

# Pre-Conception Counselling in Graves' Disease

John H. Lazarus

Centre for Endocrine and Diabetes Sciences, Cardiff University, Cardiff, UK

## Key Words

Pregnancy · Graves' disease · Counselling · Pre-conception · Lactation · Iodine · Thionamides · Radioiodine · Surgery

## Abstract

Risks to mother, fetus and neonate from untreated Graves' hyperthyroidism during gestation are compelling reasons for recommending pre-conception counselling. Pre-conception counselling should include discussion as to the optimum treatment of Graves' hyperthyroidism in women wishing to become pregnant. Thyrotropin receptor antibodies remain elevated following radioiodine therapy, so medical or surgical treatment may be preferred to avoid fetal or neonatal hyperthyroidism. A TSH level  $<2.5$  mIU/l must be achieved in women receiving  $LT_4$  before conception. The patient should be reassured that both she and the fetus can be maintained in a euthyroid state and that neonatal hyperthyroidism can be readily managed with a good outcome. The risks of antithyroid drug therapy during gestation should be fully discussed with emphasis on the very low risk (although real) of liver disease with propylthiouracil treatment and embryopathy with methimazole or carbimazole therapy. While propylthiouracil is the preferred drug for the first trimester, if it is not available other thionamides may be given. Breast-feeding while on antithyroid drugs is not contraindicated provided the dose of drug is low. The patient should also be advised of the importance of thyroid monitoring in the post-partum period.

Maternal hyperthyroidism is reported to occur at a frequency of around 0.2% [1]. This is to be contrasted with the prevalence of antithyroid peroxidase antibodies which occur in 10% of women when measured at around 12 weeks of gestation. In contrast, TSH receptor antibodies have a prevalence of around 0.01%, but neonatal hyperthyroidism occurs in 30% of TSH receptor antibody-positive women [2].

## Course of Graves' Disease during Pregnancy

Deterioration in the clinical features of Graves' disease in the first trimester of pregnancy may occur due to stimulation of the thyroid both by human chorionic gonadotropin and thyrotropin receptor-stimulating antibodies [3–5]. The markedly increased thyroid hormone-binding capacity of the serum (due to high thyroxine-binding globulin) may also contribute to the deterioration [6]. However, an improvement in Graves' disease may be expected in the second half of gestation due to the falling titre of thyroid-stimulating antibodies and possibly the presence of thyroid receptor-blocking antibodies [4]. Therefore, although hyperthyroidism is relatively rare in pregnancy, its effects may be substantial [7]. This means that thyroid function should be controlled not only in the pregnant woman with Graves' hyperthyroidism but also in her fetus.

Copyright © 2012 European Thyroid Association  
Published by S. Karger AG, Basel

This review is based on a lecture delivered at the annual meeting of The European Thyroid Association, Krakow, Poland, 2011.

## KARGER

Fax +41 61 306 12 34  
E-Mail [karger@karger.ch](mailto:karger@karger.ch)  
[www.karger.com](http://www.karger.com)

© 2012 European Thyroid Association  
Published by S. Karger AG, Basel  
2235-0640/12/0011-0024\$38.00/0  
Accessible online at:  
[www.karger.com/etj](http://www.karger.com/etj)

John H. Lazarus  
Centre for Endocrine and Diabetes Sciences, Cardiff University  
Cardiff CF14 4XN (UK)  
Tel. +44 2920 744 326  
E-Mail [Lazarus@cf.ac.uk](mailto:Lazarus@cf.ac.uk)

**Table 1.** Effects of poorly treated hyperthyroidism in pregnancy

Clinical	Mother	Pregnancy	Fetus	Neonate
Untreated/inadequate	Congestive cardiac failure Pre-eclamptic toxemia Thyroid storm	Miscarriage Abruptio Post-partum thyroid disease	Hyperthyroidism Goitre Death	Primary hyperthyroidism Secondary hypothyroidism
Antithyroid drugs			Hypothyroidism Goitre	Transient hyperthyroidism
Surgery + L-thyroxine	Hypothyroidism		Hyperthyroidism (TRAb)	Hyperthyroidism (TRAb)
<sup>131</sup> I radioiodine L-thyroxine	Hypothyroidism		Hyperthyroidism (TRAb)	Hyperthyroidism (TRAb)
Previous antithyroid drugs	Relapse post-partum			

TRAb = Thyrotropin receptor antibodies. Adapted from Laurberg et al. [7].

