Chula Med J Vol. 54 No. 3 May - June 2010

Neonatal outcomes associated with maternal treatment for Graves' disease

Pimolrat Thaithumyanon*

Santi Punnahitananda*

Thaithumyanon P, Punnahitananda S. Neonatal outcomes associated with maternal treatment for Graves' disease. Chula Med J 2010 May - Jun; 54(3): 265 - 76

Background : *Both the status of maternal Graves' disease and the methods of treatment can cause a variety of impacts on their fetuses and newborn infants.*

Objective : *To determine the clinical outcome and thyroid function test (TFT) of the infants born to the women who have been diagnosed with Graves' disease.*

Methods : *The study was performed on the infants born to mothers with Graves' disease at King Chulalongkorn Memorial Hospital between April 1999 and March 2006. They were examined and tested for serum FT_4 or T_4 and TSH levels at age ≥ 48 hours (screening tests). Infants suspected of thyroid disease would have repeated serum FT_4 and TSH test within 1 - 2 weeks. Tc99 thyroid scan was performed if congenital hypothyroidism was suspected. The infants were divided into 3 groups according to the methods of treatment their mothers had previously received. Group 1, 2, 3 were defined for maternal treatment with anti-thyroid drug, I^{131} and surgery, respectively. Comparison of clinical outcomes and TFT among these 3 groups of infants were performed.*

*Department of Pediatrics, Faculty of Medicine, Chulalongkorn University

Results : *One hundred and ninety pregnant women delivered 191 infants were enrolled. There were 131, 49 and 11 infants in group 1, 2 and 3, respectively. During pregnancy, 91 women were on propyl thiouracil (PTU), 47 on L-thyroxine and 52 were not on medication. There were more percentage of women in Group 1 who received PTU (64.6%, 12.2% and 9.1% respectively) and fewer of them (5.4%, 69.4% and 54.5% respectively) needed L-thyroxine. Among these infants, there was no statistical difference in terms of mean maternal age, gestational age, birth weight and proportion of small-for-gestational-age infants. Congenital anomalies were found in 5 infants (2.6%). Thyroid dysfunction was found in 15 infants (7.8%). Five were found with congenital hypothyroidism, 1 transient hypothyroidism, 2 fetal hyperthyroidism, 1 symptomatic hyperthyroidism and 6 asymptomatic hyperthyroidism. Screening levels of TSH and FT_4 of infants, whose mothers were taking PTU during pregnancy, were significantly higher and lower than the others ($p < 0.001$, ANOVA test). The maximum dosage of maternal PTU were also correlated significantly with the level of screening TSH ($r = 0.44$, $p < 0.001$) and screening FT_4 ($r = -0.47$, $p < 0.001$) of the infants (Pearson Correlation).*

Conclusion : *Infants born to Graves' disease mothers are at risk of congenital anomalies and thyroid dysfunction. Careful physical examination and thyroid function test should be closely monitored in these infants.*

Keywords : *Graves' disease, Thyroid function test, Free thyroxine (FT4), Thyroid stimulating hormone (TSH), Anti-thyroid drug, Radioiodine, Thyroidectomy, L-thyroxine, congenital anomalies.*

Reprint request: Thaithumyanon P. Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.

Received for publication. October 15, 2009.

พิมลรัตน์ ไทยธรรมยานนท์, สันติ ปุณณะหิตานนท์. ผลกระทบจากโรคต่อมธัยรอยด์เป็นพิษในมารดาต่อทารกแรกเกิด. จุฬาลงกรณ์เวชสาร 2553 พ.ค. – มิ.ย.; 54(3): 265 – 76

ความเป็นมา : *สภาวะการเป็นโรคต่อมธัยรอยด์เป็นพิษในหญิงตั้งครรภ์ และวิธีการรักษาที่ได้รับอาจมีผลกระทบต่อทารกในครรภ์และทารกแรกเกิด*

วัตถุประสงค์ : *เพื่อศึกษาผลกระทบทางคลินิกและการทำงานของต่อมธัยรอยด์ (thyroid function test) ทารกที่เกิดจากมารดาที่เคยได้รับการรักษาโรคต่อมธัยรอยด์เป็นพิษด้วยวิธีต่าง ๆ*

