deficit/hyperactivity disorder (ADHD; Bell *et al.*, 2014) and general problems related to social behavior and the ability to cope with stress (Buckley, 2015; Lefevre and Sirigu, 2016).

These hypotheses are based on the important roles endogenous oxytocin plays in the regulation of stress, anxiety, and social cognition and behaviors in humans (Landgraf and Neumann, 2004) and findings from animal studies showing that neonatal exposure to synthetic oxytocin leads to changes in social behavior and the oxytocinergic system in adulthood (Bales and Carter, 2003; Jia *et al.*, 2008*a*, 2008*b*; Lefevre and Sirigu, 2016). Disruptions in the

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oxytocinergic system have been implicated in a range of psychiatric disorders (Cochran *et al.*, 2013), such as ASD (Gregory *et al.*, 2009) and ADHD (Sasaki *et al.*, 2015). Genetic and epigenetic studies consistently show associations between the oxytocin receptor gene (OXTR) and ASD (Gregory *et al.*, 2009). Genetic studies have not supported a role of the OXTR in ADHD (Park *et al.*, 2010; Kalyoncu *et al.*, 2017), but youth with ADHD have lower serum levels of oxytocin than neurotypical controls (Sasaki *et al.*, 2015).

It is unclear whether perinatal exposure to synthetic oxytocin has deleterious effects in humans. The widespread use of synthetic oxytocin and its importance to obstetric practice makes it imperative to investigate this question by reviewing and analyzing all accessible data. No systematic reviews of the evidence linking perinatal oxytocin to neurodevelopmental outcomes in offspring have been published. Thus, we aimed to provide a comprehensive overview of research on neurodevelopmental outcomes in offspring related to the obstetric use of oxytocin that systematically and critically evaluates the currently available evidence. We sought to answer the following question: Is perinatal synthetic oxytocin associated with increased neurodevelopmental problems in human offspring? If perinatal synthetic oxytocin increases the risk of neurodevelopmental problems, this knowledge may incentivize the more judicious use of oxytocin in obstetrics. Null findings, although unable to rule out an association, are just as important to disseminate as significant findings, especially to calm concerns after the publication of several papers linking, at least putatively, perinatal synthetic oxytocin use to neurodevelopmental problems in offspring (Wahl, 2004; Plothe, 2009; Gialloreti *et al.*, 2014).

Methods

We conducted a systematic literature search according to MOOSE Guidelines for Meta-Analyses and Systematic Reviews of Observational Studies (Stroup *et al.*, 2000).

Search strategy

We searched the databases Web of Science, Medline, and EMBASE up to 25 August 2017, for studies on the administration of synthetic oxytocin in the perinatal period without language or date restrictions. For EMBASE, we used the terms 'Pitocin®' or 'Syntocinon®' or 'synthetic oxytocin' and 'labour/labor' or 'birth' or 'perinatal' or 'prenatal' or 'obstetric'. In Web of Science, we combined the search terms used in the EMBASE search with 'delivery' and 'augment*' or 'induc*'. For MEDLINE, we used the EMBASE search terms in addition to 'antepartum'. We also manually searched the reference lists of papers that matched the eligibility criteria and one review article (Bell *et al.*, 2014). We contacted authors of included studies to request any unpublished studies and results. As of 9 September 2018, two new relevant studies emerged.

Inclusion and exclusion criteria

To be included in the review, publications had to meet the following criteria: (1) describe original research, (2) report results on the association between perinatal synthetic oxytocin exposure and any childhood neurodevelopmental outcome, and (3) written in English. Neurodevelopmental outcomes include all disorders within the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5; American Psychiatric Association, 2013) or F-diagnoses in the *International Statistical Classification of Diseases and Related Health Problems* (ICD-10; World Health Organization, 1992) and supplementary somatic diagnoses for delayed development (R41.8, R62, R62.0, R62.9) and dimensional measures of psychiatric symptom severity. We included studies that examined pharmacological augmentation even if studies did not explicitly report synthetic oxytocin, as it is the primary pharmacological method for augmentation. We excluded studies that described pharmacological induction without specifying the use of oxytocin, as prostaglandins are the recommended first-choice pharmacological preparation for certain indications of induction (World Health Organization, 2011). In cases of publications using the same sample and outcomes, we retained publications with the earliest publication date and excluded later publications.

