Abnormal stimulation of the thyrotrophin receptor during gestation

Patrice Rodien1,2,5, Nicola Jordan2, Anne Lefèvre2, Julien Royer2, Claudine Vasseur1,3, Frédérique Savagner2,4, Aline Bourdelot1,4 and Vincent Rohmer1,2,4

1Service d’Endocrinologie, 2INSERM EMI U0018, 3Service de Gynécologie Obstétrique, Centre Hospitalier Universitaire d’Angers and 4Université d’Angers, Angers, France

5To whom correspondence should be addressed at Service d’Endocrinologie Centre Hospitalier Universitaire d’Angers, 4 rue Larrey, 49033 Angers cedex 01, France. E-mail: PaRodien@chu-angers.fr

Pregnancy induces physiological alterations in thyroid function which may make difficult the interpretation of results of thyroid hormone measurement. A state of hyperstimulation of the thyroid gland is common in early pregnancy. In a few cases, thyroid hormone values will deviate from the normal range, which corresponds to the gestational transient thyrotoxicosis. This syndrome is closely associated with hyperemesis gravidarum. The relationship between the two syndromes, demonstrated by epidemiological studies, has been illustrated by an exceptional case of familial recurrent gestational thyrotoxicosis presenting as hyperemesis gravidarum due to hypersensitivity of the thyrotrophin receptor to hCG. However, the exact mechanisms of hyperemesis gravidarum have not yet been identified. Gestational transient thyrotoxicosis has to be distinguished from Graves’ disease, because the latter is associated with potential maternal and fetal complications when thyrotoxicosis is not controlled, whereas the former has usually a favourable outcome. The existence of other cases of thyroid hypersensitivity or hCG endowed with abnormal thyrotrophic activity is suspected. They may be identified only by assessment of the thyroid function in cases of hyperemesis gravidarum. The identification of these cases would be helpful to understand the mechanisms of specificity of glycoprotein hormone receptors.

Key words: hyperemesis gravidarum/pregnancy/thyrotoxicosis/thyrotrophin receptor

Introduction

Thyroid function is known to be altered during normal pregnancy through several mechanisms (Glinoer, 1997). An increase in iodine clearance leads to hyperstimulation of the gland to compensate for a relative iodine deficiency. An increase in the thyroxine-binding globulin (TBG), induced by estrogens, leads to a temporary and moderate decrease in free thyroxine concentration, which, by negative feedback on the pituitary, provokes an increase in thyroid stimulating hormone (TSH) secretion and hyperstimulation of the thyroid. The variation in concentration of albumin may also disturb equilibrium between free and protein-bound thyroxine.

Furthermore, the appearance and increase of hCG is responsible for thyroid stimulation.

From thyroid hyperstimulation to thyrotoxicosis

The normal evolution of thyroid function during pregnancy

The long-standing knowledge of hCG thyrotrophic activity in vitro (Carayon et al., 1980; Hershman et al., 1988; Tomer et al., 1992) is illustrated in vivo in cases of hypersecretion of hCG such as molar pregnancy (Hershman and Higgins, 1971; Kenimer et al., 1975; Hershman, 1992; Yoshimura et al., 1994b), or multiple pregnancy (Grun et al., 1997). It has also been demonstrated in normal singleton pregnancies by longitudinal studies in large cohorts of pregnant women, conducted by Glinoer et al. (1990). The data collected in this work lead to the description of normal thyroid hormone kinetics, changes in thyroid volume during pregnancy and changes observed in cases of pre-existing thyroid disease (Glinoer et al., 1991).

TSH and hCG follow opposite variation, with ‘mirror curves’ (Figure 1). The thyroid volume increases during pregnancy, especially in countries where iodine supplies are insufficient, and declines after delivery, but does not return to the pre-gestational state in all women. Thus, goitre may persist after several pregnancies (Glinoer et al., 1992). Autoimmune diseases of the thyroid improve during gestation but are usually exacerbated post-partum. Occurrence of post-partum thyroiditis can, up to a certain point, be predicted by the presence of thyroid antibodies before, or during early pregnancy (Glinoer et al., 1991).
Although the variations of thyroid function during gestation have been nicely studied by Glinoer et al., reference values for thyroid hormones according to age of pregnancy are still frequently unavailable. As a consequence, diagnosis of true hyperthyroidism is frequently based on multiple sequential measurements of TSH and thyroxine to distinguish it from moderate transient self-resuming hyperthyroxinaemia with decreased TSH related to the peak of hCG secretion. In addition, free thyroid hormone assays may be disturbed by changes that occur during pregnancy, such as an increase in binding proteins, haemodilution, increased free fatty acid concentration and a decrease in albumin concentration (Ekins, 1993; Stockigt, 2001). Reference ranges should therefore be established for these assays according to age of pregnancy as proposed in several studies (Ball et al., 1989; Panesar et al., 2001; Price et al., 2001). According to Glinoer (1997), close to 20% of pregnant women will have a suppressed TSH, 2% will have a suppressed TSH with increased thyroxine concentration, and in 1% of pregnant women, suppressed TSH and hyperthyroxinaemia will be associated with clinical hyperthyroidism. Only a few of these cases will require antithyroid treatment, usually for a limited period. This frequency of hyperthyroidism, whether subclinical or overt, is higher than the frequency (0.1–0.2%) found in other series (Mestman, 1998). However, it should be remembered that few studies have followed prospectively a large cohort of pregnant women, and that many studies were mainly addressing the question of Graves’ disease during pregnancy, or considered hyperthyroidism only when clinical signs were present. Furthermore, depending on the age of pregnancy when a unique sampling is performed in transversal studies, peak of hCG and nadir of TSH may be missed, and consequently frequency of suppressed TSH and/or elevated thyroxine may be underestimated. In a more recent prospective study, the frequency of transient gestational hyperthyroidism (suppressed TSH and elevated free thyroxine) reached 11% for Asian women (Yeo et al., 2001). In contrast, in another large study, using dried blood spots, a lower frequency of 0.285% was found, also in an Asian population (Tanaka et al., 1998).

