Hypothyroidism and first-trimester spontaneous miscarriages

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Summary

Objective: To evaluate the association between hypothyroidism and first-trimester spontaneous miscarriages and to explain the mechanism. *Materials and Methods:* Patients admitted between October and May 2011 with threatened miscarriage in the first trimester were analyzed and levels of progesterone and thyroid hormones as T3, T4, and thyroid-stimulating hormone (TSH) were estimated. Once hypothyroidism was diagnosed, patients were treated with sodium levothyroxine (LT4) as substitution and outcomes were observed. *Results:* Measurement of progesterone was useful for predicting the outcome of threatened miscarriage The results showed that progesterone (P) = 14.74 ng/ml is selected as predictive value to judge whether the fetal treatment was successfully or not. When serum P value is above 14.74ng/ml before treatment, it may favour a miscarriage, if the serum P value is below 14.74 ng/ml, miscarriage is unlikely; its sensitivity and specificity are high. The risk for miscarriage in patients diagnosed with hypothyroidism in which LT4 substitution was similar to the level observed in the controls, and P between the two groups had no distinct difference. The mechanism explaining the risk of miscarriage increased by thyroid disorders remains unclear, which needs advanced research. *Conclusion:* Screening of thyroid disorders has important clinical significance in early pregnancy, and substitution of LT4 to those who are in the early pregnancy with hypothyroidism could reduce the risk of miscarriage.

Keywords: Hypothyroidism; Pregnancy; Miscarriage; Thyroid autoimmunity; Progesterone.

Introduction

The incidence of hypothyroidism in women of child bearing age is approximately 2% to 4% [1,2], which has an increasing tendency in recent years. The endocrine function of the thyroid and autoimmune disorders can significantly affect the pregnancy itself, leading to adverse pregnancy outcomes [3,4]. Abortion is one of the early complications, but the mechanism explaining the risk of miscarriage increased by thyroid disorders remains unclear. Most scholars agreed that once hypothyroidism was diagnosed, patients should be treated with sodium levothyroxine (LT4) as substitution as soon as possible, as early diagnosis and treatment can ameliorate pregnancy outcomes. In this study, thyroid disorders were screened in patients with threatened miscarriage in the first trimester. Once hypothyroidism was diagnosed, the patients were treated with LT4 as substitution, and outcomes were observed. References that pathological mechanisms explain the risk of miscarriage increased by hypothyroidism were reviewed at home and abroad.

Materials and Methods

General information

As shown in Table 1, between October, 2010, and March, 2012, a total of 164 women underwent threatened miscarriage in the first trimester, during their first diagnosis at maternity clinics in the Fourth Hospital of Hebei Medical University. The patients were 22-38 years of age and had suppressed menstruation 27-74 days. One hundred twenty-nine cases voluntarily accepted the thyroid function tests, had complete follow-up data, had no previous history of thyroid disease, had no significant surgical complications, and with confirmed single birth by B-ultrasound examination, were divided into two groups according to thyroid function, one was normal thyroid function group including 70 cases, who were 22-38 years of age, with suppressed menstruation for 29-74 days, and that were undergoing their first to third pregnancy. The other was hypothyroidism group including 59 cases, who were 22-30 years of age, with suppressed menstruation from 27-70 days, and that were undergoing their first to third pregnancy. Due to the fact that the age distribution of patients was non-normal, the Wilcoxon test was used for comparison and a $p > 0.05$ was judged as statistically significant.

Diagnostic criteria

The American Thyroid Association and the reference standard for diagnosis and treatment of thyroid disease guidelines recommend that the upper limit of serum thyroid stimulating hormone (TSH), in early pregnancy (less than 12 weeks of pregnancy), is 2.5 mU / l [5].

Specimen collection

Serum human chorionic gonadotropin (hCG), estradiol (E2), and progesterone (P) were measured in 164 patients, who were for the first time diagnosed in the present hospital, with threatened miscarriage in the first trimester, and included 129 patients with serum TSH, free triiodothyronine (T3) and free thyroxine (T4) monitored at the same time, which were sent to the clinical laboratory for quantitative analysis.

Therapeutic considerations

Serum hCG, E2 and P were measured in patients with threatened miscarriage, when serum P was above 25 ng/ml, threatened miscarriage was considered not caused by endocrine factors, and not treated with drugs. If serum P was between 10 and 30 ng/ml, progesterone was injected intramuscularly between 20 and 40 mg once a day, dydrogesterone was taken 10 mg twice a day, serum P and β-hCG were monitored once a week and B ultrasound was examined every two weeks. Progesterone was stopped when

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Table 1. — *The clinical data between normal group and hypothyroidism group.*

Groups	N. of cases	Age (mean ± SD	Pregnancies (n.)	Suppressed menstruation (days)
Normal group	70	27.66 ± 3.40	1 - 3	29 - 74
Hypothyroidism	59	25.66 ± 2.15	1 - 3	27 - 70

$p > 0.05$ has no statistical significance.

serum P was above 30 ng/ml, while dydrogesterone was continue taken as usual until 12 weeks of pregnancy. When serum P was below 10 ng/ml, it was considered that there was little significance for miscarriage, and outcomes were observed. Embryo development was observed by B ultrasound examination in all objects on a periodical inspection.

