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## Case Report

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# Prenatal Exposure to Fluconazole: An Identifiable Dysmorphic Phenotype

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**BACKGROUND:** Fluconazole is a triazole antifungal used to treat mycotic infections. Fluconazole is reported to act as a teratogen when used continuously at a dosage of 400–800 mg daily. Fluconazole embryopathy was previously reported in 4 cases. The common features that were also seen in the current case include multiple synostosis (including craniosynostosis and digital synostosis), congenital heart defects, skeletal anomalies, and recognizable dysmorphic facial features. **CASE:** We report the case of a 9-month-old male born to a 30-year-old woman following a 37-week pregnancy. The pregnancy was complicated by maternal human immunodeficiency virus (HIV) infection and multiple drug exposures, including fluconazole (400 mg/day) until the fifth month and then from 6 months to term, efavirenz, nevirapine, methadone, dapson, pentamidine, and trimethoprim-sulfamethoxazole. At birth the infant had seizures related to neonatal abstinence syndrome and was noted to have multiple congenital anomalies. On examination at age 9 months, he had craniosynostosis secondary to coronal and lambdoidal suture closures, shallow orbital region, hypoplastic supraorbital ridges, hypertelorism, and mild ptosis. He had radioulnar synostosis and metacarpophalangeal-proximal interphalangeal symphalangism of D2–D5 bilaterally. **CONCLUSIONS:** The findings of cranial synostosis, multiple symphalangism, and long-bone abnormalities in our case are typical of other reported cases of fluconazole embryopathy. Our patient showed no evidence of embryopathy due to efavirenz, and he did not have the features of Antley-Bixler or other craniosynostosis syndromes. We review the literature regarding the teratogenic effects of prenatal exposure to fluconazole and provide additional evidence that prenatal fluconazole exposure has a clearly identifiable phenotype. *Birth Defects Research (Part A) 73:919–923, 2005.*

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**Key words:** fluconazole embryopathy; teratogenicity; craniosynostosis; P450 reductase

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## INTRODUCTION

Fluconazole is a widely prescribed drug for the treatment of vaginal candidiasis and is given as a single 150-mg dose. Its use during pregnancy has not been reported to have any apparent teratogenic effects. Fluconazole is also used to treat more serious systemic mycotic infections at higher dosages (400–800 mg a day) for prolonged periods of time. There are 4 reported cases of children born after high-dosage (400–800 mg/day) prenatal exposure to fluconazole during the first and second trimesters of pregnancy who had a distinctive pattern of malformations (Lee et al., 1992; Pursley et al., 1996; Aleck and Bartley, 1997). We present a fifth case and review the literature regarding

the teratogenicity of high-dose exposure to fluconazole during the first and second trimesters of pregnancy.

## CASE REPORT

Our patient was born to a 30-year-old mother of Aboriginal background. The pregnancy was complicated by ma-

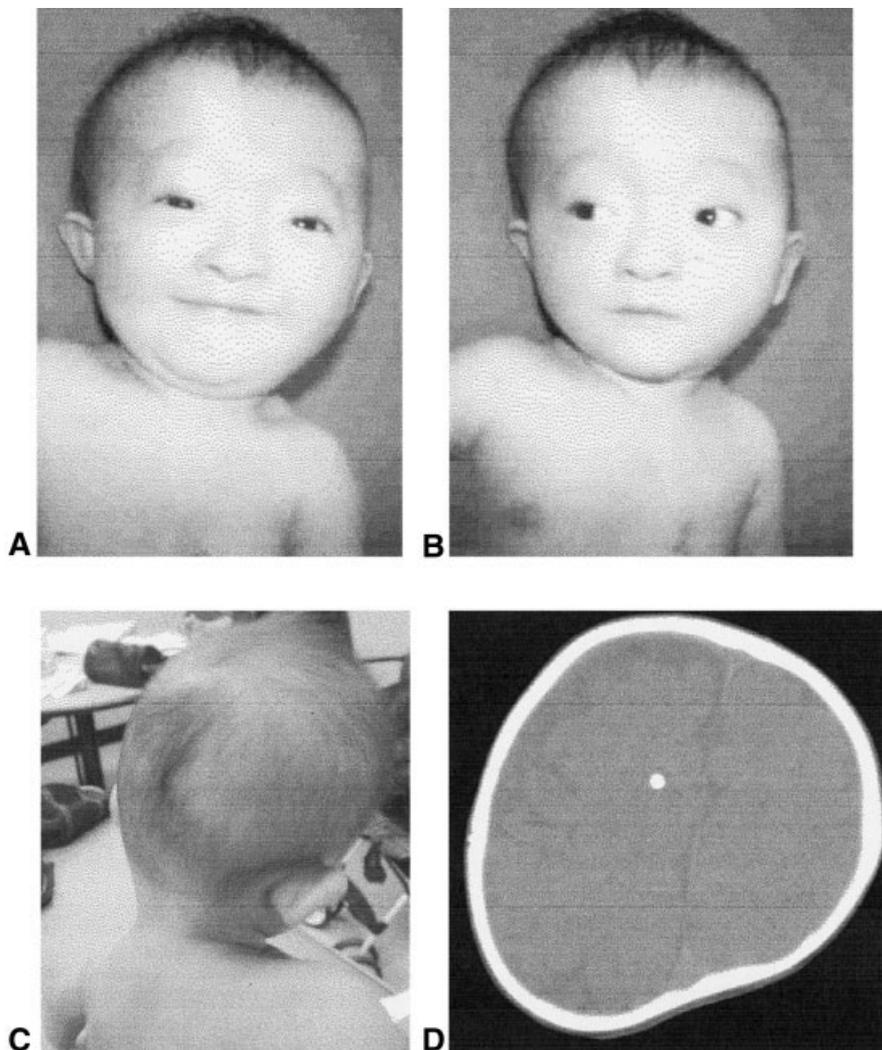
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This case and a review of the literature were presented at the 44th Annual Meeting of the Teratology Society, Vancouver, Canada, 2004.