To be included in a meta-analysis, two or more studies had to have the same outcome. Equivalent ICD and DSM diagnoses with different names (e.g. ADHD and disturbances of hyperactivity and attention) were regarded as the same outcome. Included studies also had to report a risk estimate or data that would enable us to calculate a risk estimate (e.g. frequencies or percentages).

Study selection procedure

First, the first author imported search results into Endnote X8 and removed duplicates. Then, she reviewed primary titles and abstracts to select articles for further scrutiny. For the retained articles, the first author obtained the full text and imported the references into Review Manager 5.3 (The Cochrane Collaboration, 2014). Next, the first and second authors independently read full texts to determine eligibility. In cases of disagreement, the first and second authors discussed the specific articles to reach consensus. If consensus could not be reached, the last author broke the tie.

Data collection

We extracted the following information from included studies: author, year of publication, study design, country in which the study was conducted, mode of oxytocin administration, level of measurement for exposure, outcome criteria, comparison group type, sample and group size, percentage of females, children's ages at follow-up, risk estimates [i.e. odds ratios, risk ratios, rate ratios, and standard errors (S.E.) or confidence interval (CI), when S.E. not available], and control variables (Table 1).

Quality assessment

We assessed study quality using the Newcastle-Ottawa Quality Assessment Scales (NOS) for case-control and cohort studies (Wells *et al.*, 2010). NOS ratings informed our interpretations of the sensitivity analyses. We made modifications to the NOS based in part by issues raised about the scale (Stang, 2010). The first and second authors independently rated studies within three categories: *selection, comparability,* and *exposure* (for case-control studies) or *outcome* (for cohort studies). The last author decided the final score on any discrepant scores. Total scores could range from 0 to 11. We grouped the scores into intervals of low (0–3), moderate (4–7) and high (8–11) study quality. The *selection* section consists of four items (Table 2), for which studies could receive one star per item.

For groups to be judged as *comparable* within studies, analyses needed to be adequately adjusted: either confounding variables

https://doi.org/10.1017/S0033291718003021 Published online by Cambridge University Press

Table 1. Characteristics of studies

Author, Year	Study design	Country	Outcome criteria	Comparator	Exp. meas. level	Mode of admin.	Total N	Cases/ exposed n	Controls/ nonexposed n	Female % cases/ exposed	Female % controls/ nonexposed	Age, years	NOS
Cognitive functioning													
Freedman *et al.* (2015)	Cohort	USA	Ravens Matrices	Non-exposed	Di	OT-ind	265	34	231	not reported	not reported	5, 9–11	6*
			Peabody Picture Vocabulary Test										6
Gonzalez-Valenzuela *et al.* (2014)	Cohort	ES	Battelle Developmental Inventory	Non-exposed	Di	OT-ind or aug	148	84	64	50%	45.3%	5	3
Child problem behavior													
Guastella *et al.* (2018)	Cohort	AU	CBCL	Non-exposed	2 and 3 cat and continuous	OT-ind and/or aug	1350–2070	148–462	906–1359	45.3%	50.5%	5, 8, 10, 14, 17	7
ADHD													
Henriksen *et al.* (2015)	Cohort	DK	ICD-10 or prescription	Non-exposed	Di	aug	5 46 146	1 39 473	4 06 673	46.4%	49.5%	0–8	8
Kurth and Haussmann (2011)	CC	USA & CA	DSM-IV-TR	Non-affected sibling or non-affected, unrelated	Di	OT-ind or aug	172	88	84	35.2%	47.7%	3–25	5*
Silva *et al.* (2014)	CC	AU	DSM-IV/ICD-10	Non-exposed	Di	OT-ind	960	324	636	19.4%	20.9%	0–10	7
						OT-aug	450	120	330	17.5%	23%		
ASD													
Al-Ayadhi (2005)	CC	SA	DSM-IV	'Healthy' children	Di	OT-ind	154	77	77	6.2%	6.2%	3.5–14	0
Gale *et al.* (2003)	CC	USA	DSM-IV/ADOS	Boys with and without intellectual disability	Di	OT-ind	66	41	25	0%	0%	6–16	3
Gregory *et al.* (2013)	Cohort	USA	DSM-IV	Non-exposed	Di	aug	3 16 290	88 796	2 27 494	48.8%	49.1%	7–18	8*
Guastella *et al.* (2018)	Cohort	AU	DSM-IV	Non-exposed	Di	OT-ind or aug	2228	761	1467	45.3%	50.5%	17	5
Herrera *et al.* (2017)	CC	USA	DSM-IV-TR	Children without ASD	4 dose cat.	OT-ind or aug	11 487	2294	9193	20.2%	20.2%	2–16	9
Smallwood *et al.* (2016)	CC	USA	DSM-IV-TR	Neurotypical children	Di	OT-aug	205	101	104	10%	10%	2–25	1*
Weisman *et al.* (2015)	Cohort	DK	ICD-10	Non-exposed	Di	OT-ind	5 57 040	18 374	5 38 666	47.8%	48.6%	3–12	11
					Di	OT-aug		1 49 246	4 07 794	46.5%	49.4%		11*

