

Fluconazole-Associated Birth Defects: A Comprehensive Review

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Conflicts of interest: None to disclose

Key words: fluconazole, congenital abnormality, pregnancy, pregnancy complications, antifungal agents, teratogens

Abstract

Background: The August 2013 publication of a large historical cohort study in the *New England Journal of Medicine* has reignited interest in the potential teratogenic effects of fluconazole when used in pregnant females. Fluconazole is an effective and commonly-utilized antifungal medication. Thus, maternal and fetal exposure to fluconazole is expected in the general population, and pharmacists are expected to counsel patients regarding any risks to their prescribed treatment.

Methods: A literature review of all published literature indexed to PubMed (January 1966 to October 2013) and *International Pharmaceutical Abstracts* (January 1975 to October 2013) including fluconazole and teratogenic effects and published in the English language was conducted.

Results: Fourteen publications were included for analysis including case reports (n=7), cross-sectional research (n=2), and historical cohort studies (n=5).

Conclusion: There appears to be little to no fetal risk resulting from a single dose or short duration antifungal therapy with fluconazole. However, prolonged high-dose fluconazole therapy has increased potential to confer teratogenic effects. In those cases, the risks of such therapy should be weighed against potential benefits.

Introduction

Initially introduced to the market in January 1990, fluconazole (FLU) is extensively used, especially as a 150 mg single dose for treatment of vaginal candidiasis. Guidelines published by the Infectious Diseases Society of America (IDSA) suggest FLU treatment for a wide variety of fungal infections. In candidiasis and cryptococcal disease, FLU is often listed as a primary therapy option. Fluconazole is efficacious for the treatment of a wide range of candidal infections including nonneutropenic candidemia, suspected candidiasis in urinary tract infections, and pulmonary cryptococcosis.^{2,3}

Fluconazole exhibits excellent cerebrospinal fluid penetration, with concentrations exceeding 70% of serum values in dosages from 50 to 400 mg/day.⁴ As a result, FLU also has a prominent place in the treatment of numerous types of fungal central nervous system infections such as meningitis, often as a step down therapy after initial treatment with amphotericin B (AmB).^{2,3} Guidelines for antifungal therapy for blastomycosis, coccidioidomycosis, and histoplasmosis also list FLU as a primary, adjunct, or secondary treatment option.⁵⁻⁷

Though FLU has been suspected of being a teratogen since as early as 1992, it is still frequently used during pregnancy. Depression of the T-cell mediated immune response, high estrogen levels, reduced vaginal pH, and increased vaginal glycogen concentrations place pregnant women at an increased risk of vaginal candidiasis, which is easily treated with FLU.^{8,9} Additionally, the risk of dissemination of disease and mortality from coccidioidomycosis and coccidioidal meningitis is significantly higher in pregnant women.¹⁰ Despite its popularity, FLU is thought to cross the placenta and achieve detectable or even therapeutic concentrations in amniotic fluid as well as fetal tissue and cord blood. This property of FLU led to the preference of AmB deoxycholate or lipid formulations of AmB by most published guidelines for susceptible fungal infections in pregnancy. The guideline preference for AmB is specifically directed toward pregnant females in the first trimester, which is the most critical period for development of embryonic and fetal malformations.⁹

In August 2011, the U.S. Food and Drug Administration (FDA) issued a safety announcement concerning the use of FLU in pregnancy. On the basis of several published case reports in humans¹¹⁻¹⁴, and animals showing similar causative effects¹⁵, the FDA changed the pregnancy category of FLU from category C to category D for all indications except FLU 150 mg as a single dose for treatment of vaginal candidiasis, citing trends of "a rare and distinct set of birth defects in infants whose mothers were treated with the drug during the first trimester of pregnancy".¹⁶ The FDA noted that these defects

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included a short, broad head, abnormal looking face, abnormal development of the skullcap, oral cleft, bowing of the thigh bones, thin ribs and long bones, muscle weakness and joint deformities, and congenital heart disease.¹⁶

Created in 1980, the FDA's drug-associated pregnancy risk categories, which consist of the letter designations of A, B, C, D, or X, are assigned according to the known or potential fetal harm associated with drug therapy. Category A represents the least proven harm, while category X represents definitive fetal harm that outweighs any benefit of use in pregnant women. The change from category C to category D for most indications of FLU reflected what the FDA believed to be positive evidence of fetal risk in human studies, rather than evidence of risk from only animal studies.¹⁶

In August 2013, the *New England Journal of Medicine* published a registry-based historical cohort study by Mølgaard-Nielsen et al. which assessed congenital malformations outcomes after exposure to FLU during the first trimester of pregnancy.¹⁷ The goal of this article is to conduct a comprehensive literature review that incorporates this most recent data with the other published literature regarding the safety of FLU in pregnancy, with the outcome of teratogenicity as a specific focus.

