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Research Letter

Concordant myelomeningocele in dizygotic twins conceived by intracytoplasmic sperm injection, *in vitro* fertilization, and embryo transfer

Chih-Ping Chen [a,b,c,d,e,f,*], Yuh-Ming Hwu [a], Chen-Yu Chen [a], Yi-Ning Su [g,h], Tzu-Hung Lin [h], Yu-Ling Kuo [i], Schu-Rern Chern [b], Wayseen Wang [b,j]

[a] *Department of Obstetrics and Gynecology, Mackay Memorial Hospital, Taipei, Taiwan*
[b] *Department of Medical Research, Mackay Memorial Hospital, Taipei, Taiwan*
[c] *Department of Biotechnology, Asia University, Taichung, Taiwan*
[d] *School of Chinese Medicine, College of Chinese Medicine, China Medical University, Taichung, Taiwan*
[e] *Institute of Clinical and Community Health Nursing, National Yang-Ming University, Taipei, Taiwan*
[f] *Department of Obstetrics and Gynecology, School of Medicine, National Yang-Ming University, Taipei, Taiwan*
[g] *Department of Obstetrics and Gynecology, School of Medicine, Taipei Medical University, Taipei, Taiwan*
[h] *Dianthus Maternal Fetal Medicine Clinic, Taipei, Taiwan*
[i] *Department of Obstetrics and Gynecology, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan*
[j] *Department of Bioengineering, Tatung University, Taipei, Taiwan*

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A 36-year-old, gravida 3, para 1 woman had suffered from secondary infertility. Her husband was aged 37 years. She and her husband were healthy and nonconsanguineous, and there was no family history of congenital malformations. The woman did not have diabetes mellitus. Her HbA1c and blood sugar were within the normal limits. She denied any recent infections or exposure to teratogens during this pregnancy. This was her third pregnancy, and it was achieved by intracytoplasmic sperm injection (ICSI), *in vitro* fertilization (IVF), and embryo transfer (ET). Two embryos were implanted, and a twin pregnancy was achieved. Prenatal ultrasound at 12 weeks of gestation revealed a dichorionic and diamniotic twin pregnancy. The pregnancy was uneventful until 20 weeks of gestation when level II ultrasound revealed ventriculomegaly, club feet, and concordant myelomeningocele in the twins. Amniocentesis revealed a karyotype of 46,XX in the twins, and array comparative genomic hybridization analysis revealed no genomic imbalance. Her pregnancy was subsequently terminated, and two abnormal female cotwins with concordant lumbosacral myelomeningocele and club feet were delivered (Fig. 1). Cytogenetic analysis of the cord blood of the twins revealed a karyotype of 46,XX in each cotwin. A methylenetetrahydrofolate reductase (*MTHFR*) C677T single-nucleotide polymorphism analysis of the maternal blood revealed an *MTHFR* 677CT heterozygous genotype in the mother. A molecular zygosity test confirmed dizygotic twinning (Fig. 2).

Monozygotic twinning is well known to be associated with neural tube defects (NTDs) [1]. However, concordance of NTD in dizygotic twins is uncommon [2–6]. Deak et al [6] found a male:female ratio of 0.82 in individuals affected with NTDs. They reported that among the twins affected with NTDs, two of five monozygotic twins were concordant, whereas only three of 35 dizygotic twins were concordant.

A peculiar aspect of the present case is the association of concordant myelomeningocele with dizygotic twins conceived by ICSI and IVF–ET. Källén et al [7] reported an increased risk for congenital malformations after different IVF methods. In a study of 16,280 IVF children of which 30% were conceived after ICSI, Källén et al [7] found that 8% had a congenital malformation, 5% had a relatively severe condition, and an additional risk increase was observed in NTDs, choanal atresia, and alimentary tract atresia; in addition, the odds ratios (ORs) with 95% confidence intervals (CIs) for anencephaly, spina bifida, and any NTD were 7.6 (95% CI: 2.5–7.7), 5.1 (95% CI: 3.4–7.8), and 4.8 (95% CI: 3.3–6.9), respectively. Källén et al [8] concluded that in infants born after IVF, a slightly increased risk for congenital malformation persists; for NTDs, cardiac septal defects, and esophageal atresia, they found an increased risk in their continuous series studies. Ben-Ami et al [9] reported an increased risk of anencephaly in twins. Ben-Ami et al [10] concluded that twin pregnancies conceived by assisted reproductive technology (ART) constitute a high-risk group for anencephaly because of the synergistic effect of twinning and

* Corresponding author. Department of Obstetrics and Gynecology, Mackay Memorial Hospital, 92, Section 2, Chung-Shan North Road, Taipei, Taiwan.
E-mail address: cpc_mmh@yahoo.com (C.-P. Chen).

