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Twin Pregnancy with Holoprosencephaly in One Fetus and Down Syndrome in the Other

In this case report, we present a dizygotic twin pregnancy with two different major anomalies one of which was a fetus with multiple congenital anomalies consisting of alobar holoprosencephaly, cleft lip and palate, enlarged echogenic kidneys and clubfoot. The other fetus with early asymmetrical growth restriction and sandal gap sign suggesting Down syndrome which was confirmed after birth.

Keywords: Twins, Holoprosencephaly, Down Syndrome

Introduction

The risk of congenital anomalies in twins is approximately twice as high as singletons.[1] The rate of congenital anomalies is higher for all major types of anomalies, except for chromosomal abnormalities.[2] Major malformations occur in approximately 2.12% of infants of a twin gestation while it is 1.05% in singletons. The rates of minor malformation in twins and singletons are 4.13% and 2.45%, respectively.

The increased incidence of anomalies in twins has been proven to be entirely due to the increased rate of anomalies in monozygotic (MZ) twins.[3] In comparison to singletons, dizygotic (DZ) twins are not at increased risk for anomalies.[4] Congenital anomalies in monochorionic (MC) twins have twice the prevalence of singletons and occur more common in dichorionic (DC) twins than in singletons.[5]

Case Presentation

In this report, we present a 34-year-old woman who was referred to Royan Institute with primary infertility. The couple were close relatives. The hormonal profile, routine laboratory tests and the hysterosalpingogram (HSG) were normal. Except for sperm morphology which was abnormal (90%), the other quantitative measurements of sperm analysis based on WHO values were normal. Both parents also had a normal karyotype.

The patient was selected as an intra-uterine insemination (IUI) candidate. After positive βHCG at 9 weeks gestation, she underwent a sonographic exam (ALOKA α-10) and two fetuses were seen with regular fetal heart rate (FHR). At 12 weeks gestation, two fetuses corresponded to 12 weeks were seen with top normal nuchal translucency (NT) (2.5 and 2 mm). At 15 weeks gestation, one of the fetuses corresponded to 13.5-14 weeks with monoventricle in the center of the brain, which was suspected of holoprosencephaly (HPE) although the other fetus seemed normal. Triple test revealed a risk of 1/162 for trisomy 21.

At 17 weeks gestation, holoprosencephaly was clearly seen as well as the midline

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Received January 5, 2010;
Revised August 23, 2010;
Accepted December 25, 2010.

Iran J Radiol 7(4): 221-224

facial defect and unilateral clubfoot. Both kidneys were larger than normal with an echogenic pattern, one fetus corresponding to 15.5 weeks and the other to 16-17 weeks. Selective reduction was done for the holoprosencephalic fetus at 18 weeks (Fig. 1).

At 20 weeks gestation, the second twin corresponded to 18.5 weeks and in the serial sonography that was performed at 20-33 weeks, growth retardation developed until there was a 5-week growth retardation at 33 weeks. The volume of amniotic fluid was normal and grade two placenta was identified in all sonographies. In Doppler study, reversed diastolic flow was seen in the umbilical artery. The last sonography was carried out at 33 weeks gestation, which corresponded to 28 weeks with 1400 g weight. At this stage, asymmetric IUGR in the background of chromosomal abnormality was suspected and the sandal gap sign was only seen in the minor diagnostic criteria. At least 2 weeks later, after premature rupture of membranes, a 1700 g baby boy was born by cesarean section.

Regarding the specific facies with hypotonia and sandal gap between the fingers, the baby was suspected of Down syndrome which was subsequently confirmed by the karyotype (Fig. 2). The baby was hospitalized several times and finally, he died at the age of 8 months due to recurrent respiratory infections.

Discussion

The purpose of this paper was to present a unique case, which has not been reported so far. To our best knowledge, so far, three monozygotic and five dizygotic pairs have been reported, in which at least one twin was diagnosed with holoprosencephaly.[6] We present this case because of the low incidence of two simultaneous major anomalies in DZ twin pregnancy

