Ultrasound in pregnancy and non-right handedness: meta-analysis of randomized trials

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KEYWORDS: meta-analysis; non-right handedness; safety; ultrasound

ABSTRACT

Objective To study the association between exposure to ultrasound in pregnancy and non-right handedness in children with available data from randomized trials.

Methods Follow-up data of 8865 children aged 8–14 years from three randomized trials on routine ultrasonography at 15–20 weeks’ gestation were available. Handedness was assessed through questionnaires to the parents and classified according to five, 10 or 11 questions. Children not classified as right handed were regarded as non-right handed.

Results There was a statistically significant increased prevalence of non-right handedness in ultrasonographically screened children compared with controls (odds ratio (OR) 1.15; 95% CI, 1.03–1.29). The results in subgroups according to gender are consistent with the overall results, with no significant differences between boys and girls. Among boys, the association became stronger when an exploratory analysis according to ultrasound exposure before 19–22 weeks’ gestation was done (OR 1.30; 95% CI, 1.10–1.53).

Conclusion There is a statistically significant – albeit weak – association between ultrasound screening during pregnancy and being non-right handed later in life.

INTRODUCTION

Ultrasoundography has been used in obstetrics for five decades with no proven harmful effects, and systematic reviews of the epidemiological literature on ultrasound safety have been reassuring. The only controversy has been an unexplained weak association with non-right handedness among boys.

The first meta-analysis demonstrating an association between exposure to ultrasound and non-right handedness was published in 1999. There was no statistically significant difference in the prevalence of non-right handedness between children screened by ultrasound and controls (odds ratio (OR) 1.13; 95% CI, 0.97–1.32), but there was a difference in a subgroup analysis of boys (OR 1.26; 95% CI, 1.03–1.34). In the most recent Cochrane review (2010) a conservative approach towards subgroup analysis is advocated. The Cochrane review reports no association between ultrasound exposure and non-right handedness in an intention-to-treat analysis of all children (OR 1.12; 95% CI, 0.92–1.36) and does not include a gender-specific subgroup analysis. A review by the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) in collaboration with the World Health Organization (WHO) adopted a less conservative analytical approach and included two randomized trials and two cohort studies. The ISUOG–WHO review confirms the findings from the first meta-analysis, and adds: ‘When boys were considered separately, there was a weak association between ultrasound screening and being non-right handed, both in the randomized trials (OR 1.26; 95% CI, 1.03–1.34) and in the cohort studies (OR 1.17; 95% CI, 1.07–1.28)’.

A follow-up study of a Finnish randomized trial was published in 2011. At first glance this study appears reassuring since there is no difference in non-right handedness between ultrasound-screened children and controls (OR 1.16; 95% CI, 0.98–1.37), nor in a subgroup analysis of boys (OR 1.12; 95% CI, 0.89–1.41).

The aim of the present study was to explore the association between exposure of the fetus to ultrasound and non-right handedness in a meta-analysis of the available randomized trials.

METHODS

The literature was searched extensively by the authors of the ISUOG–WHO review (October 2007) and the Cochrane review (September 2009). A PubMed search with the search phrases ‘ultrasound’, ‘handedness’ and

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Accepted: 11 May 2011

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Ultrasound exposure

In a study carried out in Norway in 1979–81, women were randomly allocated to ultrasound screening at 18 and 32 weeks’ gestation or standard antenatal care. Linear real-time ultrasound machines (ADR 3120, Tempe, AZ, USA) were used. The median exposure time for the first routine scan was 3 min. A Swedish trial in which pregnant women were randomized to ultrasound screening at 15 weeks’ gestation or a control group was carried out in 1985–7. Real-time ultrasound equipment (Hitachi EUB 22, EUB 25, EUB 26, EUB 400 (Maidenhead, UK) and Siemens Imager 2380 (Erlangen, Munich, Germany)) were used. Exposure times were not recorded individually, but booking interval was 15 min. A Finnish trial in which women were randomized to ultrasound screening at 16–20 weeks’ gestation or standard care was carried in 1986–7. Real-time equipment (Hitachi EUB 400, Kretz Combison 320 (Medison-Kretztechnik, Linz, Austria) and Aloka SS 13–280 (Tokyo, Japan)) was used. Exposure times were not recorded.

