NUTRITION INTERVENTIONS FOR HYPEREMESIS GRAVIDARUM

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ABSTRACT OF THESIS

OBJECTIVE: To determine whether enteral and parenteral nutrition support are safe and effective ways to provide nutrition to women with hyperemesis gravidarum and whether enteral and parenteral nutrition support improve maternal and fetal health outcomes during hyperemesis gravidarum.

DESIGN: Academy of Nutrition and Dietetics Evidence Analysis Project

METHODS: The Academy of Nutrition and Dietetics Evidence Analysis process was used to critically analyze current research on hyperemesis gravidarum. This process uses an objective and transparent methodology to assess food and nutrition-related science. It incorporates five steps: 1) Formulate evidence analysis question, 2) Gather and classify evidence, 3) Critically appraise each article, 4) Summarize the evidence, and 5) Write and grade the conclusion statement.

RESULTS: Eight studies evaluating the use of nutrition support in women with hyperemesis gravidarum between the years 2001 and 2015 were analyzed. Four studies focused on enteral nutrition and four focused on parenteral nutrition. The four studies evaluating enteral nutrition demonstrated that enteral nutrition is well tolerated, safe, and associated with positive pregnancy outcomes, including weight gain and delivery of healthy, term infants. Three of the studies evaluating parenteral nutrition showed that use of parenteral nutrition can be safe and effective in women with hyperemesis gravidarum. One of these studies associated parenteral nutrition with a lower rate of adverse pregnancy outcomes. One study, however, showed a significant increase in serious complications directly related to parenteral nutrition use in women with hyperemesis gravidarum.

CONCLUSION: Enteral and parenteral nutrition are both shown to be successful ways to provide nutrition to women suffering from hyperemesis gravidarum, leading to favorable pregnancy outcomes. Enteral nutrition is a safe, effective, and well-tolerated form of nutrition support in women with hyperemesis gravidarum. Parenteral nutrition treatment for women with hyperemesis gravidarum was associated with a lower rate of adverse pregnancy outcomes. Complications have been experienced with the use of parenteral nutrition in these patients. This research was given a limited/weak grade due to the weak study designs.

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CHAPTER 1: INTRODUCTION

Nutrition during pregnancy significantly impacts a child and mother's health. The likelihood of having a healthy baby improves when a woman implements healthy behaviors before and during pregnancy, including good nutrition. Poor nutritional status can lead to poor fetal development, birth defects, and chronic health problems in both the child and mother. [1]

Health and nutrition status can be affected by different conditions, such as nausea and vomiting. Nausea and vomiting is common during pregnancy and affects up to 70-85% of pregnant women. Hyperemesis gravidarum, which is described as uncontrolled vomiting requiring hospitalization, severe dehydration, muscle wasting, electrolyte imbalance, ketonuria, and weight loss of more than 5% of body weight, affects 0.3 to 2.3% of all pregnancies.[2]

Dietary intake of specific nutrients has been shown to be altered in pregnant women with nausea and vomiting, specifically decreases in protein, vitamin B12, magnesium, and zinc, as well as increases in proportion of carbohydrates as a percentage of total energy intake.[3] Weight loss of greater than 15% of pre-pregnancy weight has been shown in women with hyperemesis, indicating it is a form of prolonged starvation in pregnancy.[4] Nausea and vomiting can lead to Mallory-Weiss tears (tear of the lower part of the esophagus or upper part of the stomach) and esophageal rupture, as well as neurological disturbances and even maternal death, if not treated. About 1-5% of women with hyperemesis need to be hospitalized. In addition, this can lead to adverse fetal outcomes, including babies who are small for gestational age (SGA) and premature.[2,3,4,5] It is thought that the

adverse outcomes are an effect of low weight gain occurring with nausea and vomiting rather than hyperemesis itself.[2]

Women with hyperemesis gravidarum can also experience other sources of distress because of severe nausea and vomiting, including time lost from work, psychological distress, marital problems, financial hardship, inability of self care, and overall decreased quality of life.[2,6] Because of the detrimental effects nausea and vomiting during pregnancy can have upon a woman and baby, effective treatments are critical.

Rationale

The purpose of this research was to critically analyze the evidence on effective nutrition treatments for severe nausea and vomiting during pregnancy, specifically hyperemesis gravidarum. The objectives were to determine the quality and strength of evidence that exists for nutrition interventions for severe nausea and vomiting during pregnancy using the Academy of Nutrition and Dietetic's (AND) Evidence Analysis (EA) process, identify gaps and needs for future research, and to summarize the evidence to be translated for the dietetic professional.

Potential Significance

This research has the potential to significantly improve the nutrition status of women with the most severe form of nausea and vomiting during pregnancy. Many women and infants are in need of treatment, as 70 to 85% of pregnancies are affected by nausea and vomiting and up to 2.3% of pregnancies are affected by hyperemesis gravidarum.

Research Questions

The research questions used to conduct this EA project were as follows: "Are enteral and parenteral nutrition support safe and effective ways to provide nutrition to women with hyperemesis gravidarum? Do enteral and parenteral nutrition support improve maternal and fetal health outcomes during hyperemesis gravidarum?"

Sub-Problems

The objectives of this research were: 1. Determine the level of evidence that exists for nutrition interventions for hyperemesis gravidarum using the AND's EA process, 2. Identify gaps of knowledge and needs for future research, and 3. Summarize evidence to be translated for the dietetic professional. This research involved assessing enteral and parenteral nutrition and each of their effectiveness separately for treating hyperemesis gravidarum. How do they compare to each other in treating hyperemesis gravidarum?

Limitations, Delimitations, and Assumptions

Limitations

Completing studies on pregnant women has many limitations. For example, there are ethical limitations in conducting studies on this population. In addition, there are a limited number of pregnant women at specific medical sites with nausea and vomiting, so sample sizes may be small. The women who do have nausea and vomiting may not give consent to be part of a study. Because of these reasons, there are a limited number of studies available to review. In addition, some women's nausea and vomiting may resolve on its own, which makes it challenging to determine the etiology of hyperemesis. If a study is done using nutrition

interventions, it may be unknown whether the intervention treatment was effective, or whether the nausea and vomiting resolved on its own. Honesty of the subjects following specific nutrition restrictions may also be a limitation.

Delimitations

This research was limited to studies among women with severe nausea and vomiting during pregnancy (hyperemesis gravidarum.) It only looked at studies analyzing nutrition interventions (not drug or herb treatments.) In addition, this research only looked at articles completed after the year 2000 and written in English.

Assumptions

This research assumed that women followed treatments and diets prescribed to them. It also assumed that the women are not also following other treatments or diets not prescribed to them by the researchers.

Definitions:

Apgar Score: Evaluation of a newborn infant's physical status by assigning numeric values (0-2) to each of 5 criteria: 1) heart rate, 2) respiratory effort, 3) muscle tone, 4) response to stimulation, and 5) skin color; a score of 8-10 indicates the best possible condition.[7]

Central Venous Catheter (CVC): Tube surgically inserted into a vein in the central circulation (usually the superior vena cava). Commonly used for long-term IV therapy, nutritional support, or chemotherapy.[7]

Electrolyte: Any compound that, in solution, conducts electricity and is decomposed (electrolyzed) by it; an ionizable substance in solution.[7]

Electrolyte imbalance: Physiologic disorder in which there are fewer or more than normal levels of serum electrolytes.[7]

Enteral nutrition*:* Provision of nourishment by means of a tube into the stomach or intestine.[7]

Fetus: The product of conception from the end of the eighth week to the moment of birth.[7]

Gastroenterology: The medical specialty concerned with the function and disorders of the gastrointestinal tract, including stomach, intestines, and associated organs.[7]

Gastroscopy: Inspection of the inner surface of the stomach through an endoscope.[7]

Gestational age: The age of a fetus expressed in elapsed time since the first day of the last normal menstrual period.[7]

Hyperemesis gravidarum: Nausea and vomiting during pregnancy severe enough to result in dehydration, acidosis, and weight loss. May require hospitalization; if untreated, can be fatal.[7]

Ileus: Mechanical, dynamic, or adynamic obstruction of the intestines; may be accompanied by severe pain, abdominal distention, vomiting, absence of passage of stool, and often fever and dehydration.[7]

Intravenous (IV): through the veins.[7]

Jejunostomy: Operative establishment of an opening from the abdominal all into the jejunum, usually with creation of a stoma on the abdominal wall.[7]

Ketonuria: Enhanced urinary excretion of ketone bodies.[7]

Mallory-Weiss Tear: Laceration of the lower end of the esophagus associated with bleeding or penetration into the mediastinum; usually caused by severe retching and vomiting.[7]

Nasogastric: Pertaining to or involving the nasal passages and the stomach.[7]

Nasogastric tube: A tube used for feeding or suctioning stomach contents; inserted through the nose and down the esophagus into the stomach.[7]

Nasojejunal: Pertaining to or involving the nasal passages and the jejunum.[7]

Nasojejunal tube: A tube used for feeding; inserted through the nose and into the jejunum.[7]

Peripherally inserted central catheter (PICC): Tube inserted into the superior vena cava through a peripheral vein.[7]

Pneumothorax: The presence of air or gas in the pleural cavity.[7]

Preterm Infant: An infant with gestational age of fewer than 37 completed weeks.[7]

Short Bowel Syndrome: Complex of symptoms that can result whenever the absorptive surface of the small bowel is reduced, as in massive or multiple small bowel resections. Symptoms include diarrhea, weight loss, malabsorption, anemia, and vitamin, mineral, and electrolyte abnormalities.[7]

Small for Gestational Age (SGA): Infant whose birth weight is below the tenth percentile for gestational age.[7]

Refeeding Syndrome: A metabolic complication that occurs when nutritional support is given to a severely malnourished patient. Metabolism changes from a catabolic to anabolic state. Insulin is released on carbohydrate intake, causing a cellular uptake of potassium, phosphate, and magnesium. When the serum

concentrations of these electrolytes are reduced, serious complications can occur, such as arrhythmias.[8]

Total parenteral nutrition (TPN): Providing the body with nutrition intravenously.[7]

Chapter 2: Literature Review

Introduction

Nutrition during pregnancy significantly impacts a child and mother's health. The likelihood of having a healthy baby improves when a woman implements healthy behaviors before and during pregnancy, including good nutrition. Healthy pre-pregnancy weight, appropriate weight gain during pregnancy, intake of a variety of foods, appropriate vitamin and mineral supplementation, avoidance of alcohol and other harmful substances, and safe food handling are all important factors leading to a healthy pregnancy outcome. Poor nutrition status can lead to poor fetal development, birth defects, and chronic health problems in both the child and mother. [1]

Nausea and vomiting during pregnancy

Nausea and vomiting during pregnancy can affect the health and nutrition status of both the mother and the baby. Nausea and vomiting is common during pregnancy and affects up to 70-85% of pregnant women. Hyperemesis gravidarum, which is described as uncontrolled vomiting requiring hospitalization, severe dehydration, muscle wasting, electrolyte imbalance, ketonuria, and weight loss of more than 5% of body weight, affects 0.3 to 2.3% of all pregnancies.[2]

Altered dietary intake of specific nutrients has been shown among pregnant women with nausea and vomiting. Specifically, changes in diet have included decreases in protein, vitamin B12, magnesium, and zinc, as well as increases in proportion of carbohydrates as a percentage of total energy intake.[3] Weight loss of greater than 15% of pre-pregnancy weight has been shown in women with

hyperemesis, indicating it is a form of prolonged starvation in pregnancy.[4] Nausea and vomiting can lead to Mallory-Weiss tears (tear of the lower part of the esophagus or upper part of the stomach) and esophageal rupture, as well as neurological disturbances and even maternal death if not treated. About 1% to 5% of women with hyperemesis need to be hospitalized.[2] In addition, this can lead to adverse fetal outcomes, including babies who are small for gestational age and premature.[2,3,4,5] It is thought that the adverse outcomes are an effect of low weight gain occurring with nausea and vomiting rather than hyperemesis itself.[2]

Women can also experience other sources of distress associated with hyperemesis gravidarum, including time lost from work, psychological distress, marital problems, financial hardship, inability of self care, and overall decreased quality of life.[2,6]

Effective treatments are critical for hyperemesis gravidarum because of the detrimental effects it has on woman and baby. The purpose of this literature review is to critically analyze the evidence on effective nutrition interventions for hyperemesis gravidarum.

Background

The cause of hyperemesis gravidarum is not evident, as the pathogenesis is not completely understood. Some factors that may lead to nausea and vomiting include hormonal changes, gastrointestinal (GI) dysfunction, thyrotoxicosis, serotonin, hepatic abnormalities, autonomic nervous dysfunction, nutritional deficiencies, asthma, allergies, Helicobacter pylori infection, and psychosomatic causes.[2] One study suggested that a moderate intake of water and consumption of a

healthy diet including vegetables and fish is associated with a lower risk of developing hyperemesis. In this study patients without hyperemesis consumed 20% higher allium vegetables, 16% higher fish and seafood, and 9% higher drinking water than patients with hyperemesis.[9] Another study found that the most significant condition prior to pregnancy in women with prolonged hyperemesis gravidarum was allergies, indicating that there may be an autoimmune component affecting hyperemesis.[10] This same study also found that the most significant lifestyle choice linked to prolonged hyperemesis was a restrictive diet, such as a lactose-free diet or a vegetarian diet.[10]

Current treatment and practice

Various treatments have been used to relieve pregnant women of nausea and vomiting during pregnancy depending on the severity of the symptoms. Some of these treatments include: diet, lifestyle, intravaneous fluids, medications, supplementing with thiamine and ginger, nasogastric enteral feeding, total parenteral nutrition, hypnosis, and acupuncture.[2,9]

For mild to moderate nausea and vomiting, modified diet and lifestyle, supplemental ginger and thiamine, and antiemetics, and steroids are often used. Diet treatments involve altering the size and number of meals consumed throughout the day. This includes consuming smaller amounts of food and fluid more often to prevent mild nausea and vomiting from getting worse. Patients are also advised to limit fat intake and consume solid carbohydrate meals, such as soda crackers since fat is relatively difficult to digest and may aggravate upset stomachs. Women are encouraged to avoid foods and types of food preparation that trigger nausea.[2]

For women with severe nausea and vomiting, or hyperemesis, medications, including antiemetics and steroids, may be used.[2, 11] In addition, intravaneous (IV) fluids are used for rehydration. This includes replacing electrolytes, such as potassium that may be lost due to vomiting and poor intake.[2] Enteral or parenteral nutrition is also needed in severe cases.[2,11]

Enteral and parenteral nutrition

For patients who are unable to sustain their nutritional status with an oral diet, the alternative is nutrition support through enteral or parenteral nutrition. Enteral nutrition refers to feeding through the gastrointestinal tract via a tube, catheter, or stoma that delivers nutrients beyond the oral cavity. Enteral nutrition is recommended for patients who cannot feed themselves adequately yet have a functioning gastrointestinal tract. Enteral feeding is contraindicated if patients have medical conditions that affect the gastrointestinal tract, such as diffuse peritonitis, gastrointestinal feeding, and obstruction or ileus that prevents contents from passing through the intestine.[12,13]

Research has demonstrated many advantages of enteral nutrition, including cost effectiveness, reduced hospital length of stay, reduced surgical interventions, reduced rate of infectious complications in critically ill patients, improved wound healing, and maintenance of gastrointestinal function. Disadvantages include the potential difficulty of administration and poor tolerance. Complications can include underfeeding or overfeeding, electrolyte imbalance, hyperglycemia, and refeeding syndrome. [13]

Parenteral nutrition (PN), also called total parenteral nutrition (TPN), is the administration of nutrients directly into circulation, bypassing the digestive tract. Parenteral nutrition is recommended when a patient is not able to meet nutritional needs either by an oral diet or with enteral nutrition. Clinical conditions that might require parenteral nutrition include the inability to digest and absorb nutrients, such as with bowel resection or short bowel syndrome, intractable vomiting, as in hyperemesis gravidarum, GI tract obstruction, impaired GI motility, and abdominal trauma or injury.[13]

Parenteral nutrition complications can be severe, but can be prevented through patient monitoring. Many of the complications associated with enteral nutrition can also occur with parenteral nutrition. Patients on parenteral nutrition can also experience gastrointestinal symptoms such as cholestasis, in which bile accumulates in the gallbladder. Lack of enteral stimulation can also cause atrophy of intestinal cells, leading to increased permeability to bacteria and increased risk of infection.[13] In addition, brief elevations in liver enzymes can occur if PN is administered for several weeks. Patients receiving PN can also develop serious infections and have a higher risk of infection compared to patients receiving oral or enteral nutrition.[13]

Research is important to determine the best way to treat hyperemesis gravidarum. This literature review focuses on nutrition interventions for this condition. The following research articles examine the effectiveness of enteral and parenteral nutrition for treatment of nausea and vomiting during pregnancy.

Nutrition interventions

Enteral feeding

Enteral nutrition is one method to provide nutrition. Four articles evaluated the use of enteral nutrition in the treatment of hyperemesis gravidarum. The first article, by Stokke et al, is a retrospective cohort study, which compared maternal outcomes (weight gain during hospitalization and pregnancy) in a cohort of tube fed women with hyperemesis gravidarum and in women receiving different fluid and nutritional therapies for hyperemesis. It also compared fetal outcomes (birthweight and gestational age at delivery) between the different nutrition interventions.[14]

All patients with the diagnosis nausea and vomiting during pregnancy who were discharged from the Department of Gynecology at Haukeland University Hospital in Bergen, Norway, from 2001 to 2011 were assessed retrospectively. Women with the diagnosis hyperemesis gravidarum, admitted at <20 weeks gestation, and had two of three criteria: dehydration, weight loss, and ketonuria/electrolyte disturbances, were included in this cohort study.[14]

According to treatment guidelines, antiemetic drugs were started on admission. All women received initial intravenous rehydration with saline or five percent glucose with electrolyte supplementation. If women could not restart food intake within two to three days after rehydration, peripheral parenteral nutrition began with 1-1.5 liters of protein/fat/glucose solutions with about 1000 calories or half of the estimated total energy needs. Nutritional status was monitored with daily food charts, weight measurements, and assessment of vomiting.[14]

If the patient's condition did not improve, her oral intake remained at none or very low levels, or her weight continued to decrease after two to three days of parenteral supplementation, an enteral feeding tube was recommended. The tube was placed through the nose and advanced to the jejunum by gastroscopy. A commercial enteral nutrition was started at 20 mL per hour and advanced by 20 mL every 8 hours up to 80 mL per hour, which provided 2000 mL per 24 hours and 2000 calories. Peripheral parenteral nutrition continued until the tube feeding reached the goal. Patients were encouraged to eat and drink while receiving tube feeding.[14]

Patient characteristics, including age, parity, ethnicity, earlier hyperemesis pregnancies, weight and height, and type and duration of fluid and nutritional regimens were pulled from hospital records. Details regarding the pregnancy after discharge (continuation of nutritional therapy, pregnancy outcome, and maternal weight gain), along with fetal outcomes and placental weight were collected from maternal records and delivery charts.[14]

Weight before pregnancy was self-reported and cross-checked with the maternity record. Women were weighed on each hospital admission and discharge. Birthweight was evaluated by Norwegian sex-specific smoothed centile charts for singletons and SGA was defined as <10th percentile.[14]

Five hundred fifty-seven women met the inclusion criteria. The women were divided into three groups based on the main type of fluid/nutrition treatment provided: 273 (49%) received fluids, 177 (32%) received nutritional solution by

peripheral catheter, and 107 (19%) received enteral nutrition by jejunal tube (nine of these women also received TPN.) [14]

Women receiving enteral nutrition compared to those given only intravenous supplementation lost significantly more weight at the time of admission (5.0 kg, 95% CI 4.0-5.0 compared with 4.0 kg, 95% CI 4.0-4.0, p <0.001) and had a shorter length of gestation at the time of admission of 8.0 weeks (95% CI 7.7-8.6), compared with 9.0 weeks (95% CI 8.7-9.3, p < 0.001, Mann-Whitney *U*-tests). Four hundred fifty-five (87%) of the women were admitted during their first trimester.[14]

The median length of hospitalization was two days in the fluid group, four days in the peripheral nutrition group, and 13 days for the enteral nutrition group (p < 0.0001, Kruskal-Wallis test). Nutrition therapy was provided for a median of two days (95% CI 2-2, range 1-37 days) for the peripheral nutrition group, while the enteral nutrition group received tube feeding for a median of five days (95% CI 4-6 days, range 0-41 days) in addition to peripheral nutrition for a median of four days (95% CI 3-5 days, range 1-31 days). Forty-six women (43%) had a tube replacement.[14]

Tube-fed women's weight loss increased to a median of 5.5 kg (95% CI 0.5-6.0) from admission to start of nutrition. Eighty-four percent of these women lost > 5% of their pre-pregnancy weight, but gained a median of 0.8 kg (95% CI 0.5-1.0) compared with no weight changes in the other two treatment groups (p = 0.005, Kruskal-Wallis test). The tube-fed group had significantly greater weight loss before treatment and significantly greater weight gain during hospitalization compared to

the two other groups. Even though the women in the tube-fed group had greater initial weight loss, they had a similar total weight gain as the other groups.[14]

The enteral tubes were mostly well tolerated by the women. Eight women (7%) asked to remove the tube due to discomfort. Fifty-eight women's (54%) tubes inadvertently came out due to clogging (n=4) and forceful vomiting (n=46). One of the nine women on TPN developed a pneumothorax, two had their CVC removed due to infection, and one women had to have her catheter removed because of obstruction (n=4, 44% with catheter removal). [14]

Pregnancy outcomes were similar across groups in terms of abortion rates, twin rates, gestational age, birthweight, preterm birth, low birthweight, or SGA infants (all $p > 0.05$, Kruskal-Wallis or chi-squared tests.) The women with >5% weight loss before treatment had no increased risk of preterm birth, SGA, or abnormal placenta/birthweight ration (all $p \geq 0.05$, chi-squared test), but women who gained < 7kg during their pregnancy had significantly more SGA babies (20% vs 7%) ($p < 0.001$, chi-squared test), in addition to having significantly smaller placentas and larger placenta/birthweight ratios.[14]

The nutritional regimen had no significant impact as a risk factor for fetal growth restriction when adjusting for parity, ethnicity, and weight gain during pregnancy. Weight gain <7 kg was the strongest risk factor or SGA (odds ratio 3.68; 95% CI 1.89-7.18, $p < 0.001$). [14]

The authors concluded that women hospitalized for hyperemesis gravidarum who were treated with enteral nutrition had reversal of weight loss and attained

weight gain during the remainder of the pregnancy in a comparable way to women receiving either only intravenous fluid or peripheral parenteral nutrition.[14]

This has been the largest study showing results of enteral feeding for nutrition management of severe hyperemesis gravidarum, showing that it is a feasible and beneficial way of providing nutrition. The study used cases of hyperemesis over a 10 year period and had a large sample of women to assess.[14]

The study does have some limitations. Because it is a retrospective cohort study, different aspects of the treatment cannot be assessed, such as patient acceptability of different nutritional methods. This study is representative of a Norwegian population, so may not be representative of different ethnicities, as only 25% of the patients are of non-Caucasian ethnicity. In addition, this study did not assess smoking habits. Previous studies have shown that women with hyperemesis have a lower prevalence of smoking than those without emesis, so this could have an impact on the results.[14]

Even with the study's limitations, it still offers promising evidence for the use of tube feeding to provide nutrition for patients with hyperemesis gravidarum.[14]

Another study that focused on enteral nutrition, by Sumona et al, is a case series, assessing the feasibility and efficacy of surgically placed feeding jejunostomy in women with hyperemesis gravidarum who failed standard therapy. Patients in this study were referred for gastroenterology consultation for hyperemesis gravidarum, either as an inpatient or outpatient at Women & Infants Hospital, which has one of the largest cohorts of pregnant patients in the United States. From 1998 to 2005, 1,323 patients were treated at this hospital for hyperemesis gravidarum.

