CASE-CONTROL STUDY OF FOOD INTAKE, NAUSEA AND VOMITING OF PREGNANT WOMEN

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Acknowledgements

Present trial was performed at the Women Clinic, KK, at Haukeland University Hospital during the period of May 2012 and May 2014. Sixty-nine participants were recruited to the trial from Haukeland University Hospital, Stavanger University Hospital and Førde Hospital, in addition to some health care centers in Bergen. I would like to thank all the participants and all the nurses at the recruiting hospitals, as well as the physicians and gynecologists and other involved in the recruitment and data collection of present study.

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Abstract

Background: Severe pregnancy induced nausea and vomiting, also known as Hyperemesis gravidarum (HG), can lead to significant reduced quality of life (QOL) and of food intake. Untreated this can potentially harm both mother and foetus. An English questionnaire, PUQE, identifies women severely affected with HG. Our aim in present study was to investigate whether scores from a Norwegian translated version of PUQE; SUKK (SvangerskapsUtløst Kvalme Kvantifisering) was associated with severity of nausea and vomiting of pregnancy (NVP) and the nutritional intake of women with HG (cases) compared to a group of healthy pregnant women (controls).

Methods: A prospective observational case-control study was conducted in Western-Norway: Bergen, Stavanger and Førde, during May 2013-January 2014. A total of 69 pregnant woman participated; 38 hospitalised patients with hyperemesis gravidarum and 31 healthy pregnant controls. The participants answered the SUKK questionnaire and a question of QOL, in addition to report their nutritional intake over a period of 24-hours. SUKK and QOL scores and food intake were calculated and compared.

Results: Women with HG had a lower gestational age (median 65 versus 83 days, p=0.004), and larger weight-change from pre-pregnant (median -3 kg vs. +2kg, p<0.001) compared to the healthy controls. Otherwise the groups were similar regarding pre-pregnant BMI, age, gravidity, and weight at inclusion. Furthermore, the HG patients had significant higher SUKK-score (median 13, 95% CI [11-14] vs 7, 95% CI [4-8]), lower QOL score (median score 3 vs. 6) and lower energy intake (median 957 kcal vs. 1651 kcal) compared to controls (all p<0.001). SUKK-score was inversely correlated to nutritional intake of all variables measured ($p\leq$0.004). SUKK scores in the HG group were measured at both admission and discharge. At discharge SUKK score had decreased to median six (95% CI [5-8]) and QOL score increased to 6.5, (both p<0.001) compared to values at admission.

Conclusion: The Norwegian version of PUQE; SUKK gives a robust indicator of severe hyperemesis gravidarum. There is a strong invers correlation of the SUKK scores and the nutritional intake of the women in the two groups. SUKK score improved after treatment of HG. Thus, PUQE/SUKK has been validated to assess HG severity and effect of treatment in a Norwegian population. Additionally, the food intake of the two groups were significantly different in all measured nutrients.

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List of Abbreviations

NVP:	Nausea and vomiting of pregnancy
HG:	Hyperemesis gravidarum
PUQE:	Pregnancy Unique Questionnaires of Emesis and Nausea
QOL:	Quality of life
SUKK:	Svangerskapsutløst kvalme kvantifisering / Pregnancy induced nausea quantification
BMI:	Body Mass Index
KCAL:	Kilo calories
E%:	Percentages of energy intake
CARB:	Carbohydrates
CI:	Confidence Interval

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1. Introduction

1.1 Nausea and Vomiting in Pregnancy

Nausea and vomiting occur in approximately 80 % of all pregnancies (1). It is mostly self-limiting, however leading to reduced quality of life (2). Women with even a moderate form of nausea and vomiting of pregnancy (NVP) can become emotional distressed and depressed (3-5). About 0.3-1.5 % of pregnant women have a more serious condition called Hyperemesis Gravidarum (HG) (6). In 1968, Fairwether defined Hyperemesis as "Vomiting occurring in pregnancy for the first time before the twentieth week of gestation, and of such severity as to require the patient's admission to hospital, the vomiting being unassociated with such coincidental condition as appendicitis, pyelitis, etc." (7). Women with HG can have a problematic situation regarding intake and retaining food and beverage. Low food intake in combination with frequent vomiting can lead to dehydration, metabolic imbalance, nutrition deficiency and weight loss. There have been tested several theories, among others hormonal status (6, 8, 9) and psychological causes (10). However, the etiology of HG remains unknown, despite decades with lots of interest and research (3). Even though, some maternal factors such as high pre-pregnancy weight, previous pregnancy with HG, low age (11, 12) and genetics (13, 14) appears to be involved with development of HG.

1.2 Challenges for mother

1.2.1 Decreased nutrition intake

Nausea and vomiting may influence amount and choices of food intake in pregnant women (15). Insufficient food intake and/or vomiting during pregnancy can lead to anemia as well as deficiencies of multiple nutrients. There are few investigations exploring the effect of nausea and vomiting during pregnancy in relation to food intake. In a study of Latva-Pukkila and colleagues, 187 women reported their food habits during first trimester of pregnancy, 134 women with NVP and 53 without (15). They reported statistically significant lower meat intake and a lower energy percent provided by protein in the NVP group as well as higher energy percent provided by carbohydrates compared to healthy pregnant women. There was also a tendency towards a lower intake of vegetables in the NVP group. Meat is a god source of Vitamin B12 and Magnesium. These components were also statistically significant reduced in the NVP group compared to the control group of healthy pregnant women.

A study from South Africa of 20 pregnant women with HG compared to 20 healthy pregnant women reported a 50% decrease in most of nutrients as well as total energy intake (16).

In a Mother and Child cohort study from Norway investigating 51 000 pregnancies, they concluded that woman with NVP had significantly different food intake compared to healthy pregnant women (1). They reported that the NVP group had a higher energy intake, with a higher energy percent intake of carbohydrates and added sugar. With a higher intake of sugar- and artificial sweetener-containing soft drinks compared to the nausea without vomiting and the symptom free groups.

1.2.2 Impact of nutritional status

When nutritional and energy demands are met by food intake, the nutritional status is adequate (17). Weight loss can be an indicator of declining nutritional level (18). During pregnancy the weight is a composite of both mother and fetus, thus designated weight charts have been specified throughout pregnancy.

1.2.2.1 Weight gain

Recommendations of weight gain are depending on the pre-pregnancy weight (19); Women with low body mass index (BMI), <20 kg/m^2, should gain between 12.5 and 18 kg during the pregnancy (20). Normal weighted women, with a BMI between 20 and 26, are recommended to gain between 11.5 and 16 kg. Women with overweight, BMI between 26 and 29, should gain between seven and 11.5 kg and those with a BMI over 30 should gain less than six kg during the pregnancy. Women with HG have a two-fold higher risk of low weight gain compared to healthy women (21).

Additionally, it has been developed recommendations of weight gain during the different stages of pregnancy for women with normal pre-pregnancy weight (22). The recommendation is set to be 840 g (12 g per day) during the first ten weeks, 3.4 kg (48 g per day) during the weeks from week ten to twenty, 4.5 kg (64 g per day) during the weeks from twenty to thirty and four kg (57 g per day) during the last ten weeks.

1.2.2.2 Food intake

Nutritional status is associated to food intake, even absorption and metabolism is influent factors. The food-intake can be quantified in several ways. Ideally, the intake of food and drinks should be registered consecutively during several days, including both weekdays and weekends. Another proper method is to perform a diet interview collecting the medical and dietary history and assessing the pregnant woman's attitudes towards her food and drink intake and appetite (23). Together with a meticulous recollection of her food intake during the last 24-hours, this interview may give a good understanding of their nutritional status. A

proper food interview is somewhat time-consuming. Alternatively, the patient must write down her food intake during three to four of days. Designated food-diaries exist where the most common food and drink components can be checked consecutively (24). A prospective real-time registration is generally evaluated as the most exact, minimizing recall bias (25). The nutritionist will then be able to analyze the diary and estimate total energy intake as well as macro- and micronutritional composition. Computer programs may facilitate this evaluation, enabling to access even micronutrient intake. Blood tests (s-prealbumin, albumin, glucose, electrolytes and transferrin) can give supplemental information (17) of the short term nutritional status (25).

1.2.3 Nutritional requirements

Adequate nutritional intake during pregnancy is important to insure good growth and development of fetus and to promote good maternal health (19). Pregnant women should follow the general food recommendations (17), however, they must be careful with some sorts of food that can contain bacteria or other contaminants (26).

During the gestational period metabolic demands increases due to growth of the fetus, placenta, maternal tissues growth (27). The severe food deprivation during the World War II has given us a great understanding of the necessity of adequate food intake to prevent pregnancy complications and poor birth outcome (28). The famine during the years of the war led to higher rates of spontaneous abortions, stillbirths and neonatal births. For the surviving children during this period, there were observed lower birth weight and birth lengths. In addition, there were higher rates of congenital malformations.

During pregnancy the metabolic demands increases by 15% (28). This requires a higher energy intake. In healthy pregnant women this is usually good regulated by the feeling of hunger and/or reduced energy expenditure (19). During the first trimester the energy requirements is only slightly increased (+10 kcal/day) compared to non-pregnant women (28). During the second and third trimester, it increases with about 340 kcal and 452 kcal extra per day, respectively.

1.2.4 Recommendations of nutrients

1.2.4.1 Protein

The protein requirement rises during pregnancy (28). This is caused by the syntheses of maternal and fetal tissue growth. The daily recommendations are 71 g protein per day,

compared to 46 g per day for non-pregnant women (29). In energy percentage (E%), the recommendation is set to be between 10 to 20 E% of the total energy intake (30).

1.2.4.2 Carbohydrate

To maintain appropriate blood glucose and prevent ketosis the recommendations of carbohydrates is set to be between 135 g and 175 g per day (28). Recommended E% intake of carbohydrates is set to be between 46 and 60 E% of total energy intake (30).

1.2.4.3 Lipids

There are no daily recommendations of total lipid intake either for pregnant nor non-pregnant women (28). However, there are recommendations of the essential poly-unsaturated fatty acids omega 3 (1.4 g per day) and omega 6 (13 g per day) (29). The recommended E% intake of fat is set to be between 25 and 40 E% of total energy intake (30).

In analogue with only marginally increased total energy requirements during the first trimester, this amounts to these three macronutrients as well (30).

1.2.5 Recommendations of micronutrients

Some of the micronutrients have the same recommendations for pregnant women as for non-pregnant women (28). These are Vitamin D, Vitamin E, Vitamin K, Calcium, Biotin, Phosphorus and Fluoride.

Micronutrient with an increased requirement during pregnancy are (28);

Vitamin A (+ 10%)
Vitamin C (+ 13%)
Thiamin (+ 27%)
Riboflavin (+27%)
Niacin (+ 29%)
B6 (+ 36%)
Folate (+ 50%. In Norway the recommendation is 400 µg both for women in childbearing age and during the first three months of pregnancy)
Pantothenic acid (+ 20%)
Vitamin B_{12} (+ 8%)
Choline (+ 6%)
Magnesium (+ 13%)
Iron (+ 50%)

Zinc	(+ 38%)
Iodine	(+ 47%)
Selenium	(+ 9%)

1.2.6 Wellbeing

Symptoms of HG have an undesirable impact of the overall wellbeing of pregnant women (5, 31). Women with HG describe their condition as a feeling of helplessness, and describe a reduced physical and emotional well-being (5) and it is associated with depression (3) and anxiety (32). In some extreme cases of HG, women chose to terminate the pregnancy (3). For most women with HG the symptoms subsides during second trimester. However, Fejzo and colleagues reported that women with high pregnancy weight loss (>15% of pre-pregnancy weight) due to HG had increased recovery time (>1month after delivery) compared to woman with less weight loss or weight gain during pregnancy (33).

1.2.7 Social consequences

When women experience extreme nausea and vomiting, they find it troublesome to function in daily activities, family and social settings and in work situations (5, 34). HG often requires hospital treatment (1, 31, 35), being the most common reason for hospitalization in early pregnancy (36). Including days or weeks with sick leave, this condition has a significant economic impact as well (37).

1.2.8 Pregnancy complications

Women with nausea and vomiting and poor weight gain have been reported as having increased risk of pregnancy-induced hypertension, gestational diabetes and preeclampsia (4). Nausea and vomiting has generally been linked with reduced risk of miscarriage (38), a similar association has also been reported in HG (39). Depue and co-workers reported a reduced rate of spontaneous abortions and stillbirths in women with HG compared to women without extreme nausea and vomiting (39).

1.2.9 Maternal mortality and time-trends

Inadequate treatment of HG may cause severe or mortal consequences for the woman (4, 40). Wernicke's encephalopathy and central pontine myelinolysis, might be an end outcome (41). Before the introduction of intravenous treatment with fluid replacement in the 1950's, there were high rates of mortality caused by HG. Between 1930 and 1960 the mortality rate dropped from 159 per million to three per million pregnancy (7, 42). After introduction of

antiemetic medication, intravenous treatment and parental nutrition, HG is no longer a mortal disease (43).

1.3 Neonatal and pregnancy outcomes

1.3.1 Pregnancy outcome

Several studies have evaluated HG and NVP in relation to pregnancy outcomes. Conclusions are conflicting (4, 21, 44). Some studies report an increased risk of complications such as preterm labor, low birth weight, birth defects (45, 46) and a higher rate of stillbirths (4). However in a study by Rosenboom and colleagues it was commented that the women presenting with HG had underlying socioeconomic risk factors that largely explained their increased risk of these pregnancy complications (46).

1.3.2 Growth development

A cohort study from Norway concluded that there was an inverse correlation between HG and large for gestational age and very preterm birth (47). Hyperemesis babies had slightly lower birth weight and gestational age. They also reported an association between HG and perinatal death, however no associations between HG and stillbirth or neonatal death. A retrospective cohort study from Canada concluded that total weight gain >/< 7 kg during pregnancy was an essential factor for pregnancy outcomes (21). Women with HG and a weight gain less than 7 kg during pregnancy had statistically significant higher risk of having a preterm delivery, a child with low birth weight or an infant small for gestational age (SGA) compared to women with HG, with a weight gain over 7 kg.

1.3.3 Long-term consequences

Poor nutritional status during pregnancy may effect fetal growth and diseases later in life (48). Barker and his colleague suggested a hypothesis that severe malnutrition during critical periods of pregnancy might program the fetus for metabolic alterations exposing the child at risk of developing diabetes and cardiovascular disease later in life (49). Barker's hypothesis was developed among others after observations from the Dutch famine 1944 World War II with extremely restricted caloric intakes (400-800 kcal/day, mimicking the situation in Hyperemesis pregnancies). Pregnancies during this period had significantly increased risks of intrauterine growth restriction and the offspring had higher risks of developing coronary heart disease later in life (50). Studies of long term consequences on children of mothers with HG have reported an increased risk of developing depression, bipolar disorder and anxiety (51).

Other long-term evaluations indicated that they have a higher nonverbal intelligence score (52).

1.4 Treatment of NVP/HG

The severity of the symptoms is the basis of the treatment of NVP and HG (4). It is important to exclude other diagnosis before starting any treatment program (53) since pathological conditions such as urinary infection, gastrointestinal diseases, endocrine disorders and neurological diseases might also lead to nausea and vomiting.