Of 1115 ultrasonographically screened 9-year-old Norwegian children, 37 (3.3%) had never been exposed to ultrasound during pregnancy. In the control group of 1046 women, 65 (6.2%) had been scanned before 22 weeks and 200 (19.1%) had been scanned at least once during pregnancy. In the Swedish trial 2482 women (of whom 32 (1.3%) women did not attend for a scan) were allocated to ultrasound scanning at 15 weeks. In the non-screening group of 2511 women, 103 (4.1%) had a scan before 19 weeks and 786 (31.3%) had a later scan. In the Finnish trial 4691 women were randomized to ultrasound screening at 16–20 weeks. In the screening group 1.6% of women had no scan at all during pregnancy, 22.6% had an additional scan before 16 weeks and 35.6% an additional scan after 20 weeks. In the control group of 4619 women, 54% were scanned before 21 weeks and 77% were scanned during pregnancy.

Analysis of handedness according to exposure status has been previously done with data from the Norwegian and Swedish trials. New and unpublished data from the Finnish trial were kindly provided by K. Heikkinen to be included in an exploratory analysis in the present meta-analysis. Children exposed to ultrasound before 19 weeks (Swedish trial) or 22 weeks (Norwegian and Finnish trials) were considered as exposed, and children who were exposed to ultrasound after 19–22 weeks were considered to be non-exposed.

Classification of handedness

In the Norwegian study a questionnaire included 21 questions about which hand the child preferred to use while performing various tasks in their daily activities. The response options were right hand, equally often with either hand or left hand. Parents were instructed not to respond if they had never observed the child do the task in question. The questionnaire was returned by 2161 (89%), however, complete data on all 21 handedness questions were only available for 1210 of the children (50% of the original total). It was decided to use only 10 of the 21 questions, as a result of which ‘complete’ data were available for 1663 children (68% of the original total eligible children). A child was classified as right handed (or left handed) if at least 9 of 10 questions were answered as such. Children were classified as non-right handed if they were not right handed, thereby including all children who were left handed.

In the Swedish study a questionnaire included 11 questions on the dominant hand. Ten questions were the same as those selected in the Norwegian trial, and one extra question – on the preferred hand when using a toothbrush – was added. The response options were: always right hand, most often right hand, equally often either hand, most often left hand or always left hand. The questionnaires were returned for 3265 (70% of the original total eligible children) children. Only children for whom the parents had answered at least 10 of the 11 questions on the preferred hand were included in the analysis, and these data were available for 3052 (66%) children. A child was classified as right handed if at least 10 of the 11 questions were answered with always right hand or most often right hand. Children not classified as right handed were regarded as non-right handed.

In the Finnish study a questionnaire included five questions on the dominant hand. Parents indicated which hand the child used when writing, throwing a ball, holding scissors, holding a knife and holding a spoon. The response options were right hand, left hand or both hands equally often. Handedness data were available for 4150 children (48% of the original total eligible children). Handedness was classified according to a laterality quotient based on the Edinburgh Handedness Inventory, and children were classified as right handed if all five questions were answered with right hand (laterality quotient of +100). All other children were classified as non-right handed.

Statistical analysis

Comparisons were made between children in the ultrasound screening and the non-screening groups according to the intention-to-treat principle and with subgroup analyses for boys and girls separately. An exploratory analysis according to ultrasound exposure before 19–22 weeks’ gestation with gender subgroups was also done. Analysis was done using the Cochrane Review Manager (RevMan), version 5.1 (The Nordic Cochrane Centre, The Cochrane Collaborative Group, 2011, Copenhagen, Denmark). Estimates are given as Peto OR with 95% CIs or as Mantel–Henschel fixed risk difference (RD) also with 95% CIs.
RESULTS

There was a statistically significant difference in the prevalence of non-right handedness between the ultrasound-screened children and controls (OR 1.15; 95% CI, 1.03–1.29) (Figure 1 and Table 1). Looking at the subgroups according to gender, there was a statistically significant increase in non-right handedness among the boys (OR 1.20; 95% CI, 1.03–1.39), but not the girls (OR 1.10; 95% CI, 0.93–1.30). However, the CIs overlap, there is no heterogeneity between the two groups and, therefore, the results in both subgroups are consistent with the overall result. The RD between ultrasound-screened children and controls was 0.02 (95% CI, 0.00–0.03).

