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Women with Subclinical Hypothyroidism Are at Low Risk of Poor Pregnancy Outcome in Japan

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Maternal subclinical hypothyroidism may be associated with adverse pregnancy outcomes, although not consistently across regions. Here, we sought to determine the effect of elevated thyroid-stimulating hormone (TSH) on pregnancy outcomes in Japanese women without known medical complications. TSH was determined by dried blood spots at 8-20 weeks of gestation, and 3.0-10.0 μU/mL of TSH was considered as elevated TSH (eTSH). A retrospective study involving 167 cases of eTSH was conducted. Five hundred and seventy eight of controls with normal TSH and without thyroid antibodies were selected. We compared a composite adverse maternal outcome comprised of spontaneous abortion, premature delivery, gestational diabetes mellitus (GDM), placental abruption, and pregnancy-induced hypertension, as well as composite adverse neonatal outcome including stillbirths, heavy for date, light for date, and a low Apgar score (< 7) at 5 minutes between two groups. The incidence of GDM was significantly higher in eTSH ($p < 0.01$); however, composite adverse maternal and neonatal outcome did not differ between groups ($p = 0.19$ and $p = 0.50$, respectively). Although 27 out of 167 cases in eTSH have antibodies, composite adverse outcome did not differ between eTSH with antibodies and controls ($p = 0.64$ and $p = 0.50$, respectively). Additionally, composite adverse maternal and neonatal outcome did not differ between the group larger than the median of TSH in eTSH ($n = 81$) and controls ($p = 0.43$ and $p = 0.98$, respectively). Thus, elevated TSH is not associated with overall adverse pregnancy outcomes in women without known medical complications.

Keywords: adverse outcome; anti-thyroid antibodies; pregnancy; subclinical hypothyroidism; thyroid-stimulating hormone
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Introduction

Nearly 10% thyroid dysfunction was documented in a thyroid function survey using a general health checkup system for adults in Japan, and of these, subclinical hypothyroidism (SCH) accounted for half of the observed thyroid dysfunctions (Kasagi et al. 2009). This suggested that considerable numbers of pregnant women might be associated with undiagnosed SCH. In fact, it has been reported that the prevalence of SCH was 2-5% in pregnant women (American College of Obstetricians and Gynecologists 2015). As a result, this relatively high incidence of SCH raises the possibility that SCH may lead to deterioration of neurodevelopment of infants and perinatal outcomes such as observed in pregnant women with overt hypothyroidism.

The main causes of SCH comprise inappropriate iodine intake and thyroid autoimmunity. Inappropriate iodine intake that leads to iodine deficiency or excess is dependent on region or ethnicity (Andersson et al. 2012; Zimmermann and Andersson 2012; Aguayo et al. 2013). Conflicting results regarding neurodevelopment in infants may be due to iodine intake that differs by region or ethnicity. Additionally, a much broader range of normal thyroid-stimulating hormone (TSH) levels has been identified in different regions (Negro and Stagnaro-Green 2014). Furthermore, overdiagnosis of SCH by levels of TSH in pregnant women may also affect the results of neurodevelopmental assessments. Investigation of thyroid autoimmunity showed that the prevalence of positive thyroid antibodies in Japanese low-risk pregnancies is less than 7% (Orito et al. 2009). On the other hand, a high prevalence of positive thyroid antibodies has been observed outside of Japan (Stricker et al. 2007; Han et al. 2013; Quinn et al. 2014). Taking these epidemiological studies into account, it is necessary to investigate morbidity with respect to SCH by region.

According to a recent review, SCH adversely affects obstetric outcomes including increasing pregnancy loss,

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premature delivery, and gestational hypertension (Maraka et al. 2016). In contrast, it was reported that in a prospective cohort study of pregnant women, SCH at the first trimester was not associated with adverse pregnancy outcomes after 20 weeks (Ong et al. 2014). Thus, there have been conflicting data concerning the impact of SCH on obstetrical outcomes. Regional features may contribute to differences in adverse obstetrical outcomes in pregnant women; however, there are no data concerning the impact of SCH on perinatal outcomes in Japan. Therefore, in the beginning, we conducted a study to determine the effect of maternal TSH levels on pregnancy adverse events.

Materials and Methods

We conducted a multi-institutional retrospective study of women who were diagnosed as elevated maternal TSH levels until 20 weeks of gestation and compared the incidence of known pregnancy outcomes with pregnant women without elevated TSH from January 2013 to April 2016 in two private hospitals in the suburbs of Tokyo. Approval for the study was obtained from the constituted Ethics Committee of Kyorin University (H27-033), the Tokyo Health Service Association, and the Tokyo Association of Obstetrics and Gynecology, including two private hospitals.