**Table 2.** Recommended iodine intake during pregnancy and lactation and categorization of iodine nutrition adequacy based on urinary iodine excretion

Population group	Median urinary iodine concentration	Category of iodine intake
Pregnant women <sup>a</sup>	250 µg/day	
Lactating women <sup>a</sup>	250 µg/day	
Pregnant women	<150 µg/l	Insufficient
	150–249 µg/l	Adequate
	250–499 µg/l	More than adequate
	>500 µg/l	Excessive
Lactating women	<100 µg/l	Insufficient
	>100 µg/l	Adequate

<sup>a</sup> Recommended intake.

## Factors Affecting Pregnancy in Graves' Disease

### Risks and Complications

The risks of untreated or poorly treated Graves' hyperthyroidism in pregnancy may be seen in the mother and the fetus [8, 9]. Maternal risks include increased incidence of miscarriage, placental abruption and pre-term delivery. In addition, untreated disease may be associated with congestive heart failure, the increased incidence of pre-eclampsia and even thyroid storm. Fetal risks of poorly treated Graves' disease include fetal hyperthyroidism as well as neonatal hyperthyroidism. Important complications also include prematurity, intrauterine growth retardation and fetal death or stillbirth. There is also an increased incidence of fetal abnormalities. The risks of Graves' hyperthyroidism in pregnancy are further illus-

trated in table 1, where it is seen that the untreated or inadequately treated disease leads to complications in the mother, complications in pregnancy and fetal and neonatal adverse effects. Even if the mother is on antithyroid drugs, the fetus may develop hypothyroidism or goitre and the neonate may have transient hyperthyroidism. If the mother has previously been treated with surgery and is on levothyroxine therapy, she may develop hypothyroidism and both the fetus and neonate are at risk of hyperthyroidism due to the continuing presence of thyrotropin receptor-stimulating antibodies. A similar situation occurs if the mother had previously received radioiodine and is also on levothyroxine therapy. If the mother has had previous treatment with antithyroid drugs she may be at risk of relapse.

### Iodine Requirements

In the case of all pregnant women, with or without thyroid disease, it should be remembered that the recommended iodine intake during pregnancy and lactation should be 250 µg/day (table 2), which corresponds to a urinary iodine concentration of approximately 150 µg/l [10]. Although there has been a significant increase in the use of universal salt iodisation in the last 20 years, some countries, including for example the United Kingdom [11], are still iodine-deficient.

From the foregoing considerations it is apparent that counselling in Graves' disease during pregnancy is very desirable. The administration of counselling should be either by the endocrinologist or obstetrician, or even specialist nurse. It can be performed during the management of Graves' hyperthyroidism in women of child-bearing age who are not, but wish to become pregnant. It may be given during pre-conception in women with Graves' dis-

ease who are on or off antithyroid therapy and also during pregnancy. It should be noted that there is no specific evidence base for counselling at this point in time. Nevertheless, there has been considerable discussion and debate around the management of Graves' disease in pregnancy, most notably at the meetings of the American Thyroid Association together with the Food and Drug Administration in Washington, D.C., in 2009 [12], The International Thyroid Congress in Paris in 2010, and recently at the annual meeting of The European Thyroid Association in Krakow in 2011. However, there have been no publications on counselling derived from these meetings.

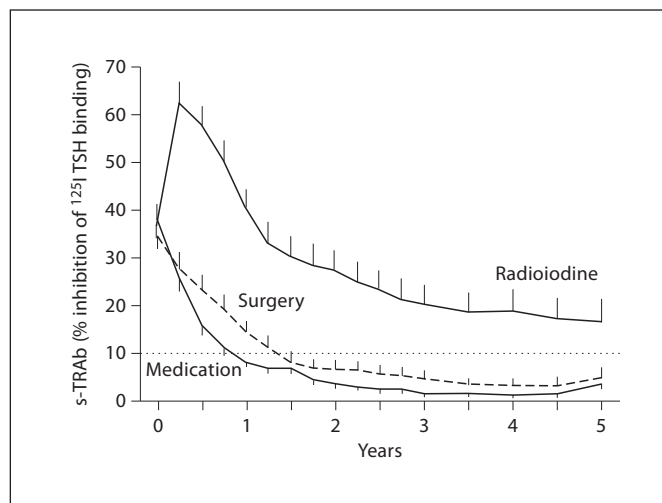
### Treatment of Graves' Hyperthyroidism in Women of Childbearing Age

