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Comparison of brain apparent diffusion coefficient value in naturally and assisted conceived newborns

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Background: **Our aim was to assess the value of brain apparent diffusion coefficient (ADC) in Intra Cytoplasmic Sperm Injection (ICSI) and spontaneously conceived preterm singletons.**
Methods: **Twenty ICSI-conceived preterm singletons and 20 gestational age matched spontaneously conceived preterm singletons were studied. All subjects underwent diffusion-weighted imaging (DWI). The main outcome measure was the brain ADC value in the in ICSI-conceived and naturally conceived newborns.** ***Results:*** **Children born after ICSI had an increased ADC value than the controls. The ADC values of ICSI-conceived singletons were higher than those of spontaneously conceived singletons at cerebellum, corpus striatum, frontal lobe, occipital lobe, and temporal lobe white matter. The mean Apgar score, birth weight, height, and head circumference of ICSI children were found to be similar to naturally conceived children.** ***Conclusions:*** **Measuring ADC value may be a promising marker in identifying neurological outcome of ICSI-conceived newborns.**

Keywords: Apparent diffusion coefficient, intra cytoplasmic sperm injection, newborn

Introduction

Increasing use of assisted reproductive technology (ART) has raised concerns about its effects on intellectual and motor developments of children. Studies comparing rates of congenital malformations in naturally conceived children with those in children conceived following ICSI have shown a 30–40% increase in rates of congenital malformations, preterm birth and low birth weighted born after ICSI [1,2]. However, there is conflicting information regarding the abnormalities of neural and intellectual development of children born after ART. In the current literature, there are limited studies with discordant results on this issue [3–5]. The vast majority of the available data suggests that there is no difference in the neurodevelopmental well being of singleton ICSI children when compared to naturally conceived children [4,6]. However, a few studies have reported concerns regarding neurodevelopment in ART children [7–9]. The effect of *in vitro* fertilization (IVF) or ICSI on the developing human brain is unclear. With the advent of fetal MRI, fetal brain abnormality is now more frequently detected than in the past. MRI provides information on general brain morphology, but microstructural changes that may play a prognostic role are beyond the resolution of that technique. These changes may theoretically be revealed by diffusion-weighted magnetic resonance imaging (DWI). DWI is a relatively new technique and has proved useful in the detection of acute ischemic changes [10]. DWI is sensitive to the random translational motion (diffusion) of water molecules in tissue. Even subtle pathological damage should disrupt the tissue architecture increasing the mobility of water molecules and giving diffusion imaging the potential to probe structural changes that are inaccessible to other MR (Magnetic resonance) techniques [11]. This method provides the opportunity to measure quantitative values related to the microstructure and biophysical status of the cerebral tissues [12]. In this study, possible ultrastructural changes were investigated with DWI in a cohort ICSI-conceived singletons and gestational age matched spontaneously conceived singletons. Our preliminary findings of DWI on the naturally conceived children and children conceived following ICSI are presented.

Materials and methods

Twenty ICSI-conceived singletons and 20 gestational age matched spontaneously conceived singletons were investigated using a 1.5-Tesla MR scanner. The gestational age of both groups were varied between 22 and 35 weeks. Both of the groups were selected from infants who were born in our clinic during the study. We included the infants delivered only with cesarean section to exclude the possible confounding effects of vaginal delivery on the brain and to homogenize the groups. The cesarean section indications were preterm birth and/or preterm premature rupture of membranes in the ICSI-conceived group as well as the spontaneously conceived cases. The cases with multiple pregnancy, preclampsia, intrauterine growth restriction, placenta previa, placental abruption, antenatal bleeding and term pregnancy above 37 weeks of gestation were excluded from the study. The ART history of patients including information on underlying causes of infertility and types of fertility treatment, namely, conventional IVF or ICSI, number of embryos transferred, and whether the embryos transferred were fresh or frozen and thawed were recorded from patient files. Thirteen of the 20 subjects, who had been diagnosed for primary infertility, were subject to the long protocol and the other 7 were subject to the antagonist protocol, and then the procedure followed by ICSI to each of them. Fresh embriyo was transferred to each subject. In addition to conventional techniques, DWI was performed in

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the first 10 days of their life after cesarean birth for understanding whether it can distinguish ischemic changes from the reversible condition of vasogenic (interstitial) edema. It was obtained using a single-shot echo-planar imaging sequence (TR/TE: 4393/81 ms; slice thickness: 5 mm; interslice gap: 1 mm; FOV: 230 mm; matrix size: 128 × 256; b values: 0 and 1000 s/mm^2). Apparent diffusion coefficient values were measured in the white matter (WM) of the right cerebellum, left cerebellum, right frontal, left frontal, right occipital, left occipital, right temporal and left temporal lobes. ADC values were also measured in the pons, right and left corpus striatum, right and left thalamus (Figure 1). The MRI images were evaluated by a single radiologist blinded to the groups. The study was performed according to the guidelines of the Helsinki Declaration on human experimentation and was approved by the local ethics committee.

