Hyperemesis gravidarum, a literature review

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Hyperemesis gravidarum (HG) is a condition causing severe nausea and vomiting in early pregnancy often resulting in hospital admission. The incidence of HG is approximately 0.5% of live births, said to be higher in multiple pregnancies, hydatidiform mole and other conditions associated with increased pregnancy hormone levels. Both the aetiology and pathogenesis of HG remain unknown. We conducted a literature review (1966-now) to summarize the current evidence on the aetiology and pathogenesis of HG. The potential role of pregnancy-related hormones such as progesterone, estrogen and HCG has been widely studied; however, various other hormones such as leptin, placental growth hormone, prolactin, thyroid and adrenal cortical hormones have been implicated in the aetiology of HG. In addition to endocrinological hypotheses, the rationale and evidence considering infectious, immunological, psychological, metabolic and anatomical causes for HG have been analysed here. Many studies suffer from the low number of patients included, the variable definition used for HG and varying assay methodology used in studies of hormone measurement. This review highlights the need for more extensive studies addressing the pathogenesis and aetiology of HG.

Key words: HCG/hyperemesis gravidarum/nausea/pregnancy/vomiting

Introduction

Up to 80% of all pregnant women experience some form of nausea and vomiting during their pregnancy (NVP) (Gadsby *et al*., 1993). Hyperemesis gravidarum (HG) is a condition of intractable vomiting during pregnancy, leading to fluid, electrolyte and acid–base imbalance, nutrition deficiency and weight loss often severe enough to require hospital admission (Fairweather, 1968). HG, like NVP, typically occurs between the 4th and the 10th week of gestation, with resolution by 20 weeks of gestation. In approximately 10% of HG patients, symptoms will persist throughout pregnancy (Gadsby *et al*., 1993). Estimates of the incidence of HG vary from 0.3 to 1.5% of all live births, with most authors reporting an incidence of 0.5% (Kallen, 1987; Tsang *et al*., 1996). It is widely believed that the rate varies across different cultures (Jordan *et al*., 1995). Despite decades of research, the cause of these conditions remains unknown, and the relationship between NVP and HG is still unclear.

Because the great majority of pregnant women experience discomfort due to nausea and vomiting, a functional role of NVP is often considered. It has been hypothesized that morning sickness protects the embryo by causing pregnant women to physically vomit and subsequently avoid foods that contain teratogenic and abortifacient chemicals, especially toxic chemicals in strong-tasting vegetables, caffeinated beverages and alcohol (Flaxman and Sherman, 2000).

HG is most prevalent during, but certainly not limited to, the first trimester of pregnancy when both the placenta and the corpus luteum are producing hormones and the body is adapting to the pregnant state (Figure 1). Investigators have tried to relate these factors to the pathogenesis of HG, and various pregnancy-related hormones have been considered (Figure 2). Other pathogenic mechanisms and causes have been hypothesized and studied in the pathogenesis of HG as well, but consensus about the cause and mechanism has not been reached until now. Until the discovery of the aetiology and pathogenesis of HG, treatment and patient care will remain empirical and therefore suboptimal. This article is a narrative review of the theories and the current evidence on the aetiology and pathogenesis of HG.

Hyperemesis gravidarum

It is commonly believed that HG is of little consequence since it is usually self-limited, but before the introduction of i.v. fluid treatment, the mortality from HG was 159 deaths per million births in Great Britain (Michelini, 2002). Even now, dehydration (accompanied by orthostatic symptoms), metabolic and electrolyte disturbance are relatively commonly seen complications in patients with severe HG. Cases with advanced vitamin and metabolite disturbances with complications such as Wernicke's encephalopathy, central pontine myelinolysis, vasospasm of cerebral arteries,
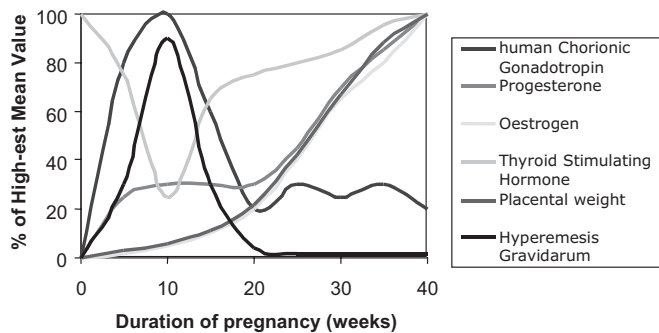
Figure 1. Relative levels of maternal hormones and incidence of hyperemesis gravidarum (HG) according to the duration of human pregnancy. [Modified from Austin and Short (ed.) (1984) Reproduction in Mammals, Book III: Hormonal Control of Reproduction. Cambridge University Press, Cambridge, UK.]
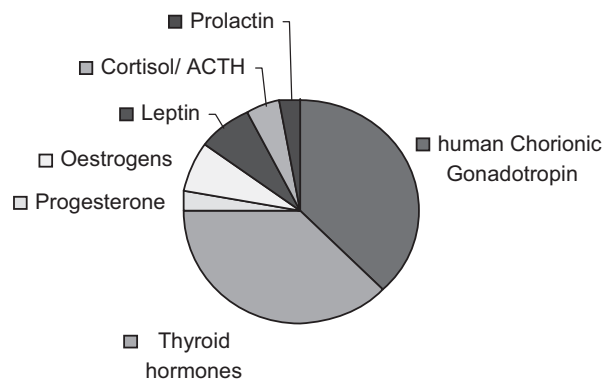

Figure 2. Publications since 1990 comparing various hormone levels of hyperemesis gravidarum (HG) patients in studies in which a control group has been included ($n = 40$). ACTH, adrenocorticotropic hormone.

rhabdomyolysis, coagulopathy and peripheral neuropathy are reported with some regularity (Peeters *et al.*, 1993; Kanayama *et al.*, 1998; Robinson *et al.*, 1998; Fukada *et al.*, 1999; Togay-Isikay *et al.*, 2001). In addition, pneumomediastinum and esophageal rupture as a consequence of mechanical forces have occurred in HG patients (Liang *et al.*, 2002). Severe nausea and vomiting remain the third leading cause for hospitalization during pregnancy (Bennett *et al.*, 1998; Miller, 2002). It is estimated that 206 h are lost from paid work for each woman who has nausea and vomiting during early pregnancy (Mazzotta *et al.*, 2000).

