CEOG Clinical and Experimental Obstetrics & Gynecology

Original Research

Relationship between subclinical hypothyroidism during pregnancy and hypertensive disorder complicating pregnancy and its poor prognosis

W.X. Chen, L.Y. Tang

Department of obstetrics, Shanghai Changning Maternal & Infant Health Hospital, Shanghai (China)

Summary

Objectives: Pregnancy-induced hypertension syndrome (PIH) is a common disease of pregnant women. This study explored the correlation between subclinical hypothyroidism (SCH) and PIH and the prognosis of patients with PIH. *Materials and Methods:* The study included 180 pregnant women were divided into three groups, including PIH+SCH group, PIH+non-SCH group, and normal group. Immunofluorescence method was used to detect thyroid stimulating hormone (TSH). Student's *t*-test and chi-square test were used to analyze the difference between two groups. Pearson correlation analysis was used to assess the correlation between two variables. *Results:* Systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) were all significantly upregulated in PIH+SCH group compared with those in normal group and PIH+ non-SCH groups (all $p < 0.05$) and SCH had a close relationship with SBP ($r^2 = 0.2163$, $p = 0.0002$). The incidences of postpartum hemorrhage, premature delivery, abortion, FGR, and pregnancy anemia were all cleary increased in PIH+non-SCH, and PIH+SCH groups, compared with those in normal group, respectively (8.3, 10, 13.3,1 8.3, 23.3; 13.3, 23.3, 26.7, 35, and 36.7 *vs*.1.7, 5, 3.3, 1.7, and 5.1 (all $p < 0.05$). The incidences of premature delivery, abortion, FGR, and pregnancy anemia were significantly higher in PIH+SCH group than PIH+non-SCH group (23.3, 26.7, 35, and 36.7 *vs*. 10, 13.3, 18.3, 23.3 (all $p < 0.05$). Moreover, serum TSH level was significantly increased in high gestational week group compared with low gestational week group (6.86 ± 0.78 *vs*. 5.79 ± 0.45, $p < 0.05$) and SBP, DBP, and MAP were all remarkably elevated in high gestational week group compared with low gestational week group (167.6 ± 12.4 *vs*. 150.9 ± 10.8; 108.5 ± 11.4 *vs*. 95.2 ± 11.2; 121.8 ± 13.6 *vs*. 110.0 ± 12.3 (all $p < 0.05$). In addition, compared with those in low TSH group, the incidences of postpartum hemorrhage, premature delivery, abortion, FGR, and pregnancy anemia were all obviously increased in high TSH group (all $p < 0.05$). *Conclusion:* SCH had a close association with PIH and poor prognosis during pregnancy.

Key words: Subclinical hypothyroidism; Pregnancy-induced hypertension syndrome; Thyroid stimulating hormone; Systolic blood pressure.

Introduction

Pregnancy-induced hypertension syndrome (PIH) is a unique and common disease in pregnant women [1]. Due to the severity of PIH, the impact on mother and child are also quietly different. Over the past years, in spite of the achievement of prevention and treatment of this disease at home and abroad, the maternal mortality is still at a relative high level. The occurrence of PIH is associated with vascular endothelial cell injury and disorders of synthesis of vascular cytokines [2, 3]. In order to protect the health of the mother and child, reducing perinatal mortality and achieving the purpose of eugenics, it is extremely important to conduct relative investigations of the incidence of PIH and its independent risk factors.

Hypothalamus - pituitary - thyroid axis is involved in the process of regulation of human blood pressure and thyroid hormone on cardiovascular function [4, 5]. Some studies have shown that there is a close association between thyroid function and blood pressure, and increased systemic vascular resistance is the main mechanism for elevated blood pressure caused by hypothyroidism or hyperglycemia [6, 7]. Triiodothyronine (T3) directly plays a role in the aortic endothelial cells and vascular smooth muscle cells, which leads to vasodilatation; lack of T3 may cause increased vascular resistance in hypothyroidism or hyperthyroidism [8, 9]. Hypothyroidism can also cause sodium homeostasis abnormalities, sympathetic nervous system activation, decreased glomerular filtration rate and other changes, which may be involved in the diastolic blood pressure-based hypertension [10, 11].