Laboratory methods

Thyroid function for pregnant women has been evaluated by dried blood spots test in two hospitals for almost 40 years, since the dried blood spots method to detect thyroid disease is known to be a reliable screening test (Irie et al. 1975; Hearn and Hannon 1982). For the dried blood spot method, at around the first checkup after conception (8-20 weeks of gestation), venous blood is obtained for the initial blood test and is simultaneously spotted onto filter paper. Spotted filter papers are then sent to the laboratory of the Tokyo Health Service Association. Serum level of TSH is performed by ELISA (FUJIREBIO Inc., Tokyo, Japan) and microsomal and thyroglobulin antibodies are also assayed using a semi-quantitative microtiter particle agglutination test (Serodia-ATG and Serodia-AMC, FUJIREBIO Inc., Tokyo, Japan). Prior to the current study, we performed a pilot study to assess the correlation between maternal serum TSH (2.6-6.0 μU/mL) and TSH using the dried blood spot test for 17 pregnant women. Maternal serum TSH was linearly correlated ($R^2 = 0.83$) with 3.0 μU /mL or more of the level of TSH by dried blood spot test.

Participants in the study

In this study, we determined elevated TSH as TSH level between 3.0 and 10.0 μU/mL using dried blood spots until 20 weeks of gestation, because the current upper limit of serum TSH at the first and second trimester is considered to be 2.5-3.0 μU/mL (Stagnaro-Green et al. 2011). During the study period, excluded from the study were cases involving a known medical history that included thyroid disease, diabetes mellitus, collagen disease, and chronic hypertension. A total of 167 women with elevated TSH (eTSH) were thus enrolled in this study. No cases of 167 women were treated with levothyroxine during pregnancy. Controls were selected by identifying women without subclinical hypothyroidism ($0.1 < TSH < 3.0$ μU/mL using dried blood spots), thyroid antibodies, and other known medical disorders including hyperthyroidism, diabetes mellitus, collagen disease, and chronic hypertension. Each case was almost matched regarding age and parities with at least three controls from two private clinics. A total of 578 controls were enrolled in this study.

Data collection

The following antenatal characteristics, mode of delivery, and maternal adverse outcomes were collected: maternal age, parity (primipara), BMI before pregnancy, spontaneous abortion before 22 weeks of gestation, gestational diabetes mellitus (GDM), pregnancy-induced hypertension (PIH), intrauterine fetal death (IUFD), placental abruption (Abruption), and premature delivery (less than 37 weeks). GDM was diagnosed if one or more of these readings were elevated in the 75 g oral glucose tolerance test: plasma glucose level at fasting $\geq$ 92 mg/dl, at 1 hour $\geq$ 180 mg/dl, and at 2 hours $\geq$ 153 mg/dl. PIH included preeclampsia and gestational hypertension. Preeclampsia was diagnosed when hypertension (systolic blood pressure $\geq$ 140 mmHg or diastolic blood pressure $\geq$ 90 mmHg) and proteinuria (dipstick $\geq$ 1+) developed after 20 weeks of gestation. Gestational hypertension was diagnosed when hypertension (systolic blood pressure $\geq$ 140 mmHg or diastolic blood pressure $\geq$ 90 mmHg) without proteinuria developed after 20 weeks of gestation. Abruption was clinically determined by the presence of retro-placental hematoma and clinical presentations with any one or combination of genital bleeding, abdominal pain, PIH, premature labor, premature rupture of membrane, IUFD, or non-reassuring fetal status. Emergency cesarean deliveries occurred due to maternal or fetal indication for termination of pregnancy. Maternal indications to terminate pregnancy included arrest of labor and severe PIH. Severe PIH was defined as persistent severe hypertension (blood pressure $\geqq$ 160/110 mmHg), oligouria (< 500 ml/day), low platelet count (< 100,000/mm^3), HELLP syndrome (hemolysis, elevated liver enzyme, and low platelets), pulmonary edema or eclampsia. Fetal indications to terminate pregnancy included non-reassuring fetal heart rate patterns (NRFS; recurrent late decelerations, recurrent severe variable decelerations, or prolonged deceleration). The following neonatal characteristics and adverse outcomes were also collected: birth weight (g), light for date (LFD), heavy for date (HFD), and a low Apgar score < 7 at 5 minutes. LFD and HFD were defined as sex-specific birth weight less than the 10th percentile or above the 90th percentile for gestational age according to the Japanese standard singleton growth curve (Itabashi et al. 2010).

