PREALBUMIN AS A NUTRITIONAL MARKER IN NORMAL AND HYPEREMESIS PREGNANCIES – A CASE-CONTROL STUDY

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Abstract

Objective: Hyperemesis gravidarum (HG) affects 1% of pregnancies and is potentially harmful for mother and foetus. Prealbumin is a marker of nutritional status. We wanted to investigate whether prealbumin level was associated with severity and nutritional risks of NVP (nausea and vomiting in pregnancy).

Methods: A case-control study including 92 hospitalized patients with hyperemesis gravidarum and 32 healthy controls. Serum Prealbumin was correlated to clinical and biochemical nutritional parameters, including 24h recall food-diary.

Results: HG patients had longer gestational length than controls (median 8.6 versus 7.0 weeks, $p<0.001$). Otherwise, the groups were similar regarding pre-pregnant BMI, parity, proportion of earlier pregnancies complicated with HG in and weight at inclusion. The prealbumin levels were significant lower in HG versus controls: median 0.19 g/L versus 0.23 g/L (95% CI 0.18-0.20 and 0.19-0.25, $p<0.001$). Compared to the control group HG patients had significantly lower 24h energy intake (median 653 kcal versus 1790, $p<0.001$), larger weight-change at inclusion (median –3 kg versus +1 kg, $p<0.001$), higher percentage of ketonuria +3 (69% versus 3% $p<0.001$) and higher PUQE-score (Pregnancy Unique Quantification of Emesis and nausea) median 13, 95% CI 13-14 versus 6, 95% CI 5-8). Prealbumin level , 24 h caloric and protein intake significantly decreased while weight-loss and ketonuria increased across severity of NVP as classified by the three tiered PUQE-score <6, 7-12 and 13-15 (all p $\leq$ 0.004). Prealbumin level was significantly correlated to 24 h protein intake, Pearson Correlation =0.401 (p= 0.001, two-tailed).

Conclusion: Prealbumin-measuring validates patients with severe NVP/HG as being at high nutritional risk.

Abstrakt

Bakgrunn: Uttalt svangerskapskvalme, Hyperemesis gravidarum (HG),er en tilstand som rammer ca. 1% av alle gravide. Ubehandlet kan tilstanden føre til alvorlige væske-/elektrolyttforstyrrelser og underernæring hos kvinnen. Det kan bli farlig både for mor og barn. Prealbumin brukes som markør på underernæring. Vi ønsket å vurdere om prealbumin nivå hos gravide samsvarer med alvorlighetsgrad og ernæringsmessige risiko ved svangerskapskvalme.

Metode: En case-kontroll studie blant 92 innlagte pasienter med hyperemesis gravidarum og 32 friske kontroller. Serum prealbumin ble korrelert til kliniske og biokjemiske ernærings parametre, inkludert 24-timers matinntak.

Resultater: HG pasienter hadde lengre svangerskapslengde enn kontrollene (median 8,6 versus 7,0 uker, p <0,001). Ellers var gruppene like angående pre-gravid BMI, paritet, andel med HG i tidligere svangerskap og vekt ved inklusjon. Prealbuminnivåene var signifikant lavere i HG versus kontroller: median 0,19 g / L sammenlignet med 0,23 g / L (95% CI 0,18-0,20 og 0,19 - 0,25, p<0.001). Sammenlignet med kontrollgruppen hadde HG pasienter signifikant lavere 24-timers energiinntak (median 653 kcal versus 1790, p <0,001), større vekt-endring ved inklusjon (median -3 kg versus +1 kg, p <0,001) høyere prosentandel av ketonuri + 3 (69% versus 3% p <0,001) og høyere SUKK-skår (SvangerskapsUtløst Kvalme Kvantifisering) median 13, 95% CI 13-14 versus 6, 95% CI 5-8). Prealbuminnivå, 24-timers kalori- og proteininntak sank betydelig mens vekttap og ketonuri økte med økende alvorlighetsgrad av svangerskapsutløst kvalme klassifisert som tre kategorier SUKK-skår: <6, 7-12 og 13-15 (alle p ≤0.004). Prealbuminnivået var signifikant korrelert til 24-timer protein inntak, Pearson korrelasjon = 0,401 (p = 0,001, to-sidig).

Konklusjon: prealbumin-måling validerer at pasienter med alvorlig svangerskapsutløst kvalme/ hyperemesis gravidarum utsatt for høy ernæringsmessig risiko.

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List of Abbreviations

BMI: Body mass index

CI: Confidence interval

CRL: Crown-rump length

CRP: C-reactive protein

EN: Enteral nutrition

E%:   Percent of energy intake

FCT: Food composition table

HG: Hyperemesis gravidarum

LBW: Low birth weight

MUAC: Mid-upper arm circumference

NVP: Nausea and vomiting of pregnancy

PN: Parenteral nutrition

PUQE: Pregnancy-Unique Quantification of Emesis and nausea

QOL: Quality of life

RCT: Randomized control trials

RDI: Recommended daily intake

REK: Regional Ethical Committee

SGA: Small for gestational age

SUKK: Svangerskaps Utløst Kvalme Kvantifisering

TPN: Total parenteral nutrition

WHO: World Health Organization

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1 Introduction

1.1 Hyperemesis Gravidarum

1.1.1 Definition and diagnoses

Hyperemesis gravidarum (HG) is from the Greek *hyper-*, meaning excessive, and *emesis*, meaning vomiting, and the Latin *gravidarum*, meaning "pregnant [woman]". Therefore, hyperemesis gravidarum means "excessive vomiting of pregnant women".

Nausea and vomiting in pregnancy (NVP) is a very common condition that accompanies early pregnancies of up to 91% of women (1). It is often considered to be a "rite of passage" for woman providing reassurance that pregnancy proceeds well (2, 3). HG is a fairly rare and extreme form of NVP, with distinct features and outcomes. HG occurs in 0.3 – 3.6% of pregnancies with an average of 1.1% (1).

A standard definition of HG is based on the American Council on Pharmacy and Chemistry 1956 conclusions and was given by Fairweather in 1968 in his review "Nausea and Vomiting in Pregnancy": as an "intractable vomiting and disturbed nutrition, such as alteration of electrolyte balance, loss of weight of 5 percent or more, ketosis and acetonuria" (4). However, the diagnosis is usually made clinically, based on typical presentation and exclusion of other causes of nausea and vomiting in the pregnant woman (5).

The symptoms of NVP generally occur between 5th and 10th gestational weeks (6, 7) with a peak at week 12 (5). Most women experience relief of symptoms by 20 weeks' gestation. However, 10% to 20% of pregnant women have symptoms of NVP up to the end of the pregnancy (5).

Despite the symptoms of NVP usually resolve spontaneously, the symptoms of HG are severe and can affect all aspects of a woman's life: physical, psychological and social (8, 9). HG is the most common reason for hospitalization during the first part of pregnancy (9, 10).

1.1.2   Aetiology

The aetiology of NVP and HG is poorly understood (3, 11, 12), although some biological, physiological, psychological and sociocultural factors are thought to be contributory factors (12). Other theories suggest NVP is the body's natural mechanism that prevents the intake of potentially noxious food (13, 14). In general, the cause is thought to be multifactorial (15).

1.1.3 Risk factors

Risk factors of HG include female fetal sex, younger maternal age (5), multifetal pregnancy, nulliparity, obesity (5, 9, 16), pre-pregnancy body mass index (BMI) less than 18,5 kg/m^2 (underweight) or more than 25 kg/m^2 (overweight) (5) , metabolic disturbances, a history of HG in a previous pregnancy, trophoblastic disorders, psychological disorders (such as anorexia nervosa or bulimia) (9, 16) and lower socioeconomic status. In addition, there is a growing evidence that *Helicobacter pylori* infection is a factor in the development of HG (17).

1.1.4 Challenges for the woman

1.1.4.1 Changes in quality of life

Women with HG suffer both mentally and physically (18). Smith et al. showed definitive connection of NVP with negative effects on different areas of life (6). Using Quality of Life (QOL) data, Lacasse et al. found that QOL for women with moderate to severe NVP (HG) was similar to women with myocardial infarction or breast cancer (19). Several studies show a definite correlation between HG and poor QOL (6, 8, 20). Moreover, women often feel disbelieved by health care professionals and their family members regarding severity of their symptoms and how much suffering this condition actually causes (9, 21).

Many women suffering from HG decide to change their plans for current or future pregnancy. Seventy six percent of women with a history of the condition reported modifying their reproductive plans; many get a fear of pregnancy (9). A Norwegian 10-year cohort of women hospitalized due to HG described 27/558 (5%) of women decided to terminate their pregnancy (induced abortion) (22).

1.1.4.2 Decreased nutritional intake

Due to both nausea and vomiting, women may suffer from insufficient food and fluid intake during their illness. This can lead to dehydration, electrolyte and metabolic imbalance, nutritional deterioration, and weight loss (23, 24).

A South-African study of 20 patients with HG compared to 20 healthy controls showed that mean dietary intake of most of the main nutrients were 50% less than the recommended daily intake (RDI), significantly different from the control group's intake. The majority of the HG patients had also suboptimal blood levels of thiamine, riboflavin, vitamin B$_6$, vitamin A and retinol-binding protein (25). A Norwegian study of 37 HG women and 31 healthy controls

confirmed significantly lower dietary intake of the HG patients as compared to the healthy pregnant women (20).

In a survey of 819 women affected by HG, 26.1% had lost more than 15% of their pre-pregnancy weight. The women with this large weight-loss had more severe accompanying symptoms such as anemia, hypotension, retinal hemorrhage, hematemesis, gallbladder dysfunction, retinal failure and liver dysfunction (26).

One of the most serious complications to poorly treated HG is Wernicke's encephalopathy. This is caused by thiamine deficiency and can lead to permanent neurologic dysfunction and even death (27).

1.1.5 Pregnancy outcomes

Despite most of the effects of HG are maternal, the pregnancy outcomes may be affected. There are both short and long-term risks for the fetus.

1.1.5.1 Low birth weight

As demonstrated by a meta-analysis performed by Vennendaal et. al. (28), HG pregnancies are associated with increased risk of small for gestational age (SGA) and low birth weight (LBW) (<2500 g) babies as well as preterm delivery (<37 weeks gestation). In their research, Dodds et al. found that affected women with weight gain of less than 7 kg were more likely to deliver SGA babies with LBW or preterm deliveries, compared to women with normal pregnancies. However, women with HG, who had a pregnancy weight gain of 7 kg or more, had the same risks of LBW, SGA or preterm delivery as healthy women (29). In the Norwegian study of 558 HG pregnancies, weight gain <7 kg was an independent risk factor for SGA or LBW (22). Thus, it seems justifiable to imply the low catch-up weight gain as the cause of the poor perinatal outcomes rather than the nausea and vomiting itself (29).
LBW increases the risk for health complications in early life and has been found to be related to increased risks of adult diseases such as coronary heart disease, hypertension, and type 2 diabetes (30). LBW was on the second place in the list of causes leading to death in US infants in 2006 (31).

1.1.5.2 Other complications

Other studies have reported an association between HG and different anomalies including undescended testicles, trisomy 21, hip dysplasia, and skeletal or central nervous system anomalies. However, in a resent meta-analysis congenital malformations were not statistical significantly increased in HG compared to control pregnancies (28).

1.1.5.3 Long-term outcomes

There are few follow-up studies of children whose mothers had HG during pregnancy. Thus it is difficult to conclude whether HG affects further life of these children or not. Several publications have demonstrated NVP and HG to be associated with decreased rates of miscarriages when compared to women without these symptoms (14, 32).

There is one study reporting that infants of women affected with severe HG (lasting at least until third trimester of pregnancy) have colic and irritability more often than infants of women with shorter lasting or no HG (33). A survey by Ayyavoo and colleagues shows that offspring of women with HG have decreased insulin sensitivity and increased fasting glucose values, that could mean these people are at risk for developing diabetes mellitus (34).

However, a Scandinavian registry-based nested case-control study of 14 805 HG women cases concluded that hyperemesis does not seem to increase cancer risk of offspring (35).

1.1.6   Management of NVP and HG

All women suffering from NVP and HG should receive advice on managing their symptoms by lifestyle and dietary changes, non-pharmacological or pharmacological approaches (36). The severity of symptoms is a determinant of treatment of NVP and HG (37). Before starting any treatment program, other diseases causing nausea or vomiting should be excluded (24, 36).

Identifying HG as the extreme form of symptoms of NVP, management is usually guided by the same recommendations and algorithms existing for the treatment of NVP (5).

1.1.6.1 Dietary and lifestyle strategies

To our knowledge, there are no studies confirming that changes in lifestyle and diet can minimize the symptoms of HG. However, some guidelines based on clinical knowledge are developed. According to these guidelines, changes in food and fluid intake and daily routines can eliminate the symptoms of mild NVP and to some extent help women with HG achieve an increased dietary intake (16, 36, 38). A consumption of small frequent portions of food and drinks throughout the day is often recommended (16, 36, 39, 40). Cold drinks between each food intake can help to prevent dehydration (36). It is also presumed useful to increase dietary fiber intake (36) and eat food low in fat and acids (16). Additionally, electrolyte-replacement drinks and oral nutritional supplements are also advised as a mean to maintain electrolyte balance and an adequate calorie intake (16, 36, 40). Snacks rich in protein (such as nuts, seeds or dairy) can help to balance blood sugar level and calm down stomach acid (36, 41, 42).

Replacement of hot spicy food by chilled food can prevent nausea caused by odors (16, 23, 36).

The main lifestyle recommendations are to avoid stress and get plenty of sleep and rest (16, 36, 43). Women diagnosed with HG most often require hospitalization. Although women should not be completely isolated from visitors, heavy fragrances (e.g. perfumes or flowers) or smelly food should be limited.

1.1.6.2 Pharmacologic therapies

Antiemetic drugs are commonly used to reduce the symptoms of NVP. They can be used separately or in different combinations (36).

Pharmacologic treatments include:

- vitamin B_6 (pyridoxine)
- anthihistamines (dimenhydrinate, diphenhydramine, doxylamine, hydroxyzine, meclizine)
- phenothiazines (prochlorperazine, promethazine)
- dopamine antagonists (droperidol, metoclopramide, trimethobenzamide)
- 5-hydroxytryptamine$_3$ receptor antagonists (ondansetron)
- glucocorticoids (3, 36)

Despite medications in general are advised to be used carefully during pregnancy, it is considered that the most common antiemetics are safe for mother and fetus. However, the Norwegian Health Authorities have recently issued a warning, restricting Metoclopramide use to a maximum of 5 days (due to possible neurological complications for the women) (24). Ondansetron is preferably not instituted before 10 weeks of gestation (after organogenesis is completed as there are some reports linking this medication to congenital heart defects . Corticosteroids has not been studied in sufficiently large and consistent studies to make valid meta-analyses regarding effects in HG and thus is presently used as "last resort" (44).

1.1.6.3 Intravenous therapies

Due to decreased intake of food and water and excessive loss by vomiting, HG patients are at risk of being dehydrated and may experience electrolyte imbalance. Women who are dehydrated and unable to tolerate oral fluids require intravenous fluid therapy (45). Most patients respond positive to treatment by intravenous fluids (46).

Even in cases of significant ketonuria and hyponatremia, a normal saline (0.9 % sodium chloride) is preferable to dextrose solution or more concentrated solutions of saline (47). In

order to prevent Wernicke encephalopathy, all women, who have experienced vomiting lasting 3 weeks or more, should receive thiamine supplementation to their intravenous infusions (47). In cases of hypokalemia, potassium chloride can be added to infusions (45).

1.1.6.4 Nutritional supplements

If a woman is not responding to antiemetic treatment and rehydration therapy and have persistent weight loss, enteral or parenteral nutrition is required (36, 46, 47). Currently, women suffering from HG often do not receive sufficient nutritional attention (48). The focus of the treatment is usually in correction of dehydration and electrolyte imbalance, and enteral tube feeding is sometimes described as a treatment of last resort (3, 22).

