Maternal Thyroid Function in the First Twenty Weeks of Pregnancy and Subsequent Fetal and Infant Development: A Prospective Population-Based Cohort Study in China

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Context: There are a few prospective population-based cohort studies evaluating the effects of maternal thyroid dysfunctions on fetal and infant developments, but they are inconsistent.

Objective: The objective of the study was to investigate the effects of maternal thyroid dysfunction on fetal and infant development.

Setting and Participants: The study was nested within a prospective population-based China-Anhui Birth Defects and Child Development study. A total of 1017 women with singleton pregnancies participated in this study. Maternal serum samples in the first 20 wk of pregnancy were tested for thyroid hormones (TSH and free T_4). Pregnant women were classified by hormone status into percentile categories based on laboratory assay and were compared accordingly.

Main Outcomes: Outcomes included fetal loss, malformation, birth weight, preterm delivery, fetal stress, neonatal death, and infant development.

Results: Clinical hypothyroidism was associated with increased fetal loss, low birth weight, and congenital circulation system malformations; the adjusted odds ratios [95% confidence interval (CI)] were 13.45 (2.54–71.20), 9.05 (1.01–80.90), and 10.44 (1.15–94.62), respectively. Subclinical hypothyroidism was associated with increased fetal distress, preterm delivery, poor vision development, and neurodevelopmental delay; the adjusted odds ratios (95% CI) were 3.65 (1.44–9.26), 3.32 (1.22–9.05), 5.34 (1.09–26.16), and 10.49 (1.01–119.19), respectively. Isolated hypothyroxinemia was related to fetal distress, small for gestational age, and musculoskeletal malformations; the adjusted odds ratios (95% CI) were 2.95 (1.08–8.05), 3.55 (1.01–12.83), and 9.12 (1.67–49.70), respectively. Isolated hyperthyroxinemia was associated with spontaneous abortion; the adjusted odds ratio (95% CI) was 6.02 (1.25–28.96). Clinical hyperthyroidism was associated with hearing dysplasia; the adjusted odds ratio (95% CI) was 12.14 (1.22–120.70).

Conclusions: Thyroid dysfunction in the first 20 wk of pregnancy may result in fetal loss and dysplasia and some congenital malformations. **(*J Clin Endocrinol Metab* 96: 3234–3241, 2011)**

Over the last 2 decades, the link between maternal thyroid dysfunction during pregnancy and adverse pregnancy outcomes has been a subject of considerable interest (1–6). Overt hypothyroidism and thyrotoxicosis have a well-documented impact on female fertility, pregnancy outcomes, and offspring development (7–10). Mild maternal thyroid dysfunction has been reported to be associated with spontaneous abortion (9), fetal death (11),

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Abbreviations: BMI, Body mass index; CI, confidence interval; fT4, free T_4; hCG, human chorionic gonadotropin; MCH, maternal and child health; SGA, small for gestational age.

preterm delivery (10, 11), small head circumference and low birth weight (2), and impaired neuropsychological development (4, 9, 12). In addition, a low maternal T_4 level is a risk factor for breech presentation (13), whereas maternal hyperthyroidism increases the incidence of hip dysplasia (14). Despite these health impacts, women with thyroid dysfunction during pregnancy have rarely been diagnosed or appropriately treated in China. Furthermore, a large study in China conducted by Teng *et al.* (15) indicated an increase in the prevalence of overt hypothyroidism and subclinical hypothyroidism with increased iodine intake. Salt has been iodized throughout China since 1996; we have subsequently observed an increasing number of patients with thyroid disorders. Shi *et al.* (16) reported that in some areas with adequate iodine availability, 42.63% of pregnant women have iodine deficiency.