1.4.1 Diet and lifestyles modification

Mild nausea may be alleviated by changes in diet and lifestyle modifications (4, 15). Common food recommendations are to have frequent and small meals (54, 55) of low energy food and higher proportion of daily energy intake by proteins (56). In addition, to prevent dehydration, it is important to drink between meals (54). Stress might worsening the symptoms of pregnancy induced nausea and vomiting and should be avoided (57). Additionally, spicy food and food with strong odors should be avoided as they can lead to worsening of symptoms (54). Studies have proposed that taking vitamins before and in the beginning of pregnancy can prevent severe NVP (58, 59). Women are additionally recommended to eat some dry crackers in the morning before getting up in the morning (31).

1.4.2 Antiemetic medications

Antiemetic drugs can alleviate nausea and vomiting during pregnancy as well as nausea in other conditions. Antiemetic drugs has been in common use since the 1960's (60). In general, any medication should be used with caution during pregnancy, however the most common antiemetics (antihistamines and prochlorperazin) have been used for decades and are considered safe (53). The Norwegian Health Authorities have recently issued a warning restricting Metoclopramide use to a maximum of 5 days (due to neurological complications for the mother) nevertheless this has not been highlighted in other European or US guidelines.

1.4.3 Fluid and electrolyte replacement

Due to both reduced intake and excessive loss by vomiting, HG patients are at risk of being dehydrated and may experience electrolyte imbalances. Most patients respond well to treatment by intravenous fluids (61). If the patient has been vomiting for two weeks or more, it might be necessary to supplement with vitamin B6 and Thiamin (55) to avoid neurological complications such as Wernicke's encephalopati. During rehydration, hyponatremia should be avoided as this may cause central pontine myolysis (62), a neurological disease.

1.4.4 Nutrition supplements

Women who, despite treatment by intravenous fluid and electrolytes or antiemetics, continues to lose weight, should be considered for enteral or parenteral feeding (61, 63).

1.4.4.1 Enteral Nutrition

If the woman is undernourished or has inadequate food intake for the last 7-10 days, enteral nutrition (EN) should be considered(64). A feeding tube can be inserted by gastroscopy through the nose and down to the jejunum (upper part of the intestine). Designated enteral nutrition solution should be delivered continuously by infusion pump, starting at a low velocity and gradually increasing until 2 l is given during 24 hours (53). When the condition is improved, the woman may continue the enteral feeding at home. At the time where she has resumed normal oral food intake for two days, the enteral tube may be removed. If enteral feeding does not lead to any improvement and the woman keeps on losing weight, parenteral nutrition (PN) should be offered (65).

1.4.4.2 Parenteral Nutrition

Parenteral nutrition (PN) is when nutritional solution is delivered directly to the patient's blood via a catheter inserted into a vein (66). PN is preferred when the woman cannot tolerate food through the gastrointestinal system (65). A parenteral nutritional supplement (1-1.5 l) can be administered by peripheral venous cannula, total 1000 kcal or half of daily energy requirement (53). If adequate nutrition is not resumed within a few days enteral tube feeding is recommended (67, 68). A peripheral vein is preferred for treatment lasting a short period of time (days) and might be administered in parallel with correction of fluid and electrolyte imbalance (53), and while initiating the enteral feeding. When the treatment is prolonged, parental feeding should be delivered through a central vein (66), either by peripheral inserted central line (PICC) line or by central venous catheter (CVC). The parenteral solution does not contain any micronutrients (as opposed to enteral solutions). Therefore, vitamins and minerals must be added to the parenteral solution before administration, to prevent nutritional deficiencies. For those women who do not improve by PN or EN supplements, total parental nutrition (TPN) might be required (31). TPN signifies that most of or all of daily nutritional requirements are delivered by the venous route. Early startup with treatment of TPN in women with HG has been associated with a lower rate of adverse pregnancy outcome (40). However, TPN and PICC are associated with a risk of catheter related complications such as bacteremia, sepsis and thrombosis (69), as well as complications due to lack of enteral

nutritional activity (metabolic disturbances) (70). This is therefore a last resort treatment to be considered when all other treatment options have failed (61).

1.4.4.3 Thiamin supplement

Thiamin is a water soluble vitamin and has relatively short time storage, as it has no major tissue for storage (25). The vitamin is rapidly excreted in the urine. Thiamin is important in the carbohydrate metabolism. Deficiency of the vitamin can develop quickly and can lead to fatal consequences for the mother, eg. Wernicke's encephalopathy (71). Women with sever NVP might be advised to consume carbohydrate rich food (eg. Crackers) to alleviate the nausea symptoms (31).This makes the catabolism of the vitamin even quicker.

1.5 Assessment of nausea and vomiting

Good tools to distinguish between HG and normal pregnancy induced nausea and vomiting, may give us a better understanding of the severity and predict what kind of treatment the pregnant woman needs. When women with HG receive precise treatment early, it may reduce the severity of the symptoms (34). There is no single measure to evaluate the severity of nausea and vomiting (e.g. blood test); however, there are questionnaires that can give a composite score proportional to the reported rate of sickness. Nausea and vomiting are common during the first trimester of pregnancy, it is therefore helpful to have an easy questionnaire to help to quantify the symptoms, determine level of treatment needed and evaluate the effect of the treatment.

The Rhode's Score is an eight-tier questionnaire developed primarily to evaluate nausea and vomiting during cancer treatment (72). Later this questionnaire have been validated for use to distinguish between regular nausea of pregnancy and the severe form of NVP, HG (73). Additionally, a McGill Pain Questionnaire were modified to a nausea questionnaire, named The Nausea Questionnaire, for measuring the severity of nausea and vomiting during cancer treatment and later validated to measure the severity of pregnancy induced nausea and vomiting (74). The Nausea Questionnaire involves three different questionnaires. Moreover, there is another questionnaire, the Hyperemesis Impact of Symptoms Questionnaire (HIS) which is a clinical tool developed to access both physically and psychological symptoms of HG (2). The strategy of this questionnaire is to figure how well the women with HG can handle different life situations during extreme nausea and vomiting. It contains ten questions and thus is a comprehensive questionnaire. Nevertheless, the utility of HIS has not yet been tested in the clinical evaluation of HG patients. Furthermore, it has been developed QOL

related questionnaire, the Health-Related Quality of Life questionnaire, NVPQOL (75). This questionnaire involves 30 questions regarding emotions, limitations, fatigue, physical symptoms and aggravating factors of HG.

In general, the larger and more complex a questionnaire is, the more time consuming and less user-friendly it is. Thus Pregnancy Unique Questionnaire of Emesis (PUQE), a three-tier questionnaire reporting hours of nausea, times of vomiting and times of retching episodes, was developed (76). The PUQE questionnaire originates from the Rhodes scores and has been validated to have very good correlation with the scores of the Rhodes questionnaire when evaluating pregnant patients with nausea and vomiting (77). The original PUQE evaluates symptoms during 12 hours. Consequently night –hours/sleep would unsystematic be included depending on the actual time of presenting the questionnaire. Therefore, a 24 hour modified questionnaire has been developed and validated (78). Furthermore, the PUQE questionnaire has been modified to measure the severity of nausea and vomiting of the first trimester of pregnancy (79). All of these versions of PUQE also include a question of the wellbeing, Quality of Life (QOL). QOL is a generic question that involves both the physical and emotional wellbeing of the pregnant woman.

Furthermore, the PUQE score is correlated with inability of taking iron containing vitamin supplementation in pregnancy, risk of hospitalization due to NVP/HG and increased health care costs due to NVP and HG (80). PUQE has been evaluated in several studies to assess the severity of nausea and vomiting of pregnancies in English populations (76, 78, 80-82).

We are not aware of other questionnaires regarding nausea and vomiting in pregnancy being in general clinical use. None of these questionnaires have been validated in relation to the woman's food intake. Neither have any of these pregnancy related questionnaires been evaluated in Norway. Thus in present study, we have translated the PUQE-24, from English to Norwegian, and named it SUKK: SvangerskapsUtløst Kvalme Kvantifisering.

2. Aims and Hypothesis

The severity of nausea and vomiting varies between women during the first trimester of pregnancy. By measuring the severity of the condition, it might facilitate the right treatment at an early point. The PUQE questionnaire has been validated in several versions and is considered as a valid and easy tool to measure the severity of pregnancy induced nausea and vomiting (78, 80, 82). However, this questionnaire has never been used in a Norwegian population. Neither, has the PUQE questionnaire been compared to the food intake of women affected by NVP or HG. Food consumption before conception (83) and in the beginning of the pregnancy may play a role in development of pregnancy induced nausea and vomiting (1).

Our aims in present study are to:

- Validate the translated version of PUQE: SUKK in a Norwegian population
- Compare food intake of pregnant women with severe nausea and vomiting to healthy pregnant women
- Compare the scores from the SUKK questionnaire to the reported food intake of the participating women.
- Compare the SUKK scores at admission to the scores at discharge of the hospitalized women.

3. Methods and materials

3.1 Study design

This study was a prospective case-control study investigating the severity of nausea and vomiting in pregnancy and the nutritional intake of women hospitalized due to HG (cases) as compared to healthy pregnant women (controls). Information from the participants was collected prospectively by questionnaires and food diaries.

The 24 hours English PUQE (*Appendix 1*) was translated by an authorized translator to Norwegian (*Appendix 2)* and afterwards the Norwegian version was translated back to English (*Appendix 3*). The author of the original PUQE, Gideon Koren, (76) has approved the English translation based on the Norwegian version (*Appendix 4*).

3.2 Study population

During Mai 2013 to January 2014, a total of 69 pregnant women participated. Of these, 38 were hospitalised patients with hyperemesis gravidarum and 31 healthy controls.

The HG group:

Women in the HG group were recruited at Haukeland University Hospital, Førde Hospital and Stavanger University Hospital.

Inclusion criteria

- hospitalized by HG
- defined as extreme nausea and vomiting in pregnancy
- at least two out of three criteria
    - dehydration
    - weight loss
    - electrolytes imbalances/ketonuria
- a pregnancy length of maximum 16 weeks.

Women were invited to participate in the study the first morning after hospital admission.

Exclusion criteria

- native language other than Norwegian
- other diseases causing nausea and vomiting during pregnancy.

Control group:

Women were recruited by invitation from out-patient gynaecologists, primary health care physicians, health care centres and nutritionists. Information about the study and inclusion forms was also available as posters at information boards at the campus of the University in Bergen and at Haukeland University Hospital for self-recruitment.

Inclusion criteria

- healthy pregnancy
- a pregnancy length of maximum 16 weeks

Exclusion criteria

- inability to understand and write/read Norwegian

3.3 Demographic data

Data regarding age, number of previous pregnancies with NVP or HG, gestational age at inclusion (if possible performed by sonographic determination), height and pre-pregnancy weight as well as weight at inclusion were collected together with the questionnaires (Appendix 5).

3.4 Questionnaires and variables

Information of HG patients' and control group's severity of nausea and vomiting (SUKK-score), quality of life (QOL-score) and nutritional intake were collected by a three-question SUKK questionnaire, a one question QOL score and a 24 hours prospective food-registration ticking list. The HG patients filled out the SUKK and QOL questionnaires twice, first when they were admitted to hospital and secondly when they were discharged. The questionnaires were delivered in pre-paid envelopes.

Question one (Q1) was a question regarding how many hours during the last 24 hours the pregnant woman felt nausea. Where the alternative answers were; not nausea at all (1p), nausea less than one hour (2p), nausea between two and three hours (3p), nausea between four and six hours (4p) and nausea over six hours (5 p).

Question two (Q2) was a question regarding how many episodes during the last 24 hours the pregnant woman vomited. Where the alternative answers were; did not vomit at all (1p),

vomited one to two times (2p), vomited between two and three times (3p), vomited between four and six times (4p) and vomited over six times (5 p).

Question three (Q3) was a question regarding how many episodes during the last 24 hours the pregnant woman retched or had dry heaves without bringing anything up. Where the alternative answers were; did not retch or dry heaves at all (1p), retched or dry heaves one to two times (2p), retched or dry heaves between two and three times (3p), retched or dry heaves between four and six times (4p) and retched or dry heaves over six times (5 p).

Summarizing the scores of the three SUKK questions (Q1-3), we got a total SUKK score from three to 15 points. A score between 3-6 points was defined as mild NVP, 7-12 points as moderate NVP and scores from 13 points and above was classified as severe NVP/HG.

QOL was a question rating the woman's well-being at present as compared to before the start of this pregnancy. QOL was measured by an 11 point rating scale with a range between zero and ten, where a score of zero was a well-being assessed as the worst possibly imaginable and a score of ten was a measure equalling as good as she felt before the start of this pregnancy. A similar question has been used in the validation of the original PUQE (80). SUKK scores and QOL score were compared between HG patients and controls, and for HG patients at admission and discharge.

3.5 Dietary assessment

Food and drink intake during 24 hours was prospectively registered. Using a food list form slightly simplified from the Norwegian national recommendation for prevention and treatment of malnutrition (Appendix 6) (24). Including 38 regular food items and drinks (Appendix 7). The food and drink items were listed with a normal size portion (e.g. 150 ml semi skimmed milk, one egg, one cup of yoghurt etc.). The participant ticked out consecutively how many servings of each item they consumed during the 24 hours of registration. Foods or beverages not listed in the registry form could be added manually.

3.6 Dietary analysis

Energy, macronutrients (fat, protein, carbohydrates and fiber) and micronutrients (vitamin D, vitamin C, vitamin B_{12}, calcium, iron, magnesium and sodium) were calculated from the reported food intake form using "Dietist XP" version 2012 (Kost och Näringsdata, Bromma, Sweden). Dietist XP is a dietary analysis computer program based on the Swedish National Food Agency (NFA, Livsmedelsverket) register of food items. Dinner, dessert, soup, cakes

and toppings for bread slices were specified per portion. Thus to perform the nutritional calculations for each of these food categories we constructed a mean nutrient intake out of four different common Norwegian choices.

3.7 Statistical analysis

Statistical analysis of data were performed by using the statistic program IBM SPSS (Statistical Package for the Social Sciences) Statistics version 21 (IBM, Armonk, NY). Statistical significance was set at $p< 0.05$. All tests were two-sided. Chi square test was used to compare categorical variables. Due to small, not normally distributed data samples (38 and 31 participants), we used non-parametric tests to compare the linear variables; Mann-Whitney U test for two groups, while Kruskal-Wallis test was used for comparing three or more groups. For related groups Wilcoxon Signed Rank Test was performed. Testing for confounding factors was performed by multiple linear correlation (ANOVA) after checking regression of standardized residuals. Bivariate linear correlations were compared by Spearmans's Rank correlation.

Values for energy, macro- and micronutrients were calculated for each participant and compared between the two groups; women with HG and healthy control women. In addition, the nutrient intake was compared to the three categories of SUKK scores (mild, moderate and severe NVP). The participants' food intake were also compared with the recommendations of nutrient intake for pregnant women (84). Energy percent of protein, carbohydrates and fat were measured in both groups. Macronutrients intakes were expressed in energy percentage (E%), grams (g) and percentage of daily-recommended intake. Micronutrients intakes were expressed in grams (g), milligrams (mg) or micrograms (μg), in addition to percentage of the daily recommendations.