The Statistical Package for Social Sciences, version 11.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Normality of continuous variables in groups was tested by the Shapiro–Wilk test. Since the variables did not show a normal distribution, Mann–Whitney *U*-test was used for comparison. The data were presented as mean ± SD. For all comparisons, statistical significance was defined by $p < 0.05$.

Results

The gestational week, Apgar score, birth weight, fetal length, and head circumference of ICSI conceived children were found to be similar to naturally conceived children. The mean ADC values were measured bilaterally in the gray and white matter. The groups were compared according to the average ADC values for each region. The ICSI children had significantly higher ADC values in the cerebellum, corpus striatum, frontal lobe, occipital lobe and temporal lobe than the naturally conceived children. The ADC values of pons and were similar in ICSI and control newborns. Demographic characteristics and mean ADC values of the ICSI-conceived and the spontaneously conceived singletons are given in Table I.

Discussion

A number of prospective controlled studies, based upon interviews or neurological examination, did not find any difference in neurological outcome between ICSI and spontaneously conceived children. Ponjaert-Kristoffersen et al. [13] investigated the development of 5-year-old ICSI conceived children using the Weschler preschool and primary scales of intelligence and found no significant difference in the groups. Pinborg et al. [6] assessed the prevalence of neurological sequelae in Denmark in a nation wide cohort of singleton and twin pregnancies achieved with IVF/ICSI techniques and in population based control group of naturally conceived children. They found that twin ART pregnancies had similar risk of neurological sequelae with the singleton ART pregnancies as well as the naturally conceived peers. The group of Norfolk reported the follow-up of 110 IVF children compared with a control group of spontaneously conceived children. No difference was found for neurological and psychomotor evaluation [4].

However, most of these studies excluded children born <32 weeks of gestation, thus excluding many children at higher risk of neurological morbidity. An Australian study suggested that 1-year-old children born following ICSI were more likely to exhibit delayed development than children born following IVF or natural conception [7]. Dutch study has reported a lower mean IQ in 5- to 8-year-old ICSI singletons compared to naturally conceived singletons [8]. Studies from Scandinavia have reported 1.6 to 3.7 fold increased risk of cerebral palsy in IVF children compared to naturally conceived children [9,14,15].. Ericson and colleagues reported an increased risk of hospital admission due to epilepsy in IVF children compared to spontaneously conceived children aged 1–11 years [9].

The vast majority of studies investigating growth beyond the neonatal period have not found any difference between ICSI and spontaneously conceived children. The weight, height, and head circumference of IVF and ICSI children at the ages of 6–12 months [16], 1–3 years [17], 5 years [18], 8 years [19], and 6–12 years [20] have been reported to be within normal limits. In line with the previous studies, in present study gestational week, Apgar score, birth weight, fetal length, and head circumference of ICSI conceived children were found to be similar to naturally conceived children.

Various studies have demonstrated that singleton children born after ICSI are at increased risk of preterm delivery, low birth weight, neonatal mortality, and neonatal intensive care unit admission when compared to spontaneously conceived singleton controls [21–23]. In present study, the differences between groups with regard to the incidences of hospitalization rates, respiratory complications, hyperbilirubinemia and hypoglycemia were insignificant. Incidence of low birth weight newborns was similar.

