Research

Antenatal corticosteroid administration and attention-deficit/hyperactivity disorder in childhood: a regression discontinuity study

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Abstract

Background: Antenatal corticosteroids reduce respiratory morbidity in preterm infants, but their use during late preterm gestation (34–36 weeks) is limited because their safety for longer-term child neurodevelopment is unclear. We sought to determine if fetuses with higher probability of exposure to antenatal corticosteroids had increased rates of prescriptions for attention-deficit/hyperactivity disorder (ADHD) medication in childhood, using a quasiexperimental design that better controls for confounding than existing observational studies.

Methods: We identified 16 358 children whose birthing parents were admitted for delivery between 31 + 0 (31 weeks, 0 days)

and 36 + 6 weeks' gestation in 2000–2013, using a perinatal data registry from British Columbia, Canada, and linked their records with population-based child ADHD medication data (2000–2018). We used a regression discontinuity design to capitalize on the fact that pregnancies presenting for delivery immediately before and immediately after the clinical cut-off for antenatal corticosteroid administration of 34 + 0 weeks' gestation have very different levels of exposure to corticosteroids, but are otherwise similar with respect to confounders.

Results: Over a median follow-up period of 9 years, 892 (5.5%) children had 1 or more dispensations of ADHD

medication. Children whose birthing parents were admitted for delivery just before the corticosteroid clinical cut-off of 34 + 0 weeks' gestation did not appear to be more likely to be prescribed ADHD medication than those admitted just after the cut-off (rate ratio 1.1, 95% confidence interval [CI] 0.8 to 1.6; 1.3 excess cases per 100 children, 95% CI –2.5 to 5.7).

Interpretation: We found little evidence that children with higher probability of exposure to antenatal corticosteroids have higher rates of ADHD prescriptions in childhood, supporting the safety of antenatal corticosteroids for this neurodevelopmental outcome.

A ntenatal corticosteroid administration to prevent neonatal respiratory morbidity and death has long been recommended for pregnancies with threatened preterm delivery before 34 weeks' gestation.[1,2] Although evidence has shown that antenatal corticosteroids are also effective in preventing neonatal morbidity at late preterm gestation (34–36 weeks),[3] their routine use at these ages is more controversial.[4,5] Serious respiratory morbidity and death become less common with advancing gestation,[6,7] so the potential harms of corticosteroids, including their unknown impact on child neurodevelopment, become a more important consideration than earlier in gestation.[8–10]

High-quality evidence on the safety of antenatal corticosteroid administration for child neurodevelopment is scarce. Evidence from follow-up of randomized trials has generally been reassuring, but is limited by high losses to follow-up and small

sample sizes.[11–14] Several observational studies have explored the association between antenatal corticosteroids and child neurodevelopment,[15,16] but their findings are prone to confounding.[5] Further, they have tended to focus on rare neurodevelopmental conditions such as cerebral palsy,[15] and our understanding of the association with common neurodevelopmental outcomes such as attention-deficit/hyperactivity disorder (ADHD) is limited. Repeat courses of antenatal corticosteroids have been linked with increased hyperactivity in animal research[17] and with increased attention problems in children at age 2 years in 1 randomized trial,[18] supporting the importance of investigating this outcome.

In this study, we aimed to investigate whether children with a higher probability of in-utero exposure to antenatal corticosteroids were more likely to be prescribed ADHD medications.

Methods

Study design

We used a regression discontinuity design, which is a quasi-experimental approach that exploits how treatment decisions often differ above and below a clinical cut-off or threshold that is somewhat arbitrary. Individuals immediately on either side of the cut-off tend to be highly similar except for their probability of receiving treatment; therefore, comparisons of individuals immediately above and below the threshold can provide evidence for causal effects of the intervention that may be less confounded than direct comparisons of individuals who did or did not receive treatment, as in standard observational studies.[19,20] For example, during our study period, a Canadian clinical practice guideline recommended that pregnancies with threatened preterm delivery should be treated with antenatal corticosteroids up to 33 + 6 (33 weeks, 6 days) weeks' gestation, but not at 34 + 0 weeks or later.[21] Thus, infants just below and just above the 34-week threshold have very different probabilities of exposure to antenatal corticosteroids, but are otherwise very similar with respect to confounder characteristics.