Differences in assays and methodology, in the time of sampling, as well as population characteristics may be responsible for these discrepancies, although the totally different values are puzzling.

**The thyrotrophin receptor (TSHR)**

Although the thyrotrophin receptor coding sequence was cloned in 1989 (Parmentier et al., 1989), the precise structure of the receptor is still hypothetical. Our current understanding is based on models derived from crystallized receptors belonging to the same family, crystallised homologous proteins, or derived from directed engineered mutagenesis experiments and natural mutations found in human diseases (Szkudlinski et al., 2002). TSHR is the obligatory path of thyroid regulation by TSH (Vassart and Dumont, 1992). It transduces the positive signal for hormone synthesis, thyroid differentiation and thyroid proliferation. TSHR is a member of the seven transmembrane domain G protein-coupled receptor family. It signals through the cyclic AMP and inositol phosphate pathways. Together with FSH and LH/hCG receptors, it defines a subgroup. Like other G protein-coupled receptors, the receptors for glycoprotein hormones (TSH, LH/hCG, FSH) consist of a serpentine (transmembrane) domain, but in contrast to other receptors (i.e. adrenergic receptors, or rhodopsin), they harbour a large extracellular domain (Parmentier et al., 1989). This extracellular domain is known to be the hormone binding site, whilst the serpine domain is deemed to be responsible for transduction of the signal and coupling to the G protein (Nagayama et al., 1991).

The three glycoprotein hormone receptors display strong homology, and are thought to be derived from a common ancestor gene (Moyle et al., 1994), as are the ligands themselves (Grossmann et al., 1997). The strongest homologies are found in the serpine domain, whilst the extracellular domains are more distantly related, in keeping with the specific hormone binding site being located in this part of the receptor. Because of the proximity between the ligands and between the receptors, cross-activation is possible in vitro at high concentrations of these hormones (Grossmann et al., 1997). However, the concentration required for one hormone to activate illegitimately one related receptor is so high that it is not reached under normal conditions in vivo. This is true except during gestation where the hCG concentration around weeks 10–12 reaches a level whereby it can activate the TSHR. This explains the moderate transient increase in thyroxine concentration and subsequent decrease of TSH (Harada et al., 1979; Glinoer, 1997). Twin pregnancies, molar pregnancies and spontaneous unexplained hypersecretion of hCG lead to amplification of a normal phenomenon with a stronger, sometimes prolonged, thyroid stimulation. The TSHR is the regular target of TSH, a marginal target that poorly accommodates hCG, and the central victim target of TSHR antibodies present in Graves’ disease.

**Graves’ disease during pregnancy**

Graves’ disease is a paradigm of abnormal hyperstimulation of TSHR, and subsequently of thyroid cell function and proliferation. Hyperthyroidism is due to the presence of autoantibodies directed to TSHR that are able to stimulate it. The goitre is a consequence of this hyperstimulation, as well as hyperthyroidism (Weetman, 2000). Management of Graves’ disease during pregnancy is
hyperthyroidism during post-partum (Amino et al., 1982; Tamaki et al., 1993), the possible difficulty of obtaining and maintaining euthyroidism, and the usual relapse of hyperthyroidism during post-partum (Amino et al., 1982; Weetman, 2000). Uncontrolled hyperthyroidism during pregnancy is associated with severe maternal and fetal complications (Davis et al., 1989; Mestman, 1998).

 Adjustment of the treatment is necessary

Due to the transplacental crossing of antithyroid drugs, high doses are not recommended and thyroid surgery is sometimes necessary, when euthyroidism cannot be achieved with low doses of antithyroid drugs (Lazarus, 2002). High doses of antithyroid drugs may lead to fetal goitre and hypothyroidism. Although a teratogenic effect has never been unequivocally demonstrated, cases of aplasia cutis congenita and of complex fetal malformation have been reported in babies born to women treated for hyperthyroidism by methimazole during pregnancy (Mandel and Cooper, 2001).