3.8 Ethical considerations

The Norwegian Regional Ethical Committee (REK Norway) and the Institutional Board have approved this study (2013/465). All participants signed consent to participate (Appendix 8). The study was registered at ClinicalTrials.gov (NCT01836835). Analyses of all data were anonymously. All data were stored electronically on a designated research server in accordance with the institutional research rules.

4. Results

4.1 Participants

During the inclusion period there were 85 women hospitalized at Haukeland University Hospital, Førde Hospital and Stavanger University Hospital due to HG. Thirteen women were excluded according to criteria i.e. they were not able to understand Norwegian, leaving 72 eligible patients. 34 women did not join the study either declining or not being asked to participate. Finally, 38 patients with HG were included as cases in present study, a participation rate of 53%. From Haukeland University Hospital 22 of 42 eligible patients were included. A participation rate of 52%. From Førde Hospital, eight of eleven eligible HG patients (73%) were included and from Stavanger University Hospital, eight of 19 eligible HG patients (42%) were included. We did not have exact information of how many controls were potentially eligible or how many were actually invited to participate, with the exception of one private gynaecologist where seven of 23 women (30%) finally returned their inclusion forms. In total 150 questionnaires were administered to those aiming at including healthy pregnant women. Thirty-three were filled in and returned, as a response rate of 22 %. Two women were excluded due to gestational age over 16 weeks, finally 31 were included to the study as control patients. The flow of participants in the study is described in **Figure 1**.

Figure 1 Flow chart of participating women

Approximately 150 questionnaires were delivered out. Thirty-tree were filled in and returned. Two were excluded due to gestational age over 16 weeks, finally 31 were included to the study as control patients.

In the HG group, QOL question was missing for one patient at inclusion and three patients at discharge. One lacked SUKK scores at discharge. Nutrition diary was lacking from one HG

patient. One of the control cases had not registered weight at inclusion, otherwise all data were complete.

4.2 Demographic

Demographic data for the patients and controls was presented in **Table 1**. Age, number of pregnancies, HG in former pregnancies and BMI before pregnancy was not significantly different between patients and controls. Women with HG had a statistically significant shorter gestational age (median 65 days, 95% CI 60-74), compared to the healthy controls (median 83 days, 95% CI 71 -90, p= 0.004) and had lost median 3 kg (95% CI -4 to -3) while the controls had gained median 2 kg (95% CI 0.5-2, p<0.001). Calculating weight change per gestational week the normal pregnant women gained median 0.13 kg/week (95% CI 0.06-0.17) while the hyperemesis patients lost 0.35 kg/week (95% CI -0.42 to -0.25 p<0.001).

Adjusting for gestational age in multiple regressions (ANOVA), diagnosis (HG as compared to controls) was still an independent factor of OR 4.8 for weight loss (95% CI 3.4-6.1) while gestational age was not an independent factor.

Table 1 Characteristics of the participants

Variables	**HG n=38 Median (95% CI)**	**Healthy Controls n=31 Median (95% CI)**	***P* value Mann-Whitney U Test**
Age	28 (25-30)	30 (27-32)	0.174
Gravidity (number pregnancies)	2 (2)	2 (1-2)	0.434
Number previous pregnancy with HG[a]	0.5 (0-1)	0 (0-0)	0.189
BMI before pregnancy (Kg/m^2)	24.9 (22.4-26.7)	23.3 (22.3-25.5)	0.286
Weight at inclusion (Kg)[b]	65.3 (57-73)	67.3 (63-70)	0.493
Weight change (Kg)[b]	-3 (-4- -3)	2 (0.5-2)	<0.001
Weight change per week (kg/week)[bc]	-0.35(-0.42- -0.25)	0.13 (0.06-0.17)	<0.001
Height (cm)	167 (164-169)	167 (165-170)	0.633
Gestational age (days) at inclusion	65 (60-74)	83 (71-90)	0.004

[a] Excluding nulliparous, n=11 in HG group and n=13 in controls [b] Weight missing for one control
[c] Weight change per week from pre-gravid to inclusion.
HG: Hyperemesis Gravidarum
BMI: Body Mass Index
CI: Confidence interval

4.2.1 Demographic data compared to a 10-year cohort

Comparing demographic data of the HG group of our study to a ten-year cohort from Haukeland University Hospital, including 558 women with HG, we found similar background information (**Table 2**).

Table 2 Clinical characteristics of historical controls of patients with hyperemesis gravidarum as compared to present study's participants with HG

Variables	**Historical cohort n=558 Median (Mean)**	**Study cohort n=38 Median (mean)**	***P* value (Mann-Whitney U Test)**
Age (years)	28 (28.0)	28 (27.9)	0.989
Gravidity(number pregnancies)	2 (2.5)	2 (2.0)	0.437
BMI before pregnancy (Kg/m^2)	23.5 (24.4)	24.9 (25.3)	0.236
Weight at admission (kg)	61.0 (63.1)	65.3(67.7)	0.088
Weight loss (kg)	4.0 (4.2)	3.0(3.3)	0.089
Gestational age (weeks)	8 (9.0)	9.3 (10.1)	0.085
Gravidity [a]	Number (%)	Number (%)	*P* value
Gravida 1	175 (31)	8 (21)	0.182
Gravida ≥2	383 (69)	30 (79)	
HG in former pregnancy [ab]			
No	240 (63)	17 (56)	0.514
Yes	143 (37)	13 (43)	
Weight loss admission [a]			
≤5% of pre pregnant weight	225 (40)	21 (55)	0.070
>5% of pre pregnant weight	333 (60)	17 (45)	

(85) [a] Chi square test [b] Nulliparous women were excluded, n=383 women in Historical Cohort and n=30 women in present study
HG: Hyperemesis Gravidarum
BMI: Body Mass Index
CI: Confidence interval

4.3 SUKK score

Each of the separate questions in the SUKK questionnaire was statistically significantly higher in the HG group compare to the control group (**Table 3**). The median SUKK score for patients was 13 (95% CI 11-14) while controls had a median of seven (95% CI 5-8, $p<0.001$). SUKK scores were inversely related to the women's weight change: low scores associated with weight gain at inclusion and high SUKK scores were associated with weight loss ($p<0.002$). Adjusting for gestational age SUKK score was still a statistical significant factor of -0.6 (95% CI -0.8 to -0.4, $p<0.001$ ANOVA).

Using SUKK score as a predictor for being hospitalized with HG (binary logistic regression), SUKK score had a hazard ratio of 1.9 (95% CI 1.4-2.7, $p<0.001$) even when adjusted for gestational age.

Table 3 SUKK Questionnaires of HG group and control patients

Variables	**HG** **n = 38** **Median** **(95% CI)**	**Healthy Controls** **n = 31** **Median** **(95% CI)**	***P* value** **Mann-Whitney U Test**
Question 1 (Length nausea)	5 (5-5)	3 (2-4)	<0.001
Question 2 (Rate vomiting)	4 (3-4)	1 (1-1)	<0.001
Question 3 (Rate retching)	4 (4-5)	2 (1-2)	<0.001
PUQE/SUKK score	13 (11-14)	7 (5-8)	<0.001
Quality of life[ab]	3 (2-4)	6 (4.5-8)	<0.001
SUKK score severity[c]	Number (%)	Number (%)	*P*-value
Mild NVP (score <7)	1 (2.6)	15 (48.4)	<0.001
Moderate NVP (score 7-12)	15 (39.5)	15 (48.4)	
Severe NVP (score ≥13)	22 (57.9)	1 (3.2)	

[a] Missing data for one HG patient in the HG group [b] missing data of three participants in the control group
[c] Chi-square test
HG: Hyperemesis gravidarum
NVP: Nausea and vomiting in pregnancy
PUQE: Pregnancy-unique quantification of emesis and nausea
SUKK: Norwegian PUQE: Pregnancy induced nausea quantification
CI: Confidence interval

4.3.1 SUKK score inversely correlates to QOL

SUKK scores can define three categories of nausea and vomiting; low SUKK score = Mild NVP with scores between three and six points, moderate SUKK score = moderate NVP with scores between seven and twelve points and high SUKK score = Severe NVP/HG with thirteen or more points. These three SUKK categories inversely correlate to women's rating of QOL (**Table 4**); Mild SUKK category had median QOL score of 8 (95% CI 7-9.5), moderate SUKK had score of 4.5 (95% CI 3-5) and high SUKK had QOL score of 3 (95% CI 1.5-4.5, $p<0.001$). SUKK score and QOL score were significantly linearly inversely correlated both at inclusion ($r = -0.681$, $p<0.001$) as well as at discharge ($r = -0.638$ $p<0.001$ Spearman's rank correlation).

Table 4 QOL score in the three groups of SUKK score categories

Variable	Mild NVP Median (95% CI) n=16	Moderate NVP Median (95 % CI) n=29	Severe NVP/HG Median (95% CI) n=23	*P*-value Kruskal-Wallis test
QOL[a]	8 (7-9.5)	4.5 (3-5)	3 (1.5-4)	<0.001

NVP: Nausea and vomiting of pregnancy
HG: Hyperemesis Gravidarum
QOL: Quality of life
CI: Confidence interval

4.3.2 Change in SUKK score and QOL during hospital treatment

There was a statistical significant reduction in SUKK scores in the HG group comparing the questionnaires at hospitalization and discharge. SUKK score at hospitalization decreased from median thirteen (95% CI 11-14) to median six (95% CI 5-8, p <0.001) at discharge (**Table 5**).

In accordance, the QOL score increased from median three (95% CI 2-4) to median seven (95% CI 6-8, p<0.001 Wilcoxon Signed Rank test). At discharge the HG group had SUKK scores and QOL no different from those of the healthy pregnant controls (p=0.5 and p=0.8 respectively) (**Table 6**).

Table 4 Data of women with HG during hospitalization and at discharge

Variables	HG hospitalization n=38 Median (95% CI)	HG discharged n=37 Median (95% CI)	P-value Wilcoxon Rank test
Question 1 (length of nausea)	5 (5-5)	3 (2-4)	<0.001
Question 2 (rate vomiting)	4 (3-4)	1 (1-1)	<0.001
Question 3 (rate retching)	4 (4-5)	2 (1-2)	<0.001
Total SUKK score	13 (11-14)	6 (5-8)	<0.001
Quality of life (QOL) score [ab]	3 (2-4)	7 (6-8)	<0.001
SUKK score severity[c]	Number (%)	Number (%)	P-value
Mild NVP (score<7)	1 (2.6)	20 (54.1)	0.760
Moderate NVP (7-12)	15 (39.5)	16 (43.2)	
Severe NVP (score ≥ 13)	22 (57.9)	1 (2.7)	

[a] Data of one participant during hospitalization is missing [b] Data of three participants at discharge are missing [c] chi square test
HG: Hyperemesis Gravidarum
SUKK: Norwegian PUQE, Pregnancy induced nausea quantification
NVP: Nausea and vomiting of pregnancy
CI: Confidence interval

Table 5 SUKK questionnaires at discharge in HG patients and control patients

Variables	**HG at discharge n=38 Median (95% CI)**	**Healthy Controls n = 31 Median (95% CI)**	***P*-value Mann-Whitney U test**
Question 1 (Length nausea)	3 (2-4)	3 (2-4)	0.714
Question 2 (Rate vomiting)	1 (1-1)	1 (1-1)	0.873
Question 3 (Rate retching)	2 (1-2)	2 (1-2)	0.456
PUQE/SUKK score	6 (5-8)	7 (5-8)	0.833
Quality of life[ab]	7 (6-8)	6 (4.5-8)	0.509
SUKK score severity[c]	Number (%)	Number (%)	*P*-value
Mild NVP (score <7)	20 (51.4)	15 (48.4)	0.896
Moderate NVP (score 7-12)	16 (43.2)	15 (48.4)	
Severe NVP (score ≥13)	1 (2.7)	1 (3.2)	

[a] data missing of one participant at discharge [b] data missing of 3 control participants [c] Chi square test
HG: Hyperemesis gravidarum
PUQE: Pregnancy-Unique Quantification of Nausea and Emesis
SUKK: Norwegian PUQE, Pregnancy induced nausea quantification
NVP: Nausea and vomiting of pregnancy
CI: Confidence interval

4.4. Nutritional intake

Median values of nutrient intake in the HG group and control group respectively are presented in **table 7**. All calculated parameters; total energy intake, amount of macro- and micronutrients were statistically significant lower in the group of women with HG compared to the group of healthy pregnant women (all p <0.001).

Table 6 Nutritional intake in women with HG and in healthy control group

Variables	**HG n=37 Median (95% CI)**	**Healthy Controls n=31 Median (95% CI)**	***P* Value Mann-Whitney U test**
Energy intake (kcal)	989.5 (709-1233)	1651.5 (1558-1880)	<0.001
Protein (g)	27.6 (17.9-37.7)	63.2 (51.1-69.1)	<0.001
Fat (g)	36.1 (21.8-47.2)	66.3 (47.6-77.2)	<0.001
Carbohydrates (g)	147.2 (98.7-165.0)	195.4 (167.1-226.7)	0.001
Vitamin D (µg)	1.2 (0.6-1.4)	2.2 (1.4-3.4)	<0.001
Vitamin C (mg)	48.8 (29.0-64.5)	110.5 (74.0-154.0)	<0.001
Vitamin B12 (µg)	0.8 (0.5-1.0)	2.6 (2.0-3.2)	<0.001
Calcium (mg)	292.7 (181-333)	685.0 (545-737)	<0.001
Iron (mg)	3.1 (2.1-4.0)	6.95 (5.8-8.5)	<0.001
Magnesium (mg)	127.6 (71.9-156.8)	259.7 (227.6-300.8)	<0.001
Sodium (mg)	1348.0 (892.8-1564.5)	1997.0 (1665-2268)	<0.001
Fiber (g)	8.0 (5.9-10.0)	18.5 (13.9-23.5)	<0.001

HG: Hyperemesis Gravidarum
Kcal: Kilo calories
CI: Confidence interval

Median values of energy percentage of the macronutrients and percentage of recommended intake of both macro- and micronutrients are presented in **table 8**. The differences between the two groups were statistically significant in all parameters, except for energy percentage of fat intake. The women with HG had altered their diet; consuming a significantly higher proportion of carbohydrates, lower protein proportion, however unaltered fat proportion.

