Clinical Policy: Hyperemesis Gravidarum Treatment

Reference Number: CP.MP.34 Coding Implications
Date of Last Revision: 02/22 Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Hyperemesis gravidarum is a term reserved to describe the most severe cases of nausea and vomiting in pregnancy (NVP) which results in the inability to rehydrate and replenish nutritional reserves. A diagnosis of hyperemesis gravidarum is best made based on objective findings such as moderate to large ketonuria and weight loss. Weight loss of 5% or greater is often described as diagnostic of hyperemesis gravidarum, but is not to suggest that measures to improve nausea and vomiting should not be undertaken prior to this. Hyperemesis gravidarum tends to begin earlier in pregnancy and last longer than those patients with less severe NVP.

When the step-approach algorithm does not allow for continued adequate hydration of the patient, intravenous (IV) infusion or subcutaneous (SQ) micropump infusion of ondansetron can allow for treatment until the patient can reliably take oral medications. The ability to perform activities of daily living, tolerate most food intake, and take oral medications are measures that objectively and subjectively instruct the practitioner as to the value of these therapies. When these therapies have allowed the patient to return to the above states of function, they can be discontinued. Oral therapies can be used in conjunction with IV and SQ infusion, if tolerated. There is not a place for continuous, long-term IV or SQ infusion of medications to manage hyperemesis if the patient is functioning as described above.

Policy/Criteria

I. It is the policy of health plans affiliated with Centene Corporation® that hyperemesis gravidarum treatment is **medically necessary** when meeting the following criteria:

A. IV infusion of metoclopramide or ondansetron, or SQ micropump infusion of ondansetron for the treatment of intractable hyperemesis gravidarum (must meet all):

1. Failed at least one drug in each step of the step therapy approach in Table 1 below;
2. Other potential causes of nausea and vomiting have been ruled out;
3. Clinical signs of hyperemesis gravidarum, including nausea and vomiting, have been persistent for ≥ 3 weeks;
4. Within this time there has been documented weight loss and dehydration or electrolyte abnormalities.

Infusion may be approved at 2-week intervals based on the patient's response to therapy.

1. Non-responder - If no improvement with injectable/IV antiemetics, they should be discontinued.
2. Responder - When the patient has minimal vomiting and nausea and no dehydration for five days, therapy can be discontinued.
3. Partial responder - If the patient does not meet non-responder or responder criteria, the therapy should continue. An additional 10-14 days are recommended before further reauthorization is required.

B. Home enteral therapy for maternal weight loss secondary to hyperemesis (must meet all):

1. Attempted and failed the step therapy approach listed in Table 1 below;
2. Other potential causes of nausea and vomiting have been ruled out;
3. Clinical signs of hyperemesis gravidarum, including nausea and vomiting, have been persistent for ≥ 3 weeks;
4. Within this time, there has been documented weight loss and dehydration or electrolyte abnormalities;
5. Enteral therapy is started in the hospital.

Therapy may be approved at intervals of 5 to 21 days, based on the individual member's/enrollee's needs.

Background

Hyperemesis gravidarum and nausea and vomiting of pregnancy (NVP) are self-limiting problems given appropriate time, dietary adjustments, intensive support, and counseling. Presentation is often a symptomatic issue and not an issue of dehydration. Intense nausea with small amounts of emesis needs to be differentiated from true hyperemesis and associated dehydration. Therapeutic decisions should be based on the clinical presentation and objective findings.

Step-therapy approaches that begin with monotherapy and add medicines with different mechanisms of anti-emetic action are the most effective treatment regimes. A step-therapy algorithm should result in satisfactory treatment for the majority of patients with "hypernausea" or hyperemesis gravidarum. Time, oral intake, psychotherapy, education, and intensive support should allow for the patient to eventually return to a state where the patient can again function and eat properly.