Using the gestational age cut-off of 33 + 6 weeks, we have previously shown that the regression discontinuity design can produce estimates of the short-term benefits of antenatal corticosteroids comparable to those of randomized trials, with a 19% lower risk of neonatal respiratory morbidity or death[22] compared with the 20% reduction in the primary respiratory outcome reported in the Antenatal Late Preterm Steroids trial.[3]

Study population

We included all live, singleton births to pregnant individuals admitted for delivery between 31 + 0 weeks' and 36 + 6 weeks' gestation in British Columbia, Canada, from April 2000 to March 2013 (irrespective of reason for admission). We linked population-based medical records from the BC Perinatal Data Registry, which contains abstracted records for more than 99% of births in the province, with the PharmaNet register, which contains records of all outpatient prescriptions.[23,24] We also linked coverage records and basic census geo-data from BC Vital Statistics and Medical Services.[25,26] Linkages were conducted using names, birthdates and Medical Services Plan numbers (a unique identifier for provision of universal health care). We obtained records from PharmaNet, BC Vital Statistics and Medical Services from April 2000 to March 2018, ensuring 5 or more years of follow-up for all individuals.

Exposure

Our primary exposure was gestational age at the time of hospital admission, as we hypothesized that this better approximated the timing of decision-making on antenatal corticosteroid administration than gestational age at delivery. Gestational age in days was estimated using last menstrual period, confirmed or revised with early ultrasonography.[27]

We limited our cohort to births with a day-specific, ultrasonography-confirmed estimate of gestational age. Validation work has established that about 85% of births at this time had a prenatal ultrasonography;[28] however, day-specific estimates were available for only 56% of the population because, before 2008, information

on gestational age by ultrasonography was abstracted in completed weeks only, not days. Moreover, scans done after 20 + 0 weeks are not abstracted. As most births with missing day-specific estimates from ultrasonography were missing owing to administrative reasons, we do not believe that this introduced meaningful bias.[22]

Antenatal corticosteroid administration

Antenatal corticosteroid administration is documented in the BC Perinatal Data Registry as a binary variable indicating administration of any corticosteroid during the delivery admission for the purpose of fetal lung maturation. We used this variable for descriptive purposes only, as our primary exposure was the gestational age at admission for delivery rather than individual-level corticosteroid exposure.

Outcomes

Our primary outcome was the dispensation of 1 or more medications categorized under N06B in the Anatomical Therapeutic Chemical classification, which corresponds to "psychostimulants, agents used for ADHD, and other nootropics." This category includes all first-line ADHD medications recommended by the Canadian Paediatric Society.[29] We also evaluated 2 or more dispensations of N06B medications as a secondary outcome. We classified infant deaths as having experienced the outcome to avoid selection bias (i.e., infants who did not receive corticosteroids may not have survived to develop ADHD).

Statistical analysis

We calculated descriptive characteristics of the study population using means with standard deviations, medians with interquartile ranges (IQR) or frequencies with percentages. We calculated week- and day-specific proportions to describe patterns of antenatal corticosteroid administration and ADHD dispensations by gestational age. We used a regression discontinuity design[30] to compare rates of ADHD prescriptions among children whose birthing parents were admitted just before and just after 34 + 0 weeks' gestation (< 34 + 0 v. ≥ 34 + 0 weeks). The model effectively estimates the effect of routine antenatal corticosteroid administration as the difference in outcome rate immediately before versus immediately after the discontinuity, controlling for underlying gestational age trends before and after the discontinuity separately (illustrated in Appendix 1, Figure S1, available at www.cmaj.ca/lookup/doi/10.1503/cmaj.211491/tab-related-content). The estimate produced by the model is analogous to an intention-to-treat effect, because it reflects the impact of antenatal corticosteroid administration as it occurs in a real-world setting (in which imperfect adherence to corticosteroid recommendations occurs because of insufficient time to administer corticosteroids before delivery, incomplete courses and mistimed administration).

