Hyperthyroidism as a Potential Risk Factor for Placental Abruption: A Case Control Study

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Abstract

Background

Overt hyperthyroidism and hypothyroidism are associated with pregnancy complications; however, most women with these conditions are diagnosed before conception and are under treatment during pregnancy, especially in the developed countries. The purpose of this study was to investigate pregnancy complications among these women.

Methods

A retrospective case-control study was conducted, and data on 3824 pregnant women who gave birth at Nagoya University Hospital located in Japan from 2005 to 2014 was collected. The pregnancy outcomes were divided and compared among three groups: the control group ($n = 3709$), the hyperthyroidism group ($n = 52$) and the hypothyroidism group ($n = 63$). Risk factors for placental abruption were also evaluated in singleton pregnancies ($n = 3588$) by multivariable logistic regression analysis. Moreover, in hyperthyroidism, thyroid function was also compared between successful and failed placentation group, and the latter group included placental abruption and preeclampsia.

Results

The incidence of placental abruption was significantly higher in hyperthyroidism than in control and hypothyroidism groups ($p < 0.01$). Hyperthyroidism was independently associated with an increased risk of placental abruption (adjusted odds ratio = 12.52, 95% confidence interval = 2.91–53.88). Thyroid stimulating hormone (TSH) was significantly lower in failed placentation group than in successful placentation group ($p < 0.05$).

Conclusion

According to the results of our study, pregnancy outcomes in women with treated hypothyroidism were comparable with those in women without thyroid disease. Conversely, women with treated hyperthyroidism showed an independent risk of placental abruption, which might be related with lower TSH level at early gestation. However, further research is required to validate our findings.

Background

Thyroid diseases, including hyper- and hypothyroidism, are common disorders in women of childbearing age. When left untreated, they can have adverse effects on maternal and neonatal outcomes. A large cohort study demonstrated that primary hypothyroidism was associated with increased pregnancy complications including preeclampsia [odds ratio (OR) = 1.47, 99% confidence intervals (CI) = 1.20–1.81], gestational diabetes (OR = 1.57, 99% CI = 1.33–1.86), preterm birth (OR = 1.34, 99% CI = 1.17–1.53), induction of labour (OR = 1.15, 99% CI = 1.04–1.28), and caesarean section (prelabor, OR = 1.31, 99% CI = 1.11–1.54; after spontaneous labor OR = 1.38, 99% CI = 1.14–1.66) [1]. It also revealed that

hyperthyroidism was associated with preeclampsia (OR = 1.78, 99% CI = 1.08–2.94), preterm birth (OR = 1.81, 99% CI = 1.32–2.49), and induction of labour (OR = 1.40, 99% CI = 1.06–1.86). A meta-analysis reported that both overt hypo- and hyperthyroidism were associated with an increase in OR for preterm birth (OR = 1.24, 95% CI = 1.17–1.31 and OR = 1.19, 95% CI = 1.12–1.26, respectively) [2]. Most women in developed countries with hyper- or hypothyroidism are diagnosed and treated before conception and only few studies have reported the pregnancy outcomes in such cases [3]. Therefore, the diagnosis and treatment of thyroid disease, before and during pregnancy, is recommended to minimise adverse outcomes [4]. Although most women are already on medication, the effect of treated hyper- or hypothyroidism on pregnancy outcomes remains unknown.

In the present study, we investigated the pregnancy outcomes of women with thyroid disease who had been diagnosed and treated prior to their pregnancy: birth weight, caesarean section, Apgar scores and the obstetric complications including preterm labour, preeclampsia, low birth weight, premature rupture of membranes (PROM), placenta previa, placenta abruption and preterm birth. We also focused on the placental abruption, which is a main cause of maternal and neonatal mortality and morbidity.