ADHD, attention deficit/hyperactivity disorder; admin, administration; ASD, autism spectrum disorder; aug, labor augmentation; cat., category; CBCL, Child Behavior Checklist; CC, case control; Di, dichotomous; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; DSM-IV-TR, DSM-IV, Text Revision; Exp. Meas., exposure measurement; ICD-10, International Classification of Diseases 10th revision; ind, labor induction; OT, oxytocin; NOS, Newcastle-Ottawa Assessment Scales for case-control and cohort studies. Two sample sizes reported for one study indicate the different samples sizes for labor inductions and augmentations. Age is in years at follow-up.

* = statistically significant harmful association.

Table 2. Modified Newcastle–Ottawa Quality Assessment Scale for case-control and cohort studies

Author, Year	Selection					Comparability				Exposure			
	Case def. adequacy	Rep. of cases	Select. of controls	Def. of controls	Subtotal	Maternal psych. Hx	Maternal SES	Indications for OT	Subtotal	Ascert of exp	Same ascert.	Non-resp. rate	Subtotal
Al-Ayadhi (2005)	/	/	/	/	0	/	/	/	0	/	/	/	0
Gale *et al.* (2003)	*	/	/	*	2	/	/	/	0	/	*	/	1
Herrera *et al.* (2017)	*	*	*	*	4	/	*	*	2	*	*	*	3
Kurth and Haussmann (2011)	*	/	*	*	3	/	/	/	0	*	*	/	2
Silva *et al.* (2014)	*	*	*	/	3	/	*	/	1	*	*	*	3
Smallwood *et al.* (2016)	/	/	/	*	1	/	/	/	0	/	/	/	0
For cohort studies													
	Exposed cohort rep	Select. of non-exposed	Ascert. of exp.	Outcome not present at study start	Subtotal	Maternal psych. Hx	Maternal SES	Indications for OT	Subtotal	Assess. of outcome	Adequate length of FU	FU adequate	Subtotal
Freedman *et al.* (2015)	*	*	*	/	3	/	*	/	1	*	*	/	2
Gonzalez-Valenzuela *et al.* (2014)	/	*	/	/	1	/	/	/	0	*	*	/	2
Gregory *et al.* (2013)	*	*	*	*	4	/	*	*	2	*	*	/	2
Guastella *et al.* (2018)	*	*	*	*	4	/	/	/	0	*	*	/	1
Henriksen *et al.* (2015)	*	*	*	*	4	/	*	*	2	*	/	*	2
Weisman *et al.* (2015)	*	*	*	*	4	**	*	*	4	*	*	*	3

Ascert., Ascertainment; Assess., Assessment; Def., definition; Exp, exposure; FU, follow-up period; Maternal psych. Hx, maternal history of psychiatric illness; Rep., representativeness; resp., response; Select., selection; SES, socioeconomic status.
Note: Adequate follow-up of cohorts ⩾80%.
* fulfilled criteria. / did not fulfill criteria.

had to be included in the statistical models or individuals had to be matched on the confounding variables. We decided on the specific criteria for comparability after identifying the studies to include in the review, as these criteria depend on the outcomes of individual studies. For comparability, studies could receive 0–4 stars. Studies could earn two stars if analyses adjusted for maternal psychiatric history. Studies could earn one more star if they controlled for socioeconomic status (i.e. income or maternal education). Studies could receive an additional star if they controlled for two or more other potential confounders: hypertensive disorders during pregnancy, preterm premature rupture of membranes, rhesus incompatibility, maternal diabetes, size for gestational age, length of labor, maternal BMI, maternal age, and maternal race, ethnicity or immigrant status.

For the final study quality criterion, studies could earn one star for each of the three items on *exposure or outcome*. We deemed follow-up of cohorts adequate if at least 80% of the cohort was included in the follow-up or if attrition was independent of exposure and outcome (Hartling *et al.*, 2012).

