

## Association between combined use of epidural analgesia and oxytocin administration during labor and offspring outcomes: a narrative review and proposal

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### ABSTRACT

Studies have suggested that the administration of epidural analgesia (Epi) and oxytocin (OT) during labor affects offspring outcomes. However, the effects of their combined use remain unclear. This article aimed to review the outcomes of offspring exposed to Epi and OT, identify research gaps, and discuss future research directions. We searched the MEDLINE/PubMed, Web of Science, and Cochrane Library databases to identify studies describing offspring outcomes in the Epi, OT, Epi-OT, and control groups. We included one systematic review, six cohort studies, and one case-control study. The offspring outcomes at birth did not differ between the Epi-OT and Epi groups. In the first hour of life, the pre-feeding and sucking behaviors of the Epi-OT group showed an inverse correlation. At 2 days of age, the breastfeeding behavior and skin temperature patterns differed significantly between the Epi-OT and other groups. At 4 days of age, hyperbilirubinemia was more prevalent in the Epi-OT versus control group. Behavioral scores at 1 month differed little among the Epi-OT, Epi, and control groups. No eligible studies examined 1 month to 1 year of life. From 1 to >13 years of age, the risk of autism spectrum disorder was higher in the Epi and Epi-OT groups versus the control group. Most eligible studies were small and observational without randomization, and the results were inconsistent. Additional large cohort studies of various aspects of offspring development are required to assess the long-term effects of Epi-OT administration.

Keywords: epidural analgesia, opioids, oxytocin administration, offspring outcome, development

#### Abbreviations:

ASD: autism spectrum disorder

CI: confidence interval

Epi: epidural analgesia

Epi-OT: exposure to both epidural analgesia and oxytocin

NBAS: Neonatal Behavioral Assessment Scale

NICU: neonatal intensive care unit

OT: oxytocin

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## INTRODUCTION

Epidural analgesia (Epi) is widely administered and recommended for pain relief during labor in many countries<sup>1</sup> and used in more than 70% of deliveries in the United States.<sup>2</sup> Some studies have investigated the association between Epi use and offspring outcomes.<sup>3,4</sup> Moreover, several studies have examined the association between Epi and neurological development and the risk of autism spectrum disorder (ASD) in offspring.<sup>5-9</sup> A recent meta-analysis showed that the long-term neurobiological effects of Epi administered to laboring women may predispose the offspring to ASD.<sup>10</sup>

Oxytocin (OT), a peptide molecule produced in the hypothalamus and secreted by the pituitary gland, induces uterine contractions during childbirth and stimulates breast milk production.<sup>11</sup> Synthetic OT, which has the same structure as endogenous OT, is widely used to induce or augment labor. Nearly one-third of all term deliveries in England involve the induction of labor.<sup>12</sup> The reported neonatal outcomes immediately after birth in relation to OT administration remain controversial.<sup>13-17</sup> Furthermore, similar to Epi, the long-term effects of exogenous OT administration on later social and neurological developments, such as bipolar disorder and ASD, have been studied.<sup>18-20</sup>

Epi use reportedly increases OT administration by more than two-fold,<sup>21</sup> and their biological interactions were previously demonstrated.<sup>22-24</sup> While many studies have examined their individual effects on offspring with promising results, little is known about their interactions and the effects of their combined use on offspring. Therefore, we conducted this narrative review to overview the outcomes of a group of offspring exposed to both Epi and OT during delivery, identify existing research gaps, and propose areas of future research.

