Case Report

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

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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.

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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
(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 woman (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 non-consanguineous 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
imperforate anus/anal atresia, 25% for genitourinary anomalies, 40—80% for cardiac malformations, 50—80% for tracheoesophageal fistula, 50—80% for renal anomalies, and 40—50% for limb malformations [1]. The present case had radial ray defects with radial aplasia, thumb aplasia/hypoplasia, and bilateral arthrogryposis of the hands. Radial ray defects include partial or complete absence of the radius and the first carpal and metacarpal bones and the two phalanges of the thumb, and occur in 1:30,000 live births [28,29]. Prenatal diagnosis of radial ray defects should prompt detailed fetal anatomy scans to assess growth restriction, abnormal digits, vertebral defects, anal atresia, tracheo-esophageal fistula, cardiac abnormalities, facial anomaly, thumb abnormality, and renal anomalies, including differential diagnosis of VACTERL association, trisomy 18, trisomy 13, Cornelia de Lange syndrome, Holt—Oram syndrome, Robert syndrome, Fanconi anemia, thrombocytopenia-absent-radius (TAR), acrofacial dysostosis, and Baller—Gerald syndrome [28].

The present case had VACTERL association and hydrocephalus but no history of familial inheritance, no PTEN or HOXD13 mutations, no chromosomal abnormality, no genomic imbalance, and no heterotaxy. Chromosomal abnormalities associated with VACTERL association include distal 13q deletion [7], 5q11.2 deletion [16], a complex supernumerary ring chromosome 18 [18], microdeletion at 16q24.1 [15], microduplication at 22q11.21 [22], and microduplications at 1q41, 2q37.3, and 8q24.3 [24]. Cases with VACTERL-H (OMIM 276950) have been reported [30–38]. VACTERL-H has been described in association with autosomal recessive inheritance [30,31,35], X-linked VACTERL-H with FANCB mutations and Fanconi anemia [36,38], autosomal recessive inheritance (FANCD1/BRCA2) with Fanconi anemia [37], X-linked VACTERL association with or without hydrocephalus (VACTERL X; OMIM 314390), and autosomal dominant heterozygous PTEN mutation [6]. Reardon et al [6] reported a H61D mutation in the PTEN gene in a child with VACTERL association including ventriculomegaly, macrocephaly, tracheoesophageal fistula, and bilateral radial hand anomalies. PTEN (OMIM 601728) is a tumor-suppressor gene and PTEN mutations have been associated with tumor-predisposing syndrome and PTEN hamartoma syndrome. Garcia-Barceló et al reported a heterozygous de novo 21-bp deletion in a polyalanine tract in the HOXD13 gene in a 17-year-old girl with VACTERL association [14]. HOXD13 (OMIM 142989) is a homeobox gene that plays a role in limb development. VACTERL X is associated with X-linked visceral heterotaxy-1 (OMIM 306955), which is caused by mutation in or deletion of the ZIC3 gene. Wessels et al [19] reported VACTERL association and X-linked heterotaxy but no hydrocephalus in a male infant with polyalanine expansion in the ZIC3 gene. Chung et al [21] reported VACTERL-H and X-linked heterotaxy in a four-generation family in which affected males had a 1.3-Mb deletion of Xq26.3 including the ZIC3 gene. ZIC3 (OMIM 300265) encodes a zinc-finger transcription factor that functions in the earliest stages of left—right body axis formation. Loss-of-function FANCB mutations result in X-linked VACTERL-H and Fanconi anemia complementation group B (OMIM 300514) in affected males [36,38]. FANCB (OMIM 300515) is mapped to Xp22.2 and encodes a Fanconi anemia protein. Affected males with FANCB mutations are predicted to manifest major phenotypic signs of ventriculomegaly, bilateral absent thumbs and radii, vertebral defects, renal agenesis, and growth retardation, and less frequent signs of brain, pituitary, eye, and ear malformations, esophageal, duodenal, and anal atresia, tracheo-esophageal fistula, lung segmentation defects, and small genitalia, in addition to Fanconi anemia. In patients with microdeletions of the FOX gene cluster (FOXF1, MTHFS, FOXC2, and FOXL1) at 16q24.1, VACTERL association has been observed with vertebral anomalies, esophageal, duodenal and anal atresia, congenital heart defects, and urinary tract malformations, in addition to alveolar capillary dysplasia with misalignment of pulmonary veins (OMIM 265380) [15,17]. FOXF1 (OMIM 601089) encodes forkhead-related activator 1, which is a transcription factor. FOXF1 mutations are responsible for alveolar capillary dysplasia and multiple congenital anomalies [15].

The peculiar aspect of the present case is the association of VACTERL-H with assisted reproductive technology (ART). Sunagawa et al [39] reported concomitant occurrence of VACTERL association in dichorionic twin fetuses conceived by intracytoplasmic sperm injection (ICSI) and ET. In a German case—control study, Zwink et al [40] found a significantly increased risk of anorectal malformations after IVF [odds ratio (OR) 10.9; 95% confidence interval (CI) 6.2—19] and after ICSI (OR 7.5; 95% CI 4.6—12.2), and OR of 4.9, 11.9, and 7.9 for isolated anorectal malformations, anorectal malformations with associated anomalies, and anorectal malformations with VATER/VACTERL association, respectively. It is well known that monozygotic twinning is associated with early embryonic structural developmental defects such as sirenomelia, holoprosencephaly, anencephaly, exstrophy of the cloaca, and VACTERL association [41,42]. Recent investigations have shown increased congenital anomalies after ART [40,43—49]. We previously reported sirenomelia, limb-body wall complex, Cantrell syndrome, and anencephaly in pregnancies conceived via IVF-ET [50—52]. This case provides evidence of the occurrence of VACTERL-H in pregnancy after IVF-ET.

In conclusion, prenatal diagnosis of radial ray defects in fetuses conceived by ART should include a differential diagnosis of VACTERL association with anorectal malformation. VACTERL-H may occur in pregnancy after IVF-ET.

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References


Reference