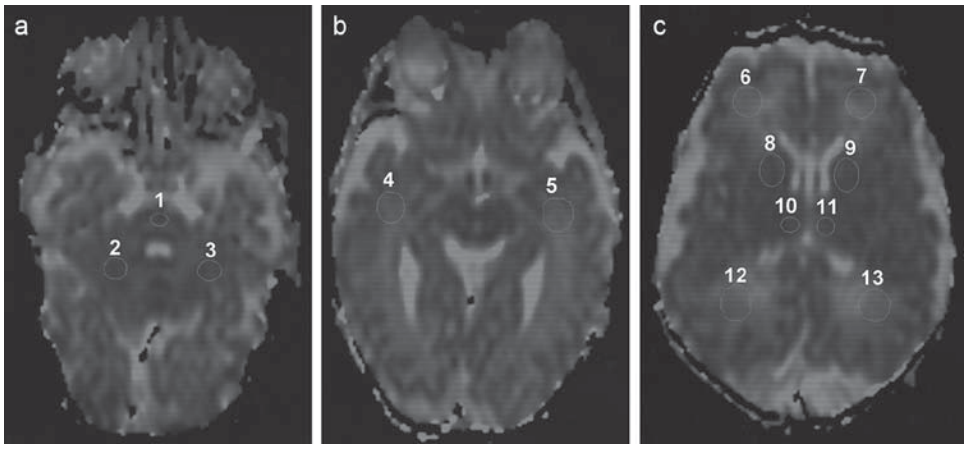

Figure 1. (a-c) DW image and ADC measurements of different areas of the brain are shown. ADC measurements were made in pons (1), bilateral frontal (6,7), temporal (4,5), occipital (12,13), cerebellar (2,3) white matter, bilateral thalamus (10,11) and bilateral corpus striatum (8,9) in locations designated with a circle.

Table I. Demographic characteristics and average apparent diffusion coefficient (ADC) values in ICSI and control newborns.

ADC region	IVF/ICSI newborns ($n = 20$)	Control newborns ($n = 20$)	p value
Age (year)	29.0 ± 4.9	31.1 ± 2.3	0.072
Gestational week	33.7 ± 2.3	33.1 ± 2.2	0.314
Birth weight (kg)	2102.6 ± 631.6	2121.5 ± 880.3	0.547
Apgar	9.0 ± 0.9	8.80 ± 0.7	0.529
Fetal length (cm)	43.5 ± 2.9	41.7 ± 4.7	0.157
Head circumference	33.1 ± 2.2	32.0 ± 2.5	0.076
Pons	$981.2 \pm 81.9 \times 10^{-6}$	$946.9 \pm 83.3 \times 10^{-6}$	0.183
Right cerebellum WM	$1215.2 \pm 47.7 \times 10^{-6}$	$1069.1 \pm 108.3 \times 10^{-6}$	0.001
Left cerebellum WM	$1220.0 \pm 56.8 \times 10^{-6}$	$1096.05 \pm 95.4 \times 10^{-6}$	0.001
Right corpus striatum	$1233.0 \pm 72.3 \times 10^{-6}$	$1152.4 \pm 67.6 \times 10^{-6}$	0.001
Left corpus striatum	$1234.15 \pm 64.7 \times 10^{-6}$	$1153.35 \pm 71.4 \times 10^{-6}$	0.001
Right thalamus	$1143.8 \pm 76.0 \times 10^{-6}$	$1104.6 \pm 99.0 \times 10^{-6}$	0.127
Left thalamus	$1135.7 \pm 79.5 \times 10^{-6}$	$1107.3 \pm 95.6 \times 10^{-6}$	0.253
Right frontal lobe WM	$1787.4 \pm 100.6 \times 10^{-6}$	$1449.4 \pm 99.5 \times 10^{-6}$	0.001
Left frontal lobe WM	$1755.0 \pm 91.0 \times 10^{-6}$	$1443.9 \pm 99.2 \times 10^{-6}$	0.001
Right occipital lobe WM	$1753.4 \pm 70.5 \times 10^{-6}$	$1445.3 \pm 103.0 \times 10^{-6}$	0.001
Left occipital lobe WM	$1766.2 \pm 79.8 \times 10^{-6}$	$1420.8 \pm 87.3 \times 10^{-6}$	0.001
Right temporal lobe WM	$1644.2 \pm 57.1 \times 10^{-6}$	$1355.4 \pm 107.6 \times 10^{-6}$	0.001
Left temporal lobe WM	$1631.6 \pm 68.8 \times 10^{-6}$	$1343.9 \pm 124.8 \times 10^{-6}$	0.001

ADC, apparent diffusion coefficient; IVF, *in vitro* fertilization.

Diffusion-weighted imaging provides important information in evaluating the microstructure and biophysical status of brain and intracranial lesions. The random motion of water molecules, also known as Brownian motion, is restricted only by their local environment, such as cellular structures, cell walls and orientation of the local tissue bundles. It has been suggested that DWI and ADC values can provide information on tissue integrity in the brain [24]. ADC values give crucial data for distinction between cytotoxic and vasogenic edema, and a variety of lesions including tumors, cysts, hamartomas, leukodystrophies, infections and others [24]. Even where subtle pathological damage disrupts the tissue architecture, the increased mobility of water molecules is detected by DWI. The net diffusion of the molecules is called the ADC. ADC reflects the structural properties of the cellular compartments of the tissue studied and provides a rotationally invariant measurement of the total diffusion of water within a tissue. It is a particularly sensitive detector of acute ischemic changes. Besides true diffusion images, ADC maps reveal signal differences between lesions and normal brain tissue [12,24]. Images are provided in a short period of time and there is no need to utilize contrast material. Although there are several studies investigating neurodevelopmental outcome in ART children, this study is the first DWI work on ICSI children.