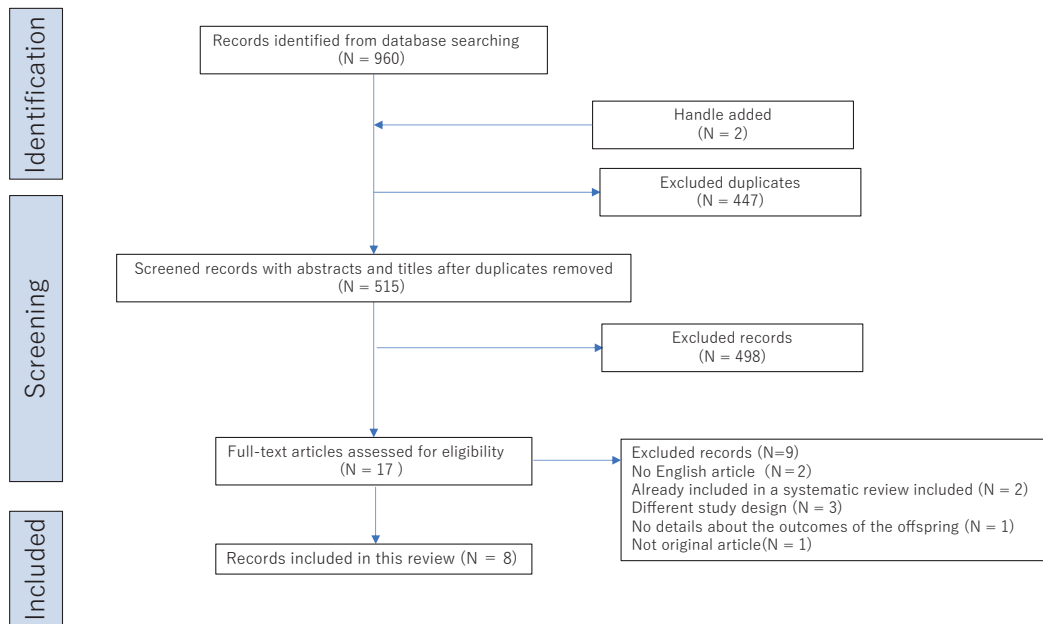
## MATERIALS AND METHODS

### *Research question*

What are the offspring outcomes of exposure to combined Epi and OT during labor?

### *Search strategy and eligibility criteria*

The search aimed to review the outcomes of offspring of mothers exposed to the combined use of Epi and OT and included all relevant evidence of short- and long-term offspring outcomes. It included the MEDLINE/PubMed, Web of Science, and Cochrane Library databases. The Medical Subject Headings (MeSH) search terms “oxytocin,” “administered,” “epidural,” “anesthesia,” “analgesia,” and “offspring” along with the listed indications were used to search the databases. A manual search of the reference lists of the retrieved articles yielded additional studies. Duplicate studies were removed. The titles and abstracts of all studies were screened by independent reviewers (including A.T.), and relevant full-text reviews were performed independently of the primary research question of each study (A.T. and Y.T.). The search was conducted on September 22, 2023. Only full-text human studies published in English were included. Exclusion criteria were non-English publication, case report design, previous inclusion in a systematic review or meta-analysis, and lack of relevance to the topic (eg, either Epi or OT was included as a covariate but not examined in combination use, Epi was compared with another type of anesthesia). Reasons for exclusion were non-English publication (n = 2), previous inclusion in a systematic review (n = 2), different study design (n = 3), lack of details about offspring outcomes (n = 1), and non-original article (n = 1; Figure 1).



**Fig. 1** Flowchart for selecting studies from the MEDLINE/PubMed, Web of Science, and Cochrane Library databases

## RESULTS

The search yielded 960 studies. After the exclusion of 447 duplicate studies and the elimination of 515 studies based on the title and abstract screening, 17 studies were analyzed. The studies were reviewed in full; of them, eight investigated the outcomes in the offspring of mothers exposed to both Epi and OT during labor (Epi-OT group; Figure 1). These eight studies included one systematic review, six cohort studies, and one case-control study. This systematic review investigated the neonatal outcomes of the Epi-OT group. Two studies reported from birth to 1 hour after birth, two studies reported from birth to 2 days after birth, one study reported from birth to 4 days after birth, one study reported from birth to 1 month after birth, and one study reported from 1 year to 13 years (Table 1).

