Prenatal ultrasound - epidemiological studies

Introduction

Ultrasound has been used in obstetrics for four decades with no proven harmful effects. However, absence of evidence of harm is not evidence of absence of harm. Thus, it is necessary to study the effect of prenatal ultrasound exposure on human populations directly before any definitive statements regarding risk can be made.

Epidemiological studies may be divided into observational and experimental studies (see figure 1). Descriptive studies are suitable for generating new hypotheses about associations between exposure and disease, whereas analytical studies are designed to test such hypotheses. The randomized controlled trial is the best way to examine possible cause-effect relationships in human populations. Evidence based medicine is usually derived from systematic review of data obtained from randomized controlled trials and/or observational studies.

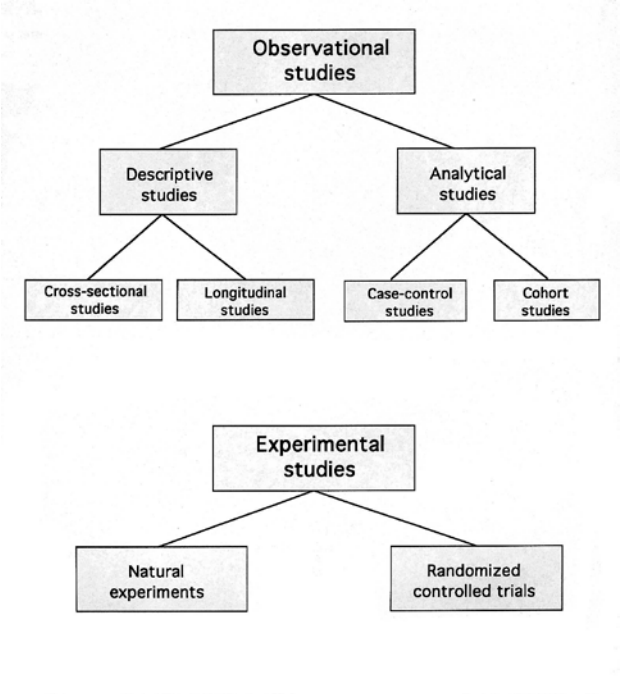

Figure 1. Classification of epidemiological studies

Evidence based medicine

Two systematic reviews of epidemiological studies of the safety of ultrasound in pregnancy have been published [1,2]. The Cochrane review [2] included all registered published and ongoing randomized controlled trials and quasi-randomized trials (up to September 2009), but no analytical studies. The ISUOG-WHO review [1] included 16 randomized controlled trials, 13 cohort and 12 case-control studies published between January 1950 and October 2007 that assessed any type of short- and long term effects of at least one exposure to ultrasound during pregnancy. The outcomes assessed included maternal outcomes, perinatal outcomes, childhood growth, neurological development and school performance, non-right handedness, childhood malignancies, intellectual performance and mental diseases after childhood [1].

Ultrasound exposures

There is one important caveat about the data from epidemiological studies. The acoustic outputs from modern devices have increased 10-15 fold during the last two decades [3], and most epidemiologic evidence derives from B-mode scanners in commercial use 20-25 years ago. If adverse effects of ultrasound during pregnancy are dependent on exposure conditions, one must acknowledge that the available epidemiological evidence is of limited relevance to current practice.

Outcomes studied

Birth weight

The question of whether ultrasound exposure in utero leads to reduced birth weight has probably been given more attention than any other perinatal outcome.

Two systematic reviews have concluded that there is no evidence that ultrasound exposure *in utero* affects birth weight [1,2].

Perinatal mortality or morbidity

The main reason for introducing ultrasound into antenatal care is to try to reduce perinatal mortality and/or morbidity. However, from a safety perspective it is just as important to demonstrate that ultrasound exposure in pregnancy does not increase perinatal mortality or morbidity. Based on the randomized trials and cohort studies to date there is no evidence that ultrasound exposure *in utero* influences perinatal morbidity or mortality [1,2].

Childhood malignancies

When the outcome under study is rare, such as with childhood malignancies, any approach other than the case-control design is unsuitable. For childhood malignancies there are data from 8 studies including more than 14 000 children [1,4]. There is no evidence that ultrasound exposure *in utero* is associated with childhood malignancies.