Data analysis

We firstly compared the incidence of each adverse maternal and neonatal outcome between two groups. We then compared a composite adverse maternal outcome comprised of spontaneous abortion, premature delivery, GDM, placental abruption, and PIH, as well as composite adverse neonatal outcomes including IUFD, HFD, LFD, and a low Apgar score (< 7) at 5 minutes between two groups. Mothers or newborns who had experienced any of the adverse outcomes were considered to have experienced the composite outcome. Thus, the composite outcome excluded duplications. We also evaluated the effect of thyroid autoimmunity (i.e., the presence of thyroid antibodies) on both composite outcomes. In addition, we divided eTSH into two subgroups according to the second quartile of TSH (median), and then compared both composite outcomes between the group larger than the median and controls. Comparisons between groups were made using the χ^2 test. Data are expressed as number, incidence (%), or mean ± SD. Probability values < 0.05 were considered significant.

Results

The average serum TSH in eTSH was 3.7 ± 0.7 μU/mL. The median of TSH in eTSH was 3.4 μU/mL (Fig. 1). Twenty-seven of 167 (16%) women with eTSH had thyroid antibodies. A comparison of antenatal characteristics between groups showed similarities for maternal age, parity, history of spontaneous abortion including at least two losses, and BMI (Table 1).

The percentage of emergency cesarean section deliveries did not differ between eTSH and controls (8% vs. 7%, p = 0.64). Six of 13 emergency cesarean sections were the result of maternal indication in the eTSH group. Instead, 34 of 39 emergency cesarean sections were the result of maternal indication in controls. As shown in Table 2, the incidence of GDM was significantly higher in eTSH than in controls (6% vs. 0.3%, p < 0.01). However, the composite adverse maternal outcome did not differ between groups (14% vs. 10%, p = 0.19). Likewise, the composite adverse neonatal outcome did not differ between groups (14% vs.

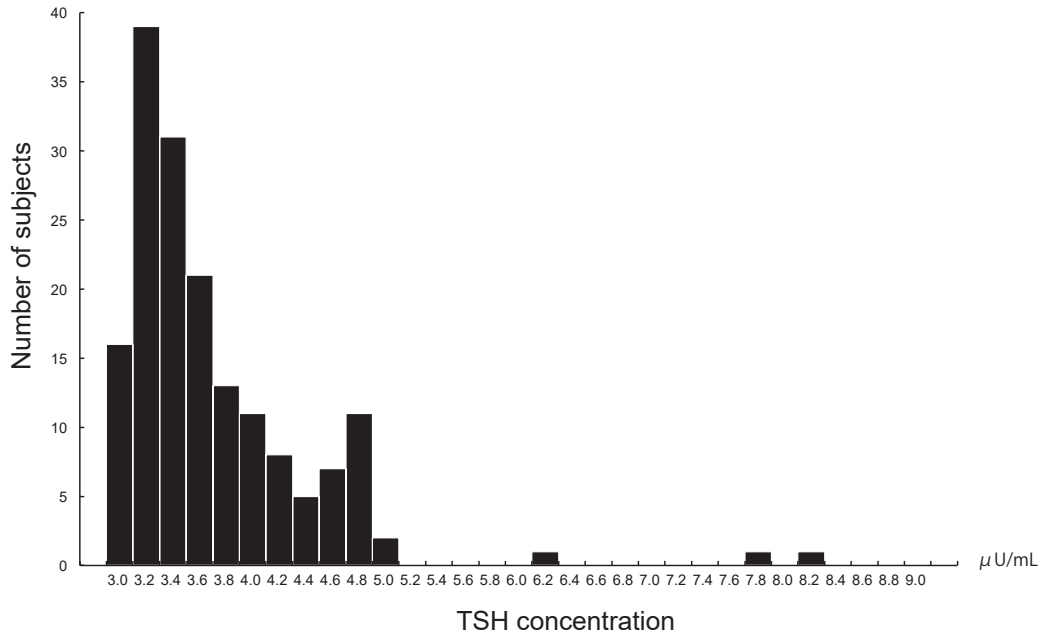

Fig. 1. Frequency distribution of TSH in eTSH.
Frequency distribution of TSH in the elevated TSH (eTSH) group. The second quartile of TSH (median) was 3.4 μU/mL, which was determined by a dried blood spot test for the screening of thyroid dysfunction.

Table 1. Demographic data of study groups.