Hyperemesis gravidarum was diagnosed if a woman had persistent nausea and vomiting that could not be explained by other conditions, as well as one or more of the following: weight loss of >5% of prepregnancy body weight, ketonuria, multiple emergency room visits for dehydration, and/or inability to tolerate oral intake.[15]

Patients were treated with the center's treatment algorithm for hyperemesis gravidarum. If the women had persistent weight loss despite intravenous (IV) hydration, IV ondansetron, IV ranitidine or pantoprazole, and IV metoclopramide, they were offered jejunostomy placement. Patients were excluded if they were in the third trimester of pregnancy or if they had contraindications to surgery.[15]

A feeding jejunostomy was placed in the second trimester of pregnancy after informed consent was granted. Enteral feedings started within 24 hours of tube placement. A registered dietitian calculated calorie needs using the Harris-Benedict equation plus 300 calories for pregnancy. They used an isotonic, high-protein formula for all patients. Feeding rates and times were adjusted based on patient tolerance and preference. Feeding times varied from 12 to 24 hours. After tube feeding was initiated, nutrition counseling continued. Women were encouraged to eat and drink as tolerated along with tube feedings. In addition, patients were offered psychological support to help cope with this condition. Once patients could tolerate feedings at goal rate, they were discharged from the hospital with the jejunostomy in place.[15]

Between 1998 and 2005, five patients accepted jejunostomy placement. One patient had jejunostomy placement twice for consecutive pregnancies. All the women had singleton pregnancies. Three patients had hyperemesis gravidarum in

previous pregnancies and three had a history of fetal losses due to hyperemesis gravidarum. The mean body weight loss from prepregnancy weight was 7.9% (range, 4.0% to 15.9%). [15]

The jejunostomy tubes were placed between 12 and 26 weeks gestation (median 14 weeks). The tubes were in place for a mean duration of 19 weeks (range, 8 to 28 weeks). Four jejunostomy tubes stayed in place until delivery. One tube fell out at 30 weeks and was not replaced, and one tube was removed at 34 weeks due to a patient's wish because of emotional distress. For the tube that fell out, however, it was suspected that it might have been due to tampering to restrict weight gain, as the patient was known to have anorexia nervosa. Maternal weight gain was attained in five of six pregnancies. All pregnancies resulted in term deliveries (range, 36 to 40 weeks gestation) of healthy infants. The mean infant birth weight was 2.99 kg (range, 2.27 to 4.00 kg). [15]

Jejunostomy related complications included late tube dislodgement involving simple replacement. There were no intra-operative or immediate postoperative complications, as well as no cases of delayed infection, bleeding, preterm labor, or congenital abnormalities. All patients experienced continued nausea and vomiting, needing continued standard therapy in addition to tube feeding. In five of six pregnancies, patients could be sustained on oral anti-emetics. One patient required IV hydration and IV medications.[15]

The authors concluded that providing nutrition via jejunostomy is a potentially safe, effective, and well-tolerated form of nutrition support intervention for women with hyperemesis gravidarum.[15]

This study, which is one of a few assessing nutrition support during pregnancy, is able to show relative safety and effectiveness of enteral feeding via jejunostomy for patients with hyperemesis gravidarum. It was completed at a unique center, which is a high-volume obstetric hospital with a gastroenterology division that focuses on gastrointestinal disorders during pregnancy. This study is limited due to the small number of cases as well as its retrospective design. In addition, it only assessed patients at one center, so it may not be generalized to all patients with hyperemesis gravidarum. Overall, this study provides promising evidence that enteral nutrition can safely provide nutrition for patients with hyperemesis gravidarum, avoiding complications associated with parenteral nutrition.[15]

In a preliminary study by Vaisman et al, researchers examined the feasibility and the preferability of feeding patients with hyperemesis gravidarum via an intrajejunal route to overcome vomiting, weight loss, and relative malnutrition.[16]

Fifty-two women were hospitalized with hyperemesis gravidarum in Tel-Aviv Sourasky Medical Center in Tel-Aviv, Israel from January 2000 to May 2002. They all suffered from severe vomiting (> 5 times per day), electrolyte abnormalities, persistent ketonuria, and weight loss. The women did not to respond to outpatient dietary changes and antiemetic medications.[16]

On admission, all patients were treated with IV fluids, electrolyte imbalances were treated, and metoclopramide or promethazine was given through an IV for nausea. Eleven of these patients continued to vomit, lose weight, and were still unable to eat or drink. All of these patients agreed to receive nasojejunal (NJ)

feeding. Osmolite solution (1 kcal/mL) was given by continuous infusion for 24 hours, starting at 40 mL per hour and increased as tolerated by 20 mL per hour per day, until a maximum rate of 100 mL per hour was reached for a total of 2400 mL per day for all patients. Two patients developed diarrhea and were switched to a semi-elemental formula (Progestamil). From day three and on, patients were encouraged to drink and eat along with tube feeding. The main goal was termination of vomiting and tolerable oral intake of 1000 calories per day. When vomiting stopped and caloric intake surpassed 1000 kilocalories per day, tube feeding was discontinued.[16]

Mean weight loss in the hospital was 2.2 kg (+/- SD 1.1 kg). None of the patients had evidence of esophagitis, gastritis, or ulceration. Symptoms of nausea and vomiting ceased as early as 48 hours after insertion of the tube, but vomiting and retching stopped completely after 1-13 days (mean $\pm$SD, 5$\pm$4 days). The length of the NJ tube feeding for all 11 women ranged from one to 21 days. Six patients started tolerating oral intake after three to four days and the rest started later, mostly due to fear of recurring vomiting. Weight loss stopped in all patients on tube feeding.[14] The authors concluded that NJ enteral feeding is an effective option in women with hyperemesis gravidarum.[16]

This study is one of few studies assessing enteral feeding on patients with hyperemesis. However, this was a preliminary study with the objective of testing the feasibility of this treatment. All patients received the same treatment, so there was no control group and the sample size was small. Larger studies will need to be conducted to test the effectiveness of this treatment. However, this study provides

promising results for a successful treatment in pregnant women with severe nausea and vomiting.[16]

The last article assessing enteral nutrition for patients with hyperemesis gravidarum describes two cases in which nasojejunal tubes were placed in patients with severe hyperemesis gravidarum.[15] In the first case study, a 31-year-old-patient with her first pregnancy was admitted at 25 weeks gestation with persistent vomiting and epigastric pain thought to be due to reflux esophagitis and had been unable to eat or drink for several days. She was started on H2 antagonists, intravenous fluids, and antiemetics. She was then referred to the nutrition team and TPN was recommended, while preparations for enteral feeding access were made. Parenteral feeds were started after a peripherally inserted central catheter (PICC) was inserted. Then, a nasojejunal tube was inserted and it was discovered that the esophagus, stomach, and duodenum were normal.[17]

The patient was still unable to eat at one week after admission and had not eaten for several days. At this point, the original nasojejunal tube had become dislodged and had been removed. In addition, the PICC line was looking infected and also had to be removed. She was still not tolerating oral food two weeks after admission and was dehydrated and nauseated with ketonuria. In addition, her weight decreased by 3.7 kg.[17]

Another nasojejunal tube was inserted and enteral feeding was initiated and tolerated well. The patient reached the goal feeding rate within four days. Around 10 days post-insertion, the first tube became blocked and was replaced. The patient was discharged around three weeks after admission, after she was trained in the use

of the tubes. About one week after discharge, the second tube became blocked and was replaced after being in place for 17 days. The third tube was replaced after about 20 days.[17]

The last tube remained in place until labor at 36 weeks gestation when a normal three-kilogram baby boy was delivered. She tolerated the enteral feeds well and feeding goals were met, despite continued nausea and inability to tolerate oral feeds.[17]

The second case study involved a 34-year-old-patient that was admitted to the hospital at eight weeks gestation during her second pregnancy. She had been vomiting for 17 days and was not able to eat or drink. Oral metoclopramide and cyclizine did not relieve her symptoms. She was dehydrated, positive for urinary ketones, and had lost 10 kilograms in weight. The ultrasound showed a normal size fetus. Blood tests were normal, except for mildly elevated liver function tests.[17]

The patient improved clinically and biochemically after receiving intravenous fluids and cyclizine, but was still unable to eat or drink and her weight continued to drop another 0.6 kilograms five days after admission. The nutrition team was then consulted and a nasojejunal tube was placed five days after admission. Enteral feeding started, was well tolerated, and goal feedings were met four days later. The patient was trained on the tube and discharged 12 days after admission.[17]

The tube became displaced about one month later. She had been tolerating oral anti-emetics and was eating four times a day with little nausea and the tube was removed. One month later, her weight was up 2.8 kg from her admission weight. The

fetus grew normally throughout the remainder of the pregnancy. At 39 weeks, the patient had gained another 31.8 kg and she delivered a four-kilogram male.[17]

These two cases demonstrated both advantages and potential problems with nasojejunal tube feeding. The first case also showed some of the problems with parenteral nutrition. This article is limited in that it is a case study, only assessing two patients. However, it still shows promising results in using enteral nutrition to treat women with hyperemesis gravidarum.[17]

Studies by Erick, Hsu et al, and Serrano et al all assessed the use of enteral nutrition in women with hyperemesis, but were published before the year 2000, so were not included in the analysis for this research. The article by Erick was a case study evaluating the use of enteral nutrition in a woman with hyperemesis gravidarum. The woman delivered a healthy male after receiving feeding through a jejunostomy tube. Erick concluded that psychological and physiological factors could hinder an enteral feeding intervention.[22] The article by Hsu et al assessed seven women with hyperemesis gravidarum. Enteral feeds were well tolerated among these women and nausea and vomiting improved within 24 hours of nasogastric tube placement. They all gave birth to full term, normal-weight infants. The authors concluded that enteral feeding appears to be effective in alleviating nausea and vomiting and delivering adequate nutrition.[23] The article by Serrano et al was a case study on two women with hyperemesis gravidarum. The women both received enteral nutrition support and delivered healthy infants. The authors concluded that enteral nutrition support in women with hyperemesis is cost

effective, well tolerated, and has no major complications. The women's nutritional goals were met and the infants achieved proper fetal growth and development.[24]

The article by Lord et al is a review of the use of enteral nutrition in women with hyperemesis gravidarum. The authors concluded that gastric enteral nutrition is a safe and effective method to maintain nutrition and hydration and helps relieve symptoms of hyperemesis gravidarum.[25]

Parenteral feeding

Parenteral nutrition is another method to provide nutrition. Four studies evaluated the use of parenteral nutrition in treating hyperemesis gravidarum. The first one is a retrospective cohort study completed by Peled et al, which assessed pregnancy outcomes among women with hyperemesis gravidarum and examined whether the outcomes were related to the provision of total parenteral nutrition (TPN) support in early pregnancy.[18]

The study included all pregnant women who were hospitalized with the diagnosis of hyperemesis gravidarum during their first trimester between 1997 and 2011. Only women with singleton pregnancies who delivered at gestational age of >24 weeks were included. Pregnancy outcomes were compared to a control group of women with singleton pregnancies, matched by maternal age and parity in a 3:1 ratio. Subgroup analysis was done to compare pregnancy outcome between women with hyperemesis gravidarum who either received or did not receive TPN support.[18]

Pregnancy outcomes were extracted from a comprehensive perinatal database in the Rabin Medical Center in Petach Tikva, Israel. Outcomes included: 1) pregnancy complications (gestational diabetes, preeclampsia, and placental

abruption); 2) delivery outcomes (gestational age at delivery, labor induction, and cesarean section, meconium); and 3) perinatal outcomes [birth weight, composite morbidity, 5-min Apgar score, neonatal death, admission to neonatal intensive critical unit (NICU), respiratory distress syndrome (RDS), necrotizing enterocolitis (NEC), jaundice requiring phototherapy, and hypoglycemia.] [18]

TPN support included supplementation of fluid, fat, protein and essential amino acids, and glucose with supplementation of essential minerals, as well as antiemetic drugs.[18]

During the study period, 599 women with a singleton pregnancy were admitted with hyperemesis gravidarum and delivered in the medical center. Of these women, 122 received TPN support. Women in the hyperemesis and control groups were similar in terms of the medical and obstetrical background characteristics.[18]

Women with hyperemesis had a significantly higher rate of preeclampsia, preterm delivery, and labor induction. Neonates in the hyperemesis group had a significantly lower birth weight and birth weight percentile and a significantly higher rate of birth weight <10th percentile. They also had a significantly higher rate of composite neonatal morbidity, NICU admission, five minute Apgar score less than seven, and RDS.[18]

Provision of TPN was associated with a lower rate of preterm delivery and a lower rate of labor induction than women with hyperemesis who did not receive TPN. Neonates of mothers who received TPN had a higher birth weight, a higher

birth weight percentile, a lower rate of birth weight <10th percentile, and a lower rate of composite morbidity and NICU admission.[18]

The authors concluded that hyperemesis gravidarum is an independent risk factor for preterm delivery, fetal growth restriction, and adverse short-term neonatal outcome. They also found that TPN support in early pregnancy for women with hyperemesis is associated with lower rate of adverse pregnancy outcome.[18]

There were many strengths of the study, including that it was a large sample size. There was a uniform set of criteria used to define hyperemesis gravidarum, as well as uniform treatment protocols and criteria for TPN support as all of the patients were treated at the same medical center. Further, the researchers used a wide spectrum of different components of neonatal outcome.[18]

One major limitation is that the study design is retrospective. Data regarding the possible confounders such as pre-pregnancy BMI and pregnancy weight change were not available. Overall, this study provides support for a promising treatment for women with hyperemesis gravidarum.[18]

The next study on parenteral nutrition is a report on two cases, by Christodoulou et al, in which two women with hyperemesis gravidarum were successfully treated with peripheral parenteral nutrition.[19]

The first patient is a twenty-seven year old woman at 10 weeks and four days gestation, admitted to the Obstetrics Department for hyperemesis gravidarum and a small amount of vaginal bleeding. She was treated with bed rest, intravenous fluids, intravenous metoclopramide, and temporary cessation of oral intake. Dimenhydrinate was substituted for metoclopramide due to a reported intolerance

or allergy. She had a decrease in vomiting after a few days and was discharged with orders to avoid excessive amounts of food and fluids.[19]

The patient was readmitted a few weeks later at 14 weeks and five days gestation with intractable vomiting, dehydration, and exhaustion. She was not able to drink and keep down even small amounts of water or tea. She had weakness, malaise, mild epigastric tenderness, and a small amount of sludge in the gallbladder. The uterus and fetus were normal. She continued to have nausea and persistent vomiting despite receiving intravenous fluids and dimenhydrinate and discontinuing oral diet. Her epigastric pain also became more severe. An endoscopy showed third degree esophagitis and erosive gastritis of the fundus, which could be due to intractable vomiting.[19]

Ranitidine was started and peripheral parenteral nutrition was recommended. She received a one-liter bag every 12 hours for a total of two bags per day. She tolerated the treatment very well and recovered quickly. Less than a day after the start of peripheral parenteral nutrition, nausea and vomiting decreased and her condition improved. She received parenteral nutrition for 12 days and had no significant problems in the last months of her pregnancy. At 39 weeks gestation she vaginally delivered a healthy female baby with a weight of 2860 grams. [19]

The second patient is a thirty-three year old at eight weeks and three days gestation, admitted to the Obstetrics Department with severe hyperemesis gravidarum. She reported an allergy to metoclopramide. Her abdomen and fetus were within normal limits. She was given intravenous fluids and dimenhydrinate,

and discontinued oral intake. The patient also received intravenous solutions of amino acids and glucose preparations peripherally, but her symptoms did not significantly improve. Her nausea, epigastric discomfort, and vomiting worsened.[19]

After a gastroenterological consultation, peripheral parenteral solution began at 11 weeks and five days gestation at the same regimen as the previous patient, along with 500 mL of normal saline daily. Her symptoms and nutritional status quickly improved. She received peripheral parenteral nutrition for 14 days and was discharged a few days later, and did not have any more significant problems for the remainder of her pregnancy. At 39 weeks and four days gestation, she vaginally delivered a healthy, female baby with a weight of 3065 grams.[17] A few days later, she developed a breast abscess and was treated with antibiotics and local surgical drainage.[19]

These two case studies demonstrated that peripheral parenteral nutrition can be a safe and effective regimen to provide nutrition support to women with hyperemesis gravidarum. This study is limited in that it is a case study, only assessing two patients. However, it still shows promising results in using peripheral parenteral nutrition to treat women with hyperemesis gravidarum.[19]

Another study assessing parenteral nutrition, by Folk et al, is a retrospective design, comparing a group of women with hyperemesis gravidarum needing hospitalization and TPN support to a group also hospitalized, but did not receive TPN support. The purpose was to compare the two groups for the degree of illness and to detect complications related to TPN and to any potential risk factor for the development of hyperemesis gravidarum.[20]

The researchers completed a retrospective chart review for patients with a diagnosis of hyperemesis gravidarum admitted to Crouse Hospital in Syracuse, New York, a tertiary hospital for the central New York region, from January 1995 to December 1998. They identified a total of 166 patients and reviewed 192 admissions. They gathered information on age, gravidity and parity, marital status, gestational age, number of admissions, length of admissions, methods of nutritional support utilized, serum albumin levels, serum potassium, thyroid function, pregnancy complications, and pregnancy outcome.[20]

They reviewed medical records of 166 subjects. TPN was utilized in 27 (16%) of these subjects; so 139 of the subjects did not receive TPN. The overall incidence of medical and obstetric complications not directly related to TPN management was similar, 43% for the non-TPN group, compared to 41% for the TPN group. The researchers noted an increase in the incidence of complications related to TPN use for the TPN group, from 41% to 67%. The percentage of subjects with no complications was 57% for the non-TPN group and 33% for the TPN group.[20]

The incidence of preeclampsia, intrauterine growth restriction, preterm delivery, pregnancy termination, abruption, emergency delivery, abnormal serum screening, liver or gallbladder dysfunction, pyelonephritis, sepsis, pulmonary embolism, and depression was similar in both groups. The incidence of multiple gestation, fetal death, thyroid dysfunction, urinary tract infection, acute renal failure, and pneumonia was elevated in the TPN group as compared to the non-TPN group ($P<0.05$ for each complication.) Complications directly related to TPN use

were also reviewed. The incidence of line-related sepsis was elevated at 25%. The incidence of other potentially life-threatening complications, such as line-related thrombosis and bacterial endocarditis was about three percent each.[20]

There was no difference in objective laboratory measures between the TPN group and the non-TPN group. There were a few medical and obstetric conditions that were statistically more likely in the TPN group, but overall the incidence of complications not directly related to TPN was not significantly different between the two groups.[20]

The researchers did not find any differences when comparing maternal age, gravidity, parity, marital status, or gestational age at the time of inpatient admission. Sixty-eight of 98 (69%) multiparous patients had an antecedent pregnancy complicated by loss, either a spontaneous abortion, induced abortion, or fetal death.[20]

Ten of the 27 patients who received TPN had it initiated by established, documented criteria that comprised weight loss over at least four weeks, failed conservative therapy (including intravenous hydration), a variety of antiemetic medications, and persistent laboratory findings, such as electrolyte abnormalities and low serum albumin levels. For 17 of the patients, these criteria were either not documented or not followed strictly. All of the women in the TPN group had a central line placed and were prescribed nutritional support based on a combination of carbohydrate, lipid, and protein calories with electrolyte replacement.[20]

Twenty-seven of the total 166 subjects were managed with TPN and 139 were not. The incidence of a number of obstetric and medical complications was

significantly increased for the TPN group ($P<0.05$) when compared to the non-TPN group, including multiple gestation, fetal death, thyroid disease, urinary tract infection, acute renal failure, and pneumonia. Serum potassium, albumin, bicarbonate, and thyroid stimulating hormone levels were similar between the two groups and were similar to normal ranges for women during pregnancy.[20]

The incidence of obstetric and medical problems not related to TPN use was not significantly different between the two groups. The incidence of obstetric and medical complications directly related to TPN use was significantly different between the two groups. The overall incidence of complications increased by greater than 2.5 fold with TPN. These complications included a 25% incidence of TPN-related line sepsis and potentially lethal events, such as TPN-related line thrombus formation and bacterial endocarditis. It is not clear, however, if the TPN group had a larger disease burden from complications or laboratory abnormalities, so it is hard to warrant the additional risk taken with TPN use.[20]

Sixty-nine percent of the multiparous subjects had previous pregnancy complicated by loss. For the general population, an incidence of spontaneous first and second trimester loss of 10 to 15% has been reported. The fetal death rate is reported as 7.5 per 1,000 births in the United States. This increased incidence of a previous pregnancy complicated by loss in women using TPN seems to be prominently elevated when compared to the general reproductive population, indicating that a history of a previous pregnancy loss may be a risk factor for the development of hyperemesis gravidarum in a later pregnancy.[20]

This study concluded that the TPN and non-TPN groups were similar in the impact and severity of hyperemesis gravidarum. There appeared to be a significant increase in serious complications directly related to TPN use. The study also suggested that a history of fetal loss in a previous pregnancy might be a risk factor for hyperemesis gravidarum.[20]

One of the study's strengths is that it had a relatively large number of subjects with hyperemesis gravidarum treated with TPN. In addition, the comparison group of subjects who did not receive TPN were treated at the same hospital center during the same period.[20]

A limitation of this study is that the study design is retrospective. In addition, incomplete records that did not permit all patients admitted during the study period to be selected as subjects for this study likely introduced selection bias. Selection bias was also likely in the TPN group as some of the subjects were referrals from other hospitals within the center's referral region. Furthermore, there did not appear to be well-defined criteria for the initiation of TPN management. In addition, there did not seem to be a consistent approach to additional therapy past hydration support and antiemetics, such as use of steroids or enteral feeding, prior to the initiation of TPN management.[20]

The final study on parenteral nutrition is a case report by Ghani on a 34-year-old woman admitted at eight weeks gestation with vomiting. She had clinical signs of dehydration on admission, but her renal and liver functions were normal. She was given intravenous fluids and intramuscular antiemetics, but her condition did not improve in a week. Other diseases were excluded.[21]

To decrease the risk of venous thromboembolism, the patient was started on heparin prophylaxis and given compression stockings to wear at the beginning of the second week. Acupuncture was attempted, but did not help much. Intravenous Ondansetron was started, which slightly decreased her symptoms. The use of steroids were considered, but never started.[21]

At the end of the second week, the vomiting continued and TPN began. Vitamin B6 was also started. TPN was stopped after three weeks when the patient's nausea and vomiting spontaneously resolved. She was discharged home when she was tolerating diet and fluids freely.[21]

A 20-week ultrasound showed a normal fetus. As the patient delivered her first baby by emergency caesarean section for failure to progress in the first stage of labor, she delivered this baby by elective caesarean section. At 38 weeks gestation, a 3340 gram, female baby was born in good condition.[21]

This article demonstrated that TPN can be used as an effective treatment for hyperemesis gravidarum. However, this study is limited in that it is a case study on only one patient.[21]

Oral nutrition

The articles by Javidi et al, Viljoen et al, Ding et al, Saberi et al, and Jednak et al evaluated mild nausea and vomiting of pregnancy, so were not included in the analysis for this research.

Javadi et al was a clinical trial that assessed the effects of vitamin B6 and ginger in treating pregnancy nausea. The authors concluded that both vitamin B6 and ginger equally reduced symptoms of nausea and vomiting of pregnancy.[26] Both

articles by Viljoen et al and Ding et al are systematic reviews assessing the effectiveness and safety of ginger for the treatment of nausea and vomiting of pregnancy. Viljoen et al concluded that ginger did not significantly affect vomiting episodes nor pose a risk for side effects of adverse effects during pregnancy.[27] On the other hand, Ding et al concluded that ginger is a safe and effective treatment for nausea and vomiting of pregnancy. However, there remains uncertainty about the maximum safe dose of ginger, proper duration of treatment, and potential drug-herb interactions.[28] Saberi et al is a randomized, placebo-controlled trial that evaluated the effectiveness of ginger in the treatment of nausea and vomiting of pregnancy. The authors concluded that ginger was effective for the relief of mild to moderate nausea and vomiting in pregnant women at less than 16 weeks gestation.[29]

The final excluded study by Jednak et al was a controlled study that determined which meal characteristics offer the greatest reduction in symptoms in women with first trimester nausea and whether these meals have specific effects on electrogastrographic parameters. The authors concluded that protein meals selectively reduce nausea and gastric slow wave dysrhythmias in first trimester pregnancy.[30]

Conclusion

Overall, there is a lack of research on nutrition interventions in treating hyperemesis gravidarum. This literature review found eight total studies on treatment of hyperemesis gravidarum with nutrition support. The first four assessed enteral nutrition and the last four assessed parenteral nutrition. Most of the studies generally have a small sample size or are case studies with only one or

two patients. In addition, most are retrospective in nature. All of the studies demonstrated that both enteral and parenteral nutrition can be effective nutritional interventions for hyperemesis gravidarum. Complications for both were found in the studies.