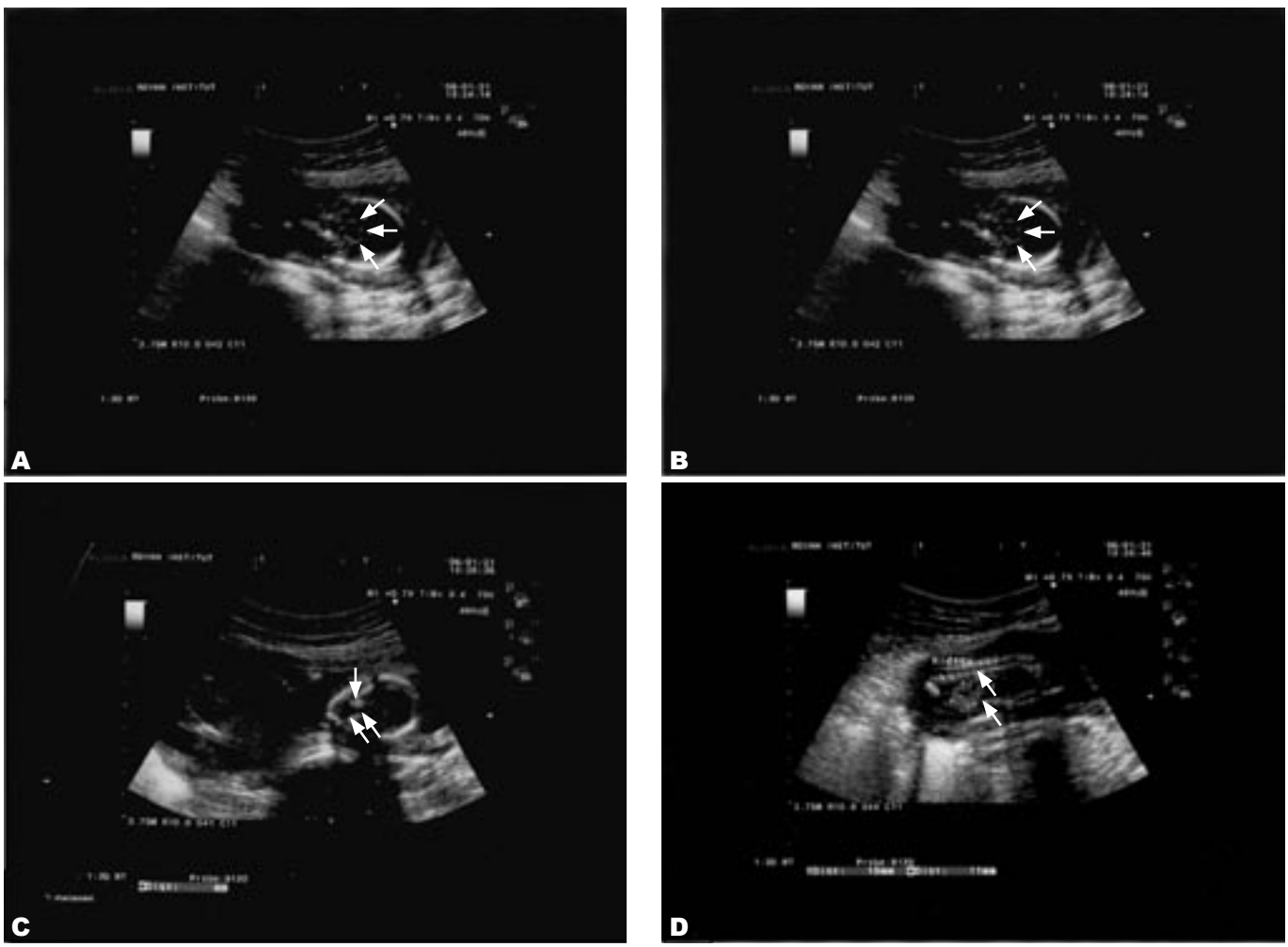

Fig. 1. A 34-year-old woman with twin pregnancy. In the brain sonography, arrows indicate
A. The first fetus with the typical holoprosencephalic picture.
B. A monoventricle and fused thalami.
C. A midline facial cleft palate.
D. An enlarged echogenic kidney.