Table 7 Nutrient intake and percentage of daily-recommended intake in the two groups

Variables	**HG n=37 Median (95% CI)**	**Healthy Controls n=31 Median (95% CI)**	***P* Value Mann-Whitney U test**	***Percent of daily requirement Intake of HG women***	***Percentage of daily require-ment of Controls***
Energy (kcal)[a]	990 (720.5-1233.0)	1648 (1558-1880)	< 0.001	40.4%	67%
Protein (g)[b]	27.6 (17.9-37.7)	62.6 (51.1-68.5)	<0.001	39%	88%
Fat (g)[c]	36.1 (21.8-47.2)	64.9 (47.6-76.1)	<0.001		
Carb (g)[d]	147.2 (98.7-165)	195.9 (167.1-226.7)	0.001	95%	126%
Vitamin D (µg)	1.2 (0.6-1.4)	2.1 (1.4-3.4)	<0.001	12%	21%
Vitamin C (mg)	48.8 (29-64.5)	110.5 (74-154)	<0.001	57.4%	129.4%
Vitamin B12 (µg)	0.8 (0.5-1)	2.6 (2-3.2)	<0.001	40%	130%
Calcium (mg)	293 (181-333)	673 (545-730)	<0.001	32.5%	74.8%
Iron (mg)	3.1 (2.1-4)	6.7 (5.8-8.5)	<0.001	20.7%	44.7%
Magnesium (mg)	127.6 (71.9-156.8)	258.6 (227.6-285.6)	<0.001	45.6%	92.1%
Sodium (mg)	1348 (893-1565)	1961 (1665-2268)	<0.001	27%	38%
Fiber (g)	8 (5.9-10)	18.5 (13.9-23.5)	<0.001	26.7%	61.7%
Protein (E%)[e]	11.4 (9.3-12.1)	15.2 (14.7-16.1)	<0.001	57-114%	76-152%
Fat (E%)[f]	33.1 (29.0-38.0)	35.9 (33.0-38.7)	0.285	82.8-132.4%	89.8-144%
Carb (E%)[g]	55.3 (50.4-58.4)	48.1 (47.0-52.1)	0.008	92.2-123%	80.2-107%

[a] Recommended energy intake of pregnant women depends among other by their pre-pregnancy weight, daily level of activity. In present study a calculation of daily energy intake were set to 2450 calories. [b] Recommended protein intake of pregnant women is set to 71 g per day (28) [c] There are no recommendations on total fat intake per day. [d] Recommended daily intake of carbohydrates is set to be between 135 and 175 g per day to maintain normal blood glucose (28). Calculated percentage of daily carbohydrate intake recommendation is in this case set to the mean of 135 and 175 g: 155 g. [e] Recommended protein intake is between 10 and 20 E% of total energy intake (84) [f] Recommended fat intake is between 25 and 40 E% of total energy intake (30) [g] Recommended carbohydrate intake is between 45 and 60 E% of total energy intake (30).

HG: Hyperemesis Gravidarum
NVP: Nausea and vomiting of pregnancy
E%: Energy percentage
Carb: Carbohydrate
CI: Confidence interval

4.4.1 Energy intake

The Norwegian Health board recommends healthy women to have an energy intake of between 2150 kcal for inactive women and 2400 kcal for active women (86). A cutoff were set to be the mean of these recommendations; 2275 kcal. In addition, during the first trimester the daily need is about 10 kcal extra per day and in the second trimester 340 extra kcal per day (28).

When comparing the energy intake (kcal) of the three SUKK categories (low, moderate and severe NVP/HG) to the recommended energy intake during the first and second trimester we found statistically significant difference in energy intake in the first trimester. However, there was no significant differences in the energy intake for the patients in the second trimester (**Table 9**). Similarly, when comparing energy intake in first and second trimester in the HG group to the control group, we found a significantly difference at first trimester in HG patients compared to controls (**Table 10**).

Table 8 Sufficient energy intake due to gestational age and SUKK categories

Variables	Sufficient energy intake	SUKK mild n=16	SUKK moderate n=29	SUKK severe NVP n=23	*P*-value Chi-square test
1th trimester[a]	Yes	3	1	0	0.016
	No	7	25	19	
2nd trimester[b]	Yes	0	1	0	0.571
	No	6	3	4	

[a] Sufficient energy intake of 1th Trimester were an energy intake of 2285 calories a day or above.
[b] Sufficient energy intake of 2nd trimester were an energy intake of 2615 calories a day or above.

Table 9 Sufficient energy intake related to gestational age and diagnose

Variables	Sufficient energy intake	HG group n=37	Control Group n=31	*P*-value Chi-square test
1. Trimester[a]	Yes	0	4	0.026
	No	32	19	
2. Trimester[b]	Yes	1	0	0.429
	No	5	8	

[a] Sufficient energy intake of 1th Trimester were an energy intake of 2285 calories a day or above.
[b] Sufficient energy intake of 2nd trimester were an energy intake of 2615 calories a day or above.

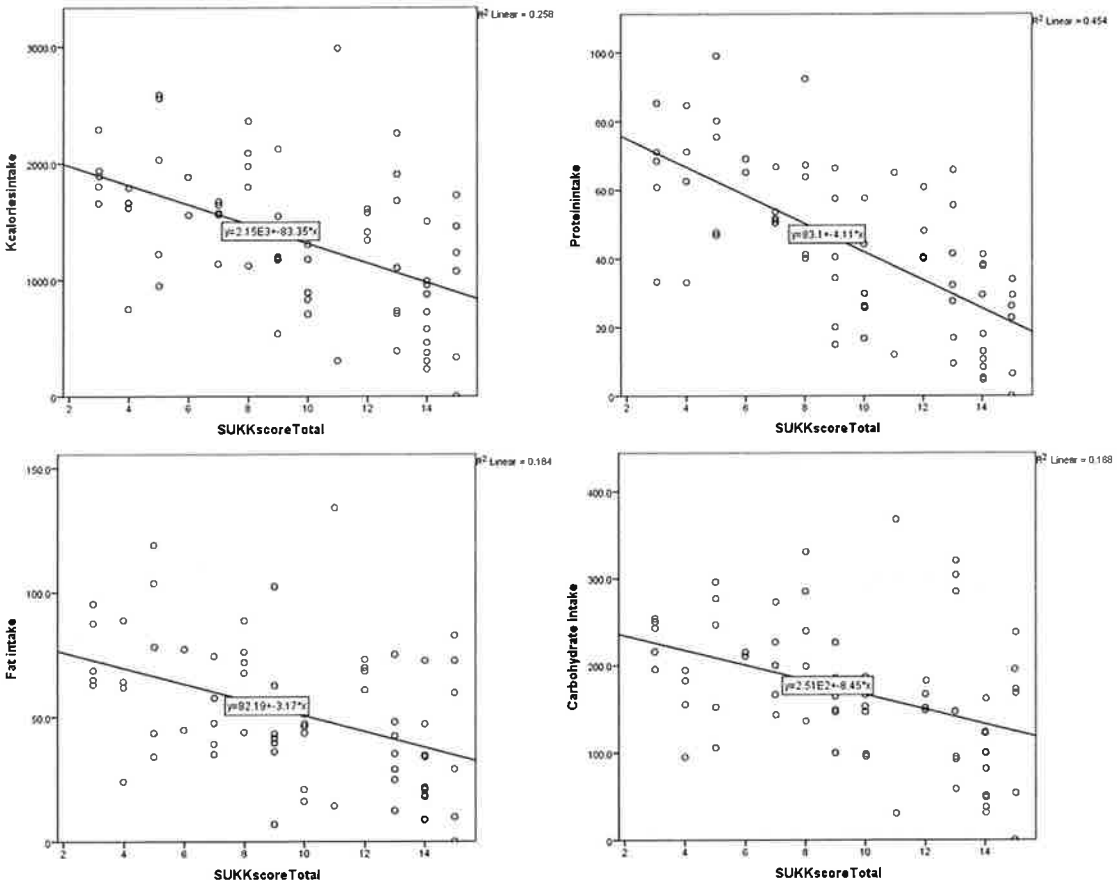
When comparing the three SUKK categories (mild, moderate and severe NVP/HG) with nutrient intake we found statistical significantly decrease of all measured nutritional variables as the SUKK scores increased (**Table 11**). Scatterplots of energy and macronutrients can deepen this significant reduction (**Fgure 2**).

Table 10 Nutrient intake distributed by SUKK scores categories

Variables	**Mild NVP** SUKK score 3-6 n=16 **Median (95%CI)**	**Moderate NVP** SUKK score 7-12 n=29 **Median (95% CI)**	**Severe NVP/ HG** SUKK score ≥13 n= 23 **Median (95% CI)**	***P*-value Kruskal-Wallis test**
Energy (Kcal)	1796 (1558-2031)	1408 (1171-1605)	877.5 (459-1233)	<0.001
Protein (g)	68.8 (47.7-80)	47.5 (39.9-57.4)	26.2 (10.6-33.9)	<0.001
Fat (g)	66.8 (44.9-88.9)	47.6 (41.5-68.4)	29.1 (18.8-47.2)	0.001
Carbohydrate (g)	213.0 (155.6-250.6)	166.8 (148.8-199.5)	100.4 (58.7-168.5)	0.004
Vitamin D (µg)	2.4 (1.4-4.7)	1.7 (1.3-2.2)	0.7 (0.3-1.3)	<0.001
Vitamin C (mg)	103.8 (67-161.5)	75.0 (52.5-132)	48.8 (15-64.5)	<0.001
Vitamin B_{12} (µg)	2.9 (2-3.5)	1.8 (0.9-2.1)	0.5 (0.3-1.1)	<0.001
Calcium (mg)	700.5 (454-896.3)	491.0 (329.2-673)	228.0 (180-396.5)	<0.001
Iron (mg)	8.5 (5.2-9.9)	5.3 (4-6.2)	2.9 (1.2-3.7)	<0.001
Magnesium (mg)	277.4 (203.9-332.2)	209.1 (143-241.5)	110.3 (57.7-170.9)	<0.001
Sodium (mg)	2058.5 (1665-2488.5)	1729 (1315.5-2035.5)	1267 (722-1532)	<0.001
Fiber (g)	19.9 (13-28.1)	13.3 (9.7-18)	7.6 (4.8-10)	<0.001

NVP: Nausea and vomiting of pregnancy
HG: Hyperemesis gravidarum
SUKK: Svangerskapsutløst kvalme kvantifisering
CI: Confidence interval

Figure 2 Scatterplots of energy intake and macronutrient intake of the participants distributed on their SUKK scores.



These four scatterplots shows the energy (calories), protein (g), fat (g) and carbohydrate (g) intake respectively distributed on the SUKK scores of all the participating women. The lines in the scatterplots show the trend of the scattering.

5 Discussion

This thesis aims to validate the SUKK questionnaire, a Norwegian version of the pregnancy specific PUQE questionnaire, as a tool to determine the severity of nausea and vomiting in pregnancy (NVP). The SUKK scores are compared between normal pregnant women and a group of hospitalized women due to hyperemesis gravidarum. In addition, we examine a 24 hours nutritional intake of all the women participating in the study. In the following part, a discussion of the methodology of current study follows before the discussion of results and a short conclusion is presented.

5.1. Methodological discussion

5.1.1 Study design and method

The current study is an observational prospective case-control study. Despite the fact that randomized controlled trials (RCTs) are considered as the gold standard of evidence-based medical studies (87, 88), RCTs are not always the best choice of a study design due to ethical reasons or are not possible to conduct for certain investigations (89). In such cases, a prospective observational case-control study may be the best method to address certain kinds of questions. According to Chung and colleagues, retrospective case-control studies have a level of III of an evidence rating scale (90). Whereas RCTs, prospective cohort studies, and systematic reviews of these have an evidence of level I and II. In present study, our aim is to evaluate associations between women with HG compared to healthy pregnant women. Severe NVP/HG is a relatively seldom diagnose (6). A traditional cohort study would therefore have to be very large (>2800 pregnant women) to meet the estimated number of 28 patients with HG. A case-control study is deemed more efficient and realistic to perform in the time-period available for inclusion. Still, due to slow recruitment at our department of gynecology and obstetrics, Hukeland University Hospital, we had to add two other hospitals to meet the estimated number of patients.

To validate this pregnancy emesis questionnaire both presumably healthy pregnant women as well as those most severely affected had to be included. As hyperemesis gravidarum is relatively rare, encompassing 0.3-1.5 of pregnant women (6), a case-control design was deemed most appropriate.

An authorized translator translated the PUQE questionnaire to Norwegian and the Norwegian questionnaire was independently translated to English to verify that the original content is kept. This is in line with general recommendations of validating questionnaires. Before

starting the study, a pilot of one pregnant woman answered the SUKK questionnaire, the QOL question and completed the food diary to ensure that the questions are understandable and the food-list manageable.

5.1.2 Collected data

The participating women in present study have answered questions regarding their background information, their severity of the symptoms of NVP or HG and information of their food intake by questionnaires and a 24 hours prospective ticking-list. Misclassification and false self-reported information can make biases in the outcome of the study. Generally, a woman's information regarding pregnancy details (number of pregnancies, gestational age and earlier pregnancy complications such as hyperemesis) are considered valid. These data are self-reported on the Norwegian pregnancy record (Helsekort for gravide) and basis for reports to the compulsory Norwegian national birth registry (Fødselsregisteret). Self-reported weight and height may be a sensitive matter for over weighted women. Women tend to under report their actual weight and over report their height to get a lower BMI (91). We did not find a significant difference in BMI at inclusion between the two groups. If hyperemesis patients generally are heavier and thus under report their weight, a difference from normal pregnant women may be masked. To ensure a correct weight measurement the same scale should have been used for all women (patients and controls, before pregnancy and at inclusion). However, this was not feasible.

5.1.3 Estimation of nutritional intake

Nutritional intake can be assessed in several ways, either by collecting data of intake retrospectively (24 hours recall, food frequency questionnaire or diet history) or by summarizing prospective data (weighed diet diary, estimated diet diary or checklist/diary). Food and nutrient intake vary from day to day. A proper way to get a good view of the participants' food intake would be to have a food record for several days (usually three to seven days) and make an average of the recorded days (92). Whereas a 24 hours recall of one day is not considered to be representative for a person's dietary habits (93, 94). In present study we aim to compare the food intake to the score of the SUKK questionnaire which measured the severity of NVP over 24 hours, thus a registration of food intake of 24 hours is considered as enough.

A proper food interview with each of the study's participants to assess information of their situation and have a 24-hour recall of their food intake is cost- and time consuming (25). This

would be possible to perform for the hospitalized patients. However this is considered to significantly hamper the inclusion of normal pregnant patients. Using different evaluation methods for patients and controls would be a major bias. Thus, we chose to use a self-reported food diary. It was considered easiest for the participants to tick off specified standard food and drink items rather than writing each food element themselves.

The food and drink list in present study is a slightly modified from recommended in the Norwegian national nutritional recommendation (24). The food items are typical "Norwegian", thus food items mostly used by other ethnic groups are not included. Since our goal was to validate a Norwegian questionnaire, we decided to include native Norwegian. Participants could write missing items but this was seldom done which verified the list as valid for our investigational cohort.

The instructions are to fill in the list consecutively starting from the morning at inclusion as a real-time procedure to minimize recall bias. The SUKK questionnaires and the food list are supposed to relate to the same day to measure an association between the food intake and the SUKK scores. We cannot control if these were actually filled out at the same day, since the questionnaires were delivered to the participating women to fill out at home or during the start and at the end of the hospital treatment. Still the very good correlation between dietary intake and SUKK scores gives us reason to believe that this information is collected at the same day. Similarly, we cannot control if some of the information regarding questionnaires and food diaries are supplemented in retrospect.

5.1.4 Study population

Each year approximately 50-60 women with HG are admitted to Haukeland University Hospital, of which 25% is of non-Caucasian ethnicity and often not native Norwegian speaking. Inclusion period was eight months, leaving an estimated 30 women with hyperemesis and fully able to understand and answer a Norwegian questionnaire. Because of a slow inclusion rate by the end of September 2013, two other hospitals on the west coast of Norway, Stavanger University Hospital and Førde Hospital, were invited to recruit hospitalized patients with HG to the study from October 2013-January 2014.

