Retrospective analysis of the effects induced by maternal thyroid dysfunction on obstetrical complications and outcomes

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Abstract

Background: Abnormal concentrations of maternal thyroid hormones are risk factors for some obstetrical complications. However, the influence induced by different types of maternal thyroid dysfunction on obstetrical complications and outcomes is still controversial.

Methods: A total of 17219 pregnant women were drawn for a thyroid function test, including TSH and fT4. All participants were divided into 7 groups, on the basis of their blood tested results, and their pregnancy outcomes were followed up. The isolated hypothyroxinemia group was further divided into 2 cohorts, according to whether they receive levothyroxine. Pregnant complications and outcomes in two cohorts were observed and analyzed.

Results: A total of 2621 (15.22%)were identified to have abnormal thyroid function, including 1150 with subclinical hypothyroidism, 526 with gestational transient thyrotoxicosis (GTT), 419 with subclinical hyperthyroidism, 336 with isolated hypothyroxinemia, 78 with hyperthyroidism and 76 with hypothyroidism. Compare to control group, subclinical hypothyroidism, subclinical hyperthyroidism, isolated hypothyroxinemia and hypothyroidism groups presented higher incidence in one or more complications of pregnancy, while, GTT and drug-controlled hyperthyroidism had little significant effect on pregnancy complications. In isolated hypothyroxinemia group, there were no significant difference outcomes between cohorts using levothyroxine and not treatment.

Conclusions: Our results showed a high incidence rate of thyroid dysfunction in pregnant women, and subclinical hypothyroidism is most common, followed by GTT. In general, pregnant women with thyroid dysfunction presented high risk of pregnancy complications. Isolated hypothyroxinemia in pregnant women is a matter of concern and treatment with levothyroxine couldn't improve pregnancy outcomes and obstetrical complications.

Background

Normal maternal thyroid function is crucial for a normal pregnancy and fetal growth. During pregnancy, maternal thyroid dysfunction induced pregnancy complications and influences the fetal developments in utero and later in life [1–3]. According to the values of thyroid stimulating hormone (TSH) and free tetraiodothyronine (fT4), thyroid disorders in pregnancy were included subclinical hypothyroidism, hypothyroidism, isolated hypothyroxinemia, subclinical hyperthyroidism, and thyrotoxicosis [4–6]. On this basis, thyrotoxicosis can be divided into overt hyperthyroidism and gestational transient thyrotoxicosis (GTT) according to etiology [5].

The thyroid dysfunction is one of the most common complications of pregnancy. The reported frequencies of various thyroid dysfunctions in pregnancy are difference because of different research objects and methods in previous studies [7–10]. And the influence induced by different types of maternal thyroid dysfunction on pregnancy complications and outcomes is still controversial [6, 11]. For example, some studies found that subclinical hypothyroidism and isolated hypothyroxinemia were related to the increase of adverse obstetric outcomes risk [12, 13], but the others did not find a significant correlation [14, 15].Therefore, more clinical observation and data are necessary for research.

Not only the effects isolated hypothyroxinemia on pregnant complications are indeterminacy, but also there is no consensus on whether they should receive levothyroxine. According to American Thyroid Association (ATA) pregnancy guidelines in 2017 [7], the isolated hypothyroxinemia should not be treated, however, it was an opposite conclusion in European Thyroid Association (ETA) guidelines for the management of subclinical hypothyroidism in pregnancy and children [16]. In China, the guidelines give advices that neither recommend nor opposed to treatment of levothyroxine for pregnant women with isolated hypothyroxinemia in early pregnancy [17].

In this study, we performed a survey of the prevalence of thyroid dysfunction in the local situation of southern China. We also analyzed the incidence rates of obstetrical complications and pregnant adverse outcomes among different thyroid function groups. In additional, we assessed the effects of levothyroxine replacement on adverse outcomes in pregnant women with isolated hypothyroidism.

Methods

Patients

The descriptive study is based on a retrospective study and conducted in which is a third class maternal and child health care hospital Clinical data of 17869 pregnant women, who were admitted to Dongguan maternal and Child Health Hospital in Guangdong Province of China, were collected from January 2018 to March 2020. Exclusion criteria are as follows: (1) women with twin pregnancy, (2) women with a history of thyroid disease, (3) women with loosed to follow-up.17219 cases were enrolled (Fig. 1). The ethics committees of the Dongguan maternal and Child Health Hospital had granted Ethical approval for this study. All participants had signed informed consent.

