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Influence of screening and intervention of hyperthyroidism on pregnancy outcome

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Abstract. – OBJECTIVE: To discuss the influence of screening and intervention of hyperthyroidism on pregnancy outcome.

PATIENTS AND METHODS: The clinical data of 122 pregnant women who had been confirmed with hyperthyroidism from April 2012 to July 2014 in the Weifang People's Hospital were analyzed retrospectively (25 untreated, 97 treated). 60 with normal pregnancy check were randomly selected as control group. The pregnancy outcomes of the two groups of patients were analyzed.

RESULTS: Among 10,427 pregnant women, 122 of them were diagnosed with hyperthyroidism, the prevalence of hyperthyroidism and subclinical hyperthyroidism were 0.44% and 0.73%. The occurrence of adverse maternal, obstetric complication, and adverse perinatal infant of the untreated group was higher than that of the treated group, and the inter-group differences were of statistically significance ($p<0.05$). However, the comparison of treated group and control group showed that there was no statistical significance in occurrences of adverse maternal, obstetric complication, and adverse perinatal infant ($p>0.05$).

CONCLUSIONS: Timely screening for gestational thyroid disease and actively intervention treatment can significantly improve the outcome of pregnancy.

Key Words:
Pregnancy, Hyperthyroidism, Screening, Intervention, Pregnancy outcome.

Introduction

As a common endocrine disease existed in women in the reproductive period, hyperthyroidism is caused by hypersecretion of thyroid hormones and featured by increased excitability or hypermetabolism of circulation, nerve, and digestion system. Diffuse toxic goiter (Graves' disease) is one of the most common causes of such disease, accounting for about 85%. It is more common in women of childbearing age, and women's occurrence is about 4 to 6 times of men. Hyperthyroidism in pregnancy is very rare, with an occurrence rate from 0.02% to 0.1% as shown in some literature[1,2]. In recent years, with the development of medical and health care, people's enhanced awareness of health and standardization of examination during pregnancy, hyperthyroidism's harm to pregnant women has attracted increasing attention. Pregnancy with severe hyperthyroidism is a high-risk pregnancy. If pregnant patients with hyperthyroidism are not properly treated, adverse pregnancy outcome can be easily caused, such as premature birth, abortion, stillbirth and fetal abnormalities, which may lead to severe complications such as congestive heart-failure, pregnancy hypertension, hyperthyroidism crisis, infection, placental abruption, anemia and premature rupture of fetal membranes. Except for gestational diabetes mellitus, pregnancy complicated by hyperthyroidism is the second major reason for increased pregnant women and fetal fatality rate[3,4]. Control of hyperthyroidism in pregnancy is the key to reduce adverse pregnancy outcome of hyperthyroidism patients in pregnancy. In this study, hyperthyroidism screening of patients receiving routine pregnancy check in our hospital was conducted. The clinical data of 122 patients diagnosed as hyperthyroidism in pregnancy were retrospectively analyzed. The influence of screening and intervention of hyperthyroidism on pregnancy outcome was discussed.

Patients and Methods

Patients

The 10,427 pregnant women receiving routine pregnancy check in Weifang People's Hospital from April 2012 to July 2014 were collected, 122 of which were diagnosed with hyperthyroidism. Among them, 97 cases were treated by standard

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therapy, 25 cases were not given standard treatment due to various reasons. The 60 cases with normal pregnancy check were randomly selected as control group.

Inclusion criteria

Research objects were selected according to the standard recommended by American College of Clinical Biochemistry (NACB): (1) no history of drug administration (excluding estrogen) which may have an effect on thyroid function; (2) no previous history, family history of thyroid disease, no previous history of autoimmune disease; (3) thyroid is normal in size without enlargement; (4) no *hyperemesis gravidarum*, trophoblastic cell disease, preeclampsia; (5) singleton pregnancy; (6) antithyroglobulin antibody (TgAb), thyrotropin receptor antibody (TRAb) are negative. Another 60 healthy pregnant women receiving routine pregnancy check in the same period in our hospital were selected for normal control.