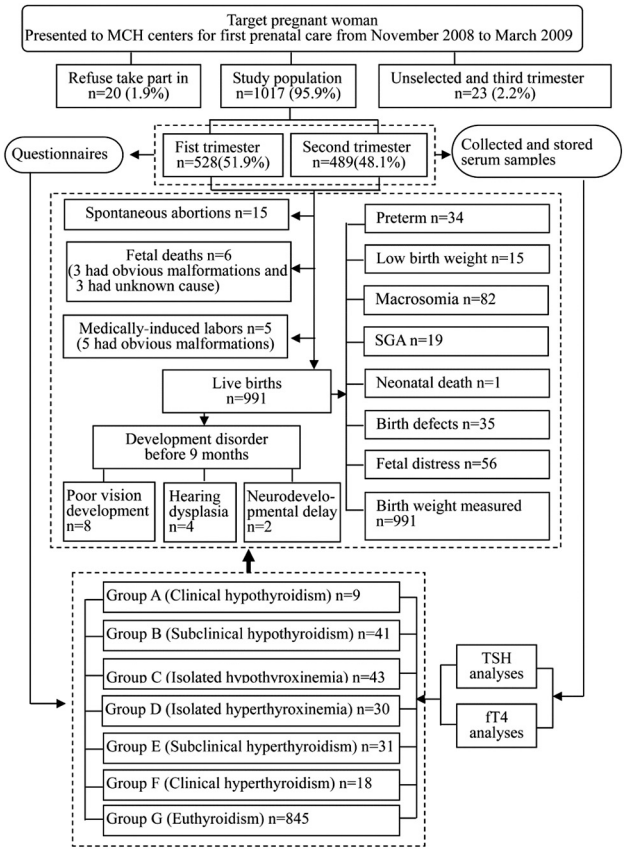
There are several prospective cohort studies that have evaluated the effects of maternal thyroid dysfunction on offspring (2, 11, 12, 17–19). However, none of those studies examined all types of thyroid dysfunction and its effects on fetal, neonatal, and infant development. Additionally, few studies explored the relationships between different types of maternal thyroid dysfunction and different system malformations. Thus, we conducted a prospective, population-based cohort study in China.

Subjects and Methods

Study population

Our study was nested within a prospective cohort study of pregnant women from the China-Anhui Birth Defects and Child Development cohort study, which was designed to investigate the association between maternal environmental exposure and birth defects and child development. We chose 23 maternal and child health (MCH) centers in 12 cities in Anhui Province (China) between October 2008 and December 2010. Before October 2010, 20308 pregnant women who presented to 23 MCH centers for their first prenatal care agreed to participate in the China-Anhui Birth Defects and Child Development cohort study.

In the present study, the participants were recruited in Ma'anshan city. Between November 2008 and March 2009, pregnant women living in the city were invited to participate when they presented to MCH centers for their first prenatal visit. Among the 1060 pregnant women who were invited, 1040 women 20–42 yr of age agreed to participate (response rate 98.1%) in the study. In this sample, 23 women who had thyroid disease, plural gestations, or were longer than 20 wk of gestation were excluded. A total of 1017 women in the first 20 wk of pregnancy were recruited in the present study (Fig. 1). The cohort has been followed up for more than 19 months since enrollment in the study. These pregnant women were given a written letter explaining the purpose and procedure of the study. They completed a self-administered questionnaire, which was collected and checked by the nurses immediately. Additionally, blood was collected for research, and the separated serum was stored at −80 C for subsequent biochemical analysis. Ethical approval was obtained from the Biomedicine Ethical Committee of Anhui Medical University (approval no. 2007002). A written informed consent was obtained from all eligible women who agreed to participate in this study.



Group A: TSH over 95th percentile for gestational age, fT4 under 5th percentile for gestational age
Group B: TSH over 95th percentile for gestational age, fT4 between 5th and 95th percentiles for gestational age
Group C: TSH between 5th and 95th percentiles for gestational age, fT4 below 5th percentile for gestational age
Group D: TSH between 5th and 95th percentiles for gestational age, fT4 over 95th percentile for gestational age
Group E: TSH under 5th percentile for gestational age, fT4 between 5th and 95th percentiles for gestational age
Group F: TSH under 5th percentile for gestational age, fT4 over 95th percentile for gestational age
Group G (Reference group): TSH between 5th and 95th percentiles for gestational age, fT4 between 5th and 95th percentiles for gestational age