Several studies have indicated that thyroid dysfunction can increase the risk of hypertension. The changes of thyroid stimulating hormone (TSH) in serum are most rapid and most obvious in thyroid function abnormalities, and TSH level is the most accurate and sensitive indicators of reflection of thyroid function [12]. With the rise of TSH levels, systolic and diastolic blood pressure is linearly increased, and the higher the level of TSH, the higher the incidence of hypertension [13]. During pregnancy, the

Published: 15 February 2020

Clin. Exp. Obstet. Gynecol. - ISSN: 0390-6663
XLVII, n. 1, 2020
doi: 10.31083/j.ceog.2020.01.4975

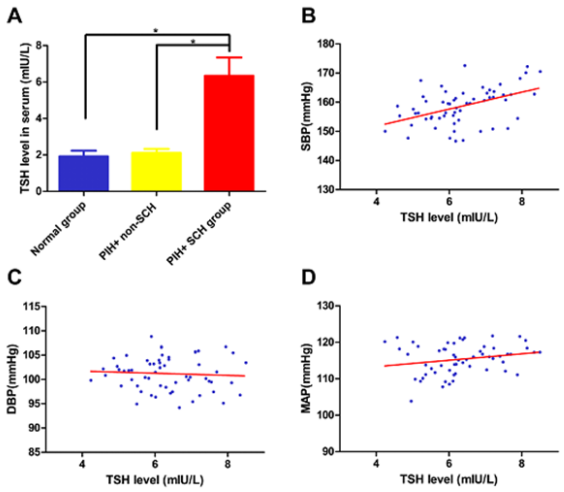

Figure 1. — Relationship between SCH during pregnancy and PIH. (A) the serum level of TSH in three groups. (B) Relationship between SCH andSBP. (C) Relationship between SCH and DBP. (D) Relationship between SCH and MAP.

thyrotropin effect of human chorionic gonadotropin (hCG) leads to a decrease in TSH, which is most pronounced at 8-12 weeks of gestation, and causes a lower TSH level than the lower level of the general population (0.4 mIU/L) [14]. Over the past decades, emerging evidence showed that subclinical hypothyroidism (SCH) is associated with PIH [15]. Yet, the relationship between subclinical hypothyroidism during pregnancy and hypertensive disorder, complicating pregnancy, and its prognosis remain to be clarified. In this study, the authors aimed to analyze the relationship between subclinical hypothyroidism during pregnancy and hypertensive disorder complicating pregnancy, and its prognosis, which could provide more comprehensive data for the future investigation of PIH and SCH.

Materials and Methods

The study included 180 pregnant women recruited from Shanghai Changning Maternal &Infant Health Hospital during January 2012 to January 2015, which divided into three groups, including PIH+SCH group, PIH+non-SCH group, and normal group. The baseline information of three groups is presented in Table 1.

The study was approved by the local Research Ethics Committee of Shanghai Changning Maternal &Infant Health Hospital, and all participants gave written informed consent. Written informed consent was also obtained from the patients/participants (delete as appropriate) for publication of their individual details and accompanying images in this manuscript.

Gestational hypertension was defined as blood pressure more than 140/90 mm Hg without proteinuria after 20 weeks gestation. Exclusion criteria were combined cardiopulmonary, liver, kidney, and other important organs diseases.

According to the guidelines for the diagnosis and treatment of pregnancy and postpartum thyroid diseases of American thyroid association at 2011 and Chinese guidelines for the diagnosis and treatment of thyroid diseases, SCH was defined as TSH between 2.5~10 mIU/L^{-1} and FT4 at normal reference range. Exclusion criteria were: 1) combined cardiopulmonary, liver, kidney, and other important organs diseases, 2) hypothyroidism patients: TSH more than 2.5~10 mIU/L^{-1}, and FT4 < 12 pmol/L.

Fasting venous blood of the three groups of pregnant women was collected, obtaining the serum after centrifuging and stored in refrigerator. Radioimmunoassay was used to detect the triiodothyronine (FT3) and free thyroxine (FT4) and immunofluorescence method was used to detect TSH.

SPSS 19.0 statistical software package was used for statistical processing, of which, measurement data was repressed by mean ± standard deviation (x ± s) using *t*-test and count data expressed as a percentage using chi-square test. Pearson correlation analysis was used to assess the correlation between two variables. $P < 0.05$ was considered statistically significant.