Methods

Study participants

The study samples were retrospectively recruited from medical records at a single tertiary care institute, Nagoya University Hospital in Japan. The inclusion criteria for this study was women who gave birth at Nagoya University Hospital located in Japan from 2005 to 2014. Patients who treated thyroid diseases at other hospitals were also included when their treatment information from the hospital were provided. The exclusion criteria for this study was as follows: less than 22 weeks of gestation at birth, and incomplete medical records. Subjects were divided into three groups, namely, the control group: those without thyroid disease (n = 3709); the hyperthyroidism group: those who were diagnosed and treated for hyperthyroidism (n = 52); and the hypothyroidism group: those who were diagnosed and treated for hypothyroidism (n = 63). In the hyperthyroidism, 23 patients (44.2%) were treated by oral propylthiouracil, and 12 patients (23.1%) were treated by oral methimazole. All of subjects in the control group were not screened for thyroid function before pregnancy.

Clinical Information

Demographic data included maternal age, information on gravidity and parity, method of conception, and history of chronic maternal disease. In-vitro fertilization and embryo transfer and intracytoplasmic sperm injection were defined as assisted reproductive technology (ART), and ovarian stimulation methods and intrauterine insemination (IUI) were defined as other treatment. The clinical information on number of babies, gestational age at delivery, birth weight, foetal position at delivery, mode of delivery, Apgar scores at both 1 min and 5 min, and pregnancy complications including preterm labour, preeclampsia, PROM,

placenta abruption, placenta previa, and preterm birth was also collected as maternal and neonatal outcomes. Birth weight was categorised into three groups: <1500 g; 1500–2500 g; and $\geq$ 2500 g and Apgar scores were divided into two groups: $\leq$ 6; $\geq$ 7.

Preeclampsia was defined as persistent hypertension ($> 140/90$ mm Hg) and proteinuria (> 300 mg/24 h) after 20 weeks of gestation. Preterm birth was defined as delivery between 22 and 36 weeks of gestation. Gestational ages were calculated based on the last menstrual period, and subsequently confirmed by crown-rump length, when the fertilisation date was unknown.

Sub-analysis

To determine whether hyperthyroidism was a risk factor of placental abruption, multiple pregnancies were excluded from study population for multiple logistic regression analysis. Additionally, 11 women were also excluded from the control group for the lack of data. Overall, the analysis was performed in singleton pregnancies including the control ($n = 3540$) and the hyperthyroidism ($n = 48$). Univariate and multiple logistic regression analysis were performed to estimate the ORs and 95% CI of placental abruption for binary prognostic variables including hyperthyroidism as follows: maternal age, parity, method of conception, gestational age at birth, birth weight, hypertension, diabetes mellitus, psychiatric disease, preterm labour, preeclampsia, premature rupture of membranes, and placenta previa.

The hyperthyroidism group was further divided into the two subgroups; the failed placentation group: those with preeclampsia or placental abruption and the successful placentation group: those who were not complicated with preeclampsia or placental abruption. To assess the effect of thyroid function including stimulating hormone (TSH), free T_3 (FT_3 ; triiodothyronine) and free T_4 (FT_4 ; thyroxine) and thyroid stimulating hormone receptor autoantibody (TRAb) positivity on placentation, these were compared in that two subgroups. However, these data were partially lacked in the part of the hyperthyroidism group, because they were treated at other institutes during pregnancy. In the hyperthyroidism group, 34 patients (65.4%) had data of TSH, FT_3 and FT_4 at the early gestation; from conception to 14 weeks of gestation, because it is thought to be the period of placental development. For the data of TRAb during the pregnancy, 36 patients (69.2%) had the results in the hyperthyroidism group.

Statistical analysis

All statistical analyses were performed using the SAS (version 9.4, SAS Institute Inc., Cary, North Carolina, USA) software program and JMP pro 14 (JMP, Tokyo, Japan). Continuous variables are presented as median (range) and p values were calculated by Kruskal-Wallis test. Categorical variables are presented as number (percentage) and p values were calculated by Fisher's exact test or chi-square test as appropriate. A p value of < 0.05 was considered to be significant.

