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Case Report

VACTERL association with hydrocephalus in a fetus conceived by *in vitro* fertilization and embryo transfer

Chih-Ping Chen [a,b,c,d,e,f,g,*], Tung-Yao Chang [h], Yi-Yung Chen [a], Schu-Rern Chern [b], Jun-Wei Su [a,i], 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 Medicine, Mackay Medical College, New Taipei City, Taiwan*
[d] *Department of Biotechnology, Asia University, Taichung, Taiwan*
[e] *School of Chinese Medicine, College of Chinese Medicine, China Medical University, Taichung, Taiwan*
[f] *Institute of Clinical and Community Health Nursing, National Yang-Ming University, Taipei, Taiwan*
[g] *Department of Obstetrics and Gynecology, School of Medicine, National Yang-Ming University, Taipei, Taiwan*
[h] *Taiji Fetal Medicine Center, Taipei, Taiwan*
[i] *Department of Obstetrics and Gynecology, China Medical University Hospital, Taichung, Taiwan*
[j] *Department of Bioengineering, Tatung University, Taipei, Taiwan*

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Abstract

Objective: We present a case of VACTERL association with hydrocephalus (VACTERL-H) in a fetus conceived by *in vitro* fertilization (IVF) and embryo transfer (ET) and review the literature.

Case report: A 35-year-old woman presented with multiple fetal anomalies at 22 weeks of gestation. She and her husband were non-consanguineous and there was no family history of congenital malformations. This was her second pregnancy conceived via IVF-ET. Two embryos had been implanted and only one survived. She underwent chorionic villus sampling at 17 weeks of gestation because of oligohydramnios and advanced maternal age. Cytogenetic analysis revealed a karyotype of 46,XY, and array comparative genomic hybridization analysis revealed no genomic imbalance. Prenatal ultrasound at 21 weeks of gestation revealed a singleton with fetal biometry equivalent to 18 weeks, ventriculomegaly, a small cerebellum, and a ventricular septal defect. Level II ultrasound showed a single umbilical artery, scoliosis, a right club hand, radial aplasia, and renal agenesis. The parents elected to terminate the pregnancy at 22 weeks of gestation, and a fetus was delivered with bilateral arthrogryposis, right radial aplasia, a club hand and thumb aplasia, hypoplasia of the left thumb, scoliosis, and an imperforate anus. The clinical findings were consistent with the diagnosis of VACTERL-H. Molecular analysis of *PTEN*, *FANCB*, and *HOXD13* genes revealed no mutation.

Conclusion: Prenatal diagnosis of radial ray defects in fetuses conceived by assisted reproductive technology should include a differential diagnosis of VACTERL association with anorectal malformation. VACTERL-H may occur in pregnancy after IVF-ET.

Keywords: assisted reproductive technology; hydrocephalus; *in vitro* fertilization; prenatal diagnosis; VACTERL association

Introduction

VACTERL association (OMIM 192350) occurs in 1/10,000–1/40,000 infants and is an acronym to describe the non-random association of at least three of the following core abnormalities: vertebral defects (V), anal atresia (A), cardiac defects (C), tracheo-esophageal fistula (TE), renal anomalies