Statistical analysis

We conducted meta-analyses using Review Manager 5.3 (The Cochrane Collaboration, 2014). As ASD and ADHD are relatively rare outcomes, with 2 and 5% prevalence rates, we treated odds ratios, risk ratios (RR), and rate ratios as comparable estimates of the relative risk (Symons and Moore, 2002). We used adjusted risk estimates if studies reported these or we could obtain them from the authors. If not, we used the raw data available in the publication. Due to under-reporting and misclassification of induction and augmentation in medical records in many countries (Lain, 2012), we combined separate estimates for induction and augmentation from mutually exclusive samples. Otherwise, the augmentation estimates were entered first and exchanged with the induction estimates in analyses.

We used random effect models to estimate pooled RRs to account for heterogeneity (Shadish and Haddock, 2009). I^2 estimated the homogeneity of the RRs (Higgins *et al.*, 2003). A low amount of heterogeneity is associated with $I^2 \leqslant 25\%$, moderate heterogeneity begins at 50%, and a high amount starts at 75% (Higgins *et al.*, 2003). To test the robustness of our results and handle heterogeneity, we removed studies one at a time, re-ran the analysis each time, and sequentially removed the studies responsible for the greatest decrease in I^2 until I^2 was 25% or below (Patsopoulos *et al.*, 2008). When studies reported separate risk estimates for female and male offspring, we tested subgroup differences. Given the small number of studies, recommended tests of publication bias were not feasible (trim and fill, funnel plots).

Results

Our search in electronic databases yielded 2581 titles, and our manual search of bibliographies yielded 18 additional titles (Fig. 1). We excluded 152 duplicates and 2423 titles based on title or abstract. We reviewed 25 full-text articles for eligibility, of which 12 studies met inclusion criteria, with four different outcomes: cognitive functioning ($n = 2$), problem behavior ($n = 1$), ADHD ($n = 3$), and ASD ($n = 7$). Seven of the 12 authors we contacted responded. Two authors are preparing new data for publication, but no author made unpublished data available for this review. Three authors provided additional information on study characteristics (Table 1). Table 2 provides an overview of the quality assessments of the included studies.

Perinatal oxytocin and cognitive impairment

The earliest published study did not support an association between use of oxytocin and developmental delay (RR 1.46; 95% CI 0.79–2.71; Gonzalez-Valenzuela *et al.*, 2014). Risk estimates were significant for mothers under the age of 28 and over 35 years, in infants born after non-instrumental deliveries, and infants born without anesthesia. However, CIs were even wider for these estimates. A second study, which only investigated oxytocin exposure by means of induction, found that exposed children scored 0.45 (95% CI −2.12 to 1.23; $p = 0.60$) standard deviation units lower on a test of receptive vocabulary (IQ scores) and 0.14 (95% CI −0.26 to −0.03; $p = 0.02$) standard deviation units lower on a test of problem-solving ability (z-scores) than the children not exposed to induction with oxytocin (Freedman *et al.*, 2015).

Perinatal oxytocin and problem behavior

One study examined the relationship between oxytocin-induced and/or -augmented labor and parent-rated child behavior and emotional problems at five time points during childhood and adolescence (Guastella *et al.*, 2018). At age 10, the oxytocin-augmented group had a higher percentage of children with a Child Behavior Checklist (CBCL; Achenbach, 1991) T-score of 60 or above (23.3%) than the oxytocin-induced (17.8%) and no-oxytocin groups (16.4%). A Chi-squared test indicated a significant difference between groups ($p = 0.04$). However, oxytocin exposure was not a significant predictor of dichotomous or continuous CBCL scores at any age. Based on a subsample of 542 children, higher oxytocin dosage was associated with a slight increased risk of a CBCL score of 60 or above (OR 1.03, 95% CI 1.01–1.06).

