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CASE REPORT

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Variable phenotypic expression of Apert syndrome in monozygotic twins

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Key Clinical Message

Apert syndrome in monozygotic twins can lead to different phenotypic expression of the disease in the two fetuses. Apert syndrome can be associated with congenital left diaphragmatic hernia and cleft palate.

KEYWORDS

Apert syndrome, congenital diaphragmatic hernia, craniosynostosis, fetal autopsy, fetal ultrasound, monozygotic twins

1 | INTRODUCTION

We report a second case of Apert syndrome in monozygotic twins affected by the same mutation but with different clinical characteristics. The typical malformations were identified for both fetuses. In addition, fetus A presented a congenital left diaphragmatic hernia and a cleft palate.

Apert syndrome is an acrocephalosyndactyly characterized by craniosynostosis, midface hypoplasia, and extremities anomalies and caused by heterozygous mutation in the Fibroblast Growth Factor 2 (FGFR2) gene. The estimated incidence of Apert syndrome is reported to be 1/100 000 to 1/160 000.[1] We report a case of a prenatal diagnostic of Apert syndrome in monozygotic twins affected by the same mutation but with different clinical characteristics.

2 | CASE HISTORY

This is a second pregnancy in a 32-year-old woman without medical or familial history. The antenatal diagnostic of Apert syndrome was made at 30 weeks of gestation during a detailed ultrasound (US) investigation. The typical malformations were identified by two- (2D) and three-dimensional (3D) US for both fetuses: facial dysmorphia including: hypertelorism, midface hypoplasia, craniosynostosis with brachycephaly, micrognathia, down-slanting palpebral fissures (Figures 1 and 3), and symmetric limbs' extremities abnormalities (mitten hand, enlarged and varus big toe) of the four extremities (Figures 2 and 3). In addition, fetus A presented a congenital left diaphragmatic hernia and a cleft palate (Figure 3). Craniosynostosis (coronal suture synostosis and open sagittal and lambdoid sutures) was confirmed by a