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**Figure 1.** A and B: Dysmorphic features. C: Asymmetric skull due to premature lambdoid synostosis. D: Computed tomography scan image showing an asymmetric skull.

ternal human immunodeficiency virus (HIV) infection and multiple medication exposures. The mother was treated with fluconazole at 800 mg/day for vaginal candidiasis from before conception until the fifth month and again from 6 months of gestation to delivery. She also received 600 mg of efavirenz daily until 16 weeks, then 400 mg of nevirapine daily until delivery, and 90 mg daily of methadone, pentamidine, and Septra (trimethoprim-sulfamethoxazole).

Our patient was born at 37 weeks 3 days via spontaneous vaginal delivery. His birth weight was 3045 gm (50%), birth length was 51 cm (>98%), and head circumference was 32 cm (10%). At birth he had craniosynostosis, asymmetric facies, dysmorphic features, and joint contractures of the digits, wrists, elbows, knees, and ankles. His karyotype was 46, XY (450 band resolution). His neonatal period was complicated by neonatal abstinence syndrome with mild seizures, *Streptococcus pneumoniae*, and bacteremia.

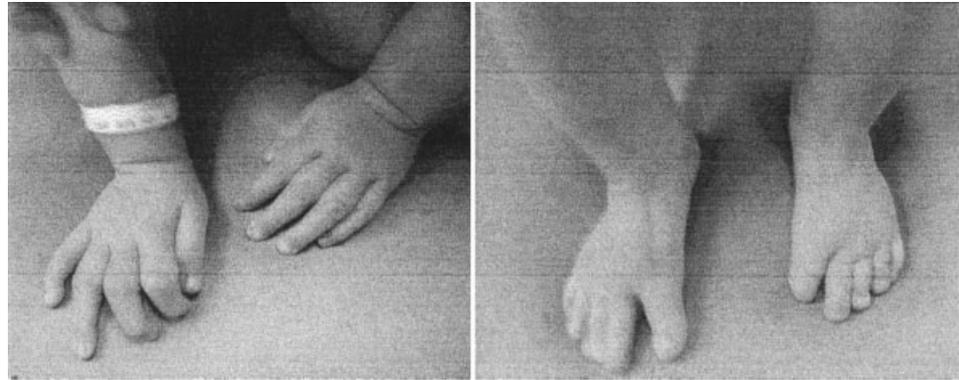
Over the next 9 months, he showed worsening cranial asymmetry with premature closure of the coronal and lambdoid sutures and developmental delay. He had 1 episode of tonic clonic seizures. An electroencephalogram

showed mild to moderately diffuse cerebral dysfunction. He is receiving antiseizure medication. A hearing test showed moderate bilateral hearing loss. An abdominal ultrasound examination showed that he had a duplicated left collecting system.