Study design

All participants were fasting measured serum levels of TSH and fT4 in the morning using an electrochemiluminescence immunoassay with a Cobas Elecsys 601 system (Roche Diagnostics, Switzerland). According to the gestational age-specific reference intervals for serum thyroid hormone levels in Chinese population [12,13], reference intervals for TSH in the first, second and third trimesters of pregnancy were 0.09 to 4.52, 0.45 to 4.32, 0.80 to 4.98 mIU/L, respectively. Similarly, reference intervals for fT4 were 13.15 to 20.78, 9.77 to 18.89, and 9.05 to 15.22 *pmol*/L, respectively. All participants were divided into 7 groups: (1) Overt hypothyroidism was defined as TSH level higher than normal reference range and fT4 level lower than normal range. (2) Subclinical hypothyroidism was defined as TSH level higher than normal reference range with normal fT4 range. (3) Isolated hypothyroxinemia was defined as normal TSH and fT4 level lower than normal fT4 range. (4) Subclinical hyperthyroidism was defined as lower than normal TSH value with normal fT4 value. (5) Overt hyperthyroidism was defined as TSH level lower than normal reference range and fT4 level higher than normal fT4 range. (6) Gestational transient thyrotoxicosis was defined as TSH level lower than normal reference range and fT4 level higher than normal fT4 range, and exclude hyperthyroidism by endocrinologist. (7) Controls group was defined as normal concentration of TSH and fT4. The patients with hyperthyroidism, hypothyroidism and subclinical hypothyroidism were treated with levothyroxine as soon as they were diagnosed. Levothyroxine was used in the patients with isolated hypothyroxinemia according to their wishes.

Outcome Measure

All of the participants received tests for serum TSH and fT4 at the first antenatal, and completed all examinations and treatments needed for pregnancy in our hospital. Pregnant women related information, complications and outcomes were collected via medical records of inpatient and outpatient. Gestational age was evaluated by early ultrasound, and all pregnancy complications and fetus situations were diagnosed according indicators, such as preeclampsia, postpartum hemorrhage (PPH), gestational diabetes mellitus (GDM), premature rupture of membranes (PROM) and Apgar score of newborn.

Statistical analysis

Statistical analysis was performed using SPSS 22.0 version (IBM USA). Descriptive variables were expressed as mean ± SD. The measurement data and numeration data were statistically analyzed with *t*-test and chi-square test or Fisher's exact test, respectively. $P < 0.05$ was considered statistically significant.

Results

Incidence rate of thyroid dysfunction

As listed in Table 1, we identified a total of 2621(15.22%) abnormal thyroid function pregnancy, which included 1150 subclinical hypothyroidism, 76 overt hypothyroidism, 336 isolated hypothyroxinemia, 419 subclinical hyperthyroidism, 78 overt hyperthyroidism and 562 gestational transient thyrotoxicosis. The average age of all participants was 30.2 years. There was no statistically difference in aged factors between the abnormal thyroid function groups and the control group.

Table 1
Frequency of biochemical thyroid function pregnancy in the total cohort

	N	%	Age	*P*-Value
Subclinical hypothyroidism	1150	6.68%	29.27 ± 5.1	0.287
Overt hypothyroidism	76	0.44%	30.7 ± 5.2	0.822
Isolatedhypothyroxinemia	336	1.95%	31.5 ± 4.9	0.395
Subclinical hyperthyroidism	419	2.43%	29.4 ± 5.1	0.225
Overt hyperthyroidism	78	0.45%	30.4 ± 4.9	0.496
Gestational transient thyrotoxicosis	562	3.26%	29.4 ± 5.5	0.905
Normal thyroid function	14598	84.78%	30.1 ± 4.8	-
Total	17219	100%	30.2 ± 5.3	

