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Associations of maternal serum transthyretin concentration with pregnancy and birth outcomes

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Abstract

Objective This study aims to explore the association of maternal serum transthyretin (TTR) concentrations with adverse pregnancy and birth outcomes, as well as the variations in TTR concentrations across different gestational weeks in relation to these outcomes.

Methods This retrospective cohort study included 6,584 women who delivered at The Second Affiliated Hospital of Wenzhou Medical University between January 1, 2022 and January 30, 2024. Logistic regression and Restricted cubic spline (RCS) models were applied to evaluate the association between TTR levels and the risk of complications, based on TTR quartile analyses. Locally estimated scatter plot smoothing (LOESS) curves were performed to provide a graphical representation of the relationship between TTR levels and gestational weeks.

Results Significant negative correlations were observed between maternal TTR levels and the risk of gestational diabetes mellitus (GDM), preeclampsia (PE), liver disease, anemia during pregnancy, and preterm delivery (all $P < 0.001$). The RCS models revealed a non-linear relationship between TTR levels and maternal comorbidities, including anemia (adjusted OR 0.992 [95% CI 0.990–0.994]; $P = 0.017$), liver disease (adjusted OR 0.991 [95% CI 0.988–0.994]; $P < 0.001$), hypothyroidism (adjusted OR 0.999 [95% CI 0.996–1.001]; $P = 0.023$) and preterm delivery (adjusted OR 0.986 [95% CI 0.983–0.989]; $P < 0.001$). The LOESS curves indicated a declining trend in TTR concentrations during the third trimester of pregnancy.

Conclusion Maternal TTR concentrations showed an inverse linear association with the incidence of GDM and PE. Moreover, complex non-linear relationships were identified with TTR levels and comorbidities such as liver disease, anemia, hypothyroidism during pregnancy, and preterm delivery.

Keywords Serum transthyretin, Maternal comorbidities, Non-linear relationship, Gestational diabetes mellitus, Preeclampsia

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Introduction

Transthyretin (TTR), also known as prealbumin, is a 56-kDa homotetrameric protein that binds to thyroid hormone and retinol-binding protein [1, 2]. In humans, approximately 90% of serum TTR is synthesized in the liver, with concentrations ranging from 200 to 400 mg/L [3]. Disruption of the tetrameric structure's stability can lead to systemic deposition of TTR monomers. The deposition of TTR is implicated in the pathogenesis of transthyretin-related amyloidosis, a progressive disorder primarily affecting cardiac and neurological systems [4]. Contemporary studies predominantly investigate the association between TTR and neurological disorders, such as Parkinson's disease, schizophrenia, and depression [5–7]. Additionally, the synthesis of TTR is significantly influenced by protein and energy intake, positioning TTR as a potential biomarker for nutritional status assessment [8].

However, there is a paucity of data regarding alterations in TTR concentration during pregnancy and its relationship to pregnancy-related complications and comorbidities. As with many other important functions of TTR that have been discovered recently, current evidence suggests a role for TTR in female reproduction, encompassing both normal and pathological states [9]. Notably, TTR levels in the endometrium and uterine secretions typically increase prior to implantation and throughout gestation, likely in response to elevated progesterone levels, which may contribute to maintaining a healthy pregnancy [10]. Recent research has demonstrated that TTR is secreted by trophoblasts in significantly greater quantities during the first trimester of pregnancy, predominantly entering the maternal circulation. TTR is also hypothesized to facilitate the active transport of maternal thyroid hormones to the developing fetus [11, 12]. Previous study has suggested that TTR plays a crucial role in the pathophysiology of preeclampsia and GDM [13–16]. Additionally, TTR served as a biomarker for nutrition and may be associated with anemia in pregnancy and preterm delivery [17, 18]. Given the emerging findings regarding TTR synthesis and expression in the placenta, further research is warranted to explore the diverse roles proposed for TTR during pregnancy.

This retrospective study aimed to investigate the potential association between TTR concentration with adverse pregnancy and birth outcomes, as well as the temporal expression of TTR in serum throughout pregnancy. Our findings provide insight into the role of TTR in pregnancies complicated by various pathological conditions, thereby contributing to a more comprehensive understanding of its impact on maternal and fetal health.

Methods

Study population

Participants in this retrospective study included pregnant women who delivered at the Second Affiliated Hospital of Wenzhou Medical University between January 1, 2022, and January 30, 2024. The inclusion criteria for this study were women aged ≥ 16 years at the time of delivery, who had a live singleton birth and did not undergo assisted conception. Finally, 6,584 women were included in the analysis to examine the relationship between TTR concentration and pregnancy complications (Fig. 1). Participants were categorized into four quartiles according to TTR levels measured within two weeks before delivery. Additionally, we collected 21,383 TTR data at various gestational weeks to investigate the temporal changes in TTR concentration associated with different complications. Data were extracted from electronic medical records maintained in the hospital's Medical Record Room database. This study was approved by the Ethics Committee of the Second Affiliated Hospital of Wenzhou Medical University. Since it was a retrospective study, informed consent from participants was not required.

