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PREGNANCY AND DRUG

# Pregnancy outcome following in utero exposure to azathioprine: A French comparative observational study

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**Summary**
*Aim of the study.* — To evaluate whether azathioprine exposure during pregnancy increases the risk of birth defects and prematurity.
*Method.* — Prospective comparative observational study using the French pregnancy database TERAPPEL. To evaluate birth defects, outcomes of pregnancies exposed to azathioprine during the 1st trimester were prospectively assessed and compared to that of pregnancies exposed to another drug used for the same indications. Secondly, the rate of preterm births was compared between fetuses exposed to azathioprine at least during the third trimester and those exposed during the first trimester only.

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**Results** From 447 requests for a risk assessment for women receiving azathioprine during pregnancy, 193 pregnancies meet inclusion criteria. One hundred and twenty-four of them were exposed to azathioprine during the 1st trimester and were compared to that of 124 pregnancies exposed to another drug used for the same indication. Azathioprine use during the first trimester was not statistically associated with the risk of all birth defects ([7.3% vs. 5.4%]; [OR = 1.36; 95%CI: 0.44—4.20]) nor with major birth defects (5.2% vs. 1.8% [OR = 2.96; 95%CI: 0.56—15.64]). The rate of preterm births (22.5% vs. 27.3%, $P = 0.579$) was similar regardless of the exposure period to azathioprine (at least during the third trimester or during the first trimester only).
*Conclusions.* — This study confirms that first trimester exposure to azathioprine is not associated with an elevated rate of birth defects and that the high rate of preterm births among women exposed to azathioprine is probably explained by the underlying maternal disease.



## Abbreviations

| | |
|---|---|
| 6-MP6 | mercaptopurine |
| 6-MMP | methylmercaptopurine |
| 6-TGN | 6-thioguanine |
| AZA | azathioprine |
| CNIL | French national commission of informatics and liberties |
| DNA | deoxyribonucleic acid |
| GW | gestational weeks |
| IBD | inflammatory bowel diseases |
| ICD | International classification of diseases |
| LBW | low birth weight |
| LMP | last menstrual period |
| RNA | ribonucleic acid |

## Introduction

Azathioprine (AZA), a purine analog, is used in the treatment of autoimmune disorders, such as inflammatory bowel diseases (IBD) and as part of immunosuppressive regimens to prevent transplant rejection [1—4]. After oral administration, AZA is quickly converted to 6-mercaptopurine (6-MP), which is further metabolized leading to the formation of 6-thioguanine (6-TGN), 6-methyl-MP (6-MMP) and thiouric acid [5]. AZA and 6-TGN cross the placenta, whereas 6-MMP does not [6,7]. Animal studies have shown that AZA can lead to congenital abnormalities, such as limb defects, ocular anomalies and cleft palate [8—11]. The summary of product characteristics of azathioprine for pregnancy says that ''AZA can cause fetal harm when administered to a pregnant woman and should not be given during pregnancy without careful weighing of risk versus benefit. Whenever possible, its use in pregnant patients should be avoided''. Nevertheless, data from humans suggest a risk in third trimester but also that the benefit of treatment for the mother outweighs the potential risk for the fetus and newborn [12].

Studies examining the effect of maternal AZA exposure on pregnancy outcome report conflicting results, but a lot of data suggest that thiopurines have little effect, if any, on the fetus [13—23]. In addition, the deleterious consequences on both the mother and fetus of any disease relapse resulting from the discontinuation of thiopurine during pregnancy should be taken into consideration [24,25].

Thus, the primary objective of this study was to compare the rate of all and major birth defects in fetuses exposed in utero to AZA during the first trimester of pregnancy and in those exposed to another immunosuppressant used for a similar indication. It is often impossible to determine whether the high rate of low birth weight (LBW) and prematurity among babies born to AZA-treated women result from treatment or maternal illness because AZA is used to treat women with severe illness. Thus, the secondary endpoint was to compare the birth weight and gestational age at delivery of infants exposed in utero to AZA during the first trimester only and those exposed at least during the third trimester.

## Methods

All requests for risk assessment for AZA exposure during pregnancy registered in the French pregnancy database between 1 January 1989 and 15 May 2012 were selected.

Data were obtained from requests made by physicians or patients asking to a French regional pharmacovigilance center to carry out a risk assessment for drug exposure during pregnancy. All these requests are recorded in the French pregnancy database TERAPPEL approved by the French National commission of informatics and liberties (CNIL), registered under the number: 816—257 [26]. Women were informed about the computerization of their data and could oppose it. Collected information included maternal age, gravidity, parity, the number of previous spontaneous and induced abortions, smoking and alcohol consumption habits, drug(s) dose, indication, and maternal medical history, duration of pregnancy using the date of the last menstrual period (LMP) or the date of conception estimated from ultrasound examination. Data on the outcome of pregnancy was obtained after the expected date of delivery from structured telephone interviews and/or questionnaires mailed

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