Archives of Gynecology and Obstetrics (2019) 300:347–353
https://doi.org/10.1007/s00404-019-05192-y

MATERNAL-FETAL MEDICINE

# Hyperemesis gravidarum and adverse pregnancy outcomes

Niv Agmon[1] · Shanny Sade[1] · Gali Pariente[1] · Reut Rotem[2] · Adi Y. Weintraub[1]

Received: 24 February 2019 / Accepted: 7 May 2019 / Published online: 16 May 2019


## Abstract

**Purpose** To assess adverse pregnancy outcomes in patients complicated with mild or severe Hyperemesis Gravidarum (HG).

**Methods** A retrospective cohort study of women aged 18–45 with a singleton pregnancy that were admitted to the gynecological ward at the Soroka University Medical Center due to HG between the years 2013–2016 and gave birth at the same hospital was conducted. During the study period 89 patients met the inclusion criteria and comprised the study group. Women without HG who gave birth at the same time period comprised the comparison group ($n=91$). Univariate analysis was carried out using Chi square or Fisher's exact test for nominal variables, and $T$ test for numeric variables. Significance was defined as a $P$ value $<0.05$.

**Results** Women with HG were more likely to have experienced HG in a previous pregnancy. Rate of amniotic fluid abnormalities was significantly lower in the study group. However, rates of all other pregnancy complications were comparable between the groups. A sub-analysis of the HG group comparing mild and severe cases demonstrated no significant differences in rates of adverse pregnancy outcomes between the groups.

**Conclusions** In this retrospective cohort study no association was demonstrated between HG and adverse pregnancy outcomes regardless of HG severity. Women with severe nausea and vomiting during pregnancy can be reassured that HG is not associated with unfavorable maternal and neonatal outcomes.

**Keywords** Hyperemesis gravidarum · Elevated liver enzymes · Electrolyte disturbances · Poor maternal weight gain · Ketonuria · Adverse pregnancy outcomes

## Introduction

Nausea and vomiting are common during the first trimester of pregnancy, affecting up to 90% of women. Although generally considered benign, these symptoms may impair the patient's quality of life. For most affected women, resolution is achieved during the second trimester, and for 91% of affected women complete resolution occurs before 20 weeks of gestation [1]. Hyperemesis gravidarum (HG) is a complication of pregnancy, characterized by severe nausea and vomiting. HG may lead to dehydration, weight loss and electrolyte imbalance with an increased rate of hospitalization [1, 2]. The etiology of HG is not completely understood and several theories have been proposed in an attempt to explain this condition. These include among others, genetic predisposition [3, 4], evolutionary adaptation (the vomiting in early pregnancy provided a survival advantage maybe through avoidance from dietary teratogenic substances) [5] and effects of hormonal and nutrient levels such as human chorionic gonadotropin (hCG) [5], estrogen [5], and vitamin B deficiencies [6]. Multiple gestations, hydatiform mole and non-use of multivitamins are recognized as risk factors for HG [1] but they do not account for the majority of cases.

Three main clinically significant issues stand at the core of HG. First, the documented prevalence of HG is highly variable ranging between 0.3 and 3% of pregnancies [5, 6]. Ethnic differences and different diagnostic criteria have been implied to account at least in part for this variation. Secondly, although the term HG is commonly used in clinical practice, there is no clear and widely accepted diagnostic criteria to define HG, nor a classification system differentiating

✉ Reut Rotem
reutah86@gmail.com

[1] Department of Obstetrics and Gynecology, Soroka University Medical Center, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel

[2] Department of Obstetrics and Gynecology, Shaare Zedek Medical Center, Jerusalem Affiliated with the Hebrew University Medical School of Jerusalem, Jerusalem, Israel

HG by the degree of severity [5, 7]. Finally, the association between HG and adverse pregnancy outcomes remains an issue of great controversy [7–11]. This applies to both maternal complications and neonatal outcomes such as placental dysfunction disorders (e.g., intrauterine growth restriction, preeclampsia, and stillbirth).

Given this lack of clarity, we aimed to investigate the association between HG and adverse pregnancy outcomes. We also attempted to differentiate HG by the degree of severity and to investigate whether this is clinically significant for outcome.