Therapy for hypothyroidism

In 129 patients, once hypothyroidism (including clinical hypothyroidism and subclinical hypothyroidism) was diagnosed, patients returned to the Hospital of Endocrinology as soon as possible and treated with LT4 as substitution, serum TSH, FT3, and FT4 were monitored every four weeks [6] and the levothyroxine dosage was adjusted accordingly.

Statistical methods

SPSS13.0 software was used, means were compared using the Wilcoxon rank sum test, P values were determined using receiver operating characteristic curve (ROC curve), the miscarriage rate between normal thyroid function group and hypothyroidism group which was treated with LT4 were compared using fourfold tables of the chi-square test and a $p < 0.05$ was judged as statistically significant.

Results

Among 164 cases of threatened miscarriage patients after treatment, 116 of them were tocolysed successfully, another 48 resulted in inevitable abortion, serum P levels were compared between the two groups and a $p < 0.01$ was judged as statistically significant (Table 2). Through ROC curve calculations, the group with a higher p value with higher sensitivity and specificity was selected as the predictive value to judge whether the fetal treatment was successfully or not in patients with threatened miscarriage, that is 14.74 ng/ml, with a sensitivity of 87.9% and a specificity of 72.9%.

According to the screening results of thyroid function, 129 patients were divided into two groups, of which 70 cases with normal thyroid function, whose progesterone levels of M (Q) was 18. 29 (12.28) ng/ml, distributed non-normal, other 59 hypothyroidism patients that had a normal P value distribution, whose P values (mean ± SD) were 22.18 ± 11.795 ng/ml.

P levels of the two groups were compared using the Wilcoxon rank sum test, the results of $p < 0.05$ confirmed that the P levels between the two groups had no distinct difference.

In the group of 129 cases with threatened miscarriage, there were 70 cases with normal thyroid function, including 59 cases of miscarriage and 46 cases of tocolytic failure. Among another 24 cases with hypothyroidism given sodium levothyroxine (LT4) substitution, 46 cases had miscarriages and 13 cases experienced tocolytic failure.

Table 2. — *Comparison of progesterone between miscarriage successful group and the inevitable abortion group*

Groups	N. of cases	Progesterone value
Miscarriage group	116	24.34 ± 9.56
Inevitable abortion group	48	10.95 ± 6.37

$p < 0.01$ has statistical significance

Table 3. — *Comparison of progesterone levels between normal thyroid function group and hypothyroid treatment group.*

Groups	N. of cases	Progesterone level (mean ± SD ng/ml
Normal thyroid function	70	18.29 (12.28)
Hypothyroidism with treatment	59	22.18 ± 11.795

Table 4. — *Comparison of the miscarriage rate between normal thyroid function group and hypothyroid treatment group.*

Groups	miscarriage successfully (cases)	Tocolytic failure (n.)
Normal thyroid function	46	24
Hypothyroidism with treatment	46	13

Fourfold tables of the chi-square test was used with SPSS13.0 software to carry out the result, that is: $x^2 = 2.349$ and $p = 0.125$, which is considered that the risk for miscarriage in patients diagnosed with hypothyroidism which LT4 substitution was similar to the level observed in the controls.

Discussion

The cause of threatened miscarriage is very complex, including endocrine diseases, autoimmune diseases, genetic abnormalities, and anatomic abnormalities et al. About 20% of threatened miscarriage is due to endocrine factors. P during pregnancy is very important to maintain normal pregnancy, which can affect the permeability of uterine smooth muscle to reduce the concentration of intracellular potassium, and increase the sodium ion concentration, resulting

in the relaxation of muscle fibers, the excitability decreasing, while reducing the sensitivity of pregnant uterus to oxytocin, and uterine contractions, so that zygote can grow and develop normally in the womb. For some reason, the low level of serum P values would lead to threatened abortion or miscarriage.