**Table 1** Overview of research studies

Source	Aim	Participants	Groups of medical intervention			Age	Study design	Epidural analgesia	Oxytocin administration protocol	Offspring outcomes
			Epi-OT	Epi	OT					
Costley et al, <sup>27</sup> 2013	To determine whether augmentation using Epi and OT will decrease the incidence of operative deliveries, reduce foetal and maternal morbidity.	A total of 319 infants born vaginally and their mothers who used Epi during labour were randomized into 2 groups as follows; OT group (n=154) and a placebo treatment group (n=165).	○	○	○	On birth	Systematic review and meta-analysis	Bupivacain	Initial infusion started from 2 mU/min and dose was doubled every 20 minutes up to rate of 16 mU/min (1989). Initial rate was 2 mu/min, increasing every 15 min to the following up to 2 mU/min (1995).	No statistically significant differences between the Epi and Epi-OT groups in Apgar scores less than seven at five minutes (RR, 3.06, 95% CI, 0.13-73.33; two studies, 319 women) and admission to a neonatal intensive care unit (RR, 1.07, 95% CI, 0.29-3.93; two studies, 319 women).
Brimdyr et al, <sup>28</sup> 2015	To describe the effect of Epi and OT for breastfeeding during the first one hour of skin-to-skin contact on infants.	A total number of 63 low-risk full-term infants; the control group (n=10), the Epi group (n=16), the OT group (n=12), and the Epi-OT group (n=25).	○	○	○	During the first hour of life	Cohort study	Ropivacaine, fentanyl	Infusion increased by 1 mU/minute every 30 minutes, up to 24 mU/minute.	No differences in birthweight ( $P = 0.11$ ), gestational age ( $P = 0.46$ ) and one- and five-minute Apgar scores ( $P = 0.64$ , $P = 0.65$ ) in four groups. Epidural analgesia showed strong inverse correlations with the achieving suckling ( $P = 0.01$ ) and the amount of oxytocin ( $P = 0.046$ ).
Brimdyr et al, <sup>29</sup> 2019	To describe the effect of Epi and OT for breastfeeding behaviour during the first one hour of skin-to-skin contact on infants.	A total number of 63 low-risk full-term infants; the control group (n=10), the Epi group (n=16), the OT group (n=12), and the Epi-OT group (n=25)	○	○	○	During the first hour of life	Cohort study	Fentanyl	No data	Epi-OT group reached significantly lower stages of Widstrom's 9 Stages by the end of the first hour than the control and the OT group (mean stage $5.47 \pm SD 1.4$ vs $7.10 \pm 1.7$ ; $P = 0.03$ , and vs $7.17 \pm 1.1$ ; $P = 0.01$ ).

Source	Aim	Participants	Groups of medical intervention			Study design	Epidural analgesia	Oxytocin administration protocol	Offspring outcomes
			Epi-OT	Epi	OT im				
Jonas et al. <sup>31</sup> 2007	To assess the influence of Epi and OT during birth for the skin temperature pattern in neonate on two days after birth.	A total number of 47 full-term low-risk infants whose mothers were Swedish speaking in primipara; the OT group (n=9), the Epi-OT group (n=20), and the control group (n=18).	○	○	○	○	Sufentanyl	No data	The Epi-OT group showed significantly higher body temperatures compared to the control group (mean ± SE, 35.07 ± 0.26 °C vs 34.19 ± 0.26 °C, <i>P</i> = 0.025) at the start. The Epi-OT group showed significantly negative temperature difference between the start and first ten minutes (mean ± SE, -0.62 ± 0.22 °C, <i>P</i> = 0.019) whereas the control group and the OT groups showed significantly increasing between the start and first ten minutes (mean ± SE, 0.91 ± 0.2 °C; <i>P</i> = 0.001 and 1.47 ± 0.37 °C, <i>P</i> = 0.008).
Takahashi et al. <sup>32</sup> 2021	To explore the association between the quality of breastfeeding behaviors and Epi/OT use for mother duration of delivery.	A total number of 41 low-risk full-term infants whose mothers were Swedish-speaking in primiparity; the control group (n=13), the OT group (n=5), the OT-im group (n=8), the Epi group (n=5) and the Epi-OT groups (n=10).	○	○	○	○	Bupivacain, sufentanyl	The oxytocin infusion started from 10 IU in 500 mL, giving rise to a concentration of 20 mIU/mL (OT group). 10 IE oxytocin was administered by intramuscular injection (OT im group).	The control group showed a significantly longer duration of rooting than the other four groups. The median of total IBFAT scores were the lowest in the Epi group (8 vs the control group; 10 vs, the OT group; 10 vs the OT im group; 10.5 vs the Epi-OT group; 9). The Epi-OT group showed significantly lower scores than the control group in (medians, interquartile ranges Q25-Q75; 2, 1-2 vs 1, 0-2, <i>P</i> = 0.02).
Sima et al. <sup>34</sup> 1975	To explore prenatal factors for the risk of neonatal jaundice.	A total number of 138 infants (46 in full-term and pre-term infants who diagnosed as hyperbilirubinemia) and matched controls (n=92).	○	○	○	○	No data	No data	Hyperbilirubinemia case was independently associated with oxytocin administration for induction compared to the control group (52.2% vs 28.3%, <i>P</i> <0.01) and Epi use (39.1% vs 15.2%, <i>P</i> <0.01). More hyperbilirubinemia infants in the Epi-OT group than the control group ( $\chi^2 = 3.18, P < 0.05$ ).

