

Research Article

Levels of Thyroid Peroxidase Antibodies is Higher in Threatened Abortion

Kadar Tiroid Peroksidase Antibodi lebih Tinggi pada Abortus Iminens

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Abstract

Objective: To assess the relationship between the incidence of threatened abortion with serum levels of TPO antibodies.

Methods: This was cross-sectional study involving subjects 40 cases and 40 controls. The study was conducted September 2012 to November 2012. The difference in the levels of thyroid peroxidase antibody was tested by Mann-Whitney test.

Result: In this study, hypothyroidism was found only in the abortion group, as many as 6 subjects (15%) and subclinical hypothyroidism was more prevalent in threatened abortion group, found in 2 people (5%), compared to normal pregnant group, found in only 1 person (2.5%). This study revealed a significant difference in the mean levels of TPO antibodies in the threatened abortion and normal pregnancy group. The mean levels of TPO antibodies in threatened abortion group was 91.76 ± 133.18 IU/ml with the lowest level of 14.41 IU/ml and the highest levels of 534.47 IU/ml while in the normal pregnancy group found an average 12.97 ± 3.91 IU/ml with the lowest value 2.02 IU/ml and the highest value of 20.78 IU/ml. In this study, subjects with TPO antibody levels ≥ 125 IU/ml, all of them experienced threatened abortion ($n = 7$) and found the risk of miscarriage by 2.212-fold compared with subjects with TPO levels < 125 IU/ml.

Conclusion: There are differences in the levels of TPO antibodies in patients with threatened abortion and in normal pregnancies, with average levels of TPO antibodies in imminent abortion group is higher than normal pregnancy group. There is a relationship between TPO antibody levels ≥ 125 IU/ml with the incidence of threatened abortion, with the risk of threatened abortion increasing 2.212 times.

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Keywords: threatened abortion, thyroid peroxidase antibody (TPO)

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Abstrak

Tujuan: Mengetahui hubungan antara kejadian abortus iminens dengan kadar TPO antibody dalam serum.

Metode: Penelitian ini menggunakan rancangan penelitian cross sectional/belah lintang dengan subjek 40 kasus dan 40 kontrol. Penelitian dimulai September 2012 sampai November 2012. Perbedaan kadar thyroid peroxidase antibody serum dan data lain yang bersifat numeric diuji dengan uji Mann-Whitney.

Hasil: Dalam penelitian ini hipotiroid hanya ditemukan pada kelompok abortus yaitu 6 orang (15%) demikian halnya dengan hipotiroid subklinis lebih banyak ditemukan pada kelompok abortus yaitu 2 orang (5%) dibandingkan kelompok hamil normal hanya ditemukan 1 orang (2,5%). Pada penelitian ini ditemukan perbedaan bermakna rerata kadar TPO antibody pada kelompok abortus iminens dan kelompok hamil normal. Rerata kadar TPO antibody pada kelompok threatened abortion $91,76 \pm 133,18$ IU/ml dengan kadar terendah 14,41 IU/ml dan kadar tertinggi 534,47 IU/ml sedangkan pada kelompok hamil normal ditemukan rerata $12,97 \pm 3,91$ IU/ml dengan nilai terendah 2,02 IU/ml dan nilai tertinggi 20,78 IU/ml. Dalam penelitian ini subjek dengan kadar TPO antibody ≥ 125 IU/ml kesemuanya mengalami abortus iminens ($n = 7$) dan didapatkan risiko terjadinya abortus sebesar 2,212 kali lipat dibandingkan dengan subjek dengan kadar TPO < 125 IU/ml.

Kesimpulan: Terdapat perbedaan kadar TPO antibody pada pasien dengan abortus iminens dibandingkan pada kehamilan normal, dengan rerata kadar TPO antibody pada kelompok abortus iminens lebih tinggi dibandingkan kelompok hamil normal. Terdapat hubungan antara kadar TPO antibody ≥ 125 IU/ml dengan kejadian abortus iminens, dengan risiko sebesar 2,212 kali untuk terjadinya threatened abortion.

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Kata kunci: abortus iminens, thyroid peroxidase antibody (TPO antibody)

INTRODUCTION

Abortion is a common event in pregnancy and about 80% of spontaneous abortions occur in the first trimester of pregnancy. The causes of abortion, such as genetics, anatomy, infection, endocrine disorders, autoimmune factors, and external environmental exposures such as cigarette smoke, alcohol, and toxic substances.¹⁻⁴

The presence of antithyroid antibodies in the first trimester of pregnancy was significantly associated with an increased incidence of abortion. Women with antithyroid antibodies may have normal thyroid gland function, but at greater risk for the occurrence of spontaneous abortion. Some studies indicate that women with recurrent miscarriage had higher levels of antithyroid antibodies higher than women who did not have recurrent miscarriage.