Methods

A comprehensive literature search was conducted to identify relevant literature regarding use of FLU during pregnancy and any potential association with congenital malformations. The databases included in the search were PubMed (January 1966 to October 2013) and International Pharmaceutical Abstracts (January 1975 to October 2013). For PubMed, keywords, exploded terms, truncation, and controlled terminology were used. The following search terms were used, both individually and in combination: "Fluconazole [Mesh]", "pregnancy [Mesh]", "congenital abnormalities [Mesh]", "abnormalities, drug-induced [Mesh]", "antifungal agents/adverse effects [Mesh]", "pregnancy complications [Mesh]", "pregnancy complications, infectious [Mesh]", "teratogens [Mesh]", "Fluconazole", "abnormalities", "pregnancy", "birth", "congenital", "malformations", and "teratogens". For International Pharmaceutical Abstracts, keyword searching and truncated derivations of the keywords were exclusively used. Additional references were identified through a bibliographic search of included references.

Studies were included for analysis if they were conducted in humans, examined an association between FLU use in pregnancy and congenital malformations as either a primary or secondary endpoint, and were available in English as a full-text article. Clinical trials, cohorts, case-controls, cross-

sectionals, case series, case reports, and letters to the editor were all considered for analysis. In total, 14 references ultimately met the criteria for inclusion in this analysis.

Results

The association between FLU use during pregnancy and congenital malformations has been assessed in various types of published literature. These studies are summarized in Table 1.

Case Reports

Eight individual cases were identified where FLU use during pregnancy was studied in relation to the development of congenital malformations. The earliest of these was presented by Lee et al. in 1992¹¹, who reported the case of a premature infant born at 27-weeks to a 22-year-old mother who was treated for disseminated coccidioidomycosis with FLU 400 mg per day from before conception through delivery. The mother was in her second pregnancy, and she had a history of coccidioid meningitis dating back to her first pregnancy. After treatment with 2600 mg intravenous AmB and 131.5 mg intrathecal AmB, she was placed on FLU and remained on the medication through delivery due to late detection of her pregnancy at 23-weeks gestation. Upon cesarean birth, the infant displayed multiple congenital malformations, including craniosynostosis, contractures of both upper and lower extremities, humeral-radial fusion, bowed tibia and femur, incomplete or shortened digits, and cleft palate. These abnormalities produced a poor prognosis that led to withdrawal of life support and death of the infant. The authors were unable to differentiate their findings from Antley-Bixler syndrome, but suggested possible causation due to similar abnormalities in animal studies with FLU.¹¹

The same 22-year old mother described by Lee et al.¹¹ had two subsequent pregnancies that were reported by Pursley et al.¹² in 1996. During her third pregnancy, the patient was nonadherent to therapy, delivered a healthy boy, and resumed FLU therapy. She then remained on a regimen of FLU 400 mg/day for coccidioid meningitis when she was yet again discovered to be 4-months pregnant (gravida 4), upon which FLU therapy was discontinued. The female baby, born at full term, was found to have multiple craniofacial malformations (cleft palate, tracheomalacia, low ears, rudimentary epiglottis, and proptosis), multiple cardiac defects (ventricular septal defect and pulmonary artery hypoplasia), and multiple skeletal malformation (bowed femurs, clavicular fracture, thin and wavy ribs, absent distal phalanx, and arachnodactyly). The infant died at 3 months of age from pneumonia, presumably secondary to tracheomalacia.¹²

Pursley et al.¹² also reported the case of a 25-year old mother treated for coccidioidal meningitis with FLU 800 mg/day through delivery at 38 weeks gestation (with a FLU hiatus during weeks 7-9). Congenital abnormalities found upon examination were as follows: flattened occiput, brachycephaly, trigonocephaly, supraorbital ridge hypoplasia, bitemporal narrowing, open cranial sutures, large anterior fontanel, maxillary hypoplasia, short ear helices, micrognathia, exotropia, bowed femurs, diffuse osteopenia, thin ribs, clavicles, and long bones, long metacarpals and phalanges, hypoplastic facial bones, craniofacial disproportion, slanted orbital roofs, tetralogy of Fallot, patent ductus arteriosus, right and left pulmonary artery hypoplasia, patent foramen ovale, and large ventricular septal defect.¹²

