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EDITORIALS

Epidural labour analgesia and autism spectrum disorder: is the current evidence sufficient to dismiss an association?

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Summary

Findings from a population-based study using a sibling-matched analysis published in this issue of the *British Journal of Anaesthesia* indicate that epidural labour analgesia is not associated with an increased risk of autism spectrum disorder. These findings are consistent with those from three other population-based studies that used similar methodological approaches. Cumulatively, these robust, high-quality epidemiological data support the assertion that there is no meaningful association between epidural labour analgesia and autism spectrum disorder in offspring.

Keywords: autism spectrum disorder; epidural analgesia; labour; neurodevelopmental disorders; offspring

Neuraxial labour analgesia (most commonly epidural analgesia) is the most effective form of pain relief during labour.[1] Data from the USA indicate that in 2015 a high proportion (73%) of pregnant individuals received epidural labour analgesia.[2] Despite its gained popularity, findings from early observational studies have linked epidural labour analgesia to unfavourable maternal and perinatal outcomes, for example an increased risk of Caesarean delivery and long-term back pain.[3,4] Subsequent RCTs and meta-analyses have determined that these associations are not causal and are most likely explained by residual confounding, confounding by indication, or selection bias.[1,5–7] For example, abnormal labour (or dystocia) has been linked to an increased risk of Caesarean delivery.[8] However, because abnormal labour is more painful than normal labour, and women who experience increased pain in labour are more likely to request epidural labour analgesia, confounding by indication is the most likely explanation for the purported link between epidural labour analgesia and the increased risk of Caesarean delivery.[8] More recently, epidemiological studies, including a study in

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this issue of the *British Journal of Anaesthesia* by Ren and colleagues,[9] have explored whether there is an association between epidural labour analgesia and an increased risk of autism spectrum disorder and other neurodevelopment disorders in offspring.[10–13]

What are the clinical features and aetiology of autism spectrum disorder?

We summarise the main clinical features and aetiology of autism spectrum disorder to provide clinical and scientific context for exploring a possible association between epidural labour analgesia and autism spectrum disorder, a neurodevelopmental disorder characterised by pronounced deficits in social communication and repetitive and restricted behaviours. A diagnosis of autism spectrum disorder often presents substantial challenges for families and caregivers; compared with individuals with other neurodevelopmental disorders, individuals with autism spectrum disorder achieve lower levels of education, employment, and independent living.[14,15] Given these challenges, an association between epidural labour analgesia and an increased risk of neurodevelopment disabilities in offspring, such as autism spectrum disorder, may deter pregnant individuals from requesting epidural analgesia.

The aetiology of autism spectrum disorder is complex. Specifically, current neurobiological models conceptualise autism spectrum disorder as the result of atypical brain development, with a focus on disrupted brain connectivity.[16,17] Brain connectivity is an important concept in cognitive and social neuroscience. Although early models of brain function posited that individual brain regions underlie distinct cognitive functions, it is now widely accepted that complex cognitive and social functions are the result of coordinated neural activity between spatially distributed brain regions. For example human social function, such as comprehending a story or identifying a person's face,[18] is thought to rely on coordinated activity throughout a network of brain regions distributed across the frontal, temporal, parietal, and occipital lobes. Accordingly, atypical connectivity within these 'social brain' networks may cause disruptions in social function, such as those seen in autism spectrum disorder. Current neurobiological models of autism spectrum disorder further posit that disruptions in brain connectivity arise during early stages of brain development. For example studies have shown that functional and structural brain connectivity in high-risk 6-month-old children predicts whether they will be diagnosed with autism spectrum disorder at age 2 yr,[19] and cross-sectional studies have shown that aberrant patterns of brain connectivity are prominent throughout the life span in affected individuals.[20] Neurobiological evidence from animal models of autism suggests that disruptions in brain connectivity in autism spectrum disorder stem from one or more abnormal neurodevelopmental events, including neurogenesis, neuronal migration, and synaptogenesis.[21]

The disorder is linked with multiple genetic and environmental factors[22]; current estimates for the heritability of autism spectrum disorder are between 50% and 80%.[23–25] Genetics research has implicated rare and common inherited variation and *de novo* mutation,[26,27] whereas findings from studies of environmental variations have implicated advanced parental age, maternal conditions, and exposure to toxins. Exposure to perinatal factors, including birth asphyxia, breech or transverse presentation, and pre-eclampsia, has also emerged as a potential risk for autism spectrum disorder; however, the population-attributable risk for perinatal factors is estimated to be small (0.3%).[28] In addition, medication exposure during pregnancy has been implicated as a risk factor, including exposure to valproic acid, an anticonvulsant, and asthma medications.[29,30] Importantly, the majority of risk factors associated with autism spectrum disorder occur before birth.[22]

Is there an association between epidural labour analgesia and autism spectrum disorder risk in offspring?