Neurological development, dyslexia and speech development

These outcomes have been studied in two controlled trials with more than 5 200 children [5,6,7], one case-control study with 214 children [8] and one cohort study with 806 children [9]. Overall the results suggest that it is unlikely that prenatal ultrasound can "cause harm to the developing fetal brain".

School and intellectual performance

School performance has been studied in two controlled trials with almost 6 500 children [6,10]. There is no evidence that ultrasound exposure *in utero* is associated with poor school performance. In a Swedish cohort study of 7 999 prenatally ultrasound exposed and 197 829 unexposed men aged 18 years, there was an increased risk of subnormal intellectual performance among exposed men [11]. However, this association was probably confounded by sociogeographical factors, and the authors stated that: "*the study failed to demonstrate a clear association between ultrasound and intellectual performance*" [11].

Autism and mental disease in adult life

The proportion of children diagnosed with autism spectrum disorders (ASD) has increased. There is evidence that environmental factors may play a role, and that the initiating process leading to ASD originates during fetal life. In theory, antenatal ultrasound may be a risk factor for ASD. However, a case-control study with 362 singletons born 1995-1999 with a diagnosis of ASD was compared to 393 controls [12]. The study demonstrated no association between antenatal ultrasound and ASD. In a Swedish cohort study of 370 945 individuals there was no association between prenatal ultrasound and schizophrenia (odds ratio 1.47, 95% CI 0.99-2.16) or other psychoses (odds ratio 1.03, 95% CI 0,80 -1.33) [13].

Handedness

There is, however, one statistically significant association between prenatal ultrasound exposure and behavior that holds up through all epidemiological studies and systematic reviews. The controversy is handedness.

The first meta-analysis demonstrating an association between ultrasound and non-right handedness was published in 1999 [14]. There was no statistically significant difference in the prevalence of non-right handedness among all children, but there was a difference in a subgroup analysis of boys. The Cochrane review reports no association between ultrasound and non-right handedness in an intention-to-treat analysis of all children and abstains from doing a gender specific subgroup analysis [2]. The ISUOG-WHO review [1] has adopted a less conservative analytical approach and included two randomized

trials [15,16,17] and two cohort studies [18,19]. The ISUOG-WHO review confirmed the findings from the first meta-analysis [14], and added: *"When boys were considered separately, there is 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)"* [1].

A follow-up study of a Finnish randomized trial was published in 2011 [20]. At first glance this study appeared reassuring since there was no difference in non-right handedness between ultrasound screened children and controls, nor in a subgroup analysis of boys [20]. However, when the results of the Finnish trial was included in a new meta-analysis of three randomized controlled trials, there was a statistically significant increased prevalence of non-right handedness in ultrasound screened children compared with controls (OR 1.14, 95% CI 1.02 – 1.28) [21]. The results in subgroups analysed according to gender were consistent with overall results with no significant differences between boys and girls, but among boys the association became stronger when an exploratory analysis according to ultrasound exposure before 19-22 weeks was carried out (OR 1.30, 95% CI 1.10– 1.53) [21].

The conclusion must be that five epidemiological studies report a 15% increase in the likelihood of sinistrality (in particular among males), and no other epidemiological evidence contradicts this association. The discussion of prenatal ultrasound and left-handedness is complex. An editorial explores this issue in detail [22]. A statistical association between ultrasound and left-handedness should not lead to the conclusion that ultrasound causes harm to the developing brain. The current biological understanding of handedness is limited and partly contradictory to the epidemiological evidence [22].

Conclusions

Epidemiological studies have demonstrated no confirmed associations between prenatal ultrasound and adverse perinatal outcomes, childhood malignancies, neurological development, dyslexia, speech development, school performance, intellectual performance and adult mental disease. However, there is a weak statistical significant association between prenatal ultrasound and being non-right handed. This does not mean that there must be a causal relationship. Given the dearth of epidemiological studies involving modern ultrasound scanners, we will have to live with uncertainty regarding ultrasound safety in the years to come.

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