Sener [24] studied the ADC values in the normal brain parenchyma and those in a variety of lesions in 310 cases. Brain disorders were classified based on their ADC values, taking the ADC value of the normal brain white matter as the principal category. For infants up to 2 years of age, the mean ADC values were as follows: unmyelinated white matter, 1.64 ± 0.17; myelinated white matter, 0.90 ± 0.12; basal ganglia, thalami, 0.98 ± 0.11; and cerebellar parenchyma, 0.97 ± 0.13 (all values in $\mu m^2/ms$). Righini et al. [25] determined the first ADC values of the fetal brain in 15 fetuses with gestational age ranging from 22 to 35 weeks using DWI. Mean ADC values were detected as 1.96 ± 0.1 $\mu m^2/ms$ in frontal white matter, 1.95 ± 0.1 $\mu m^2/ms$ in occipital white matter and 1.56 ± 0.1 $\mu m^2/ms$ in basal ganglia. When median ADC values and the gestational age were compared, only basal ganglia ADC values showed a negative correlation with age.

In this study, the brain ADC values of the ICSI-conceived singletons were significantly higher than the spontaneously conceived singletons in many locations. This condition did not represent normalization but an abnormality. This may associated with decreased myelinization that develops as a natural consequence of the vasogenic edema. It has been well documented that acute infarction related to cytotoxic edema is characterized by a marked decrease in diffusion, and also that increased interstitial water related to vasogenic edema shows increased diffusion [26]. The increase in the ADC of cerebral tissue has been shown in diseases leading to vasogenic edema such as acidosis, breakdown of the brain vasculature and decreased myelinization. The shift of water from the intracellular space to the extracellular space by leading to a decrease in the intracellular space and increase in the extracellular space, cause the increase of ADC values and hypointensity on DWI in vasogenic edema. In the ICSI conceived subjects ADC value of cerebellum, corpus striatum, frontal, occipital and temporal lobes were higher as compared to those gestational age matched spontaneously conceived children. The high value of ADC shows the excess of extracellular fluid in this location. This condition may be explained by vasogenic (interstitial) edema or other conditions leading to extracellular fluid accumulation. The high value of ADC in ICSI newborns can suggest the brain maturation and neuro-axonal myelinization develop at a slower rate or later than in the spontaneously conceived children.

The brain of the preterm infant is substantially different from the neonatal brain in basic structure and connectivity. Preterm brain has a transient synapse-rich subplate, high extracellular matrix content, and growing long fiber systems [27]. Using myelin basic protein staining which shows ongoing myelination, Kostovic et al. [27] found myelination in the white matter of the parietal, occipital, and temporal lobes. Given that the mid fetal and late fetal phases are crucial periods for the growth, development and target finding of axonal pathways, damage caused by hypoxia/ischemia or other factors during this time may led to abnormalities in neuronal pathway formation in ICSI children. ICSI-conceived singletons may trigger acidosis and the breakdown of the brain vasculature, resulting in vasogenic edema. Recent DWI study, Partridge et al. [28] showed increased fractional anisotropy values in the corpus callosum and internal capsule, which may be a sign of a particular stage of corpus callosum fiber organization. DWI may distinguish ischemic changes from the reversible condition of vasogenic edema [29].

Yet, dealing with single measurements and a small population of ICSI-conceived newborn are the basic limitations of this study need to be taken into account while analyzing this particular observation. Since our analyses are based on single measurements of brain ADC, the results may not reflect the relationship over time properly. It would be interesting to measure serial changes of brain ADC values in ICSI- conceived and naturally- conceived newborns to further clarify the role of DWI in the newborn brain development. In spite of these limitations, as a first clinical trial, this study was able to detect a difference in the ADC values, as being higher in ICSI babies than in the control subjects. If this argument could be supported by further studies, then the ADC value in the subjects may be a promising marker in identifying neurological outcome of ICSI-conceived newborns. Correlation of postmortem data with ADC value in ICSI and naturally conceived fetuses is the most promising approach for the determination of the etiology and the improvement of treatment for patients with neurological and cognitive disorders. However, long-term prospective trials on the correlation of ADC values and

neurological outcome are necessary to exploit the full benefit of that novel technique in ICSI conceived children.

***Declaration of Interest*:** The authors declare no conflicts of interest.

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