

Does umbilical cord length – an indirect measure of fetal activity – predict hyperactivity in grade school children?

[Clinical Science Research]

Does Umbilical Cord Length -- An Indirect Measure of Fetal Activity – Predict Hyperactivity in Grade School Children? Jennifer Leung MD, Andrew Adesman MD, Sarah Keim PhD MA MS; Department of Pediatrics, North Shore-Long Island Jewish Health System/Cohen Children's Medical Center

Abstract:

Despite common concerns among expectant mothers of fetal overactivity and increasing worries about ADHD in preschool and grade school children, there has been no large-scale prospective study analyzing the relationship between fetal hyperactivity and later childhood hyperactivity (HA), impulsivity (IMP), or inattention (IA). The National Collaborative Perinatal Project (NCPP) followed >59,000 pregnancies with child follow-up to 8 years and collected over 6,800 data items per pregnancy/child dyad. We used the standardized measure of umbilical cord length (UCL) at birth as an objective indirect measure of fetal activity and analyzed its association with later standardized behavioral ratings of HA, IMP, and IA by a psychologist at ages 4 and 7 years as well as a speech-and-language pathologist at age 8 years. By excluding children with specific neurodevelopmental risk factors (e.g., cerebral palsy, mental retardation) and with missing UCL, we limited analyses to 25,485 term offspring. Multivariate statistical analysis was performed, with logistic regression models based on 5-cm increase in cord length; odds ratios were adjusted for sex, socioeconomic index, race, maternal age, smoking during pregnancy, and parity. We found that UCL is not associated with later childhood IMP and/or HA at ages 4, 7, or 8 years. A slight inverse association with UCL and IA was noted at age 7 years (odds ratio [OR] 0.979; 95% confidence interval [CI] 0.961-0.997) and again at 8 years (OR 0.942; 95% CI 0.891-0.996). This statistical finding, though consistent at 2 different age points, is likely insignificant clinically since there was less than a 2 cm difference in UCL between groups with and without inattention, in context of mean cord lengths near 60 cm and standard deviations of 13 cm. Because no association between UCL at birth and assessments of IMP and/or HA at ages 4, 7, or 8 years was found in our analysis of NCPP's large scale, prospective, longitudinal data set, parents (and expectant parents) can be reassured that fetal hyperactivity is not likely associated with later childhood ADHD.

Introduction:

Attention-deficit/hyperactivity disorder (ADHD) is among the most prevalent childhood disorder worldwide and occurs in 5% of children (Polanczyk et al., 2007). ADHD is a multifactorial disorder with strong genetic underpinnings (Gustafsson & Kallen, 2010) and neuroanatomical abnormalities, both of which suggest a prenatal origin. Core symptoms include inattention, impulsivity, and hyperactivity, which have a negative impact on a child's academic

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and social emotional development (Pliszka & AACAP Work Group on Quality Issues, 2007).

As a result, the potential role of early diagnosis and treatment of ADHD is paramount, and there may even be subtle indicators as early as the fetal period (Gustafsson & Kallen, 2010).

Fetal activity is often seen as a clinical marker of neurological integrity, and monitoring gross fetal activity has been useful in assessing of fetal health (Rayburn et al., 1983). Expectant parents often worry about fetal activity and question whether it is a predictor of later childhood development. But although fetal *hypo*activity has been associated with short umbilical cord length and neurodevelopmental disorders (Moessinger et al., 1982), the clinical implications of fetal *hyper*activity are less clear. There has been a retrospective report on the positive association between fetal hyperactivity and childhood hyperactivity (Accardo et al., 1997), but inevitably, maternal reports are subject to recall bias. To date, there has been no large-scale, *prospective* analysis of fetal hyperactivity or umbilical cord length (UCL) and later hyperactivity.

The National Collaborative Perinatal Project (NCPP), 1959-1974, is a large-scale prospective cohort study of pregnancy and child health with follow-up to age 8 years. Altogether, over 59,000 pregnancies were followed with prenatal visits every 8 weeks, with a total of 6,700 data items per pregnancy/child dyad. By virtue of its immense size, rigorous data collection, and extended multi-disciplinary follow-up, the NCPP provides a unique data set and extraordinary opportunity to explore the relationship between obstetric factors and long-term developmental outcome. Using data from the NCPP, our goal is to examine the relationship between umbilical cord length (UCL) as an objective but indirect measure of fetal activity and later childhood hyperactivity (HA), impulsivity (IMP), and inattention (IA). Our primary

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hypothesis is that children with longer UCL are more active in utero and thus more likely to later exhibit signs of HA and IMP. Our secondary hypothesis is that children with longer UCL are more active in utero and thus more likely to later exhibit signs of IA.