Table 1. — *The baseline information of the three groups.*

Characteristics	PIH+SCH (n = 60)	PIH+non-SCH (n = 60)	Normal group	*p* value
Age (years)	27.9 ± 5.9	27.5 ± 6.2	28.2 ± 6.7	> 0.05
Nation				
Han	58	55	57	> 0.05
Minority	2	5	3	
Registered residence				
Urban	30	32	27	> 0.05
Rural	30	28	33	
Gestational week	28.5 ± 6.9	28.9 ± 7.1	26.3 ± 6.4	> 0.05
BMI (kg/m^2)	27.2 ± 5.4	28.2 ± 4.3	28.4 ± 6.4	> 0.05

Table 2. — *Arterial blood pressure in three groups.*

	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)
Normal group	113.3 + 10.4	86.4 + 7.9	90.4 + 8.2
PIH+non-SCH	147.2 + 5.6[a]	95 + 3.7[a]	105.7 + 4.1[a]
PIH+SCH group	158.4 + 6.5[ab]	101.2 + 3.4[ab]	115.3 + 3.9[ab]

[a]p < 0.05 (compared with normal group). [b]p < 0.05 (compared with PIH+non-SCH).

Results

The 180 pregnant women were divided into three groups, including PIH+SCH group, PIH+non-SCH group, and normal group. The arterial blood pressure of three groups, including systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), was analyzed to assess the changes of arterial blood pressure in PIH with/without SCH. As shown in Table 2, compared with those in normal group, SBP, DBP, and MAP were all significantly upregulated in PIH+SCH group and PIH+non-SCH group, respectively (Table 2). In addition, SBP, DBP, and MAP were all higher in PIH+SCH group than those in PIH+non-SCH group. Therefore, SCH were associated with high blood pressure during pregnancy.

To further validate the association between SCH during

Table 3. — *Comparison of pregnancy outcome between three groups.*

	Normal group (n=60)	PIH+non-SCH (n=60)	PIH+SCH group (n=60)
Postpartum hemorrhage	1 (1.7)	5 (8.3)[a]	8 (13.3)[a]
Premature delivery	3 (5)	6 (10)[a]	14 (23.3)[ab]
Abortion	2 (3.3)	8 (13.3)[a]	16 (26.7)[ab]
FGR	1 (1.7)	11 (18.3)[a]	21 (35)[ab]
Placental abruption	1 (1.7)	3 (5.1)	4 (6.8)
Pregnancy anemia	3 (5.1)	14 (23.3)[a]	22 (36.7)[ab]

FGR: fetal growth restriction. [a]$p < 0.05$ (compare with normal group). [b]$p < 0.05$ (compared with PIH+non-SCH).

Table 4. — *Comparison of pregnancy outcome in different TSH level.*

	Low TSH group (n=32)	High TSH group (n=28)
Postpartum hemorrhage	2 (6.3)	6 (21.4)[a]
Premature delivery	3 (9.4)	11 (39.3)[a]
Abortion	4 (12.5)	12 (42.9)[a]
FGR	5 (15.6)	16 (57.1)[a]
Placental abruption	2 (6.3)	2 (7.1)
Pregnancy anemia	6 (18.8)	16 (57.1)[a]

FGR: fetal growth restriction. [a]$p < 0.05$ (compared with normal group).

pregnancy and PIH, the authors conducted Pearson correlation analysis to evaluate the correlation between SCH and PIH. As shown in Figure 1A, the serum level of TSH was significantly higher in PIH+SCH group than that in PIH+non-SCH and normal group (6.34 + 1.01 *vs.* 2.11+ 0.22, 1.92+0.31, $p < 0.01$). Yet, there is no obvious difference of TSH level between PIH+non-SCH and normal group ($p > 0.05$). Moreover, as shown in Figure 1B, SCH had a positive correlation with SBP (r^2=0.2163, p = 0.0002). However, SCH had no significant correlation with DBP and MAP (r^2= 0.004, p = 0.624, r^2 = 0.048, and p = 0.094) (Figures 1C, 1D). These results indicated that SCH had a relationship with PIH,especially SBP.