Source	Aim	Participants	Groups of medical intervention				Study design	Epidural analgesia	Oxytocin administration protocol	Offspring outcomes
			Epi-OT	Epi	OT	Control				
Murray et al, <sup>35</sup> 1981	To evaluate the effects of Epi-dosing on healthy neonates using the Neonatal Behaviour Assessment Scale (NBAS).	A total number of 60 full-term babies; the Epi group (n=20), the Epi with OT group (n=20), and the control group (n=15).	○	○	○	○	Bupivacaine with epinephrine	No data	On the first day, there were significant differences in NBAS between the control and both the Epi and the Epi-OT groups in the motor process ( $P < 0.01$ ), and state control ( $P < 0.05$ ), and physiological response ( $P < 0.01$ ), as well as their total score ( $P < 0.01$ ). The Epi-OT group showed significantly lower values in motor behaviour on the NBAS than the Epi group (mean score, 23 vs 32; $P < 0.01$ ). However, these differences were attenuated as the day progressed. At the one month of life, there was no difference in the NBAS between the three groups (mean score, 64 vs 81 vs 72, in control, Epi, and Epi-OT groups; $P > 0.05$ ).	
Qiu et al. <sup>37</sup> 2023	To assess the association between the use of Epi and OT and the risk of ASD in children.	A total number of 205 994 singleton births with vaginal deliveries; the Epi group (n=49 679), the OT group (n=13 607), the Epi-OT group (n=104 201), and the control group (n=38 507).	○	○	○	○	No data	No data	Compared to the control group, the HRs for ASD were 0.90 (95% CI, 0.78–1.04), 1.20 (95% CI, 1.09–1.32), and 1.30 (95% CI, 1.20–1.42) in the OT, Epi, and Epi-OT groups respectively. The HR for ASD in the Epi-OT group was significantly higher than in the OT group ( $P = 0.02$ ).	

ASD: autism spectrum disorder

HR: hazard ratio

RR: risk ratio

IBFAT: Infant Breastfeeding Assessment Tool

Epi: epidural analgesia

Epi with OT group: infants from mothers exposed to both intravenous oxytocin and Epi

Epi group: infants from mothers exposed Epi without intravenous oxytocin

OT group: infants from mothers exposed intravenous oxytocin without Epi

OT-im group: infants from mothers exposed intramuscular oxytocin without Epi

Control group: infants from mothers exposed to neither intravenous

### *At birth*

A Cochrane review of two randomized controlled trials<sup>25,26</sup> examined the offspring outcomes of the Epi-OT group.<sup>27</sup> This study found no statistically significant differences between offspring in the Epi-OT group and those who received Epi without oxytocin during labor (Epi group) in terms of 5-minute Apgar score of <7 (risk ratio, 3.06; 95% confidence interval [CI], 0.13–73.33) or admission to the neonatal intensive care unit (NICU; risk ratio, 1.07; 95% CI, 0.29–3.93).<sup>27</sup>

### *First hour of life*

Two cohort studies examined the same offspring in different analyses: one focused on the achievement of suckling behavior<sup>28</sup> and the other focused on the offsprings' behaviors in terms of Widström's nine stages,<sup>29</sup> which describe the progression of newborn behavior during skin-to-skin contact with the mother during the first hour of life.<sup>30</sup> The offspring were divided into four groups: exposure to neither OT nor Epi (control), exposure to intravenous OT without Epi (OT), Epi, and Epi-OT.<sup>28,29</sup> There were no intergroup differences in birth weight ( $P = 0.11$ ), gestational age ( $P = 0.46$ ), and 1- and 5-minute Apgar scores ( $P = 0.64$  and  $P = 0.65$ , respectively).<sup>28,29</sup> However, for the Epi group, strong inverse correlations were found between the amount of fentanyl administered and achievement of suckling ( $P = 0.01$ ) and the amount of OT ( $P = 0.046$ ).<sup>28</sup> The Epi-OT group reached significantly lower stages of Widström's nine stages by the end of the first hour than the control and OT groups (mean  $\pm$  standard deviation,  $5.47 \pm 1.4$  vs  $7.10 \pm 1.7$ ,  $P = 0.03$  vs  $7.17 \pm 1.1$ ,  $P = 0.01$ , respectively).<sup>29</sup>

