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

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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
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 perinatal 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 (e.g., 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 neurobehavorial 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 (≥ 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), ≥2500 g birth weight, ≥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.
Infants were then video recorded in the crib for 5 min, beginning at 45 min after birth, to allow for later coding of behavioral states (in the original study). Infants did not bottle- or breast-feed prior to data collection. Standard of care ophthalmic antibiotic ointment and vitamin K injections were postponed by nursing staff until one hour after birth when our observations were completed. A study team member extracted study variables from the medical records (e.g., total dosage of synOT for induction and/or augmentation, epidural exposure, gestational age, birth weight, and duration of active labor).

For the present study, video recordings were reexamined to code for prefeeding cue frequency using the following procedure. Videos were downloaded into INTERACT Version 2 software (Mangold, 2010, Germany) and video recordings were segmented into 60 five-second epochs. Each epoch was coded for the observed prefeeding cues listed and de-identified each infant as having a low, medium, or high level of prefeeding organization, using tertiles of the distribution to define these levels.

2.2.2. Reliability

Coding the frequency of prefeeding cues was performed by a member of the team (primary rater). Video recordings contained no identifiers of synOT group exposure. To establish inter-rater reliability, an independent coder (secondary rater) trained in scoring prefeeding cues, coded a random 10% (n = 5) of infant video recordings. Coding of each five-second epoch resulted in 60 coded epochs per infant. At this stage, average inter-rater agreement of prefeeding cue frequency over 300 epochs was 90% (ranging from 79% to 94%) and the median kappa value was 0.72 (ranging from 0.52 to 0.78) [46]. When prefeeding cues were summarized, as described in the section above, into a categorical variable with values for low, medium, and high prefeeding organization, values between the two coders matched exactly for four of five infants. For one infant, the prefeeding organization level was rated as medium by the primary rater and low by the secondary rater. However, the low and medium categories were collapsed for analysis (see next section), thus the two raters showed exact agreement for the dependent variable as it was used in the analysis.

2.3. Statistical analysis

All analyses were carried out using PASW Statistics 17, Release Version 17.0 (SPSS, Inc., 2009, Chicago, IL, www.spss.com). Bivariate analysis was performed using two sample t-tests (continuous variables) and chi-square tests (categorical variables) to compare characteristics of...
infants exposed and unexposed to synOT. Descriptive statistics were used to summarize the number of epochs (of 60) in which each type of prefeeding cue was observed. Crude Poisson regression models with robust standard errors [47] were estimated for each cue type to quantify the bivariate relationship between exposure to synOT and the count of epochs during which each cue was observed. Incidence rate ratios (IRR) and 95% confidence intervals were reported from those models to represent the difference in individual prefeeding cue frequency for infants exposed versus unexposed to synOT. Once the summary prefeeding organization variable was constructed (as described above) multivariable analysis was performed using binary logistic regression to compare the odds of low/medium versus high levels of prefeeding organization between infants exposed and unexposed to synOT (n = 47). The low and medium categories were necessarily collapsed for analysis because none of the unexposed infants had low levels of prefeeding organization. Infant sex, gestational age, birth weight, duration of labor, and epidural analgesia exposure were controlled for in the initial model due to their plausible role as confounders, then backward selection was performed using likelihood ratio testing to achieve a more parsimonious model. Race was not considered in the initial model because it did not relate to prefeeding organization in bivariate analysis, and there were only three infants who were non-Hispanic and non-African-American. Though not significant, labor duration and epidural exposure were retained in the final model because they were conceptualized as important control variables for the relationship between synOT and prefeeding organization. Frequently labor induction (the initiation of contractions) with synOT will be longer in duration than labor augmentation (the maintenance of contractions), translating to a longer time of fetal exposure to synOT; but in our data, induced labors were not significantly longer in duration than augmented labors. To be cautious and confirm that our results were not influenced by the inclusion of synOT inductions (n = 6) along with synOT augmentations in the exposure group, a sensitivity analysis was performed excluding those 6 infants. An additional sensitivity analysis was conducted to confirm that our results were not dependent on categorizing level of prefeeding organization, in which we used the log transform of the continuous prefeeding organization score as the dependent variable in an ordinary least squares regression. All statistical tests were two-sided with an alpha level of 0.05.

3. Results

The prefeeding cues most commonly observed in this sample of 47 infants were mouthing/rooting, tonguing and empty sucking, which were observed in a mean of 25, 19, and 16 epochs per infant, respectively, out of a total of 60 epochs per infant. Prefeeding cues representing higher levels of organization, such as sustained hand to mouth contact and sucking on hand, were observed less frequently (mean of 10 epochs each) (Table 3). After summing, the mean total prefeeding organization score was 74.7 (44.8), with a range of 15–171. Infants exposed to synOT had a significantly lower incidence of epochs in which brief hand to mouth cues and sustained hand to mouth activity with no sucking were observed (IRR (95% CI) = 0.6 (0.4, 0.9) and 0.5 (0.2, 0.9), respectively) (Table 3).

