Safety of azathioprine use during pregnancy

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Abstract

Question Quite a few of my female patients with rheumatic diseases and inflammatory bowel disease are using azathioprine. They are afraid to take a "cancer drug" during pregnancy. What is known about the risks?

Answer An increasing body of evidence from prospective cohort studies suggests that azathioprine is safe for the fetus during pregnancy.

Sécurité de l'utilisation de l'azathioprine durant la grossesse

Résumé

Question Un bon nombre de mes patientes souffrant de maladies rhumatismales et de maladies inflammatoires de l'intestin prennent de l'azathioprine. Elles ont peur de prendre un médicament «anticancéreux» durant la grossesse. Que savons-nous de ses risques?

Réponse Un nombre croissant de données scientifiques tirées d'études prospectives de cohortes laissent entendre que l'azathioprine est sécuritaire pour le fœtus durant la grossesse.

Azathioprine (AZA) is a cytotoxic antimetabolite that is used to inhibit purine synthesis, which is especially important for leukocytes and lymphocytes.[1] After nonenzymatic reduction to 6-mercaptopurine, further metabolism occurs before thioguanine nucleotides are formed.[2] Thioguanine nucleotides are responsible for inhibiting DNA synthesis, thus causing cytotoxicity to cells.[3] Although anomalies occurred in rodents exposed to the drug in utero, AZA has not been identified as a human teratogen. Although not a teratogen, AZA metabolism is characterized by some genetic variation,[4] and this should be taken into consideration when establishing dosages in order to prevent maternal toxicity.

Azathioprine during pregnancy

Several studies and large case series investigated pregnancy outcomes of women exposed to AZA and other immunosuppressants during pregnancy. Most women exposed to AZA during pregnancy were treated following renal transplantation. In more than 400 reported pregnancies, there were very few anomalies reported.[5-7] The rate of malformation was not higher than would be expected in the general population and there was no pattern or consistency in the malformations that occurred.

A study of 42 pregnancies of women with autoimmune hepatitis reported that 14 of the pregnancies were exposed to AZA.[8] There were no significant differences in the outcomes of these pregnancies versus pregnancies exposed to other drugs. While a small Danish cohort study suggested an increased risk of malformations, prematurity, and perinatal mortality following maternal use of AZA or 6-mercaptopurine during the first trimester of pregnancy,[9] the National Transplantation Pregnancy Registry in 2002 did not report increased malformations among infants whose mothers were exposed to the drug. They did, however, note an increased prematurity rate.[10] A multicentre study of 189 pregnancies exposed to AZA compared with 230 unexposed pregnancies also found no difference in the malformation rate between groups. Conversely, they found an association with lower birth weight, gestational age, and prematurity.[11]

Other authors reported no malformations or adverse pregnancy risks in nearly 150 infants whose mothers were taking AZA for immune conditions, such as inflammatory bowel disease (IBD) or systemic lupus erythematosus.[12,13] However, a recent study of 476 pregnancies with AZA exposure, mostly for IBD and systemic lupus erythematosus, suggested an association between AZA exposure and atrial or ventricular septal defects.[14] When women exposed to other medications were removed from the analysis, the odds ratio decreased slightly but remained statistically significant (odds ratio 2.82, 95% confidence interval 1.13 to 5.82). The authors acknowledged that effects of underlying maternal disease cannot be eliminated and the finding could have been accidental owing to many comparisons made in the study.[14]

Recently, Motherisk conducted a meta-analysis of the fetal safety of thiopurines for treatment of IBD during pregnancy and reported on 494 patients with IBD exposed to thiopurines and 2782 IBD controls (J. Hutson, oral communication, September 2011). Compared with IBD controls, the incidence of prematurity increased among women with IBD receiving thiopurines during pregnancy. When compared with the children of healthy women, the children of those receiving thiopurines had increased risk of congenital malformations, but there was no increased risk when compared with IBD controls. The authors concluded that the associations between thiopurines and prematurity and congenital malformations were likely owing to the confounding effect of disease activity.

Immune function and neurodevelopment

One study evaluated the immune system function of 9 children exposed to immunosuppressants in utero. This group was compared with 14 infants of untreated mothers with similar diseases during pregnancy. Although only 1 of the infants was exposed to AZA, none of the exposed children had immune parameters that were significantly different from unexposed controls. These agents did not appear to alter the developing immune system.[15] However, more data and long-term follow-up are needed.

Another ongoing Motherisk study on child neurodevelopment following in utero exposure to AZA is being conducted. Preliminary results showed no significant difference in full-scale, verbal, and performance IQs between 4 groups of infants born to mothers exposed to AZA, corticosteroids, or other medications, or unexposed healthy mothers.[16] In addition, preliminary results show no association between AZA exposure in utero and neurocognitive impairment in the children.

Conclusion

Based on all available information, there is no evidence that AZA exposure is associated with congenital malformations, spontaneous abortions, or stillbirth, but the number of reported cases might not be sufficient to detect a small increase in baseline rates in the general population. Although it was recently suggested that there was a slightly increased risk of atrial or ventricular septal defects with AZA exposure, this should be weighed against possible consequences of discontinuing AZA and possible disease relapse or transplant rejection during pregnancy. Although incidences are unknown, risks of other adverse pregnancy outcomes such as intrauterine growth retardation and immunosuppression have been reported. It is important to note that most reports evaluating AZA involve concomitant maternal medications and women suffering from serious underlying diseases, which in and of themselves might have effects on pregnancy outcomes.

Competing interests
None declared

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