In the wake of research that implicated both perinatal factors and medication exposure as potential risk factors, a population-based study by Qiu and colleagues[12] reported a 37% increased risk of autism spectrum disorder in children of mothers who received epidural labour analgesia. Similar to the aforementioned methodological concerns linking epidural labour analgesia with outcomes such as Caesarean delivery and back pain, the characteristics of women who chose epidural labour analgesia were markedly different than those of women who did not. Despite attempts to control for these differences in the statistical analysis, critics opined that residual confounding bias was a likely explanation for the main findings.[31,32] Indeed, several professional organisations, including the Royal College of Anaesthetists, the Society for Obstetric Anesthesia and Perinatology, and the American College of Obstetricians and Gynecologists, issued cautionary statements about assuming a causal relationship between epidural labour analgesia and autism spectrum disorder in offspring.[33,34]

Since publication of the Qiu and colleagues study and the writing of this editorial,[12] three population-based cohort studies have been published that included a larger set of maternal, obstetric, and infant characteristics as potential confounders of the association between epidural labour analgesia and autism spectrum disorder risk.[10,11,13] These studies varied in country of origin (Denmark, Canada), exposure and outcome classification, and follow-up periods for diagnoses (Table 1). In two studies, no association was found between epidural labour analgesia and autism spectrum disorder risk after adjustment for potential confounders.[11,13] In the third study,[10] a small increase in risk was observed in the fully adjusted model (adjusted hazard ratio [HR]=1.10; 95% confidence interval [CI]=0.99–1.20) that barely met the threshold for statistical significance.[1]

Unmeasured, or poorly measured, clinical, genetic, and environmental factors likely explain the positive association between epidural labour analgesia and autism spectrum disorder risk reported by Qiu and colleagues.[12] Hanley and colleagues[10] and Wall-Wieler and colleagues[13] accounted for possible confounding by unmeasured environmental and genetic factors shared within families by applying a sibling-

[1] After writing this editorial, an observational study was published by Straub et al (JAMA Netw Open. 2021;4(12): e2140458.) which examined 2 large public health utilization datasets from the United States. The authors did not find evidence of a strong association between epidural labour analgesia and an increased risk of autism spectrum disorder. A very weak association was observed, likely explained by residual confounding.'

Table 1 Summary details of studies investigating the potential association between epidural labour analgesia and autism spectrum disorder. *Denominator is deliveries. †Denominator is children. ‡In the discordant analysis where only women were included if they had ≥2 children with ≥1 child with ASD and ≥1 other child not diagnosed with ASD; adjusted HR=1.07; 95% CI=0.87–1.30. ASD, autism spectrum disorder; CI, confidence interval; ELA, epidural labour analgesia; HR, hazard ratio; ICD, International Classification of Diseases; OR, odds ratio.

	Hanley	Mikkelsen	Wall-Weiler	Qiu
Study population	388 254 singleton vaginal deliveries in 258 472 women in British Columbia, Canada	479 178 liveborn offspring born to 338 449 women in Denmark	123 175 singleton vaginal deliveries in Manitoba, Canada	147 895 singleton vaginal deliveries born to 119 973 women in hospitals within an integrated healthcare system in Southern California, USA
Study period	2000–14; follow-up period until diagnosis of ASD, death, or study end date December 31, 2016	2006–13; follow-up period from first birthday until ASD diagnosis, death, emigration, diagnosis of disorder inherently linked to ASD, or study end date December 31, 2017.	2005–16; follow-up period after the offspring reached at least 18 months of age until April 1, 2019. Offspring were censored because of death or emigration.	2008–15; follow-up period from first birthday until ASD diagnosis, last date of health plan enrolment, death, or study end date, December 31, 2018.
Data source/classification for ELA	British Columbia Perinatal Data Registry	Codes within the Danish Patient Register	Codes within the Manitoba Hospital Abstracts dataset	Procedure notes and pharmacy data in patients' electronic medical records
Data source/classification for ASD	Diagnoses data made by trained paediatrician, psychiatrist, or psychologist within the British Columbia Autism Assessment Network or private practitioners in Britsh Columbia.	ICD-10 codes for any of the following disorders: autistic disorder; atypical autism; Asperger syndrome; other pervasive developmental disorder	At least 1 ICD-9 diagnosis code for the following disorders: autism disorder; Asperger syndrome; pervasive developmental disorder	An ICD-9 diagnosis code for the following disorders: autism disorder; Asperger syndrome; or pervasive developmental disorder, or an equivalent code used by the healthcare network from two separate healthcare encounters
Total number of offspring diagnosed with ASD	5192 (1.34%)	6428 (1.3%)	2257 (1.8%)	2524 (1.7%)
Event rate (%) of ASD in ELA group	1710/111 480* (1.53%)	1409/92 900† (1.5%)	985/47 011 (2.1%)	2039/105 710 (1.9%)
Event rate (%) of ASD in non-ELA group	3482/276 774* (1.26%)	5019/386 278† (1.3%)	1272/76 164 (1.7%)	485/38 176 (1.3%)
Unadjusted OR or HR (95% CI)	HR=1.32 (1.24–1.40)	HR=1.29 (1.21–1.37)	HR=1.25 (1.15–1.36)	HR=1.48 (1.34–1.65)
Fully adjusted OR or HR (95% CI)	HR=1.09 (1.00–1.15)	HR=1.05 (0.98–1.11)	HR=1.08 (0.97–1.2)	HR=1.37 (1.23–1.53)
Fully adjusted HR in sibling analysis (95% CI)	HR=1.10 (0.99–1.20)‡	Not done	HR=0.97 (0.78–1.22)	Not done