Number	eTSH 167	Controls 578	p
TSH (mean)	3.7 ± 0.7 μU/mL	1.4 ± 0.7μU/mL	< 0.01
TSH antibody (%)	27 (16)	0	
Microsome antibody	26	0	
Thyroglobulin antibody	8	0	
Maternal Age (yr)	29.7 ± 5.5	29.0 ± 5.5	0.16
Primipara (%)	95 (57)	298 (52)	0.26
History of spontaneous abortion (%)	26 (16)	81 (14)	0.61
(at least two losses)	3	14	0.53
BMI	22.0 ± 3.7	21.4 ± 3.9	0.11

Results are expressed as number, incidence (%), or mean ± SD.
eTSH, the group of elevated TSH.

Table 2. The perinatal outcome of women complicated with eTSH and controls.

		eTSH	Controls	p
		167	578	
Mother	Composite adverse outcome	23 (14)	59 (10)	0.19
	Spontaneous abortion	2	3	0.34
	Premature delivery	7	21	0.74
	GDM	10 (6)	2 (0.3)	< 0.01
	Abruption	1	1	0.35
	PIH	7	33	0.44
Newborn	Composite adverse outcome	23 (14)	92 (16)	0.50
	IUFD	0	0	-
	LFD	5	16	0.87
	HFD	17	71	0.46
	Low Apgar score < 7 at 5 minutes	1	7	0.50

Results are expressed as number or incidence (%). Comparisons between groups were made using χ^2 tests. Mothers or newborns who had experienced any one of the adverse outcomes were considered to have experienced the composite outcome.
eTSH, the group of elevated TSH; GDM, gestational diabetes mellitus; PIH, pregnancy-induced hypertension; IUFD, intrauterine fetal death; abruption, placental abruption; LFD, light for date; HFD, heavy for date.

16%, p = 0.50).

When the presence of thyroid antibodies was considered, the composite maternal and neonatal outcomes did not differ between eTSH with antibodies (n = 27) and controls (7% vs. 10%, p = 0.64; 11% vs. 16%, p = 0.50, respectively). Furthermore, maternal and neonatal composite outcomes did not differ between the subgroup with larger than the median TSH (n = 81) and controls (7% vs. 10%, p = 0.43; 16% vs. 16%, p = 0.98, respectively).

Discussion

Japan represents a region in which inhabitants (including pregnant women) generally experience appropriate rather than excessive iodine intake according to World Health Organization criteria (Fuse et al. 2011). It was also reported that the median urinary iodine concentration of pregnant women in Japan was 224 μg/L, and it was more than adequate range for iodine intake according to epidemiological criteria for assessing iodine nutrition (Andersson et al. 2012; Fuse et al. 2013). According to a hospital-based study in Japan, SCH might be induced by iodine excess during early pregnancy (Orito et al. 2009). Furthermore, we need to consider the effect of autoimmunity on thyroid function because 16% of pregnant women with eTSH had TSH antibodies according to our study. The prevalence of positive thyroid antibodies is low compared to that of Australian pregnant women with SCH (41-67%) (Blumenthal et al. 2016). Consequently, SCH in Japan might be caused by iodine excess. Thus, the cause responsible for the observed differences between regions varies, and a region-specific investigation is therefore essential in order to define the effect of SCH on perinatal outcome. Currently, there are no data regarding the effect of SCH on perinatal outcome in Japan. We therefore conducted the present study and showed that elevated TSH that was determined by dried blood spot method and detected until mid pregnancy was not associated with composite adverse maternal and neonatal outcome.

Several studies regarding the effect of SCH on pregnancy outcome have been conducted in countries outside of Japan. SCH adversely affects obstetric outcomes with increasing pregnancy loss, premature delivery, and gestational hypertension (Chen et al. 2014; Maraka et al. 2016). On the other hand, SCH detected at the first trimester was not associated with adverse pregnancy outcomes after 20 weeks (Ong et al. 2014). These conflicting results may be due to different causes of SCH in each country.

In Japan, as mentioned above, the main cause of SCH might be excess intake of iodine with low prevalence of thyroid autoimmunity. According to a hospital-based study in Japan, SCH might be induced by an iodine excess during early pregnancy, but there was no association between serum TSH above 4.9 μU/ml during early pregnancy and child developmental testing (Orito et al. 2009). It is also reported that children born to women with hypothyroidism at early pregnancy and whose condition was restored to a normal thyroxine concentration by late pregnancy had a normal neurodevelopmental outcome (Momotani et al. 2012). We showed that elevated TSH detected until mid pregnancy was not associated with an overall adverse pregnancy event when considering low prevalence of thyroid autoimmunity. It may be that under a low prevalence of thyroid autoimmunity, SCH induced by iodine excess is not associated with adverse pregnancy and neonatal neurodevelopmental outcome.