Information regarding the women's ethnicity is not collected. A meta-analysis of global rates of HG reported that there were differences in the occurrences of HG in geography (95). In addition, a Norwegian study of variation of prevalence of HG reported a 3.3-3.4 fold higher risk of developing HG in women born in Africa, India and Sri Lanka than ethnical Norwegian

women (96). As the aim of study is to validate a questionnaire in Norwegian, the participants have to be well knowledgeable, preferable native speaking, of Norwegian. Thus, participants would be assumed to be mainly Norwegian or Scandinavian.

The physicians and study nurses at the hospitals in Bergen, Førde and Stavanger recruited the included participants with HG to the present study. All the participants with HG are included while being hospitalized. Local health care persons, gynecologists and nutritionists included pregnant women to the control group, in addition to self-recruitment of women who saw the information of the study at lookups at Haukeland University Hospital and the University of Bergen. By recruiting the case group at a hospital and the control group in general health care centers and by self-recruitment we may have measured a referral bias (25). Some of the women in the control group have as high SUKK score and low nutritional intake as those in the HG group. One can speculate that those being interested in participating in a study regarding nausea in pregnancy might be more than average affected by this complains. Still, the control group are significantly less affected by nausea and vomiting than the HG patients. Also in the HG group, some patients have as low SUKK scores as those in the control group. Since patients would start the registration/answering questionnaires the following morning the medication and fluid/nutritional regimen started at admission might already have alleviated some of their symptoms. This could lead to an underestimation of the differences between the groups. For the control group there is no reason to believe such a consequent change from the day they were handed the questionnaires (inclusion) and to start of the filling in the following day.

The percentages of participating women are 53% of women hospitalized for HG and in the control group about 22% of those who were asked consented to participate in the study. We may have measured a self-selection bias as there might be a higher interest in food and health by the people willing to participate in a study compared to the general population (25, 97). For the hospitalized patients, very few of those asked actually declined participation. During summer holiday and weekends patients were more prone to never being asked to participate. Participating patients were not significantly different from a meticulously collected 10-year cohort of HG patients from Dpt. Of Gynecology and Obstetrics, Haukeland University Hospital, regarding age, number of former pregnancies of gestational age at admittance to hospital. See Table 2. We did find that significantly more of the women in the HG study cohort reported any former pregnancy affected by hyperemesis; this would be in line with those most affected by a disease wanting to participate in a study concerning that disease. Still

we consider the HG group as representative for Norwegian women hospitalized due to hyperemesis gravidarum.

Regarding the control, group their representatively is more difficult to assess. Severe NVP/HG is a relatively rare disease. By increasing the numbers of healthy control women per woman with HG, an increased statistical power of the investigation of current study could have been achieved (89).

The inclusion period of present study are eight months. This is limited by the time-frame of finishing this master thesis. Extending the inclusion period might perhaps have given us a larger case and control group and increase the statistical power of the study (89).

Exclusion criteria are set to be gestational age over 16 weeks or other causes of nausea and vomiting. Accepting a higher gestational age more controls than patients would probably be included as HG is most prevalent in the first trimester. This could increase the gestational age difference between the two groups of participants.

5.1.5 Dietary assessment

The food intake is registered prospectively by each participant crossing out the type of food they consumed on a food list during a period of 24 hours. 24-hour food intake is a relatively short time of food registration to give a good view of the participant's food intake. The food intake may vary from day to day in a wide range. In addition, the severity of nausea may change from day to day; therefore, a registration of between three to seven days would give us a somehow better observation of their mean food intake. However, as the intention is to validate the SUKK regimen at admittance to hospital, the food diary should reflect the same interval (24 hours). Thus, a 24 hours registration of food intake is considered as enough.

The food list contains 38 types of regular food and drinks. The portion sizes are listed as regular size portions. Therefore, there are no need for the participants to weight or calculate any food or drinks sizes. This is an easy way of preforming a food registration. However, miscalculations can easily occur since the portion size can differ widely between the participants. This could be regulated in a better way by making the participants report the size or the weight the food and beverages they consumed. Nevertheless, the more time-consuming the registration process is the harder is it to make the participants complete the food registration. Thus, we chose to make it as easy as possible with the food registration and the

portions sizes, to make sure that we got enough participants in the two groups for doing analysis.

The amount and the types of food that were consumed the day of registration can be affected by the fact that is supposed to be registered, thus certain types of food considered to be unhealthy for pregnant women might be avoided the day of registration. In addition, some may even omit to register everything they eat. Women do have a tendency to under report what they have eaten (98).

There were no details other than dinner, soup, cake and desserts in these categories at the registration form. The participants could report how many portions they had the day of registration without specifying what they ate. To have this analyzed we made an average value of four regular Norwegian dinners and soups and three average cakes and desserts (Appendix 9). Dinner is the main course of the day and constitutes a large part of the nutrients when analyzing their food intake, this might bias the analysis. In addition, a regular Norwegian diet consists of a lot of bread during the different meals of the day (99). The food list contains different sorts of bread, nevertheless there are no places for them to fill in what they use as toppings on the bread. The calculation of toppings is an average from three different toppings. Furthermore, the food list give no information about their meal frequency. It is reported that women should eat small and frequent meals to avoid nausea and vomiting during pregnancy (54). A registration form where they can write what they eat and drink, how it is prepared (boiled, fried with oil, etc.), portion sizes (1 slice of bread, 100 g, 2 dl, etc.) and at what time they eat it would give us a better view of their food intake.

However given these limitations we do not find that they should significantly bias one group (controls or HG) in favor of the other, thus when we find significantly differences between the groups regarding nutritional intake this is considered valid.

5.1.6 Statistical methods

5.1.6.1 Sample size

The sample size are determined by using data from the Canadian study (80) with a mean PUQE score of 11+/- 3 in the HG group and 9.0 +/-2.2 in controls group, with an alpha = 5% (two sided) and a power of 80%. A sample size of 28 in each group are calculated. Similarly using energy intake measured in a South-African case-control study (16) a sample size of 28 would yield a 100% power to detect differences in nutritional intake.

Approximately 60 pregnant women are hospitalized at Haukeland University Hospital during a 12 months period. This gives us about 40 patients during the inclusion period of eight months. Omitting the non-native Norwegians, 30 participants should be eligible. When accrual was slow we invited two other departments from western Norway to participate and succeeded in including more than 30 women both in the patient (n=38) as well as the control arm (n=31). The number of 69 participants in current study are much higher number than the other study comparing NVP and nutrient intake of pregnant women with 20 participants in each group (16). Also comparing to the initial PUQE validation study (80), our HG group is larger.

5.1.6.2 Statistical analyses

The *p*-value of the statistical analyses are in most analyses lower than 0.001. This means that the statistical significant level is high, and that there are large differences between the two groups. Thus, the chance of a type II error is low. Cases with missing data are excluded in present study.

5.2 Discussion of results

The current study's key findings are 1) the Norwegian translation of PUQE: SUKK significantly discriminated between normal pregnancy related nausea and vomiting and the severe hyperemesis gravidarum. 2) Nutrient intake of the women in the HG group is statistically significant lower compared to the women in the control group.
3) SUKK scores correlates inversely to self-reported nutritional intake and weight gain.
4) HG patients experienced a reduction of their SUKK scores and increased score of QOL from hospitalization until discharge which are statistically significant.

5.2.1 Validated SUKK

The PUQE questionnaire, originally developed in Canada, has been extensively tested in English and French speaking populations (80-82, 100), demonstrating PUQE score to be significantly associated with severity of NVP, poor quality of life, insufficient vitamin intake and increased costs of treatment (need for hospitalization). PUQE has also been used in NVP studies performed in Indonesisan (101), Spanish (78), Turkish (102) and Italian (103). At present, no studies using the PUQE questionnaire in any Scandinavian country or language have been published.

5.2.2 SUKK score

The Canadian HG patients (80) had significantly higher SUKK/PUQE scores (mean 11) as compared to (nine in) the outpatient NVP group. These findings have been verified in our study comparing Norwegian women hospitalized for HG with healthy pregnant women.

We have used a 24 hours scoring (rather than the initial 12 hours scoring) as recommended by Ebrahimi *et. al* (78) to avoid biases due to sleeping patterns/time of initiating scoring. PUQE has even been validated to accurately distinguish severity of nausea during the entire first trimester of pregnancy (82). However, the severity of nausea and vomiting can change from day to day. The HG patients were recruited to our study when they felt sick and sought hospital treatment and filled out the questionnaire the day following admittance to hospital. While the women of the control group filled out the questionnaires after attending local health care system for generally follow-up in pregnancy. This may bias the scores of SUKK in favor of increasing the difference between groups.

The scores of the SUKK questionnaire in present study are inverse correlated to the QOL rating. This was similar to the Canadian study (80), where the low PUQE group had median QOL score of 5.7, moderate PUQE had 4.2 and high PUQE score 2.2.

5.2.3 High SUKK scores identify women at high nutritional risk

The PUQE score has been indirectly validated to correlate with reduced dietary intake of vitamin supplements as a surrogate marker (80). To our knowledge no study have directly evaluated PUQE in regards to a comprehensive nutritional intake. In our study, the SUKK scores correlated inversely to the women's nutritional intake during 24 hours. Comparing to the group of healthy control women, statistical significant lower levels of all nutrients analyzed are found in the HG group. This correlates to what van Stuijvenberg and colleagues reported in their study in 1995, except of their lack of statistically significant differences in Vitamin C and Vitamin B_{12} (16). Their 24 hours recall by food interview estimated caloric intake of 1813 kcal for controls and 443 for HG patients. Similarly, our estimations were 1652 and 990 kcal.

Compared to recommended values for caloric intake none of the women with SUKK scores $\geq$13 reached recommended intake. In addition when women are actually vomiting it is likely that parts of the food eaten thus will be unavailable for digestion, leaving the high score group with even less actual nutritional intake. Thus a high SUKK score is consistent with a woman being at serious nutritional risk.

The different weight changes (weight loss in the high SUKK score group compared to increased weight in the lower score groups) strengthen the SUKK score as predictor of insufficient nutrition. As in other studies comparing HG patients with healthy controls it has been difficult to ensure similar gestational age (2). However, when adjusting for gestational age we still find a significant poorer weight development for women with high SUKK scores.

The estimated nutritional intakes for our control group are lower than those reported for the Norwegian women in the large Mother and Child cohort (104). Women without any symptoms of nausea during pregnancy have a mean intake of energy of 2529 kcal, the group with nausea, without vomiting, had 2489 and those with NVP had 2722 kcal. The Mother and Child cohort assess nutritional intake as a mean of the whole pregnancy from start to filling in two food frequency questionnaires (FFQ) midways in their pregnancy (week 15 and between weeks 18 to 22 of gestation). It is reasonable to believe that the FFQ in reality is more representative for their food intake during second trimester than during first trimester. The validation of their FFQ was actually correlated to weighed food diaries and energy expenditure measurements performed during 15-16 gestational week (105). We are not aware of studies actually measuring energy intake during first trimester in a Norwegian population.

Thus even though underreporting of nutritional intake is common also for pregnant women (105), we consider our measured values for the normal pregnant patients most likely as valid.

5.2.4 SUKK scores and QOL normalizes during hospital stay

To our knowledge, the current study is the first to directly compare scores of SUKK at hospitalization to discharge. Only one study has evaluated PUQE scores during hospital treatment by evaluating a 5 days crossover RCT of clonidine versus placebo in 12 hospitalized HG patients (103). The PUQE scores were reported as mean during the days of each medication regimen, not at discharge.

The English questionnaire, PUQE, has been validated in the Norwegian translated form, SUKK. As the Scandinavian population is quite similar regarding health and pregnancy demographics, it is reasonable that the results will be valid in Sweden and Denmark as well. The Scandinavian languages are also quite similar, thus with only minor changes of spelling the questionnaire should be able to be used in the other two countries.

Strengths of present study are that we have used validated questionnaires regarding both nausea and vomiting of pregnancy and food intake, furthermore the translation of the Norwegian version of the questionnaire are validated and accepted by the author of the original questionnaire. The participants of the present study filled out the questionnaires in real-time, this strengthens the trial as recall biases is minimized. In addition, the size of the participating women with the rare diagnose, HG, in this study is relatively large. Comparing the data of our study to a 10-year cohort from Haukeland University Hospital, demographic data of women with HG were not significantly different.

A weakness of present study is that using questionnaires it is not possible to collect additional information of the participants, as in an interview. Moreover, if there are any ambiguities regarding the questionnaire, the participants might not find it convenient to contacting us to clarifying what information we ask for. It would strengthen our study if we increased the food registration period from 24 hours to three to seven days. Additionally, collecting information about the participants' activity level would be beneficial to compare to their energy intake.

5.3 Conclusion

This prospective case-control trial demonstrated that the Norwegian translated version of PUQE, SUKK, is valid as a clinical tool to distinguish between regular morning sickness and

severe NVP/HG. Moreover, it demonstrated that there was a strong inverse correlation between the scores of the SUKK questionnaire and the self-reported food intake and weight gain at inclusion for the participating women. Furthermore, it demonstrated that after hospital treatment the SUKK scores decreases, and the quality of life score, QOL, increases. In addition, the women with hyperemesis gravidarum (case group) had a statistically significant lower nutrient intake of all measured compounds compared to the healthy women (control group).

5.4 Future perspectives

A validated Norwegian version of the SUKK scoring system can be beneficial for further research regarding nausea and vomiting during pregnancy in a Scandinavian population. In further studies evaluating treatment regimens SUKK scores should be used as one marker of efficacy. Additionally, the questionnaire should be validated for diagnostic of severity of nausea and vomiting by a clinical study on routine treatment of hyperemesis gravidarum.

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Norwegian PUQE (Pregnancy Unique Questionnaire of Emesis) validates to identify patients with hyperemesis gravidarum and poor nutritional intake; a case-control study

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Abstract

Objective: The English questionnaire PUQE identifies women severely affected with hyperemesis gravidarum (HG). Our aim was to investigate whether scores from the translated version; SUKK (SvangerskapsUtløst Kvalme Kvantifisering) was associated with severity of hyperemesis and nutritional intake of Norwegian pregnant women.

Methods: A prospective case-control study was conducted in Western-Norway: Bergen, Stavanger and Førde, during May 2013-January 2014. Totally 69 pregnant woman were included. Of these 38 were hospitalised patients with HG and 31 were healthy controls. Nausea of pregnancy was investigated by a SUKK-score, QOL-score and nutritional intake of a 24-hours prospective registration.

Results: HG patients had shorter gestational age compared to controls (median 65 versus 83 days, p=0.004), and larger weight-change from pre-pregnant weight (median -3 kg vs. +2kg, p<0.001). Otherwise the groups were similar regarding pre-pregnant BMI, age, gravidity, and weight at inclusion. Compared to the controls, HG patients had significant higher SUKK-score (median 13, 95% CI [11-14] vs. 7, 95% CI [4-8]), lower QOL score (median score 3 vs. 6) and lower energy intake (median 957 kcal vs. 1651 kcal, all p<0.001). SUKK-score was inversely correlated to nutritional intake and QOL-score (all $p\leq$0.004). At discharge SUKK-score decreased to median six (95%CI [5-8]) and QOL score increased to median 6.5, (both p<0.001) compared to values at admission.