In most patients, i.v. fluid therapy, vitamin supplementation and electrolyte imbalance correction are sufficient to relieve symptoms and prevent serious complications. When patients fail to respond, antiemetic therapy is also administered. In a systematic review, seven randomized controlled trials testing different methods of treatment in HG patients were identified, including oral ginger root extract, oral or injected corticosteroids or injected adrenocorticotrophic hormone (ACTH), i.v. diazepam and acupuncture. None of the treatments for HG showed any evidence of benefit (Jewell and Young, 2003). In protracted cases of HG refractory to pharmacological therapy, nasogastric feeding or total parenteral nutrition has been used to maintain adequate maternal nutrition and well being (Ghani, 2003). Nevertheless, sometimes all forms of conventional treatment fail or the maternal condition becomes life threatening

and termination of pregnancy is required. Elective termination of approximately 2% of pregnancies complicated by HG has been reported (Jarnfelt-Samsioe *et al.*, 1983; Mazzotta *et al.*, 1996).

Not only can HG be a life-threatening illness for the mother, adverse pregnancy outcomes such as lower birthweight, preterm delivery and foetal malformation have been observed in the offspring of HG patients (Depue *et al.*, 1987; Kallen, 1987; Chin and Lao, 1988; Gross *et al.*, 1989; Zhang and Cai, 1991). At the same time, protective effects of HG for some conditions have been described; women with HG were found to have a lower risk for foetal loss and nonsyndromic oral clefts (Depue *et al.*, 1987; Weigel and Weigel, 1989; Bashiri *et al.*, 1995; Czeizel *et al.*, 2003).

Aetiology

The hypothesis that endocrine factors are the primary cause for HG is often cited. Theories on how pregnancy hormones could cause HG assert that patients who develop HG may be exposed to higher levels of hormones during early pregnancy. Alternatively HG patients might be more vulnerable to their effects, HG patients possibly producing specific subtypes or isoforms of hormones that are associated with HG. Because HG is most prevalent in weeks when both the placenta and the corpus luteum produce hormones, progesterone and HCG in particular are thought to be associated with HG.

HCG

HCG is often stated as the most likely cause of HG. This is because the highest incidences of HG occur at the time HCG has its peak level and because HG has a higher incidence in conditions said to be associated with elevated HCG levels, namely twin and molar pregnancies, pregnancies of female foetuses and those with down syndrome (Danzer *et al.*, 1980; Goodwin *et al.*, 1994; Askling *et al.*, 1999; del Mar Melero-Montes and Jick, 2000; Basso and Olsen, 2001; Furneaux *et al.*, 2001; James, 2001; Steier *et al.*, 2004).

How HCG could cause HG remains unclear, but proposed mechanisms include a stimulating effect on the secretory processes in the upper gastrointestinal tract (GIT) or by stimulation of thyroid function because of its structural similarity to thyroid-stimulating hormone (TSH), as will be discussed below (Panesar, 1999; Hershman, 2004).

Twenty-three studies investigating the relation between HCG and HG by comparing circulating HCG levels in HG patients could be identified in a literature search (1968–2004). Of the 15 studies published since 1990, 11 showed a significantly higher level of serum HCG in HG patients than in controls (Figure 3). All studies were prospective comparative studies with pregnant controls, eight out of fifteen matched for gestational age.

Supporters of this theory have tried to explain the dissenting results by differences in the assay methodology used. Diversity in assays to investigate the HCG level has been used to compare HCG levels between HG patients and controls, and HCG assays can differ remarkably in their ability to detect HCG subunits, isoforms or metabolites (Berger *et al.*, 1993; Cole, 1997).

A different explanation for the inconsistent finding of elevated HCG levels in HG patients is that HG is not simply caused by elevated HCG levels but that specific isoforms of HCG are causing HG. This theory has been supported by the finding that HG patients displayed increased HCG concentrations in the more
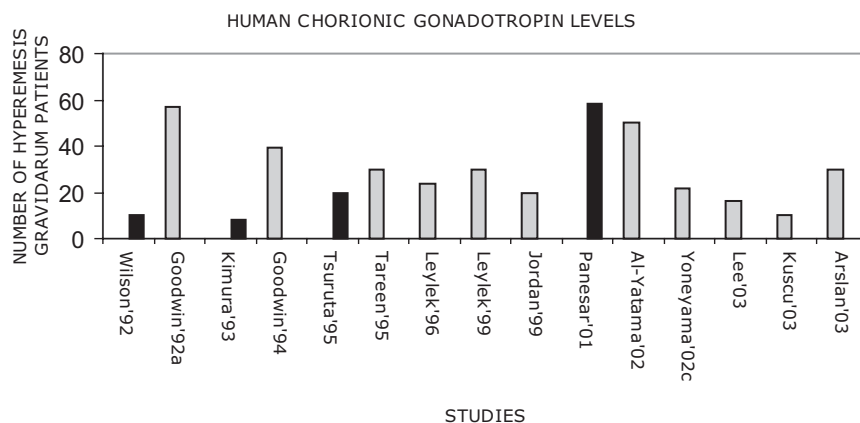
HUMAN CHORIONIC GONADOTROPIN LEVELS

Figure 3. Studies evaluating the role of HCG in hyperemesis gravidarum (HG) published since 1990. Grey: studies with significantly higher HCG levels in patients with HG compared with controls. Black: no significant difference in HCG levels between HG patients and controls.

acidic half (pH < 4) of the chromatofocusing pH range than seen in control subjects (Jordan *et al.*, 1999). In a study by Tsuruta *et al.* (1995), HG patients had significantly increased levels of the HCG fraction that contains HCG with asialo-carbohydrate chains.

Different isoform patterns of HCG can be the result of either long-term environmental influences or genetic factors. This might be the explanation for the difference in incidence of HG that has been observed between populations. A higher incidence of HG has been observed in New Zealand Pacific Island women, United Kingdom Indian and Pakistani, Asian and African American women compared with ethnic European women and lower incidences in American Indian and Eskimo populations (Klebanoff *et al.*, 1985; Jordan *et al.*, 1995, 1999; Price *et al.*, 1996; Vilming and Nesheim, 2000; Michelini, 2002).

