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Intrauterine Exposure to Clomiphene and Neonatal Persistent Hyperplastic Primary Vitreous

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ABSTRACT A 4-year-and-10-month-old girl was diagnosed shortly after birth with persistent hyperplastic primary vitreous (PHPV). Her mother took clomiphene 100 mg daily for approximately 4 weeks and discontinued the drug once she had a positive pregnancy test. The exact time of gestation was not clear. Clomiphene is an estrogen antagonist effective in the treatment of anovulation. Various ocular side effects have been described in women taking the drug, including decreased vision, mydriasis, flashing lights, central scotoma, photophobia, diplopia, allergic reactions, retinal vasospasms, detachment posterior vitreous, and possibly posterior subcapsular cataracts. These occur in 1.5–10% of patients taking clomiphene. The potential effects of clomiphene on the fetus have been investigated in five animal studies. Cataracts were observed in fetal mice and rats, but not in monkeys. In humans, a case of congenital retinal aplasia was described. The possibility of clomiphene-induced congenital PHPV should be considered, especially in pregnant women who are taking a high and prolonged dose. *Teratology 60:143–145, 1999.* © 1999 Wiley-Liss, Inc.

Persistent hyperplastic primary vitreous (PHPV) refers to a spectrum of manifestations caused by the persistence after birth of various portions of the fetal hyaloid vascular system and associated fibrovascular tissue. During the development of the eye, the hyaloid artery extends from the optic disk to the posterior aspect of the lens; it sends branches into the vitreous (vasa hyaloida propria) and ramifies to form the posterior portion of the vascular capsule of the lens (tunica vasculosa-lentis). The posterior portion of the hyaloid system normally regresses by the seventh fetal month and the anterior portion by the eighth fetal month. Small remnants of the system, such as a tuft of tissue at the disk (Bergmeister papilla) or a tag of tissue on the posterior capsule of the lens (Mittendorf dot), are common findings in healthy persons. More extensive remnants and associated complications constitute PHPV (Behrman et al., '96).

The retrolenticular tissue can invade the lens cortex through capsular defects, causing a posterior subcapsular cataract. The condition is usually unilateral and can be associated with vitreous hemorrhage and retinal detachment. Persistent remnants of the hyaloid arteries in abortive forms are commonly associated with mild fibrovascular changes found on the optic disc. In more severe cases, they are associated with retinal distortion, congenital retinal folds, or congenital retinal detachments (Collins, '82). Children with fetal alcohol syndrome may exhibit PHPV (Stromland, '94).

Clomiphene is widely used to induce ovulation. In general, its administration in the recommended dose (50 mg/day for 5 doses; if unsuccessful, another 100 mg/day for 5 doses is recommended) (Compendium of Pharmaceuticals and Specialties, '99) has not been associated with evidence-based proof of human embryopathy. We describe a case of PHPV after maternal exposure to large amounts of clomiphene, and discuss the plausibility of a cause-and-effect relationship.

CASE REPORT

A 4-year-and-10-month-old girl with bilateral PHPV came to the attention of a clinical geneticist when her mother requested genetic counseling for recurrence risks for another pregnancy.

She was the product of a second pregnancy to nonconsanguineous Anglo-Saxon parents. The mother, 33 years old, and her husband had been investigated for infertility. She required clomiphene for ovulation induction and took the drug for approximately 3 months, resulting in a pregnancy which ended in a miscarriage. Following the miscarriage, she restarted clomiphene 100 mg daily for approximately 4 weeks, and discontinued it once she had a positive pregnancy test. The

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estimated period of exposure was 3 weeks of gestation. No other medications were taken, and she did not report using alcohol or recreational drugs, although she smoked cigarettes for approximately 6 weeks into the pregnancy. The pregnancy was complicated by mild gestational diabetes. The proband was born at full term, weighing 2.9 kg. Shortly after birth, the mother noted abnormal eye movements in the baby which were subsequently diagnosed as nystagmus. The infant was assessed at the British Columbia Children's Hospital in Vancouver at age 5 months. A study of the eye ultrasound at that time confirmed the presence of a cone of thick tissue extending from the retina to both lenses. The lenses were unremarkable, and posteriorly a hyperechoic curvilinear structure was also present. These findings were consistent with bilateral persistent hyperplastic vitreous.

A clinical assessment revealed a normal neurologic examination, but the impression was of severe visual impairment. The child demonstrated wide nystagmus and roving eye movements. She had evidence of minimal vision, appreciating only light and darkness. Her vision was insufficient to allow assessment with preferential looking tests at that age.

However, at age 10 months, her preferential looking acuity at 38 cm was 1.2 cycles per degree, a Snellen equivalent of 20/540. At age 18 months, her preferential looking acuity improved to a 20/270 Snellen equivalent. A computed tomography (CT) scan of the brain at age 3 years was normal. Ocular views confirmed the ultrasound findings. Her most recent visual assessment demonstrated binocular visual acuity of 20/200.

