MRI Characteristic of Cerebral White Matter Maturation Patterns in Normal Infants of Assisted Reproductive

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Abstract

Background Assisted reproductive technology (ART) such as in-vitro fertilization (IVF) and embryo transfer (ET) has been essential in the treatment of infertility, and the number of children born after these procedures has now passed 5 million worldwide. Children born after medically assisted reproduction are at higher risk of adverse birth outcomes than are children conceived naturally. In this study, we leveraged MRI technology to investigate whether ART pregnancy methods: intracytoplasmic sperm injection (ICSI) and ET have any effect on the brain development of offspring by comparing with the NAT pregnancy method.

Methods A total of 75 infants were recruited in the study from 3 conception groups: 25 children born after ICSI, 25 children born after IVF-ET and 25 children born after natural pregnancy. Magnetic resonance imaging (MRI) scans provide exceptionally detailed information on how the human brain changes throughout childhood, adolescence, and old age. The use of MRI in the evaluation of the developing brain is well established.

Results The results of routine brain scans on T1WI and T2WI showed that there was no significant difference among the 5-7, 11-13, and 23-25 months of infants among ET, ICSI, and NAT groups. The MRI values fluctuate at different time points indicating that they may change with the development of the brain. However, they are on a similar level for different conception groups supporting our previous statistical analysis that MRI values of ICSI and ET groups are not significantly different from NAT.

Conclusions The results showed that there was no significant difference in brain development patterns between different modes of conception, which proved that ART does not affect the development of brain myelin in fetuses and infants.

Background

Assisted reproductive technology (ART) such as in-vitro fertilization (IVF) and embryo transfer (ET) has been essential in the treatment of infertility. ART such as conventional IVF, and especially intracytoplasmic sperm injection (ICSI), in which a spermatozoon is directly injected into an oocyte, allow couples whose sperm characteristics are impaired to obtain a pregnancy. ICSI was demonstrated to be much safer and more effective than other micro insemination techniques. Therefore, ICSI is now synonymous with micro insemination. ET and ICSI play a vital role amongst the various fertility treatments that are currently available. With both procedures, the natural process of conception is bypassed, the mechanical and hormonal manipulations of the embryo and the women have led to concern for the health of the offspring.

ICSI was originally introduced in 1992 as a modification of conventional in vitro fertilization (IVF).[1] Overall, ICSI was used in 65.1% of all fresh IVF cycles (embryos transferred without being frozen; n = 1,395,634) performed. The use of ICSI increased from 36.4% in 1996 to 76.2% in 2012.[2] Although ART helps millions of persons achieve pregnancy, ART is associated with potential health risks for both mothers and infants. Risks to the infant include preterm birth, low birth weight, death, and greater risk for congenital disabilities and developmental disability.[3, 4] The effect of assisted reproductive on the developing human brain is still not apparent, e the fact that IVF and ICSI were introduced more than 40 and 25 years ago.[1, 5] Some studies reported that there was no difference in placental weight and cord size between natural pregnancy and IVF pregnancy; [6] IVF/ICSI did not increase the risk for severe cognitive impairment or neuromotor handicaps; [7, 8] white matter maturation patterns in IVF-ET, ICSI and natural pregnancy (NAT) were still not clear.

Brain development is an ongoing process in fetal and infancy. Striking morphological changes have been observed as early as at the fourth gestational week (GW), the brain develops from a tubular structure to a complication. Early brain development, particularly from the mid-fetal stage to 2 years after birth, is probably the most dynamic in life. Structural changes of the brain during early development result from precisely regulated molecular and cellular processes including neurogenesis and neuronal migration, synapse formation, dendritic arborization, axonal growth, pruning and myelination [9].

Magnetic resonance imaging (MRI) scans provide exceptionally detailed information on how the human brain changes throughout childhood, adolescence, and old age. The use of MRI in the evaluation of the developing brain is well established. Current knowledge of early brain development originated from histological studies. The MRI image includes T1 and T2 weighted imaging, and diffusion-weighted images (DWI) reveal different aspects of microstructural changes as well as myelination processes. This is owing to the MRI can be detected the content of the water molecule and direction of diffusion using diffusion imaging and relaxometry imaging [10]. Diffusion tensor imaging (DTI) is a special kind of DWI, has been used extensively to study the white matter tractography. It has been widely used to investigate changes of white matter at different stages of brain development and their relationship to cognitive ability in early life. DTI allows quantitative analysis of brain microstructure based on patterns of water diffusion [11–14] and has shown promise for early prognosis of developmental outcome [15–18]. Mature models of white matter (WM) in infant development are widely available and are very useful for regions of interest (ROI)-based analyses of WM. DTI is a unique in vivo imaging technique that allows three-dimensional visualization of the WM anatomy in the brain.