The current state of research suggests a relationship between HG and high HCG levels; however, the role HCG plays in the pathogenesis of HG remains unclear. Care must be exercised in concluding that the relationship is causal because other conditions associated with high HCG levels, such as choriocarcinoma, do not typically result in nausea and vomiting, and many pregnant women with high HCG levels do not suffer from HG. In addition, the substantial proportion of patients with HG in which symptoms continue beyond the first trimester when HCG levels are falling, and also the observation that HCG administration as luteal phase support or to trigger oocyte maturation does not cause symptoms or an increase of HG or NVP, mitigate against the hypothesis of HCG as the sole factor in the aetiology of HG.

Progesterone

Given that the hormonal activity of the corpus luteum is highest in the first trimester when HG is more common, researchers have looked for an association between HG and progesterone levels. Several researchers have found abnormal serum progesterone levels in HG patients. Jarnfelt-Samsioe (1987) in a literature review described that among selected hormones measured in pregnant women, those with nausea and vomiting in early pregnancy had significantly lower progesterone levels. Others measured significantly higher progesterone levels in a relatively small group of HG patients compared with control patients matched for gestational

age (Yoneyama *et al.*, 2002b). However, not all investigators could find a correlation between the level of progesterone and severity of nausea or vomiting in prospective cohort studies (Soules *et al.*, 1980; Masson *et al.*, 1985; Lagiou *et al.*, 2003), and Fairweather (1968) described no relief of symptoms after progesterone treatment in a cohort of women with NVP.

The conclusions from these studies are not convincing as the data are derived from NVP patients as well as HG patients, and small numbers of patients are included. Pregnancies with iatrogenic-elevated progesterone levels, such as pregnancies with multiple corpora lutea caused by controlled ovarian stimulation (COS), or pregnancies in which progesterone is administered for luteal phase support do not exhibit an increased incidence of HG, suggesting that high progesterone levels (endogenous or exogenous) alone do not cause HG.

Estrogens

HG is more prevalent in a number of conditions that are associated with high estrogens levels, such as a higher body mass index (Depue *et al.*, 1987), first pregnancy (Fairweather, 1968) and undescended testicles in the foetus (Kallen, 1987). In addition, a higher incidence of testicular carcinoma has been observed in the offspring of mothers who suffered from HG during pregnancy (Depue *et al.*, 1987; Kallen, 1987). These findings, coupled with the fact that nausea is a common side effect of estrogen treatment, support the hypothesis that estrogen may be causally related to HG.

Estrogen has effects on several mechanisms that could modulate factors causing HG. High estrogen levels cause slower intestinal transit time and gastric emptying, and result in an increased accumulation of fluid caused by elevated steroid hormones. A shift in pH in the GIT could lead to the manifestation of a subclinical *Helicobacter pylori* infection, which could be related to gastrointestinal symptoms (Walsh *et al.*, 1996; Kocak *et al.*, 1999).

Several studies have been published to confirm abnormal estradiol (E_2) levels in patients with HG. A couple of prospective cohort studies were conducted to compare mean estrogen levels between HG patients and a matched control group. A few found significantly elevated mean estrogen levels in HG patients (Depue *et al.*, 1987; Yoneyama *et al.*, 2002b), one study also observed a trend

529

towards higher E_2 levels in HG patients (Goodwin *et al.*, 1992a), but others could not confirm these findings (Fairweather, 1968; Jordan *et al.*, 1999). To our knowledge, no studies have been published to date that found a relationship between the severity of HG and the E_2 level. However, in a retrospective survey, a strong correlation has been observed between women suffering from nausea in pregnancy and nausea during the use of oral contraceptives, an estrogen-related side effect, supporting the hypothesis that HG patients might be more sensitive to the effects of estrogens (Jarnfelt-Samsioe *et al.*, 1983).

Other types of pregnancy-specific estrogens, such as estriol (E_3), have also been considered in the pathogenesis of NVP, but no difference in serum levels could be observed in two prospective cohort studies with patients suffering from nausea and vomiting (Jarnfelt-Samsioe *et al.*, 1986; Lagiou *et al.*, 2003). No trials have been published which studied the level of E_3 specifically in HG patients.

Even though under the influence of estrogen numerous adaptations to pregnancy are made, some of which might cause nausea or vomiting, the suggested mechanisms do not provide a satisfactory explanation why the symptoms in HG patients are so much more severe or why HG is most prevalent during the first trimester, because estrogen levels rise progressively during pregnancy. The fact that pregnancies induced by COS in assisted reproduction techniques (ART) when circulating estrogen levels are very high is not associated with a higher incidence of HG makes it less likely that HG is simply caused by high estrogen levels as well as progesterone.

Thyroid hormones

The thyroid gland is physiologically stimulated during early pregnancy. Sometimes, thyroid hormone values will deviate from the normal range, leading to a state which is referred to as gestational transient thyrotoxicosis (GTT). GTT has been observed in up to two thirds of women suffering from HG (Goodwin *et al.*, 1992b). To study whether GTT and HG are causally related, we examined thyroxine (T_4) and TSH levels in HG patients. Of the 15 prospective comparative studies comparing T_4 levels of HG patients with those of asymptomatic controls, eight were matched for gestational age, and eleven showed significantly higher T_4 levels in the HG group. Nine out of the thirteen prospective comparative studies investigating TSH levels showed significantly higher TSH levels in the HG group (Figures 4 and 5).

