Exogenous oxytocin administration during labor and autism spectrum disorder

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BACKGROUND: Oxytocin is a neuropeptide hormone that plays a key role in social behavior, stress regulation, and mental health. Synthetic oxytocin administration is a common obstetrical practice, and importantly, previous research has suggested that intrapartum exposure may increase the risk of neurodevelopmental disorders, such as autism spectrum disorder.

OBJECTIVE: This study aimed to examine the association between synthetic oxytocin exposure during labor and autism spectrum disorder diagnosis in the child.

STUDY DESIGN: This population-based retrospective cohort study compared 2 cohorts of children: (1) all children born in British Columbia, Canada between April 1, 2000 and December 31, 2014 (n=414,336 births), and (2) all children delivered at Soroka University Medical Center in Be'er-Sheva, Israel between January 1, 2011 and December 31, 2019 (n=82,892 births). Nine different exposure groups were examined. Cox proportional hazards models were used to estimate crude and adjusted hazard ratios of autism spectrum disorder in both cohorts on the basis of induction and/or augmentation exposure status. To further control for confounding by indication, we conducted sensitivity analyses among a cohort of healthy, uncomplicated deliveries and among a group that was induced only for postdates. In addition, we stratified our analyses by infant sex to assess for potential sex differences.

RESULTS: In the British Columbia cohort, 170,013 of 414,336 deliveries (41.0%) were not induced or augmented, 107,543 (26.0%) were exposed to oxytocin, and 136,780 (33.0%) were induced or augmented but not exposed to oxytocin. In the Israel cohort, 51,790 of 82,892 deliveries (62.5%) were not induced or augmented, 28,852 (34.8%) were exposed to oxytocin, and 2250 (2.7%) were induced or augmented but not exposed to oxytocin. On adjusting for covariates in the main analysis, significant associations were observed in the Israel cohort, including adjusted hazard ratios of 1.51 (95% confidence interval, 1.20–1.90) for oxytocin-augmented births and 2.18 (95% confidence interval, 1.32–3.57) for those induced by means other than oxytocin and not augmented. However, oxytocin induction was not significantly associated with autism spectrum disorder in the Israel cohort. In the Canadian cohort, there were no statistically significant adjusted hazard ratios. Further, no significant sex differences were observed in the fully adjusted models.

CONCLUSION: This study supports that induction of labor through oxytocin administration does not increase the risk of autism spectrum disorder in the child. Our international comparison of 2 countries with differences in clinical practice regarding oxytocin administration for induction and/or augmentation suggests that previous studies reporting a significant association were likely confounded by the underlying indication for the induction.

Key words: autism spectrum disorder, international comparison, labor augmentation, labor induction, oxytocin, perinatal epidemiology

Introduction

Oxytocin, a neuropeptide hormone produced by the hypothalamus, enhances social behavior and bonding, promotes stress regulation, and improves mental health.[1] Oxytocin also promotes the progress of labor and delivery by initiating uterine contractions during labor, and synthetic oxytocin is often given during labor induction and augmentation.[2] Worldwide, up to 50% of induced deliveries use synthetic oxytocin.[3,4] Lower plasma levels of oxytocin have been reported in children diagnosed with autism spectrum disorder (ASD) compared with neurotypical children.[5] Oxytocin, which crosses the placenta, is hypothesized to desensitize and down-regulate oxytocin receptors, thereby increasing the risk of neurodevelopmental disorders, including ASD.[6–8] Thus, intrapartum administration of synthetic oxytocin has raised concerns about a possible association with increased risk of ASD in the exposed child.

The evidence linking synthetic oxytocin to ASD is contradictory. Although certain studies have reported no association,[9,10] others have reported elevated odds ratios[11,12] or hazard ratios (HRs).[13] Importantly, the quality of previous studies is varied; thus, these contradictory results may be explained by confounding indications for oxytocin administration (eg, induction for fetal or maternal health concerns that may themselves be associated with increased risk of ASD), dose and duration of oxytocin administration, or quality of the ASD case ascertainment method.[14] Infant sex may also be important, given that previous studies have found an association between intrapartum oxytocin and ASD in males but not in females.[15,16]

Considering the widespread use of oxytocin in labor, further research is warranted into the potential association between intrapartum synthetic oxytocin exposure and diagnosis of ASD. This study aimed to address the main methodological limitations of previous work

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AJOG MFM at a Glance

Why was this study conducted?

Research evidence linking intrapartum synthetic oxytocin administration to autism spectrum disorder (ASD) in children is contradictory, possibly because of methodological limitations such as confounding by indication and quality of ASD case ascertainment. Considering the widespread use of oxytocin in labor, and reports of lower plasma levels of oxytocin among children with ASD, this obstetrical exposure warrants further investigation.

Key findings

Induction of labor through oxytocin administration does not increase the risk of ASD in children.

What does this add to what is known?

Our international comparison of population-based data from British Columbia, Canada and Israel suggests that previous studies reporting a significant association between induction with oxytocin and ASD were likely confounded by the underlying indication for induction.

by: (1) using high-quality clinical data on ASD diagnosis and oxytocin exposure; (2) including data on many potential confounders; and (3) controlling for potentially confounding indications for induction. A notable contribution to existing literature is our comparison of population-based data from British Columbia (BC), Canada, where oxytocin is regularly used for induction and augmentation, and hospital-based data from a large maternity hospital in Israel, where oxytocin is primarily used for augmentation and rarely for induction. This comparison enabled us to determine whether intrapartum exposure to oxytocin was associated with increased risk of ASD regardless of indication for induction or augmentation.

Materials and Methods

Study design, data sources, and study population

Our 2 retrospective cohorts included: BC, Canada (population of ~5.1 million) and Soroka University Medical Center (SUMC) in Be'er-Sheva in Israel's southern district (population of ~1.2 million). Our Canadian cohort included children born between April 1, 2000 and December 31, 2014 and followed up until clinical diagnosis of ASD, death, or the study end date of December 31, 2016. Canadian data sources included clinical ASD diagnostic data from the BC Autism Assessment Network (median age at assessment: 5.4 years)[17] and data from the BC Ministry of Education, the BC Perinatal Data Registry,[18] the BC Consolidation File,[19] and BC Vital Statistics.[20] Ethics approval for the Canadian analysis was obtained from the University of British Columbia Clinical Research Ethics Board.

