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Androgens and hyperemesis gravidarum: a case–control study

Ragnhild Helseth [a,*], Merethe Ravlo [b], Sven M. Carlsen [c,d], E. Eszter Vanky [b,e]

[a] Department of Internal Medicine, Drammen Hospital, Vestre Viken, 3004 Drammen, Norway
[b] Department of Obstetrics and Gynecology, St. Olav's Hospital, Trondheim University Hospital, 7006 Trondheim, Norway
[c] Unit for Applied Clinical Research, Department of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology, 7489 Trondheim, Norway
[d] Department of Endocrinology, St. Olav's Hospital, Trondheim University Hospital, 7006 Trondheim, Norway
[e] Department of Laboratory Medicine, Children's and Women's Health, Norwegian University of Science and Technology, 7489 Trondheim, Norway

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ABSTRACT

Objective: The pathogenesis of hyperemesis gravidarum (HG) is probably multifactorial, involving several hormones. Androgen concentrations are reported to correlate positively with emesis gravidarum. Hypothesizing a continuum between emesis gravidarum and HG, we investigated androgen concentrations in women with HG.

Study design: In a case–control study, 32 women hospitalized for HG were compared with 29 control women scheduled for elective surgical abortion. Control women were matched for age, gestational length, body mass index (BMI) and parity. Patient characteristics and concentrations of dehydroepiandrosterone sulphate (DHEAS), androstenedione, testosterone, sex hormone binding globulin (SHBG), free testosterone index (FTI), androstanediol glucuronide (ADG), progesterone, TSH, free T3 and T4, beta-hCG, ferritin, insulin, estradiol and estriol were compared using Mann–Whitney tests and multivariate linear regression analyses.

Results: Women with HG had higher concentrations of ADG (8.49 ± 4.19 vs. 6.19 ± 1.77 pmol/L; $p = 0.015$), estradiol (2.39 ± 1.36 vs. 1.60 ± 9.30 nmol/L; $p = 0.009$) and ferritin (186 ± 138 vs. 117 ± 94 pmol/L; $p = 0.040$) compared with control women. Androstenedione (5.34 ± 2.82 vs. 6.86 ± 2.67; $p = 0.004$) and insulin (63.7 ± 35.0 vs. 75.3 ± 25.8; $p = 0.050$) concentrations were lower in women with HG. DHEAS, testosterone, FTI, SHBG, estriol, progesterone, beta-hCG, TSH, free T3 and free T4 concentrations did not differ between the groups. In multivariate regression analyses HG was associated with high concentrations of ADG ($p = 0.026$) and low concentrations of androstenedione ($p = 0.018$).

Conclusion: Steroid hormone homeostasis may be altered in women with HG. HG may be associated with high ADG and low androstenedione concentrations.

1. Introduction

Hyperemesis gravidarum (HG) is a condition in early pregnancy with persistent vomiting, more than 5% weight loss, electrolyte disturbances, ketonuria and dehydration [1,2]. HG affects 0.3–2.3% of pregnancies [3–7] and often develops from the less severe and much more prevalent condition emesis gravidarum [8]. Rarely, untreated HG may evolve into a life-threatening condition with major metabolic derangements. Adverse fetal outcomes such as small-for-gestational-age (SGA) and preterm birth are associated with HG and poor maternal weight gain [9].

The pathogenesis of HG is unknown. A great variety of central nervous system, hormonal, placental, immunological, gastrointestinal and psychological factors has been suggested [7,10]. As severe nausea and vomiting are more often observed in pregnancies with complete hydatidiform moles with no fetus than in normal singleton pregnancies [11,12], factors originating from the placenta are probably involved in the pathogenesis of HG.

The incidence of HG is highest those weeks when both the placenta and the corpus luteum produce hormones [7]. Endocrine factors are thus highlighted as potential important factors for disease development.

Concentrations of human chorionic gonadotropin (hCG) have a peak at the same time as HG occurs. Conditions associated with high hCG concentrations, such as twin pregnancies and female offspring, are more prevalent in women with HG. High progesterone concentrations also coincide with HG, and have also been suggested as a contributing factor to HG development. However, both high and low progesterone concentrations, as well as no association between progesterone concentrations and HG development have been reported [7].

* Corresponding author at: Messepromenaden 4, 0279 Oslo, Norway. Tel.: +47 97 14 95 18; fax: +47 22119181.
E-mail address: ragnhild.helseth@gmail.com (R. Helseth).

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Overstimulation of the thyroid gland, either by the ordinary thyroid-stimulating hormone (TSH) or more probably by hCG due to its structural similarity to TSH, is reported frequently in women with HG [7,13].

Despite the continuous rise in estrogens throughout pregnancy, which does not correspond with the early peak in HG incidence, estrogens are suggested to be involved in HG pathogenesis. HG is more prevalent in obese women and during the 1st trimester of pregnancy, both conditions characterized by high estrogens [7]. Estrogens are further linked to gastric dysrhythmias, which are associated with nausea [14]. In the present study, controls were matched for age, gestational age, BMI and parity.

All in all, the mechanism for HG development is most probably multifactorial and several hormones may be involved.