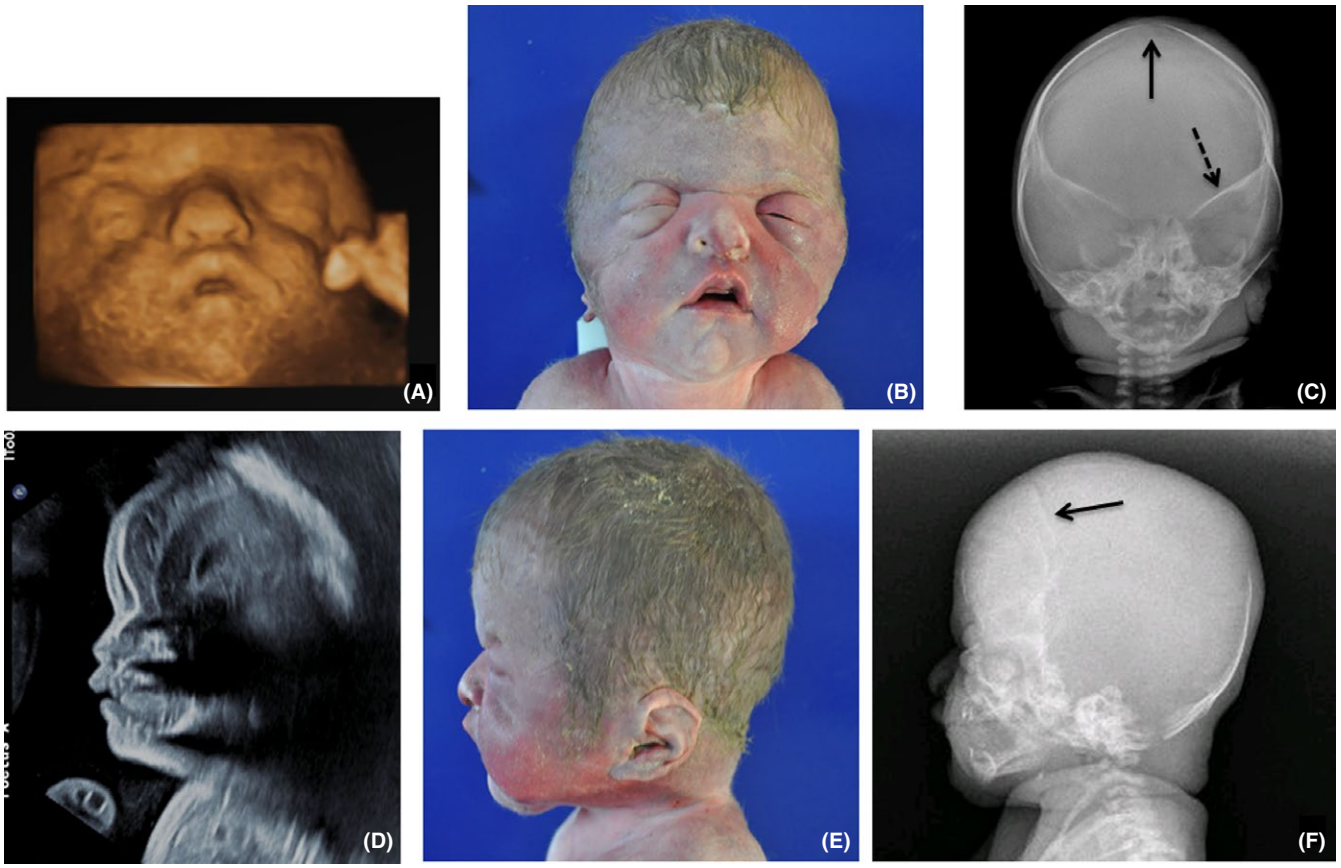

FIGURE 1 Craniosynostosis and facial dysmorphia. Prenatal 3D US (A), postmortem examination, (B) and radiography (C) of fetal face. Lateral view in prenatal 2D US (D), postmortem (E), and radiography (F). B and E. Hypertelorism, midface hypoplasia, micrognathia, downslanting palpebral fissures. C. Frontal view showing biparietal widening, hypertelorism, upward sloping orbital margins, sphenoid wings (dotted arrow) and open sagittal suture (arrow). F. Lateral views showing brachycephalic skull, highly arched orbital roofs and characteristic appearance of the coronal sutures (arrow)

fetal CT scan in both fetuses. A termination of the pregnancy was performed at 30 + 5 weeks of gestation. A postmortem exam confirmed the US abnormalities and found in addition a gallbladder agenesis and a right bifid collecting system in fetus B only. Postmortem skeletal radiography confirmed the abnormalities previously described in US and CT scan. The same heterozygous mutation was detected in both fetuses: c.755C>G, p.Ser252Trp (S252W) in exon 8 of FGFR2 as described by Wilkie et al.[2]

3 | DISCUSSION

To our knowledge it is only the second report of monozygotic twins affected by Apert syndrome after those described by Breugem et al in 2008.[3] In these two reports, both fetuses had the same genetic heritage (S252W mutation) but a different phenotypic expression of Apert syndrome, suggesting, for example, the influence of epigenetic phenomena. In the previously published case, the craniostenosis was different between the two fetuses, whereas in our description, the twins' skull's structures were similar and only visceral abnormalities were different. The correlation between genotype and phenotype is not clearly established in FGFR2 mutation. According to the review of 26 patients with S252W mutation made by Park et al, phenotypic expression is variable, all of the patients had a craniosynostosis, hypertelorism, midface hypoplasia, a hand or a foot syndactyly. Only 15 of them had cleft palate, 14 had a central nervous system abnormalities, four had a cardiac defect, and three had urogenital abnormalities.[4] S252W mutation was implicated already in two patients associated with congenital diaphragmatic hernia.[5,6] A third report of a patient with Apert syndrome in association with congenital diaphragmatic hernia was described with P253R mutation of FGFR2.[6]