Method

Patient selection

A total of 75 infants were recruited in the study from 3 conception groups: 25 children born after ICSI, 25 children born after IVF-ET and 25 children born after natural pregnancy. The study was conducted in Hangzhou Jianggan District People's Hospital. This study was approved by the ethics committee of Hangzhou Jianggan District People's Hospital, and the informed written consent for participation were obtained from all the parents of the involved children.

(exclusion criteria: The assisted conception group excluded patients with frozen egg cycle, donor egg cycle, and loss of follow-up. Inclusion criteria: no central nervous system abnormalities in prenatal and postnatal examinations. No central nervous system diseases during perinatal. All cases were reviewed through medical records and telephone follow-up to understand the perinatal complications in the three groups.)

Data collection

All fetuses of 28-32 GW and 33-37 GW and newborns were scanned by T2WI and DWI. All infants were scanned by T1WI, T2WI, and DWI at 5-7, 11-13 and 23-25months. So we collected MRI data from the above 6 time points for each infant. A circular ROI with the approximately 10mm^2 area was positioned for measurement by two neuroradiologists. We selected six brain regions in the unbiased atlas as shown in this study including anterior limb of internal capsule (ALIC), posterior limb of internal capsule (PLIC), corona radiata (CR), frontal white matter (FWM), white matter of parietal lobe (PWM), and occipital white matter (OWM). Left and right regions of anatomical locations are combined, giving a total of 12 regions in infants of 5-7, 11-13 and 23-25months at T1WI, T2WI, DTI image and in fetuses of 28-32GW, 33-37GW, newborns on T2WI and DWI images. Figure 1 shows the positions of the ROIs.

Statistical analysis

We conducted all analyses using R version 3.5.1. A value of $p < 0.05$ was considered statistically significant in all tests. The data were removed if they were greater than 1.5 interquartile range (IQR) above the upper quartile or less than 1.5 IQR below the lower quartile. The normality of distribution was determined by using qqnorm. The homogeneity of variance was evaluated by the bartlett test. All data were expressed as mean ± standard deviation (M ± SD) in the supplement. The nonparametric test “wilcox” was used to investigate if the MRI values are significantly different in the three pregnancy groups: ISCI, ET, and NAT at each of the 6-time point separately [19].

Result

Data clean

IQR was calculated from MRI values for each conception group. The value was considered as an outlier if it fell 1.5 IQR above the upper quartile or 1.5 IQR below the lower quartile in the same measure, time and brain area. We dropped nine outliers from 6 groups (supplementary table1).

No significant difference among conception groups by comparing MRI values of six brain regions together

Before we applied statistical methods to check the significance of differences of MRI values from ICSI, ET and NAT conception groups, we did qqnorm to check the data normality. The qqnorm figures showed the data are off normal distribution (supplementary figure 1). And so, we decided to use nonparametric test Wilcox to find out if the differences in MRI values were significant. The p values of MRI values: ADC, T2WI, T1, T2, and FA at 6 time points for the comparisons of ICSI vs NAT and ET vs. NAT are summarized in Table 1 and Table 2. All the p values of ADC and T2 at the ages of fetuses 28-32 weeks, 32-37 weeks, and newborn infants are greater than 0.05 (Table1) and the corresponding values of ADC and T2WI were shown as mean±SD in supplementary table1-3. All the p values of T1, T2, and FA at the ages of infants 5-7 months, 11-13 months and 23-25 months are greater than 0.05 as well (Table 2) and the corresponding values of T1 and T2 were shown as mean±SD in supplementary table4-6. These results suggest that the differences between ISCI and NAT and the differences between ET and NAT are not significant.