Sequentially, to assess the correlation between pregnancy outcome and SCH, the authors analyzed the pregnancy outcome data from three groups. As shown in Table 3, compared with those in normal group, the incidences of postpartum hemorrhage, premature delivery, abortion, FGR, and pregnancy anemia were all obviously increased in PIH+ non-SCH and PIH+SCH group, respectively ($p < 0.05$). These results demonstrate that PIH is significantly associated with a poor prognosis during pregnancy. Moreover, in order to make a comparison between PIH+non-SCH and PIH+SCH group, the authors found that the incidences of premature delivery, abortion, FGR, and pregnancy anemia were significantly higher in PIH+SCH group than in the PIH+non-SCH group (all $p < 0.05$). These conclusions indicated that SCH was also correlated with a poor prognosis during pregnancy. Next, to make a deeper exploration for TSH level and arterial blood pressure in different gestational week during pregnancy, the authors divided PIH+SCH group into two subgroups, including low gestational week group (n=27) and high gestational week group

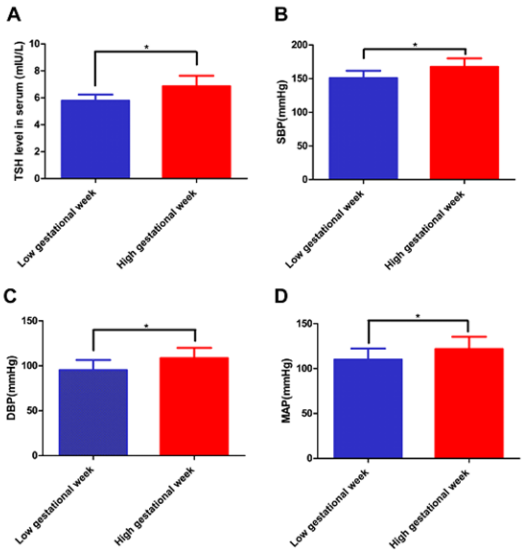

Figure 2. — TSH level and arterial blood pressure in different gestational weeks. (A) the serum level of TSH in two groups. (B) SBP in two groups. (C) DBP in two groups. (D) MAP in two groups.

(n=33). As shown in Figure 2A, serum TSH level was significantly increased in high gestational week group compared with low gestational week group (6.86 ± 0.78 *vs.* 5.79 ± 0.45, $p < 0.05$). Moreover, the arterial blood pressures, including SBP, DBP, and MAP, were all remarkably elevated in high gestational week group compared with low gestational week group (167.6 ± 12.4 *vs.* 150.9 ± 10.8; 108.5 ± 11.4 *vs.* 95.2 ± 11.2; 121.8 ± 13.6 *vs.* 110.0 ± 12.3; all $p <$

0.05). The present results indicate that gestational week was positively correlated with TSH level and arterial blood pressure. Then, the authors further explored the effect of different TSH levels on pregnancy outcome in the patients with PIH+SCH. In this study, the PIH+SCH group was divided into two subgroups, including low TSH group (n=32) and high TSH group (n=28). As showed in Table 4, compared with those in low TSH group, the incidences of postpartum hemorrhage, premature delivery, abortion, FGR, and pregnancy anemia were all obviously increased in high TSH group (all $p < 0.05$). These results showed that poor pregnancy outcome was closely associated with TSH in patients with PIH+SCH.

Discussion

Due to occult onset and lack of specificity in clinical manifestations, hypothyroidism and SCH are easily overlooked. In particular, the diagnosis of SCH mainly relies on the results of the laboratory, which could easily lead to missed diagnosis [16]. The thyroid of the fetus begins to secrete thyroid hormone from the 12th week of pregnancy, and thyroid function is established completely after 20 weeks. Within 20 weeks, the thyroid hormone of fetal development needs is mainly from the mother, in which period, if the thyroid function of the mother is normal, it could provide adequate amounts of thyroid hormone into the fetus through the placenta [17, 18].

Thyroid dysfunction could lead to mother and child hazards [19]. In this study, the results showed that compared with those in normal group and PIH+non-SCH group, SBP, DBP, and MAP were all significantly upregulated in PIH+SCH group. SCH was in relation to SBP and a poor prognosis during pregnancy.

As known, PIH is characterized by high blood pressure (HBP) [20]. Over the past decades, several studies have shown that HBP, including SBP, DBP, and MAP, were significantly elevated with PIH [21-23]. In this study, a similar conclusion indicated that compared with those in normal group, SBP, DBP, and MAP were all significantly upregulated in PIH+SCH group and PIH+non-SCH group, respectively. Moreover, several studies have shown that thyroid dysfunction can increase the risk of hypertension [24, 25]. TSH level is the most accurate and sensitive indicator, which could reflect the thyroid function [26]. With rising of TSH levels, systolic and diastolic blood pressure was linearly increased: the higher the level of TSH, the higher the incidence of hypertension [27].

