Risk of malformations and other outcomes in children exposed to fluconazole *in utero*

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Aim Fluconazole is an active drug systematically used in the oral treatment of vaginal candidiasis and other fungal diseases. We examined the risk of malformations and other birth outcomes following pregnancy related exposures.

Method From 1 January 1991 to 31 December 1996 we identified 165 women who had taken fluconazole just before or during pregnancy in the Pregnancy Outcome Section of the North Jutland Pharmacoepidemiological Prescription Database, Denmark, which is linked to the Danish Medical Birth Registry. We compared their birth outcomes (malformation, low birth weight and preterm delivery) with the outcomes among 13 327 women who did not receive any prescriptions during their pregnancies.

Results The prevalence of malformation was 3.3% (four cases) among the 121 women, who had used fluconazole in the first trimester, and 5.2% (697 cases) in offspring to controls (odds ratio: 0.65, 95% confidence limits: 0.24–1.77). Furthermore, we did not find any significantly elevated risk of preterm delivery (odds ratio: 1.17, 95% confidence limits: 0.63–2.17) and low birth weight (odds ratio: 1.19, 95% confidence limits: 0.37–3.79).

Conclusion The study showed no increased risk of congenital malformations, low birth weight or preterm birth in offspring to women who had used single dose fluconazole before conception or during pregnancy.

Keywords: fluconazole, malformations, pregnancy, safety

Introduction

Vaginal candidiasis is a frequent disease in women of childbearing age. Fluconazole is an antifungal drug used in systematical treatment of vaginal candidiasis and other fungal diseases [1]. Despite extensive use of fluconazole, the effects on the human embryo and foetus during organogenesis have only been partly evaluated [2, 3]; but since 1992 malformations have been reported [4–7]. The similarity of the malformations of these cases compared with those described in mice and rats exposed to fluconazole has led to the suggestion that fluconazole

causes a characteristic pattern of human malformations including craniofacial, skeletal, and cardiac malformations [6]. The lack of adequate data has created uncertainty about the safety of fluconazole in pregnancy. We therefore conducted a population-based follow-up study to compare the prevalence of malformations and other outcomes among fetuses exposed to fluconazole with those not exposed to any prescriptive drugs during pregnancy.

Methods

We used the Pregnancy Outcome Section of the Danish North Jutland Pharmaco-Epidemiological Prescription Database to identify exposures and outcomes [8, 9]. Data in this section are based on record linkage between the

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population-based prescription database and the Danish Medical Birth Registry.

Exposure data

The North Jutland Pharmaco-Epidemiological Prescription Database The population-based Pharmaco-Epidemiological Prescription Database of the County of North Jutland, Denmark, initiated on 1 January 1991, was used to identify 176 prescriptions for fluconazole for all singleton pregnant women in the county who gave birth in the period from 1991 to 96. The database includes $\approx 35\,000$ pregnant women from a population of about 490 000 inhabitants ($\approx 9\%$ of the Danish population). The county is served by 33 pharmacies equipped with a computerized accounting system from which data are sent to the health insurance administration of the Danish National Health Service. The National Service provides tax-supported health care for all inhabitants of the country. Besides guaranteeing free access to general practitioners, hospitals and public clinics, the insurance programme 50–75% of the costs associated with the purchase of most prescriptive drugs. The information is transferred to the prescription database from the accounting system maintained by the pharmacies and includes the customer's personal identification number (which incorporates date of birth), the type of drug prescribed according to the anatomical therapeutical chemical (ATC) classification system, and the date of the prescription. In Denmark fluconazole is mainly used to treat vaginal candidiasis with a single tablet of 150 mg.

Outcome data

The Danish Medical Birth Registry We linked the data to the Danish Medical Birth Registry, which contains information on all births in Denmark since 1 January 1973 by means of the personal identification number [10]. Data on all births are recorded by the midwives and doctors responsible for the deliveries. The main variables in the registry are maternal age, birth weight, length at birth, birth order, gestational age and smoking status.

The Regional Hospital Discharge Registry Since data on congenital malformations are only coded as present or absent by the midwives in the Medical Birth Registry, there were many missing values regarding congenital malformations in the Medical Birth Registry, we decided to use the Regional Hospital Discharge Registry to extract information on congenital malformations. Established in 1977, the Registry transfers data to the nationwide registry where 99.4% of all discharges from Danish medical hospitals are recorded. Recorded information includes civil registration number, dates of

admission and discharge, surgical procedure(s) performed, and up to 20 discharge diagnoses, classified according to the Danish version of the International Classification of Diseases, 8th revision until the end of 1993; after that time the 10th classification [11]. The children were followed in the registry until the end of 1997. The codes for congenital malformations in the ICD8 were 740.00–759.99 and Q0.00–Q99.9 in the ICD10.

Record linkage between exposure and outcome data

Use of the 10-digit personal identification number (CPR-number), which is assigned to all citizens shortly after birth by the Danish Civil Registration System, ensured a complete prescription history for each pregnant woman.