In 1996, Wiesinger et al.¹⁸ described the case of a 24-year old female admitted at 16-weeks gestation with *Candida* sepsis. After failing an AmB test dose, the patient was placed on intravenous FLU therapy (400 mg/day), which was continued for 16 days, at which time she was converted to oral FLU therapy, which continued for an additional 34 days. At 39-weeks gestation the patient delivered a healthy female baby.¹⁸

Aleck and Bartley¹³ reported another case of congenital malformation attributed to FLU exposure in 1997, describing a 27-year old mother treated with 400mg/day FLU for coccidioidal meningitis. Due to clinical deterioration, the patient's dose was increased to 800 mg/day. Approximately 4 weeks after the dose increase, the patient was determined to be pregnant, with an estimated gestation of 9 weeks; at that time FLU therapy was discontinued and AmB initiated. Due to further clinical deterioration, at approximately 22-weeks gestation, FLU therapy was reinstated (1200 mg/day) and the AmB was discontinued. At 31-weeks gestation, the patient delivered a male infant. The baby was found to have multiple congenital malformations including soft calvarium, widely separated cranial sutures, prominent forehead, mild exorbitism, small hemangioma on the tip of the nose, posteriorly angulated ears with over folded helices, bilateral radiohumeral synostosis, and dysplastic hips.¹³

Lopez-Rangel and Van Allen¹⁴ reported another case in 2005 of a 9-month-old male infant born to a mother treated for vaginal candidiasis with FLU 800 mg per day from before conception to the 5th month of gestation and again from the 6th month of gestation to delivery. Upon birth, multiple congenital malformations were present. Many of these abnormalities were consistent with those identified in other cases, such as craniosynostosis, proptosis and other recognizable dysmorphic facial features, contractures, and joint synostosis. Other malformations included multiple

sympalangism, mild to moderately diffuse cerebral dysfunction, moderate bilateral hearing loss, and short first toe. In this infant, a cardiac examination returned normal results. The mother was a 30-year-old Aboriginal diagnosed with human immunodeficiency virus (HIV) infection leading to multiple medication exposures, including efavirenz, nevirapine, methadone, dapson, pentamidine, and trimethoprim-sulfamethoxazole. The infant's neonatal period was also complicated by mild seizures due to neonatal abstinence syndrome, *Streptococcus pneumoniae*, and bacteremia.¹⁴

Two additional cases reported briefly in letters to the editor yielded mixed findings with exposure to FLU during pregnancy. Sanchez and Moya¹⁹ confirmed multiple congenital malformations upon 32-week ultrasonography and post-birth echocardiography of an infant who died 7 days post-birth after being born to a 38-year-old-primigravida exposed to a single dose of FLU 150 mg near conception. In contrast, Krcmery et al.²⁰ failed to observe any abnormalities in an 18-month follow-up exam of a child born to a 24-year-old pregnant woman at 41-weeks gestation after exposure to FLU 600 mg per day for 21 days starting in the 14th week of pregnancy. The mother was switched to FLU for *Torulopsis glabrata* fungemia after developing intolerance to AmB on the first day of therapy.

Cross-Sectional Studies

Inman et al.²¹ conducted a survey of prescribers of FLU. Of the 14,421 surveys returned, there were 289 pregnancies reported. These reported pregnancies were divided into three groups: Group 1 received a single 150 mg dose of FLU (n=275), Group 2 received multiple (undefined number) 50 mg doses (n=3) and Group 3 received multiple (undefined number) 150 mg doses (n=11). There were five cases of fetal abnormality, all of which were from Group 1. The authors were able to determine the approximate time of exposure to FLU relative to last menstrual period (LMP) for this sample and reported each case of malformation as follows: bilateral nephrosis with FLU exposure 12-weeks pre-LMP, hooded prepuce and minimal hypospadias with FLU exposure 15 weeks pre-LMP, proximal hypospadias and bifid scrotum with FLU exposure 8 weeks pre-LMP, minor finger webbing and 3 short fingers on the other hand with FLU exposure 1 week pre-LMP, and still birth along with Edwards Syndrome (i.e. Trisomy 18 and cardiac abnormalities) with FLU exposure 26-weeks pre-LMP.²¹

Campomori and Bonati²² briefly reported in a letter to the editor regarding 16 pregnant women who had contacted a drug information center concerned about possible teratogenic effects of FLU. The estimated mean FLU

exposure was 291 mg (median 300 mg, range 150-1000), beginning at 4 ± 6 weeks gestation (range 1-26 weeks), with a duration of therapy of 1 ± 0.3 weeks. Fifteen of the pregnancies resulted in normal, unremarkable births; one pregnancy involving twins ended in stillbirth, however no malformations were reported.²²