TT4 levels are gradually increased during pregnancy due to the increased concentration of thyroxine-binding globulin (TBG), which begins at 6-8 weeks of gestation and reaches its peak at 20 weeks of gestation and continues until childbirth [28]. Due to the effect of hCG, TSH decreases during pregnancy, which is most pronounced at 8-12 weeks of gestation and caused the TSH level to decrease than the lower limit of the general population (0.4 mIU/L) [14].

Wang *et al.* [29] found that TSH levels in serum was correlated positively with SBP and DBP. Consistently, in the present study, SBP, DBP, and MAP were all higher in PIH+SCH group than those in PIH+non-SCH group. Moreover, the serum level of TSH was significantly higher in PIH+SCH group than that in PIH+non-SCH and normal group. In addition, SCH had a closely positive correlation with SBP. However, SCH had no significant correlation with DBP and MAP. Over the past decades, emerging evidence showed that PIH was associated with poor prognosis of pregnant women [30, 31]. In this study, the present results indicated the incidences of postpartum hemorrhage, premature delivery, abortion, FGR, and pregnancy anemia which all obviously increased in PIH+non-SCH and PIH+SCH groups, compared to those in normal group, respectively. More and more studies demonstrated that SCH was associated with poor prognosis of pregnant women [32]. Gur *et al.* [33] showed that hemoglobin (Hb) of pregnant women was obviously lower in the SCH group than control group, indicating a high rate of postpartum hemorrhage. Liu *et al.* [34] found that pregnancy women with SCH are at an increased risk of miscarriage between four and eight gestational weeks.

A consistent conclusion showed that the incidences of premature delivery, abortion, FGR, and pregnancy anemia were significantly higher in PIH+SCH group than in PIH+non-SCH group, which indicated that SCH was correlated with a poor prognosis during pregnancy. In addition, the present authors sequentially analyzed the difference between low TSH group and high TSH group in PIH+SCH group, which demonstrated that the incidences of postpartum hemorrhage, premature delivery, abortion, FGR, and pregnancy anemia were all obviously increased in high TSH group compared to those in low TSH group, and the difference was statistically significant. These results indicate that SCH is positively correlated with a poor prognosis during pregnancy. Of note, TSH level is dramatically altered during pregnancy [35]. De Zoysa *et al.* [36] indicated that TSH level in the first trimester was 1.30 μIU/mL and significantly increased to 1.60 μIU/mL at the third trimester, which indicated that TSH level was gradually increased during pregnancy. In the present study, the authors first explored the relationship between TSH level and different gestational weeks during pregnancy, in which, serum TSH level was significantly increased in high gestational week group compared with to low gestational week group. Sequentially, they also found that the arterial blood pressures, including SBP, DBP, and MAP, were all remarkably elevated in high gestational week group compared with low gestational week group. These findings were further corroborated with SCH which has a close relation with PIH and poor prognosis during pregnancy.

In conclusion, the present authors found that SCH had a close relation with PIH and could lead to a poor prognosis

during pregnancy. The present data could provide a novel perspective to explore the association between PIH and SCH and assess its effect on the prognosis during pregnancy.

Acknowledgements

This study was supported by the "study of subclinical hypothyroidism in pregnancy and hypertensive disorder complicating pregnancy and its correlation of severe outcomes" (201440431).

References

[1] Moodley J.: "Potentially increasing rates of hypertension in women of childbearing age and during pregnancy—be prepared!" *Cardiovasc. J. Afr.*, 2011, *22*, 330.

[2] Conti E., Zezza L., Ralli E., Caserta D., Musumeci M.B., Moscarini M., Autore C., Volpe M.: "Growth factors in preeclampsia: a vascular disease model. A failed vasodilation and angiogenic challenge from pregnancy onwards?" *Cytokine Growth Factor Rev.*, 2013, *24*, 411.

[3] Heimrath J., Czekanski A., Krawczenko A., Dus D.: "The role of endothelium in the pathogenesis of pregnancy-induced hypertension". *Postepy Hig. Med. Dosw. (Online)*, 2007, *61*, 48.