During the first trimester of gestation, and beyond this period, the fetus is dependent, especially for development of the brain, on thyroid hormones transferred from the mother’s blood (Morreale de Escobar et al., 2000). Maternal hypothyroidism may thus be deleterious to the fetus. In particular, it may be associated with lower performance in IQ and psychometric tests in offspring (Kung and Jones, 1998), may lead to complex control of thyroid function of the fetus and the new born (Clavel et al., 1990; Orgiazzi, 2000).

Improvement of Graves’ disease is not obligatory

Usually, as with many other autoimmune diseases, Graves’ disease improves during pregnancy, allowing for discontinuation of antithyroid drugs. However, this optimistic description of the outcome of Graves’ disease during pregnancy does not consider the frequent worsening of hyperthyroidism during the first trimester, due in part to the thyroid-stimulating activity of hCG (Amino et al., 1982; Tamaki et al., 1993), the possible difficulty of obtaining and maintaining euthyroidism, and the usual relapse of hyperthyroidism during post-partum (Amino et al., 1982; Weetman, 2000). Uncontrolled hyperthyroidism during pregnancy is associated with severe maternal and fetal complications (Davis et al., 1989; Mestman, 1998).

Which guidelines?

For all these reasons, pregnancy is usually inadvisable in patient with Graves’ disease until a state of stable euthyroidism has been achieved (Weetman, 2000; Lazarus, 2002). When pregnancy occurs in a patient affected by Graves’ disease, hormonal and immunological status should be assessed as soon as possible, to allow for a follow-up schedule to be organized. Since the risk of fetal hyperthyroidism is determined by the transplacental transfer of TSHR antibodies (Clavel et al., 1990; Peleg et al., 2002), a follow-up of TSHR antibody concentration is useful. The proposed guidelines (Laurberg et al., 1998), will probably have to be modified owing to the availability of more sensitive second generation assays for TSHR antibodies (Costagliola et al., 1999).

Assessment of the thyroid status of a fetus, when the mother is receiving treatment for active Graves’ disease, may be difficult since the presence of a goitre may be due either to TSHR antibodies or to antithyroid drugs, and cord blood sampling is sometimes necessary (Volumenije et al., 2000; Nachum et al., 2003), although such an invasive approach is controversial (Kilpatrick, 2003). Therefore, it is preferable to obtain a careful preconception evaluation of the thyroid status of a woman currently treated for or with a past history of Graves’ disease. A management strategy is then better defined by a multidisciplinary approach with contributions from endocrinologists, obstetricians trained in ultrasound assessment of fetal thyroid, and paediatricians.

One important and still debated issue is to determine if thyroid function should be assessed in every pregnant woman or better still in women planning to become pregnant (Lazarus, 2002; Poppe and Glinoer, 2003). The devastating effects of hyperthyroidism for the mother and the fetus when it remains unrecognized or uncontrolled constitute a further reason to discuss such a proposal.

Gestational transient hyperthyroidism

As mentioned previously, in a minority of normal pregnant women, the concentration of thyroxine will increase above the upper normal value, leading to suppression of TSH. This gestational transient thyrotoxicosis can be viewed as a spill-over of the normal thyroid hyperstimulation due to cross-stimulation of TSHR by hCG. Many of the symptoms present in these women, asthenia, exercise-associated dyspnea and tachycardia, are so common during early pregnancy that they are hardly regarded as abnormal. However, some features should arouse suspicion: nervousness, tremor, failure to gain weight, or even weight loss are frequent in such cases. Because vomiting is also frequently present, reduced food intake is usually proposed as an explanation for the absence of weight gain, and the most severe cases are usually associated with hyperemesis gravidarum, which can be further misleading. The frequency of unremarkable symptoms, although compatible with the diagnosis of hyperthyroidism, certainly contributes to variation in the prevalence of hyperthyroidism during pregnancy in different studies. Frequencies range from 2.4% (Glinoer et al., 1990) to 11% (Yeo et al., 2001). A much lower frequency is found in the study of Tanaka et al. (1998) may be due to sampling late in pregnancy, up to 14 weeks. This form of thyrotoxicosis is, by definition, transient, and it is a common observation that spontaneous normalization of early suppressed TSH occurs in <2–3 weeks (Yeo et al., 2001; and our unpublished data).

Distinction between gestational transient thyrotoxicosis and Graves’ disease is essential. Goitre is usually but not necessarily absent in the former and no past history of thyroid disease is reported by the patient or her family. Ophthalmic examination reveals no abnormality, in contrast to Graves’ disease. Hormonal measurements do not help to distinguish the two diseases, at first sampling. Antithyroid antibodies are usually absent in gestational transient thyrotoxicosis. In particular, TSHR antibodies are absent.