Our Israeli cohort included children whose mothers were members of the Clalit Health Services (CHS) system and who were delivered at SUMC in Be'er-Sheva, Israel between January 1, 2011 and December 31, 2019. CHS is Israel's largest healthcare maintenance organization serving ~70% of the citizens in southern Israel. Most births in southern Israel are delivered at SUMC, which is the only medical center where children insured by CHS can receive an ASD diagnosis (ie, high correspondence with mothers insured by CHS). Children were followed up until clinical diagnosis of ASD, death, or the study end date of December 31, 2021. Data were obtained from the computerized database of SUMC that includes detailed information on antenatal, intrapartum, and postpartum maternal and infant care for all hospital deliveries. Clinical ASD diagnostic data were obtained from the autism database of the Azrieli National Centre for Autism and Neurodevelopment Research,[21] which contains data on nearly all children diagnosed with ASD at SUMC. In Israel, over half of the children are diagnosed with ASD before the age of 3, and >90% receive their diagnosis before the age of 6. Ethics approval for the Israeli analysis was obtained from the SUMC Helsinki committee.

We excluded nonsingleton pregnancies because they have a unique set of inherent risks that differentiate them from singleton pregnancies. Further, we excluded cesarean deliveries because oxytocin is not administered for planned cesarean delivery, and emergency cesarean deliveries are already indicated as higher risk. We removed these deliveries with the aim of constructing a low-risk cohort with as little confounding as possible. Finally, we excluded pregnancies that were both induced by means other than oxytocin and augmented by means other than oxytocin because these pregnancies lack relevance to the research question.

Exposure assessment

We examined 9 different exposure groups that were not mutually exclusive: (1) those who received no induction or augmentation of labor by any means (reference group); (2) those who received oxytocin in any form (either for induction or augmentation); (3) those who were induced with oxytocin; (4) those who were augmented by oxytocin; (5) those who were both induced and augmented by oxytocin; (6) those who were augmented with oxytocin without induction (went into labor spontaneously); (7) those who were induced by other means (including prostaglandins, artificial rupture of membranes, or another method, not specified) and augmented with oxytocin; (8) those who were induced by other means and not augmented; and (9) those who were not induced but who were augmented using other means.

Outcome

In BC, diagnostic assessment for ASD has been standardized within the BC Autism Assessment Network since 2004 and must be informed by 2 instruments: the Autism Diagnostic Observation Schedule (ADOS or ADOS-2) and the Autism Diagnostic Interview-Revised (ADI-R). The assessment also draws on

clinical history, evaluation of developmental status, and reports from schools and other relevant clinicians. Private practitioners (ie, pediatricians, psychiatrists, or psychologists) can also diagnose children in BC using the same assessment tools. We identified cases diagnosed by private practitioners through linkage to data held by the BC Ministry of Education.

In Israel, diagnosis of ASD requires diagnostic assessments by a developmental psychologist and either a pediatric neurologist or child psychiatrist according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria. All participating children at SUMC completed an intake interview, assessment with the ADOS-2 test, and a cognitive evaluation using either the Bayley Scales of Infant and Toddler Development, third edition (Bayley-III) or the Wechsler Preschool and Primary Scale of Intelligence, version 3 (WPPSI-III).

Covariates

We included the following maternal sociodemographic variables: maternal age, neighborhood income quintile (Canada), socioeconomic status quintile (Israel), and location of residence (urban, semiurban, or rural; Canada) or ethnicity (Bedouin, Jewish; Israel). We also examined pregnancy conditions and risk factors that could have influenced fetal health, including: nulliparity, smoking during pregnancy, gestational or preexisting diabetes mellitus, pregnancy-induced hypertension, or other types of hypertension (including hypertensive renal disease, proteinuria, high blood pressure, or a prescription for antihypertensive medication). Under labor and delivery characteristics, we included year of delivery, epidural use, and administration of antibiotics during labor and delivery. Neonatal characteristics included were sex, birthweight, gestational age, small-for-gestational-age, large-for-gestational-age,[22] and presence of a congenital malformation (ICD-10-CM [International Classification of Diseases, Tenth Revision, Clinical Modification] codes of Q00 to Q99).

Statistical analysis

We compared the characteristics across exposure groups using standardized mean difference (SMD), which is the absolute value in the difference in means of a covariate across the various exposure groups divided by the standard deviation in the exposed group. On the basis of previous guidelines, a difference in covariates is considered too different for reliable comparison if the SMD is >0.1.[23] We then estimated associations between induction and augmentation status and ASD in the child using Cox proportional hazards models, and calculated robust standard error estimates by clustering between multiple deliveries to the same mother. We added the 4 classes of covariates sequentially to the regression models to understand which covariates were important confounders in the relationship between oxytocin induction and augmentation status and ASD. Model 1 adjusted for maternal sociodemographic characteristics. Model 2 added pregnancy conditions and risk factors. Model 3 additionally controlled for labor and delivery features. Finally, Model 4 added the neonatal characteristics.

To better control for confounding by indication, we performed a healthy cohort subgroup analysis, excluding maternal and neonatal conditions that could be associated with ASD and labor induction and/or augmentation. We performed an additional sensitivity analysis among the healthy cohort using only Canadian data in which we included only postdate inductions, eliminating all inductions done for concerns regarding fetal or maternal health. These detailed data on indication for induction were not available in Israel. We also stratified by infant sex. All analyses used R statistical software (R Core Team, Vienna, Austria).[24]