วิธีการ : *ทำการศึกษาโดยการติดตามทารกแรกเกิดที่เกิดจากมารดามีประวัติเป็นโรคต่อมธัยรอยด์เป็นพิษจำนวน 190 คนที่โรงพยาบาลจุฬาลงกรณ์ ระหว่างเดือนเมษายน พ.ศ. 2542 ถึงมีนาคม พ.ศ. 2549 ทารกทุกคนได้รับการตรวจร่างกายอย่างละเอียด และเจาะเลือดตรวจวัดระดับ TSH, FT_4 หรือ T_4 ในซีรั่มเมื่ออายุ ≥ 48 ชั่วโมง (ระดับตรวจกรอง) ทารกที่มีผลตรวจผิดปกติหรือสงสัยจะเป็นโรคเกี่ยวกับต่อมธัยรอยด์ จะได้รับการตรวจเลือดซ้ำและตรวจ Thyroid scan (Tc99) ถ้าสงสัยโรคต่อมธัยรอยด์บกพร่องแต่กำเนิด (Congenital hypothyroidism) ภายในเวลา 1 – 2 สัปดาห์ แบ่งทารกเป็น 3 กลุ่มตามวิธีการรักษาที่มารดาเคยได้รับ กลุ่ม 1, 2, 3 คือมารดารักษาด้วยยา anti-thyroid, น้ำแร่ I^{131} และผ่าตัดต่อมธัยรอยด์ตามลำดับ เปรียบเทียบผลกระทบทางคลินิกและการทำงานของต่อมธัยรอยด์ในทารกทั้ง 3 กลุ่ม*

ผลการศึกษา : *จากจำนวนหญิงตั้งครรภ์ทั้งหมด 190 คนมีเพียงคนหนึ่งคลอดลูกแฝดสอง ทำให้มีทารกจำนวน 131, 49 และ 11 คน ในแต่ละกลุ่มเรียงตามลำดับ ขณะตั้งครรภ์มารดา 91คนรับประทานยา anti-thyroid 49 คน รับประทานยา L-thyroxine และ 52 คนมีต่อมธัยรอยด์ทำงานปกติไม่ต้องรับยาอะไร มารดากลุ่ม 1 จำนวน 84 คน (ร้อยละ 64.6) ยังคงต้องรับประทานยา anti-thyroid แต่มารดากลุ่ม 2 และ 3 เกิดภาวะต่อมธัยรอยด์ทำงานบกพร่อง (hypothyroidism) มากกว่ากลุ่ม 1 อย่างมีนัยสำคัญทางสถิติ ($p < 0.0001$) มีจำนวน 7 คน (ร้อยละ5.4) 34 คน (ร้อยละ 69.4) และ 6 คน (ร้อยละ 54.5) ของกลุ่ม1, 2 และ 3 ตามลำดับ ต้องรักษาด้วยยา L-thyroxine เปรียบเทียบค่าเฉลี่ยอายุมารดา อายุครรภ์ น้ำหนักแรกเกิด และสัดส่วนทารกน้ำหนักต่ำกว่าอายุครรภ์ (small for gestational age) ของทั้ง 3 กลุ่มไม่แตกต่างกัน พบทารกพิการแต่กำเนิด 4 รายในกลุ่ม 1 และ 1 ราย ในกลุ่ม 2 ทารก 15 คน (ร้อยละ 7.8) มีต่อมธัยรอยด์*

ทำงานผิดปกติ ซึ่งวินิจฉัยเป็น Congenital thyroidism 5 คน Transient hypothyroidism 1 คน Fetal hyperthyroidism 2 คน Symptomatic hyperthyroidism 1 คน และ Asymptomatic hyperthyroidism 6 คน ทารกที่มารดาได้รับยา anti-thyroid ขณะตั้งครรภ์มีระดับตรวจกรอง TSH สูงกว่าและระดับตรวจกรอง FT_4 หรือ T_4 ต่ำกว่ากลุ่มที่มารดาได้รับยา L-thyroxine ($p < 0.001$) ขนาดยา anti-thyroid ที่มารดาได้รับมีความสัมพันธ์กับระดับตรวจกรอง TSH และ FT_4 ($r = 0.44$ และ $r = -0.47$, $p < 0.001$ ตามลำดับ) (Pearson Correlation)

สรุป : *มารดาเป็นโรคต่อมธัยรอยด์เป็นพิษ เสี่ยงที่จะคลอดลูกที่มีความพิการแต่กำเนิดและมีต่อมธัยรอยด์ทำงานผิดปกติ ควรตรวจร่างกายทารกอย่างละเอียดและตรวจระดับการทำงานของต่อมธัยรอยด์ทารกแรกเกิดเหล่านี้อย่างใกล้ชิด*