Various mechanisms might be involved in the stimulation of thyroid function during pregnancy. Under the influence of estrogens, the production of thyroid-binding globulin increases and T_4 metabolism is slowed, causing a transient decrease in free T_4 level.
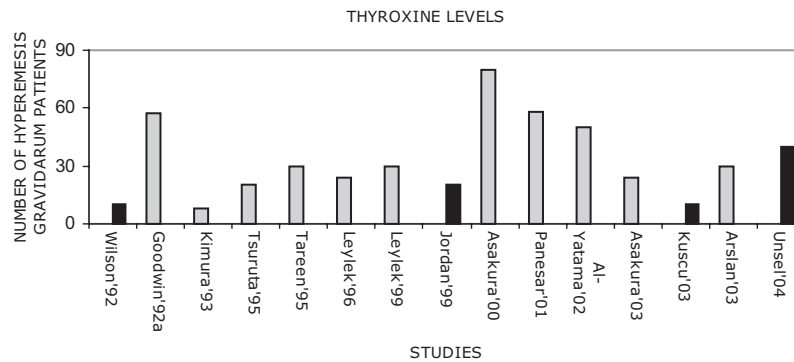

Figure 4. Studies evaluating the role of free thyroxine (T_4) in hyperemesis gravidarum (HG) published since 1990. Grey: studies with significantly higher T_4 levels in patients with HG compared with controls. Black: no significant difference in T_4 levels between HG patients and controls.
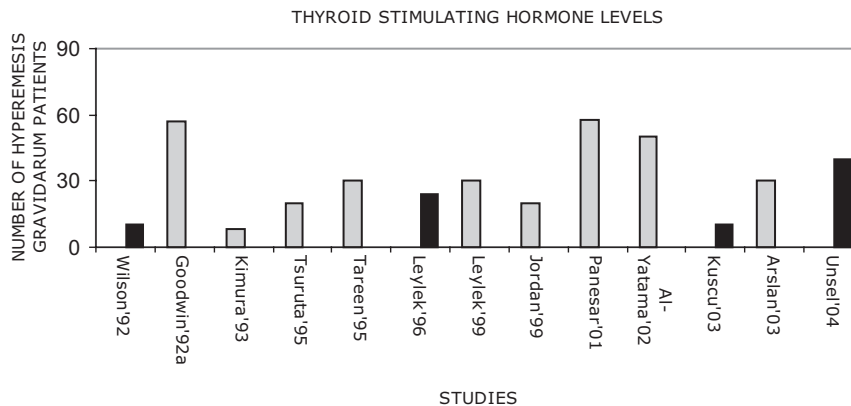

Figure 5. Studies evaluating the role of thyroid stimulating hormone (TSH) in hyperemesis gravidarum (HG) published since 1990. Grey: studies with significantly lower TSH levels in patients with HG compared with controls. Black: no significant difference in TSH levels between HG patients and controls.

Higher renal iodine clearance causes stimulation of the thyroid to compensate for a relative iodine deficiency (Glinoer, 1997). Decreased albumin and increased free fatty acid concentrations affect the binding of thyroid hormones to carrier proteins (Stockigt, 2001). Because of its structural similarity to TSH, increased HCG levels can cause excessive stimulation of the thyroid gland (Kimura *et al*., 1993).

It has been suggested that the high incidence of transient hyperthyroidism in HG patients is caused by elevated circulating HCG levels, thyroid hormone receptors hypersensitive for HCG or the production of a type of HCG that is more potent in stimulating the thyroid gland. During peak HCG levels in normal pregnancy, serum TSH levels fall and are a mirror image of the HCG peak, free triiodothyronine and T4 levels being significantly elevated at this time (Harada *et al*., 1979; Glinoer *et al*., 1990). These findings imply that HCG plays an important role in causing hyperthyroidism and is supported by the finding of thyroid hyperstimulation in cases of molar and multiple pregnancies, conditions associated with higher HCG levels (Hershman and Higgins, 1971; Grun *et al*., 1997).

Hypersensitive TSH receptors have been observed in a family with gestational hyperthyroidism and HG. Family members suffered from HG recurrently during pregnancies with HCG levels within the normal range. They were found to have a mutation in the extracellular domain of the TSH receptor that made it responsive to normal HCG levels (Rodien *et al*., 2004).

The converse hypothesis that transient hyperthyroidism in HG could be caused by a variant of HCG with increased thyroid stimulating activity was supported by the finding that the HCG fraction containing asialo-carbohydrate chains was significantly increased in a population of HG patients with gestational thyrotoxicosis compared with a control group of pregnant women with no emesis (Tsuruta *et al*., 1995). In addition, five cases have been reported of patients with gestational thyrotoxicosis and HG with circulating asialo-HCG with high thyrotropic bioactivity (Yamazaki *et al*., 1995).

Hyperthyroidism has been associated with the severity of HG. In a follow-up study, HG patients with hyperthyroidism were more likely to have abnormal electrolyte levels, increased liver enzyme levels and more severe vomiting (Goodwin *et al*., 1992a). Tsuruta *et al*. (1995) and Kimura *et al*. (1993) found that the thyroid stimulating activity levels correlated with the severity of NVP.

Evidence supports a relationship between HCG levels and GTT, but the exact role in HG is, however, obscure. Whether HCG level can participate in the triggering of vomiting or be a parallel consequence of hypersecretion of HCG is not known. Other causes of hyperthyroidism like Graves' disease do not cause HG-like symptoms. In addition, hyperthyroidism is more prevalent but not exclusive to HG patients, and many HG patients do not suffer from hyperthyroidism.

Leptin

Leptin is a circulating hormone which acts as an afferent satiety signal to regulate body weight and has a structure similar to that of cytokines. A relationship between leptin and HG was originally based on the notion that leptin was exclusively expressed in white adipose tissue and its main function was to play a crucial role in reducing appetite and raising the consumption of energy by inter-

acting with other factors such as cortisol, thyroid hormones and insulin (Halaas *et al*., 1995; Considine and Caro, 1996).

However, later reports showed that leptin is expressed in several other structures, such as the hypothalamus (Morash *et al*., 1999), pituitary (Jin *et al*., 2000), fundal gastric epithelium (Bado *et al*., 1998), skeletal muscle (Wang *et al*., 1998), mammary epithelium (Smith-Kirwin *et al*., 1998) and the placenta (Masuzaki *et al*., 1997; Senaris *et al*., 1997). Elevated leptin levels have been observed in several pregnancy-related conditions such as preeclampsia (Mise *et al*., 1998; McCarthy *et al*., 1999; Vitoratos *et al*., 2001), hypertension (Vitoratos *et al*., 2001; Canatan *et al*., 2004) and gestational diabetes mellitus (Qiu *et al*., 2004). Three prospective cohort studies comparing serum leptin levels between HG patients and controls did not show a statistically significant difference (Arslan *et al*., 2003; Lee *et al*., 2003; Unsel *et al*., 2004). Supporters of the leptin theory stated that this could be a false negative finding due to a negative energy balance in HG patients, a dramatic decrease in leptin levels being observed in other situations with a negative energy balance, such as fasting (Boden *et al*., 1996; Kolaczynski *et al*., 1996; White *et al*., 1997).