Current guidelines indicate that the optimal time to conceive is once a euthyroid state is reached [13]. Pre-pregnancy counselling for all patients with hyperthyroidism or a history of hyperthyroidism is imperative and use of contraception until the disease is controlled is strongly recommended. Prior to conception, a hyperthyroid patient may be offered ablative therapy (radioiodine or surgery) or medical therapy [6, 14].

#### Counselling

Any woman who is pregnant but who has no medical condition has concerns about her pregnancy and wishes reassurance that everything is progressing normally. However, when a pregnant woman has a concurrent medical condition these concerns are heightened. In relation to hyperthyroidism and pregnancy, a woman may well have questions and worries such as: What is the best treatment for my Graves' disease? My baby will be born a cretin, I must have an abortion, I cannot take tablets during pregnancy. Can I breast-feed? Should I take kelp tablets? Can I have more children? This list is just an illustrative example of possible queries and anxieties that a pregnant woman with Graves' disease may have and is not exhaustive. Therefore, the aims of counselling in this situation would be: (1) discussion of the therapeutic choice for treatment of Graves' hyperthyroidism (antithyroid drugs or surgery or radioiodine); (2) reassurance with regard to the management of her Graves' disease during pregnancy, and (3) the delivery of information with regard to possible effects of Graves' hyperthyroidism on the fetus and neonate with appropriate reassurance.

If a woman is not pregnant but has Graves' disease and wishes to become pregnant in the future, ablative therapy



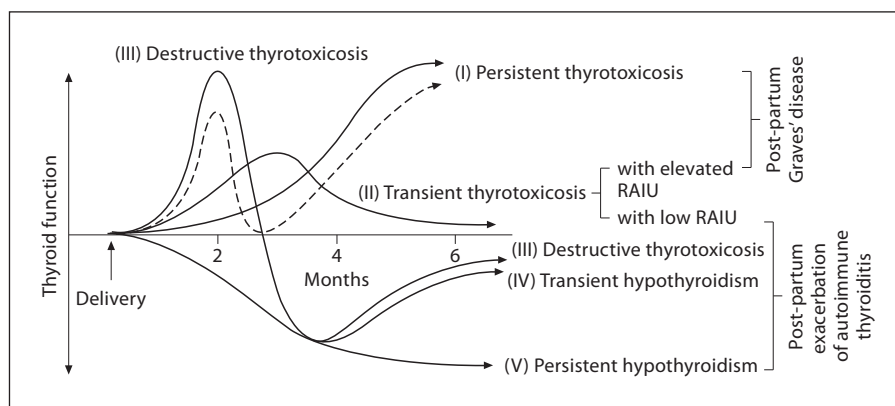
**Fig. 1.** Variations in TSH receptor antibodies in serum (mean  $\pm$  SEM) in patients with Graves' hyperthyroidism receiving radioiodine surgery or medical therapy. Patients were kept euthyroid with LT<sub>4</sub>. After therapy, all values were significantly higher for the radioiodine group when compared with values for the medical or surgical therapy groups ( $p < 0.01$ ). From Laurberg et al. [16].

may be offered. A pregnancy test prior to therapy is now routine practice if the woman is going to receive radioiodine. In addition, conception should be delayed until 6 months following therapy in order to adjust the thyroxine dose to target values for pregnancy (serum TSH 0.3–2.5 mIU/l). The 6-month period is recommended in relation to the complete clearance of radioiodine from the body following therapy. Recent guidelines recommend an upper limit of TSH at conception of 2.5 mIU/l [13] and it has been noted that in up to a half of women in one study the TSH level was  $>2.5$  mIU/l at conception [15].

With regard to thyroid receptor antibody measurement, it should be remembered that following radioiodine there is an increase in TRAb titres that may last for 12 months followed by a gradual fall [16]. This is in contrast to post-surgical therapy where there is usually (but not always) an immediate and gradual disappearance of TRAb levels. In fact, these considerations suggest that surgery may be a better choice for patients with high TRAb titres who wish to become pregnant (fig. 1), although TRAb may persist after thyroidectomy in some patients.