Conclusion: The SUKK questionnaire has been validated as a robust indicator of severe pregnancy induced nausea and vomiting in addition to measure insufficient nutrient intake in Norwegian women.

Abbreviations

NVP: Nausea and vomiting of pregnancy

HG: Hyperemesis gravidarum

QOL: Quality of life

PUQE: Pregnancy Unique Questionnaires of Emesis and Nausea

SUKK: Svangerskapsutløst kvalme kvantifisering / Pregnancy induced nausea quantification

BMI: Body Mass Index

E%: Percentages of energy

KCAL: Kilo calories

CI: Confidence Interval

Key message

The English pregnancy unique questionnaire, PUQE, has been translated and tested in a Norwegian population. PUQE was validated to identify women with severe hyperemesis gravidarum, poor quality of life and reduced nutrient intake.

Introduction

Nausea and vomiting occur in up to 80% of all pregnancies (1). It is mostly self-limiting, however leading to reduced quality of life (2). About 0.3-1.5 % of pregnant women have a more serious condition called Hyperemesis Gravidarum (HG) (3). HG was in 1968 defined as "Vomiting occurring in pregnancy for the first time before the twentieth week of gestation, and of such severity as to require the patient's admission to hospital, the vomiting being unassociated with such coincidental condition as appendicitis, pyelitis, etc." (4). The etiology of HG is unknown (5).

Intake and retaining food and beverage can be problematic for patients with HG. Persistent low food intake and/or frequent vomiting can lead to dehydration, metabolic imbalance, nutrition deficiency and weight loss. Severe weight loss in early pregnancy or insufficient catch-up weight, have been linked with unfavorable fetal outcomes, such as preterm delivery and small for gestational age (6-8). Previous studies have demonstrated that women with a sever nausea and vomiting of pregnancy (NVP) have reduced intake of specific food types (meat, vegetables) (9) and lower intake of energy and most nutrients (10). In addition, a higher intake of energy provided by sugar has been reported (1, 9).

No single measurement can easily define or quantify the severity of pregnancy induced nausea and vomiting. Tools to distinguish between regular nausea during pregnancy and the severe NVP/HG have been developed (2, 11-15). PUQE was the first questionnaire developed to measure the severity of pregnancy-induced nausea and vomiting (11). This questionnaire has been validated and used in several trials (11-13, 15, 16). PUQE has additionally been validated in different versions. This includes versions that measure the time and episodes of nausea, vomiting and retching of the last 12 hours (11), during the first trimester (13), and a version measuring symptoms during the last 24 hours (15).

To our knowledge, the direct relation between PUQE score and the patient's nutritional intake has not yet been evaluated in any study. Likewise, the changes in PUQE score from admission to hospital and discharge have not been described. PUQE has been used in several languages besides English; Indonesian (17), Turkish (18), Italian (19), French (13) and Spanish (15). No Norwegian version had yet been developed.

The aims of this study are to validate the Norwegian version of PUQE: SUKK in a Norwegian population and compare the food intake of women with severe NVP/HG to healthy pregnant women. In addition, we want to compare the scores of the SUKK questionnaire of the HG patients at admission and discharge from hospital.

Material and methods

Study design, population and setting

This study was a prospective case-control trial to validate the Norwegian version of PUQE. Additionally we investigated the severity of NVP and the nutritional intake of women hospitalized due to severe NVP/HG (cases) compared to healthy pregnant women (controls). Women with HG were recruited at Bergen University Hospital, Førde Hospital and Stavanger University Hospital. Participants in the control group were recruited at health care centers in Bergen, in addition to self-recruitment from information on look-ups at Haukeland University Hospital and the Campus of University of Bergen. Inclusion period was between first of May 2013 and end of January 2014. The inclusion criteria of the HG group were women hospitalized by HG with at least two out of three criteria; dehydration, weight loss or electrolytes imbalances/ketonuria. Inclusion criteria of the control group were a healthy pregnancy. Participants were excluded if they had native language other than Norwegian, other diseases causing nausea and vomiting during pregnancy and a gestational age over 16 weeks.

SUKK Questionnaire

The 24 hours English PUQE was translated by an authorized translator to Norwegian and afterwards the Norwegian version was translated back to English. The author of the original PUQE, Gideon Koren, (11)(11)(11) has approved the English translation based on the Norwegian version.

The Questionnaire measures the physically symptoms of nausea and vomiting by three questions, additionally it measures the psychological aspect by rating the wellbeing.

Variables

Information regarding participants' severity of nausea and vomiting (SUKK-score), quality of life (QOL-score) and nutritional intake were collected by a three-question questionnaire, a question of quality of life (QOL), and a 24 hours prospective food-ticking list. The HG

patients filled out the questionnaire twice, both when they were admitted to and discharged from hospital.

Question one (Q1), two (Q2) and three (Q3) was regarding how many hours or episodes during the day the pregnant woman felt nausea, vomited and retched. There were five alternative answers to each question. QOL was rating of the women's wellbeing at inclusion compared to before start of pregnancy.

Food and drink intake during 24 hours was registered using a food list form slightly simplified from the Norwegian national recommendation for prevention and treatment of malnutrition (20), including 38 regular food items and drinks. Dinner, dessert, soup, cakes, desserts and toppings for bread slices were specified by per portions. Thus to perform the nutritional calculations for each of these food categories we constructed a mean nutrient intake out of four different common Norwegian choices.

Outcome measurements

Summarizing scores of the SUKK questionnaire (Q1-3) gave a total SUKK score between 3 and 15 points. A score between 3-6 points was defined as mild NVP, 7-12 points as moderate NVP and scores $\geq$13 points was classified as severe NVP/HG. Energy, macronutrients (fat, protein, carbohydrate, fibre) and some micronutrients (vitamin D, vitamin C, vitamin B_{12}, calcium, magnesium, iron and sodium) were calculated.

Study size

Using data of a Canadian study (12) with a mean PUQE score of 11 $\pm$ 3 in the HG group and 9 $\pm$ 2.2 in the control group, with an alpha = 5% (two sided) and a power of 80%, a sample size of 28 in each group were calculated. Similar using energy intake measured in a South-African study (10) a sample size of 28 would yield a 100% power to detect differences in nutritional intake.

Statistical methods

Statistical analysis of data was performed using the statistic program IBM SPSS (Statistical Package for the Social Sciences) Statistics version 21 (IBM, Armonk, NY). A p-value < 0.05 was considered statistically significant. All tests were two-sided. Chi square test was used to compare categorical variables. Due to small, not normally distributed data samples we used non-parametric tests to compare the linear variables; Mann-Whitney U test for two groups, while Kruskal-Wallis test was used if three of more groups were compared. For related groups Wilcoxon Signed Rank Test was performed. Testing for confounding factors was

performed by multiple linear correlations (ANOVA) after checking regression of standardized residuals. Missing data were excluded.

SUKK-scores and QOL score were compared between HG patients and controls and for HG patients at admission and discharge.

Values for energy, macro- and micronutrients were calculated for each participant and compared between the two groups. In addition, the nutrient intake was compared between the three groups with different SUKK scores (mild, moderate and severe NVP/HG). The participants' food intake was also compared with the recommendations for nutrient intake for pregnant women (21). Reported nutrient intake was calculated using a nutrient analysis program, Dietist XP (version 2012, Kost och Näringsdata, Bromma, Sweden). Dietist XP is based on the Swedish National Food Agency (NFA, Livsmedelsverket).

Ethical consideration

The study was approved by Norwegian Regional Ethical Committee (REK Norway) and the Institutional Board (2013/465). All participants signed consent to participate. The study was registered at ClinicalTrials.gov (NCT01836835).

Results

During the inclusion period 85 women were hospitalized at Haukeland University Hospital, Førde Hospital and Stavanger University Hospital due to HG. Of these patients 38 were included to the study, 34 declined to participate, and 13 were excluded due to language (**Figure 1**). 150 questionnaires were distributed to those including healthy pregnant women. 33 healthy women replied the questionnaire. Of these, two were excluded due to gestational age above 16 weeks, and totally 31 women were included as control group.

There were no significant differences in demographic variables between the HG group and the healthy controls, except from weight change which was reduced in the HG group and increased in the control group ($p<0.001$), and gestational age which were higher in the control group ($p=0.004$) (**Table 1**). When adjusting for gestational age in multiple regressions (ANOVA), diagnosis (HG as compared to controls) was still an independent factor for weight loss (OR 4.8, 95% CI 3.4-6.1) while gestational age was not an independent factor.

SUKK scores are increased in patients with HG

Women in the HG group had significantly increased SUKK score ($p<0.001$) and decreased QOL score compared to healthy controls (**Table 2**). 57.9% of the patients in the HG group were categorized as severe NVP compared to 3.2% in the control group.

Calculated energy and nutrient intake were significantly lower in the HG group compared to healthy controls, except for analysis of energy percentage intake of fat ($p=0.285$) (**Table 3**). Additionally, intake of nutrients compared to daily recommended intake are presented in **Table 3**. SUKK categories (mild, moderate and severe NVP/HG) were compared to women's rating of QOL score and nutrient intake. QOL score and nutrient intake inversely correlated to the SUKK categories (**Table 4**). Furthermore, the SUKK scores of HG patients at admission were significantly higher compared to their scores at discharge. QOL score were significantly increased at discharge (**Table 5**). At admission, 97% of the HG group were in the moderate to severe category of NVP, at discharge the percentage of women in these categories had decreased to 45%.

In the HG group, QOL question was missing for one patient at inclusion and three patients at discharge. One lacked SUKK scores at discharge. Nutrition diary was lacking from one HG patient. One of the control cases had not registered weight at inclusion, otherwise all data were complete.

Discussion

The main results of this study are a validated Norwegian version of PUQE: SUKK, a significantly lower food intake in HG group compared to control group. Additionally, an inverse correlation between three categories (mild, moderate and severe NVP/HG) of SUKK scores in relation to food intake. Furthermore, HG patients had a significantly reduction in SUKK scores and increase of QOL score at discharge compared to scores when hospitalized.

The participants of this study have answered questions regarding their background information, their severity of the symptoms of NVP and information of food intake by questionnaires and a 24 hours food ticking-list. Misconceptions of questionnaire and false self-reported information can make biases in the outcome of the study. Self-reported weight and height may be a sensitive matter for over weighted women. Women tend to under report their actual weight and over report their height to get a lower body mass index (BMI) (22).

We did not find a significant difference in BMI at inclusion between the two groups. To ensure a correct weight measurement the same scale should have been used for all women (patients and controls, before pregnancy and at inclusion), however this was not feasible.

In this study, we aim to compare the food intake to the score of the SUKK questionnaire. The questionnaire and the food intake list measured the severity of NVP and the nutrient intake over 24 hours. A proper food interview with each of the study's participants to assess information of their situation and have a 24-hour recall of their food intake is cost- and time consuming (17). This may be possible to perform for patients at hospital, however it is consider to significantly hamper the inclusion of normal pregnant women as control group. Using different evaluation methods for patients and controls could make a major bias. Thus, we chose to use a self-reported food diary. Furthermore, the SUKK questionnaire and the food list were supposed to relate to the same day to measure an association between the food intake and the SUKK scores. We cannot control if the questionnaire and the food intake list are actually filled out at the same day. Still, the very good correlation between dietary intake and SUKK scores gives us reason to believe that this information is collected at the same day.

Hospital nurses recruited hospitalized participants with HG. Healthy pregnant women are included to the control group by local health care staff, gynecologists and physicians. In addition to self-recruitment, where they found information of the study at lookups at Haukeland University Hospital and the campus of University of Bergen. By recruiting the case group at a hospital and the control group in general health care centers and by self-recruitment we may have measured a referral bias (23). Some of the women in the control group have as high SUKK score and low nutritional intake as those in the HG group. One can speculate that those being interested in participating in a study regarding nausea in pregnancy might be more than average affected by this complains. Some patients in the HG group have as low SUKK scores as those in the control group. Since patients started answering the questionnaires the following morning after medication and fluid/nutritional regimen started. At admission their symptoms might already have alleviated. This could lead to an underestimation of the differences between the two groups. Still, the participants of the control group were in general significantly less affected by nausea and vomiting than the HG patients.

The percentages of participating women are 61% of those hospitalized for HG and in the control group about 22% of those who had been asked consented to participate in the study. We may have measured a self-selection bias as there might be a higher interest in food and health by the people willing to participate in a study compared to the general population (23, 24).

The portion sizes at the food list are listed as regular portions. Portion size can differ widely between the participants. This may bias the calculation of food intake. Furthermore, the amount and the types of food that are consumed the day of registration can be affected by the fact that it is supposed to be registered. In addition, some may omit to register everything they eat. Women have a tendency to under report what they eat (25).
There are no details other than dinner, soup, cake and desserts in these categories at the registration form. To analyze this we made an average value of four regular Norwegian dinners and soups and three average cakes and desserts. Dinner constitutes of a large part of the nutrients of their food intake, this might bias the analysis. In addition, a regular Norwegian diet consists of several meals of bread during a day (26). The food list contains different sorts of bread, without toppings on the bread slices. The calculation of toppings is an average from three different toppings. Furthermore, the food list gives no information about their meal frequency. A rapid meal frequency is reported to be essential to avoid pregnancy induced nausea (27). A registration form where they can write what they eat and drink, how it is prepared (boiled, fried with oil, etc.), portion sizes (1 slice of bread, 100 g, 2 dl, etc.) and at what time they eat it may give us a better view of their food intake. However, given these limitations we do not find that they should significantly bias one group (controls or HG) in favor of the other, thus this is considered valid.

The PUQE scores of the Canadian HG patients (12) had significantly higher SUKK/PUQE scores (mean 11) as compared to the outpatient NVP group (mean 9). These findings are verified in our study comparing the hospitalized women with HG to healthy pregnant women. However, the severity of nausea and vomiting can vary. The HG patients are recruited to our study at a time when they feel sick and search hospital treatment, whereas they filled out the questionnaire the day following admittance to the hospital. The women of the control group filled out the questionnaires after attending local health care system for generally follow-up in pregnancy. This may bias the scores of SUKK in favor of increasing the difference between

the two groups.

The scores of the SUKK questionnaire in this study are inverse correlated to the QOL rating. This is similar to the Canadian study (12), where the low PUQE group had median QOL score of 5.7, moderate PUQE had 4.2 and high PUQE score 2.2.

To our knowledge, no study has evaluated PUQE in regards to nutritional intake. In our study, a high SUKK score is consistent with a woman being at serious nutritional risk. The weight changes (weight loss in the high SUKK score group compared to increased weight in the lower score groups) strengthen the SUKK score as a predictor of insufficient nutrition. The estimated nutritional intakes for our control group are lower than those reported for the Norwegian women in the large Mother and Child cohort (28). Furthermore, this is the first study to compare scores of PUQE/SUKK at hospitalization to discharge. Only one study has evaluated PUQE scores during hospital treatment by evaluating a 5 days crossover RCT of clonidine versus placebo in 12 hospitalized HG patients (19).