## Material and methods

### Setting

We conducted a retrospective cohort study at the Soroka University Medical Center (SUMC). SUMC is a large university medical facility, and the sole tertiary hospital in the Negev (the southern region of Israel) which provides obstetrical care and delivery services for the entire population of southern Israel (695,300 residents in 2015). It is estimated that approximately 98% of deliveries in the district take place at SUMC [12]. The study was approved by the local institutional ethics committee of SUMC in accordance with the principles of the Declaration of Helsinki (SOR-17-0148). In accordance with Ministry of Health regulations, the institutional ethics committee did not require written informed consent because the data were obtained anonymously from medical records, with no direct participation of patients.

### Study population

All women aged 18–45 with a singleton pregnancy and a diagnosis of HG that were admitted to the gynecological ward and gave birth at the SUMC between the years 2013–2016, were included in the study. Data were retrieved from the patient's computerized medical records. Diagnosis of HG was determined by an obstetrician–gynecologist, according to the International Classification of Diseases 9th revision (ICD-9).The comparison group consisted of healthy parturient that delivered subsequently to a patient from the study group, therefor avoiding selection bias. The study population included patients from two main ethnic groups, Jewish and Bedouin Arabs. The prevalence of Lack of Prenatal Care (LOPC) and adverse obstetrical outcomes is known to be higher in the Bedouin Arab population [13], to prevent selection bias both groups are equally presented in this study.

Severe HG was defined as patients diagnosed with HG and who presented at least two of the following criteria [8, 11].

(1) Three or more hospitalizations due to HG during the first half of pregnancy.
(2) Elevated liver enzymes [aspartate transaminase (AST) and alanine transaminase (ALT)], on at least one liver function assay.
(3) Abnormal levels of sodium or potassium on at least one blood chemistry assay.
(4) Total weight gain of less than 7 kg during pregnancy, calculated as the difference between measurements at first trimester and on the day of delivery.
(5) Ketonuria, defined as positive urine ketone bodies on urine dipstick examination.

Patients with BMI lower than 18, patients with a reported history of gastric or duodenal ulcer due to *Helicobacter pylori* infection, patients with a reported history of gastrointestinal tract diseases prior to pregnancy (including: irritable bowel syndrome, inflammatory bowel disease and gastroesophageal reflux disease), patients with known congenital gastrointestinal tract defects or liver or kidney disease prior to pregnancy and patients with chronic hyperthyroidism subjected to medical treatment were excluded from the study.

### Definitions

Amniotic fluid disorders were diagnosed using ultrasonography. Polyhydramnios was defined as amniotic fluid index (AFI) of 24 cm or more, and oligohydramnios was defined as AFI of 5 cm or less. Gestational diabetes mellitus was defined as 'type A1' for women who were managed with dietary and lifestyle modifications only, and 'type A2' for those who were managed with medical therapy. Preterm delivery was defined as delivery occurring before 37 completed weeks of gestation. Small for gestational age (SGA) neonates were defined as birth weight lower than the 10th percentile. Postpartum hemorrhage was diagnosed by the physicians in the labor and delivery ward in symptomatic women who suffered from clinically significant hemorrhage or alternatively who had a blood loss of over 500 ml for vaginal deliveries or over 1000 ml in cesarean deliveries. Perinatal death was defined as any fetal death occurring during or before labor, or any neonatal death occurring within 1-month post labor. Laboratory examinations were collected upon presentation to the emergency department prior to delivery or within the first day of admission. Human chorionic gonadotropin levels were measured during the first trimester.

### Statistical analysis

Data analysis was conducted using SPSS version 21. Numeric variables with a normal distribution were described by mean and standard deviation. Numeric variables that are not normally distributed were represented

by values of median and range. Categorical variables were represented as proportions. A Univariate analysis was performed using Chi square or the Fisher's exact test for nominal variable, and *T* test for numeric variables displaying normal distribution. Significance was defined as a *P* value < 0.05. Initially, all women with HG (regardless of severity) were compared to women without HG. Later, women with mild HG were compared to those with severe HG.