In an exploratory analysis according to ultrasound exposure before 19–22 weeks’ gestation, the association between ultrasound and non-right handedness was strengthened for boys (OR 1.30; 95% CI, 1.10–1.53), but it was unchanged for children overall (OR 1.17; 95% CI, 1.03–1.32) (Figure 2 and Table 2).

There was an association between ultrasound screening in pregnancy and being non-right handed in this meta-analysis of available randomized trials, with a 15% increase in the prevalence of non-right handedness in ultrasound-screened children.

Number needed to treat (NNT) can be calculated from the observed risk difference (NNT = 1/RD). Thus, it may be estimated that 50 fetuses need to be scanned to give one non-right handed child or that 33 boys need to be scanned to give one non-right handed boy.

Meta-analyses are commonly updated when new trials are published. However, trial sequential analysis has been criticized\(^ {10} \). This is the second meta-analysis on ultrasound and handedness, and adding the new trial shifted the association from non-significant to significant ($P = 0.02$). There is a possibility that a random error may have occurred because of too sparse data or repetitive testing of data. However, the available epidemiological evidence points in the same direction – towards a positive association between ultrasound scanning and non-right handedness. If one also considers cohort studies\(^ {6,7} \), as was done in the ISUOG–WHO systematic review\(^ 1 \), the association is similar (OR 1.17; 95% CI, 1.07–1.28), and there are no epidemiological studies proving otherwise. The risk of publication bias (negative studies not reported) is small. The Cochrane Library has identified a limited number of randomized controlled trials of ultrasound screening in pregnancy, and children from four of 11 trials have been followed up\(^ 2 \).

The acoustic outputs from modern ultrasound machines have increased 10–15-fold during the last few years\(^ 11 \), and most epidemiologic evidence derives from B-mode scanners in commercial use 20–25 years ago. There is little epidemiological information on the use of color-flow or pulsed-wave Doppler. Number of scans per pregnancy and exposure times have increased over time in most countries. If the adverse effects of ultrasound during...
pregnancy are dose dependent, one must acknowledge that the available epidemiological data are limited.12

A strength of the randomized study design is that there is no need to control for possible confounding factors in intention-to-treat analyses. In an exploratory analysis, however, one should control for possible confounding. This was not done in the present meta-analysis, but it has been done previously in the individual trials. In the Norwegian study the association between ultrasound exposure and non-right handedness became stronger after adjusting for family predisposition for left handedness.4 In the Swedish and Finnish studies several possible confounding factors, such as family history of left handedness and smoking (both trials) and maternal age, education and perinatal asphyxia (Swedish trial) were controlled for. The odds ratios remained practically unchanged.5,8

The response rate to the handedness questionnaire was around 70% in the Norwegian and Swedish trials and around 50% in the Finnish trial. There were no differences in response rates between randomized groups, and no reason to believe that a higher response rate would have changed the results materially. Thus, the results are probably valid for children exposed to ultrasound equipment in common use in the 1980s, but the results are not necessarily generalizable to the use of ultrasound during pregnancy today.

The ‘cross-over’ between randomized groups in the Norwegian and Swedish trials was small. Only 1–3% of screened children were never scanned during pregnancy, and 20–30% of control-group children were scanned at least once. This was quite different in the Finnish trial. In the control group 54% of women were scanned before 21 weeks and 77% were scanned during pregnancy.9 The extensive use of ultrasound in the Finnish control group may have influenced the results, because a possible adverse effect of ultrasound will be ‘diluted’. This also illustrates an important problem for future research. It is important to assess medical technology at the correct point in time. It should not be done too early (before the potential of the technology is fully explored) and not too late (when no technology-free control group can be established). The time has passed since randomized controlled trials with ‘ultrasound-free’ control arms can be done.

In general, left handers are no different from right handers. However, sinistrality can be associated with pathological conditions, and this can best be explained by a very small group in whom left handedness is caused by early brain damage.13 In developed countries the prevalence of left handedness (writing hand) has gradually increased from around 2% in 1900 to 10–15% in 2000.14 This may be because the cultural pressure has decreased (being left handed has become more socially acceptable), but also because exposure to adverse environments and pathogenic insults may have increased prevalence rates. A wide range of pathogenic risk factors have been proposed, including low birth weight, birth stress and ultrasound exposure.14

**Table 2** Non-right handedness (NRH) among boys and girls compared according to ultrasound exposure before 19–22 weeks’ gestation.