Gestational transient thyrotoxicosis is usually of short duration and spontaneously resolves with the decline of hCG (Goodwin et al., 1997).
et al., 1992a; Wilson et al., 1992; Yeo et al., 2001). In many cases, symptoms have vanished before the patient obtains a medical interview. Very rarely, severity of thyrotoxicosis will require specific treatment (Jeffcoate and Bain, 1985; Glinoer, 1997). Besides sedative drugs and beta-blocking drugs, antithyroid drugs can be necessary to lower the thyroid hormone concentration rapidly. However, a careful follow-up is mandatory, since the rapid spontaneous resolution of thyrotoxicosis with a decline in hCG concentration will be followed by hypothyroidism if antithyroid drugs are unduly maintained. Only in exceptional cases is treatment of thyrotoxicosis required beyond week 20–22 of gestation in gestational transient thyrotoxicosis. Furthermore, since severe thyrotoxicosis is frequently associated with hyperemesis and dehydration, hormonal tests should be rapidly verified after correction of water and electrolyte disturbances to avoid overestimation of thyroid hormones concentration. Outcome is usually favourable in gestational transient thyrotoxicosis, which further stresses the need for its distinction from Graves’ disease and the avoidance of unnecessary and potentially deleterious treatment.

Figure 2. Familial gestational thyrotoxicosis. Schematic diagram of the thyrotrophin receptor (TSHR) showing the location of the mutated residue K183R in the extracellular domain. Increased sensitivity to hCG of the mutant TSHR (K183R) when compared to the wild-type TSHR, as shown by the accumulation of the second messenger cAMP in response to increasing doses of hCG. Reproduced with permission from Rodien et al., 1998. ©1998 Massachusetts Medical Society. All rights reserved.

Trophoblastic thyrotoxicosis: an extreme gestational ‘transient’ thyrotoxicosis

Hydatidiform moles and choriocarcinomas secrete a large amount of hCG. They can present clinically as severe hyperemesis gravidarum. Clinical hyperthyroidism may also occur. Interestingly, the ‘classic’ presentation of hydatidiform mole as trophoblastic thyrotoxicosis (Hershman and Higgins, 1971; Kenimer et al., 1975; Hershman, 1992; Yoshimura et al., 1994b) has become extremely rare with early detection of molar pregnancies (Coukos et al., 1999), due to better access to ultrasound and hormonal tests.

An unusual case of hyperemesis gravidarum and gestational thyrotoxicosis caused by a mutation of the TSHR broadening its specificity

We had the opportunity to study a family in which at least two women experienced hyperthyroidism, presenting as hyperemesis gravidarum, during several pregnancies (Rodien et al., 1998). The mother had been given a diagnosis of Graves’ disease during her...
third gestation. Her two previous pregnancies, complicated by hyperemesis, had terminated in miscarriage. During the third gestation tremor, tachycardia and nervousness associated with hyperemesis led to thyroid function tests which revealed hyperthyroidism. The patient was treated with antithyroid drugs throughout pregnancy, hyperemesis resolved, and she delivered a healthy female baby. Surprisingly enough, the ‘Graves’ disease’ improved in the post-partum period allowing for discontinuation of antithyroid drugs. The following pregnancy was also complicated by hyperemesis and hyperthyroidism, which required treatment with antithyroid drugs, and was followed by recovery of a normal thyroid function post-partum, without any relapse later. The daughter had a similar story: hyperemesis early in pregnancy, two miscarriages, hyperthyroidism lasting throughout the two following pregnancies, and a normal thyroid function between pregnancies. She had a small diffuse goitre, no Graves’ ophthalmopathy, no thyroid peroxidase or thyroglobulin antibodies, and no TSHR antibodies. The absence of antibodies, occurrence of hyperthyroidism only during gestation and improvement in the post-partum period suggested that Graves’ disease was unlikely. hCG concentration was within the normal range during gestation. Abnormal hCG, with increased thyrotrophic activity, was hypothesized but ruled out by in vitro tests.

A heterozygous mutation of the TSHR gene was identified in the mother and the daughter. The mutation resulted in exchange of lysine for arginine at position 183. This residue is located in the extracellular domain of the receptor, in a region thought to be in contact with the ligand according to three-dimensional models (Kajava et al., 1995) (Figure 2a). An alteration of the interaction with the bona fide ligand and related hormones could thus be expected. When expressed in vitro in eukaryotic cells, and compared to the wild-type TSHR, the mutant TSHR showed increased sensitivity to hCG (Figure 2b). Although hypersensitivity to hCG had been demonstrated, its molecular basis was still poorly understood. Recently, a series of mutations of residue 183 has been produced, and the mutated receptors tested for sensitivity to hCG. Any mutation of residue 183 was able to increase sensitivity to hCG in vitro, provided the mutated receptor was expressed at the cell surface (Smits et al., 2002). Computerized models predicted an interaction between the lysine 183 and a glutamate located in proximity in the three-dimensional structure of the extracellular domain. It appeared that the mutation of lysine 183 disrupted the interaction with glutamate 157, allowing the negatively charged glutamate to interact with the positive charges of hCG. Further extensive mutagenesis has identified a series of charged residues in the extracellular domain of TSHR which are involved in the ligand specificity (Smits et al., 2003a).