Forty-four percent of infants whose mothers were exposed to intrapartum synOT had a low level of prefeeding organization (score ranging from 13 to 44), while none of the unexposed infants had low levels. In contrast, only 25% of synOT exposed infants demonstrated a high level of prefeeding organization (score ranging from 90 to 171), compared to 63.6% of unexposed infants (Fig. 1). There were no significant differences in the level of prefeeding organization by infant characteristics, duration of labor, or epidural exposure (data not shown). In a multivariable binary logistic regression model, after adjusting for duration of labor and epidural analgesia exposure, infants whose mothers were exposed to intrapartum synOT were at 11.5 times the odds of demonstrating low/medium versus high levels of prefeeding organization compared to infants whose mothers were unexposed (95% CI = 1.8, 73.3) (Table 4). Our sensitivity analysis (n = 41) excluding synOT inductions resulted in the same significant conclusions (OR = 10.8, 95% CI = 1.6, 71.5). Our sensitivity analysis, treating level of prefeeding organization as a continuous variable, resulted in a significant (p = 0.01) negative beta coefficient for synOT after controlling for the covariates (data not shown).

4. Discussion

Newborn neurobehavioral cues may be sensitive to intrapartum synthetic oxytocin. Our findings suggest an association between synOT exposure and a decreased level of prefeeding organization one hour after birth. Analyses controlled for potential confounding factors including exposure to epidural analgesia and duration of labor. It is unknown if our findings point to a direct or indirect drug effect. It is possible that the infants exposed to synOT experienced borderline subclinical hypoxia (i.e., oxygen deprivation) from excessively strong uterine contractions; although, our study was designed to exclude infants with any clinical conditions and known indicators of a compromised infant (e.g., diagnosed fetal distress, low Apgar score, positive pressure ventilation, low birth weight, late preterm, forceps/vacuum extraction, cesarean). Due to the significant research gap on newborn behavior after exposure to synOT, it is too early...
to hypothesize a mechanism of action explaining our findings, but we can suggest avenues for future research.

First, it is important to consider whether exogenous oxytocin is able to reach the fetal brain. Fetal sources of oxytocin come from both fetal production, and maternal oxytocin (crossing the placenta with little degradation) passing through the fetus’ immature blood brain barrier [48,49]. The proportion of maternal–fetal sources is still unknown, as evidence in the rat species demonstrates that fetal oxytocin is primarily supplied by a maternal source [49], but in humans the fetus may be the primary contributor [30].

Endogenous oxytocin is clearly a necessary and sufficient powerful mechanism for fetal neuroprotection against mild hypoxia (i.e., oxygen deprivation) during the normal birth process [37]. Animal experiments (in vitro and in vivo) demonstrate that the fetal neuroprotection is due to an oxytocin-mediated near-term transient switch in the action of gamma-aminobutyric acid (GABA) from excitatory to inhibitory in the hippocampus and neocortex [38,49]. Optimal GABA function is critical for normal wiring of neurons during early human development [51]; but oxytocin’s neuroprotection via the GABA switch may only occur within a limited range of physiologic concentration [52]. For instance, immature hippocampal cell culture viability was measured after differential oxygen–glucose deprivation periods. Neurons were treated with exogenous oxytocin to demonstrate a neuroprotective dose–response. Oxytocin concentration of 1 μM prevented a decrease in cell viability, whereas both low and high concentrations of oxytocin resulted in significantly less neuroprotection against oxygen–glucose deprivation.

A direct drug effect of synOT on fetal neurobehavior is plausible due to findings from prairie vole pup experiments. For instance, a single high dosage injection of synOT (n = 12), administered to pups within 24 h of birth, interfered with normal adult pair-bonding; whereas a single low dosage injection (n = 14) facilitated normal adult pair-bonding [18]. In another study, a single injection of synOT or oxytocin antagonist (n = 9–15 per sex), administered to pups within 24 h of birth, resulted in significantly different sex-specific behavioral responses to stress [19]. Additionally, preliminary data suggest that oxytocin receptor gene expression may be epigenetically altered in maternal and fetal prairie voles after intrapartum synOT [20]. Taken together, these findings support a plausible hypothesis that synOT may partially silence oxytocin receptor gene transcription, thus changing expression and production of oxytocin, which in turn could influence oxytocin-dependent behaviors. Thus, changes in DNA methylation of the oxytocin receptor gene after exposure to synOT may be one mechanistic pathway to pursue with further research.

Contrary to findings in the literature on prefeeding cues and systemic opioid analgesia [7,10], we found no relationship between level of prefeeding organization and exposure to epidural analgesia; although, this may have been due to our small sample size. Two prior reports of a significant prefeeding cue and analgesia association may have been influenced by synOT; although, Widstrom et al. [53] did not address whether synOT was included in analysis, and Widstrom et al. [10] did not describe whether the sample was exposed to synOT.

