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Research report

Oxytocin-augmented labor and risk for autism in males

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HIGHLIGHTS

- The use of synthetic oxytocin to induce and/or augment labor is on the rise.
- Exposure to synthetic oxytocin may have adverse effects on the infant's development.
- Oxytocin-augmented labor is modestly associated with risk for autism in males.
- Yet, caution is warranted when interpreting findings.

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ABSTRACT

The use of synthetic oxytocin (OT) to induce and/or augment labor and delivery is on the rise. Maternal exposure to OT during birth may have adverse effects on the infant's development, including increased risk for autism. Yet, studies that test this biologically plausible association and whether it is modified by sex are limited and show inconsistent findings. To this end, we conducted an epidemiological analysis, including all singleton live births in Denmark between 2000 and 2009 ($N = 557{,}040$), with a follow-up through 2012. A total of 2110 children in this cohort were subsequently diagnosed with autistic disorder according to the ICD-10-DCR. Augmentation of labor with OT was modestly associated with an increased risk for autism in males (HR 1.13; 95% CI, 1.00–1.26; $P = 0.04$), but not in females (0.99; 0.77–1.27; $P = 0.95$). Among males exposed to OT augmentation, 560 were subsequently diagnosed with autistic disorder, and among those not exposed, 1177 met criteria for autism (incidence rate 103.2 and 81.4 per 100,000 person-years, respectively). Our findings suggest a modest association between OT-augmented labor and risk for autism in males. However, given the known benefits of using synthetic OT during labor and delivery caution is warranted when interpreting the findings. Future studies should also investigate dose-dependent effect of OT on infant's development.

1. Introduction

According to the last nation-wide US census, it is estimated that about 1 in 68 children in the US is diagnosed with autism spectrum disorder (ASD), which is defined as impairment in social interaction and communication and the presence of restricted interests and repetitive behaviors [1]. ASD is reported to occur in all racial, ethnic, and socioeconomic groups, and is almost five times more common among boys than in girls [2]. Whereas the etiology, biology and consequently the molecular origins of ASD remain largely elusive, it is widely agreed upon that both genetic *and* environmental factors contribute to the development of the disorder [3].

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Recently, obstetrical and delivery-related conditions have gained much interest, highlighting the potential contribution of several pre- and peri-natal elements to the emergence of ASD [4,5]. For example, epidemiological studies have revealed that low birth weight, low 5-min APGAR score, preterm birth, low birth weight for gestational age [6,7], as well as labor induction (stimulating uterine contraction prior to the onset of spontaneous labor) and labor augmentation (i.e., increasing uterine contraction during a spontaneous onset labor) [8], are associated with increased risk for ASD.

Most labor inductions/augmentations nowadays are performed using synthetic oxytocin (OT), which is called Pitocin. An estimated 50–70% of women who undergo labor induction receive exogenous OT [9,10], and two large European studies demonstrated that 30–50% of women in spontaneous labor benefited from OT augmentation during the course of labor [10,11]. Despite the known benefits of using synthetic OT during labor and delivery, exposure to synthetic OT has been shown to associate also with several adverse outcomes in the mother and the offspring. For example, exogenous OT may alter initiation of breastfeeding, probably due to impaired pulsatile secretion of OT and receptor desensitization, and may alter the maternal neural architecture during the sensitive period of birth [12–14]. Studies have also shown that an excess of circulating OT can desensitize OT receptors by several underlying mechanisms, therefore decreasing the beneficial effects of its natural secretion and action within the central nervous system [15,16]. Similarly, experimental paradigms in mammalian models that manipulated the OT system in the perinatal period documented lifelong changes in social behavior and related repertoire [17].

Naturally occurring OT is synthesized primarily in the hypothalamus, from where it transfers (also through diffusion) to different parts of the brain, or is being released via the pituitary gland to the blood stream [12]. Copious animal and human studies, spanning decades-long research, have consistently shown the role for OT in the initiation, maintenance, and facilitation of social behavior and motivation [e.g., 18,19]. Specifically, the OT system was found to underlay parental care and parent-infant reciprocal engagement [20,21], alongside other evolutionary-significant processes [22], such as the ability to accurately infer the mental states of others or to engage in social\reciprocal interaction with the surrounding environment [23]. Given its established role in social repertoire, research has also started to explore the involvement of the OT system in the pathophysiology of autism [24,25], as well as its potential as a therapeutic agent [26,27].