Perinatal oxytocin and ADHD

Three studies, with a total of 5 47 278 participants, investigated the association between perinatal oxytocin and an ADHD diagnosis. The smallest study found that oxytocin-induction or augmentation posed a slight increased risk for ADHD (Kurth and Haussmann, 2011), whereas the remaining two studies showed no increased or decreased risk (Silva *et al.*, 2014; Henriksen *et al.*, 2015). Pooling the estimates of the three studies suggested that oxytocin-induction and/or –augmentation is not associated with ADHD in offspring (see Fig. 2). The pooled estimates remained effectively unchanged after replacing the partially adjusted estimate with the fully adjusted estimate of one study (Silva *et al.*, 2014), and subsequently replacing the estimate for oxytocin-induction with the oxytocin-augmentation estimate (results not shown; Silva *et al.*, 2014). Heterogeneity among the estimates was high, possibly due to methodological differences among the studies. Risk estimates from the first study were based on unadjusted analyses (Kurth and Haussmann, 2011), whereas the second and third studies reported adjusted risk estimates (Silva *et al.*, 2014; Henriksen *et al.*, 2015) The studies also differed in definitions of oxytocin exposure and ADHD, follow-up length, and female/male sample composition (Table 1).

Two studies (Kurth and Haussmann, 2011; Silva *et al.*, 2014) reported data for a subgroup analysis on sex. The separate estimates for females (RR 1.22; 95% CI 0.27–5.55) and males (RR 1.28–95% CI 0.67–2.44) and the difference between them ($p =$

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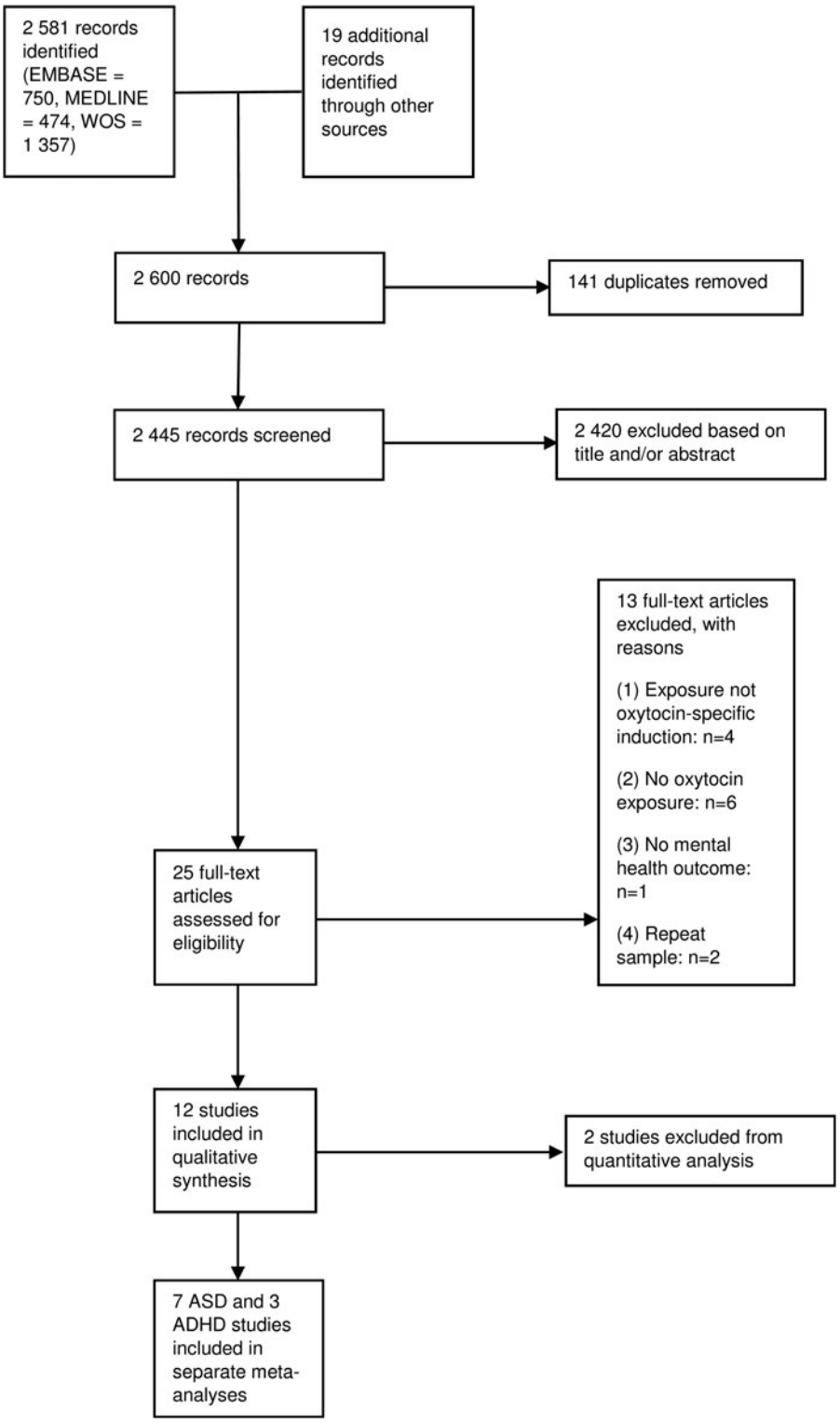

Fig. 1. Flowchart of study selection process.

