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Rare occurrence of Tetralogy of Fallot in dizygotic twins conceived via in vitro fertilisation

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Brief Report

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Abstract

An increased incidence of CHD has been noted in twin gestations and in infants conceived using assisted reproductive technologies. However, CHD in these populations remains understudied and the mechanisms underlying these phenomena remain unclear. We present the case of twins conceived via in vitro fertilisation both with Tetralogy of Fallot and additional cardiac and extracardiac malformations.

Current reproductive trends show a rise in twin pregnancies attributable both to the advancing age of childbearing mothers and the increased use of assisted reproductive technologies like in vitro fertilisation.[1] Assisted reproductive technologies have been associated with a greater likelihood of twin gestations and a higher incidence of malformations, including CHD and extracardiac malformations. Regardless of the method of conception, however, twin gestations themselves have been associated with an increased risk of congenital malformations.[1–4] We present the case of dizygotic twins conceived via in vitro fertilisation both with Tetralogy of Fallot and additional cardiac and extracardiac malformations.

Case presentation

Twins A (male) and B (female) were conceived via in vitro fertilisation to a 32-year-old G2P1 with a past medical history of psoriasis and an obstetric-gynecological history notable for septate uterus, endometriosis status post-adhesiolysis, and a therapeutic abortion by dilatation and curettage 8 years prior to conception for unspecified reasons. Paternal medical history was non-contributory and family histories were negative for CHD and congenital malformations. In vitro fertilisation was utilised due to subfertility resulting from fallopian tube adhesions secondary to endometriosis. Two embryos were transferred in order to increase the chances of conception. Embryos were fertilised using maternal eggs and paternal sperm (i.e. non-donor embryos). Since fertilisation and embryonic transfer were performed at an outside facility, the precise embryonic age at time of transfer was unavailable upon chart review and patient interview.

Pregnancy was complicated by a subchorionic haemorrhage at gestational week 10 that did not warrant medical intervention and by intrauterine growth restriction in both twins. Substance use, including prescription medications, was negative and no history of sexually transmitted diseases was reported. Group B streptococcus status was unknown and intrapartum antibiotic prophylaxis was administered.

In light of the use of artificial reproduction technology, routine ultrasound was performed bimonthly throughout pregnancy to evaluate for malformations. Structural cardiac anomalies were noted in twin A at 25 weeks gestation and in twin B at 30 weeks gestation; Tetralogy of Fallot was diagnosed in twin A at 30 weeks gestation and twin B at 33 weeks gestation. Amniocentesis performed at 27 weeks and was negative for trisomies 13, 18, and 21, but further genetic testing was deferred due to cost. Postnatal evaluation confirmed the initial diagnoses and revealed additional abnormalities: right-sided aortic arch and pelvic kidney in twin A, and atrial septal defect and unilateral radial polydactyly in twin B.

Delivery of both twins occurred uneventfully via scheduled cesarean section at 36 weeks gestation. APGAR scores were 8 and 9 at 1 and 5 minutes, respectively, in both infants. The postpartum course and infantile period were unremarkable in both twins. Successful surgical repair of Tetralogy of Fallot was performed in both twins at 6 months.

Discussion

Twin gestation has been associated with a higher incidence of congenital malformations, including CHD, in both naturally conceived pregnancies and those conceived using assisted reproductive technologies.[1,5] Large-scale population studies and meta-analyses have shown

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that the incidence of CHD in assisted reproductive technologies, including inductive medications and procedures like in vitro fertilisation, is between 1 and 3%, with a slightly larger percentage being affected with both CHD and extracardiac malformations.[5,6] Variability in the incidence of malformations between different methods of assisted reproductive technology, if any, is unknown, and therefore most studies do not differentiate between the technologies utilised.[5,7] Among all twin gestations, the incidence of malformations appears to be greater in monozygotic than in dizygotic twins and is more likely to occur in only one twin.[1–4] The twins in the present study represent a deviation from this paradigm.

Tetralogy of Fallot is the most common cyanotic CHD, accounting for 7–10% of all CHD.[8] The pathogenesis of Tetralogy of Fallot is complex and has yet to be fully elucidated, but proposed mechanisms include neural crest cell mutations and epigenetic modifications like imprinting.[5,9] Like other CHD, potential risk factors include embryonic stress and underlying chromosomal abnormalities.[6,10] Increased levels of embryonic stress associated with assisted reproductive technologies and multiple gestations themselves have been proposed as mechanisms that may induce or unmask previously silent genetic mutations.[1,5–10] Tetralogy of Fallot has classically been associated with 22q11 deletions (DiGeorge syndrome) and, more recently, has been noted in several specific gene variants, including NKX2.5, GATA4, and TBX5. Interestingly, chromosomal anomalies such as trisomies or inherited syndromes are thought to contribute to less than 15% of Tetralogy of Fallot cases in infants conceived spontaneously and only around 20% of cases in infants conceived using assisted reproductive technology.[3,6] In the present case, genetic testing beyond amniocentesis for trisomies 13, 18, and 21 was deferred, therefore precluding the possibility of more precisely determining a genetic predisposition.

We consider the most likely etiology of the malformations in this case to be a previously unrecognised genetic abnormality that was unmasked by increased levels of embryonic stress during gestation from potential placental insufficiency secondary to subchorionic haemorrhage, the process of in vitro fertilisation, and the twin gestation itself. The fact that both twins were born with Tetralogy of Fallot and additional congenital malformations suggests that an underlying genetic abnormality was contributory. However, the absence of family history of congenital malformations and the negative amniocentesis results makes a predictable inherited chromosomal anomaly such as trisomy less likely. Teratogenic effects stemming from medication use or an infectious etiology are other well-recognised etiologies of congenital malformations but are also unlikely in this case since that the mother did not report medication or substance use during pregnancy and since her prenatal testing was unremarkable.

This case is unique in that it represents the possible convergence of several causes of congenital malformations discussed in the literature, including genetic abnormalities and stress-induced mutations in assisted reproductive technologies and twin gestations. On the other hand, this case diverges from the norm of congenital mutations occurring most commonly in a single twin and in monozygotic pregnancies. More research is required to more clearly elucidate the mechanisms underlying malformations and CHD in multiple gestations and in infants conceived via assisted reproductive technologies. As previous studies have noted, it is difficult to separate potential confounding factors between subfertility, the use of assisted reproductive technologies, and twin gestations. It is possible that the same factors that lead families to use assisted reproductive technology are also associated with subfertility, congenital malformations, and/or twinning.[1,5]

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Conflicts of Interest. None.

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