We implemented our regression discontinuity model using pooled log binomial regression. Individuals were censored at the end of follow-up (Mar. 31, 2018) or if they moved out of province. We used triangular weighting to assign the greatest weight to infants delivered immediately on either side of the cut-off at 34 + 0 weeks, and the least weight to those furthest away from the cut-off (31 + 0 and 36 + 6 weeks). We bootstrapped 95% confidence intervals (CIs). We used the model coefficients to estimate the number of excess

ADHD prescriptions per 100 children by age 13 years (i.e., the absolute difference in cumulative risk) at the point of the discontinuity, with bootstrapped 95% CIs. Our pre-analysis plan and statistical code are available online (https://osf.io/4exfq/).

Sensitivity analyses

We conducted standard checks to verify model assumptions.[31] We evaluated trends in maternal–fetal characteristics to ensure that they changed smoothly across gestation, evaluated whether a quadratic term for gestational age improved model fit, and altered the gestational age time window (bandwidth) on either side of 34 + 0 weeks included in our analyses. Finally, we controlled for male fetal sex as a confounder and included a product term between sex and before and after the cut-off.

Ethics approval

Results

We identified 294 807 live, singleton births with a day-specific, ultrasonography-confirmed estimate of gestational age. We excluded 278 449 births (94.5%) admitted for delivery after 36 + 6 weeks' or before 31 + 0 weeks' gestation, leaving 16 358 (5.5%) pregnancies for analysis. Over the 16 358 pregnancies, 2594 (15.8%) were admitted before 34 + 0 weeks and 13 764 (84.1%) were admitted at 34 + 0 weeks or later. The median duration of follow-up was 9 (IQR 7–13) years.

Table 1: Descriptive characteristics of pregnancies admitted for delivery between 31 + 0 and 36 + 6 weeks' gestation, British Columbia, Canada, 2000–2013			
	No. (%) of pregnancies*		
Characteristic	Total *n* = 16 358	Admission before 34 wk *n* = 2594	Admission at or after 34 wk *n* = 13 764
Age of gestational parent, yr, mean ± SD	31.2 ± 5.7	31.5 ± 5.7	31.1 ± 5.7
Nulliparous	8129 (49.7)	1367 (52.7)	6762 (49.1)
Pre-pregnancy BMI (kg/m²)†	24.5 ± 5.5	24.5 ± 5.4	24.4 ± 5.5
Smoking in pregnancy	1878 (11.5)	288 (11.1)	1590 (11.6)
Neighbourhood income quintile			
1 (lowest)	3581 (21.9)	551 (21.7)	3030 (22.0)
2	3419 (20.9)	587 (23.1)	2832 (20.6)
3	3235 (19.8)	493 (19.4)	2742 (19.9)
4	3115 (19.0)	466 (18.3)	2649 (19.3)
5 (highest)	2401 (14.7)	383 (15.1)	2018 (14.7)
Missing	607 (3.7)	114 (4.4)	493 (3.6)
Hypertensive disorder of pregnancy	2543 (15.6)	501 (19.3)	2042 (14.8)
Diabetes in pregnancy	2811 (17.2)	499 (19.2)	2312 (16.8)
Iatrogenic delivery‡	7204 (44.0)	1151 (44.4)	6053 (44.0)
Gestational age at delivery, wk			
31	350 (2.1)	350 (13.5)	–
32	629 (3.9)	629 (24.3)	–
33	1074 (6.6)	1074 (41.4)	–
34	1942 (11.9)	357 (13.8)	1585 (11.5)
35	3497 (21.4)	93 (3.6)	3404 (24.7)
36	7806 (47.7)	51 (2.0)	7755 (56.3)
37	936 (5.7)	24 (0.9)	912 (6.6)
38	79 (< 1)	8 (0.3)	71 (0.5)
≥ 39	45 (< 1)	8 (0.3)	37 (0.3)
Male fetus	9243 (56.5)	1522 (58.7)	7721 (56.1)
Birthweight, g, mean ± SD	2671 ± 534	2110 ± 486	2777 ± 473

Note: BMI = body mass index, SD = standard deviation.
*Unless indicated otherwise.
†Among 11 973 pregnancies with BMI available.
‡Delivery after prelabour cesarean or labour induction.