Clinical data and laboratory measurements of bioassay

Maternal baseline characteristics encompassed maternal age at delivery, gestational age at delivery, parity, pre-pregnancy Body Mass Index (BMI), marital status, educational level, and the presence of chronic hypertension, pregestational diabetes, and hepatitis virus carrying status. Our primary outcomes of interest included antepartum comorbidities, intrapartum and fetal complications. Gestational diabetes mellitus (GDM) was diagnosed by 75-g oral glucose tolerance test (OGTT) conducted at 24–28 gestational weeks and if one or more of the following glucose levels were exceeded: 5.1 mmol/L at fasting, 10.0 mmol/L at 1-hour, 8.5 mmol/L at 2-hour intervals [19]. Preeclampsia (PE) was defined as the onset of hypertension (a systolic blood pressure ≥ 140 mmHg and/or a diastolic blood pressure ≥ 90 mmHg) occurring after 20 weeks of gestation, accompanied by new-onset proteinuria or other end-organ dysfunction [20]. Gestational hypertension was identified as a rise in blood pressure after 20 weeks of gestation, without the presence of proteinuria [21]. The study also considered liver disease, anemia, and hypothyroidism during pregnancy that were either induced or exacerbated by pregnancy. Liver disease during pregnancy in this study encompassed conditions where there was no pre-existing liver disease, but elevated liver biochemical and/or function tests developed during pregnancy, such as intrahepatic cholestasis of pregnancy (ICP) and related conditions. The definition of anemia in pregnancy was a hemoglobin concentration (Hb) < 110 g/L [22]. The diagnosis of primary hypothyroidism in pregnant women was based upon increased

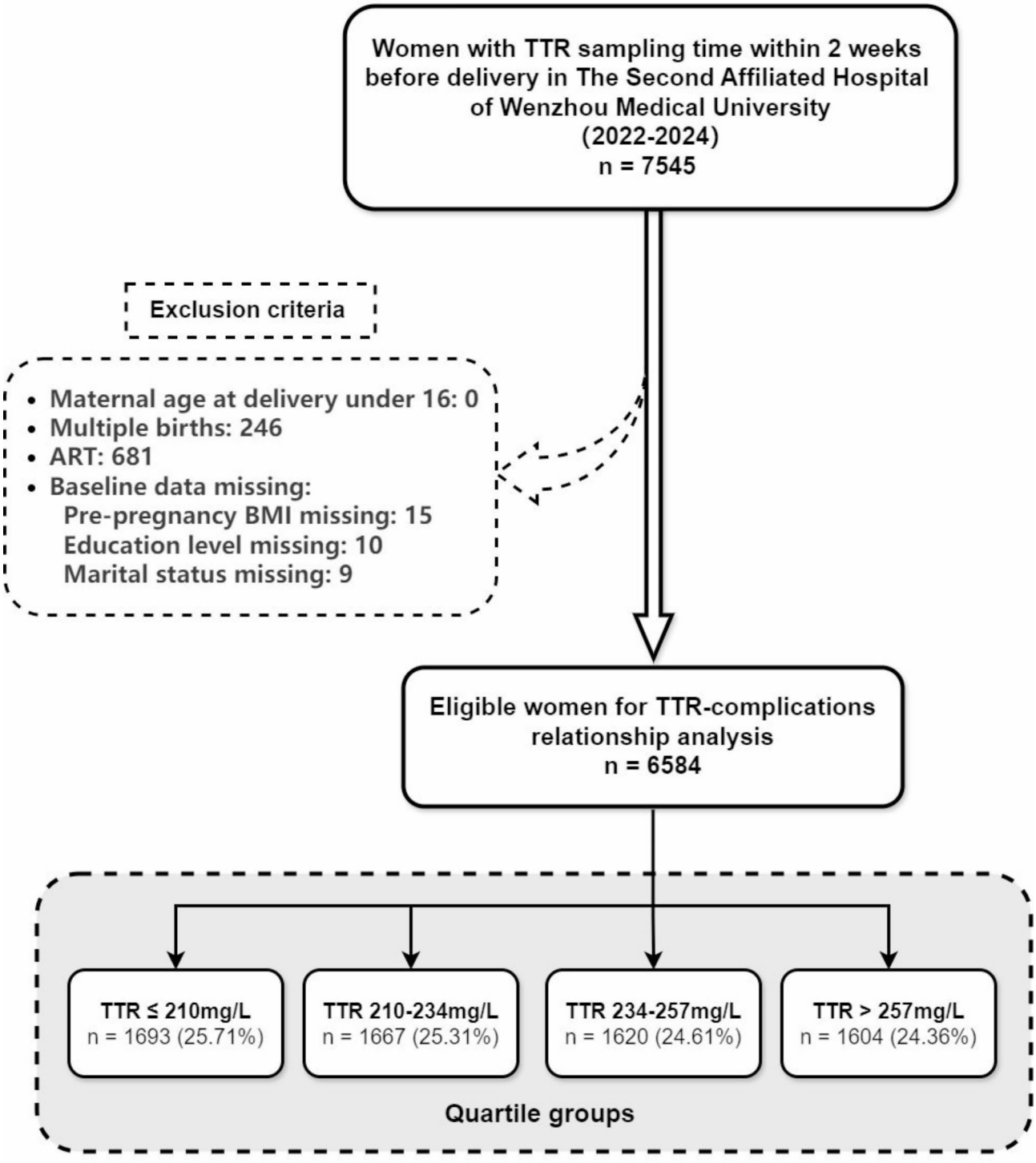

Fig. 1 Flow chart of sample selection. BMI, body mass index; TTR, transthyretin; ART, assisted reproductive technology

serum TSH concentrations, determined using trimester-specific TSH reference ranges for pregnant women [23, 24]. Blood loss exceeding 500 ml after vaginal delivery, or 1000 ml after cesarean delivery within 24 h postpartum was classified as postpartum hemorrhage [25]. The diagnosis of Intraamniotic infection (IAI) was recommended by the National Institute of Child Health and Human Development Workshop expert panel. Deliveries occurring before 37 weeks of gestation were defined as preterm births [26]. The control group consisted of pregnant women without any of the above-mentioned conditions.