Results

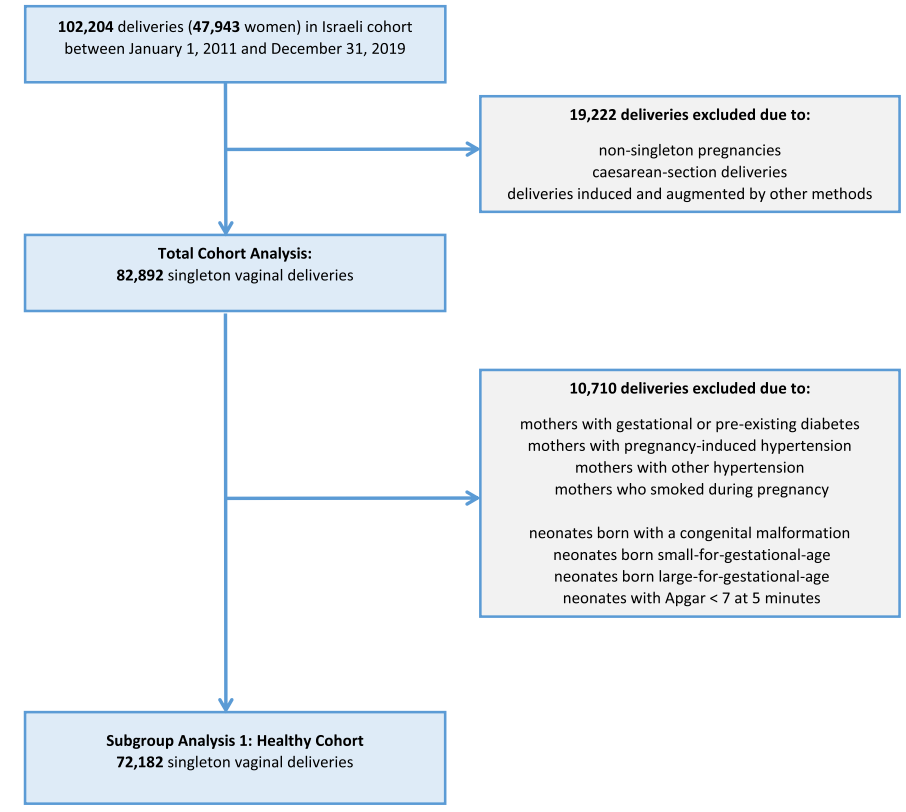
The initial cohort included 617,570 deliveries of 391,215 women in BC between April 1, 2000 and December 31, 2014, and 102,204 deliveries of 47,943 women in Israel between January 2011 and December 2019. As outlined in Figures 1 and 2, after exclusions, the total cohort for the primary analysis included 414,336 and 82,892 births in BC and Israel, respectively. In BC, 170,013 (41.0%) of these deliveries were not induced or augmented, 107,543 (26.0%) were exposed to oxytocin during induction and/or augmentation, and 136,780 (33.0%) were induced or augmented but not exposed to oxytocin. In Israel, 51,790 (62.5%) of these deliveries were not induced or augmented, 28,852 (34.8%) were exposed to oxytocin during induction and/or augmentation, and 2250 (2.7%) were induced or augmented but not exposed to oxytocin. The children were followed up for a mean of 8.43 years in the BC cohort and 4.33 years in the Israeli cohort.

Although we examined 9 groups, as outlined in the methods section above, for parsimony, Tables 1 (Israel) and 2 (Canada) present characteristics across the 4 primary groups of interest: the unexposed group and the groups induced, augmented, and both induced and augmented by oxytocin. In both Israel and Canada (Tables 1 and 2), all 3 exposed groups were more likely to have diabetes mellitus and pregnancy-induced hypertension, and to have received an epidural compared with the unexposed group. In addition, in Israel (Table 1), the 3 exposed groups were more likely to be of Jewish ethnicity, to belong to a higher socioeconomic status quintile, and to be nulliparous at birth compared with the nonexposed group. In Canada (Table 2), the 3 exposed groups were more likely to live in urban areas and less likely to be nulliparous at birth compared with the nonexposed group.

Compared with the unexposed groups, the oxytocin-induced group had a more recent year of delivery in both countries, and a higher rate of small-for-gestational-age neonates only in Israel. The oxytocin-augmented group had a lower maternal age than

FIGURE 1
Cohorts and exclusion criteria for Israel

A



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the unexposed group in Israel and a longer length of first stage of labor in both countries. The oxytocin-induced and augmented group also had a more recent delivery year in both countries and a higher rate of small-for-gestational-age neonates in Israel.

When assessing the crude associations between oxytocin induction and/or augmentation and risk of ASD in the total cohort, we found that any oxytocin exposure, any oxytocin augmentation, oxytocin augmentation without induction, and oxytocin augmentation in people who were induced by other means were all associated with increased unadjusted HRs in both Canada and Israel (Table 3). In Canada, where oxytocin is the primary method for induction, we also observed a significant association of oxytocin induction and both oxytocin induction and augmentation with the risk of ASD (HR, 1.26; 95% confidence interval [CI], 1.17−1.35; and HR, 2.38; 95% CI, 1.06−5.32; respectively). In Israel, where other means of induction are more commonly used than oxytocin, the association between other induction without augmentation and ASD was significant (HR, 2.37 [95% CI, 1.46−3.85]).

Although adjustment for covariates attenuated the HRs in both countries, many associations remained statistically significant in Israel, including adjusted HRs (aHRs) of 1.51 (95% CI, 1.20−1.90) for oxytocin-augmented births and 2.18 (95% CI, 1.32−3.57) for those induced by other means and not augmented. In contrast, none of the associations remained statistically significant in the fully adjusted models in Canada. In Canada, most of the observed associations were no longer significant after adjusting for labor and delivery factors (Model 3; eTable 8).

In the analysis stratified by child sex, the findings were consistent for the male offspring (eTable 2). For the female offspring, no significant associations were observed between any exposure group and ASD in the fully adjusted models for both Canada and Israel (eTable 3).

