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Epidemiology

Associations of maternal iodine status and thyroid function with adverse pregnancy outcomes in Henan Province of China

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ABSTRACT

Objective: The study aimed to explore the effects of maternal iodine status and thyroid diseases on adverse pregnancy outcomes.

Methods: A prospective study was conducted on 2347 pregnant women, who provided 2347 urinary samples tested for iodine, 1082 serum samples tested for thyroid function, and 2347 questionnaires about demographic information. Their pregnancy outcomes were recorded and compared between different urinary iodine concentration (UIC) and thyroid function groups.

Results: Pregnant women with UIC between 150 and 249 μg/L had lower incidences of preeclampsia (adjusted odds ratio (OR) 0.12, 95% CI: 0.01-0.87), placenta previa (adjusted OR 0.06, 95% CI: 0.01-0.69) and fetal distress (adjusted OR 0.10, 95% CI: 0.02-0.64) than the reference group (UIC < 50 μg/L). Women with UIC between 100 and 149 μg/L had lower risks of abnormal amniotic fluid (adjusted OR 0.32, 95% CI: 0.12-0.87) and fetal distress (adjusted OR 0.08, 95% CI: 0.01-0.82). Women with UIC above 249 μg/L had a significant higher rate of abnormal amniotic fluid (adjusted OR 0.38, 95% CI: 0.16-0.89). Clinical and subclinical hypothyroidism during pregnancy increased the risk of preterm delivery by 4.4 times (P = 0.009) and 3.0 times (P = 0.014), respectively. Isolated hypothyroxinemia had increased odds of having macrosomia (adjusted OR 2.22, 95% CI: 1.13-4.85). Clinical hyperthyroidism was significantly associated with miscarriage (adjusted OR 2.12, 95% CI: 1.92-96.67) and fetal distress (adjusted OR 9.53, 95% CI: 1.05–81.81). Subclinical hyperthyroidism had a significant association with umbilical cord entanglement (adjusted OR 3.82, 95% CI: 1.38-10.58). Isolated hyperthyroxinemia was associated with preterm delivery (adjusted OR 4.73, 95% CI: 1.49-15.05).

Conclusions: Maternal iodine status and thyroid diseases during pregnancy were associated with adverse pregnancy outcomes.

1. Introduction

Iodine is an essential ingredient of thyroid hormones (TH) [1,2]. Fetus obtains a fraction of maternal iodine and TH by placenta and amniotic fluid. Iodine requirement during pregnancy is sharply increased by about 50% [3], including increased production of thyroid hormone, increased iodine excretion, and fetus needs [4].

Chronic iodine deficiency can result in hypothyroidism, and then cause multiple adverse pregnant outcomes [5].Severe iodine deficiency in pregnant women is associated with endemic cretinism, spontaneous abortion, preterm delivery, and stillbirth, low birth weight (LBW), fetal growth restriction (FGR) and neurological damage [6,7]. However, the detrimental impact of mild-to-moderate maternal iodine deficiency on pregnancy outcomes remains controversial [8–10]. Charoenratana C et al. [8] and Brucker-Davis [11] suggested that the impact of mild iodine deficiency was unstable and mediated.

Subclinical hypothyroidism (SCH) is the most common thyroid disease of pregnant women. SCH has been reported to be associated with spontaneous abruption, preterm delivery, placenta abruption and impaired neural development [12–14]. The main complications of clinical hypothyroidism include fetal loss, low birth weight and congenital deficits [15]. Maternal hyperthyroidism is a rare disease, which can increase the risk of gestational hypertension, stillbirth, preterm delivery and intrauterine growth restriction [16,17].

Previous studies have assessed the association of maternal thyroid dysfunction on poor pregnancy outcomes. However, few studies evaluate the effects of maternal iodine status and all types of thyroid diseases on pregnancy outcomes. Therefore, we conducted a prospective

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cohort study to investigate the associations of maternal iodine status and thyroid function on pregnancy outcomes in China.

2. Matertial and methods

2.1. Study population

A prospective cohort study was conducted in Henan Province of China. Between July and September 2015, pregnant women were recruited from 28 maternity hospitals. In each hospital, 100 pregnant women were sequentially enrolled and followed up after delivery. Inclusion criteria were: i) singleton birth; ii) no chronic diseases; iii) no thyroid disease or usage of thyroid drugs; iv) residents in Henan Province; v) being easy to follow up. All the pregnant women were asked to complete a questionnaire and donate a urine sample for testing iodine in the first visit. Half of the pregnant women were selected to draw blood and tested for thyroid function at the same time. Questionnaire information included gestational age at sampling, maternal age, education, socioeconomic status, health and obstetric history, height and pre-gestation weight, working time during pregnancy. In our study population, those who had no maternal urinary sample (n = 109), who had uncompleted questionnaire (n = 89), who had plural gestation (n = 5), and who were lost to follow up (n = 142) were excluded. Finally, a total of 2347 pregnant mothers were included (Fig. 1). Among them, they provided 2347 urinary samples and questionnaires, and 1082 serum samples.

The survey was approved by the medical ethics committee from Henan Provinical Center for Disease Control and Prevention in China. Written informed consent was obtained from all individual participants included in the study.

