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Increased risk of intrahepatic cholestasis of pregnancy in SLE women exposed to azathioprine.

Intrahepatic cholestasis of pregnancy (ICP) is linked to adverse maternal and fetal outcomes. Emerging data from inflammatory bowel disease cohorts and a 2024 FDA safety report suggest a strong association between thiopurines and ICP. This is concerning as azathioprine (AZA), a thiopurine, is the immunosuppressive of choice in SLE pregnancies. However, evidence in SLE is limited to a 2025 administrative study reporting a 3-fold increased ICP risk with AZA, without considering disease activity or thiopurine metabolites. In a multi-centre prospective cohort study, we aimed to evaluate the risk of ICP in AZA-exposed versus unexposed SLE pregnancies.

The Lupus in prEGnAnCY cohort is conducted at SLICC centres in Canada, South Korea, Peru, and Mexico. Pregnant SLE women are followed at predefined visits (<17, 20–24, 30–34 weeks gestation, and 8–12 weeks postpartum). Since ICP occurs after 20 weeks, only pregnancies with a second-trimester visit were included and followed up until delivery. AZA exposure was modelled as time-varying and primary outcome was iatrogenic delivery for ICP or spontaneous preterm birth occurring after ICP diagnosis. Multivariable Cox proportional hazards models with frailties adjusted for maternal demographics, co-morbidities, disease activity, and glucocorticoid use. At the Montreal site, thiopurine metabolites were measured at each visit, with shunting defined using established cut-offs.

Of 127 SLE pregnancies, 46 were AZA-exposed and 81 unexposed. Ten distinct ICP cases occurred: 8 among AZA-exposed (17.4%, 95%CI 9.1–30.7) and 2 among unexposed (2.5%, 95% CI 0.7–8.6). None had preexisting liver disease nor prior ICP. AZA exposure was associated with a substantially increased risk of ICP (unadjusted HR 9.1, 95% CI 1.9–44.5; adjusted HR 11.9, 95% CI 2.2–65.1). All ICP cases with metabolite data (4/4) exhibited second-trimester shunting. Among all pregnancies with second-trimester metabolite data (n=22), 36.4% (95% CI 19.7–57.0) were shunting, and 50.0% (95% CI 21.5–78.5) of these developed ICP. No ICP occurred with tacrolimus alone (n=14). All ICP pregnancies resulted in live births, although AZA-exposed cases tended to have higher bile acid levels, earlier delivery, and lower birth weight for gestational age.

This is the first prospective multi-centre cohort study to demonstrate a substantially increased risk of ICP in SLE pregnancies exposed to AZA. Shunting in the second trimester appears to be a strong predictor of ICP. These findings underscore the importance of thiopurine metabolite monitoring in SLE pregnancies and warrant heightened clinical vigilance for ICP when prescribing AZA in this population.