คำสำคัญ : *โรคต่อมธัยรอยด์เป็นพิษ, การทำงานของต่อมธัยรอยด์, ระดับตรวจกรอง FT_4, โรคต่อมธัยรอยด์บกพร่องแต่กำเนิด, ยา L-thyroxine, ตรวจวัดระดับ TSH, ยา anti-thyroid.*

Graves' disease is an autoimmune condition in which thyroid stimulating immunoglobulin (TSI) develops spontaneously, leading to excessive production and release of thyroid hormone and subsequently hyperthyroidism. In pregnant women, it may influence the fetuses and their neonatal hypothalamic-pituitary-thyroid system. Both the status of maternal Graves' disease and the methods of treatment can have a variety of impacts on the fetuses and newborn infants. Women who remain on anti-thyroid drugs during pregnancy are, therefore, exposed to increased risks of maternal and fetal complications, particularly miscarriage, still birth and neonatal hypothyroidism. It has been known that by 20 weeks of gestational age, fetal thyroid gland is well responsive to TSI and to anti-thyroid drugs that are readily transferred from the mother to the fetus. [1]

There are 3 recognized methods of treatment for hyperthyroidism: anti- thyroid drugs, radioiodine and surgery (thyroidectomy). The current anti-thyroid drugs include propylthiouracil (PTU), methimazole (MMI) and carbimazole; they are associated with side-effects and a high relapse rate. They reduce thyroid hormone synthesis by inhibiting the oxidation and organic binding of thyroid iodide. The use of radioiodine in women of child bearing age for treatment of hyperthyroidism is increasing. [2] Although it can be used in all age groups other than children, it should be avoided in pregnancy and during lactation. [3] Because of the oncogenic potential of radioiodine and the potential risks of genetic damage to the offspring after radioiodine (I^{131}) treatment[4], its safety still remains a matter of great concerns. Clinically, thyroidectomy achieves a high rate of remission, but hypothyroidism develops in about 60% of the patients, and TSI can remain in the blood stream after the thyroid gland has been removed. [5] Therefore, even with a proper medical or surgical treatment, neonates born to women with previously treated Graves' diseases are still at risk for thyroid dysfunction resulting either from transferred maternal TSI or the potential complications associated with each therapeutic method the mothers have received. However, studies of this impact on Thai infants are quite limited. In this report we performed an observational study on infants born to mothers who had treated Graves' disease in order to determine their thyroid function test (TFT) and the neonatal outcome.

Methods

This is a prospective observational study on infants born to mothers who had Graves' disease at King Chulalongkorn Memorial Hospital between April 1999 and March 2006. The methods of treatment of Graves' disease the mothers had received and the pertinent information during the present pregnancy were collected from obstetric records and/or obtained after delivery. This information included the latest maternal TFT and the maximum dosage of PTU or L-thyroxine taken during their last trimester, especially symptoms and signs related to Graves' disease. All infants were examined thoroughly and had TSH screening or thyroid function test at age $\geq$ 48 hours (screening test). Thyroid function test (TFT) consisted of serum free thyroxine (FT_4), or thyroxine (T_4) and thyroid stimulating hormone (TSH) levels. Screening TSH > 20 mU/L, T_4 < 7 mg/L, and FT_4 <1ng/dl were defined as abnormal screening TFT. Infants with abnormal test or suspected thyroid disease would have repeated TFT and physical examination was

weekly taken within 1- 2 weeks after the screening test until it became normal or diagnosis was made. An ancillary test, such as bone age and thyroid scan, using technetium pertechnetate (Tc 99), was performed for confirmation of the diagnosis of congenital hypothyroidism. Criteria for diagnosis of thyroid diseases were based on serum FT_4 or T_4 and TSH levels according to the reference values. [6,7] Asymptomatic hyperthyroid infants were observed and serum TSH and FT_4 were monitored closely until they returned to normal without treatment or at least 3 - 4 months if they remained asymptomatic. They were treated if any symptom of hyperthyroidism should occur. Unexplainable persistent fetal tachycardia in Grave's disease mother that responded to maternal treatment of anti-thyroid drug was defined as fetal hyperthyroidism. Transient neonatal hypothyroidism was defined as an asymptomatic infant with prolonged hypothyroxinemia and hyperthyrotropinemia of

