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Original article

Effect of maternal thyroid hormone levels in late pregnancy on risk of singleton low birth weight

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Abstract. *Background and aim:* To explore the effect of maternal thyroid hormone levels in late pregnancy on the risk of singleton low birth weight (LBW). *Methods:* A total of 3757 puerperae who gave birth from September 2019 to October 2020 were divided into case group (n=249, <2500 g) and control group (n=3508, >2500 g). The baseline clinical data of puerperae were collected, and the thyroid hormone levels were compared. The factors with differences were incorporated into LASSO-logistic multivariate regression analysis, the associations between clinical data and thyroid hormone levels were analyzed, and the predictive efficiencies of thyroid hormones for the risk of LBW were assessed using receiver operating characteristic (ROC) curves. *Results:* Case group had lower level of free triiodothyronine (FT3) and higher levels of free thyroxine (FT4) and thyroid-stimulating hormone (TSH) than those of control group (P<0.05). The results of LASSO-logistic regression analysis showed that FT3, FT4 and TSH levels were independent influencing factors for the risk of singleton LBW. The FT3 level was negatively correlated with premature labor, gestational hypertension, gestational anemia and fewer prenatal examinations, the FT4 level was positively correlated with premature labor and placenta previa, and the TSH level had positive correlations with premature labor, gestational hypertension and gestational anemia. According to ROC analysis, the FT3, FT4 and TSH levels had high predictive efficiencies for the risk of LBW. *Conclusion:* The decreased level of maternal FT3 and increased levels of FT4 and TSH in late pregnancy raise the risk of singleton LBW.

Key words: thyroid hormone; pregnancy; low birth weight

Introduction

Birth weight is an important index measuring the status of nutrition and development of fetuses in the uterus, and also an important index reflecting the social economy, sanitary status and maternal/child health care status of a country or region (1). The risk of low birth weight (LBW), defined as neonatal birth weight less than 2500 g, is closely related to the perinatal infant mortality and the occurrence and development of chronic diseases (2). LBW can inhibit neonatal growth and cognitive development, severely affecting neonatal health. There are many influencing factors for the neonatal birth weight, the most important of which are the *in utero* growth rate and the duration of pregnancy (3). Thyroid hormones are of great importance for the normal fetal growth and development, and they can stimulate the metabolism of all tissues in the human body (4). The levels of fetal thyroid hormones in early pregnancy depend on the levels of maternal thyroid hormones, and they are still affected by the mother at about 18-20 weeks of pregnancy even though the fetal thyroid function becomes mature (5). With physiological changes in the maternal thyroid function during pregnancy, the levels of thyroid hormones change accordingly, and the body's demand for thyroid hormones

rises. The change in maternal thyroid hormone levels has close associations with pregnancy outcome and fetal growth and development (6). It has been shown that hypothyroidism in pregnant women can result in premature labor, LBW, intellectual and motor impairment, and even perinatal infant death in severe cases (7). Current research mostly focuses on the effect of the maternal thyroid function in early pregnancy on fetal development, but the maternal thyroid hormone levels in late pregnancy remain to be further explored. This study aims to explore the effect of maternal thyroid hormone levels in late pregnancy on the risk of LBW.

Methods

A total of 3757 puerperae who gave birth in our hospital from September 2019 to October 2020 were selected as the subjects according the following inclusion criteria: 1) singleton live birth, and 2) complete clinical data. Exclusion criteria were as follows: 1) puerperae complicated with other vital organ diseases, 2) those with fetal chromosomal variation found in prenatal examinations, or 3) those receiving artificial inducement of labor. This study had been approved by the Ethics Committee of our hospital, and all the puerperae and their families participated voluntarily in the study and signed the informed consent.

The general data of all puerperae were collected, including gestational age, gestational week, childbearing history, physical health status and prenatal examination results. After 28 gestational weeks, 5 mL of fasting venous blood was drawn from each puerpera, placed in an anticoagulant tube and centrifuged at 3000 r/min for 15 min at room temperature. Then the isolated serum was stored at -20°C for the detection of levels of free triiodothyronine (FT3), free thyroxine (FT4) and thyroid stimulating hormone (TSH). The levels of serum FT3 and FT4 were detected using a Cobas E602 analyzer, and the TSH level was detected using a Cobas E601 analyzer. After successful labor, the newborn was wiped clean with disinfectant wipes, and weighed flat on an electronic baby scale in a quiet state.

Standardized prenatal examinations referred to at least 5 prenatal examinations during pregnancy. Premature labor was defined as labor after 28 weeks and before 37 weeks of gestation. LBW infants were those with birth weight of less than 2500 g. The puerperae who gave birth to LBW infants were enrolled as case group, and the remaining puerperae as control group.