In contrast, the main cause of SCH in overseas is

iodine deficiency with a high prevalence of thyroid autoimmunity (Stagnaro-Green et al. 1990; Andersson et al. 2012; Blumenthal et al. 2016). The synergistic effect of iodine deficiency and autoimmunity may have a substantial influence on maternal and fetal outcome. Indeed, women with normal thyroid function and positive thyroid antibodies had an increased risk of having a miscarriage (Thangaratinam et al. 2011). The presence of thyroid autoimmunity increased the risk of preeclampsia and poor perinatal mortality (van den Boogaard et al. 2011). Moreover, the treatment for pregnant women with elevated TSH (> 2.5 mIU/l) and thyroid peroxidase antibodies reduced the risk of an adverse perinatal outcome involving miscarriage, preeclampsia, placental abruption, and preterm labor (Negro et al. 2010). Pregnant women with thyroid peroxidase antibodies alone or with subclinical hypothyroidism were more prone to preterm delivery (Kumru et al. 2015). It is therefore important to recognize the influence of SCH is dependent on conditions of each country.

In the current study, the incidence of GDM in eTSH was significantly higher than that of controls (Table 2; 6% vs. 0.3%, $p < 0.01$). The low incidence of GDM in our controls is partially due to low-risk population. In general, the incidence of GDM is 3-4% (Hunt and Schuller 2007). Still, the incidence of GDM in our eTSH is twice as frequent as that of the general population. Nevertheless, the incidence of HFD in the group of eTSH (10%) was comparable to that of our controls (12%). Therefore, there was a difference in the incidence of GDM between groups, although we think there is no significant impact on overall pregnancy adverse outcome. Presently, SCH is thought to be associated with GDM (Tudela et al. 2012; Toulis et al. 2014). On the other hand, it is reported that women who had elevated TSH without thyroid peroxidase antibody in the first trimester do not show increased incidence of GDM (Ying et al. 2016). According to our current study, the prevalence of positive thyroid antibodies is low (16%) in the group of eTSH. Despite the low prevalence of antibody, the incidence of GDM was relatively high in our study. Thus, further investigation is needed to elucidate the relationship between the incidence of GDM and SCH with or without thyroid autoimmunity. Again, a region-specific investigation is therefore essential in order to define the effect of elevated TSH on perinatal outcome.

We also found no difference in the incidence of emergency cesarean delivery between groups (8% vs. 7%, $p = 0.64$). Increased operative deliveries including cesarean section were reported in low-risk pregnancies with increased TSH and decreased free T4, and a less efficient uterine contraction was thought to be a cause of the failure to progress to a normal delivery (Monen et al. 2015). In the current study, 6 of 13 emergency cesarean sections were the result of maternal indication in the eTSH group. In contrast, 34 of 39 emergency cesarean sections were a result of maternal indication in controls. That is, there were frequent emergency cesarean sections for fetal indications in the SCH group. In our study, the incidences of PIH, Abruption, LFD, HFD, and a Low Apgar score < 7 at 5 minutes did not differ between eTSH and control groups. Consequently, the reason for the increased incidence of emergency cesarean delivery for fetal indication remains unclear. NRFS may be more frequently seen in eTSH, however, we did not conduct a full investigation of intrapartum fetal heart rate pattern in both groups. Further investigation is therefore needed to elucidate the relationship between increased operative deliveries and eTSH.

This study has some limitations. First, it was conducted in two private hospitals mainly dealing with low-risk cases. Consequently, there may be a bias for selecting study group and controls. More hospitals need to be included for a thorough study of thyroid dysfunction and the relevance of adverse perinatal events in low-risk cases. Second, we did not investigate direct serum thyroid function and free T4 in all mothers who visited the private clinics. In a strict sense, our series of eTSH is not classified as a category of SCH. The outcome of pregnancy should be verified using direct serum thyroid function. Third, we noticed the low incidence of GDM in our controls, perhaps as a result of a bias in the selection of the control from the two private hospitals. If information is available such as a family history of DM, then we may verify the existence of selection bias. A close association between gestational diabetes mellitus and a family history of DM has been reported (O'Sullivan et al. 1973). Unfortunately, we did not obtain information relating to a possible family history of DM.

In conclusion, we demonstrated that elevated TSH that was determined by dried blood spot method and detected until mid gestation was not associated with overall adverse pregnancy outcomes in Japanese women without known medical complications. Under the present situation involving various advantages and disadvantages concerning SCH screening during pregnancy as observed in different countries, it is important to recognize the features of SCH based on region. The investigation of direct serum thyroid function is needed in a larger number of participants from, not only the suburbs of Tokyo, but also other regions of Japan.

Conflict of Interest

The authors declare no conflict of interest.

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