#### PHYSICAL EXAMINATION

At the age of 9 months, our patient's height was 72.3 cm (50th centile), weight was 8.65 kg (25th centile), and head circumference was 44.6 cm (25th–50th centile). Examination of his head showed that he had marked asymmetry of the skull secondary to coronal and left lambdoid synostosis. He had bulging of the right parietal and flattening in the left lambdoid area. He had brachycephaly with a broad frontal area. He had dysmorphic features with asymmetric facies, a broad forehead, and high arched eyebrows with hypoplastic supraorbital ridges and bilateral shallow orbital regions (Fig. 1A, B and C). He had bilateral epicanthic folds, hypertelorism, and mild ptosis. He also had a low nasal bridge with a short pear-shaped nose, and the nasal tip

**Figure 2.** Contractures of the distal and proximal interphalangeal joints and shortening of the first toe bilaterally.



was deviated to the right. His palate was normal. His jaw line appeared shorter on the right than on the left, and his chin pointed to the right. His neck had mild torticollis on the right. His ears were cupped, with decreased helical folding. The right ear was higher than the left, and the left ear was more anterior. His chest was normally formed, and the sternum was of normal length. The lungs were clear upon auscultation. The cardiac examination was normal. The abdominal examination showed no abnormalities. The genitourinary examination showed normal male genitalia with 2 descended testes. Examination of his spine showed mild kyphosis in the lower thoracic area and a deep sacral dimple. An extremities examination showed synostosis of the joints of the metacarpophalangeal proximal and distal intraphalangeal joints in digits 2–5 (Fig. 2; left panel). There was distal tapering of the digits and a spatula-like appearance to the distal digital area. There was an elbow dimple on the right, with mild limitation of pronation and supination on the left. He had normal range of motion of the hips and knees. There was a linear crease extending from the base of the big toe to the ankle (Fig. 2; right panel), where the tendon would run. There was shortening of the first toes bilaterally, which was more prominent on the left than on the right. There was bilateral synostosis of the shortened first toes (Fig. 2; right panel). The neurological examination showed normal tone and strength. The cranial nerves were intact, and reflexes were brisk in the lower legs and normal in the upper extremities. There were 2 beats of clonus at the ankles and a downgoing Babinski reflex.

**Computed Tomography Scan**

Spiral 1-mm images of the skull were obtained after surgical correction of synostosis and shunting for the purposes of a 3-dimensional (3D) reconstruction. Images of the brain were reconstructed using this data set and compared with those from a previous study. The cranial vault was markedly asymmetric (Fig. 1D). The ventricular system had been shunted, and the ventricles remained decompressed with no evidence of shunt dysfunction. The 3D images of the skull failed to demonstrate any normal coronal or lambdoid suture on the left. However, even on the right side the coronal and lambdoid sutures were barely visible, and the superior sagittal sinus was also only barely visible anterior to the fontanel.

**DISCUSSION**

Four cases of fluconazole embryopathy have been reported (Lee et al., 1992; Pursley et al., 1996; Aleck and Bartley, 1997). All of the reported children had multiple congenital anomalies, including craniosynostosis, multiple synostoses, absent first toes, and characteristic facial features (Table 1). The features seen in our patient are very similar to those reported in the previous studies. Our patient also had craniosynostosis, dysmorphic features, and multiple congenital anomalies. The karyotypes in 2 of the published reports and our patient were normal.

The exposure to fluconazole varied in each case. Case 1 was a female child born to a 22-year-old woman (gravida 1) with coccidioidal meningitis treated with fluconazole

**Table 1**  
Features of Reported Cases of Children Born After Prenatal Fluconazole Exposure

	Lee et al. (1992) Case 1	Pursley et al. (1996) Case 2 and 3	Aleck and Bartley (1997) Case 4	Our case Case 5	Total
Craniosynostosis	1	2	1	1	5
Proptosis	0	2	1	1	4
Cleft palate	0	2	0	0	2
Contractures	1	2	1	1	6
Joint synostosis	1	2	1	1	5
Short thumbs	1	2	0	0	4
Short 1st toe	1	2	0	1	4

Table 2  
Gestational Age of Prenatal Fluconazole Exposure and Doses

	Lee et al. (1992) Case 1	Pursley et al. (1996) Case 2	Case 3	Aleck and Bartley (1997) Case 4	Our case Case 5
Time of treatment in gestation	0–23 weeks	0–7 weeks (9 weeks–term)	0–19 weeks	0–4 weeks 4–9 weeks 22 weeks–term	0–23 weeks 27–term
Fluconazole dose	400 mg/day	800 mg/day 800 mg/day	400 mg/day	400 mg/day 800 mg/day 1200 mg/day	800 mg/day 800 mg/day