matched design. Sibling-matched designs have advantages over conventional observational studies by reducing bias caused by residual confounding by unmeasured variables that are consistent within families. In the sibling-matched analyses,[10,13] the 95% CIs for the effect estimates for the association between epidural labour analgesia and autism spectrum disorder risk overlapped the null (no increased risk in women who receive epidural labour analgesia), providing further evidence of an unmeasured confounding effect in the initial cohort analyses. In yet another recent observational study of more than 220 000 mother–offspring pairs in Scotland, Kearns and collegues[35] found no statistically significant associations between epidural labour analgesia and abnormal assessment of offspring motor, social, or communication development outcomes within the first 2 yr of life.

The new study by Ren and colleagues[9] provides further evidence to support the absence of a meaningful association between epidural labour analgesia and autism spectrum disorder risk. The authors performed a population-based cohort study comprising 624 952 liveborn singleton births to investigate links between autism spectrum disorder and other neurodevelopmental disorders (including specific developmental disorder [SDD], attention deficit hyperactivity disorder [ADHD], intellectual disability [ID], and epilepsy) with epidural labour analgesia. By linking several population-wide Danish databases, the investigators accounted for a very large set of prepregnancy, socioeconomic, pregnancy, and labour-related confounders, and any parental history of psychiatric disease. After adjusting for potential confounders, the risk of autism spectrum disorder in offspring was increased by 11% in women who used epidural labour analgesia (HR=1.11; 95% CI, 1.04–1.18). However, the increased risk associated with epidural labour analgesia was not observed in a sibling-matched analysis (HR=1.03; 95% CI, 0.84–1.27). Findings from the main analyses were similar in all sensitivity analyses, which included more restrictive cohort selection (e.g. only vaginal deliveries, only offspring with a favourable perinatal outcome), and a more restrictive classification of neurodevelopmental disorders (e.g. an offspring diagnosis made only by psychiatrists). The investigators also observed no dose–response relationship between the duration of epidural labour analgesia and autism spectrum disorder risk. No associations between epidural labour analgesia and the other neurodevelopmental outcomes were identified in the sibling-matched analyses.

The findings of Ren and colleagues[9] are important for several reasons. First, the study is population-specific and has excellent longitudinal data capture. Second, outcomes were classified using International Classification of Disease codes version 10 which the authors state have high positive predictive value for neurodevelopmental disorders within the Danish population.[9] Third, the methodological approach accounted for varying types of bias, including confounding bias, immortal time bias, and potential outcome misclassification. Fourth, the null associations observed in the sibling-matched analyses are consistent with those observed by the two prior studies that performed a sibling-matched analysis.[10,13] Fifth, the absence of meaningful associations between epidural labour analgesia and other neurodevelopmental disorders provides further evidence suggesting that epidural labour analgesia may not have detrimental effects on neurodevelopment. Sixth, the study used identical data sources and approaches for classifying epidural labour analgesia and autism spectrum disorder as the recent study by Mikkelsen and colleagues.[11] Interestingly, the reported adjusted hazard ratios differed slightly between the studies from Ren and colleagues[9] and Mikkelsen and colleagues[11] (adjusted HR=1.11; 95% CI, 1.04–1.18; adjusted HR=1.05; 95% CI, 0.98–1.11, respectively).[9,11] A different selection of confounders and analytic strategies may explain the small between-study difference in the magnitude of the reported association. Despite these differences, the point estimates in the main models in both studies were close to the null and are likely accounted for by residual confounding. However, these differences serve to emphasise the importance of replication in the scientific method, and the need for detailed descriptions of study methods.

