A congenital brain tumor associated with assisted in vitro fertilization

Case report

ASHA DAS, M.D., CHARLES SIMMONS, M.D., AND MOISE DANIELPOUR, M.D.

Maxine Dunitz Neurosurgical Institute; and Department of Pediatrics, Cedars-Sinai Medical Center, Los Angeles, California

In this report the authors describe the clinical features of a rare neonatal anaplastic astrocytoma in the setting of in vitro fertilization (IVF). The infant had been conceived using IVF and was born full term to a 29-year-old prima gravi-da mother. At birth, the baby boy was irritable and demonstrated poor feeding. Cranial ultrasonography and magnetic resonance imaging revealed an echogenic mass in the left hemisphere with midline shift and hydrocephalus. Gross-total resection of an anaplastic astrocytoma was followed by chemotherapy with temozolomide and vincristine. Previous cases of neonatal brain tumors occurring in the setting of assisted reproduction are reviewed. A possible association between IVF and congenital neuroepithelial tumors is highlighted.

KEY WORDS • congenital brain tumor • neuroepithelial tumor • in vitro fertilization • pediatric neurosurgery

PEDIATRIC brain tumors comprise 15 to 20% of all primary brain tumors. Of these tumors, congenital or neonatal ones are thought to be extremely rare, accounting for 0.5 to 1.9% of tumors diagnosed in childhood. The definitions of congenital or neonatal brain tumors vary. Stricter definitions indicate that a neonatal tumor is one diagnosed within the first 2 months of life; however, other authors have proposed broader definitions that include as neonatal tumors those diagnosed even after 1 year of age, provided the symptoms can be traced back to the neonatal period. Broader definitions account for the higher incidence of tumors in newborns reported in some series. For the purposes of our study, we have selected only brain tumors occurring in children of 2 months of age or younger, because of the profound differences in histological subtypes of brain tumors encountered in children 2 months of age or younger and those older than 1 year of age. The limited environmental influences on tumorigenesis present at this age may help identify possible causal factors in patients with neonatal brain tumors. We report a case of congenital brain tumor in the setting of assisted reproduction and highlight a possible increased risk of tumorigenesis in the setting of IVF.

Case Report

History and Examination. This baby boy was a full-term product of a 29-year-old prima gravi-da mother. After approximately 5 years of infertility, conception was achieved via intrauterine insemination. Apart from infertility, neither parent had any unusual family or medical history. Ovulation was induced by clomiphene and gonadotropin, and the transferred embryos were fresh. Prenatal ultrasonography revealed abnormal findings during the middle of the third trimester with the presence of a fetal nuchal fold. Amniocentesis was performed which, by report, revealed a 46 XY karyotype. Apgar scores at 1 and 5 minutes were 9 and 9. At birth, the infant was alert but irritable and exhibited poor feeding. Cephalohematoma and caput succedaneum were noted in the left occipital region. A right undescended testis, web neck, and widely spaced nipples were also observed. The left pupil was 4 mm and the right pupil was 2 mm dilated. Motor, sensory, and deep tendon reflex examinations were within normal limits. Cranial ultrasonography and MR imaging revealed a left hemispheric complex mass with hydrocephalus, hemorrhage, and displacement of the midline to the right hemisphere (Fig. 1).

Operation. On Day 4 of life, the infant underwent a craniotomy with resection of the tumor. Intraoperatively, the tumor was noted to be extremely hemorrhagic.

Histopathological Examination. An astrocytic neoplasm with anaplastic features of brisk mitosis and focal necrosis was resected. The tumor cells were immunohistochemically positive for glial fibrillary acidic protein and negative for chromogranin, synaptophysin, p53, epithelial membrane

Abbreviation used in this paper: IVF = in vitro fertilization.
antigen, desmin, and estrogen and progesterone markers. A high MIB-1 labeling index of more than 50% was observed. Immunostaining showed that the tumor did not stain for neurofilament and reticulin. Eosinophilic granular bodies were present (Fig. 2).