Cohort Studies

Five cohort studies were identified that investigated the association of FLU with various birth defects. The first of these was conducted in 1996 by Mastriacovo et al.²³, who designed a prospective cohort study of women who contacted one of three Teratology Information Services centers in Italy during pregnancy. The exposure group consisted of 226 women who had been exposed to FLU during the first trimester. The control group consisted of 452 women who had not been exposed to FLU during pregnancy. Of the parameters examined (i.e., induced abortions, miscarriages, stillbirths, congenital anomalies, prematurity, low birth weight, cesarean section, and long hospital stay), FLU exposure during the first trimester was only significantly associated with induced abortions [OR = 5.06 (95% CI, 2.28-11.21)]. Odds ratios for nonsignificant variables were as follows: miscarriages [OR = 1.21, (95% CI, 0.67-2.21)], stillbirths [OR = 0.36 (95% CI, 0.03-3.90)], congenital anomalies [OR = 1.07 (95% CI, 0.41-2.77)], prematurity [OR = 1.73 (95% CI, 0.60-4.97)], low birth weight [OR = 0.92 (95% CI, 0.38-2.19)], cesarean section [OR = 0.91 (95% CI, 0.60-1.40)], and long hospital stay [OR = 0.87 (95% CI, 0.57-1.29)].²³

In 1999, Jick²⁴ used the United Kingdom's General Practice Research Database to identify 234 women who had been exposed to FLU during the first trimester of pregnancy. Of those exposures, 92% received a single 150 mg dose of FLU, and the study group was matched by age and general practice with 1,629 women without exposure to FLU or otherazole medications during pregnancy. The study found no significant increased risk of malformations for FLU users compared with nonusers, with polydactyly-syndactyly, heart defects, and spina bifida among the abnormalities present.²⁴

Sørensen et al.²⁵ identified 121 Danish women who had taken FLU during the first trimester of their pregnancies and had subsequently given birth to either a live or stillborn infant. All pregnancies in North Jutland County from January 1, 1991, to December 31, 1996, were included in the study, a sample representative of 9 percent of the Danish national population during that time. These pregnancies were identified using the Danish Medical Birth Registry (DMBR), which tracks all live and still births in Denmark since January 1, 1973, and stores data collected by midwives and doctors attending deliveries. The DMBR follows infants up until one year of age,

so it may be used along with the Danish National Registry of Patients (DNRP) to ascertain birth defect data.²⁵

Sørensen et al.²⁵ identified FLU exposure during the first trimester using computerized prescription databases. Though the authors were unable to determine daily medication regimens or cumulative doses of FLU received, they assumed that most subjects were given a single 150 mg FLU tablet based on patterns and standards of vaginal candidiasis treatment in Denmark at the time. The study found no significant association between FLU use and congenital malformations, both in the crude RR [0.62 (95% CI, 0.23-1.68)] and in a RR adjusted for maternal age, birth order, gestational age, and maternal smoking status [0.65 (95% CI, 0.24-1.77)]. Additionally, FLU use was found to have a nonsignificant association with low birth weight [RR = 1.17 (95% CI 0.37-3.70)] and with preterm delivery [RR = 1.13 (95% CI, 0.61-2.09)]. None of the malformations were duplicative, with congenital hip dislocation, lacrimal stenosis, partial syndactyly, and ventricular septum deficiencies each appearing in one infant. However, the study was not powered to detect more than a 1.8-fold increased risk of malformations, and the study design did not include spontaneous abortions or abortions performed due to prenatal diagnoses of malformation.²⁵

Nørgaard et al.²⁶ published a 2008 study that expanded on the work of Sørensen et al.²⁵, using the DMBR to identify women from four Danish counties who gave birth to either live or stillborn infants after the 20th week of gestation. The study encompassed 31 percent of the country's population, and depending on the county, set a date range from either 1991, 1996, or 1998, through 2005. Fluconazole exposure during the first trimester was identified using computerized prescription databases, and all women in the study group (N=1,079) received a "short-course," or 1 to 4 days, of FLU therapy with cumulative exposures of either 150mg (74%), 300mg (22%), 350mg (2%), or 600mg (2%). Exclusions listed in the study were congenital hip dislocation, undescended testes, and known chromosomal aberrations such as Down's syndrome. The crude prevalence odds ratio (POR) for the study group compared to pregnancies not exposed to FLU (N=170,453) was found to be nonsignificant [1.1 (95% CI, 0.8-1.5)], as was a POR adjusted for maternal smoking status, parity, maternal age, and prescriptions for antiepileptics and maternal diabetes [1.0 (95% CI, 0.8-1.4)]. No significant associations or definitive trends were found when congenital abnormalities were analyzed individually, though some malformations occurred multiple times within the study group, including cardiovascular, craniofacial, and musculoskeletal abnormalities, along with club foot and neural tube defects.²⁶