less than 3 weeks. Infants with confirmed diagnosis of congenital hypothyroidism were treated with L-thyroxine as soon as possible. The infants were divided into 3 groups according to the previous methods of maternal treatment for Graves' diseases. Group 1, 2, 3 were defined based on the types of maternal treatment with anti-thyroid drug, radioiodine (I^{131}) and surgery (thyroidectomy), respectively. Comparison of clinical outcomes and TFT among these 3 groups of infants were performed. Statistical analyses were performed with a PC statistics package (SPSS, Chicago, Ill). Chi-square test and Odd Ratio were used for comparison of discrete variables. ANOVA tests were used for comparison of continuous variables as appropriate. Pearson correlation analysis was performed to assess linear associations between maternal dosage of anti-thyroid drug and screening thyroid function test of the infants. Value of $p < 0.05$ was considered significant.

Results

During a period of 7-year data collection, 190 pregnant women with history of Graves' disease were enrolled. There were 130, 49 and 11 women in Group 1, 2 and 3, respectively. All women delivered singleton infant except 1 mother of Group 1 who delivered a pair of twins. Therefore, there were 131 infants in Group1. Twenty-four infants were low-birth weight (birth weight < 2500 grams) and 14 of them were small for gestational age (SGA). Among these 3 groups, there was no statistical difference in terms of mean maternal age, gestational age, birth weight, and incidence of SGA infants. Screening TSH level of Group1 infants was significantly higher than those of group 2 infants. But the TSH levels of Group 2 and 3 were not statistical different (Table 1). Duration between the onset of Graves' disease and the time at delivery was reported in 144 mothers (75.8%). The average time was 5.4 ± 4.6 years (range 2 months - 20 years). The duration in each group was 3.9 ± 4.0, 7.4 ± 4.4 and 10.2 ± 5.2 years in Groups 1, 2, and 3, respectively (Table 2). Graves' disease was first diagnosed during the present pregnancy in 7 women (between 2-7 months of pregnancy) and they were well controlled with anti-thyroid drugs. All of them delivered normal term infants with normal TFT except 2 infants who developed fetal hyperthyroidism during their last trimester. The average time of radioiodine treatment in Group 2 women was approximately 5.2 ± 3.8 years (range 1 month-14 years) before

Table 1. Data on characteristics of the mothers and infants.

	Group 1 n = 131	Group 2 n = 49	Group 3 n = 11	Total n = 191
Maternal age, y.	29.4 ± 6.6	31.4 ± 5.1	32.3 ± 6.3	30.1 ± 6.0
Infants' BW, g.	2973 ± 502	3060 ± 415	2947 ± 440	2995 ± 477
Infants' GA, wks.	38.7 ± 1.8	38.7 ± 1.8	38.8 ± 1.2	38.7 ± 1.8
Number of SGA, (%)	9 (6.87)	3 (6.12)	2 (18.18)	14 (7.33)
Screening TSH, (mU/L)	26.40 ± 39.80*	10.17 ± 16.94*	12.40 ± 14.17	21.43 ± 34.95

*p-value = 0.02

Table 2. Duration between the onset of maternal Graves' disease and time of delivery.

Group	n	Duration (years)	
		Mean+ SD	Range
Antithyroid drug (1)	89	3.9 ± 4.0*, **	0.2 - 20
Radioiodine (2)	46	7.4 ± 4.4 * ,***	1.5 - 17
Surgery (3)	9	10.2 ± 5.2 **, ***	4 - 18

*, ** p-value < 0.001

*** p-value > 0.05

pregnancy. During pregnancy, 91 women were on anti-thyroid drugs (all were PTU) 47 were on L-thyroxine and 52 were euthyroid without medication. Percentage of women needed PTU during pregnancy in Group 1 was significantly higher than those in the other two groups. On the contrary, the percentage of women in Group 2 and 3 who needed L-thyroxin was higher than those in Group 1 (Table 3). One hundred

Table 3. Maternal medications during pregnancy.

