Handedness in the Helsinki Ultrasound Trial

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KEYWORDS: confounders; handedness; prenatal ultrasound; randomized trial

ABSTRACT

Objectives To determine whether exposure to prenatal ultrasound increases non-right-handedness in boys.

Methods The association between exposure to prenatal ultrasound and handedness was tested, using logistic regression analysis, in the Helsinki Ultrasound Trial data. We applied an intention-to-treat approach in this analysis of a subset of 4150 subjects whose parents answered a follow-up questionnaire on handedness when the children were aged 13–15 years, and who had......

Results The odds ratio for non-right-handedness was 1.16 (0.98–1.37) for all subjects, 1.12 (0.89–1.41) for boys and 1.24 (0.97–1.58) for girls.

Conclusions We could not confirm the hypothesis that prenatal ultrasound exposure increases non-right-handedness in boys.

recent meta-analysis of four studies, including two RCTs (OR, 1.26) and two cohort studies (OR, 1.17), indicated that males who were exposed to prenatal ultrasound were more likely to be NRH than were males who were not exposed to prenatal ultrasound. Thus, the effect of prenatal ultrasound exposure on handedness, especially among boys, needs further investigation. The aim of this study was to investigate whether prenatal exposure to ultrasound is associated with an increase of NRH in boys. If this was found to be the case, it could support the common belief that boys may be more vulnerable than girls to prenatal insults.

METHODS

Our study was a RCT based on the randomized Helsinki Ultrasound Trial and the detailed study design has been described in a previous paper. This trial investigated the effect of ultrasound screening on perinatal mortality, randomizing into cases or controls on an intention-to-treat basis 9310 pregnant women at the time of their first visit to the prenatal clinic in 1985–1987. Of these 9310 pregnancies, 8662 delivered successfully. When preparing the questionnaires in 1999, we were able to trace addresses for 7773 mothers who had been randomized into prenatal ultrasound (n = 3915) and control (n = 3858) groups.

There is some evidence that the determination of human handedness takes place during prenatal development and genetic effects have been reported to explain about one quarter of the variance in handedness. It is also well known that left-handedness is more prevalent among males. Furthermore, although non-right-handedness (NRH) is a natural phenomenon in general, it may result from a brain injury.

Two previous randomized controlled trials (RCTs) have raised concern that NRH might be increased in males who have been exposed to prenatal ultrasound. A recent meta-analysis of four studies, including two RCTs (OR, 1.26) and two cohort studies (OR, 1.17), indicated that males who were exposed to prenatal ultrasound were more likely to be NRH than were males who were not exposed to prenatal ultrasound. Thus, the effect of prenatal ultrasound exposure on handedness, especially among boys, needs further investigation. The aim of this study was to investigate whether prenatal exposure to ultrasound is associated with an increase of NRH in boys. If this was found to be the case, it could support the common belief that boys may be more vulnerable than girls to prenatal insults.

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The handedness of offspring was measured by means of a parental report as part of a longer questionnaire that included the Child Behavior Checklist designed by Achenbach and Edelbrock. There was a yes/no question about familial left handedness (existence of another left-handed member of the family). Parents indicated whether their child used their left or right hands or both hands equally when performing five activities: writing, throwing a ball, holding scissors, holding a knife and holding a spoon. We calculated the laterality quotient (LQ) based on the Edinburgh Handedness Inventory method. The difference between the right- and left-hand scores was divided by their sum and the result was multiplied by 100. This formula yielded a LQ that ranged from -100 (totally left-handed) to +100 (totally right-handed). We categorized subjects as right-handed when the LQ was +100, the rest being NRH. We used a LQ of +70 as an alternative cut-off as well as NRH based on writing-hand alone to test whether the particular classification of NRH used would affect our analysis. When a woman had responded regarding more than one child, only one, selected arbitrarily, was included in the study.

The study was approved by the ethics committee of Helsinki University Central Hospital.