0.96) were non-significant (see online Supplementary eFig. S1). Heterogeneity was high for both group estimates ($I^2 = 91\%$; $I^2 = 89\%$), which is likely due to the opposite directions of the estimates from the two studies. Replacing the estimate for oxytocin-induction with the oxytocin-augmentation estimate did not change results (results not shown).

In the sensitivity analysis, removing the first study (Kurth and Haussmann, 2011), removed the smallest study, moved the estimate closer to one (RR 0.98–95% CI 0.77–1.25), and reduced heterogeneity to a moderate amount ($I^2 = 40\%$). Due to the small number of studies, it was not possible to reduce heterogeneity below the threshold.

Perinatal oxytocin and ASD

Seven studies, with a total of 8 87 470 participants, investigated the association between perinatal oxytocin and ASD in children.

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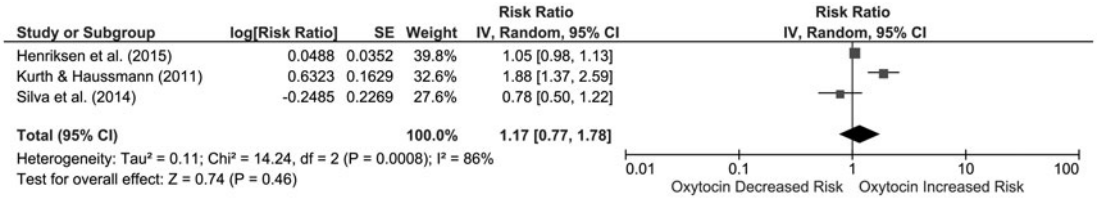

Fig. 2. Relationship between perinatal synthetic oxytocin use and risk of attention-deficit/hyperactivity disorder (ADHD) using a meta-analysis of comparative epidemiological studies. Data are presented as risk ratios (RRs). Squares indicate the RR estimates and whiskers their 95% confidence interval. The center of the diamond represents the pooled RR and the corners the 95% confidence interval. An RR greater than 1 indicates a higher risk of ADHD in those exposed to perinatal oxytocin.

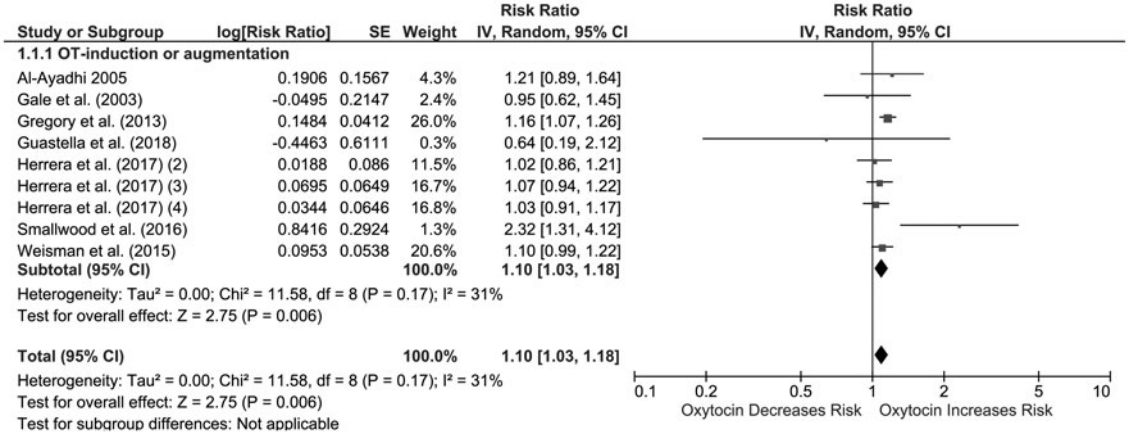

Fig. 3. Relationship between perinatal synthetic oxytocin use and risk of autism spectrum disorder (ASD) using a meta-analysis of comparative epidemiological studies. This analysis uses the estimate for labor augmentation from Weisman *et al.*, 2015. Data are presented as risk ratios (RRs). Squares indicate the RR estimates and whiskers their 95% confidence interval. The center of the diamond represents the pooled RR and the corners the 95% confidence interval. An RR greater than 1 indicates a higher risk of ASD in those exposed to perinatal oxytocin.

