Letters

RESEARCH LETTER

Oral Fluconazole in Pregnancy and Risk of Stillbirth and Neonatal Death

Although treatment with oral fluconazole during pregnancy is generally discouraged,[1] approximately 4% of pregnant women in the United States use fluconazole.[2] There are concerns that fluconazole use may be associated with stillbirth, particularly in doses above those commonly used for the treatment of vaginal candidiasis (150 mg, administered once or twice). In a nationwide Danish study,[3] any fluconazole exposure was not associated with an increased risk of stillbirth, but the estimate had limited precision (hazard ratio [HR], 1.32 [95% CI, 0.82-2.14]); exposure to doses above 300 mg was associated with stillbirth (HR, 4.10 [95% CI, 1.89-8.90]).

We investigated if fluconazole use during pregnancy is associated with stillbirth and neonatal death.

Methods | Nationwide register data were used to identify all pregnancies with singleton live births and stillbirths in Sweden (July 2006-December 2014) and Norway (January 2005-December 2015). We excluded pregnancies with missing maternal personal identification number, missing or implausible gestational age, nonresidence in the country, prescription for fluconazole within 28 days before conception, and prescription for any nonfluconazole oral azole antifungal between 28 days before conception and delivery. The study was approved by the respective research ethics committees. Informed consent was waived.

The primary outcomes were stillbirth (fetal loss after 22 completed weeks; except during July 2006-June 2008 in Sweden, when it was defined as after 28 completed weeks) and neonatal death (0-27 days after live birth) associated with any fluconazole exposure at any time during pregnancy, as defined by filled prescriptions. Secondary analyses investigated outcomes by fluconazole dose.

Using logistic regression, propensity scores were estimated in each country data set. Fluconazole-exposed and unexposed pregnancies were matched (1:10) on age and propensity scores. A distinct matched cohort was created for analyses of stillbirth (based on live births and stillbirths) and neonatal death (based on live births). The cohort for analysis of stillbirth also included gestational day at fluconazole exposure as a matching criterion.[3] Following matching, data from the 2 countries were pooled for analysis. Sensitivity analyses restricted to Sweden were conducted including a broader set of covariates in the propensity score. Cox and Poisson regression were used to estimate HRs for stillbirth and risk ratios (RRs) for neonatal death, respectively (SAS [SAS Institute], version 9.4).

Results | From a cohort of 1 485 316 pregnancies (852 959 in Sweden and 632 357 in Norway), 10 669 exposed and 106 690 unexposed pregnancies were included in the matched analysis of stillbirth, and 10 640 exposed and 106 387 unexposed pregnancies in the matched analysis of neonatal death. Baseline characteristics were well balanced between groups (**Table 1**).

There were 2.7 stillbirths per 1000 exposed pregnancies and 3.6 per 1000 unexposed pregnancies (HR, 0.76 [95% CI, 0.52-1.10]), and 1.2 neonatal deaths per 1000 exposed pregnancies and 1.7 per 1000 unexposed pregnancies (RR, 0.73 [95% CI, 0.42-1.29]; **Table 2**). Results were similar for doses of 300 mg or less and for more than 300 mg. Sensitivity analyses with a broader set of covariates in the propensity score were consistent with the primary analyses.

Discussion | In this cohort study, fluconazole use in pregnancy was not associated with significantly increased risks of stillbirth or neonatal death. The outcome of neonatal death has not been reported previously, to our knowledge. An increased risk of stillbirth suggested by the Danish study[3] for any fluconazole exposure or for doses more than 300 mg was not confirmed. This study included twice the number of fluconazole-exposed pregnancies from 2 countries, although the number exposed to higher doses was still small. However, in both studies, CIs were wide and, for any exposure, neither result was statistically significant. The previous result may have been due to chance.

The possibility of confounding cannot be excluded; of concern would be unmeasured confounders that could bias results toward no increased risk. Filled prescriptions were used to define drug exposure; any nonuse of fluconazole would bias results toward the null.