Treatment with antithyroid drugs (carbimazole/methimazole or propylthiouracil (PTU)) is acceptable either before pregnancy or during pregnancy. However, the risks of antithyroid therapy must be discussed carefully with the patient. There is a possibility of relapse in the first tri-

**Fig. 2.** Development of post-partum thyroid dysfunction. RAIU = Radioiodine uptake. Adapted from Amino and Kubota [23].



mester and post-partum in previously treated women [17, 18]. If hyperthyroidism occurs in the first trimester, gestational transient thyrotoxicosis must be differentiated from Graves' disease. In this regard, a human chorionic gonadotropin level, FT<sub>3</sub>/FT<sub>4</sub> ratio and thyroid receptor antibody tests are useful [17]. If a woman is on antithyroid drugs for more than 2 years, she will probably require drug therapy through gestation. Recently there has been extensive discussion about the side effects of carbimazole/methimazole and PTU in pregnancy [12, 19]. Recognition of liver disease in patients on PTU has resulted in the recommendation that PTU should only be used for the first trimester. It is preferred in the first trimester to carbimazole or methimazole due to the occurrence of so-called methimazole embryopathy in patients on a thionamide drug in the first trimester during organogenesis in the fetus. It should be stressed that both the liver problems with PTU and the methimazole embryopathy are rare and do not negate the use of these drugs in pregnancy. If PTU is not available or the patient is intolerant of that drug, it is acceptable to proceed with methimazole or carbimazole in the lowest possible effective dose.

#### Breast-Feeding

With regard to breast-feeding in a woman receiving antithyroid drugs, it should be noted that both PTU and MMI are secreted in human milk [20]. If the dose of MMI is <20 mg/day or that of PTU <250 mg/day, the risk to the infant is practically negligible. Because of the already mentioned side effects of PTU, methimazole is the preferred drug during lactation. In general, there is no evidence to advise mothers against breast-feeding when taking antithyroid drugs [21]. There are several studies indicating no long-term effects on the neonate or in child development [19].

#### Can We Reassure the Mother that Her Baby Is Going to Be Normal after She Has Taken Antithyroid Drugs?

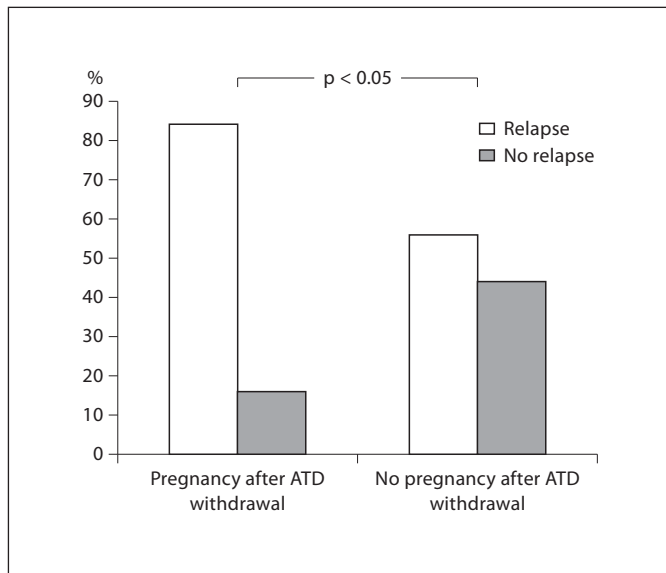
There is an incidence of transient hyperthyroidism of 1–5%. Transient neonatal hypothyroidism may occur, rarely. Both these conditions can be managed very satisfactorily. As noted, aplasia cutis and methimazole embryopathy are rare but can occur if methimazole is given in the first trimester. Recently there has been an association of antithyroid drug use in pregnancy and development dysplasia of the hip [22], this requires confirmation however.

#### What about the Mother, Will She Be Subject to Any Complications after Delivery?

Thyroid receptor antibodies fall during gestation but they do rise in the post-partum as do thyroid peroxidase antibodies. Of those women with antithyroid peroxidase antibodies, 50% will develop post-partum thyroiditis with associated risks of transient hyper- and hypothyroidism (fig. 2). Hence there is a requirement for a careful monitoring post-partum for any woman with Graves' disease [23]. According to Rotondi et al. [24], there is an increased incidence of relapse of Graves' hyperthyroidism in women who had had a pregnancy after previous antithyroid drug withdrawal compared to those women who did not become pregnant following their antithyroid drug withdrawal (fig. 3).