Obstetrical complications and pregnancy outcomes of thyroid dysfunction

Multiple complications and outcomes of pregnancy were analyzed among 17219 pregnant women from 7 groups (Table 2). The top 4 prevalent thyroid dysfunction was subclinical hypothyroidism, gestational transient thyrotoxicosis, subclinical hyperthyroidism and isolated hypothyroxinemia, respectively. However, hypothyroidism and hyperthyroidism had a similarly lower incidence rate in our study. Compared with control group, subclinical hypothyroidism group presented a higher rate of GDM, preeclampsia, PROM and therapeutic abortion related to fetal diseases ($P < 0.05$);the incidence of gestational transient thyrotoxicosis group had no significant difference in the obstetrical complications and pregnant outcomes ($P > 0.05$); in subclinical hyperthyroidism group, there was no significant difference in the adverse outcomes except of GDM ($P > 0.05$); in isolated hypothyroxinemia group, the incidence of spontaneous abortion, premature livery, preeclampsia, gestational diabetes(GDM), macrosomia, breech presentation were more likely ($P < 0.05$); in hypothyroidism group, the incidence rates of PPH and preeclampsia were increased significantly ($P < 0.05$); and in overt hyperthyroidism treated with drugs had little significant effect on pregnancy complications and outcomes ($P > 0.05$).

Table 2
Comparison of the incidence of obstetrical complications in pregnant women between the normal thyroid function group and the abnormal thyroid function groups

		SCH[b]	Hypothyroidism	IH[c]	subclinical hyperthyroidism	Hyperthyroidism	GTT[d]	Normal
spontaneous abortion	N	17	4	27	8	1	7	195
	%	1.04%	2.60%	3.54%	1.91%	1.33%	1.24%	1.34%
	P	0.107	0.277	**0.003**	0.315	1	0.852	
Premature delivery	N	96	10	47	33	9	44	1286
	%	8.33%	12.99%	13.86%	7.88%	12.00%	7.82%	8.80%
	P	0.587	0.197	**0.001**	0.508	0.33	0.217	
Therapeutic abortion related to fetal diseases[a]	N	15	1	1	4	1	7	102
	%	1.30%	1.30%	0.29%	0.95%	1.33%	1.24%	0.70%
	P	**0.022**	0.419	0.733	0.543	0.411	0.127	
GDM	N	185	11	105	114	20	145	3265
	%	16.06	14.29%	30.97%	27.21%	26.67%	25.75%	22.35%
	P	**0.000**	0.09	**0.003**	**0.019**	0.371	0.058	
preeclampsia	N	80	7	29	10	3	14	457
	%	6.96%	9.21%	8.63%	2.39%	3.85%	2.49%	2.65%
	P	**0.000**	**0.003**	**0.000**	0.387	0.737	0.391	
PROM	N	323	13	69	85	15	111	3088
	%	28.04%	16.88%	20.35%	20.29%	20.00%	19.72%	21.14%
	P	**0.000**	0.361	0.725	0.672	0.809	0.416	
PPH	N	31	6	15	18	0	14	428
	%	2.69%	7.79%	4.42%	4.30%	0.00%	2.49%	2.93%
	P	0.642	**0.012**	0.109	0.104	0.283	0.539	
Macrosomia	N	33	4	18	12	2	20	476
	%	2.86%	5.19%	5.31%	2.86%	2.67%	3.55%	3.26%
	P	0.466	0.321	**0.037**	0.653	0.773	0.701	0.466
Breech presentation	N	43	1	23	18	2	17	581
	%	3.73%	1.30%	6.78%	4.30%	2.67%	3.02%	3.98%

[a] Therapeutic abortion related to fetal diseases, Lethal or multiple malformation of ultrasound or chromosome abnormality for fetal.

[b] Subclinical hypothyroidism

[c] Isolated hypothyroxinemia

[d] Gestational transient thyrotoxicosis

[e]Apgar score of newborn less or equal to 7 points

		SCH[b]	Hypothyroidism	IH[c]	subclinical hyperthyroidism	Hyperthyroidism	GTT[d]	Normal
	P	0.681	0.664	**0.000**	0.743	0.771	0.252	
Intrauterine fetal death	N	3	1	0	1	0	2	23
	%	0.26%	1.30%	0.00%	0.24%	0.00%	0.36%	0.16%
	P	0.434	0.119	-	0.493	-	0.237	
Neonatal asphyxia[e]	N	8	0	1	1	0	2	55
	%	0.70%	0.00%	0.30%	0.24%	0.00%	0.36%	0.38%
	P	0.071	-	0.640	1.000	-	1.000	
Newborn weight	Mean	3.21 ± 0.41	3.22 ± 0.44	3.32 ± 0.40	3.27 ± 0.39	3.31 ± 0.39	3.22 ± 0.40	3.24 ± 0.40
	P	0.193	0.665	0.48	0.409	0.733	0.275	

[a] Therapeutic abortion related to fetal diseases, Lethal or multiple malformation of ultrasound or chromosome abnormality for fetal.