Statistical analysis

All analyses were accomplished by using SPSS 24.0 (IBM Corp., Armonk, NY, USA) and R x64 4.4.1 (R Foundation for Statistical Computing). The normality of the continuous TTR variable was assessed using the Anderson-Darling test. The test results revealed that the distribution of the TTR variable significantly departed from normality. The TTR concentrations in pregnant women were evaluated both as a continuous variable (effect as per concentration in mg/L) and as quartiles: <210, 210–234, 234–257, >257 mg/L, with the first quartile (Q1), representing the lowest TTR concentrations, serving as the base reference. Descriptive statistics were reported as medians with interquartile ranges (IQR) for continuous variables, and as percentages for categorical variables. To compare differences in baseline characteristics across TTR quartiles, the chi-square test was applied to categorical variables, while the Kruskal-Wallis test was used for continuous variables that did not meet the assumption of normality. Additionally, we employed logistic regression to assess the relationship between TTR concentration and adverse pregnancy and birth outcomes, while adjusting for potential confounding factors. To further investigate the dose-response relationships between maternal TTR concentration and complications, we applied a restricted cubic spline (RCS) regression model, with four assumed knots at the 5th, 35th, 65th and 95th percentiles. The distribution of TTR was illustrated using histograms. Finally, we analyzed the association between TTR concentration and gestational weeks using a locally estimated scatterplot smoothing (LOESS) curve. Statistical significance was set at 0.05.

Result

The comparisons of baseline characteristics

The median serum TTR concentration during pregnancy was 224 mg/L (IQR, 210–257) in this study. The baseline characteristics of the 6,584 participants, stratified by maternal TTR concentration quartiles, were presented in Table 1. The median maternal age was 30.0 years (IQR, 27.0–33.0), and the median pre-pregnancy BMI was 20.7 kg/m² (IQR, 19.1–22.9). Overall, 96.6% of the women were married, and 53.8% of the participants were primiparas. Among the participants, 0.9% had chronic hypertension, 1.3% had pregestational diabetes, and 4.9% were carriers of the hepatitis virus. A positive correlation was noted across the TTR concentration quartiles with respect to gestational age, and pre-pregnancy BMI. Conversely, negative correlations were observed with parity, pregestational diabetes, and the prevalence of hepatitis virus carriage. Nevertheless, there were no significant differences in maternal age, maternal education level, child sex or the prevalence of chronic hypertension among the TTR concentration stratification groups.

Association of TTR levels with maternal complications

Table 2 investigated the association between maternal TTR levels and various pregnancy-related complications, delineating their incidence rates across distinct TTR level categories. Maternal complications including GDM, PE, liver disease and anemia manifested significant correlations with maternal TTR levels, irrespective of whether TTR levels were categorized by quartiles or treated as a continuous variable (all $P<0.05$). After adjusting for confounding variables, we found that pregnant women with elevated circulating TTR concentrations tended to have lower risk of developing the aforementioned complications (all $P<0.001$). Specifically, women with serum

Table 1 Characteristics of participants according to quartiles of maternal TTR concentration in pregnancy

	Total (*n* = 6584)	≤ 210 (*n* = 1693)	210 < X ≤ 234 (*n* = 1667)	234 < X ≤ 257 (*n* = 1620)	> 257 (*n* = 1604)	*P*-value
Maternal age (years)	30.0 (27.0–33.0)	30.0 (27.0–33.0)	30.0 (27.0–33.0)	30.0 (27.0–33.0)	30.0 (27.0–33.0)	0.051
Gestational age (weeks)	38.9 (38.3–39.3)	38.7 (38.1–39.3)	38.9 (38.4–39.4)	38.9 (38.3–39.3)	38.9 (38.3–39.3)	**< 0.001**
Parity (1 or more versus 0)	3547 (53.8)	979 (57.8)	892 (53.5)	838 (51.7)	838 (52.2)	**0.001**
Pre-pregnancy BMI (kg/m^2)	20.7 (19.1–22.9)	20.6 (18.8–22.9)	20.6 (19.1–22.7)	20.8 (19.1–23.1)	20.9 (19.2–23.1)	**0.001**
Marital status (yes versus no)	6360 (96.6)	1634 (96.5)	1613 (96.8)	1569 (96.9)	1544 (94.1)	0.790
Maternal education level						0.060
Primary or less	81 (1.2)	21 (1.2)	22 (1.3)	23 (1.4)	15 (0.9)	
Secondary	3904 (59.3)	967 (57.1)	967 (58.0)	970 (59.9)	1000 (62.3)	
University degree	2599 (39.5)	705 (41.6)	678 (40.7)	627 (38.7)	589 (36.7)	
Child sex (male)	3484 (52.9)	925 (54.6)	885 (53.1)	831 (51.3)	843 (52.6)	0.281
Chronic hypertension (yes versus no)	61 (0.9)	14 (0.8)	13 (0.8)	20 (1.2)	14 (0.9)	0.513
Pregestational diabetes (yes versus no)	89 (1.3)	37 (2.2)	18 (1.1)	22 (1.4)	12 (0.8)	**0.003**
Hepatitis virus carrying status (yes versus no)	324 (4.9)	122 (7.2)	97 (5.8)	59 (3.6)	46 (2.9)	**< 0.001**

Bold values indicate $P<0.05$.