In 2013 Mølgaard-Nielsen et al.¹⁷ conducted a registry-based historical cohort study of all live births in Denmark for the period January 1, 1996 through March 31, 2011 using the DMBR to assess for congenital malformation outcomes after exposure to FLU during the first trimester of pregnancy. Fluconazole exposure during the first trimester was identified using computerized prescription databases, resulting in a FLU exposure group of 7,352 cases. For the non-exposure group, there were 968,236 cases. The primary endpoint was major birth defect; a composite endpoint comprising 15 birth defects thought to be associated with azole antifungals. Additionally, exposure to FLU was assessed for each component of the surrogate primary endpoint. Exposure to itraconazole or ketoconazole in the first trimester was also assessed. The individual defects that comprised the primary endpoint were as follows: craniosynostosis; cleft palate alone; cleft lip, cleft palate, or both; other craniofacial defects; middle-ear defects; limb defects; limb-reduction defects; polydactyly; syndactyly; diaphragmatic hernia; any heart defects; tetralogy of Fallot; pulmonary-artery hypoplasia; ventricular septal defects; and hypoplastic left heart. The authors failed to find increased risk of overall major birth defect due to FLU exposure during the first trimester [crude POR = 1.10 (95% CI, 0.96-1.27)]. Among the individual birth defects, oral FLU during the first trimester was associated with an increased incidence of tetralogy of Fallot [crude POR = 3.21 (95% CI, 1.52-6.81)]. No significant association was found with exposure to itraconazole or ketoconazole and risk of birth defects [crude POR itraconazole = 1.24 (95% CI, 0.81-1.90); crude POR ketoconazole = 1.07 (95% CI, 0.26-4.37)]. A subanalysis that included terminated pregnancies found a significant association between exposure to FLU and hypoplastic left heart [adjusted POR = 2.82 (95% CI, 1.23-6.45)] when “proportion of terminated pregnancies was assumed to be doubled among the exposed pregnancies”.¹⁷

Discussion

The results of the primary literature document that FLU has been implicated in causing congenital malformations, especially when administered in high doses over a prolonged duration of therapy.

A comprehensive literature review of the literature identified fourteen citations evaluating or discussing FLU use in pregnancy and congenital malformations. Six citations (four case reports, one case series comprised of two cases, and one cross-sectional study) associated FLU exposure during pregnancy with congenital malformations. Seven citations (three registry based cohort studies, one prospective cohort study, one case report, two letters to the editor) found no association between FLU exposure and birth defects. One

citation (a registry-based cohort study) found no association between oral FLU exposure during the first trimester of pregnancy and major birth defects as a composite measure, but when examining individual birth defects the investigators did find an increased incidence of tetralogy of Fallot. Those citations linking FLU exposure with congenital malformations implicated its use in the development of craniofacial, skeletal, cardiac, and genitourinary malformations, among others.

A number of references^{11,14,19} noted similarities between the malformations associated with FLU teratogenicity and those associated with Antley-Bixler syndrome, an autosomal recessive disorder of poorly understood etiology. Antley-Bixler syndrome has been associated with mutations in cytochrome P450 oxidoreductase^{27,28} and CYP51 (lanosterol-14 demethylase)^{29,30} among other mutations. As reported by Lee et al.¹¹, the phenotype characteristics associated with Antley-Bixler syndrome include craniofacial malformations such as brachycephaly, craniosynostosis, and midfacial hypoplasia; skeletal malformations such as radiohumeral synostosis, femoral bowing/fractures, thin ribs, arachnodactyly, syndactyly; and genitourinary malformations such as vaginal atresia and renal abnormalities, in addition to other malformation such as hydrocephalus, atrial septal defects, preauricular tags, and hemangioma.¹¹

The possible teratogenic effects of FLU appear to be highly dependent upon the dose, duration of exposure, and timing of exposure relative to conception. The paucity of significant findings among the five cohort studies can most likely be attributed to the dose and duration of FLU, since the total FLU exposure in these studies rarely exceeded 300 mg. In contrast, the case reports and case series reporting negative FLU effects consisted of prolonged exposure (several months in duration) to high doses (400-1200 mg/day). There was only one case report of congenital malformations after a single 150 mg dose of FLU¹⁹, promulgating theories on whether other confounding variables could have been contributory to the negative outcome.

