

10 Bar-Oz B et al. Pregnancy outcome after in utero exposure to itraconazole: a prospective cohort study. *Am J Obstet Gynecol* 183, 617-20, 2000

Type of study	Prospective cohort
Where	Canada
When	1989-1998
Characteristics of the starting cohort	Exposed pregnancies ascertained from reports to the international pharmacovigilance department of the manufacturer of itraconazole
Ascertainment of drug exposure	Data reported by the treating physician at the time of exposure
Exposure definition	<ul style="list-style-type: none"> - Intake during the first trimester of pregnancy - Daily doses: 50-800mg (median 200mg) - Mean duration of drug therapy: 8.5 ± 12.4 days - Total dose during the first trimester: 200-18,600mg (median 800mg)
Size of the studied cohort	<p>Exposed to the studied drug: 198 women recruited (229 exposed: excluded: 5 second trimester exposures, 26 timing of exposure unknown), 156 livebirths</p> <p>Unexposed reference group: 198 women recruited, 187 livebirths</p>
Exposed cohort	Newborns exposed to a specific drug
Control cohort	Newborns not exposed to any known teratogens, whose mothers during pregnancy contacted the Motherisk Program, a Canadian teratogen information service (acceptable exposures included acetaminophen, dental radiography, penicillins, prenatal vitamins, or no exposures)
Pregnancy outcome/malformations ascertainment	Pregnancy outcome reports sent to the manufacturer by the treating physician (spontaneous/therapeutic abortion, perinatal/neonatal complications, gestational age at delivery, birth weight, presence/identity of any birth defects)
Malformations definition	Major malformation: any structural abnormality with serious medical, surgical, or cosmetic consequences
Prevalence of malformations among control offspring	4.8%
Analysis	<ul style="list-style-type: none"> - Data for both groups presented as mean \pm SD - Categorical data: chi-square analysis or Fisher's test; continuous variables: Student t test and the Mann-Whitney rank sum test - RR and 95% CI were calculated - Exposed patients and the control subjects matched for maternal age (within 2 years), last menstrual period (within 6 months), gravidity, parity, alcohol/smoking status
Strengths	<ul style="list-style-type: none"> - Data reported by the treating physician at the time of exposure - Outcomes ascertained prospectively, recorded by treating physician in exposed group - Standardized data collection forms - Information on other drug exposures, timing/dose of maternal drug therapy - Information on reproductive end points (spontaneous/therapeutic abortions, fetal death) - Evaluation of the study's power analyses
Weaknesses	<ul style="list-style-type: none"> - Ascertainment of exposure was different in the groups - Not specified if ascertainment of pregnancy outcome was similar in the groups, probably not - The time of the ascertainment after delivery was not indicated - Not indicated if the staff at the follow up interview was unaware of the exposure status of the women in the control group - No information about women who refused to participate

Main results

The study supports the hypothesis that the use of itraconazole during pregnancy is safe. The rate of major malformations in the study group was 3.2%, compared with 4.8% in the control group (P=0.64; RR 0.67, 95% CI 0.2-1.9). The rate of any pregnancy loss was higher in the exposed group (RR 1.75, 95% CI 1.5-2.1). Birth weight was lower in the itraconazole group. Gestational age at birth, rate of preterm delivery, Apgar scores at 1 and 5 minutes, and neonatal complications were comparable between the groups