BMI, body mass index; TTR, transthyretin.

Values are percentages for categorical variables and median (interquartile range) for continuous variables

Table 2 Adjusted associations of maternal TTR concentration in pregnancy with antepartum complications

	TTR (mg/L)	As continuous	Quartiles			
			Q1: ≤210	Q2:210 < X ≤ 234	Q3:234 < X ≤ 257	Q4:>257
GDM	n (%)	1097 (16.7)	352 (20.8)	261 (15.7)	266 (16.4)	218 (13.6)
	OR (95%CI)	0.995 (0.993,0.996)	1.00	0.72 (0.60,0.87)	0.75 (0.62,0.90)	0.59 (0.48,0.71)
	P	**< 0.001**		**< 0.001**	**0.002**	**< 0.001**
PE	n (%)	279 (4.2)	130 (7.7)	64 (3.8)	54 (3.3)	57 (3.6)
	OR (95%CI)	0.989 (0.986,0.993)	1.00	0.54 (0.39,0.75)	0.40 (0.28,0.57)	0.43 (0.31,0.61)
	P	**< 0.001**		**< 0.001**	**< 0.001**	**< 0.001**
Gestational hypertension	n (%)	254 (3.9)	78 (4.6)	58 (3.5)	61 (3.7)	57 (3.6)
	OR (95%CI)	0.998 (0.994,1.001)	1.00	0.77 (0.54,1.10)	0.81 (0.57,1.15)	0.76 (0.53,1.10)
	P	0.146		0.152	0.245	0.128
Liver disease	n (%)	330 (5.0)	139 (8.2)	76 (4.6)	45 (2.8)	70 (4.4)
	OR (95%CI)	0.991 (0.988,0.994)	1.00	0.54 (0.41,0.72)	0.33 (0.23,0.46)	0.52 (0.38,0.70)
	P	**< 0.001**		**< 0.001**	**< 0.001**	**< 0.001**
Anemia	n (%)	797 (12.1)	268 (15.8)	220 (13.2)	179 (11.1)	130 (8.1)
	OR (95%CI)	0.992 (0.990,0.994)	1.00	0.81 (0.66,0.99)	0.65 (0.52,0.80)	0.45 (0.36,0.56)
	P	**< 0.001**		**0.037**	**< 0.001**	**< 0.001**
Hypothyroidism	n (%)	513 (7.8)	158 (9.3)	114 (6.8)	119 (7.3)	122 (7.6)
	OR (95%CI)	0.999 (0.996,1.001)	1.00	0.73 (0.57,0.94)	0.78 (0.61,1.01)	0.81 (0.63,1.04)
	P	0.223		**0.016**	0.056	0.093

CI, confidence interval; OR, odds ratio; TTR, transthyretin; GDM, gestational diabetes mellitus; PE, preeclampsia.

Models were adjusted for child's sex, maternal age, pre-pregnancy BMI, marital status, education level, parity, gestational age, hepatitis virus carrying status, chronic hypertension and pregestational diabetes

Table 3 Adjusted associations of maternal TTR concentration in pregnancy with intrapartum complications

	TTR (mg/L)	As continuous	Quartiles			
			Q1: ≤210	Q2:210 < X ≤ 234	Q3:234 < X ≤ 257	Q4:>257
Postpartum hemorrhage	n (%)	270 (3.1)	62 (3.7)	54 (3.2)	44 (2.7)	47 (2.9)
	OR (95%CI)	0.996 (0.993,1.000)	1.00	0.83 (0.57,1.21)	0.70 (0.47,1.03)	0.76 (0.52,1.13)
	P	0.065		0.341	0.072	0.175
IAI	n (%)	187 (2.8)	63 (3.7)	45 (2.7)	47 (2.9)	37 (2.3)
	OR (95%CI)	0.998 (0.994,1.001)	1.00	0.90 (0.60,1.35)	1.03 (0.69,1.54)	0.78 (0.51,1.20)
	P	0.194		0.620	0.889	0.265
PROM	n (%)	1090 (16.6)	286 (16.9)	274 (16.4)	285 (17.6)	258 (16.1)
	OR (95%CI)	1.001 (0.999,1.003)	1.00	1.06 (0.88,1.28)	1.18 (0.98,1.42)	1.05 (0.87,1.27)
	P	0.314		0.538	0.086	0.611
Placenta previa	n (%)	109 (1.7)	34 (2.0)	26 (1.6)	20 (1.2)	30 (1.9)
	OR (95%CI)	1.001 (0.997,1.006)	1.00	1.05 (0.61,1.82)	0.90 (0.50,1.61)	1.38 (0.81,2.35)
	P	0.566		0.852	0.715	0.236

CI, confidence interval; OR, odds ratio; TTR, transthyretin; IAI, Intraamniotic infection; PROM, premature rupture of membranes.