In conclusion, there appears to be little to no fetal risk resulting from a single dose or short duration antifungal therapy with FLU; however, prolonged high-dose FLU therapy, such as that required for the treatment of coccidioidal meningitis, has potential for teratogenic effects and the risk of therapy must be weighed against the benefits.

References

1. Clinical Pharmacology. Tampa (FL): Gold Standard. [accessed 10/23/13]. <http://clinicalpharmacology-ip.com.ezproxy.samford.edu/Default.aspx>.
2. Pappas PG, Kauffman CA, Andes D, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;48(5):503-535.
3. Perfect JR, Dismukes WE, Dromer F, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2010;50(3):291-322.
4. Tucker, RM, Williams PL, Arathoon EG, et al. Pharmacokinetics of fluconazole in cerebrospinal fluid and serum in human coccidioidal meningitis. *Antimicrob Agents Chemother*. 1988;32(3):369-373.
5. Chapman SW, Dismukes WE, Proia LA, et al. Clinical practice guidelines for the management of blastomycosis: 2008 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2008;46(12):1801-1812.
6. Galgiani JN, Ampel NM, Blair JE, et al. Coccidioidomycosis. *Clin Infect Dis*. 2005;41(9):1217-1223.
7. Wheat LJ, Freifeld AG, Kleiman MB, et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2007;45(7):807-825.
8. Grigoriou O, Baka S, Makrakis E, Hassiakos D, Kapparos G, Kouskouni E. Prevalence of clinical vaginal candidiasis in a university hospital and possible risk factors. *Eur J Obstet Gynecol Reprod Biol*. 2006;126(1):121-125.
9. Sobel JD. Use of antifungal drugs in pregnancy: a focus on safety. *Drug Saf*. 2000;23(1):77-85.
10. Smale LE, Waechter KG. Dissemination of coccidioidomycosis in pregnancy. *Am J Obstet Gynecol*. 1970;107(3):356-361.
11. Lee BE, Feinberg M, Abraham JJ, Murthy AR. Congenital malformations in an infant born to a woman treated with fluconazole. *Pediatr Infect Dis J*. 1992;11(12):1062-1064.
12. Pursley TJ, Blomquist IK, Abraham J, Anderson HF, Bartley JA. Fluconazole-induced congenital anomalies in three infants. *Clin Infect Dis*. 1996;22(2):336-340.
13. Aleck KA, Bartley DL. Multiple malformation syndrome following fluconazole use in pregnancy: report of an additional patient. *Am J Med Genet*. 1997;72(3):253-256.
14. Lopez-Rangel E, Van Allen MI. Prenatal exposure to fluconazole: an identifiable dysmorphic phenotype. *Birth Defects Res A Clin Mol Teratol*. 2005;73(11):919-923.
15. Tiboni GM, Iammarrone E, Giampietro F, Lamonaca D, Bellati U, Di Ilio C. Teratological interaction between the bis-triazole antifungal agent fluconazole and the anticonvulsant drug phenytoin. *Teratology*. 1999;59(2):81-87.
16. FDA Drug Safety Communication: Use of long-term, high-dose Diflucan (fluconazole) during pregnancy may be associated with birth defects in infants. <http://www.fda.gov/Drugs/DrugSafety/ucm266030.htm>. Accessed October 15, 2013.
17. Mølgaard-Nielsen D, Pasternak B, Hviid A. Use of oral fluconazole during pregnancy and the risk of birth defects. *N Engl J Med*. 2013;369(9):830-839.
18. Weisinger EC, Mayerhofer S, Wenisch C, Breyer S, Graninger W. Fluconazole in *Candida albicans* sepsis during pregnancy: case report and review of the literature. *Infection*. 1996;24(3):263-266.
19. Sanchez JM, Moya G. Fluconazole teratogenicity [letter to the editor]. *Prenat Diagn*. 1998;18(8):862-863.
20. Krcmery V Jr, Huttova M, Masar O. Teratogenicity of fluconazole [letter to the editor]. *Pediatr Infect Dis J*. 1996;15(9):841.
21. Inman W, Pearce G, Wilton L. Safety of fluconazole in the treatment of vaginal candidiasis. A prescription-event monitoring study, with special reference to the outcome of pregnancy. *Eur J Clin Pharmacol*. 1994;46:115-118.
22. Campomori A, Bonati M. Fluconazole treatment for vulvovaginal candidiasis during pregnancy [letter to the editor]. *Ann Pharmacother*. 1997;31(1):31.
23. Mastriacovo P, Mazzone T, Botto LD, et al. Prospective assessment of pregnancy outcomes after first trimester exposure to fluconazole. *Am J Obstet Gynecol*. 1996;175(6):1645-1650.
24. Jick SS. Pregnancy outcomes after maternal exposure to fluconazole. *Pharmacotherapy*. 1999;19(2):221-222.
25. Sørensen HT, Nielsen GL, Olesen C, et al. Risk of malformations and other outcomes in children exposed to fluconazole in utero. *Br J Clin Pharmacol*. 1999;48(2):234-238.