Table 1: Nausea and vomiting in pregnancy step-therapy

If there is not improvement after the first step, proceed to the next. Dosages and frequency may be adjusted based on tolerability and improvement in symptoms.

- Initial therapy, one of the following:
  - Pyridoxine (vitamin B_6) 10-25 mg by mouth (PO) every 6-8 hours;
  - Ginger 250 mg capsules four times daily;
  - Pyridoxine (vitamin B_6) 10-25 mg and doxylamine (Unisom) (**Note**: an extended-release combination product is preferred)
    - Pyridoxine 10-25 mg and doxylamine 12.5 mg PO every 6-8 hours (equivalent to Diclegis);
    - Pyridoxine 10mg and doxylamine 10mg combination product, 2 tablets at bedtime, up to 4 daily;
    - Pyridoxine 20mg and doxylamine 20mg combination product, 1 tablet at bedtime, up to 2 daily;
  - Dimenhydrinate (Dramamine) 25-50 mg PO every 4-6 hours;
  - Promethazine 12.5 – 25 mg PO, rectal suppository or IM every 4-6 hours;
  - Prochlorperazine 5 to 10 mg PO, IM or IV every 6 -8 hours, or 25 mg rectally twice daily;
  - Diphenydramine 25 to 50 mg PO or 10 to 50 mg IV every 4 to 6 hours as needed;
  - Meclizine 25 mg PO every 4 to 6 hours as needed;

  - Trimethobenzamide 200 mg every 6-8 hours, IM.
- Step 2, one of the following:
  - Metoclopramide (Reglan) 5 - 10 mg PO, intramuscularly, or IV, three times daily or four times daily;
  - Ondansetron (Zofran) 4 or 8 mg PO twice daily or three times daily. Zofran oral disintegrating tablets may be more useful;
  - Dimenhydrinate 50 mg IV (in 50 ml saline, over 20 minutes), every 4-6 hours;
  - Promethazine, 12.5-25 mg IV every 4-6 hours.

Failed outpatient management, multiple hospitalizations, electrolyte disturbances, and/or persistent weight loss might necessitate long term venous access for fluid and electrolyte replacement and possible supplemental nutrition. The overall percentage of patients with nausea and vomiting in pregnancy requiring parenteral nutrition or IV anti-emetic therapy is very small.

Complications
Hyperemesis gravidarum is an extreme form of nausea and vomiting of pregnancy occurring in approximately 0.3-3% of pregnancies.[1, 14] However, its effects are rarely the cause of fetal morbidity or mortality or of maternal mortality. It is the most common cause of hospitalization in the first half of the pregnancy.[2]

Some reported maternal complications of hyperemesis gravidarum are:
- Wernicke's encephalopathy
- Beriberi
- Central pontine myelinolysis
- Hepatic insufficiency
- Acute tubular necrosis
- Peripheral neuropathy
- Traumatic damage to the esophagus, retina, or spleen secondary to vomiting

Management
There is no single accepted method of management of NVP and hyperemesis gravidarum. Commonalities are the treatment of the nausea itself, hydration, and alteration in diet. Frequent, small meals, higher protein, lower carbohydrate meals, and meals that are higher in liquid content all have some scientific validity to lessen the problem.

Fear of medication is one of the most common reasons for under-treatment of NVP, however, common oral therapies have been shown to be safe. There is more potential for harm when there is untreated hyperemesis gravidarum that leads to hospitalization and risk for iatrogenic problems such as IV site infection than there are risks related to treatments for hyperemesis gravidarum. Untreated hyperemesis gravidarum also increases the chance that an underlying undiagnosed problem other than NVP could worsen.

There is one FDA-approved prescription drug for the treatment of NVP, Diclegis, which was approved on April 9, 2013. Diclegis is a combination of doxylamine succinate 10mg and pyridoxine hydrochloride (Vit B6) 10mg. Doxylamine and pyridoxine are both available in over-the-counter formulations. Off-label uses of many other drugs have been supported by the literature and ACOG in regard to safety.