Because of the importance of nutrition during pregnancy and the detrimental effects severe nausea and vomiting can have on mothers and babies, evidence for effective treatments are needed. More prospective studies need to be completed to determine the most safe and effective nutrition intervention for hyperemesis gravidarum. This includes studies on both enteral and parenteral nutrition, as well as studies comparing one to the other. However, it is challenging to complete prospective studies due to ethical limitations in conducting studies on this population. In addition, there are a limited number of pregnant women at specific medical sites with nausea and vomiting, so it may be difficult to obtain large sample sizes.

It is important to determine the optimal time to initiate enteral or parenteral nutrition, to assess the best tube placement for enteral nutrition, and evaluate patient acceptability of different nutrition interventions. Further trials are needed for evidence on the effectiveness of this treatment.

Even though more research is needed, the studies in this review provide building evidence for effective nutritional interventions for hyperemesis gravidarum. The articles show promising evidence for successful use of enteral and parenteral nutrition to treat women with severe nausea and vomiting during pregnancy.

CHAPTER 3: METHODS

Methodology

This research was completed using the Academy of Nutrition and Dietetics' (AND) Evidence Analysis process. The Academy of Nutrition and Dietetics' Evidence Analysis Library (EAL) is a "synthesis of the best, most relevant nutritional research on important dietetic practice questions." It uses "an objective and transparent methodology to assess food and nutrition-related science."[31]

The EAL was developed by AND for AND members using detailed methods and electronic tools throughout the process to allow objectivity, transparency, and reproducibility of the whole process. It has been recognized by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) and adapted by the Food and Drug Administration (FDA) to assess health claims placed on food labels.[32]

This process involves five steps: 1) Formulate evidence analysis question, 2) Gather and classify evidence, 3) Critically appraise each article, 4) Summarize the evidence and, 5) Write and grade the conclusion statement.[10] This process has been used to summarize current research related to nutrition interventions for hyperemesis gravidarum.[32]

Formulate Evidence Analysis Question

The first step in the EA process is to formulate a question for evidence analysis. It is important to pinpoint issues where scientific evidence is needed to inform and guide the nutrition professional. Asking focused questions helps to accomplish this by making clear connections between what knowledge is needed for

practice and what scientific research already exists. The nutrition care process (NCP) can be a helpful tool to help create questions, which includes four phases called ADIME (assessment, diagnosis, intervention, monitoring, and evaluation.) The NCP helps determine what outcomes are expected from an intervention. [32] For example, whether or not enteral nutrition helps relieve symptoms of hyperemesis gravidarum and where gaps in the literature exist.

For this research, the following questions were formulated: "Are enteral and parenteral nutrition support safe and effective ways to provide nutrition to women with hyperemesis gravidarum? Do enteral and parenteral nutrition support improve maternal and fetal health outcomes during hyperemesis gravidarum?"

The answers to this question will help guide professionals in providing the best treatment for women with this condition.

Gather and Classify Evidence

After the question is formed, the next step in this process is to gather research, which involves creating a search plan with inclusion and exclusion criteria, conducting a search using various databases, reviewing citations and abstracts, gathering articles meeting criteria, and constructing a search plan and results through detailed examination of included and excluded articles. The goal of this step is to find the best available research to answer the research question and develop a final list of articles to be abstracted, as well as a list of excluded articles along with reasons for their exclusion.[32]

After the planning is complete, the search is conducted.[23] For this research project, PubMed was used to search for articles. Search terms included pregnancy,

nutrition, nausea and vomiting, hyperemesis, hyperemesis gravidarum, nutrition support, enteral nutrition, and parenteral nutrition. Inclusion criteria were studies published in English and studies on pregnant women with severe nausea and vomiting. Exclusion criteria were any review or meta-analysis articles, studies published before 2000, studies on mild nausea and vomiting during pregnancy, studies on other conditions associated with nausea and vomiting, and studies also analyzing drug and herb treatment.

The research is first divided into primary research (original studies) and secondary research (review, meta-analysis, and/or synthesis of previously reported studies). This project only analyzed primary research. Next, the articles are classified based on research design. The type of research question asked establishes best research design to pursue. A randomized controlled trial (RCT) is the most appropriate type of research design for this research question because it is treatment based. Classifying the studies helps to give a picture of the types of studies and level of evidence available, in addition to organizing the articles for the next step of the analysis process. Table 1 shows the hierarchy and classification of studies.

Table 1: Hierarchy and Classification of Studies

Primary Reports		Secondary Reports	
A	Randomized Controlled Trial Cluster Randomized Trial Randomized Crossover Trial	M	Meta-analysis or Systematic review Decision analysis Cost-benefit analysis Cost-effectiveness study
B	Prospective Cohort Study Retrospective Cohort Study		
C	Non-Randomized Controlled Trial Non-Randomized Crossover Trial Case-Control Study Time Series Study Diagnostic, Validity or Reliability Study	R	Narrative review (Review article) Consensus statement Consensus report
D	Non-Controlled Trial Case Study or Case Series Other Descriptive Study Cross-Sectional Study Trend Study Before-After Study	X	Medical opinion

(Academy of Nutrition and Dietetics Evidence Analysis Library, 2012)

This particular search found seventeen studies during the search, with eight studies meeting the inclusion and exclusion criteria: three retrospective cohort studies, four case studies, and one case series. [32] Listed below are the articles that met search criteria:

Included Articles:

1. Stokke, Guro, et al. Hyperemesis gravidarum, nutritional treatment by nasogastric tube feeding: a 10-year retrospective cohort study. *Acta obstetricia et gynecologica Scandinavica*. 2015; (94): 359-367.

2. Saha, Sumona, et al. Feeding jejunostomy for the treatment of severe hyperemesis gravidarum: a case series. *Journal of Parenteral and Enteral Nutrition*. 2009; (33): 529-534.

3. Vaisman N, Kaidar R, Levin I, Lessing JB. Nasojejunal feeding in hyperemesis gravidarum – a preliminary study. *Clin Nutr*. 2004; (23): 53-57.

4. Pearce, C. B., et al. Enteral nutrition by nasojejunal tube in hyperemesis gravidarum. *Clinical Nutrition*. 2001; (20): 461-464.

5. Peled Y, Melamed N, Hiersch L, Pardo J, Wiznitzer A, Yogev Y. The impact of total parenteral nutrition support on pregnancy outcome in women with hyperemesis gravidarum. *J Matern Fetal Neonatal Med*. 2014 Jul; 27 (11): 1146-1150.

6. Christodoulou DK, Katsanos KH, Makrydimas G, Tsanadis G, Tsianos EV. Peripheral parenteral nutrition in protracted hyperemesis gravidarum-report of two cases and a literature review. *Acta Gastro-Enterologica Belgica.* 2008; (71): 259-262.

7. Folk JJ, Leslie-Brown HFM, Nosovitch JT, Silverman RK, Aubry RH. Hyperemesis gravidarum: outcomes and complications with and without total parenteral nutrition. *J Reprod Med*. 2004; (49): 497-502.

8. Ghani R. The use of total parenteral nutrition in protracted hyperemesis gravidarum. *J Obstet Gynaecol*. 2003; (23): 199-201.

Table 2 shows articles that were excluded from analyses and the reasons why.

Table 2: Excluded Articles from the Literature Search

Article	***Reason Excluded***
Erick M. Nutrition via jejunostomy in refractory hyperemesis gravidarum: a case report. *J Am Diet Assoc. 1997*; (97):1154-1156.	Published before 2000
Lord L, Pelletier K. Management of hyperemesis gravidarum with enteral nutrition. *Nutrition Issues in Gastroenterology.* 2008; (63): 15-31.	Review article
Hsu J, Clark-Glena R, Nelson D, Kim C. Nasogastric enteral feeding in the management of hyperemesis gravidarum. *Obstetrics and Gynecology.*	Published before 2000

1996; (88): 343-346.	
Serrano P et al. Enteral nutrition by percutaneous endoscopic gastrojejunostomy in severe hyperemesis gravidarum: a report of two cases. *Clinical Nutrition.* 1998; (17); 135-139.	Published before 2000
Javadi EHS, Salehi F, Mashravi O. Comparing the effectiveness of vitamin B6 and ginger in treatment of pregnancy-induced nausea and vomiting. *Obstetrics and Gynecology International.* 2013; (2013): 1-4.	Assesses mild nausea and vomiting, analyzes vitamin B6 and ginger treatments
Viljoen E, Visser J, Koen N, Musekiwa A. A systematic review and meta-analysis of the effect and safety of ginger in the treatment of pregnancy-associated nausea and vomiting. *Nutrition Journal.* 2014; (13); 1-14.	Systematic review and meta-analysis
Ding M, Leach M, Bradley H. The effectiveness and safety of ginger for pregnancy-induced nausea and vomiting: a systematic review. *Women and Birth.* 2013; (26): e26-e30.	Systematic review
Saberi F, Sadat Z, Abedzadeh-Kalahroudi M, Taebi M, Effect of ginger on relieving nausea and vomiting in pregnancy: a randomized, placebo-controlled trial. *Nur Midwifery Stud.* 2014; (3): 1-6.	Assesses mild nausea and vomiting, analyzing ginger
Jednak et al. Protein meals reduce nausea and gastric slow wave dysrhythmic activity in first trimester pregnancy. *American Journal of Physiology-Gastrointestinal and Liver Physiology.* 1999; (277); 855-861.	Assesses mild nausea and vomiting, analyzing oral diet, also published before 2000

Critically Appraise Each Article

After the evidence is gathered and classified, the next step is to critically appraise each article. Each article is reviewed using an Evidence Worksheet

developed by AND (Appendix A). This worksheet is used to abstract key information for future reference, identify study details that allow determination of study quality, summarize major findings, record the author's conclusion, note reviewer's comments about the study limitations and applicability, and note the funding source. A quality criteria checklist is used to determine a rating for each research article. This helps to identify criteria for sound scientific research and is used to assign an overall rating to the study. The Evidence Analysis Manual provides instructions and tips for using the Evidence Worksheet and quality criteria checklist.[32]

Summarize the Evidence

After the articles are critically appraised, the next step is to summarize evidence. This step comprises two parts: the Overview Table (Appendix B) and the narrative synthesis. These both involve combining relevant and scientifically valid information into a brief summary, allowing comparison of the studies. This information is transferred from the Evidence Worksheets. The table includes the authors and publication year, outcomes and measurements of interest, important sample characteristics and comparison factors, implications for practice, and limitations of findings.[32]

The next part involves writing the evidence summary. This summary compares the articles to each other, identifying common patterns in the research. Components of the evidence summary includes the overall summary statement, comparison factors statements, methodological statements, and outcome impact statements.[32]

Write and Grade the Conclusion Statement

The final step in the evidence analysis process is to grade the strength of the evidence of nutrition interventions for hyperemesis gravidarum. The research is combined into a conclusion statement answering the evidence analysis questions, "Are enteral and parenteral nutrition support safe and effective ways to provide nutrition to women with hyperemesis gravidarum? Do enteral and parenteral nutrition support improve maternal and fetal health outcomes during hyperemesis gravidarum?"

Last, the strength of the evidence supporting the conclusion statement is given a grade. This analysis is added to the evidence on what nutrition interventions are effective in treating hyperemesis gravidarum. Table 3 describes the conclusion grades. [32]

Table 3: Conclusion Grading Table

Strength of Evidence Elements	Grades				
	I Good	II Fair	III Limited	IV Expert Opinion Only	V Grade Not Assignable
Quality • Scientific rigor/validity • Considers design and execution	Studies of strong design for question Free from design flaws, bias and execution problems	Studies of strong design for question with minor methodological concerns, OR Only studies of weaker study design for question	Studies of weak design for answering the question OR Inconclusive findings due to design flaws, bias or execution problems	No studies available Conclusion based on usual practice, expert consensus, clinical experience, opinion, or extrapolation from basic research	No evidence that pertains to question being addressed
Consistency Of findings across studies	Findings generally consistent in direction and size of effect or degree of association, and statistical significance with minor exceptions at most	Inconsistency among results of studies with strong design, OR Consistency with minor exceptions across studies of weaker design	Unexplained inconsistency among results from different studies OR single study unconfirmed by other studies	Conclusion supported solely by statements of informed nutrition or medical commentators	NA
Quantity • Number of studies • Number of subjects in studies	One to several good quality studies Large number of subjects studied Studies with negative results have sufficiently large sample size for adequate statistical power	Several studies by independent investigators Doubts about adequacy of sample size to avoid Type I and Type II error	Limited number of studies Low number of subjects studied and/or inadequate sample size within studies	Unsubstantiated by published research studies	Relevant studies have not been done
Clinical Impact • Importance of studied outcomes • Magnitude of effect	Studied outcome relates directly to the question Size of effect is clinically meaningful Significant (statistical) difference is large	Some doubt about the statistical or clinical significance of the effect	Studied outcome is an intermediate outcome or surrogate for the true outcome of interest OR Size of effect is small or lacks statistical and/or clinical significance	Objective data unavailable	Indicates area for future research
Generalizability To population of interest	Studied population, intervention and outcomes are free from serious doubts about generalizability	Minor doubts about generalizability	Serious doubts about generalizability due to narrow or different study population, intervention or outcomes studied	Generalizability limited to scope of experience	NA

(Academy of Nutrition and Dietetics Evidence Analysis Library, 2012)

CHAPTER 4: RESULTS

Maternal and fetal health outcomes following the use of parenteral and enteral nutrition support during hyperemesis gravidarum is provided in a few retrospective cohort studies, as well as some case studies. This analysis included eight studies evaluating the use of nutrition support in women with hyperemesis gravidarum between the years 2001 and 2015. Four studies focused on enteral nutrition and four focused on parenteral nutrition. Below is a summary of each of these studies.

Relevant Findings: Stokke, et al., 2015

This retrospective cohort study compared maternal and fetal outcomes between women with hyperemesis gravidarum who received tube feeding and women who received different fluid and nutrition therapies. One comparison group received intravenous fluids and the other group received nutritional solution by peripheral catheter. Women treated with enteral nutrition had significantly greater weight loss on admission (median 5.0 kg) and prior to the start of nutrition support (5.5 kg) than the control group (4.0 kg) ($p<0.001$). Enteral nutrition was given for up to 41 days during hospitalization (median 5 days), resulting in an average 0.8 kg weight gain compared with no weight changes in the other two treatment groups (95% CI 0.5-1.0, $p = 0.005$).[14] Women treated with enteral nutrition had similar weight gain during pregnancy and similar incidence of preterm birth and small-for-gestational age compared with the other two groups. All women with <7 kg of weight gain had a higher risk of birthweight <2500 g and small-for-gestational-age infants (odds ratio 3.68, 95% CI 1.89-7.18, $p<0.001$). Pregnancy outcomes were

similar across groups in terms of abortion rates, twin rates, gestational age, birthweight, preterm birth, low birthweight, and SGA infants (all p >0.05).[14]

The enteral tubes were mostly well tolerated by the women. Eight women (7%) asked to remove the tube due to discomfort. Fifty-eight women's (54%) tubes inadvertently came out due to clogging (n=4) and forceful vomiting (n=46). One of the nine women on TPN developed a pneumothorax, two had their CVC removed due to infection, and one women had to have her catheter removed because of obstruction (n=4, 44% with catheter removal). [14]

The authors concluded that compared with other fluid and nutrition regimens, enteral tube feeding for women with hyperemesis gravidarum is associated with adequate maternal weight gain and favorable pregnancy outcomes.[14]

Research Quality Rating

This study was classified in study class B and received a positive (+) research quality rating.

Relevant Findings: Sumona, et al., 2009.

This case series assessed the feasibility and efficacy of surgically placed jejunostomy feeding tubes (J tube) in women with hyperemesis gravidarum who failed standard therapy.[15] Six J tubes were placement at the Women & Infants Hospital between 1998 and 2005 in women with hyperemesis gravidarum. One patient had a J tube placed twice for consecutive pregnancies. The mean body weight loss from prepregnancy was 7.9% (range of 4.0% to 15.9%).[15]

The J tubes were placed between 12 and 26 weeks gestation (median of 14 weeks). Maternal weight gain was realized in five of six pregnancies. The J tubes were placed for a mean of 19 weeks (range, 8-28 weeks). Four J tubes stayed in place until delivery. All pregnancies resulted in term deliveries (range, 36-40 weeks of gestation) of healthy infants. The mean infant birth weight was 2995 grams (range, 2270-4000 grams). The only tube-related complication was tube dislodgement in two patients requiring simple replacement.[15]

The authors concluded that providing nutrition through a jejunostomy feeding tube is a potentially safe, effective, and well-tolerated method of nutrition support therapy in women with hyperemesis gravidarum.[15]

Research Quality Rating

This study was classified in study class D and received a neutral (∅) research quality rating.

Relevant Findings: Vaisman, et al., 2004.

This case study examined the feasibility and the preferability of feeding patients with hyperemesis gravidarum via an intrajejunal route to overcome vomiting, weight loss, and relative malnutrition.[16]

Mean weight loss in the hospital was 2.2 kg, with a standard deviation of 1.1 kg. None of the patients had evidence of esophagitis, gastritis, or ulceration. Symptoms of nausea and vomiting ceased as early as 48 hours after insertion of the tube, but vomiting and retching stopped completely after 1-13 days (mean $\pm$SD, 5$\pm$4 days). The length of the NJ tube feeding for all 11 women ranged from one to 21 days. Six patients started tolerating oral intake after three to four days and the rest

started later, mostly due to fear of recurring vomiting. Weight loss stopped in all patients on tube feeding.[16]

In three cases, the tube came out due to vomiting after one to four days, and in one case the tube was blocked after 18 days. There were no complications associated with enteral feeding in these subjects.[16]

The authors concluded that enteral feeding through a nasojejunal tube can be an effective way to provide nutrition in women with hyperemesis gravidarum.[16]

Research Quality Rating

This study was classified in study class D and received a negative (-) research quality rating.

Relevant Findings: Pearce, et al., 2001.

This case study evaluated the use of enteral nutrition in two patients with hyperemesis gravidarum.[17]

Both patients had severe cases of hyperemesis gravidarum and were dehydrated, malnourished, and had ketonuria. The first patient tolerated enteral nutrition well and her feeding goals were met after the first two nasojejunal tubes had been dislodged. She delivered a normal, three-kilogram baby boy at 36 weeks gestation. The second patient tolerated enteral feeding, but her tube became displaced about one month after she was at home on enteral feeds. At that point she was eating four times a day with little nausea, so the tube was removed. She delivered a four-kilogram, normal baby boy at 39 weeks.[17]

The authors concluded that enteral feeding can be an alternative to parenteral feeding to provide nutrition to women with hyperemesis gravidarum. It is well tolerated, cost effective, and has a low rate of complication.[17]

Research Quality Rating

This case study was classified in study class D and received a neutral (∅) research quality rating.

Relevant Findings: Peled, et al., 2014.

This retrospective cohort study assessed pregnancy outcomes among women with hyperemesis gravidarum and examined whether the outcomes were related to the provision of total parenteral nutrition (TPN) support during early pregnancy.[18]

Compared to women without hyperemesis, women with hyperemesis had a significantly higher rate of preeclampsia (1.3% versus 0.5%, p=0.04), preterm delivery at less than 37 and 34 weeks (10.9% versus 6.9%, p<0.001 and 4.7% versus 1.6%, p<0.001, respectively.) Neonates in the hyperemesis group had a significantly lower birth weight (3074 $\pm$ 456 grams versus 3248 $\pm$ 543 grams, p<0.001), birth weight percentile (44.8 $\pm$28.3 versus 52.4 $\pm$ 27.0, p<0.001), and a significantly higher rate of birth weight <10th percentile (12.7% versus 6.8%, p<0.001). They also had a significantly higher rate of composite neonatal morbidity (8.7% versus 3.8%, p<0.001), NICU admission (7.2% versus 2.5%, p<0.001), five minute Apgar score less than seven (0.7% versus 0%, p<0.001), and RDS (2.7% versus 1.2%, p<0.01).[18]

Provision of TPN was associated with a lower rate of preterm delivery at <37 weeks and < 34 weeks (6.2% versus 12.8% and 1.7% versus 5.9%, respectively, p=0.02 for both) and a lower rate of labor induction (7.3% versus 13%, p=0.045)

compared to women with hyperemesis who did not receive TPN. Neonates of mothers who received TPN compared to those who did not, had a higher birth weight (3145 ± 487 grams versus 3056 ± 443 grams, p=0.03), a higher birth weight percentile (49.6% ± 27.1% versus 43.6% ± 28.6%, p=0.03), a lower rate of birth weight <10th percentile (7.9% versus 14.7%, p=0.02), and a lower rate of composite morbidity (4% versus 10.7%, p=0.008), and NICU admission (3.4% versus 8.8%, p=0.02).[18]

The authors concluded that hyperemesis gravidarum in pregnancy is a risk factor for preterm delivery, fetal growth restriction, and adverse short-term neonatal outcome. TPN treatment for women with hyperemesis gravidarum in early pregnancy is associated with lower rate of adverse pregnancy outcome.[18]

Research Quality Rating

This case study was classified in study class B and received a neutral (∅) research quality rating.

Relevant Findings: Christodoulou, et al., 2008.

This case study evaluated the use of peripheral parenteral nutrition in two women with hyperemesis gravidarum.[19]

The patient in Case 1 tolerated the treatment well and had a fast recovery. She received parenteral nutrition for 12 days and had no significant problems for the remainder of her pregnancy. At 39 weeks gestation, she delivered a healthy female baby weighing 2860 grams.[19]

The patient in Case 2 also had a quick recovery with improvement of her symptoms and nutritional status. She received parenteral nutrition for 14 days and

was discharged a few days later. At 39 weeks and 4 days gestation, she delivered a healthy female baby weighing 3065 grams.[19]

The authors concluded that a short course of a standardized commercial regimen of peripheral parenteral nutrition can be a successful way to provide nutrition to women with hyperemesis gravidarum.[19]

Research Quality Rating

This case study was classified in study class D and received a neutral (∅) research quality rating.

Relevant Findings: Folk, et al., 2004.

This retrospective cohort study evaluated the obstetric and medical complications in patients with hyperemesis gravidarum, comparing those who were treated with total parenteral nutrition (TPN) to those who did not receive TPN.[20]

TPN was used in 27 of 166 subjects (16%). The overall occurrence of medical and obstetric complications not directly related to TPN management was similar between the two groups. There was an increase in the occurrence of complications related to TPN use for the TPN group from 41% to 67%. This includes the incidence of line-related sepsis, which was noticeably elevated at 25%. The incidence of other potentially life-threatening complications, such as line-related thrombosis and bacterial endocarditis was about 3% each. Compared to the non-TPN group, the TPN group had a higher incidence of multiple gestation (3.1% versus 1.5%), fetal death (6.3% versus 0%), thyroid dysfunction (18.8% versus 5.2%), urinary tract infection (31.3% versus 10.4%), acute renal failure (3.1% versus 0%), and pneumonia (3.1% versus 0%) ($p<0.05$ for each complication). For obstetric and medical complications

not directly related to TPN use, the odds ratio for complications shows no significant difference between with groups. With the addition of complications directly related to TPN use, including line-related sepsis, line-related thrombosis, and bacterial endocarditis, the odds ratio becomes statistically significant, showing an additional risk attributable to TPN use.[20]

Sixty-eight of 98 multiparous subjects (69%) had a prior pregnancy complicated by loss, either a spontaneous abortion, induced abortion, or fetal death. Criteria were not followed strictly or not documented for the remaining 17 subjects who received TPN.[20]

The authors concluded that there was a significant increase in serious complications directly related to TPN use in women with hyperemesis gravidarum. In addition, it revealed that a history of fetal loss in a prior pregnancy might be a risk factor for hyperemesis gravidarum.[20]

Research Quality Rating

This retrospective cohort study was classified in study class B and received a neutral (∅) research quality rating.

Relevant Findings: Ghani, et al., 2003.

This case study assessed whether total parenteral nutrition (TPN) could be used successfully to treat a patient with protracted hyperemesis gravidarum.[21]

TPN was given for three weeks and then nausea and vomiting stopped. The patient was discharged after she was able to eat and drink. She delivered a healthy, 3340-gram female baby at 38 weeks gestation.[21]

The authors concluded that TPN can be successfully used in a patient with severe hyperemesis gravidarum.[21]

Research Quality Rating

This case study was classified in study class D and received a neutral (Ø) research quality rating.