<table>
<thead>
<tr>
<th>Study group</th>
<th>Ultrasound group (n)</th>
<th>Controls (n)</th>
<th>Weight (%)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NRH</td>
<td>Total</td>
<td>NRH</td>
<td>Total</td>
</tr>
<tr>
<td>Boys</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finland</td>
<td>274</td>
<td>1545</td>
<td>71</td>
<td>468</td>
</tr>
<tr>
<td>Norway</td>
<td>97</td>
<td>424</td>
<td>73</td>
<td>424</td>
</tr>
<tr>
<td>Sweden</td>
<td>167</td>
<td>822</td>
<td>123</td>
<td>752</td>
</tr>
<tr>
<td>Subtotal*</td>
<td>538</td>
<td>2791</td>
<td>267</td>
<td>1644</td>
</tr>
<tr>
<td>Girls</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finland</td>
<td>242</td>
<td>1660</td>
<td>66</td>
<td>477</td>
</tr>
<tr>
<td>Norway</td>
<td>65</td>
<td>422</td>
<td>47</td>
<td>393</td>
</tr>
<tr>
<td>Sweden</td>
<td>100</td>
<td>774</td>
<td>103</td>
<td>704</td>
</tr>
<tr>
<td>Subtotal†</td>
<td>407</td>
<td>2856</td>
<td>216</td>
<td>1574</td>
</tr>
<tr>
<td>Total‡</td>
<td>945</td>
<td>5647</td>
<td>483</td>
<td>3218</td>
</tr>
</tbody>
</table>

*Heterogeneity: chi-square = 0.56; df = 2 (P = 0.76); I² = 0%; test for overall effect: Z = 3.05 (P = 0.002).
†Heterogeneity: chi-square = 3.00; df = 2 (P = 0.22); I² = 33%; test for overall effect: Z = 0.322 (P = 0.75).
‡Heterogeneity: chi-square = 6.85; df = 5 (P = 0.23); I² = 27%; test for overall effect: Z = 2.50 (P = 0.01); test for subgroup differences: chi-square = 3.25; df = 1 (P = 0.07); I² = 69.3%.

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The origins of human handedness and brain lateralization are unknown. There is currently no agreement in the literature as to whether left handedness is caused predominantly by genetic influence, through an intrauterine hormonal influence on the developing brain or other environmental influences. Medland et al. studied 25 732 twin families and reviewed 35 twin studies and found that additive genetic effects accounted for 25% of the variance of handedness, with the remainder accounted for by non-shared environmental factors. The right-shift theory of handedness developed by Annett puts more emphasis on genetic influence than on intrauterine environment. If this model is correct, it is not biologically plausible that ultrasound can influence brain lateralization in a developing fetus. Also, there is evidence that laterality is present in early pregnancy (before the time of routine ultrasound). Hepper et al. found that handedness in ‘thumb-sucking’ fetuses at 15 weeks gestation could be related to handedness at age 10–12 years, somewhat more strongly for ‘right-handed’ than ‘left-handed’ fetuses.

On the other hand, in a model proposed by Geschwind and Galaburda it is theoretically conceivable that ultrasound exposure may modify or influence neuronal migration in the developing fetal brain. In addition, Ang et al. demonstrated that exposure to a commercially available ultrasound device was capable of producing disturbed neuronal migration in fetal mouse brains. The exposure times were extensive (up to 420 min) and not comparable with standard obstetrical practice. Nevertheless, disturbed neuronal migration in mouse brains after exposure to modern ultrasound devices and epidemiological evidence of non-right handedness with old ultrasound devices indicate that ultrasound during pregnancy may influence neuronal migration and handedness.

A possible gender difference as indicated by the results of the randomized trials should be played down. In general, boys are more often left-handed than girls. Subgroup analyses should always be viewed with caution, and there is no heterogeneity between the subgroups in this meta-analysis (Figures 1 and 2 and Tables 1 and 2). Since we have no biological understanding of a possible association between prenatal ultrasound exposure and handedness, any speculation on a gender specific effect of ultrasound should be abandoned.

In conclusion, there is a weak statistically significant association between ultrasound screening and being non-right handed, but this does not mean that there must be a causal relationship. The current biological understanding of handedness is limited and partly contradictory of the epidemiological evidence. We will have to live with uncertainty regarding ultrasound safety in the years to come.

REFERENCES