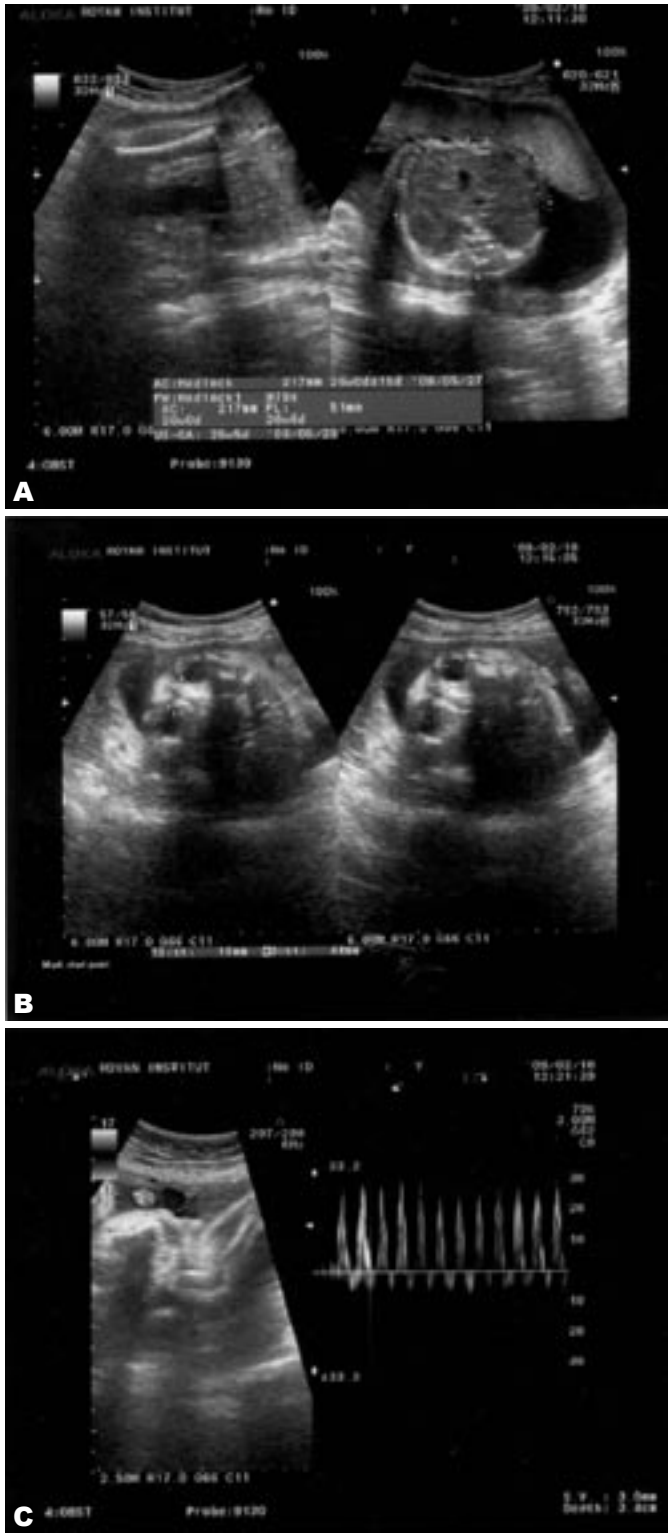

Fig. 2. A Sonography of the same patient at 32 weeks gestational age.
A. Sonography reveals the second fetus with a biometric measurement corresponding with 25-26 weeks.
B. Hypotelorism IOD=16 mm and OOD=44 mm.
C. Spectral wave flow in the umbilical artery with a reverse diastolic flow.
IOD: Inner ocular distance. This measurement is 18 mm at 32.5 weeks gestation.
OOD: Outer ocular distance. This measurement is 52 mm at 32.5 weeks gestation.

in infertile patients.

Kurtz et al.[7] described the first case of prenatal recognition of HPE by ultrasound in 1980. HPE has three major types based on severity, alobar, semilobar and lobar. The earliest diagnoses of holoprosencephaly for alobar HPE, semilobar HPE, and lobar HPE were reported at 9.5, 13 and 21 weeks, respectively.[8-10]

We detected semilobar holoprosencephaly in 15 weeks gestation. Unfortunately, amniocentesis had not been performed before reduction because this procedure was expensive.

There is no evidence to suggest that delayed ovulation or delayed fertilization is associated with the risk of holoprosencephaly.

Two published papers suggest that almost one half of holoprosencephalic cases are associated with choromosomal anomalies and the other half have normal karyotypes. The most common of these chromosomal anomalies was trisomy 13.[6]

Dalal et al.[11] presented a case report of a twin pregnancy with Robert syndrome and Edward syndrome and concluded that karyotyping of both fetuses would be warranted when one of the twins is found to have major malformation. This was supported by our finding in this case.

Because holoprosencephaly (HPE) was associated with multiple anomalies such as enlarged echogenic kidneys, cleft palate and club foot, we do expect a higher chance of choromosomal abnormalities in the first fetus, but the patient preferred reduction without amniocentesis. As pregnancy progressed, we mentioned the probability of chromosomal abnormality in the second fetus, but unfortunately in spite of all the recommendations, the patient preferred continuing her pregnancy without amniocentesis because of the probability of miscarriage. According to the records, miscarriage rate in twins is twice as high as singletons after amniocentesis.[12]

Because of the increased use of assisted reproductive technologies and the trend of delayed childbearing, twin pregnancies have risen dramatically. Those who use ART have a 25% chance or more for conceiving twins. Furthermore, women over 35 years of age are three times more likely to spontaneously conceive twins than younger women. Twin pregnancies pose numerous management problems; for example, they are at higher risk both for chromosomal abnormality and structural defect for each individual co-twin. Dalal et

al has mentioned the limited value of serum screening of Down syndrome in twins, "because of the unaffected co-twin's masking of the abnormal maternal serum distribution seen in singleton analyses".[11] However, it is still ambiguous to what extent the increasing risk of congenital anomalies in assisted reproductive technology (ART) treated pregnancies is related to the underlying infertility and to what extent it is due to the treatment itself.[5]

Another significant aspect of this case was a reversed diastolic flow in the umbilical artery (ARED flow) in the second fetus, in which Down syndrome was proven after birth. The prediction of any association between reversed diastolic flow in the umbilical artery and chromosomal abnormalities needs to be proven based on more comprehensive Doppler studies on fetuses with chromosomal abnormalities.

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