Results

The demographic data of the control (n = 3709), hyperthyroidism (n = 52) and hypothyroidism (n = 63) groups are shown in Table 1. The percentage of ART in the hypothyroidism group was higher than those of the control and hyperthyroidism groups ($p = 0.019$). There were no significant differences in other characteristics like maternal age, gravidity, parity, and chronic maternal diseases among the control, hyperthyroidism, and hypothyroidism groups.

Table 1
Demographic data of pregnancies

	Control (n = 3709)	Hyperthyroidism (n = 52)	Hypothyroidism (n = 63)	<i>p</i> Value
Maternal age, years	33 (15–52)	33 (25–42)	33 (22–43)	0.070
Gravida				0.531
0	1438 (38.8)	24 (46.2)	26 (41.3)	
≥ 1	2270 (61.2)	28 (53.9)	37 (58.7)	
Missing value	1 (0.0)	0 (0.0)	0 (0.0)	
Parity				0.215
0	2084 (56.2)	34 (65.4)	40 (63.5)	
≥ 1	1625 (43.8)	18 (34.6)	23 (36.5)	
Conception				0.004
natural	2958 (79.8)	45 (86.5)	40 (63.5)	
ART	363 (9.8)	6 (11.5)	13 (20.6)	
Other treatment	388 (10.5)	1 (1.9)	4 (15.9)	
Maternal chronic diseases				
Hypertension	31 (0.8)	0 (0.0)	0 (0.0)	1.000
DM	82 (2.2)	1 (1.9)	2 (3.2)	0.764
Psychiatric disease	194 (5.2)	1 (1.9)	5 (7.9)	0.387
Continuous variables are presented as median (range) and <i>p</i> values were calculated by Kruskal-Wallis test. Categorical variables are presented as number (percentage) and <i>p</i> values were calculated by Fisher's exact test. ART, assisted reproductive technology; DM, diabetes mellites.				

Pregnancy outcomes were compared among the control, hyperthyroidism, and hypothyroidism groups (Table 2) and no significant differences were observed in the birth weight, foetal position at delivery, and mode of delivery. However, the incidence of placental abruption in the hyperthyroidism group was significantly higher than in the control and hypothyroidism groups ($p < 0.01$). The hyperthyroidism group

also showed a higher incidence of preeclampsia as compared to the control and hypothyroidism groups, although the difference was not significant ($p = 0.063$). The number of cases with Apgar scores of ≤ 6 at 1 min and 5 min were significantly different among the control, hyperthyroidism, and hypothyroidism groups ($p = 0.010$ and $p = 0.013$, respectively), and those in the control were higher than the hyper- and hypothyroidism groups. The differences in the incidences of preterm labour, PROM, low birth weight, and placenta previa among the control, hyperthyroidism, and hypothyroidism groups were not significant. The incidence of preterm birth in the hypothyroidism group was lower than that in the control and hyperthyroidism groups, but this again was not significant ($p = 0.064$).