Methods

Clinical Diagnosis

(1) Past medical history;

(2) Clinical symptoms;

Due to severe changes in the mother's internal environment during pregnancy, there may be similar symptoms with hyperthyroidism, so it should be firstly decide whether it is a normal metabolic change in pregnancy. Common hyperthyroidism symptoms include diffuse goiter, with palpable tremor and hearable vascular murmur, heat intolerance, sweating, and erubescence. The special wetting eye disease is one of the symptoms in Graves' disease such as palpitation, tachycardia beyond the normal range, prominent eyes, polyphagia but lose weight in different degrees, involuntary activities, hand and foot trembling.

(3) Treatment and follow-up history.

Laboratory Diagnosis

Specimen collection: 3 mL of fasting venous blood sample was collected and placed at room temperature for 1 h; then it was store it at -80°C refrigerator for central detection.

Detection methods: Modular analytic 170 electrochemiluminescence immunoassay analyzer system provided by Roche Diagnostics Company (Berlin, Germany) and the corresponding reagents were used to measure free thyroid triiodothioate (FT3) and free thyroxine (FT4). FT3 reference value ranges from 0.5 to 44 pmol/L; FT4 reference value ranges from 11.5 to 23.0 pmol/L. The kit (Tianjin Hao Yang Biological Manufacture Co., Ltd, Tianjin, China) was used to detect thyroid-stimulating hormone (TSH). TSH reference value range: 0.25-4.0 mIU/L. The kit (Heraeus, Hanau, Germany) was used to detect thyroid peroxidase antibody (TPOAb). TPOAb reference value range: 0-15 IU/L.

Diagnostic criteria

1) Clinical hyperthyroidism: hyperthyroidism in pregnancy has certain specificity, so diagnosis is mainly based on serum FT4, FT3, TSH. TSH < 0.25 mU/L, FT3 and/or FT4 levels increased. 2) Subclinical hyperthyroidism: excluding other factors influencing TSH level, TSH test value is below the reference value, while FT3, FT4 levels are normal. 3- TPoAb(+): TPoAb > 9.0 U/mL; TPoAb(-):TPoAb < 0.25 U/mL. See Table I for specifics[5].

Table I. The normal range of TSH and FT4 during the pregnant period.

	Reagent company	Early pregnancy	Mid pregnancy	Late pregnancy
TSH (mU/L)	DPC 1	0.13~3.93	0.26~3.50	0.42~3. 85
	Abbott 2	0.03~3.6	0.27~3.8	0.28~5.07
	Roche 2	0.05~5.17	0.39~5.22	0.6~6.84
	Bavar 3	0.03~4.51	0.05~4.50	0.47~4.54
FT4 (pmol/L)	DPC 1	12.00~23.34	11.20~21.46	9.80~18.20
	Abbott 2	11.49~18.84	9. 74~17.15	9.63~18.33
	Roche 2	12.91~22.35	9. 81~17.26	9.12~15.71
	Bavar 3	11.80~21.00	10.6~17.60	9.20~16.70

Hyperthyroidism in pregnancy has certain specificity, so diagnosis is mainly based on serum FT4, FT3, TSH. TSH < 0.25 mU/L, FT3 and/or FT4 levels increased. Subclinical hyperthyroidism: excluding other factors influencing TSH level, TSH test value is below the reference value, while FT3, FT4 levels are normal. 3- TPoAb(+): TPoAb > 9.0 U/mL; TPoAb(-):TPoAb < 0.25 U/mL.

Table II. Population prevalence.