FIG. 1. Flow chart of the study population. Group A included a TSH greater than the 95th percentile for gestational age and a fT4 less than the fifth percentile for gestational age. Group B included a TSH greater than the 95th percentile for gestational age and a fT4 between the fifth and 95th percentiles for gestational age. Group C included a TSH between the fifth and 95th percentiles for gestational age and a fT4 below the fifth percentile for gestational age. Group D included a TSH between the fifth and 95th percentiles for gestational age and a fT4 greater than the fifth percentile for gestational age. Group E included a TSH less than the fifth percentile for gestational age and a fT4 between the fifth and 95th percentiles for gestational age. Group F included a TSH less than the fifth percentile for gestational age and a fT4 greater than the 95th percentiles for gestational age. Group G (reference group) included a TSH between the fifth and 95th percentiles for gestational age and a fT4 between the fifth and 95th percentiles for gestational age.

Laboratory assay

Maternal serum samples were assayed for levels of TSH and free T_4 (fT4), using chemiluminescent immunoassays on an au-

tomated platform (LIAISON analyzer; DiaSorin SpA., Saluggia, Italy) in the Department of Clinical Laboratory in the First Affiliated Hospital of Anhui Medical University in October 2010 (thus far, all of the cohort infants were >9 months of age). The functional sensitivity of TSH was 0.004 mIU/liter. The measured concentrations of TSH were between 0.004 and 100 mIU/liter. The normal range for TSH was 0.3–3.6 mIU/liter (2.5th and 97.5th percentiles). The measured concentrations of fT4 were between 0.1 and 10 ng/dl. The normal range for fT4 was 0.8–1.7 ng/dl (first and 99th percentiles). The intraassay coefficient of variation of serum TSH and fT4 was 0.7–1.9 and 1.1–2.4%, respectively. The interassay coefficient of variation of serum TSH and fT4 was 1.6–5.2 and 2.9–4.8%, respectively.

Categorization of the study population

The data were categorized using percentiles for gestational age of our own laboratory values for the following reasons: 1) the reference values given by the manufacturer of the analyzer apply to a nonpregnant population, and these values may differ from the values in a pregnant population (18); 2) the reference intervals may differ for pregnant women at different gestational ages (20, 21); 3) The variations of TSH and fT4 reference intervals are caused by many factors, such as ethnic background, methods of analysis, iodine status, rigor for selection of normal subjects, and calculation method (22); and 4) the current study is based on a population large enough to create independent reference values (Table 1). In this study, the pregnant women with serum concentrations of TSH and fT4 between the fifth and 95th percentiles were considered to have normal thyroid function because the serum TSH level will be affected by freezing, thawing, and storage (17, 23). The series of gestational age-specific reference intervals for TSH and fT4 (median, fifth, and 95th percentiles) are presented in Table 1.

The subjects were divided into seven groups with respect to thyroid hormone levels, as follows: group A (n = 9, clinical hypothyroidism), a TSH greater than the 95th percentile for gestational age and a fT4 less than the fifth percentile for gestational age; group B (n = 41, subclinical hypothyroidism), a TSH greater than the 95th percentile and a fT4 between the fifth and 95th percentiles; group C (n = 43, isolated hypothyroxinemia), a TSH between the fifth and 95th percentiles and a fT4 less than the fifth percentile; group D (n = 30, isolated hyperthyroxinemia), a TSH between the fifth and 95th percentiles and a fT4 greater than the 95th percentile; group E (n = 31, subclinical hyperthyroidism), a TSH less than the fifth percentile and a fT4 between the fifth and 95th percentiles; group F (n = 18, clinical hyperthyroidism), a TSH less than the fifth percentile and a fT4 greater than the 95th percentile; and group G (n = 845, reference group), a TSH and fT4 between the fifth and 95th percentiles. Groups A–F were compared with group G (reference group) separately in the analyses.