* 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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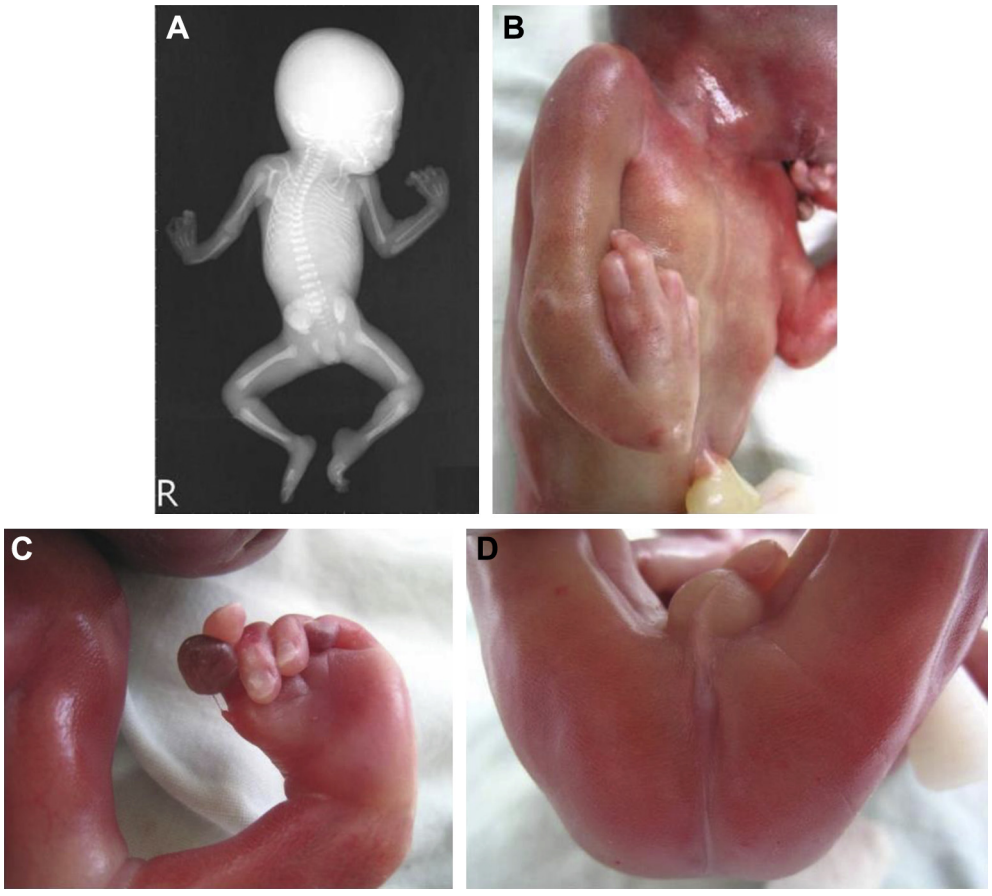

Fig. 1. (A) X-Ray of the fetus at birth. (B) Radial ray defects of the right upper limb and absence of the right thumb. (C) Left thumb hypoplasia. (D) Imperforate anus.

(R), and limb defects (L) [1]. Approximately 90% of VACTERL association cases occur sporadically, whereas 10% of cases involve familial inheritance [2]. Genetic factors associated with VACTERL association include mitochondrial dysfunction, respiratory chain deficiency, chromosomal deletions or duplications, and mutations in *HOXD13*, *ZIC3*, *PTEN*, *FANCB*, and *FOXF1* genes [3–24]. Here we describe our experience of prenatal diagnosis of VACTERL association with hydrocephalus (VACTERL-H) in a fetus conceived by *in vitro* fertilization (IVF) and embryo transfer (ET) and review the literature.

Case report

A 35-year-old women (gravida 2, para 0) presented with multiple fetal anomalies at 22 weeks of gestation. The woman's husband was 35 years old. She and her husband were nonconsanguineous and there was no family history of congenital malformations. The woman did not have diabetes mellitus during this pregnancy. She had experienced one spontaneous abortion and had suffered from infertility. This was her second pregnancy conceived via IVF-ET. Two embryos had been implanted and only one survived. She underwent chorionic villus sampling at 17 weeks of gestation because of oligohydramnios and advanced maternal age. Cytogenetic analysis revealed a karyotype of 46,XY, and an array comparative genomic hybridization analysis revealed no genomic imbalance. Prenatal ultrasound at 21 weeks of gestation revealed a singleton with fetal biometry equivalent to 18 weeks, ventriculomegaly, a small cerebellum, and a ventricular septal defect (VSD). Level II ultrasound showed a single umbilical artery, scoliosis, a right club hand, right radial aplasia, and right renal agenesis. The parents elected to terminate the pregnancy at 22 weeks of gestation, and a 342-g malformed fetus was delivered with bilateral arthrogryposis, right radial aplasia, a right club hand, aplasia of the right thumb, hypoplasia of the left thumb, scoliosis, and an imperforate anus (Fig. 1). The clinical findings were consistent with the diagnosis of VACTERL-H. Molecular analysis of *PTEN*, *FANCB*, and *HOXD13* genes revealed no mutation.

Discussion

With the advent of fetal ultrasonography, prenatal diagnosis of VACTERL association is possible in the second trimester [25–28]. The present case exhibited multiple abnormalities such as scoliosis, an imperforate anus, VSD, unilateral renal agenesis and radial ray defects, and hydrocephalus. In patients with VACTERL association, the frequency of the core abnormalities is 60–80% for vertebral anomalies, 55–90% for