Medications	Group 1 n = 130	Group 2 n = 49	Group 3 n = 11	OR (95%CI)	p-value
PTU	84 (64.6%) *,+	6 (12.2%) *	1 (9.1%) +	* 13.2 (5.2,33.4) + 18.5 (2.3,148.9)	* <.0001 + <.001
L-thyroxin	7 (5.4%) **, ++	34 (69.4%) **	6 (54.5%) ++	** .03 (.009, .07) ++ .05 (.01, .19)	** < .0001 ++ <.0001
None	39 (30%)	9 (18.4%)	4 (36.4%)		ns

ns = no significance

and forty-one women (74.2%) were clinically euthyroid; 58 women (30.5%) had goiter; and, 17 (8.9%) of them still had exopthalmos. Results of TFT during the last trimester were available from 67 women (35.3%). Mean ± SD of their serum TSH, FT4 and FT3 were 3.52 ± 7.28 mU/L,1.49 ± 1.22 ng/dl and 3.23 ± 2.44 nmol/L, respectively. Among infants born to women who were on L-thyroxine, there was no abnormal screening TFT or anomaly. All of these mothers were on L-thyroxine only 1 tablet (50 mcg) per day. Congenital anomalies were found in 4 infants of Group 1 and 1 infant of Group 2. The mothers of 3 infants with scalp cutis aplasia or hydronephrosis or toes syndactyly, were taking PTU during pregnancy. Mothers of the other 2 infants with achondroplasia or gastroscisis were euthyroid with no medication. Forty-three infants (22.5%) had abnormal high TSH screening levels (>20 mU/L). Thyroid dysfunction was found in 15 infants (7.8%). There were 5 cases of congenital hypothyroidism, 1 of transient hypothyroidism, 2 of fetal hyperthyroidism, 6 of asymptomatic hyper-thyroidism and 1 of symptomatic hyperthyroidism (Table 4). Screening TSH of all asymptomatic hyperthyroidism and one fetal hyperthyroidism were >20 mU/L. The infant with transient congenital hypothyroidism was a low-birth weight infant (2320 grams) whose serum TSH and FT4 level gradually returned to normal at 24-day old and remained within normal range until 3 months of age. His thyroid scan showed normal appearance. Repeated TFT of the other 25 infants with abnormal high TSH screening levels became normal between 7-17 days after birth. Thyroid scan was performed on 3 of them who showed normal glands. They remained asymptomatic up until 2-3 months of age. Three other infants with high screening TSH level were lost to follow up. Etiologies of 5 infants with congenital hypothyroid were: 3 dyshormonogenesis and one each of ectopic and agenetic thyroid. All infants with thyroid dysfunction except one with symptomatic hyperthyroidism were born to Group 1 mothers; only 2 were exposed to intrauterine anti-thyroid drug. Two infants with fetal hyperthyroidism were successfully treated with anti-thyroid drug administrated to their mothers. They were asymptomatic. However, high screening TSH and FT_4 levels were still noted in one of them which became normal in one week. Diagnosis of Graves' disease in one woman was made after fetal hyperthyroidism was noted at 32-week gestation. The symptomatic hyperthyroid infant was a normal term female infant born to a euthyroid mother in Group 3. Her screening TSH was 0.02 mU/L and FT_4 was 1.9 ng/dl. She became irritable, and had tachycardia with poor weight gain and her serum FT_4 rose up to 3.90 ng/dl at the age of 18 days which hospitalization was needed. She demonstrated a good response to a 2-week course of small dose PTU treatment. Six infants with asymptomatic hyperthyroidism were followed up closely without treatment. Their screening TSH was abnormally high (39 - 200mU/L) and FT4 were 0.2 - 1.3 ng/dl. Hyperthyroidism was diagnosed at age between 5 - 21 days. They remained asymptomatic and their TFT return to normal within 2 months. Both screening TSH and FT_4 levels of infants whose mothers were on anti-thyroid drugs during pregnancy were significantly higher and lower respectively than those infants whose mothers were on L-thyroxine or no medication ($p < 0.001$, for both, ANOVA test) (Table 5). Percentage of infants with abnormal screening TFT stratified according to type of medications taken by

their mothers during pregnancy were shown in table 6.The maximum dosage of maternal anti-thyroid drug was also significantly correlated with the level of screening TSH (r = 0.44, p< 0.001) and screening FT_4 (r = -0.47, p< 0.001), (Pearson Correlation).

Table 4. Fetal and neonatal outcomes.

	Group 1	Group 2	Group 3	Total, n
Cong. anomalies	1 Cutis aplasia 1 Gastroschisis 1 Achondroplasia 1 Hydronephrosis	1 Syndactyly toes	No	5 (2.6%)
Thyroid dysfunction	5 Cong. hypothyroid 1 Trans. hypothyroid 2 Fetal hyperthyroid 6 Asymp. hyperthyroid	No	1 Symp. hyperthyroid	15 (7.8%)

Table 5. Screening levels (Mean + SD) of TSH ,T_4 and FT_4 of the infants of mothers with medication during pregnancy.