Pregnant outcomes

The pregnancy outcomes included birth weight; spontaneous abortion (fetal loss after enrollment but before 20 completed weeks of gestation); fetal death (intrauterine fetal demise after 20 completed weeks of gestation); medically induced labor (termination of pregnancy because of serious maternal or fetal risks, such as anencephaly); malformations (nervous system, eye, ear, and face, circulatory system, reproductive system, urinary system, musculoskeletal, and others); fetal distress (based on fetal heart rate variability analysis); preterm delivery (a live birth before 37 completed weeks of gestation); low birth weight (<2500 g); macrosomia (≥4000 g); small for gestational age (SGA); and neonatal death (death within the first 28 d of life).

Infant developmental disorders, including infant vision, hearing, and neurological, were screened by child health care providers and were then diagnosed by related medical specialists. Vision development was tested initially with automatic optometry equipment to screen for poor vision development at 6 months of age in the MCH center at Ma'anshan City. If the result was abnormal, the infant was screened for a second time at 9 months of age. If the result was still abnormal, then the infant was diagnosed as poor vision development at the First Affiliated Hospital of Anhui Medical University. Infant hearing development was tested initially using auditory brain stem response at 42 d of age at the MCH center of Ma'anshan City. If the result was abnormal, then the infant was screened again at 3 months of age. If the result was still abnormal, then the infant was diagnosed as hearing dysplasia at the First Affiliated Hospital of Anhui Medical University. Neurodevelopment was tested using the Chinese Bayley Scales of Infant Development before 6 months of age by child health care providers.

Data on other characteristics

All pregnant women received a pregnancy questionnaire at the first antenatal visit at MCH centers. The questionnaire included the following potential confounding factors: maternal social demographic information (age, education level, and annual income of parents); reproductive histories (spontaneous abortion, medical abortion, induced abortion, medically induced labor; intrauterine fetal demise or stillbirth; extrauterine pregnancy, and malformation); thyroid disease history; method of conception (spontaneous or assisted conception requiring the use of reproductive technology); and body mass index (BMI; based on the preconception height and weight).

Statistical analysis

All statistical analyses were performed using the Statistical Package of Social Sciences and Problem Solutions (SPSS, version 13.0; SPSS, Inc., Chicago, IL). Bilateral Fischer's exact test was used to compare two different rates if the number of measures in

TABLE 1. Reference intervals (median, fifth, and 95th percentiles) for thyroid hormone levels in pregnant women

Gestational week	n	TSH (mIU/liter)			fT4 (ng/dl)		
		Fifth	Median	95th	Fifth	Median	95th
5–8	88	0.340	1.370	4.230	0.808	1.090	1.332
9–12	440	0.056	1.265	3.819	0.753	0.976	1.289
13–16	385	0.206	1.500	3.770	0.745	0.932	1.180
17–20	104	0.411	1.940	4.345	0.661	0.847	1.180

anyone group was less than 5. Continuous variables were compared by Student's *t* test. Logistic regression analysis was used to assess the associations between different types of maternal thyroid dysfunction and different obstetric outcomes after adjustment for confounders (maternal age, parity, and BMI).

Results

Study population

In the first 20 wk of pregnancy, the following diagnoses were established: 0.9% (nine of 1017) for clinical hypothyroidism; 4.0% (41 of 1017) for subclinical hypothyroidism; 4.2% (43 of 1017) for isolated hypothyroxinemia; 2.9% (30 of 1017) for isolated hyperthyroxinemia; 3.0% (31 of 1017) for subclinical hyperthyroidism; 1.8% (18 of 1017) for clinical hyperthyroidism; and 83.1% (845 of 1017) for euthyroidism (TSH and fT4 between the fifth and 95th percentiles). There were significant differences between groups A–F and the reference group with respect to maternal age and BMI. The pregnant women in group A were younger (24.3 ± 3.1 yr) than those in the reference group (26.8 ± 3.3 yr), whereas the pregnant women in groups D and E were older (28.0 ± 3.8 and 28.9 ± 3.9 yr, respectively). Group C had a higher BMI (21.6 ± 2.6 kg/m^2) than those in the reference group (20.2 ± 2.3 kg/m^2). However, parity and a history of adverse pregnant outcomes between the reference group and groups A–F were not significantly different.