26. Nørgaard M, Pedersen L, Gislum M, et al. Maternal use of fluconazole and risk of congenital malformations: a Danish population-based cohort study. *J Antimicrob Chemother.* 2008;62(1):172-176.
27. Adachi M, Tachibana K, Asakura Y, et al. Compound heterozygous mutations of cytochrome P450 oxidoreductase gene (POR) in two patients with Antley-Bixler syndrome. *Am J Med Genet.* 2004; 128A:333-339.
28. Fluck CE, Tajima T, Pandey AV, et al. Mutant P450 oxidoreductase causes disordered steroidogenesis with and without Antley-Bixler syndrome. *Nat Genet.* 2004;36(3):228-230.
29. Reardon W, Smith A, Honour JW, et al. Evidence for digenic inheritance in some cases of Antley-Bixler syndrome? *J Med Genet.* 2000; 37:26-32.
30. Kelley RI, Kratz LE, Glaser RL, et al. Abnormal sterol metabolism in a patient with Antley-Bixler syndrome and ambiguous genitalia. *Am J Med Genet.* 2002; 110:95-102.

Table 1 – Summary of studies related to fluconazole use in pregnancy and congenital malformations

Reference	Design	Exposure ^a	Patients ^b	Outcome
<i>Fluconazole associated with increased risk</i>				
Lee 1992 ¹¹	Case Report	FLU 400 mg/day from before conception through delivery for coccidioidal meningitis	22 yo black secundigravida with disseminated coccidioidomycosis giving caesarean birth to a female infant after 27 weeks	Multiple congenital malformations leading to death post-birth, including craniosynostosis, contractures, humeral-radial fusion and other skeletal anomalies, and cleft palate
Pursley 1996 ¹²	Case Report	Case 1: 800mg/day through 38 weeks for coccidioidal meningitis Case 2: 400mg/day through 4 months gestation for coccidioidal meningitis	Case 1: 25 yo giving caesarean birth to male infant after 38 weeks Case 2: 22 yo multiparous female whose 2 nd gestation was described by Lee et al. 4 th gestation (Case 2) was full term	Case 1: Multiple congenital malformations including skeletal defects (especially cranial and long bone) and cardiac defects (including tetralogy of Fallot, patent ductus arteriosus, and patent foramen ovale) Case 2: Multiple congenital malformations leading to death at 3 months, including tracheomalacia, cleft palate, proptosis, other various skeletal malformations, ventricular septal defect, pulmonary artery hypoplasia
Aleck 1996 ¹³	Case Report	Week 0-4: 400mg/day Week 5-9: 800mg/day Week 22-31: 1200mg/day for coccidioidal meningitis	27 yo multiparous female giving caesarean birth after 31 weeks	Soft calvarium, widely separated cranial sutures, prominent forehead, mild exorbitism, small hemangioma on tip of nose, posteriorly angulated ears with over folded helices, bilateral radiohumeral synostosis, dysplastic hips
Lopez-Rangel 2005 ¹⁴	Case Report	FLU 800 mg/day from before conception to 5th month and from 6th month to delivery for vaginal candidiasis	30 yo HIV+ Aboriginal female on multiple medications giving vaginal birth to male infant after 37 weeks	Multiple congenital malformations in infant at 9 months, including: craniosynostosis, proptosis and other recognizable dysmorphic facial features, contractures, skeletal anomalies, and joint synostosis
Sanchez 1998 ¹⁹	Letter – Case Report	FLU 150 mg single dose near conception for vaginal candidiasis	38 yo primigravida giving caesarean birth to a male infant after 39 weeks	Multiple congenital malformations leading to death at 7 days post-birth, including occipital encephalocele, severe hypoplasia of cervical vertebrae, and heart defects
Inman 1994 ²¹	Cross-sectional	Group 1: 150mg x 1 (n=275) Group 2: 50 mg course (n=3) Group 3: 150 mg x ≥2 (n=11)	Survey of prescribers for patients receiving FLU who became pregnant	Group 1: 5 cases of fetal abnormality -FLU exposure 12 weeks prior to last menstrual period: bilateral hydronephrosis -FLU exposure 15 weeks prior to last menstrual period: hooded prepuce, minimal hypospadias - FLU exposure 8 weeks prior to last menstrual period: proximal hypospadias, bifid scrotum -FLU exposure 1 week prior to last menstrual period: minor finger webbing, 3 short fingers -FLU exposure 26 weeks prior to last menstrual period: still born, Edwards Syndrome Group 2: no fetal abnormalities Group 3: no fetal abnormalities