	Number	Hypothyroidism	Subclinical hypothyroidism	Hyperthyroidism	Subclinical hyperthyroidism	Total
Early pregnancy	1855	107	106	31	22	266
Mid pregnancy	4311	43	238	15	43	339
Late pregnancy	4261	129	231	0	11	377
Total	10427	279	581	46	76	982

The 10427 selected research objects were screened. A total of 982 patients were detected with thyroid disease, including 122 patients with hyperthyroidism, 76 of which were patients with subclinical hyperthyroidism, 46 patients with clinical hyperthyroidism. There were 860 patients with hypothyroidism, including 581 patients with subclinical hypothyroidism and 279 patients with clinical hypothyroidism.

Intervention therapy

For patients with thyroid dysfunction in pregnancy, timely and appropriate intervention should be given according to the American Thyroid Society's program to reduce the occurrence of adverse pregnancy outcomes. Patients with mild hyperthyroidism are allowed to not receive drug treatment. Anti-thyroid drugs are mainly thiourea drugs including: methylthiouracil (MTU), propylthiouracil (PTU) of thiouracils, methimazole (MMI) and carbimazole (CMZ) of imidazole. Propylthiouracil and methimazole are commonly used. Anti-thyroid drugs make TSH level in normal range of the corresponding pregnant stage, while FT4 is close to or slightly higher than the upper limit of normal value. As T3-type hyperthyroidism in pregnant women can be expressed as normal maternal TT3 with increased fetal TSH, it is not recommended to take TT3 as a test index. Patients should be scheduled for review to have timely grasp of thyroid function changes. Drug dose should be adjusted according to the actual situation, which can be reduced to maintenance dose after gradual stabilization. Take PTU as an example, it can be seen that the commonly used dose in treatment period is 150-300 mg, while the maintenance dose can be 50-150 mg. In principle, the dose is the minimum dose that can control the symptoms to avoid the effect on fetal nervous system. Overtreatment can easily cause low thyroid function and neonatal goiter[4].

Follow-up Indicators

FT3, FT4, TSH detections were conducted monthly, to be respectively recorded. The pregnancy outcome of the three groups and the corresponding clinical data were recorded, such as pregnancy time, hypertension of pregnancy, hyperthyroid heart disease, premature birth, abortion, post-partum hemorrhage. Newborn's situation was recorded, including low birth weight, neonatal asphyxia, neonatal hyperthyroidism, and neonatal hypothyroidism.

Statistical Analysis

The SPSS 18.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The measurement data were expressed as mean ± standard deviation ($X \pm S$), with *t*-test for comparison between groups. The count data was expressed as rate, with χ^2-test for comparison between groups, with $p<0.05$, indicating that there is statistical significance.

Results

Thyroid disease prevalence

The 10427 selected research objects were screened. A total of 982 patients were detected with thyroid disease, including 122 patients with hyperthyroidism, 76 of which were patients with subclinical hyperthyroidism, 46 patients with clinical hyperthyroidism. There were 860 patients with hypothyroidism, including 581 patients with subclinical hypothyroidism and 279 patients with clinical hypothyroidism (see Table II). The prevalence rates were 0.73% (76/10427), 0.44% (46/10427), 5.58% (581/10427) and 2.68% (279/10427), respectively.

Clinical Data Statistics

The clinical data of the treated group, untreated group and control group were compared. According to statistical analysis, there can find no statistically significant difference between the treated group and the untreated group in hyperthyroidism classification and diagnosis time. The information is balanced (Table III).

Table III. Comparison of the general clinical data among three groups.

	Indexes	Untreated Group (n=25)	Treated group (n=97)	Control group (n=60)	F/χ^2	p
	Age	27.0±1.3	27.4±2.1	27.3±2.1	2.131	0.119
	BIM $\bar{x}\pm s$	24.2±1.5	23.7±2.2	23.9±2.4	0.261	0.761
Hyperthyroidism	Mild	13	58	-		
Classification	Moderate	9	22	-	1.966	0.374
	Severe	3	17	-		
The time	Before pregnancy	16	69	-	0.479	0.489
of diagnosis	After pregnancy	9	28	-		

According to statistical analysis, there can find no statistically significant difference between the treated group and the untreated group in hyperthyroidism classification and diagnosis time.

