



## Fetal exposure to synthetic oxytocin and the relationship with prefeeding cues within one hour postbirth

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### ABSTRACT

**Background:** Prefeeding cues are oral-motor neurobehaviors that communicate feeding readiness, and the ability to self-comfort and regulate behavioral state. Intrapartum and newborn procedures have been associated with altered frequency and emergence of prefeeding cues soon after birth. Intrapartum synthetic oxytocin is commonly used for labor induction/augmentation in the US, yet there is little research on potential effects on infant neurobehavioral cues.

**Aims:** To explore whether fetal exposure to synthetic oxytocin was associated with the infant's level of prefeeding organization shortly after birth.

**Study design:** Cohort.

**Subjects:** A convenience sample of 47 healthy full-term infants (36 exposed and 11 unexposed to intrapartum synthetic oxytocin) was studied.

**Exclusion criteria:** Fetal distress, vacuum/forceps, cesarean, and low Apgar.

**Outcome measures:** Videotapes of infants (45–50 min postbirth) were coded for frequency of eight prefeeding cues, and analyzed by level of prefeeding organization.

**Results:** In general, fewer prefeeding cues were observed in infants exposed *versus* unexposed to synOT and differences were significant for brief and sustained hand to mouth cues [incidence rate ratio (95% CI) = 0.6 (0.4, 0.9) and 0.5 (0.2, 0.9), respectively]. Forty-four percent of exposed infants demonstrated a low level of prefeeding organization, compared to 0% from the unexposed group. In contrast, 25% of exposed *versus* 64% of unexposed infants demonstrated high prefeeding organization. After adjusting for covariates, exposed infants were at 11.5 times (95% CI = 1.8–73.3) the odds of demonstrating low/medium *versus* high levels of prefeeding organization compared to unexposed infants.

**Conclusions:** Newborn neurobehavioral cues may be sensitive to intrapartum synthetic oxytocin.

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### 1. Introduction

Infant prefeeding cues communicate a readiness to feed. Prefeeding cues are also organized, oral-motor neurobehaviors that reflect the infant's ability to self-comfort and regulate behavioral state [1–4]. In the period soon after birth, infant prefeeding cues may relate to early successful breastfeeding [5–8]. Intrapartum and newborn procedures (e.g., labor pain medication, newborn gastric suctioning, and newborn bathing) have been associated with altered frequency and emergence of infant prefeeding cues in the first two hours after birth [7,9,10]. Intrapartum procedures (e.g., intramuscular opioids, epidural, and cesarean surgery) have also been associated with measures of newborn feeding, such as reduced breastfeeding initiation [11], less exclusive breastfeeding upon hospital discharge [12], attenuated sucking behavior

[13], and lower neurobehavioral organization [14]. Synthetic oxytocin (synOT), a common intrapartum procedure to augment labor contractions, has an estimated 57% prevalence rate in the United States [15]. Yet, there is limited published investigation of newborn behavior and feeding outcomes after exposure to intrapartum synOT [16,17]. For example, in a pilot study of 20 healthy newborns exposed to intrapartum synOT and epidural, less sucking activity was observed in newborns exposed to higher *versus* lower intrapartum synOT dosage ( $p = 0.03$ ) [17]. Additionally, three months after birth, there was less exclusive breastfeeding in women exposed to higher *versus* lower intrapartum synOT dosage ( $p = 0.04$ ). An epidemiology study ( $n = 44,000$ ) found that immediate postpartum administration of synOT significantly related to a 6–8% reduction in breastfeeding at 48 h postpartum [16]. These correlational findings, along with data from animal studies (suggesting that young developing behavioral systems can be sensitive to perinatal synOT [18–20]), support the need for further research on potential developmental effects from synOT.

Prefeeding cues can be categorized as mouthing (an open gaping mouth), rooting (head turning to one side with an open mouth), tonguing

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or licking (tongue darting out of the mouth), sucking (empty sucking, or sucking on the tongue, fingers or hand), hand swiping at the mouth, and hand to mouth contact [7,9,10,21–26]. Multiple investigators have described the high frequency of prefeeding cues that emerge in the first hour after birth [7,9,10,21–25]. In most of those studies, infants were placed skin-to-skin on the mother. Under these conditions, the presence of prefeeding cues was associated with successful feeding at the breast approximately one hour after birth [7,10,21,23–25]. The time from birth to the initiation of each prefeeding cue varies between studies, ranging from 3 to 21 min for mouthing and rooting, 15 min for sucking, 15–27 min for tonguing, and 12–34 min for hand to mouth activity [7,10,24,25]. Research findings on neonatal hand to mouth activity demonstrate a relationship with the infant's capacity to self-comfort [2]. For instance, being able to maintain hand to mouth sucking activity is considered a more organized behavior than repeated episodes of swiping at the mouth. Infants who can maintain hand to mouth sucking activity are self-regulating their behavior. Frequently this means they are able to transition more easily from a fussy or crying state to a calmer behavioral state.

While prefeeding cues in the first hour after birth may reflect an infant's emerging neurobehavioral capacity to maintain contact with an oral stimulus and subsequently begin sucking [2,4,27], meaningful consequences of more- or less-organized prefeeding cues have only been studied in the preterm population. For instance, infants who display a greater frequency of prefeeding cues demonstrate more alertness, improved feeding efficiency, and shorter hospital stays [1,3,28]. Little is known about the specific role of prefeeding cues in successful breastfeeding, although one descriptive study ( $n=40$ ) found that the hand to mouth cue triggered mouthing, rooting, and sucking activity; and a greater number of prefeeding cues were significantly associated with aiding latch and sustained breastfeeding [6].