Adrenal cortex

In 1953, Wells (1953) observed a reduction of symptoms when using corticosteroid therapy for the treatment of HG. Fairweather (1968) stated that both symptoms and anatomical changes in the adrenal cortex in HG subjects were found to be very similar to those in Addison's disease and adrenal cortex insufficiency in animals. These findings resulted in the hypothesis that adrenal cortex insufficiency was related to HG. This would be caused by either insufficient ACTH production or the inability of the hypothalamic-pituitary-adrenal axis to respond to the increased demands for adrenal output in early pregnancy.

The hypothesis was supported by the finding of significantly lower serum cortisol levels in vomiting patients compared with pregnant controls (Jarnfelt-Samsioe *et al*., 1986). However, other trials suggested an activated hypothalamic-pituitary-adrenal axis in HG patients. Kauppila *et al*. (1976) measured higher ACTH and cortisol levels in HG patients before and after insulin-induced hypoglycaemia than in controls in a prospective controlled trial with 24 patients. la Marca *et al*. (1998) and Unsel *et al*. (2004) measured elevated mean serum cortisol levels in HG patients compared with asymptomatic pregnant women in prospective cohort studies. However, in a meta-analysis of randomized controlled trials, corticosteroid and ACTH administration were not shown to relieve symptoms (Jewell and Young, 2003).

Overactivity of the hypothalamic-pituitary-adrenal axis appears to be associated with HG, but it is not clear whether it is actually involved in the pathogenesis. Increased ACTH and cortisol levels have also been observed in women with starvation, anorexia and bulimia nervosa, this being interpreted as a protective mechanism to conserve energy in starvation (Gorozhanin and Lobkov, 1990; Hasegawa, 2001).

Growth hormone and prolactin

Decreased basal human growth hormone (hGH) and elevated basal prolactin levels were reported in HG patients after the administration of gonadotrophin-releasing hormones in a prospective, randomized, double-blinded, controlled trial with 32 patients, but

the results were not statistically significant (Ylikorkala *et al.*, 1976). Lagiou *et al.* (2003) prospectively measured prolactin levels in pregnant women and observed a significantly lower levels in women who developed nausea and vomiting.

Later studies showed prolactin and hGH production by extrapituitary tissues, including the endometrium and syncytiotrophoblast cells, during pregnancy (Igout *et al.*, 1993; Wu *et al.*, 1995; Ben-Jonathan *et al.*, 1996; Brosens *et al.*, 1999; Tseng and Mazella, 1999). These findings imply that the changes in hGH and prolactin levels in HG patients may reflect endometrial and placental hormone production rather than changes in the pituitary gland secretion (Ylikorkala *et al.*, 1979). Further studies are required to establish the role of endometrial prolactin and placental hGH in HG patients.

Placental serum markers

Schwangerschafts protein 1 (SP1) or pregnancy specific β-1 glycoprotein, a placental protein secreted in the maternal circulation from the earliest weeks of pregnancy, is used as a maternal serum marker in the screening for down syndrome (MacIntosh *et al.*, 1993). In a prospective cohort study, to evaluate the predictive effect of early pregnancy markers, SP1 levels were found to correlate with vomiting during pregnancy (Kauppila *et al.*, 1984), a finding not confirmed in a later study (Masson *et al.*, 1985). To our knowledge, no other studies that have investigated SP1 or any other placental serum markers in combination with NVP or HG have been published to date.

Immunology

During pregnancy, changes in the humoral and cell-mediated immune systems occur. Probably the most important aspect of these changes is to protect the foetus and decidua from disruption by the maternal immune system. It has been suggested that changes of the physiological immune response to pregnancy cause pregnancy-related disorders.

In accordance with this hypothesis, HG has been regarded as the result of an overactivated immune system, which could in part be related to pregnancy hormone synthesis (Minagawa *et al.*, 1999). In a prospective cohort study, Sekizawa *et al.* (2001) measured an increased concentration of foetal DNA in the plasma of HG patients compared with matched asymptomatic pregnant women, both groups carrying a single male foetus, suggesting a relationship between HG and immunological interaction between mother and foetus. Immunological factor levels have been studied, and several were found to be higher in HG patients and had positive correlations with changes in hormone levels. Kuscu *et al.* (2003) observed increased interleukin-6 (IL-6) levels in HG patients and a positive correlation between IL-6 levels and β-HCG in a prospective case–control study. Kaplan *et al.* (2003) prospectively compared the IL-1, IL-2, IL-6, IL-8 and tumour necrosis factor-alpha (TNFα) levels between women with HG, pregnant and non-pregnant controls and found a significantly higher level of TNFα in HG patients.

Yoneyama *et al.* (2002b) studied the T-helper 1/T-helper 2 balance and observed a shift towards T-helper 2 dominance in HG patients accompanied by the elevation of progesterone and estrogen levels compared with a matched control group. Leylek *et al.* (1999) found significantly higher immunoglobulin G (IgG), IgM, C3, C4 levels and lymphocyte count in HG patients in a comparative

study. They also observed a positive correlation between IgG and IgM levels, and the prevalence of hyperthyroidism in HG patients and β-HCG levels were found to correlate with the lymphocyte count, IgM and C3. Minagawa *et al.* (1999) observed higher natural killer and extra-thymic T-cell levels in HG patients, and Yoneyama *et al.* (2002a, 2004) reported increased plasma 5′-nucleotidase and serum adenosine deaminase activities and increased plasma adenosine concentrations in HG patients.

Starvation normally causes suppression of immune functions, but these findings rather support an activated immune system in HG. It cannot be concluded from these preliminary findings whether the immune response is a cause or a reaction to HG but because HG is a self-limited condition these seemingly random elevations in immune factors could be part of a compensatory reaction to limit the progression of HG. The precise significance of correlated changes in hormone levels remains unclear.