Serum P has been used as key indicators to judge the threatened abortion prognosis; this study also confirmed that serum progesterone levels play in a very important role in predicting threatened abortion pregnancy outcome. In this study, P value of 14.74 ng/ml was used as the predictive value to judge whether the treatment in patients with threatened miscarriage was successful or not. When serum P value was above 14.74 ng/ml before treatment, it may have led to a miscarriage, if the serum progesterone value was below 14.74 ng/ml, miscarriage was unlikely and its sensitivity and specificity was high. Positive treatment can be given to patients with threatened miscarriage who may have a good prognosis, those with poor prognosis should be offered an earlier termination of pregnancy earlier to avoid the meaningless miscarriage and over-treatment, or missed abortion caused by excessive miscarriage which may lead to secondary coagulation disorders, while avoiding the waste of medical resources and consuming energy and financial resources of the patients.

Pregnant women with hypothyroidism can lead to adverse pregnancy outcomes, such as spontaneous abortion, anemia, gestational hypertension, placental abruption, postpartum hemorrhage, preterm birth, low birth weight, neonatal respiratory distress syndrome, and fetal death miscarriage is one of the early complications [7,8]; however, the mechanism explaining the risk of miscarriage increased by thyroid disorders remains unclear. Currently, there are five hypotheses regarding the mechanism of this effect as following: The first theory states that the miscarriage risk appears to be not directly related to thyroid autoimmunity (TAI), but to immune imbalance [9]. According to the second theory, the increased risk of miscarriage should be attributed to the direct action of the thyroid autoantibody on the placenta, which has been validated in animal models [10-12], but still needs to be confirmed in human models. The third theory postulates that the increased risk of miscarriages is a result of a subtle deficiency in thyroid hormone concentrations due to a decreased adaptability of the thyroid gland to the increased demands of pregnancy, in the presence of TAI. With lower thyroid hormone levels and higher maternal TSH levels in pregnancy, the risk of miscarriage is increased. In a randomized controlled trial [13], the risk for miscarriage in patients with diagnosed TAI with LT4 substitution was significantly lower and similar to the levels observed in the healthy controls [14]. The fourth theory argued is that thyroid autoantibody positive rate is increases when women are older, since increased age is an independent risk factor for miscarriage [15], and TAI is attributed to the age factor. The last theory is corpus luteum hypothesis [16] which states that there are a variety of antibodies in the plasma of TAI, which could inhibit hCG action on its receptors, located in corpus luteum, by the immune cross-reactivity, this inhibition could cause luteal phase defect and lead to a decrease in steroid hormones production, such as P and estrogen, result in spontaneous miscarriages.

The results of this research support the third theory that the risk for miscarriage in patients with diagnosed hypothyroidism with LT4 substitution was significantly reduced and similar to the level observed in the healthy controls, and *p* between the two groups had no distinct difference, but not yet deny the corpus luteum hypothesis, to analyze the reasons: (1) the cause of spontaneous abortion is very complicated, mostly attributed to embryonic chromosomal factors, while the proportion of luteal phase defect caused by endocrine factors which is caused by hypothyroidism is very small, and could not rule out the interference of other factors; (2) in this study, considering economic conditions of patients, autoimmune thyroid antibody was not routinely estimated in patients who were in the group, and thyroid antibody was one of the independent risk factors increasing the abortion rate. The positive rate level of antibodies also affected the final result [17,18]; (3) the sample size was small and larger-scale clinical studies should be conducted to confirm the hypothesis.

At present, it has caused a high degree of attention in the medical profession that pregnant women with hypothyroidism lead to adverse pregnancy outcomes for both mother and child, and the incidence of hypothyroidism has increased each year, which is reported to be from 2% to 5% [19,20], and the thyroid antibody-positive rate reported is approximately 10% -15%. As early as 1999, the American Association of Clinical Endocrinologists proposed to screen TSH routinely for pregnant women and all planned pregnancies. Whether all pregnant women should have their TSH and thyroid antibody screened, is still controversial. Current evidence-based medicine does not yet support the screening of all pregnant women for thyroid function, but recommends to screen TSH in pregnant women with high risk for thyroid disease, such as the following: (1) hyperthyroidism, hypothyroidism, PPT, or partial hepatectomy, history of thyroid; (2) a family history of thyroid disease; (3) thyroid nodules; (4) thyroid-associated antibodies (known) positive; (5) hyperthyroidism or hypothyroidism symptoms or clinical signs, and accompanied with anemia, high cholesterol and low sodium aciduria; (6) diabetes type 1; (7) other autoimmune diseases; (8) infertile women should screen TSH as part of infertility associated with this; (9) head and neck history of radiation therapy; (10) miscarriage or preterm birth history [20].

Most scholars agree that patients with clinical or subclinical hypothyroidism once diagnosed should be treated with LT4 as substitution as early as possible, and variety of adverse pregnancy outcomes can be prevented and improved. Results of the research confirmed that the risk for

miscarriage in patients with diagnosed hypothyroidism in which LT4 substitution was similar to the level observed in the controls.