We have previously reported that raised maternal androgen concentrations are associated with nausea and vomiting in otherwise uncomplicated pregnancies [15]. Clinical experience suggests a continuum from nausea, via emesis gravidarum to HG. Accordingly, we hypothesized that androgen concentrations are also increased in women with HG, and we compared androgens and a variety of other potentially relevant hormones in women hospitalized for HG with women scheduled for elective surgical abortion in a case–control study.

2. Materials and methods

2.1. Study population

Patients hospitalized for hyperemesis gravidarum at the Department of Gynecology and Obstetrics, St. Olav's Hospital, in the period from June 2002 to September 2004 were included ($N = 32$). Thirty women scheduled for elective abortion were recruited as controls. One control had to be excluded due to missing serum samples. Controls were matched for maternal age, gestational age, BMI and parity. All pregnancies were singletons.

In the HG group all participants had ketonuria. Only one had normal electrolyte concentrations, two women had elevated hematocrit concentrations and five had elevated alanine aminotransferase (ALAT) concentrations.

Signed written informed consent was obtained from all participants before inclusion, and The Declaration of Helsinki was followed throughout the study. The Committee for Medical Research Ethics of Health Region IV, Norway approved the study.

2.2. Investigations

Venous blood samples were drawn from an antecubital vein, centrifuged at room temperature within 30 min and stored at −80 °C until analysis. Samples were taken the first morning after hospitalization in HG patients, and between 8:00 and 11:00 A.M. after an overnight fast in controls. Women in the HG group were asked about their use of medication for nausea and vomiting.

2.3. Laboratory methods

Serum testosterone and androstenedione were extracted by organic solvent (dichloromethane for testosterone and ethyl ether for androstenedione). Testosterone was quantified by ELISA technique (DRG Instruments GmbH, Marburg/Lahn, Germany). For androstenedione quantification, Coat-A-Count RIA kits (Diagnostic Products Corporation, Los Angeles, CA, USA) were used. TSH, free T3, free T4, sex hormone binding globulin (SHBG), estradiol, estriol, dehydroepiandrosterone sulphate (DHEAS), progesterone, insulin, beta-human chorionic gonadotropin (beta-hCG), ferritin, and androstanediol glucuronide (5α-androstane-3α, 17β-diol-glucoronide; ADG) were measured by the ELISA method using kits and reagents from the producer (DRG instruments, Marburg, Germany). All measures were carried out as single estimations in a single kit. The intra-assay coefficients of variation (CV) were 6.4% for testosterone, 5.0% for androstenedione, 8.0% for TSH, 5.4% for FT4, 5.6% for FT3, 7.9% for SHBG, 5.8% for estradiol, 8.8% for estriol, 5.1% for DHEAS, 7.5% for progesterone, 5.2% for insulin, 6.5% for beta-hCG, 7.9% for ferritin, and 5.0% for ADG. Free testosterone index (FTI) was calculated as total testosterone divided by SHBG and multiplied by a constant of 100.

2.4. Statistical analysis

All statistical procedures were carried out using the software SPSS Statistics version 20 (IBM Corporation, NY 10589, USA). Values were reported as means and standard deviations (SD) as the variables were not markedly skewed. Because the investigated variables and biomarkers did not all follow the normal distribution, we chose a conservative approach to avoid type 1 statistical errors and used the Mann–Whitney test to compare groups. Multivariate linear regression analyses were used to identify endocrine predictors of HG. Endocrine variables with $p \leq 0.1$ in the Mann–Whitney tests comparing values in the HG group and controls were included in the multivariate linear regression analyses. *P*-values ≤ 0.05 were considered significant. No adjustment for multiple testing was applied.

3. Results

3.1. Baseline characteristics

We found no differences in baseline characteristics of women hospitalized for HG and controls (Table 1). In the HG group 28

Table 1
Characteristics of women with hyperemesis gravidarum and control women.

	Hyperemesis gravidarum		Controls		*P*-value[a]
	N	Mean ± SD	*N*	Mean ± SD	
Age (years)	31	27.1 ± 4.5	29	28.0 ± 3.9	0.42
Height (cm)	28	167.0 ± 6.5	26	169.6 ± 4.8	0.095
Previous pregnancies (no.)	31	2.3 ± 1.2	29	2.8 ± 1.4	0.072
Parity (no.)	31	0.7 ± 0.8	29	1.4 ± 2.1	0.085
Weight before pregnancy (kg)	29	67.3 ± 12.8	28	64.8 ± 13.1	0.17
Weight at inclusion (kg)	29	65.1 ± 14.5	29	65.5 ± 12.1	0.79
First nausea (weeks)	30	5.2 ± 1.3	6	5.0 ± 0.5	0.39
Gestational age (days)	29	58 ± 12	29	58 ± 14	0.96
Sick leave due to nausea (yes/no)	26	14/12	29	1/28	<0.0005
Vomiting this pregnancy (yes/no)	31	30/1	29	10/19	<0.0005
Nausea in previous pregnancy (yes/no)	30	20/10	28	18/10	1.00

[a] Mann–Whitney tests for independent samples or two-sided Fischers exact test as appropriate.
cm, centimeter; no., number; kg, kilogram; SD, standard deviation; parity, no. of former deliveries.