GIT

Helicobacter pylori *infection*

An increased incidence of *H. pylori* infection has been observed in HG patients and thus has become a candidate aetiological factor. In a total of eleven prospective case–control studies, five of which were matched, the incidence of *H. pylori* infection in HG patients was measured, the great majority showing a significantly increased infection rate in HG patients than in controls (Figure 6). Only one study used histological examination of mucosal biopsy, considered to be the gold standard for testing *H. pylori* infection, as a diagnostic tool. In this study, 95% of all HG patients tested positive for *H. pylori* compared with 50% in the control group (Bagis *et al.*, 2002). They also found significantly higher *H. pylori* densities in the gastric antrum and corpus in HG patients. The density of *H. pylori* could be correlated with the severity of symptoms and might be an explanation for the difference between ordinary 'morning sickness' and severe HG. By contrast, Erdem *et al.* (2002) could not find a correlation between serum *H. pylori* IgG concentration and duration of HG symptoms although histological examination of mucosal biopsy was not used.

Helicobacter pylori infection in pregnant women could be caused by changes in the gastric pH or pregnancy-related changes in the immune system. A manifestation of subclinical *H. pylori* infection could be the result of a change in gastric pH because of an increased accumulation of fluid caused by elevated steroid hormones in pregnant women (Kocak *et al.*, 1999). Changes in humoral and cell-mediated immunity during pregnancy could cause an increased susceptibility to *H. pylori* infection in pregnancy, these effects possibly being more pronounced in HG patients (Lanciers *et al.*, 1999).

A relationship between HG and *H. pylori* infection is supported by reports of five cases of women with HG who did not respond to standard HG management, but therapy with *H. pylori* treatment resulted in a complete relief of symptoms (El Younis *et al.*, 1998; Jacoby and Porter, 1999). As far as we are aware, no randomized controlled trials evaluating this treatment strategy have been published to date.

An association between *H. pylori* and HG could be a possible explanation for the observed variation in the incidence of HG in different ethnic groups because *H. pylori* infection rates also differ markedly between distinct populations (Taylor and Blaser, 1991).
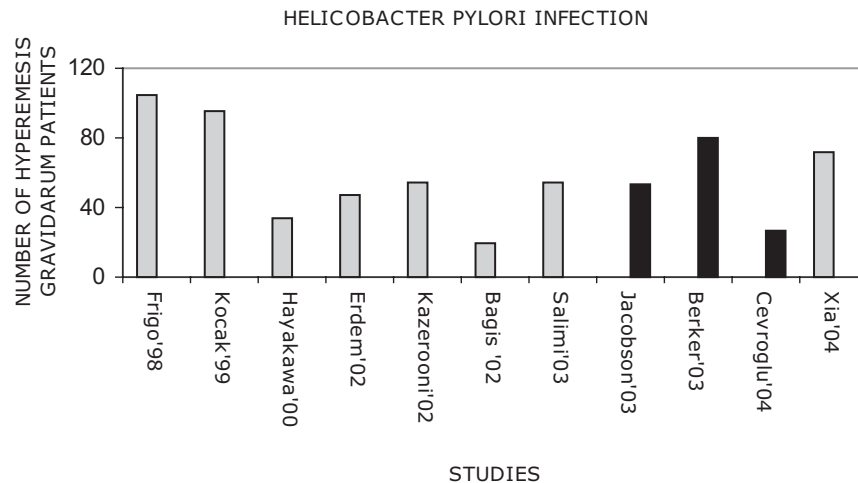
HELICOBACTER PYLORI INFECTION

Figure 6. Studies evaluating the role of *Helicobacter pylori* in hyperemesis gravidarum (HG). Grey: studies with a significantly higher infection rate in HG patients compared with controls. Black: no significant difference seen in infection rate between HG patients and controls.

However, this hypothesis is susceptible to confounding factors such as lower socioeconomic status, which has been implicated in both HG and *H. pylori* infection (Wolkind and Zajicek, 1978; Patel *et al*., 1994). Karaca *et al*. (2004) found supportive evidence for a possible association between socioeconomic status and *H. pylori* infection in pregnant women with HG in a prospective comparative study with asymptomatic pregnant women.

Although *H. pylori* infection has been observed more often in patients with HG, most pregnant women with *H. pylori* infection remain asymptomatic. The idea that susceptibility to *H. pylori* is secondary to steroid levels or changes in the immune system does not provide a satisfactory explanation. If the infection is causally related to elevated steroid hormones, effects would be most pronounced at the end of pregnancy, whereas immune functions appear to be activated in HG patients and these are unlikely to cause greater susceptibility to infection. It seems more likely that damage to the upper GIT due to excessive vomiting increases susceptibility to subclinical *H. pylori* infection.

Gastric and intestinal motility

During pregnancy, sex steroids cause abnormal activity in gastric and colonic smooth muscle, leading to slower small intestinal and colonic transit times and slow gastric emptying that may cause nausea (Kumar, 1962; Bruce *et al*., 1987; Datz *et al*., 1987; Hutson *et al*., 1989; Koch *et al*., 1990). Maes *et al*. (1999) tried to relate these observations to HG by measuring gastric emptying in HG patients and controls, and in contrast to the expected finding, they observed an increase in gastric emptying in HG patients. This finding, along with the knowledge that the strongest effects of estrogens and progesterone would be expected at the end of pregnancy, does not support the hypothesis that HG and gastrointestinal motility disorders are related.

Lower esophageal sphincter pressure

Many women have symptoms of gastrointestinal reflux during their pregnancy (Marshall *et al*., 1998; Rayburn *et al*., 1999). These symptoms could be the result of progressive decrease in lower esophageal sphincter pressure (LESP; Bainbridge *et al*.,

1984; Al Amri, 2002). Several studies documented evidence for a causal relationship between LESP and increases of estrogen and progesterone levels in combination with an enlarging uterus (Brock-Utne *et al*., 1981; Bainbridge *et al*., 1984; Dodds *et al*., 1987; Baron and Richter, 1992). However, later studies did not uniformly confirm these findings (Van Thiel *et al*., 1976; Van Thiel and Wald, 1981; Alvarez-Sanchez *et al*., 1999). Some authors have hypothesized that there is a relationship between a decreased LESP and HG, but there is little evidence supporting this hypothesis. Additionally, HG is most pronounced during the first trimester of pregnancy, and the decrease in LESP is more severe in the end of pregnancy, thus mitigating against this hypothesis.