1.1.6.4.1   Enteral Nutrition

Enteral nutrition (EN, given as tube feeding) is a way of delivering liquid and feeding through the gastrointestinal tract. Enteral nutrition can be given to the patients by nasogastric or nasojejunal tube. Enteral nutrition is considered to be more natural and a safer alternative of the intravenous nutrition, having none of the serious complications related to central catheters (such as thrombosis, infection or pneumothorax)(49). Tube feeding is recommended as first-line nutritional treatment in pregnancy (3, 39). Some observational studies show that the enteral tube feeding can effectively treat dehydration and malnutrition and alleviate nausea and vomiting symptoms in HG patients (48). In a Norwegian 10-year cohort study of 558 women hospitalized for HG it was found that women treated with EN achieved a reversal of their weight loss and during the remaining of the pregnancy gained weight in a similar amount as women who received either only intravenous fluid or peripheral parenteral nutrition (22).

A gastric feeding tube can be inserted through the nose and manually gently be pushed forward as the patient actively swallow and thus be brought down to the stomach (ventricle). A jejunal feeding tube has to be positioned by gastroscopy to allow for passing the tube through the pylorus down to the jejunum (upper part of the intestine) (22).

Designated enteral nutrition (EN) solution should be delivered continuously by infusion pump, starting at a low velocity and gradually increasing until approximately 2 litres is given during 24 hours (24). After the patient's general condition has improved and she handles the equipment herself she may continue enteral feeding at home. When the woman has resumed normal oral food intake throughout two days, the enteral tube can be removed. If enteral feeding does not lead to any improvement and the woman continues to lose weight, parenteral nutrition (PN) should be considered (50).

1.1.6.4.2 Parenteral Nutrition

Parenteral nutrition (PN) is feeding a person intravenously, bypassing the usual process of eating and food absorption by the gut. The person receives nutritional formulae that contain nutrients such as glucose, amino acids, lipids and added vitamins and dietary minerals (51). PN is preferable when the woman cannot tolerate food through the gastrointestinal system (50). For treatment lasting a short period, a peripheral vein catheter is preferred and can be administered in parallel with correction of fluid and electrolyte imbalance and while initiating the enteral feeding (24). Due to vulnerability of peripheral veins it is rarely possible to achieve the infusion volume aimed for if all nutritional needed should be delivered through a peripheral catheter. Thus, when the treatment is prolonged, total parenteral nutrition (TPN) should be delivered through a central vein, either by peripheral inserted central line (PICC-line) or by central venous catheter (CVC) (51).

Basically, the parenteral solutions do not contain any micronutrients. Therefore, in order to prevent nutritional deficiencies, minerals and vitamins should be added to the parenteral solution before infusion (49).

For those women who do not improve by EN or PN supplements, total parenteral nutrition (TPN) might be required (52, 53). TPN means that most of or all of daily nutritional requirements are delivered by the venous route. However, TPN should only be used as a last resort when all other treatments have failed, as it can be associated with severe complications such as thrombosis, metabolic disturbances and infection (54).

1.1.6.5 Psychological support

Many NVP/HG suffers still report lack of support from their health care providers (55). The role of psychotherapy for managing HG is not well understood. Psychological therapy is not essential but may be suitable for women who are interested and find it helpful. Online support groups are also available (5). A study from Iran, including 86 pregnant women with moderate NVP found that adding 3 weeks of psychological intervention to a medical therapy gives positive therapeutic outcome (56).

1.1.7 Assessment of the severity of HG

Good clinical assessment tools can be helpful in the validation of the severity of NVP and impact of symptoms. The Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) index is a 3-item questionnaire that characterizes the severity of NVP. It is available in 3 forms in order to evaluate the severity of symptoms during tree different time periods: last 12 hours, last 24 hours and since the beginning of pregnancy (PUQE, PUQE-24, and modified

PUQE respectively) (57, 58). These questionnaires are validated in many countries (58), including Norway (20). PUQE-24 questionnaire is translated to Norwegian as Svangerskaps Utløst Kvalme Kvantifisering (SUKK). In this study a strong inverse correlation between the scores of the PUQE questionnaire and the self-reported food intake and weight gain at inclusion for the participating women was demonstrated (20). PUQE-scores of 13 or more is a significant indicator for hospitalization and necessity of nutritional status evaluation (59). The PUQE-questionnaire also includes one question regarding impact of nausea/vomiting on the woman's general well-being/quality of life. It has been demonstrated that this QOL-item is inversely correlated to the PUQE-score (20, 58). Both the PUQE-score and the QOL-score demonstrated to normalize after treatment/hospitalization in the Norwegian study (20).

To further assess the physical and psychosocial impact of HG, another questionnaire, the Hyperemesis Impact of Symptoms Questionnaire has been developed and validated but has not reached as wide spread use as the PUQE-score. It includes 10 questions about activities of daily living and psychosocial stress (21).

1.2   Nutritional status of pregnant woman

1.2.1 Energy requirements of pregnant woman

According to the World Health Organization (WHO) "the energy requirement of pregnant woman is the level of energy intake from food that will balance her energy expenditure when the woman has a body size and composition and level of physical activity consistent with good health, and that will allow for the maintenance of economically necessary and socially desirable physical activity. In pregnant woman the energy requirement includes the energy needs associated with the deposition of tissues consistent with optimal pregnancy outcome." (60).

Caloric expenditure is not distributed evenly throughout the pregnancy; it is only slightly increased during first trimester but increases significantly in the second and third trimesters (61). The total energy cost of pregnancy is considered to be 325 MJ, distributed as 375, 1200, 1950 kJ/day, for the first, second and third trimesters retrospectively (62).

Nutritional status is adequate when nutritional and energy requirements are covered by food intake (63). The weight of a pregnant woman consists of weight of the mother and the fetus. Weight loss can be an indicator of declining nutritional level (64).

1.2.2 Weight gain recommendations

At this time the WHO does not have recommendations on total weight gain or rate of weight gain during pregnancy. However, the US Institute of Medicine has established guidelines for weight gain during pregnancy based on pre-pregnancy BMI (65). Women with low BMI $<18,5$ kg/m^2, should gain between 12.7 and 18.2 kg during the pregnancy. Normal weight women, with BMI between 18.5 and 24.5 kg/m^2, are recommended to gain between 11.4 and 15.9 kg. Women with overweight, whose BMI is between 25 and 29.9 kg/m^2 should gain 6.8 – 11.4 kg and the obese women with BMI over 30 kg/m^2 should gain between 5.0 and 9.1 kg during pregnancy (65). Women with HG have doubled their risk of low weight gain during pregnancy compared to healthy women (29).

1.2.3 Nutritional requirements

Pregnancy is a decisive period when maternal nutrition and lifestyle plays important roles (31). An adequate nutritional intake during pregnancy is important to ensure proper growth and development for fetus and to promote good maternal health (66). Despite the old sayings that pregnant women should "eat for two", an intake of 2200 – 2900 kcal/day is recommended, that is only about 10 – 15% extra as compared to non-pregnant women (67). General increase in calories should be as follows: the first trimester require only 10 kcal extra per day; during the second trimester an additional 340 kcal/day are recommended; for the third trimester the recommendation is 452 kcal/day (68, 69). However, Nordic Nutrition Recommendations 2012 give slightly different figures: 103 kcal, 329 kcal and 537 kcal extra for the first, second and third trimesters respectively (70).

Pregnant women should mostly follow general food recommendations (63, 66), with the exceptions to avoid some sorts of food that can contain bacteria or other contaminants (71).

1.2.4 Recommendations of nutrients

The recommended balance of energy sources during pregnancy is the same as for non-pregnant women (72).

1.2.4.1 Proteins

Due to extra syntheses of maternal tissues and growth of the fetus, the protein requirement rises during pregnancy (61, 69). The daily recommendation for protein is 71 g/day, compared to 46 g/day for non-pregnant woman (73). The recommended percent of the energy derived from the protein per day (E%) is set to be 10 to 20 E% of the total energy intake (74).

1.2.4.2 Carbohydrates

In order to prevent ketosis and maintain appropriate blood glucose, it is recommended to consume between 135g and 175g carbohydrates per day (69). Recommended E% intake of carbohydrates is set to be 46 – 60 E% of total energy intake (74).

1.2.4.3 Lipids

There are no daily recommendations of total lipid intake either for pregnant or non-pregnant women. Nevertheless, the recommendations for daily intake of the essential poly-unsaturated fatty acids are set to be 1.4 g/day for omega-3 and 13 g/day for omega-6 (73). The recommended E% intake of fat is between 25 and 40 E% of total energy intake (74).

1.2.5   Recommendations of micronutrients

The recommendations of micronutrients, given by the Norwegian Directorate of Health are presented in Table 1. The recommended value of some micronutrients for pregnant woman are the same as for non-pregnant. These micronutrients are Vitamin D, Vitamin B_{12}, Potassium, Magnesium and Iron (74). Although Folate intake recommendation for pregnant women is the same as for non-pregnant, the risk of fetal neural tube anomalies are significantly increased with insufficient intake, thus routinely daily supplementation of 400µg folate is a general recommendation in Norway (74).

The requirement of other vitamins and minerals are higher for pregnant women in comparison with non-pregnant.

Table 1 Recommended daily intake (RDI) of micronutrients for pregnant and non-pregnant women, given by the Norwegian Directorate of Health (74)

Micronutrient	RDI for pregnant woman	RDI for non-pregnant woman (18 – 60 years)
Vitamin A, RAE[a]	800 (+14%)	700
Vitamin D, µg	10	10
Vitamin E, µ-TE[b]	10 (+25%)	8
Thiamin, mg	1.5 (+36%)	1.1
Riboflavin, mg	1.6 (+23%)	1.3
Niacin, NE[c]	17 (+13%)	15
Vitamin B_6, mg	1.4 (+17%)	1.2
Folate, µg	400	400
Vitamin B_{12}, µg	2.0	2.0
Vitamin C, mg	85 (+13%)	75
Calcium, mg	900 (+12.5%)	800
Phosphorus, mg	700 (+17%)	600
Potassium, g	3.1	3.1
Magnesium, mg	280	280
Iron, mg	15	15
Zink, mg	9 (+29%)	7
Copper, mg	1.0 (+11%)	0.9
Iodine, µg	175 (+17%)	150
Selenium, µg	60 (+20%)	50

[a] Retinol activity equivalents (RAE); 1 RAE = 1 µg retinol = 12 µg β-carotene.
[b] α-tokoferolequivalents; 1 α-tokoferolequivalent (α-TE) = 1 mg RRR-α-tokoferol
[c] Niacinequivalents; 1 niacinequivalent (NE) = 1 mg niacin = 60 mg tryptofan.

1.2.6 Assessment of nutritional status

Nutritional status is always associated with food intake. However, absorption and individual metabolism are factors that should be taken into consideration.

1.2.6.1 Food-intake quantification

Different methods and types of questionnaires are used for dietary assessment (75).

Dietary records: the best result, meaning the most representative for one individual, is achieved if all intake of food and drinks is registered consecutively during several days, including both weekdays and weekends. The respondent writes down all food and drinks he/she consumes during these three – four days, or ticks off a specially designed food form (75). Although this method is useful in planned investigations like nutritional surveys, the use in the hospital may be less useful. There is also the possibility that the dietary intake is influenced by the recording. Another method is a *food-intake interview* by a designated nutritionist, where the respondent's food intake for two or more days is collected. As such an interview is time consuming and is not applicable for all situations, *a 24-hour dietary recall* can be used. This is a questionnaire, where respondent is asked to remember and write down all food and beverages that were consumed during the last 24 hours. Specific tick-off forms may be constructed to make the registration easier and pictograms may be added to demonstrate different portions/sizes of servings (76). A nutritionist will then be able to analyze the information collected and estimate total energy intake as well as macro- and micro nutritional composition (76). The disadvantage of this method can be in incorrect estimation of portion size or under-/over reporting food consumed.

Food-frequency questionnaire asks respondents about their usual frequency of consumption of particular food. Such forms collects information only about frequency of eaten foods with no other details (75).

1.2.6.2 Physical methods of nutritional status evaluation

The best method for assessing the adequacy of maternal energy intake is to monitor weight change (72). During pregnancy, the weight will encompass both mother and fetus, but fetal growth/weight gain will normally be assessed by measuring uterine growth (symphysis-fundus measure) or by sonography.

 BMI is a simple index of weight-for-height that is commonly used to classify underweight, overweight and obesity in adults. It is defined as the weight in kilograms divided by the square of the height in meters. The normal range of BMI is 18.5 – 24.99 kg/m^2 (77). For pregnant women BMI before pregnancy must be used for classification.

Mid upper arm circumference (MUAC) is one more parameter that is often used for detecting malnutrition (65). In general, MUAC is considered to be a good indicator of lean mass.

Additionally, the study showed that there is an association between small MUAC of mother and increased risk of infants with LBW (65). No universal MUAC cut-off points are established. Different values of MUAC cut-offs are used for different regions. Nevertheless, it is recommended to use a MUAC cut-off <22 cm as an indicator of a LBW risk and as an entry criterion for nutritional programs (78). It is however, questionable, how quickly the MUAC will change upon low dietary intake.

1.2.6.3 Laboratory assessment of undernutrition

Some blood and urine tests can give additional information of the short-term nutritional status (63).

Ketonuria

One of the markers of undernutrition is ketonuria - a high level of the ketones in the urine (79). Generally, ketonuria occurs when high amounts of fat and fatty acids are metabolized and ketone bodies that are not metabolized are excreted in the urine. That can be due to low supply of carbohydrates from the diet. In such a hunger state, the body uses fatty acids from adipose tissue as an alternative energy source. However, other reasons (diabetes mellitus, increased metabolism etc.) can be a cause of a high ketones level (80).

Prealbumin

Serum prealbumin level can also be used as a marker of malnutrition. Prealbumin is a protein that is produced in the liver and gastrointestinal mucosa (81). Prealbumin composition compared to the other proteins of the body has one of the highest number of essential amino acids, that makes it a distinct marker for protein synthesis. If dietary protein is of poor biologic value or insufficient in amount, or if total calorie intake is low, dietary amino acids must be oxidized as fuel. That decreases synthesis of prealbumin (82). Because the half-life of prealbumin is just two days, the serum level reflects rapid changes in visceral protein status (83). The normal range of prealbumin in blood for women younger than 50 years is 0.23 – 0.39 g/L (84). Lower prealbumin scores mean that a patient is at risk for malnutrition and needs careful assessment (82).

Prealbumin is easily quantified by laboratory instruments available in majority of hospitals and is less affected by liver disease than other serum proteins (81).

To our knowledge, there are few studies about the use of prealbumin as a nutritional marker in pregnant women in general and in pregnant women suffering from HG. One study of 30 pregnant women from 1984 concluded that prealbumin can also be used as a nutritional

marker during pregnancy (85). Specific reference values of prealbumin level in blood during pregnancy have not been developed.

2 Aims and Hypothesis

Monitoring of the nutritional status among pregnant women is important to ensure optimal conditions for growth and development. Women suffering from HG are known to have poor nutritional status (20, 22-25). Pregnancy is characterized by a number of physiological changes leading to changes in many serologic parameters (blood values) (86). That is why reference values that are provided for the adult non-pregnant female population are not necessarily valid during pregnancy. Biochemical parameters that have been validated for use in the assessment of nutritional status during pregnancy are scarce. Especially values during first trimester, the period when hyperemesis is most prevalent, are lacking. In line with our general effort to heighten awareness of nutritional therapy as an important part of treatment for HG patients, we wanted to elucidate different aspects of nutritional status monitoring.

Our main aim in present study is to investigate if prealbumin level in pregnancy is associated with severity and nutritional risks of NVP.

The secondary aims are:

- To evaluate if prealbumin level in early pregnancy in healthy women correspond to the reference range for non-pregnant women.

- To analyze if prealbumin level correlates with self-reported dietary intake.

- To evaluate if prealbumin level correlates with the degree of nausea / vomiting measured by PUQE-scores.