Pregnant outcomes

The frequencies of offspring outcomes are listed in Fig. 1. Among a total of 1017 pregnant women with singleton pregnancies, there were 15 spontaneous abortions (1.5%), six fetal deaths (0.6%) in which three had obvious malformations and three had unknown causes, five pregnant women with medically induced labors (0.5%) in which all had obvious malformations, and 991 live-born infants (97.4%). Among those live-born infants, there were 56 cases of fetal distress (5.7%), 34 premature deliveries (3.4%), 15 low-birth-weight infants (1.5%), 82 infants weighing 4000 g or more (8.2%), 19 SGA infants (1.9%), 35 infants with birth defects (3.5%), one neonatal death (0.1%), eight infants with poor visual development (0.8%), four infants with hearing dysplasia (0.4%), and two infants with neurodevelopment delay (0.2%). In total, 43 fetuses or live births had obvious malformations [4.2% (43 of 1017)].

Maternal thyroid dysfunction and outcomes of fetus

Tables 2 and 3 show that in the pregnant women with clinical hypothyroidism (group A), there was a significant

TABLE 2. Outcomes of fetuses and live births grouped according to maternal thyroid hormone status

Pregnancy outcomes	Reference group	Group A	Group B	Group C	Group D	Group E	Group F	*P* value
Fetus[a]	n = 845	n = 9	n = 41	n = 43	n = 30	n = 31	n = 18	
Spontaneous abortions	11 (1.3)	0	2 (4.9)	0	2 (6.7)		0	0.133
Fetal deaths	4 (0.5)	1 (11.1)	0	0	0	1 (3.2)	0	0.040
Medically induced labors	4 (0.5)	1 (11.1)	0	0	0	0	0	0.068
Fetal loss	19 (2.2)	2 (22.2)[b]	2 (1.9)	0	2 (3.7)	1 (3.2)	0	0.030
Nervous system malformations	3 (0.4)	0	0	0	0	0	0	1.000
Eye, ear, and face malformations	5 (0.6)	0	0	0	0	0	0	1.000
Circulation system malformations	11 (1.3)	1 (11.1)	0	2 (4.7)	0	1 (3.2)	1 (5.6)	0.054
Reproductive system malformations	1 (0.1)	0	0	0	0	0	0	1.000
Urinary system malformations	1 (0.1)	0	0	0	0	0	0	1.000
Musculoskeletal malformations	6 (0.7)	0	0	2 (4.7)	0	0	1 (5.6)	0.091
Other malformations	10 (1.2)	0	0	0	0	0	0	1.000
Total malformations	37 (4.4)	1 (11.1)	0	2 (4.7)	0	1 (3.2)	2 (11.1)	0.275
Infant[c]	n = 826	n = 7	n = 39	n = 43	n = 28	n = 30	n = 18	
Birth length (cm)	50.0 ± 1.0	49.9 ± 0.4	49.6 ± 1.5[b]	49.9 ± 0.9	50.1 ± 1.0	50.2 ± 1.1	49.7 ± 0.7	0.099
Head circumference (cm)	33.9 ± 1.1	33.7 ± 2.2	33.2 ± 1.7[b]	34.0 ± 1.4	33.8 ± 0.9	33.6 ± 1.2	33.4 ± 0.6	0.010
Chest circumference (cm)	33.3 ± 1.6	33.3 ± 2.4	32.8 ± 1.7	32.9 ± 1.4	33.1 ± 1.3	32.4 ± 1.8[b]	33.5 ± 1.5	0.215
Fetal distress infants	39 (4.7)	1 (14.3)	6 (15.4)[b]	5 (11.6)	3 (10.7)	1 (3.3)	1 (5.6)	0.019
Preterm births	34 (4.1)	0	5 (12.8)[b]	1 (2.3)	0	0	2 (11.1)	0.096
Low-birth-weight infants	15 (1.8)	1 (14.3)	2 (5.1)	1 (2.3)	0	1 (3.3)	0	0.164
Macrosomia infants	82 (9.9)	0	1 (2.6)	3 (7.0)	1 (3.6)	4 (13.3)	0	0.453
SGA infants	19 (2.3)	1 (14.3)	0	3 (7.0)	2 (7.1)	2 (6.7)	1 (5.6)	0.025
Neonatal death	1 (0.1)	0	0	0	0	0	0	1.000
Infants with poor vision development	8 (1.0)	0	2 (5.1)	1 (2.3)	0	0	1 (5.6)	0.104
Infants with hearing dysplasia	4 (0.5)	0	0	0	0	0	1 (5.6)	0.257
Infants with neurodevelopmental delay	2 (0.2)	0	1 (2.6)	0	0	0	0	0.331