The PUQE score has been indirectly validated to correlate with reduced dietary intake of vitamin supplements as a surrogate marker (12). To our knowledge no study has directly evaluated PUQE in regards to a comprehensive nutritional intake. In this study, the SUKK scores correlated inversely to the women's nutritional intake during 24 hours. Comparing to the group of healthy control women, statistical significant lower levels of all nutrients analyzed were found in the HG group. This correlates to what van Stuijvenberg and colleagues reported in their study in 1995, except of their lack of statistically significant differences in Vitamin C and Vitamin B_{12} (10). Their 24 hours recall by food interview estimated an energy intake of 1813 kcal for controls and 443 calories for HG patients. Similarly, our estimations were 1652 and 990 kcal respectively.

None of the women with SUKK scores $\geq$13 reach the recommended intake of energy and nutrients. In addition, when women are vomiting it is likely that parts of the food they eat will be unavailable for digestion, leaving the high SUKK score group with even less actual nutritional intake. Thus, a high SUKK score is consistent with a woman being at serious nutritional risk. The different weight changes strengthen the SUKK score as predictor of insufficient nutrition.

The estimated nutritional intake for our control group are lower than those reported for the Norwegian women in the large Mother and Child cohort (28). We are not aware of studies measuring energy intake during first trimester in a Norwegian population. Thus even though underreporting of nutritional intake is common also for pregnant women (29), we consider our measured values for the normal pregnant patients most likely as valid.

Conclusion

We have demonstrated that the Norwegian translated version of PUQE, SUKK, is valid as a clinical tool to distinguish between regular morning sickness and HG. Additionally, it demonstrated that there are a strong inverse correlation between the SUKK scores and the self-reported food intake for the participating women. Furthermore, it demonstrated that after hospital treatment the SUKK scores decreases and the QOL score increases.

Future perspectives

A validated Norwegian version of the SUKK scoring system can be beneficial for further research regarding nausea and vomiting during pregnancy in a Scandinavian population. In further studies evaluating treatment regimens SUKK scores should be used as one marker of efficacy. Additionally, the questionnaire should be validated for diagnostic of severity of nausea and vomiting by a clinical study on routine treatment of hyperemesis gravidarum.

Acknowledgements

We would like to thank all the participating women who have contributed to this study. Additionally, we want to thank the nurses at Haukeland University Hospital, Førde Hospital and Stavanger University Hospital who recruited hospitalized women with hyperemesis gravidarum. Furthermore, we want to thank the physicians and gynecologists who recruited the healthy women as the control group of the study.

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Tables and figure

Table 1 Information of the participants

Variables	**HG n=38 Median (95% CI)**	**Healthy Controls n=31 Median (95% CI)**	***P* value Mann-Whitney U Test**
Age	28 (25-30)	30 (27-32)	0.174
Gravidity (number pregnancies)	2 (2)	2 (1-2)	0.434
Number former pregnancy with HG[a]	0.5 (0-1)	0 (0-0)	0.189
BMI before pregnancy (Kg/m²)	24.9 (22.4-26.7)	23.3 (22.3-25.5)	0.286
Weight Inclusion (Kg)[b]	65.3 (57-73)	67.3 (63-70)	0.493
Weight change inclusion (Kg) [b]	-3 (-4- -3)	2 (0.5-2)	<0.001
Height (cm)	167 (164-169)	167 (165-170)	0.633
Gestational age (days)	65 (60-74)	83 (71-90)	0.004

[a]Excluding nullipara, n=11 in HG group and n=13 in controls [b]Weight missing for one healthy control
HG: Hyperemesis Gravidarum
BMI: Body Mass Index
CI: Confidence interval

Table 2 SUKK Questionnaires of intervention group and control patients

Variables	**HG n = 38 Median (95% CI)**	**Healthy Controls n = 31 Median (95% CI)**	***P* value Mann-Whitney U Test**
Question 1 (Length nausea)	5 (5-5)	3 (2-4)	<0.001
Question 2 (Rate vomiting)	4 (3-4)	1 (1-1)	<0.001
Question 3 (Rate retching)	4 (4-5)	2 (1-2)	<0.001
PUQE/SUKK score	13 (11-14)	7 (5-8)	<0.001
Quality of life[a]	3 (2-4)	6 (4.5-8)	<0.001
SUKK score severity[b]	Number (%)	Number (%)	*P*-value
Mild NVP (score <7)	1 (2.6)	15 (48.4)	<0.001
Moderate NVP (score 7-12)	15 (39.5)	15 (48.4)	
Severe NVP (score ≥13)	22 (57.9)	1 (3.2)	

[a]Missing data for one HG patient in the intervention group, [b] Chi-square test

NVP: Nausea and vomiting in pregnancy

PUQE: Pregnancy Unique Quantification of Emesis and Nausea

SUKK: Svangerskapsutløst Kvalme Kvantifisering, Pregnancy induced nausea quantification

CI: Confidence interval

Table 3 Nutrient intake and daily-recommended intake in the two groups

Variables	HG n=37 Median (95% CI)	Healthy Controls n=31 Median (95% CI)	*P* Value Mann-Whitney U test	Intervention Percent of daily requirement	Controls Percentage of daily Requirement
Energy (kcal)[a]	989.5 (720.5-1233.0)	1648.0 (1558-1880)	< 0.001	40.4%	67%
Protein (g)[b]	27.6 (17.9-37.7)	62.6 (51.1-68.5)	<0.001	39%	88%
Fat (g)[c]	36.1 (21.8-47.2)	64.9 (47.6-76.1)	<0.001		
Carb (g)[d]	147.2 (98.7-165)	195.9 (167.1-226.7)	0.001	95%	126%
Vitamin D (µg)	1.2 (0.6-1.4)	2.1 (1.4-3.4)	<0.001	12%	21%
Vitamin C (mg)	48.8 (29-64.5)	110.5 (74-154)	<0.001	57.4%	129.4%
B12 (µg)	0.8 (0.5-1)	2.6 (2-3.2)	<0.001	40%	130%
Calcium (mg)	292.7 (181-333)	673 (545-730)	<0.001	32.5%	74.8%
Iron (mg)	3.1 (2.1-4)	6.7 (5.8-8.5)	<0.001	20.7%	44.7%
Magnesium(mg)	127.6 (71.9-156.8)	258.6 (227.6-285.6)	<0.001	45.6%	92.1%
Sodium (mg)	1348 (892.8-1564.5)	1961 (1665-2268)	<0.001	27%	38%
Fiber (g)	8 (5.9-10)	18.5 (13.9-23.5)	<0.001	26.7%	61.7%
Protein (E%)[e]	11.4 (9.3-12.1)	15.2 (14.7-16.1)	<0.001	57-114%	76-152%
Fat (E%)[f]	33.1 (29.0-38.0)	35.9 (33.0-38.7)	0.285	82.8-132.4%	89.8-144%
Carb (E%)[g]	55.3 (50.4-58.4)	48.1 (47.0-52.1)	0.008	92.2-123%	80.2-107%

[a] Recommended energy intake of pregnant women depends among other by their pre-pregnancy weight, daily level of activity. In this study a calculation of daily calorie intake were set to 2450 calories. [b] Recommended protein intake of pregnant women is set to 71 g per day (30) [c] There are no recommendations on gram of fat per day. [d] Recommended daily intake of carbohydrates is set to be between 135 and 175 g per day to maintain normal blood glucose (30). Calculated percentage of daily carbohydrate intake recommendation is in this case set to mean of 135 and 175 g: 155 g.[e] Recommended protein intake is set to be between 10 and 20 E% of total energy intake (21) [f] Recommended fat intake is set to be between 25 and 40 E% of total energy intake (31) [g] Recommended carbohydrate intake is set to be between 45 and 60 E% of total energy intake (31).

Carb: Carbohydrate
HG: Hyperemesis Gravidarum
NVP: Nausea and vomiting of pregnancy
E%: Energy percentage
CI: Confidence interval

Table 4 SUKK categories compared to QOL score and nutritional intake

Variables	Mild NVP Median (95% CI) n=16	Moderate NVP Median (95 % CI) n=29	Severe NVP/HG Median (95% CI) n=23	P-value Kruskal-Wallis test
QOL[a]	8 (7-9.5)	4.5 (3-5)	3 (1.5-4)	<0.001
Energy (Kcal)	1796 (1558-2031)	1408 (1171-1605)	877.5 (459-1233)	<0.001
Protein (g)	68.8 (47.7-80)	47.5 (39.9-57.4)	26.2 (10.6-33.9)	<0.001
Fat (g)	66.8 (44.9-88.9)	47.6 (41.5-68.4)	29.1 (18.8-47.2)	0.001
Carbohydrate (g)	213.0 (155.6-250.6)	166.8 (148.8-199.5)	100.4 (58.7-168.5)	0.004
Vitamin D (µg)	2.4 (1.4-4.7)	1.7 (1.3-2.2)	0.7 (0.3-1.3)	<0.001
Vitamin C (mg)	103.8 (67-161.5)	75.0 (52.5-132)	48.8 (15-64.5)	<0.001
Vitamin B_{12} (µg)	2.9 (2-3.5)	1.8 (0.9-2.1)	0.5 (0.3-1.1)	<0.001
Calcium (mg)	700.5 (454-896.3)	491.0 (329.2-673)	228.0 (180-396.5)	<0.001
Iron (mg)	8.5 (5.2-9.9)	5.3 (4-6.2)	2.9 (1.2-3.7)	<0.001
Magnesium (mg)	277.4 (203.9-332.2)	209.1 (143-241.5)	110.3 (57.7-170.9)	<0.001
Sodium (mg)	2058.5 (1665-2488.5)	1729 (1315.5-2035.5)	1267 (722-1532)	<0.001
Fiber (g)	19.9 (13-28.1)	13.3 (9.7-18)	7.6 (4.8-10)	<0.001

[a] Data of QOL score of one patient in the Moderate NVP category is missing
NVP: Nausea and vomiting of pregnancy
HG: Hyperemesis Gravidarum
QOL: Quality of Life
CI: Confidence interval

Table 5 Data of women with HG during hospitalization and discharge

Variables	HG hospitalization n=38 Median (95% CI)	HG discharged n=37 Median (95% CI)	P-value Wilcoxon Rank test
Question 1 (length of nausea)	5 (5-5)	3 (2-4)	<0.001
Question 2 (rate vomiting)	4 (3-4)	1 (1-1)	<0.001
Question 3 (rate retching)	4 (4-5)	2 (1-2)	<0.001
Total SUKK score	13 (11-14)	6 (5-8)	<0.001
Quality of life (QOL) score [ab]	3 (2-4)	7 (6-8)	<0.001
SUKK score severity[c]	Number (%)	Number (%)	P-value
Mild NVP (score<7)	1 (2.6)	20 (54.1)	0.760
Moderate NVP (7-12)	15 (39.5)	16 (43.2)	
Severe NVP (score ≥ 13)	22 (57.9)	1 (2.7)	

[a] Data of one participant during hospitalization is missing [b] Data of three participants at discharge are missing [c] Chi square test
HG: Hyperemesis Gravidarum
SUKK: Svangerskapsutløst Kvalme Kvantifisering/Pregnancy induced nausea quantification
NVP: Nausea and vomiting of pregnancy
CI: Confidence interval

Figure 1

Approximately 150 questionnaires were delivered out. Thirty-tree were filled in and returned. Two were excluded due to gestational length over 16 weeks; finally 31 were included to the study as control patients.

Appendix I The original PUQE questionnaire

1. In the last 12 hours, for how long have you felt nauseated or sick to your stomach				
Not at all (n=1)	1 hour or less (n=2)	2 to 3 hours (n=3)	4 to 6 hours (n=4)	More than 6 hours (n=5)
2. In the last 12 hours, have you vomited or thrown up				
7 or more times (n=5)	5 to 6 (n=4)	3 to 4 (n=3)	1 to 2 (n=2)	I did not throw up (n=1)
3. In the last 12 hours, how many times have you had retching or dry heaves without bringing anything up				
No time (n=1)	1 to 2 (n=2)	3 to 4 (n=3)	5 to 6 (n=4)	7 or more (n=5)

Total score: (Summary of *n*) no symptoms 0–3, mild 4–6; moderate 7–12; severe ⩾13

APPENDIX II

Oversettelse fra engelsk

Modifisert graviditetsspesifikk indeks for kvantifisering av kvalme og oppkast

Sett ring rundt det svaret som best beskriver din situasjon det siste døgnet.

1. Gjennomsnittlig for hver dag, hvor lenge er du kvalm eller dårlig i magen?

> 6 timer 5 poeng	4-6 timer 4 poeng	2-3 timer 3 poeng	≤1 time 2 poeng	Ikke i det hele tatt 1 poeng

2. Gjennomsnittlig for hver dag, hvor mange ganger kaster du opp?

≥7 ganger 5 poeng	5-6 ganger 4 poeng	3-4 ganger 3 poeng	1-2 ganger 2 poeng	Ikke i det hele tatt 1 poeng

3. Gjennomsnittlig for hver dag, hvor mange ganger brekker du deg eller har tørrbrekninger?

≥7 ganger 5 poeng	5-6 ganger 4 poeng	3-4 ganger 3 poeng	1-2 ganger 2 poeng	Ikke i det hele tatt 1 poeng

Totalskåre (summen av svarene på 1, 2 og 3): mild NVP ≤6, moderat NVP 7-12, alvorlig NVP ≥13.

STATSAUTORISERT TRANSLATØR · INA TJUGEN · NORGE · BERGEN · ENGELSK - NORSK

Rett oversettelse bekreftes.
Bergen, 30. januar 2013.

Ina Tjugen
Statsautorisert translatør
Allegro språktjenester

APPENDIX III

Translation from Norwegian

Modified pregnancy-specific index for quantifying nausea and vomiting

Circle the answer that best describes your situation during the past 24 hours.

1. On average every day, for how long are you nauseous or have an upset stomach?

> 6 hours 5 points	4-6 hours 4 points	2-3 hours 3 points	≤1 hour 2 points	Not at all 1 point

2. On average every day, how often do you vomit?

≥7 times 5 points	5-6 times 4 points	3-4 times 3 points	1-2 times 2 points	Not at all 1 point

3. On average every day, how many times do you wretch or have dry heaves?

≥7 times 5 points	5-6 times 4 points	3-4 times 3 points	1-2 times 2 points	Not at all 1 point

Total score (sum of the answers to 1, 2 and 3): mild NVP ≤6, moderate NVP 7-12, serious NVP ≥13.

GOVERNMENT AUTHORISED TRANSLATOR · RAGNHILD WAAGE · NORGE · BERGEN · ENGLISH NORWEGIAN - NORWEGIAN ENGLISH

True translation confirmed.
Bergen, 31 January 2013,

Ragnhild Waage
Government Authorised Translator
Allegro AS Language Services

Appendix IV Approval of back translated version of PUQE

From: Gideon Koren [mailto:gidiup_2000@yahoo.com]
Sent: 12. February 2013 01:32
To: Trovik, Jone
Copy: Vikanes, Ase Vigdis
Subject: Re: Validation of the 24-h PUQE form in Norwegian?