Conclusion Statement

Questions:

Are enteral and parenteral nutrition support safe and effective ways to provide nutrition to women with hyperemesis gravidarum? Do enteral and parenteral nutrition support improve maternal and fetal health outcomes during hyperemesis gravidarum?

Conclusion:

Safety and Effectiveness

Enteral and parenteral nutrition are both shown to be successful ways to provide nutrition to women suffering from hyperemesis gravidarum, leading to favorable pregnancy outcomes.

Enteral nutrition is a potentially safe and effective form of nutrition support in women with hyperemesis gravidarum. All four studies focusing on enteral nutrition exhibited enteral nutrition to be mostly well tolerated, with limited complications. Minor complications, such as tube dislodgement and clogging occurred. On the other hand, serious complications have been experienced with the use of parenteral nutrition in these patients, including pneumothorax, serious infections, and line obstruction. The comparison of complications between enteral

nutrition and parenteral nutrition need to be discussed with patients considering these methods of nutrition support during hyperemesis gravidarum.

Maternal and Fetal Health Outcomes

Weight loss due to hyperemesis gravidarum was shown to stop in patients on tube feeding in three studies. Women treated with enteral nutrition had similar weight gain during pregnancy and similar incidence of preterm birth and SGA infants compared with other groups receiving other nutrition and fluid regimens in one study. Pregnancy outcomes, including gestational age, birthweight, preterm birth, low birthweight, and SGA infants were similar among women receiving enteral nutrition, intravenous fluids, and nutrition by peripheral catheter in one study.

Parenteral nutrition treatment for women with hyperemesis gravidarum was also associated with a lower rate of adverse pregnancy outcomes compared to women not receiving parenteral nutrition in one study. Women receiving parenteral nutrition had a lower rate of preterm delivery at less than 37 and 34 weeks (6.2% versus 12.8% and 1.7% versus 5.9%, respectively) and a lower rate of labor induction (7.3% versus 13%) compared to women with no parenteral nutrition in one study. Neonates of mothers receiving parenteral nutrition had higher birthweights, higher birthweight percentiles, lower rate of birthweights <10th percentile, lower rate of composite morbidity, and lower rate of NICU admission in one study.

Study rating and design

Out of the eight studies reviewed, one study had a positive rating, six had a neutral rating, and one had a negative rating. Three studies were retrospective cohort studies and five were case studies. Table 4 summarizes the results.

Grade III: Limited/Weak

This research was given a limited/weak grade based on the weak study designs.

Table 4: Summary of Results

Study	**Study Design (N)**	**Treatment**	**Maternal Outcomes**	**Fetal Outcomes**
Stokke et al	Retrospective cohort study (n=557)	Enteral nutrition	Weight gain	Birthweight
Sumona et al	Case series (n=6)	Enteral nutrition	Weight gain	Weeks gestation, birthweight
Vaisman et al	Case study (n=11)	Enteral nutrition	Cessation of symptoms and weight loss	NA
Pearce et al	Case study (n=2)	Enteral nutrition	NA	Weeks gestation, birthweight
Peled et al	Retrospective cohort study (n=599)	Parenteral nutrition	Preterm delivery, labor induction	Birthweight, composite morbidity, NICU admission
Christoldoulou et al	Case Study (n=2)	Parenteral nutrition	NA	Weeks gestation, birthweight
Folk et al	Retrospective cohort study (n=166)	Parenteral nutrition	Obstetric and medical complications	Fetal death
Ghani et al	Case study (n=1)	Parenteral nutrition	Cessation of symptoms	Weeks gestation, birthweight

CHAPTER 5: DISCUSSION

Evidence Summary

Overall Summary Statement

Eight studies were reviewed using AND's Evidence Analysis criteria. All eight studies evaluated the use of nutrition support in women with hyperemesis gravidarum, four assessed enteral nutrition and four assessed parenteral nutrition. All of the studies concluded that nutrition support can be a successful way to provide nutrition to patients with hyperemesis gravidarum. Enteral nutrition was well tolerated with limited complications. Enteral nutrition led to alleviation of nausea and vomiting and also stopped weight loss. Some patients receiving parenteral nutrition did show some complications, such as infections, but parenteral nutrition was also associated with positive pregnancy outcomes. It was associated with a lower rate of adverse pregnancy outcomes compared to women who did not receive parenteral nutrition, including a lower rate of preterm delivery and lower rate of labor induction. Neonates of mothers on parenteral nutrition had a higher birthweight percentile, lower rate of composite morbidity, and a lower rate of NICU admission compared to neonates of mothers who did not receive parenteral nutrition.

Comparison Factors Statements

Four of the studies indicated that enteral nutrition was an effective method to provide nutrition support in women with hyperemesis gravidarum, as it was well tolerated, led to positive pregnancy outcomes, alleviated nausea and vomiting, and stopped weight loss. The remaining four studies showed that parenteral nutrition

was effective, leading to positive pregnancy outcomes. The Stokke et al and Folk et al studies both showed that parenteral nutrition can increase risk of complications, such as pneumothorax, infections, line-related thrombosis, and bacterial endocarditis compared to women not receiving parenteral nutrition. Stokke et al, Sumona et al, Vaisman et al, and Pearce et al revealed minor complications of enteral nutrition, including tube dislodgement and clogging, but also demonstrated that these were easily resolved and that the use of tube feeding led to favorable pregnancy outcomes of healthy, normal weight infants. All eight of the studies demonstrated that nutrition support can be a successful way to provide nutrition in these patients.

Methodological Statements

Three of the studies were retrospective cohort studies, which fall into study class B, the highest study design classification of this review. Studies with more highly valued design such as prospective or randomized controlled trials have not been conducted on the use of nutrition support in the HG population. Stokke et al evaluated 557 women total, of whom 273 women received fluids intravenously, 177 received nutritional solution by peripheral catheter, and 107 received enteral nutrition by jejunal tube. The second retrospective cohort study by Peled et al had the largest number of subjects of all the studies in this review. They evaluated a total of 599 subjects, 122 who received TPN and 477 who did not receive TPN. 1797 women were in a control group. The final retrospective cohort study by Folk et al completed a chart review of a total of 166 patients, comparing 27 subjects who received TPN to 139 subjects who did not.

Five of the studies were case studies, which fall into study class D, the lowest classification of this review. Saha et al studied five women who received enteral nutrition during pregnancy for hyperemesis gravidarum, for a total of six patients evaluated as one patient had a J tube placed in two different pregnancies during the study period. Vaisman et al studied eleven patients who received enteral nutrition during pregnancy for hyperemesis gravidarum. Pearce et al assessed two patients with hyperemesis gravidarum who received enteral nutrition. Christodoulou et al assessed two patients with hyperemesis gravidarum who received parenteral nutrition. The last case study by Ghani et al had the smallest sample, with one patient who received parenteral nutrition during pregnancy for hyperemesis gravidarum. These study designs were all observational, as the researchers did not manipulate interventions. Because the studies were not randomized, controlled trials, cause and effect cannot be determined.

Outcome Impact Statements

The articles evaluating the use of enteral nutrition demonstrate that enteral nutrition can be a safe and effective way to provide nutrition support to women with hyperemesis gravidarum and can improve maternal and fetal health outcomes. The articles demonstrated that enteral nutrition was well tolerated, cost effective, and low rate of complication and women receiving enteral nutrition delivered healthy, normal weight infants. One article showed that women receiving enteral nutrition had an average weight gain of 0.8 kg compared to no weight changes in groups receiving intravenous fluids and nutrition solution by peripheral catheter. The enteral nutrition group also had a similar incidence of small-for-gestational-age

infants and preterm births as the other two groups. They also found that the enteral tubes were mostly well tolerated and that a few patients on TPN experienced pneumothorax, infection, and obstruction of the line.[14] Another study found that symptoms of nausea and vomiting stopped as early as 48 hours after insertion of an enteral tube and vomiting and retching completely stopped after one to 13 days. Weight loss stopped in all of the patients in this study.[16]

The articles evaluating the use of parenteral nutrition can improve maternal and fetal outcomes. Most deliveries of women on parenteral nutrition were of healthy infants. In one study parenteral nutrition was associated with a lower rate of preterm delivery and lower rate of labor induction compared with women who did not receive parenteral nutrition. Neonates of mothers who received parenteral nutrition compared to those who did not had a higher birthweight, a higher birthweight percentile, a lower rate of composite morbidity, and NICU admission.[18] Some safety concerns were brought up with the use of parenteral nutrition. In one study, the incidence of line-related sepsis, line-related thrombosis, and bacterial endocarditis increased with the use of parenteral nutrition. Parenteral nutrition was also associated with a higher incidence of fetal death, thyroid dysfunction, urinary tract infection, acute renal failure, and pneumonia compared to women who did not receive parenteral nutrition.[20]

Strengths and Limitations

Stokke et al has been the largest study showing results of enteral feeding for nutrition management of severe hyperemesis gravidarum, showing that it is a

feasible and beneficial way of providing nutrition. The study used cases of hyperemesis over a 10 year period and had a large sample of women to assess.[14]

The study did have some limitations. Because it was a retrospective cohort study, different aspects of the treatment cannot be assessed, such as patient acceptability of different nutritional methods. This study is representative of a Norwegian population, so may not be representative of different ethnicities, as only 25% of the patients are of non-Caucasian ethnicity. In addition, this study did not assess smoking habits. Previous studies have shown that women with hyperemesis have a lower prevalence of smoking than those without emesis, so this could have an impact on the results.[14]

Sumona et al is one of a few studies assessing nutrition support during pregnancy. It was completed at a unique center, which is a high-volume obstetric hospital with a gastroenterology division that focuses on gastrointestinal disorders during pregnancy. This study was limited due to the small number of cases as well as its retrospective design. In addition, it only assessed patients at one center, so it may not be generalized to all patients with hyperemesis gravidarum.[15]

Vaisman et al is also one of few studies assessing enteral feeding on patients with hyperemesis. However, this was a preliminary study with the objective of testing the feasibility of this treatment. All patients received the same treatment, so there was no control group and the sample size was small.[16]

Pearce et al demonstrated both advantages and potential problems with nasojejunal tube feeding. It also revealed some of the problems with parenteral

nutrition. This article was limited in that it was a case study, only assessing two patients.[17]

There were many strengths of the Peled et al study, including that it was a large sample size. There was a uniform set of criteria used to define hyperemesis gravidarum, as well as uniform treatment protocols and criteria for TPN support as all of the patients were treated at the same medical center. Further, the researchers used a wide spectrum of different components of neonatal outcome.[18]

One major limitation is that the study design was retrospective. Data regarding the possible confounders such as pre-pregnancy BMI and pregnancy weight change were not available.[18]

Christodoulou et al demonstrated that peripheral parenteral nutrition can be a safe and effective regimen to provide nutrition support to women with hyperemesis gravidarum. This study was limited in that it is a case study, only assessing two patients.[19]

Folk et al had a relatively large number of subjects with hyperemesis gravidarum treated with TPN. In addition, the comparison group of subjects who did not receive TPN were treated at the same hospital center during the same period.[20]

A limitation of this study is that it was retrospective. In addition, incomplete records that did not permit all patients admitted during the study period to be selected as subjects for this study likely introduced selection bias. Selection bias was also likely in the TPN group as some of the subjects were referrals from other hospitals within the center's referral region. Furthermore, there did not appear to be well-defined criteria for the initiation of TPN management. In addition, there did

not seem to be a consistent approach to additional therapy past hydration support and antiemetics, such as use of steroids or enteral feeding, prior to the initiation of TPN management.[20]

Ghani et al demonstrated that TPN can be used as an effective treatment for hyperemesis gravidarum. However, this study was limited in that it is a case study on only one patient.[21]

Excluded Studies

Some articles found in the search for this review were excluded from the analysis because they did not meet the inclusion criteria. Articles were not included if they were published before the year 2000, if they were not original research, or if they studied mild rather than severe nausea and vomiting of pregnancy.

The studies by Erick, Hsu et al, and Serrano et al, which were all published before the year 2000, also showed that enteral nutrition can be a safe and effective way to provide nutrition to a woman with hyperemesis, leading to favorable maternal and fetal outcomes. Hsu et al noted that enteral nutrition has less potential for serious complications and is substantially cheaper than total parenteral nutrition. This study also made the observation that the presence of the tube may play some role in alleviating symptoms of hyperemesis gravidarum. Erick demonstrated that psychological and physiological factors might hinder an enteral nutrition intervention.[24, 25, 26]

The review article by Lord et al also concluded that enteral nutrition can be a safe and effective method to provide nutrition and hydration and help relieve symptoms of hyperemesis gravidarum.[27]

The studies by Javadi et al, Viloen et al, Ding et al., Saberi et al, and Jednak et al assessed mild nausea and vomiting, evaluating the use of ginger, vitamin B6, and protein in alleviating symptoms.[28, 29, 30, 31, 32]

EAL Process

The EA process was an effective and organized way to sort through the research available on treatment for hyperemesis. This process allowed me to determine what research was completed on treatments for hyperemesis and efficiently analyze each article. I was not able to determine definite practice recommendations from the results of this process, however, due to the nature of the study designs on this topic, as there were no randomized controlled studies completed.

Implications for Future Research

Because nutrition significantly impacts a child and mother's health, research is needed on the best method to provide nutrition to women with hyperemesis gravidarum. Future prospective studies, including randomized controlled trials, need to be completed to strengthen the evidence for the use of enteral and parenteral nutrition in patients with hyperemesis gravidarum. For example, a study that randomizes hyperemesis gravidarum patients into a group for parenteral nutrition, a group for enteral nutrition, and a group with no nutrition support would allow the two methods to be compared to each other, as well as each compared to no nutrition support. Outcomes to be measured should include complications, weight gain, maternal outcomes, and infant outcomes, so that researches can determine whether the benefits of nutrition support outweigh the risks and to

determine which route is the safer and/or more effective way to provide nutrition support during hyperemesis gravidarum.

Because of the challenges with studying the pregnant population, it is difficult to complete randomized, controlled studies. For example, there are ethical limitations of giving pregnant women certain treatments, as the effects on the fetus are unknown. Pregnant women also may not consent to being part of a study. In addition, there are a limited number of pregnant women with hyperemesis gravidarum at specific medical sites. At this point there is some initial evidence for positive pregnancy outcomes with the use of nutrition support, both for enteral and parenteral nutrition in women with hyperemesis gravidarum. The known benefits and risks should be communicated with the health care team and patient when deciding on which method to provide nutrition is best for the patient.

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Evidence Worksheet for Primary RESEARCH Article

Citation:	Stokke, Guro, et al. Hyperemesis gravidarum, nutritional treatment by nasogastric tube feeding: a 10- year retrospective cohort study. *Acta obstetricia et gynecologica Scandinavica*. 2015; (94): 359-367.
Study design:	Retrospective cohort study (10 years)
Study Class (A,B,C,D)	Study Class B
Research Quality Rating	Plus/Positive +
Purpose/Population Studied/Practice Studied	
Research purpose:	The research purpose was to compare maternal outcomes in a cohort of enterally tube-fed women with hyperemesis gravidarum and in a group of women receiving different fluid and nutritional therapies for hyperemesis. The second objective was to compare fetal outcomes between the different nutritional treatment modules.
Inclusion criteria:	Inclusion criteria were all patient files with International Classification of Diseases version 10 (ICD-10) diagnosis O21: Nausea and vomiting during pregnancy, for women discharged from the Department of Gynecology, Haukeland University Hospital in Bergen, Norway during 2002-2011. Women with severe hyperemesis gravidarum (diagnosis O21.1 Hyperemesis with metabolic disturbance), admitted at <20 weeks of gestation and with two of three criteria: dehydration, weight loss, and ketonuria/electrolyte disturbances were included in the study.
Exclusion criteria (conditions that make individual ineligible)	Any patients who did not meet the inclusion criteria were not included in the study.
Recruitment	N/A
Blinding used:	N/A
Description of study protocol	Patients with hyperemesis were treated with antiemetics, hydration, and electrolyte substitution. If food intake did not restart after rehydration within two to three days, peripheral parenteral nutrition started. Enteral nutrition was started if the woman's condition did not improve after 2-3 days of peripheral parenteral nutrition. Peripheral parenteral nutrition continued until enteral nutrition reached the goal volume. Women were encouraged to eat and drink alongside the tube and could be discharged with ongoing tube feeding when they mastered using the equipment. Hospital records were used to obtain patient characteristics.
Intervention:	The cohort was divided into three groups according to the main type of fluid/nutrition regimen given: peripheral fluid intravenously (n=273), parenteral nutrition by peripheral line (n=177) and enteral nutrition by gastroscopically placed nasojejunal tube (n=107). The last group also included nine women also getting TPN following enteral feeding.
Statistical analysis:	Correlations between the three major interventions and clinical categorical variables were done by the Pearson's chi-squared test unless any of the cells had an expected count of <5, when Fisher's exact test was used. Kruskal-Wallis tests were used for comparing continuous variables between the three interventions. If enteral nutrition was compared with the two other regimens combined as one category, the Mann-Whitney *U*-test was used. Dichotomizing total weight-gain during pregnancy as <7 or >7 kg was done in accordance with a former cohort study presenting

	weight gain <7 kg as a risk for poor pregnancy outcome. Weight changes were also stratisfied in relation to trimester of first admission. Binary logistic regression was used to estimate the impact of the nutritional regimens on the odds ratio for an SGA baby, adjusting for relevant factors from univariate analysis (parity, ethnicity, and maternal weight gain during pregnancy). Probabilities of <0.05 were considered significant.
Timing of measurements:	Gestational age was estimated from ultrasound assessment either on admission or calculated from routine second-trimester sonography screening. The woman's weight before pregnancy was self-reported on first admission and cross-checked with information from the maternity record. The women were weighed on each hospitalization admission and discharge.
Dependent variables:	Dependent variables included weight gain during hospitalization and pregnancy, birthweight, and gestational age at delivery.

Independent variables	Independent variables included number of days on peripheral nutrition, enteral nutrition, and central nutrition.
Control Variables	Control variables included age, gravity, parity, BMI before pregnancy, admission weight, weight lost at admission, gestational weeks, ethnicity, hyperemesis gravidarum in previous pregnancy, weight loss at start of treatment, weight gain to discharge, number of admissions, and number of days in hospital.
Initial n	557 women met the inclusion criteria. Fluids were given intravenously to 273 women (49%) and nutritional solution by peripheral catheter was given to 177 (32%). Enteral nutrition by jejunal tube was given to 107 women (19%). Nine of these also received TPN.
Final n (attrition)	557 women completed the study.
Age	The median age of women receiving fluid intravenously, peripheral nutrition, and enteral nutrition were 27, 28, and 29 respectively.
Ethnicity (if given)	The majority of the women included in the study were Caucasian : 73% receiving fluid intravenously were Caucasian, 75% receiving parenteral nutrition were Caucasian, and 76% of the women receiving enteral nutrition were Caucasian. The remaining women were listed as "other."
Other relevant demographics:	The median number of pregnancies of women was 2. The median number of previous deliveries of women was 1. 27% of women receiving fluid intravenously had HG in a previous pregnancy, 40% of women receiving parenteral nutrition had HG in a previous pregnancy, and 56% of women receiving enteral nutrition had HG in a previous pregnancy.
Anthropometrics:	The median BMI of women receiving fluids intravenously, peripheral nutrition, and enteral nutrition was 23.6, 23.4, and 23.5 respectively. The median admission weight of women receiving fluids intravenously, peripheral nutrition, and enteral nutrition was 61 kg, 61 kg, and 60.5 kg respectively.
Location:	The study took place in Bergen, Norway.
Summary of Results:	Women treated with enteral nutrition had significantly greater weight loss on admission (median 5.0 kg) and on the start of nutrition (5.5 kg) than the other groups (4.0 kg) ($p<0.001$). Enteral nutrition was given for up to 41 days during hospitalization (median 5 days), resulting in a 0.8 kg weight gain (95% CI 0.5-1.0, $p = 0.005$). Women treated with enteral nutrition had similar weight gain during pregnancy and similar incidence of preterm birth and small-for-gestational age compared with the other groups. Women with <7 kg of weight gain had a higher risk of birthweight <2500 g and small-for-gestational-age infants (odds ratio 3.68, 95% CI 1.89-7.18, $p<0.001$).
Author's Conclusions	
Author conclusion:	Compared with other fluid and nutrition regimens, enteral tube feeding for women with hyperemesis gravidarum is associated with adequate maternal weight gain and favorable pregnancy outcomes.
Reviewer comments:	*This is the largest study investigating enteral nutrition as a major part of the nutritional treatment of severe hyperemesis gravidarum. The study used 10 years worth of data and provides a valid evaluation of enteral nutrition as a treatment of severe hyperemesis gravidarum.* *The main limitation in this study was that it was a retrospective design. This study was not able to assess patient acceptability of different nutritional methods due to the retrospective design. This study is also only representative of a Norwegian population, which was 75% Caucasian. Many ethnic groups were underrepresented. In addition, smoking habits were not evaluated as a risk factor for SGA in this study. Further, because of the sequential routine proceedings adding levels of nutritional support, the three treatment groups are not mutually exclusive, so results should be interpreted cautiously.*

	Prospective studies need to be completed to evaluate the optimal time to initiate enteral nutrition, to assess the best tube placement, and assess patient acceptability of different nutrition treatments.

Table 3.2.a. Quality Criteria Checklist: Primary Research

RELEVANCE QUESTIONS					
Citation: Stokke, Guro, et al. Hyperemesis gravidarum, nutritional treatment by nasogastric tube feeding: a 10- year retrospective cohort study. *Acta obstetricia et gynecologica Scandinavica*. 2015; (94): 359-367.		YES	NO	UNCLEAR	NA
1. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	1	X			
2. Did the authors study an outcome (dependent variable) or topic that the patients / clients / population group would care about?	2	X			
3. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice?	3	X			
4. Is the intervention or procedure feasible (NA for some epidemiological studies)?	4	X			
If the answers to all of the above relevance questions are "yes", the report is eligible for designation with a plus (+) on the Evidence Quality Worksheet, depending on answers to the following validity questions.					
VALIDITY QUESTIONS					
1. Was the research question clearly stated?		YES	NO	UNCLEAR	NA
1.1 Was the specific intervention(s) or procedure (independent variable(s)) identified?	1.1	X			
1.2 Was the outcome(s) (dependent variable(s)) clearly indicated?	1.2	X			
1.3 Were the target population and setting specified?	1.3	X			
2. Was the selection of study subjects / patients free from bias?		YES	NO	UNCLEAR	NA
2.1 Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	2.1	X			
2.2 Were criteria applied equally to all study groups?	2.2	X			
2.3 Were health, demographics, and other characteristics of subjects described?	2.3	X			
2.4 Were the subjects /patients in a representative sample of the relevant population?	2.4	X			
3, Were study groups comparable?		YES	NO	UNCLEAR	NA
3.1 Was the method of assigning subjects / patients to groups described and unbiased? (Method of randomization identified if RCT)	3.1	X			

3.2 Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	3.2	X			
3.3 Were concurrent controls used? (Concurrent preferred over historical controls.)	3.3				X
3.4 If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	3.4	X			
3.5 If case control study, were potential confounding factors comparable for cases and controls? If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.	3.5				X
3.6 If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g. "gold standard")?	3.6				X
4. Was method of handling <u>withdrawals</u> described?		**YES**	**NO**	**UNCLEAR**	**NA**
4.1 Were follow up methods described and the same for all groups?	4.1				X
4.2 Was the number, characteristics of withdrawals (i.e. dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80 %.)	4.2				X
4.3 Were all enrolled subjects/patients (in the original sample) accounted for?	4.3	X			
		YES	**NO**	**UNCLEAR**	**NA**
4.4 Were reasons for withdrawals similar across groups?	4.4				X
4.5 If diagnostic test, was decision to perform reference test not dependent on results of test under study?	4.5				X
5. **Was <u>blinding</u> used to prevent introduction of bias?**		**YES**	**NO**	**UNCLEAR**	**NA**
5.1 In intervention study, were subjects, clinicians / practitioners and investigators blinded to treatment group, **<u>as appropriate</u>**?	5.1				X
5.2 Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	5.2				X
5.3 In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	5.3	X			
5.4 In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	5.4				X

5.5 In diagnostic study, were test results blinded to patient history and other test results?	5.5					X
6. Were intervention / therapeutic regimens / exposure factor or procedure and any comparison(s) described in detail? Were intervening factors described?		YES	NO	UNCLEAR		NA
6.1 In RCT or other intervention trial, were protocols described for all regimens studied?	6.1					X
6.2 In observational study, were interventions, study settings, and clinicians / provider described?	6.2	X				
6.3 Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	6.3	X				
6.4 Was the amount of exposure and, if relevant, subject / patient compliance measured?	6.4		X			
6.5 Were co-interventions (e.g., ancillary treatments other therapies) described?	6.5	YES X	NO	UNCLEAR		NA
6.6 Were extra or unplanned treatments described?	6.6		X			
6.7 Was the information for 6.4, 6.5, 6.6 and 6.7 assessed the same way for all groups?	6.7	X				
6.8 In diagnostic study, were details of test administration and replication sufficient?	6.8					X
7. Were outcomes clearly defined and the measurements valid and reliable?		YES	NO	UNCLEAR		NA
7.1 Were primary and secondary endpoints described and relevant to the question?	7.1	X				
7.2 Were nutrition measures appropriate to question and outcomes of concern?	7.2	X				
7.3 Was the period of follow-up long enough for important outcome(s) to occur?	7.3	X				
7.4 Were the observations and measurements based on standard, valid, and reliable data collection instruments / tests / procedures?	7.4	X				
7.5 Was the measurement of effect at an appropriate level of precision?	7.5	X				
7.6 Were other factors accounted for (measured) that could affect outcomes?	7.6	X				
7.7 Were the measurements conducted consistently across groups?	7.7	X				
8. Was the statistical analysis appropriate for the study design and type of outcome indicators?		YES	NO	UNCLEAR		NA
8.1 Were statistical analyses adequately described and the results reported appropriately?	8.1	X				
8.2 Were correct statistical tests used and assumptions of test not violated?	8.2	X				
8.3 Were statistics reported with levels of significance and/or confidence intervals?	8.3	X				

8.4 Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	8.4				X
		YES	NO	UNCLEAR	NA
8.5 Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g. multivariate analyses)?	8.5	X			
8.6 Was clinical significance as well as statistical significance reported?	8.6	X			
8.7 If negative findings, was a power calculation reported to address type 2 error?	8.7				X
9. **Are <u>conclusions</u> supported by results with biases and limitations taken into consideration?**	**YES**	YES	NO	UNCLEAR	NA
9.1 Is there a discussion of findings?	9.1	X			
9.2 Are biases and study limitations identified and discussed?	9.2	X			
10. Is bias due to study's <u>funding or sponsorship</u> unlikely?	**YES**	YES X	NO	UNCLEAR	NA
10.1 Were sources of funding and investigators' affiliations described?	10.1	X			
10.2 Was there no apparent conflict of interest?	10.2	X			

SYMBOL

MINUS/NEGATIVE (-)
If most (six or ore) of the answers to the above validity questions are "no," the report should be designated with a minus (-) symbol on the Evidence Quality Worksheet.