Statistical methods

Using logistic regression analysis, we first tested all children together and then boys and girls separately because of the known higher prevalence of NRH in boys. Testing boys alone also directly addressed the initial hypothesis presented by Salvesen and Eik-Nes. According to their meta-analysis based on Norwegian and Swedish follow-up studies, if boys alone were analyzed according to intention-to-treat, the OR for NRH was 1.26 (95% CI, 1.03–1.54). We also carried out per-protocol analysis (analysis according to actual exposure status), which would be expected to show the size of any effect but at the risk that it may be confounded. We then carried out subgroup analysis according to trimester(s) during which exposure occurred (Model 1), using 85 days and 170 days as cut-offs for the start of the second and third trimesters, respectively, and then introduced as confounders smoking status and handedness of any first-degree relative (Model 2). Smoking status was pooled into three classes: non-smokers (reference group), mothers who had stopped because of pregnancy and current smokers. We also investigated dose–response effects, which would be particularly important if the intention-to-treat analysis showed an association between prenatal ultrasound exposure and handedness. Multiple selection correction was used because of hypothesis generation. Among individuals there were subgroups such as controls that had ultrasound during pregnancy and cases that had extra exposure when they were exposed to ultrasound mostly outside the planned time window. This is why some combined subgroup analyses with respect to exposure were carried out.

There was no significant difference in randomization status between subjects with or without handedness data. Because of the known genetic effects on handedness, we included familial NRH (at least one NRH first-degree relative) as a covariate in the logistic regression analyses. Maternal smoking during pregnancy was also included as a covariate to control for possible pathological effects on handedness.

RESULTS

Of the 7773 initially randomized eligible subjects for whom contact details could be traced, 4174 bypassed date-of-birth and gender checks against information available from birth records and CPR (Central Population Registry) records. Of these, 24 had missing LQ data. Our analysis thus included 4150 subjects (2013 boys and 2137 girls), i.e. 53% of those contacted. Of these, 2112 (981 boys and 1131 girls) were cases and 2038 (1032 boys and 1006 girls) were controls.

There was a significant sex difference in the prevalence of NRH between boys and girls (Table S1 online). Using a LQ of +100 to define right-handedness, the prevalence of NRH was 17.1% in boys and 14.4% in girls (chi-square = 5.81, P = 0.02) and using a LQ of +70, the prevalence of NRH was 13.2% in boys and 10.0% in girls (chi-square = 10.1, P = 0.002). Based on writing hand alone, the prevalence of NRH was significantly higher in boys (10.1%) than in girls (7.5%) (chi-square = 8.75, P = 0.003).

Prenatal ultrasound exposure did not increase the probability of NRH (defined as LQ ≠ 100): OR, 1.16 (95% CI, 0.98–1.37) (Table 1). The result was similar using the alternative +70 LQ cut-off. Similarly, there was no effect of ultrasound exposure on handedness when boys and girls were analyzed separately. The results were similar when analyzing writing hand alone (Table S2).

Table 2 shows the per-protocol subgroup analyses for girls and boys separately. Logistic regression analyses indicated there to be no trimester-specific ultrasound exposure effect on handedness, either in boys (Table 3) or in girls (Table 4). Instead, having at least one NRH first-degree relative significantly increased the probability of NRH in both sexes (P < 0.05). Moreover, maternal smoking cessation because of pregnancy increased the probability of NRH in boys (P < 0.05), but this effect was not evident when familial NRH was included in the analysis. Similar results to those obtained for analysis according to LQ of +100 were obtained when the LQ cut-off was +70 or when writing handedness alone was considered (Tables S3–8 online). However, the effect of maternal smoking cessation because of pregnancy in boys was not significant when we used the LQ cut-off of +70 or writing handedness alone.

DISCUSSION

Although NRH was significantly more common in boys than in girls, we could not confirm an association...
Table 1 Association between prenatal exposure to ultrasound and handedness, analyzed by intention-to-treat using logistic regression (n = 4150)

<table>
<thead>
<tr>
<th>LQ cut-off/subgroup</th>
<th>Controls</th>
<th>Cases</th>
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</thead>
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<tr>
<td></td>
<td>n</td>
<td>NRH (n)</td>
</tr>
<tr>
<td>All LQ + 100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>2038</td>
<td>300</td>
</tr>
<tr>
<td>Boys</td>
<td>1032</td>
<td>169</td>
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<tr>
<td>Girls</td>
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<td>131</td>
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<tr>
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<td></td>
</tr>
<tr>
<td>All</td>
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<td>221</td>
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<tr>
<td>Boys</td>
<td>1032</td>
<td>131</td>
</tr>
<tr>
<td>Girls</td>
<td>1006</td>
<td>90</td>
</tr>
</tbody>
</table>

Handedness was defined using a laterality quotient (based on Edinburgh Handedness Inventory method\textsuperscript{12}), those at or above the cut-off being defined as right-handed and those below it as non-right-handed (NRH). OR, odds ratio.