### *Second day of life*

Two cohort studies assessed the outcomes of the Epi-OT group on the second day of life.<sup>31,32</sup> The skin temperature of the infants was assessed for 30 minutes when in skin-to-skin contact with their mothers.<sup>31</sup> Another study showed offspring behavior with duration of rooting and assessed their feeding behavior and suckling quality using the Infant Breast Feeding Assessment Tool,<sup>32</sup> which assesses infant state, readiness, rooting, latching, suckling behaviors, and maternal satisfaction with the breastfeeding experience.<sup>33</sup> In the first experiment, the offspring were divided into the OT, Epi-OT, and control groups. The Epi-OT group had a significantly higher body temperature than the control group (mean  $\pm$  standard error [SE],  $35.07 \pm 0.26$  °C vs  $34.19 \pm 0.26$  °C,  $P = 0.025$ ) when the offspring were placed in skin-to-skin contact with their mothers.<sup>31</sup> In addition, the Epi-OT group showed a significantly lower temperature difference between the start of breastfeeding and 10 minutes into the session (mean  $\pm$  SE,  $-0.62 \pm 0.22$  °C,  $P = 0.019$ ) whereas the control and OT groups showed significantly increasing temperatures between the start of breastfeeding and 10 minutes into the session (mean  $\pm$  SE,  $0.91 \pm 0.2$  °C,  $P = 0.001$ ; and  $1.47 \pm 0.37$  °C,  $P = 0.008$ ).<sup>31</sup>

A later study assessed the feeding behavior quality of the infants in the control, Epi, Epi-OT, OT, and intramuscular OT without Epi groups.<sup>31</sup> In that study, offspring in the control group had a significantly longer rooting duration than those in the other four groups.<sup>32</sup> The median total Infant Breast Feeding Assessment Tool scores were lowest in the Epi group (Epi, 8; control, 10; OT, 10; intramuscular OT without Epi, 10.5; Epi-OT, 9). The Epi-OT group showed significantly lower Infant Breast Feeding Assessment Tool scores than the control group, especially for rooting (median [interquartile range], 2 [1–2] vs 1 [0–2], respectively;  $P = 0.02$ ).<sup>32</sup>

### *Fourth day of life*

One case-control study was conducted in the hospital at 4 days after birth to evaluate prenatal factors related to the risk of neonatal jaundice and hyperbilirubinemia in the offspring.<sup>34</sup> Compared to control, hyperbilirubinemia was independently associated with OT administration (52.2% vs

28.3%,  $P < 0.01$ ) and Epi use (39.1% vs 15.2%,  $P < 0.01$ ).<sup>34</sup> More infants in the Epi-OT versus the control group had hyperbilirubinemia ( $\chi^2 = 3.18$ ,  $P < 0.05$ ).<sup>34</sup>

#### *Birth to 1 month of age*

One observational study assessed neonatal outcomes from birth to 1 month of age by assessing neonatal behavior using the Neonatal Behavioral Assessment Scale (NBAS),<sup>35</sup> a neurobehavioral assessment tool that was designed to describe newborns' responses to their new environment and document their behavioral repertoire.<sup>36</sup> On the first day of life, the Epi and Epi-OT groups showed significantly lower NBAS scores than the control group in terms of motor process ( $P < 0.01$ ), state control ( $P < 0.05$ ), and physiological response ( $P < 0.01$ ) as well as total score ( $P < 0.01$ ).<sup>35</sup> In addition, the Epi-OT group showed significantly lower motor behavior scores on the NBAS than the Epi group (mean, 23 vs 32;  $P < 0.01$ ).<sup>35</sup> By the fifth day of life, the differences in NBAS scores among the three groups were smaller, but the Epi and Epi-OT groups showed significantly poorer state organization than the control group ( $P < 0.05$ ).<sup>35</sup> Moreover, the Epi-OT group showed significantly fewer feedings than those in the Epi group (mean, 7.5 vs 6.6,  $P < 0.05$ ) and fewer minutes of crying per day than those in the Epi group (mean, 105.0 vs 71.4,  $P < 0.05$ ).<sup>35</sup> Although the Epi and Epi-OT groups received fewer feedings per day than the control group (mean, 66 vs 67 vs 93 times;  $P < 0.05$ ) at 3 weeks of age, no differences were noted between the Epi and Epi-OT groups.<sup>35</sup> Finally, at 1 month of life, there was no difference in NBAS scores among the three groups (mean, 64 vs 81 vs 72 in the control, Epi, and Epi-OT groups, respectively;  $P > 0.05$ ).<sup>35</sup>

#### *One month to 1 year*

There were no studies in this area of infants from 1 month to 1 year of age.