Methods

Participants

Altogether, the NCPP followed 59,407 pregnancies. We limited analyses to the 25,485 offspring for whom UCL and follow-up data to at least age 7 years was available and who met no exclusionary criteria. Obstetric/perinatal exclusion criteria include prematurity (<37 weeks gestation), SGA, LGA, oligo- or polyhydramnios, or multiple gestation (prior or current pregnancy). Children were also excluded if other neurological risk factors were present (e.g., congenital malformations, blindness, deafness, 5-minute Apgar ≤ 2 , mental retardation, Down syndrome, CP, non-febrile seizures, microcephaly, or neurologist rating of “neurologically abnormal” at neonatal exam, 4 months, or 7 years). Table 1 lists the number of subjects who satisfied one or more exclusionary criteria.

Procedures

Given there were no direct maternal reports of fetal hyperactivity, UCL was used as an indirect biometric marker of fetal activity (Moessinger et al, 1982). The outcome variables were ratings of HA, IMP, and IA during testing by a psychologist at ages 4 and 7 years on a 1 to 5 point scale (Table 2), and with independent assessments by a speech-language pathologist at age 8 years on a “Yes/No” scale (Table 2). Each outcome variable was assessed as individual variables (HA, IMP, or IA), as well as combined variables (HA+IMP, or HA+IMP+IA). The

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psychological test battery included the Stanford-Binet Intelligence Scale at 4 years, and the Wechsler Intelligence Scale for Children and the Wide Range Achievement Test at age 7 years. The final 8-year speech, language, and hearing evaluation was limited to about half the total sample.

Multivariate statistical analysis was performed. The results of logistic regression models were based on a 5-cm increase in cord length. All Odds Ratios (OR) were adjusted for sex, socioeconomic index, race, maternal age, smoking during pregnancy, and parity. Critical alpha level was set at $p \leq 0.05$ for all analyses.

Results

With respect to our primary hypothesis, there is no relationship between UCL and ratings of HA and/or IMP as individual or combined variables at ages 4, 7, or 8 years. The unadjusted and adjusted odds ratios for HA and/or IMP at 4, 7, and 8 years of age are listed in Table 3, with all 95% confidence intervals inclusive of the OR of 1. Although the unadjusted odds ratio for the combined variable HA+IMP+IA was statistically significant (OR 1.029, 95% CI 1.000-1.058), this significance was lost after the OR was adjusted (OR 1.028, 95% CI 0.999, 1.058) (Table 3).

With respect to our secondary hypothesis, there is an unexpected inverse relationship between UCL and ratings of IA at ages 7 and 8 years. Specifically, the adjusted OR for IA at ages 7 and 8 years are 0.979 (95% CI 0.961-0.997) and 0.942 (95% CI 0.891-0.996), respectively. This statistical finding, though consistent at 2 different age points, is likely insignificant clinically because there was less than a 2 cm difference in UCL between groups

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with and without inattention, in context of mean cord lengths near 60 cm and standard deviations of 13 cm (Table 4).

Discussion

Despite common concerns among expectant mothers of fetal hyperactivity and increasing concern about ADHD in children, there has been no large-scale prospective study analyzing the relationship between fetal hyperactivity or UCL and later childhood HA, IMP, and/or IA. We utilized data from the NCPP, a large-scale prospective study, which provided a monumental sample size of > 25,000 subjects, even after the exclusion of those with neurodevelopmental risk factors. However, contrary to our primary hypothesis, a longer UCL was *not* associated with HA and/or IMP when assessed during testing at ages 4, 7, and 8 years. This lack of association is significant on a clinical and practical basis given the high degree of parental concern over fetal activity (Cote-Arsenault et al., 2006). If UCL is a reasonable indirect biometric marker for activity level, then parents who report fetal hyperactivity may be reassured knowing there is no increased association with observed hyperactivity and/or impulsivity when tested individually at ages 7 and 8 years.

Two prior small prospective studies have also found no association between intrauterine fetal movements and activity at either at 3-18 months (Rayburn et al., 1983) or at 6 years (Niederhofer & Reiter, 2004). First, Rayburn et al. (1983) used data gathered from fetal movement charts recorded by 931 patients. Patients were asked to keep a daily record of any perceived strong fetal movements, described as “kicks,” “stretches,” “rolling,” or “balling up.” Fetal hyperactivity was defined as 40 or more movements perceived per hour for at least 14 days shortly before delivery. Follow-up exams obtained on 24 of the infants between the ages of 3

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and 18 months, with a mean age of 9 months, showed no unusual growth, developmental, or temperamental patterns. Unlike the Rayburn study that only had a single follow-up visit at an average age of less than a year, our study had multiple points of follow-up (ages 4, 7, and 8 years) and is also more pertinent given the extended follow-up into the school-age child.