SPSS 23.0 and R 4.0.2 software were used for statistical analysis. Kolmogorov-Smirnov test of normality was conducted on continuous data. The normally distributed continuous variables were expressed as ($\bar{x}$ ± s), and whether they had statistically significant differences between two groups was detected by *t* test. Categorical variables were expressed as frequency (percentage), and whether they had statistically significant differences between two groups was detected by c^2 test. The influencing factors for LBW were explored by LASSO-logistic regression analysis, Spearman rank correlation test was conducted between thyroid hormone levels and clinical data, and the predictive efficiencies of thyroid hormones for the risk of LBW were assessed using receiver operating characteristic (ROC) curves. $P<0.05$ was considered statistically significant, and the test level was set at $\alpha=0.05$.

Results

The basic data of puerperae such as age, gestational week, pregnancy-labor history, mode of delivery and concurrent diseases were compared between the two groups. As shown in Table 1, the proportions of puerperae who had old age, premature labor, gestational hypertension, gestational anemia and placenta previa, and received prenatal examinations less than 5 times in case group were significantly higher than those in control group, and the differences were statistically significant ($P<0.05$). No statistically significant differences were found in the mode of delivery, primipara or not, and the proportion of puerperae with gestational diabetes mellitus between the two groups ($P>0.05$).

The maternal thyroid hormone levels in late pregnancy were compared between the two groups. As shown in Table 2, case group had a lower level of FT3 and higher levels of FT4 and TSH than control group ($P<0.05$).

Old age, premature labor, gestational hypertension, gestational anemia, times of prenatal

Table 1. Baseline clinical data of puerperae

Item	Case group (n=249)	Control group (n=3508)	t/c^2	P
Mode of delivery [n(%)]			0.173	0.677
Vaginal delivery	54 (21.69)	722 (20.58)		
Caesarean section	195 (78.31)	2786 (79.42)		
Old age [n(%)]			4.164	0.041
Yes	90 (36.14)	1052 (29.99)		
No	159 (63.86)	2456 (70.01)		
Premature labor [n(%)]			153.774	0.000
Yes	217 (87.15)	98 (2.79)		
No	32 (12.85)	3410 (97.21)		
Primipara [n(%)]			3.532	0.060
Yes	87 (34.94)	1438 (40.99)		
No	162 (65.06)	2070 (59.01)		
Gestational hypertension [n(%)]			31.057	0.000
Yes	17 (6.83)	59 (1.68)		
No	232 (93.17)	3449 (98.32)		
Gestational diabetes mellitus [n(%)]			0.795	0.373
Yes	29 (11.65)	347 (9.89)		
No	220 (88.35)	3161 (90.11)		
Gestational anemia [n(%)]			8.831	0.003
Yes	114 (45.78)	1276 (36.37)		
No	135 (54.22)	2232 (63.63)		
Prenatal examinations <5 times [n(%)]			7.328	0.007
Yes	26 (10.44)	214 (6.10)		
No	223 (89.56)	3294 (93.90)		
Placenta previa			8.739	0.003
Yes	6 (2.41)	24 (0.68)		
No	243 (97.59)	3484 (99.32)		

examinations, placenta previa, and levels of FT3, FT4 and TSH as independent variables, and LBW or not as a dependent variable were incorporated into the LASSO-Logistic regression analysis model (Figure 1). The optimal λ value was selected by cross-validation, and the folding times were 10. In the left figure, the lower abscissa shows the logarithmic value of λ, the upper abscissa shows the number of nonzero coefficient variables entering the model, and the ordinate is the target parameter. The right figure displays the screening of each independent variable with the change in λ value. With the increase in the λ value, the degree of model compression rose, the number of independent variables entering the model declined,

Table 2. Maternal thyroid hormone levels in late pregnancy

Item	Case group (n=249)	Control group (n=3508)	t	P
FT3 (pmol/L)	1.57±0.65	2.93±0.52	9.158	0.000
FT4 (pmol/L)	13.62±5.39	9.15±4.79	14.106	0.000
TSH (mIU/L)	4.93±0.57	1.86±0.23	17.585	0.000

FT3: Free triiodothyronine; FT4: free thyroxine; TSH: thyroid stimulating hormone.