#### *Over 1 year*

A large cohort study of 205,994 singleton vaginal births investigated the risk of ASD from 1 year to 13 years. The study included the control ( $n = 38,507$ ), Epi ( $n = 49,679$ ), OT ( $n = 13,607$ ), and Epi-OT ( $n = 104,201$ ) groups.<sup>37</sup> Compared to the control group, the hazard ratio for ASD was 1.20 (95% CI, 1.09–1.32) in the Epi group and 1.30 (95% CI, 1.20–1.42) in the Epi-OT group, respectively, and 0.90 (95% CI, 0.78–1.04) in the OT group after the adjustment for potential confounders.<sup>37</sup> A significant interaction was observed between Epi and OT in terms of ASD risk ( $P = 0.02$ ), with the hazard ratio for ASD in the Epi-OT group being significantly higher than that in the OT group ( $P = 0.02$ ).<sup>37</sup>

## DISCUSSION

This narrative review identified eight studies of neurological and biobehavioral outcomes in the Epi-OT group. Regarding neonatal outcomes at birth, such as Apgar score or NICU admission, no differences were noted between the Epi-OT and Epi groups,<sup>27</sup> or among the control, OT, and Epi-OT groups.<sup>28,29</sup> Regarding infants' pre-feeding and suckling behaviors during the first hour of life, a strong inverse correlation was found in the Epi-OT group.<sup>28,29</sup> At 2 days after birth, the breastfeeding behavior and skin temperature patterns in the Epi-OT group were significantly different from those in the other three groups.<sup>31,32</sup> At 4 days of age, more patients in the Epi-OT group versus the control group had hyperbilirubinemia.<sup>34</sup> From the first day to 1 month of age, the effects of Epi and synthetic OT on neonatal behavior, particularly motor behavior, were strongest on the first day, but this trend was attenuated by the fifth day.<sup>35</sup> At 1 month of age,



the Epi-OT group showed no differences in NBAS scores from the Epi or the control groups.<sup>35</sup> Between 1 month and 1 year of age, no eligible studies were conducted in this area. From 1 to 13 years of age, the risk of ASD was higher in the Epi and Epi-OT than the control group, while it remained unchanged in the OT group.<sup>37</sup>

All outcomes described above are suggested to be associated with neurodevelopmental impairments.<sup>38-53</sup> The development of ASD, a neurobiological condition characterized by deficits in social communication, restricted interests, and repetitive behaviors,<sup>54</sup> is influenced by both genetic and environmental factors that affect the developing brain.<sup>55,56</sup> Although more than 1,000 genes are suggested to be associated with ASD, most variations have only a small effect on its risk, and there is insufficient evidence to prove their causal relationship with ASD.<sup>57</sup> Several environmental factors are also associated with ASD, including maternal smoking, air pollution exposure, and vitamin intake; however, there is insufficient evidence of their causal association with ASD.<sup>58</sup> Low Apgar scores are reportedly associated with neurological delay or cerebral palsy, and NICU admission is a prognostic factor for long-term cognitive status in offspring.<sup>38,39</sup> Regarding ASD, limited evidence has shown an association between low Apgar scores and NICU admission<sup>40-42</sup>; however, these factors often result from preterm birth or low birth weight, which are associated with a risk of neurological problems including ASD.<sup>42,43,59</sup> Feeding and suckling behaviors affect differentiation of the oropharyngeal and cranial nerves, which in turn affect neurological development.<sup>44,52,53</sup>

Suckling behavior reportedly reflects neonatal development, and neonatal behavior during the first hour after birth is influenced by fetal development.<sup>60</sup> Feeding difficulties as well as oral, motor, and sensory problems are common in individuals with ASD.<sup>45,46</sup> Body and skin temperatures are regulated by the hypothalamus. Studies have shown that temperature instability in newborns is associated with neurodevelopmental disorders.<sup>47,61</sup> Persistent hyperbilirubinemia can cause jaundice in newborns, leading to brain damage and neurological abnormalities such as hearing loss and motor delay.<sup>62</sup> Additionally, neonatal hyperbilirubinemia is reportedly associated with an increased risk of ASD.<sup>48,49</sup> Moreover, NBAS scores are correlated with neurological development, and low scores are an early indicator of later developmental difficulties.<sup>63,64</sup> Lower NBAS scores are also associated with an increased risk of ASD.<sup>50,51</sup>