3 Methods and materials

3.1 Study design

This study was originally designed as a prospective case-control study investigating the nutritional intake and nutritional status of women hospitalized with diagnosed HG (cases) as compared to healthy pregnant women (controls) included during August 2015 - April 2016. To increase number of HG patients with available prealbumin analyses, it was decided to include into the analyses the relevant information for HG patients, hospitalized at Haukeland University Hospital during 2013 – 2015 included in other research studies (Gastric tube feeding study and PUQE-validation study). Information regarding these patients was collected from the questionnaires filled out by the participants and from the patients' hospital cases files.

Nutritional parameters (weight, serum prealbumin and ketonuria) were compared between patient and control groups. Nutritional intake was assessed by food diaries.

3.2 Study population

A total 125 of pregnant women participated in present study. Of these, 92 were hospitalized patients with hyperemesis gravidarum and 32 were healthy controls.

The HG group:

Women in the HG group were recruited at the gynecological department of Haukeland University Hospital.

Inclusion criteria

- Hospitalized due to HG: prolonged nausea and vomiting in pregnancy characterized by at least two out of three criteria:

  - dehydration

  - weight loss

  - electrolytes imbalances/ketonuria

- A pregnancy length of less than 16 weeks.

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

Exclusion criteria

  Women with insufficient Norwegian language skills to properly understand consent form and questionnaires.

The control group:

Pregnant women referred to the gynecological outpatient clinic at Haukeland University Hospital due to any other reason than NVP. This could also include women referred for pregnancy termination and women investigated for threatening miscarriage.

Inclusion criteria

- Healthy viable pregnancy

- A pregnancy length of less than 16 weeks

Exclusion criteria

- Inability to understand and write/read Norwegian

- PUQE-score of 13 or more

3.3 Demographic data

At inclusion, participants were asked to fill out a questionnaire collecting general information (Appendix I). These parameters were age, gestational age at inclusion, ethnicity, weight before pregnancy, education, number of previous pregnancies with and without HG, number of deliveries and number of miscarriages. Gestational age at inclusion was estimated according to the last date of menstrual period (a.m Naegele) and confirmed by sonography results at the date of inclusion (Crown-rump length (CRL); Terminhjulet) collected from the patients' case files.

Further, collected background information was compared to a ten-year cohort from Haukeland University Hospital (22), including 558 women with HG.

3.4 Assessment of physical parameters

During anthropometrical measurements, the participants were wearing light clothing and no shoes. Weight was obtained by a scale (kg) and height was measured by stadiometer (cm). BMI (kg/m^2) was calculated as the weight (m) in kilograms divided by the square of the height (h) in meters: BMI = m/h^2.

3.5 Laboratory assessments

At inclusion, blood samples and urine specimen were collected from participating women. For HG patients these analyses were repeated at the discharge from the hospital.

Ketonuria

To determine the presence of the ketones in the urine a rapid urine test was used (Cobas Combur 7 Test Strips, Roche Diagnostics Limited, Rotkreuz, Switzerland). This involves

dipping a test strip with colored fields into an urine sample for one second. After 60 seconds, comparing the subsequent color of the test strip with a color table, the concentration of the ketones in the urine is determined. Unchanged color of the test strip means absence of any ketones in the urine. Changed color shows the presence of ketones. Intensity of the color displays the concentration. Ketonuria measures from 0 to 3+. The test is substantially more sensitive for acetoacetic acid (detection limit 5 mg/dL = 0.5 mmol/L) than for acetone (detection limit about 40 mg/dL = 7 mmol/L) (87).

Prealbumin

Blood samples were used to determine serum prealbumin and C-reactive protein (CRP). CRP was analyzed to avoid prealbumin values elevated due to infection. Analyses were performed in the routine Laboratory for Clinic Biochemistry, Haukeland University Hospital.

Serum prealbumin was analysed using an immunoturbidometric assay (CV 5.5%) (Cobas Integra 400, Roche Diagnostics Limited, Rotkreuz, Switzerland), that measures increasing sample turbidity caused by the formation of insoluble immune complexes when antibody to prealbumin is added to the sample (88).

For CRP analyses, serum was obtained by collecting blood into Vacutainer Tubes with no additive (Becton Dickinson). Serum high sensitive-CRP was measured by an immunoturbidometric assay run on Roche-Hitachi modular system.

3.6 Questionnaires and variables

Information of HG patients' and control group's severity of nausea and vomiting (PUQE-score) and nutritional intake during the last 24 hours were collected by the three-questions SUKK-questionnaire (translated to Norwegian version of PUQE-24 questionnaire) and a food registration ticking list (Appendix II). The HG patients filled out the PUQE and 24-hours registration questionnaires twice, first when they were admitted to the hospital and secondly when they were discharged. The control group filled out questionnaires only once at inclusion.

Question one (Q1) was a question regarding the quantity of hours during the last 24 hours the pregnant woman felt nausea. The alternative answers were: not any nausea (1p), nausea less than one hour (2p), nausea between two and three hours (3p), nausea between four and six hours (4p) and nausea lasting more than six hours (5p).

Question two (Q2) was a question regarding the quantity of episodes of vomiting that the pregnant woman had experienced during the last 24 hours. The alternative answers were: did not vomit at all (1p), vomited one or two times (2p), vomited between three and four times (3p), vomited between five and six times (4p) and vomited more than six times (5p).

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

Summarizing the scores of the three PUQE questions (Q1–3), leads to a total PUQE-score from 3 to 15 points. Result between 3 and 6 points was defined as mild NVP, 7 – 12 points as moderate NVP and patients with scores 13 and above were classified as having severe NVP/HG in line with former studies (57).

3.7 Dietary assessment

Food and drink intake during the last 24 hours before inclusion was registered retrospectively by using of 24-hour food recall questionnaire. HG patients also filled out the same form before discharge from the hospital. The assessment was done using a food list form slightly simplified from the Norwegian national recommendation for prevention and treatment of malnutrition (Appendix III) (89). The form included 38 regular food items and drinks that were listed with a normal size portion (e.g. one egg, one piece of bread, one cup of yoghurt etc.) (Appendix II). In order to improve the participants' accuracy in reporting portion sizes, an evaluated booklet with photograph series of 13 food items with known portion weight was used (Appendix IV, Ungkost 3, edited by Mattilsynet). Participants ticked out consecutively how many servings of each item they consumed for breakfast, lunch, dinner and supper during the last 24 hours. Foods and beverages not listed in the registry form could be added manually. To make the food record as precise as possible, the participants were assisted by nutritionist student (Olga Zybkina) or study nurse while filling out the questionnaires.

3.8 Dietary analysis

Energy, macronutrients (fat, proteins, carbohydrates and fiber) and micronutrients (vitamins, micro and macro elements) were calculated from the reported food intake form using a diet planner Kostholdsplanleggeren (kostholdsplanleggeren.no) (90). That is an educational calculation program designed to display, calculate and compare the nutritional content of

foods, dishes, meals and daily and weekly intake (menus). The program is intended for use in diet education, nutrition counseling, and for those who want to evaluate and plan own diet. Diet Planner is developed by the Norwegian Directorate of Health and the Norwegian Food Safety Authority and is based on The Norwegian Food Composition Table (FCT). FCT provides information concerning the nutrient- and energy content of the most commonly consumed foods in Norway (91). The FCT's nutritional values are compiled from chemical analyses performed in Norwegian quality-assured laboratories, provided by the industry or extrapolated from foreign food composition tables. The FCT is an important tool in governmental food policy and management, education and public health promotion and for health workers and researchers. The table is also used by the food industry as the basis of nutrient declarations and in food production.

3.9 Power calculation

In line with a former study assessing differences in PUQE-score and nutritional intake between HG and healthy pregnant women it was found that 28 patients in each group represent 80% and 100% power to find significant differences (20). The sample size are determined using data from the Canadian study (57) with a mean PUQE-score with 11 +/-3 in the HG group and 9.0 +/-2.2 in control group, with an alpha = 5% (two sided) and a power of 80%. Similarly, using a data of South-African case-control study (25), a sample size of 28 would give a 100% power to detect differences in nutritional intake. We did not have any prealbumin values to estimate from in these studies. However, if we assumed that they were equally different between these two groups as PUQE-score and nutritional intake, minimum of 30 patients in each group was needed. To achieve this number of HG patients with available prealbumin values during the time of inclusion available for this master project, information from patients admitted to the department of gynecology during September 2013-July 2015 was also collected.

3.10 Statistical analysis

Statistical analysis of data was performed by using the statistic program IBM SPSS (Statistical Package for the Social Sciences) Statistics version 23 (IBM, Armonk, NY, USA). Statistical significance was set at $p<0.05$. All tests were to-sided. Chi-squared test was used to compare categorical variables. The linear variables were compared by non-parametric tests: Mann-Whitney U test for two groups, while Kruskal-Wallis test was used for comparing three or more groups. Pearson Correlation test was performed for prealbumin concentration in blood and protein intake.

3.11 Ethical considerations

The Norwegian Regional Ethical Committee (REK Norway) has approved this study (REK 2015/894) (Appendix V). The study is registered at ClinicalTrials.gov NCT02619188. Additional information regarding the routine prealbumin/ketonuria values from HG patients admitted to the department during an earlier study (REK 2013/465) or as a part of a quality assessment project evaluating nasogastric tube-feeding (Haukeland Hospital Personal Security Officer 2015/8991) has also been included in this evaluation.

All participants signed consent of participation (Appendix VI). All data were anonymized before they were stored electronically on a designated research server in accordance with the institutional research rules. Analyses of all data were done after anonymization.

4 Results

4.1 Participants

During the inclusion period from the 3rd September 2015 to 18th April 2016, 49 women were hospitalized due to HG at Department of Gynaecology, Haukeland University Hospital. Of them, 16 women were included in the study. Thus, participation rate was 33%. Reasons for not joining the study were mainly not being asked to participate due to language difficulties or weekend hospitalization (not actively recruiting). Very few women actively declined to participate. For one patient food-intake registration is missing. In addition, from the two studies 2013-2015 (PUQE evaluation and Gastric tube investigation) data from 76 patients was collected retrospectively and included into the analyses. Fourteen of them had filled out food-intake questionnaires (in the PUQE-validation study) (20).

As a control group for the present study, 203 healthy pregnant women were assessed for eligibility. Of these, 50 women (25%) agreed to join and filled out PUQE-24 and food intake forms and 36 of them completed blood analyses for prealbumin. Four women were excluded from the control group due to PUQE-score ≥13. Finally, data from 32 healthy controls was analysed.

The main reasons for not being included was language barrier (not sufficiently reading and understanding Norwegian), study person not present at out-patient ward (not actively recruiting), age <16 years of age or the woman was not considered sufficient healthy psychosocial or physical. Only a minority of women actively declined to participate.

Thus in total 124 pregnant women participated in present study. Of these, 92 were hospitalized patients with hyperemesis gravidarum and 32 healthy controls. The flow of participants in the study is shown in Figure 1.

Hyperemesis Gravidarum group

```
┌──────────────────────────┐      ┌──────────────────────────┐      ┌──────────────────────────┐
│ Hospitalized with HG *    │      │ Hospitalized with HG in  │      │ Hospitalized with HG     │
│ from 04.09.14 to 29.06.15 │      │ 2013 -2014 and included in│      │ from 03.09.2015 to 18.04.2016│
│ and included in Gastric   │      │ PUQE** - validation study │      │ n=49                     │
│ tube study                │      │ n=22                      │      │                          │
│ n=71                      │      │                           │      │                          │
└──────────────────────────┘      └──────────────────────────┘      └──────────────────────────┘
```

Excluded n=9:
- no prealbumin blood test

Excluded n=8:
no prealbumin blood tests

Excluded n=32:
-not meeting inclusion creteria
-refused to partisipate
-not asked
-other

Included **n=62**
(No food-intake registration)

Included **n=14**

Included **n=16**

Missing food-intake registration n=1

n=29
with food-intake registration and prealbumin blood test

Healthy control group

Assessed for eligibility
from 03.09.2015 to 22.12.2015
n=203

Excluded n=153:
- not meeting inclussion criteria
-refused to partisipate

Filled out questionnaires
n=50

Excluded:
- n=14 - missing blood test
- n=4 - PUQE-score>=13

Analyzed **n=32**

*HG Hyperemesis Gravidarum

**PUQE Pregnancy unique quantification of emesis and nausea.

Figure 1: Inclusion process, women hospitalized due to HG and healthy control women in study evaluating prealbumin as a nutritional marker in early pregnancy.

4.2 Clinical characteristics

Clinical data for the patients and controls is presented in Table 2. Age, number of pregnancies and deliveries, and number of former pregnancies complicated by HG were not significantly different between HG and control groups. Physical parameters such as weight before pregnancy, weight at inclusion, height and BMI were also not significantly different in two groups. Women with HG had a statistical significant longer gestational age (median 8.6 weeks, 95% CI 8.3-9), compared to the healthy controls (median 7 weeks, 95% CI 6.6-8.1).

Table 2 Clinical information from patients hospitalized for HG* and healthy pregnant women

Variables	HG*patients n=92 (Median 95% CI)		Controls n=32 (Median 95% CI)		*p*-value Mann-Whitney U Test
Age	28	(27 – 30)	26	(22 – 30)	0.127
Gravidity (number pregnancies)	2	(2 – 2)	1	(1 – 3)	0.209
Parity	1	(0 – 1)	0	(0 – 1)	0.192
HG in former pregnancies (number)[a]	1	(0 – 1)	2	(0 – 3)	0.087
Weight pre-pregnant (kg)[b]	66.7	(61.5 - 69.0)	59.0	(54.0 - 67.0)	0.140
BMI[c] before pregnancy (kg/m²)	23.5	(22.4 - 24.4)	21.6	(20.1 - 24.5)	0.122
Weight Inclusion (kg)[d]	63.9	(58.6 - 68.1)	61.0	(54.0 - 72.0)	0.896
Height (cm)[e]	166	(164 - 169)	165	(162 – 170)	0.622
Gestational length (weeks)	8.6	(8.3 - 9.0)	7.0	(6.6 - 8.1)	<0.001

Hyperemesis Gravidarum,
[a]Excluding nullipara, n=32 in HG* group and n=18 in controls,
[b]Pre-pregnant weight missing for five HG patients and one healthy control,
[c]BMI: Body Mass Index, information missing for eight HG patients and one healthy control,
[d]Weight inclusion missing for two HG patients,
[e]Height missing for four HG patients

4.3 Demographic data of HG patients compared to a 10-years cohort

Comparing demographic data of the HG group of our study to a former ten-year cohort of 558 women with HG hospitalized at Haukeland University Hospital (22), we found similar background information (Tables 3 - 4).

We compared all the HG patients included in our analyses to the historical cohort (Table 3). Age, BMI at admission, weight at admission, number of pregnancies and deliveries, gestational age and ethnicity were not significantly different compared to the historical cohort. More than half of HG patients in both groups (59.7% in historic cohort and 50.6% in present study cohort) lost more than 5% of pre-pregnant weight.

Table 3 Clinical characteristics of historical cohort of patients with hyperemesis gravidarum as compared to all present study's participants with HG

Variables	Historical cohort n=558 Median (Mean)	Study cohort n=92 Median (Mean)	P value (Mann-Whitney U Test)
Age (years)	28 (28.0)	28 (28.4)	0.474
BMI[a] before pregnancy (kg/m^2)	23.5 (24.4)	23.6 (23.9)	0.826
Weight at admission (kg)	61.0 (63.0)	64.9 (64.1)	0.370
Weight loss (kg)	4.0 (4.2)	3.0 (2.6)	0.002
Gestational age (weeks)	8.7 (9.5)	8.6 (9.3)	0.608
	Number (%)	*Number (%)*	*P value Chi-squared test*
Ethnisity			
Caucasian	412 (73.8%)	53 (65.4%)	0.112
Other	146 (26.2%)	28 (34.6%)	
Gravidity			
Primigravida	175 (31.4%)	33 (35.5%)	0.430
Multigravida	383 (68.6%)	60 (64.5%)	
Parity			
Nullipara	240 (43.0%)	46 (41.8%)	0.817
Parous	318 (57%)	64 (58.2%)	
HG in earlier pregnancies[b]			
No	240 (62.7%)	32 (43.2%)	0.002
Yes	143 (37.3%)	42 (56.8%)	
Weight loss at admission[a]			
≤5% of pre pregnant weight	225 (40.3%)	43 (49.4%)	0.109
>5% of pre pregnant weight	333 (59.7%)	44 (50.6%)	

HG: Hyperemesis Gravidarum
[a]BMI: Body Mass Index
[b]Excluded nullipara, n=383 women in historical cohort and n=14 women in present study.

