A 28-year-old woman without medical history developed at 16 weeks of gestation fever (39°C), agranulocytosis (neutrophil count = 76/mm³), anemia (hemoglobin [Hb] = 8.2 g/dl), and hepatic cytolytic (aspartate aminotransferase [ASAT], 395 IU/liter; alanine aminotransferase [ALAT], 454 IU/liter [normal values < 50]); gamma glutamyl transpeptidase [GGT], 30 IU/liter; total bilirubin, 31 μmol/liter; free bilirubin, 5 μmol/liter; alkaline phosphatase, 270 IU/liter). Bone marrow aspiration revealed aplastic anemia. An extensive viral and immunological work-up, including anti-cytomegalovirus (CMV), anti-Epstein-Barr virus (EBV), anti-hepatitis A, B, and C, anti-HIV-1/2, anti-human T-lymphotropic virus 1 and 2 (HTLV-1/2), anti-parvovirus B19, anti-nuclear, anti-DNA, anti-extractable nuclear antigens, anti-mitochondrial, anti-LKM1, anti-ribosomal, and anti-smooth muscle antibodies, and CMV, EBV, human herpesvirus 8 (HHV-8), and HHV-6 viremia, was negative. Autoimmune aplastic anemia was suspected, and intravenous polyvalent immunoglobulins (1 g/kg of body weight/day) and oral cyclosporine (150 mg/day) were prescribed. At day 12 of neutropenia, invasive aspergillosis was diagnosed (maxillary sinusitis, periorbital cellulitis, pulmonary nodule on computed tomography with positive Aspergillus antigenemia [index = 0.67], and acute-angle branching septate hyphae on meatotomy and ethmoido-maxillar drainage samples) (1). Sinus cultures at 4 days yielded on chloramphenicol-gentamycin Sabouraud agar colonies of Aspergillus identified by matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) as Aspergillus flavus (2). The strain was considered sensitive to all tested azoles (3). MICs through Etest were as follows: itraconazole, 0.500 μg/ml; voriconazole, 0.190 μg/ml; amphotericin B, 0.750 μg/ml; posaconazole, 0.190 μg/ml. Intravenous liposomal amphotericin B was initiated (3 mg/kg/day). Neutropenia recovery was observed at day 21, with simultaneous major local extension requiring median maxillectomy. Treatment was switched to oral voriconazole (200 mg twice daily [BID]). The plasma trough concentration at day 7 was in the therapeutic range (1.38 mg/liter, single dosage) (4). Clinical and radiological improvement was obtained. Voriconazole was prescribed for 5 months and stopped after clinical/radiological resolution, 1 month after delivery.

Close fetal evaluations, including karyotype, were normal. The patient gave birth to a male baby at 35 weeks of gestation. Weight at birth was normal according to the term (2.550 kg), and the Appgar score was 10/10 (at 1 ½ min). Clinical examination, neurological development, and growth at the 6-month follow-up visit were normal.

Voriconazole is anazole displaying fungidal activity against Candida spp., Cryptococcus neoformans, Aspergillus spp., and molds with limited susceptibility to other antifungal agents (5). The use of azoles in pregnancy is limited because of embryotoxic/teratogenic effects in rodents (6). In humans, a sustained high dose of fluconazole during the first trimester and beyond is associated with major congenital craniofacial, skeletal, and cardiac abnormalities (7–9). Data regarding voriconazole are extremely scarce (10). The manufacturer reports embryotoxic/teratogenic effects in rabbits and rats at 0.3 and 6 times the human recommended dose, respectively (cleft palates, hydrourephrosis, reduced ossification, fetal mortality). Whether voriconazole crosses the human placenta is unknown but likely given its low molecular weight. Voriconazole is labeled category D (fetal risk, which may be outweighed by maternal benefit in specific situations) (5).

This is, to our knowledge, the first report on the use of voriconazole in pregnancy. Voriconazole administered after the first trimester appeared safe. However, before further confirmation comes, voriconazole should be considered in pregnancy after the first trimester only in life-threatening cases without alternative.

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There are no transparency declarations related to this article.

REFERENCES