As expected for a cohort of preterm births, hypertensive disorders of pregnancy and diabetes were common ($n = 2543$, 15.6% and $n = 2811$, 17.2%, respectively), and 7204 (44.0%) infants had an iatrogenic delivery (Table 1). Although pregnancies admitted before 34 + 0 weeks were moderately more likely than those admitted 34 weeks or later to be nulliparous (53.0% v. 49.3%, respectively), have a hypertensive disorder of pregnancy (19.3% v. 14.8%, respectively) or have diabetes (19.2% v. 16.8%, respectively), these characteristics (and others) changed smoothly across our gestational age range (Appendix 1, Figure S2), with no abrupt changes at 34 + 0 weeks' gestation that could introduce confounding.

Patterns of antenatal corticosteroid administration

Pregnancies admitted before 34 + 0 weeks' gestation were 24 times more likely to be exposed to corticosteroids than those admitted later (Figure 1). Antenatal corticosteroid administration decreased sharply at 34 + 0 weeks, from about 50% of pregnancies admitted before 34 + 0 to less than 2% for those admitted after the cut-off. The decrease occurred primarily over a 4-day period for admissions between 33 + 4 and 34 + 0 weeks.

Patterns of attention-deficit/hyperactivity disorder medication dispensing

About 1 in 20 children were prescribed 1 or more medications for ADHD, with a median age at first prescription of 8 years (Table 2). Three-quarters ($n = 676$, 75.7%) of dispensation were to boys. Children with ADHD medication prescriptions filled a median of 11 dispensations, of which nearly two-thirds (63.9%) were for methylphenidate hydrochloride.
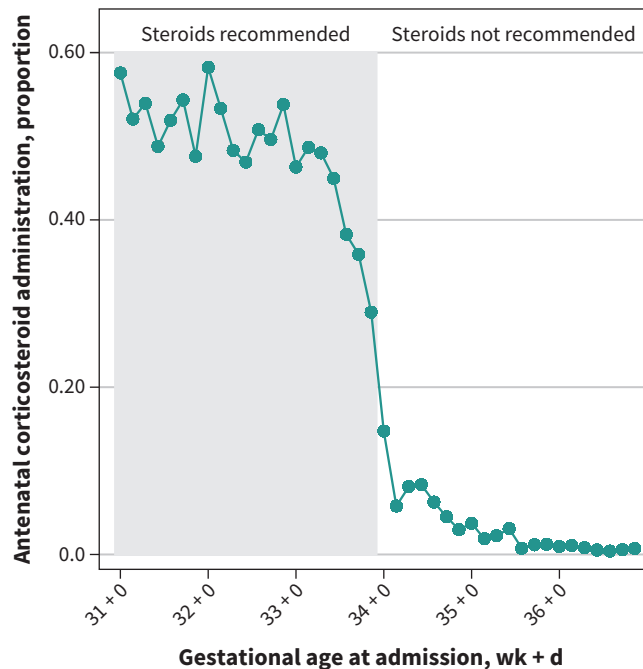
Regression discontinuity analysis

Figure 2 shows the crude prevalence of ADHD prescriptions by gestational week at admission. Although prescriptions decreased steadily with advancing gestational age (from 9.4% in children born at 31 weeks to 5.8% for those born at 36 weeks), no abrupt difference distinguished between children whose birthing parents were admitted for delivery just before versus just after 34 + 0 weeks' gestation (6.8% at 33 weeks v. 6.8% at 34 weeks). This was confirmed in the regression discontinuity analysis (Figure 3 and Table 3), which found no clinically meaningful difference in ADHD medication dispensation rates between children whose birthing parents were admitted just before versus just after 34 + 0 weeks (rate ratio 1.1, 95% CI 0.8 to 1.6; 1.3 excess cases per 100 children by age 13, 95% CI −2.5 to 5.7). Results were similar for the secondary outcome of 2 or more dispensations.