No significant difference in the comparisons of MRI values from six brain regions separately except ICSI vs. NAT of fetus FWM in PLIC

The Wilcox tests for MRI values from all brain regions reveals that ISCI and ET are not significantly different from NAT. However, whether the MRI values would be different among conception groups in a particular brain region or at a certain age are still unknown.

Therefore we did the Wilcox test for MRI values from each brain region separately and the p values were shown in Table 4. Except that the comparison in PLIC of ICSI vs. NAT has p-value 0.09, all other 81 comparisons with p values >0.05 indicating that it is not significantly different among conception groups by comparing MRI values in different brain regions separately.

Fluctuation of MRI values with brain developmental stages

Comparisons of MRI values among the conception groups show that ICSI and ET are not significantly different from NAT in all combined brain regions or each investigated brain region separately. However, whether the MRI values changes at different time points are still not clear. Therefore, we made candle plots of MRI values at the 3-time points of fetus or infant for each brain region (Figure 2).

ADC values in the ALIC, CR, and OWM regions (red candles) were dispersed at 28-32 weeks of the fetus from any conception group (Figure 2). ADC values in the PWM region fluctuate largely with lowest ADC values at 33-37 weeks of the fetus. ADC values in the PLIC region show an increasing trend with increasing gestational ages. The probable reasons causing the dispersion of AD values described below. During the process of myelinization of normal WM, the contents of cholesterol and lipid gradually increase, and its hydroxyl and ketone are based on the set of water molecules. The development of neuronal cells and colloids leads to a decrease in the activity space of water molecules, and the ADC value should be reduced. However, the individual difference of fetal myelination is relatively large, and the stability of ADC value for moving fetal imaging measurement is difficult to be guaranteed. Therefore, the observations of the variation pattern of ADC values during the period of the fetus still need to be verified by a large number of live study data.

The results of T2 showed that ALIC, PLIC, and PWM increased first and then decreased with the increase of gestational ages, while FWM and OWM showed a gradual decline with the increase of gestational ages. Although the T2 values in CR region at 28-32 weeks had the largest dispersions which masked the trend along gestational ages, the average T2 values in CR region at 28-32 weeks had a similar pattern as in ALIC, PLIC, and PWM regions.

The results of routine brain scans on T1WI and T2WI showed that there was no significant difference among the 5-7, 11-13, and 23-25 months of infants among ET, ICSI, and NAT groups. T1 values in ALIC, PLIC, and FWM regions of infants decreased gradually with the increase of months. The data of T1 in the PWM region at 5-7 months in the ICSI group is relatively dispersed, however, the overall trend in all 3 infant ages declines. The T2 values of 5-7 months and 11-13 months infants were the same except for the region of OWM, and the T2 values of 23-25 months infants were significantly lower than those of 5-7 months and 11-13 months infants. OWM decreased gradually with the increase of infant ages. These results indicated that the myelin formation in the OWM region might be earlier than other parts.

In addition to 6 brain regions: ALIC, PLIC, CR, FWM, PWM and OWM, we collected values from FA map in another 11 regions including: genu of corpus callosum (GCC), splenium of corpus callosum (SCC), external capsule (EC), longitudinal fasciculus (SLF), Inferior longitudinal fasciculus (ILF), corticospinal tract (CST), optic radiations (OR), ftemporal white matter (TWM), caudate nucleus head (CNH), thalamus (THA), lenticular nucleus (LN).

In the 5-7, 11-13, and 23-25 months of infants born through ET, ICSI and NAT, the values in the 17 brain regions on the FA map indicate are not significantly different between infants with different conception methods at the same time point. The FA values in PLIC, GCC, and TWM regions all showed an increasing trend with the increase of ages. The FA values in SCC, SLF, ILF, CSF, and OR regions were mostly the same between 5-7 and 11-13months infants but slightly increased in 23-25 months. FA values in ALIC region at 5-7 months are higher than 11-13months and 23-25months, while the values of 11-13 and 23-25 months are almost equal. It is noteworthy that FA values in FWM region decreased with the increase of infants ages. Overall, the MRI values fluctuate at different time points indicating that they may change with the development of the brain. However, they are on a similar level for different conception groups supporting our previous statistical analysis that MRI values of ICSI and ET groups are not significantly different from NAT.