Extent evidence suggests a dysregulation of the oxytocinergic system in ASD, although the exact underlying processes responsible for this remain largely unknown. For example, lower plasma levels of OT have been reported in children with ASD [28,29], and abnormal plasma OT and vasopressin have been identified in mothers of ASD-affected children [30]. These studies imply that an abnormal synthesis of these hormones may be related to ASD. Moreover, reduced expression of the OT receptor has been associated with an epigenetic characteristic of the OT system in rodents, namely, methylation of the OT-receptor (*OXTR*) promoter region [31], and variations in *OXTR* expression and methylation patterns have been found to associate with differentiated socio-cognitive propensities, including ASD symptomology [32–35]. Based on this line of findings, showing that exposure to OT during birth alter infant's DNA methylation, and that specific genomic and epigenomic patterns are associated with ASD phenotype, it was postulated that OT-driven epigenetic change during delivery is likely to dysregulate the offspring's brain neuropeptide systems, consequently leading to atypical brain development [15,36].

Interestingly, a retrospective analysis of more than 3000 women delivering full-term infants between 2009 and 2011 has shown that the use of synthetic OT during labor (either induction or augmentation) was independently associated with adverse neonatal outcomes and unexpected admission to the neonatal intensive care unit (NICU) for more than 24 h. Moreover, the researchers found an association between OT-augmented delivery and neonates' APGAR score less than 7 at five minutes (Tsimis et al., Presentation at the ACOG Annual Conference, May 2013). In addition, statistical analysis of 625,042 births in the state of North Carolina, including more than 5500 children at risk for ASD, showed that induction and/or augmentation during childbirth is associated with increased odds of attending a specialized educational program for children with special needs, especially those diagnosed with ASD [8]. In contrast, two earlier studies showed no association between peripartum OT administration and a subsequent ASD diagnosis in offspring. However, gender was not considered in one of the analyses [37], while the other was based on a small sample size [38], which makes it difficult to interpret the validity and generalizability of the reported findings.

Having that, alongside the biological plausibility of an association between exposure to OT during birth and alternations in the offspring's brain neuropeptide systems and subsequent neurodevelopment, we thought to examine whether exposure to OT during labor and delivery will be associated with increased risk for autism diagnosis. To this aim, we conducted an epidemiological analysis using the Danish Civil Registration System (DCRS), and the Danish Medical Birth Register (DMBR). The analysis included all singleton live births in Denmark between 2000 and 2009 ($N = 557{,}040$), with a follow-up of 100% of the cohort through 2012. We hypothesized that exposure to OT during labor and delivery will be associated with increased risk for autism. Based on the well-documented gender bias in autism and the results of the earlier study by Gregory et al. [8], we further postulated that the association between peripartum use of OT and autism would be more robust among males.

2. Materials and methods

2.1. Data sources

The DCRS holds information on the 10-digit personal identification number, sex, date and place of birth, and continuously updated information on vital status, and also the parent's personal identifiers for all persons in Denmark. The personal identification number is used in all other registers, which enables accurate linkage of data between registers for cohort members and their parents. Data from DCRS was merged with data from several other registers including the DMBR. The DMBR records information on birth weight, birth complications, mode of delivery, APGAR score and other obstetrical and perinatal data. The Integrated Database for Longitudinal Labour Market Research (IDA) holds yearly data on a number of variables affecting socioeconomic status. The Danish Psychiatric Central Research Register (DPCR) holds data on all admissions to Danish psychiatric in-patient facilities and from 1995 also data on outpatient visits and for each admission and visit clinical diagnoses according to the Danish modification of International Classification of Diseases, 8th revision (ICD-8) during 1969–1993, and since 1994 the International Classification of Diseases, 10th revision, Diagnostic Criteria for Research (ICD-10-DCR) [39]. The Danish National Patient Register (DNPR) holds similar data from all somatic hospital departments.

2.2. Participants

We identified a cohort of all singleton live births in Denmark by Danish parents from January 1st 2000 through December 31st 2009 (557,040 births) who were alive and living in Denmark at their 1st birthday. The individuals were followed from their 1st birthday