Does an association between epidural labour analgesia and autism spectrum disorder have biologic plausibility?

In their study, Qiu and colleagues[12] cited indirect findings from previous animal and human studies to provide evidence of biological plausibility. In a cited animal study,[36] which comprised a small number (11 treated and eight non-exposed) term rhesus monkeys, the investigators used epidural bupivacaine doses that are substantially higher (0.5% bupivacaine, 0.6 mg kg^{-1} infusion over 20 min) than those used in modern obstetric anaesthetic practice. Findings were mixed; no between-group differences were observed in neonatal abnormalities or specific cognitive defect, but several between-group behavioural differences were observed. To our knowledge, this study has never been replicated. Qiu and colleagues also cited three studies in humans to support the assertion that epidural analgesia exposure is linked to autism spectrum disorder.[37–39] However, all three studies failed to account for confounder bias.[37–39]

Epidural labour analgesia causes fever in a subset of women; the aetiology is currently not clear, but the mechanism is likely inflammatory.[40] A recent review confirmed the link between epidural analgesia and fever, and a link between intrapartum fever and neonatal brain injury.[41] However, current evidence is insufficient to link epidural-related maternal fever to poor neurological outcome in offspring. Reassuringly, Qiu and colleagues[12] did not identify an association between intrapartum fever and offspring autism spectrum disorder.

What do these studies' findings mean for patients and clinicians?

Findings of the most recent epidemiological studies, including the study by Ren and colleagues,[9] should help allay the fears of pregnant individuals, families, and their care providers about a perceived risk of offspring autism spectrum disorder from receiving epidural labour analgesia.[42] However, the impact of flawed research on patients' opinions and beliefs about medical interventions should not be underestimated. The most well-known example is the effect of flawed research purporting an association between vaccines and autism spectrum disorder. The increase in the number of parents refusing or delaying vaccination for their children, resulting in outbreaks of vaccine-preventable and potentially fatal disease, have been serious and long-lasting.[43] Although it is not clear whether

pregnant individuals will be less likely to consider epidural labour analgesia based on the media attention given to the positive association between epidural labour analgesia and autism spectrum disorder reported by Qiu and colleagues,[12] this would be unfortunate, particularly for the subset of parturients who likely benefit from epidural labour analgesia, such as those with comorbidities and those at increased risk for intrapartum Caesarean delivery. Fortunately, publication of the non-confirmatory studies occurred soon after the Qiu and colleagues[12] study. Until we know more, anaesthetists and other childbirth professionals should continue to highlight the important benefits of epidural labour analgesia to pregnant individuals during prenatal office visits and in prenatal classes.

Do we need more replication studies?

There are now four high-quality population-based studies which applied similar methodological approaches and reported very similar findings in the main analyses.[9–11,13] Furthermore, three sibling-based analyses confirmed that unmeasured genetic and environmental factors play an important role in explaining any positive association between epidural labour analgesia and autism spectrum disorder risk.[9,10,13] Given the consistency and totality of these findings, plus the recent additional evidence by Kearns and colleagues,[35] we believe that there is now sufficiently robust, high-quality epidemiological data to support the assertion that there is no meaningful association between epidural labour analgesia and autism spectrum disorder. Cumulatively, these studies answered the appropriate call by Qui and colleagues[12] for further research to confirm their findings, but with results that instead refuted their original finding of a positive association between epidural labour analgesia and offspring autism spectrum disorder risk. The findings of the follow-up studies remind us to be cautious when examining statistical inference within initial exploratory analyses and to base any take-home messages and generalisations on cumulative knowledge rather than the findings of a single study.[44]

We acknowledge that proving or refuting cause and effect, that is whether epidural labour analgesia is an aetiologic factor for autism spectrum disorder, is not possible because a clinical trial that randomises women to receive epidural labour analgesia with 'sham' epidural analgesia is unethical, immoral, and therefore unfeasible. Nonetheless, the accumulating epidemiological data indicate no clear association between epidural labour analgesia and autism spectrum disorder risk in offspring. These data should provide sufficient reassurance to care providers when counselling pregnant individuals about the risks of epidural labour analgesia.

Authors' contributions

AJB, DAA, CAW: drafting manuscript and final approval of manuscript.

Declarations of interest

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