However, there was a statistically significant difference in amount of kilos, lost by the two groups' patients (Historical cohort: median 4.0 kg, present study cohort: median 3.0 kg, p = 0.002 Mann-Whitney U test). The number of former pregnancies complicated by HG was also statistically significantly higher in the combined group of HG patients in present study in comparison to historical cohort (56.8% and 37.3% respectively, p = 0.002 Mann-Whitney U test).

Comparing background information of the three groups of HG patients included in our study gave us similar results (Table 4). Age, BMI before pregnancy, weight at admission, weight loss and gestational age was not statistically significant different between those three groups.

65% of HG patients were Caucasian (21% of HG patients were of African origin). Among the control group, 90% of participants were Caucasian.

Table 4 Clinical characteristics of all groups of present study's participants with HG

Variables	Study cohort, included Sept.2015-Apr.2016, n=16 Median (95% CI)	Study cohort , (Gastric tube study) included Sept.2014-Jun.2015, n=62 Median (95% CI)	Study cohort, (PUQE-validation study) included Mai 2013 - Jan 2014, n=14 Median (95% CI)	p-value Kruskal-Wallis test
Age (years)	29 (27 – 31)	28 (26 – 30)	26.5 (22 - 23)	0.656
BMI[a] before pregnancy (kg/m^2)	24.4 (21.5 – 26.7)	23.5 (22.1 – 24.3)	22.8 (20.5 – 26.5)	0.487
Weight at admission[b] (kg)	68.3 (58 – 75.8)	62.0 (56 – 68.1)	57.0 (52 - 75)	0.706
Weight loss (kg)	2.1 (4.2 – 1.3)	3.6 (4.6 – 2)	3.0 (4.3 - 0)	0.599
Gestational age (weeks)	8.3 (7.1 – 10.7)	8.5 (8 – 9)	9.3 (7 - 13)	0.455

[a]BMI is missing for eight gastric tube study patients
[b]Weight is missing for two gastric tube study patients
HG: Hyperemesis Gravidarum
PUQE: Pregnancy Unique Quantification of Emesis
BMI: Body Mass Index
CI: Confidence Interval

4.4 Nutritional parameters

All the nutritional parameters were statistically significantly different between HG patients and the healthy control group (Table 5). Women with HG had lost median 3 kg (95% CI -4 to -2) while the controls had gained median 1 kg (95% CI 0 - 2), this in spite of the control group

was included at one week shorter pregnancy duration (Table 1). PUQE-score was statistically significantly higher in HG group (median 13, 95% CI 13 - 14, p<0.001 Mann-Whitney U test) compared to the healthy controls (median 6, 95% CI 5 - 8). Prealbumin concentration in blood was significantly lower among HG patients (median 0.19 g/L 5% CI 0.18 - 0.20, p<0.001 Mann-Whitney U test) compared to the healthy controls (median 0.23 g/L, 95% CI 0.19 - 0.25). Stem and Leaf plot at Figure 2 demonstrates this difference. Women from the control group had no ketonuria (median 0, 95% CI = 0); while in urine of HG patients ketones were present at inclusion (median 2+, 95% CI 2 - 3). Caloric and protein intakes estimated in the control group were significantly higher (median 1790 kcal, 95% CI 1350 - 2247 and 84g, 95% CI 55.3 - 104.1, respectively) as compared to HG group (median 653 kcal, 95% CI 387 - 1066 and 21.1g, 95% CI 10.6 - 31.2 respectively, all p-values <0.001 Mann-Whitney U test).

Table 5 Nutritional parameters from patients hospitalized for HG* and healthy pregnant women

Variable	HG*patients n=92, (Median 95% CI^)		Controls n=32, (Median 95% CI)		*p*-value Mann-Whitney U Test
Weight change from pre-conception to inclusion (kg)[a]	-3	(-4 - -2)	1	(0 – 2)	<0.001
PUQE-score[b]	13	(13 – 14)	6	(5 – 8)	<0.001
Prealbumin (g/L)	0.19	(0.18 – 0.20)	0.23	(0.19 – 0.25)	<0.001
Ketonuria[c]	2	(2 – 3)	0	(0 – 0)	<0.001
24h Caloric intake[d] (kcal)	653	(387 – 1066)	1790	(1350 – 2247)	<0.001
24h Protein intake[d] (g)	21.2	(10.6 – 31.2)	84.0	(55.3 – 104.1)	<0.001

*HG: Hyperemesis Gravidarum,
^CI: Confidence Interval,
PUQE: Pregnancy Unique Quantification of Emesis,
[a]Weight change is missing for 6 HG patients and one healthy control,
[b]PUQE-score is missing for 13 HG patients,
[c]Ketonuria is missing for 2 HG patients,
[d]Caloric intake and protein intake is available for 29 HG patients.
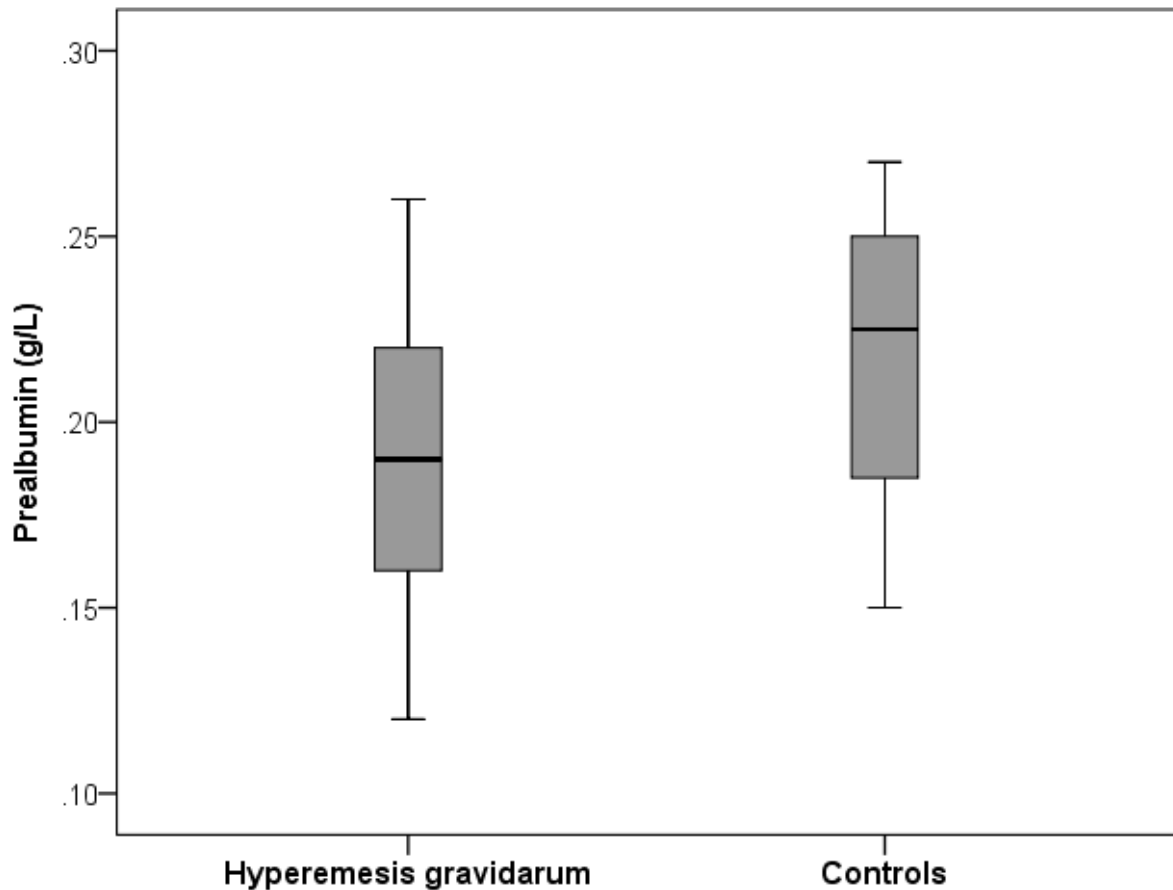
Figure 2: Stem and Leaf plot. Prealbumin concentration (g/L) in blood of Hyperemesis gravidarum and healthy control groups' participants.

4.5 Nutritional parameters compared to severity of NVP/HG

PUQE-scores can be categorized as to describe three degrees of severity of NVP: low PUQE-score = Mild NVP with scores between three and six points, moderate PUQE-score = moderate NVP with scores between seven and twelve points and high PUQE-score = Severe NVP/HG with scores from thirteen to fifteen points (57). This three-tiered PUQE categorization correlated significantly with all the major nutritional parameters (Table 6). The more severe NVP, the worse nutritional characteristics patients had. Prealbumin level goes down, ketonuria rises, weight loss is more pronounced and caloric and protein intake is significantly lower in the HG group.

Table 6 Nutritional parameters compared to PUQE-24*-score severity.
Study of 79 HG patients and 32 healthy pregnant women.

Variable	Mild NVP[a] PUQE-score <7 n=17 (Median 95% CI[π])	Moderate NVP PUQE-score 7-12 n=40 (Median 95% CI)	Severe NVP/HG PUQE-score 13-15 n=54 (Median 95% CI)	*p*-value Kruskal-Wallis test
Prealbumin (g/L)	0.23 (0.19 – 0.25)	0.20 (0.18 – 0.23)	0.19 (0.18 – 0.20)	0.004
Ketonuria[b]	0 (0 – 0)	1 (0 – 2)	2 (2 – 3)	<0.001
Weight change from pre-conception to inclusion (kg)[c]	1 (0 – 3)	-1 (-2.6 – 0.8)	-4 (-4.4 – -2.1)	<0.001
Caloric intake (kcal/24h)[d]	1917 (1531 – 2247)	1194 (834 – 2239)	437 (332 – 871)	<0.001
Protein intake (g/24h)	90.8 (64.6 – 104.1)	47.6 (30.5 – 67)	15.4 (8.3 – 30.9)	<0.001

*PUQE: Pregnancy-Unique Quantification of Emesis and nausea,
^Hyperemesis Gravidarum,
[π]CI: Confidence Interval;
[a]NVP: Nausea and vomiting of pregnancy;
[b]Ketonuria is missing for 1 patient;
[c]Weight change is missing for 6 patients;
[d]Caloric and Protein intake is missing for 47 patients.

Scatterplot of prealbumin concentration in blood of the two groups of participants (HG and control) (Figure 3) illustrates significant negative correlation between PUQE-score and prealbumin level.
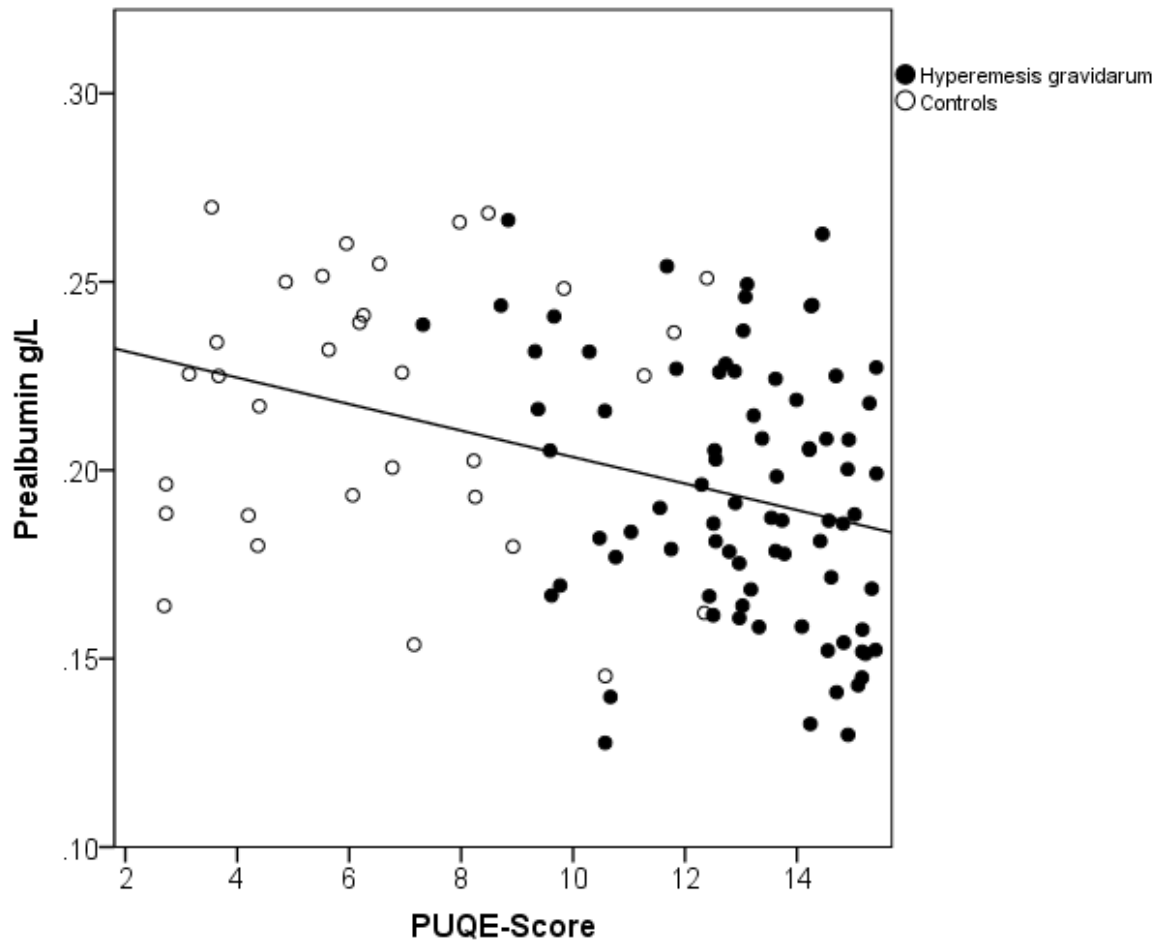
Figure 3: Severity of emesis and nausea in pregnancy measured as PUQE-score (Pregnancy Unique Quantification of Emesis and nausea) anticorrelates with serum Prealbumin measurements in women with Hyperemesis gravidarum (HG) and healthy pregnant controls.

4.6 Nutritional parameters compared to weight change at inclusion

Comparing nutritional parameters to gross weight change (weight loss, unchanged or gain) of all the participants of the study (Table 7), we found that prealbumin level is significantly lower in patients with reported weight loss at inclusion (Median 0.19, CI 95% 0.18 – 0.20). Similarly, ketonuria is more severe in patients with weight loss (Median 2, CI 95% 2 – 3), as compared to those who had weight gain (Median 0, CI 95% 0 – 1). Calculated caloric intake and protein intake was statistically significantly different in the three groups (p=0.009 and p= 0.001 Kruskal-Wallis test, respectively)

Table 7 Nutritional parameters compared to weight change at inclusion.
Study of 85 HG* patients and 32 healthy pregnant women.

Variable	Weight loss n=71 (Median 95% CI^)	Weight unchanged n=13 (Median 95 % CI)	Weight gain n=33 (Median 95% CI)	*p*-value Kruskal-Wallis test
Prealbumin (g/L)	0.19 (0.18 – 0.20)	0.20 (0.17 – 0.25)	0.23 (0.19 – 0.24)	0.005
Ketonuria[a]	2 (2 – 3)	0 (0 – 2)	0 (0 – 1)	<0.001
24h Caloric intake[b] (kcal)	834 (459 – 1502)	1366 (387 – 2349)	1593 (1253 – 2568)	0.009
24h Protein intake[b] (g)	25.5 (14.9 – 43.5)	38.1 (10.6 – 98.5)	76.5 (52.4 – 106.4)	0.001

[a]Ketonuria is missing for 1 patient
[b]Caloric and protein intake is missing for 50 patients
Hyperemesis Gravidarum
^*Confidence Interval*

4.7 Nutritional intake

Comparing nutritional intake of two groups of HG patients (PUQE-validation study HG patients, and present study HG patients) included in our analyses we have not found statistically significant difference in any of these parameters (Table 8). Despite the fact, that estimated carbohydrate intake (Median 99.4g, 95% CI 53.9 – 304 in PUQE-validation study and median 75.4g, 95% CI 18.5 – 162.4 in present study) and general caloric intake (Median 719.5 kcal, 95% CI 387 – 1909 and 489 kcal, 95% CI 194 – 1066 in PUQE-validation and present studies respectively) seemed to be slightly higher in PUQE-validation study group, a non-parametric Mann-Whitney U test showed this to be not significant (p-value = 0.134 both for carbohydrate and caloric intakes).