Models were adjusted for child's sex, maternal age, pre-pregnancy BMI, marital status, education level, parity, gestational age, hepatitis virus carrying status, chronic hypertension and pregestational diabetes

TTR in the quartile 210–234 mg/L (Q2) had significantly lower odds of experiencing hypothyroidism during pregnancy compared to those in the lowest serum TTR quartile ≤ 210 mg/L (Q1), with an adjusted OR of 0.73 (95% CI: 0.57–0.94; $P = 0.016$). Additionally, no significant association was found between TTR concentration and the incidence of gestational hypertension.

Table 3 analyzed the relationship between maternal TTR levels and intrapartum complications, including postpartum hemorrhage, IAI, PROM and placenta previa. After adjusting for potential confounding factors, no significant correlations were identified between TTR levels and these complications, regardless of whether TTR concentration was analyzed as a continuous variable or categorized by quartiles (all $P > 0.05$).

Figures 2 and 3 presented the RCS and LOESS curves for specific pregnancy and fetal complications that demonstrate a significant association with maternal TTR concentration as identified by logistic regression analyses presented in Tables 2 and 4. The risk of GDM and PE exhibited a linear relationship with maternal TTR concentration, with risk progressively decreasing as TTR levels increased, which was consistent with the findings in Table 2. The study revealed an approximately