[b] Subclinical hypothyroidism

[c] Isolated hypothyroxinemia

[d] Gestational transient thyrotoxicosis

[e]Apgar score of newborn less or equal to 7 points

Treatment Of Isolated Hypothyroxinemia With Levothyroxine

40 out of 336 gravidas in the isolated hypothyroxinemia group received treatment with levothyroxine and maintained fT4 at a normal level (Table 3). The incidences of spontaneous abortions, premature delivery, and preeclampsia in women who received levothyroxine treatment was lower than in women who did not receive treatment, but the difference was no significant ($P > 0.05$). Similarly, the rest of obstetrical complications had no represents statistical difference between 2 groups ($P > 0.05$).

Table 3
Comparison of the incidence of obstetrical complications between treated women and non-treated women in the isolated hypothyroxinemia group

	Treated gravidas (n = 40)	Untreated gravidas (n = 296)	*P*-Value
Spontaneous abortion	1	11	1.000
Premature delivery	4	43	0.438
Therapeutic abortion related to fetal diseases	1	0	0.119
GDM	13	92	0.856
preeclampsia	3	26	1.000
PROM	9	60	0.743
PPH	4	11	0.089
Macrosomia	2	15	1.000
Breech presentation	3	20	0.745
Neonatal asphyxia	0	1	1.000
Newborn weight	3.32 ± 0.40	3.29 ± 0.36	1.000

Discussion

We have performed a survey of the incidence of thyroid disorders during pregnancy in local situation of southern China. The results of the survey indicated that thyroid dysfunction is a common disorder among local pregnant women. In fact, at least one in seven pregnant women suffers from thyroid disorder. The results of study are approximately consistent with the latest meta-analysis results that showed the prevalence of overt hypothyroidism, isolated hypothyroxinemia, and sub-clinical hyperthyroidism to be 0.5%, 2.05%, and 2.18% [18]. But compared with the meta-analysis which showed the prevalence of subclinical hypothyroidism and hyperthyroidism to be 3.47% and 0.91%, the subclinical hypothyroidism revealed the higher frequency (6.68%) and the hyperthyroidism revealed the lower frequency (0.45%) in our study. In Denmark, the incidence rates of subclinical hypothyroidism and hyperthyroidism were 5.3% and 1.6%, respectively [19]. In previous studies of China, the prevalence of subclinical hypothyroidism and clinical hyperthyroidism was reportedly 5.27% and 0.4%, respectively [17]. We believed the results might be due to the iodine intake of residents in different area, and classification of thyroid status by different criteria, the other reason for this phenomenon may was that we did not refer to the status of thyroid peroxidase antibody (TPO-Ab) in our study. We also determined the prevalence of gestational transient thyrotoxicosis along with endocrinologists (3.26%). It was occasionally difficult to distinguish GTT from hyperthyroidism, which be distinguished by several clinical and laboratory differences [5]. GTT was related to the high level of hCG (Human chorionic gonadotropin) secreted by the placenta, which was often manifested as hyperemesis and not ordinarily require intervention. Its appearance was a physiological process, not an immune abnormality; its thyrotropin receptor (TRAb) often showed negative results [20].

In the study reported herein, there were various impacts on adverse pregnancy outcomes in different thyroid dysfunction groups. The pregnant women with hypothyroidism showed more common preeclampsia and postpartum hemorrhage. Compared with control group, overt hypothyroidism increased the incidence rates of spontaneous abortion, premature delivery, therapeutic abortion related to fetal diseases and macrosomia, and overt hyperthyroidism increased the incidence rates of premature delivery, therapeutic abortion related to fetal diseases, GDM and preeclampsia. However, the difference was not significant ($P > 0.05$). We considered that the main reasons might be related to using levothyroxine or propylthiouracil (PTU) once the hypothyroidism or hyperthyroidism was diagnosed. Many of previous studies showed that untreated hypothyroidism and

hyperthyroidism can cause serious adverse consequences for the pregnant women and fetal [6, 12, 21–23], however, if the maternal hyperthyroidism was adequately treated, prognosis was well [5, 23]. According to the existing guidelines [7], all participants identified as overt hyperthyroidism and hypothyroidism were treated immediately and kept TSH in an ideal range continuously in our study. Our results reflect the obstetrical outcomes of pregnant women with treated hypothyroidism and hyperthyroidism.