#### Discussion

This review has highlighted the importance of counselling patients with Graves' disease who wish to become pregnant or who are pregnant. Although counselling may induce concerns in both pregnant women and those



**Fig. 3.** Relapsing Graves' hyperthyroidism was observed in 21 of 25 patients who had a pregnancy after ATD withdrawal (84.0%) and in 70 of 125 patients who did not become pregnant since ATD withdrawal (56.0%) ( $\lambda^2$  and Fisher's exact test;  $p < 0.05$ ). From Rotondi et al. [24].

wishing to become pregnant, appropriate discussion with the patient will alleviate many of their worries. For example, the risks and benefits of any treatment for Graves' disease prior to conception can be confirmed; the appropriate drug therapy during pregnancy can also be indicated. Reassurance can be given to the mother that while the baby does have a slight risk of transient hyperthyroidism, there is no other specific cause for concern. There is

certainly no reason to suggest an abortion and there is also no indication that the woman should not take anti-thyroid drugs during pregnancy. On balance, there is a strong argument to be made in favour of counselling a woman who has Graves' disease and wishes to achieve pregnancy or is already pregnant.

Breast-feeding should be encouraged, providing that the dose of antithyroid drugs is reasonably low. Concern about iodine levels may be expressed but the best way of ensuring adequate iodisation during pregnancy is by iodine supplements rather than proprietary preparations such as kelp.

Lastly, a woman may be concerned as to whether she can have further pregnancies in view of her thyroid disease. Although Graves' disease may relapse or she may be required to take levothyroxine following ablative therapy, there is no evidence that further pregnancies are contraindicated.

In conclusion, counselling for a woman previously treated for Graves' disease or currently receiving treatment who wishes to become pregnant or who is already at any stage of gestation is highly desirable and should be mandated. The major topics to be discussed with her are therapy before and during pregnancy, possible effects on fetus and neonate and breast-feeding. It is imperative that adequate monitoring and follow-up be implemented following delivery.

### Disclosure Statement

The author has no conflicts of interest to disclose.

### References

- Lazarus JH: Thyroid function in pregnancy. *Br Med Bull* 2011;97:137–148.
- Zuppa AA, Perrone S, Sindico P, Alighieri G, Antichi E, Carducci C, Romagnoli C: Fetal and neonatal outcomes in infants of mothers with TSH receptor antibody positivity in pregnancy. *Pediatr Med Chir* 2009;31:72–77.
- Tamaki H, Itoh E, Kaneda T, Asahi K, Mitsuda N, Tanizawa O, Amino N: Crucial role of serum human chorionic gonadotropin for the aggravation of thyrotoxicosis in early pregnancy in Graves' disease. *Thyroid* 1993;3:189–193.
- Kung AW, Jones BM: A change from stimulatory to blocking antibody activity in Graves' disease during pregnancy. *J Clin Endocrinol Metab* 1998;83:514–518.
- Amino N, Izumi Y, Hidaka Y, Takeoka K, Nakata Y, Tatsumi KI, Nagata A, Takano T: No increase of blocking type anti-thyrotropin receptor antibodies during pregnancy in patients with Graves' disease. *J Clin Endocrinol Metab* 2003;88:5871–5874.
- Krassas GE, Poppe K, Glinoeir D: Thyroid function and human reproductive health. *Endocr Rev* 2010;31:702–755.
- Laurberg P, Bournaud C, Karmisholt J, Orgiazzi J: Management of Graves' hyperthyroidism in pregnancy: focus on both maternal and foetal thyroid function, and caution against surgical thyroidectomy in pregnancy. *Eur J Endocrinol* 2009;160:1–8.
- Mestman JH: Hyperthyroidism in pregnancy. *Best Pract Res Clin Endocrinol Metab* 2004;18:267–288.
- Casey BM, Leveno KJ: Thyroid disease in pregnancy. *Obstet Gynecol* 2006;108:1283–1292.
- Andersson M, de Benoist B, Delange F, Zupan J: Prevention and control of iodine deficiency in pregnant and lactating women and in children less than 2 years old: conclusions and recommendations of the technical consultation. *Public Health Nutr* 2007;10:1606–1611.
- Vanderpump MPJ, Lazarus JH, Smyth PP, Laurberg P, Holder RL, Boelaert K, Franklyn JA: Iodine status of UK schoolgirls: a cross-sectional survey. *Lancet* 2011;377:2007–2012.

