COMMITTEE OPINION

Labor Induction or Augmentation and Autism

ABSTRACT: Functional oxytocin deficiency and a faulty oxytocin signaling pathway have been observed in conjunction with autism spectrum disorder (ASD). Because exogenous synthetic oxytocin commonly is administered for labor induction and augmentation, some have hypothesized that synthetic oxytocin used for these purposes may alter fetal oxytocin receptors and predispose exposed offspring to ASD. However, current evidence does not identify a causal relationship between labor induction or augmentation in general, or oxytocin labor induction specifically, and autism or ASD. Recognizing the limitations of available study design, conflicting data, and the potential consequences of limiting labor induction and augmentation, the Committee on Obstetric Practice recommends against a change in current guidance regarding counseling and indications for and methods of labor induction and augmentation.

Autism spectrum disorder (ASD) is characterized by social and communicative developmental deficits and repetitive, restrictive, or unusual behaviors (1). Autism spectrum disorder includes the diagnosis of autism, Asperger syndrome, and pervasive developmental disorder not otherwise specified (1–2). Approximately 1 in 88 American children is affected by ASD, although the reported prevalence varies widely, exhibiting a 4:1 male predominance and racial and ethnic variation (3). Although the cause of ASD is unclear, it demonstrates a strong genetic predisposition and multifactorial influences. A wide variety of exposures, including many perinatal factors, have been linked to ASD but the suggested associations in many cases are weak, inconsistent, or both among studies, and cannot be equated with a cause and effect relationship (4–9).

Recent research suggests a role for endogenous oxytocin in normal human social and cognitive behavioral development (10). Functional oxytocin deficiency and a faulty oxytocin signaling pathway have been observed in conjunction with ASD (11). Because exogenous synthetic oxytocin commonly is administered for labor induction and augmentation, some have hypothesized that synthetic oxytocin used for these purposes may alter fetal oxytocin receptors and predispose exposed offspring to ASD (12).

Studies to date that have investigated a potential link between oxytocin and ASD have a number of limitations, such as small size, retrospective data collection, and limited control for possible confounding variables. Such characteristics reduce the value of these studies and suggest the need for more research. Among nine studies summarized by Guinchat et al in a 2012 review (13), three studies (7–9) demonstrated a weak but significant association between labor induction and autism in univariate analysis, and six studies (6, 14–18) found no such association. Only one study found an association that persisted after adjustment for potentially confounding variables (7). A 2011 meta-analysis found insufficient evidence to suggest an association between labor induction or augmentation and an increased risk of autism (odds ratio [OR], 1.21; 95% confidence interval [CI], 0.9–1.62) (19).

A larger 2013 analysis reported an increased odds ratio of autism among children born following induced or augmented labor (20). Data for this study were obtained from the North Carolina Detailed Birth Record and Education Research databases linked with children's school records and included 5,500 children with autism (as indicated in their educational records) from among 625,042 live births. Among males, multivariate logistic regression showed a weak association between ASD

diagnosis and labor induction and augmentation (induced and augmented [OR, 1.35; 95% CI, 1.1–1.66]; induction only [OR, 1.18; 95% CI, 1.08–1.3]; and augmentation only [OR, 1.15; 95% CI, 1.05–1.25]); in contrast, among females, ASD diagnosis was modestly associated with labor augmentation only (OR, 1.18; 95% CI, 1.02–1.36); but not with induction or both (20). If risks like these were substantiated in future work, it would represent an attributable risk of approximately 2 per 1,000 for male offspring (95% CI, 1–3 per 1,000) and 3 per 10,000 for female offspring (95% CI, -2–8 per 10,000) for induction or augmentation of labor (20).

Although the Gregory study suggested an association between ASD and labor induction or augmentation, the study design could not determine if such findings were truly a result of cause and effect. This was recognized by the authors, who noted that interpretation of their findings was limited by missing data regarding important potential confounders, the use of education as a proxy for socioeconomic status, and a lack of data regarding induction indications and methods. They concluded that the "results are not sufficient to suggest altering the standard of care regarding induction or augmentation…though additional research is warranted" (20).

Subsequent to its publication, the Gregory study has been criticized because of limitations in defining the exposure and the outcome of interest (21). Critics note that investigators did not know the specific individual or combination of agents that were used for labor induction or augmentation. The critics also note that the American Psychiatric Association reported an editorial error in the criteria listed for the diagnosis of pervasive developmental disorder not otherwise specified in the *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*; an error potentially leading to overdiagnosis during much of the time covered by the Gregory study (21).

In addition to recognizing limitations of available evidence, it is important to view any concerns about an association between labor induction or augmentation and ASD in the context of obstetric practice. Labor induction and augmentation are common in contemporary obstetric practice. Reducing indicated oxytocin use for labor augmentation or induction (eg, when delivery is deemed necessary or when labor is not progressing appropriately) would increase the cesarean delivery rate and could adversely affect maternal or neonatal health.