Sensitivity analyses

Results were similar after shortening the gestational age window to 14 days on either side of the discontinuity of 34 + 0 weeks (Appendix 1, Table S1). After shortening the gestational age window to 7 days, the model estimated a significantly increased risk of childhood prescriptions for ADHD medications among infants born just before 34 + 0 weeks (rate ratio 2.5, 95% CI 1.3 to 4.4). However, as shown in Appendix 1, Figure S3, this result appeared to be driven by an estimated increase in risk between 33 + 0 and 33 + 6 weeks (i.e., an upward slope line), which is counter to the

Figure 1: Rate of antenatal corticosteroid administration by gestational age at admission of 16 358 pregnancies admitted for delivery between 31 + 0 and 36 + 6 weeks' gestation, British Columbia, Canada, 2000–2013.

Table 2: Patterns of childhood prescriptions of medications for attention-deficit/hyperactivity disorder among children of 16 358 pregnancies admitted for delivery between 31 + 0 and 36 + 6 weeks' gestation in British Columbia, Canada, 2000–2013

Characteristic	No. (%) of pregnancies* $n = 16\ 358$
≥ 1 prescription	892 (5.5)
Age at first prescription, yr, median (IQR)†	8 (6–10)
≥ 1 prescription among children aged ≥ 13 yr‡	449 (8.2)
No. of dispensations, median (IQR)†	11 (4–31)
Estimated total number of d of treatment (total d supplied for all medications, per child), median (IQR)†	362 (118–1041)
Type of medication, no. (%) of total dispensations	
Methylphenidate hydrochloride	12 069 (63.9)
Atomoxetine hydrochloride	1936 (10.3)
Dextroamphetamine sulfate	1717 (9.1)
Dextroamphetamine-amphetamine	939 (5.0)
Lisdexamfetamine dimesylate	2223 (11.8)
Total dispensations	18 884