(400 mg/day) from prior to conception until 23 weeks of gestation. Case 2 was a male child born to a 25-year-old woman with *coccidioides immitis* meningitis treated with 800 mg/day of fluconazole from before conception until 7 weeks of gestation, and then from 9 weeks of gestation until delivery. Case 3 was a female sibling of the patient described by Lee et al. (1992). Her mother had been treated with 400 mg/day of fluconazole until the fourth month of pregnancy. Case 4 was a male child born to a 27-year-old mother who had been treated with 400 mg/day of fluconazole for *coccidioides meningitis* until the fifth week of pregnancy, when the dosage was increased to 800 mg/day. The pregnancy was recognized at 9 weeks of gestation, and the fluconazole was discontinued but restarted at 22 weeks at a dosage of 1200 mg/day until delivery. The dosages of fluconazole in the previously reported cases were comparable to those administered to our patient's mother, who received 400 mg/day of oral fluconazole during the first and second trimesters (Table 2).

Fluconazole is a highly selective inhibitor of fungal cytochrome P-450 (sterol C-14 alpha-demethylation, CYP). It binds to the fungal p450 enzymes and stops the cells from making ergosterol, the main component of the cell wall. Fluconazole teratogenicity has been reported in animal models. Mice show embryonic death and rib, craniofacial, skeletal, and palatal anomalies when treated with 3–20 times the maximum human dose of fluconazole (Tiboni et al., 1999). In humans a single fluconazole oral dosage of 150 or 200 mg/day in the first trimester has not been related to an increased incidence of congenital anomalies (Jick, 1999).

Few studies have examined the continuous use of fluconazole during pregnancy. The long-term daily use of fluconazole in pregnancy was studied by Campomori and Bonati (1997) in a group of 17 women. The median time of treatment was during the second trimester, the average total dosage was 291 mg/day, and no malformations were reported. These dosages and median time of treatment are lower than those reported for the above-described patients with multiple congenital anomalies. In another case, a mother was treated with a high dosage of fluconazole (600 mg/day for 21 days) starting at a gestational age of 14 weeks, and she delivered a normal infant (Krcmery et al., 1996). This last case, in contrast to the ones reviewed here, was not exposed during the first trimester, providing evidence for the crucial timing of fluconazole exposure and its teratogenic effects.

Other pregnancy exposures of concern in our case were related to prenatal exposure to efavirenz, a nonnucleoside reverse transcriptase inhibitor. The teratogenicity of efavirenz has not been fully established. The Antiretroviral

Pregnancy Registry 2001 ([www.apregistry.com](http://www.apregistry.com)) does not list any major congenital anomalies reported in children born to mothers receiving efavirenz treatment, but there is 1 case report of a child exposed to efavirenz who had a meningomyelocele (Fundaro et al., 2002). Animal studies have reported malformations in 3 of 20 cynomolgus monkeys, including microphthalmia, anencephaly, and cleft palate (USP, 2002; [www.micromedex.com](http://www.micromedex.com)). Our patient did not have any features that could be related to efavirenz teratogenicity.

The features seen in fluconazole embryopathy have been compared with those of Antley-Bixler syndrome. The Antley-Bixler phenotype has been associated with mutations in *FGFR2* (Chun et al., 1998), abnormal sterol metabolism, mainly lanosterol-14 demethylase (CYP51) (Reardon et al., 2000; Kelley et al., 2002) and P450 oxidoreductase (POR), mutations (Adachi et al., 2004; Fluck et al., 2004).

POR is a flavoprotein that donates electrons to microsomal cytochrome P450. Mutations in POR explain the decrease in lanosterol-14 demethylase (CYP51) activity described in Antley-Bixler syndrome (Adachi et al., 2004; Fluck et al., 2004). Fluconazole, as mentioned above, is a selective inhibitor of fungal cytochrome P-450 (sterol C-14 alpha-demethylation CYP), which explains the common pathogenesis leading to phenocopies. This POR-mediated toxicity was previously demonstrated in the case of retinoids (Otto et al., 2003).

In summary, a single fluconazole dose of 150–200 mg appears to be safe at any point in gestation. However, fluconazole appears to be teratogenic at daily dosages of 400–800 mg during the first half of pregnancy, and its teratogenicity may be related to mutations in the *POR* gene. Furthermore, fluconazole embryopathy has a very distinct phenotype, including craniosynostosis, characteristic facial features, digital synostosis, multiple contractures, and aplasia/hypoplasia of the first thumbs and toes.

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