Thyroid autoimmune disorder characterized by the presence of antithyroid antibodies, notably thyroid peroxidase (TPO) and thyroglobulin antibody (TG) antibodies. Marai and Lejeune in 1988 suggested that TPO antibodies are the most common antibodies found in patients with recurrent miscarriage.⁵⁻⁷

This study analyze the differences in levels of TPO antibodies in patients with threatened abortion with patients with normal pregnancies, and the relationship between TPO antibody levels with the incidence of threatened abortion. The objective of this study was to assess the relationship between the incidence of threatened abortion with TPO antibody levels in serum.

In early pregnancy there is an increase in renal blood flow and filtration glomerulus resulting in increased plasma iodide clearance. This has led to a decrease in plasma concentrations of iodide and increasing the iodide body's needs. Thyroid hormone (TH) is transported in the serum and attached to three proteins with non-covalent bound namely T₄ binding globulin (thyroxine binding globulin/TBG), albumin, and transtiretin (formerly known as pre-albumin), about two-thirds of the normal serum T₄ carried by TBG.⁸⁻¹¹

In pregnancy, changes in total thyroid hormone levels is a direct consequence of the apparent increase in serum TBG, total T₄ and T₃ levels increased significantly during the first half of pregnancy. Serum T₄ levels increased significantly between 6 to 12 weeks, further progress will be slowly, and become stable around the mid-gestation, whereas the increase in serum T₃ occurred more progressive. T₃ and T₄ total reaches plateau at 20 weeks of gestation and remains until term pregnant. Because of the increased affinity of TBG for T₄ up to 20-fold when compared with T₃, T₄ levels change following the changes in TBG occurs rapidly.^{10,11}

The process of forming the thyroid hormones is started by pumping process/active iodide trapping that pumped into the cells and thyroid glands follicle that stimulated by TSH and hCG. The concentration of free iodide is concentrated in the glandular cells up to 30-40 times. Endoplasmic reticulum and Golgi apparatus synthesize and secrete the glycoprotein molecule called thyroglobulin into the follicle glands. Each molecule thyroglobulin will integrate with iodide to form thyroid hormone namely thyroid hormone thyroxine (T₄) and triiodo-

thyronine (T₃). The synthesized thyroid hormone then stored in the thyroid gland.

The initial stage of the formation of thyroid hormones is the iodide ion alteration to form oxidized iodine (oxidation of iodide ion). The thyroid peroxidase enzyme catalyzes this process. This enzyme is located in the apical membrane of cells whose function is to placed oxidized iodine in the cell, right on the place that thyroglobulin molecules released from the Golgi apparatus and through the cell membrane into the storage area. If the peroxidase system was hampered, it will decrease the speed of formation of thyroid hormone. This inhibition may occur because the effect of thyroid peroxidase antibodies.¹²⁻¹⁴

Several studies suggest that primary hypothyroidism is associated with antithyroid antibodies that affect fertility and spontaneous abortion. Hypothyroid condition characterized by a TSH ≥ 6 mIU/l and free T₄ (FT₄) ≤ 0.8 ng/dl. Pregnant women with hypothyroidism also have an increased risk of obstetric complications such as intra-uterine fetal death, gestational hypertension, placental solutio, and unfavorable perinatal conditions.¹⁵

Subclinical hypothyroidism occurs more frequently in pregnant women with positive antithyroid antibodies with serum TSH levels were normal before conception. Subclinical hypothyroidism is characterized by a TSH ≥ 6 mIU/l and FT₄ levels within the normal range (0.8 - 2.2ng/dl). Klein et al conducted a retrospective study on a data bank of serum from 2000 pregnant women with gestational age 15-18 weeks and found that 2.5% of all pregnant women had TSH concentrations above normal, and one-tenth develop hypothyroid. They also found that pregnant women with positive antithyroid antibodies had a 5-fold risk for the occurrence of subclinical hypothyroidism.¹⁴⁻¹⁷

Stagnaro-Green et al in 1990 and Glinoe in 1991 were the first to report a strong correlation between positive antithyroid antibodies and the risk of spontaneous abortion in euthyroid women. The relative risk of abortion is 2-4 times greater in women with positive antithyroid antibodies.