Discussion

With the development of imaging technology, MR has become an essential means to evaluate fetal brain development and diagnose congenital brain diseases. Myelination is an essential maturation process in human brain development. Understanding the development of myelin has important clinical and physiological significance. Magnetic resonance imaging technology can not only directly display the development process of each structure and the appearance or disappearance of temporary structures, but also evaluate the maturity of various tissues by different signal intensity.

The measurement of relaxation time in fetuses' and infants' brains can reflect changes in water content in various parts of the brain, and then evaluate the development of the brain. In this study, the T2 signal values of the deep and superficial white matter of infants and fetal with different pregnancy modes were measured and compared. The results showed that there was no significant difference in the developmental patterns of different conception fetuses. The T2 signal values of ALIC, PLCI, CR, and PWM first increased and then decreased with the growth of gestational age, while FWM and OWM gradually decreased. This is basically the same as that shown by Dobbing et al., the water content of the human brain reaches up to 90% in the fetal period, 88% at full term, and 82% at six months after birth [20].

With the increase of gestational age, T2 signal value showed a gradually decreasing trend. Since the fetal movement and the long T1WI imaging time were considered to affect the image quality and lead to the measurement inaccuracy of T1 signal value. The T1 signal value was not included for fetus in this study.

Apparent diffusion coefficient (ADC) is the average of the diffusion size of water molecules in the human body; it represents the comprehensive micro-movement of brain tissue. ADC maps provide quantitative measures of water diffusion within brain tissue. Because of the short imaging time, it is suitable for fetal examination. In this study, the ADC values of deep and superficial white matter were measured and compared in fetuses and neonates from three different conception groups in three gestational ages.

Diffusion tensor imaging (DTI) is a more advanced diffusion imaging, in which tensor is introduced based on DWI imaging. DTI analyses the three-dimensional shape of the diffusion, also known as diffusion tensor. The diffusion tensor of white matter or gray matter tracts should be considered as a three-dimensional structure with three principal diffusivities associated with three mutually perpendicular principal directions. DTI provides measurable metrics of diffusion characteristics, including fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD), each of which provides quantitative characteristics for the underlying diffusivity of the brain. Given the degree of anisotropic diffusion in white matter – due to tissue barriers such as axonal fibers and the myelin sheath – FA, MD, RD, and AD provide indirect markers of white matter microstructure. FA value, one of the main parameters of DTI, refers to the proportion of the anisotropic components of water molecules in the whole diffusion tensor, reflecting the diffusion direction. Brain tissue is composed of gray matter and white matter, not homogeneous tissue, so the diffusion process of water molecules in brain tissue shows obvious anisotropy and changes with the development and maturity of white matter fiber bundles. DTI can perform non-invasive studies on the molecular diffusion characteristics of brain tissue in vivo, showing the changes in the fine structure of the living brain, clearly showing the diffusivity of the white matter fiber bundle and the degree of myelination.

Myelination is an essential part of the brain development process. The FA values of three groups' infants with different conception modes and at different months of age showed no significant differences. PLIC, GCC, and TWM all showed a trend of FA increasing gradually with the increase of age. The values of SCC, SLF, ILF, CSF, and OR were the same in 5-7 and 11-13months infants but slightly increased in 23-25months. ALIC shows that the FA of 5-7 months is higher than 11-13 and 23-25months, while the values of 11-13 and 23-25months are substantially equal. The development trend of the white matter region of the brain in this study is consistent with the confirmation of a large number of studies that the FA value gradually increases with the progress of myelin sheath, which can reflect the maturity of the brain [21, 22].

The MRI values in ALIC, CR, FWM regions fluctuate relatively large. Considering that the brain develops until 10 years old and some regions may develop late in some individuals, our investigating duration from 5 to 25 months might be too narrow and early, which may lead to a large fluctuation of MRI values. However, it should be meaningful and necessary to confirm this study in a larger sample set and longer follow uptime. FA values in different gray matter areas were significantly different from those in infants at months old. The main consideration is that the gray matter of the brain is arranged in many directions and irregular, and the degree of anisotropy is reduced. For example, there are a large number of white matter fiber bundles in the thalamus, such as subthalamic radiation, central thalamic radiation, and thalamic anterior spokes, etc., so the gray matter FA value fluctuates and changes greatly [23-30].