Healthy cohort subgroup analysis

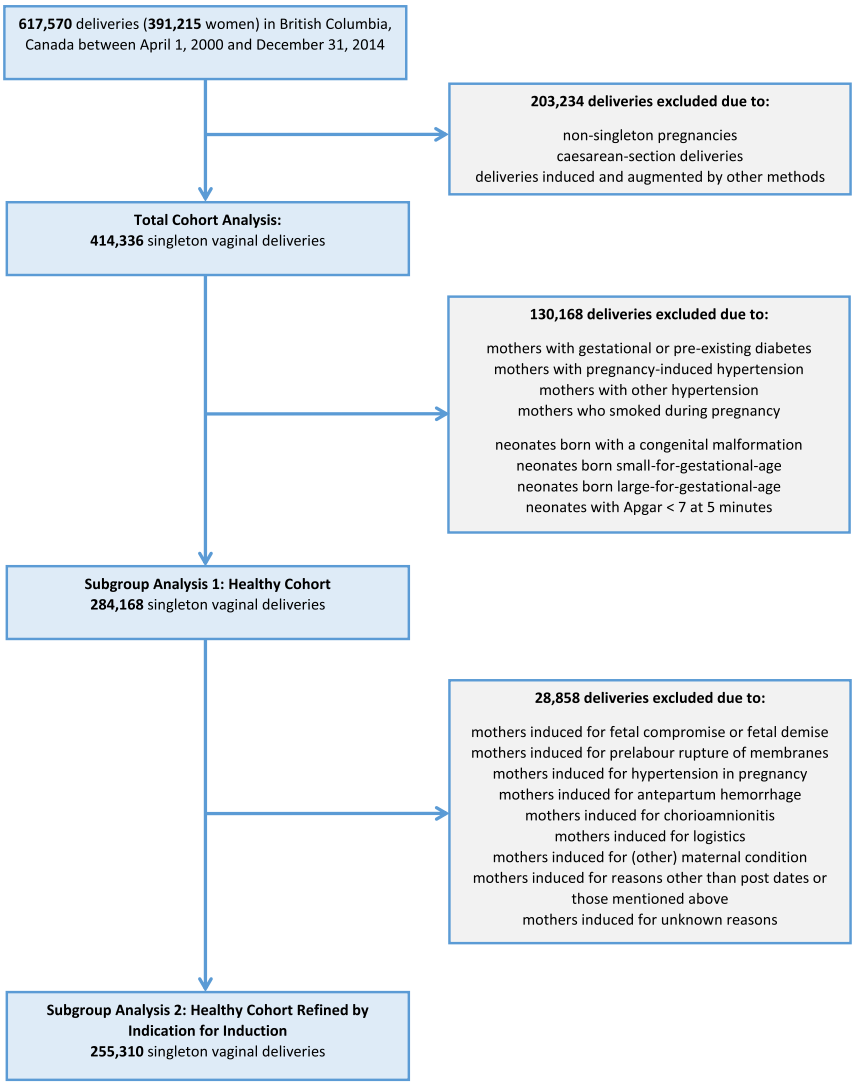
After excluding maternal and neonatal conditions that could be associated with ASD, we also observed an increased risk of ASD in offspring exposed to any oxytocin, oxytocin augmentation, oxytocin augmentation without induction, and other means of induction with oxytocin augmentation compared with the unexposed group in both Canadian and Israeli cohorts in the unadjusted analysis, with unadjusted HRs ranging from 1.32 (95% CI, 1.22−1.43) to 2.69 (95% CI, 1.76−4.10) (Table 4). On adjusting for covariates, the associations were attenuated and lost statistical significance in the Canadian cohort. In Israel but not Canada, any oxytocin exposure, oxytocin augmentation, oxytocin augmentation without induction, and other means of induction without augmentation remained significantly associated with ASD in the fully adjusted models (aHR ranging from 1.51 [95% CI, 1.16−1.95] to 2.02 [95% CI, 1.16−3.52]). Supplemental eTables 4 and 5 show the healthy cohort subgroup analyses stratified by offspring sex.

Sensitivity analysis

To further control for confounding by indication, the Canadian analysis including only postdate inductions revealed significant associations between any oxytocin exposure, oxytocin induction, oxytocin augmentation, and oxytocin augmentation without induction and ASD in unadjusted models (HRs ranging from 1.29 [95% CI,

FIGURE 2
Cohorts and exclusion criteria for British Columbia, Canada

B



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1.02−1.61] to 1.32 [95% CI, 1.20−1.45]) (eTable 1). No statistically significant associations remained following adjustment for covariates. Results were consistent when stratified by sex (eTables 6 and 7).

Comment

Principal findings

In this population-based retrospective cohort study, no associations were found in the primary analysis between oxytocin induction and risk of ASD in the child after adjusting for maternal sociodemographic characteristics, pregnancy conditions and risk factors, labor and delivery characteristics, and neonatal characteristics.

Clinical implications

On the basis of our international comparison, we observed important differences in oxytocin use between our 2 cohorts that shed light on a probable confounding by indication leading to the association between oxytocin induction and ASD. Although oxytocin was the most common means of induction in BC, it was not commonly chosen as the method for induction in Israel. Thus, the statistically significant unadjusted association in Canada, coupled with the significant fully adjusted association with induction by other means in Israel, could together be interpreted as resulting from confounding by indication for induction. In addition, our findings illustrate that on controlling for characteristics associated with dysfunctional labor and infection (eg, epidural and antibiotic use) in Model 3, the associations are substantially attenuated and lose significance, further indicating confounding by indication. Finally, this hypothesis is further strengthened by our finding of no association in the group that was induced only for postdates. Together, these results propose that the common obstetrical practice of administering oxytocin for labor induction is unlikely to increase the risk of ASD.

Research implications

Oxytocin augmentation remained significantly associated with ASD in the fully adjusted models in Israel; however, this association was fully attenuated in Canada. Considering these findings, we cannot rule out the possibility that augmentation of labor with oxytocin may be associated with increased risk of ASD in the child. Thus, further research should examine the relationship between augmentation with oxytocin and ASD and compare it with other means of augmentation.

Results in the context of what is known

The finding that oxytocin use in labor was not significantly associated with increased risk of ASD is supported by other large population studies.[25,26] Although there are many contradictory reports in the existing literature, including several studies that find a significant and positive association,[11−13] it seems that studies that best controlled for confounding factors tended to report no significant association. For example, Oberg et al[10] conducted a large