Comparison of Pregnancy Outcomes and Perinatal Infant Outcome Among the Three Groups

The occurrence rate of adverse pregnancy outcomes, obstetric complications (pregnancy hypertension, hyperthyroid heart disease, hyperthyroidism crisis, premature birth, abortion, and postpartum hemorrhage), and perinatal infant outcomes (low birth weight, neonatal asphyxia, neonatal hyperthyroidism, neonatal hypothyroidism) in untreated group are higher than those of the normal group. The difference is statistically significant ($p<0.05$). There is no statistical significance between the treated group and the normal group in adverse pregnancy outcome, obstetric complication rate and perinatal infant adverse outcome ($p>0.05$) (see Table IV).

Discussion

The thyroid gland is one of the most important endocrine organs of the human body. By secretion of thyroid hormones, thyroid gland regulates metabolism, growth rate, controls the speed of energy use, produces protein, adjusts the body's sensitivities to other hormones and other body system[6]. Substances required for fetal growth and development in the maternal body, including the thyroid hormones with important significance for its nervous system, are all from the mother. Hyperthyroidism will inevitably affect the normal development of the fetus and its health. Thyroxine binding globulin (TBG) during pregnancy will increase TT4, TT3 (FT4, FT3 levels do not change much). Human chorionic gonadotropin (HCG) increases from the 1th week after pregnancy and

Table IV. Comparison of pregnancy outcomes and perinatal infant outcome among three groups [n (%)].

Indexes	Untreated Group (n=25)	Treated group (n=97)	Control group (n=60)	F/χ^2	p
Hypertension of pregnancy	7 (28.00)	6 (6.18)	1 (1.67)	13.45*	0.001
Hyperthyroid heart disease	4 (16.00)	1 (1.03)	0 (0.00)	12.16*	0.001
Hyperthyroidism crisis	4 (16.00)	0 (0.00)	0 (0.00)	13.63*	<0.001
Abortion	3 (12.00)	7 (7.22)	0 (0.00)	10.01*	0.002
Premature birth	8 (32.00)	0 (0.00)	5 (8.33)	10.24*	0.004
Postpartum hemorrhage	3 (12.00)	0 (0.00)	0 (0.00)	10.01*	0.002
Low birth weight	9 (36.00)	6 (6.18)	3 (5.00)	15.92*	>0.001
Neonatal asphyxia	7 (28.00)	6 (6.18)	3 (5.00)	10.04*	0.005
Neonatal hyperthyroidism	4 (16.00)	1 (1.03)	0 (0.00)	11.19*	0.001
Neonatal hypothyroidism	4 (16.00)	1 (1.03)	0 (0.00)	11.19*	0.001

Note: *Fisher exact probability; a) The occurrence rate of adverse pregnancy outcomes, obstetric complications and perinatal infant outcomes in untreated group are higher than those of the normal group ($p<0.05$); b) There is no statistical significance between the treated group and the normal group in adverse pregnancy outcome, obstetric complication rate and perinatal infant adverse outcome ($p>0.05$).