Hyperemesis gravidarum and gestational hyperthyroidism: a single disease?

Morning sickness is a common feature of early pregnancy, regarded as an undesirable but normal effect of gestation, which usually requires no treatment except for anti-emetic drugs. Due to its frequency and self-limitation, the putative mechanisms are given little attention. The role of estrogens has been proposed but is debated (Depue et al., 1987; Lagnou et al., 2003).

In some women, vomiting may be so frequent that it can no longer be named morning sickness, since no food intake is possible, with subsequent weight loss, dehydration, and sometimes life-threatening electrolytic disturbances. This defines hyperemesis gravidarum.

Frequency ranges from 0.15 to 1% of pregnancies. Variation in frequency is dependent on definition (Bashiri et al., 1995; Tsang et al., 1996; Nelson-Piercy et al., 2001); some authors define hyperemesis gravidarum as severe vomiting requiring hospitalization (Wilson et al., 1992; Tsang et al., 1996) which leads to a higher frequency (up to 1.5%), whereas others apply a more stringent definition which includes hydroelectrolytic disorders, ketosis, and weight loss >5% of non-pregnant weight (Goodwin et al., 1992a).

Treatment usually requires admission to hospital, sometimes in an intensive care unit, for rehydration, anti-emetic and sedative drugs; corticosteroids seem to improve outcome (Nelson-Piercy et al., 2001). In most cases this supportive treatment is effective, the syndrome resolves, and pregnancy then continues.

The mechanisms of hyperemesis gravidarum are poorly understood. The syndrome is favoured by hypersecretion of hCG (Jeffcoate and Bain, 1985; Goodwin et al., 1992b), although normal concentrations of hCG have also been reported (Depue et al., 1987). However, if hCG levels are higher in a group of women with hyperemesis gravidarum, there is no clear threshold, since the normal range of hCG concentration is extremely large. Some pregnant women with extremely high hCG concentrations will not experience any hyperemesis whereas some with normal hCG will. For the same reason, no excessive estrogen concentration has been demonstrated in hyperemesis gravidarum, although estrogen in high doses is known to provoke vomiting and higher estrogen concentrations have been found in women with hyperemesis gravidarum (Depue et al., 1987; Goodwin et al., 1992b).

Hyperemesis gravidarum is frequently associated with both clinical and biological hyperthyroidism (Bouillon et al., 1982; Swaminathan et al., 1989; Goodwin et al., 1992a). Thyroxine levels have been correlated with severity of hyperemesis gravidarum (Goodwin et al., 1992b), and with hCG concentrations. The exact role of hyperthyroidism in hyperemesis gravidarum is, however, obscure. Whether it can participate in the triggering of vomiting or be a parallel consequence of hypersecretion of hCG is not known. However, suppressed TSH was found in 70%, at most, of patients with hyperemesis gravidarum (Goodwin et al., 1992a), whereas in other studies, thyroid parameters were not significantly different between patients with hyperemesis gravidarum and control pregnant women (Wilson et al., 1992). hCG concentration was also comparable between patients and controls in several studies (Depue et al., 1987; Swaminathan et al., 1989; Wilson et al., 1992). Separate effects of a common cause, excessive hCG secretion, have been discussed as mechanisms of gestational thyrotoxicosis and hyperemesis gravidarum, with thyroid hyperstimulation and ovarian hyperstimulation (with subsequent hyperestrogenia) respectively (Goodwin et al., 1992b). Absence of hyperthyroidism, of hyperemesis gravidarum, or dissociation between the two syndromes in many patients with very high levels of hCG suggest that different predisposing factors contribute to them.

The case we reported would suggest a direct relationship between hyperthyroidism and hyperemesis gravidarum, since
P. Rodien et al.

treatment of thyrotoxicosis led to disappearance of vomiting. On the other hand, vomiting is not a common manifestation of thyrotoxicosis in the non-pregnant patient although this has been reported (Rosenthal et al., 1976), nor of Graves’ disease during pregnancy. In addition, in the study of Goodwin et al. (1992b), some patients still had vomiting after correction of hyperthyroidism, and even hypothyroid patients can be hyperemetic.

Noteworthy, not all patients with gestational thyrotoxicosis will have hyperemesis gravidarum, which does not suggest a causal role of hyperthyroxinaemia. Recently, a study of metabolism in hyperemesis gravidarum, has shown a decrease in basal metabolic rate, which is not the expected profile in thyrotoxicosis, making a direct causal role of thyrotoxicosis unlikely. However, correction of hydroelectrolytic disorders induced an increase in basal metabolic rate, favoured by the thyrotoxic state (Chihara et al., 2003). It has been debated whether hyperemesis gravidarum is associated with a favourable outcome or with complications for the fetus (Depue et al., 1987; Nelson-Piercy et al., 2001). It seems that besides lower birthweight in some studies, there was no increase in premature labour or malformation (Bashiri et al., 1995; Tsang et al., 1996). A protective effect of hyperemesis gravidarum for some malformation has been reported without clear explanation (Boneva et al., 1999; Czeizel et al., 2003). This contrasts with the complications reported with thyrotoxicosis during pregnancy (Mestman, 1998), although the thyrotoxicosis in the case of hyperemesis gravidarum may not last long enough to induce these complications.