A thyroid peroxidase antibody is one of the specific serological marker for diagnosing autoimmune thyroid disease. Thyroid peroxidase antibodies produced by lymphocytes B through T-cell dependent mechanism. In recent years, it is known that thyroid peroxidase antibodies known as an epitope

which is highly dependent of the three-dimensional structure of the enzyme molecule TPO. Thyroid peroxidase antibodies immunodominant section are limited by two surfaces containing different but adjacent epitope. In 1989, Ruf and Carayons localize places on human antigen-TPO and TPO antibodies discovered four domains that is interact with domain A through D of the enzyme TPO. However, in future studies only two domains dominant antigen which have a bond that is domain A and B. Through the action of the enzyme is inhibited by TPO antibodies. This suggests that these two parts form the immunodominant regions of human-TPO.¹⁸

Wakim et al in 1994 in his study suggested that thyrotropin and thyroid hormone receptor found in ovarian granulose cells and the hormones T₄ and T₃ in the follicle. T₄ increases gonadotropin action on the luteinizing process so that stimulates the secretion of progesterin. Deficiency of thyroid hormone at the level of the ovary will affect gonadal dysfunction. Formation of thyroid hormone needed for the role of the TPO enzyme for oxidation iodide ion and iodide thyroglobulin organofication with oxidized iodide to form the thyroxine hormone (T₄) and triiodothyronine (T₃). TPO antibodies, through it binding with domains A and B in the TPO enzyme, will inhibit the action of this enzyme in the process of oxidation and organofication that resulted in a decrease serum concentrations of thyroid hormones.^{18,19}

There are differences in the levels of TPO antibodies in patients with threatened abortion than in normal pregnancies.

There is a relationship between high levels of maternal antibodies TPO high (≥ 125 IU/ml) and the incidence of threatened abortion

METHODS

This study is a cross sectional study, held in Obstetrics and Gynecology Department at RSUP Dr. Kariadi Semarang, Puskesmas Halmahera and Puskesmas Ngesrep Semarang. The examination of TPO antibody was held in Laboratorium GAKI-Medical Faculty of Diponegoro University from September 2012 until November 2012. Subject of this study was women diagnosed with threatened abortion on 8-20 weeks of gestational age.

Inclusion criterias were women ≤ 35 y.o diag-

nosed with threatened abortion on 8-20 weeks of gestational age, and noticed fetal plate, normotension, normoweight, no previous abortion, no systemic infection no abdominal trauma, agreed for blood examination and signing the informed consent form. The control group consist of patients with normal pregnancy, meeting inclusion criterias, willing to be the subject of study and signing the informed consent form.

Patient meeting the inclusion criteria received counseling and a questionnaire. The blood sample was taken from v. Mediana cubiti, and placed in reaction glass without EDTA, then the blood must be centrifuged immediately to separate the serum. After centrifuged, thyroid peroxidase antibodies will be in a stable condition in the serum for up to 7 days in the refrigerator (2-8°C) or 6 months with a temperature of -20°C. Obtained blood samples will be examined to measure serum levels of TPO antibodies by enzyme-linked immunosorbent technique assay (ELISA) with a unit of measure IU/ml.

The difference in the levels of thyroid peroxidase antibody was tested by Mann-Whitney test.

RESULT

The study was conducted in the RSUP Dr. Kariadi, RSUD Tugurejo, Puskesmas Ngesrep and Puskesmas Halmahera Semarang, from September 2012 to October 2012, involved 80 subjects, that is pregnant women 8 to 20 weeks who fulfilled the study criteria. There are 22 subjects obtained from RS Dr. Kariadi Semarang, 24 subjects from RSUD Tugurejo, 15 subjects from Puskesmas Halmahera, and 19 subjects from Puskesmas Ngesrep. Based on the history and examination performed, the study subjects were divided into two groups of 40 pregnant women accompanied by signs of threatened abortion and 40 normal pregnant women as a control group.

In threatened abortion group, the mean levels of antibody TPO is 91.76 ± 133.18 IU/ml, with the lowest level is 14.41 IU/ml and the highest level is 534.47 IU/ml, with a median of 33.73 IU/ml. In normal pregnant group, the mean levels of TPO antibodies is 12.97 ± 3.91 IU/ml, with the lowest level is 2.02 IU/ml and the highest level is 20.78 IU/ml, with a median of 13.23 IU/ml.

Table 1. Antibody TPO Level in Threatened Abortion and Normal Pregnancy Group.