NEUTRAL (ø)
*If the answers to validity criteria questions **2, 3, 6, and 7** do not indicate that the study is exceptionally strong, the report should be designated with a neutral (ø) symbol on the Evidence Quality Worksheet.*

PLUS/POSITIVE (+)
*If most of the answers to the above validity questions are "Yes" including criteria **2, 3, 6, and 7 and at least one additional "yes",(the report should be designated with a plus symbol (+) on the Evidence Quality Worksheet.***

Evidence Worksheet for Primary RESEARCH Article

Citation:	Saha, Sumona, et al. Feeding jejunostomy for the treatment of severe hyperemesis gravidarum: a case series. *Journal of Parenteral and Enteral Nutrition*. 2009; (33): 529-534.
Study design:	Case series
Study Class (A,B,C,D)	Study Class D
Research Quality Rating	Neutral ∅
Purpose/Population Studied/Practice Studied	
Research purpose:	This study assessed the feasibility and efficacy of surgically placed feeding jejunostomy (J tube) in women with hyperemesis gravidarum (HG) refractory to standard therapy.
Inclusion criteria:	The inclusion criteria included inpatients and outpatients referred for gastroenterology consultation for HG between 1998 and 2005 at Women & Infants Hospital in Providence, Rhode Island. Women were diagnosed with HG if they had persistent severe nausea and vomiting that could not be explained by other conditions and one or more of the following: weight loss of >5% of prepregnancy weight, ketonuria, multiple emergency room visits for dehydration, and/or inability to tolerate oral intake.
Exclusion criteria (conditions that make individual ineligible)	Women were excluded if they were in the third trimester of pregnancy or if they had contraindications to surgery.
Recruitment	N/A
Blinding used:	N/A
Description of study protocol	Women with hyperemesis gravidarum who did not improve with standard therapy were recommended to get a jejunostomy for enteral nutrition. Tube feeding was given at a rate to meet caloric needs calculated by the Harris-Benedict equation plus added calories for pregnancy. These women were monitored throughout the rest of their pregnancy.
Intervention:	The intervention is placing a J tube and providing enteral nutrition in women with HG.
Statistical analysis:	N/A
Timing of measurements:	Prepregnancy weight and weight at the start of the intervention were taken and the woman's weight, gestational age, and infant birth weight were measured at delivery.
Dependent variables:	Dependent variables included maternal weight change, gestational age at delivery, and infant's birth weight.

Independent variables	The independent variable was the duration of jejunostomy placement.
Control Variables	N/A
Initial n	Five patients accepted J tube placement from 1998 to 2005 at the Women & Infant's Hospital. One patient had J tube placement for two consecutive pregnancies.
Final n (attrition)	Five women completed the study, for a total of six patients studied as one patient had a J tube placed in two different pregnancies during the time period studied.
Age	Age ranged from 19 to 37.
Ethnicity (if given)	Not given
Other relevant demographics:	Gravida ranged from 1 to 11; parity ranged from 0 to 3; 4 of the patients had hyperemesis in a previous pregnancy, weeks gestations ranged from 12 to 26.
Anthropometrics:	Prepregnancy weight ranged from 112 to 190, pre-intervention weight ranged from 104 to 172, and percent weight loss ranged from 3.1 to 15.6.
Location:	The study took place in Providence, Rhode Island.
Summary of Results:	Five patients received J tube placement at the Women & Infants Hospital between 1998 and 2005. One patient had a J tube placed twice for consecutive pregnancies. Three patients had a history of HG in previous pregnancies and three had a history of fetal losses as a result of HG. The mean body weight loss from prepregnancy was 7.9% (range of 4.0% to 15.9%). The J tubes were placed between 12 and 26 weeks gestation (median of 14 weeks). Maternal weight gain was realized in 5 of 6 pregnancies. The J tubes were placed for a mean of 19 weeks (range, 8-28 weeks). Four J tubes stayed in place until delivery. All pregnancies resulted in term deliveries (range, 36-40 weeks of gestation) of healthy infants. The mean infant birth weight was 2995 grams (range, 2270-4000 grams). The only tube-related complication was tube dislodgement in two patients requiring simple replacement.
Author's Conclusions	
Author conclusion:	This case series offers evidence of the relative safety and usefulness of feeding jejunostomy in patients with HG. This study provides an example of how EN avoids the catheter-related complications associated with PN.
Reviewer comments:	*This study provided evidence for the safety and efficacy of jejunostomy feedings for women with HG.* *This study is limited in that it only examined six patients and was retrospective in nature. It also only assessed patients at one center, so the findings may not be simply generalized to women in other locations.* *Controlled studies need to be done to provide further evidence for the use of jejunostomy feedings for women with HG.*

Table 3.2.a. Quality Criteria Checklist: Primary Research

RELEVANCE QUESTIONS					
Citation: Saha, Sumona, et al. Feeding jejunostomy for the treatment of severe hyperemesis gravidarum: a case series. *Journal of Parenteral and Enteral Nutrition*. 2009; (33): 529-534.		YES	NO	UNCLEAR	NA
1. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	1	X			
2. Did the authors study an outcome (dependent variable) or topic that the patients / clients / population group would care about?	2	X			
3. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice?	3	X			
4. Is the intervention or procedure feasible (NA for some epidemiological studies)?	4	X			
If the answers to all of the above relevance questions are "yes", the report is eligible for designation with a plus (+) on the Evidence Quality Worksheet, depending on answers to the following validity questions.					
VALIDITY QUESTIONS					
3. Was the research question clearly stated?		YES	NO	UNCLEAR	NA
1.1 Was the specific intervention(s) or procedure (independent variable(s)) identified?	1.1	X			
1.2 Was the outcome(s) (dependent variable(s)) clearly indicated?	1.2	X			
1.3 Were the target population and setting specified?	1.3	X			
4. Was the selection of study subjects / patients free from bias?		YES	NO	UNCLEAR	NA
2.2 Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	2.1	X			
2.3 Were criteria applied equally to all study groups?	2.2	X			
2.4 Were health, demographics, and other characteristics of subjects described?	2.3	X			
2.4 Were the subjects /patients in a representative sample of the relevant population?	2.4	X			
3, Were study groups comparable?		YES	NO	UNCLEAR	NA
3.1 Was the method of assigning subjects / patients to groups described and unbiased? (Method of randomization identified if RCT)	3.1				X
3.2 Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	3.2				X
3.3 Were concurrent controls used? (Concurrent preferred over historical controls.)	3.3				X

3.4 If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	3.4				X
3.5 If case control study, were potential confounding factors comparable for cases and controls? If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.	3.5				X
3.6 If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g. "gold standard")?	3.6				X
8. Was method of handling <u>withdrawals</u> described?		YES	NO	UNCLEAR	NA
4.1 Were follow up methods described and the same for all groups?	4.1				X
4.3 Was the number, characteristics of withdrawals (i.e. dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80 %.)	4.2				X
4.3 Were all enrolled subjects/patients (in the original sample) accounted for?	4.3	X			
		YES	NO	UNCLEAR	NA
4.5 Were reasons for withdrawals similar across groups?	4.4				X
4.5 If diagnostic test, was decision to perform reference test not dependent on results of test under study?	4.5				X
9. **Was <u>blinding</u> used to prevent introduction of bias?**		YES	NO	UNCLEAR	NA
5.5 In intervention study, were subjects, clinicians / practitioners and investigators blinded to treatment group, **<u>as appropriate</u>**?	5.1				X
5.6 Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	5.2				X
5.7 In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	5.3				X
5.8 In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	5.4				X
5.5 In diagnostic study, were test results blinded to patient history and other test results?	5.5				X
10. Were intervention / therapeutic regimens / exposure factor or procedure and any comparison(s) described in detail? Were intervening factors described?		YES	NO	UNCLEAR	NA

6.1 In RCT or other intervention trial, were protocols described for all regimens studied?	6.1				X
6.7 In observational study, were interventions, study settings, and clinicians / provider described?	6.2	X			
6.8 Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	6.3	X			
6.9 Was the amount of exposure and, if relevant, subject / patient compliance measured?	6.4		X		
6.10Were co-interventions (e.g., ancillary treatments other therapies) described?	6.5	YES X	NO	UNCLEAR	NA
6.11Were extra or unplanned treatments described?	6.6		X		
6.7 Was the information for 6.4, 6.5, 6.6 and 6.7 assessed the same way for all groups?	6.7	X			
6.8 In diagnostic study, were details of test administration and replication sufficient?	6.8				X
11. Were outcomes clearly defined and the measurements valid and reliable?		YES	NO	UNCLEAR	NA
7.2 Were primary and secondary endpoints described and relevant to the question?	7.1	X			
7.2 Were nutrition measures appropriate to question and outcomes of concern?	7.2	X			
7.7 Was the period of follow-up long enough for important outcome(s) to occur?	7.3	X			
7.8 Were the observations and measurements based on standard, valid, and reliable data collection instruments / tests / procedures?	7.4	X			
7.9 Was the measurement of effect at an appropriate level of precision?	7.5	X			
7.10Were other factors accounted for (measured) that could affect outcomes?	7.6		X		
7.7 Were the measurements conducted consistently across groups?	7.7	X			
11. Was the statistical analysis appropriate for the study design and type of outcome indicators?		YES	NO	UNCLEAR	NA
8.6 Were statistical analyses adequately described and the results reported appropriately?	8.1				X
8.7 Were correct statistical tests used and assumptions of test not violated?	8.2				X
8.8 Were statistics reported with levels of significance and/or confidence intervals?	8.3				X
8.9 Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	8.4				X
		YES	NO	UNCLEA	NA

				R	
8.10Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g. multivariate analyses)?	8.5		X		
8.6 Was clinical significance as well as statistical significance reported?	8.6		X		
8.7 If negative findings, was a power calculation reported to address type 2 error?	8.7				X
12. **Are <u>conclusions</u> supported by results with biases and limitations taken into consideration?**	**YES**	YES	NO	UNCLEAR	NA
9.1 Is there a discussion of findings?	9.1	X			
9.2 Are biases and study limitations identified and discussed?	9.2	X			
13. Is bias due to study's <u>funding or sponsorship</u> unlikely?	**YES**	YES	NO	UNCLEAR	NA
10.1 Were sources of funding and investigators' affiliations described?	10.1	X			
10.2 Was there no apparent conflict of interest?	10.2	X			

SYMBOL

MINUS/NEGATIVE (-)
If most (six or ore) of the answers to the above validity questions are "no," the report should be designated with a minus (-) symbol on the Evidence Quality Worksheet.

NEUTRAL (ø)
*If the answers to validity criteria questions **2, 3, 6, and 7** do not indicate that the study is exceptionally strong, the report should be designated with a neutral (ø) symbol on the Evidence Quality Worksheet.*

PLUS/POSITIVE (+)
*If most of the answers to the above validity questions are "Yes" including criteria **2, 3, 6, and 7 and at least one additional "yes",(** the report should be designated with a plus symbol (+) on the Evidence Quality Worksheet.*

Evidence Worksheet for Primary RESEARCH Article

Citation:	Vaisman N, Kaidar R, Levin I, Lessing JB. Nasojejunal feeding in hyperemesis gravidarum – a preliminary study. *Clin Nutr*. 2004; (23): 53-57.
Study design:	Case Study
Study Class (A,B,C,D)	D
Research Quality Rating	Negative (-)
Purpose/Population Studied/Practice Studied	
Research purpose:	The purpose of this preliminary study was to test the feasibility and the preferability of feeding patients with hyperemesis gravidarum (HG) via an intrajejunal rather than a parenteral route to overcome vomiting of nutrients, weight loss, and malnutrition.
Inclusion criteria:	Inclusion criteria included women who were hospitalized between January 2000 and May 2002 for HG. They experienced severe vomiting (more than five vomiting episodes a day), electrolyte abnormalities (hyponatremia and hypokalemia), ketonuria, and weight loss. These symptoms failed to respond to outpatient dietary changes and antiemetic medications.
Exclusion criteria (conditions that make individual ineligible)	Patients were excluded if they did not meet the inclusion criteria.
Recruitment	N/A
Blinding used:	N/A
Description of study protocol	Eleven women with HG agreed to a nasojejunal tube for enteral feeding after their symptoms continued after treatment with intravenous fluids and antiemetics. After three to four days, patients were encouraged to eat and drink along with the tube feeding.
Intervention:	The intervention studied was the effectiveness of tube feeding through an NJ tube for women with HG.
Statistical analysis:	N/A
Timing of measurements:	Weight was taken on admission, before tube insertion, on tube removed, and on discharge.
Dependent variables:	The dependent variable was weight change.

Independent variables	The independent variable was NJ tube feeding.
Control Variables	N/A
Initial n	Eleven patients entered the study.
Final n (attrition)	Eleven patients completed the study.
Age	Age was not listed.
Ethnicity (if given)	Ethnicity was not given.
Other relevant demographics:	Patient's gestation ranged from six weeks to 13 weeks.
Anthropometrics:	Weight on admission ranged from 48 kg to 85.7 kg.
Location:	The study took place at the Tel-Aviv Sourasky Medical Center in Tel-Aviv, Israel.
Summary of Results:	Mean weight loss during hospitalization before the start of enteral feeding was 2.2 ±1.1 kg (range 0.9 to 5.1 kg). Within the first 48 hours after tube insertion, there was a decrease in the amount of vomiting. Vomiting stopped entirely after a mean of 5±4 days (range of 1 to 13 days). Six patients who stayed on tube feeding for more than four days had weight gain. The tube was removed in 4 to 21 days when vomiting stopped and the woman had sufficient oral intake of at least 1000 kcal per day. For three women the tube was ejected by recurrent vomiting after 1 to 4 days, and was blocked for one woman. The tube was not replaced for these women and they did not continue vomiting. There were no other complications noted with enteral feeding in these patients.
Author's Conclusions	
Author conclusion:	The results of the study indicate that NJ enteral feeding can be an effective treatment for women with HG.
Reviewer comments:	*This study provides evidence of the effectiveness of enteral feeding as a treatment for HG.* *This study is limited in that it only assessed 11 patients at one facility. In addition, there were no control subjects.*

Table 3.2.a. Quality Criteria Checklist: Primary Research

RELEVANCE QUESTIONS					
Citation: Vaisman N, Kaidar R, Levin I, Lessing JB. Nasojejunal feeding in hyperemesis gravidarum – a preliminary study. *Clin Nutr*. 2004; (23): 53-57.		YES	NO	UNCLEAR	NA
1. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	1	X			
2. Did the authors study an outcome (dependent variable) or topic that the patients / clients / population group would care about?	2	X			
3. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice?	3	X			
4. Is the intervention or procedure feasible (NA for some epidemiological studies)?	4	X			
If the answers to all of the above relevance questions are "yes", the report is eligible for designation with a plus (+) on the Evidence Quality Worksheet, depending on answers to the following validity questions.					
VALIDITY QUESTIONS					

5. Was the research question clearly stated?		YES	NO	UNCLEAR	NA
1.1 Was the specific intervention(s) or procedure (independent variable(s)) identified?	1.1	X			
1.2 Was the outcome(s) (dependent variable(s)) clearly indicated?	1.2	X			
1.3 Were the target population and setting specified?	1.3	X			
6. Was the selection of study subjects / patients free from bias?		YES	NO	UNCLEAR	NA
2.3 Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	2.1	X			
2.4 Were criteria applied equally to all study groups?	2.2	X			
2.5 Were health, demographics, and other characteristics of subjects described?	2.3		X		
2.4 Were the subjects /patients in a representative sample of the relevant population?	2.4	X			
3, Were study groups comparable?		YES	NO	UNCLEAR	NA
3.1 Was the method of assigning subjects / patients to groups described and unbiased? (Method of randomization identified if RCT)	3.1				X
3.2 Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	3.2				X
3.3 Were concurrent controls used? (Concurrent preferred over historical controls.)	3.3				X
3.4 If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	3.4				X
3.5 If case control study, were potential confounding factors comparable for cases and controls? If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.	3.5				X
3.6 If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g. "gold standard")?	3.6				X
12. Was method of handling withdrawals described?		YES	NO	UNCLEAR	NA
4.1 Were follow up methods described and the same for all groups?	4.1				X
4.4 Was the number, characteristics of withdrawals (i.e. dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80 %.)	4.2				X

4.3 Were all enrolled subjects/patients (in the original sample) accounted for?	4.3	X			
		YES	NO	UNCLEAR	NA
4.6 Were reasons for withdrawals similar across groups?	4.4				X
4.5 If diagnostic test, was decision to perform reference test not dependent on results of test under study?	4.5				X
13. **Was <u>blinding</u> used to prevent introduction of bias?**		YES	NO	UNCLEAR	NA
5.9 In intervention study, were subjects, clinicians / practitioners and investigators blinded to treatment group, **<u>as appropriate</u>**?	5.1				X
5.10Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	5.2				X
5.11In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	5.3				X
5.12In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	5.4				X
5.5 In diagnostic study, were test results blinded to patient history and other test results?	5.5				X
14. Were intervention / therapeutic regimens / exposure factor or procedure and any comparison(s) described in detail? Were intervening factors described?		YES	NO	UNCLEAR	NA
6.1 In RCT or other intervention trial, were protocols described for all regimens studied?	6.1				X
6.12In observational study, were interventions, study settings, and clinicians / provider described?	6.2	X			
6.13Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	6.3	X			
6.14Was the amount of exposure and, if relevant, subject / patient compliance measured?	6.4	X			
6.15Were co-interventions (e.g., ancillary treatments other therapies) described?	6.5	YES X	NO	UNCLEAR	NA
6.16Were extra or unplanned treatments described?	6.6		X		
6.7 Was the information for 6.4, 6.5, 6.6 and 6.7 assessed the same way for all groups?	6.7	X			
6.8 In diagnostic study, were details of test administration and replication sufficient?	6.8				X

15. Were outcomes clearly defined and the measurements valid and reliable?		YES	NO	UNCLEAR	NA
7.3 Were primary and secondary endpoints described and relevant to the question?	7.1	X			
7.2 Were nutrition measures appropriate to question and outcomes of concern?	7.2	X			
7.11Was the period of follow-up long enough for important outcome(s) to occur?	7.3	X			
7.12Were the observations and measurements based on standard, valid, and reliable data collection instruments / tests / procedures?	7.4	X			
7.13Was the measurement of effect at an appropriate level of precision?	7.5	X			
7.14Were other factors accounted for (measured) that could affect outcomes?	7.6		X		
7.7 Were the measurements conducted consistently across groups?	7.7	X			
14. Was the statistical analysis appropriate for the study design and type of outcome indicators?		YES	NO	UNCLEAR	NA
8.11Were statistical analyses adequately described and the results reported appropriately?	8.1				X
8.12Were correct statistical tests used and assumptions of test not violated?	8.2				X
8.13Were statistics reported with levels of significance and/or confidence intervals?	8.3				X
8.14Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	8.4				X
		YES	NO	UNCLEAR	NA
8.15Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g. multivariate analyses)?	8.5		X		
8.6 Was clinical significance as well as statistical significance reported?	8.6		X		
8.7 If negative findings, was a power calculation reported to address type 2 error?	8.7				X
15. **Are conclusions supported by results with biases and limitations taken into consideration?**		YES	NO	UNCLEAR	NA
9.1 Is there a discussion of findings?	9.1	X			
9.2 Are biases and study limitations identified and discussed?	9.2		X		

16. Is bias due to study's <u>funding or sponsorship</u> unlikely?		YES	NO	UNCLEAR	NA
10.1 Were sources of funding and investigators' affiliations described?	10.1		X		
10.2 Was there no apparent conflict of interest?	10.2		X		

SYMBOL
MINUS/NEGATIVE (-) *If most (six or ore) of the answers to the above validity questions are "no," the report should be designated with a minus (-) symbol on the Evidence Quality Worksheet.*
NEUTRAL (ø) *If the answers to validity criteria questions **2, 3, 6, and 7** do not indicate that the study is exceptionally strong, the report should be designated with a neutral (ø) symbol on the Evidence Quality Worksheet.*
PLUS/POSITIVE (+) *If most of the answers to the above validity questions are "Yes" including criteria **2, 3, 6, and 7 and at least one additional "yes",(the report should be designated with a plus symbol (+) on the Evidence Quality Worksheet.*

Independent variables	The independent variable was the duration of jejunostomy placement.
Control Variables	N/A
Initial n	Five patients accepted J tube placement from 1998 to 2005 at the Women & Infant's Hospital. One patient had J tube placement for two consecutive pregnancies.
Final n (attrition)	Five women completed the study, for a total of six patients studied as one patient had a J tube placed in two different pregnancies during the time period studied.
Age	Age ranged from 19 to 37.
Ethnicity (if given)	Not given
Other relevant demographics:	Gravida ranged from 1 to 11; parity ranged from 0 to 3; 4 of the patients had hyperemesis in a previous pregnancy, weeks gestations ranged from 12 to 26.
Anthropometrics:	Prepregnancy weight ranged from 112 to 190, pre-intervention weight ranged from 104 to 172, and percent weight loss ranged from 3.1 to 15.6.
Location:	The study took place in Providence, Rhode Island.
Summary of Results:	Five patients received J tube placement at the Women & Infants Hospital between 1998 and 2005. One patient had a J tube placed twice for consecutive pregnancies. Three patients had a history of HG in previous pregnancies and three had a history of fetal losses as a result of HG. The mean body weight loss from prepregnancy was 7.9% (range of 4.0% to 15.9%). The J tubes were placed between 12 and 26 weeks gestation (median of 14 weeks). Maternal weight gain was realized in 5 of 6 pregnancies. The J tubes were placed for a mean of 19 weeks (range, 8-28 weeks). Four J tubes stayed in place until delivery. All pregnancies resulted in term deliveries (range, 36-40 weeks of gestation) of healthy infants. The mean infant birth weight was 2995 grams (range, 2270-4000 grams). The only tube-related complication was tube dislodgement in two patients requiring simple replacement.
Author's Conclusions	
Author conclusion:	This case series offers evidence of the relative safety and usefulness of feeding jejunostomy in patients with HG. This study provides an example of how EN avoids the catheter-related complications associated with PN.
Reviewer comments:	*This study provided evidence for the safety and efficacy of jejunostomy feedings for women with HG.* *This study is limited in that it only examined six patients and was retrospective in nature. It also only assessed patients at one center, so the findings may not be simply generalized to women in other locations.* *Controlled studies need to be done to provide further evidence for the use of jejunostomy feedings for women with HG.*