## Results

A total of 104 women were admitted with the diagnosis of HG to the gynecology ward between the years 2013–2016. Twelve women were excluded from the study prior to data collection (four deliveries outside SUMC, three abortions, two no-documented deliveries, and three gastrointestinal tract diseases). Another four women were excluded after the data collection due to multiple gestation (three from the study group and one from comparison group). Of 180 women that were included in the study, 89 were diagnosed with HG and comprised the study group, while 91 deliveries of healthy women following a delivery of a patient with HG comprised the comparison group.

Demographic and clinical characteristics of the study population are displayed in Table 1. Women with HG were of comparable age and parity to those without HG. No statistically significant differences were noted in the rates of smoking, psychiatric disorders and thyroid dysfunction disorders between the two groups. Women with HG were more likely to have experienced HG in a previous pregnancy (12.4% vs 0%, $P = 0.001$).

Pregnancy-related complications are displayed in Table 2. The mean number of hospitalization days due to HG in the study group was $5.79 \pm 6.22$ days. Mean weight gain during pregnancy was not significantly different between the groups.

Apart from the rate of amniotic fluid abnormalities that was significantly lower in the study group, rates of all other pregnancy complications that were evaluated were similar between the groups.

Laboratory values of patients in the study groups are displayed in Table 3. Three laboratory values were found to be significantly higher in the study group: hematocrit, hemoglobin and ALT (Table 3). Thyroid-Stimulating Hormone (TSH) values were found to be significantly lower in the HG group. Mean urine ketone bodies in urine dipstick test was $3.2 \pm 1.3$ in HG group, compared with no urine ketone bodies in the comparison group. No significant differences were noted between the two groups in all other measured laboratory values.

**Table 1** Demographic and clinical characteristics of patients with and without hyperemesis gravidarum

| Variables | HG ($N = 89$) | No HG ($N = 91$) | *P* value |
|---|---|---|---|
| Ethnicity *N* (%) | | | |
| Bedouin | 38 (42.7%) | 55 (60.4%) | 0.057 |
| Jewish | 50 (56.2%) | 35 (38.5%) | |
| Other | 1 (1.1%) | 1 (1.1%) | |
| Maternal age *N* (%) | | | |
| 18–25 | 42 (47.2%) | 28 (30.8%) | 0.075 |
| 26–35 | 41 (46.1%) | 56 (61.5%) | |
| > 35 | 6 (6.7%) | 7 (7.7%) | |
| Parity *N* (%) | | | |
| Multiparous | 55 (61.8%) | 68 (74.7%) | 0.062 |
| Nulliparous | 34 (28.2%) | 23 (25.3%) | |
| Previous miscarriages *N* (%) | 27 (30.3%) | 20 (22.0%) | 0.202 |
| Previous C/S *N* (%) | 16 (18.0%) | 11 (12.1%) | 0.269 |
| HG in previous pregnancy *N* (%) | 11 (12.4%) | 0 (0.0%) | 0.001 |
| Chronic medication therapy *N* (%) | 4 (4.5%) | 11 (12.1%) | 0.065 |
| Smoking *N* (%) | 2 (2.2%) | 3 (3.3%) | 0.511 |
| Psychiatric disorders *N* (%) | 7 (7.9%) | 3 (3.3%) | 0.156 |
| Chronic HTN *N* (%) | 1 (1.1%) | 1 (1.1%) | 0.746 |
| ART *N* (%) | 7 (7.9%) | 2 (2.2%) | 0.079 |
| Thyroid dysfunction *N* (%) | 2 (2.2%) | 5 (5.5%) | 0.231 |

*C/S* caesarean section, *HG* hyperemesis gravidarum, *HTN* hypertension, *ART* assisted reproductive technique

Maternal and neonatal outcomes are summarized in Table 4. No statistically significant differences were found in pregnancy outcomes between the groups.

We performed a subgroup analysis, and divided patients with HG into mild and severe HG (Table 5) (laboratory values are presented Appendix 1). TSH was found to be significantly lower in the severe HG group. No significant difference in maternal and neonatal outcomes was found between the subgroups of HG.

## Discussion

This study aimed at investigating whether an association between HG and adverse pregnancy outcomes exists. No statistically significant association was demonstrated between HG and several adverse pregnancy outcomes that were evaluated. Our findings remained consistent after further dividing women with HG into severe and mild presentations.