Dear Dr Trovik:
Thank you for adopting our PUQE -24 to Norwegian.
I carefully checked the back-translated version and have found it to perfectly reflect the original English text.
All the best
gkoren

Gideon Koren MD, FRCPC, FACMT

Director, The Motherisk Program

The Hospital for Sick Children,

Professor of Pediatrics,Pharmacology, Pharmacy and Medical Genetics

The University of Toronto,

Professor of Medicine, Pediatrics and Physiology/Pharmacology

and the Ivey Chair in Molecular Toxicology

The University of Western Ontario

APPENDIX V

SUKK-S **Svangerskaps Utløst Kvalme Kvantifisering –Spørreskjema**

Sett ring rundt det svaret som best beskriver din situasjon det siste døgnet (det samme du fylte ut matinntaksskjemaet)

1: Gjennomsnittlig for hver dag, hvor lenge er du kvalm eller dårlig i magen

> 6 timer 5 poeng	4-6 timer 4 poeng	2-3 timer 3 poeng	≤1 time 2 poeng	Ikke i det hele tatt 1 poeng

2: Gjennomsnittlig for hver dag, hvor mange ganger kaster du opp

≥ 7 ganger 5 poeng	5-6 ganger 4 poeng	3-4 ganger 3 poeng	1-2 ganger 2 poeng	Ikke i det hele tatt 1 poeng

3: Gjennomsnittlig for hver dag, hvor mange ganger brekker du deg eller har tørrbrekninger*?

≥ 7ganger 5 poeng	5-6 ganger 4 poeng	3-4 ganger 3 poeng	1-2 ganger 2 poeng	Ikke i det hele tatt 1 poeng

(*Brekning uten at noe kommer opp)

Vurdering av velbefinnende:.....

På en skala fra 0-10, angi ditt generelle velbefinnende nå; 0= verst tenkelig, 10= like bra som jeg hadde det før jeg ble gravid.

- - - - - - - - - - - - -

Noen bakgrunnsopplysninger:

Min f.dato:.....

Detter er mitt svangerskap nr:....

Jeg har hatt uttalt svangerskapskvalme i ..... svangerskap før

Jeg er .....cm høy, veide før svangerskapet.....kg og i dag veier jeg .....kg

Jeg er nå gravid med siste menstruasjonsdato:.....

(evt svangerskapslengde i dag hvis du allerede har vært til ultralyd:.....uker.....dager)

Dato skjemaene er utfylt:.....

APPENDIX VI

MATVARE	ENHET	MENGDE SPIST	KCAL	SUM KCAL	PROTEIN	SUM PROTEIN
Kneipp/grovbrød	½ skive *		90		3	
Loff	½ skive *		85		2	
Rundstykke	½ stk *		130		5	
Knekkebrød	1 stk *		120		3	
Frokostblanding	1 pors u/melk		132		5	
Corn flakes	1 pors u/melk		70		0	
Havregrøt	1 pors		170		8	
Risgrøt	1 pors		185		8	
Egg	1 stk		80		7	
Yoghurt(Duo kar.)	1 beger		230		5	
Yoghurt (frukt)	1 beger		160		6	
Is	1 beger		290		5	
Eple	1 stk		45		0	
Banan	1 stk		100		1	
Appelsin	1 stk		40		1	
Middag	1 pors		350		19	
Dessert	1 pors		150		4	
Suppe (salt)	1 pors		80		3	
Havresuppe (melk)	1 kopp 100 ml		75		4	
Havresuppe (vann)	1 kopp 100ml		9		0	
Kake	1 stk		220		4	
Tørr kjeks	1 stk		40		1	
H-melk, kefir	1 glass		100		5	
Lettmelk, Biola	1 glass		70		5	
Sk. melk (søt/sur)	1 glass		50		5	
Appelsinjuice	1 glass		70		1	
Saft, brus	1 glass		60		0	
Sukkerbit	1 stk		8		0	
Sjokolade	1 stk (60 g)		340		5	
Nutridrink	1 boks		300		12	
Nutridrink Protein	1 boks		300		20	
Fresubin Protein Energy Drink	1 boks		300		20	
Nutridrink Juicestyle	1 boks		300		8	
Resource Addera Plus	1 boks		250		8	
Fresubin ProvideXtra	1 boks		300		8	
Til sammen						

* Inkludert smør/margarin og pålegg.

Beregnet energibehov for å opprettholde vekten: Aktuell vekt x 30 kcal: .....

Beregnet proteinbehov: Aktuell vekt x 1 gram protein: .....

Ved ønsket vektoppgang er det behov for et høyere inntak! Sist oppdatert 10.12.09

APPENDIX VII

MATVARE	ENHET	ANTALL/MENGDE SPIST
Kneipp/grovbrød	1/2 skive*	
Loff	1/2 skive*	
Rundstykke	1/2 skive*	
Knekkebrød	1 stk*	
Frokostblanding	1 porsj u/melk	
Corn flakes	1 porsj u/melk	
Havregrøt	1 porsjon	
Risgrøt	1 posjon	
Egg	1 stk	
Yoghurt	1 beger	
Youghurt(duokartong)	1 beger	
Is	1 beger	
Eple/Appelsin	1 stk	
Banan	1 stk	
10 druer	1 porsjon	
Middag	1 porsjon	
Dessert	1 porsjon	
Suppe(salt)	1 porsjon	
Havresuppe(melk)	1 porsjon	
Havresuppe(vann)	1 porsjon	
Kake/vaffelplate	1 stk	
Tørr kjeks	1 stk	
Bolle	1 stk	
Evt annen mat:		
H-melk, kefir	1 glass/1,5 dl	
Lettmelk/Biola	1 glass/1,5 dl	
Skummet melk(søt/sur)	1 glass/1,5 dl	
Appelsinjuice	1 glass/1,5 dl	
Saft/Brus	1 glass/1,5 dl	
Vann/Farris/sukkefri brus	1 glass/1,5 dl	
Kaffe/Te u sukker	1 glass/1,5 dl	
Vin	1 glass/1,5 dl	
Øl	1 glass/1,5 dl	
Næringsdrikk	1 boks	
Evt. annen drikke:		
Sukkerbit	1 stk	
Karameller/drops	1 stk	
Sjokolade (60g)	1 stk	
Peanutter	15g/ca 20stk	
Potetgull	15g/1dl	
Evt. annet "ekstra":		

Skjemaet fylles ut for ett døgn. Marker etter hvert som du spiser og drikker med å krysse av for den enkelte matenhet (X evt I).
Spiser du mindre enn en enhet anføres det, f.eks 1/2 glass skriv 1/2

APPENDIX VIII

SUKK-S – 05.04.2013

Forespørsel om deltakelse i forskningsprosjektet

"SUKK-S"

Svangerskaps Utløst Kvalme Kvantifisering- Spørreskjemautprøving

Bakgrunn og hensikt
Dette er et spørsmål om du vil delta i en forskningsstudie for å teste et spørreskjema angående svangerskapskvalme. Skjemaet skal benyttes til å skille alvorlig fra ufarlig svangerskapskvalme. Spørreskjemaet SUKK (SvangerskapsUtløstKvalmeKvantifisering) er oversatt fra engelsk til norsk. Du som får skjemaet tilsendt hjem eller utlevert på helsestasjon er utvalgt som antatt frisk gravid (kontrollguppe). Du som får skjemaet på Kvinneklinikken er henvist til oss pga. uttalt svangerskapskvalme. Det er Kvinneklinikken, Haukeland Universitetssjukehus som er ansvarlig for gjennomføringen av undersøkelsen.

Hva innebærer deltagelse i studien?
SUKK-spørreskjemaet med tre spørsmål relatert til kvalme i svangerskap og matinntaksskjema skal fylles ut (kryss av for hva du har spist og drukket ett døgn). Hvis du er innlagt for uttalt svangerskapskvalme vil vi også be om at skjema fylles ut på nytt før utskrivelsen. Behandlingen du vil få i avdelingen blir ellers den samme som alle med svangerskapskvalme får, uansett om du deltar eller ikke i studien. Det tas ingen ekstra prøver fra deg som deltar men vi innhenter opplysninger fra fødejournalen din om hvor mye du veier ved nedkomsttidspunkt samt barnets fødselsvekt.

Mulige fordeler og ulemper
For deg som er innlagt med uttalt svangerskapskvalme vil spørreskjemaet og matinntaksregistreringen kunne gi legene ekstra informasjon om din tilstands alvorlighetsgrad. For deg som er kontrollpasient vil neppe skjemautfyllingen medføre noen sannsynlig fordel, men vi trenger svar fra friske gravide for å kunne vurdere om skjema er brukbart til de med alvorlig svangerskapskvalme. Ulempen ved å delta er det lille ekstra arbeid som utfylling av skjema medfører for den enkelte kvinne.

Hva skjer med informasjonen om deg?
Informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger gjennom en navneliste. Det betyr at opplysningene er avidentifisert.

Det er kun autorisert personell knyttet til prosjektet som har adgang til navnelisten og som kan finne tilbake til deg. Opplysningene vil bli slettet etter 10 år.
Det vil ikke være mulig å identifisere deg i resultatene av studien når disse publiseres.

Frivillig deltakelse
Det er frivillig å delta i studien. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke til å delta i studien. Dette vil ikke få konsekvenser for din videre behandling. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Om du nå sier ja til å delta, kan du senere trekke tilbake ditt samtykke uten at det påvirker øvrige behandling. Dersom du senere ønsker å trekke deg eller har spørsmål til studien, kan du kontakte Dr. Jone Trovik tlf 55974200 / 004792425171

Ytterligere informasjon om studien finnes i kapittel *A – utdypende forklaring av hva studien innebærer.*
Ytterligere informasjon om personvern og økonomi finnes i kapittel B – *Personvern og økonomi.*

Samtykkeerklæring følger etter kapittel B.

Kapittel A- utdypende forklaring om hva studien innebærer

- **Bakgrunn og hensikt**
- Kvalme i svangerskapet er svært vanlig, som oftest forbigående og uten alvorlige konsekvenser for kvinnen eller barnet. Hos ca. 1% av gravide er kvalmen så uttalt (Hyperemesis Gravidarum) at de får utilstrekkelig næringsinntak, blir uttørket (dehydrert) og må innlegges på sykehus for behandling. Ubehandlet kan mor bli alvorlig syk og barnet få økt risiko for dårlig tilvekst og å bli født for tidlig. Det finnes et engelsk spørreskjema som kan fastsette alvorlighetsgrad av svangerskapskvalme. Nå har vi fått oversatt skjemaet til norsk, men før det kan tas i bruk rutinemessig må vi undersøke om skjemaet faktisk skiller ufarlig svangerskapskvalme fra alvorlig svangerskapskvalme hos norske kvinner.

  Vi vil derfor be deg om å delta i denne studien med å fylle ut SUKK-skjemaet samt ett døgn skrive opp hva du faktisk spiser og drikker på vedlagt ernæringsskjema slik at vi kan sammenlikne svaret på SUKK-skjemaet med ditt faktiske næringsinntak.

- Du som får skjemaet tilsendt hjem eller utlevert på helsestasjon er utvalgt som antatt frisk gravid (kontrollguppe). Vennligst returner utfylt spørreskjema og matregistreringsskjema sammen med signert samtykkeskjema i vedlagt frankert svarkonvolutt.
- Du som får skjemaet på Kvinneklinikken er henvist til oss pga. uttalt svangerskapskvalme. Hvis du blir innlagt i avdelingen vil vi be om at du fyller ut skjemaet nå ved innleggelsen samt pånytt under oppholdet/før du blir uskrevet for å se om kvalme/næringsinntak er blitt bedre.

- Forskning på helseopplysninger relatert til pasienters diagnose, behandling og prognose er avgjørende for å sikre befolkningen en høy kvalitet på helsetjenestetilbudet. Ved Helse Bergen HF/Haukeland universitetssykehus arbeider vi kontinuerlig med å oppnå ny kunnskap om sykdom i svangerskap og underliv. For å kunne utføre denne forskningen er vi avhengig av pasientenes samtykke. Det er helt frivillig å delta. Den behandling du får på Kvinneklinkken vil være den samme uavhengig av om du deltar i studien eller ikke.

Kapittel B - Personvern og økonomi

Personvern
Opplysninger som registreres om deg er det du fyller ut på SUKK-skjemaet samt matinntaksregistreringen, dessuten din og barnets vekt ved nedkomst.

Helse-Bergen ved administrerende direktør er databehandlingsansvarlig.

Rett til innsyn og sletting av opplysninger om deg og sletting av prøver
Hvis du sier ja til å delta i studien, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har videre rett til å få korrigert eventuelle feil i de opplysningene vi har registrert. Dersom du trekker deg fra studien, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner.

Økonomi
Studien er finansiert gjennom forskningsmidler fra Helse-Vest

Informasjon om utfallet av studien
Når studien er avsluttet (ved utgangen av 2014) vil du kunne få tilsendt et resyme av resultatene.

Samtykke til deltakelse i studien

Jeg er villig til å delta i studien

(Signert av prosjektdeltaker, dato)

Jeg ønsker tilsendt resultatresyme på følgende adresse:

(fylles ut dersom du ønsker dette tilsendt)

Vi bekrefter å ha gitt informasjon om studien

Bergen 01.05.2013

Jone Trovik
Overlege KKB, PhD
Prosjektleder
jone.trovik@helse-bergen.no

Guro Stokke
Ass.lege KKB
Prosjektmedarbeider
guro.stokke@helse-bergen.no

Dersom du ønsker ytterligere informasjon er du velkommen til å kontakte pr epost eller tlf 55974200 (KK, Haukeland Universitetssjukehus)

Appendix IX

Average nutrient contents in Norwegian regular dinners, soups, toppings, cakes and desserts.

Based on four different dinner types an average of nutrient intake of one portion of dinner were made:

- Meatballs with potatoes, carrot, broccoli and sauce
- Fish gratin, potatoes and vegetables
- Chicken, salad and rice
- Pork meat, pasta and vegetables

Average soup nutrients were based on four different soup types:

- Fish soup
- Tomato soup
- Cauliflower soup
- Fruit soup

Based on three different toppings on slices of bread an average of topping nutrients were made:

- Butter, white cheese and paprika
- Mayonnaise and ham
- Margarine and jam

Based on four different cakes an average of nutrient content in a portion of cake were made:

- Macaroon cake
- Waffle
- Pancake
- Cheese cake

Based on three different desserts an average of nutrient content of desserts were made:

- Gel and vanilla sauce
- Chocolate pudding
- Fruit compote

Average	Kcal	Protein	Fat	Carbs	vit d, ug	vit c, mg	b12	Ca, mg	Fe, mg	Mg, mg	NaCl, mg	Fiber, g
Dinner	488	28	13	60,5	0,55	46	0,9	162	2,4	95	1139	6
Soup	98	3,3	1,6	17	0	7	0,1	56	0,5	37	700	1,4
Topping	99	2,4	8,3	3,7	0,28	7	0,1	42	0,1	3,3	114	0,23
Cake	215	5	11	23	0,7	0,75	0,33	55	0,55	16,8	214	1
Dessert	207	3,5	5,9	35	0	1	0,2	81,3	0,4	18	53	0,43

Portion sizes and types of food for this calculations were obtained from "Standardkost" chap. 11 in *Kosthåndboken Veileder I ernæringsarbeid I helse- og omsorgstjenesten.* IS-1972. Helsedirektoratet. Oslo