**Postoperative Course.** Subsequently, chemotherapy with temozolomide and vincristine was administered for 1 year with no evidence of recurrent tumor in the baby, who is currently 28 months old.

**Discussion**

In several series, no increased incidence of cancer was observed in children who are the products of assisted reproductive technology. Although the incidence of malignancies may not be increased, a greater than expected proportion of specific subtypes can be observed. For example, several authors have highlighted a possible association between IVF and embryonal and neuroectodermal tumors, neuroblastoma, and retinoblastoma. These observations indicate a possible association between specific subsets of tumors and assisted reproductive technology.

In most studies of congenital brain tumors, teratomas are the most common tumor type, accounting for one third to more than one half of brain tumors in children younger than the age of 2 months. Astrocytomas represent less than 10% of congenital intracranial tumors. After 2 months of age, the incidence of teratomas decreases dramatically to 0.5 to 1.8% of childhood brain tumors, of which tumors of neuroepithelial origin predominate. The four most common neuroepithelial tumors are medulloblastomas, astrocytomas, choroid plexus papillomas, and ependymoma/ependymoblastomas.

There are only two reported cases of congenital brain tumors occurring after IVF. In one case, the neonate was a product of IVF with ovulation induced by clomiphene and gonadotropin and presented at 2 months of age with hydrocephalus. Magnetic resonance imaging revealed a right temporoparietal mass, which was totally resected to reveal a gliosarcoma. Of note, the patient’s postoperative course was characterized by diffuse intravascular coagulation, and the child died on postoperative Day 3. Authors of a second case described a child conceived using IVF who presented in the third trimester with a choroid plexus papilloma, which was resected at age 5 days. A total of three patients makes it difficult to draw any definitive conclusions; however, we think that our case report and the two additional cases of congenital brain tumors occurring in the setting of IVF are remarkable. Using assisted reproductive technologies, 109,519 live-birth infants were born between 1997 and 2000 in the US. (The other two case reports of congenital brain tumors occurring after IVF were published in 2000 and 2002 from countries other than the US.) Although the worldwide rates of IVF are unavailable, an extremely generous extrapolation could project that, using assisted reproductive technologies, 3 million live-birth infants were delivered worldwide between 1997 and 2003. We know that
In vitro fertilization and congenital brain tumors

congenital brain tumors are very rare, with an incidence estimated at 0.34 per 1 million live births. Because more than one half of brain tumors in children younger than 2 months of age are teratomas, we might expect to have fewer than 1.7 congenital neuroepithelial brain tumors per 3 million live births.

All three of the aforementioned congenital brain tumors were neuroepithelial tumors in a population in which brain tumors are exceedingly rare and are typically teratomas. This observation raises the question of a possible increased risk of specific congenital malignancies in the setting of IVF. We know that many of the phases of assisted reproduction, including the use of fertility drugs to stimulate multiple folliculogenesis, the process of oocyte retrieval and preparation of spermatozoa, the growth of embryos in culture medium, and the freezing and thawing of embryos, have a potential harmful effect on the developing embryo. Alternatively, the relative risk of genetic abnormality among infertile couples may predispose their offspring to malignancies. This latter point may be in line with other reports that show a very significant increase and reproducible risk of abnormalities in this population. For example, a link between IVF and other genetic disorders, including such imprinting disorders as Beckwith-Wiedemann syndrome and Angelman syndrome, has been reported.

Conclusions

We report a possible excess of neuroepithelial tumors among congenital brain tumors occurring in the setting of IVF, suggesting that certain aspects of the IVF procedure might be important in tumorigenesis. These observations have implications in relation to genetic counseling for those undergoing IVF, screening of central nervous system development, and the interpretation of abnormal prenatal neuroimaging findings.

Disclaimer

The authors have no financial interest in the subject under discussion.

References


Manuscript received February 3, 2005. Accepted in final form August 16, 2005.

Address reprint requests to: Asha Das, M.D., Eisai Medical Research, 55 Challenger Road, Ridgefield Park, New Jersey 07601. email: Asha_Das@eisai.com