The association between HG and pregnancy complications has long been debated. Our findings are in accordance with the findings of four other studies which assessed more than 82,000 subjects combined [7–10]. Koudijs et al. [10]

**Table 2** Pregnancy complications in patients with and without hyperemesis gravidarum

| Variables | HG ($N=89$) | No HG ($N=91$) | $P$ value |
|---|---|---|---|
| No. of admissions (mean ± SD) | 1.67 ± 1.49 | b | |
| Total no. of days of admission[a] (mean ± SD) | 5.79 ± 6.22 | b | |
| Weight gain during pregnancy (mean ± SD) | 10.12 ± 7.28 | 9.72 ± 6.25 | 0.776 |
| Amniotic fluid disorders | | | |
| Oligohydramnios | 1 (1.1%) | 3 (3.3%) | 0.005 |
| Polyhydramnios | 1 (1.1%) | 5 (5.5%) | |
| Chorioamnionitis *N* (%) | 1 (1.1%) | 0 (0.0%) | 0.494 |
| Preeclampsia *N* (%) | | | |
| Mid | 0 (0.0%) | 1 (1.1%) | 0.368 |
| Severe | 1 (1.1%) | 0 (0.0%) | |
| Gestational hypertension *N* (%) | 1 (1.1%) | 4 (4.4%) | 0.191 |
| Gestational diabetes mellitus *N* (%) | | | |
| A1 | 0 (0.0%) | 3 (3.3%) | 0.081 |
| A2 | 0 (0.0%) | 2 (2.2%) | |

*No.* number

[a]Due to hyperemesis gravidarum

[b]Women without hyperemesis gravidarum were not admitted

**Table 3** Laboratory values of patients with and without hyperemesis gravidarum

| Variables | HG ($N=89$) | No HG ($N=91$) | $P$ value |
|---|---|---|---|
| Beta HCG (mean ± SD) | 22,456.67 ± 42,746.85 | 2939.00 ± 37,188.06 | 0.544 |
| TSH (mean ± SD) | 1.25 ± 0.95 | 1.75 ± 0.89 | 0.002 |
| T3 (mean ± SD) | 3.21 ± 0.69 | 3.31 ± 0.82 | 0.772 |
| T4 (mean ± SD) | 2.56 ± 4.29 | 3.67 ± 6.50 | 0.499 |
| Amylase (mean ± SD) | 76.52 ± 34.58 | 80.20 ± 25.25 | 0.176 |
| Lipase (mean ± SD) | 26.50 ± 24.54 | 16.00 ± 12.2 | 0.676 |
| AST (mean ± SD) | 28.20 ± 22.57 | 19.42 ± 6.90 | 0.310 |
| ALT (mean ± SD) | 37.44 ± 41.05 | 11.14 ± 4.41 | < 0.001 |
| Potassium (mean ± SD) | 3.86 ± 0.39 | 4.08 ± 0.40 | 0.148 |
| Sodium (mean ± SD) | 135.33 ± 2.50 | 136.57 ± 1.27 | 0.199 |
| Creatinine (mean ± SD) | 0.50 ± 0.08 | 0.59 ± 0.08 | 0.005 |
| Hematocrit (mean ± SD) | 36.96 ± 2.50 | 34.70 ± 3.58 | < 0.001 |
| Hemoglobin (Mean ± SD) | 12.78 ± 0.98 | 11.40 ± 1.40 | < 0.001 |
| Lymphocytes count (mean ± SD) | 2.20 ± 0.77 | 2.00 ± 2.21 | 0.406 |
| Neutrophils count (mean ± SD) | 7.27 ± 7.29 | 8.17 ± 2.47 | 0.268 |
| Urine ketone bodies (mean ± SD) | 3.20 ± 1.34 | 0 | < 0.001 |

*HCG* human chorionic gonadotropin, *TSH* thyroid stimulating hormone, *T3* triiodothyronine, *T4* thyroxine, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase

conducted a prospective cohort study that included more than 2000 women, of them more than 350 were diagnosed with HG. They found no associations between HG and miscarriage, gestational hypertension, preeclampsia, and stillbirth. The authors found that severe HG was associated with a significant decrease in birth weight of 172 g, although no association was found between HG and small for gestational age (SGA) neonates or neonates weighing less than 2500 g.