One puzzling feature of hyperemesis gravidarum is its variable frequency in different ethnic groups (Jordan et al., 1995), occurring at a much higher frequency in the Asian population than in the Caucasian population (Vangen et al., 1999). Cases of recurrent hyperemesis gravidarum with recurrent thyrotoxicosis have been reported (Jeffcoate and Bain, 1985; Nader and Mastrobattista, 1996; Jordan et al., 1999), and gestational thyrotoxicosis occurs with the highest frequency in populations where hyperemesis gravidarum is also reported with high frequency (Price et al., 1996; Vangen et al., 1999; Yeo et al., 2001). When patients with hyperemesis gravidarum are excluded from the population studied, there is no difference in thyroid function between Asian and European pregnant women (Price et al., 2001). This suggests, at least, a common predisposing genetic background, if not a unique disease. Most severe cases of hyperemesis gravidarum are associated with the most severe thyrotoxicosis, again suggesting a common background or common mechanisms, which may just be attributed to the role of hCG, since the most severe cases usually are associated with the highest hCG levels (Goodwin et al., 1992b).

The ambiguous role of hCG

A high hCG level in women affected with hyperemesis gravidarum and gestational transient thyrotoxicosis (Jeffcoate and Bain, 1985; Goodwin et al., 1992b) is not an obligatory finding (Depue et al., 1987; Kennedy et al., 1992a; Kimura et al., 1993). Failure to observe this higher hCG concentration may be due to the study design, when transversal or case-control studies are performed, because blood sampling may have been performed too late in some cases. Contradictory results of studies which aimed at correlating the concentration of hCG with the severity of hyperemesis gravidarum or gestational thyrotoxicosis may also be due in part to differences in the ability of the hCG assays to measure all the isoforms of hCG, including nicked hCG, or to detect only intact forms (Cole et al., 1993b). Furthermore, as pregnancy progresses, the proportion of altered or nicked hCG varies (Cole et al., 1993a). The role of abnormal forms of hCG is more controversial. A high thyrotrophic activity in the serum of patients with gestational thyrotoxicosis has been found by several groups (Kennedy et al., 1992a,b; Kimura et al., 1993). However, some authors did not agree with the involvement of hCG in this thyrotoxic activity (Kennedy et al., 1992a). Furthermore, when trying to identify the isoforms of hCG endowed with the thyrotrophic activity, several groups have obtained contradictory results. Increased desialylated (basic) forms of hCG have been demonstrated by Tsuruta et al. (1995) in gestational thyrotoxicosis, whereas Jordan et al. (1999) have demonstrated an increase in acidic forms of hCG in hyperemesis gravidarum. Unusual glycosylation patterns of hCG are common in hydatidiform moles which frequently present as hyperemesis gravidarum (Yoshimura et al., 1994b; Yamazaki et al., 1995). In a more recent study, Talbot et al. did not find any specific profile of hCG isoforms in gestational thyrotoxicosis, but found a correlation between more acidic fractions and thyroid hormones (Talbot et al., 2001) as did Jordan et al., in contrast with the results of Tsuruta et al., showing a correlation between basic forms and thyroid hormones. The in vitro thyrotoxic activity of the different forms of hCG has also been tested. The hCG of hydatidiform moles is endowed with a higher thyrotrophic activity in vitro (Hershman, 1992; Pekary et al., 1993); it was found that basic forms, such as asialo-hCG, were more potent thyroid stimulators than acidic forms (Yoshimura et al., 1994b). Interestingly, the thyrotrophic activity of basic forms of hCG was also demonstrated in normal pregnant women (Ballabio et al., 1991). Yamazaki et al. (1995) demonstrated an increase in thyrotrophic activity of deglycosylated hCG. Again, contradictory results were obtained by several groups, when studying the thyrotoxic activity of hCG. Hoermann et al. (1994) described an antagonistic effect of asialo-hCG on TSHR. However, it appears now, with the use of recombinant human TSHR, that hCG is able to stimulate TSHR (Tomer et al., 1992; Yoshimura et al., 1993), and that many discrepancies were due to the use of different assays, and sometimes to variable sensitivity of thyroid cells from different species (Amir et al., 1985; Hershman et al., 1988; Hoermann et al., 1991; Hoermann et al., 1995). Nicked hCG appears to be a more potent stimulator for TSHR (Yoshimura et al., 1994a). These differences in in vitro activity may not translate easily in increased or decreased activity in vivo, since clearance rates are also different between the different isoforms. More basic forms have a shorter half-life than acidic forms (Hoermann et al., 1993). Increased acidic fractions may thus compensate for a decreased in vitro activity by a prolonged half-life in vivo, whereas basic forms with increased activity may explain some cases of gestational thyrotoxicosis despite hCG concentrations in the normal range. In addition, there is a change, around week 13 of gestation, in the isoforms of hCG, with an increase in more basic forms which should lead to modification in both the half-life of the hormone and its bioactivity (Wide et al., 1994). When looking for a correlation between isoforms of hCG and estrogen concentrations, Jordan et al. (1999) found a better correlation between basic forms and estrogens, in contrast to the correlation between acidic forms and thyroid hormones, and between acidic forms and...
Hypersensitivity of the TSHR to hCG can be produced by various pregnancy mechanisms. A call for a careful evaluation of thyroid function during gestation is obvious, in this study, a difference in hCG concentration between patients with hyperemesis gravidarum and controls was apparent. Interestingly, in this study, a difference in hCG concentration between patients with hyperemesis gravidarum and controls was obvious only in patients of Samoan origin and not in patients of European origin (Jordan et al., 1999). It is thus difficult to draw out a clear picture of the mechanisms of increased action of hCG in hyperemesis gravidarum and in gestational thyrotoxicosis. Whatever the exact mechanism of increased thyrotrophic activity of hCG, it is fascinating to consider the fact that evolution has selected a hormone with potentially dangerous effects. In animal species, chorionic gonadotrophin is present only in primates and equids (Grossmann et al., 1997). The ease with which stimulation of TSHR by hCG at high concentration can occur would suggest that during evolution, the minimal barrier has been selected to prevent such a cross-stimulation. To what purpose was the appearance and maintenance of such a dangerous hormone due?