Table 3.2.a. Quality Criteria Checklist: Primary Research

RELEVANCE QUESTIONS					
Citation: Saha, Sumona, et al. Feeding jejunostomy for the treatment of severe hyperemesis gravidarum: a case series. *Journal of Parenteral and Enteral Nutrition*. 2009; (33): 529-534.		YES	NO	UNCLEAR	NA
1. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	1	X			
2. Did the authors study an outcome (dependent variable) or topic that the patients / clients / population group would care about?	2	X			
3. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice?	3	X			
4. Is the intervention or procedure feasible (NA for some epidemiological studies)?	4	X			
If the answers to all of the above relevance questions are "yes", the report is eligible for designation with a plus (+) on the Evidence Quality Worksheet, depending on answers to the following validity questions.					
VALIDITY QUESTIONS					
7. Was the research question clearly stated?		YES	NO	UNCLEAR	NA
1.1 Was the specific intervention(s) or procedure (independent variable(s)) identified?	1.1	X			
1.2 Was the outcome(s) (dependent variable(s)) clearly indicated?	1.2	X			
1.3 Were the target population and setting specified?	1.3	X			
8. Was the selection of study subjects / patients free from bias?		YES	NO	UNCLEAR	NA
2.4 Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	2.1	X			
2.5 Were criteria applied equally to all study groups?	2.2	X			
2.6 Were health, demographics, and other characteristics of subjects described?	2.3	X			
2.4 Were the subjects /patients in a representative sample of the relevant population?	2.4	X			
3, Were study groups comparable?		YES	NO	UNCLEAR	NA
3.1 Was the method of assigning subjects / patients to groups described and unbiased? (Method of randomization identified if RCT)	3.1				X
3.2 Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	3.2				X
3.3 Were concurrent controls used? (Concurrent preferred over historical controls.)	3.3				X

3.4 If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	3.4				X
3.5 If case control study, were potential confounding factors comparable for cases and controls? If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.	3.5				X
3.6 If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g. "gold standard")?	3.6				X
16. Was method of handling withdrawals described?		YES	NO	UNCLEAR	NA
4.1 Were follow up methods described and the same for all groups?	4.1				X
4.5 Was the number, characteristics of withdrawals (i.e. dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80 %.)	4.2				X
4.3 Were all enrolled subjects/patients (in the original sample) accounted for?	4.3	X			
		YES	NO	UNCLEAR	NA
4.7 Were reasons for withdrawals similar across groups?	4.4				X
4.5 If diagnostic test, was decision to perform reference test not dependent on results of test under study?	4.5				X
17. **Was blinding used to prevent introduction of bias?**		YES	NO	UNCLEAR	NA
5.13In intervention study, were subjects, clinicians / practitioners and investigators blinded to treatment group, **as appropriate**?	5.1				X
5.14Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	5.2				X
5.15In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	5.3				X
5.16In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	5.4				X
5.5 In diagnostic study, were test results blinded to patient history and other test results?	5.5				X
18. Were intervention / therapeutic regimens / exposure factor or procedure and any comparison(s) described in detail? Were intervening factors described?		YES	NO	UNCLEAR	NA

6.1 In RCT or other intervention trial, were protocols described for all regimens studied?	6.1				X
6.17In observational study, were interventions, study settings, and clinicians / provider described?	6.2	X			
6.18Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	6.3	X			
6.19Was the amount of exposure and, if relevant, subject / patient compliance measured?	6.4		X		
6.20Were co-interventions (e.g., ancillary treatments other therapies) described?	6.5	YES X	NO	UNCLEAR	NA
6.21Were extra or unplanned treatments described?	6.6		X		
6.7 Was the information for 6.4, 6.5, 6.6 and 6.7 assessed the same way for all groups?	6.7	X			
6.8 In diagnostic study, were details of test administration and replication sufficient?	6.8				X
19. Were outcomes clearly defined and the measurements valid and reliable?		YES	NO	UNCLEAR	NA
7.4 Were primary and secondary endpoints described and relevant to the question?	7.1	X			
7.2 Were nutrition measures appropriate to question and outcomes of concern?	7.2	X			
7.15Was the period of follow-up long enough for important outcome(s) to occur?	7.3	X			
7.16Were the observations and measurements based on standard, valid, and reliable data collection instruments / tests / procedures?	7.4	X			
7.17Was the measurement of effect at an appropriate level of precision?	7.5	X			
7.18Were other factors accounted for (measured) that could affect outcomes?	7.6		X		
7.7 Were the measurements conducted consistently across groups?	7.7	X			
17. Was the statistical analysis appropriate for the study design and type of outcome indicators?		YES	NO	UNCLEAR	NA
8.16Were statistical analyses adequately described and the results reported appropriately?	8.1				X
8.17Were correct statistical tests used and assumptions of test not violated?	8.2				X
8.18Were statistics reported with levels of significance and/or confidence intervals?	8.3				X
8.19Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	8.4				X
		YES	NO	UNCLEA	NA

				R	
8.20Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g. multivariate analyses)?	8.5		X		
8.6 Was clinical significance as well as statistical significance reported?	8.6		X		
8.7 If negative findings, was a power calculation reported to address type 2 error?	8.7				X
18. **Are <u>conclusions</u> supported by results with biases and limitations taken into consideration?**	**YES**	YES	NO	UNCLEAR	NA
9.1 Is there a discussion of findings?	9.1	X			
9.2 Are biases and study limitations identified and discussed?	9.2	X			
19. Is bias due to study's <u>funding or sponsorship</u> unlikely?	**YES**	YES	NO	UNCLEAR	NA
10.1 Were sources of funding and investigators' affiliations described?	10.1	X			
10.2 Was there no apparent conflict of interest?	10.2	X			

SYMBOL

MINUS/NEGATIVE (-)
If most (six or ore) of the answers to the above validity questions are "no," the report should be designated with a minus (-) symbol on the Evidence Quality Worksheet.

NEUTRAL (ø)
*If the answers to validity criteria questions **2, 3, 6, and 7** do not indicate that the study is exceptionally strong, the report should be designated with a neutral (ø) symbol on the Evidence Quality Worksheet.*

PLUS/POSITIVE (+)
*If most of the answers to the above validity questions are "Yes" including criteria **2, 3, 6, and 7 and at least one additional "yes",(the report should be designated with a plus symbol (+) on the Evidence Quality Worksheet.***

Evidence Worksheet for Primary RESEARCH Article

Citation:	Pearce, C. B., et al. Enteral nutrition by nasojejunal tube in hyperemesis gravidarum. *Clinical Nutrition*. 2001; (20): 461-464.
Study design:	Case study
Study Class (A,B,C,D)	D
Research Quality Rating	Neutral (∅)
Purpose/Population Studied/Practice Studied	
Research purpose:	The purpose of this study was to evaluate enteral nutrition in patients with hyperemesis gravidarum (HEG).
Inclusion criteria:	Two patients with HEG were studied.
Exclusion criteria (conditions that make individual ineligible)	N/A
Recruitment	N/A
Blinding used:	N/A
Description of study protocol	Nasojejunal tubes were placed in two patients with hyperemesis for enteral feedng.
Intervention:	Effectiveness of enteral tube feeding was evaluated in two patients with HEG.
Statistical analysis:	N/A
Timing of measurements:	N/A
Dependent variables:	N/A

Independent variables	N/A
Control Variables	N/A
Initial n	Two patients
Final n (attrition)	Two patients
Age	Patient one was 31 years old and patient two was 34 years old.
Ethnicity (if given)	Ethnicity was not provided
Other relevant demographics:	No other demographics were described.
Anthropometrics:	Patient one weighted 105.7 kg on admission and patient two weighed 94.4 kg on admission.
Location:	The study took place at Queen Alexandra Hospital in Portsmouth, UK.
Summary of Results:	Both patients had severe cases of HEG and were dehydrated, malnourished, and had ketonuria. They were both provided enteral nutrition and had normal pregnancies and babies.
Author's Conclusions	
Author conclusion:	These two cases demonstrate the advantages and potential problems with nasojejunal feeding.
Reviewer comments:	*This study is one of few examining the effectiveness of enteral nutrition for patients with HEG.* *This study is limited in that it is a case study in which only two patients were assessed. Controlled studies need to be completed to gather more evidence on the use of enteral nutrition in patients with HEG.*

Table 3.2.a. Quality Criteria Checklist: Primary Research

RELEVANCE QUESTIONS					
Citation: Pearce, C. B., et al. Enteral nutrition by nasojejunal tube in hyperemesis gravidarum. *Clinical Nutrition*. 2001; (20): 461-464.		YES	NO	UNCLEAR	NA
1. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	1	X			
2. Did the authors study an outcome (dependent variable) or topic that the patients / clients / population group would care about?	2	X			
3. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice?	3	X			
4. Is the intervention or procedure feasible (NA for some epidemiological studies)?	4	X			
If the answers to all of the above relevance questions are "yes", the report is eligible for designation with a plus (+) on the Evidence Quality Worksheet, depending on answers to the following validity questions.					
VALIDITY QUESTIONS					
9. Was the <u>research question</u> clearly stated?		YES	NO	UNCLEAR	NA
1.1 Was the specific intervention(s) or procedure (independent variable(s)) identified?	1.1	X			
1.2 Was the outcome(s) (dependent variable(s)) clearly indicated?	1.2	X			

1.3 Were the target population and setting specified?	1.3	X			
10. Was the selection of study subjects / patients free from bias?		YES	NO	UNCLEAR	NA
2.5 Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	2.1				X
2.6 Were criteria applied equally to all study groups?	2.2	X			
2.7 Were health, demographics, and other characteristics of subjects described?	2.3		X		
2.4 Were the subjects /patients in a representative sample of the relevant population?	2.4	X			
3, Were study groups comparable?		YES	NO	UNCLEAR	NA
3.1 Was the method of assigning subjects / patients to groups described and unbiased? (Method of randomization identified if RCT)	3.1				X
3.2 Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	3.2				X
3.3 Were concurrent controls used? (Concurrent preferred over historical controls.)	3.3				X
3.4 If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	3.4				X
3.5 If case control study, were potential confounding factors comparable for cases and controls? If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.	3.5				X
3.6 If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g. "gold standard")?	3.6				X
20. Was method of handling withdrawals described?		YES	NO	UNCLEAR	NA
4.1 Were follow up methods described and the same for all groups?	4.1				X
4.6 Was the number, characteristics of withdrawals (i.e. dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80 %.)	4.2				X
4.3 Were all enrolled subjects/patients (in the original sample) accounted for?	4.3	X			
		YES	NO	UNCLEA	NA

				R	
4.8 Were reasons for withdrawals similar across groups?	4.4				X
4.5 If diagnostic test, was decision to perform reference test not dependent on results of test under study?	4.5				X
21. **Was <u>blinding</u> used to prevent introduction of bias?**		YES	NO	UNCLEAR	NA
5.17In intervention study, were subjects, clinicians / practitioners and investigators blinded to treatment group, **<u>as appropriate</u>**?	5.1				X
5.18Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	5.2				X
5.19In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	5.3				X
5.20In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	5.4				X
5.5 In diagnostic study, were test results blinded to patient history and other test results?	5.5				X
22. Were intervention / therapeutic regimens / exposure factor or procedure and any comparison(s) described in detail? Were intervening factors described?		YES	NO	UNCLEAR	NA
6.1 In RCT or other intervention trial, were protocols described for all regimens studied?	6.1				X
6.22In observational study, were interventions, study settings, and clinicians / provider described?	6.2	X			
6.23Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	6.3	X			
6.24Was the amount of exposure and, if relevant, subject / patient compliance measured?	6.4	X			
6.25Were co-interventions (e.g., ancillary treatments other therapies) described?	6.5	YES X	NO	UNCLEAR	NA
6.26Were extra or unplanned treatments described?	6.6	X			
6.7 Was the information for 6.4, 6.5, 6.6 and 6.7 assessed the same way for all groups?	6.7	X			
6.8 In diagnostic study, were details of test administration and replication sufficient?	6.8				X
23. Were <u>outcomes</u> clearly defined and the measurements valid and reliable?		YES	NO	UNCLEAR	NA
7.5 Were primary and secondary endpoints described and relevant to the question?	7.1	X			

7.2 Were nutrition measures appropriate to question and outcomes of concern?	7.2	X			
7.19Was the period of follow-up long enough for important outcome(s) to occur?	7.3	X			
7.20Were the observations and measurements based on standard, valid, and reliable data collection instruments / tests / procedures?	7.4	X			
7.21Was the measurement of effect at an appropriate level of precision?	7.5	X			
7.22Were other factors accounted for (measured) that could affect outcomes?	7.6		X		
7.7 Were the measurements conducted consistently across groups?	7.7	X			
20. Was the <u>statistical analysis</u> appropriate for the study design and type of outcome indicators?		**YES**	**NO**	**UNCLEAR**	**NA**
8.21Were statistical analyses adequately described and the results reported appropriately?	8.1				X
8.22Were correct statistical tests used and assumptions of test not violated?	8.2				X
8.23Were statistics reported with levels of significance and/or confidence intervals?	8.3				X
8.24Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	8.4				X
		YES	**NO**	**UNCLEAR**	**NA**
8.25Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g. multivariate analyses)?	8.5				X
8.6 Was clinical significance as well as statistical significance reported?	8.6				X
8.7 If negative findings, was a power calculation reported to address type 2 error?	8.7				X
21. **Are <u>conclusions</u> supported by results with biases and limitations taken into consideration?**	**YES**	**YES**	**NO**	**UNCLEAR**	**NA**
9.1 Is there a discussion of findings?	9.1	X			
9.2 Are biases and study limitations identified and discussed?	9.2		X		
22. Is bias due to study's <u>funding or sponsorship</u> unlikely?	**YES**	**YES**	**NO**	**UNCLEAR**	**NA**
10.1 Were sources of funding and investigators' affiliations described?	10.1	X			
10.2 Was there no apparent conflict of interest?	10.2	X			
SYMBOL					

MINUS/NEGATIVE (-) *If most (six or ore) of the answers to the above validity questions are "no," the report should be designated with a minus (-) symbol on the Evidence Quality Worksheet.*
NEUTRAL (ø) *If the answers to validity criteria questions **2, 3, 6, and 7** do not indicate that the study is exceptionally strong, the report should be designated with a neutral (ø) symbol on the Evidence Quality Worksheet.*
PLUS/POSITIVE (+) *If most of the answers to the above validity questions are "Yes" including criteria **2, 3, 6, and 7 and at least one additional "yes",(the report should be designated with a plus symbol (+) on the Evidence Quality Worksheet.*

Evidence Worksheet for Primary RESEARCH Article

Citation:	Peled Y, Melamed N, Hiersch L, Pardo J, Wiznitzer A, Yogev Y. The impact of total parenteral nutrition support on pregnancy outcome in women with hyperemesis gravidarum. *J Matern Fetal Neonatal Med*. 2014 Jul; 27 (11): 1146-1150.
Study design:	Retrospective cohort study
Study Class (A,B,C,D)	B
Research Quality Rating	NEUTRAL (ø)
Purpose/Population Studied/Practice Studied	
Research purpose:	What is the pregnancy outcome among women with hyperemesis gravidarum and is the outcome related to provision of TPN support in early pregnancy?
Inclusion criteria:	Inclusion criteria included: all pregnant women who were hospitalized with the diagnosis of hyperemesis gravidarum between 1997 and 2011. Only women with singleton pregnancies who subsequently delivered in the Rabin Medical Center in Retach Tikva, Israel at gestational age of >24 weeks were included in the analysis. A control group included women with singleton pregnancies who gave birth immediately after each of the index hyperemesis gravidarum deliveries, matched by maternal age and parity.
Exclusion criteria (conditions that make individual ineligible)	Anyone who did not meet the inclusion criteria was excluded.
Recruitment	Women hospitalized at Rabin Medical Center with hyperemesis gravidarum were included in the study. The control group included women who gave birth immediately after each of the hyperemesis deliveries.
Blinding used:	This was a retrospective study, so there was no blinding.
Description of study protocol	Pregnancy outcomes of women with hyperemesis were compared to pregnancy outcomes of a control group of women with singleton pregnancies. Pregnancy outcomes were also compared between women with hyperemesis who received TPN to those with hyperemesis who did not receive TPN. TPN was started if clinical symptoms or laboratory tests did not resolve after intravenous fluids and antiemetic drugs were given, if oral intake was not tolerated within 72 hours, or if the woman had more than 10% decrease in weight from pre-pregnancy weight.
Intervention:	This was a retrospective study, so there was no intervention done. Pregnancy outcomes of women with hyperemesis were compared to pregnancy outcomes of a control group of women with singleton pregnancies. Pregnancy outcomes were also compared between women with hyperemesis who received TPN to those with hyperemesis who did not receive TPN. These outcomes were obtained from a database.
Statistical analysis:	Student's *t*-test was used to compare continuous variables between groups and X^2 test and Fisher's exact test were used for categorical variables. Step-wise multivariate logistic regression analysis was used to adjust the association of hyperemesis with adverse pregnancy outcome for potential confounders. Differences were considered significant if the p value was less than 0.05.

Timing of measurements:	The researchers looked at data from pregnant women who were hospitalized with hyperemesis between 1997 and 2011, along with controls who gave birth during that same time period.
Dependent variables:	Dependent variables included pregnancy outcomes, which comprised of pregnancy complications (gestational diabetes, preeclampsia, and placental abruption), delivery outcomes (gestational age at delivery, labor induction, caesarean section, and meconium), perinatal outcome (birth weight, composite morbidity, 5-minute Apgar < 7, neonatal death, admission to NICU, RDS, NEC, jaundice requiring phototherapy, and hypoglycemia).

Independent variables	The independent variables were whether or not the woman had hyperemesis and also whether or not the woman with hyperemesis received TPN.
Control Variables	Multivariate logistic regression was used to adjust the association between hyperemesis gravidarum and several outcome measures for potential confounders, including maternal age, parity, chronic hypertension, diabetes, fetal sex, and a history of caesarean section.
Initial n	Overall admissions for hyperemesis were 946. Of these, 635 were delivered in the Rabin Medical Center, and of these 599 were singleton pregnancies. 1797 controls were matched by maternal age and parity to the women with hyperemesis.
Final n (attrition)	The final number of subjects in the study group with hyperemesis was 599 (122 who received TPN and 477 with no TPN). 1797 women were in the control group.
Age	Overall average maternal age of women with hyperemesis was 28.8, average age of women with hyperemesis who did not receive TPN was 28.9, and average age of women with hyperemesis who received TPN was 28.7 years old. Average age of women in the control group was 28.8 years old.
Ethnicity (if given)	Ethnicity was not given.
Other relevant demographics:	Nine hundred twenty-one (51.3%) women in the control group were nulliparous. Fifty-five (9.2%) women with hyperemesis had a previous caesarean section (42 (10%) with no TPN and 13 (7.3%) with TPN). One hundred seventy-one (9.5%) women in the control group had a previous caesarean section. Three (0.5%) women with hyperemesis had diabetes (3 (0.7%) with no TPN and zero with TPN). Twenty-three (1.3%) women in the control group had diabetes. Three (0.5%) women with hyperemesis had chronic hypertension (3 (0.7%) with no TPN and zero with TPN). Eleven (0.6%) women in the control group had chronic hypertension.
Anthropometrics:	Anthropometrics were not given.
Location:	The study took place in Petach Tikva, Israel.
Summary of Results:	122 of 599 women with HEG received TPN during the study. Women with HEG had a higher incidence of severe preeclampsia (1.3% vs 0.5%, $p = 0.04$) and a higher rate of preterm delivery at less than 37 and 34 weeks (10.9% vs 6.9%, $p<0.001$ and 4.7% vs 1.6%, $p<0.001$, respectively). The use of TPN during early pregnancy was associated with a lower rate of preterm delivery at less than 37 or 34 weeks, and a lower rate of labor induction. Neonates of mothers with HEG had lower birth weight (3074 $\pm$ 456 g vs 3248 $\pm$ 543 g, $p<0.001$), higher rate of birth weight <10% percentile (12.7% vs 6.8%, $p<0.001$), and a higher rate of neonatal morbidity (8.7% vs 3.8%, $p<0.001$). These associations persisted after adjusting for possible cofounders, and were most notable among women with HEG who did not receive TPN.
Author's Conclusions	
Author conclusion:	1. Hyperemesis in pregnancy is a risk factor for preterm delivery, fetal growth restriction, and adverse short-term neonatal outcome. 2. TPN treatment for women with HEG in early pregnancy is associated with lower rate of adverse pregnancy outcome.
Reviewer comments:	*There were many strengths of the study, including that it was a large sample size. There was a similar set of criteria used to define hyperemesis gravidarum, as well as similar treatment protocols and criteria for TPN support, as all of the patients were treated at the same medical center. Further, the researchers used many different components of neonatal outcome.* *This study has some limitations. Because this study was retrospective, data regarding possible confounders was not available. Future prospective studies are needed to provide more evidence for the effectiveness of using parenteral nutrition for the treatment of hyperemesis gravidarum.*

Table 3.2.a. Quality Criteria Checklist: Primary Research

RELEVANCE QUESTIONS					
Citation: Peled Y, Melamed N, Hiersch L, Pardo J, Wiznitzer A, Yogev Y. The impact of total parenteral nutrition support on pregnancy outcome in women with hyperemesis gravidarum. *J Matern Fetal Neonatal Med*. 2014 Jul; 27 (11): 1146-1150.		YES	NO	UNCLEAR	NA
1. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	1	X			
2. Did the authors study an outcome (dependent variable) or topic that the patients / clients / population group would care about?	2	X			
3. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice?	3	X			
4. Is the intervention or procedure feasible (NA for some epidemiological studies)?	4	X			
If the answers to all of the above relevance questions are "yes", the report is eligible for designation with a plus (+) on the Evidence Quality Worksheet, depending on answers to the following validity questions.					
VALIDITY QUESTIONS					
11. Was the research question clearly stated?		YES	NO	UNCLEAR	NA
1.1 Was the specific intervention(s) or procedure (independent variable(s)) identified?	1.1	X			
1.2 Was the outcome(s) (dependent variable(s)) clearly indicated?	1.2	X			
1.3 Were the target population and setting specified?	1.3	X			
12. Was the selection of study subjects / patients free from bias? As per answers to subquestions below, selection was free from bias, but groups were not comparable (and thus study was biased)		YES	NO	UNCLEAR	NA
2.6 Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	2.1	X			
2.7 Were criteria applied equally to all study groups?	2.2				X
2.8 Were health, demographics, and other characteristics of subjects described?	2.3	X			
2.4 Were the subjects /patients in a representative sample of the relevant population?	2.4	X			
3, Were study groups comparable?		YES	NO	UNCLEAR	NA
3.1 Was the method of assigning subjects / patients to groups described and unbiased? (Method of randomization identified if RCT) *!*	3.1				X
3.2 Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	3.2	X			

3.3 Were concurrent controls used? (Concurrent preferred over historical controls.)	3.3	X				
3.4 If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	3.4	X				
3.5 If case control study, were potential confounding factors comparable for cases and controls? If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.	3.5					X
3.6 If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g. "gold standard")?	3.6					X
24. Was method of handling <u>withdrawals</u> described?		YES	NO	UNCLEAR	NA	
4.1 Were follow up methods described and the same for all groups?	4.1					X
4.7 Was the number, characteristics of withdrawals (i.e. dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80 %.)	4.2					X
4.3 Were all enrolled subjects/patients (in the original sample) accounted for?	4.3	X				
		YES	NO	UNCLEAR	NA	
4.9 Were reasons for withdrawals similar across groups?	4.4					X
4.5 If diagnostic test, was decision to perform reference test not dependent on results of test under study?	4.5					X
25. **Was <u>blinding</u> used to prevent introduction of bias?**		YES	NO	UNCLEAR	NA	
5.21In intervention study, were subjects, clinicians / practitioners and investigators blinded to treatment group, **<u>as appropriate</u>**?	5.1					X
5.22Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	5.2					X
5.23In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	5.3	X				
5.24In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	5.4					X
5.5 In diagnostic study, were test results blinded to patient history and other test results?	5.5					X
26. Were intervention / therapeutic regimens / exposure factor or procedure and any comparison(s) described in detail? Were intervening factors described?		YES	NO	UNCLE	NA	