In contrast to our findings, Peled et al. [11] found HG to pose an independent risk factor for preterm delivery and intrauterine growth restriction. However, that study was subjected to selection bias, since 311 patients (32.9%) of the 946 women diagnosed with HG, were excluded from the study due to delivery in another facility. Furthermore, no exclusion criteria were defined, raising the possibility that other known etiologies for nausea and vomiting such as hyperthyroidism, chronic medication therapy and psychiatric disorders, may have confounded the diagnosis and the results. Fejzo et al. [14] demonstrated an association between HG and low birth weight, preterm birth and SGA neonates. However, this was

**Table 4** Obstetrical and neonatal outcomes in patients with and without hyperemesis gravidarum

| Variables | HG ($N=89$) | No HG ($N=91$) | $P$ value |
|---|---|---|---|
| Gestational age at delivery (mean ± SD) | 38.83 ± 2.26 | 39.11 ± 2.61 | 0.44 |
| Preterm birth *N* (%) | 8 (9.0%) | 9 (9.9%) | 0.836 |
| Birth weight (mean ± SD) | 3076.06 ± 449.97 | 3178.90 ± 559.32 | 0.176 |
| SGA *N* (%) | 5 (5.6%) | 2 (2.2%) | 0.213 |
| Placental abruption *N* (%) | 1 (1.1%) | 0 (0.0%) | 0.494 |
| C/S N (%) | 15 (16.9%) | 13 (14.3%) | 0.635 |
| Apgar score < 7 at 1 min *N* (%) | 9 (10.1%) | 5 (5.6%) | 0.256 |
| Apgar score < 7 at 5 min *N* (%) | 2 (2.2%) | 1 (1.1%) | 0.5 |
| pH (mean ± SD) | 7.30 ± 0.95 | 7.29 ± 0.92 | 0.23 |
| PPH *N* (%) | 1 (1.1%) | 1 (1.1%) | 0.746 |
| Perinatal mortality *N* (%) | 2 (2.2%) | 1 (1.1%) | 0.22 |
| Number of post-delivery admission days (median, mode) | 3 (3) | 3 (3) | 0.484 |

*SGA* small for gestational age, *C/S* caesarean section, *PPH* postpartum hemorrhage

**Table 5** Obstetrical outcomes for mild and severe hyperemesis gravidarum

| Variables | Mild HG ($N=46$) | Severe HG ($N=43$) | $P$ value |
|---|---|---|---|
| Gestational age at delivery (mean ± SD) | 39.06 ± 1.55 | 38.59 ± 2.82 | 0.495 |
| Preterm birth *N* (%) | 4 (8.7%) | 4 (9.3%) | 0.974 |
| Birth weight (mean ± SD) | 3108.48 ± 362.04 | 3041.39 ± 509.40 | 0.332 |
| SGA *N* (%) | 1 (2.2%) | 4 (9.3%) | 0.160 |
| Placental abruption *N* (%) | 0 (0.0%) | 1 (2.3%) | 0.202 |
| C/S *N* (%) | 6 (13.0%) | 9 (20.9%) | 0.528 |
| Apgar score < 7 at 1 min *N* (%) | 4 (8.7%) | 5 (11.6%) | 0.417 |
| Apgar score < 7 at 5 min *N* (%) | 0 (0.0%) | 2 (4.7%) | 0.198 |
| pH (mean ± SD) | 7.31 ± 0.10 | 7.30 ± 0.89 | 0.434 |
| PPH *N* (%) | 1 (2.2%) | 0 (0.0%) | 0.62 |
| Perinatal mortality *N* (%) | 0 (0.0%) | 2 ( 4.7%) | 0.192 |
| Number of post-delivery admission days (median) | 3 (3) | 3 (3) | 0.78 |

*SGA* small for gestational age, *C/S* caesarean section, *PPH* postpartum hemorrhage

a questionnaire-based case–control study and was subject to potential recall bias.

Opposed to the previously reported association between HG and anemia related to nutritional deficiencies [2], our study demonstrated significantly higher hematocrit and hemoglobin levels in the HG group. Significantly higher levels were further demonstrated in severe cases of HG compared with mild cases. We believe that these findings might be explained at least in part by hemoconcentration secondary to vomiting and dehydration in the severe cases of HG. This was also supported by significantly higher urine ketone bodies in this group. This association may imply the use of high levels of hemoglobin and hematocrit as an indicator for severe cases of HG in future studies.