Further studies of this rare disease may help to improve the knowledge on the phenotypic expression of S252W mutation. Animal model may also help to understand pathogenesis: Nitrofen model in rat with congenital diaphragmatic hernia provide evidence that FGFR2 is playing an active role in fetal lung development.[9]

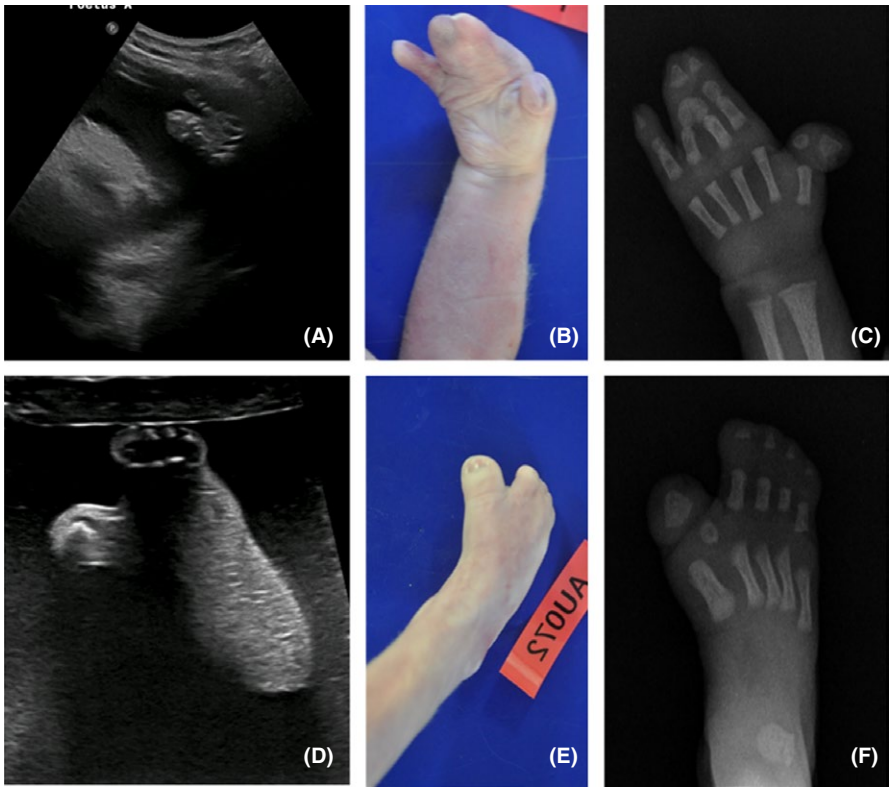

FIGURE 2 Abnormalities of the limbs. Prenatal 2D US (A and D), postmortem examination, (B and E) and radiography (C and F). D, E, and F. Enlarged and varus big toe of fetal foot. A, B, and C. Mitten hand with membranous syndactyly of fingers 2-3 and bony syndactyly of fingers 3-4