TABLE 1
Characteristics by oxytocin induction and augmentation status for Israel

Variable	Not induced or augmented N=51,790	Induced labor with oxytocin N=710	SMD (oxytocin-induced vs unexposed)	Augmented labor with oxytocin N=28,668	SMD (oxytocin-augmented vs unexposed)	Induced and augmented with oxytocin N=526	SMD (oxytocin-induced and augmented vs unexposed)
Maternal sociodemographic characteristics							
Age, mean y (SD)	28.8 (5.7)	28.5 (5.7)	0.053	28.0 (5.5)	0.149	28.5 (5.7)	0.051
Age categories, n (%)			0.034		0.145		0.038
<20	1928 (3.7)	31 (4.4)		1491 (5.2)		23 (4.4)	
20–29	28,794 (55.6)	397 (55.9)		17,385 (60.6)		298 (56.7)	
30–39	19,491 (37.6)	264 (37.2)		9155 (31.9)		189 (35.9)	
≥40	1569 (3.0)	18 (2.5)		635 (2.2)		16 (3.0)	
Income quintile, n (%)			0.263		0.243		0.304
1	33,457 (64.7)	347 (49.2)		14,786 (51.7)		240 (46.1)	
2	4423 (8.6)	94 (13.3)		3135 (11.0)		80 (15.4)	
3	7849 (15.2)	155 (22.0)		5916 (20.7)		118 (22.6)	
4	4420 (8.6)	78 (11.1)		3721 (13.0)		59 (11.3)	
5	1533 (3.0)	31 (4.4)		1024 (3.6)		24 (4.6)	
Ethnicity, n (%)			0.342		0.278		0.394
Bedouin	35,179 (67.9)	365 (51.4)		15,629 (54.5)		257 (48.9)	
Jewish	16,611 (32.1)	345 (48.6)		13,039 (45.5)		269 (51.1)	
Pregnancy conditions and risk factors							
Parity, n (%)			0.610		0.591		0.679
Nulliparous	7503 (14.5)	288 (40.6)		11,370 (39.7)		230 (43.7)	
Multiparous	44,275 (85.5)	422 (59.4)		17,296 (60.3)		296 (56.3)	
Smoked during pregnancy, n (%)	319 (0.6)	7 (1.0)	0.041	262 (0.9)	0.034	6 (1.1)	0.056
Diabetes mellitus, n (%)	181 (0.3)	26 (3.7)	0.238	418 (1.5)	0.117	20 (3.8)	0.244
Pregnancy-induced hypertension, n (%)	818 (1.6)	68 (9.6)	0.354	1113 (3.9)	0.142	52 (9.9)	0.363
Other hypertension, n (%)	131 (0.3)	5 (0.7)	0.065	163 (0.6)	0.049	5 (1.0)	0.090
Labor and delivery characteristics							
Year of delivery, n (%)			0.102		0.080		0.133
2010–2014	22,079 (42.6)	271 (38.2)		11,202 (39.1)		201 (38.2)	

(continued)

TABLE 1
Characteristics by oxytocin induction and augmentation status for Israel *(continued)*

Variable	Not induced or augmented N=51,790	Induced labor with oxytocin N=710	SMD (oxytocin-induced vs unexposed)	Augmented labor with oxytocin N=28,668	SMD (oxytocin-augmented vs unexposed)	Induced and augmented with oxytocin N=526	SMD (oxytocin-induced and augmented vs unexposed)
2015–2019	29,711 (57.4)	439 (61.8)		17,466 (60.9)		325 (61.8)	
Epidural, n (%)	6894 (13.3)	333 (46.9)	0.787	13,379 (46.7)	0.782	287 (54.6)	0.967
Antibiotics during labor, n (%)	2169 (4.2)	28 (3.9)	0.012	1233 (4.3)	0.006	17 (3.2)	0.051
Neonatal characteristics							
Sex, n (%)			0.066		0.037		0.087
Male	25,997 (50.2)	380 (53.5)		14,917 (52.0)		287 (45.4)	
Female	25,786 (49.8)	330 (46.5)		13,750 (48.0)		239 (54.6)	
Birthweight, mean g (SD)	3198 (475)	3157 (541)	0.079	3241 (456)	0.093	3150 (551)	0.093
Gestational age, mean wk (SD)	39.1 (1.8)	39.4 (1.8)	0.179	39.3 (1.6)	0.119	39.4 (1.8)	0.175
Small-for-gestational-age, n (%)	2018 (3.9)	78 (11.0)	0.272	1191 (4.2)	0.013	64 (12.2)	0.308
Large-for-gestational-age, n (%)	1808 (3.5)	24 (3.4)	0.006	1111 (3.9)	0.020	19 (3.6)	0.007
Congenital malformation, n (%)	39 (0.1)	0 (0)	0.039	19 (0.1)	0.003	0 (0)	0.039
Length of follow-up, mean y (SD)	4.40 (2.5)	4.18 (2.3)	0.093	4.20 (2.4)	0.080	4.12 (2.2)	0.121

SMD, standardized mean difference.

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population-based study, including a sibling analysis to account for unmeasured environmental and genetic factors. They reported a significant association between labor induction (method not specified) and ASD in their main cohort, but no association was present in their sibling analysis.[10] The lack of association in the sibling analysis supports the assertion that the association between oxytocin induction and augmentation and ASD may be a result of confounding, particularly confounding by the indication for induction or augmentation. The Oberg et al[10] findings also suggest that unmeasured differences between groups could have an important role and may explain the positive relationship between oxytocin augmentation and ASD that persists in the Israel cohort.

Strengths and limitations

Our study is strengthened by the international comparison and the high quality of the case ascertainment data in both BC and Israel, where we had access to clinical data on ASD diagnosis made by specialists trained in assessing ASD, an improvement over the use of health administrative data to confirm a case of ASD.[27] This study was limited by its observational design; thus, residual confounding likely remains, particularly in the relationship between oxytocin augmentation and ASD that persists in the Israel data. This is evident when comparing the Israel cohort characteristics of the oxytocin augmentation −exposed and unexposed groups. Significant differences existed in ways that would predispose toward a worse prognosis for women exposed to oxytocin augmentation, such as likelihood of diabetes mellitus and pregnancy-induced hypertension. The observational design also limits causal inferences in this potential relationship. Finally, the lack of information on genetics and dose/duration of oxytocin exposure meant that we were unable to exclude children with known genetic causes of ASD or analyze dose −response associations.