Table 1 Cont – Summary of studies related to fluconazole use in pregnancy and congenital malformations

Reference	Design	Exposure ^a	Patients ^b	Outcome
<i>Fluconazole associated with decreased risk, or no difference between exposures and non-exposures</i>				
Wiesinger 1996 ¹⁸	Case Report	400mg/day IV beginning at 16 weeks gestation for 18 days, followed by 400mg/day PO for 34 days	Candida sepsis	Healthy female infant
Krcmery 1996 ²⁰	Letter – Case Report	FLU 600 mg/day for 21 days starting in 14th week of pregnancy for fungemia	24 yo female giving birth to infant after 41 weeks	No malformations present at 18 month follow-up exam
Campomori 1997 ²²	Letter – Cross-sectional	Mean exposure 291mg (median 300mg, range 150-1000), with a mean duration of 1 ± 0.3 weeks	16 pregnant females who contacted a drug information center regarding teratogenic effects of FLU	15 healthy, normally developed babies (1 set of stillbirth, but not malformed twins)
Mastriacovo 1996 ²³	Prospective Cohort	Mean total exposure = 200 mg ▪ Study group - FLU in first trimester for vaginal candidiasis (n=226) ▪ Control group – non-exposure to FLU (n=452)	Italian women who contacted one of three Teratology Information Services centers from January 1992 through June 1994.	Congenital abnormality OR = 1.07 (95% CI, 0.41-2.77). Induced abortion OR = 5.06 (95% CI, 2.28-11.21).
Jick 1999 ²⁴	Registry-based historical cohort	▪ Study group - Short-course FLU in first trimester (N=234) for vaginal candidiasis ▪ Control group – non-exposure toazole drug (N=1,629)	British women giving birth to live infants	Malformations present at birth resulting in treatment verified in clinical records: - 4 births in study group (1.7%) and 26 births in control group (1.6%) - RR = 1.1 (95% CI, 0.4-3.3) - No duplicate malformations in study group
Sørensen 1999 ²⁵	Registry-based historical cohort	▪ Study group - FLU use in first trimester (N=121) for vaginal candidiasis ▪ Control group – non-exposure to prescription drugs (N=13,327)	Danish women giving birth to live or stillborn infants	Malformations registered until study end: - 4 births in study group (3.3%) and 697 births in control group (5.2%) - Crude RR = 0.62 (95% CI, 0.23-1.68) - No duplicate malformations in study group
Nørgaard 2008 ²⁶	Registry-based historical cohort	▪ Study group - Short-course FLU in first trimester (N=1,079) for vaginal candidiasis ▪ Control group – non-exposure to FLU (N=170,453)	Danish women giving birth to live or stillborn infants after 20 weeks gestation	Malformations registered in first year of life: - 44 births in study group (4.1%) and 6,152 births in control group (3.6%) - Crude POR = 1.1 (95% CI, 0.8-1.5) - No significant correlations or trends among individual abnormalities analyzed - Common abnormalities in study group included cardiovascular, musculoskeletal, and craniofacial malformations

Table 1 Cont – Summary of studies related to fluconazole use in pregnancy and congenital malformations

Reference	Design	Exposure ^a	Patients ^b	Outcome
<i>Fluconazole was associated with both negative and positive results</i>				
Mølgaard-Nielsen 2013 ¹⁷	Registry-based historical cohort	▪ Study group - FLU in first trimester (N=7,352) ▪ Control group – non-exposure to FLU (N=968,236)	All live births in Denmark (01/01/1996 – 03/31/2011)	Malformations registered in first year of life: - 210 in study group (2.86%) and 25,159 in control group (2.60%) - Crude POR = 1.10 (95% CI, 0.96-1.27) Tetralogy of Fallot - 7 (0.10%) vs 287 (0.03%) - Crude POR = 3.21 (95% CI, 1.52-6.81)

^aShort-course = 1 to 4 days, ^byo=years old, OR = odds ratio, POR= prevalence odds ratio