[4] Medici M., Visser W.E., Visser T.J., Peeters R.P.: "Genetic determination of the hypothalamic-pituitary-thyroid axis: where do we stand?" *Endocr. Rev.*, 2015, *36*, 214.

[5] Leow M.K.: "A Review of the Phenomenon of Hysteresis in the Hypothalamus-Pituitary-Thyroid Axis". *Front. Endocrinol. (Lausanne)*, 2016, *7*, 64.

[6] Jabbar A., Pingitore A., Pearce S.H., Zaman A., Iervasi G., Razvi S.: "Thyroid hormones and cardiovascular disease". *Nat. Rev. Cardiol.*, 2017, *14*, 39-55.

[7] Sun X., Sun Y., Li W.C., Chen C.Y., Chiu Y.H., Chien H.Y., Wang Y.: "Association of thyroid-stimulating hormone and cardiovascular risk factors". *Intern. Med.*, 2015, *54*, 2537.

[8] Ojamaa K., Balkman C., Klein I.L.: "Acute effects of triiodothyronine on arterial smooth muscle cells". *Ann. Thorac. Surg.*, 1993, *56*, S61.

[9] Broderick T.J., Wechsler A.S.: "Triiodothyronine in cardiac surgery". *Thyroid*, 1997, *7*, 133.

[10] Gonzalez Gil L., de la Sierra A.: "Prevalence of hypertension and other cardiovascular risk factors in subjects with subclinical hypothyroidism". *Med. Clin. (Barc.)*, 2017, *148*, 35.

[11] Arshad A.R., Tipu H.N., Paracha A.I.: "The impact of hypertension on lipid parameters in type 2 diabetes". *J. Pak. Med. Assoc.*, 2016, *66*, 1262.

[12] Feng X., Cao X., Zhao S., Wang X., Hua X., Chen L.: "Exposure of Pregnant Mice to Perfluorobutanesulfonate Causes Hypothyroxinemia and Developmental Abnormalities in Female Offspring". *Toxicol. Sci.*, 2017, *155*, 409.

[13] Gomez-Zamudio J.H., Mendoza-Zubieta V., Ferreira-Hermosillo A., Molina-Ayala M.A., Valladares-Salgado A., Suarez-Sanchez F., *et al.*: "High Thyroid-stimulating Hormone Levels Increase Proinflammatory and Cardiovascular Markers in Patients with Extreme Obesity". *Arch. Med. Res.*, 2016, *47*, 476.

[14] Moleti M., Trimarchi F., Vermiglio F.: "Thyroid physiology in pregnancy". *Endocr. Pract.*, 2014, *20*, 589.

[15] Nazarpour S., Ramezani Tehrani F., Simbar M., Azizi F.: "Thyroid dysfunction and pregnancy outcomes". *Iran J. Reprod. Med.*, 2015, *13*, 387.

[16] Voigtlander R., Fuhrer D.: "Subclinical hypothyroidism - laboratory finding or disease?" *Dtsch. Med. Wochenschr.*, 2016, *141*, 1134.

[17] Wadzinski T.L., Geromini K., McKinley Brewer J., Bansal R., Abdelouahab N., Langlois M.F., *et al.*: "Endocrine disruption in human placenta: expression of the dioxin-inducible enzyme, CYP1A1, is correlated with that of thyroid hormone-regulated genes". *J. Clin. Endocrinol. Metab.*, 2014, *99*, E2735.

[18] Nishioka E., Hirayama S., Ueno T., Matsukawa T., Vigeh M., Yokoyama K., *et al.*: "Relationship between maternal thyroid-stimulating hormone (TSH) elevation during pregnancy and low birth weight: a longitudinal study of apparently healthy urban Japanese women at very low risk". *Early Hum. Dev.*, 2015, *91*, 181.

[19] Andersen S.L., Laurberg P., Wu C.S., Olsen J.: "Attention deficit hyperactivity disorder and autism spectrum disorder in children born to mothers with thyroid dysfunction: a Danish nationwide cohort study". *BJOG*, 2014, *121*, 1365.

[20] Anthony J., Damasceno A., Ojjii D.: "Hypertensive disorders of pregnancy: what the physician needs to know". *Cardiovasc. J. Afr.*, 2016, *27*, 104.