One study reported three separate risk estimates for three dosage categories (Herrera *et al.*, 2017). Another study reported separate risk estimates for oxytocin-induction and -augmentation, but the induction and augmentation groups were not mutually exclusive (Weisman *et al.*, 2015), which precluded including both estimates in the same meta-analysis. Using the estimate for induction (Weisman *et al.*, 2015), the pooled estimate was RR 1.08; 95% CI 1.00–1.18 (see online Supplementary eFig. S2). Heterogeneity among the estimates was significant, possibly stemming from definitions of oxytocin exposure. Using the estimate for augmentation instead of the induction estimate (Weisman *et al.*, 2015), did not change the point estimate (RR 1.10; 95% CI 1.04–1.17; see Fig. 3). Heterogeneity was reduced, but still just above threshold ($I^2 = 27\%$). Excluding one study (Smallwood *et al.*, 2016) eliminated heterogeneity ($I^2 = 0\%$) and provided a less biased estimate as it reduced inconsistency and removed a study with a quality score of one out of 11 (RR 1.10; 95% CI 1.05–1.16). Heterogeneity may have been reduced as the two largest studies defined oxytocin exposure similarly (Gregory *et al.*, 2013; Weisman *et al.*, 2015).

The subgroup analysis on sex, pooling five estimates for females and six for males from three and four studies, respectively (see online Supplementary eFig. S3; Gale *et al.*, 2003; Gregory *et al.*, 2013; Herrera *et al.*, 2017; Weisman *et al.*, 2015), suggested that the magnitude of risk did not significantly differ between the sexes ($p = 0.17$). The pooled estimate for females was RR 1.17–95% CI 1.05–1.30, with no indication of heterogeneity ($I^2 =$ 0%). However, the wide CI for the individual female estimates may account for the homogeneity among the estimates. The pooled estimate for male offspring was RR 1.07; 95% CI 1.00–1.15, with negligible heterogeneity ($I^2 = 23\%$).

Discussion

Several individual studies have concluded that oxytocin used to induce and augment labor increases the risk of specific psychiatric symptoms and disorders. Our systematic search of the literature revealed that few studies have examined associations between perinatal oxytocin use and neurodevelopmental outcomes in offspring. Outcomes include cognitive impairment, problem behavior, ADHD, and ASD diagnoses.

Current findings for cognitive impairment are inconclusive, as they were based on only two studies that used different scales to measure cognitive abilities. Furthermore, the quality of the two studies on cognitive impairment was low to moderate. The significant associations between perinatal oxytocin and child problem behavior (internalizing and externalizing) were small and came from a single study of moderate quality that included many statistical tests (Guastella *et al.*, 2018). For ADHD, three studies of moderate to high quality were identified, and the meta-analyses did not support an association between perinatal oxytocin and ADHD. Our finding is consistent with the results of a recent cohort study on the association between perinatal synthetic oxytocin use and dimensionally measured ADHD symptoms (Stokholm *et al.*, 2018). This cohort study was not included in our meta-analysis as it used a subsample of an included population-based study (Henriksen *et al.*, 2015). The lack of an

https://doi.org/10.1017/S0033291718003021 Published online by Cambridge University Press

association between perinatal synthetic oxytocin and ADHD is not surprising given the absence of a known link between ADHD and the oxytocinergic system. Studies have failed to find an association between oxytocin and ADHD, but they have supported oxytocin's role in symptoms marked by problems in social behavior (Gregory *et al.*, 2009; Sasaki *et al.*, 2015).

