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Research Letter

Ursodeoxycholic Acid May Have Limited Effectiveness for Hypercholanemia Caused by Sodium Taurocholate Cotransporting Polypeptide Deficiency in Pregnancy: A Retrospective Study

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Ursodeoxycholic acid (UDCA) may have limited effectiveness in treating hypercholanemia caused by sodium-taurocholate cotransporting polypeptide deficiency (NTCPD) in pregnancy. This research letter summarizes our clinical observations and proposes a mechanistic hypothesis to account for these findings, calling for a systematic reevaluation of current clinical practice.

Sodium-taurocholate cotransporting polypeptide (NTCP) is a transport protein located on the basolateral membrane of hepatocytes, and plays a critical role in the uptake of bile acids from portal blood.[1] Loss-of-function variants in the *SLC10A1* gene lead to NTCP deficiency (NTCPD)—a recently recognized inborn error of bile acid metabolism characterized by persistent hypercholanemia.[2,3] Although published reports describe only a small number of pregnancies affected by this condition,[4-6] evidence from our center and from broader population screening suggests that NTCPD may be more prevalent than previously recognized. For instance, in some regions of southern China, the *SLC10A1* variant allele frequency is 11.72%, with an estimated carrier frequency of 20.69%.[7] Data from our cohort also suggest that NTCPD accounts for approximately half of the cases of hypercholanemia in pregnancy (50%, 6/12 in our pilot study[4] and 59.68%, 151/253 in the current dataset [unpublished data]). In clinical practice, however, this disorder is often diagnosed as intrahepatic cholestasis of pregnancy (ICP),[6] largely because both conditions present with hypercholanemia—defined as a fasting total bile acid (TBA) level ≥ 10 μmol/L—and because awareness of NTCPD among clinicians remains limited.

Because ICP is associated with adverse maternal and fetal outcomes, current clinical guidelines in the United States and China recommend UDCA for the treatment of maternal symptoms of ICP.[8,9] Consequently, many pregnant women with NTCPD currently receive UDCA therapy. However, we have observed persistent hypercholanemia despite treatment in these patients.

This study was conducted at the Guangdong Women and Children Hospital and used data from our registered project (Registration No.: MR-44-24-021219; Ethics Approval No.: 202101129). Hypercholanemia was defined as a fasting TBA level ≥ 10 μmol/L. TBA normalization was defined as a fasting TBA level < 10 μmol/L. NTCPD was diagnosed using a single-tube, TaqMan-based four-color fluorescence quantitative polymerase chain reaction assay targeting the c.800C>T (p.Ser267Phe) and c.263T>C (p.Ile88Thr) variants, which account for 98.94% of all *SLC10A1* variants in the Guangdong population. NTCPD was defined as either biallelic variants at a single locus or compound heterozygous variants. Participants were identified through the outpatient system using diagnoses of "intrahepatic cholestasis of pregnancy" or "cholestasis" combined with "pregnancy". Among 253 pregnant women with hypercholanemia, 151 were diagnosed with NTCPD. Of the 253 patients, 188 delivered at our hospital, including 113 with NTCPD (93 treated with UDCA and 20 without UDCA) and 75 with non-NTCPD (58 treated with UDCA and 17 without UDCA). Clinical data and pregnancy outcomes were retrospectively collected. The treatment group was defined as patients who received UDCA continuously for at least 2 weeks during pregnancy. The primary outcome was normalization of TBA levels at delivery. Continuous variables were compared using the Mann–Whitney U test, and categorical variables were compared using Fisher's exact test.

Our retrospective clinical data raise concerns about the effectiveness of UDCA in this population. In a 2022 pilot study, only one of six pregnancies affected by NTCPD and treated with UDCA achieved normalization of total bile acids at delivery.[4] A similarly low normalization rate was observed in our larger, more recent cohort of 113 NTCPD pregnancies (case series and data

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Table 1. TBA outcomes by UDCA use in NTCPD and non-NTCPD groups (preliminary unadjusted data)

Variables	NTCPD with UDCA (*n* = 93)	NTCPD without UDCA (*n* = 20)	Non-NTCPD with UDCA (*n* = 58)	*P* value[1]	*P* value[2]
TBA levels at birth[a] (μmol/L)	22.9 (15.5, 34.9)	17.1 (12.6, 21.9)	23.9 (13.3, 38.8)	0.042	0.532
Peak TBA level during pregnancy[a] (μmol/L)	34.5 (25.8, 52.7)	24.5 (16.7, 32.0)	32.1 (20.6, 45.8)	0.004	0.096
TBA normalization at birth[b], *n* (%)				0.605	0.002
Yes	5 (5.4)	2 (10)	13 (22.4)		
No	88 (94.6)	18 (90)	45 (77.6)		

[a]Data are presented as medians and quartiles. Intergroup comparisons used the Mann–Whitney U test. [b]Data are presented as percentages. Intergroup comparisons used Fisher's exact test. *P* value[1]: NTCPD with UDCA compared with NTCPD without UDCA. *P* value[2]: NTCPD with UDCA compared with non-NTCPD with UDCA. TBA normalization was defined as a fasting TBA level < 10 μmol/L. NTCPD, sodium-taurocholate cotransporting polypeptide deficiency; TBA, total bile acid; UDCA, ursodeoxycholic acid.

under review). Among 93 UDCA-treated pregnancies affected by NTCPD, only five (5.4%) achieved TBA normalization, and a previously reported patient with NTCPD also showed no response to UDCA therapy.[5] In contrast, the TBA normalization rate was 10% (2/20) among the untreated NTCPD patients, and this difference was not statistically significant ($P = 0.605$). Among patients treated with UDCA, TBA normalization was achieved in only 5.4% of NTCPD patients, compared with 22.4% of non-NTCPD patients ($P = 0.002$). Furthermore, NTCPD patients treated with UDCA had higher maternal bile acid levels at delivery than those who did not receive UDCA treatment ($P = 0.042$). However, it is important to note that the treated patients also had higher peak TBA levels during pregnancy ($P = 0.004$), suggesting potential confounding by disease severity (Table 1). These findings represent preliminary unadjusted associations, and these data do not establish that UDCA worsens hypercholanemia based on these data alone.