Several intrapartum and newborn procedures have been identified as predictors of prefeeding cue frequency in the first one to two hours after birth [7,9,25]. Gastric suctioning ( $n=11$ ), versus no gastric suctioning ( $n=10$ ), resulted in significantly less hand to mouth activity and delayed sucking activity [25]. This finding may be due to a direct disturbance of oral-motor nerves. Infants bathed ( $n=17$ ), versus not bathed ( $n=31$ ), within the first hour after birth displayed significantly less hand to mouth activity [9]. This finding may be due to a stress-induced interruption of emerging neurobehavioral cues or infant fatigue. Exposure to labor pain analgesia (i.e., epidural/pudendal with bupivacaine, or intramuscular opioids) ( $n=18$ ), versus no medication ( $n=10$ ), resulted in significantly less hand to mouth, tonguing, and sucking activity [7], and an increased time to locate the nipple [10]. These findings may be due to a direct or indirect drug effect on neurobehavioral organization.

Administration of synOT is an intrapartum procedure used for the induction (initiation) and augmentation (maintenance) of uterine contractions. Use of synOT is associated with an increased risk of fetal adverse effects due to the risk of fetal anoxia from excessive uterine activity, with subsequent need for cesarean surgery [29,30]. Due to the heightened risk for significant harm, intrapartum synOT is on the “high alert medication” list [31]. The endogenous form of oxytocin is a paraventricular neuroendocrine peptide that supports normal function of uterine contractility [32] and lactation [33], and has a major role in the development of affiliative, bonding, and parenting behaviors [34]. Endogenous oxytocin also exerts a powerful regulating effect on numerous systems (i.e., autonomic, immune, cardiovascular, and stress reactivity) that interact to support critical neurobehavioral functions in early human development [35,36]. Endogenous oxytocin is known to promote fetal neural protection against mild hypoxic conditions during labor and birth [37,38]. As with other systems critical to early development, oxytocin regulation and expression is modifiable through environmental influence [35,36].

In numerous non-human species, perinatal manipulation of the oxytocin system has modified gene expression and prosocial behaviors associated with oxytocin [39,40]. Administration of perinatal synOT directly to prairie vole offspring has resulted in altered offspring behavior (with

some aberrant, dose-dependent, life-long effects) [18–20,41]. There is recent correlational evidence in humans warranting further investigation of potential adverse effects related to intrapartum synOT exposure, but the studies focus on outcomes in childhood and not infancy. For instance, in a multiple regression model ( $n=172$ ), including 21 relevant variables, intrapartum synOT was the only significant predictor of increased childhood attention deficit disorder ( $p<0.009$ ) [42]. Additionally, authors of a meta-analysis reported a 72% increased risk of autism related to induction of labor in three clinical studies, but this association was not found in four population studies [43]. These human studies need replication.

Despite the common use of intrapartum synOT in the US, and emerging lines of evidence suggesting the need for further research on potential short- and long-term behavioral effects in young animals and humans after exposure to synOT, there has been little investigation of intrapartum synOT's relationship with newborn human behavior, including prefeeding cues shortly after birth. Therefore, the aim of this exploratory study was to examine whether fetal exposure to intrapartum synOT was associated with a lower level of prefeeding organization 45–50 min postbirth.

## 2. Method

### 2.1. Participants

In 2007–2008 a convenience sample of 86 healthy low-risk pregnant women were recruited, at an inner-city community hospital in the United States, as part of another study exploring associations among maternal epidural analgesia, newborn nutritive sucking patterns, maternal/fetal cortisol levels, and newborn behavioral state organization [44]. The women gave permission for their newborn infants to be video recorded. The study protocol was approved by the ethical review boards of the participating hospital and the authors' university. English- and Spanish-speaking women ( $\geq 18$  years) were included if they had an uncomplicated vaginal birth, and received either epidural analgesia (with fentanyl and bupivacaine), or no labor pain medication of any type. Inclusion criteria for infants included: full-term gestation (37–42 weeks), no evidence of persistent fetal distress (defined as bradycardia  $< 110$ , tachycardia  $> 170$ , late decelerations, or poor variability),  $\geq 2500$  g birth weight,  $\geq 7$  Apgar at 1 and 5 min, a cephalic birth without forceps or vacuum extraction, no positive pressure ventilation, and no observable chromosomal abnormalities (e.g., cleft palate). Of the 86 enrolled, four women withdrew from the study before labor began, one infant was transferred to a brightly lit nursery, four video malfunctions occurred, and 30 women/infants became ineligible (two women reported their age incorrectly, one pregnancy complication, one vacuum extraction, one low Apgar, five received IV analgesia during labor, seven cesareans, three delivered at a non-study site hospital, and ten instances when the research team was not notified of the birth). Thus, the final sample available for this study was 47 healthy, low-risk, vigorous, full-term infants. Of the 36 mothers exposed to synOT, 30 received synOT to augment (maintain) labor contractions, and 6 received synOT to both induce and augment labor contractions. Infant characteristics are displayed in Table 1. The sample was nearly equally distributed between Black and Latino infants, with one Asian and two White infants. All infants demonstrated 1 minute Apgars of 8 or 9. Mean birth weight was 3.4 kg (SD = 0.4). Infants whose mothers were administered intrapartum synOT were significantly heavier at birth than infants whose mothers were not exposed to synOT, but no other significant differences were seen by exposure status.

### 2.2. Procedure and measures

At the study site, standard of care was for nurses to observe infants in the infant warmer for the first 20 min after birth, and then give the swaddled infants to their mothers. Study protocol began at 40 min after birth when infants were placed supine in a crib (in the mother's dimly lit room), and allowed to rest undisturbed by themselves for 5 min.

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