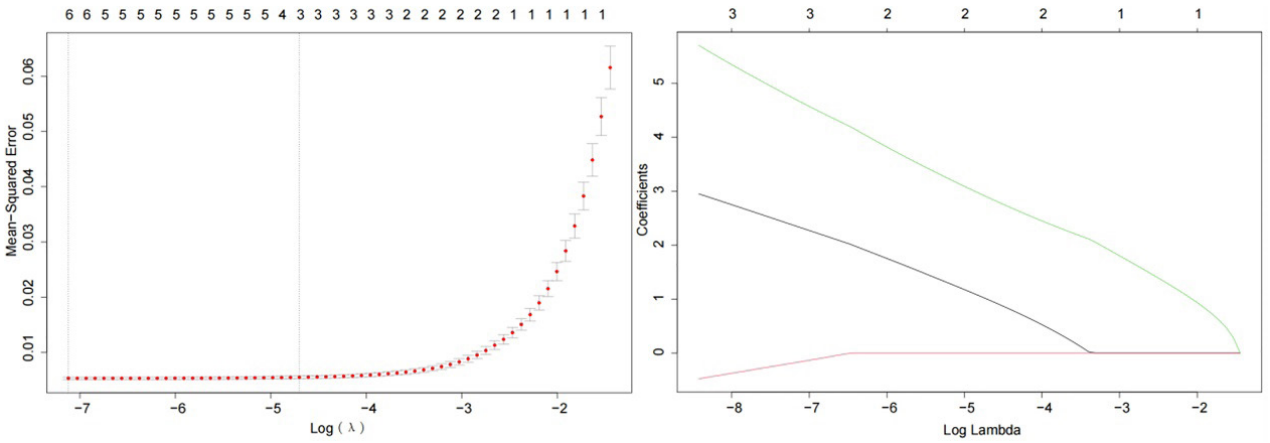

Figure 1. Selection of variables by LASSO-Logistic regression model. The optimal value was determined in the LASSO model by 10-fold cross-validation and the minimum criterion (left figure). LASSO coefficient curve of maternal clinical features (right figure).

and the ability of the model to select major variables became stronger. The value of lambda.1se was 0.009, in which case FT3, FT4 and TSH entered the model.

Correlation analysis was conducted between the age and gestational week of puerperae and the maternal thyroid hormone levels in late pregnancy. It was found that the FT3 level was negatively correlated with premature labor, gestational hypertension, gestational anemia and fewer prenatal examinations, the FT4 level was positively correlated with premature labor and placenta previa, and the TSH level had positive correlations with premature labor, gestational hypertension and gestational anemia (Table 3).

The predictive efficacy of thyroid hormones for the risk of LBW was assessed using ROC curves. The results showed that the area under the ROC curve (AUC), sensitivity and specificity of TSH were 0.868, 78.3% and 83.5%, respectively. The AUC, sensitivity and specificity of FT4 were 0.851, 78.1% and 80.2%, respectively. The AUC, sensitivity and specificity of FT3 were 0.791, 68.4% and 85.7%, respectively (Figure 2).

Discussion

Birth weight is not only an important index for *in utero* growth and development of fetuses and their adaptation to the uterine environment, but also a basic index reflecting the neonatal health status, and LBW is an important cause of neonatal death (8). Research suggests that there are approximately 20 million LBW infants every year globally, and the risk of LBW in developing countries is twice that in developed countries (9). According to a survey, the morbidity rate of pregnancy complicated with subclinical hypothyroidism is 2-10% in China (10), which may lead to a variety of

Table 3. Correlations between basic data and thyroid hormone levels

Item		Old age	Premature labor	Gestational hypertension	Gestational anemia	Prenatal e xamination <5 times	Placenta previa
FT3	*r*	-0.010	-0.240	-0.046	-0.029	-0.026	0.003
	P	0.433	0.000	0.000	0.031	0.049	0.837
FT4	*r*	0.013	0.127	0.013	0.005	0.022	0.029
	P	0.319	0.000	0.347	0.730	0.099	0.027
TSH	*r*	0.026	0.258	0.074	0.030	0.008	0.026
	P	0.050	0.000	0.000	0.023	0.549	0.054

FT3: Free triiodothyronine; FT4: free thyroxine; TSH: thyroid stimulating hormone.

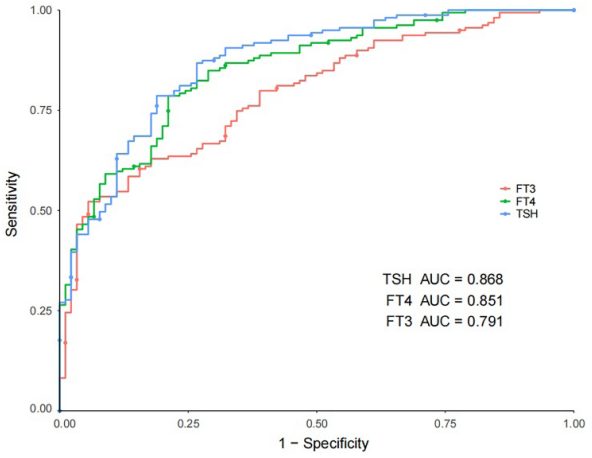

Figure 2. Predictive efficiencies of FT3, FT4 and TSH for risk of LBW using ROC curves. FT3: Free triiodothyronine; FT4: free thyroxine; LBW: low birth weight; ROC: receiver operating characteristic; TSH: thyroid stimulating hormone.