Table 8 Comparison of the nutritional intake in the HG* patients recorded 24 hours prospectively (PUQE-validation study) and 24 hours retrospectively (present study)

Variables	Study cohort, PUQE^-N study, included May 2013 – Jan.2014, n=14 Median (95% CI¤)		Study cohort, included Sept.2015 – Apr.2016, n=15 Median (95% CI)		*p*-value Mann-Whitney U Test
Protein (g)	22	(10.6 – 55.4)	21.2	(4.6 – 31.2)	0.270
Fat (g)	21.4	(12.4 – 72.6)	17.6	(5.9 – 28.8)	0.186
Carbohydrates (g)	99.4	(53.9 - 304)	75.4	(18.5 – 162.4)	0.134
Caloric intake (kcal)	719.5	(387 – 1909)	489	(194 - 1066)	0.134

*HG: Hyperemesis Gravidarum
^PUQE: Pregnancy Unique Quantification of Emesis
¤CI: Confidence Interval

Median values of nutrients' intake, median values of energy percentage of the macronutrients and percentage of recommended intake of both macro- and micronutrients are presented in Table 9. All nutritional parameters except vitamin C intake were statistically significantly different between HG patients and the healthy pregnant control group.

Table 9 Nutritional intake calculated from 24h self-reported food-intake form and percentage of daily-recommended intake in the HG[*] and control groups

Variables	HG[*]		Controls		P-value
	n=28 Median (95% CI[¤])	Percent of RDI[#]	n=32 Median (95% CI)	Percent of RDI	Mann-Whitney U test
Energy (kcal)[a]	653 (387 - 1066)	27%	1790 (1350 – 2247)	73%	<0.001
Protein (g)[b]	21.2 (10.6 – 31.2)	30%	84 (55.3 -104.1)	118%	<0.001
Fat (g)[c]	21 (12.4 – 28.8)	-	67.7 (45.9 – 104.8)	-	<0.001
Carb' (g)[d]	95.4 (54 – 162.3)	62%	193.5 (150.5 – 244.1)	125%	0.001
Vitamin D (µg)	0.5 (0.3 – 1.0)	5%	2.7 (1.2 – 5.5)	27%	0.001
Vitamin C (mg)	32.2 (10.5 – 102)	38%	26.5 (10 – 58)	31%	0.465
Vitamin B$_{12}$ (µg)	0.6 (0.4 – 1.3)	30%	4.6 (2.3 - 6.2)	230%	<0.001
Calcium (mg)	195 (119.5 – 428)	22%	727 (427 – 1087)	81%	0.001
Iron (mg)	2.1 (1.3 – 3.3)	14%	8.2 (5.9 – 9.8)	55%	<0.001
Magnesium (mg)	66 (54 – 163)	24%	228 (179 – 322)	81%	<0.001
Sodium (mg)	909 (667 – 1348)	19%	2783 (1573 – 3262)	57%	<0.001
Fiber (g)	5.9 (2.8 – 8.7)	20%	12.5 (8.3 – 18.8)	42%	<0.001
Protein (E%^)[e]	12 (10 – 14)	-	17.5 (16 – 20)	-	<0.001
Fat (E%)[f]	28 (21 – 34)	-	36 (33 – 42)	-	0.004
Carb (E%)[g]	56 (45 – 65)	-	47 (41 – 54)	-	0.022

[a]Recommended energy intake of pregnant women depends among other on their pre-pregnancy weight and daily level of activity. At present study, the estimated recommended level of daily energy intake was set as 2450 kcal. [b]Recommended protein intake of pregnant women is set as 71 g per day (71). [c]There are no recommendations on total fat intake per day. [d]Recommended daily intake of carbohydrates is set to be between 135 and 175g per day to maintain normal blood glucose (71). Calculated percentage of daily carbohydrate intake recommendation is in this case set to the mean of 135 and 175 g: 155g.
[e]Recommended protein intake is between 25 and 40 E% of total energy intake (73).
[f]Recommended fat intake is between 25 and 45 E% of total energy intake (73).
[g]Recommended carbohydrate intake is between 45 and 60 E% of total energy intake (73).
*HG: Hyperemesis Gravidarum
[¤]CI: Confidence interval
[#]RDI: Recommended Daily Intake
^E%: Energy percentage
'Carb: Carbohydrates

4. 8 Energy intake

The recommended energy intake for healthy pregnant women, set by the Norwegian Health board is between 2150 kcal for inactive women and 2400 kcal for active women (74). A cut

off was determined as the mean of these values: 2275 kcal. Additionally, for pregnant women during the first trimester the daily need is approximately 10 kcal extra per day and in the second trimester 340 kcal extra per day (74).

Comparing the energy intake (kcal) between groups with the three PUQE categories (mild, moderate and severe NVP/HG) to the recommended energy intake during the first and the second trimester, we found no statistically significant difference in proportion of women with sufficient energy intake in the first and the second trimesters (Table 10). However, the results shows, that the higher PUQE-score patients have, the larger proportion have insufficient energy intake. Comparing energy intake in the first and the second trimester in the HG group to control group, the significant difference was found in the first trimester (Table 11). Moreover, the results show that the majority of control group women (75%) and almost all the HG patients (97%) have insufficient self-reported energy intake.

Table 10 Sufficient energy intake related to gestational age and PUQE* categories for 29 women hospitalized due to HG[§] and 32 healthy pregnant controls

Variables	Sufficient energy intake	PUQE* 3 – 6 n = 17	PUQE 7 – 12 n = 24	PUQE 13 – 15 n = 20	p-value Chi-squared test
1st trimester[a]	Yes	3	5	0	0.093
	No	13	16	18	
2nd trimester[b]	Yes	0	1	0	0.549
	No	1	2	2	

[a]Sufficient energy intake for the 1st trimester is estimated as 2285 kcal a day or above.
[b]Sufficient energy intake for the 2nd trimester is estimated as 2615 kcal a day or above.
*PUQE: Pregnancy Unique Quantification of Emesis and nausea
[§]HG: Hyperemesis Gravidarum

Table 11 Self-reported 24h energy intake in pregnant women, categorized as if meeting national recommendations (sufficient) and related to gestational age and diagnose of HG*

Variables	Sufficient energy intake	HG* group n = 29	Control group n = 32	p-value Chi-squared test
1st trimester[a]	Yes	0	8	0.007
	No	24	23	
2nd trimester[b]	Yes	1	0	0.624
	No	4	1	

[a]Sufficient energy intake for the 1st trimester is estimated as 2285 kcal a day or above.
[b]Sufficient energy intake for the 2nd trimester is estimated as 2615 kcal a day or above.
HG: Hyperemesis Gravidarum

Table 12 Self-reported 24h energy intake in pregnant women, categorized as if meeting national recommendations (sufficient) and related to prealbumin level and diagnose of HG*

Variables	Sufficient energy intake[a]	HG*group n = 29	Control group n = 32	p-value Chi-square test
Low prealbumin (<0.23 g/L)	Yes	1	4	0.096
	No	18	12	
Normal prealbumin (≥0.23 g/L)	Yes	0	4	0.086
	No	10	12	

[a]Sufficient energy intake for the 1st trimester is 2285 kcal a day or above. Sufficient energy intake for the 2nd trimester is 2615 kcal a day or above.
HG: Hyperemesis Gravidarum

4.9 Protein intake

Although, there were not found significant differences in energy intake of HG patients and control group with low or normal prealbumin levels (Table 12), statistically significant difference in protein intake of both groups appeared (Table 13).

Prealbumin level was significantly correlated to 24 h protein intake, Pearson Correlation =0.401 (p = 0.001, two-tailed). Figure 4 demonstrates this significant correlation.
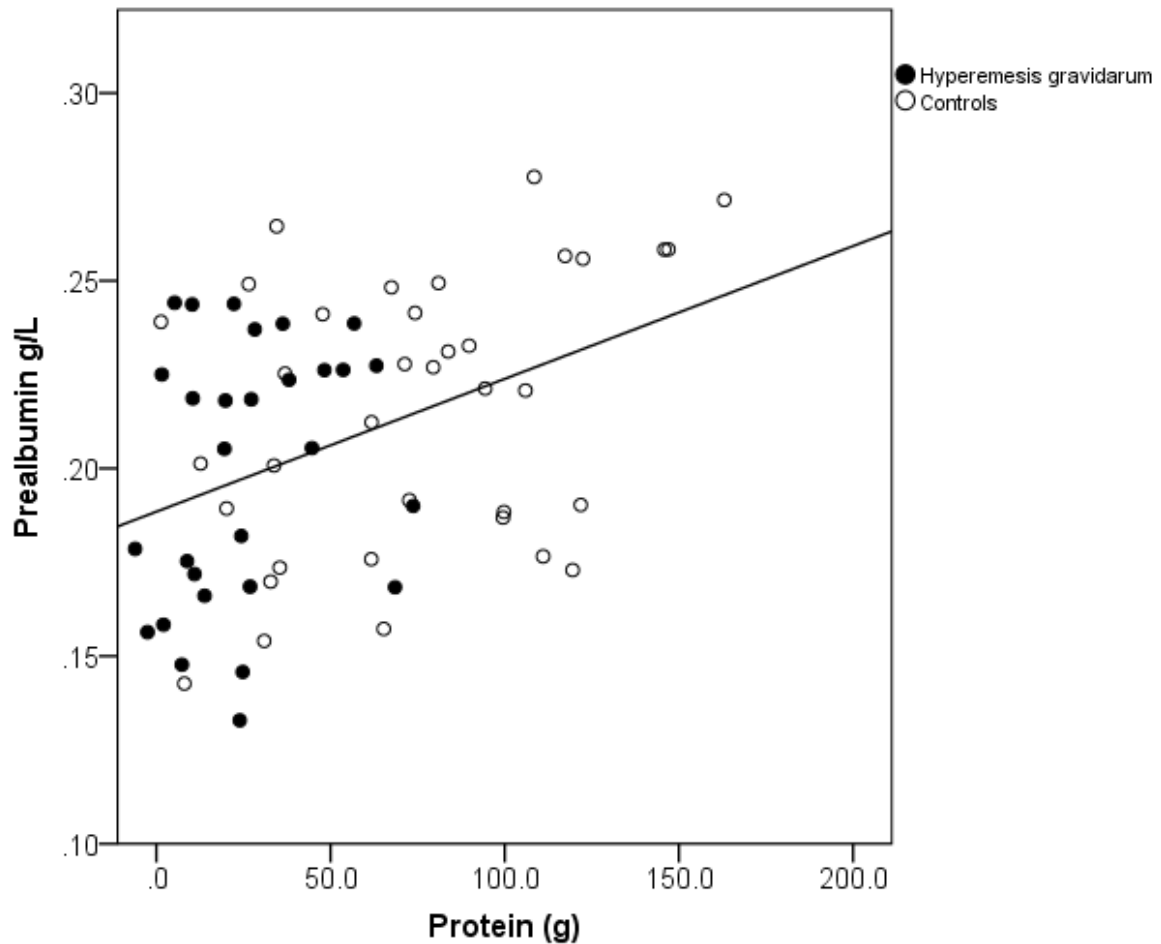
Figure 4: Protein intake (g) correlates with serum prealbumin measurements in women with Hyperemesis gravidarum (HG) and healthy pregnant controls.

Table 13 Estimated 24h protein intake in pregnant women, categorized as if meeting national recommendations (sufficient) and related to prealbumin level and diagnose

Variables	Sufficient protein intake[a]	HG group n = 29	Control group n = 32	p-value Chi-square test
Low prealbumin (<0.23 g/L)	Yes	0	7	0.001
	No	19	9	
Normal prealbumin (≥0.23 g/L)	Yes	0	10	0.001
	No	10	6	

[a]Sufficient protein intake for pregnant women is set to be 71g per day.

5 Discussion

This thesis aimed to validate whether serum prealbumin level is associated with severity and nutritional risks of nausea and vomiting in pregnancy. Prealbumin levels in blood were compared between healthy pregnant women and women hospitalized due to hyperemesis gravidarum. We did find that serum prealbumin was significantly lower in HG than healthy controls. Prealbumin levels decreased with increased severity of NVP (measured as PUQE-score) and correlated with self-reported 24h energy- as well as protein intake.

5.1 Methodological discussion

5.1.1 Study design and method

The current study is an observational case-control study where the data from the participants was collected using retrospective (last 24 hours)questionnaire forms. Although, randomized controlled trials (RCTs) are considered to be the gold standard of the evidence-based medical studies evaluating interventions (92, 93), RCTs are not possible to perform for all kinds of research or are not always the best choice of a study design because due to ethical reasons (94). Our study is not an interventional study but an observational/epidemiologic study where RCT is not an option. According to Chang and colleagues, RCTs, prospective cohort studies and systematic review of these have high level of evidence (I and II). While retrospective studies, case-control studies and systematic review of these have a level of III of evidence rating scale (95). A prospective study thus would be preferable.

The aim of present study was to evaluate the difference in nutritional parameters of two groups of pregnant women: healthy pregnant compared to those whose pregnancy is completed with HG. As severe NVP/HG is a relatively rare diagnose, occurring in 1% of pregnancies (1), a traditional cohort study would therefore have to be very large (more than 2800 pregnant women) to meet the estimated number of 28 patients with HG. That is why, a case-control study is considered more efficient and realistic to perform within the time period available for inclusion. Nevertheless, because of the slow recruitment of the HG patients at the department of gynecology and obstetrics, Haukeland University Hospital, information from patients admitted to the department during 2013-july 2015 was also collected. As retrospective studies and case-control studies have an equal level of evidence (96), the bias between two groups of HG patients we have studied is supposed to be minimal.

Before starting study enrollment, the nutritional master student was given instructions on how to make anthropometrical measurements and take urine test. Training on assisting women in

answering food-intake questionnaire to ensure that the food-list was manageable was completed before meeting patients. The same food-list had been used in a former study by our group (20) and proven to contain relevant food and fluid items.

5.1.2 Study population

Each year approximately 50 – 60 women are admitted to Haukeland University Hospital with a diagnose HG. Of them, 25% is of non-Caucasian ethnicity and often not Norwegian speaking (20). Inclusion period was eight months, leaving an estimate number of 30 women with HG and fully able to understand and answer questionnaires in Norwegian.

We asked our participants about their ethnicity. Despite the fact, that only women able to understand Norwegian were included, only 65% of HG patients were Caucasian (21% of HG patients were of African origin). Among the control group, 90% of participants were Caucasian. Our results are in line with meta-analyses done by Einarson and colleagues, who reported that there were differences in the occurrences of HG in geographic areas (97). Additionally, a Norwegian study of variations of prevalence of HG by country of birth stated a 3.3 – 3.4 fold higher risk of developing HG in women born in Africa, India and Sri Lanka than ethnical Norwegian women (98).

Both groups (HG and control) were recruited at Haukeland University Hospital; HG while being hospitalized at the gynecological department and controls while referred to the gynecological out-patient clinic. Our PUQE-validation study (20) included healthy controls when attending their general practitioner for routine pregnancy care. It was demonstrated in that study that healthy pregnant women do not contact health practitioners before the end of the first trimester, it is later than hyperemesis patients are usually hospitalized (11.8 and 9 gestational weeks respectively) (20). To include a control group with a gestational length more representative of early/mid first trimester, more in line with when hyperemesis in general is diagnosed, it was decided to assess for eligibility also women attending the out-patient clinic for pregnancy termination consultation. The majority of these patients are present their consultation before ninth gestational week. Norwegian women have a 30 % lifetime risk to conduct pregnancy termination (99). Pregnancy termination is considered a less stigmatizing "condition" during last years. Norwegian REK has formerly permitted to recruit women applying for pregnancy termination for research evaluating blood analyses (100). We specifically raised the issue whether it was ethical justifiable to ask this group of women to participate with our Regional Ethical Board and got their approval. However,

women with psychosocial burdens (such as drug addictions or psychiatric conditions) were considered ineligible and would not be asked to participate.