- 12 Bahn RS, Burch HS, Cooper DS, Garber JR, Greenlee CM, Klein IL, Laurberg P, McDougall IR, Rivkees SA, Ross D, Sosa JA, Stan MN: The role of propylthiouracil in the management of Graves' disease in adults: report of a meeting jointly sponsored by the American Thyroid Association and the Food and Drug Administration. *Thyroid* 2009;19: 673–674.
- 13 Stagnaro-Green A, Abalovich M, Alexander E, Azizi F, Mestman J, Negro R, Nixon A, Pearce EN, Soldin OP, Sullivan S, Wiersinga W: American Thyroid Association Taskforce on Thyroid Disease during Pregnancy and Postpartum: Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. *Thyroid* 2011;21: 1081–1125.
- 14 Marx H, Amin P, Lazarus JH: Pregnancy plus: hyperthyroidism and pregnancy. *Br Med J* 2008;336:663–667.
- 15 McClain MR, Lambert-Messerlian G, Had-  
dow JE, Palomaki GE, Canick JA, Cleary-  
Goldman J, Malone FD, Porter TF, Nyberg  
DA, Bernstein P, D'Alton ME, FaSTER Re-  
search Consortium: Sequential first- and  
second-trimester TSH, free thyroxine, and  
thyroid antibody measurements in women  
with known hypothyroidism: a FaSTER trial  
study. *Am J Obstet Gynecol* 2008;199:129.e1.
- 16 Laurberg P, Wallin G, Tallstedt L, Abraham-  
Nordling M, Lundell G, Tørring O: TSH-re-  
ceptor autoimmunity in Graves' disease after  
therapy with anti-thyroid drugs, surgery, or  
radioiodine: a 5-year prospective random-  
ized study. *Eur J Endocrinol* 2008;158:69–75.
- 17 Tagami T, Hagiwara H, Kimura T, Usui T,  
Shimatsu A, Naruse M: The incidence of ges-  
tational hyperthyroidism and postpartum  
thyroiditis in treated patients with Graves'  
disease. *Thyroid* 2007;17:767–772.
- 18 Okamura K, Hagio N, Bandai S, Fujikawa M,  
Sato K, Iida M: The influence of pregnancy  
on the clinical course of Graves' disease with  
special reference to the change in TSH recep-  
tor antibody and the long-term prognosis.  
International Thyroid Congress, Paris 2010,  
abstr. 0270.
- 19 Azizi F, Amouzegar A: Management of hy-  
perthyroidism during pregnancy and lacta-  
tion. *Eur J Endocrinol* 2011;164:871–876.
- 20 Muller AF, Drexhage HA, Berghout A: Post-  
partum thyroiditis and autoimmune thy-  
roiditis in women of childbearing age: recent  
insights and consequences for antenatal and  
postnatal care. *Endocr Rev* 2001;22:605–  
630.
- 21 Karras S, Tzotzas T, Kaltsas T, Krassas GE:  
Pharmacological treatment of hyperthy-  
roidism during lactation: review of the liter-  
ature and novel data. *Pediatr Endocrinol Rev*  
2010;8:25–33.
- 22 Ishikawa N: The relationship between neo-  
natal developmental dysplasia of the hip and  
maternal hyperthyroidism. *J Pediatr Orthop*  
2008;28:432–434.
- 23 Amino N, Kubota S: Thyroid disease after  
pregnancy: postpartum thyroiditis; in Wass  
JA, Stewart PM (eds): *Oxford Textbook of  
Endocrinology and Diabetes*, ed 2. Oxford,  
Oxford University Press, 2011, pp 552–557.
- 24 Rotondi M, Cappelli C, Pirali B, Pirola I,  
Magri F, Fonte R, Castellano M, Rosei EA,  
Chiovato L: The effect of pregnancy on sub-  
sequent relapse from Graves' disease after a  
successful course of antithyroid drug thera-  
py. *J Clin Endocrinol Metab* 2008;93:3985–  
3988.