Table 2 Association between prenatal exposure to ultrasound and handedness, analyzed according to exposure and sex using logistic regression

<table>
<thead>
<tr>
<th>Group</th>
<th>No ultrasound exposure</th>
<th>Ultrasound exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>NRH (n)</td>
</tr>
<tr>
<td>Boys</td>
<td></td>
<td></td>
</tr>
<tr>
<td>True controls\textsuperscript{†} and cases with no scan</td>
<td>263</td>
<td>44</td>
</tr>
<tr>
<td>Drop-ins and cases with extra scans\textsuperscript{‡}</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Cases per-protocol\textsuperscript{§}</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Girls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>True controls\textsuperscript{†} and cases with no scan</td>
<td>270</td>
<td>49</td>
</tr>
<tr>
<td>Drop-ins and cases with extra scans\textsuperscript{‡}</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Per-protocol cases\textsuperscript{§}</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Handedness was defined using a laterality quotient (based on Edinburgh Handedness Inventory method\textsuperscript{12}) cut-off of +100, i.e. those with LQ + 100 were defined as right-handed and those with LQ below this as non-right-handed (NRH). *Confidence limits corrected for 24 separate tests. †True controls were those randomized to the control group that did not receive a scan. ‡‘Drop-ins’ were controls that were scanned; ‘cases with extra scans’ underwent extra scans, including outside weeks 16–20. §Per-protocol cases were cases that were scanned only as planned, during weeks 16–20. OR, odds ratio.
correct use is generally believed to be sufficient to ensure safety in human applications. Many of the concerns regarding ultrasound safety are historically based, with a lot of the available epidemiological data having been gathered more than 20 years ago. Speculations regarding ultrasound safety in humans also refer to the difficulty in precisely calculating wave characteristics such as wave amplitude fluctuations and excessive local temperature increases, as well as potential unknown vulnerabilities of the growing tissue, possible bone–tissue interactions and maternal fever, which could lead to a vulnerable rise of temperature. Experimental animal research has indicated that ultrasound may affect neuronal migration in the growing fetus. However, the finding is not generalizable to prenatal ultrasound scanning in humans, because, in animal trials, the proportion of ultrasound exposure to body size differs from that in human scanning. Moreover, the time and amount of exposure tend to be more regulated in medical use.

The efficiency of devices in clinical practice has improved considerably in recent years. Yet such speculations regarding risk are needed, if only to remind us that there are still things we do not know for sure. Sometimes, risk is a matter of thresholds, and this is addressed by the ALARA (As Low As Reasonably Achievable) principle.

In conclusion, we could not confirm the association between handedness and prenatal ultrasound exposure. Our results suggest that other factors, such as familial left-handedness, may contribute to the determination of handedness.

ACKNOWLEDGMENTS

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REFERENCES


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AQ2 How about ‘We applied an intention-to-treat approach in this analysis of a subset of 4150 subjects whose parents answered a follow-up questionnaire on handedness when the children were aged 13–15 years, and who had….’ – let’s complete this regarding the LQ at proof stage.

AQ3 Is S8 ok or are we having S9 too?

AQ4 Note refs were out of order. You may wish to check them.

AQ5 I’ve added ‘If this were found to be the case, it could support the common belief that boys may be more vulnerable than are girls to prenatal insults.’ – is this what you meant by the last bit of your reply to query HB6?

AQ6 I’ve reworded to add the children’s ages: During 2001–2002, when the children were aged 13–15 years,

AQ7 ‘We used a LQ of +70 as an alternative cut-off as well as NRH based on writing-hand alone to test…’ – is this what you meant me to put?

AQ8 I’m sorry – I’m not sure I understand your reply to my query here. I was wondering if you wanted to add ‘intention to treat’ anywhere in this first paragraph – did you think I meant you should not be using the term??

AQ9 Do you want to add anywhere that subjects had up to eight scans?

AQ10 As suggested, this paragraph has been moved from earlier in the methods. We can decide whether it fits here in the stats bit at proof stage.

AQ11 Instead of ‘bypassed’ could you mean ‘passed’? Also, did you want me to add anything else regarding 4174/4150 numbers?

AQ12 Regarding your changes to numbers in Table S1 – are any changes required here in the paper?

AQ13 I’m sorry I’m not sure what you mean – where should it say ‘(adjusted OR in both sexes)’?

AQ14 ‘Tables S38 online’ – is this now ok or did you mean some to be added to the next sentence? Also, do you mean you want to delete table S9 (which was S5)?

AQ15 77 changed to 69 – is that all you wanted here?

AQ16 Is this paragraph now as you want it?

AQ17 Please provide the full page range for Reference 16.
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