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Asymmetry of fetal cerebral hemispheres: in utero ultrasound study

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Abstract

***Background*—Slight morphological asymmetry of the cerebral hemispheres has been observed in fetal and newborn brains. In adults, sex differences in hemispheric asymmetry have also been reported.**

***Objective*—To establish whether cerebral hemisphere asymmetry correlates with sex in fetuses.**

***Methods*—Left-right cerebral hemisphere asymmetry, and the correlation with sex, were studied in 51 male and 51 female fetuses of 20–22 weeks gestation, using diagnostic ultrasound scanning.**

***Results*—A total of 102 fetuses were examined. The diameter of the left hemisphere was larger than that of the right, in both female and male fetuses. The mean (SEM) diameter of the left hemisphere was 2.804 (0.174) cm in female fetuses and 2.781 (0.287) cm in male fetuses; the corresponding values for the right hemisphere were 2.627 (0.192) cm and 2.681 (0.267) cm. There was no sex related difference between hemispheric diameters. The interhemispheric difference was significant for both sexes: male fetuses, p = 0.017; female fetuses, p = 0.016.**

***Conclusions*—Left-right fetal brain asymmetry, as measured by in utero ultrasound examination, is apparent at 20–22 weeks gestation regardless of sex.**

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Keywords: in utero; ultrasound; cerebral asymmetry; brain

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Anatomical asymmetry in the adult brain has been established for over 100 years.[1–5] Differences in hemispheric length have been measured indirectly in skulls.[6 7] Brain asymmetry has been observed at postmortem examination,[8–12] as well as in conventional neurological studies using pneumoencephalograms,[13 14] cerebral angiograms,[15–18] computed tomography (CT) scans,[19] and magnetic resonance imaging.[20] Sex differences in hemispheric asymmetry have also been found.[21–23] Some studies showed less asymmetry in women than in men.[24 25] Slight morphological asymmetry of the cerebral hemispheres has also been observed in fetal and newborn brains.[9 10 25 26] This was found to be less pronounced in female than in male fetuses.[27]

The aim of this study was to measure the cerebral hemispheres in male and female fetuses during pregnancy using diagnostic ultrasound scanning, and to establish whether asymmetry correlates with sex.

Subjects and methods

The study group comprised pregnant women with the following criteria: history of regular menses with a 28 day cycle; a known date at which the last normal menstrual period began; absence of any maternal disease and clinically normal fetus at term; documented gestational age based on ultrasound measurement of crown-rump length in the first trimester of pregnancy below 12 weeks of gestation.

Hemispheric measurements were obtained during routine ultrasound examination at the Ultrasound Unit, Department of Obstetrics and Gynecology, The Chaim Sheba Medical Center. Each fetus was examined only once between 20 and 22 weeks gestation. Ultrasonographic examinations were performed using a 3.5–5 MHz curvilinear transducer (Elscint ESI 3000, Haifa, Israel). Hemispheric measurements were obtained from the axial section of the fetal head at the level used for biparietal diameter measurement.[28] Landmarks of this plan included the thalami in the centre and the cavum septum pellucidum anteriorly. Freeze frame ultrasound capabilities and electronic on-screen calipers were used for cerebral hemispheric measurements. The cursors were placed at the inner edge of the parietal bone and on the mid-line falx cerebri.

The images of the fetal head were presented to a single observer (RA), care being taken to ensure that images did not include fetal genitals. Fetal sex was determined ultrasonographically by a second independent observer. The laterality of the fetal cerebral hemisphere (right or left) was determined by establishing the fetal head position in utero and by abdominal viscera, respectively. In all neonates the sex was confirmed by examining the newborn medical records.

STATISTICAL METHODS

Data are presented as mean (SEM). Variables were compared using the paired Student's *t* test. Intraobserver variability is expressed by mean absolute differences. $p < 0.05$ was considered significant.

Results

The sonograms of 102 consecutive fetuses that met the inclusion criteria were reviewed. In all 102 cases, determination of fetal sex and hemispheric measurements were successfully performed, and sex identification was confirmed. The left hemispheres of both male and female fetuses were larger than the right. The mean (SEM) diameters of the left and right hemispheres of 51 male fetuses were 2.781 (0.287) cm and 2.681 (0.267) cm respectively

Table 1 Diameters of right and left hemispheres of 20–22 week fetuses

	Right hemisphere (cm)	*Left hemisphere (cm)*	*p Value between hemispheres*
Male (n=51)	2.681 (0.267)	2.781 (0.287)	0.017
Female (n=51)	2.627 (0.192)	2.804 (0.174)	0.016
p Value between sexes	0.51	0.82	

Values are mean (SEM).