Note: IQR = interquartile range.
*Unless indicated otherwise.
†Among 892 children with at least 1 prescription.
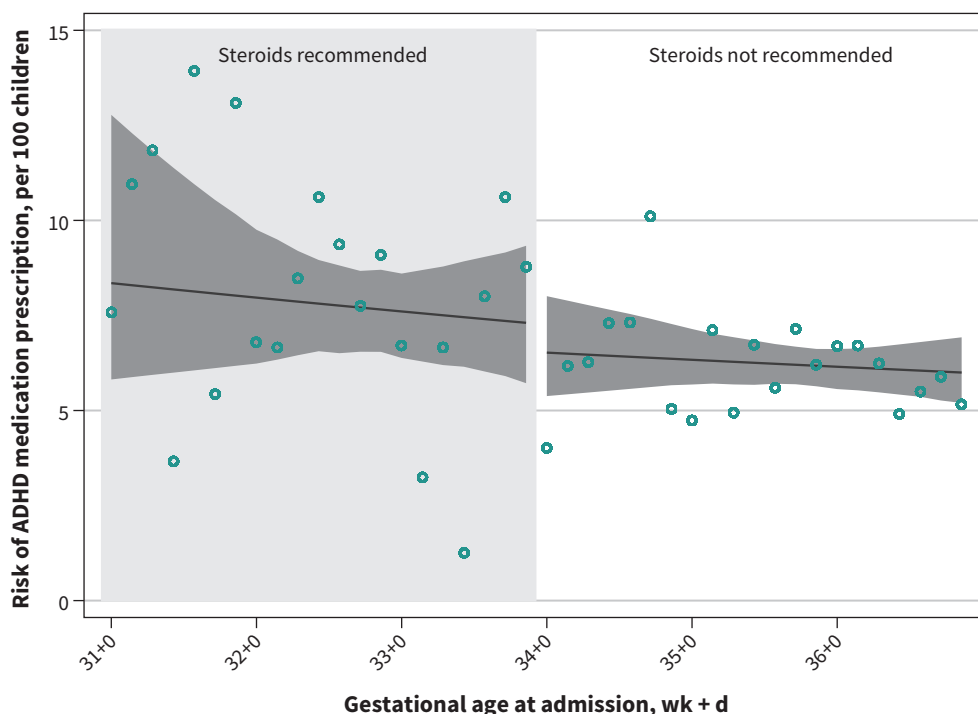‡Among 5458 children with 13 or more years of follow-up.
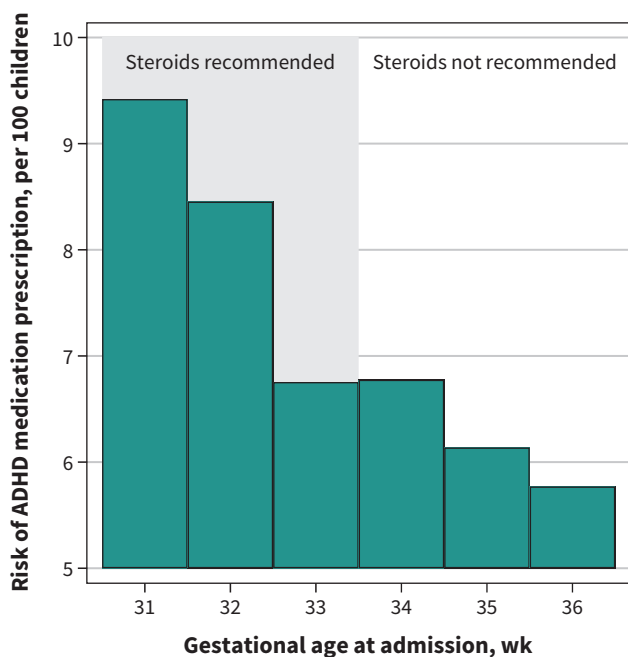
Figure 2: Risk of childhood prescription of medication for attention-deficit/hyperactivity disorder (ADHD) per 100 children, by gestational age (in weeks) at hospital admission (between 31 + 0 and 36 + 6 weeks) for delivery of 16 358 children in British Columbia, Canada, 2000–2013.

more plausible pattern of decreasing risk in adverse neurodevelopmental outcomes with advancing gestational age. We therefore believe this result reflects numerical instability associated with estimating a trend using only 7 data points (days) rather than a true increase in risk. Controlling for sex in the model had no meaningful impact (Appendix 1, Table S1), nor was there evidence for effect measure modification by sex ($p = 0.4$).

Interpretation

In this population-based study of children whose birthing parents were admitted for delivery between 31 + 0 and 36 + 6 weeks' gestation, we found little evidence of an increased risk of ADHD medication prescription among children of pregnant individuals admitted for delivery just before the clinical cut-off for antenatal corticosteroid administration of 34 + 0 weeks (i.e., with high probability of exposure to antenatal corticosteroids), compared with those admitted just after this cut-off (i.e., with minimal exposure to antenatal corticosteroids). These findings provide reassurance to clinicians and families concerned about the longer-term safety of antenatal corticosteroids for more subtle neurodevelopment outcomes such as ADHD.

Two cohort studies that followed patients who had completed randomized trials comparing single-course antenatal corticosteroids to placebo have evaluated subsequent risk of ADHD. A follow-up of the 1969–1974 Auckland steroid trial found no significant

Figure 3: Risk of prescriptions of medication for attention-deficit/hyperactivity disorder (ADHD) per 100 children, by gestational age at hospital admission (between 31 + 0 and 36 + 6 weeks) for delivery of 16 358 children in British Columbia, Canada, 2000–2013. Circles indicate observed day-specific values; solid line indicates the smoothed estimate of risk of prescription with 95% confidence interval (dark grey shaded area).