Many existing studies had demonstrated that subclinical hypothyroidism also had adverse effects on pregnancy outcomes, for example preeclampsia, GDM, spontaneous abortion, premature delivery, although the effects were less than overt hypothyroidism [24–26]. But in Mannisto's study, the results showed that maternal subclinical hypothyroidism was not related to adverse pregnant outcomes [27]; and Cleary-Goldman also reported similar results [14]. In our study, the incidence of preeclampsia, GDM, PROM, therapeutic abortion related to fetal diseases were increased. But the incidence of spontaneous abortion, macrosomia, PPH, premature delivery breech presentation, intrauterine fetal death did not show significant increasing in subclinical hypothyroidism group than control group. Inconsistent research conclusions might be related to the timing of levothyroxine use, but we tend to think that the effects of subclinical hypothyroidism on pregnancy outcomes were complex and worthy of further study.

There was no dispute that subclinical hyperthyroidism and gestational transient thyrotoxicosis had little adverse effects on pregnancy outcome and obstetrical complications [20, 21, 28], our results are also consistent with the conclusions.

It is worth noting that the effects isolated hypothyroxinemia on gravidas and fetus. At present, there were few studies on the relationship between the isolated hypothyroxinemia and adverse pregnant outcomes, and the results of studies were controversies [29–31]. Some studies have reported increased risk of premature delivery, fetal distress, and premature rupture of membranes and higher mean birth weight in isolated hypothyroxinemia [32]. However, other studies have reported no increased risk of alteration in the offspring of women with isolated hypothyroxinemia [33]. In our study, the incidences of spontaneous abortion, premature delivery, GDM, preeclampsia, macrosomia, breech presentation were significantly higher in isolated hypothyroxinemia than those euthyroidism ($P < 0.05$). Our results played a role in complementing clinical data for the study of isolated hypothyroxinemia.

As for the treatment of hypothyroxinemia, there was still no consensus in the guidelines [7, 16], so that in the face of patients with isolated hypothyroxinemia, the decision to use levothyroxine often based on clinician's experience or patient's wishes rather than objective evidence. There was a large pregnant population suffered from isolated hypothyroxinemia if calculated by the incidence rate of 1.95%. Therefore, the significance of levothyroxine in isolated hypothyroxinemia urgently needs to be confirmed. The results of our study suggested that it was not significant improved on pregnancy outcomes and obstetrical complications by using levothyroxine ($P > 0.05$), although the incidence rate of spontaneous abortion, premature delivery and preeclampsia is lower in isolated maternal hypothyroxinemia group than control group.

Conclusion

In conclusion, our study revealed the incidence of thyroid disorders during pregnancy in local situation of southern China, showing a high frequency of subclinical hypothyroidism but low frequency of hypothyroidism and hyperthyroidism. We observed that different kinds of thyroid dysfunction have different effects on obstetrical complications and pregnant outcomes. Isolated hypothyroxinemia had various adverse effects on pregnancy; the pregnant women with isolated hypothyroxinemia should be concerned and received medical intervention [34]. Perhaps, we should look for and treated for cause of maternal, such as irrelevant iodine nutrition or deficiency iron [35–37], rather than add levothyroxine simply.

Abbreviations

ATA: American Thyroid Association; ETA: European Thyroid Association; fT4: Free tetraiodothyronine; GDM: Gestational diabetes mellitus; GTT: Gestational transient thyrotoxicosis; hCG : Human chorionic gonadotropin; IH: Isolated hypothyroxinemia; PPH: Preeclampsia, postpartum hemorrhage; PROM: Premature rupture of membranes; PTU: Propylthiouracil; SCH: Subclinical hypothyroidism; TPO-Ab: Thyroid peroxidase antibody; TRAb: Thyrotropin receptor; TSH: Thyroid stimulating hormone

Declarations

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Authors' contributions

SMN: Data collection and Manuscript writing. WXH: Data collection and analysis. FYY: Study design. LCN and LJW: Data analysis. CJS: Study design and manuscript revision. DBM: Supervision. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated and analyzed during the current study are not publicly available due hospital regulations but are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Written informed consent was obtained from each participant and the program was approved by the Research Ethics Committee of Dongguan Maternal and Children Hospital (reference: DGFYECHU-2020012).