Values are mean (SD) or n (%). *P* values when comparing groups A–F together with the reference group.

[a] The number of fetus in different group.

[b] $P < 0.05$ when comparing groups A-F separately with the reference group.

[c] The number of infant in different group.

TABLE 3. Estimated risks of pregnancy outcomes in association with maternal thyroid dysfunction (presented as odds ratios)

Pregnancy outcomes	Thyroid status	n (%)	Univatiate OR (95% CI)	Adjusted OR (95% CI)
Spontaneous abortions	Reference group	11 (1.3)	1.0	
	Group D	2 (6.7)	5.42 (1.15–25.59)	6.02 (1.25–28.96)
Fetal deaths	Reference group	4 (0.8)	1.0	
	Group A	1 (11.1)	26.28 (2.64–261.94)	44.24 (3.85–507.87)
Medically induced labors	Reference group	4 (0.5)	1.0	
	Group A	1 (11.1)	26.28 (2.64–261.94)	44.24 (3.85–507.87)
Fetal loss	Reference group	19 (2.2)	1.0	
	Group A	2 (22.2)	12.42 (2.42–63.77)	13.45 (2.54–71.20)
Circulation system malformations	Reference group	11 (1.3)	1.0	
	Group A	1 (11.1)	9.477 (1.09–82.37)	10.44 (1.15–94.62)
Musculoskeletal malformations	Reference group	6 (0.7)	1.0	
	Group C	2 (4.7)	6.82 (1.34–34.84)	9.12 (1.67–49.70)
Fetal distress infants	Reference group	39 (4.7)	1.0	
	Group B	6 (15.4)	3.67 (1.45–9.28)	3.65 (1.44–9.26)
	Group C	5 (11.6)	2.66 (0.99–7.12)	2.95 (1.08–8.05)
Preterm births	Reference group	34 (4.1)	1.0	
	Group B	5 (12.8)	3.43 (1.26–9.31)	3.32 (1.22–9.05)
Low-birth-weight infants	Reference group	15 (1.8)	1.0	
	Group A	1 (14.3)	9.01 (1.02–79.54)	9.05 (1.01–80.90)
SGA infants	Reference group	19 (2.3)	1.0	
	Group C	3 (7.0)	3.19 (0.91–11.21)	3.55 (1.01–12.83)
Infants with poor vision development	Reference group	8 (1.0)	1.0	
	Group B	2 (5.1)	5.53 (1.13–26.94)	5.34 (1.09–26.16)
Infants with hearing dysplasia	Reference group	4 (0.5)	1.0	
	Group F	1 (5.6)	12.09 (1.28–113.93)	12.14 (1.22–120.70)
Infants with neurodevelopmental delay	Reference group	2 (0.2)	1.0	
	Group B	1 (2.6)	10.84 (0.96–122.22)	10.49 (1.01–119.19)

OR adjusted for maternal age, parity, and BMI. OR, Odds ratio.

increase in fetal loss [adjusted odds ratio 13.45; 95% confidence interval (CI) 2.54–71.20]. Those women had a 26.28-fold higher risk of fetal death or medically induced labor when compared with the reference group. The differences persisted after adjusting for these confounders (adjusted odds ratio 44.24; 95% CI 3.85–507.87, Table 3). Pregnant women in group D had a 5.42-fold higher incidence of spontaneous abortions than the reference group. The risk was higher after adjusting for maternal age, parity, and BMI (adjusted odds ratio 6.02; 95% CI 1.25–28.96, Table 3).