Clinical genetic assessment at age 4 years found her head circumference, height, and weight to be at the 50th percentile. She had a pleasant-looking, nondysmorphic, and round face with a pointed chin. Bilateral fifth-finger clinodactyly was noted, with otherwise normal extremities. There were no abnormalities of the thorax and no evidence of organ abnormalities, and she had normal female genitalia.

The family history was negative for congenital malformations, miscarriages, or stillbirths. A second cousin of the proband was reported to be "legally blind." She had been adopted out of the family, and records were not available.

DISCUSSION

Although persistent hyperplastic vitreous is rare, bilateral hyperplastic primary vitreous is exceedingly rare. Familial occurrence has been reported, and it is sometimes associated with known syndromes, or neurological abnormalities (Traboulsi et al., '86; Frydman et al., '85; Wang and Phillips, '73; Lin et al., '90).

In this case, the mother had been treated with clomiphene continuously for 4 weeks prior to the knowledge of her pregnancy. Clomiphene is an estrogen antagonist effective in the treatment of anovulation. Ocular side effects (decreased vision, mydriasis, flashing lights, central scotoma, photophobia, diplopia, allergic reactions, retinal vasospasms, detachment posterior vitreous, and possibly posterior subcapsular cataracts) are seen in 1.5–10% of patients taking clomiphene. Ocular symptoms can be severe enough to require some patients to discontinue use of the drug. Except for detachment of the posterior vitreous and posterior subcapsular cataracts, which are not proven side effects, all others are reversible within a few days after discontinuation of the drug (Fraunfelder, '82).

In a review by Bernstein ('70), clomiphene citrate typically caused blurred vision and entopic phenomena, which suggests some effects on either the retina or the optic nerve. In women these ocular effects are dose-related, with a minimal dose of 50 mg/day or less if any symptom formation is to be expected. The incidence also varies with the duration of a single course of therapy, being as high as 5% when the drug is taken for 21 days or more (Bernstein, '70).

A case of congenital retinal aplasia associated with prenatal exposure was described by Laing et al. ('81). The mother received clomiphene citrate at a 50-mg daily dose from the fifth to the ninth days of the menstrual cycle for two successive cycles.

The potential ophthalmic effects of clomiphene on the fetus have been investigated in animal studies in rats and monkeys. Cataracts were observed in fetal rats, but not in monkeys: Eneroth et al. ('70) showed that the formation of congenital cataracts is dose-dependent in rats. Congenital cataracts were absent in the 2 mg/kg exposed group, present in 3 of the 128 examined fetuses at 10 mg/kg, and in 61% of the 50 mg/kg and 200 mg/kg group. The only other ocular anomalies observed were a few colobomas among the 50–200 mg/kg exposed group. Courtney and Valerio ('68) treated 18 monkeys with 1–4 mg/kg/day clomiphen for several days during the embryonic period and found no defect in the fetuses.

The potential association between congenital cataracts and PHPV has been discussed in several animal and human case studies. Several authors reported the concurrence of PHPV and cataracts in dogs (Boeve et al., '89; Gelatt, '73; Ori et al., '98). Haddad et al. ('78) documented that among 62 human cases of PHPV, 10 (16%) also had cataract. They observed that the initially clear lens in infants with PHPV may become opacified shortly after the posterior capsule of the lens ruptures. They noted that the detection on slit-lamp examination of a well-vascularized opaque tissue behind the lens may not be appreciated if a cataract is present. When opacification of the lens occurs at a very early stage before a diagnosis of PHPV has been established, such a finding may lead to incorrect diagnosis of a congenital cataract. Thus a lens opacity, when associated with PHPV, may be simply interpreted as a cataract.

The mother in the present case received larger than the recommended doses of clomiphene for a longer time than usual. She received a dose of 100 mg continuously for 4 weeks, substantially longer than the recommended 50 mg/day for 5 days followed by 100 mg/day

for an additional 5 days in unsuccessful cases (Canadian Pharmaceutical Association, Compendium of Pharmaceuticals and Specialties, '99). Although her daily dose was substantially lower (1.5 mg/kg) than the one causing cataracts in mice (10 mg/kg), rodents generally have higher clearance rates of drugs than humans (Nau, '86). As a regulatory rule, women should not be exposed to a dose which is larger than 1% of the no-effect level (NOEL) in the most sensitive animal species (Dourson and Stara, '83). In this case, 1% of the NOEL would translate to 0.02 mg/kg of clomiphene, substantially smaller than the dose given to the patient. Thus, with evidence suggesting that the eye is quite sensitive to the adverse effects of clomiphene, one has to consider the possibility that clomiphene might have played a role in the pathogenesis of PHPV in this case. It is prudent to adhere to the recommended dosages and suggested length of treatment when clomiphene is used for ovulation induction.

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