Consent for publication

Not applicable.

Competing interests

The authors report no competing interest.

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Figures

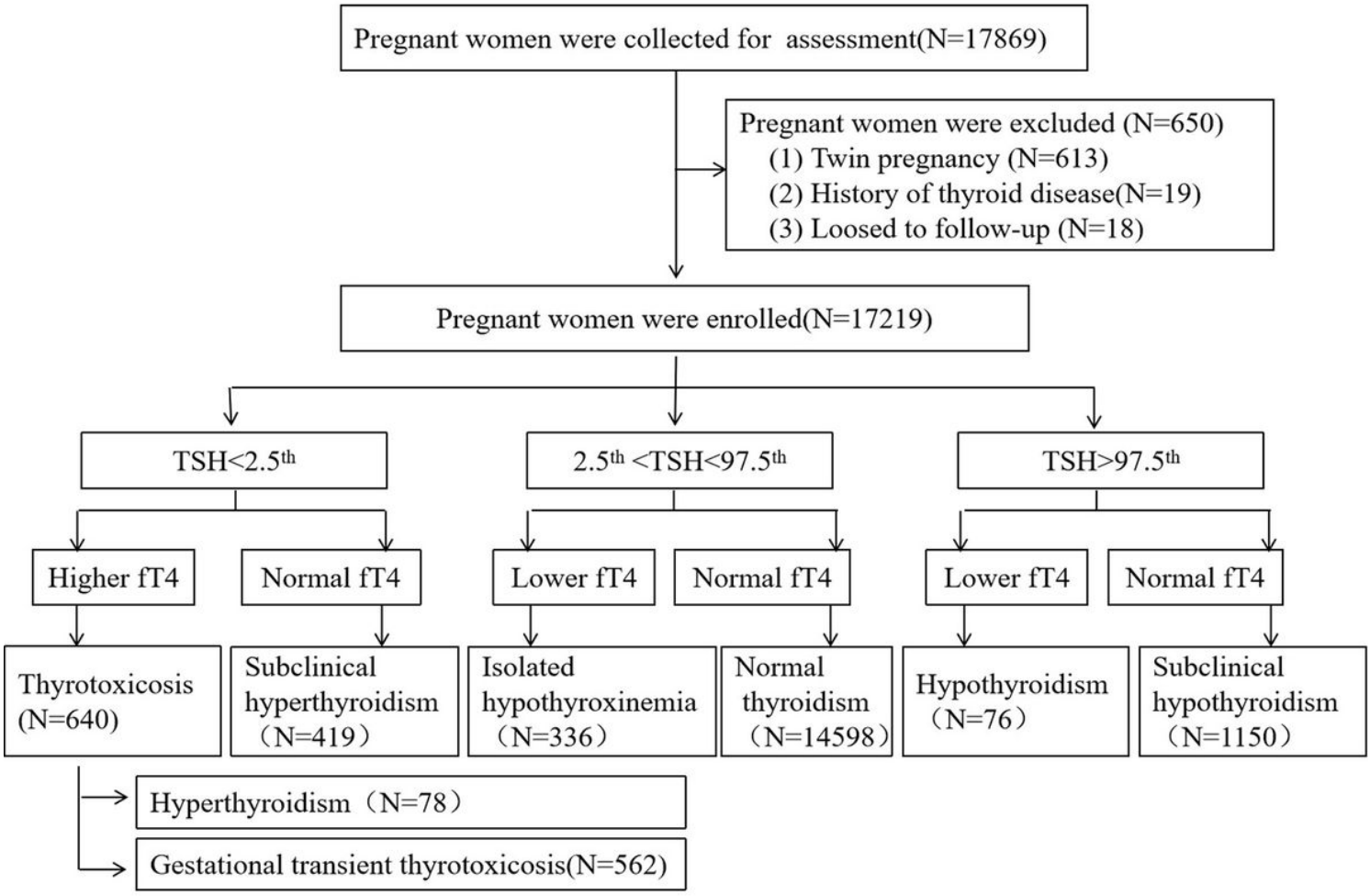

Figure 1

Flow chart