The T1, T2, ADC, and FA values are all relative ratios. Various studies reported that there is no uniform standard for selecting the exact location, boundary, size, and shape of the ROI. Different magnetic resonance manufacturers, field strengths, models, sequences, scanning parameters, etc. some indexes particularly sensitive to position, and the size of the ROI, often appear error and uncertainty [31-35]. Therefore, the change rules of these values are more meaningful, which can be mutually verified in different studies.

In summary, the T1, T2, ADC, and FA signal values can be used to detect the diffusion of water molecules in living fetal and infant brain tissue, which can be used to evaluate the developmental maturity of white matter in children. This research will be used to evaluate the brain development of fetuses and infants in different stages of the natural conception group, IVF or ET conception group and ICSI conception group. The results showed that there was no significant difference in brain development patterns between different modes of conception, which proved that ART does not affect the development of brain myelin in fetuses and infants.

Abbreviations

Assisted reproductive technology (ART)

In-vitro fertilization (IVF)

Intracytoplasmic sperm injection (ICSI)

Embryo transfer (ET)

Magnetic resonance imaging (MRI)

Diffusion-weighted images (DWI)

Diffusion tensor imaging (DTI)

Anterior limb of internal capsule (ALIC)

Posterior limb of internal capsule (PLIC)

Corona radiata (CR)

Frontal white matter (FWM)

White matter of parietal lobe (PWM)

Occipital white matter (OWM).

Interquartile range (IQR)

Genu of corpus callosum (GCC)

Splenium of corpus callosum (SCC)

External capsule (EC)

longitudinal fasciculus (SLF)

Inferior longitudinal fasciculus (ILF)

Corticospinal tract (CST)

Optic radiations (OR)

Ftemporal white matter (TWM)

Caudate nucleus head (CNH)

Thalamus (THA)

Lenticular nucleus (LN)

Apparent diffusion coefficient (ADC)

Fractional anisotropy (FA)

Mean diffusivity (MD)

Radial diffusivity (RD)

Axial diffusivity (AD)

Declarations

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Authors' contributions

All authors have made substantial contributions to the entire image analysis procedures including data acquisition, image analysis, and classification. XW and JW contributed equally to this work, were major contributors in writing and revising the manuscript. LZ, XC, YW, and QX participated in collecting data and performed the statistical analysis. ZZ supervised the entire procedures and helped to draft the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used in this study are available from the corresponding author on reasonable request.

Ethics declarations

Ethics approval and consent to participate

The study was conducted in Hangzhou Jianggan District People's Hospital. This study was approved by the ethics committee of Hangzhou Jianggan District People's Hospital, and the informed written consent for participation were obtained from all the parents of the involved children.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Due to technical limitations, tables are only available as a download in the supplemental files section