Although the data on fluconzazole use in pregnancy suggest no increased risk of stillbirth, additional studies should be conducted and the collective body of data[3-5] scrutinized by drug authorities before recommendations to guide clinical decision making are made, and weighed against the benefits of therapy.

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Table 1. Baseline Characteristics of Women Included in Matched Cohorts for Analyses of Stillbirth and Neonatal Death Associated With Fluconazole Use During Pregnancy, Sweden and Norway, 2005-2015[a]

Characteristics	Main Analysis (Sweden and Norway), No. (%)[b]				Sensitivity Analysis (Sweden), No. (%)			
	Stillbirth[c]		Neonatal Death[d]		Stillbirth[c]		Neonatal Death[d]	
	Fluconazole (n = 10 669)	Unexposed (n = 106 690)	Fluconazole (n = 10 640)	Unexposed (n = 106 387)	Fluconazole (n = 7440)	Unexposed (n = 74 400)	Fluconazole (n = 7418)	Unexposed (n = 74 157)
Gestational day at first prescription of fluconazole, median (IQR)	90 (19-195)		90 (19-195)		118 (21-204)		118 (21-204)	
Country								
Sweden	7440 (69.7)	74 400 (69.7)	7418 (69.7)	74 167 (69.7)	7440 (100.0)	74 400 (100.0)	7418 (100.0)	74 157 (100.0)
Norway	3229 (30.3)	32 290 (30.3)	3222 (30.3)	32 220 (30.3)				
Age, y								
≤24	1698 (15.9)	16 980 (15.9)	1694 (15.9)	16 940 (15.9)	1079 (14.5)	10 790 (14.5)	1076 (14.5)	10 760 (14.5)
25-29	3238 (30.4)	32 380 (30.4)	3233 (30.4)	32 330 (30.4)	2233 (30.0)	22 330 (30.0)	2231 (30.1)	22 310 (30.1)
30-34	3505 (32.9)	35 050 (32.9)	3494 (32.8)	34 939 (32.8)	2476 (33.3)	24 760 (33.3)	2467 (33.3)	24 670 (33.3)
35-39	1833 (17.2)	18 330 (17.2)	1827 (17.2)	18 262 (17.2)	1342 (18.0)	13 420 (18.0)	1337 (18.0)	13 352 (18.0)
≥40	395 (3.7)	3950 (3.7)	392 (3.7)	3916 (3.7)	310 (4.2)	3100 (4.2)	307 (4.1)	3065 (4.1)
Year of delivery								
2005-2008	2552 (23.9)	25 448 (23.9)	2547 (23.9)	25 515 (24.0)	1663 (22.4)	14 382 (19.3)	1659 (22.4)	16 346 (22.0)
2009-2011	3406 (31.9)	33 845 (31.7)	3397 (31.9)	33 814 (31.8)	2627 (35.3)	26 889 (36.1)	2620 (35.3)	25 799 (34.8)
2012-2015	4711 (44.2)	47 397 (44.4)	4696 (44.1)	47 058 (44.2)	3150 (42.3)	33 129 (44.5)	3139 (42.3)	32 012 (43.2)