TABLE 2
Characteristics by oxytocin induction and augmentation status for British Columbia, Canada

Variable	Not induced or augmented, N N=170,013	Induced labor with oxytocin N=42,328	SMD (oxytocin-induced vs unexposed)	Augmented labor with oxytocin N=66,756	SMD (oxytocin-augmented vs unexposed)	Induced and augmented with oxytocin N=1541	SMD (oxytocin-induced and augmented vs unexposed)
Maternal sociodemographic characteristics							
Age, mean y (SD)	30.33 (5.5)	30.67 (5.6)	0.060	30.00 (5.5)	0.062	31.54 (5.4)	0.222
Age categories, n (%)			0.080		0.057		0.208
<20	5623 (3.3)	1229 (2.9)		2440 (3.7)		28 (1.8)	
20–29	71,838 (42.3)	17,443 (41.2)		29,842 (44.7)		545 (35.4)	
30–39	87,178 (51.3)	21,689 (51.2)		32,466 (48.6)		878 (57.0)	
≥40	5374 (3.2)	1967 (4.6)		2008 (3.0)		90 (5.8)	
Income quintile, n (%)			0.053		0.041		0.130
1	39,176 (23.8)	10,444 (25.6)		16,166 (25.2)		404 (28.9)	
2	33,676 (20.5)	8689 (21.3)		13,444 (20.9)		298 (21.3)	
3	33,367 (20.3)	7882 (19.3)		12,365 (19.3)		245 (17.5)	
4	31,784 (19.3)	7449 (18.2)		11,904 (18.5)		248 (17.7)	
5	26,392 (16.1)	6365 (15.6)		10,318 (16.1)		205 (14.6)	
Location of residence, n (%)			0.182		0.209		0.613
Urban	111,945 (66.4)	31,325 (74.6)		50,176 (75.8)		1385 (90.5)	
Semiurban	34,925 (20.7)	6743 (16.1)		9889 (14.9)		90 (5.9)	
Rural	21,820 (12.9)	3934 (9.4)		6136 (9.3)		56 (3.7)	
Pregnancy conditions and risk factors							
Parity, n (%)			0.221		0.566		0.280
Nulliparous	101,448 (59.7)	20,634 (48.7)		21,701 (32.5)		706 (45.8)	
Multiparous	68,556 (40.3)	21,693 (51.3)		45,054 (67.5)		835 (54.2)	
Smoked during pregnancy, n (%)	15,005 (8.8)	4521 (10.7)	0.063	6623 (9.9)	0.038	98 (6.4)	0.093
Diabetes mellitus, n (%)	9470 (5.6)	4933 (11.7)	0.218	5471 (8.2)	0.104	279 (18.1)	0.396
Pregnancy-induced hypertension, n (%)	2093 (1.2)	4515 (10.7)	0.407	3061 (4.6)	0.201	111 (7.2)	0.300
Other hypertension, n (%)	1471 (0.9)	2986 (7.1)	0.321	2062 (3.1)	0.160	100 (6.5)	0.302

(continued)

TABLE 2
Characteristics by oxytocin induction and augmentation status for British Columbia, Canada *(continued)*

Variable	Not induced or augmented, N N=170,013	Induced labor with oxytocin N=42,328	SMD (oxytocin-induced vs unexposed)	Augmented labor with oxytocin N=66,756	SMD (oxytocin-augmented vs unexposed)	Induced and augmented with oxytocin N=1541	SMD (oxytocin-induced and augmented vs unexposed)
Labor and delivery characteristics							
Year of delivery, n (%)			0.129		0.054		1.905
2000–2004	53,316 (31.4)	10,840 (25.6)		19,406 (29.1)		0	
2005–2009	56,300 (33.1)	14,890 (35.2)		23,396 (35.0)		0	
2010–2014	60,397 (35.5)	16,598 (39.2)		23,954 (35.9)		1541 (100.0)	
Epidural, n (%)	23,971 (14.1)	22,100 (52.2)	0.885	46,554 (69.7)	1.365	976 (63.3)	1.171
Antibiotics during labor, n (%)	37,757 (22.2)	18,658 (44.1)	0.478	25,998 (38.9)	0.369	638 (41.4)	0.421
Length of first-stage labor, mean h (SD)	5.59 (4.34)	5.40 (4.32)	0.044	10.77 (6.76)	0.912	5.78 (4.44)	0.043
Neonatal characteristics							
Sex, n (%)			0.008		0.016		0.013
Male	85,159 (50.1)	21,371 (50.5)		33,977 (50.9)		782 (50.7)	
Female	84,849 (49.9)	20,957 (49.5)		32,779 (49.1)		759 (49.3)	
Birthweight, mean g (SD)	3401.35 (511.38)	3360.30 (549.25)	0.077	3430.52 (491.01)	0.058	3318.06 (521.38)	0.161
Gestational age, mean wk (SD)	38.75 (1.74)	38.61 (1.90)	0.078	38.99 (1.66)	0.142	38.45 (1.76)	0.174
Small-for-gestational-age, n (%)	11,080 (6.5)	3256 (7.7)	0.046	4538 (6.8)	0.011	128 (8.3)	0.068
Large-for-gestational-age, n (%)	5352 (3.1)	1541 (3.6)	0.027	2099 (3.1)	<0.001	44 (2.9)	0.017
Congenital malformation, n (%)	8065 (4.7)	2528 (6.0)	0.055	3529 (5.3)	0.025	61 (4.0)	0.039
Length of follow-up, mean y (SD)	8.37 (4.53)	7.90 (4.39)	0.105	8.17 (4.48)	0.044	2.73 (0.73)	1.736

SMD, standardized mean difference.

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TABLE 3
Associations between induction and augmentation status and risk of autism spectrum disorder in offspring in the total cohort

Exposure group/number of observations	Country	Exposed, n (%)	Unadjusted risk difference	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratios (95% CI)[a]
No induction or augmentation (reference)					
Number of children	Israel	51,790			
	Canada	170,013			
ASD cases	Israel	177 (0.3)	0.0000	1.00	1.00
	Canada	2202 (1.3)	0.0000	1.00	1.00
Any oxytocin exposure (induction or augmentation)					
Number of children	Israel	28,852	80,642		
	Canada	107,543	277,556		
ASD cases	Israel	208 (0.7)	0.0038	2.20 (1.80–2.69)	1.51 (1.20–1.89)
	Canada	1723 (1.6)	0.0031	1.27 (1.19–1.35)	1.04 (0.96–1.13)
Oxytocin-induced					
Number of children	Israel	710	52,500		
	Canada	42,328	212,341		
ASD cases	Israel	5 (0.7)	0.0036	2.15 (0.88–5.24)	1.41 (0.57–3.51)
	Canada	667 (1.6)	0.0028	1.29 (1.18–1.41)	1.04 (0.94–1.15)
Oxytocin-augmented					
Number of children	Israel	28,668	80,458		
	Canada	66,756	236,769		
ASD cases	Israel	207 (0.7)	0.0038	2.21 (1.80–2.70)	1.51 (1.20–1.90)
	Canada	1062 (1.6)	0.0030	1.26 (1.17–1.35)	1.03 (0.94–1.13)
Oxytocin induction and oxytocin augmentation					
Number of children	Israel	526	52,316		
	Canada	1541	171,554		
ASD cases	Israel	4 (0.8)	0.0042	2.34 (0.87–6.30)	1.40 (0.51–3.88)
	Canada	6 (0.4)	−0.0091	2.38 (1.06–5.32)	1.43 (0.63–3.24)