Table 2
Obstetric outcomes of pregnancies

	Control (n = 3709)	Hyperthyroidism (n = 52)	Hypothyroidism (n = 63)	<i>p</i> Value
Number of babies				0.498
singleton	3552 (95.8)	48 (92.3)	61 (96.8)	
twin	150 (4.0)	4 (7.7)	2 (3.2)	
triplets	7 (0.2)	0 (0.0)	0 (0.0)	
Birth Weight* (g)	2860 (270–4648)	2834 (1182–3812)	3000 (1226–3714)	0.200
Fetal position at delivery				0.633
cephalic	3476 (89.8)	53 (94.6)	58 (89.2)	
breech	302 (7.8)	3 (5.4)	4 (6.2)	
others	86 (2.2)	0 (0.0)	3 (4.6)	
missing value	9 (0.2)	0 (0.0)	0 (0.0)	
Mode of delivery				0.476
Vaginal delivery	1813 (48.9)	25 (48.1)	31 (49.2)	
Vacuum	222 (6.0)	7 (13.5)	4 (6.4)	
Forceps	46 (1.2)	0 (0.0)	1 (1.6)	
Elected cesarean section	959 (25.9)	10 (19.2)	13 (20.6)	
Emergent cesarean section	669 (18.0)	10 (19.2)	14 (22.2)	
Apgar Score at 1min*				0.010
≤ 6	435 (11.2)	3 (5.4)	1 (1.5)	
≥ 7	3438 (88.8)	53 (94.6)	64 (98.5)	
Apgar Score at 5min*				0.013
≤ 6	224 (5.8)	0 (0.0)	0 (0.0)	
≥ 7	3649 (94.2)	56 (100.0)	65 (100.0)	

Data are presented as number (percentage) and median (range) and *p* values were calculated by Fisher's exact and Kruskal-Wallis test, respectively. In mode of delivery, χ^2 test was used. *Birth weight, Apgar scores and low birth weight were analyzed on numbers of babies (Control, n = 3873; Hyperthyroidism, n = 56; Hypothyroidism, n = 65).

	Control (n = 3709)	Hyperthyroidism (n = 52)	Hypothyroidism (n = 63)	<i>p</i> Value
Pregnancy complication				
Preterm labor	481 (13.0)	8 (15.4)	8 (12.7)	0.879
Preeclampsia	167 (4.5)	6 (11.5)	3 (4.8)	0.063
Low birth weight*	918 (23.7)	12 (21.4)	9 (13.9)	0.169
PROM	155 (4.2)	2 (3.9)	3 (4.8)	0.930
Placenta previa	154 (4.2)	1 (1.9)	0 (0.0)	0.221
Placenta abruption	18 (0.5)	3 (5.7)	0 (0.0)	< 0.01
Preterm birth	601 (16.2)	6 (11.5)	4 (6.4)	0.064
Data are presented as number (percentage) and median (range) and <i>p</i> values were calculated by Fisher's exact and Kruskal-Wallis test, respectively. In mode of delivery, χ^2 test was used. *Birth weight, Apgar scores and low birth weight were analyzed on numbers of babies (Control, n = 3873; Hyperthyroidism, n = 56; Hypothyroidism, n = 65).				

To determine whether hyperthyroidism was a risk factor of placental abruption, other valuables were examined among singleton pregnancies (n = 3588, Fig. 1). Factors found to increase placental abruption included hyperthyroidism (crude OR = 11.48, 95% CI: 2.91–45.36), preterm labour (crude OR = 3.44, 95% CI: 1.27–9.32), and preeclampsia (crude OR = 4.80, 95% CI: 1.49–15.72) (Fig. 1. upper panel). While gestational age $\geq$ 37 weeks (crude OR = 0.09, 95% CI: 0.03–0.22), birth weight $\geq$ 1500 g (1500–2500 g and $\geq$ 2500 g; crude OR = 0.22 and 0.06, 95% CI: 0.07–0.71 and 0.02–0.16, respectively) decreased placental abruption (Fig. 1. upper panel). After multivariate analysis, hyperthyroidism (adjusted OR, aOR = 12.52, 95% CI: 2.91–53.88) was found to be independently associated with an increased risk of placental abruption, conversely, gestational age $\geq$ 37 weeks (aOR = 0.12, 95% CI: 0.04–0.40) was associated with a decreased risk (Fig. 1. lower panel).

In the hyperthyroidism subgroup, serum TSH levels in the failed placentation group were significantly lower than those in the successful placentation group (p = 0.043, Fig. 2A). Additionally, although fT₃ and fT₄ were higher in the failed group, the difference was not significant (Fig. 2B - C). In comparison of TRAb positivity, no significant difference was detected between the two groups (successful placentation – 16/28; 57.1%, failed placentation – 6/8; 75.0%, p = 0.441).