Thus we managed to enroll a control group of much lower gestational age than the previous study (7 weeks, compared to 11.8). Participants with median 8.6 gestational weeks in the HG group and 7 gestational weeks in control group, give us a desired cohort representative of pregnant women in first trimester.

Blood test for determination of prealbumin is already a routine test for hospitalized hyperemesis patients. Pregnant women, attending the gynecological out-patient clinic (control group) will usually have a blood test performed. Thus, some extra vials of blood will not present any higher risk for patient.

The actual participation rate was 33% of hospitalized HG patients and 25% of controls. We may have encountered a self-selection bias, as it may be a higher interest in food and health in people willing to join the study as compared to the general population (101). Among hospitalized women almost none of those who were asked to participate, actually declined. To consider if our study cohort is representative for women hospitalized due to HG in general, we compared it to a 10-years cohort of HG patients from Department of Gynecology and Obstetrics, Haukeland University Hospital (22). Age, BMI at admission, weight at admission, number of pregnancies and deliveries, gestational age and ethnicity were not significantly different (See Table 3). The HG patients participating in this study had significantly higher proportion of women with earlier HG pregnancies (57% as compared to 37% in the historical 10-year cohort). Thus, women having experienced the debilitating effects of HG possibly are more willing to participate in studies regarding that condition. This goes in line with a statement that people are more willing to participate in studies investigating disease they have (102).

The participation rate of controls should ideally be higher. Including healthy volunteers for studies are always challenging. Taking into account the possible emotional burden of an unwanted pregnancy we would definitely avoid these women should feel any pressure to participate. In that way a low participation rate is reassuring that those participating really consented without any hesitation. By increasing the number of healthy control women per women with HG, an increased statistical power of the results could have been achieved (94).

To determine a robust reference range for a blood analysis 120 cases are recommended to include as a minimum. We did not manage to include this number of healthy pregnant women within the inclusion period.

5.1.3 Collected data

The women participating in this study have filled out their background information, answered the questions regarding the severity of the symptoms of NVP they had (PUQE-form) and reported their food and fluid intake during the 24 hours before inclusion. Misclassification and false self-reported information can lead to biases in the outcome of the study. However, the assistance of the participants in filling out questionnaires by the study personnel should raise accuracy of the answers. Generally, women's answers regarding pregnancy details (number of pregnancies, gestational age and previous pregnancy complications such as HG) are considered valid. These data is self-reported on the Norwegian pregnancy record (Helsekort for gravide) and is a basis for reports to the compulsory Norwegian national birth registry (Fødselsregisteret). Pre-pregnant weight was self-reported in our questionnaires, as weight at inclusion was measured by study personnel. Overweight women tend to under report their actual weight and over report their height, leading to a lower estimated BMI, in addition, underweight women tend to over report their weight. (96). However, the median BMI of our participants was 23.5 kg/m^2 and 21.6 kg/m^2 for HG and control groups respectively, that is lower than the cut-off for BMI indicating overweight (25.0 kg/m^2). To ensure a correct weight measurement the same scale should have been used before pregnancy and at inclusion. Unfortunately, this was not realizable. However to reduce within-group variation the same/one weight was used for weighing the HG patients at inclusion (in the department) and one weight for all the controls (in the out-patient department).

Prealbumin blood test and urine tests for ketones were performed using methods that are used routinely in Haukeland University Hospital. The prealbumin analyses were performed at the laboratory of clinical biochemistry while urine dip-stix analyses were performed by nurses at the ward (in-patient or out-patient).

Prealbumin may be elevated due to concomitant conditions such as infection. To control for this CRP was measured concomitantly. No patients had CRP ≥10.

5.1.4 Estimation of nutritional intake

For nutritional intake estimation, different methods are available. Data can be collected retrospectively (24-hours recall, food frequency questionnaire or diet history) or prospectively (estimated diet diary, checklist or weight diet diary). Food intake of any person varies from day to day and a 24-hours food recall is not necessarily considered to be representative for a person's mean dietary habits (102). To get a better picture a several days food (3 to 7 days) record should be performed and average values calculated (104). However, in a study of nutritional intake of 160 women, Bingham and colleagues found, that the 16-days weight record and food frequency questionnaire were not noticeably better in describing individual's diet than 24–hours questionnaire (103).

The aim of thepresent study was to evaluate correlation between the food intake and PUQE-score and serum prealbumin level. Serum prealbumin as a nutritional marker has a quite short half-life of 2 days (81). That means that changes in diet give rather quick changes in prealbumin concentration in blood. Moreover, PUQE-score is measured by questionnaire, evaluating the severity of NVP during the last 24 hours. Thus, a registration of last 24 hours food intake is considered to be the most relevant for this particular study.

5.1.5 Dietary assessment

The food intake was registered using a specially designed tick-off form. The food list contained 38 types of regular food and drinks (Appendix II), there were also space to write down extra information (types of dinner or desert, topping on bread, etc.). Every participant was assisted thoroughly during the filling out of the food-intake form. Special booklet with pictures of portion sizes of different foods helped participants to estimate amount of food they have eaten. This is an easy way of performing a food registration. We have chosen such form of food-registration to achieve more accurate data collection and to get enough participants in the two groups for making analyses. Despite the fact, that booklet with portion sizes minimizes mistakes in portion size measurement, miscalculation can occur. Sometimes, even photos of different food portion sizes were not sufficient for participants to accurately estimate amount of eaten food. In addition, some of the participants might forget to register some foods or consciously or unconsciously do not register particular types of "unhealthy" food. Women in general have a tendency to underreport what they have eaten (105). Moreover, NVP can differ from day to day and influence food intake. However, in our former study (20) we have documented that self-reported food intake anticorrelated with rate

of NVP (measured as PUQE-score). Thus, our modified food-frequency chart and the NVP-questionnaire reporting from the same immediate preceding 24 hours period and related to a prealbumin-value taken the morning immediate following this 24-hour period seem a most appropriate comparison.

However, given the limitations described, we considered the inclusion of study population and methods used as not being significantly biased. Thus, when we found significantly differences between the nutritional intake in HG and control groups, this is considered valid.

In general the female population in Bergen/Hordaland is not significantly different form those in the rest of Norway. In this regard, we consider our findings to be of relevance for a Norwegian pregnant population in general.

5.1.6 Statistical analyses

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

5.2 Discussion of results

The present study key findings are: 1) serum prealbumin level correlates negatively with PUQE-score (the more severe NVP/HG the lower prealbumin concentration in blood was measured); 2) nutrient intake of the HG patients is statistically significant lower than the nutrient intake of the control group; 3) serum prealbumin level significantly correlated to 24-hour protein intake; 4) NVP in any grade influence nutritional intake of pregnant women in the first trimester (nutritional intake for the majority of HG and control patients is lower than recommended values).

5.2.1 Serum prealbumin level

Serum prealbumin level of HG group (0.19 g/L) is statistically significant lower than in control group (0.23 g/L). However, control group women also have rather low concentration of prealbumin in blood. Normal value of serum prealbumin for non-pregnant women younger than 50 years is 0.23 – 0.39 g/L (84). Lower prealbumin scores mean that a patient is at risk for malnutrition and needs careful assessment (82). To our knowledge, there are no studies about using prealbumin as a nutritional marker during pregnancy, except one from 1984 (106). That study led the authors to suggest that prealbumin level in blood can be used as a nutritional marker in pregnant women as well as in non-pregnant. Reference values of serum prealbumin for pregnant women in the first trimester have not been specifically developed. As prealbumin values of 120 healthy pregnant women are needed to robustly estimate a normal range of prealbumin concentration in blood for pregnant women in the first trimester (107), we did not manage to fulfil this criterion during the time-frame of present study.

5.2.2 Pregnant women in first trimester are at nutritional risk

According to a previous study from our group (20), PUQE-score correlates inversely to the women's nutritional intake during 24 hours. Our present study also confirms a strong inverse correlation between PUQE-score and caloric intake. Compared to the healthy control group, statistically significant lower levels of all nutrients except vitamin C are found in the HG group. This is in line with what Stuijvenberg and colleagues reported in their study from 1995 (25), except for their lack of statistically significant difference not only for vitamin C but also for vitamin B_{12} values. Their 24-hours food-intake recall determined 1813 kcal for controls and 443 kcal for HG patients. In comparison, our estimations were 1790 kcal and 653 kcal.

Compared to recommended values of energy intake, none of the pregnant women with PUQE-score≥13 reached recommended intake of calories. Moreover, none of the pregnant woman in the first trimester diagnose as HG reached recommended values in energy or protein intake. The fact, that when woman is actually vomiting, parts of food eaten will be not accessible for digestion, leaves the high-score group with even lower actual nutritional uptake. Thus, high PUQE-score is compatible with women being at high nutritional risk. As a prealbumin level inversely correlates with a PUQE-score, we can consider that it can be used as a marker of malnutrition in HG pregnancies.

The differences in weight changes (patients with the weight loss had the lowest prealbumin level, oppositely, patients with weight gain had the highest prealbumin level) strengthen our statement of prealbumin being a marker of insufficient nutrition.

Despite the fact that patients in our HG group have very low caloric intake, 56% of the energy they consumed was from carbohydrates. This result supports findings from the Mother and Child study that women with severe NVP/HG consume most of their calories from carbohydrates (mostly added sugars) (24). Opposite, energy percent from protein intake is very low in HG group (12 E%, compared to recommended 25 – 40 E%). However, according to food recommendations during pregnancy accomplished by NVP/HG high protein intake is recommended. It is suggested that food high in protein may help to reduce symptoms of nausea (36, 41).

The control group of healthy pregnant women had statistically significant higher nutritional intake compared to the HG group. Nevertheless, the majority of the control women (75%) had insufficient self-reported energy intake as compared to recommended values. Prealbumin level in blood of control women is at the lower border of normal range. These facts allow us to suggest that the majority of pregnant women, due to NVP during the first trimester, maybe more at nutritional risk than generally acknowledged.

5.3 Conclusion

This case-control study demonstrated that there was a strong correlation between serum prealbumin level and protein/energy intake. Thus, prealbumin measuring can be used to identify patients with severe NVP/HG- as being at high nutritional risk. Additionally, we found statistically significant differences in all the nutritional parameters between healthy women and women suffering from HG.

5.4 Future perspectives

Reference values of prealbumin concentration in blood for pregnant women in the first trimester should be developed. A deeper analysis of micronutrients intake can give better picture of nutritional status of HG patients.

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SUKK-M; STUDIE OM KVALME OG ERNÆRINGSMARKØRER

VED HYPEREMESISSVANGERSKAP

SPØRRESKJEMA v/inklusjon   1. trimester

Fødselsnummer	Mobiltlf.	Dato utfylt:
Fornavn	Etternavn	Løpenr.
Dato siste menstruasjon	Svangerskapsuke (i dag)	Termin ultralyd
Regelmessig menstruasjon JA☐ NEI ☐	Sykluslengde Antall dager	Termin Naegele

Etnisitet: Afrikansk ☐ Arabisk ☐Asiatisk ☐ Kaukasisk («Europeisk») ☐

Vekt før graviditet (kg): _____   Vekt uke ----- (kg):_____

Høyde(cm)   _____

Ketoner i urin: ……… (sykepleier fører på det)

Utdannelse (år)

☐ ≤ 12 (tom videregående) ☐13-16 (3-årig høyskole e.l.) ☐ ≥ 17 (>5 år på Høyskole/universitet)

Tidligere svangerskap

Hvor mange ganger har du vært gravid _____   Hvor mange barn har du _____

Fødselsår for barna: _____   _____   _____   _____

Har du hatt mye svangerskapskvalme (Hyperemesis) i tidligere svangerskap JA ☐   NEI ☐

Hvis JA antall svangerskap med Hyperemesis   _____

Evt antall tidlige spontanaborter (< uke 12) _____

SUKK-S   Svangerskaps Utløst Kvalme Kvantifisering –Spørreskjema
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	4-6 timer	2-3 timer	≤1 time	Ikke i det hele tatt
5 poeng	4 poeng	3 poeng	2 poeng	1 poeng

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

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

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

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

1

BRUKER DU:

Faste medikamenter (spesifiser) _____

Kvalmestillende medikamenter (spesifiser)_____

Multivitamintilskudd mer enn 3 dager/uke?

Nå?   *NEI* ☐   *JA* ☐ *Preparatnavn*_____

Før svangerskapet?   NEI ☐   JA ☐ **Antall mndr**_____

Jerntilskudd mer enn 3 dager/uke?

Nå?   *NEI* ☐   *JA* ☐ *Preparatnavn*_____

Før svangerskapet?   NEI ☐   JA ☐ **Antall mndr**_____

Folat tilskudd (0,4 mg) mer enn 3 dager / uke ?

Nå?   *NEI* ☐   *JA* ☐ *Preparatnavn*_____

Før svangerskapet?   NEI ☐   JA ☐ **Antall mndr**_____

Tran/annet omega-3 tilskudd mer enn 3 dager / uke?

Nå?   *NEI* ☐   *JA* ☐ *Preparatnavn*_____

Før svangerskapet?   NEI ☐   JA ☐ **Antall mndr**_____

Naturlegemidler mer enn 3 dager / uke?

Nå?   *NEI* ☐   *JA* ☐ *Preparatnavn*_____

Før svangerskapet?   NEI ☐   JA ☐ **Antall mndr**_____

Helsekostprodukter mer enn 3 dager / uke?