**Extension of the concept of illegitimate stimulation**

A call for a careful evaluation of thyroid function during pregnancy

Hypersensitivity of the TSHR to hCG can be produced by various mutations (Smits et al., 2003a), which is in contrast with the unique case we described previously. It may be explained in two ways. First, severity of hyperthyroidism may be incompatible with a normal outcome of pregnancy, and miscarriage may occur early enough to prevent any diagnosis of hyperthyroidism. Second, it is possible that moderate forms of gestational hyperthyroidism are overlooked when masquerading as hyperemesis gravidarum, or because clinical symptoms of hyperthyroidism—dyspnea, palpitations, nervousness—are non-specific, and do improve when hCG declines.

The fragility of specificity of the TSHR makes it unlikely that the family described previously is unique, unless the phenotype is too severe to allow for a normal pregnancy. However, mutations of the TSHR have been sought unsuccessfully by other groups in cases of gestational thyrotoxicosis (Yeo et al., 2001). It should be stressed that in these cases, gestational thyrotoxicosis was transient, in contrast to the first case.

The association of hyperthyroidism with hyperemesis gravidarum is known and this is usually looked for in severe forms associated with clinical signs of thyrotoxicosis. However, simultaneous measurement of hCG is rarely performed. Diagnosis is then hyperemesis gravidarum, as some authors have suggested, with moderate hyperthyroidism, treated by rest, correction of electrolytic disorders, anti-emetic drugs, and sometimes corticosteroids (Nelson-Piery et al., 2001). In contrast to several authors (American College of Obstetrics and Gynecology, 2002; Tan et al., 2002), we would propose a systematic measurement of thyroid hormones and TSH as an evaluation of patients affected by hyperemesis gravidarum, with simultaneous measurement of hCG, for the following reasons:

(i) Gestational hyperthyroidism due to thyroid hypersensitivity to hCG can be suspected only by demonstration of hyperthyroidism, in the absence of thyroid autoimmunity, simultaneous with a normal concentration of hCG. As shown in Figure 3, it may be expected that pregnant women would be separated into three groups according to free thyroxine and hCG values: normal women, women with excessive hCG secretion, women with abnormal hCG or with thyroid hypersensitivity. Indeed, a careful review of published studies suggests that some patients either have a thyroid gland hypersensitive to hCG, or secrete hCG endowed with a higher thyrotrophic activity (Goodwin et al., 1992b; Kimura et al., 1993; Tsuruta et al., 1995). Glycosylation differences may be the cause, but mutations of α or β subunit of hCG may also be involved.

Whether such a diagnosis would change the management of the patient is not known, but it is expected that identification of such patients with a hypersensitive thyroid would help in understanding the molecular basis of specificity and mechanisms of activation of the glycoprotein hormone receptors.