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6.1 In RCT or other intervention trial, were protocols described for all regimens studied?	6.1				X
6.27In observational study, were interventions, study settings, and clinicians / provider described?	6.2	X			
6.28Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	6.3	X			
6.29Was the amount of exposure and, if relevant, subject / patient compliance measured?	6.4		X		
6.30Were co-interventions (e.g., ancillary treatments other therapies) described?	6.5	YES X	NO	UNCLEAR	NA X
6.31Were extra or unplanned treatments described?	6.6	X			
6.7 Was the information for 6.4, 6.5, 6.6 and 6.7 assessed the same way for all groups?	6.7	X			
6.8 In diagnostic study, were details of test administration and replication sufficient?	6.8				X
27. Were outcomes clearly defined and the measurements valid and reliable?		YES	NO	UNCLEAR	NA
7.6 Were primary and secondary endpoints described and relevant to the question?	7.1	X			
7.2 Were nutrition measures appropriate to question and outcomes of concern?	7.2	X			
7.23Was the period of follow-up long enough for important outcome(s) to occur?	7.3	X			
7.24Were the observations and measurements based on standard, valid, and reliable data collection instruments / tests / procedures?	7.4	X			
7.25Was the measurement of effect at an appropriate level of precision?	7.5	X			
7.26Were other factors accounted for (measured) that could affect outcomes?	7.6	X			
7.7 Were the measurements conducted consistently across groups?	7.7	X			
23. Was the statistical analysis appropriate for the study design and type of outcome indicators?		YES	NO	UNCLEAR	NA
8.26Were statistical analyses adequately described and the results reported appropriately?	8.1	X			
8.27Were correct statistical tests used and assumptions of test not violated?	8.2	X			
8.28Were statistics reported with levels of significance and/or confidence intervals?	8.3	X			
8.29Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	8.4				X
		YES	NO	UNC	NA

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8.30Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g. multivariate analyses)?	8.5	X			
8.6 Was clinical significance as well as statistical significance reported?	8.6	X			
8.7 If negative findings, was a power calculation reported to address type 2 error?	8.7				X
24. **Are <u>conclusions</u> supported by results with biases and limitations taken into consideration?**		YES	NO	UNCLEAR	NA
9.1 Is there a discussion of findings?	9.1	X			
9.2 Are biases and study limitations identified and discussed?	9.2	X			
25. Is bias due to study's <u>funding or sponsorship</u> unlikely?		YES	NO	UNCLEAR	NA
10.1 Were sources of funding and investigators' affiliations described?	10.1	X			
10.2 Was there no apparent conflict of interest?	10.2	X			
SYMBOL					
MINUS/NEGATIVE (-) *If most (six or ore) of the answers to the above validity questions are "no," the report should be designated with a minus (-) symbol on the Evidence Quality Worksheet.*					
NEUTRAL (ø) *If the answers to validity criteria questions **2, 3, 6, and 7** do not indicate that the study is exceptionally strong, the report should be designated with a neutral (ø) symbol on the Evidence Quality Worksheet.*					
PLUS/POSITIVE (+) *If most of the answers to the above validity questions are "Yes" including criteria **2, 3, 6, and 7 and at least one additional "yes",(** the report should be designated with a plus symbol (+) on the Evidence Quality Worksheet.*					

Evidence Worksheet for Primary RESEARCH Article

Citation:	Christodoulou DK, Katsanos KH, Makrydimas G, Tsanadis G, Tsianos EV. Peripheral parenteral nutrition in protracted hyperemesis gravidarum-report of two cases and a literature review. *Acta Gastro-Enterologica Belgica.* 2008; (71): 259-262.
Study design:	Case study
Study Class (A,B,C,D)	D
Research Quality Rating	Neutral *(∅)*
Purpose/Population Studied/Practice Studied	
Research purpose:	Is parenteral nutrition an effective treatment for hyperemesis gravidarum (HG)?
Inclusion criteria:	The two case study patients had severe cases of HG.
Exclusion criteria	N/A
Recruitment	N/A
Blinding used:	N/A
Description of study protocol	Case 1 is of a pregnant 27-year-old female with HG at 10 weeks and 4 days gestation. She was discharged after a few days after treatment of hydration and antiemetics, but then readmitted at 14 weeks and 5 days gestation for severe exacerbation of HG with intractable vomiting, dehydration, and exhaustion. Ranitidine and peripheral parenteral nutrition were started. Case 2 is of a 33-year-old female with severe HG at 8 weeks and 3 days gestation. Treatment included discontinuation of oral intake, administration of intravenous fluids, and dimenhydrinate. She also received intravenous solutions of amino acids and glucose via a peripheral vein. At 11 weeks and 5 days gestation, a peripheral parenteral solution was started.
Intervention:	Peripheral parenteral nutrition was provided to two women with severe symptoms of HG.
Statistical analysis:	N/A
Timing of measurements:	Measurements were taken on admission. The authors did not discuss other measurements.
Dependent variables:	N/A

Independent variables	N/A
Control Variables	N/A
Initial n	2 females
Final n (attrition)	2 females were studied
Age	Case study patient 1 was 27 and case study patient 2 was 33.
Ethnicity (if given)	Ethnicity was not given
Other relevant demographics:*)*	None provided
Anthropometrics:	None provided
Location:	Department of Obstetrics and Gynecology in, Medical School, University of Ioannina, Greece.
Summary of Results:	The patient in Case 1 tolerated the treatment well and had a fast recovery. Her symptoms decreased and her condition improved dramatically in less than one day after the start of peripheral parenteral nutrition. She received parenteral nutrition for 12 days and had no significant problems for the remainder of her pregnancy. At 39 weeks gestation, she delivered a healthy female baby weighing 2860 grams. The patient in Case 2 also had a quick recovery with improvement of her symptoms and nutritional status. She received parenteral nutrition for 14 days and was discharged a few days later. She did not have any more significant problems for the remainder of her pregnancy. At 39 weeks and 4 days gestation, she delivered a healthy female baby weighing 3065 grams.
Author's Conclusions	
Author conclusion:	Treatment of severe cases of HG can be successful with a short course of a standardized, commercial regimen of peripheral parenteral nutrition.
Reviewer comments:	*This study shows that peripheral parenteral nutrition can be a safe and effective treatment in patients with severe HG.* *This case study only assessed 2 patients. More controlled studies need to be done to provide evidence for the use of nutrition support in patients with HG.*

Table 3.2.a. Quality Criteria Checklist: Primary Research

RELEVANCE QUESTIONS					
Citation: Christodoulou DK, Katsanos KH, Makrydimas G, Tsanadis G, Tsianos EV. Peripheral parenteral nutrition in protracted hyperemesis gravidarum-report of two cases and a literature review. *Acta Gastro-Enterologica Belgica.* 2008; (71): 259-262.		YES	NO	UNCLEAR	NA
1. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	1	X			
2. Did the authors study an outcome (dependent variable) or topic that the patients / clients / population group would care about?	2	X			
3. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice?	3	X			
4. Is the intervention or procedure feasible (NA for some epidemiological studies)?	4	X			
If the answers to all of the above relevance questions are "yes", the report is eligible for designation with a plus (+) on the Evidence Quality Worksheet, depending on answers to the following validity questions.					
VALIDITY QUESTIONS					
13. Was the research question clearly stated?		YES	NO	UNCLEAR	NA
1.1 Was the specific intervention(s) or procedure (independent variable(s)) identified?	1.1	X			
1.2 Was the outcome(s) (dependent variable(s)) clearly indicated?	1.2	X			
1.3 Were the target population and setting specified?	1.3	X			
14. Was the selection of study subjects / patients free from bias?		YES	NO	UNCLEAR	NA
2.7 Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	2.1				X
2.8 Were criteria applied equally to all study groups?	2.2				X
2.9 Were health, demographics, and other characteristics of subjects described?	2.3		X		
2.4 Were the subjects /patients in a representative sample of the relevant population?	2.4	X			
3, Were study groups comparable?		YES	NO	UNCLEAR	NA
3.1 Was the method of assigning subjects / patients to groups described and unbiased? (Method of randomization identified if RCT)	3.1				X
3.2 Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	3.2				X
3.3 Were concurrent controls used? (Concurrent preferred over historical controls.)	3.3				X

3.4 If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	3.4				X
3.5 If case control study, were potential confounding factors comparable for cases and controls? If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.	3.5				X
3.6 If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g. "gold standard")?	3.6				X
28. Was method of handling withdrawals described?		YES	NO	UNCLEAR	NA
4.1 Were follow up methods described and the same for all groups?	4.1				X
4.8 Was the number, characteristics of withdrawals (i.e. dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80 %.)	4.2				X
4.3 Were all enrolled subjects/patients (in the original sample) accounted for?	4.3	X			
		YES	NO	UNCLEAR	NA
4.10Were reasons for withdrawals similar across groups?	4.4				X
4.5 If diagnostic test, was decision to perform reference test not dependent on results of test under study?	4.5				X
29. **Was blinding used to prevent introduction of bias?**		YES	NO	UNCLEAR	NA
5.25In intervention study, were subjects, clinicians / practitioners and investigators blinded to treatment group, **as appropriate**?	5.1				X
5.26Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	5.2				X
5.27In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	5.3				X
5.28In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	5.4				X
5.5 In diagnostic study, were test results blinded to patient history and other test results?	5.5				X
30. Were intervention / therapeutic regimens / exposure factor or procedure and any comparison(s) described in detail? Were intervening factors described?		YES	NO	UNCLEAR	NA

6.1 In RCT or other intervention trial, were protocols described for all regimens studied?	6.1				X
6.32In observational study, were interventions, study settings, and clinicians / provider described?	6.2	X			
6.33Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	6.3	X			
6.34Was the amount of exposure and, if relevant, subject / patient compliance measured?	6.4	X			
6.35Were co-interventions (e.g., ancillary treatments other therapies) described?	6.5	YES X	NO	UNCLEAR	NA
6.36Were extra or unplanned treatments described?	6.6	X			
6.7 Was the information for 6.4, 6.5, 6.6 and 6.7 assessed the same way for all groups?	6.7	X			
6.8 In diagnostic study, were details of test administration and replication sufficient?	6.8				X
31. Were outcomes clearly defined and the measurements valid and reliable?		YES	NO	UNCLEAR	NA
7.7 Were primary and secondary endpoints described and relevant to the question?	7.1	X			
7.2 Were nutrition measures appropriate to question and outcomes of concern?	7.2	X			
7.27Was the period of follow-up long enough for important outcome(s) to occur?	7.3	X			
7.28Were the observations and measurements based on standard, valid, and reliable data collection instruments / tests / procedures?	7.4	X			
7.29Was the measurement of effect at an appropriate level of precision?	7.5	X			
7.30Were other factors accounted for (measured) that could affect outcomes?	7.6		X		
7.7 Were the measurements conducted consistently across groups?	7.7				
26. Was the statistical analysis appropriate for the study design and type of outcome indicators?		YES	NO	UNCLEAR	NA
8.31Were statistical analyses adequately described and the results reported appropriately?	8.1				X
8.32Were correct statistical tests used and assumptions of test not violated?	8.2				X
8.33Were statistics reported with levels of significance and/or confidence intervals?	8.3				X
8.34Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	8.4				X
		YES	NO	UNCLEA	NA

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8.35Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g. multivariate analyses)?	8.5				X
8.6 Was clinical significance as well as statistical significance reported?	8.6				X
8.7 If negative findings, was a power calculation reported to address type 2 error?	8.7				X
27. **Are <u>conclusions</u> supported by results with biases and limitations taken into consideration?**		YES	NO	UNCLEAR	NA
9.1 Is there a discussion of findings?	9.1	X			
9.2 Are biases and study limitations identified and discussed?	9.2		X		
28. Is bias due to study's <u>funding or sponsorship</u> unlikely?		YES	NO	UNCLEAR	NA
10.1 Were sources of funding and investigators' affiliations described?	10.1	X			
10.2 Was there no apparent conflict of interest?	10.2	X			
SYMBOL					
MINUS/NEGATIVE (-) *If most (six or ore) of the answers to the above validity questions are "no," the report should be designated with a minus (-) symbol on the Evidence Quality Worksheet.*					
NEUTRAL (ø) *If the answers to validity criteria questions **2, 3, 6, and 7** do not indicate that the study is exceptionally strong, the report should be designated with a neutral (ø) symbol on the Evidence Quality Worksheet.*					
PLUS/POSITIVE (+) *If most of the answers to the above validity questions are "Yes" including criteria **2, 3, 6, and 7 and at least one additional "yes",(** the report should be designated with a plus symbol (+) on the Evidence Quality Worksheet.*					

Evidence Worksheet for Primary RESEARCH Article

Citation:	Folk JJ, Leslie-Brown HFM, Nosovitch JT, Silverman RK, Aubry RH. Hyperemesis gravidarum: outcomes and complications with and without total parenteral nutrition. *J Reprod Med*. 2004; (49): 497-502.
Study design:	Retrospective cohort
Study Class (A,B,C,D)	B
Research Quality Rating	Neutral (∅)
Purpose/Population Studied/Practice Studied	
Research purpose:	The purpose of the study was to evaluate the obstetric and medical complications in patients with hyperemesis gravidarum, comparing those who were treated with total parenteral nutrition (TPN) and those who did not receive TPN.
Inclusion criteria:	Patients were included in the study if they were admitted to Crouse Hospital in Syracuse, New York between January 1995 and December 1998 and had a diagnosis of hyperemesis gravidarum.
Exclusion criteria (conditions that make individual ineligible)	Patients were excluded if they did not meet the inclusion criteria.
Recruitment	N/A
Blinding used:	N/A
Description of study protocol	An anonymous chart review was completed on 166 patients. The researchers gathered information on age, gravidity and parity, marital status, gestational age, number of admissions, methods of nutritional support used, serum albumin levels, serum potassium, thyroid function, pregnancy complications, and pregnancy outcomes.
Intervention:	A chart review was completed on patients with hyperemesis gravidarum, comparing those who were treated with TPN and those who did not receive TPN.
Statistical analysis:	Odds ratios were used to compare the incidence of medical and obstetric complications unrelated to TPN use between the non-TPN and TPN groups, as well as the incidence of medical complications directly related to TPN use. The odds ratios were calculated by the Cornfield method with 95% confidence limits.
Timing of measurements:	Timing of measurements was not provided.
Dependent variables:	Dependent variables were the incidence of various complications.

Independent variables	Independent variables were TPN treatment and non-TPN treatment.
Control Variables	N/A
Initial n	192 admissions were reviewed.
Final n (attrition)	166 subjects were reviewed.
Age	Age was not provided
Ethnicity (if given)	Ethnicity was not provided
Other relevant demographics:*)*	Demographics were not provided
Anthropometrics:	Anthropometrics were not provided
Location:	The study took place in Syracuse, New York
Summary of Results:	TPN was used in 27 of 166 subjects (16%). The overall occurrence of medical and obstetric complications not directly related to TPN management was similar. They noted an increase in the occurrence of complications related to TPN use for the TPN group from 41% to 67%. The incidence of multiple gestation, fetal death, thyroid dysfunction, urinary tract infection, acute renal failure, and pneumonia was elevated ($p<0.05$ for each complication) in the TPN group compared to the non-TPN group. The occurrence of line-related sepsis was elevated at 25% in patients with TPN. For complications directly related to TPN use, the odds ratio is statistically significant, showing an additional risk attributable to TPN use. 68 of 98 (69%) had a prior pregnancy complicated by loss, either a spontaneous abortion, induced abortion, or fetal death. Criteria were not followed strictly or not documented for the remaining 17 subjects who received TPN.
Author's Conclusions	
Author conclusion:	This study showed a significant increase in serious complications directly related to TPN use. The study also revealed that a history of fetal loss in a prior pregnancy might be a risk factor for hyperemesis gravidarum.
Reviewer comments:	*This study had a relatively large number of subjects with hyperemesis gravidarum managed with TPN. These subjects were compared to subjects who did not receive TPN, but were treated at the same hospital for hyperemesis gravidarum during the same time period.* *One limitation of the study is that it is retrospective. There was likely selection bias in that there were incomplete records that did not allow all patients admitted during the study period to be chosen as subjects for this study. Further, some of the subjects in the TPN group were referrals from other hospitals within the center's referral region. The kinds of obstetric or medical complications these patients had is not known.* *In addition, there did not seem to be clear selection criteria for the start of TPN. There also did not seem to be a consistent approach to additional therapy outside of intravenous fluids and antiemetics, before the start of TPN management.* *Overall, prospective, controlled studies need to be completed to determine the effectiveness and safety of using TPN to treat patients with hyperemesis gravidarum.*

Table 3.2.a. Quality Criteria Checklist: Primary Research

RELEVANCE QUESTIONS					
Citation: Folk JJ, Leslie-Brown HFM, Nosovitch JT, Silverman RK, Aubry RH. Hyperemesis gravidarum: outcomes and complications with and without total parenteral nutrition. *J Reprod Med*. 2004; (49): 497-502.		YES	NO	UNCLEAR	NA
1. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	1	X			
2. Did the authors study an outcome (dependent variable) or topic that the patients / clients / population group would care about?	2	X			
3. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice?	3	X			
4. Is the intervention or procedure feasible (NA for some epidemiological studies)?	4	X			
If the answers to all of the above relevance questions are "yes", the report is eligible for designation with a plus (+) on the Evidence Quality Worksheet, depending on answers to the following validity questions.					
VALIDITY QUESTIONS					
15. Was the research question clearly stated?		YES	NO	UNCLEAR	NA
1.1 Was the specific intervention(s) or procedure (independent variable(s)) identified?	1.1	X			
1.2 Was the outcome(s) (dependent variable(s)) clearly indicated?	1.2	X			
1.3 Were the target population and setting specified?	1.3	X			
16. Was the selection of study subjects / patients free from bias?		YES	NO	UNCLEAR	NA
2.8 Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	2.1	X			
2.9 Were criteria applied equally to all study groups?	2.2		X		
2.10Were health, demographics, and other characteristics of subjects described?	2.3		X		
2.4 Were the subjects /patients in a representative sample of the relevant population?	2.4	X			
3, Were study groups comparable?		YES	NO	UNCLEAR	NA
3.1 Was the method of assigning subjects / patients to groups described and unbiased? (Method of randomization identified if RCT)	3.1	X			
3.2 Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	3.2			X	
3.3 Were concurrent controls used? (Concurrent preferred over historical controls.)	3.3				X

3.4 If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	3.4			X	
3.5 If case control study, were potential confounding factors comparable for cases and controls? If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.	3.5				X
3.6 If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g. "gold standard")?	3.6				X
32. Was method of handling <u>withdrawals</u> described?		YES	NO	UNCLEAR	NA
4.1 Were follow up methods described and the same for all groups?	4.1				X
4.9 Was the number, characteristics of withdrawals (i.e. dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80 %.)	4.2				X
4.3 Were all enrolled subjects/patients (in the original sample) accounted for?	4.3	X			
		YES	NO	UNCLEAR	NA
4.11Were reasons for withdrawals similar across groups?	4.4				X
4.5 If diagnostic test, was decision to perform reference test not dependent on results of test under study?	4.5				X
33. **Was <u>blinding</u> used to prevent introduction of bias?**		YES	NO	UNCLEAR	NA
5.29In intervention study, were subjects, clinicians / practitioners and investigators blinded to treatment group, **<u>as appropriate</u>**?	5.1				X
5.30Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	5.2				X
5.31In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	5.3	X			
5.32In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	5.4				X
5.5 In diagnostic study, were test results blinded to patient history and other test results?	5.5				X
34. Were intervention / therapeutic regimens / exposure factor or procedure and any comparison(s) described in detail? Were intervening factors described?		YES	NO	UNCLEAR	NA

6.1 In RCT or other intervention trial, were protocols described for all regimens studied?	6.1				X
6.37In observational study, were interventions, study settings, and clinicians / provider described?	6.2	X			
6.38Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	6.3			X	
6.39Was the amount of exposure and, if relevant, subject / patient compliance measured?	6.4		X		
6.40Were co-interventions (e.g., ancillary treatments other therapies) described?	6.5	YES X	NO	UNCLEAR	NA
6.41Were extra or unplanned treatments described?	6.6		X		
6.7 Was the information for 6.4, 6.5, 6.6 and 6.7 assessed the same way for all groups?	6.7	X			
6.8 In diagnostic study, were details of test administration and replication sufficient?	6.8				X
35. Were outcomes clearly defined and the measurements valid and reliable?		YES	NO	UNCLEAR	NA
7.8 Were primary and secondary endpoints described and relevant to the question?	7.1	X			
7.2 Were nutrition measures appropriate to question and outcomes of concern?	7.2				X
7.31Was the period of follow-up long enough for important outcome(s) to occur?	7.3			X	
7.32Were the observations and measurements based on standard, valid, and reliable data collection instruments / tests / procedures?	7.4			X	
7.33Was the measurement of effect at an appropriate level of precision?	7.5			X	
7.34Were other factors accounted for (measured) that could affect outcomes?	7.6		X		
7.7 Were the measurements conducted consistently across groups?	7.7			X	
29. Was the statistical analysis appropriate for the study design and type of outcome indicators?		YES	NO	UNCLEAR	NA
8.36Were statistical analyses adequately described and the results reported appropriately?	8.1	X			
8.37Were correct statistical tests used and assumptions of test not violated?	8.2	X			
8.38Were statistics reported with levels of significance and/or confidence intervals?	8.3	X			
8.39Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	8.4				X
		YES	NO	UNCLEA	NA

				R	
8.40Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g. multivariate analyses)?	8.5				X
8.6 Was clinical significance as well as statistical significance reported?	8.6	X			
8.7 If negative findings, was a power calculation reported to address type 2 error?	8.7				X
30. **Are <u>conclusions</u> supported by results with biases and limitations taken into consideration?**		YES	NO	UNCLEAR	NA
9.1 Is there a discussion of findings?	9.1	X			
9.2 Are biases and study limitations identified and discussed?	9.2	X			
31. Is bias due to study's <u>funding or sponsorship</u> unlikely?		YES	NO	UNCLEAR	NA
10.1 Were sources of funding and investigators' affiliations described?	10.1	X			
10.2 Was there no apparent conflict of interest?	10.2	X			
SYMBOL					
MINUS/NEGATIVE (-) *If most (six or ore) of the answers to the above validity questions are "no," the report should be designated with a minus (-) symbol on the Evidence Quality Worksheet.*					
NEUTRAL (ø) *If the answers to validity criteria questions **2, 3, 6, and 7** do not indicate that the study is exceptionally strong, the report should be designated with a neutral (ø) symbol on the Evidence Quality Worksheet.*					
PLUS/POSITIVE (+) *If most of the answers to the above validity questions are "Yes" including criteria **2, 3, 6, and 7 and at least one additional "yes",(** the report should be designated with a plus symbol (+) on the Evidence Quality Worksheet.*					

Evidence Worksheet for Primary RESEARCH Article

Citation:	Ghani R. The use of total parenteral nutrition in protracted hyperemesis gravidarum. *J Obstet Gynaecol*. 2003; (23): 199-201.
Study design:	Case Study
Study Class (A,B,C,D)	D
Research Quality Rating	Neutral (∅)
Purpose/Population Studied/Practice Studied	
Research purpose:	This case study assessed whether total parenteral nutrition could be used successfully to treat a patient with protracted hyperemesis gravidarum.
Inclusion criteria:	This included one patient with hyperemesis gravidarum.
Exclusion criteria (conditions that make individual ineligible)	N/A
Recruitment	N/A
Blinding used:	N/A
Description of study protocol	A 34-year-old woman was admitted at eight weeks gestation with vomiting. Here condition did not improve, despite receiving intravenous fluids and a combination of antiemetics. TPN was started at the end of the second week. TPN continued for three weeks while her symptoms continued. At this point, her nausea and vomiting stopped. She was discharged home once she was easily tolerating diet and fluids.
Intervention:	The use of TPN was assessed in a patient with hyperemesis gravidarum.
Statistical analysis:	N/A
Timing of measurements:	Timing of measurements was not given.
Dependent variables:	Pregnancy outcome