The safety of ondansetron for NVP has been questioned and was most recently evaluated in a retrospective review of 1.8 million women enrolled in Medicaid from three months before to one month after delivery. After accounting for confounders, the risk of cardiac or congenital malformations overall was not increased with first-trimester exposure to ondansetron. However, there was a small increase (2.7 in 10,000 births) in the incidence of oral cleft. Given the small increased risk, and the apparent efficacy for treating NVP, ondansetron may be classified as an appropriate treatment option after other options have failed.

Step-therapy approaches that add medicines with different mechanisms of anti-emetic action are the most effective treatment regimes. Decisions for need for home IV hydration should be made alongside decisions for treatment of nausea and vomiting. IV hydration alone, with SQ/IV medication, or following SQ/IV medication regimes often play a necessary role. Clinicians should include measures of hydration (specific gravity, rapid weight loss, ketonuria) in their assessment of the patient's status and not rely only on the verbal reports of nausea and vomiting when considering ongoing care. When considering long term IV or SQ access for severe hyperemesis treatment, the risks must be weighed against the benefits carefully. Risks of PICC line complications in the gravid patient have been documented.

A 2007 study[4] looked at three treatment methods for ninety-four patients that were stratified into: 1) management with intravenous medication alone, 2) management with nasogastric or nasoduodenal tube, and 3) management with placement of a PICC line. The enteral and parenteral nutrition patients also had medical therapy. All patients in the IV therapy group had at least two medications. Five of the thirty-three patients with a PICC line also had TPN. Each patient was admitted for the treatment of nausea and vomiting, ketonuria, and electrolyte disturbances. The authors described the differences as "striking." The study showed that serious complications, i.e., bacteremia, sepsis, and thrombosis, were observed in the *majority* of the PICC line group. There were three fetal losses in the PICC line group, including an intrauterine demise at 20 weeks that resulted from infection of a PICC line placed at 12 weeks. There were no significant differences in neonatal outcomes in regards to fetal weight at delivery, gestational age at delivery, and Apgar scores. There were more admissions to the NICU in the PICC line group. The authors concluded that due to severe, life-threatening complications, the use of PICC lines for the management of hyperemesis is rarely indicated and, except in specific circumstances, should be avoided.

A nutritional strategy that is often underutilized is enteral feeding using pediatric nasogastric tubes. This has been used with success in patients with intractable nausea, vomiting, weight loss, and hospitalization. One study looked at seven patients who had strong gustatory and olfactory cues who used enteral feedings. In each case there was improvement within 24 hours. Six patients were discharged with continued out-patient enteral feeds. Oral liquids were tolerated by all patients within 2-5 days.[5] Another study showed that patients treated for hyperemesis gravidarum with enteral tube feeding had favorable pregnancy outcomes and appropriate maternal weight gain.[15]

In an updated practice bulletin, ACOG reports, "There is limited evidence regarding the clinical efficacy of the use of continuous subcutaneous microinfusion pumps to administer

metoclopramide or ondansetron for the treatment of nausea and vomiting of pregnancy. Moreover, adverse effects with the use of continuous subcutaneous pumps were seen in 11–31% of selected patients." [9] In addition, UpToDate does not recommend the use of a SQ pump for delivery of metoclopramide; however, Zofran via a microinfusion pump appears to be a reasonable alternative route for treating severe nausea and vomiting of pregnancy, although adverse side effects are common.[10] Both conclude that SQ microinfusion pumps of these antiemetic therapies do not appear to be cost effective when compared with conventional treatment alternatives, including periodic hospitalization. Ondansetron and metoclopramide IV are both included in the treatment algorithm for persistent symptoms.