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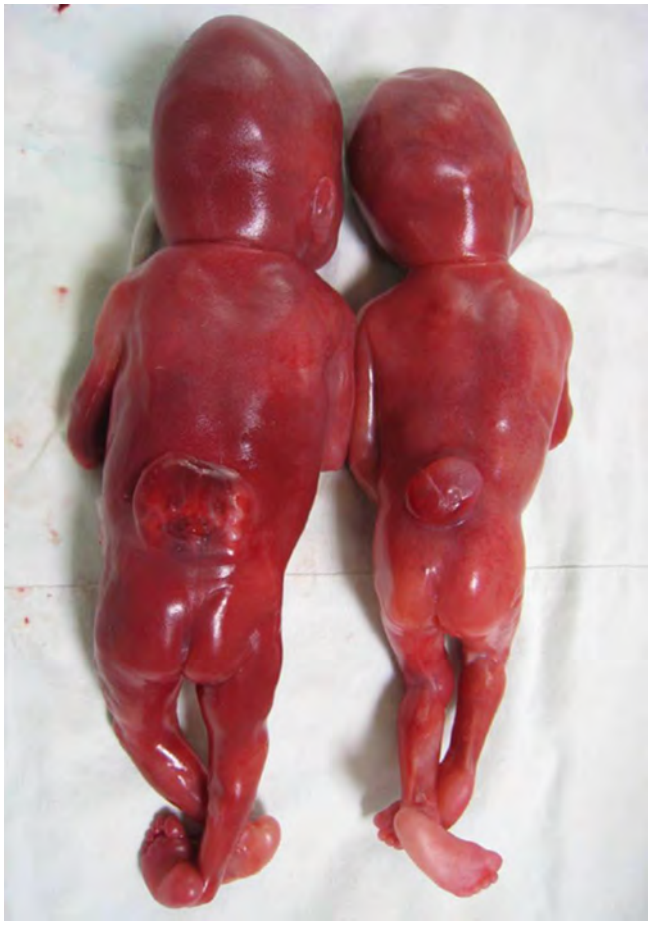

Fig. 1. Concordant lumbosacral myelomeningocele in the twins.

ART. In a study of 1154 pregnancies diagnosed with severe fetal anomaly, Ben-Ami et al [10] found that 43 fetuses (3.7%) had anencephaly, and anencephaly was diagnosed in 9/78 (11.5%) twin pregnancies of which 8/45 (17.8%) were ART conceived and 1/33 (3%) were spontaneously conceived. Ben-Ami et al [10] calculated an OR of 6.6 (95% CI: 2.8–15.3, $p < 0.01$) for anencephaly in correlation with the combination of ART conception and twinning.

Our case additionally provides evidence that twinning and ART can be associated with concordant myelomeningocele in the twin fetuses born after ICSI and IVF–ET. We suggest careful perinatal investigations of birth defects in pregnancies achieved by ART, including a sonographic screening of fetal spine to exclude myelomeningocele.

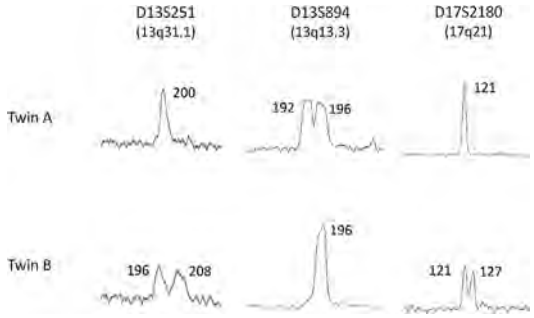

Fig. 2. Polymorphic DNA marker analysis shows dizygotic twinning.

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