Independent variables	TPN administration
Control Variables	N/A
Initial n	One patient was studied.
Final n (attrition)	One patient was studied.
Age	A 34-year-old woman was studied.
Ethnicity (if given)	Ethnicity was not given.
Other relevant demographics:	None given
Anthropometrics:	None provided
Location:	Department of Obstetrics and Gynecology, Blackpool Victoria Hospital, UK
Summary of Results:	TPN was given for three weeks and then nausea and vomiting stopped. The patient was discharged after she was able to eat and drink. She delivered a healthy, female baby at 38 weeks gestation.
Author's Conclusions	
Author conclusion:	In severe cases of hyperemesis gravidarum, TPN or tube feeding is needed to maintain adequate nutrition. This case showed a successful use of TPN in a patient with severe hyperemesis gravidarum.
Reviewer comments:	*This case provides some evidence for the successful use of TPN in a patient with hyperemesis gravidarum.* *This study just assessed one patient. More controlled studies need to be completed with more patients to provide a larger body of evidence for the use of nutrition support in patients with hyperemesis gravidarum.*

Table 3.2.a. Quality Criteria Checklist: Primary Research

RELEVANCE QUESTIONS					
Citation: Ghani R. The use of total parenteral nutrition in protracted hyperemesis gravidarum. *J Obstet Gynaecol*. 2003; (23): 199-201.		YES	NO	UNCLEAR	NA
1. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies)	1	X			
2. Did the authors study an outcome (dependent variable) or topic that the patients / clients / population group would care about?	2	X			
3. Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice?	3	X			
4. Is the intervention or procedure feasible (NA for some epidemiological studies)?	4	X			
If the answers to all of the above relevance questions are "yes", the report is eligible for designation with a plus (+) on the Evidence Quality Worksheet, depending on answers to the following validity questions.					
VALIDITY QUESTIONS					
17. Was the research question clearly stated?		YES	NO	UNCLEAR	NA
1.1 Was the specific intervention(s) or procedure (independent variable(s)) identified?	1.1	X			
1.2 Was the outcome(s) (dependent variable(s)) clearly indicated?	1.2	X			
1.3 Were the target population and setting specified?	1.3	X			
18. Was the selection of study subjects / patients free from bias?		YES	NO	UNCLEAR	NA
2.9 Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	2.1				X
2.10Were criteria applied equally to all study groups?	2.2				X
2.11Were health, demographics, and other characteristics of subjects described?	2.3		X		
2.4 Were the subjects /patients in a representative sample of the relevant population?	2.4	X			
3, Were study groups comparable?		YES	NO	UNCLEAR	NA
3.1 Was the method of assigning subjects / patients to groups described and unbiased? (Method of randomization identified if RCT)	3.1				X
3.2 Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	3.2				X
3.3 Were concurrent controls used? (Concurrent preferred over historical controls.)	3.3				X

3.4 If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	3.4				X
3.5 If case control study, were potential confounding factors comparable for cases and controls? If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.	3.5				X
3.6 If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g. "gold standard")?	3.6				X
36. Was method of handling withdrawals described?		YES	NO	UNCLEAR	NA
4.1 Were follow up methods described and the same for all groups?	4.1				X
4.10Was the number, characteristics of withdrawals (i.e. dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80 %.)	4.2				X
4.3 Were all enrolled subjects/patients (in the original sample) accounted for?	4.3	X			
		YES	NO	UNCLEAR	NA
4.12Were reasons for withdrawals similar across groups?	4.4				X
4.5 If diagnostic test, was decision to perform reference test not dependent on results of test under study?	4.5				X
37. **Was blinding used to prevent introduction of bias?**		YES	NO	UNCLEAR	NA
5.33In intervention study, were subjects, clinicians / practitioners and investigators blinded to treatment group, **as appropriate**?	5.1				X
5.34Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	5.2				X
5.35In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	5.3				X
5.36In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	5.4				X
5.5 In diagnostic study, were test results blinded to patient history and other test results?	5.5				X
38. Were intervention / therapeutic regimens / exposure factor or procedure and any comparison(s) described in detail? Were intervening factors described?		YES	NO	UNCLEAR	NA

6.1 In RCT or other intervention trial, were protocols described for all regimens studied?	6.1				X
6.42In observational study, were interventions, study settings, and clinicians / provider described?	6.2	X			
6.43Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	6.3	X			
6.44Was the amount of exposure and, if relevant, subject / patient compliance measured?	6.4	X			
6.45Were co-interventions (e.g., ancillary treatments other therapies) described?	6.5	YES X	NO	UNCLEAR	NA
6.46Were extra or unplanned treatments described?	6.6	X			
6.7 Was the information for 6.4, 6.5, 6.6 and 6.7 assessed the same way for all groups?	6.7				X
6.8 In diagnostic study, were details of test administration and replication sufficient?	6.8				X
39. Were <u>outcomes</u> clearly defined and the measurements valid and reliable?		YES	NO	UNCLEAR	NA
7.9 Were primary and secondary endpoints described and relevant to the question?	7.1	X			
7.2 Were nutrition measures appropriate to question and outcomes of concern?	7.2				X
7.35Was the period of follow-up long enough for important outcome(s) to occur?	7.3	X			
7.36Were the observations and measurements based on standard, valid, and reliable data collection instruments / tests / procedures?	7.4	X			
7.37Was the measurement of effect at an appropriate level of precision?	7.5	X			
7.38Were other factors accounted for (measured) that could affect outcomes?	7.6		X		
7.7 Were the measurements conducted consistently across groups?	7.7				X
32. Was the <u>statistical analysis</u> appropriate for the study design and type of outcome indicators?		YES	NO	UNCLEAR	NA
8.41Were statistical analyses adequately described and the results reported appropriately?	8.1				X
8.42Were correct statistical tests used and assumptions of test not violated?	8.2				X
8.43Were statistics reported with levels of significance and/or confidence intervals?	8.3				X
8.44Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	8.4				X
		YES	NO	UNCLEA	NA

				R	
8.45Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g. multivariate analyses)?	8.5				X
8.6 Was clinical significance as well as statistical significance reported?	8.6				X
8.7 If negative findings, was a power calculation reported to address type 2 error?	8.7				X
33. **Are <u>conclusions</u> supported by results with biases and limitations taken into consideration?**		YES	NO	UNCLEAR	NA
9.1 Is there a discussion of findings?	9.1	X			
9.2 Are biases and study limitations identified and discussed?	9.2		X		
34. Is bias due to study's <u>funding or sponsorship</u> unlikely?		YES	NO	UNCLEAR	NA
10.1 Were sources of funding and investigators' affiliations described?	10.1		X		
10.2 Was there no apparent conflict of interest?	10.2	X			
SYMBOL					
MINUS/NEGATIVE (-) *If most (six or ore) of the answers to the above validity questions are "no," the report should be designated with a minus (-) symbol on the Evidence Quality Worksheet.*					
NEUTRAL (ø) *If the answers to validity criteria questions **2, 3, 6, and 7** do not indicate that the study is exceptionally strong, the report should be designated with a neutral (ø) symbol on the Evidence Quality Worksheet.*					
PLUS/POSITIVE (+) *If most of the answers to the above validity questions are "Yes" including criteria **2, 3, 6, and 7 and at least one additional "yes",(** the report should be designated with a plus symbol (+) on the Evidence Quality Worksheet.*					

APPENDIX B: OVERVIEW TABLE

Author, Year, Study Design, Class, Rating	Study Purpose	Study Population	Intervention	Outcomes	Conclusions	Limitations
Stokke et al, 2015	The research purpose was to compare maternal outcomes in a cohort of enterally tube fed women with hyperemesis gravidarum and in a group of women receiving different fluid and nutritional therapies for hyperemesis. The second objective was to compare fetal outcomes between the different nutritional treatment modules.	557 women with hyperemesis gravidarum completed the study. The median age of women receiving fluid intravenously, peripheral nutrition, and enteral nutrition was 27, 28, and 29 respectively.	The cohort was divided into three groups according to the main type of fluid/nutrition regimen given: peripheral fluid intravenously (n=273), parenteral nutrition by peripheral line (n=177) and enteral nutrition by gastroscopically placed nasojejunal tube (n=107). The last group also included nine women also getting TPN if following enteral feeding.	Women treated with enteral nutrition had significantly greater weight loss on admission (median 5.0 kg) and prior to the start of nutrition supported (5.5 kg) than the control group (4.0 kg) ($p<0.001$). Enteral nutrition was given for up to 41 days during hospitalization (median 5 days). The resulting in an average 0.8 kg weight gain compared with no weight change in the other two treatment groups (95% CI 0.5 to 1.0, $p=0.005$).[14] Women treated with enteral nutrition had similar weight gain during pregnancy and similar incidence of preterm birth and small for gestational age compared with the other two groups. All women with <7 kg of weight gain had a higher risk of birthweight <2500 g and small for gestational age infants (odds ratio 3.68, 95% CI 1.89 to 7.18, $p<0.001$). Pregnancy outcomes were similar across groups in terms of abortion rates, twin rates,	Compared with other fluid and nutrition regimens, enteral tube feeding for women with hyperemesis gravidarum is associated with adequate maternal weight gain and favorable pregnancy outcomes.	The main limitation in this study was that it was a retrospective design. This study is also only representative of a Norwegian population, which was 75% Caucasian. Many ethnic groups were underrepresented. In addition, smoking

				preterm birth, low birthweight, and SGA infants (all p >0.05). The enteral tubes were mostly well tolerated by the women. Eight women (7%) asked to remove the tube due to discomfort. Fifty-eight women's (54%) tubes inadvertently came out due to clogging (n=4) and forceful vomiting (n=46). One of the nine women on TPN developed a pneumothorax, two had their CVC removed due to infection, and one women had to have her catheter removed because of obstruction (n=4, 44% with catheter removal).		not evaluated as a risk factor for SGA in this study. Further, because of the sequential routine proceedings adding levels of nutritional support, the three treatment groups are not mutually exclusive, so results should be interpreted cautiously.
Sumona et al, 2009 Case Study Class: D Rating: ∅	This study assessed the feasibility and efficacy of a surgically placed feeding jejunostomy (J tube) in women with hyperemesis gravidarum (HG) refractory to	Five women with hyperemesis gravidarum completed the study, for a total of six patients studied as one patient had a J tube placed in two different pregnancies	Women with hyperemesis gravidarum had J tubes placed and were provided enteral nutrition.	Six J tubes were placement at the Women & Infants Hospital between 1998 and 2005 in women with hyperemesis gravidarum. One patient had a J tube placed twice for consecutive pregnancies. The mean body weight loss from prepregnancy was 7.9% (range of 4.0% to 15.9%). The J tubes were placed between 12 and 26 weeks gestation (median of 14	Providing nutrition through a jejunostomy feeding tube is a potentially safe, effective, and well-tolerated method of nutrition support therapy in	This study is limited in that it only examined six patients and was retrospective in nature. It also only assessed patients at one center, so the findings may not be

	standard therapy.	during the time period studied. Age ranged from 19 to 37.		weeks). Maternal weight gain was realized in five of six pregnancies. The J tubes were placed for a mean of 19 weeks (range, 8>28 weeks). Four J tubes stayed in place until delivery. All pregnancies resulted in term deliveries (range, 36>40 weeks of gestation) of healthy infants. The mean infant birth weight was 2995 grams (range, 2270>4000 grams). The only tube>related complication was tube dislodgement in two patients requiring simple replacement.	women with hyperemesis gravidarum.	simply generalized to women in other locations.
Vaisman et al, 2004 Case Study Class: D Rating: >>	The purpose of this preliminary study was to test the feasibility and the preferability of feeding patients with hyperemesis gravidarum via an intrajejunal rather than a parenteral route to overcome	Eleven women with hyperemesis gravidarum completed the study.	The intervention studied was the effectiveness of tube feeding through an NJ tube for women with hyperemesis gravidarum.	Mean weight loss in the hospital was 2.2 kg, with a standard deviation of 1.1 kg. None of the patients had evidence of esophagitis, gastritis, or ulceration. Symptoms of nausea and vomiting ceased as early as 48 hours after insertion of the tube, but vomiting and retching stopped completely after 1>13 days (mean +SD, 5+4 days). The length of the NJ tube feeding for all 11 women ranged from one to 21 days. Six patients started tolerating oral intake after three to four days and the next	This study indicates that enteral feeding through a nasojejunal tube can be an effective way to provide nutrition in women with hyperemesis gravidarum.	This study is limited in that it only assessed 11 patients at one facility. In addition, there were no control subjects.

	vomiting!of! nutrients,! weight!loss,! and! malnutrition.!			started!later,!mostly!due!to! fear!of!recurring!vomiting.! Weight!loss!stopped!in!all! patients!on!tube!feeding.! ! In!three!cases,!the!tube!came! out!due!to!vomiting!after!one! to!four!days,!and!in!one!case! the!tube!was!blocked!after!18! days.!There!were!no! complications!associated!with! enteral!feeding!in!these! subjects.! !		
Pearce(et(al,(2001(! Case!Study! ! Class:!D! ! Rating:!∅!	The purpose of this study was to evaluate enteral nutrition in patients with hyperemesis gravidarum.!	Two!women! with! hyperemesis! gravidarum! were!studied,! one!woman! was!31!years! old!and!the! other!was!34! years!old.!	Effectiveness!of! enteral!tube! feeding!was! evaluated!in! two!patients! with! hyperemesis! gravidarum.!	Both!patients!had!severe! cases!of!hyperemesis! gravidarum!and!were! dehydrated,!malnourished,! and!had!ketonuria.!The!first! patient!tolerated!enteral! nutrition!well!and!her!feeding! goals!were!met!after!the!first! two!nasojejunal!tubes!had! been!dislodged.!She!delivered! a!normal,!three>kilogram! baby!boy!at!36!weeks! gestation.!The!second!patient! tolerated!enteral!feeding,!but! her!tube!became!displaced! about!one!month!after!she! was!at!home!on!enteral!feeds.! At!that!point!she!was!eating! four!times!a!day!with!little! nausea,!so!the!tube!was! removed.!She!delivered!a! four>kilogram,!normal!baby!	This!study! demonstrates! that!enteral! feeding!can! be!an! alternative!to! parenteral! feeding!to! provide! nutrition!to! women!with! hyperemesis! gravidarum.!It! is!well! tolerated,!cost! effective,!and! has!a!low!rate! of! complication.!	This!study!is! limited!in!that! it!is!a!case! study!in! which!only! two!patients! were! assessed.!

				boy!at!39!weeks.!		
Peled(et(al,(2014(! Retrospective! Cohort!Study! ! Class:!B! ! Rating:!∅!	The!purpose! of!this!study! was!to! evaluate!the! pregnancy! outcome! among! women!with! hyperemesis! gravidarum! and!the! outcome! related!to! provision!of! TPN!support! in!early! pregnancy.!	The!number! of!women! studied!with! hyperemesis! was!599.!The! control!group! included! 1797!women.!! ! Overall! average! maternal!age! of!women! with! hyperemesis! was!28.8,! average!age!of! women!with! hyperemesis! who!did!not! receive!TPN! was!28.9,!and! average!age!of! women!with! hyperemesis! who!received! TPN!was!28.7! years!old.! Average!age! of!women!in! the!control! group!was! 28.8!years! old.!	Pregnancy! outcomes!of! women!with! hyperemesis! were!compared! to!pregnancy! outcomes!of!a! control!group!of! women!with! singleton! pregnancies.! Pregnancy! outcomes!were! also!compared! between! women!with! hyperemesis! who!received! TPN!to!those! with! hyperemesis! who!did!not! receive!TPN.! These! outcomes!were! obtained!from!a! database.!	Compared!to!women!without! hyperemesis,!women!with! hyperemesis!had!a! significantly!higher!rate!of! preeclampsia!(1.3%!versus! 0.5%,!p=0.04),!preterm! delivery!at!less!than!37!and! 34!weeks!(10.9%!versus! 6.9%,!p<0.001!and!4.7%! versus!1.6%,!p<0.001,! respectively.)!Neonates!in!the! hyperemesis!group!had!a! significantly!lower!birth! weight!(3074!+!456!grams! versus!3248!+!543!grams,! p<0.001),!birth!weight! percentile!(44.8!+28.3!versus! 52.4!+!27.0,!p<0.001),!and!a! significantly!higher!rate!of! birth!weight!<10th!percentile! (12.7%!versus!6.8%,! p<0.001).!They!also!had!a! significantly!higher!rate!of! composite!neonatal!morbidity! (8.7%!versus!3.8%,!p<0.001),! NICU!admission!(7.2%!versus! 2.5%,!p<0.001),!five!minute! Apgar!score!less!than!seven! (0.7%!versus!0%,!p<0.001),! and!RDS!(2.7%!versus!1.2%,! p<0.01).! ! Provision!of!TPN!was! associated!with!a!lower!rate!	Hyperemesis! gravidarum!in! pregnancy!is! a!risk!factor! for!preterm! delivery,!fetal! growth! restriction,! and!adverse! short>term! neonatal! outcome.!TPN! treatment!for! women!with! hyperemesis! gravidarum!in! early! pregnancy!is! associated! with!lower! rate!of! adverse! pregnancy! outcome.!	Because!this! study!was! retrospective,! data! regarding! possible! confounders! was!not! available.! Future! prospective! studies!are! needed!to! provide!more! evidence!for! the! effectiveness! of!using! parenteral! nutrition!for! the!treatment! of! hyperemesis! gravidarum.!

				weeks!and!<!34!weeks!(6.2%! versus!12.8%,!p<0.02,! respectively)!and!a!lower!rate! of!labor!induction!(7.3%! versus!13%,!p=0.045)! compared!to!women!with! hyperemesis!who!did!not! receive!TPN.!Neonates!of! mothers!who!received!TPN! compared!to!those!who!did! not,!had!a!higher!birth!weight! (3145!+!487!grams!versus! 3056!+!443!grams,!p=0.03),!a! higher!birth!weight!percentile! (49.6%!+!27.1%!versus!43.6%! +!28.6%,!p=0.03),!a!lower!rate! of!birth!weight!<10th! percentile!(7.9%!versus! 14.7%,!p=0.02),!and!a!lower! rate!of!composite!morbidity! (4%!versus!10.7%,!p=0.008)! and!NICU!admission!(3.4%!		
Christodoulou(et(al,(2008(! Case!Study! ! Class:!D! ! Rating;!∅!	The!purpose! of!this!study! was!to! evaluate! whether! parenteral! nutrition!is! an!effective! treatment!for! hyperemesis! gravidarum.!	Two!women! with! hyperemesis! gravidarum! were!studied.! The!woman!in! case!one!was! 27!years!old! and!the! woman!in! case!2!was!33! years!old.!	Peripheral! parenteral! nutrition!was! provided!to!two! women!with! severe! symptoms!of! hyperemesis! gravidarum.!	The!patient!in!Case!1! tolerated!the!treatment!well! and!had!a!fast!recovery.!She! received!parenteral!nutrition! for!12!days!and!had!no! significant!problems!for!the! remainder!of!her!pregnancy.! At!39!weeks!gestation,!she! delivered!a!healthy!female! baby!weighing!2860!grams.! ! The!patient!in!Case!2!also!had! a!quick!recovery!with!	A!short! course!of!a! standardized! commercial! regimen!of! peripheral! parenteral! nutrition!can! be!a! successful! way!to! provide! nutrition!to!	This!case! study!only! assessed!two! patients.! More! controlled! studies!need! to!be!done!to! provide! evidence!for! the!use!of! nutrition! support!in!

				improvement!of!her! symptoms!and!nutritional! status.!She!received! parenteral!nutrition!for!14! days!and!was!discharged!a! few!days!later.!At!39!weeks! and!four!days!gestation,!she! delivered!a!healthy!female! baby!weighing!3065!grams.!	women!with! hyperemesis ! gravidarum.!	patients!with ! hyperemesis! gravidarum.!
Folk(et(al,(2004(! Retrospective! Cohort!Study! ! Class:!B! ! Rating:!∅!	The!purpose! of!the!study! was!to! evaluate!the! obstetric!and! medical! complications! in!patients! with! hyperemesis! gravidarum,! comparing! those!who! were!treated! with!total! parenteral! nutrition! (TPN)!and! those!who! did!not! receive!TPN.!	One!hundred! sixty>six! women!with!a! hospital! admission!for! hyperemesis! gravidarum! were! assessed.!	A!chart!review! was!completed! on!patients! with! hyperemesis! gravidarum,! comparing! those!who!were! treated!with! TPN!and!those! who!did!not! receive!TPN.!	TPN!was!used!in!27!of!166! subjects!(16%).!The!overall! occurrence!of!medical!and! obstetric!complications!not! directly!related!to!TPN! management!was!similar! between!the!two!groups.! There!was!an!increase!in!the! occurrence!of!complications! related!to!TPN!use!for!the! TPN!group!from!41%!to!67%.! This!includes!the!incidence!of! line>related!sepsis,!which!was! noticeably!elevated!at!25%.! The!incidence!of!other! potentially!life>threatening! complications,!such!as!line> related!thrombosis!and! bacterial!endocarditis!was! about!3%!each.!Compared!to! the!non>TPN!group,!the!TPN! group!had!a!higher!incidence! of!multiple!gestation!(3.1%! versus!1.5%),!fetal!death! (6.3%!versus!0%),!thyroid! dysfunction!(18.8%!versus!	This!study! showed!a! significant! increase!in! serious! complications! directly! related!to! TPN!use!in! women!with! hyperemesis! gravidarum.! In!addition,!it! revealed!that! a!history!of! fetal!loss!in!a! prior! pregnancy! might!be!a! risk!factor!for! hyperemesis! gravidarum.!	One!limitation! of!the!study!is! that!it!is! retrospective.! There!was! likely! selection!bias! in!that!there! were! incomplete! records!that! did!not!allow! all!patients! admitted! during!the! study!period! to!be!chosen! as!subjects!for! this!study.! Further,!some! of!the! subjects!in! the!TPN! group!were! referrals!from! other!

				(31.3%!versus!10.4%),!acute! renal!failure!(3.1%!versus! 0%),!and!pneumonia!(3.1%! versus!0%)!(p<0.05!for!each! complication).!For!obstetric! and!medical!complications! not!directly!related!to!TPN! use,!the!odds!ratio!for! complications!shows!no! significant!difference!between! with!groups.!With!the! addition!of!complications! directly!related!to!TPN!use,! including!line>related!sepsis,! line>related!thrombosis,!and! bacterial!endocarditis,!the! odds!ratio!becomes! statistically!significant,! showing!an!additional!risk! attributable!to!TPN!use.! ! Sixty>eight!of!98!multiparous! subjects!(69%)!had!a!prior! pregnancy!complicated!by! loss,!either!a!spontaneous! abortion,!induced!abortion,!or! fetal!death.!Criteria!were!not! followed!strictly!or!not! documented!for!the! remaining!17!subjects!who! received!TPN.!		within!the! center's! referral! region.!The! kinds!of! obstetric!or! medical! complications! these!patients! had!is!not! known.!! ! In!addition,! there!did!not! seem!to!be! clear! selection! criteria!for! the!start!of! TPN.!There! also!did!not! seem!to!be!a! consistent! approach!to! additional! therapy! outside!of! intravenous! fluids!and! antiemetics,! before!the! start!of!TPN! management.!!
Ghani(et(al,(2003(	This!case! study!	One!34>year> old!woman!	The!use!of!TPN! was!assessed!in!	TPN!was!given!for!three! weeks!and!then!nausea!and!	This!study! demonstrated!	This!study! just!assessed!

! Case!Study! ! Class:!D! ! Rating:!∅!	assessed! whether!total! parenteral! nutrition! could!be!used! successfully! to!treat!a! patient!with! protracted! hyperemesis! gravidarum.!	with! hyperemesis! gravidarum! was!assessed.!	a!patient!with! hyperemesis! gravidarum.!	vomiting!stopped.!The!patient! was!discharged!after!she!was! able!to!eat!and!drink.!She! delivered!a!healthy,!3340> gram!female!baby!at!38!weeks! gestation.!	a!successful! use!of!TPN!in! a!patient!with! severe! hyperemesis! gravidarum.!
one!patient.! More! controlled! studies!need! to!be! completed! with!more! patients!to! provide!a! larger!body!of! evidence!for! the!use!of! nutrition! support!in! patients!with! hyperemesis! gravidarum.!					