reaches the peak at the 8th-10th week. If not increase sustainably, normal serum hCG changes will not lead to clinical hyperthyroidism, but there is great possibility of transient hyperthyroidism. HCG can inhibit pituitary-thyroid axis, which has a mirror image relationship with thyrotropic hormone (TSH), so pregnancy can aggravate symptoms of hyperthyroidism[3,7-9]. Therefore, prompt intervention is a must for hyperthyroidism in pregnancy. Van den Boogaard et al[10-11], after careful study, reckon that if hyperthyroidism in pregnancy is well controlled, it will not have a great impact on pregnancy. Otherwise, if the condition is severe or is not well controlled, probability of abortion, pregnancy hypertension, premature birth, perinatal death will be greatly improved. Thus, in maternal prenatal examination, screening and timely intervention of hyperthyroidism are very important. This study screened thyroid function of 10,427 pregnant women, finding that occurrence rate of hyperthyroidism in pregnancy was 1.17%, wherein the occurrence rate of clinical hyperthyroidism was 0.44%, while that of subclinical hyperthyroidism was 0.73%. The occurrence of abnormal thyroid function in pregnancy is on the rise according to related literature, of which occurrence of hyperthyroidism in pregnancy is low, ranging from 0.02% to 0.1%[1]. In this study, statistics of occurrence of hyperthyroidism in pregnancy differs greatly from the above data, because our hospital is a regional medical center with many high-risk pregnant women. Influence of hyperthyroidism on pregnancy outcome mainly depends on whether the patients receive regular treatment as well as on hyperthyroidism degree. If no systemic treatment is received or hyperthyroidism is severe, it can cause embryos to stop development in early pregnancy, eventually leading to abortion. In mid and late pregnancy, the occurrence of pregnancy hypertension is 3.5 times that of normal pregnant women, and neonatal premature birth is 5.8 times higher[12-14]. For the maternal body, uncontrolled hyperthyroidism may lead to hyperthyroid heart disease or even hyperthyroidism crisis. Hyperthyroid heart disease is mostly caused by long-term toxicity of high T4 hyperlipidemia on myocardial cell. Hyperthyroidism crisis occurrence can make maternal death rate reach 25% or above. The stress and pain stimulation during maternal delivery are common inducing factors[15]. Sustained high maternal thyroid hormone can exert negative feedback regulation of pituitary-thyroid axis, leading to lower tricarboxylic acid cycle level and lower energy. Fetus is prone to premature birth due to lack of energy, while increased thyroid hormone secretion can lead to sustained neuromuscular excitability, blood vessel spasm, increased uterine contraction, causing such adverse pregnancy outcomes as premature birth, abortion, postpartum hemorrhage, low birth weight, neonatal asphyxia, neonatal hyperthyroidism, neonatal hypothyroidism. With occurrence of premature birth reaching 11% to 25%, and intrauterine death rate reaching 8% to 15%[10-12,16-19]. Maternal and fetal thyroid system are interrelated. The mother's thyroid hormone levels will affect fetal thyroid development. In particular, thyroid hormone receptor can directly pass the placenta. Thus, maternal thyroid dysfunction can lead to neonatal hyperthyroidism or hypothyroidism[19,20]. In this study, of the 122 women with hyperthyroidism in pregnancy, 97 underwent systematic treatment, 25 failed for various reasons. Comparison of pregnancy outcome, complications and perinatal outcome of treated and untreated group reveals that pregnancy hypertension, hyperthyroid heart disease, hyperthyroidism crisis, premature birth and other adverse pregnancy outcomes, occurrence of obstetric complications and neonatal perinatal adverse outcomes (low birth weight, neonatal asphyxia, neonatal hyperthyroidism, neonatal hypothyroidism) of treated group are lower than those of untreated group. The difference is statistically significant ($p<0.05$), which corresponds to the literature reports[13-16]. The results of this study also demonstrate that failure to positively control hyperthyroidism in pregnancy will cause serious harm to the mother and perinatal infant. After standard treatment, satisfactory pregnancy outcome can result. Also, due to the unique biological role of thyroid hormones, early screening, especially thyroid function monitoring in the early pregnancy, and intervention after abnormal thyroid function, will mean great significance for maternal, neonatal health, especially growth and development of neonatal bone, brain and reproductive organ[19-23].

Conclusions

Early screening of thyroid-related diseases among pregnant women and active intervention based on the screening results can significantly improve their thyroid function, reduce hyperthyroidism-induced adverse pregnancy outcome and complications, and significantly improve maternal and infant safety.

Ethics Committee Approval

The above cases were confirmed by the hospital ethics committee approval and their families signed informed consent.

Conflict of interest

The authors declare no conflicts of interest.

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