Nå?   *NEI* ☐   *JA* ☐ *Preparatnavn*_____

Før svangerskapet?   NEI ☐   JA ☐ **Antall mndr**_____

Røyker du? NEI ☐ JA ☐ Hvis Ja, hvor mange sigaretter/dag _____

Er det noen andre i husstanden som røyker? **NEI ☐ JA ☐**   Antall sigaretter/dag: _____

Hvis du røykt før du ble gravid, når sluttet du? Dato _____

Bruker du snus? Ja ☐   Nei ☐

Hvis ja, hvor lenge har du brukt snus _____(antall år, evt mnd)

Hvis ja, hvor mye snuser du _____ (antall pr dag)

Hvis du snuste før du ble gravid, når sluttet du å snuse? Dato _____

Hvor mye snuste du _____ (antall pr dag)

2

APPENDIX II   Food-intake form

SUKK-M   Egenrapportert matinntaksskjema Inklusjon

MATVARE	ENHET	ANTALL/	MENGDE	SPIST		
		FROKOST	LUNSJ	MIDDAG	KVELDS	
Kneipp/grovbrød	1 skive m/					
Loff	1 skive m/					
Rundstykke	1 skive m/					
Knekkebrød	1 stk m/					
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					
Juice:	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 forrige/siste døgn. Marker for hvert måltid, og husk om du spiste/ drakk utenom måltid. Kryss av for hver enkelte matenhet (X evt I). Spiste du mindre enn en enhet f.eks 1/2 glass; skriv 1/2.   *Inkludert pålegg   Skriv + ved smør på skiver

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 før et høyere inntak!   Sist oppdatert 10.12.09

*Bildehefte
med porsjonsstørrelser*

DETTE BILDET VISER STØRRELSEN PÅ TALLERKENENE SOM ER BRUKT I BILDEHEFTET
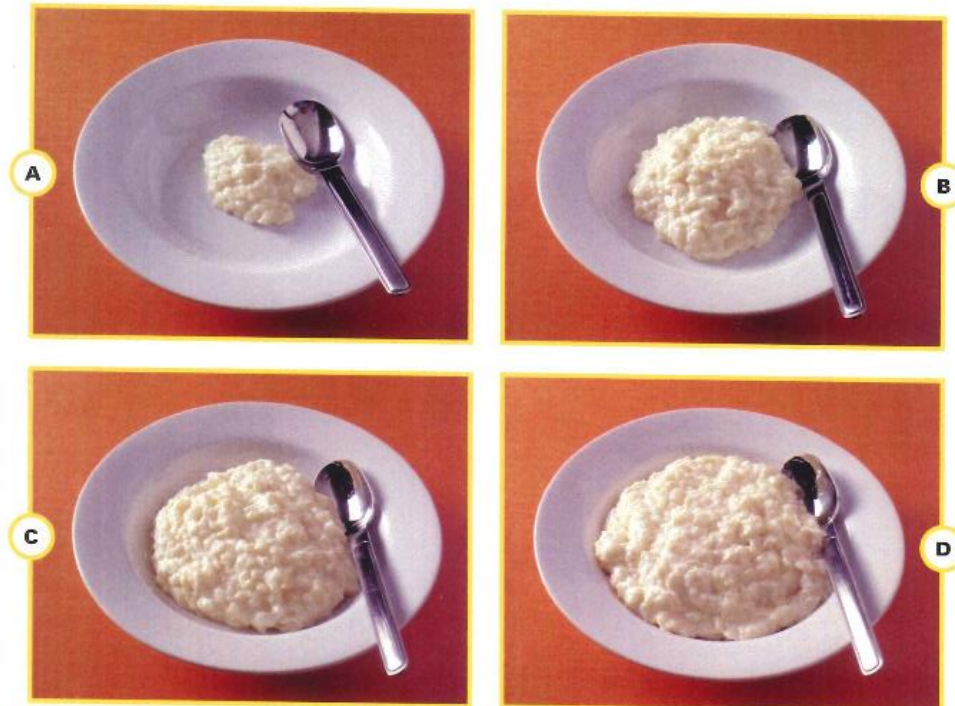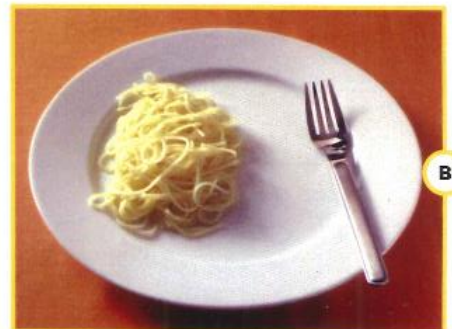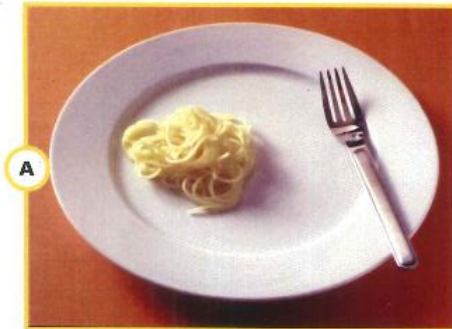

1. GLASS
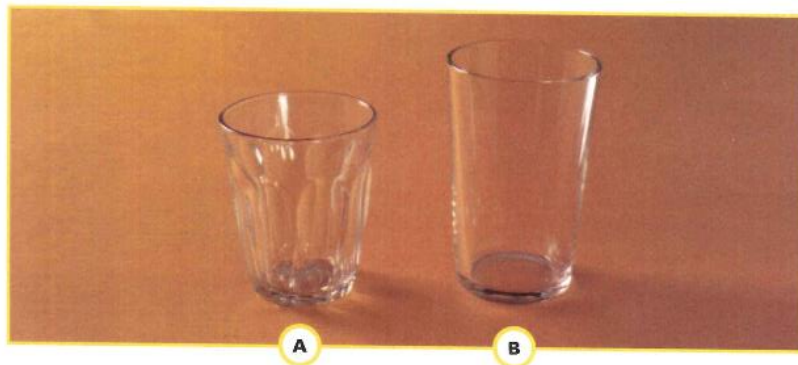
2. BRØDTYKKELSE
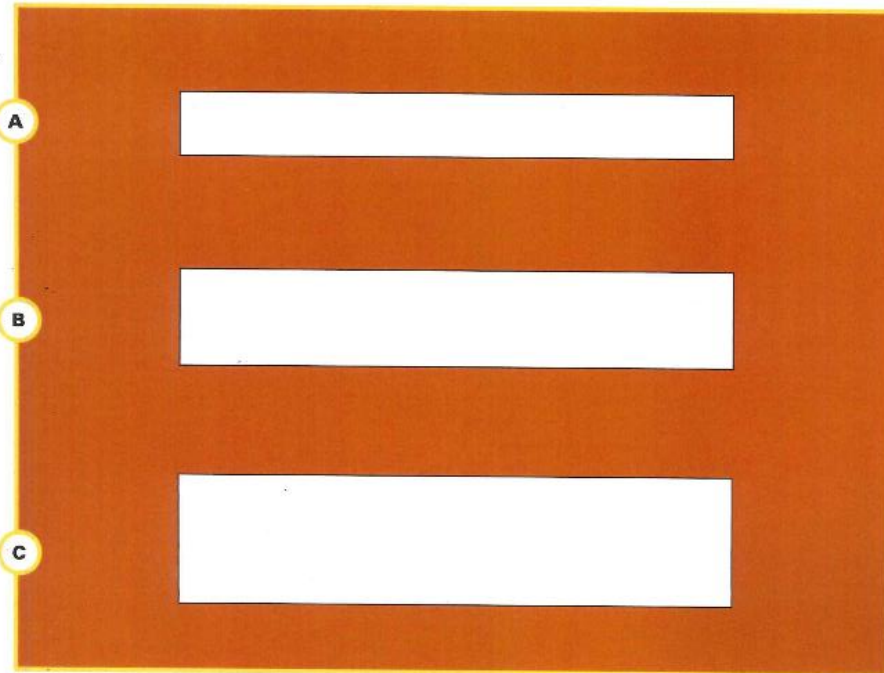
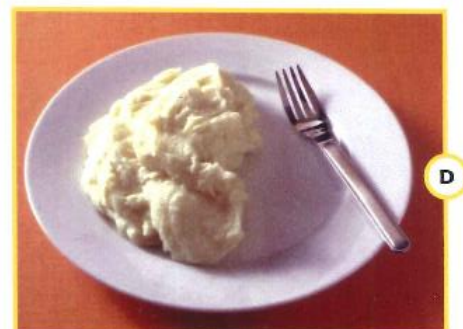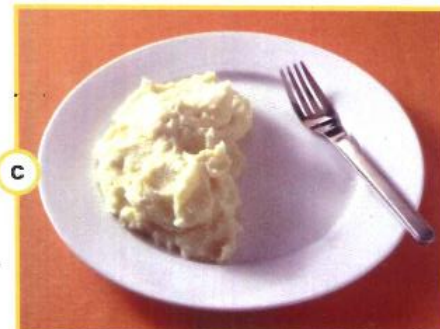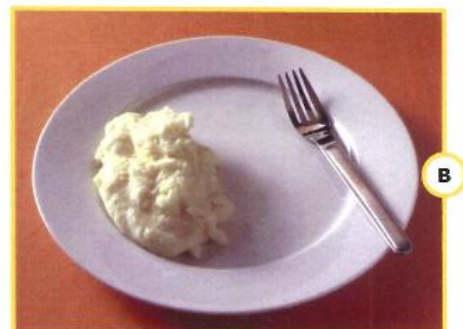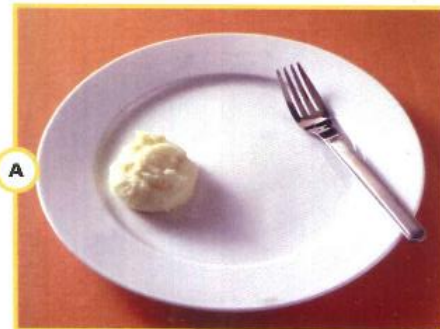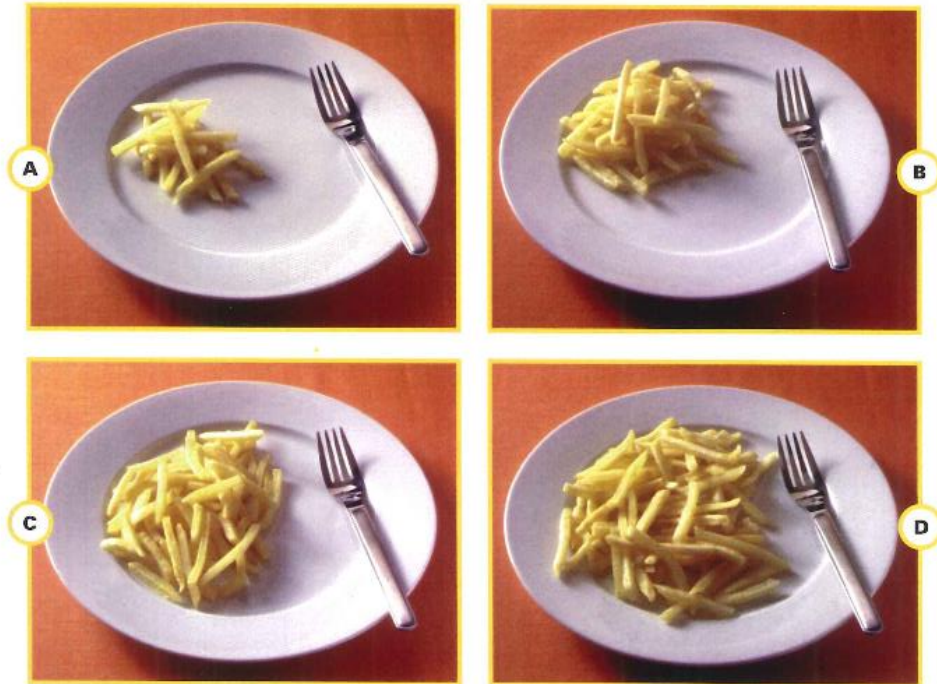## 3. SMØR/MARGARIN PÅ BRØD
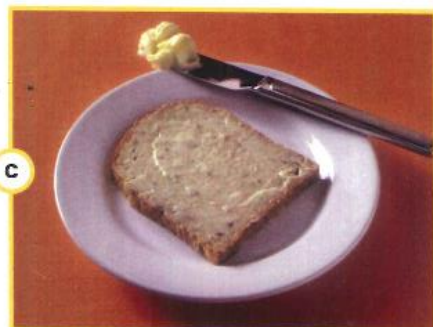
4. CORNFLAKES (FROKOSTBLANDING)
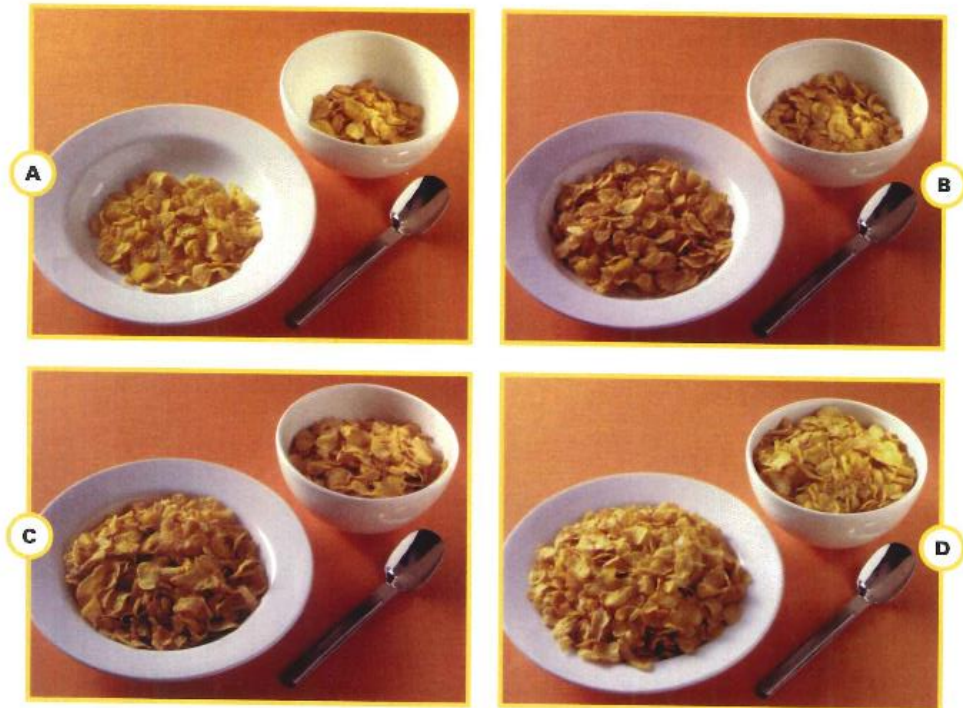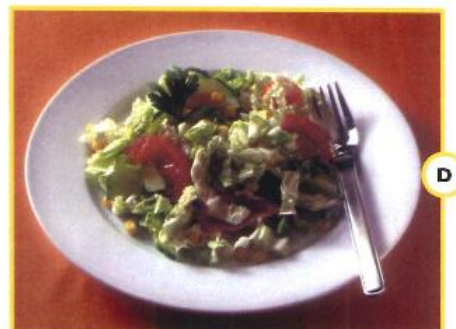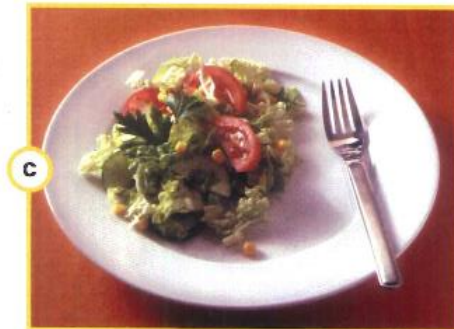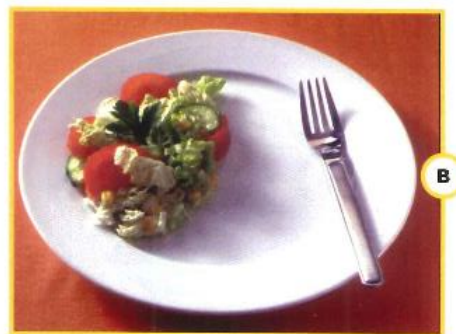

5. GRØT

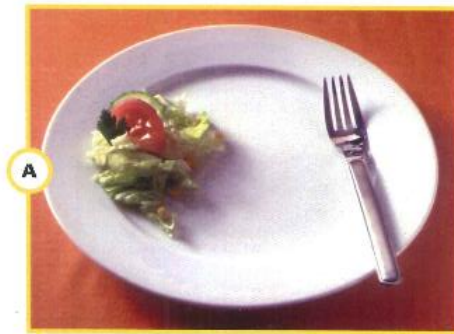## 6. SPAGHETTI / PASTA (RIS)
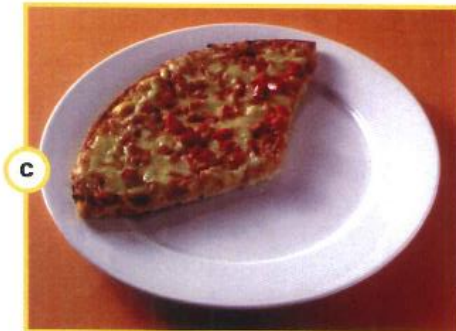