	Maternal medication during pregnancy					
		Anti-thyroid		L-Thyroxin		No drug
TSH, mu/L	n = 92	33.5 ± 39.7*,**	n = 47	8.5 ± 6.0*	n = 52	11.7 ± 34.5**
T_4, mg/L	n = 21	12.8 ± 6.4	n = 4	16.6 ± 5.3	n = 5	16.0 ± 6.2
FT_4, ng/dl	n = 37	1.4 ± 0.7# ,***	n = 26	2.1 ± 0.4#	n = 12	2.0 ± 0.5***

*, # p-value < 0.001, ** p-value < 0.005, *** p-value < 0.05

Table 6. Percentage of infants with abnormal screening TFT stratified according to their maternal medication during pregnancy.

Test	Number of infants			
	Anti-thyroid (%)	L-thyroxin (%)	No drug (%)	Total (%)
TSH>20mU/L	41.0 (38/92)*,**	6.4 (3/47)*	3.8 (2/52)**	22.5 (43/191)
T_4<7mg/dl	19.1 (4/21)	0	0	13.3 (4/30)
FT_4<1ng/dl	29.7 (11/37)	0	0	14.7 (11/75)

*, ** p < 0.001

Discussion

This study demonstrates higher recurrent rate of Graves' disease during pregnancy among women who have been previously treated with anti-thyroid drugs than those women with radioiodine or surgical treatment. Thyroid gland ablation effect of anti-thyroid drugs is probable not as extensive as the effect of the other 2 methods. Therefore, with increased metabolism during pregnancy, the symptoms and signs of hyperthyroid can reoccur. Maternal hypothyroidism as indicated by the need of L-thyroxine, a common adverse effect of radioiodine or thyroidectomy is found in 34/49 (69.4%) and 6/11 (54.5%) of Group 2 and 3, respectively. Only 7 out of 130 women (5.4%) in Group 1 develop hypothyroidism which is significantly less than the others. However, these women's thyroid function is well controlled with a small dose of L-thyroxine and no adverse effect on their offspring is noted. Radioiodine is contraindicated during pregnancy and breast feeding. Therapeutic administration of radioiodine (I^{131}) to the mother will usually result in fetal hypothyroidism. So, it is necessary to have pregnancy test prior to I^{131}treatment for women in child-bearing age. Moreover, it is recommended that pregnancy should be postponed for at least 120 days after I^{131} therapy.[4] Read et al.[8] reported long-term outcomes of Graves' disease patients who had been treated with radioiodine when they were aged less than 20-year-old and found that their pregnancies did not result in any unusual number of congenital anomalies or spontaneous abortion. One woman in our study received I^{131} about 1 month prior to pregnancy, and she delivered a normal male infant. Although, toe syndactyly is the only abnormality found in one infant whose mother has been previously treated with I^{131}. We think this anomaly is probable not related to the radioactive iodine and the I^{131} activity should not remain in the maternal tissues at the time of conception, since all these mothers received I^{131} treatment before their pregnancies. However, the safety of this method of treatment is still needed to be verified.

Infants born to mothers in Group 1 seemed to have more adverse outcomes than the others. The prevalence of congenital anomalies is 3% and 2% in Group 1 and 2, respectively. The mothers of 2 infants with anomalies (1 scalp cutis aplasia and 1 hydronephrosis) were still taking propyl thiouracil (PTU) throughout their pregnancies. Although, cutis aplasia and choanal atresia have been reported in the infants whose mothers were on methimazole.[9,10] So far, the association between anti-thyroid drugs and congenital anomalies has not been confirmed.