Nordic country of birth	8110 (76.0)	81 168 (76.1)	8087 (76.0)	80 915 (76.1)	5567 (74.8)	56 248 (75.6)	5550 (74.8)	55 859 (75.3)
Living with partner	9812 (92.0)	98 064 (91.9)	9784 (92.0)	97 757 (91.9)	6880 (92.5)	69 126 (92.9)	6859 (92.5)	69 068 (93.1)
Parity								
1	3981 (37.3)	39 937 (37.4)	3974 (37.4)	39 857 (37.5)	2904 (39.0)	29 948 (40.3)	2898 (39.1)	30 003 (40.5)
≥2	2234 (20.9)	22 075 (20.7)	2226 (20.9)	21 922 (20.6)	1546 (20.8)	14 166 (19.0)	1540 (20.8)	14 413 (19.4)
History of stillbirth or neonatal death	106 (1.0)	840 (0.8)	106 (1.0)	864 (0.8)	69 (0.9)	521 (0.7)	69 (0.9)	536 (0.7)
History of major birth defect	255 (2.4)	2216 (2.1)	255 (2.4)	2258 (2.1)	199 (2.7)	1631 (2.2)	199 (2.7)	1624 (2.2)
Diabetes	181 (1.7)	1424 (1.3)	180 (1.7)	1462 (1.4)	126 (1.7)	1038 (1.4)	125 (1.7)	1029 (1.4)
Cancer diagnosis in past 6 mo	11 (0.1)	45 (<0.1)	11 (0.1)	54 (0.1)	6 (0.1)	50 (0.1)	6 (0.1)	29 (<0.1)
In vitro fertilization drug in past 3 mo	530 (5.0)	5121 (4.8)	530 (5.0)	5171 (4.9)	406 (5.5)	3683 (5.0)	406 (5.5)	3687 (5.0)
No. of prescription drugs in past 6 mo								
1-2	3932 (36.9)	39 373 (36.9)	3919 (36.8)	39 258 (36.9)	2686 (36.1)	27 322 (36.7)	2676 (36.1)	27 094 (36.5)
3-4	1915 (18.0)	19 151 (18.0)	1909 (17.9)	19 041 (17.9)	1328 (17.9)	13 262 (17.8)	1324 (17.9)	13 172 (17.8)
≥5	1708 (16.0)	17 003 (15.9)	1703 (16.0)	17 027 (16.0)	1377 (18.5)	13 094 (17.6)	1373 (18.5)	13 410 (18.1)
Educational level, y[e]								
≤9					815 (11.0)	7789 (10.5)	809 (10.9)	7372 (9.9)
10-12					2715 (36.5)	27 035 (36.3)	2708 (36.5)	26 876 (36.2)
≥13					3910 (52.6)	39 576 (53.2)	3901 (52.6)	39 909 (53.8)
Smoking[e]					477 (6.4)	4106 (5.5)	475 (6.4)	4026 (5.4)
BMI, mean (SD)[e]					24.6 (4.5)	24.5 (4.3)	24.6 (4.5)	24.5 (4.3)
Immunodeficiency[e]					35 (0.5)	302 (0.4)	35 (0.5)	279 (0.4)
No. of outpatient hospital contacts in past year[e]								
1-2					2469 (33.2)	25 330 (34.1)	2461 (33.2)	25 178 (34.0)
≥3					1976 (26.6)	19 169 (25.8)	1970 (26.6)	19 171 (25.9)
No. of hospital admissions in past year[d]								
1-2					1229 (16.5)	11 933 (16.0)	1225 (16.5)	12 009 (16.2)
≥3					80 (1.1)	670 (0.9)	79 (1.1)	667 (0.9)