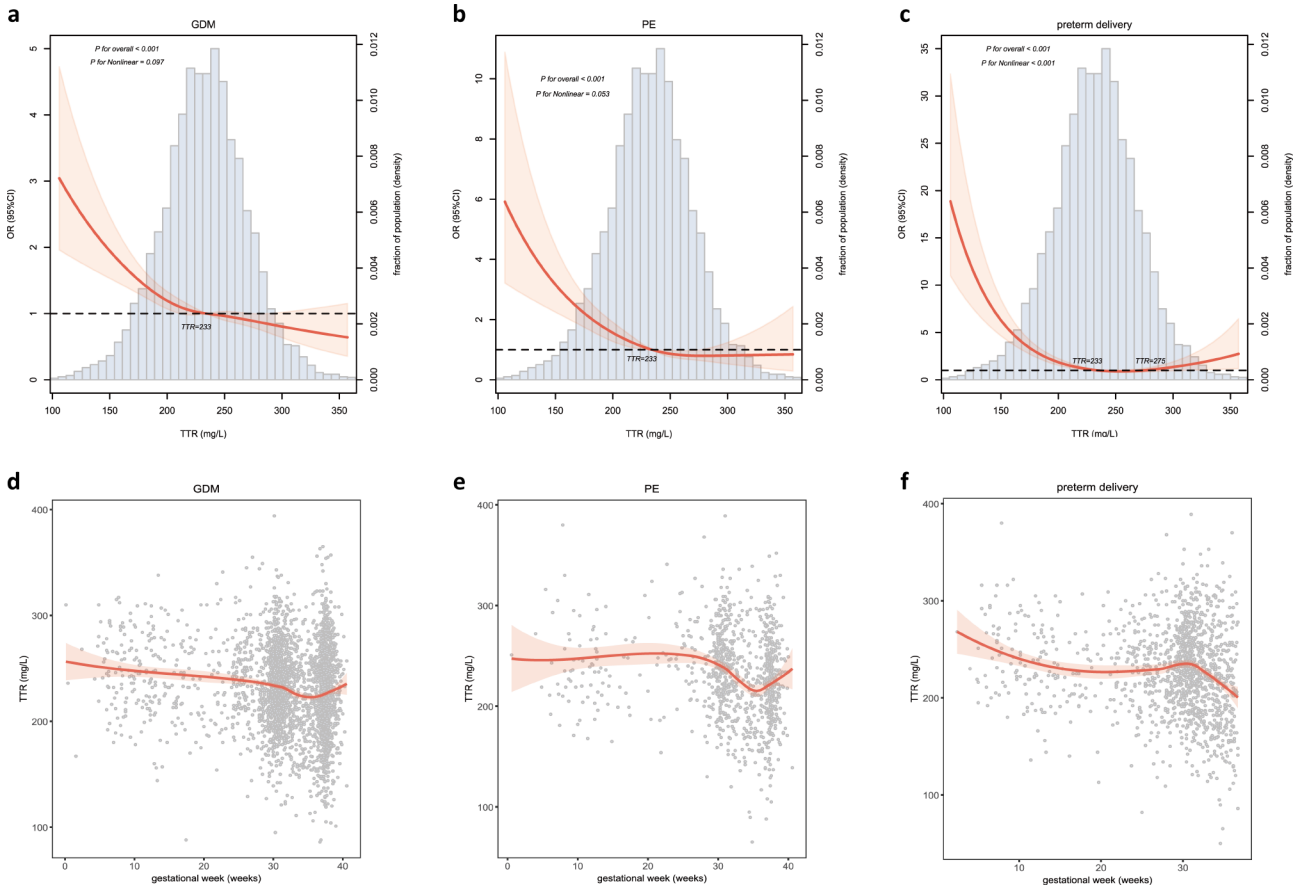

Fig. 2 The association of serum TTR concentration with prevalence risks and gestational week-related changes in GDM, PE and preterm delivery. CI, confidence interval; OR, odds ratio; TTR, transthyretin; GDM, gestational diabetes mellitus; PE, preeclampsia. **a ~ c**: Restricted cubic spline curve showing the relationship between TTR and GDM, PE, preterm delivery. TTR 233 mg/L was selected as the reference level. The solid lines indicate adjusted odds ratios (OR) and the light red areas indicate 95% confidence intervals (CI). Knot positions were set at 5%, 35%, 65%and 95% of the distribution of TTR. The histogram shows the distribution density of TTR in the population. **a, b**: Adjusted for child sex, maternal age, pre-pregnancy BMI, marital status, education level, parity, gestational age, hepatitis virus carrying status, chronic hypertension and pregestational diabetes. **c:** Adjusted for child sex, maternal age, pre-pregnancy BMI, marital status, education level, parity, hepatitis virus carrying status, chronic hypertension and pregestational diabetes. **d ~ f**: Scatter plot showing the distribution of data for TTR and gestational week. Smoothing lines with locally estimated scatter plot smoothing were drawn in red (confidence interval in light red)

U-shaped nonlinear relationship between TTR concentration and both liver disease (P for Nonlinear < 0.001), and hypothyroidism (P for Nonlinear = 0.023). Furthermore, a nonlinear decreasing trend in the risk of anemia during pregnancy was observed as maternal TTR levels increased (P for Nonlinear = 0.017), exhibiting an initial slow decline followed by a more pronounced decrease.

The LOESS curve analysis indicated that TTR levels gradually decreased with each advancing week of pregnancy up to approximately the 30th week, after which a sharp decline was observed, reaching a nadir around the 35th week of gestation. Subsequently, TTR levels trended upward towards the end of gestation; however, they did not surpass the levels observed during the first trimester (Fig. 2d). This pattern was particularly pronounced in cases of PE. This contrasted with the control group, in which the curve was remarkably stable without significant fluctuations (supplementary Fig. 1).

Association of TTR levels with fetal complications

The study identified a nonlinear relationship between maternal TTR levels and the risks of preterm delivery (P for Nonlinear < 0.001), characterized by an U-shaped curve (Fig. 2c). The analysis showed that maternal TTR levels < 233 mg/L were associated with a reduced risk of preterm delivery, while levels > 275 mg/L were linked to an increased risk. The LOESS curve revealed a downward trend in maternal TTR concentration as pregnancy progressed, with a notable acceleration in this decline observed around the 30th weeks of gestation. By the time of delivery, maternal TTR levels had decreased to approximately 200 mg/L.