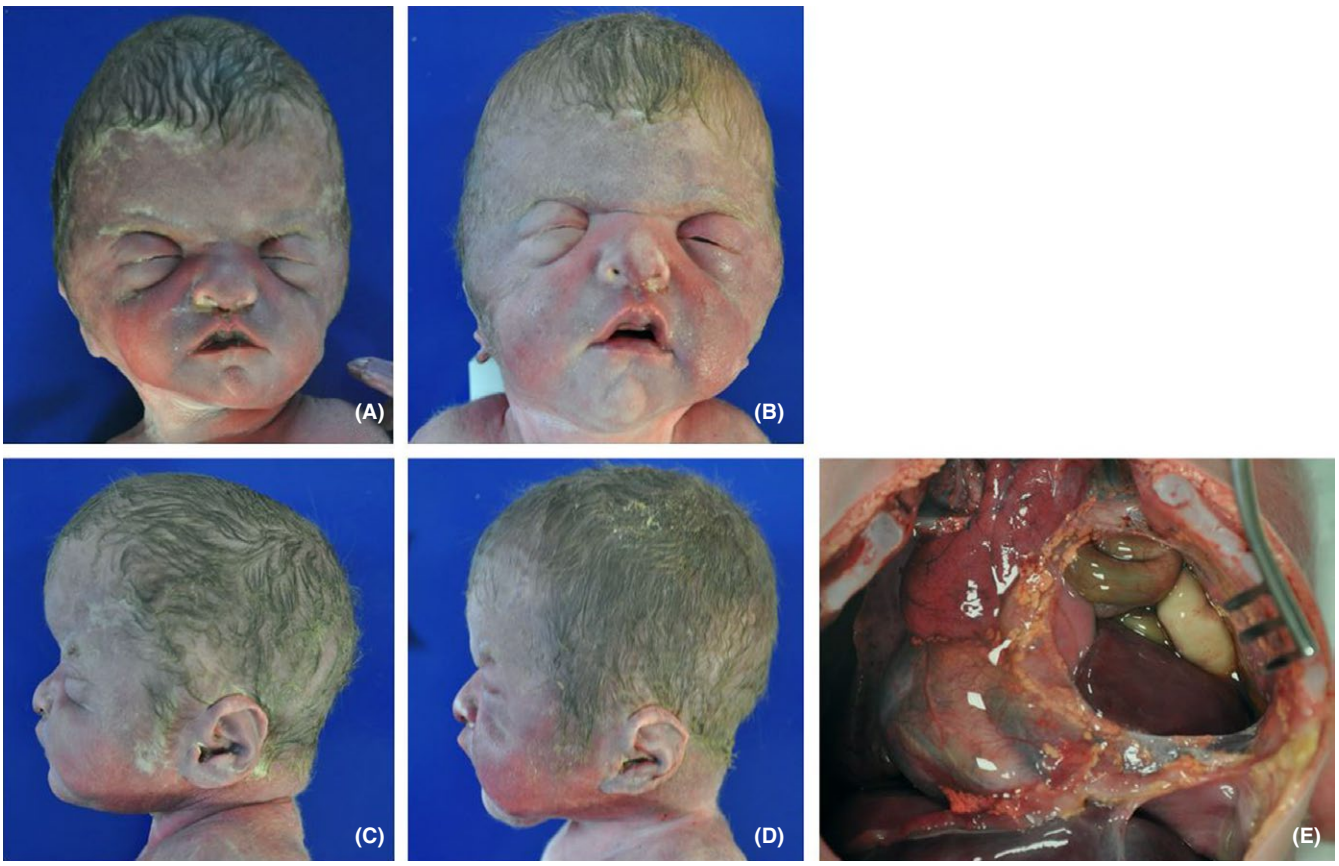

FIGURE 3 Phenotypic comparison of the two fetuses. Postmortem examination of fetus B (frontal view A, lateral view C) and fetus A (frontal view B, lateral view D, left congenital diaphragmatic hernia E)

For these twins, Apert syndrome was highly suspected before molecular genetic testing. Usually, craniosynostosis syndromes are diagnosed in the first month of newborn life. In this case, the US sign leading to a detailed US investigation was a congenital diaphragmatic hernia in one fetus of this monochorionic pregnancy. FGFR-related craniosynostosis disorders differed mainly by extremities anomalies: In Crouzon syndrome, extremities are normal, contrary to Apert and Pfeiffer syndromes.[10] Antenatal diagnostic allows being more specific on fetus' prognosis: In Crouzon syndrome, intellectual development is normal against Apert syndrome. In order to confirm the diagnosis, a targeted prenatal testing based on clinical findings may be valuable.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTION

MD, CB, DM, J-PM, OK, EP-G: contributed to data collection and interpretation and manuscript writing. PB-S: contributed to data acquisition and interpretation and manuscript writing. LL: contributed to data interpretation and manuscript writing and revising. OM: conceived the study and contributed to manuscript writing and revising.

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