7. POTETMOS

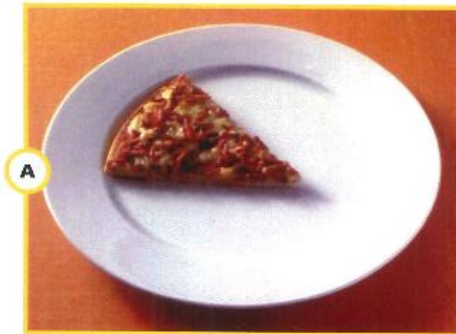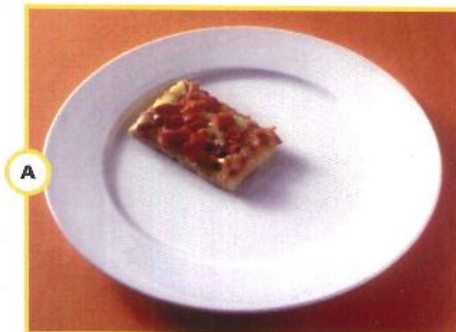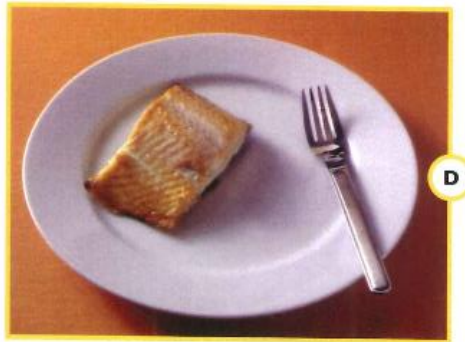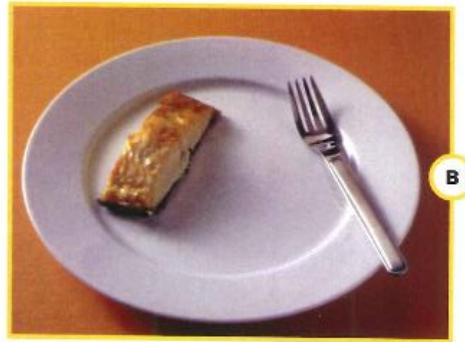## 8. POMMES FRITES

9. GRØNNSAKSBLANDING (RÅKOST)
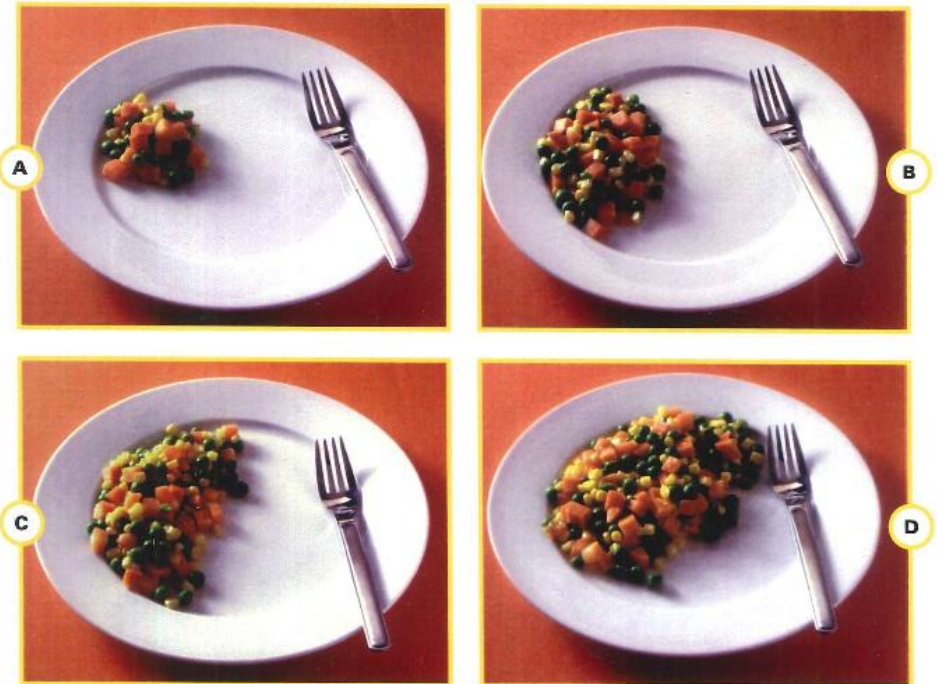
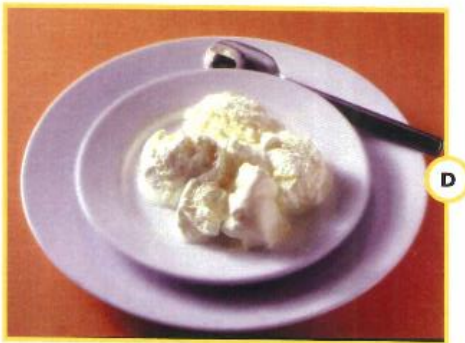## 10. SALAT

11. KJØTTSAUS (LAPSKAUS)
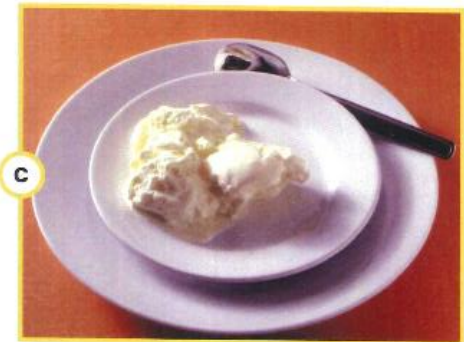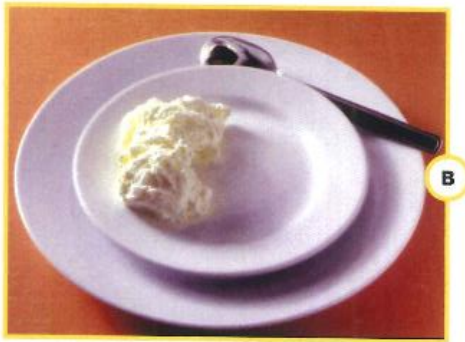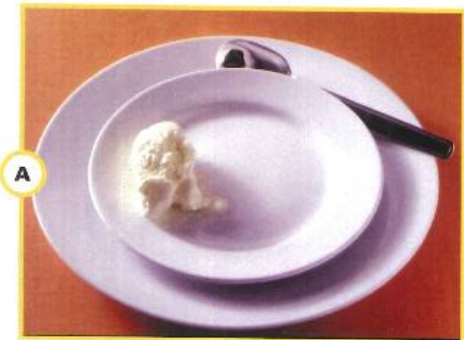
12. PIZZA, TREKANTSTYKKER

A

B

C

D

13. PIZZA, FIRKANTSTYKKER

A

B

C

D

14. FISK

15. IS (PUDDING)

Bildehefte med porsjonsstørrelser brukt i Ungkost 2000
Mengder per 25.04.2005

Bilde		A	B	C	D
1	Glass	150 g	230 g		
2	Brødtykkelse				
	Loff	21 g	35 g	50 g	
	Grovbrød	25 g	38 g	58 g	
3	Smør/margarin på brød	3 g	6 g	9 g	12 g
4	Cornflakes (frokostbland.)				
	Cornflakes	10 g	30 g	57 g	85 g
	Havregryn	22 g	65 g	124 g	189 g
	Søtet musli	23 g	69 g	131 g	199 g
	Usøtet musli, Firkorn	32 g	97 g	184 g	280 g
5	Grøt	50 g	200 g	350 g	500 g
6	Spaghetti / pasta (ris)				
	Spaghetti	34 g	68 g	160 g	250 g
	Ris	44 g	88 g	208 g	325 g
7	Potetmos	60 g	205 g	355 g	500 g
8	Pommes frites				
	Pommes frites	30 g	60 g	90 g	120 g
	Stekt potet	40 g	80 g	120 g	160 g
9	Grønnsakblanding (råkost)				
	Grønnsakblanding	40 g	80 g	120 g	160 g
	Råkost	28 g	56 g	84 g	112 g
10	Salat	33 g	52 g	100 g	175 g
11	Kjøttsaus (lapskaus)	50 g	200 g	350 g	500 g
12+13	Pizza				
	Trekantstykker	56 g	114 g	165 g	270 g
	Firkantstykker	52 g	112 g	165 g	270 g
14	Fisk				
	Rå filet	36 g	102 g	160 g	195 g
	Stekt filet	27 g	84 g	134 g	166 g
15	Is (pudding)				
	Iskrem	38 g	64 g	97 g	139 g
	Pudding	76 g	128 g	194 g	278 g

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK vest	Øyvind Straume	55978496	24.06.2015	2015/894/REK vest
			Deres dato:	Deres referanse:
			12.05.2015	

Vår referanse må oppgis ved alle henvendelser

Jone Trovik

2015/894 SUKK-M; SvangerskapsUtløst Kvalme Kvantifisering –Metodeutprøving

Forskningsansvarlig: Helse Bergen HF
Prosjektleder: Jone Trovik

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regionalkomité for medisinsk og helsefaglig forskningsetikk (REK vest) i møtet 04.06.2015.Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.)§ 10, jf. forskningsetikkloven § 4.

Prosjektomtale
Dette er en prospektiv kohortstudie for å kartlegge gravides kvalmegrad og ernæringsinntak og etablere et norsk normalmateriale for ernæringsmarkøren prealbumin i første tredjedel av svangerskap. 1% av gravide er så kvalme (hyperemesis) at de trenger sykehusbehandling. Prosjektgruppen vet at hyperemesis er assosiert med betydelig redusert næringsinntak. En måte å måle ernæringsstatus er blodprøven prealbumin. Det finnes ikke norske normalkurver for prealbumin hos gravide. Søker vil derfor registrere kvalmegrad (målt ved kvalmespørreskjemaet SUKK) og egenrapportert næringsinntak (registreringsskjema) samt prealbuminverdi hos en gruppe kvinner innlagt med hyperemesis og sammenlikne med en gruppe friske gravide fra gynekologisk poliklinikk.

Vurdering

Søknad/protokoll
Komiteen bemerker at protokollen er noe tynn, men finner den akseptabel. Komiteen vurderer prosjektet til å ha liten ulempe og anser det som forsvarlig å gjennomføre.

Informasjonsskrivet
Informasjonsskrivet må forbedres noe: Avsnittet «Hva innebærer deltagelse» må tydeliggjøres. Videre setter komiteen som vilkår at dere utarbeider et separat informasjonsskriv til kontrollgruppen.

Opprettelse av register?
Ved å signere samtykkeerklæringen aksepterer du at opplysninger kan benytt es til forskning innen svangerskapskvalme» Det virker som prosjektleder ser for seg et register om «svangerskapskvalme» som det samtykkes til her. Vi gjør oppmerksom på at et slikt register bør samtykkes til separat, og må ha konsesjon av Daratilsynet/Personvernombudet.

Prosjektslutt
Tillatelsen til å oppbevare og behandle data gjelder til prosjektslutt 01.09.2017.

Vilkår

- Revidert informasjonsskriv skal ettersendes REK vest.
- Eget informasjonsskriv for kontrollgruppen skal utarbeides og ettersendes REK vest.

Vedtak
REK vest godkjenner prosjektet på betingelse av at ovennevnte vilkår tas til følge.

Sluttmelding og søknad om prosjektendring
Prosjektleder skal sende sluttmelding til REK vest på eget skjema senest 01.03.2018, jf. hfl. § 12.Prosjektleder skal sende søknad om prosjektendring til REK vest dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. hfl. § 11.

Klageadgang
Du kan klage på komiteens vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes til REK vest. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK vest, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Med vennlig hilsen

Ansgar Berg
Prof. Dr.med
Komitéleder

Øyvind Straume
sekretariatsleder

Kopi til:postmottak@helse-bergen.no

HELSE BERGEN
Haukeland universitetssjukehus

Forespørsel om samtykke til deltagelse i et forskningsprosjekt om kvalme
SUKK-M; SvangerskapsUtløst Kvalme Kvantifisering –Metodeutprøving

Relasjon mellom kvalmeskår, egenrapportert næringsinntak og ernæringsparametre.

Bakgrunn og hensikt

Kvalme i svangerskapet er svært vanlig og som oftest forbigående 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. Det er utviklet et svangerskapsspesifikt kvalmespørreskjema (SUKK: Svangerskaps Utløst Kvalme Kvantifisering) som kan angi alvorlighetsgrad av hyperemesis. Det er vist at høy skår samsvarer med at kvinnen spiser lite. En blodprøve (Prealbumin) brukes ofte som mål på om næringsinntak har vært tilstrekkelig. Vi har imidlertid ikke gode referanseverdier for denne blodprøven hos gravide.

Vi vil derfor be deg om å delta i denne studien med å fylle ut SUKK-skjemaet og ernæringsskjemaet mhp hva du spiste og drakk siste døgn. Vi vil også ta en blodprøve for måling av Prealbumin.

Hva innebærer deltagelse i studien:
Du som får skjemaet på gynekologisk poliklinikk er utvalgt som antatt frisk gravid (kontrollguppe).
Du som får skjemaet på gynekologisk avdeling 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.

Samtykkets omfang og dine rettigheter

Ved å signere samtykkeerklæringen aksepterer du at opplysninger kan benyttes til forskning innen svangerskapskvalme. Vi registrer opplysninger anonymt, dvs uten persongjenkjennbare data. Det som registreres er din alder (år), høyde/vekt før svangerskap og på svartidspunkt og hvor lang varighet av graviditeten er.

Informasjonen som registreres om deg vil bli behandlet konfidensielt og kun bli brukt til forskning innen svangerskapskvalme. Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine

Besøksadresse: Haukeland universitetssjukehus, Jonas Liesvei 65, Postadresse: Helse Bergen HF, Postboks 1, 5021 Bergen
Telefon 05300 – Innvalg 74200   , E-post: postmottak@helse-bergen.no
Foretaksnr. NO 983974724 mva. Internett: www.helse-bergen.no

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opplysninger og prøver gjennom en navneliste. Det vil ikke være mulig å identifisere deg i forskningsresultatene når disse publiseres.

Du kan til enhver tid 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 tilbake samtykket, kan du kreve å få slettet innsamlede opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner.

Denne studien er godkjent gjennomført av REK (Regional Etisk Komite).
Vi gjør oppmerksom på at anonymiserte opplysninger kan utleveres til samarbeidende forskere ved foretakene i Helse Vest og Universitetet i Bergen. Enhver utlevering av opplysninger til samarbeidende forskere vil bli lagt frem for REK for godkjenning før dette gjøres.

Ytterligere informasjon
Når studien er avsluttet vil du kunne få tilsendt et resyme av resultatene hvis du ønsker.

Har du spørsmål tilknyttet forskningsvirksomheten, kontakt prosjektleder for SUKK: overlege, PhD Jone Trovik, Gynekologisk Avdeling, Kvinneklinikken 5021 Haukeland Universitetssjukehus Tlf 55974200 epost: jone.trovik@helse-bergen.no

Jone Trovik
Overlege, PhD
Prosjektleder

Ingrid Johanne Garnes
Klinikkleder
Kvinneklinikken

Ingeborg Bøe Engelsen
Seksjonsoverlege
Gynekologisk seksjon KK

Besøksadresse: Haukeland Universitetssykehus, Jonas Liesvei 65, Postadresse: Helse Bergen HF, Postboks 1, 5021 Bergen
Telefon 05300 – Innvalg 74200   – Telefaks   , E-post: postmottak@helse-bergen.no
Foretaksnr. NO 983974724 mva. Internett: www.helse-bergen.no

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Skjema for samtykke til forskning - Voksne over 16 år	
Forskningsområde SUKK-M; SvangerskapsUtløst Kvalme Kvantifisering –Metodeutprøving	**Prosjektnummer** <sett inn prosjektnummer>
Prosjektleders navn Jone Trovik	**Klinikk/avdeling** Kvinneklinikken/Gynekologisk avdeling

All forskningsdeltakelse er frivillig. Dersom du ønsker å delta, undertegner du denne samtykkeerklæringen. Om du nå sier ja til å delta, kan du senere når som helst og uten å oppgi noen grunn, trekke tilbake ditt samtykke uten at det påvirker din øvrige behandling. Dersom du senere ønsker å trekke deg eller har spørsmål om forskningen, kan du kontakte prosjektleder.

Jeg er villig til at prøver og opplysninger om meg brukes i forskning innen Svangerskapskvalme

Navn med blokkbokstaver	Fødselsnummer (11 siffer)

Dato	Underskrift

Dersom du ønsker tilsendt opplysninger om forskningsresultater vennligst angi adresse du vil vi skal sende dette til her:

Fylles ut av representant for forskningsområdet

Jeg bekrefter å ha gitt informasjon om forskningsområdet:

Dato	Underskrift	Brukerkode (4-tegnskode)

Eventuelle kommentarer: