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RESEARCH ARTICLE

Differential Metabolic Effects of Osteoporosis Therapies in Patients With Diabetes Mellitus: A Retrospective Cohort Study

Derya Unal,¹ Turkan Pasalı Kilit,² Kevser Onbasi³

¹Kutahya City Hospital, Department Of Internal Medicine

²Kutahya Health Sciences University, Department of Internal Medicine

³The Pearl International Hospital, Department Of Endocrinology And Metabolism

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ORCIDs of the authors:

DU : 0000-0002-7258-1452

TPK : 0000-0003-1126-7336

KO : 0000-0003-2230-9263

Abstract

Introduction: Osteoporosis is currently health problem with mortality rate that can reach 12–20%. Diabetes mellitus (DM) is one of the independent risk factors for osteoporosis. An area requiring further study during osteoporosis treatment, in which various agents are selected according to the patient, is the metabolic parameters that change with treatment. The aim of this study is to comparatively evaluate the metabolic effects of bisphosphonates and denosumab, agents commonly used in osteoporosis treatment on glucose, HbA1c, and lipid profile according to the presence of diabetes.

Methods: The data of 4552 patients who presented to our clinics between January 2011 and March 2024 and were diagnosed with osteoporosis were retrospectively reviewed. After excluding patients lost to follow-up or with missing data, 733 adult patients were included in the study. Patients were grouped according to the antiosteoporotic medication used and the presence of a diabetes diagnosis, and laboratory results before and after treatment were analyzed.

Results: Post-treatment glucose levels varied by group in both treatment arms, whereas HbA1c levels showed a statistically significant increase in non-DM ($p < 0.001$). According to subgroup analyses, bisphosphonate use did not cause significant change in HbA1c levels in non-diabetic patients, whereas denosumab use led to a significant increase in HbA1c. In contrast, the osteoporosis medications used in the diabetic patient group did not lead to a statistically significant change in metabolic parameters, although significant post-treatment decrease in triglyceride levels was recorded in the bisphosphonate group.

Conclusion: The metabolic effects of anti-osteoporotic therapies, particularly HbA1c and LDL, emerged clearly in nonDM individuals, whereas these effects were not observed in diabetic patients, likely owing to their pre-existing metabolic dysregulation. In contrast to some literature suggesting that RANKL inhibitors contribute positively to glucose metabolism, the increases in HbA1c and LDL observed in this study indicate that this issue warrants investigation through larger-scale clinical studies.

Correspondence Address: Evliya Çelebi Mahallesi Eken Paşa Cad. No:19 43100 Merkez/Kütahya.

Phone: +90 532 667 98 24 / **e-mail:** drdyunal@hotmail.com

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Introduction

Osteoporosis is the most common metabolic bone disease and mortality rate that can reach 12–20%¹⁻³. It is characterized by low bone mass and deteriorated microarchitecture.² According to data from the 2010 FRAKTÜRK study, the population prevalence of osteoporosis among individuals over 50 years of age in Türkiye is 25%, and the condition is more common in women.² Osteoporosis progresses silently until a fracture occurs and may go undetected in the absence of awareness, the most common fracture sites are the vertebrae and hip, and less frequently the arm.^{4,5} Screening and treatment of the at-risk group are particularly important for preserving independence and quality of life in the elderly population.⁶ Major risk factors include female sex, advanced age, family history, low calcium/vitamin D intake, low body mass index, early menopause, thyroid, parathyroid, and other endocrine disorders, certain medications (such as anticonvulsants, glucocorticoids, GnRH agonists/antagonists, SSRIs, thiazolidinediones, and aromatase inhibitors), and smoking/alcohol use.⁷ Diagnosis is established by dual-energy X-ray absorptiometry (DXA)-based bone mineral density (BMD) testing, with a lumbar spine, femoral neck, or total hip T-score of ≤ -2.5 .² Because of the elevated risk in this context, whether the diagnostic threshold should be set higher in diabetic patients compared with non-diabetic patients to facilitate earlier access to treatment has been debated.⁸

DM is one of the independent risk factors for osteoporosis.² It is a metabolic disease that develops as a result of impaired insulin secretion or reduced insulin action. Fracture risk is increased in both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). However, difference is that BMD is decreased in T1DM patients, whereas bone mineral density may be unchanged or even increased in T2DM patients.^{2,9} Bone structure is affected by advanced glycation end products, low bone turnover, chronic inflammation and oxidative stress, impaired osteocyte function, mineralization defects, deterioration of the developing bone microarchitecture, and the adverse effects of certain medications.¹⁰

Bisphosphonates are regarded as the first-line treatment for osteoporosis.¹¹ Although changes in metabolic effects associated with this treatment have been investigated in large-scale studies, sufficient data are still lacking.¹²⁻¹⁵ The aim of this study is to determine the impact of osteoporosis treatment prac-

tices on metabolic profiles, and to compare the effects of anti-resorptive and RANKL-inhibitor therapies on HbA1c levels and serum lipid parameters.

Material and Methods

Study Design

A total of 4552 adult patients diagnosed with osteoporosis at the endocrinology and internal medicine outpatient clinics of our institution between January 2011 and March 2024 were identified from hospital information system records. After excluding 1357 patients lost to follow-up and 2462 patients with inaccessible records or a potential source of bias (e.g., hemoglobinopathy), 733 adult patients were retrospectively analyzed. Patients were classified as having DM (n=318; based on a prior DM diagnosis, current antidiabetic medication use, or a new diagnosis at presentation) or not having DM (n=415), DM duration could not be reliably determined from the records (Figure 1). Demographic data, laboratory results (glucose, HbA1c, total cholesterol, HDL, LDL, triglycerides, creatinine, calcium, phosphorus, sodium, potassium, magnesium, vitamin D, and parathyroid hormone), and medication use were reviewed retrospectively. Glycemic parameters were measured by HPLC, biochemical markers by colorimetric methods, and hormone/vitamin D levels by chemiluminescence assay. Bone densitometry results were not analyzed, as they served only to guide treatment initiation and were not part of the study hypothesis. Patients received alendronate (oral, weekly), ibandronate (IV, four times/year), risedronate (oral, weekly), or zoledronate (IV, yearly) in the bisphosphonate group, or subcutaneous denosumab (twice yearly). Laboratory values at baseline and at 1 year were recorded; the primary endpoint was HbA1c at 1 year, while lipid profile, fasting glucose, vitamin D, renal function, and electrolytes were secondary endpoints. Statin, antidiabetic, and glucocorticoid use, smoking status, menopausal status, and height/weight were not consistently recorded and were therefore excluded from the analysis. The study was approved by the Kültahya Health Sciences University Ethics Committee (11.10.2023, no. 2023/11-35).

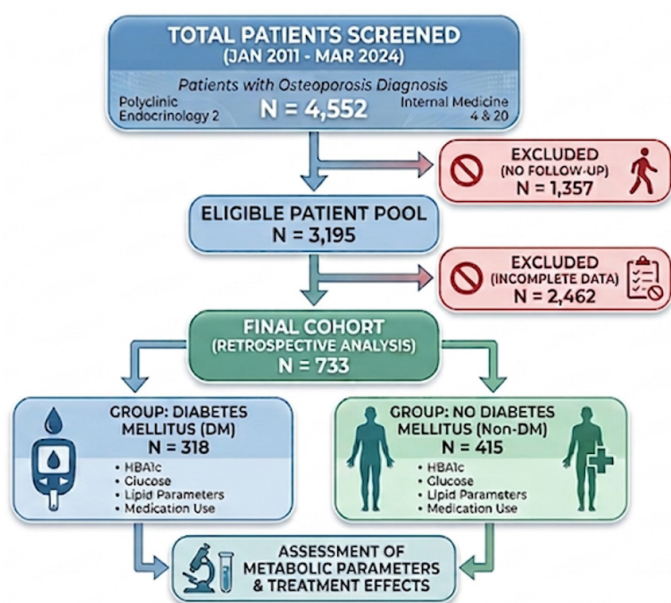


Figure 1 Flow diagram representing the selection process of

Statistical analysis

Statistical analyses were performed using SPSS v21.0. Normality was assessed with the Kolmogorov–Smirnov test. Categorical variables (sex, DM group, medication) were compared using the chi-square test. Normally distributed variables (potassium, magnesium) were analyzed using the paired-samples t-test, and pre-/post-treatment differences in these biochemical parameters were analyzed using the Wilcoxon signed-rank test. Non-normally distributed variables (age, HbA1c, glucose, lipid parameters, creatinine, calcium, phosphorus, sodium, vitamin D, and parathyroid hormone) were analyzed using the Mann–Whitney U and Wilcoxon signed-rank tests. A p-value <0.05 was considered statistically significant.

Results

A total of 733 patients were included, of whom 318 had DM. Among the non-diabetic patients (n=415), 321 (77.3%) received bisphosphonate therapy and 94 (22.7%) received denosumab, whereas among the diabetic patients (n=318), 248 (78.0%) received bisphosphonate therapy and 70 (22.0%) received denosumab. Overall, 43.6% of patients receiving bisphosphonates and 42.7% of those receiving denosumab had a diagnosis of diabetes. No statistically significant association was found between the osteoporosis treatment regimen and diabetic status ($p > 0.05$). The treatment distributions of the diabetic and non-diabetic groups were similar, and no difference indicating statistical bias or a confounding effect between the groups was detected.

In the non-diabetic group, the mean pre-treatment HbA1c was $5.59 (\pm 0.03)$ and glucose was $102 (\pm 2)$ mg/dL, while the mean post-treatment HbA1c was $5.70 (\pm 0.03)$ and glucose was $119 (\pm 5)$ mg/dL. In the DM group, the mean pre-treatment HbA1c was $6.88 (\pm 0.20)$ and glucose was $138 (\pm 8)$ mg/dL, while the mean post-treatment HbA1c was $7.02 (\pm 0.20)$ and glucose was $114 (\pm 5)$ mg/dL. In the analyses stratified by DM status, the treatment-related temporal changes in HbA1c—the primary endpoint, which did not show a normal distribution—were evaluated. No statistically significant difference was found between pre- and post-treatment HbA1c values in patients with DM. In contrast, a statistically significant increase in HbA1c levels after treatment was observed in the non-diabetic group ($p < 0.001$). Blood glucose levels also increased significantly in the non-diabetic group ($p < 0.001$).

Table 1. Baseline Characteristics

Parameters	Non DM (n=415)	DM (n=318)	p Value
Age (years), Mean $\pm$ SD	73.9 $\pm$ 0.6	75.1 $\pm$ 0.6	>0.05
Sex (Female), n (%)	365 (88.0%)	274 (86.2%)	>0.05
HbA1c (%), Mean $\pm$ SD	5.59 $\pm$ 0.03	6.88 $\pm$ 0.20	<0.001
Glucose (mg/dL), Mean $\pm$ SD	102 $\pm$ 2	138 $\pm$ 8	<0.001
Total Cholesterol (mg/dL), Mean $\pm$ SD	203.3 $\pm$ 2.0	211.1 $\pm$ 2.5	<0.05
LDL Cholesterol (mg/dL), Mean $\pm$ SD	124.5 $\pm$ 1.7	128.4 $\pm$ 2.5	>0.05
HDL Cholesterol (mg/dL), Mean $\pm$ SD	52.6 $\pm$ 0.6	50.6 $\pm$ 0.6	>0.05
Triglycerides (mg/dL), Mean $\pm$ SD	136.1 $\pm$ 3.4	163.5 $\pm$ 5.1	<0.05
Creatinine (mg/dL), Mean $\pm$ SD	0.71 $\pm$ 0.03	0.71 $\pm$ 0.02	>0.05
Calcium (mg/dL), Mean $\pm$ SD	9.5 $\pm$ 0.5	9.6 $\pm$ 0.1	>0.05
Phosphorus (mg/dL), Mean $\pm$ SD	1.3 $\pm$ 0.2	1.5 $\pm$ 0.2	>0.05
Sodium (mmol/L), Mean $\pm$ SD	138.7 $\pm$ 0.8	140.8 $\pm$ 0.7	>0.05
Potassium (mmol/L), Mean $\pm$ SD	4.5 $\pm$ 0.5	4.5 $\pm$ 0.1	>0.05
Magnesium (mg/dL), Mean $\pm$ SD	1.99 $\pm$ 0.05	2.02 $\pm$ 0.05	>0.05
Vitamin D (ng/mL), Mean $\pm$ SD	29.1 $\pm$ 1.4	29.5 $\pm$ 2.0	>0.05
Parathyroid Hormone (pg/mL), Mean $\pm$ SD	66.6($\pm$ 2.8)	66.2($\pm$ 4.0)	>0.05

In the non-diabetic group, the mean total cholesterol was 203.3 (± 2.0) mg/dL, HDL was 52.6 (± 0.6) mg/dL, LDL was 124.5 (± 1.7) mg/dL, and triglycerides were 136.1 (± 3.4) mg/dL, whereas in the DM group, the mean total cholesterol was 211.1 (± 2.5) mg/dL, HDL was 50.6 (± 0.6) mg/dL, LDL was 128.4 (± 2.5) mg/dL, and triglycerides were 163.5 (± 5.1) mg/dL. The two groups were not comparable in terms of total cholesterol and triglycerides. However, when the pre- and post-treatment total cholesterol, LDL, HDL, and triglyceride levels were compared over time within each group, no significant change was observed in any lipid parameter. A moderate positive correlation was found between the pre- and post-treatment measurements for both parameters ($p < 0.001$). No significant change in lipid parameters was observed in diabetic patients ($p > 0.05$).

At baseline, there were no differences between the groups in creatinine, calcium, phosphorus, magnesium, potassium, sodium, or parathyroid hormone levels. Among the electrolytes, no significant pre-/post-treatment difference was found for calcium, magnesium, or potassium ($p > 0.05$). Phosphorus showed a significant increase from pre- to post-treatment in both groups ($p < 0.001$). For sodium, a significant

increase was observed only in the non-diabetic group. In the non-diabetic group, the mean pre-treatment vitamin D was 29,1($\pm 1,4$) and the mean post-treatment vitamin D was 28,9($\pm 1,2$); in the DM group, the mean pre-treatment vitamin D was 29,5($\pm 2,0$) and the mean post-treatment vitamin D was 25,2($\pm 0,9$). In the non-diabetic group, the mean pre-treatment parathyroid hormone was 66,6($\pm 2,8$) and the mean post-treatment parathyroid hormone was 69,3($\pm 7,0$); in the DM group, the mean pre-treatment parathyroid hormone was 66,2($\pm 4,0$) and the mean post-treatment parathyroid hormone was 65,2($\pm 4,2$). In the bisphosphonate group, no difference was observed for HbA1c, glucose, HDL, or LDL; however, a statistically significant decrease of 5 mg/dL—not reaching the clinical target—was observed for triglycerides in diabetic patients and for total cholesterol in non-diabetic patients. In the denosumab group, the increases in glucose and HbA1c in non-diabetic patients were significant ($p < 0.05$, Table 2)

In the multiple linear regression model, no statistically significant linear association was demonstrated for any of the 11 variables potentially related to the change in HbA1c (Table 3, Figure 2).

Table 2. Pre- and Post-Treatment Changes in HbA1c and Glucose by Medication Group

		HbA1c		p	Glucose		p
		Pre-treatment	Post-treatment		Pre-treatment	Post-treatment	
Bisphosphonate	Non DM	5.61(± 0.36)	5.70 (± 0.46)	>0.05	103.9(± 2.0)	112.9(± 4.4)	>0.05
	DM	6.96(± 0.19)	7.03(± 0.24)	>0.05	144.5(± 9.9)	114.3(± 5.9)	>0.05
Denosumab	Non DM	5.52(± 0.06)	5.70(± 0.06)	<0.001	96.5(± 2.3)	139.3(± 13.3)	<0.001
	DM	6.66(± 0.30)	6.99(± 0.32)	>0.05	120.9(± 5.5)	113.2(± 9.4)	>0.05

Figure 2. Forest Plot of the Multiple Linear Regression Analysis of Variables Associated with the Change in HbA1c

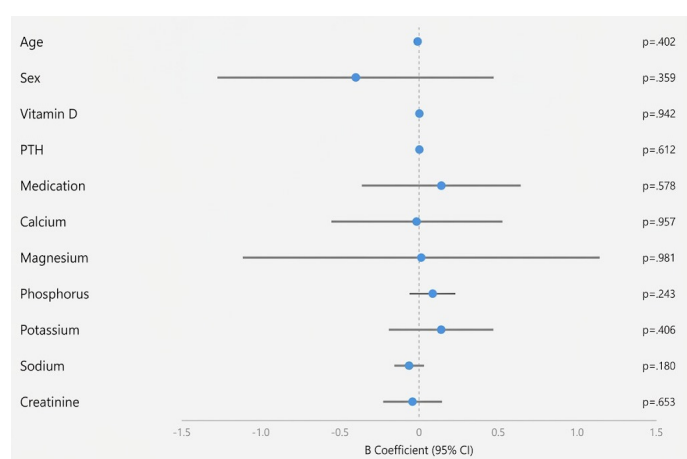


Table 3. Multiple Linear Regression Analysis of Variables Associated with the Change in HbA1c

Variable	B	Std. Error	Beta	t	95% CI Lower	95% CI Upper
(Constant)	9.170	6.821		1.344	-4.568	22.907
Age	-0.010	0.012	-0.139	-0.846	-0.034	0.014
Sex	-0.402	0.434	-0.145	-0.928	-1.276	0.471
Vitamin D	0.001	0.007	0.011	0.073	-0.014	0.015
PTH	0.002	0.003	0.080	0.510	-0.005	0.008
Medication	0.140	0.250	0.081	0.560	-0.364	0.644
Calcium	-0.015	0.269	-0.008	-0.055	-0.556	0.527
Magnesium	0.013	0.560	0.005	0.024	-1.115	1.142
Phosphorus	0.085	0.072	0.195	1.183	-0.060	0.231
Potassium	0.138	0.164	0.119	0.839	-0.193	0.469
Sodium	-0.063	0.046	-0.201	-1.362	-0.156	0.030
Creatinine	-0.042	0.092	-0.097	-0.453	-0.228	0.144

Dependent variable: Change of HbA1c

Discussion

This study was designed to evaluate the metabolic effects of anti-osteoporotic therapies. The results indicate that these effects may differ according to the presence of diabetes. A strength of our study is that, unlike much of the literature, we examined not only glucose and HbA1c but also lipid and electrolyte parameters.^{13,15,16} Other large cohort studies had a more limited scope; for instance, while Lasco et al. examined levels of electrolytes, vitamin D, or parathyroid hormone and found no significant changes, we evaluated a broader panel of metabolic parameters in the context of the use of multiple active agents over the same follow-up period.¹⁷

When the medications were examined independently, a decrease in glucose was observed in diabetic patients, which was thought to potentially be related to concurrent diabetes treatments. Although no significant difference in glucose or HbA1c was found in the bisphosphonate group, an increase in both HbA1c and glucose levels was observed in non-diabetic patients receiving denosumab. Several publications in the literature suggest that denosumab may be protective with respect to diabetes.^{16–18} In the study by Wang et al., conducted in postmenopausal women treated with denosumab and ibandronate, denosumab use was noted to contribute positively to diabetes control. It has been proposed that the effect involving an increase in GLP-1 levels together with a decrease in dipeptidyl peptidase-4 (DPP-4) levels was not observed with ibandronate, and that this effect stems from the influence of RANKL inhibitors on glucose metabolism.¹⁸ A reduced incidence of DM has been reported in geriatric patients started on denosumab therapy, and the need to investigate this finding in different countries has been emphasized.¹⁹ RANKL increases DPP-4 expression in osteoclasts, leading to more rapid degradation of GLP-1, this in turn reduces insulin secretion, increases glucagon, and promotes hyperglycemia/insulin resistance.¹⁶ Denosumab, by blocking RANKL, may reduce circulating DPP-4 and thereby increase GLP-1.²⁰ In contrast, our failure to observe a significant change in patients with diabetes suggests that this effect may vary according to the patient population. This discrepancy between our study and the existing literature highlights the need for large-scale, prospective studies that exclude confounding factors.

Regarding the evaluation of lipid parameters, the difference between the diabetic and non-diabetic

groups was considered to stem from the metabolic status of the DM group itself. In the study by Karimifard et al. (2021), osteopenic and prediabetic postmenopausal women were evaluated; triglycerides, total cholesterol, LDL, and HDL were measured before and after alendronate treatment, and no significant difference was found between the treatment and placebo groups.²¹ In the study by Lou et al., the anti-inflammatory effect of denosumab was evaluated with respect to the OPG/RANKL/RANK signaling pathway, but no significant evidence was found.¹⁵ In our study, the treatment administered was found to have a statistically significant lowering effect on total cholesterol and triglyceride levels, although this did not translate into achieving clinical targets, and no significant effect was found on HDL or LDL cholesterol levels. This may indicate that hyperlipidemia in diabetic patients is not well controlled independently of treatment.

The absence of a significant change in creatinine, calcium, magnesium, and potassium levels before and after treatment in either group suggests that the anti-osteoporotic agents used did not have a marked adverse effect on renal function or basic electrolyte balance. About phosphorus increase observed in our study cannot be directly explained by anti-resorptive therapies. This finding does not conform to the pattern of antiresorptive agents which is characterized by a transient decline in serum calcium and phosphate accompanied by a compensatory rise in parathyroid hormone. A plausible explanation is that the post-treatment assessment in our cohort did not coincide with this early time window, during which such transient changes are most likely to be detected.

Our study has several limitations. First, its retrospective design prevented access to certain data that could have influenced osteoporosis and metabolic parameters, which may have introduced bias. In particular, the inconsistent recording of glucocorticoid, statin, and antidiabetic medication use across all patients makes it difficult to distinguish whether the observed metabolic changes were directly attributable to anti-osteoporotic treatment or to concurrent changes in medication. This represents the most important limitation of our study. Larger, prospective studies are needed. Fracture assessment was not performed in this study. In addition, the reasons for inadequate control of hyperlipidemia in diabetic patients warrant investigation as an independent research topic.

In conclusion, these findings indicate that the metabolic effects of anti-osteoporotic therapies are more pronounced in non-diabetic individuals; the already elevated baseline HbA1c and glucose values in diabetic patients, together with their frequent concurrent use of antidiabetic therapy, may have pushed any additional effect of anti-osteoporotic agents below the threshold of statistical detectability. Our findings suggest that it may be reasonable to include glyce-mic parameters in routine monitoring following the initiation of denosumab, particularly in non-diabetic osteoporosis patients. In addition, the finding that denosumab therapy may produce more pronounced effects on glyce-mic and lipid parameters compared with bisphosphonates warrants further investigation.

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RESEARCH ARTICLE

Maternal and Perinatal Outcomes According to Proteinuria in Preeclampsia: A Retrospective Cohort Study

Gulnihal Reyhan Toptas,¹ Dilek Sahin¹

¹Ankara Bilkent City Hospital

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ORCID IDs of the authors:

GRT : 0000-0002-6814-8373

DS : 0000-0001-8567-9048

Abstract

Introduction: The prognostic significance of proteinuria in preeclampsia remains uncertain. This study aimed to compare maternal, laboratory, and perinatal outcomes between women with dipstick proteinuria $<2+$ and $\geq 2+$ and to evaluate the association between proteinuria $\geq 2+$ and adverse outcomes.

Methods: This retrospective cohort included 260 women with preeclampsia, categorized according to dipstick proteinuria as $<2+$ (0/1+; n=126) or $\geq 2+$ (n=134). Maternal, laboratory, and perinatal outcomes were compared between the groups. Binary logistic regression was used to evaluate the association between proteinuria $\geq 2+$ and the composite adverse neonatal outcome, adjusting for maternal age, nulliparity, and severe hypertension.

Results: Dipstick proteinuria $\geq 2+$ was present in 134 women (51.5%). Compared with the $<2+$ group, women with proteinuria $\geq 2+$ had higher blood urea nitrogen and creatinine levels and lower estimated glomerular filtration rate (all $p \leq 0.013$). Median birthweight was lower in the $\geq 2+$ group (2315 vs 2520 g; $p=0.002$), whereas gestational age at delivery and 1- and 5-minute Apgar scores did not differ significantly. The composite adverse neonatal outcome was more frequent with proteinuria $\geq 2+$ (57.5% vs 44.4%; $p=0.036$), while severe hypertension and composite adverse maternal outcome rates were similar. Proteinuria $\geq 2+$ was associated with the composite adverse neonatal outcome in the unadjusted analysis (OR 1.69, 95% CI 1.03–2.76; $p=0.036$) and in the primary adjusted model (adjusted OR 1.74, 95% CI 1.03–2.93; $p=0.037$). After gestational age at delivery was added in the sensitivity model, the association was attenuated (adjusted OR 1.40, 95% CI 0.72–2.71; $p=0.317$), while model discrimination increased from an AUC of 0.658 to 0.864.

Conclusion: Dipstick proteinuria $\geq 2+$ was associated with greater renal biochemical involvement, lower birthweight, and higher odds of a composite adverse neonatal outcome, but not with severe hypertension or the composite adverse maternal outcome. The attenuation after adjustment for gestational age at delivery suggests that the neonatal association was not independent of the timing of birth.

Correspondence Address: Üniversiteler, 1604. Cd. No: 9, 06800 Çankaya 06800 Ankara - Türkiye
Phone: +90 507 924 95 41 / **e-mail:** gulnihalreyhan@gmail.com

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Introduction

Preeclampsia is a heterogeneous multisystem disorder characterized by new-onset hypertension after 20 weeks of gestation accompanied by proteinuria and/or maternal organ dysfunction. It remains an important cause of maternal and perinatal morbidity worldwide. Current diagnostic frameworks no longer require proteinuria when other severe maternal or uteroplacental features are present, and the amount of proteinuria is not considered a severe feature in the American College of Obstetricians and Gynecologists criteria.^{1,2}

Proteinuria reflects glomerular endothelial injury and altered permselectivity arising from the systemic endothelial dysfunction of preeclampsia.³⁻⁵ Nevertheless, its prognostic meaning is uncertain. A systematic review concluded that the measured amount of proteinuria was a poor stand-alone predictor of maternal and fetal complications.⁶ Similarly, the multicenter PIERS cohort found that dipstick, protein-to-creatinine ratio, and 24-hour protein excretion had limited ability to predict adverse outcomes in isolation.⁷ Other cohorts, however, have linked higher protein excretion to earlier delivery, fetal growth restriction, low birthweight, and neonatal intensive care admission.⁸⁻¹¹ Differences in diagnostic thresholds, methods of urine assessment, gestational age, and outcome definitions probably contribute to the conflicting evidence.^{12,13}

The present study aimed to compare maternal characteristics, laboratory parameters, and perinatal outcomes between preeclamptic women with dipstick proteinuria <2+ and ≥2+. We also investigated whether proteinuria was independently associated with a composite adverse neonatal outcome.

Material and Methods

Study design and setting

This single-center retrospective cohort study was conducted in the Department of Perinatology at Ankara Bilkent City Hospital, Ankara, Türkiye. The study included women diagnosed with preeclampsia between June 2025 and June 2026

Participants and definitions

A total of 260 women coded as having preeclampsia were eligible for the present analysis. Women were categorized by urine dipstick grade as <2+ (0 or 1+; n=126) or ≥2+ (2+, 3+, or 4+; n=134). Dipstick grades were 0 in 91 women, 1+ in 35, 2+ in 44, 3+ in 50, and 4+ in 40. The ≥2+ threshold was selected a

priori in accordance with guideline-based definitions of proteinuria in preeclampsia. ACOG and ISSHP define significant proteinuria as ≥300 mg in a 24-hour urine collection or a spot urine protein-to-creatinine ratio ≥0.3 (30 mg/mmol); when quantitative methods are unavailable or rapid clinical decisions are required, a urine dipstick reading of ≥2+ may be used as a reasonable alternative.^{1,2}

Preeclampsia was defined according to ACOG criteria as new-onset hypertension after 20 weeks of gestation accompanied by proteinuria or, in the absence of proteinuria, new-onset maternal organ dysfunction or other severe features. Severe hypertension was defined as systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥110 mmHg.¹

Data collection and outcomes

Maternal age, gravidity, parity, gestational age at delivery, birthweight, Apgar scores, hematologic indices, blood urea nitrogen (BUN), creatinine, liver enzymes, bilirubin, and estimated glomerular filtration rate (eGFR) were extracted.

Severe hypertension was analyzed according to the diagnosis recorded in the database. The composite adverse maternal outcome comprised HELLP syndrome, eclampsia, maternal intensive care requirement, or maternal death. The composite adverse neonatal outcome comprised at least one of delivery before 34 weeks, birthweight <1500 g, neonatal intensive care unit (NICU) admission, 1-minute Apgar score <7, 5-minute Apgar score <7, fetal death, or neonatal death.

Statistical analysis

Normality was assessed separately in the two proteinuria groups using the Shapiro–Wilk test. Hemoglobin, which was normally distributed in both groups, is reported as mean ± standard deviation and was compared using Welch’s independent-samples t test. Other continuous variables are reported as median (minimum–maximum) and were compared using the Mann–Whitney U test. Categorical variables are reported as n/N (%) and were compared using Pearson’s chi-square test. Analyses were complete-case by variable. Two-sided p<0.05 was considered statistically significant. Because the comparisons were exploratory, p values were not adjusted for multiplicity.

Binary logistic regression was used for the composite adverse neonatal outcome. Proteinuria ≥2+ was the exposure of interest, with dipstick gra-

des 0/1+ as the reference group. Model 1 was unadjusted. Model 2 included proteinuria $\geq 2+$, maternal age, nulliparity, and severe hypertension. Covariates were selected a priori based on clinical relevance and the existing literature.¹ Model 3 additionally included gestational age at delivery to assess whether the association was independent of timing of birth; because gestational age may lie on the causal pathway, Model 3 was interpreted as an explanatory sensitivity model rather than the primary etiologic model. Results are presented as ORs with 95% CIs. Discrimination was evaluated using the area under the receiver operating characteristic curve (AUC), and calibration with the Hosmer–Lemeshow test where applicable. No model variable had missing data.

Ethical considerations

The study was approved by the Ankara Bilkent City Hospital Ethics Committee (approval no. TABED 2-26-2546; approval date: July 8, 2026). The requirement for individual informed consent was waived by the Ethics Committee due to the retrospective nature of the study. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Results

Cohort characteristics

The study included 260 women with preeclampsia, of whom 134 (51.5%) had dipstick proteinuria $\geq 2+$ and 126 (48.5%) had grades 0/1+. Maternal age was lower in the $\geq 2+$ group (median, 31.5 vs 32.5 years; $p=0.048$). Gravidity and parity were also lower in the $\geq 2+$ group (both $p\leq 0.002$) (Table 1).

Laboratory findings

Hemoglobin, white blood cell count, and platelet count did not differ significantly between the groups. Women with proteinuria $\geq 2+$ had higher BUN levels (median, 24 vs 19 mg/dL; $p<0.001$), higher creatinine levels (median, 0.60 vs 0.54 mg/dL; $p<0.001$), and lower eGFR values (median, 122 vs 126 mL/min/1.73 m²; $p=0.013$). AST, ALT, total bilirubin, and direct bilirubin levels were similar between the groups (Table 1).

Table 1. Clinical and laboratory characteristics according to dipstick proteinuria level

Variable	Proteinuria $\geq 2+$ (n=134)	Proteinuria $<2+$ (n=126)	p value
Maternal age, years	31.5 (18-46)	32.5 (19-49)	0.048
Gravidity	2 (1-7)	2 (1-9)	<0.001
Parity	0 (0-5)	1 (0-6)	0.002
Hemoglobin, g/dL	11.93 $\pm$ 1.59	12.13 $\pm$ 1.44	0.282
White blood cell count, / μ L	10800 (1440-22000)	10830 (3150-73660)	0.805
Platelet count, / μ L	238500 (58000-546000)	242500 (60000-528000)	0.864
BUN, mg/dL	24 (1-56)	19 (1-41)	<0.001
Creatinine, mg/dL	0.60 (0.30-1.35)	0.54 (0.34-1.04)	<0.001
AST, U/L	24 (5-454)	20 (7-1062)	0.059
ALT, U/L	16 (3-340)	14.5 (5-1123)	0.340
Total bilirubin, mg/dL	0.40 (0.10-1.80)	0.40 (0.20-1.90)	0.447
Direct bilirubin, mg/dL	0.10 (0.00-1.00)	0.10 (0.00-0.40)	0.208
eGFR, mL/min/1.73 m ²	122 (56-153)	126 (70-153)	0.013

Values are presented as mean $\pm$ standard deviation or median (minimum–maximum), as appropriate. Welch’s independent-samples t test was used for hemoglobin, and the Mann–Whitney U test was used for all other variables. BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate.

Maternal and neonatal outcomes

Gestational age at delivery did not differ significantly between the $\geq 2+$ and $<2+$ groups (median, 35 vs 36 weeks; $p=0.070$). Median birthweight was lower in the $\geq 2+$ group (2315 vs 2520 g; $p=0.002$), whereas 1- and 5-minute Apgar scores were similar ($p=0.560$ and $p=0.733$, respectively). Severe hypertension (45.5% vs 40.5%; $p=0.412$) and the composite adverse maternal outcome (7.5% vs 4.8%; $p=0.365$) did not differ significantly. NICU admission was more frequent in the $\geq 2+$ group, although the difference was not statistically significant (48.5% vs 38.1%; $p=0.091$). The composite adverse neonatal outcome was significantly more frequent in the $\geq 2+$ group (57.5% vs 44.4%; $p=0.036$). No fetal deaths occurred in either group. Neonatal death occurred in 2 women in the $\geq 2+$ group and 2 women in the $<2+$ group (1.5% vs 1.6%; $p=1.000$). (Table 2).

Table 2. Maternal and neonatal outcomes according to dipstick proteinuria level

Outcome	Proteinuria $\geq 2+$ (n=134)	Proteinuria $< 2+$ (n=126)	p value
Gestational age at delivery, weeks	35 (23-41)	36 (26-42)	0.070
Birthweight, g	2315 (480-4850)	2520 (520-4280)	0.002
1-minute Apgar score	7 (0-8)	7 (0-8)	0.560
5-minute Apgar score	9 (0-10)	9 (0-10)	0.733
Birthweight < 1500 g	37/134 (27.6)	17/126 (13.5)	0.005
Delivery before 34 weeks	45/134 (33.6)	30/126 (23.8)	0.082
1-minute Apgar score < 7	40/134 (29.9)	34/126 (27.0)	0.609
5-minute Apgar score < 7	14/134 (10.4)	14/126 (11.1)	0.863
Fetal death	0/134 (0.0)	0/126 (0.0)	—
Neonatal death	2/134 (1.5)	2/126 (1.6)	1.000
NICU admission	65/134 (48.5)	48/126 (38.1)	0.091
Severe hypertension	61/134 (45.5)	51/126 (40.5)	0.412
Composite adverse maternal outcome	10/134 (7.5)	6/126 (4.8)	0.365
Composite adverse neonatal outcome	77/134 (57.5)	56/126 (44.4)	0.036

Values are presented as median (minimum–maximum) or n/N (%); Pearson's chi-square test or Fisher's exact test was used for categorical variables, as appropriate.

NICU, neonatal intensive care unit.

Logistic regression analysis

In the unadjusted model, dipstick proteinuria $\geq 2+$ was associated with higher odds of the composite adverse neonatal outcome (OR 1.69, 95% CI 1.03–2.76; $p=0.036$; AUC=0.565). The association remained significant in the primary model adjusted for maternal age, nulliparity, and severe hypertension (adjusted OR 1.74, 95% CI 1.03–2.93; $p=0.037$; AUC=0.658). When gestational age at delivery was added in the sensitivity model, the proteinuria estimate was attenuated and no longer statistically significant (adjusted OR 1.40, 95% CI 0.72–2.71; $p=0.317$), whereas discrimination increased (AUC=0.864). Thus, Model 2 represented the primary adjusted association, while Model 3 described the association after accounting for gestational age at delivery; attenuation in Model 3 is compatible with, but does not establish, an intermediate role of earlier delivery (Table 3).

Table 3. Logistic regression for composite adverse neonatal outcome

Model	N	Proteinuria $\geq 2+$ OR (95% CI)	p value	AUC
Model 1: Unadjusted	260	1.69 (1.03-2.76)	0.036	0.565
Model 2: Adjusted for maternal age, nulliparity, and severe hypertension	260	1.74 (1.03-2.93)	0.037	0.658
Model 3: Model 2 + gestational age at delivery	260	1.40 (0.72-2.71)	0.317	0.864

ORs are for dipstick proteinuria $\geq 2+$ versus $< 2+$ (0/1+). AUC, area under the receiver operating characteristic curve

Discussion

The main finding was that dipstick proteinuria $\geq 2+$ identified a preeclampsia phenotype characterized by greater renal involvement, lower birthweight, and a higher frequency of adverse neonatal outcome, but not by a higher frequency of severe hypertension. Proteinuria $\geq 2+$ increased the adjusted odds of the composite adverse neonatal outcome by approximately 74% after adjustment for maternal age, nulliparity, and severe hypertension. Although maternal age, gravidity, and parity differed statistically between groups, the absolute differences were modest and may have limited clinical relevance; these findings should be viewed as baseline group characteristics rather than clinically meaningful separation. The estimate weakened after gestational age at delivery was included. This attenuation is compatible with the possibility that earlier delivery lies partly on the pathway linking proteinuria to neonatal outcome, but mediation cannot be established from these retrospective observational data.

The renal findings are biologically plausible. Glomerular endotheliosis and imbalance between angiogenic and antiangiogenic pathways increase glomerular permeability in preeclampsia.^{3,14} Accordingly, women with dipstick proteinuria $\geq 2+$ in our cohort had higher BUN and creatinine and lower eGFR. However, the absence of differences in severe hypertension or composite adverse maternal outcome supports modern diagnostic frameworks, which emphasize multisystem findings rather than proteinuria alone.^{1,6}

Our neonatal findings are consistent with the PIERS proteinuria analysis, threshold-based studies, and a recent large Brazilian cohort reporting lower birthweight, more prematurity, and greater neonatal intensive care use among women with greater proteinuria.^{7,9,10,15} By contrast, meta-analytic evidence in-

icates that neither dipstick nor quantified proteinuria has sufficient stand-alone prognostic accuracy.^{6,12,13} Accordingly, the magnitude of dipstick proteinuria should not be used alone to classify severe preeclampsia or determine timing of delivery; clinical decisions should integrate maternal symptoms, blood pressure, laboratory abnormalities, gestational age, and fetal status.

The sequential regression models help explain this distinction. Dipstick proteinuria $\geq 2+$ remained associated with adverse neonatal outcome after adjustment for maternal age, nulliparity, and severe hypertension, but not after gestational age at delivery was added. Gestational age may be a confounder, an intermediate variable, or both, depending on whether the degree of proteinuria influenced clinical timing of delivery.¹⁶ Therefore, Model 2 describes the primary adjusted clinical association, whereas Model 3 describes the association after accounting for gestational age. The observed attenuation is compatible with confounding, clinical decision-making, an intermediate role of earlier delivery, or a combination of these mechanisms and should not be interpreted as proof of mediation. Neither model establishes causality.

Strengths and limitations

Strengths include comparison within a defined preeclampsia cohort, complete data for the regression variables, explicit sequential modeling, and evaluation of discrimination and calibration. Limitations include the retrospective single-center design, use of a semiquantitative dipstick threshold rather than quantitative protein assessment. Although $\geq 2+$ was selected in accordance with guidance for situations in which quantitative testing is unavailable or rapid decisions are required, dipstick testing has limited diagnostic accuracy and may be affected by urine concentration.^{1,2} In several urgent presentations with uncontrolled hypertension, delivery or immediate management occurred before a complete and verifiable 24-hour urine collection could be obtained. The absence of consistently available 24-hour urinary protein or protein-to-creatinine ratio measurements precluded evaluation of a quantitative dose-response relationship and may have introduced exposure misclassification. In addition, the composite neonatal endpoint combined outcomes of different clinical severity and included several gestational-age-dependent components; this heterogeneity may obscure component-specific associations. The number of ad-

verse maternal events was small, precluding a stable multivariable maternal model. Multiple univariable comparisons were exploratory and not multiplicity-adjusted. Finally, external validation is required before the regression model can be used clinically.^{17, 18}

Conclusion

Among women with preeclampsia, dipstick proteinuria $\geq 2+$ was associated with renal biochemical abnormalities, lower birthweight, and approximately 74% higher adjusted odds of a composite adverse neonatal outcome, but not with severe hypertension or adverse maternal outcome. The neonatal association was attenuated after gestational age at delivery was considered. Dipstick proteinuria $\geq 2+$ should therefore be interpreted as one component of a broader maternal-fetal assessment, not as an isolated measure of severity or prognosis, and should not alone determine classification of severe preeclampsia or timing of delivery.

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RESEARCH ARTICLE

Predictive Value of a $\geq 50\%$ Decrease in Total Serum Bile Acids After Ursodeoxycholic Acid Treatment for Perinatal Outcomes in Intrahepatic Cholestasis of Pregnancy: A Retrospective Cohort Study

Resat Misirlioglu,¹ Ali Cetin¹

¹Division of Perinatology, Department of Obstetrics and Gynecology, Haseki Training and Research Hospital, University of Health Sciences, Istanbul, Türkiye

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ORCID IDs of the authors:

RM : 0009-0002-7221-0042
AC : 0000-0002-5767-7894

Abstract

Introduction: In intrahepatic cholestasis of pregnancy (ICP), risk assessment rests on bile acid concentrations measured at diagnosis or at their peak. We asked whether a prespecified $\geq 50\%$ decrease in total serum bile acids (TSBA) after ursodeoxycholic acid (UDCA) treatment predicts adverse perinatal outcomes.

Methods: We retrospectively studied 200 singleton pregnancies with ICP (TSBA ≥ 19 $\mu\text{mol/L}$) treated with UDCA between January 2020 and January 2026. Women with a $\geq 50\%$ decrease in TSBA at follow-up were classified as biochemical responders (n=135); the remainder were non-responders (n=65). The primary outcome was a composite of preterm birth, meconium-stained amniotic fluid, fetal distress, neonatal intensive care unit admission, or stillbirth. Logistic regression was adjusted for maternal age, body mass index, gestational age at diagnosis, and baseline TSBA.

Results: The composite outcome occurred in 49.6% of responders and 69.2% of non-responders (adjusted odds ratio [aOR] 0.41, 95% confidence interval [CI] 0.21-0.80, p=0.009). The percentage decrease in TSBA discriminated the composite outcome better than baseline (area under the curve 0.613 versus 0.523) or peak TSBA (0.537, p<0.001). The group difference was confined to iatrogenic preterm birth (9.6% versus 29.2%, p<0.001); spontaneous preterm birth was similar, and a composite excluding iatrogenic preterm birth showed no association (aOR 0.87, p=0.659).

Conclusion: The biochemical response to UDCA carries prognostic information beyond static bile acid values, but the association operates mainly through iatrogenic preterm delivery. Response assessment may support surveillance and counseling; it should not by itself trigger intervention.

Correspondence Address: Ugur Mumcu District No 7 34265 Istanbul - Türkiye
Phone: +90 537 431 24 11 / **e-mail:** dr.rstmsrl.34@gmail.com

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Introduction

Intrahepatic cholestasis of pregnancy (ICP) is the most common liver disease specific to pregnancy. It usually presents in the second or third trimester with maternal pruritus and a rise in total serum bile acids (TSBA).^{1,2} The maternal course is usually favorable, and symptoms resolve after delivery. For the fetus, ICP has been associated with spontaneous and iatrogenic preterm birth, meconium-stained amniotic fluid, neonatal unit admission, and stillbirth.^{3,4} In an individual participant data meta-analysis of 5269 women, the risk of stillbirth in singleton pregnancies rose steeply only at peak TSBA concentrations of 100 $\mu\text{mol/L}$ or more, and peak TSBA discriminated stillbirth well whereas transaminases did not.³ Current guidance therefore anchors delivery timing to peak TSBA.^{2,3}

Ursodeoxycholic acid (UDCA) is the drug most women with ICP receive, and it improves pruritus and biochemistry in the majority.^{2,5} What it does for the fetus is less clear. In the placebo-controlled PITCHES trial, UDCA did not reduce the primary composite of perinatal death, preterm delivery, or neonatal unit admission.⁶ An individual participant data meta-analysis later suggested a possible reduction in spontaneous preterm birth, mainly in randomized studies.⁷ How to reconcile these findings is still debated, and heterogeneity of the biochemical response to treatment is one proposed explanation.⁸

Risk assessment in practice remains static: it uses the TSBA value at diagnosis or the peak value, not the trajectory under treatment.^{2,8} Whether the response to UDCA adds prognostic information is largely untested. In a prospective Indian cohort, TSBA fell by a mean of 45.6% after UDCA, but no threshold for this change was validated against outcomes.⁹ In twin pregnancies with ICP, adding dynamic TSBA monitoring and treatment-response information improved the prediction of preterm birth.¹⁰ A decrease of at least 50% has served as a response definition in severe, treatment-refractory ICP.¹¹ Its predictive value for perinatal outcomes in singleton pregnancies is unknown.

We therefore examined whether a prespecified $\geq 50\%$ decrease in TSBA after UDCA treatment predicts adverse perinatal outcomes in women with ICP, and we compared this dynamic measure with baseline and peak TSBA. Our hypothesis was that biochemical responders would have a lower risk of the composite adverse perinatal outcome than non-responders, independent of baseline severity.

Material and Methods

Study design and setting

This retrospective cohort study was conducted in the Perinatology Unit of the Department of Obstetrics and Gynecology, Haseki Training and Research Hospital, Istanbul, Türkiye. We reviewed the records of women diagnosed with ICP between January 1, 2020, and January 1, 2026. The Ethics Committee for Non-Interventional Clinical Research of Haseki Training and Research Hospital approved the study protocol (decision number: 128-2026; date: May 13, 2026), and the study was performed in accordance with the Declaration of Helsinki. Because the design was retrospective and based on anonymized records, the committee waived the requirement for individual informed consent. Reporting follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations for cohort studies.

Participants

Eligible women were 18–45 years old, carried a singleton pregnancy, and had a confirmed diagnosis of ICP, defined as maternal pruritus with a TSBA concentration of $\geq 19 \mu\text{mol/L}$.¹² This cutoff is the pregnancy-specific upper reference limit for non-fasting TSBA derived from a large case-control study and was preferred to the historical fasting-based threshold of 10 $\mu\text{mol/L}$.¹² TSBA was measured in the non-fasting state, without a standardized fasting requirement, so the non-fasting threshold was considered the appropriate diagnostic criterion. All had started UDCA at diagnosis, had paired pretreatment and post-treatment TSBA measurements, and delivered at our center with complete perinatal follow-up data. Exclusion criteria were multiple gestation; preeclampsia, eclampsia, or gestational hypertension; pregestational or gestational diabetes mellitus; viral hepatitis or chronic liver disease; HELLP syndrome or acute fatty liver of pregnancy; cholelithiasis or other structural hepatobiliary disease; major fetal structural or chromosomal abnormality; preterm premature rupture of membranes; and missing bile acid measurements. Figure 1 shows the selection of the cohort. Hepatobiliary ultrasonography was not used to diagnose ICP; its role was to exclude gallstones, bile duct dilatation, and other structural hepatobiliary disease, and women with such findings were excluded.

Figure 1

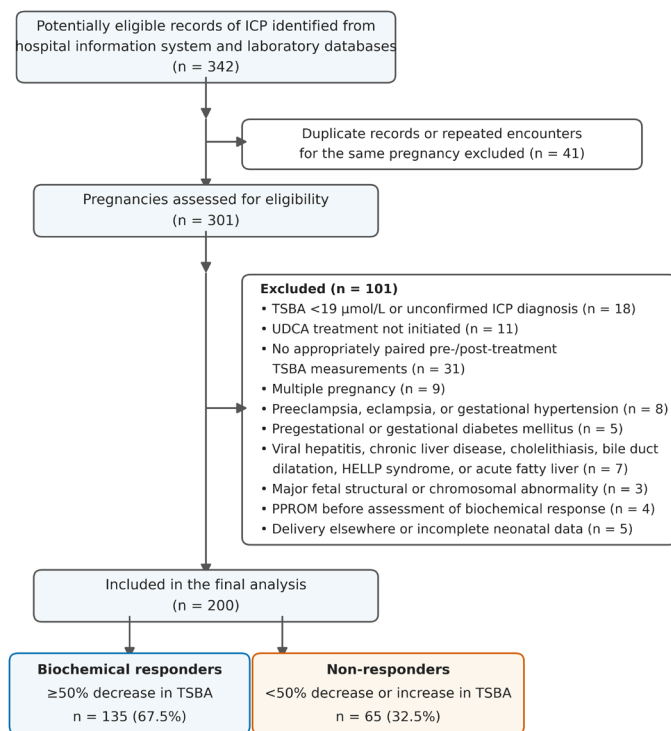


Figure 1. Flow diagram of study population selection. ICP, intrahepatic cholestasis of pregnancy; TSBA, total serum bile acids; UDCA, ursodeoxycholic acid; PPROM, preterm prelabor rupture of membranes.

Data collection

Data came from the hospital information management system, laboratory records, perinatology follow-up charts, delivery records, and neonatal files, abstracted onto a standardized case report form. We recorded maternal age, body mass index (BMI), gravidity, parity, smoking, ICP in a previous pregnancy, gestational age at diagnosis, pruritus intensity (0-10 numeric rating scale), baseline, post-treatment, and peak TSBA, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), total bilirubin, daily UDCA dose, the interval to the follow-up TSBA measurement, mode and onset of delivery, gestational age at delivery, birth weight, 1- and 5-minute Apgar scores, meconium-stained amniotic fluid, fetal distress, neonatal intensive care unit (NICU) admission and length of stay, and stillbirth. All data were anonymized before analysis.

Exposure definition and treatment

UDCA was started at diagnosis at an approximate dose of 10-15 mg/kg/day, administered orally in two or three divided doses. The usual starting dose was 500-1000 mg/day according to maternal weight,

and the dose was up-titrated at follow-up visits according to pruritus severity and the TSBA response, to a maximum of 1500 mg/day (recorded daily doses, 500-1500 mg). The biochemical response was the percentage change in TSBA, calculated as $(\text{baseline TSBA} - \text{post-treatment TSBA}) / \text{baseline TSBA} \times 100$. The follow-up measurement was obtained a median of 14 days (range 7-21 days) after treatment initiation. Women with a decrease of $\geq 50\%$ from baseline formed the responder group; women with a smaller decrease, or an increase, formed the non-responder group. The 50% threshold was prespecified in the study protocol. Peak TSBA was the highest concentration recorded during pregnancy, and disease severity was categorized by peak TSBA as mild ($<40 \mu\text{mol/L}$), moderate ($40\text{--}99.9 \mu\text{mol/L}$), or severe ($\geq 100 \mu\text{mol/L}$), in line with the risk thresholds identified in the individual participant data meta-analysis.³ During the study period, the timing of delivery followed a severity-stratified institutional approach informed by contemporary guidance:² delivery was planned at approximately 36 weeks of gestation for women with peak TSBA $\geq 100 \mu\text{mol/L}$, at 37-38 weeks for peak TSBA of $40\text{--}99.9 \mu\text{mol/L}$, and at 38-39 weeks for milder disease, with earlier delivery at the discretion of the treating clinicians for refractory pruritus, persistently rising TSBA despite treatment, or nonreassuring fetal status. Delivery decisions were therefore informed by bile acid concentrations, maternal symptoms, and the biochemical response, and were not blinded to them.

Outcomes

The primary outcome was a composite adverse perinatal outcome: at least one of preterm birth (<37 weeks), meconium-stained amniotic fluid, fetal distress (nonreassuring fetal heart rate patterns requiring obstetric intervention), NICU admission, or stillbirth. Secondary outcomes were the individual components, spontaneous and iatrogenic preterm birth analyzed separately, Apgar scores, birth weight, gestational age at delivery, and NICU length of stay. Because delivery timing may itself depend on the biochemical response, we prespecified a sensitivity analysis using an alternative composite that excluded iatrogenic preterm birth.

Statistical analysis

Analyses were performed with IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). Distributions were checked with the Shap-

iro-Wilk test. Normally distributed variables are reported as mean $\pm$ standard deviation and compared with the independent-samples *t* test; the others are reported as median (interquartile range [IQR]) and compared with the Mann-Whitney *U* test. Categorical variables are numbers (percentages), compared with the chi-square or Fisher exact test, with unadjusted odds ratios (ORs) and 95% confidence intervals (CIs) for perinatal outcomes. Multivariable binary logistic regression estimated the association between biochemical response and the composite outcome, with maternal age, BMI, gestational age at diagnosis, and baseline TSBA (per 10 $\mu\text{mol/L}$) as prespecified covariates. Gestational age at delivery lies on the causal pathway and was not entered into the models. Calibration was assessed with the Hosmer-Lemeshow test and collinearity with variance inflation factors. The percentage decrease in TSBA was also modeled continuously (per 10 percentage points), with a quadratic term to test linearity, and its incremental value was assessed with the likelihood ratio test and by comparing the areas under the receiver operating characteristic curves (AUCs) of nested models. AUCs of competing bile acid indices were compared with the DeLong method, the optimal cutoff was identified with the Youden index, and the diagnostic indices of the 50% threshold were calculated with 95% Wilson CIs. Subgroup analyses stratified by peak TSBA severity were prespecified, with a likelihood ratio test for interaction. Analyses used complete cases; missing data did not exceed 6% for any variable. Two-tailed *p* values below 0.05 were considered statistically significant; exact *p* values are reported.

Results

Study population

During the study period, 342 potentially eligible records were identified. After removal of 41 duplicate records, 301 pregnancies were assessed for eligibility and 101 were excluded; the reasons are detailed in Figure 1. The most frequent were missing paired TSBA measurements (*n*=31), TSBA <19 $\mu\text{mol/L}$ or an unconfirmed diagnosis (*n*=18), and UDCA not having been started (*n*=11). The final cohort comprised 200 women. Mean maternal age was 29.71 ± 5.34 years, mean BMI was 27.64 ± 4.68 kg/m², and the median gestational age at diagnosis was 33.75 (IQR 31.60-35.50) weeks. The median baseline TSBA was 33.35 (IQR 27.18-55.48) $\mu\text{mol/L}$. After a median interval of 14.00 (IQR 10.00-18.00) days, the

median decrease in TSBA was 65.00% (IQR 45.58-80.17%; range -1.20% to 95.30%); TSBA rose despite treatment in one woman. In total, 135 women (67.5%) reached a $\geq 50\%$ decrease and formed the responder group; 65 (32.5%) were non-responders. No stillbirth occurred, so this component of the composite outcome was not assessable.

Baseline, biochemical, and treatment characteristics

The groups were comparable for age, BMI, gravidity, parity, smoking, previous ICP, gestational age at diagnosis, and pruritus score (Table 1). Non-responders had higher baseline TSBA (median 41.60 versus 31.70 $\mu\text{mol/L}$, *p*=0.004), peak TSBA (42.80 versus 33.50 $\mu\text{mol/L}$, *p*=0.002), ALT (63.50 versus 53.80 U/L, *p*=0.023), and total bilirubin (0.77 versus 0.67 mg/dL, *p*=0.002), and severe disease was more frequent among them (16.9% versus 6.7%; overall severity distribution, $\chi^2=5.995$, *p*=0.050) (Table 2). UDCA dose and the interval to the follow-up measurement did not differ.

Table 1. Baseline maternal and clinical characteristics according to biochemical response to ursodeoxycholic acid

Characteristic	Responders ($\geq 50\%$ decrease) (<i>n</i> =135)	Non-responders (<50% decrease) (<i>n</i> =65)	<i>p</i> value
Maternal age, years, mean $\pm$ SD	29.86 $\pm$ 5.33	29.40 $\pm$ 5.39	0.570
Body mass index, kg/m ² , mean $\pm$ SD*	27.78 $\pm$ 4.49	27.35 $\pm$ 5.07	0.545
Gravidity, median (IQR)	2.00 (1.00-3.00)	2.00 (1.00-3.00)	0.469
Parity, median (IQR)	0.00 (0.00-1.00)	0.00 (0.00-1.00)	0.813
Nulliparity, <i>n</i> (%)	86 (63.7)	40 (61.5)	0.766
Smoking, <i>n</i> (%)	8 (5.9)	3 (4.6)	1.000
ICP in a previous pregnancy, <i>n</i> (%)	6 (4.4)	7 (10.8)	0.124
Gestational age at diagnosis, weeks, median (IQR)	33.50 (31.10-35.70)	34.00 (31.90-35.40)	0.403
Pruritus intensity score (0-10), median (IQR)†	5.00 (4.00-6.00)	5.00 (4.00-6.00)	0.118

SD, standard deviation; IQR, interquartile range; ICP, intrahepatic cholestasis of pregnancy. *Missing in 7 women. †Missing in 12 women. Independent-samples *t* test, Mann-Whitney *U* test, chi-square test, or Fisher exact test, as appropriate.

Table 2. Biochemical and treatment characteristics according to biochemical response to ursodeoxycholic acid

Variable	Responders (n=135)	Non-responders (n=65)	p value
Baseline TSBA, $\mu\text{mol/L}$, median (IQR)	31.70 (25.60-48.15)	41.60 (29.10-80.90)	0.004
Post-treatment TSBA, $\mu\text{mol/L}$, median (IQR)	7.90 (5.05-11.50)	30.90 (17.70-46.10)	<0.001
Peak TSBA, $\mu\text{mol/L}$, median (IQR)	33.50 (28.45-50.10)	42.80 (31.50-84.00)	0.002
Decrease in TSBA, %, median (IQR)	75.70 (64.80-85.75)	38.10 (25.80-45.20)	<0.001
Peak TSBA severity, n (%)			0.050
Mild (<40 $\mu\text{mol/L}$)	84 (62.2)	32 (49.2)	
Moderate (40-99.9 $\mu\text{mol/L}$)	42 (31.1)	22 (33.8)	
Severe (≥ 100 $\mu\text{mol/L}$)	9 (6.7)	11 (16.9)	
AST, U/L, median (IQR)	46.70 (39.00-59.95)	52.40 (42.40-62.30)	0.092
ALT, U/L, median (IQR)	53.80 (46.05-63.25)	63.50 (47.50-78.80)	0.023
GGT, U/L, median (IQR)*	22.60 (18.50-27.40)	23.10 (19.12-28.88)	0.455
Total bilirubin, mg/dL, median (IQR)†	0.67 (0.60-0.81)	0.77 (0.66-0.92)	0.002
Daily UDCA dose, mg, median (IQR)	1000.00 (1000.00-1250.00)	1000.00 (1000.00-1250.00)	0.791
Interval to follow-up TSBA, days, median (IQR)	14.00 (10.00-18.00)	14.00 (10.00-17.00)	0.863

TSBA, total serum bile acids; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; UDCA, ursodeoxycholic acid; IQR, interquartile range. *Missing in 11 women. †Missing in 9 women. Severity distribution compared with the chi-square test ($\chi^2=5.995$).

Perinatal outcomes

Table 3 and Figure 2 summarize the perinatal outcomes. The composite adverse outcome occurred in 67 of 135 responders (49.6%) and 45 of 65 non-responders (69.2%) (OR 0.44, 95% CI 0.23-0.82; $\chi^2=6.841$, $p=0.009$). Preterm birth was less frequent among responders (17.8% versus 38.5%; OR 0.35, 95% CI 0.18-0.67; $\chi^2=10.148$, $p=0.001$). Disaggregated by onset, the difference lay entirely in iatrogenic preterm birth (9.6% versus 29.2%; OR 0.26, 95% CI 0.12-0.56; $\chi^2=12.542$, $p<0.001$). Spontaneous preterm birth did not differ (8.1% versus 9.2%, $p=0.797$). Neither did meconium-stained amniotic fluid (10.4% versus 15.4%, $p=0.307$), fetal distress (17.8% versus 20.0%, $p=0.705$), NICU admission (17.8% versus 18.5%, $p=0.906$), or cesarean delivery (51.9%

versus 47.7%, $p=0.582$). Responders delivered later (median 38.10 versus 37.40 weeks, $p=0.040$) and had heavier newborns (median 3211.10 versus 3010.30 g, $p=0.030$). The 5-minute Apgar score differed statistically ($p=0.031$) with identical medians (9.00 [IQR 9.00-10.00] versus 9.00 [IQR 9.00-9.00]), and no infant had a 5-minute Apgar score below 7. Among admitted neonates, NICU stay was similar (median 5.50 versus 5.00 days, $p=0.598$).

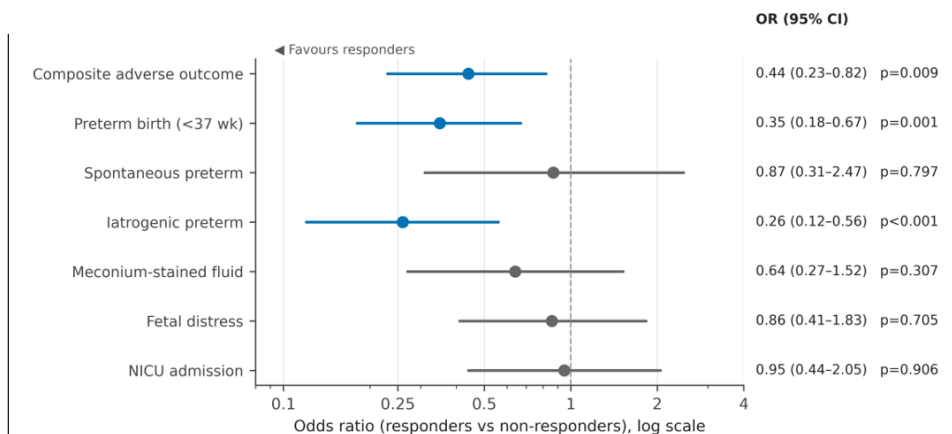
Table 3. Perinatal outcomes according to biochemical response to ursodeoxycholic acid

Outcome	Responders (n=135)	Non-responders (n=65)	OR (95% CI)	p value
Composite adverse perinatal outcome, n (%)	67 (49.6)	45 (69.2)	0.44 (0.23-0.82)	0.009
Preterm birth (<37 weeks), n (%)	24 (17.8)	25 (38.5)	0.35 (0.18-0.67)	0.001
Spontaneous preterm birth, n (%)	11 (8.1)	6 (9.2)	0.87 (0.31-2.47)	0.797
Iatrogenic preterm birth, n (%)	13 (9.6)	19 (29.2)	0.26 (0.12-0.56)	<0.001
Meconium-stained amniotic fluid, n (%)	14 (10.4)	10 (15.4)	0.64 (0.27-1.52)	0.307
Fetal distress, n (%)	24 (17.8)	13 (20.0)	0.86 (0.41-1.83)	0.705
NICU admission, n (%)	24 (17.8)	12 (18.5)	0.95 (0.44-2.05)	0.906
Stillbirth, n (%)	0 (0.0)	0 (0.0)	NA	NA
Cesarean delivery, n (%)	70 (51.9)	31 (47.7)	—	0.582
Gestational age at delivery, weeks, median (IQR)	38.10 (37.40-38.75)	37.40 (34.80-38.90)	—	0.040
Birth weight, g, median (IQR)*	3211.10 (2817.00-3487.40)	3010.30 (2623.10-3332.50)	—	0.030
1-minute Apgar score, median (IQR)†	8.00 (8.00-9.00)	8.00 (8.00-8.25)	—	0.148
5-minute Apgar score, median (IQR)‡	9.00 (9.00-10.00)	9.00 (9.00-9.00)	—	0.031
NICU length of stay, days, median (IQR)§	5.50 (4.00-8.00)	5.00 (4.00-8.25)	—	0.598

OR, odds ratio; CI, confidence interval; NICU, neonatal intensive care unit; IQR, interquartile range; NA, not assessable (no events). The composite comprised preterm birth, meconium-stained amniotic fluid, fetal distress, NICU admission, or stillbirth. *Missing in 2 neonates. †Missing in 3 neonates. ‡Missing in 2 neonates; no infant had a 5-minute Apgar score <7. §Among admitted neonates only (24 responders, 12 non-responders).

Figure 2

Figure 2. Unadjusted odds ratios (95% confidence intervals) for perinatal outcomes in biochemical responders ($\geq 50\%$ decrease in TSBA) versus non-responders. Estimates to the left of unity favor responders; the x-axis is logarithmic. NICU, neonatal intensive care unit.



Multivariable analysis

After adjustment for maternal age, BMI, gestational age at diagnosis, and baseline TSBA, a $\geq 50\%$ decrease in TSBA remained associated with lower odds of the composite outcome (adjusted odds ratio [aOR] 0.41, 95% CI 0.21-0.80, $p=0.009$) (Table 4). Later diagnosis was also associated with lower odds (aOR per week 0.89, 95% CI 0.79-0.99, $p=0.036$); baseline TSBA was not (aOR per 10 $\mu\text{mol/L}$ 1.03, 95% CI 0.94-1.13, $p=0.548$). Calibration was adequate (Hosmer-Lemeshow $\chi^2=4.97$, $p=0.761$) and all variance inflation factors were below 1.1. For preterm birth, the adjusted estimate was similar (aOR 0.35, 95% CI 0.17-0.72, $p=0.004$). Modeled continuously, each 10-percentage-point decrease in TSBA lowered the adjusted odds of the composite outcome by 19% (aOR 0.81, 95% CI 0.70-0.94, $p=0.005$), with no departure from linearity (quadratic term, $p=0.542$). Adding the response variable to the covariate-only model improved fit (likelihood ratio $\chi^2=7.09$, $p=0.008$) and raised the model AUC from 0.601 to 0.654.

Table 4. Multivariable logistic regression analyses of the association between biochemical response and adverse perinatal outcomes (n=193 complete cases)

Model / variable	aOR (95% CI)	p value
Model 1: composite adverse perinatal outcome (primary)		
$\geq 50\%$ decrease in TSBA (vs <50%)	0.41 (0.21-0.80)	0.009
Baseline TSBA, per 10 $\mu\text{mol/L}$	1.03 (0.94-1.13)	0.548
Gestational age at diagnosis, per week	0.89 (0.79-0.99)	0.036
Maternal age, per year	0.98 (0.93-1.03)	0.435
Body mass index, per kg/m^2	1.05 (0.98-1.11)	0.179
Model 2: preterm birth		
$\geq 50\%$ decrease in TSBA (vs <50%)	0.35 (0.17-0.72)	0.004
Model 3: composite outcome, TSBA decrease as continuous exposure		
Decrease in TSBA, per 10 percentage points	0.81 (0.70-0.94)	0.005
Model 4: sensitivity composite excluding iatrogenic preterm birth		
$\geq 50\%$ decrease in TSBA (vs <50%)	0.87 (0.46-1.63)	0.659

aOR, adjusted odds ratio; CI, confidence interval; TSBA, total serum bile acids. All models adjusted for maternal age, body mass index, gestational age at diagnosis, and baseline TSBA; Models 2-4 report the estimate for the exposure of interest. Gestational age at delivery was not entered as a covariate because it lies on the causal pathway. Model 1: Hosmer-Lemeshow $\chi^2=4.97$, $p=0.761$; all variance inflation factors <1.1; likelihood ratio test for adding biochemical response, $\chi^2=7.09$, $p=0.008$.

Predictive performance

Table 5 and Figure 3 present the discrimination analyses. The percentage decrease in TSBA yielded an AUC of 0.613 (95% CI 0.535-0.690) for the composite outcome, higher than baseline TSBA (0.523, 95% CI 0.441-0.604), peak TSBA (0.537, 95% CI 0.455-0.618), and post-treatment TSBA (0.583, 95% CI 0.504-0.662) (DeLong $p<0.001$ for each comparison). Figure 4 shows the distribution of the percentage decrease by outcome status. The Youden index identified an optimal cutoff at a 39.9% decrease (specificity 93.2%, sensitivity 29.5%). At the prespecified 50% threshold, a decrease below 50% predicted the composite outcome with a sensitivity of 40.2% (95% CI 31.6-49.4%), a specificity of 77.3% (95% CI 67.5-84.8%), a positive predictive value of 69.2% (95% CI 57.2-79.1%), and a negative predictive value of 50.4% (95% CI 42.0-58.7%). For preterm birth, the AUC was 0.633 (95% CI 0.542-0.725), and the threshold had a sensitivity of 51.0%, a specificity of 73.5%, and a negative predictive value of 82.2%.

Figure 3

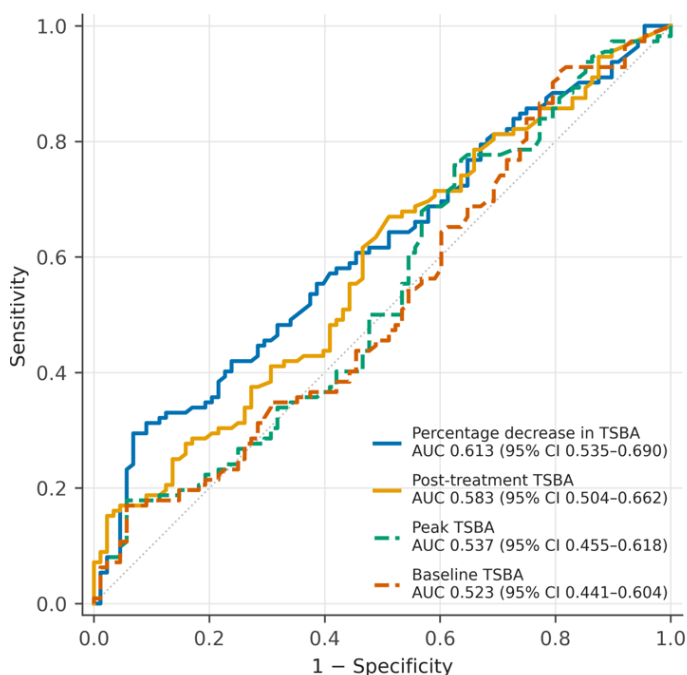


Figure 3. Receiver operating characteristic curves of the percentage decrease in TSBA, post-treatment TSBA, peak TSBA, and baseline TSBA for the prediction of the composite adverse perinatal outcome. AUC, area under the curve; CI, confidence interval.

Figure 4

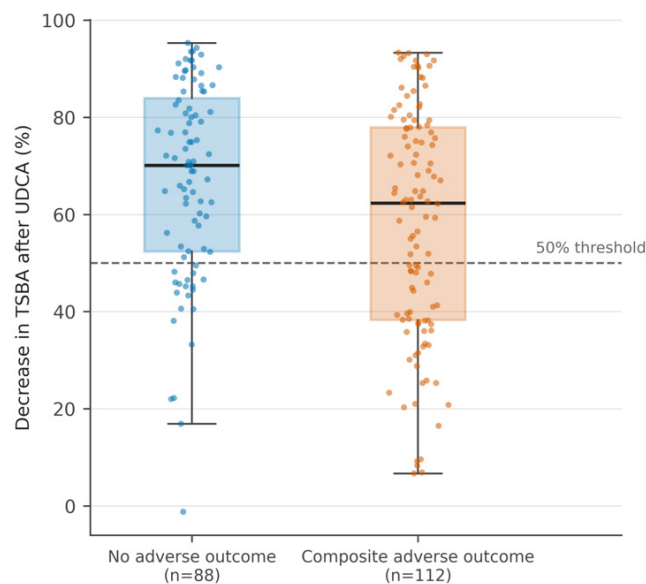


Figure 4. Distribution of the percentage decrease in TSBA after UDCA treatment according to the occurrence of the composite adverse perinatal outcome. Boxes show medians and interquartile ranges; whiskers extend to $1.5 \times$ IQR; points are individual women. The dashed line marks the prespecified 50% threshold.

Table 5. Discriminatory performance of bile acid indices for the composite adverse perinatal outcome

Index	AUC (95% CI)	DeLong p vs percentage decrease
Percentage decrease in TSBA	0.613 (0.535-0.690)	—
Post-treatment TSBA	0.583 (0.504-0.662)	<0.001
Peak TSBA	0.537 (0.455-0.618)	<0.001
Baseline TSBA	0.523 (0.441-0.604)	<0.001

AUC, area under the receiver operating characteristic curve; CI, confidence interval; TSBA, total serum bile acids. Youden-optimal cutoff for the percentage decrease: 39.9% (sensitivity 29.5%, specificity 93.2%). Prespecified <50% decrease threshold for the composite outcome: sensitivity 40.2% (95% CI 31.6-49.4%), specificity 77.3% (95% CI 67.5-84.8%), positive predictive value 69.2% (95% CI 57.2-79.1%), negative predictive value 50.4% (95% CI 42.0-58.7%).

Stratified and sensitivity analyses

Within severity strata, the composite outcome was less frequent among responders with moderate disease (35.7% versus 68.2%, $p=0.018$) but not with mild (56.0% versus 62.5%, $p=0.674$) or severe disease (55.6% versus 90.9%, $p=0.127$); the interaction was not significant ($\chi^2=4.50$, $p=0.106$). In the prespecified sensitivity analysis excluding iatrogenic preterm birth from the composite, the association disappeared (43.0% versus 46.2%; OR 0.88, 95% CI 0.48-1.59, $p=0.670$; aOR 0.87, 95% CI 0.46-1.63, $p=0.659$). The association between biochemical response and the primary composite was therefore attributable largely to its iatrogenic preterm birth component.