Regarding the potential physiological mechanisms of Epi exposure in these neonatal outcomes, the local anesthesia and opioids used for Epi was reported to diffuse from the epidural space into the fetus.<sup>65-68</sup> Epi administration for vaginal delivery reportedly affects an offspring's development,<sup>69,70</sup> while its use for cesarean delivery does not.<sup>71</sup> Bupivacaine and ropivacaine, commonly used as Epi drugs during delivery, reportedly inhibit the gamma-aminobutyric acid response in rat pyramidal neurons,<sup>72</sup> and a reduction in synaptic inputs has been implicated in an ASD model mice.<sup>73,74</sup> Opioids induce leukoencephalopathy and edema in infants<sup>67</sup> and promote autism-like behavior through hypermethylation of the glutamate receptor gene in the mouse brain.<sup>75,76</sup> Moreover, recent studies reported the DNA methylation of Epi in immune-related signaling pathways in the umbilical cord blood of offspring.<sup>77</sup> However, the mechanisms underlying the long-term effects of maternal Epi use on the fetal or neonatal brain or the later development of ASD remain unclear.

The same associations as Epi for the neurological and physiological effects of maternal OT administration on the brains of infants have been reported, such as low Apgar scores; NICU admission; pre-feeding, feeding, and neonatal behaviors; hyperbilirubinemia; and neurodevelopmental disorders such as bipolar disorder or ASD.<sup>14,78-80</sup> Although the transport of OT from maternal plasma to the placenta has been reported,<sup>81</sup> a recent review concluded that it is not expected to occur at high levels when synthetic OT is used at the recommended dose.<sup>82</sup> Regarding the potential physiological mechanisms of synthetic OT administration in terms of neonatal outcomes, studies

of rodent pup models showed that the induction of high doses of synthetic OT in dams resulted in pup brain damage in pups with oligodendrocyte cell death and microglial phagocytosis in the prefrontal cortex,<sup>83-85</sup> which is known to be associated with psychiatric disorders.<sup>86</sup> In addition, synthetic OT administration increased the methylation of OT receptors in the vole brain.<sup>87</sup> Most importantly, as with Epi, the mechanisms underlying the long-term effects of OT on the fetal or neonatal brain or subsequent ASD development remain unclear. Epi inhibits exogenous OT secretion in animals and increases the need for synthetic OT in humans.<sup>22-24</sup> However, the drug interaction effect of the combined use of Epi and OT on offspring and their neurodevelopment remains unclear.

More importantly, the medical necessity and benefits of epidural analgesia and oxytocin administration require consideration. Epidural anesthesia is beneficial for pain relief during childbirth.<sup>1</sup> Oxytocin administration according to proper protocols to induce or accelerate labor shortens delivery time and reduces the incidence of clinical chorioamnionitis.<sup>88</sup>

Some studies examined the outcomes of offspring from birth to 13 years of age exposed to both Epi and OT during labor and reported inconsistent results. However, the research in this area is insufficient. Conducting randomized controlled trials for this purpose presents ethical challenges. Most of the studies included in this review were small and observational; only one large cohort study specifically focused on ASD. Further population-based long-term cohort studies of several aspects of offspring development are needed in this area to provide additional information for both women and clinicians considering Epi and synthetic OT administration during labor.

## LIMITATIONS

This study has several limitations. First, with the exception of one systematic review that included two randomized controlled trials, most of the included studies were small and observational, which may make it difficult to exclude the possibility of bias. Second, we did not evaluate all Epi protocols (eg, anesthesia drug, dose, or duration) or OT protocols (eg, dose or duration) because they differed completely among studies, some of which lacked detailed data. Finally, we did not describe offspring developmental outcomes in terms of genetic and environmental background factors since the included studies provided limited offspring and family information.

## ARTICLE INFORMATION

### *Credit authorship contribution statement*

Tachi Asuka: Conceptualization: Writing – original draft, Writing – review and editing. Takahashi Yuki: Conceptualization, Funding acquisition, Writing – review and editing. Kotani Tomomi: Writing – review and editing.

### *Declaration of competing interests*

The authors declare no competing interests.

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*Data availability*

No data were used for the research described herein.

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