Our study demonstrated lower TSH levels in women diagnosed with HG compared to the comparison group. Further, TSH levels were significantly lower in severe cases compared with mild cases of HG, although still within the normal range for TSH values. This finding might strengthen the suspected association between human chorionic gonadotropin levels, TSH and HG [5].

In our medical center, amniotic fluid disorders may be diagnosed using ultrasonography during the obstetrical emergency room visit. Our study demonstrated lower rates of amniotic fluid disorders, both polyhydramnios and oligohydramnios, in women with HG. Considering widely different etiologies for these two clinical conditions, as well as the fact that the diagnosis is mostly given following an ultrasound examination which is operator-dependent and subjected to great inter-operator variance, we were not able to speculate regarding a plausible explanation for this finding and we assume it to be incidental.

This study holds several strengths. SUMC is a tertiary hospital, where practically all deliveries in the region take place, representing an unselected population and decreasing the risk of selection bias. Moreover, SUMC serves

some variable ethnic populations, all of which were represented in this study, thus also increasing the generalizability of our findings. In addition, only severe cases of HG leading to hospitalization were included in this study, which further highlights our findings regarding the lack of an association between HG and adverse pregnancy outcomes. Yet, this study's main limitations include its limited number of patients with HG and its retrospective design, leading to some missing data mainly regarding laboratory values.

In conclusion, in this retrospective cohort study no association was demonstrated between HG and adverse pregnancy outcomes regardless of HG severity. Women with severe nausea and vomiting during pregnancy can be reassured that HG is not associated with unfavorable maternal and neonatal outcomes. Further research investigating the association between HG and thyroid dysfunction and its clinical application is suggested.

**Acknowledgements** The authors report no sources of support for the work. This study was conducted as part of the requirements for MD degree from the Goldman Medical School at the Faculty of Health Sciences, Ben-Gurion University of the Negev.

**Authors' contribution** Niv Agmon: protocol development, data collection, data analysis, manuscript writing. Shanny Sade: protocol development, data collection, manuscript writing. Gali Pariente: protocol development, data collection, data analysis, manuscript editing. Reut Rotem: protocol development, data analysis, manuscript editing. Adi Yehuda Weintraub: protocol development, data collection, data analysis, manuscript editing.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

## Appendix

See Table 6.

**Table 6** Laboratory values for mild and severe hyperemesis gravidarum

| Variables | Mild HG ($N=46$) | Severe HG ($N=43$) | $P$ value |
|---|---|---|---|
| Beta HCG (mean ± SD) | 22,592.93 ± 51,829.97 | 22,343.11 ± 35,032.78 | 0.833 |
| TSH (mean ± SD) | 1.42 ± 0.96 | 1.05 ± 0.91 | 0.002 |
| T3 (mean ± SD) | 0.34 ± 0.68 | 0.31 ± 0.69 | 0.638 |
| T4 (mean ± SD) | 3.17 ± 5.18 | 2.06 ± 3.47 | 0.666 |
| Amylase (mean ± SD) | 76.71 ± 36.61 | 76.40 ± 34.11 | 0.405 |
| Lipase (mean ± SD) | 22.42 ± 25.18 | 29.35 ± 24.33 | 0.666 |
| AST (mean ± SD) | 19.56 ± 11.40 | 37.46 ± 27.52 | < 0.001 |
| ALT (mean ± SD) | 19.91 ± 19.82 | 55.79 ± 49.04 | < 0.001 |
| Potassium (mean ± SD) | 3.95 ± 0.30 | 3.75 ± 0.45 | 0.020 |
| Sodium (mean ± SD) | 135.95 ± 1.90 | 134.67 ± 2.88 | 0.019 |
| Creatinine (mean ± SD) | 0.50 ± 0.76 | 0.89 ± 0.13 | 0.017 |
| Hematocrit (mean ± SD) | 36.57 ± 2.28 | 37.39 ± 2.69 | < 0.001 |
| Hemoglobin (mean ± SD) | 12.63 ± 0.95 | 12.97 ± 0.99 | < 0.001 |
| Lymphocytes count (mean ± SD) | 1.76 ± 0.92 | 2.24 ± 3.04 | 0.286 |
| Neutrophils count (mean ± SD) | 6.52 ± 2.50 | 8.07 ± 10.17 | 0.219 |
| Urine ketone bodies (mean ± SD) | 2.65 ± 1.61 | 3.78 ± 0.564 | < 0.001 |