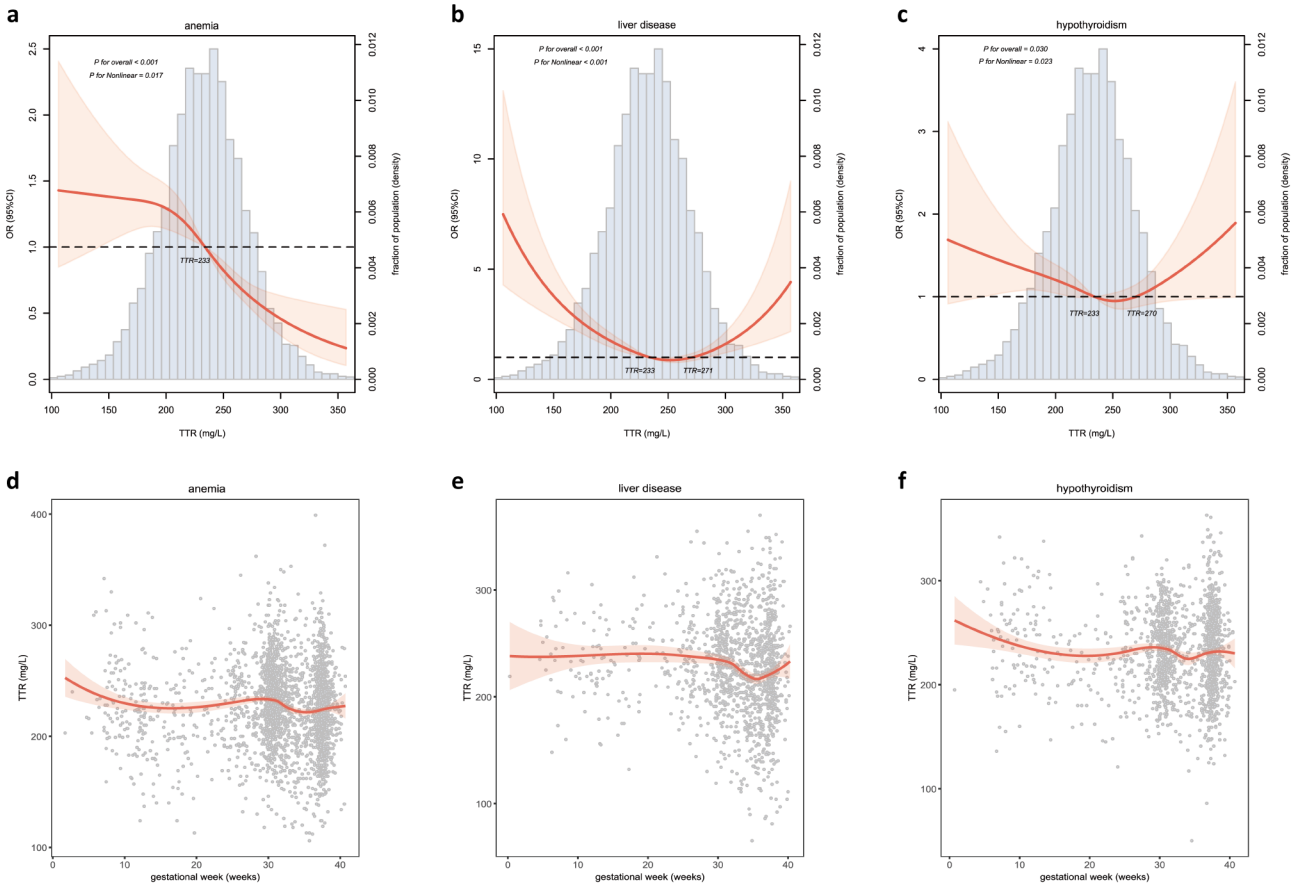

Fig. 3 The association of serum TTR concentration with prevalence risks and gestational week-related changes in anemia, liver disease, and hypothyroidism. CI, confidence interval; OR, odds ratio; TTR, transthyretin. **a ~ c**: Restricted cubic spline curve showing the relationship between TTR and anemia, liver disease, hypothyroidism. TTR 233 mg/L was selected as the reference level. The solid lines indicate adjusted odds ratios (OR) and the light red areas indicate 95% confidence intervals (CI). Knot positions were set at 5%, 35%, 65%and 95% of the distribution of TTR. The histogram shows the distribution density of TTR in the population. Adjusted for child sex, maternal age, pre-pregnancy BMI, marital status, education level, parity, gestational age, hepatitis virus carrying status, chronic hypertension and pregestational diabetes. **d ~ f**: Scatter plot showing the distribution of data for TTR and gestational week. Smoothing lines with locally estimated scatter plot smoothing were drawn in red (confidence interval in light red)

Discussion

Plasma TTR levels may fluctuate due to various factors, such as protein-calorie malnutrition, inflammatory conditions, and central nervous system disorders [27–30]. The observed initial decline followed by a subsequent increase in TTR levels in our study corresponds with existing findings that indicate a significant reduction in TTR levels during mid-pregnancy, which return to normal levels at term and postpartum. This trend is particularly pronounced in women experiencing PE and preterm birth within our study cohort.

The mechanism of the relationship between TTR concentration and GDM remains unclear. Our research indicated that TTR presence in serum during pregnancy may negatively impact GDM. It has been reported that serum TTR concentrations were higher in women with GDM, suggesting that increased levels of TTR could be involved in the development of GDM which was contrary to our findings [31]. However, the aforementioned study included only 97 pregnant women, a significantly smaller sample size compared to our study. Previous studies have shown that TTR plays a role in inhibiting the interaction between holo-RBP (RBP bound to retinol) and STRA6 [32]. Consequently, TTR may inhibit RBP-induced insulin resistance, potentially explaining why higher TTR levels may serve as a protective factor against GDM in our study [32].

Consistent with our findings, previous research has shown that the average serum TTR concentration of each gestational month in PE is significantly lower than in healthy pregnancies [33]. The characteristic of shallow trophoblast invasion is a fundamental pathological feature in PE, and TTR plays an important role in modulating the invasion and migratory capabilities of trophoblasts [1]. One research suggests that TTR could potentially regulate trophoblast proliferation or trigger apoptosis in endothelial cells [34]. In a 2013 study conducted by Kalkunte, it was demonstrated through mouse

Table 4 Presented the adjusted associations between maternal TTR levels and fetal outcomes, including preterm birth, SGA and LGA, highlighting their prevalence rates across difference TTR levels categories. In this study, 309 fetuses (4.7%) were delivered preterm. Additionally, 446 fetuses (6.8%) were SGA, while 560 fetuses (8.5%) were LGA. When maternal TTR concentration was analyzed both as a categorical variable by quartiles and as a continuous variable, a statistically significant association was observed with preterm delivery (adjusted OR 0.986 [95% CI 0.983–0.989]; $P < 0.001$). There were no significant associations observed between maternal TTR concentration and the risks of SGA or LGA (all $P > 0.05$)

	TTR (mg/L)	As continuous	Quartiles			
			Q1: ≤210	Q2:210 < X ≤ 234	Q3:234 < X ≤ 257	Q4:>257
Preterm delivery*	n (%)	309 (4.7)	144 (8.5)	57 (3.4)	54 (3.3)	54 (3.4)
	OR (95%CI)	0.986 (0.983,0.989)	1.00	0.38 (0.28,0.52)	0.34 (0.24,0.47)	0.36 (0.26,0.50)
	P	**< 0.001**		**< 0.001**	**< 0.001**	**< 0.001**
SGA**	n (%)	446 (6.8)	130 (7.7)	108 (6.5)	96 (5.9)	112 (7.0)
	OR (95%CI)	1.000 (0.998,1.003)	1.00	0.96 (0.73,1.26)	0.90 (0.68,1.20)	1.09 (0.83,1.42)
	P	0.778		0.751	0.483	0.559
LGA**	n (%)	560 (8.5)	144 (8.5)	150 (9.0)	137 (8.5)	129 (8.0)
	OR (95%CI)	0.998 (0.996,1.001)	1.00	1.04 (0.82,1.33)	0.93 (0.72,1.20)	0.88 (0.68,1.13)
	P	0.207		0.741	0.573	0.307

Table 4. Adjusted associations of maternal TTR concentration in pregnancy with fetal complications.