There is no gold standard measure of newborn neurobehavioral organization, as it is a multidimensional construct [54]. Our measure of prefeeding organization may be more sensitive to changes in the oxytocin system than measurement of the alert behavioral state. In a prior study using this sample, we found that infant alertness in the first hour after birth was not related to exposure to synOT [44]. Our measure of prefeeding organization may aid in quantifying an infant’s self-regulation, and better evaluate clinically meaningful outcomes to the mother–infant dyad. Because there is no prior research to indicate the most appropriate way to handle levels of prefeeding organization in analysis, and our distribution was highly skewed, we decided to empirically categorize total prefeeding organization scores into low, medium, and high in order to make the results more interpretable and report a meaningful measure of effect. Our sensitivity analysis confirmed that our results were not dependent on our decision to categorize prefeeding organization scores.

In light of precipitous drops in breastfeeding continuation the first week after birth reported in the US and UK [15,55], and the low US national average (33%) of exclusive breastfeeding at three months [56], prefeeding organization should be further investigated as a predictor of breastfeeding initiation and continuation. One study showed that women’s perception of their newborn’s ability to rooting and latch influences a women’s satisfaction with the breastfeeding experience [57]. Another descriptive study has investigated prefeeding cues and breastfeeding, showing that greater cues were related to better latch and sustained breastfeeding [6]. However, more research is needed to examine whether repeated measures of prefeeding cues are a reliable predictor of feeding outcomes, in addition to other clinically meaningful outcomes such as weight gain, self-regulation, and dyadic interaction.

4.1. Limitations

This is an exploratory pilot study with a small convenience sample. As an initial study on a topic that has received limited investigation, our significant findings may represent a useful indicator of pursuing these relationships in future studies. It is a limitation that power could not be calculated a priori due to no prior investigations of synOT exposure and prefeeding behavior in the literature. The relatively small sample size in this study resulted in an unstable estimate of effect with wide confidence intervals, so these findings need replication in future studies with larger samples. Despite the instability, however, statistical significance (p = 0.05) was achieved, indicating that the observed effect is likely not due to chance alone.

Our findings may not be transferable to settings where infants are placed skin-to-skin immediately after birth without interruption until feeding has finished, nor to infants born by cesarean surgery. In spite of nursing’s standard of practice at the study site to place infants in the warmer for the first 20 min after birth, there was variability in infant sensory stimulation in the 40 min between birth and data collection; but this variability would have been independent of synOT exposure. It is a strength of the study that infants had no prior exposure to breast- or bottle-feeding before data collection, and video recording conditions were tightly controlled (dim lighting, and no interaction between infant and family members or investigator).

5. Conclusion

The intrapartum administration of exogenous oxytocin has more than doubled from 1990 to 2006 [58], and animal findings suggest caution in exposing young developing systems to perinatal synOT [18–20]. Endogenous oxytocin is known to facilitate numerous systems that promote normal neurobehavioral development [35], yet there has been little research on potential effects of intrapartum synOT on human newborn behavior. To our knowledge, this is the first published investigation of intrapartum synOT exposure and human newborn behavior; with exploratory findings suggestive that exposure to intrapartum synOT may result in less organized prefeeding behavioral cues soon after birth. Further research is warranted to explore the reliability of these findings.
in a larger sample, and to determine if there is a synOT dose–behavioral response effect, as suggested by the animal literature. Research on long-term effects of intrapartum synOT should include child outcomes related to developmental social behavior (e.g., autism spectrum disorder, attention-deficit disorder, and anxiety). Long-term developmental risks can be identified using measures of early self-regulation. The feeding experience is one of the primary interactions whereby infants learn self-regulation. Our novel operational measure of prefeeding organization may aid in quantifying neurobehavioral organization and self-regulation. The evaluation of prefeeding cues may also help in the assessment of clinically meaningful outcomes related to feeding, such as feeding readiness, successful early breastfeeding, and infant weight gain.

Conflict of interest

All authors confirm that they have no financial or personal relationships with other people or organizations that could inappropriately influence their work.

Acknowledgments

We thank the parents of the infants in the study. We thank Dr. Sue Carter for her editorial review of the manuscript.

Funding

The study was supported by an Irving B. Harris Foundation Post Doctoral Fellowship. The study sponsor had no involvement in the study design, in the collection, analysis, and interpretation of the data, in writing the manuscript or in the decision to submit the manuscript for publication.

Ethical statement

The study protocol for our manuscript "Fetal exposure to synthetic oxytocin and the relationship with prefeeding cues within one hour postbirth" was approved by the ethical review boards of Mercy Hospital and Medical Center, Chicago, Illinois (subject enrollment and data collection site), and the University of Illinois at Chicago (the authors’ university). All women gave informed consent for themselves and their babies to participate. Protocol approval documents are available upon request.

References