Maternal thyroid dysfunction and fetal and infant malformations

In the current study, there were 43 fetuses or infants with obvious malformations. The most frequent malformation occurred in the circulatory system [37.2% (16 of 43)], and among them, 87.5% (14 of 16) fetuses or infants had congenital heart disease.

The offspring of group A had a 10.44-fold increased risk of circulatory system malformations than the reference group after adjusting for maternal age, parity, and BMI (Table 3). The fetuses and infants in group C had a 6.821-fold increased risk of musculoskeletal malformations when compared with the reference group. The risk was higher after controlling for these confounders (adjusted odds ratio 9.12; 95% CI 1.67–49.70, Table 3). No other associations were observed in this study.

Maternal thyroid dysfunction and outcomes of live births

The infants in group A were at a 9.01-fold increased risk of low birth weight when compared with the reference group (adjusted odds ratio 9.05; 95% CI 1.01–80.90, Table 3). The infants in group B had a smaller head circumference and shorter birth length than the reference group (Table 2). The offspring in group B also had a higher risk of premature birth (adjusted odds ratio 3.32; 95% CI 1.22–9.05), fetal distress (adjusted odds ratio 3.65; 95% CI 1.44–9.26), poor vision development (adjusted odds ratio 5.34; 95% CI 1.09–26.16), and neurodevelopmental delay (adjusted odds ratio 10.49; 95% CI 1.01–119.19) when compared with the reference group (Table 3). Compared with the reference group the incidences of fetal distress and SGA in group C were significantly higher (adjusted odds ratio 2.95; 95% CI 1.08–8.05 and 3.55; 95% CI 1.01–12.83, respectively, Tables 2 and 3), and the incidence of hearing dysplasia in group F was significantly increased (adjusted odds ratio 12.14; 95% CI 1.22–120.70, Table 3).

Discussion

There were several important findings from this prospective population-based cohort study. First, the occurrence of fetal loss (spontaneous abortion, fetal death, and medically induced labor) significantly increased in the pregnant women with clinical hypothyroidism, while the incidence of spontaneous abortion was significantly higher in pregnant women with higher fT4 (isolated hyperthyroxinemia). Second, the pregnant women with clinical hypothyroidism had a 9.48-fold greater risk of circulatory system malformations, and those with isolated hypothyroxinemia had a 6.82-fold increased risk of musculoskeletal malformations. Third, the pregnant women with subclinical hypothyroidism had a significant increase in the incidence of preterm delivery, fetal distress, SGA, poor vision development, and neurodevelopmental delay. In addition, the incidences of low birth weight and hearing dysplasia were significantly higher in infants born from pregnancies complicated by maternal clinical hypothyroidism and clinical hyperthyroidism, respectively.

In this study, the pregnant women were grouped according to maternal serum TSH and fT4 for gestational age-specific reference intervals. It is known that the serum TSH level decreases during the first trimester of pregnancy and then increases gradually. The serum fT4 level usually increases in early pregnancy and then decreases (21, 24, 25). The results of this study are consistent with other studies that suggested that the intervals of TSH and fT4 are significantly different with gestational age (12, 20, 21), even when the gestational age is only a few weeks apart. Therefore, the categorization of our study subjects was relatively accurate. Additionally, the measurement of pregnant outcomes were relatively reliable because all pregnant women had well-organized maternity care and gave birth in public hospitals.

Fetal loss was 12.42-fold greater in the pregnant women with clinical hypothyroidism compared with those from the reference group. Allan *et al.* (11) showed that TSH levels greater than 6 mU/liter were significantly associated with a higher frequency of stillbirth. Benhadi *et al.* (26) and Negro *et al.* (5) found that high maternal TSH levels were associated with an increased risk of pregnancy loss. Because TSH is inversely related to human chorionic gonadotropin (hCG) levels, women with low hCG levels are at a greater risk of child loss (27). In addition, we found that women with isolated hyperthyroxinemia had a 5.42-fold higher incidence of spontaneous abortion, but this type of thyroid dysfunction was not associated with child loss. This result demonstrates that maternal isolated hyperthyroxinemia may affect early embryonic development.