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IQR, interquartile range.

[a] All variable status as current at date of conception, unless stated otherwise.

[b] For the main analysis, matching was performed in each country separately, and the country cohorts subsequently pooled.

[c] The cohorts for the analyses of stillbirth were matched (1:10 ratio) on maternal age, propensity score, and gestational age at fluconazole exposure.

[d] The cohorts for the analyses of neonatal death were matched (1:10 ratio) on maternal age and propensity score. For the main analysis, matching was performed in each country separately, and the country cohorts subsequently pooled.

[e] Variable available only in Swedish data set; included in the expanded propensity score in the sensitivity analyses restricted to Sweden.

Table 2. Association Between Use of Oral Fluconazole During Pregnancy and Risk of Stillbirth and Neonatal Death

	Pregnancies, No.	Events, No.	Events per 1000 Pregnancies, No.	Hazard Ratio (95% CI)	Absolute Difference, No. of Events per 1000 Pregnancies (95% CI)
Stillbirth					
Unmatched cohort					
Fluconazole, overall	10 669	29	2.7	0.93 (0.65 to 1.35)	−0.2 (−1.2 to 1.2)
Unexposed	1 474 647	5109	3.5	1 [Reference]	1 [Reference]
Matched cohort					
Fluconazole, overall (main analysis)	10 669	29	2.7	0.76 (0.52 to 1.10)	−0.9 (−1.7 to 0.4)
Fluconazole, dose ≤300 mg[a]	6739	17	2.5	0.80 (0.50 to 1.28)	−0.7 (−1.8 to 1.0)
Fluconazole, dose >300 mg[a]	4543	12	2.6	0.70 (0.39 to 1.26)	−1.1 (−2.2 to 0.9)
Unexposed	106 690	387	3.6	1 [Reference]	1 [Reference]
Matched cohort, sensitivity analysis[b]					
Fluconazole, overall	7440	22	3.0	1.05 (0.68 to 1.63)	0.1 (−0.9 to 1.8)
Unexposed	74 400	218	2.9	1 [Reference]	1 [Reference]
Neonatal Death				**Risk Ratio (95% CI)**	
Unmatched cohort					
Fluconazole, overall	10 640	13	1.2	0.93 (0.54 to 1.60)	−0.1 (−0.6 to 0.8)
Unexposed	1 469 538	1941	1.3	1 [Reference]	1 [Reference]
Matched cohort					
Fluconazole, overall (main analysis)	10 640	13	1.2	0.73 (0.42 to 1.29)	−0.5 (−1.0 to 0.5)
Fluconazole, dose ≤300 mg[c]	6110	8	1.3	0.78 (0.39 to 1.59)	−0.4 (−1.0 to 1.0)
Fluconazole, dose >300 mg[c]	4530	5	1.1	0.66 (0.27 to 1.61)	−0.6 (−1.2 to 1.0)
Unexposed	106 387	177	1.7	1 [Reference]	1 [Reference]
Matched cohort, sensitivity analysis[b]					
Fluconazole, overall	7418	8	1.1	0.85 (0.41 to 1.75)	−0.2 (−0.8 to 1.0)
Unexposed	74 157	94	1.3	1 [Reference]	1 [Reference]

[a] In the stillbirth analysis, the assignment to dose category was based on a time-updated definition of cumulative fluconazole dose achieved at any single point in time during pregnancy; a pregnancy could hence contribute follow-up at risk to >1 dose category, although the outcome event could only occur once and was always attributed to the highest achieved dose category.

[b] Sensitivity analysis restricted to Sweden, including a broader set of covariates in the propensity score as shown in Table 1.

[c] In the neonatal death analysis, the assignment to dose category was based on the total dose of fluconazole during pregnancy; hence each pregnancy could contribute to only 1 dose category.

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Concept and design: All authors.
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1. Eckert LO. Clinical practice: acute vulvovaginitis. *N Engl J Med*. 2006;355(12):1244-1252.

2. Palmsten K, Hernández-Díaz S, Chambers CD, et al. The most commonly dispensed prescription medications among pregnant women enrolled in the US Medicaid program. *Obstet Gynecol*. 2015;126(3):465-473.

3. Mølgaard-Nielsen D, Svanström H, Melbye M, Hviid A, Pasternak B. Association between use of oral fluconazole during pregnancy and risk of spontaneous abortion and stillbirth. *JAMA*. 2016;315(1):58-67.

4. 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.

5. Howley MM, Carter TC, Browne ML, et al. Fluconazole use and birth defects in the National Birth Defects Prevention Study. *Am J Obstet Gynecol*. 2016;214(5):657.

COMMENT & RESPONSE

Contributions of Screening and Treatment to Mortality From Breast Cancer

To the Editor Dr Plevritis and colleagues[1] modeled the relative contributions of screening and treatment to breast cancer mortality in the United States from 2000 to 2012. The weakness of this study is insufficient follow-up time.