The second example is from a study by Niederhofer & Reiter, where they examined pregnancies for 227 women living in Austria and looked at ultrasound measurements of intrauterine fetal movements at 16 to 28 weeks and their correlation with measurements of the child's marks at age 6 years. After the child's first year of grammar school, teachers were asked to provide the child's marks, which included a behavior using a score of 1 (excellent) and 5 (not sufficient). The weaknesses of the Niederhofer study include the small sample size (227 women) and its reliance upon a single observation by ultrasound at 16-28 weeks as the measure of fetal activity. Moreover, their outcome variable of "behavior" is not specific and cannot differentiate between HA, IMP, and/or IA. In comparison, our study had >25,000 subjects, as well as an objective, aggregate, global measure of fetal activity at term (UCL). We also had multiple specific outcome variables (HA, IMP, and/or IA) that were based on observations of children at a uniform age, obtained from standardized testing by either a psychologist or speech-language pathologist.

The relationship between UCL and fetal activity has been demonstrated experimentally in multiple animal studies as well as noted in clinical populations involving different obstetric and pediatric conditions. For example, in studies conducted on rat fetuses by Moessinger et al. (1982), restriction of fetal movements either by experimentally induced oligohydramnios or fetal paralysis with curare from day 18 led to short cords. Moreover, while extrauterine pregnancies

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with fetuses free in the maternal abdominal cavity and attached to cords led to cords measuring 147% of littermate controls, extrauterine fetuses that were fixed close to the placental implantation site with little/no stretch applied to the cord had a mean cord length of 90%. Based on such results, Moessinger speculated that the UCL of the newborn infant is a reflection of past fetal activity, given adequate space for movement (Moessinger et al., 1982). In another human study by Moessinger et al. (1986), he identified 21 infants with Down's syndrome and compared each individual cord length to mean standard values derived from the same population and matched for sex, race, and gestational age. He found that infants with Down's syndrome had significantly shorter UCL (mean 45.1 cm compared with 57.3 cm for matched standards). Given that Down's syndrome is associated with hypotonicity and reduced fetal activity, this human study supports the theory that fetal motor activity influences umbilical cord growth (Moessinger et al., 1986).

There are three major limitations to our study. First, our data did not have direct maternal fetal reports. However, we argue that maternal reports are less reliable than our objective measure of UCL as a measure of fetal activity. This is supported by a study by Yawn et al. (1998), where a mail survey sent to 342 eligible women found that gestational age is reported less accurately and with different rates of recall for mothers with term (85%) and preterm (99.5%) deliveries. If an item as objective as the gestational age is inaccurately reported by term mothers, how can a subjective maternal report of fetal activity be a reliable marker? Additionally, as we saw in the study by Accardo et al. (1997), the retrospective maternal reporting of fetal activity actually showed a positive association between fetal hyperactivity and childhood hyperactivity, likely an inaccurate and misleading result given maternal reports are

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subject to recall bias. Hence, rather than maternal reports, our study used UCL, a reliable and precise objective measure of fetal activity.

The second limitation is that our outcome variables were based on psychologists' or speech-and-language pathologists' rating scales obtained in a one-on-one setting, where a child may likely be on his best behavior. Although it is possible that children with mild difficulties with inattention or restlessness in home or school may have not exhibited difficulties during testing, it is unlikely that children with more severe symptoms of ADHD would be missed. Our study environment provides the most standardized setting with reliable objective measures obtained by a trained professional. Although ratings were done at multiple locations by different observers, all assessments were protocolized with specific guidelines for scoring to insure reliability across settings.

Third and lastly, one can argue that by excluding children with cerebral palsy and mental retardation, we weaken the association between UCL as a measure of fetal activity and later development. However, in this specific study, our outcome group of interest is specifically children with signs of ADHD who are otherwise healthy with normal intelligence.

Future research opportunities are very exciting in this modern era of computer technology. We can now use electronic medical records (EMR) to access a multitude of patient information, which allows a larger sample size as well as more ease in data collection. Even more, the birth of the National Children's Study (NCS) in 2010, offers a new and large data bank for research; the NCS will examine the health of children across the US from birth to age 21 years, with plans to enroll at least 100,000 families. The NCS is the modern-day NCPP, and only time will tell what the future holds. Regardless, our current study already shows no

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association between UCL at birth and assessments of IMP and/or HA at ages 4, 7, or 8 years from our analysis of data from the NCPP's large scale, prospective, longitudinal data set. As a result, parents (and expectant parents) can be confidently reassured that fetal hyperactivity is not likely associated with later childhood ADHD.