Statistical analysis

For all pregnancies time of exposure was identified based on the reported gestational age (based on ultrasound or last menstrual period). The prescriptions filled in each trimester were included in the study. All prescriptions for fluconazole during pregnancy were thus classified in these three time windows. We used multiple regression analysis to analyse differences in birth weight of offspring of women exposed to fluconazole and made comparisons with the offspring of women not exposed to any prescriptive drugs during pregnancy. The model was adjusted for maternal age, birth order, gestational age, and smoking. We also used logistic regression models to evaluate the influence of exposure to fluconazole on the risk of malformations, low birth weight (defined as less than 2500 g) and preterm delivery (less than 37 weeks) adjusted for the same potential confounders except gestational age, which is not a confounder in this context. We used data from the first trimester to examine the risk of malformations and from first to third trimester to examine the risk of preterm delivery and low birth weight (this analysis was restricted to full term deliveries).

Results

A total of 165 pregnant women exposed to fluconazole around conception and/or in pregnancy were identified. The control group consisted of 13 327 women who did not receive any reimbursed prescriptions 30 days before or during their pregnancies. The characteristics of the women in the fluconazole and the control groups are shown in Table 1. No substantial differences regarding the main study variables between the two groups were found.

The prevalence proportion of malformations was 3.3% in the exposed and 5.2% in the control group. Table 2 shows the results of the logistic regression analysis. No

Table 1 Characteristics of the study cohort.

<i>Variable</i>	<i>Exposed to fluconazole in the first trimester (n = 121)</i>	<i>Exposed to fluconazole during pregnancy (n = 165)</i>	<i>Controls (n = 13 327)</i>
Number of prescriptions	125	176	—
Mother			
Mean age (years)	27.3	27.6	27.8
Range	17–38	17–45	13–47
Proportion of smokers (%)	33.1	31.5	28.9
Birth order			
1	54	70	7472
> 1	67	95	5855
Gestational age (weeks)			
≥ 37	113	154	12 534
34–36	6	9	540
< 34	2	2	253
Mean birth weight	3527	3538	3470
Range	1210–4920	1210–5000	500–5520
Number of malformations	4	6	697
Number of low birth weight	5	7/3*	657/209*
Number of preterm deliveries	8	11	793
Number of stillborn (before birth)	1	1	31
Number of stillborn (during birth)	0	0	15

*Full term deliveries.

elevated risk of malformation was found (odds ratio: 0.65, 95% confidence limits: 0.24–1.77). The four malformations among the exposed were congenital dislocation of the hip, lacrimal stenosis, partial syndactyly, and ventricular septum deficiency.

The proportion of preterm deliveries (6.6%) was not significantly higher than in the control group (5.7%) with an adjusted odds ratio of 1.17. When restricted to full-term infants, the proportion of low birth weight babies was 2.0% in the exposed group compared with 1.6% among the controls. By logistic regression analysis, the adjusted odds ratio for low birth weight was 1.19 (Table 2). The mean birth weight among the exposed was 58 g lower after adjustment for maternal age, birth order, gestational age and smoking.

Discussion

The use of fluconazole for prophylaxis and treatment of mycotic infections including candidiasis is widespread, also in pregnancy. We did not find any elevated risk for the main pregnancy outcomes among women exposed to fluconazole. However, the study did not have the power to detect more than 1.8 increased risk of malformations. The present data on fluconazole do not indicate any teratogenic risk, but nonteratogenicity is very difficult to prove. The indicated elevated risk of major malformations in the case reports was based upon fluconazole use in higher doses and for longer periods.

It is important to note the advantages and limitations of our study. We have a complete registration of prescriptions and births which prevents any selection bias. The proportion of coding errors is $\approx 0.2\%$ in the prescription databases [8]. We were also able to control for gestational age which is important when studying risk of malformations. The outcome data have proved to be of high validity [12] and are obtained independently of exposure information. It is well known that the discharge diagnoses can vary in quality, but it seems unlikely that there should be any differential misclassification [13]. In addition, we reviewed all hospital records of the exposed mothers around the time of birth, and did not find other malformed babies than those already recorded. Our use of routine data might be a strength since the study itself did not affect the diagnostic process, thereby introducing bias due to more surveillance of the exposed children [13].

The prevalence of malformations in our study was much higher than the prevalence in a British registry study [14] based on evaluation of the safety of anticonvulsants in pregnancy. However, the prevalence of 5.2 in our control group is close to the prevalence reported in a Hungarian study based on a nationwide registry [15]. We have used prescription data but a drug taken as a single dose is easily forgotten in a retrospective recall design; this drug is used for treatment of vaginal candidiasis, and low compliance to treatment is thus not a problem. The weaknesses of the study are not only a matter of low statistical power but also our inability to

Table 2 Pregnancy outcome in the study cohort.