(ii) Careful examination of hormonal values in patients with hyperemesis gravidarum may reveal intriguing and unexplained features. Excessive secretion of hCG is a hallmark of molar pregnancy and choriocarcinoma. However, there are some cases of excessive secretion in the absence of trophoblastic disease. Some cases have been named hyperplacentosis, due to the development of a large placenta, and could thus be assimilated to twin pregnancies for this trait (Ginsberg et al., 2001). As shown in Figure 4, other cases in which extremely high levels of hCG can be observed, leading to hyperemesis gravidarum and hyperthyroidism, do not have any satisfying explanation. The patient was referred for premature labour. She had experienced hyperemesis gravidarum lasting beyond week 20. A retrospective analysis of frozen blood samples, drawn during the preceding weeks.
allowed us to demonstrate gestational hyperthyroidism associated with extremely high hCG concentration. Thyroid function recovered after delivery. No anomaly was found in the placenta. These cases point to our limited knowledge of determinants of placental function.

(iii) Many physicians have been facing cases of recurrent hyperemesis gravidarum or gestational thyrotoxicosis, associated or not with a high hCG concentration. In some cases, a familial history of hyperemesis gravidarum is also reported (Jordan et al., 1999; Yeo et al., 2001). Careful investigation of these familial cases, as well as ethnic groups or genetic isolates with a high frequency of hyperemesis gravidarum or gestational thyrotoxicosis, should help to unveil the mechanisms of excessive hCG secretion, synthesis of an abnormal hCG or hypersensitivity to hCG. It should nevertheless be mentioned that the report of a higher frequency of gestational thyrotoxicosis in Asian women was based initially on a clinical impression (Kennedy et al., 1992b), and that different studies gave discrepant results (Kennedy et al., 1992b; Price et al., 1996; Tanaka et al., 1998; Yeo et al., 2001). For example, Goodwin et al. did not find an over-representation of Asian women in the group of patients affected by hyperemesis gravidarum. The majority of the group was constituted by hispanic patients. Some apparent differences in frequency of hyperemesis gravidarum among different ethnic groups may just reflect a bias in the population attending an institution. Some ethnic groups are loosely defined, and, as pointed out by Yeo et al.,

![Figure 4](https://academic.oup.com/humupd/article-abstract/10/2/95/617155/102)

Figure 4. (A) A case of prolonged gestational thyrotoxicosis due to a long-lasting hypersecretion of hCG, presenting initially as hyperemesis gravidarum during a fourth pregnancy. Normalization of the thyroid function had not been verified after hyperemesis had resolved. Premature labour occurred at 30 weeks. A female baby was delivered, affected by hyaline membrane disease with favourable outcome. No trophoblastic disease was found. The mother recovered rapidly from hyperthyroidism after delivery. Repeated measurement of hCG in the mother and the baby several weeks later confirmed the absence of any evolving trophoblastic disease. Normal range for free T4 is indicated. (B) Time-course of secretion of hCG in the patient and mean values in normal pregnant women according to Glinoer et al., 1990.
‘Asian women’ refers to Pakistani, Chinese, Malaysian and Japanese patients in different studies.

(iv) Activating mutations of TSHR have been found in toxic adenoma of the thyroid (Parma et al., 1997), as well as in familial cases of non-autoimmune hyperthyroidism (Duprez et al., 1994). These mutations, somatic in the first case, germinal in the latter, result in an activated TSHR in the absence of TSH, which leads to autonomy of the adenoma, or of the whole gland. It is not known whether these mutations, which usually do not affect the response to TSH, could increase the sensitivity of TSHR to hCG in the same manner as the mutation of lysine 183. In such cases, subclinical thyrotoxicosis may be exacerbated during gestation, with return to borderline hormonal values after delivery.

(v) Several cases of corticotrophin-independent Cushing’s syndrome have been reported due to abnormal sensitivity of adrenal cortex to a ligand that usually does not stimulate it (Lacroix et al., 2001). This has been shown to be due to ectopic adrenal expression of receptor normally absent from the adrenal gland. For example, food-dependent Cushing’s syndrome is due to ectopic adrenal expression of the receptor for gastric inhibitory polypeptide (GIP), a polypeptide secreted after food absorption. Similarly, a case of gestational Cushing’s syndrome has been explained by the abnormal response of adrenal cortex to hCG and LH.

By analogy, it may be postulated that some cases of gestational hyperthyroidism with normal hCG levels could be due to ectopic expression of LH/hCG receptor in the thyroid and, as a consequence, illegitimate response of the thyroid gland to hCG.

Finally, gestation, because of the extreme hormonal fluctuations, represents a challenge for specificity of hormone receptors. Mechanisms that operate at much lower hormone concentration to avoid cross-stimulation can be overwhelmed, and pregnancy provides a fascinating model of adaptation and relative resistance to overdose of hormones. Cases of illegitimate stimulation of endocrine glands are certainly more frequent than previously thought—they just need to be identified properly. Identification of such cases could improve our knowledge of other receptors similar to the way in which it has shed light on the molecular basis of specificity of TSHR and related receptors (Smits et al., 2003a; Vasseur et al., 2003).

Acknowledgements
This work has been supported by the INSERM: Programme AVENIR 2001 (P.R.) and poste vert (N.J.).

References