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Tables

Table 1: Cohort Exclusionary Criteria from Original NCPP Data Set

Exclusionary Criteria	Number
<i><u>Obstetrical/Perinatal Risk Factors</u></i>	
Multiple gestation (in pregnancy of interest)	3662
Prematurity (<37 weeks)	10013
SGA or LGA	8522
Pregnancies w/ maternal history of multiple gestation	1093
Oligohydramnios or polyhydramnios	843
Missing cord length	17821
<i><u>Neurological Risk Factors</u></i>	
Congenital malformations	1691
Apgar score ≤ 2	76
WISC < 70 (at age 7 years)	1407
Mental retardation	1386
Down syndrome	46
Cerebral Palsy	214
History of non-febrile seizures	912
Microcephaly	12
Neuro. rating “neurologically abnormal” at neonatal exam, 4 months, or 7 years	2337
Blind or deaf	125
Pregnancies in Original Sample	59,407
Final Sample Size	25,485

Note: Subject may fall into one or more exclusionary criteria.

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Table 2: Psychologist and Speech-Language Pathologist (SLP) Rating Scales for Primary Outcome Variables of Attention span, Impulsivity, & Hyperactivity at Ages 4, 7, & 8 yrs

Age	Outcome Variable	Rating
4 years & 7 years (Psych)	Duration of Attention Span	1- Attends to tasks very briefly 2- Spends short time with tasks 3- Spends adequate amount of time on tasks 4- Spends more than average time on tasks 5- Highly perseverative, unable to shift attention
	Level of Activity	1- Extreme inactivity and passivity 2- Little activity 3- Normal amount of activity 4- Unusual amount of activity and restlessness 5- Extreme overactivity and restlessness
	Nature of Activity	1- Extreme rigidity, unable to shift activity or approach to task 2- Some rigidity 3- Flexible behavioral patterns 4- Behavior frequently impulsive 5- Extremely impulsive
8 years (SLP)	Short attention span Observation by Examiner	0- No 1- Yes 9- Unknown
	Hyperactivity Observation by Examiner	0- No 1- Yes 9- Unknown
	Motor Disinhibition Observation by Examiner	0- No 1- Yes 9- Unknown

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Table 3: Results of logistic regression models – based on a 5-cm increase in cord length

Outcome variable	Unadjusted odds ratio (95% confidence interval)	Adjusted odds ratio (95% confidence interval)*
Age 4 years		
Hyperactive	1.005 (0.989, 1.021)	1.002 (0.986, 1.019)
Impulsive	1.016 (0.993, 1.039)	1.015 (0.992, 1.040)
Short attention span	0.995 (0.981, 1.010)	0.996 (0.981, 1.011)
Hyperactive and impulsive	1.018 (0.993, 1.044)	1.016 (0.990, 1.043)
Hyperactive, impulsive, and short attention	1.029 (1.000, 1.058)*	1.028 (0.999, 1.058)
Age 7		
Hyperactive	1.003 (0.985, 1.022)	0.997 (0.979, 1.016)
Impulsive	1.005 (0.979, 1.033)	1.002 (0.975, 1.030)
Short attention span	0.978 (0.961, 0.996)*	0.979 (0.961, 0.997)*
Hyperactive and impulsive	1.005 (0.974, 1.037)	1.001 (0.970, 1.033)
Hyperactive, impulsive, and short attention	1.014 (0.974, 1.055)	1.012 (0.971, 1.054)
Age 8		
Hyperactive	0.988 (0.934, 1.044)	0.975 (0.921, 1.032)
Impulsive	0.961 (0.908, 1.017)	0.959 (0.905, 1.016)
Short attention span	0.946 (0.896, 0.999)*	0.942 (0.891, 0.996)*

*statistically significant

Table 4: Mean Umbilical Cord Lengths in Groups with Statistically Significant Outcome Variables

Age	UCL (with SD) in Group With HA + IMP + IA (cm)	UCL in Group Without HA + IMP + IA (cm)	Difference (cm)
4 years	60 (12.3)	59 (13.1)	1.0

	UCL (with SD) in Group With Inattention (cm)	UCL (with SD) in Group Without Inattention (cm)	Difference (cm)
7 years	58.5 (13.3)	59.3 (13.1)	0.8
8 years	57.3 (13.1)	59.2 (13.1)	1.9

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