(p = 0.017). In 51 female fetuses, the respective diameters were 2.804 (0.174) cm and 2.627 (0.192) cm (p = 0.016) (table 1). The mean (SEM) difference between individual right and left hemisphere measurements in the male fetuses was 0.101 (0.019) cm, and in female fetuses 0.171 (0.02) cm (p = 0.64).

There were no sex related differences between left hemispheres (p = 0.82) or right hemispheres (p = 0.51).

The mean (SD) of the absolute differences between two repeated evaluations by the same observer was 0.19 (0.04) cm.

Discussion

In utero ultrasonographic measurements of brain hemispheres showed left-right fetal brain asymmetry at 20–22 weeks gestation. The left hemisphere of both sexes was significantly larger than the right. No sex related differences were found between the respective hemispheres.

Wada *et al*[11] were the first to show that the human brain is asymmetric in the fetus. They found planum asymmetry in brains of 100 fetuses and newborns between the 18th gestational week and the 18th postnatal month. LeMay and Culebras[17] used carotid arteriograms to evaluate fetal brains and showed a lower sylvian point on the left in 10 fetuses. In another study, examining photographs from the Yakovlev collection of 49 fetuses and newborn brains, theses authors, similarly to our findings, noted that the left hemisphere was longer in 24 fetuses, the right hemisphere was longer in eight fetuses, and both hemispheres were equal in length in 17 fetuses.[7] Chi *et al*[27] measured brains of 207 fetuses at a gestational age of 10–44 weeks. They showed that left-right asymmetry of the transverse temporal gyri and the temporal plane become recognisable beyond 31 weeks of gestation. LeMay and Kido[19] found cerebral asymmetry on brain CT scans of 22 infants aged less than 1 year (five of whom were less than 7 days old). Weinberger *et al*[29] measured brain volume of a portion of the frontal and occipital lobes in fetuses (20–42 weeks gestation) and infants (aged 3.5–8 months) from the Yakovlev collection. Asymmetry was present in 17 of the 20 brains examined. Photographs of 16 week fetal brains taken by Fontes[30] show asymmetry typical of adults—that is, the left sylvian fissure is longer than the right, and the right sylvian point is higher than the left. De Lacoste *et al*[31] noted that, in 21 fetal brains from the Yakovlev collection of gestational age 13–37 weeks, the two most asymmetrical regions in the developing fetal brain were roughly equivalent to prefrontal cortex and a region that included striate and extra-striate cortical areas; the latter also manifested a sex difference.

Geschwind and Galaburda[32] hypothesised that factors relating to male sex, perhaps testosterone, retarded growth on the left, so that the corresponding regions on the right side developed relatively more rapidly. However, in our study the structural differences show a laterality effect, with predominance of left hemispheric development.

To the best of our knowledge, this is the first study to show, by ultrasound, brain asymmetry, with larger left hemispheres, in fetuses at an age as early as 20–22 weeks gestation. There is only one study[33] that has shown by ultrasound behavioural asymmetry in utero, where a clear bias for sucking the right thumb was found to correlate with head turning to the same side.

The structural differences shown in this study may be related to the effect of sex hormones such as testosterone and aromatase, the key enzyme converting androgen into oestrogen, both of which are known to be involved in brain differentiation. Testosterone increases aromatase activity, neurite length, and branching of cultured hypothalamic neurones.[34 35] The sex hormones may affect brain differentiation and cause asymmetry in both sexes and thus no sex effects were found.

The neurotransmitter environment of undifferentiated cells in the developing brain and cholinesterase activity in different brain regions may also determine early differences in brain development.[36 37]

The functional implications of the present findings of an organisational role in brain development, with left hemispheric predominance and no significant sex effects, are not yet clear. They may be related to different functions of the right and left hemispheres later in adult life. We believe that a better understanding of the development of the human brain will help in the detection and interpretation of brain abnormalities and dysfunction in early life.

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