2.2. Thyroid function test

Blood samples were collected from 1082 pregnant mothers and stored in glass tubes. The samples were centrifugated and frozen at −20 °C until determination. Maternal serum samples were analyzed for TSH and free FT4 using chemiluminescence immunoassay on an automated analytic instrument. The reference range for TSH was 0.3–5.0 μIU/ml and the measured range was 0.006–100 μIU/ml. The reference range for FT4 was 8.5–22.5 pmol/L and the measured range was 2.5–100.0 pmol/L. The intra-assay coefficient of variation for TSH and FT4 was 3.6% and 4.8%.

The normal values of our pregnant women for TSH and FT4 were determined by using 5th and 95th percentiles for gestational age of our laboratory. According to the gestational age-specific reference values, 1082 pregnant women were classified into seven groups to examine the relationship between thyroid function group and pregnancy outcomes, as follows:

Group A (euthyroid group, as reference group) was defined as TSH and FT4 between the 5th and 95th percentile;

Group B (clinical hypothyroidism) was defined as TSH over the 95th percentile and FT4 below the 5th percentile;

Group C (SCH) was defined as TSH over the 95th percentile and FT4 between the 5th and 95th percentiles;

Group D (isolated hypothyroxinemia) was defined as TSH between the 5th and 95th percentiles and FT4 below the 5th percentile;

Group E (clinical hyperthyroidism) was defined as TSH below the 5th percentile and FT4 over the 95th percentile

Group F (subclinical hyperthyroidism) was defined as TSH below the 5th percentile and FT4 between the 5th and 95th percentiles;

Group G (isolated hyperthyroxinemia) was defined as TSH between the 5th and 95th percentiles and FT4 over the 95th percentile.

2.3. Urinary iodine concentration test

Urine samples were collected from 2347 pregnant mothers. The samples were sealed in plastic bottles and refrigerated at 4 °C until analysis. UIC was measured to determine iodine in urine by the acid digestion method (As3+-Ce4+ catalytic spectrophotometry) [18]. All urine samples were tested by the municipal CDC laboratories. External quality control was provided by China National Iodine Deficiency Disorders Reference Laboratory. Based on the results, the coefficients of variation for UIC in our laboratory were 2.0% at 68.2 ± 1.3 μg/L and 0.9% at 193.0 ± 10.0 μg/L. 2347 pregnant mothers who provided urinary samples were classified into five groups: < 50 μg/L, 50–100 μg/L, 100–150 μg/L, 150–249 μg/L, ≥250 μg/L to examine the relationship between UIC groups and pregnancy outcomes. UIC below 50 μg/L was defined as the reference group.

2.4. Pregnancy outcomes

Pregnancy outcomes of the study, including maternal complications, obstetric complications and neonatal outcomes, were obtained from the hospital records. Maternal complication included gestational diabetes, gestational proteinuria, gestational hypertension and preeclampsia. Obstetric complication included preterm delivery (gestational age at delivery < 37 weeks), cesarean delivery, miscarriage (a fetal loss of gestational age < 28 weeks), stillbirth (a fetal loss of gestational age ≥28 weeks), placenta previa, placenta abruption, abnormal amniotic fluid (< 300 ml or > 2000 ml), fetal distress and umbilical cord entanglement. Neonatal outcomes included gestational age at delivery, low apgar score (apgar score < 7), birth weight and length, head circumstance, low birth weight (LBW, birth weight < 2500 g), macrosomia (birth weight > 4000 g), small for gestational age (SGA, birth weight < 10th percentile).

2.5. Statistical analysis

Data were recorded with Epi-data 3.1 and analyzed with SPSS 17.0. Normally distributed data were expressed as mean and standard deviation (SD), if non-normally, expressed as median and percentiles. Group differences of normally distributed data were compared by *t*-test and ANOVA. Non-normally distributed data were compared with Mann-Whiteny *U* test or Kruskal-Wallis H-test. Categorical variables were expressed as absolute numbers and percentages. The chi-square test was used to compare the difference of categorical variables. Logistic regression models were used to calculate odds ratio (OR) and 95% confidence interval (CI) for pregnancy outcomes by UIC groups and thyroid function groups. All the odds ratios were adjusted for maternal age, education, income, and working hours. As thyroid disease can cause weight loss or gain, maternal weight was an intermediate in the relationship between thyroid disease and pregnancy outcomes. So, maternal weight was not included the logistic regression model. In UIC groups, maternal UIC below 50 was the reference group. In thyroid function groups, euthyroid group was the reference group. The significant level were set at $p < .05$.

3. Results

3.1. Maternal characteristics

Among 2347 pregnant women, the mean age, height, pre-pregnancy weight and BMI were 26.5 ± 4.3 yr, 161.3 ± 4.2 cm, 57.1 ± 7.1 kg and 22.0 ± 2.8 kg/m^2, respectively. And their mean gestational age at sampling was 27.1 ± 9.1 weeks.

The median UIC of 2347 pregnant mothers was 203.8 μg/L, which met the adequate level for pregnant women (150–249 μg/L). Maternal education and gestational age showed significant differences between different UIC groups ($P < .001$ and $P < .001$).

In the enrolled women, only 1082 pregnant mothers provided blood samples for thyroid function test. The prevalence of thyroid diseases was 1.2% clinical hypothyroidism, 3.5% subclinical hypothyroidism,