adverse pregnancy outcomes, such as LBW infants, premature labor, placental abruption, premature rupture of membranes, small-for-gestational-age infants and postpartum hemorrhage (11). Maraka *et al*. (12) analyzed the pregnancy outcomes of pregnant women with subclinical hypothyroidism in different trimesters of pregnancy, and found that pregnant women with subclinical hypothyroidism in the third trimester had a higher risk of premature labor and LBW infants than those in the first and second trimesters, suggesting that the changes in thyroid hormone levels in the third trimester have greater impact on pregnancy outcomes than those in the first and second trimesters. However, the associations between thyroid hormone levels in late pregnancy and neonatal birth weight remain unclear, so the maternal thyroid hormone levels in late pregnancy and related clinical data were analyzed in this study, hoping to find out their influence on LBW.

In this study, the proportions of puerperae who had old age, premature labor, gestational hypertension, gestational anemia and placenta previa, and received prenatal examinations less than 5 times in case group were higher than those in control group, and case group had a lower level of FT3 and higher levels of FT4 and TSH than control group. According to LASSO-Logistic regression analysis, the levels of FT3, FT4 and TSH were important influencing factors for LBW. FT3 existing in the blood in a free form is an important index for diagnosing hypothyroidism and hyperthyroidism, assessing the severity of thyroid diseases and detecting the curative effect (13). Zhou *et al*. (14) analyzed the associations between thyroid hormone levels and pregnancy outcomes among 8107 pregnant women in Wuhan, and found that the maternal FT3 level during pregnancy was associated with an increased risk of LBW. In this study, the level of FT3 in late pregnancy in case group was significantly lower than that in control group, and the results of regression analysis showed that the FT3 level was an important influencing factor for LBW. FT4 secreted by thyroid follicular cells exists in the blood in a free form, and is free from influence of thyroid hormone-binding protein, which can reflect the thyroid function more accurately than total thyroid hormone (15). Zhang *et al*. (16) revealed an association between a high FT4 level in pregnant women in late pregnancy and LBW. In this study, the FT4 level in late pregnancy in case group was higher than that in control group, and it was confirmed by LASSO regression analysis to be an important influencing factor for neonatal birth weight. Besides, TSH is the major regulator of thyroid morphological and functional status, and its level is an effective index for detecting the thyroid function (17), *i.e.*, a higher TSH level than the reference value suggests hypothyroidism, while a lower TSH level than the reference value suggests hyperthyroidism. Human chorionic gonadotropin (hCG) leads to the changes in the TSH level during pregnancy, which, with thyroid-stimulating activity, makes the TSH level decrease in the first trimester, begin to increase in the second trimester, and peak in the third trimester. A foreign study showed that there is a significant association between an increased TSH level during pregnancy and the risk of LBW (18). In a prospective cohort study on the relation between the TSH level and neonatal weight conducted by Guo *et al*. (19) among 1931 pregnant women at 28-36 weeks of gestation, a significant negative correlation was found between the TSH level in late pregnancy and the neonatal birth weight. In this study, case group had a significantly higher level of TSH than control group, and LASSO-Logistic regression analysis manifested that the TSH level was an important factor affecting the risk of LBW.

An association has been found between maternal age and LBW in a retrospective study (20), and the possible reason is that elderly puerperae have increased placental vascular damage, affecting the nutritional supply to the fetus. Gestational anemia affects the fetal blood supply during pregnancy and leads to malnutrition during fetal development, thereby resulting in LBW. According to a foreign study, premature labor has a significant association with LBW (21), the fetal weight gain reaches the peak in the third trimester, and the risk of LBW rises among newborns of less than 38 weeks of gestation. Gestational hypertension may cause arteriolar spasm in pregnant women, so that the supply of oxygen and nutrients to the placenta and uterus becomes insufficient, ultimately resulting in LBW. Moreover, the association between prenatal examinations and the risk of LBW was reported in a study in China, and the results showed that the risk of LBW in pregnant women receiving fewer prenatal examinations is 2.34 times that in pregnant women receiving standardized prenatal examinations (22). Placenta previa refers to the position of the placenta covering the internal cervical opening, and it causes repeated bleeding in pregnant women and placental insufficiency, affecting the nutritional supply, growth and development of the fetus. In this study, the proportions of puerperae who had old age, premature labor, gestational hypertension, gestational anemia and placenta previa, and received prenatal examinations less than 5 times had significant differences between case group and control group, suggesting that adequate nutrition and standardized prenatal examinations during pregnancy should be ensured for pregnant women to avoid the risk of LBW.

In conclusion, the decreased level of maternal FT3 and increased levels of FT4 and TSH in late pregnancy will raise the risk of LBW. Regardless, this study is still limited. This is a single-center study with a short research duration, which may lead to bias. Further multicenter long-term studies with larger sample sizes are ongoing in our group.

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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