Figures

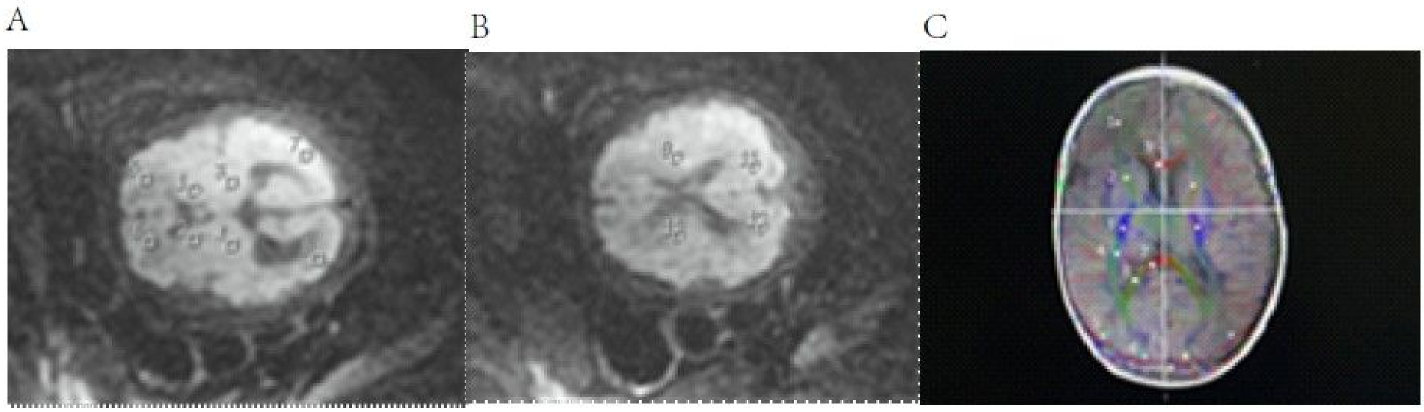

Figure 1

. MR imagine demonstrating the positions of the ROIs. A) Left regions of anatomical locations. B) Right regions of anatomical locations. C) Left and right regions of anatomical locations are combined, giving a total of 12 regions in infants of 5-7, 11-13 and 23-25months at T1WI, T2WI, DTI image and in fetuses of 28-32GW, 33-37GW, newborns on T2WI and DWI images.

