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# First-Trimester Itraconazole Exposure and Pregnancy Outcome

## A Prospective Cohort Study of Women Contacting Teratology Information Services in Italy

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## Abstract

**Background:** Itraconazole is an effective fungal treatment; however, there are few human data on prenatal exposure.

**Objectives:** To evaluate the major malformation rate in itraconazole prenatally exposed infants. The secondary objective includes evaluation of the pregnancy outcome.

**Methods:** A prospective cohort study was conducted from January 2002 to October 2006 in women who called two Italian Teratology Information Services (TIS). Pregnant women who were exposed to itraconazole during the first trimester and gave informed consent were matched with a contemporary group of pregnant women who contacted the TIS because they had undergone a non-teratogenic drug exposure during the first trimester. Information was obtained via a structured questionnaire at the time of the initial call to the TIS and no earlier than 1 month after delivery. A trained operator conducted the interview. The main outcome measure was information about major congenital anomalies, type of delivery, birth weight, and any pregnancy or neonatal complications.

**Results:** Data were collected on 206 women who called the TIS because of first-trimester exposure to itraconazole, and 207 controls. There were no significant differences in terms of major congenital anomalies in the exposed group versus the control group (3/163 [1.8%] vs 4/190 [2.1%], respectively).

There was no statistical difference in the rate of vaginal delivery between the exposed and control groups (101/162 [62.3%] vs 102/190 [53.8%]), premature birth (11/162 [6.8%] vs 15/190 [7.9%]), low birth weight (1/152 [0.7%] vs 4/175 [2.3%]) and high birth weight (10/152 [6.5%] vs 7/175 [4.0%], respectively).

The rates of live births (163/206 [79.1%] vs 190/207 [91.8%]), spontaneous abortion (23/206 [11.2%] vs 10/207 [4.8%]) and termination of pregnancy

(19/206 [9.2%] vs 7/207 [3.4%] in the exposed and control groups, respectively) were significantly different ($p < 0.05$).

**Conclusion:** First-trimester itraconazole-exposed infants were not at increased risk of major congenital anomalies, but the rates of spontaneous and induced abortion were higher in the exposed group versus the control group. Larger studies are warranted to confirm these observations.

## Background

Itraconazole is a systemically used triazole antifungal chemically related to ketoconazole and fluconazole. These drugs act by inhibiting the ergosterol biosynthesis, thereby causing disruption of the fungal cell membrane.[1] In animal studies it was shown that azole derivatives cross the placenta,[2] and that fluconazole and ketoconazole can be teratogenic at very high doses in rats.[3] In mouse and rat models, high doses of itraconazole cause an increased incidence of cleft palate and limb defects, while embryotoxic and teratogenic effects were not observed at low doses.[4] Human studies, even if not conclusive, did not show a significant increased risk associated with first trimester itraconazole exposure.[5]

Itraconazole is classified as pregnancy risk class C by the US FDA (i.e. animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks).[6] We report our experience in a prospective cohort study on pregnancies exposed to itraconazole in Italy in the period between 2002 and 2006.

## Materials and Methods

The study enrolled women who contacted two teratology information services (TIS; Telefono Rosso-TIS in Rome and CEPIG [CEntro per l'Informazione Genetica]-TIS in Padua) by telephone during their first trimester of pregnancy, from January 2002 to October 2006 because of exposure to itraconazole.

The primary point of interest was the rate of major congenital anomalies, defined as structural abnormalities of medical, surgical or cosmetic relevance. Chromosomal anomalies were excluded. Secondary endpoints included the rate of spontaneous and induced abortions, gestational age and weight at birth, type of delivery and rate of neonatal complications.

Women exposed during their first trimester to oral itraconazole therapy, who contacted one of the two TIS, were invited to participate in the study. The two TIS are members of ENTIS (European Network of Teratogen Information Services) and adopt the same methodology.[7,8] When the call was received, a similarly structured questionnaire was used by both centres to collect information about maternal age, gravidity, parity, maternal medical features and details of itraconazole therapy (dosage and timing).

A contemporary control group of women exposed only to non-teratogenic (e.g. paracetamol [acetaminophen], hair dying) substances during their first trimester was selected among patients who contacted the TIS. The exposed and control groups were matched according to maternal age, gravidity and parity, cigarette smoking, alcohol and illicit drug consumption.

Women who agreed to participate in the study and gave informed consent were enrolled. Data collection at both first contact and follow-up was performed in the same way for each cohort.

Both control and study populations were contacted by telephone at least 1 month after delivery and the information about major congenital anomalies (presence and type), delivery (gestational age and type), birth weight and neonatal complications were collected using a structured questionnaire.

All follow-ups were carried out by non-medical personnel who were specifically trained by medical staff.

Data are expressed as means and ranges, and paired data are compared by using Chi-square ($\chi^2$) analysis and Fisher's Exact test.

