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The use of azathioprine and mercaptopurine during pregnancy is associated with an increased risk of intrahepatic cholestasis of pregnancy

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Background

- **Intrahepatic cholestasis of pregnancy (ICP)** is a complication of pregnancy that is associated with **increased fetal risks including preterm birth and intra-uterine death**.
- In some studies, thiopurine use was associated with an increased the risk of developing ICP.
- Thiopurines include **mercaptopurine, azathioprine, thioguanine**
- The **objective of this study was to evaluate the current evidence for an association between thiopurines and ICP** based on literature cases, spontaneous reports and a pharmacological mechanism.

Methods

- The database of the European Medicines Agency, Eudravigilance, was used to search for **spontaneous reports on ICP following mercaptopurine, azathioprine and thioguanine exposure during pregnancy**.
- Case narratives were screened and information on the moment of diagnosis, the maximum level of bile acids and pregnancy outcomes was collected.
- **A literature search was performed** searching for case reports and cohort studies describing or evaluating the association between ICP and thiopurines as a primary or secondary outcome.
- Duplicate cases between literature and Eudravigilance were identified based on the available information and were excluded from the spontaneous reports.

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Results

- A total of **27 spontaneous reports of ICP following thiopurine use during pregnancy** were identified. This included 24 reports in which azathioprine was used and three reports following mercaptopurine exposure.
- There were no reports of ICP following thioguanine use.
- In all but nine cases the indication for thiopurine use was an inflammatory bowel disease.
- For 18 cases the week of diagnosis in pregnancy was known. **In six cases, the ICP was diagnosed <30 weeks of gestation**. In five cases it was diagnosed ≥36 weeks. The other seven cases were diagnosed between 30 and 36 weeks of gestation.
- In 14 reports, the **maximum levels of bile acids were described (mean 278 µmol/L, range 53-636 µmol/L).**
- For 18 reports the pregnancy outcome was known. This included **14 premature births and four intra-uterine deaths**.
- In literature, an **additional 51 cases** were identified of which 17 in case reports and 34 in cohort studies.

Table 1. Spontaneous reports of ICP after exposure to tioguanine during pregnancy

	N
Total number of reports	27
Used medicine	
- Azathioprine	24
- Mercaptopurine	3
- Thioguanine	0
Indication	
- Inflammatory bowel disease	18
- Systemic lupus erythematosus	2
- Other	3
- Unknown	4
Pregnancy week at diagnosis	
- <30 weeks	6
- 30-36 weeks	7
- ≥36 weeks	5
- Unknown	9
Maximum bile acids levels (µmol/L)	
- <100	1
- 100-199	4
- 200-300	3
- >300	6
- Unknown	13
Pregnancy outcome	
- Premature birth	14
- Intra-uterine death	4
- Unknown	9

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Pharmacological mechanism

- The proposed pharmacological mechanism lays in the alternation of the metabolism of thiopurines during pregnancy **(Figure 1).**
- Azathioprine and mercaptopurine are metabolized into two main (inactive) metabolites: 6-TGN and 6-MMP.
- In 'shunting' phenotypes, there is an increased metabolism to 6-MMP resulting in increased 6-MMP/6-TGN ratios. These increased ratios are associated with hepatotoxicity.
- **During pregnancy, the enzyme activity of TPMT**, responsible for the metabolism to 6-MMP, **is increased.**
- This alters the metabolism of mercaptopurine and azathioprine in **favor of 6-MMP**.
- This may result in shunting. **In up to 25% of pregnant women there is shunting during pregnancy**, independent of the phenotype prior to pregnancy.
- This explains an increased risk of ICP following azathioprine and mercaptopurine exposure during pregnancy.
- As in thioguanine metabolism, TPMT is not involved, thioguanine is thought not to increase the risk of ICP.

Conclusion

- Due to changes in the metabolism of azathioprine and mercaptopurine during pregnancy, **the risk of ICP might be increased**.
- **Awareness is essential** to early detect patients at risk of increased 6-MMP levels during pregnancy.
- **Dosage splitting or cessation of treatment may reverse the ICP**.
- This might prevent adverse pregnancy outcomes including preterm birth and intra-uterine death.

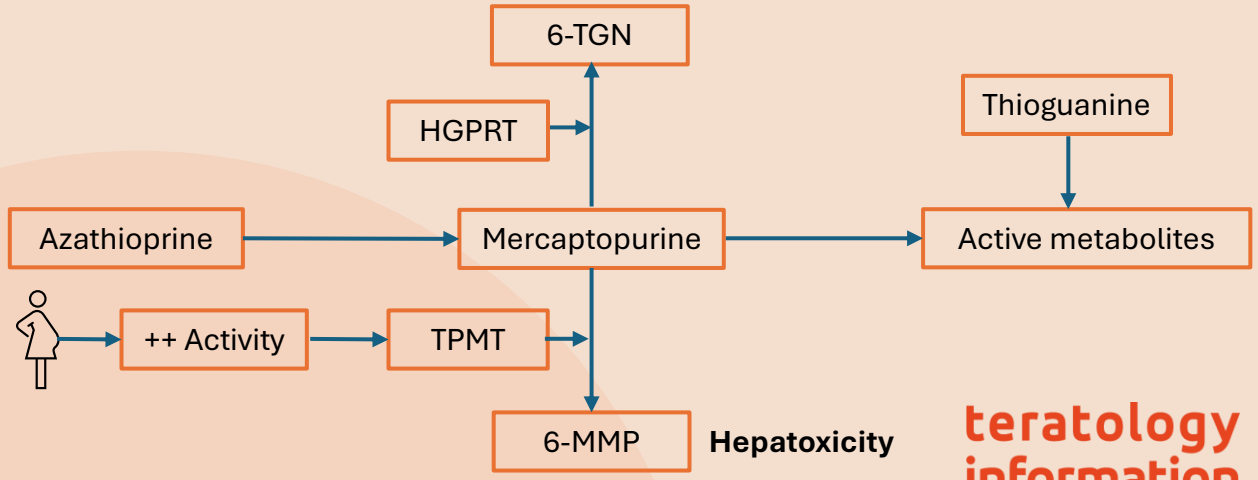

Figure 1. Summary of thiopurine metabolism.

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