*HCG* human chorionic gonadotropin, *TSH* thyroid stimulating hormone, *T3* triiodothyronine, *T4* thyroxine, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase

## References


1. Niebyl JR (2010) Clinical practice. Nausea and vomiting in pregnancy. N Engl J Med 363:1544–1550. https://doi.org/10.1056/NEJMcp1003896
2. Buyukkayaci Duman N, Ozcan O, Bostanci MÖ (2015) Hyperemesis gravidarum affects maternal sanity, thyroid hormones and fetal health: a prospective case control study. Arch Gynecol Obstet 292:307–312. https://doi.org/10.1007/s00404-015-3632-2
3. Fejzo MS, Sazonova OV, Sathirapongsasuti JF et al (2018) Placenta and appetite genes GDF15 and IGFBP7 are associated with hyperemesis gravidarum. Nat Commun 9:1178. https://doi.org/10.1038/s41467-018-03258-0
4. Fejzo MS, Myhre R, Colodro-Conde L et al (2017) Genetic analysis of hyperemesis gravidarum reveals association with intracellular calcium release channel (RYR2). Mol Cell Endocrinol 439:308–316. https://doi.org/10.1016/j.mce.2016.09.017
5. Erick M, Cox JT, Mogensen KM (2018) ACOG practice bulletin 189: nausea and vomiting of pregnancy. Obstet Gynecol 131:935. https://doi.org/10.1097/AOG.0000000000002604
6. Eliakim R, Abulafia O, Sherer DM (2000) Hyperemesis gravidarum: a current review. Am J Perinatol 17:207–218. https://doi.org/10.1055/s-2000-9424
7. Vikanes ÅV, Støer NC, Magnus P, Grjibovski AM (2013) Hyperemesis gravidarum and pregnancy outcomes in the Norwegian Mother and Child Cohort—a cohort study. BMC Pregnancy Childbirth 13:169. https://doi.org/10.1186/1471-2393-13-169
8. Dodds L, Fell DB, Joseph KS et al (2006) Outcomes of pregnancies complicated by hyperemesis gravidarum. Obstet Gynecol 107:285–292. https://doi.org/10.1097/01.AOG.0000195060.22832.cd
9. Morokuma S, Shimokawa M, Kato K et al (2016) Relationship between hyperemesis gravidarum and small-for-gestational-age in the Japanese population: the Japan Environment and Children's Study (JECS). BMC Pregnancy Childbirth 16:247. https://doi.org/10.1186/s12884-016-1041-6
10. Koudijs HM, Savitri AI, Browne JL et al (2016) Hyperemesis gravidarum and placental dysfunction disorders. BMC Pregnancy Childbirth 16:374. https://doi.org/10.1186/s12884-016-1174-7
11. Peled Y, Melamed N, Hiersch L et al (2014) The impact of total parenteral nutrition support on pregnancy outcome in women with hyperemesis gravidarum. J Matern Fetal Neonatal Med 27:1146–1150. https://doi.org/10.3109/14767058.2013.851187
12. Matok I, Gorodischer R, Koren G et al (2009) The safety of metoclopramide use in the first trimester of pregnancy. N Engl J Med 360:2528–2535. https://doi.org/10.1056/NEJMoa0807154
13. Abu-Ghanem S, Sheiner E, Sherf M et al (2012) Lack of prenatal care in a traditional community: trends and perinatal outcomes. Arch Gynecol Obstet 285:1237–1242. https://doi.org/10.1007/s00404-011-2153-x
14. Fejzo MS, Magtira A, Schoenberg FP et al (2013) Antihistamines and other prognostic factors for adverse outcome in hyperemesis gravidarum. Eur J Obstet Gynecol Reprod Biol 170:71–76. https://doi.org/10.1016/j.ejogrb.2013.04.017