CI, confidence interval; OR, odds ratio; TTR, transthyretin; SGA small for gestational age; LGA, large for gestational age.

*All models adjusted for child's sex, maternal age, pre-pregnancy BMI, marital status, education level, parity, hepatitis virus carrying status, chronic hypertension and pregestational diabetes.

**All models adjusted for child's sex, maternal age, pre-pregnancy BMI, marital status, education level, parity, gestational age, hepatitis virus carrying status, chronic hypertension and pregestational diabetes

models that the supplementation of natural TTR during the early stages of pregnancy can help prevent the onset of preeclampsia [34]. Recent studies have revealed that transthyretin misfolding and aggregation may drive the progression of preeclampsia through diverse mechanisms. Specifically, pathological aggregation of this protein has been implicated in inducing vascular endothelial dysfunction and placental ischemic injury, two hallmark pathological events in preeclampsia pathogenesis [16]. Therefore, TTR may be used as a potential biomarker for PE [35].

In addition, we observed a nonlinear relationship between maternal TTR concentration and the risk of liver disease, anemia, hypothyroidism and preterm delivery, indicating that TTR plays a complex role in these conditions. To our knowledge, this is the first study to detect TTR concentrations in relation to these specific diseases during pregnancy. Our research revealed a notable decrease in the risk of anemia with increasing maternal TTR concentrations. This novel observation aligns with the understanding of TTR's nutritional and health implications. The coexistence of malnutrition and anemia can often be attributed to similar underlying causes, including poor diet and absorption issues, suggesting a strong correlation between the two conditions. Especially, a notable 'U' shaped trends were observed among TTR levels and conditions such as liver disease, hypothyroidism and preterm delivery. This finding indicates an elevated risk for these conditions when TTR concentrations are either excessively low or exceedingly high. TTR is a highly conserved protein involved in the transportation of thyroxine (T4) and retinol-binding protein [2]. The mechanism underlying the changes in transthyretin (TTR) levels in hypothyroidism requires further investigation. It is currently believed that preterm labor arises from various causes, including infection or inflammation, decidual haemorrhage and uterine overdistension [36–38]. Inflammation is known to decrease serum TTR levels, which may elucidate the increased risk of preterm birth associated with low TTR concentrations [39]. Our study suggests that TTR has diverse roles beyond its primary function as a transport protein, warranting further investigation to understand these additional functions.

The current study has several advantages. Firstly, we conducted an analysis to explore the relationship between serum TTR levels and pregnancy-related complications, as there was limited research available on TTR levels in pregnant women. Secondly, our study utilized a comparatively large sample size from a tertiary care center. Based on these data, we comprehensively studied these most frequent pregnant complications, aiming to fill knowledge gap in the existing literature on TTR during pregnancy. Thirdly, we performed RCS curve to visually represent the potential nonlinear trend between TTR concentration and the risk of complications and LOESS curve to explore if gestational age alters TTR concentration patterns, which represented a methodological advancement.

There are several limitations to this study: Firstly, we focused on serum TTR measurements obtained within two weeks prior to delivery which remains uncertain as to whether we adequately captured the pivotal period

during pregnancy that may significantly influence the outcomes studied here. Secondly, although adjusting for a comprehensive array of confounding variables, there remain potential confounders that could not be controlled. Thirdly, the retrospective nature of this study has poor ability to establish causality, and we could not conclusively prove a direct causal relationship between TTR concentration and the occurrence of complications. Fourthly, we did not evaluate the levels of inflammatory biomarkers, but existing research suggests that plasma TTR levels may be slightly influenced by inflammation or infection [40].

Conclusion

In this study, maternal serum TTR levels were found to be a risk factor for many complications. Apart from its negative correlation with the risk of GDM and PE, significant non-linear relationships were discovered between TTR concentrations and liver disease, anemia, hypothyroidism and preterm delivery. These findings suggest a complex relationship between TTR concentrations and pregnancy-related complications. Further research is essential to explore the possible underlying mechanisms that might explain the association between TTR levels and various complications during pregnancy.

Supplementary Information

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Supplementary Material 1

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Author contributions

HZH and FW conceived and designed the study. HZH and ZYL collected and analyzed the data. ZYL and LW verified the data reported in the manuscript. HZH wrote the paper. YSZ and CQX contributed to project management and critical revision of the manuscript. All authors contributed to the interpretation of the results and assisted with critical comments and revisions of the article.

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Data availability

Upon reasonable request, the corresponding author will provide the dataset used and/or analyzed during the study.

Declarations

Ethics approval and consent to participate

Ethics Committee of the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University (2021-K-318-02) waived the need of informed consent as a retrospective study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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