Discussion

The present study revealed that hyperthyroidism had a significantly higher incidence of placental abruption and a trend for increased preeclampsia compared to the control and the hypothyroidism.

Moreover, hyperthyroidism was shown to be an independent risk factor for placental abruption by multivariate analyses.

Previous reports on population-based and case-control studies demonstrated hyperthyroidism to be associated with a high risk of preeclampsia [5–8] and placental abruption [9]. The impact of interventions for hyperthyroidism before and during pregnancy on pregnancy outcomes remains uncertain [10]. Although one study had reported a higher occurrence of adverse pregnancy complications in an untreated hyperthyroidism group compared to a treated group [11], the study population was small and placental abruption was not evaluated. They also reported a higher occurrence of hypertensive disorders of pregnancy was seen in the treated group compared to control, which was consistent with the result in this study, because preeclampsia is included in hypertensive disorders of pregnancy.

Additionally, the present study revealed that the maternal and neonatal outcomes in women with treated hypothyroidism were comparable to those in women without thyroid disease. Both overt hyperthyroidism and hypothyroidism are well-known to have adverse effects on the mother and her child [12]. ART is known to be associated with increased adverse pregnancy outcomes [13]. In this study, despite a higher prevalence of ART, cases in the hypothyroidism group were not associated with a higher incidence of adverse pregnancy outcomes as compared to controls. This result is consistent with that of a previous report [3], and suggests that hypothyroidism treatment could decrease the risk of adverse pregnancy outcomes seen in overt hypothyroidism. In this study, the hypothyroidism group also had a lower incidence of preterm birth, although this finding was not statistically significant.

Moreover, multivariate analysis firstly demonstrated that hyperthyroidism, even though they were treated by endocrinologists, was an independent risk factor for placental abruption in the present study, although several retrospective cohort studies have also reported the association of placental abruption with hyperthyroidism [9, 14]. However, whether treatment for hyperthyroidism could influence the risk of placental abruption remains unknown, because the present study could not include population of untreated hyperthyroidism. As randomised controlled trials was lacked, the impact of antithyroid interventions for hyperthyroidism pre-pregnancy or during pregnancy on important pregnancy outcomes remains unknown [9]. Additionally, GA $\geq$ 37 weeks independently decreased the aOR of placental abruption. This indicates that preterm birth (GA < 37 weeks) was also an independent risk factor of placental abruption, which is consistent with previous reports [15, 16].

As one of pathological mechanisms in the hyperthyroidism group, TSH levels at the early gestation were significantly lower in the subgroup with preeclampsia or placental abruption than the subgroup without preeclampsia or placental abruption. Recently, preeclampsia and placental abruption were reported to be associated with failed placentation due to inefficient invasion of trophoblasts after implantation [17]. Human chorionic gonadotropin from trophoblast stimulates thyroid hormones at early gestation. Thyroid hormones play a role in placentation, which is completed at almost 20 weeks of gestation [18], and T₃ is known to play a critical role in placentation by increasing trophoblasts invasion [19]. These findings led us to a hypothesis that thyroid function at early gestation would cause failed placentation related

disorders in treated hyperthyroidism. Serum FT₃ and FT₄ levels at early gestation in failed placentation group was higher than those in successful group, but the difference was not significant. These thyroid status at early gestation in failed placentation group might be similar to subclinical hyperthyroidism. The previous studies reported the association of placental abruption with subclinical hyperthyroidism at early gestation [14, 20], which was consistent with the present study. Thus, these results suggested that subclinical hyperthyroidism at early gestation, in spite of treatment prior to or during pregnancy, would cause preeclampsia or placental abruption, although further investigation is required.