## Results

We collected data on 206 women who called our TIS because of first-trimester exposure to itraconazole and 207 controls. All the pregnancies except one were singleton. The mean daily dose of drug was 182.23 ± 62.58 mg and the mean duration of therapy was 6.9 ± 6.4 days. The treatment was within the therapeutic regimen range in all cases and the main indication was vaginal mycosis.

Maternal age, gravidity, parity, cigarette smoking, alcohol abuse and drug addiction were similar in the exposed and control groups (table I). The gestational age at the time of the call was not significantly different in the two groups.

Pregnancy and neonatal outcome data are summarized in table II.

There were no differences in terms of major congenital anomalies in the exposed and control groups (3/163 vs 4/190 [1.8% vs 2.1%], respectively). In the exposed group, three children were affected with major malformations without a specific pattern of malformation: one atrial septal defect, one unilateral hydronephrosis due to ureteropelvic junction obstruction and one cerebral calcification and hepatomegaly. This latter child was affected with congenital cytomegalovirus infection. In addition, one case presented with a chromosome 17 inversion. Details of the itraconazole exposure of the mothers of these cases are shown in table III. In the control group, four cases of congenital anomalies were reported (one Dandy-Walker anomaly, one biliary atresia, one ventricular septal defect [VSD], one lip haemangioma). One child was affected with trisomy 21. There was one fetal death (unknown cause, no major malformations) in the exposed group and none in the control group.

**Table I.** Characteristics of study and control populations

| Characteristic | Itraconazole-exposed group (n = 206) | Control group (n = 207) | p-Value |
|---|---|---|---|
| Maternal age (y; mean ± SD) | 31.6 ± 5.2 | 31.6 ± 4.0 | NS |
| Gravidity (no.; mean ± SD) | 1.6 ± 0.9 | 1.5 ± 0.7 | NS |
| Parity (no.; mean ± SD) | 0.3 ± 0.7 | 0.4 ± 0.6 | NS |
| Alcohol abuse [no. (%)] | 0 (0.0) | 0 (0.0) | NS |
| Smoking [no. (%)] | 11 (5.3) | 9 (4.3) | NS |
| Drug addiction [no. (%)] | 0 (0.0) | 0 (0.0) | NS |

**NS** = not significant.

The two groups were significantly different ($p < 0.05$) in the rate of live births (163/206 vs 190/207 [79.1% vs 91.8%]), spontaneous abortions (23/206 vs 10/207 [11.2% vs 4.8%]) and terminations of pregnancy (TOP) [19/206 vs 7/207 {9.2% vs 3.4%}].

After the exclusion of TOP (19 and 7 pregnancies in exposed and control groups, respectively) the live birth rates were 87.0% and 95.0% ($p < 0.02$).

There was no statistical difference in the rate of vaginal delivery (101/162 vs 102/190 [62.3% vs 53.8%]), premature birth (11/162 vs 15/190 [6.8% vs 7.9%]), low birth weight (1/152 vs 4/175 [0.6% vs 2.3%]) and high birth weight (10/152 vs 7/175 [6.5% vs 4.0%]) between cases and controls, respectively. The mean gestational age at delivery and the birth weight were similar in the exposed and control groups (38.9 vs 39.1 weeks and 3260.5 vs 3162.0 g, respectively).

Finally, there were two cases of neonatal complications in the exposed group (one respiratory distress syndrome and one gastrointestinal disorder) and four cases in the control group (one respiratory distress syndrome, one jaundice, one neonatal seizure and one cardiac arrhythmia).

## Discussion

Itraconazole therapy is widely used as a treatment for vaginal candidiasis or other mycotic infections. Animal data have shown that itraconazole can be a teratogen in mice,[5] causing cleft palate, limb defects and axial skeletal malformations for exposure at high doses during

**Table II.** Pregnancy and neonatal outcome

| Outcome | Itraconazole-exposed group | Control group | p-Value |
|---|---|---|---|
| Total live births [no. (%)] | 163/206 (79.1) | 190/207 (91.8) | <0.05 |
| Live births excluding TOP [no. (%)] | 163/187 (87.0) | 190/200 (95.0) | <0.05 |
| Spontaneous abortion [no. (%)] | 23/206 (11.2) | 10/207 (4.8) | <0.05 |
| TOP [no. (%)] | 19/206 (9.2) | 7/207 (3.4) | <0.05 |
| Fetal death [no. (%)] | 1/206 (0.5) | 0 (0) | NS |
| Major congenital anomalies [no. (%)] | 3/163 (1.8) | 4/190 (2.1) | NS |
| Vaginal delivery [no. (%)] | 101/162 (62.3) | 102/190 (53.8) | NS |
| Gestational age at delivery (wk; mean ± SD) | 38.9 ± 2.0 | 39.1 ± 2.2 | NS |
| Birth weight (g; mean ± SD) | 3260.5 ± 549.6 | 3162.0 ± 597.1 | NS |
| Premature birth [no. (%)] | 11/162 (6.7) | 15/190 (8.0) | NS |
| Low birth weight (<2500 g) [no. (%)] | 1/152 (0.6) | 4/175 (2.3) | NS |
| High birth weight (>4000 g) [no. (%)] | 10/152 (6.5) | 7/175 (4.0) | NS |
| Neonatal complications [no. (%)] | 2/163 (1.2) | 4/175 (2.2) | NS |