Discussion

In this cohort of 200 singleton pregnancies with ICP, women who reached a prespecified $\geq 50\%$ decrease in TSBA after UDCA had lower odds of the composite adverse perinatal outcome, before and after adjustment for baseline severity (aOR 0.41). The percentage decrease behaved as a continuous, approximately log-linear predictor and separated the composite outcome better than baseline, peak, or post-treatment TSBA, although its absolute discrimination was modest. One finding qualifies all the others: the association was carried almost entirely by iatrogenic preterm birth and disappeared once iatrogenic preterm birth was excluded from the composite.

Bile acid values inform delivery decisions, and clinicians whose patients remain biochemically refractory tend to deliver earlier, in line with severity-stratified guidance.² A persistent non-response will then produce more iatrogenic preterm birth even if the biochemical change itself confers no fetal benefit. The same dynamic followed the adoption of active management strategies for ICP, which lowered stillbirth at the cost of more iatrogenic prematurity, and delivery-timing policy has been tested in a randomized design.^{13,14} We therefore do not read our data as evidence that a $\geq 50\%$ decrease protects the fetus. The response behaves as a process indicator, entangled with delivery-timing decisions, and its clinical meaning may lie mostly in marking women likely to follow a lower-intervention pathway.

The management-independent outcomes support this reading. Spontaneous preterm birth, meconium-stained amniotic fluid, fetal distress, and NICU admission were all similar between groups. PITCHES reported improved biochemistry without improved perinatal outcomes, and its secondary analysis found no subgroup with clear benefit.^{6,15} The individual participant data meta-analysis confined any possible benefit of UDCA to spontaneous preterm birth, with uncertain magnitude.⁷ Observational cohorts, in contrast, have repeatedly tied higher bile acids to preterm delivery and adverse outcomes, and our non-responders did have higher baseline and peak TSBA.^{3,16,17} The adjusted estimate suggests the response variable carries information beyond baseline severity; the sensitivity analysis shows that this information surfaces clinically through delivery decisions rather than through measurable fetal compromise.

Peak TSBA keeps its central place in risk stratification for stillbirth, and nothing here challenges it; our cohort had no stillbirths, so the gravest outcome of ICP was not assessable.^{2,3} For the broader morbidity composite, however, the dynamic measure discriminated better than either static value, and adding it improved a covariate-based model.

The biochemical efficacy we observed, a $\geq 50\%$ decrease in 67.5% of women, is consistent with randomized trials in which UDCA lowered bile acids more effectively than comparators, and with the mean 45.6% decrease reported prospectively.^{9,18,19} The 50% definition itself has precedent: in severe UDCA-refractory ICP, a $\geq 50\%$ fall defined the biochemical response to added rifampicin and occurred in 38% of treated women.¹¹ Our study provides, to our knowl-

edge, the first formal test of this threshold against perinatal outcomes in singleton ICP. The empirically optimal cutoff, a decrease of about 40%, fell close to the prespecified 50%. Even so, its diagnostic indices were modest (sensitivity 40.2%, specificity 77.3% for the composite), and its most useful property was a negative predictive value of 82.2% for preterm birth. A strong response can offer reassurance. A weak response, on its own, is not grounds for intervention.

This study has strengths. The threshold was prespecified rather than data-derived, and the exposure was also analyzed continuously with a formal linearity check. The analysis respected the causal structure: gestational age at delivery was treated as a mediator and left out of the models, spontaneous and iatrogenic preterm birth were separated, and the sensitivity composite was reported in full, an approach shaped by the recognized circularity risk when delivery decisions depend on the biomarker under study. Outcome selection was aligned with the core outcome set for ICP research.²⁰

Most limitations are inherent to the design. Retrospective, single-center data carry residual confounding, above all confounding by indication, because delivery decisions were left to the treating clinicians; this mechanism plausibly explains much of the observed association. The absence of stillbirth leaves the study uninformative for the outcome that dominates counseling in severe ICP.³ Umbilical cord arterial pH, part of the core outcome set, was unavailable.²⁰ The response rested on a single follow-up measurement taken 7 to 21 days after treatment started, without standardized fasting status or assay conditions, so some response misclassification is possible. The model was not validated externally, and the secondary analyses were exploratory, without correction for multiplicity.

Conclusion

A $\geq 50\%$ decrease in TSBA after UDCA identifies women with ICP at lower risk of a composite adverse perinatal outcome, and the dynamic response adds prognostic information beyond baseline and peak bile acid values. The association operates mainly through iatrogenic preterm delivery and reflects management decisions rather than demonstrated fetal benefit. Response assessment may provide additional information for surveillance and counseling, but should not currently be used independently to determine delivery timing. Prospective multicenter

studies with protocolized delivery criteria, standardized serial TSBA measurement, and core outcome set endpoints are needed before treatment response can guide management.

Ethical Approval

The study protocol was approved by the Ethics Committee for Non-Interventional Clinical Research of Haseki Training and Research Hospital (decision number: 128-2026; date: May 13, 2026). The study was conducted in accordance with the Declaration of Helsinki, and the requirement for individual informed consent was waived owing to the retrospective design.

Conflict of Interest and Funding

The authors declare that there is no conflict of interest. This research received no financial support from any funding agency in the public, commercial, or not-for-profit sectors.

Author Contributions

Concept and design: R.M., A.C. Data collection and processing: R.M. Statistical analysis and interpretation: R.M., A.C. Literature search: R.M. Writing of the manuscript: R.M. Critical review and supervision: A.C. Both authors read and approved the final version of the manuscript.

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CASE REPORT

Primary Pulmonary Mucinous Adenocarcinoma in a Patient with Previous Ovarian Mucinous Adenocarcinoma: A Diagnostic Challenge

Belma Gozde Ozdemir,¹ Cetin Celik¹

¹Obstetrics And Gynecology Department, Selçuk University Faculty Of Medicine, Konya, Türkiye

Abstract

Background/Aim: Primary ovarian mucinous adenocarcinoma and pulmonary mucinous adenocarcinoma are distinct entities; however, their overlapping histopathological and immunohistochemical features may create significant diagnostic challenges, particularly in distinguishing primary tumors from metastatic disease. This case report aims to highlight the diagnostic challenge of distinguishing primary pulmonary mucinous adenocarcinoma from metastatic ovarian mucinous adenocarcinoma and to emphasize the importance of integrating clinical, histopathological, and immunohistochemical findings in the differential diagnosis.

Case: A 49-year-old female patient presented with pain. Her medical history revealed that she underwent fertility-sparing surgery and debulking for a right ovarian mass in 2001, followed by chemotherapy and successful pregnancy via in vitro fertilization. Molecular analysis was negative for EGFR, ROS1, and BRAF mutations. The patient had a history of living in Kahramanmaraş for over 20 years, and environmental exposure included possible dye exposure related to her spouse's occupation. In 2017, lesions were detected in the right upper and lower lobes of the lung. Histopathological examination revealed mucinous adenocarcinoma in both lobes. Immunohistochemically, tumor cells were CK7 and CA125 positive, focally CK20 positive, and negative for TTF-1, Napsin-A, CDX2, PAX8, ER, PR, and p16. The presence of "mucinous adenocarcinoma in situ" areas in both lesions supported the diagnosis of two separate primary lung tumors rather than metastatic disease. Additionally, anthracosis and emphysematous changes were observed in the surrounding lung parenchyma.

Conclusion: Distinguishing between primary and metastatic mucinous tumors requires a comprehensive evaluation of clinical, radiological, histopathological, and immunohistochemical findings. This case highlights the diagnostic complexity of mucinous tumors and underscores the importance of a multidisciplinary approach in accurate tumor classification and management.

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ORCIDs of the authors:

BGO:0000-0002-7025-4087

CC :0000-0001-6165-5092

Correspondence Address: Beyhekim Mahallesi Alanlı Sok Beyhouse Park Sitesi 4 No: 6 Selcuklu Konya 42130 Konya - Türkiye **Phone:** +90 530 936 94 59 / **e-mail:** gzdgrgn35@gmail.com



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Introduction

Mucinous adenocarcinomas represent a heterogeneous group of epithelial malignancies characterized by abundant extracellular mucin production and diverse anatomical origins. Among these, primary ovarian mucinous adenocarcinoma and pulmonary mucinous adenocarcinoma are relatively uncommon but clinically significant entities. Despite arising in distinct organs, these tumors share overlapping histopathological features and, in some cases, similar molecular alterations, which may lead to diagnostic uncertainty, particularly in the context of synchronous lesions or suspected metastatic disease.¹ The differentiation between primary and metastatic mucinous tumors is a well-recognized challenge in oncologic pathology. Ovarian mucinous tumors, for instance, are more frequently metastatic than primary, often originating from gastrointestinal or pancreatobiliary sources. Similarly, pulmonary mucinous adenocarcinoma—previously categorized under invasive mucinous adenocarcinoma—exhibits unique clinicopathological features distinct from conventional lung adenocarcinomas, including frequent KRAS mutations and atypical immunophenotypic profiles.^{2,3} These overlapping characteristics can complicate the identification of the tumor origin when both ovarian and pulmonary lesions are present. The primary aim of this case report is to illustrate the diagnostic challenge of differentiating primary pulmonary mucinous adenocarcinoma from metastatic ovarian mucinous adenocarcinoma in a patient with a previous history of ovarian mucinous carcinoma. By presenting the clinical course, histopathological findings, and immunohistochemical profile of this rare case, we emphasize the importance of a multidisciplinary approach in achieving an accurate diagnosis and guiding appropriate clinical management.

In this study, the patient was initially operated on at Selçuk University Faculty of Medicine, and subsequently underwent pulmonary surgery at the Thoracic Surgery clinic of another center. All clinical data related to the patient were anonymized in this case report, and their identity information was kept completely confidential. The patient provided written informed consent for the use of their clinical and medical data for scientific purposes. This report is a retrospective case report and only includes an evaluation of existing clinical data. No experimental interventions or changes in patient management were

made. Therefore, in accordance with relevant legislation and institutional practices, no additional ethics committee approval is required.

Case

A 49-year-old female patient presented to this clinic with complaints of pain. Her medical history revealed that in 2001, a mass was detected in her right ovary, leading to fertility-preserving surgery and debulking. The patient underwent fertility-sparing surgery and debulking for a right ovarian mass in 2001. Final histopathological examination revealed a right-sided primary mucinous adenocarcinoma of the ovary (Grade 1, FIGO stage IA). The ovarian capsule was intact, there was no ovarian surface involvement or lymphovascular space invasion positive (LVSI), and peritoneal cytology was malign. Following this, she underwent four rounds of chemotherapy and achieved pregnancy via in vitro fertilization (IVF). Following fertility-sparing surgery, the patient received four cycles of platinum-based chemotherapy. After completion of childbearing, completion surgery was performed. Owing to the long interval since the initial treatment, detailed information regarding the specific chemotherapy regimen and the rationale for administering four cycles was not available in the medical records.

Tumor molecular analysis revealed negative results for EGFR, ROS1, and BRAF mutations. In 2017, evaluations revealed lesions in the upper and lower lobes of her right lung. Surgical and pathological examinations confirmed tumor formations consistent with mucinous adenocarcinoma in both lobes. A mass located in the right upper lobe was approximately 6 cm in diameter, showing invasion of the visceral pleura but not exceeding the elastic membrane (PL0). Intraalveolar spread was present, but no significant lymphovascular or perineural invasion was detected. Immunohistochemical examination revealed tumor cells to be positive for CK7 and CA125, focally positive for CK20, while being negative for TTF-1, Napsin-A, CDX2, Vimentin, ER, PR, PAX8, and p16. Widespread mucin positivity was also noted. A second lesion, located in the right lower lobe, was approximately 11 mm in diameter, showed intra-parenchymal localization, and did not exhibit visceral pleural invasion. Intraalveolar spread was present in this lesion as well, but no lymphovascular or perineural invasion was observed. The presence of areas of “mucinous adenocarcinoma in situ” in both tumors

supported the possibility that the lesions were two separate primary lung tumors. Additionally, emphysematous changes in the extratumor lung parenchyma, intraalveolar pigmented macrophages, and minimal anthracosis were observed. Given the patient's history of mucinous adenocarcinoma in the ovary and lung, further evaluation was conducted. The patient had resided in Kahramanmaraş for approximately 21 years and had a history of occupational dye exposure. These environmental factors were recorded as part of the patient's background history but were not considered sufficient to establish a causal relationship with the development of either malignancy. The patient has been followed for 10 years after pulmonary surgery. During this period, no evidence of local recurrence or distant metastasis has been detected on clinical or radiological follow-up. She remains alive and has not required any additional oncological treatment.

Discussion

The co-occurrence of primary ovarian mucinous adenocarcinoma and pulmonary mucinous adenocarcinoma in the same patient, especially when the lesions appear at different times, raises one of the most important diagnostic questions: Is the lesion in the lung an ovarian metastasis or an independent primary lung tumor? This distinction is difficult in mucinous tumors because both tumor groups can exhibit similar morphological patterns, abundant intracytoplasmic or extracellular mucin production, and partially overlapping immunohistochemical features. Ovarian mucinous carcinoma is also a rare subtype of epithelial ovarian cancer, and the primary-metastasis distinction in this subtype is already considered a diagnostic problem in itself.⁴ In this case, the central differential diagnosis is determining whether the lesions detected in the lung are metastatic or multifocal/separate primary pulmonary mucinous adenocarcinoma. Pulmonary invasive mucinous adenocarcinoma is defined as a specific variant of lung adenocarcinoma in current lung tumor classifications; these tumors can frequently exhibit lepidic/intraalveolar spread, display multifocal or pneumonic distribution, and have a different immunophenotype than classic non-mucinous lung adenocarcinomas. Therefore, interpreting a mucinous lesion in the lung solely based on "TTF-1 negativity" as a sign of metastasis is incorrect, as TTF-1 and Napsin A expression is often weak or negative in pulmonary invasive mucinous adenocarcinomas.⁵ The presence of CK7 positivity,

focal CK20 positivity, and TTF-1 and Napsin A negativity in the lung tumors of our case, when considered alone, does not rule out ovarian metastasis; however, it is consistent with pulmonary mucinous adenocarcinoma. The literature indicates that in most invasive mucinous lung adenocarcinomas, CK7 positivity is maintained while TTF-1 and Napsin A are frequently negative, and CK20 and even gastrointestinal markers may be expressed at variable levels in some cases. Therefore, in this tumor group, immunohistochemistry should be interpreted in conjunction with clinical, radiological, and morphological data, rather than as a "single-marker identification of origin".⁶ In the present case, the immunohistochemical profile was interpreted in conjunction with the patient's clinical history and the morphological characteristics of both pulmonary lesions. Diffuse CK7 positivity supported both pulmonary and ovarian mucinous adenocarcinoma; therefore, this marker alone was not useful in determining the primary site. Focal CK20 positivity was considered compatible with pulmonary invasive mucinous adenocarcinoma, as variable CK20 expression has been reported in this subtype, but it may also be observed in ovarian mucinous tumors with gastrointestinal differentiation. The absence of TTF-1 and Napsin-A expression did not exclude a pulmonary origin because invasive mucinous adenocarcinomas of the lung frequently demonstrate reduced or absent expression of these conventional pulmonary markers. Likewise, negative PAX8 staining did not definitively exclude an ovarian primary, since primary ovarian mucinous adenocarcinomas often lack PAX8 expression. Similarly, the absence of CDX2 expression argued against a gastrointestinal primary tumor but was insufficient to determine the site of origin on its own. Although CA125 positivity initially raised the possibility of a Müllerian origin, this marker lacks specificity and has also been reported in a subset of pulmonary adenocarcinomas. Importantly, the identification of mucinous adenocarcinoma in situ components within both pulmonary lesions strongly favored synchronous primary pulmonary mucinous adenocarcinomas rather than metastatic ovarian disease. Taken together, the immunophenotypic findings were considered supportive rather than definitive, and the final diagnosis relied on the integration of clinical history, tumor morphology, and immunohistochemical results.