Table 3: Estimated risk of childhood prescription of medications for attention-deficit/hyperactivity disorder among children born to birth parents admitted for delivery between 31 + 0 and 33 + 6 weeks' gestation versus those admitted between 34 + 0 and 36 + 6 weeks' gestation in British Columbia, Canada, 2000–2013

Prescription	Rate ratio (95% CI)	Excess cases per 100 children by 13 years of age* (95% CI)
≥ 1 dispensation	1.12 (0.8 to 1.6)	1.3 (−2.5 to 5.7)
≥ 2 dispensations	1.1 (0.7 to 1.7)	1.3 (−3.1 to 5.6)

Note: CI = confidence interval.
*Absolute difference in cumulative risk by age 13.

difference in scores on the Brown attention-deficit disorder scale in individuals with and without prenatal exposure to betamethasone (mean scores 25.6 v. 26.9, respectively).[12] A follow-up of the Antenatal Steroids for Term Elective Cesarean Section (ASTECS) trial also found no difference between study arms in hyperactivity subscale scores of a strengths and difficulties questionnaire.[14] However, the evidence from these studies is limited by low follow-up rates (17% and 47%, respectively) and small sample sizes (*n* = 192 and *n* = 407, respectively). Our findings are consistent with these randomized studies in suggesting that antenatal corticosteroid exposure does not increase the risk of ADHD, but considerably strengthens the evidence behind this conclusion through our use of a large, population-based sample that reflects the real-world impact of antenatal corticosteroid administration, combined with a robust quasiexperimental design that reduces confounding. However, a recent population-based, observational study from Finland found that children exposed to antenatal corticosteroids had increased risks of receiving a diagnosis of ADHD or conduct disorder.[16] Given that the effect size was small (a 20% increase in risk), confounding by indication could plausibly explain these findings.[10]

Limitations

Prescription of a medication used for ADHD is a different outcome than an ADHD diagnosis. A study from Ontario found that 70% of children with a chart-confirmed ADHD diagnosis were prescribed ADHD medications;[32] thus, the outcome of ADHD medication prescriptions does not reflect the incidence of ADHD. However, unlike ADHD diagnosis, ADHD medication dispensation is accurately documented in population databases and is a clinically relevant outcome in its own right, making it a more robust outcome for this study.

The regression discontinuity design estimates only the effect of an intervention at the point of the discontinuity (here, 34 + 0 weeks). Thus, our conclusions are most generalizable to gestational ages close to 34 + 0 weeks, and we caution that our conclusions may not apply to markedly different gestational ages (e.g., term gestation). Although the rate ratios from our models suggest that antenatal corticosteroids do not increase the risk of ADHD, the upper limits of our 95% CIs preclude conclusively ruling out a moderate degree of increased risk. However, the upper limits of our CIs are well below the magnitude of risks found in previous studies that generated current safety

concerns, such as the 2.1-fold increase in risk of being in the lowest quartile of academic ability, as observed in the ASTECS trial,[14] or the (nonsignificant) 5.7-fold increase in risk of cerebral palsy observed in a trial of repeat courses of antenatal corticosteroids.[33]

Finally, the regression discontinuity design depends on an assumption that exposure to antenatal corticosteroids was high among infants just before the clinical cut-off of 34 + 0 weeks, and low among infants just after (an assumption analogous to the need for high treatment adherence in a randomized trial). Our ability to document corticosteroid administration was limited by a known shortcoming in the Perinatal Registry variable for antenatal corticosteroids, which instructs coders not to indicate administration in cases where documentation on timing of administration is incomplete. We estimate that about 75% of pregnancies admitted for delivery before 34 weeks' gestation were exposed to corticosteroids (based on an unpublished chart audit of BC infants before 34 weeks' gestation,[34] and previously published national data of neonatal intensive care units from 2003–2013),[35] but cannot confirm this empirically. We also had no information on the timing or number of doses administered; it is likely that some of the pregnancies that received antenatal corticosteroids had incomplete doses or suboptimally timed administration.

Conclusion

We did not identify an association between higher probability of antenatal corticosteroid exposure and prescriptions for ADHD medications in childhood. Our findings may be useful in supporting discussions with families about the harms and benefits of antenatal corticosteroid administration, particularly at late preterm gestations, where the need for safety data is most pressing.

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