This research letter proposes the hypothesis that UDCA may have limited effectiveness in treating hypercholanemia caused by NTCPD in pregnancy. The hypothesis is based on three considerations: accumulating clinical experience with this population (5.4% TBA normalization rate during UDCA treatment), a previous report,[5] and a proposed mechanistic mismatch between UDCA's mechanism of action and the pathophysiology of NTCPD.

Following oral administration, UDCA is absorbed in the intestine and may depend substantially on NTCP for uptake into hepatocytes.[10] Once inside hepatocytes, UDCA is conjugated to form tauroursodeoxycholic acid or glycoursodeoxycholic acid. UDCA, together with its conjugates, mediates multiple anticholestatic effects, supporting its clinical use for conditions such as ICP.[11] We propose that in NTCPD, hepatocyte bile acid uptake is markedly impaired. Consequently, UDCA may not efficiently reach its site of action, potentially limiting its intracellular conjugation and downstream pathways involved in bile acid export and detoxification. This provides a potential mechanistic explanation for the observed limited biochemical response. It may also explain why some treated patients have higher total bile acid levels: UDCA itself, if its hepatic uptake is reduced, might remain in the circulation as a measurable component of the total bile acid pool. However, this proposed mechanism has not been directly demonstrated in the present study.

The findings of this analysis should be interpreted with caution. First, our data were obtained from retrospective cohorts, which are inherently susceptible to confounding by indication. The higher peak TBA observed in the treated group indicates that these patients may have had higher baseline TBA levels or more severe disease, which may account for their higher TBA concentrations at delivery. Until these confounding factors are properly controlled for, this observation cannot be interpreted as evidence supporting the lack of efficacy of UDCA. Second, the limited sample size, particularly in the untreated NTCPD group ($n = 20$), may have rendered some statistical comparisons underpowered. Total bile acids comprise a heterogeneous group of molecules with varying hydrophobicity and cytotoxicity. Which subset is most harmful to the fetoplacental unit remains unclear. Therefore, a detailed bile acid profile, beyond TBA levels alone, would provide valuable complementary information. Furthermore, our analysis relied primarily on normalization of TBA levels as a marker of treatment response. Ideally, treatment efficacy should also be evaluated against clinically meaningful endpoints, including rates of preterm birth, fetal distress, and stillbirth. Potential biochemical worsening (elevated TBA levels) should be clearly distinguished from demonstrated adverse maternal or fetal outcomes.

To resolve the current uncertainty, we propose a systematic research agenda. First, existing retrospective datasets should be expanded and refined, with meticulous documentation of reasons for non-treatment and robust adjustment for confounders. Second, a prospective, multicenter registry of pregnant patients with NTCPD should be established, capturing treatment decisions, medication adherence, and maternal and fetal outcomes from diagnosis through 42 days postpartum. Third, mechanistic studies should be integrated: paired measurements of individual bile acid profiles before and after UDCA treatment may help determine which bile acid species are associated with adverse pregnancy outcomes and whether UDCA accumulates in serum without a corresponding increase in its conjugated hepatic metabolites. Fourth, analyses should be stratified by *SLC10A1* genotype, as different variants may retain partial transport function and respond differently to therapy. Well-designed prospective studies are necessary before recommending a change in clinical practice.

In conclusion, NTCPD is an underrecognized cause of hypercholanemia in pregnancy, and the available evidence raises the

possibility that UDCA may have limited effectiveness in this condition. Both clinical observations and proposed mechanistic considerations warrant further evaluation of current practice, in which many patients with NTCPD are managed according to guidelines developed for ICP. The available data do not establish clinical harm from UDCA and do not justify discontinuation of UDCA at present. Collaborative efforts are needed to conduct well-designed, adequately powered studies to determine whether the routine use of UDCA should be reconsidered in this distinct patient population.

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Conflict of interest

The authors have no conflicts of interest related to this publication.

Author contributions

Conceptualization (XL, LZ), funding acquisition (XL), data acquisition, analysis, and interpretation (YZ, XL), supervision (XL, LZ), original draft preparation (YZ), and manuscript review and editing (XL, LZ, YZ).

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki, approved by the Committee for Medical Ethics at Guangdong Women and Children Hospital, Guangzhou, China (No. 202101129). The retrospective study was registered at MR-44-24-021219. A formal waiver of informed consent was granted in view of the use of residual blood samples, the minimal risk involved, the complete de-identification of samples, and retrospective extraction and analysis of the clinical records.

Data sharing statement

The data that support the findings of this study are not publicly available due to ethical restrictions and the terms of the data use agreement that prohibit public sharing of the data. The data used in this study are a subset of a larger ongoing research project, and the principal investigator of the parent project has not yet granted permission for public release. Researchers who are interested may contact the corresponding author for access requests, which will be reviewed by the institutional ethics committee.

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