Fluid secretion in the GIT

HG may result from the distension of the upper GIT caused by excessive secretion and accumulation of fluid in the gut lumen. Fluid secretion is a phenomenon regularly seen during pregnancy in physiological proportions, as is the case in the production of amniotic fluid and in pathological circumstances, such as hydropic swellings of chorionic villi in hydatidiform mole, ovarian hyperstimulation syndrome and polycystic ovary syndrome, conditions related to high gonadotrophin levels (Panesar, 1999). There is evidence suggesting that gonadotrophins are capable of affecting ion transport accompanied by passive fluid movement (Duchatelle and Joffre, 1990). This finding, along with the high affinity HCG binding sites seen in the pancreas and duodenum of rats, areas in which much of the upper GIT secretion originates, suggests that HG could be because of secretory effects of HCG in the upper GIT (Panesar and Poon, 1998). Studies have not yet tested this hypothesis in human HG patients.

Metabolic enzymes

Liver enzymes

Liver function abnormalities have been reported in up to 67% of HG patients, with elevations of either aspartate aminotransferase or alanine aminotransferase being observed in 50% (Wallstedt *et al*., 1990). Liver enzyme abnormalities were found to be associated

with a later onset of HG, more severe ketonuria and hyperthyroidism (Morali and Braverman, 1990; Goodwin *et al*., 1992b).

The aetiology of liver enzymes abnormalities in HG is not clear. Liver enzymes return to normal promptly when the vomiting resolves and with the resumption of adequate nutrition (Adams *et al*., 1968; Conchillo *et al*., 2002). Diagnostic tests like virus serology, ultrasonography and liver biopsy do not show abnormal features (Adams *et al*., 1968; Larrey *et al*., 1984; Orazi *et al*., 1998; Conchillo *et al*., 2002), indicating that the liver enzyme abnormalities are a result rather than the cause of HG. It has been suggested that the abnormal liver function is a combined effect of hypovolaemia, malnutrition and lactic acidosis occurring in HG (Morali and Braverman, 1990; Wolf, 1996).

Amylase

Elevated serum amylase levels have been observed in HG patients (DeVore *et al*., 1980; Goodwin *et al*., 1992b). This was confirmed by Robertson and Millar (1999) who found raised serum amylase levels in 24% of HG patients. However, all patients with elevated amylase levels had normal pancreatic amylase levels, implying that the elevated level of serum amylase in HG patients is rather the effect of excessive salivary gland, rather than pancreatic, amylase production and therefore a result rather than a cause of HG.

Nutritional deficiencies

Vitamin deficiency

Early reports mention pyridoxine deficiency in relation to HG. Studies could not show a relationship between the biochemical indicators of vitamin B6 status and the incidence or degree of morning sickness, and no studies have been identified that tested this hypothesis in HG patients. A meta-analysis of prospective, randomized, double-blind, placebo-controlled studies on pyridoxine therapy in women with NVP did not show a significant effect on vomiting (Jewell and Young, 2003).

Deficiencies in other vitamins, such as thiamine and vitamin K, have been reported in patients with HG (Robinson *et al*., 1998; Spruill and Kuller, 2002). A combination of increased demands during pregnancy, the absence of nutritional intake and malabsorption during HG are possible causes of these deficiencies (Robinson *et al*., 1998; Spruill and Kuller, 2002). The fact that similar symptoms have been reported in patients with severe starvation, and bulimia nervosa makes it even more reasonable to assume that these deficiencies are a result of the excessive vomiting in HG.

Trace element deficiency

Influences of changes in various trace elements have also been considered in the pathogenesis of HG. Trace element levels in serum and erythrocytes of HG patients have been investigated in case–control studies. Plasma zinc levels in HG patients were found to be significantly elevated (Dokmeci *et al*., 2004), significantly lower (Teksen *et al*., 2001) and not different compared with controls in a series of observational cohort studies (Lao *et al*., 1988; el Tabbakh *et al*., 1989; Swaminathan *et al*., 1989). Copper concentrations were found to be low (Dokmeci *et al*., 2004) and normal (el Tabbakh *et al*., 1989; Teksen *et al*., 2001) in HG patients compared with controls. To date, no abnormalities in magnesium concentrations in HG patients have been observed.

Although it is possible that changes in trace elements in HG patients could be explained by a combination of increased demand during pregnancy, vomiting or aggravation of existing HG by deficiency of these trace elements, a causal relation cannot be completely excluded. Zinc is essential for the catalytic activity of enzymes involved in energy nutrient metabolism and appears to regulate hormones that play key roles in metabolism (Evans *et al*., 2004), and low copper intake has been shown to alter biochemical, metabolic and endocrine function of several organs (Tapiero *et al*., 2003).

Anatomy

Women could be more prone to HG because of anatomical variations. A right-sided corpus luteum has been observed significantly more frequently in a cohort study of patients with NVP (Samsioe *et al*., 1986). A possible explanation for this finding is the difference in venous drainage between the left and right ovary causing a higher concentration of sex steroids in the hepatic portal system when the corpus luteum is situated on the right side. However, the observation of continuation of symptoms in a woman with severe HG in whom excision of a right-sided corpus luteum was performed at 12 weeks does not support this theory (Thorp *et al*., 1991).

Psychological Causes

Historically, a pregnant woman's vomiting was thought to represent various psychological conflicts. Nausea was believed to be the result of resentment against pregnancy or ambivalence of women ill-prepared for motherhood due to immaturity of personality, strong mother dependence, and anxiety and tension related to pregnancy (Farkas and Farkas, 1972; FitzGerald, 1984; Ringler and Krizmanits, 1984).

Other hypotheses state that HG is a sexual disorder resulting from sexuality aversion and a symptom of the same a pregnant woman may feel towards her mother for her sexual behaviour (Fairweather, 1968). HG has also been described as a conversion symptom, or a symptom of hysteria, neurosis or depression, and HG could be resulting from psychosocial stresses, poverty and marital conflicts (Katon *et al*., 1980, 1981; el-Mallakh *et al*., 1990; Lub-Moss and Eurelings-Bontekoe, 1997).