The present work examined the effect of six types of maternal thyroid dysfunction on different birth defects. It is worth noting that, more than one third of malformations involved the circulatory system, and offspring with maternal clinical hypothyroidism had a 9.48-fold greater risk of circulatory system malformations compared with the reference group, which is consistent with a previous report (28). Vohra *et al.* (29) speculated that the similarity between the structures of TSH and β-hCG, and it is possible that some receptor confusion causes the effects of thyroid hormones to become intertwined. However, further research is needed to determine the role of maternal thyroid dysfunction on the fetal cardiovascular system development.

We also found that offspring born from the pregnant women with isolated hypothyroxinemia had a 6.82-fold risk (95% CI 1.34–34.84) of musculoskeletal malformations. This may be explained by thyroid hormone, which plays a vital role in the normal development of bones and muscles (30). But Männistö *et al.* (17) and Casey *et al.* (2, 12) reported that maternal thyroid dysfunction was not significantly associated with a higher frequency of birth defects. A possible reason for this discrepancy is that the malformations of other studies were only from live birth infants. Another reason could be that other studies did not classify the malformations, whereas in the present study, malformations were divided into several system birth defects by the Classification and Encoding and Data Collection for Chinese Birth-defect Genetic Resources. In the present study, the incidence of total malformations for different types of maternal thyroid function was not significantly higher than the reference group. This demonstrates that different types of maternal thyroid dysfunction may affect the development of each system differently.

Different types of maternal thyroid dysfunction may also affect different developmental outcomes of offspring. For example, there was a significant effect of maternal subclinical hypothyroidism on the risk of poor visual development and neurodevelopmental delay in infants. Premature delivery and smaller head circumference were significantly associated with maternal subclinical hypothyroidism; thus, the investigation of the possible relationship between maternal subclinical hypothyroidism and impaired neurodevelopment and poor visual development is warranted. In addition, maternal subclinical hypothyroidism increased the risk of fetal distress, which is in agreement with the study of Goel *et al.* (31), who reported a higher incidence of fetal distress in pregnancies complicated by maternal hypothyroidism (subclinical hypothyroidism, euthyroid on replacement therapy, and overt hypothyroidism), and it has been suggested that hypothyroidism may exert irreversible effects on the fetus and placenta in early pregnancy that impair

their subsequent ability to tolerate stress, thereby increasing the incidence of fetal distress in labor. Fetal distress may impair infant developmental disorder of the nervous system. We also found that infants of clinical hypothyroidism were at a higher risk of low birth weight, whereas infants of isolated hypothyroxinemia were at a greater risk of SGA and fetal distress. Those adverse development outcomes demonstrate that the maternal fT4 level is important to fetal and infant physical and neuropsychological development. To our knowledge, the relationship between maternal hyperthyroidism and infant hearing development has not been reported. It has been noted that there is a high incidence of hearing dysplasia in pregnancies complicated by clinical hyperthyroidism (adjusted odds ratio 12.14; 95% CI 1.22–120.70). However, further research is needed to test this newly discovered association.

This study has two major limitations. First, although all the pregnant women in the first 20 wk of pregnancy were included, the number of patients with maternal thyroid dysfunction was small. Because many adverse pregnancy outcomes are uncommon, differences between groups may not be detected with this small sample size. Second, thyroid antibodies were not measured in this study. A recent study by Negro *et al.* (6) demonstrated that maternal thyroid antibodies are associated with negative pregnancy outcomes, so we will obtain the biochemical data in further studies.

The finding that different types of maternal thyroid dysfunctions in the first 20 wk of pregnancy were associated with different fetal and infant dysplasia adds support to the argument that routine maternal thyroid function screening should be conducted as a way to potentially improve the pregnancy outcomes and infant development, even in iodine-sufficient areas of China.

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