Conclusion

Current evidence does not identify a causal relationship between labor induction or augmentation in general, or oxytocin labor induction specifically, and autism or ASD. Recognizing the limitations of available study design, conflicting data, and the potential consequences of limiting labor induction and augmentation, the Committee on Obstetric Practice recommends against a change in current guidance regarding counseling and indications for and methods of labor induction and augmentation (22).

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington (VA): APA; 2013. ⇐

2. Levy SE, Mandell DS, Schultz RT. Autism [published erratum appears in Lancet 2011;378:1546]. Lancet 2009;374: 1627–38. [PubMed] [Full Text] ⇐

3. Prevalence of autism spectrum disorders–Autism and Developmental Disabilities Monitoring Network, 14 sites, United States, 2008. Autism and Developmental Disabilities Monitoring Network Surveillance Year 2008 Principal Investigators. Centers for Disease Control and Prevention. MMWR Surveill Summ 2012;61:1–19. [PubMed] [Full Text] ⇐

4. Hultman CM, Sparen P, Cnattingius S. Perinatal risk factors for infantile autism. Epidemiology 2002;13:417–23. [PubMed] ⇐

5. Bilder D, Pinborough-Zimmerman J, Miller J, McMahon W. Prenatal, perinatal, and neonatal factors associated with autism spectrum disorders. Pediatrics 2009;123:1293–300. [PubMed] [Full Text] ⇐

6. Brimacombe M, Ming X, Lamendola M. Prenatal and birth complications in autism. Matern Child Health J 2007; 11:73–9. [PubMed] ⇐

7. Dodds L, Fell DB, Shea S, Armson BA, Allen AC, Bryson S. The role of prenatal, obstetric and neonatal factors in the development of autism. J Autism Dev Disord 2011;41: 891–902. [PubMed] ⇐

8. Juul-Dam N, Townsend J, Courchesne E. Prenatal, perinatal, and neonatal factors in autism, pervasive developmental disorder-not otherwise specified, and the general population. Pediatrics 2001;107:E63. [PubMed] [Full Text] ⇐

9. Glasson EJ, Bower C, Petterson B, de Klerk N, Chaney G, Hallmayer JF. Perinatal factors and the development of autism: a population study. Arch Gen Psychiatry 2004;61: 618–27. [PubMed] [Full Text] ⇐

10. Ebstein RP, Israel S, Lerer E, Uzefovsky F, Shalev I, Gritsenko I, et al. Arginine vasopressin and oxytocin modulate human social behavior. Ann N Y Acad Sci 2009;1167: 87–102. [PubMed] ⇐

11. Gregory SG, Connelly JJ, Towers AJ, Johnson J, Biscocho D, Markunas CA, et al. Genomic and epigenetic evidence for oxytocin receptor deficiency in autism. BMC Med 2009; 7:62. [PubMed] [Full Text] ⇐

12. Wahl RU. Could oxytocin administration during labor contribute to autism and related behavioral disorders?--A look at the literature. Med Hypotheses 2004;63:456–60. [PubMed] ⇐

13. Guinchat V, Thorsen P, Laurent C, Cans C, Bodeau N, Cohen D. Pre-, peri- and neonatal risk factors for autism. Acta Obstet Gynecol Scand 2012;91:287–300. [PubMed] [Full Text] ⇐

14. Burstyn I, Sithole F, Zwaigenbaum L. Autism spectrum disorders, maternal characteristics and obstetric complications among singletons born in Alberta, Canada. Chronic Dis Can 2010;30:125–34. [PubMed] [Full Text] ⇐

15. Laxer G, Rey M, Ritvo ER. A comparison of potentially pathologic factors in European children with autism,

Down's syndrome, and multiple physical handicaps. J Autism Dev Disord 1988;18:309–13. [PubMed] ⇐

16. Mason-Brothers A, Ritvo ER, Pingree C, Petersen PB, Jenson WR, McMahon WM, et al. The UCLA-University of Utah epidemiologic survey of autism: prenatal, perinatal, and postnatal factors. Pediatrics 1990;86:514–9. [PubMed] ⇐

17. Maimburg RD, Vaeth M, Schendel DE, Bech BH, Olsen J, Thorsen P. Neonatal jaundice: a risk factor for infantile autism? Paediatr Perinat Epidemiol 2008;22:562–8. [PubMed] ⇐

18. Stein D, Weizman A, Ring A, Barak Y. Obstetric complications in individuals diagnosed with autism and in healthy controls. Compr Psychiatry 2006;47:69–75. [PubMed] ⇐

19. Gardener H, Spiegelman D, Buka SL. Perinatal and neonatal risk factors for autism: a comprehensive meta-analysis. Pediatrics 2011;128:344–55. [PubMed] [Full Text] ⇐

20. 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. [PubMed] [Full Text] ⇐

21. Vintzileos AM, Ananth CV. Does augmentation or induction of labor with oxytocin increase the risk for autism? Am J Obstet Gynecol 2013;209:502–4. [PubMed] [Full Text] ⇐

22. Induction of labor. ACOG Practice Bulletin No. 107. American College of Obstetricians and Gynecologists. Obstet Gynecol 2009;114:386–97. [PubMed] [*Obstetrics & Gynecology*] ⇐