

Research Letter

# Discordant anencephaly and Cantrell syndrome in monozygotic twins conceived by ICSI and IVF–ET

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A 35-year-old primigravid woman presented with a twin pregnancy at 13 weeks of gestation for evaluation of structural abnormalities in one co-twin. The woman and her husband were healthy and non-consanguineous. The husband was aged 37 years. There was no family history of congenital malformations. The woman did not have diabetes mellitus and denied any recent infections or exposure to teratogens during this pregnancy. The woman had suffered from primary infertility. This was her first pregnancy and it was achieved by intracytoplasmic sperm injection (ICSI), *in vitro* fertilization (IVF) and embryo transfer (ET). Two embryos had been implanted and a twin pregnancy was achieved. Prenatal ultrasound at 13 weeks of gestation revealed a dichorionic, diamniotic twin pregnancy with a normal co-twin and an abnormal co-twin with anencephaly and eviscerated heart, stomach, liver, and intestines. The pregnancy was uneventful until 16 weeks of gestation when uncontrolled preterm labor occurred. A 45-g normal male co-twin and a 30-g abnormal male co-twin with anencephaly and anterior abdominal wall defects with ectopia cordis and eviscerated stomach, liver, and intestines, a sternal defect, and a defect in the diaphragm were delivered (Figs. 1 and 2). Cytogenetic analysis of the fetal tissues of the normal and abnormal twins revealed a karyotype of 46,XY. Array comparative genomic hybridization revealed no

genomic imbalance in the fetuses. A molecular zygosity test confirmed monozygotic twinning (Fig. 3).

Severe midline disruption sequences associated with IVF–ET in dizygotic twins have been well reported [1–3]. However, a severe midline disruption sequence associated with IVF–ET in monozygotic twins is very unusual. Babies born by IVF–ET carry a two- to threefold increase in the frequency of monozygotic twinning than those without assisted reproductive technologies [4,5]. Hall suggested that the increased frequency of monozygotic twinning in babies born by IVF could be related to breaks in the zona pellucida due to handling or artificial holes caused by ICSI, and zona hardening caused by aging, drugs or media [6]. She also suggested that blastocytes may split during premature zona hardening or be separated by the edge of the broken or hardened zona [6]. Monozygotic twinning is associated with early embryonic midline structural defects such as holoprosencephaly malformation sequence, exstrophy of the cloaca malformation sequence, the VATERR association (vertebral defects, anal atresia, tracheo-esophageal fistula, esophageal atresia, and radial and renal dysplasia), sirenomelia, and sacrococcygeal teratoma, and only 5–20% of such cases are concordant [7–9]. It has been noted that approximately 10% of monozygotic twins are born with a congenital anomaly, which represents a two- to threefold increase in congenital anomalies in monozygotic twins compared to 2–3% of singleton newborns with an obvious major anomaly [6]. The congenital anomalies associated with monozygotic twinning include malformations (cloacal anomalies, neural tube defects, congenital heart defects, and midline anomalies), disruptions (hemifacial

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Fig. 1. (A) The normal co-twin and (B) the abnormal co-twin.

microsomia, limb reduction defects, and amyoplasia) and deformations (club feet, dislocated hips, and cranial synostosis) [6]. Severe midline ventral disruption syndrome associated with monozygotic twins includes body stalk anomaly [10–14], Cantrell syndrome [15], complex cloaca anomaly [16], omphalocele–exstrophy–imperforate anus–spinal defects (OEIS) complex [17,18], and omphalocele [19].

The peculiar aspect of the present case is the concomitant occurrence of anencephaly and Cantrell syndrome in one co-twin of monozygotic twins. Cases with concomitant neural tube and abdominal wall defects have previously been described [1,20]. Pentalogy of Cantrell has also been associated with abnormalities of the central nervous system. For instance, Polat et al reported prenatal diagnosis of pentalogy of Cantrell in two cases with craniorachischisis, polyhydramnios and club feet [21]. Chen et al reported concomitant exencephaly and limb defects associated with pentalogy of Cantrell

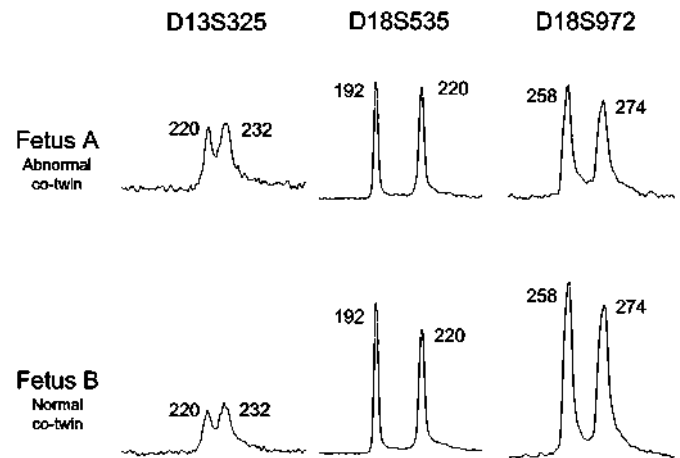


Fig. 3. Polymorphic DNA marker analysis shows monozygosity in the twins.



Fig. 2. Eviscerated heart (H, arrow), liver (L), stomach (S) and intestines (I) in the abnormal co-twin.

[1]. Cantrell et al first reported full pentalogy of a midline supraumbilical abdominal wall defect including a defect of the lower sternum, a defect of the diaphragmatic pericardium, a deficiency of the anterior diaphragm, and congenital cardiac anomalies, and suggested that such defects are related to developmental failure of a segment of the lateral mesoderm at approximately 14–18 days of embryonic life [22]. The congenital anomalies in our case are probably related to developmental defects influenced by monozygotic twinning. The recurrence risk for neural tube and abdominal defects in the next pregnancy in our case is therefore very low. The present case emphasizes the usefulness of zygosity testing in genetic counseling for discordant malformations in same-sex twins conceived by ICSI and IVF-ET.

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