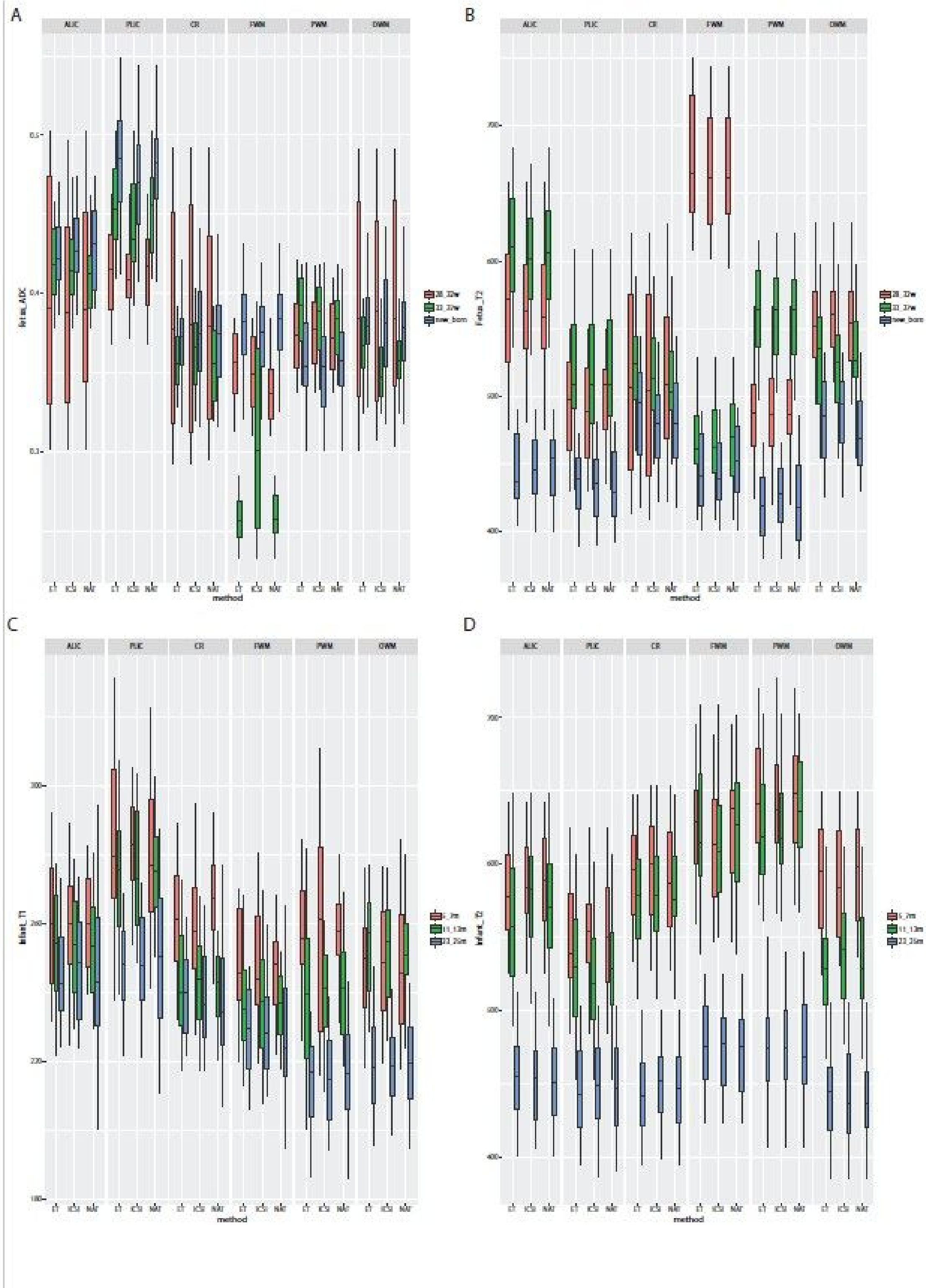

Figure 2

Candle plots of ADC (A) and T2 (B) values of fetuses and T1 (C) and T2 (D) of infants in the three conception groups: ET, ICSI and NAT at 6 brain regions: ALIC, PLIC, CR, FWM, PWM, and OWM.

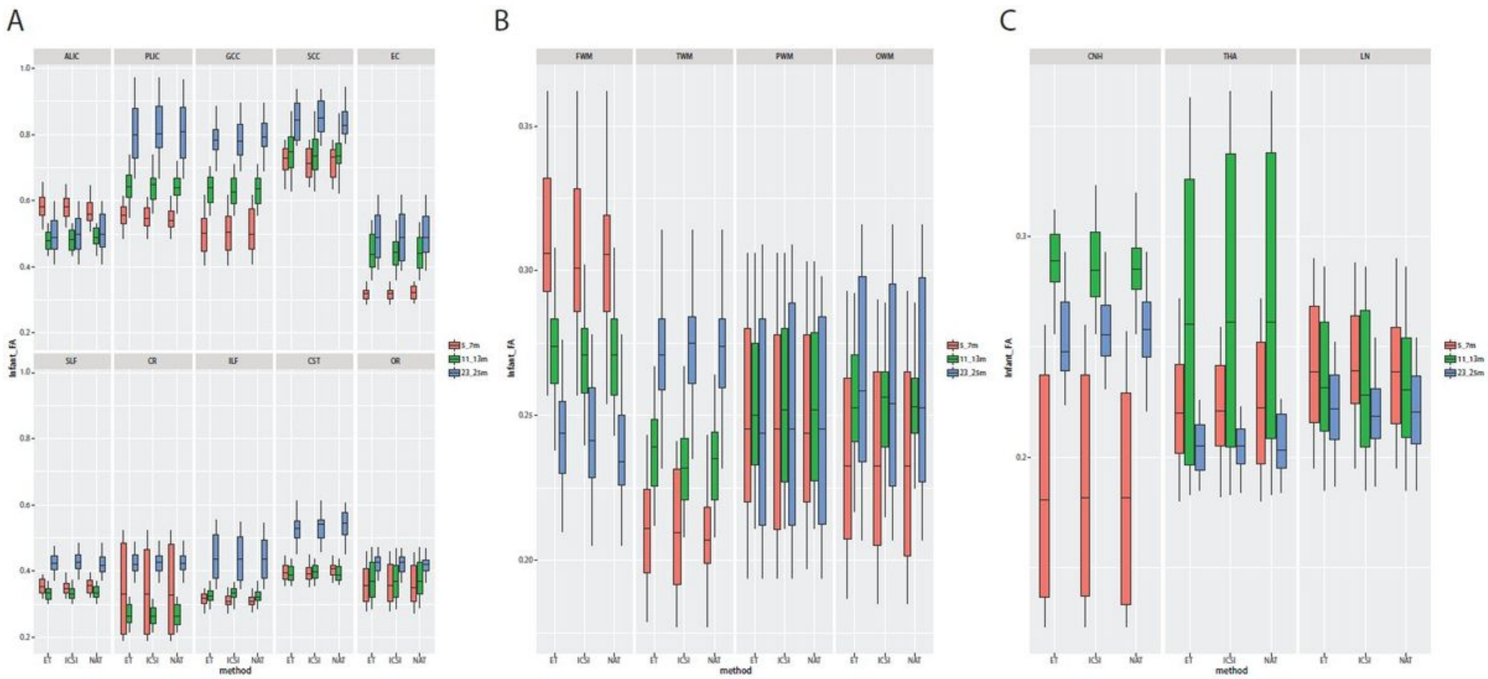

Figure 3

Analysis of FA values of three conception groups at different months of age.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- supplementfig.1.pdf
- supplement.docx
- table.xlsx
- Supplementtable.xlsx