[21] Chulkov V.S., Sinitsin S.P., Vereina N.K.: "Prognostic Value of Central Aortic Pressure in Pregnant Women With Hypertension". *Kardiologiia*, 2015, *55*, 29.

[22] Yuan T., Zhang T., Han Z.: "Placental vascularization alterations in hypertensive disorders complicating pregnancy (HDCP) and small for gestational age with HDCP using three-dimensional power doppler in a prospective case control study". *BMC Pregnancy Childbirth*, 2015, *15*, 240.

[23] Visentin S., Londero A.P., Bellamio B., Giunta G., Cosma C., Faggian D., *et al.*: "Fetal Endothelial Remodeling in Late-Onset Gestational Hypertension". *Am. J. Hypertens.*, 2016, *29*, 273.

[24] Marvisi M., Balzarini L., Mancini C., Mouzakiti P.: "Thyroid gland and pulmonary hypertension. What's the link?" *Panminerva Med.*, 2013, *55*, 93.

[25] Siviero-Miachon A.A., Spinola-Castro A.M., Guerra-Junior G.: "Detection of metabolic syndrome features among childhood cancer survivors: a target to prevent disease". *Vasc. Health Risk Manag.*, 2008, *4*, 825.

[26] Sinha R., Yen P.M.: "Cellular Action of Thyroid Hormone". *In:* De Groot L.J., Chrousos G., Dungan K., Feingold K.R., Grossman A., Hershman J.M., *et al.* (eds). South Dartmouth (MA): Endotext, 2000**.**

[27] Castillo Palma M.J., Garcia Hernandez F.J., Montero Benavides P., Gonzalez Leon R., Ocana Medina C., Sanchez Roman J.: "Thyroid dysfunction in patients with pulmonary arterial hypertension. A cohort study of 58 patients". *Med. Clin. (Barc.)*, 2009, *132*, 695.

[28] Midgley J.E., Hoermann R.: "Measurement of total rather than free thyroxine in pregnancy: the diagnostic implications". *Thyroid*, 2013, *23*, 259.

[29] Wang C.Y., Chang T.C., Chen M.F.: "Associations between subclinical thyroid disease and metabolic syndrome". *Endocr. J.*, 2012, *59*, 911.

[30] Sieroszewski P., Guzowski G.: "Prognostic value of the uterine doppler velocimetry at 20-24 gestation weeks for PIH and IUGR development in pregnancy". *Ginekol. Pol.*, 2005, *76*, 348.

[31] Matsuda R., Fujimoto T., Tamura K., Motoyama Y., Park Y.S., Nakase H.: "Case of postpartum intracerebral hemorrhage due to pregnancy induced hypertension". *No. Shinkei Geka*, 2011, *39*, 1159.

[32] Glinoer D., Spencer C.A.: "Serum TSH determinations in pregnancy: how, when and why?" *Nat. Rev. Endocrinol.*, 2010, *6*, 526.

[33] Gur E.B., Karadeniz M., Inceefe H., Tatar S., Turan G.A., Genc M., Guclu S.: "Thyroid antibodies in euthyroid and subclinical hypothyroidic pregnant women with autoimmune hypothyroidism: effects on hematological parameters and postpartum hemorrhage". *Ginekol. Pol.*, 2015, *86*, 666.

[34] Liu H., Shan Z., Li C., Mao J., Xie X., Wang W., et al.: "Maternal subclinical hypothyroidism, thyroid autoimmunity, and the risk of miscarriage: a prospective cohort study". *Thyroid*, 2014, *24*, 1642.

[35] Yu X., Chen Y., Shan Z., Teng W., Li C., Zhou W., et al.: "The pattern of thyroid function of subclinical hypothyroid women with levothyroxine treatment during pregnancy". *Endocrine*, 2013, *44*, 710.

[36] De Zoysa E., Hettiarachchi M., Liyanage C.: "Urinary iodine and thyroid determinants in pregnancy: a follow up study in Sri Lanka". *BMC Pregnancy Childbirth*, 2016, *16*, 303.

Corresponding Author:
L.Y. TANG, M.D.
Department of Obstetrics,
Shanghai Changning Maternal & Infant Health Hospital
No. 773, Wuyi Road, Shanghai (China)
e-mail: tanglongy909@126.com