Investigators have found support for a psychological pathogenesis because biological causes have not, so far, provided a satisfactory explanation; lower incidences of HG were observed during times of war and deprivation, differences in incidence are observed between cultures and the fact that hospital admission away from environmental influences with partner, family and responsibilities often reduces the vomiting (Fairweather, 1968; Schouenborg *et al*., 1992; Lub-Moss and Eurelings-Bontekoe, 1997).

Others investigators have opposed to these theories and stated that the psychological symptoms are a result of the stress and the physical burden of HG rather than a cause (Simpson *et al*., 2001; Munch, 2002).

Conclusion

The cause of HG remains unknown. Although some of the proposed mechanisms could provide a reasonable explanation, conclusive evidence for any single cause remains unconvincing (Figure 7). The lack of supporting evidence might be due to the methods used to examine the hypotheses. Many studies suffer
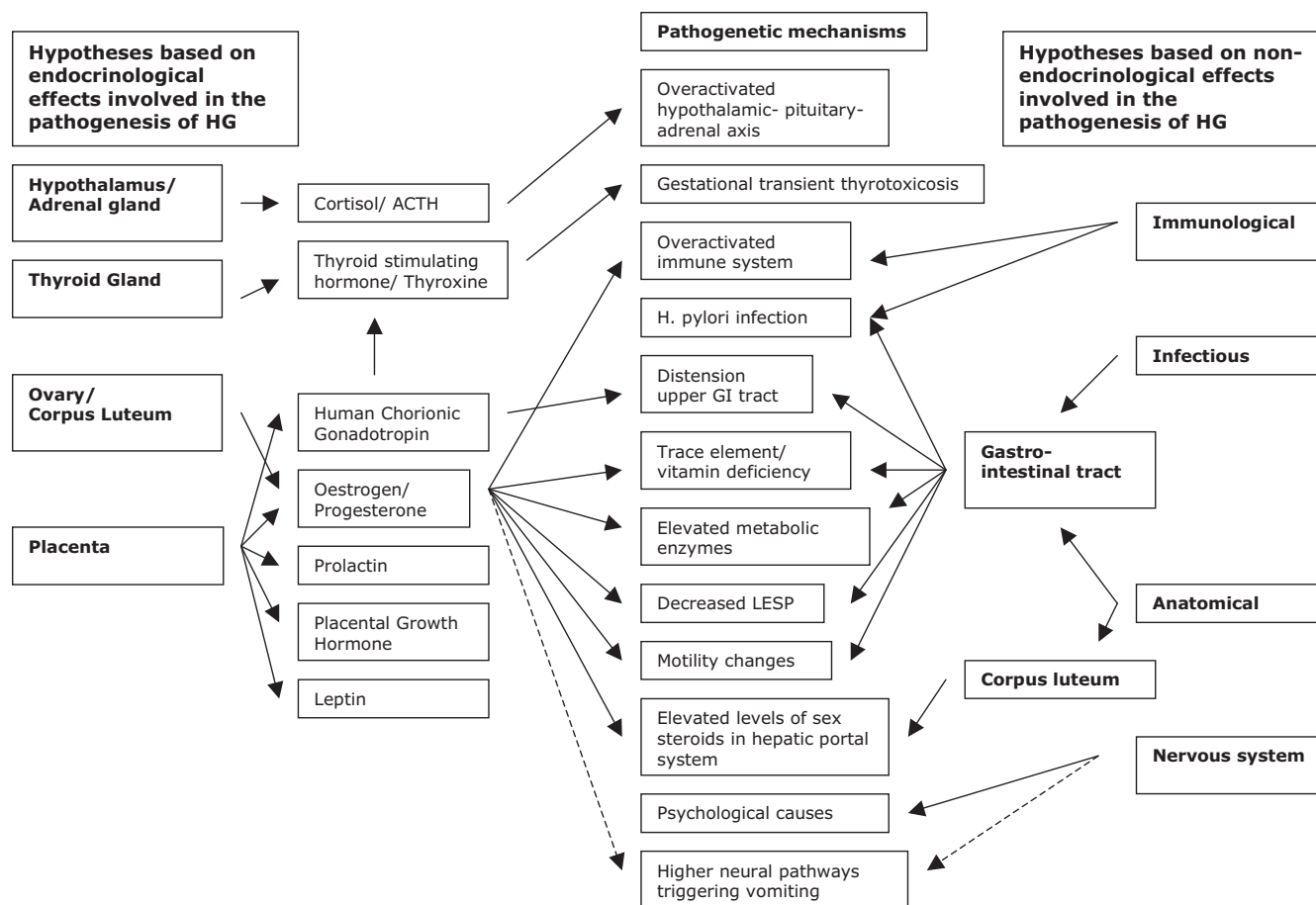
Figure 7. Interactions between endocrine influences, target organs, and functions that might be involved in the pathogenesis of hyperemesis gravidarum (HG). —→, previous publications, - - →, hypotheses; ACTH, adrenocorticotropic hormone; GIT, gastrointestinal tract; LESP, lower esophageal sphincter pressure.

from the low number of patients included, the variable definition used for HG and varying assay methodology used in studies concerning hormone measurement. Besides the methodology used in the presented studies, it is possible that the factor causing HG has not been identified yet, HG could have a multifactorial cause or HG might be the end result of various unrelated conditions.

Implications for future research

Until the pathophysiology of HG is completely understood, the treatment of HG will be symptomatic and suboptimal, and will have a profound effect on women's health and quality of life as well as a financial impact on the health care system. We conclude that there is a need for more studies on this subject. We suggest that the definition of HG should be standardized so that a homogenous group of patients is studied and the results of studies can be reliably compared, and difference in incidence between (sub) populations can be studied. We suggest a definition with stringent criteria to minimize subjective interpretation of the gravity of the condition, such as 'nausea and vomiting in pregnancy typically in the first trimester resulting in dehydration and ketonuria severe enough to justify hospital admission and require i.v. fluid therapy, after exclusion of any other causes of vomiting'.

Because the endocrine hypothesis for the aetiology of HG appears to be most plausible, the area of ART might be an interesting new field of study. Because of the changes in hormone levels in these patients, studies on incidence of HG in this patient group might lead to clues on the causal factor. In contrast to the high incidence of HG expected in these patients due to the high rate of multiple pregnancies in this group, we could only identify one single case report of HG in pregnancy following IVF/ICSI (Conchillo *et al*., 2002).

Acknowledgements

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