Both PTU and L-thyroxine taken by a mother during pregnancy may be transferred across the placenta and disturb thyroid function of the infant. PTU can temporarily suppress thyroid gland of the fetus and induce fetal goiter, transient neonatal hypothyroidism or transient hyperthyrotropinemia (elevated serum TSH with normal serum FT_4). Mestman JH[11] suggested that these effects are related to the amount of anti-thyroid medication taken by the mother during the last weeks of gestation. High doses of anti-thyroid drugs may block the infant's thyroid gland and cause hypothyroidism. It can also mask neonatal hyperthyroidism for 7 to 10 days until it has worn off. However, 2 out of 5 hypothyroid infants were not exposed to intrauterine anti-thyroid drugs and none of them developed goiter. Transient neonatal hypothyroidism and transient hyper-

thyrotropinemia (screening TSH>20 mU/L) are diagnosed in 1 and 27 infants respectively. TSH screening level of seven infants with hyperthyroidism were all higher than the normal range. They dropped quickly whereas T_4 or FT_4 rose sharply within 5 - 21 days later. We believe thyroid gland of these infants become hyperactive when the serum PTU level has subsided. Since there is no thyroid dysfunction found in infants born to the mothers who have been on L-thyroxine, small dose of L-thyroxine should give no adverse effect as shown in this report. Infant born to euthyroid pregnant woman with previous history of Graves' disease who has been treated with anti-thyroid drugs, radioiodine or surgery before pregnancy is still at risk for neonatal hyperthyroidism. [11] It is suggested that even with proper medication or surgical treatment in Graves' disease mother, thyroid stimulating immunoglobulin (TSI) remains in her blood stream and may be passed to her newborn infant. [12] Neonatal hyperthyroidism can be a transient condition induced by maternal TSI, limited by the clearance of this maternal antibody from the infant's circulation. The majority of our hyperthyroid infants do not require any treatment. They return to normal condition spontaneously as demonstrated in 6 out of 7 infants in the present report. None of their mothers were on L-thyroxine. Therefore, both fetal and neonatal hyperthyroidism in this study should be due to trans-placental transfer of TSI, although we did not measure TSI level in their mothers.

Conclusion

Infants born to Graves' disease mothers are at risk of congenital anomalies and thyroid dysfunction. Anti-thyroid drugs only block the infants' thyroid gland temporarily. Neonatal hyperthyroidism can be found regardless of the mothers' thyroid function during pregnancy. Small dose of L-thyroxine taken by the mother should not cause adverse effect on the infant. However, careful physical examination and TFT should be closely monitored in these infants.

References

1. Atkins P, Cohen SB, Phillips BJ. Drug therapy for hyperthyroidism in pregnancy: safety issues for mother and fetus. Drug Saf 2000 Sep; 23(3): 229 - 44
2. Cooper DS. Treatment of thyrotoxicosis. In: Braverman LE, Utiger RD, eds. The Thyroid: A Fundamental and Clinical Text. 6th ed. Philadelphia: Lippincott, 1991: 887 - 916
3. Gittoes NJ, Franklyn JA. Hyperthyroidism. Current treatment guidelines. Drugs1998 Apr; 55(4): 543 - 53
4. Gorman CA. Radioiodine and pregnancy. Thyroid 1999 Jul; 9(7): 721- 6
5. Miccoli P, Vitti P, Rago T, Iacconi P, Bartalena L, Bogazzi F, Fiore E, Valeriano R, Chiovato L, Rocchi R, et al. Surgical treatment of Graves' disease: subtotal or total thyroidectomy? Surgery 1996 Dec; 120(6): 1020 - 4
6. Adams LM, Emery JR, Clark SJ, Carlton EI, Nelson JC. Reference ranges for newer thyroid function tests in premature infants. J Pediatr 1995 Jan; 126(1): 122-7
7. John R, Bamforth FJ. Serum free thyroxine and free triiodothyronine concentrations in healthy fullterm, preterm and sick preterm neonates. Ann Clin Biochem 1987 Sep; 24(Pt 5): 461-5
8. Read CH Jr, Tansey MJ, Menda Y. A 36-year

retrospective analysis of the efficacy and safety of radioactive iodine in treating young Graves' patients. J Clin Endcrinol Metab 2004 Sep; 89(9): 4229 - 33

9. Becks GP, Burrow GN. Thyroid disease and pregnancy. Med Clin North Am 1991 Jan; 75(1): 121-50
10. Barwell J, Fox GF, Round J, Berg J. Choanal atresia: the result of maternal thyrotoxicosis or fetal carbimazole? Am J Med Genet 2002 Jul 22; 111(1): 55-6
11. Mestman JH. Hyperthyroidism in pregnancy. Endocrinol Metab Clin North Am 1998 Mar; 27(1): 127-49
12. McNab T, Ginsberg J. Use of anti-thyroid drugs in euthyroid pregnant women with previous Graves' disease. Clin Invest Med 2005 Jun; 28(3):127-31