Variable	Malformations			Low birth weight			Preterm delivery		
	Crude relative risk	95% CI	Adjusted relative risk	Crude relative risk	95% CI	Adjusted relative risk	Crude relative risk	95% CI	Adjusted relative risk
Number of exposures to fluconazole	1.00		1.00	1.00		1.00	1.00		1.00
Exposure to fluconazole	0.62	0.23–1.68	0.65	1.17	0.37–3.70	1.19	1.13	0.61–2.09	1.17
Birth order									
1	1.00		1.00	1.00		1.00	1.00		1.00
>1	0.83	0.71–0.97	0.83	0.59	0.44–0.78	0.53	0.81	0.70–0.94	0.76
No smoking	1.00		1.00	1.00		1.00	1.00		1.00
Smoking	1.16	0.98–1.36	1.15	3.61	2.74–4.76	3.59	1.27	1.09–1.48	1.28
Mother's age (years)									
<25	1.00		1.00	1.00		1.00	1.00		1.00
25–30	0.82	0.68–0.98	0.86	0.57	0.41–0.79	0.76	0.86	0.72–1.03	0.94
>30	0.89	0.72–1.10	1.00	0.77	0.54–1.10	1.19	1.00	0.82–1.22	1.18

control for some confounding factors. To explain the results of this study, the confounding has to be negative, which is unlikely. The study design did not identify spontaneous abortions or malformed fetuses detected at prenatal diagnoses and consequently aborted.

Our data are consistent with a recent retrospective review without control groups of pregnancies of 289 women treated with a single dose of 150 mg who were found to be pregnant or soon to become pregnant [2]. The pregnant women were identified in a prescription-event monitoring study in Britain. No foetal abnormalities were found among the exposed but the study lacked information on gestational age of exposure and had no control group. In another study based on women who contacted three Italian teratogenic information services, Mastroiacovo *et al.* compared the pregnancy outcomes of 226 women exposed to fluconazole with 452 controls [3]. The prevalence of malformations was similar in the two groups. The main limitation of this study was that the participants were self-selected by having called the Teratology Information Service for counselling.

Fluconazole is very widely used among women in the childbearing age and exposure to fluconazole is therefore a public health problem if it has any teratogenic or fetotoxic risks. The existing data provide no evidence of major risks and do not indicate that termination of pregnancies should be recommended in case of exposure.

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References

- 1 Saag MS, Dismukes WE. Azole antifungal agents: emphasis on new triazoles. *Antimicrob Agents Chemother* 1988; **32**: 1–8.
- 2 Inman W, Pearce G, Wilton L. Safety of fluconazole in the treatment of vaginal candidiasis prescription-event monitoring study, with special reference to the outcome of pregnancy. *Eur J Clin Pharmacol* 1994; **46**: 115–118.
- 3 Mastroiacovo P, Mazzone T, Botto LD, *et al.* Prospective assessment of pregnancy outcomes after first-trimester exposure to fluconazole. *Am J Obstet Gynecol* 1996; **175**: 1645–1650.
- 4 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**: 1062–1064.
- 5 Krcmery V, Huttova M, Masar O. Teratogenicity of fluconazole. *Pediatr Infect Dis J* 1996; **15**: 841.
- 6 Pursley TJ, Blomquist IK, Abraham J, Andersen HF, Bartley JA. Fluconazole-induced congenital anomalies in three infants. *Clin Infect Dis* 1996; **22**: 336–340.

- 7 Aleck KA, Bartley DL. Multiple malformation syndrome following fluconazole use in pregnancy: report of an additional patient. *Am J Med Genet* 1997; **72**: 253–256.
- 8 Olsen JH, Sørensen HT, Friis S, *et al.* Cancer risk in users of calcium channel blockers. *Hypertension* 1997; **29**: 1091–1094.
- 9 Weijin Z, Steffensen FH, Sørensen HT, Nielsen GL, Olsen J. Drug use in pregnancy in the County of North Jutland—Preliminary analyses based on 6142 pregnancies. *Int J Risk Safety Med* 1997; **10**: 189–190.
- 10 Sørensen HT, Sabroe S, Olsen J, Rothman KJ, Gillman MW, Fischer P. Birth weight and cognitive function in young adult life: historical cohort study. *Br Med J* 1997; **315**: 401–403.
- 11 Sørensen HT, Møllekjær L, Steffensen FH, Olsen JH, Nielsen GL. The risk of a diagnosis of cancer after primary deep venous thrombosis and pulmonary embolism. *N Engl J Med* 1998; **338**: 1169–1173.
- 12 Kristensen J, Langhoff-Ross J, Skovgaard LT, Kristensen FB. Validation of the Danish Birth Registration. *J Clin Epidemiol* 1996; **49**: 893–897.
- 13 Sørensen HT. Regional administrative health registries as a resource in clinical epidemiology. *Int J Risk Safety Med* 1997; **10**: 1–22.
- 14 Jick SS, Terris BZ. Anticonvulsants and congenital malformations. *Pharmacotherapy* 1997; **17**: 561–564.
- 15 Czeizel AE, Intody Z, Modell B. What proportion of congenital abnormalities can be prevented? *Br Med J* 1993; **306**: 499–503.