(continued)

TABLE 3

Associations between induction and augmentation status and risk of autism spectrum disorder in offspring in the total cohort *(continued)*

Exposure group/number of observations	Country	Exposed, n (%)	Unadjusted risk difference	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratios (95% CI)[a]
Oxytocin augmentation without induction					
Number of children	Israel	23,846	75,636		
	Canada	54,993	225,006		
ASD cases	Israel	164 (0.7)	0.0035	2.06 (1.66–2.54)	1.88 (1.87–1.90)
	Canada	879 (1.6)	0.0030	1.24 (1.15–1.34)	1.02 (0.93–1.12)
Other induction and oxytocin augmentation					
Number of children	Israel	4296	56,086		
	Canada	10,222	180,235		
ASD cases	Israel	39 (0.9)	0.0057	3.19 (2.25–4.51)	1.78 (1.20–2.64)
	Canada	177 (1.7)	0.0044	1.31 (1.12–1.53)	1.03 (0.86–1.23)
Other induction without augmentation					
Number of children	Israel	2243	54,033		
	Canada	28,946	198,959		
ASD cases	Israel	18 (0.8)	0.0046	2.37 (1.46–3.85)	2.18 (1.32–3.57)
	Canada	411 (1.4)	0.0012	1.01 (0.91–1.12)	1.02 (0.91–1.15)
Other augmentation without induction					
Number of children	Israel	7			
	Canada	107,834	277,847		
ASD cases	Israel	0			
	Canada	1306 (1.2)	−0.0008	0.91 (0.85–0.97)	0.96 (0.89–1.03)

ASD, autism spectrum disorder; *CI*, confidence interval.

[a]Adjusted for maternal age, income quintile (Canada), socioeconomic quintile (Israel), location of residence (urban, semiurban, or rural; Canada), ethnicity (Bedouin, Jewish; Israel), nulliparity, smoking during pregnancy, gestational or preexisting diabetes mellitus, pregnancy-induced hypertension, other hypertension, year of delivery, epidural, antibiotics during labor, infant's sex, birthweight, gestational age, small-for-gestational-age, large-for-gestational-age, and congenital malformation.

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TABLE 4
Associations between induction and augmentation status and risk of autism spectrum disorder in offspring among healthy mothers[a] and healthy neonates[b]

Exposure group/number of observations	Country	Exposed, n (%)	Unadjusted risk difference	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratios (95% CI)[c]
No induction or augmentation (reference)					
Number of children	Israel	45,605			
	Canada	123,178			
ASD cases	Israel	156 (0.3)	0.0000	1.00	1.00
	Canada	1379 (1.1)	0.0000	1.00	1.00
Any oxytocin exposure (induction or augmentation)					
Number of children	Israel	24,704	70,309		
	Canada	67,688	190,866		
ASD cases	Israel	168 (0.7)	0.0034	2.07 (1.66–2.57)	1.52 (1.19–1.94)
	Canada	984 (1.5)	0.0033	1.32 (1.22–1.43)	1.10 (0.99–1.21)
Oxytocin-induced					
Number of children	Israel	517	46,122		
	Canada	24,338	147,516		
ASD cases	Israel	4 (0.8)	0.0043	2.42 (0.90–6.53)	1.50 (0.54–4.14)
	Canada	337 (1.4)	0.0027	1.31 (1.16–1.47)	1.14 (1.00–1.30)
Oxytocin-augmented					
Number of children	Israel	24,558	70,163		
	Canada	44,281	167,459		
ASD cases	Israel	167 (0.7)	0.0034	2.07 (1.66–2.57)	1.52 (1.19–1.94)
	Canada	649 (1.5)	0.0035	1.33 (1.21–1.46)	1.07 (0.96–1.20)
Oxytocin induction and oxytocin augmentation					
Number of children	Israel	371	45,976		
	Canada	931			
ASD cases	Israel	3 (0.8)	0.0047	2.53 (0.81–7.92)	1.41 (0.44–4.53)
	Canada	<5			

(continued)

TABLE 4

Associations between induction and augmentation status and risk of autism spectrum disorder in offspring among healthy mothers[a] and healthy neonates[b]

(continued)

Exposure group/number of observations	Country	Exposed, n (%)	Unadjusted risk difference	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratios (95% CI)[c]
Oxytocin augmentation without induction					
Number of children	Israel	20,905	66,510		
	Canada	37,894	161,072		
ASD cases	Israel	139 (0.7)	0.0032	1.98 (1.58–2.49)	1.51 (1.16–1.95)
	Canada	556 (1.5)	0.0035	1.32 (1.19–1.45)	1.06 (0.94–1.19)
Other induction and oxytocin augmentation					
Number of children	Israel	3282	48,887		
	Canada	5456	128,634		
ASD cases	Israel	25 (0.8)	0.0042	2.69 (1.76–4.10)	1.57 (0.98–2.49)
	Canada	91 (1.7)	0.0055	1.43 (1.15–1.77)	1.22 (0.96–1.54)
Other induction without augmentation					
Number of children	Israel	1867	47,472		
	Canada	16,306	139,484		
ASD cases	Israel	14 (0.8)	0.0041	2.21 (1.28–3.82)	2.02 (1.16–3.52)
	Canada	196 (1.2)	0.0008	0.97 (0.84–1.13)	1.05 (0.90–1.23)
Other augmentation without induction					
Number of children	Israel	6			
	Canada	76,996	200,174		
ASD cases	Israel	0			
	Canada	810 (1.1)	−0.0007	0.91 (0.83–0.99)	0.94 (0.86–1.03)

ASD, autism spectrum disorder; *CI*, confidence interval.