**NS** = not significant; **TOP** = termination of pregnancy.

critical periods of susceptibility.[9] Itraconazole and the other azole derivatives are not teratogenic in rabbits.[3]

The mechanism of teratogenic effects induced by azoles is unknown. Adrenal effects via cyclooxygenase inhibition and consequential inhibition of a variety of biological mediators was hypothesized,[10] as well as the inhibitory properties on mammalian cytochrome P450 enzymes.[9,11]

There are few reports with regards to human data. Rosa[12] reported the outcomes of 70 pregnancies exposed to a single dose of itraconazole during the first trimester: no teratogenic effect was found. The FDA received 14 case reports of malformations; 4 were limb defects.[12] Chotmongkol and Sookprasert[13] reported one case of a healthy baby prenatally exposed to systemic treatment with itraconazole during first trimester. Wilton et al.[14] observed no congenital malformations among 30 children prenatally exposed to itraconazole. Similarly, a cohort study performed in a general practice research database did not identify a teratogenic effect of first-trimester itraconazole exposure among 88 children.[15] A retrospective cohort of pregnancies exposed during the first trimester showed a prevalence of 13% of congenital anomalies, but the authors postulated a reporting bias to explain the observed high prevalence.[16]

A prospective study of 198 women exposed to a median daily dosage of 200 mg itraconazole during the first trimester reported a 3.2% rate of major malformations (not above the accepted baseline risk of major anomalies), without a specific pattern.[17]

Our study is currently the largest prospective observational cohort study, collecting data from 206 patients exposed to itraconazole during the first trimester of pregnancy. Our results are in keeping with previous human reports that first-trimester itraconazole exposure at the common therapeutic dosage is not associated with increased risks of malformation. Indeed, the rate of major malformations in the study group (1.8%) was not significantly different from that in the control group (2.1%). Furthermore, there was no specific pattern of malformation.

**Table III.** Major congenital anomalies in the exposed group

| Case number | Congenital anomalies | Indication | Dosage (mg/day) | Exposure duration (week + day) |
|---|---|---|---|---|
| 1 | Cerebral calcification and hepatomegaly | Vaginal mycosis | 200 | 5 + 2 to 6 + 5 |
| 2 | Unilateral hydronephrosis | Vaginal mycosis | 100 | 3 + 4 to 4 + 3 |
| 3 | Interatrial defect | Vaginal mycosis | 100 | 1 + 2 to 3 + 0 |

The present report and the data of Bar Oz et al.[16] show a frequency of congenital anomalies in first-trimester exposed children not significantly different from the frequency in controls (1.8 vs 2.1% and 2.7 vs 2.6%, respectively).

Our data, like that of Bar Oz et al.,[16] show a significant difference in the live birth rate between cases and controls due to the increased rate of spontaneous abortions and TOPs.

In the report by Bar Oz et al.,[16] the rate of live births in the total series of itraconazole-exposed women (229, 198 of whom were exposed during the first trimester) was 78.4%, compared with 94.4% of the control group. Spontaneous abortion and fetal death rates were 12.6% and 1.5%, respectively, no different from the general population,[5] and the TOP rate was 7.5%. The authors hypothesized that the increased rate of TOP could be attributed to the maternal perception of an increased risk because of itraconazole exposure, while the increased rate of spontaneous abortions could depend on different gestational ages at the time of the call to the TIS in the control and exposed groups.

In addition, terminations in our study could possibly be related to maternal fear of increased risk of malformation due to itraconazole exposure. The rates of spontaneous abortion are in the range of general population both in the control and exposed groups,[18] but higher in the exposed group than in the controls, and this difference is statistically significant ($p < 0.05$). As the gestational age at the time of the call to the TIS was similar in the control and study groups, we cannot exclude that there may have been some false reporting: some women may have reported that the abortion was spontaneous, and using our methodology there was no way to verify this.[19]

Furthermore, we observed no differences in terms of preterm delivery, birth weight, mode or time of delivery, or other maternal or neonatal complications.

Our study was performed using prospective data collected by two TIS. Currently, this method appears to be the best source for obtaining valuable data to study drug effects in pregnancy.[20] Selection and response biases as well as the dimension of the study sample are the main limitations.

## Conclusions

Our data showed that first-trimester itraconazole-exposed infants were not at increased risk of major congenital anomalies, although the live births rate is lower in the exposed group. This is due to the rates of spontaneous and induced abortion being higher in the exposed group versus the control group. Furthermore, there was no statistical difference in the rate of vaginal delivery, premature birth, low and high birth weight, gestational age at birth and neonatal complications between cases and controls.

For the limited sample size of our population, further studies will be necessary to assess the potential risk of first-trimester itraconazole exposure.

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