Variable	Diagnose				p
	Threatened Abortion n=40		Normal Pregnancy n=40		
	Rerata	(SB)	Rerata	(SB)	
TPO antibody	91.76	(133.18)	12.97	(3.91)	0.000#

#: Mann-Whitney test

Table 2. The Relationship of TPO Antibody Levels with the Incidence of Threatened Abortion

TPO antibody level category	Threatened abortion	
	Yes	No
High (≥ 125 IU/ml) (n=7)	7 (100%)	0 (0%)
Normal (< 125 IU/ml) (n=73)	33 (45.2%)	40 (54.8%)

p = 0.006 (Chi-square test); RP = 2.212 (95% CI = 1.718 - 2.848)

Aziz et al 2002 found that TPO antibody levels ≥ 125 IU/ml had a 4-fold risk for the occurrence of abortion in pregnancy. With these limits, we assessed the relationship between high levels of TPO antibodies with threatened abortion. From the data in Table 5, by using the limitation of TPO antibody levels 125 IU/ml, showed a significant association between high levels of TPO antibodies with the incidence of threatened abortion, with TPO antibody levels ≥ 125 IU/ml had a 2.212-fold risk for the occurrence of threatened abortion (prevalence ratio/RP = 2.212; p = 0.006)

DISCUSSION

The incidence of miscarriage increases with maternal age. In women aged 20-24 years the incidence of abortion is about 12%, which was later increased to 26% in the age group > 35 years. This is presumably related to implantation failure due to poor quality embryos, chromosomal abnormalities associated with age or because of declining endometrium receptability. In this study, the subjects aged ≤ 35 years. The mean age of mothers in both groups did not differ, nor did her husband with a mean age in the two groups. Most subjects were within the reproductive age (75%). The mean gestational age in normal pregnancy group was elder than in the threatened abortion group.

Pregnant women with hypothyroidism have an increased risk of miscarriage, intra-uterine fetal

death, gestational hypertension, placental solutio, and unfavorable perinatal conditions. Klein et al found that at the age of 15-18 weeks of pregnancy 2.5% had TSH concentrations above normal, and the one-tenth developed hypothyroid. This study found hypothyroid only in abortion group is 6 people (15%) case with subclinical hypothyroidism are more common in abortion group is 2 people (5%) compared to normal pregnant group that found only 1 person (2.5%). This is consistent with research by Glinoe et al that states pregnant women with subclinical hypothyroidism and hypothyroidism had 2.5 times the risk for the occurrence of abortion.

Thyroid peroxidase (TPO) antibody is a specific serological marker for diagnosing autoimmune thyroid disease. Wakim et al found thyrotropin and thyroid hormone receptor in ovarian granulose cells and the hormones T₄ and T₃ in the follicle. T₄ increases gonadotropin action on the luteinizing process so that stimulates the secretion of progesterin. Deficiency of thyroid hormones on ovarian levels will impact on low progesterin hormone secretion. The low levels of this hormone in the first trimester of pregnancy will increase the risk of abortus. This study found significant differences in the mean levels of TPO antibodies in the threatened abortion and normal pregnancy group. The mean levels of TPO antibodies in abortion group immiens is 133.18 ± 91.76 IU/ml with the lowest level is 14.41 IU/ml and the highest levels is 534.47 IU/ml while in the normal pregnancy group found an average is 12.97 ± 3.91 IU/ml with the lowest value is 2.02 IU/ml and the highest value is 20.78 IU/ml. This is consistent with the first hypothesis that there are different levels of TPO antibodies in threatened abortion group than in the normal pregnancy group with higher average in the group of threatened abortion.

The second hypothesis is the relationship between high antibody TPO levels (≥ 125 IU/ml) and the incidence of threatened abortion. Aziz et al found the TPO antibody levels ≥ 125 IU/ml had 4 times the risk of abortion, and the mean levels of TPO antibodies in abortion group was higher than normal pregnant group. This is correspond with the second hypothesis, in this study, subjects with higher levels of TPO antibody ≥ 125 IU/ml, all of which developed threatened abortion (n = 7) and have the risk of miscarriage by 2.212-fold compared with subjects with TPO levels < 125 IU/ml.

T₄ play an important role in the luteinizing process that stimulates the secretion of progesterone that is needed to preserving pregnancy. In normal pregnancy there is sharp increase production of the T₄ at the age of 6 to 12 weeks gestation, further progress will be slow, and be stable during mid-gestation, whereas T₃ hormones increasing occur more progressive. T₃ and T₄ total reaches plateau at 20 weeks of gestation and persisted until term. Molarity ratio of T₃/T₄ must be maintained so as not to changed during pregnancy. Pregnant women with positive TPO antibodies experience inhibition the formation of hormone T₄. Negro et al provide levotiroksin (LT₄) to pregnant women with positive TPO antibodies but with normal thyroid function and found the incidence of abortion and premature births is lower 3, 9 times compared to those who did not receive therapy LT₄. Therapy LT₄ after 12 weeks of gestation did not reduce the risk of miscarriage and premature birth.

CONCLUSION

There is a significant difference in the levels of TPO antibodies in patients with threatened abortion and in normal pregnancies, with average levels of TPO antibodies in abortion group imminens is higher than in normal pregnant group. There is a relationship between TPO antibody levels ≥ 125 IU/ml with the incidence of threatened abortion, with the risk of threatened abortion increasing 2.212 times.

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