[a]Excludes mothers with gestational or preexisting diabetes, pregnancy-induced hypertension, other hypertension, or smoking during pregnancy;

[b]Excludes neonates born with a congenital malformation, small- or large-for-gestational-age, or Apgar < 7 at 5 mins;

[c]Adjusted for maternal age, income quintile (Canada), socioeconomic quintile (Israel), location of residence (urban, semiurban, or rural; Canada), ethnicity (Bedouin, Jewish; Israel), nulliparity, smoking during pregnancy, gestational or preexisting diabetes mellitus, pregnancy-induced hypertension, other hypertension, year of delivery, epidural, antibiotics during labor, infant's sex, birthweight, gestational age, small-for-gestational-age, large-for-gestational-age, and congenital malformation.

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Conclusions

This study's findings indicate that induction of labor through oxytocin administration does not increase the risk of ASD. Our international comparison, healthy cohort subanalysis, and postdates-only sensitivity analysis suggest that previous studies reporting a significant association were likely confounded by the underlying indication for induction. ■

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ajogmf.2023.101010.

References

1. Olff M, Frijling JL, Kubzansky LD, et al. The role of oxytocin in social bonding, stress regulation and mental health: an update on the moderating effects of context and interindividual differences. Psychoneuroendocrinology 2013;38:1883–94.

2. Bell AF, Erickson EN, Carter CS. Beyond labor: the role of natural and synthetic oxytocin in the transition to motherhood. J Midwifery Womens Health 2014;59:35–42.

3. Miller S, Abalos E, Chamillard M, et al. Beyond too little, too late and too much, too soon: a pathway towards evidence-based, respectful maternity care worldwide. Lancet 2016;388:2176–92.

4. Goffinet F, Dreyfus M, Carbonne B, Magnin G, Cabrol D. [Survey of the practice of cervical ripening and labor induction in france]. J Gynecol Obstet Biol Reprod (Paris) 2003;32:638–46.

5. John S, Jaeggi AV. Oxytocin levels tend to be lower in autistic children: a meta-analysis of 31 studies. Autism 2021;25:2152–61.

6. Malek A, Blann E, Mattison DR. Human placental transport of oxytocin. J Matern Fetal Med 1996;5:245–55.

7. Wahl RUR. Could oxytocin administration during labor contribute to autism and related behavioral disorders?—A look at the literature. Med Hypotheses 2004;63:456–60.

8. Gialloreti LE, Benvenuto A, Benassi F, Curatolo P. Are caesarean sections, induced labor and oxytocin regulation linked to autism spectrum disorders? Med Hypotheses 2014;82:713–8.

9. Guastella AJ, Cooper MN, White CRH, White MK, Pennell CE, Whitehouse AJO. Does perinatal exposure to exogenous oxytocin influence child behavioural problems and autistic-like behaviours to 20 years of age? J Child Psychol Psychiatry 2018;59:1323–32.

10. Oberg AS, D'Onofrio BM, Rickert ME, et al. Association of labor induction with offspring risk of autism spectrum disorders. JAMA Pediatr 2016;170:e160965.

11. Gregory SG, Anthopolos R, Osgood CE, Grotegut CA, Miranda ML. Association of autism with induced or augmented childbirth in north carolina birth record (1990-1998) and education research (1997-2007) databases. JAMA Pediatr 2013;167:959–66.

12. Smallwood M, Sareen A, Baker E, Hannusch R, Kwessi E, Williams T. Increased risk of autism development in children whose mothers experienced birth complications or received labor and delivery drugs. ASN Neuro 2016;8:1759091416659742.

13. Stokholm L, Juhl M, Talge NM, Gissler M, Obel C, Strandberg-Larsen K. Obstetric oxytocin exposure and ADHD and ASD among Danish and Finnish children. Int J Epidemiol 2021;50:446–56.

14. Lønfeldt NN, Verhulst FC, Strandberg-Larsen K, Plessen KJ, Lebowitz ER. Assessing risk of neurodevelopmental disorders after birth with oxytocin: a systematic review and meta-analysis. Psychol Med 2019;49:881–90.

15. Weisman O, Agerbo E, Carter CS, et al. Oxytocin-augmented labor and risk for autism in males. Behav Brain Res 2015;284:207–12.

16. Soltys SM, Scherbel JR, Kurian JR, et al. An association of intrapartum synthetic oxytocin dosing and the odds of developing autism. Autism 2020;24:1400–10.

17. British Columbia Ministry of Health (2021): BC Autism Assessment Network data. Population Data BC. Data Extract. MOH (2021). https://www.popdata.bc.ca/data.

18. Perinatal Services BC [creator] (2021). British Columbia Perinatal Data Registry. Population Data BC. Data Extract. PSBC (2021). http://www.perinatalservicesbc.ca/health-professionals/data-surveillance/perinatal-data-registry.

19. British Columbia Ministry of Health (2021): Consolidation file (MSP Registration & Premium Billing). Population Data BC. Data Extract. MOH (2021). http://www.popdata.bc.ca/data.

20. British Columbia Ministry of Health (2021): Vital Events Deaths. Population Data BC. Data Extract. MOH (2021). http://www.popdata.bc.ca/data

21. Dinstein I, Arazi A, Golan HM, et al. The national autism database of Israel: a resource for studying autism risk factors, biomarkers, outcome measures, and treatment efficacy. J Mol Neurosci 2020;70:1303–12.

22. British Columbia medical journal. New birth weight and gestational age charts for the British columbiae population. 2006. Available at: Https://Bcmj.org/articles/new-birth-weight-and-gestational-age-charts-british-columbia-population. Accessed September 2, 2021.

23. Stuart EA, Lee BK, Leacy FP. Prognostic score-based balance measures can be a useful diagnostic for propensity score methods in comparative effectiveness research. J Clin Epidemiol 2013;66. S84–90.e1.

24. R core team. R: a Language and Environment for Statistical Computing. 2021. Available at: https://Www.R-project.org/. Accessed May 1, 2021.

25. Herrera C, Bakian A, Fraser A, Varner MW, Esplin S, Clark EAS. Exogenous oxytocin for labor induction or augmentation and autism spectrum disorder. Am J Obstet Gynecol 2017;216:S109.

26. Clark E, Bilder D, Varner M, Esplin M, Coon H, Bakian A. Autism spectrum disorder and induced/augmented labor: epidemiologic analysis of a Utah cohort. Am J Obstet Gynecol 2015;212:S4–5.

27. Bickford CD, Oberlander TF, Lanphear NE, et al. Identification of pediatric autism spectrum disorder cases using health administrative data. Autism Res 2020;13:456–63.

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