Limitations

The main limitations of this study consisted of the study design being a cohort study and the inclusion of a single tertiary care institution. Prevalence of low Apgar scores and higher preterm births in the control group compared to the thyroid disease groups, suggests the study population belonged to a high-risk category. This could cause a bias in detecting a significant difference in adverse pregnancy outcomes. However, the multivariate analysis on the risk of placental abruption should eliminate some bias by accounting for confounding factors. Secondly, all women in the control group were not screened for thyroid dysfunction. A small but significant proportion of these women could have undiagnosed subclinical thyroid dysfunction, which may influence the results of the study. Subclinical hypothyroidism was reported to be associated with preterm birth [7], and these patients may have included in the control group. In addition, the information on the time to start treatment, the duration of treatment, and treatment adherence was also lacked, because a part of patients was treated at other hospitals before pregnancy and clinical information before pregnancy were limited. A few patients started to treatment during pregnancy, and the effect of the timing to start treatment might be minimal. Moreover, the sample size for the comparison between failed and successful placentation groups in hyperthyroidism was small. Thus, adequate TSH levels for successful placentation remains undetermined. Further prospective research with a large study population should be conducted on the effect of the intervention prior to pregnancy on pregnancy outcomes to determine the adequate management of women with hyperthyroidism who wish to pregnancy.

Conclusion

The risks of pregnancy outcomes among women with treated hypothyroidism are comparable with those in women without thyroid diseases. However, treated hyperthyroidism showed an independent risk of placental abruption. In hyperthyroidism, low serum TSH concentration at early gestation might be related to placental abruption, although further research is required in this regard.

Abbreviations

aOR, adjusted odds ratio; CI, confidence intervals; FT₃, free T₃/ triiodothyronine; FT₄, free T₄/thyroxine; GA, gestational age; OR, odds ratio; PROM, premature rupture of membrane; TSH, thyroid function including stimulating hormone.

Declarations

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Ethics approval and consent to participate

The study was approved by the ethics committee of Nagoya University Graduate School of Medicine (2015-0415). Participants did not provide written informed consent for inclusion in the study because all of data were anonymized and it was a retrospective study, in accordance with the ethical guidelines by the Japanese Ministry of Health, Labor and Welfare. However, patients had been informed them on the website of the hospital and provided an option to opt out from their medical records being used in research.

Consent for publication

Not applicable.

Availability of data and materials

The dataset that supports the conclusions is available to the corresponding author upon reasonable request.

Competing interests

The authors have no conflicts of interest to declare.

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Authors' Contributions

TKotani contributed to the conception and design of the study. TKotani, KI, TU, YM, TKobayashi, HT, and SS performed the acquisition and interpretation of data and revised it critically for important intellectual content. AH, as a statistician, contributed to the analysis of the data as a statistician. TK drafted the first version of the manuscript. SO, HK, AI, and FK contributed to interpreting the data, and revising it critically for important intellectual content. All authors gave their approval for the final version of the manuscript.

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Figures

Fig.1

Figure 1

Risk factors for placental abruption of 3588 singleton pregnancies. Reference values for odds ratio of 1.00 are as follows. Maternal age; < 25 years, Parity; nulliparity, Conception; natural, Complication; subjects without complication, Gestational age (GA) at birth; < 37 weeks, Birth weight; < 1,500 g. Circles represent mean odds ratios with bars indicating 95% confidence intervals (CIs). GA at birth, preterm labour, preeclampsia, hyperthyroidism and birth weight showed significant differences by univariate

analyses. GA at birth and hyperthyroidism also showed significant differences by multivariate analyses. OR, odds ratio; CI, confidence interval; IUI, intrauterine insemination; ART, assisted reproductive technology; GA, gestational age; DM, diabetes mellitus; PROM; premature rupture of membranes.

Figure 2

The thyroid function at early gestation was compared between successful and failed placentation group. Successful: successful placentation group, those who had no pregnancy adverse outcomes. Failed: failed placentation group, those who had preeclampsia or placental abruption. Median data [5%-95%] is shown.

*p < 0.05