On the other hand, primary ovarian mucinous carcinomas are also generally CK7 positive; CK20 and CDX2 expression may be diffuse or variable, while PAX8 is more limitedly positive compared to other Müllerian tumors and may be completely negative. Therefore, PAX8 negativity alone does not rule out primary ovarian mucinous carcinoma. Similarly, expression along the CDX2/CK20 axis can be misleading, especially in ovarian mucinous tumors approaching a gastrointestinal phenotype. Recent reviews emphasize that no single immunohistochemical panel provides absolute accuracy in differentiating primary ovarian mucinous tumors from metastatic mucinous tumors; the most reliable approach is the combined evaluation of tumor size, laterality, surface involvement, destructive stromal invasion pattern, and clinical history. From a molecular perspective, the KRAS pathway is noteworthy in both ovarian mucinous carcinoma and pulmonary invasive mucinous adenocarcinoma. Primary ovarian mucinous carcinomas frequently carry KRAS alterations, while pulmonary invasive mucinous adenocarcinoma is associated with higher KRAS mutation rates compared to other lung adenocarcinoma subtypes; conversely, EGFR mutations are less common in this subtype. Therefore, a negative result for EGFR, ROS1, and BRAF alone is not diagnostic; however, the profile does not contradict pulmonary mucinous adenocarcinoma. Nevertheless, the approach that can most strongly demonstrate a clonal relationship between the two tumors is to perform extensive comparative molecular analysis in both materials, if possible. The presence of the same specific KRAS variant and accompanying secondary alterations in both tumors may contribute to a diagnosis of metastasis, while different molecular profiles may support independent primary tumors. The immunohistochemical profile of this case highlights CA125 positivity. While CA125 is classically associated with Müllerian neoplasms, it is not specific on its own and positivity can also be reported in some lung adenocarcinomas. Therefore, CA125 positivity should not be over-interpreted as favoring ovarian origin, especially in TTF-1/Napsin A negative mucinous lung tumors. Similarly, PAX8 negativity does not definitively rule out primary ovarian mucinous carcinoma. Thus, the most appropriate approach in this case is to use the immunohistochemical panel not as an independent “decisive” factor, but as supporting data that complements the morphology and clinical context. Accompanying anthracosis, pig-

mented macrophages, and emphysematous changes in the lung parenchyma are non-specific findings that suggest additional environmental or inhalation exposure. Such changes do not directly determine whether the lung tumor is primary or metastatic; however, considering the patient’s long-term residence in Kahramanmaraş and the possible history of dye/chemical exposure related to his spouse’s occupation, they can be considered as helpful background information supporting the idea that the lung tissue is susceptible to chronic environmental exposure. However, the current literature does not specifically show that this type of exposure causes “transformation of ovarian mucinous adenocarcinoma to lung mucinous adenocarcinoma”; therefore, it is more appropriate to speak only of possible contribution, not causality, here. Although KRAS alterations are frequently reported in both ovarian mucinous adenocarcinoma and invasive mucinous adenocarcinoma of the lung, no KRAS mutation analysis was available in the present case. Therefore, any potential role of KRAS in the development or biological relationship between these tumors remains speculative and cannot be inferred from our findings. Likewise, the patient’s history of occupational dye exposure was considered part of the clinical background; however, current evidence does not support a causal association between such exposure and the occurrence of either ovarian or pulmonary mucinous adenocarcinoma. Consequently, these observations should be interpreted with caution and should not be regarded as evidence of a biological link between the two malignancies. In such cases, the final diagnosis should be made through a multidisciplinary evaluation involving a clinician, radiologist, thoracic pathologist, and gynecopathologist. The distinction between metastatic disease and synchronous primary tumors has important clinical implications. If the pulmonary lesions had been interpreted as metastases from the previous ovarian mucinous adenocarcinoma, the patient would have been considered to have recurrent metastatic ovarian cancer, resulting in different staging, systemic treatment strategies, and prognostic assessment. In contrast, establishing the diagnosis of independent primary pulmonary mucinous adenocarcinomas allows disease-specific staging and appropriate surgical management, followed by surveillance according to lung cancer guidelines. Furthermore, differentiating multiple primary tumors from metastatic disease has a direct impact on long-term follow-up, as patients require monitoring for

recurrence patterns and potential new primary malignancies specific to each tumor type. Therefore, accurate classification through integration of clinical history, imaging findings, histopathological features, and immunohistochemical results is essential for optimizing patient management and avoiding both under- and overtreatment.

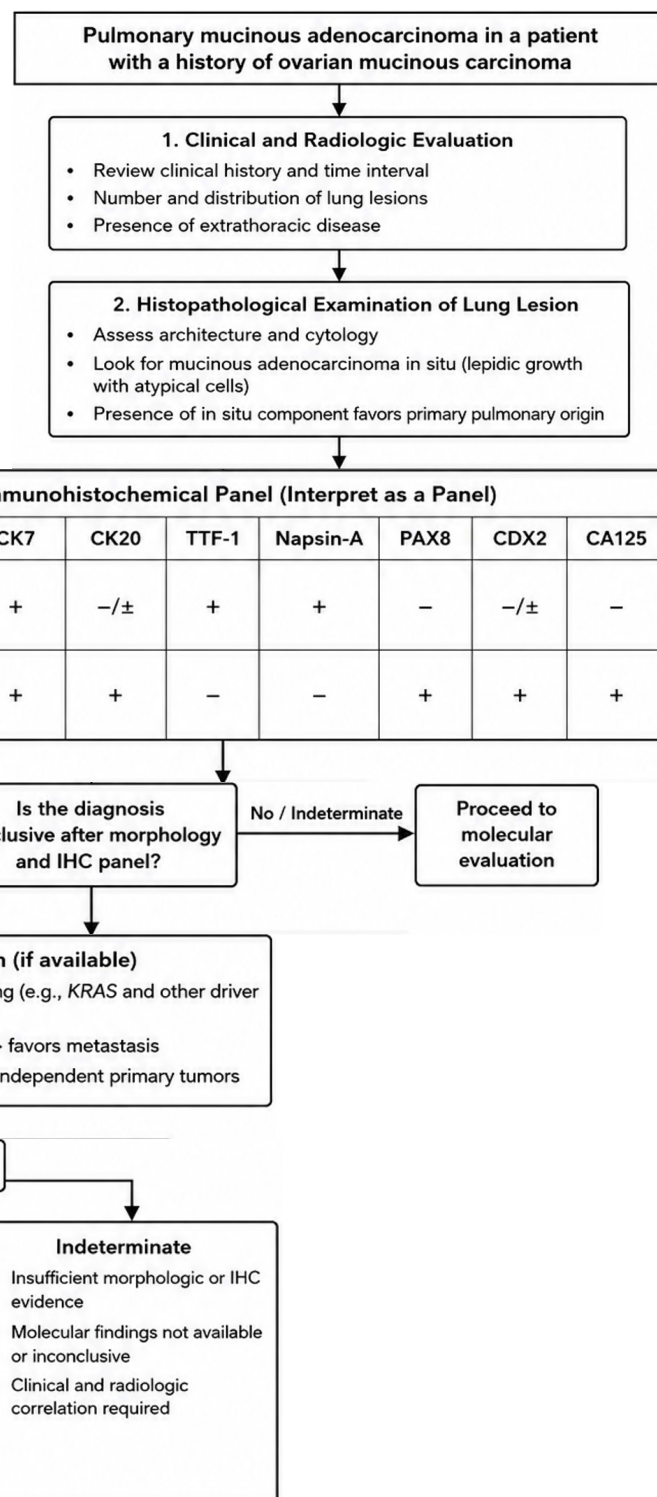
Recent studies have further emphasized that the differential diagnosis between primary and metastatic mucinous tumors cannot rely solely on morphology or immunohistochemistry. Although immunohistochemical markers such as CK7, CK20, TTF-1, Napsin-A, PAX8, CDX2, and SATB2 provide valuable diagnostic information, none demonstrates sufficient sensitivity or specificity to independently determine the site of origin in mucinous neoplasms because of their overlapping expression profiles. Consequently, current diagnostic approaches recommend interpreting immunohistochemical findings in conjunction with the patient's clinical history, radiological findings, tumor distribution, and histopathological features. In addition, advances in molecular profiling, particularly next-generation sequencing (NGS), have provided new opportunities to distinguish synchronous primary tumors from metastatic disease by evaluating shared or discordant driver mutations and clonal relationships. Comparative molecular analyses, including assessment of KRAS and other recurrent genomic alterations, may provide complementary evidence in diagnostically challenging cases. However, such analyses were not available in the present case and therefore could not be used to support the final diagnosis. Instead, the diagnosis relied on the combined interpretation of the clinical history, morphological findings, and immunohistochemical profile, highlighting the importance of a multidisciplinary approach in the evaluation of mucinous tumors.^{7,8,9}

To facilitate the differential diagnosis between primary pulmonary mucinous adenocarcinoma and metastatic ovarian mucinous adenocarcinoma, we propose a practical diagnostic algorithm based on the findings of the present case and current literature. The initial evaluation should include a comprehensive review of the patient's clinical history, previous malignancies, and radiological findings. Histopathological examination should then assess tumor morphology, growth pattern, and the presence of mucinous adenocarcinoma in situ within the pulmonary lesi-

on, as this finding favors a primary pulmonary origin. Immunohistochemical analysis, including CK7, CK20, TTF-1, Napsin-A, PAX8, CDX2, and CA125, should be interpreted as a panel rather than relying on any single marker because of the overlapping expression profiles observed in mucinous tumors. When the diagnosis remains uncertain, comparative molecular profiling, particularly assessment of shared driver alterations such as KRAS mutations by next-generation sequencing, may provide additional evidence regarding the clonal relationship between tumors. Ultimately, the final diagnosis should be established through multidisciplinary integration of the clinical, pathological, immunohistochemical, and, when available, molecular findings to ensure accurate staging and optimal patient management (Figure 1).

Figure 1: Proposed diagnostic algorithm for the differential diagnosis between primary pulmonary mucinous adenocarcinoma and metastatic ovarian mucinous adenocarcinoma.

Proposed diagnostic algorithm for differentiating primary pulmonary mucinous adenocarcinoma from metastatic ovarian mucinous adenocarcinoma. The algorithm emphasizes the integration of clinical history, histopathological findings, immunohistochemical profile, and, when available, comparative molecular analysis. In the present case, the identification of mucinous adenocarcinoma in situ in both pulmonary lesions, together with the clinicopathological and immunohistochemical findings, supported the diagnosis of independent primary pulmonary mucinous adenocarcinomas rather than metastatic ovarian disease.



Diagnosis should be established by integrating clinical, radiologic, histopathologic, immunohistochemical, and (when available) molecular findings.

IHC: Immunohistochemistry; NGS: Next-generation sequencing.

Limitations and Future Perspectives

This report has several important limitations. Firstly, the generalizability of the findings is limited due to the presentation of a single case. Secondly, the lack of re-evaluation of pathological preparations from the patient's previous ovarian tumor and the inability to perform extensive comparative molecular analyses (especially of KRAS mutation subtypes) between lung and ovarian tumors restricts the definitive establishment of a possible clonal relationship between the tumors. While immunohistochemical findings are helpful in differential diagnosis, they are not definitive diagnostic due to the overlap of markers in mucinous tumors. Future studies should be planned to include multicenter and larger patient series in similar cases, contributing to the differentiation of primary and metastatic mucinous tumors. The use of advanced molecular methods, particularly next-generation sequencing (NGS), can more clearly reveal the clonal relationship between tumors. Furthermore, standardization of immunohistochemical panels and the identification of new biomarkers can improve the accuracy of differential diagnosis. Multidisciplinary approaches integrating clinical, radiological, and pathological data will continue to be critical for accurate diagnosis and treatment planning in such complex cases. The major limitation of this case is the lack of comparative molecular analysis between the ovarian and pulmonary tumors. Therefore, a definitive conclusion regarding their clonal relationship cannot be established. Future studies incorporating comparative molecular profiling, particularly next-generation sequencing of shared driver mutations such as KRAS, may provide more definitive evidence for distinguishing metastatic disease from independent primary tumors.

Conclusion

This case highlights the diagnostic challenge of distinguishing primary pulmonary mucinous adenocarcinoma from metastatic ovarian mucinous adenocarcinoma in patients with a previous history of ovarian mucinous carcinoma. In the present case, the final diagnosis was based on the integration of the patient's clinical history, histopathological features, and immunohistochemical findings, particularly the identification of mucinous adenocarcinoma *in situ* components in both pulmonary lesions. These findings supported the diagnosis of independent primary

pulmonary tumors rather than metastatic disease. Accurate differentiation is essential because it directly influences staging, treatment planning, prognosis, and long-term follow-up. Although comparative molecular analyses were not available in this case, they may provide additional diagnostic value in selected patients with similar complex presentations. The current findings suggest that integrating such molecular investigations into routine practice could improve diagnostic accuracy, especially in cases of complex mucinous tumors. In conclusion, this case highlights the need for further molecular studies to better understand the biological behavior and origin of mucinous adenocarcinomas, and the data obtained could be guiding both in the management of similar cases and in the evaluation of potential new primary tumors that may arise in the future.

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AI Statement: No artificial intelligence (AI) tools or technologies were used in the design, analysis, or writing of this manuscript.

Data Availability: The data supporting the findings of this study are available from the corresponding author upon reasonable request. Due to patient confidentiality and privacy concerns, the data are not publicly available.