Our second set of meta-analyses found a marginal association between perinatal oxytocin and ASD in offspring. The quality of the ASD studies varied greatly. The two most influential studies were high-quality cohort studies: NOS scores of 8 and 11 (Gregory *et al.*, 2013; Weisman *et al.*, 2015). The studies adjusted for some risk factors for induction and augmentation, earning them quality points for comparability, but they did not adjust for all known risks for stimulated labor. Furthermore, one of the studies was unable to account for siblings within their sample (Gregory *et al.*, 2013). The other study calculated robust and appropriate-for-use-tests to account for siblings in the dataset (Weisman *et al.*, 2015), yet comparing discordant sibling pairs or better yet discordant cousins matched on parity, may produce more accurate results. Our marginal finding is consistent with a study that found that the association between labor induction by any means and autism disappeared when tested within siblings and in first-born children (Oberg *et al.*, 2016). Our finding also may be rendered non-significant in sibling comparison designs. Familial comparison designs control for confounding by genetic vulnerability and/or shared environmental factors, such as maternal stress during pregnancy (Weinstock, 2005). Indeed, any relationship between oxytocin-stimulated labor and ASD may be confounded by the genetic or environmental vulnerability. ASD is highly heritable, and a meta-analysis has demonstrated consistent associations between ASD and single-nucleotide polymorphisms on the oxytocin receptor gene (OXTR; Loparo and Waldman, 2015). Preliminary findings indicate that genetic vulnerability may also be inherited by other means. A study observed that a mother and a sibling of a child with ASD had a genomic deletion containing the OXTR; the child with ASD did not have this deletion, but did have increased methylation of OXTR (Gregory *et al.*, 2009). Hypermethylation is associated with decreased peripheral levels of oxytocin (Dadds *et al.*, 2014). Therefore, women with variations in the OXTR related to ASD may also produce less oxytocin, increasing their need for labor stimulation.

The current review has major strengths, such as a comprehensive search and large, pooled sample sizes in the meta-analyses, but it also has some limitations that should be considered when interpreting our findings. First, we cannot exclude the possibility of publication bias toward significant effects. Recommended methods (i.e. funnel plots, trim-and-fill) for assessing publication bias were not feasible with the small number of studies. One study had a problem with selective outcome reporting: They reported the existence of a non-significant estimate but did not report the actual risk estimate (Smallwood *et al.*, 2016). Second, the NOS is not perfect (Stang, 2010). We tried to improve the scale by increasing the number of points studies could receive for controlling for specific confounders and weighting maternal psychiatric history as a more important variable to adjust for than other potential confounders. Still, given the differences in labor induction and augmentation practices across countries, and even across different hospitals within the same country, different confounders may exist for different countries. Third, we excluded non-English-language studies for practical reasons. Our search only revealed one French study citation on the association between oxytocin-induced labor and developmental delay in psychomotor abilities (Sacrez *et al.*, 1969). We also excluded the outcomes of two studies, bipolar disorder, and autistic-like behavior, as the follow-up period extended beyond childhood (Freedman *et al.*, 2015; Guastella *et al.*, 2018). Finally, all, except one, of the existing studies were conducted in Western countries, limiting generalizability to populations in other parts of the world.

Our systematic review indicates that perinatal synthetic oxytocin poses little or no increased risk to child neurodevelopment. Thus, previous conclusions that perinatal oxytocin poses an increased risk for neurodevelopmental problems have been premature. Any future investigation of the association between oxytocin-stimulated labor and neurodevelopmental outcomes in offspring would benefit from controlling for maternal psychopathology or including a sibling or even cousin comparison. Such designs that control for confounding by genetic vulnerability and prenatal environmental factors would likely eliminate the minute association between perinatal oxytocin and ASD. Despite the lack of evidence for the increased risk of cognitive impairment, ADHD and ASD, clinicians should continue to follow clear guidelines that reduce the ubiquitous use of synthetic oxytocin due to the known physiological risks associated with the medication (World Health Organization, 2011, 2014).

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291718003021.

Acknowledgements. We would like to thank the authors who took time out of their busy schedules to respond to our request for additional information for this review. A grant awarded by the Department of Psychiatry of the Capital Region of Denmark to NNL funded this review. Role of the Funder/Sponsor: The funder had no role in the study design, collection, analysis, or interpretation of the data, writing of the manuscript, or the decision to submit the paper for publication.

Author contributions. NNL, ERL, KJP, and KSL were involved in the design of this study. NNL conducted the literature search, screened articles for inclusion, performed the meta-analyses, and wrote the first draft of the article. NNL and FCV assessed articles for eligibility and study quality. ERL settled disagreements on study quality scores. All authors were involved in determining the criteria for study quality and read and approved the final version of the article.

Conflict of interest. Although not relevant for this review, F.C.V. is the distributor of Dutch translations of ASEBA from which he receives remuneration. The remaining authors have no conflicts of interest to report.

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https://doi.org/10.1017/S0033291718003021 Published online by Cambridge University Press