In summary, thyroid function screening and treatment has a very important clinical significance in early pregnancy. By strengthening thyroid function monitoring in high-risk patients and mission to get their coordination, early diagnosis and treatment would be done to improve the perinatal outcomes in both mother and child with hypothyroidism.

References

[1] Zhang X.L., Duan Y.: "Pregnancy and hypothyroidism". *Int. J. Obstet. Gynaecol*., 2009, *36*, 30.

[2] Glinoer D., Abalovich M.: "Unresolved questions in managing hypothyroidism during pregnancy". *BMJ*, 2007, *335*, 300.

[3] Glinoer D.: "Management of hypo- and hyperthyroidism during pregnancy". *Growth Horm. IGF Res*., 2003, *13*, S45.

[4] Abalovich M., Amino N., Barbour L.A., Cobin R.H, De Groot L.J., Glinoer D., *et a1*.: "Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society Clinical Practice Guideline". *J. Clin. Endocrinol. Metab*., 2007, *9*, S1.

[5] Stagnaro-Green AÿAbalovich M Alexander E, Azizi F., Mestman J., Negro R. *et al*.: "Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and Postpartum". *Thyroid*, 2011, *21*, 1081.

[6] Yassa L., Marqusee E., Fawcett R., Alexander E.K.: "Thyroid hormone early adjustment in pregnancy (the THERAPY) trial". *J. Clin. Endocrinol. Metab.* 2010, *95*, 3234. doi: 10.1210/jc.2010-0013. Epub 2010 May 12

[7] Lazarus J.H., Kokandi A.: "Thyroid disease in relation to pregnancy: a decade of change". *Clin. Endocrinol. (Oxf)*, 2000, *53*, 265.

[8] Anselmo J., Cao D., Karrison T., Weiss R.E., Refetoff S.: "Fetal loss associated with excess thyroid hormone exposure". *JAMA*, 2004, *292*, 691.

[9] Singh A., Dantas Z.N., Stone S.C., Asch R.H.: "Presence of thyroid antibodies in early reproductive failure biochemical versus clinical pregnancies". *Fertil. Steril*. 1995, *63*, 277.

[10] Matalon S.T., Blank M., Levy Y., Carp H.J., Arad A., Burek L. *et al*.: "The pathogenic role of anti-thyroglobulin antibody on pregnancy: evidence from an active immunization model in mice". *Hum. Reprod.,* 2003, *18*, 1094.

[11] Imaizumi M., Pritsker A., Unger P., Davies T.F.: "Intrathyroidal fetal microchimerism in pregnancy and postpartum". *Endocrinology*, 2002, *143*, 247.

[12] Negro R., Formoso G., Mangieri T., Pezzarossa A., Dazzi D., Hassan H.: "Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: effects on obstetrical complications". *J. Clin. Endocrinol. Metab*., 2006, *91*, 2587. Epub 2006 Apr 18.

[13] Benhadi N., Wiersinga W., Reitsma J., Vrijkotte T., Bonsel G.: "Higher maternal TSH levels in pregnancy are associated with increased risk for miscarriage, fetal or neonatal death". *Eur. J. Endocrinol*., 2009, *160*, 985.

[14] Rai R., Regan L.: "Recurrent miscarriage". *Lancet*, 2006, *368*, 601.

[15] Toulis K.A., Goulis D.G., Venetis C.A., Kolibianakis E.M., Tarlatzis B.C., Papadimas I.: "Thyroid autoimmunity and miscarriages: The corpus luteum hypothesis". *Med. Hypotheses*, 2009, *73*, 1060. doi: 10.1016/j.mehy.2009.05.012. Epub 2009 Jun 7.

[16] Hollowell J.G., LaFranchi S., Smallridge R.C., Spong C.Y., Haddow J.E., Boyle C.A.: "2004 where do we go from here? Summary of working group discussing on thyroid functions and gestational outcomes". *Thyroid*, 2005, *15*, 72.

[17] Lazarus J.H., Kokandi A.: "Thyroid disease in relation to pregnancy: a decade of change". *Clin. Endocrinol. (Oxf),* 2000, *53*, 265.

[18] Canaris G.J., Manowitz N.R., Mayor G., Ridgway E.C.: "The Colorado thyroid disease prevalence study". Arch. Intern. Med., 2000, *160*, 526.

[19] Andrade L.J., Cruz T., Daltro C., França C.S., Nascimento A.O.: "Detection of subclinical hypothyroidism in pregnant women with different gestational ages". *Arq. Bras. Endocrinol. Metabol*., 2005, *49*, 923. Epub 2006 Mar 16.

[20] Abalovich M., Amino N., Barbour L.A., Cobin R.H., De Groot L.J., Glinoer D. *et al*.: "Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society Clinical Practice Guideline". *J. Clin. Endocrinol. Metab*., 2007, *92 (8 Suppl.)*, S1.

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