Ethics Statement: Written informed consent was obtained from the patient for the publication of this case report and accompanying clinical data. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. As this manuscript is a retrospective case report based on anonymized patient data and did not involve any experimental intervention or alteration in patient management, ethics committee approval was not required in accordance with institutional and national regulations. An ethics committee is not required; patient consent is available in signed form.

Human Consent / Patient Consent: Written informed consent was obtained from the patient for the publication of this case report and accompanying clinical data.

What is known about this topic: Primary ovarian mucinous adenocarcinoma and pulmonary mucinous adenocarcinoma are distinct tumor entities; however, they may present with overlapping histopathological and immunohistochemical features. This similarity can create significant diagnostic challenges, particularly in differentiating primary tumors from metastatic disease. Immunohistochemical markers such as CK7, CK20, TTF-1, and PAX8 are frequently used in this context, but none of these markers alone is sufficient for definitive diagnosis. In addition, both tumor types may share molecular alterations, especially involving the KRAS pathway. Therefore, accurate differentiation requires a comprehensive evaluation integrating clinical history, imaging findings, histopathological examination, and molecular data.

What this paper adds to the topic: This case report highlights the diagnostic complexity of mucinous adenocarcinomas occurring in both the ovary and lung within the same patient. The identification of mucinous adenocarcinoma in situ components in both pulmonary lesions supports the interpretation of independent primary lung tumors rather than metastatic disease. This study emphasizes that immunohistochemical findings alone are insufficient for determining tumor origin and underscores the importance of a multidisciplinary approach. Furthermore, it draws attention to the potential role of molecular analyses, particularly KRAS mutation profiling, in clarifying the clonal relationship between tumors. By presenting this rare clinical scenario, the report contributes to improving diagnostic accuracy and clinical decision-making in similar challenging cases.

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CASE REPORT

May–Thurner Syndrome in an Adolescent Male with Celiac Disease and Homozygous Factor V Leiden Mutation: A Case Report

Gul Hatice Erkol Tuncer¹, Eray Akay¹, Cagrı Ozcan², Zeliha Guzelkucuk¹, Namik Yasar Ozbek¹

¹Department Of Pediatric Hematology And Oncology, Ankara Bilkent City Hospital, Ankara, Türkiye

²Department Of Radiology, Ankara Bilkent City Hospital, Ankara, Türkiye

Abstract

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ORCIDs of the authors:

GHET:0000-0002-6189-1279

EA :0000-0002-9457-283X

CO :0009-0008-4275-3963

ZG :0000-0003-1462-6867

NYO :0000-0001-6857-0681

May–Thurner syndrome (MTS) is a rare cause of venous thromboembolism (VTE) in children and adolescents and is often underdiagnosed. Here we present an adolescent male with extensive iliofemoral deep vein thrombosis (DVT) in whom MTS was identified as one of several contributing etiological factors. His first presentation revealed acute unilateral swelling and pain in the left lower extremity following minor trauma. Doppler ultrasonography disclosed extensive acute iliofemoral DVT, and further evaluation by computed tomography angiography demonstrated extrinsic compression of the left common iliac vein by the right common iliac artery, consistent with May–Thurner syndrome. He was also found to have homozygous Factor V Leiden mutation, probable hereditary protein C deficiency, hyperhomocysteinemia, and celiac disease, together indicating a multifactorial thrombotic process. This case highlights the importance of considering anatomical venous compression syndromes in adolescents presenting with extensive and unexplained iliofemoral DVT.

Correspondence Address: 4986 Stdodurga Neighborhood, Artekent Site Ankara - Türkiye

Phone: +90 535 459 70 33 / **e-mail:** herkoll@hotmail.com



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Introduction

May–Turner syndrome (MTS) refers to compression of the left iliac vein by the right common iliac artery against the spine, which may impair venous return and predispose to venous stasis, varicosities, and deep vein thrombosis (DVT).¹ While well recognized in adults, particularly young women, MTS is rare in the pediatric population, and its diagnosis may be delayed due to low clinical suspicion.² Here we present an adolescent male with extensive iliofemoral DVT in whom MTS was identified as one of several contributing etiological factors.

Case

A 15-year-old male with no known chronic medical conditions presented with acute left lower extremity swelling and pain following minor trauma; osseous pathology was excluded. Persistent symptoms prompted Doppler ultrasonography, which demonstrated venous thrombosis and led to referral to pediatric hematology. He had no personal or family history of venous thromboembolism apart from celiac disease in one sibling.

Physical examination showed marked swelling, erythema, and tenderness of the entire left lower extremity, with a 3-cm circumferential difference (Figure 1); anthropometric measurements were normal for age (weight 52.8 kg, height 169 cm, BMI 18.49 kg/m²).



Figure 1. Clinical photograph showing swelling and circumferential difference of the left lower extremity at presentation.

Laboratory evaluation showed elevated inflammatory markers (CRP 176 mg/L; ESR 58 mm/h), with normal renal function, electrolytes, and LDH. Complete blood count was unremarkable (hemoglobin 12.7 g/dL, white blood cell count $9.97 \times 10^9/L$, platelet count $237 \times 10^9/L$, normal smear). Coagulation studies were normal (PT 13.8 s, INR 1.0, aPTT 22.8 s) except for a markedly elevated D-dimer (7.79 mg/L; reference <0.55 mg/L).

Doppler ultrasonography showed acute, totally occlusive DVT extending from the left external iliac vein through the common femoral, superficial femoral, popliteal, and proximal deep crural veins, without recanalization; the right lower extremity was normal. Subcutaneous enoxaparin (1 mg/kg every 12 hours) and compression stockings were initiated.

Given the extensive iliofemoral thrombosis without an obvious provoking factor, thrombophilia testing revealed a homozygous Factor V Leiden mutation and heterozygous MTHFR A1298C/C677T variants, with markedly elevated homocysteine (39.9 $\mu\text{mol/L}$; reference 4.7–10.3 $\mu\text{mol/L}$), low-normal vitamin B12 (361 ng/L), and unmeasured folate. Lupus anticoagulant, anticardiolipin, and anti- β_2 glycoprotein I antibodies were negative. Lipoprotein(a), antithrombin, and protein S were normal; protein C antigen and activity were decreased (26% and 35%). Family testing showed low protein C activity in the mother and sister, and repeat testing in our patient three months later remained slightly reduced (39.8%; reference 63.8–150%), supporting a true deficiency rather than acute consumption.

Given suspicion of May–Turner syndrome, CT angiography demonstrated extrinsic compression of the left common iliac vein by the right common iliac artery, causing ~70% luminal narrowing with filling defects throughout the left iliofemoral system (Figure 2); cardiovascular surgery recommended anticoagulation and follow-up without intervention.

By the second week, the patient showed clinical improvement (reduced swelling and erythema, Figure 3); serial Doppler ultrasonography showed persistent thrombosis with early partial recanalization, and D-dimer declined progressively (2.72, 1.62, 0.35 mg/L), paralleling this improvement.

Given the family history of celiac disease, tissue transglutaminase IgA was elevated, and upper gastrointestinal endoscopy confirmed celiac disease histopathologically; anticoagulation was continued.

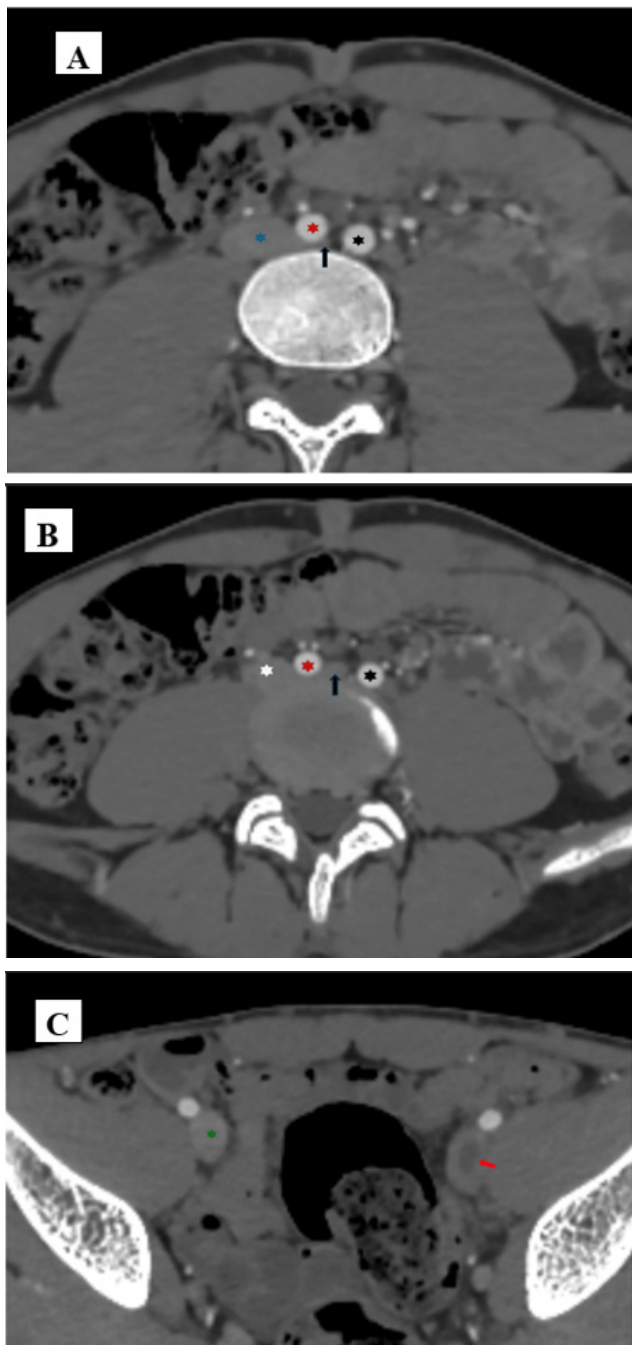


Figure 2. Computed tomography angiography showing extrinsic compression of the left common iliac vein by the right common iliac artery (black arrow), with filling defects consistent with acute thrombus in the left iliofemoral venous system (A–C, sequential axial levels).



Figure 3. At the second week of follow-up showing marked reduction in swelling and erythema of the left lower extremity.

The patient has been followed for 9 months (since December 2025), with clinical and Doppler assessment monthly for the first 3 months then every 2 months; follow-up is ongoing. At last assessment he had prominent varicose veins without pain; post-thrombotic syndrome is assessed clinically at each visit, alongside continued anticoagulation and reassessment for intervention.

Discussion

May–Thurner syndrome (MTS) is uncommon in children but represents an important, underrecognized cause of iliofemoral DVT, identified in 23.2% of non–catheter-related cases by Avila et al.² and 13.4% by Cohen et al.,³ suggesting substantial underlying venous compression in this population. Although pediatric MTS predominantly affects adolescent females, our patient was male.¹

Venous compression related to MTS should be considered a contributing factor in proximal left-sided DVT even when additional prothrombotic risk factors are present; in the cohort by Cohen et al.,³ only three patients had no identifiable prothrombotic factor at diagnosis, and a systematic review identified oral contraceptive use, antiphospholipid syndrome, protein S deficiency, and heterozygous FVL

as associated conditions.² Our patient, with no provoking factor such as central venous catheterization, had homozygous FVL, reduced protein C antigen and activity, and celiac disease, all of which may have contributed to early-onset thrombosis in the setting of underlying venous compression.

The markedly elevated CRP (176 mg/L) and ESR (58 mm/h) are unlikely to be fully explained by minor trauma alone. Extensive acute venous thrombosis can itself elicit a substantial inflammatory response through thromboinflammation and immunothrombosis,^{4,5} in which activated platelets, neutrophils, and the coagulation cascade amplify inflammation; no infectious source was identified, supporting thromboinflammation as the most plausible explanation.

Homozygous FVL confers resistance to activated protein C through a structural alteration of factor V and does not itself reduce protein C production. The persistently reduced protein C activity in our patient on repeat testing, together with reduced activity in his mother and sister, is therefore more consistent with a distinct, co-inherited (probably heterozygous) protein C deficiency than a phenotypic feature of FVL; PROC sequencing was not performed and is noted as a limitation.

The patient's markedly elevated homocysteine (39.9 $\mu\text{mol/L}$), in the context of heterozygous MTHFR A1298C/C677T variants, supports a hyperhomocysteinemia-mediated prothrombotic mechanism rather than an incidental finding.⁶ Untreated celiac disease may have further contributed via chronic intestinal inflammation and malabsorption, predisposing to B12/folate deficiency (folate not measured) and exacerbating hyperhomocysteinemia, and via systemic inflammation, which can downregulate natural anticoagulant pathways and upregulate tissue factor expression.⁷ Specifically, interleukin-6 increases tissue factor expression, interleukin-1 and TNF- α impair thrombomodulin function, and elevated plasminogen activator inhibitor-1 reduces fibrinolysis and protein C activity, offering a complementary explanation for the reduced protein C activity observed in our patient, alongside the familial deficiency discussed above.⁷

MTS was diagnosed during the second week of treatment, underscoring the importance of timely imaging in children with left-sided lower-extremity DVT, as Doppler ultrasonography or standard CT may be insufficient to confirm MTS.³ Intravascular ultrasonography offers diagnostic advantages for su-

bble iliac vein pathology⁸ but is limited by its invasive nature in pediatric use; conventional venography, MR venography/angiography, or CT venography, as performed in our patient, may therefore be used instead.⁹

No standardized recommendations exist for pediatric MTS management. In published series,⁸ most patients underwent pharmacomechanical or catheter-directed thrombolysis, partially conflicting with pediatric guidelines that generally reserve thrombolysis for limb- or life-threatening thrombosis,¹⁰ though the ASH panel noted this recommendation's evidence certainty is very low, with thrombus extent and clinical impact as key determinants; current guidelines do not specifically address MTS.¹⁰

Randomized adult trials show catheter-directed thrombolysis reduces post-thrombotic syndrome (PTS) from 55% to 37% versus anticoagulation alone,¹¹ and pediatric studies, though not MTS-specific, similarly suggest endovascular thrombolysis is safe and may reduce PTS risk,¹²⁻¹³ though risk factors for pediatric PTS remain poorly defined beyond recurrent thrombosis.²

In conclusion, May–Turner syndrome should be considered in pediatric patients with extensive left-sided iliofemoral DVT, whether provoked or unprovoked. This case illustrates that pediatric venous thrombosis may be multifactorial, resulting from the coexistence of anatomic venous compression, inherited thrombophilia, and inflammatory prothrombotic conditions. Comprehensive evaluation supported by appropriate advanced imaging is essential to avoid missed diagnoses and guide individualized management, and further prospective studies are needed to establish evidence-based recommendations.

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Conflict of Interest / Disclosures

The authors declare no conflicts of interest.

Ethical Statement

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