Coding Implications

This clinical policy references Current Procedural Terminology (CPT®). CPT® is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted 2020, American Medical Association. All rights reserved. CPT codes and CPT descriptions are from the current manuals and those included herein are not intended to be all-inclusive and are included for informational purposes only. Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

CPT® Codes	Description
96360	Intravenous infusion, hydration; initial, 31 minutes to 1 hour
96361	Intravenous infusion, hydration; each additional hour (List separately in addition to code for primary procedure)

HCPCS Codes	Description
J1240	Injection, dimenhydrinate, up to 50 mg
J2405	Injection, ondansetron HCl, per 1 mg
J2765	Injection, metoclopramide HCl, up to 10 mg
S9351	Home infusion therapy, continuous or intermittent antiemetic infusion therapy; administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and visits coded separately), per diem

ICD-10-CM Diagnosis Codes that Support Coverage Criteria

ICD-10-CM Code	Description
E51.11-E51.12	Beriberi (Dry and/or wet)
E51.2	Wernicke's encephalopathy
E86.0	Dehydration
E87.8	Other disorders of electrolyte and fluid balance, not elsewhere classified
G37.2	Central pontine myelinolysis
K72.00	Acute and subacute hepatic failure without coma
N17.0	Acute kidney failure with tubular necrosis

ICD-10-CM Code	Description
O21.0	Mild hyperemesis gravidarum
O21.1	Hyperemesis gravidarum with metabolic disturbance
O21.2	Late vomiting of pregnancy
O26.821-O26.823	Pregnancy related peripheral neuritis (1st, 2nd &/or 3rd trimester)
R63.4	Abnormal weight loss
R82.4	Acetonuria (Ketonuria)

Reviews, Revisions, and Approvals	Revision Date	Approval Date
Policy developed		03/09
Added Diclegis as new FDA approved drug for hyperemesis and clarified that Doxylamine and pyridoxine are both available as OTC meds	5/13	6/13
References reviewed and updated	6/14	6/14
Moved majority of description information to background section Converted Algorithm for treatment into Table 1 Reorganized policy/criteria section into appropriate numbering bullets and reworded section. Clarified approval intervals language. Removed prognosis and differential diagnosis sections. Clarified step therapy requirements into 2 steps	6/15	6/15
Converted to new template Added promethazine, prochlorperazine, diphenhydramine and meclizine to initial step therapy per UpToDate treatment algorithm. Reviewed by specialist.	5/16	06/16
Minor wording changes to background for clarity. References reviewed and updated.	06/17	06/17
Removed SQ micropump infusion of metoclopramide from section: Description, 1.A and C.7. Revised dosage of Dimenhydrinate in table 1, initial therapy as per ACOG/UTD. Added Trimethobenzamide IM to initial therapy table 1 per ACOG. Added Dimenhydrinate IV to Step 2 in Table 1 per ACOG. Background updated with language from ACOG Practice Bulletin #189. HCPCS codes updated.	02/18	02/18
Removed step therapy approach in I.C because it is redundant. Removed: Information about symptoms, food intake, urinary ketones, urine specific gravity, and daily weights is supplied from A, B, & C as this is not specific criteria rather just medical records.	03/18	
Added pyridoxine and doxylamine dosing options for 10/10 mg tabs 2-4 times daily, and 20/20mg tabs 1-2 times daily, per ACOG. Updated background regarding ondansetron use.	01/19	02/19
Background: Under step therapy Step 1 section on pyridoxine/doxylamine, noted that an extended release pyridoxine/doxylamine combination product is preferred. Other minor	12/19	2/20

Reviews, Revisions, and Approvals	Revision Date	Approval Date
revisions to the background with no impact on criteria. References reviewed and updated. Specialist review.		
Annual review. Removed criteria for TPN and codes S9364, S9365, S9366, S9367 and S9368. References checked and updated. Replaced "member" with "members/enrollees."	01/21	02/21
Annual review. References reviewed, updated with AMA format. Updated background with no impact to criteria. Changed "Last Review Date" in the header to "Date of Last Revision" and "Date" in the revision log header to "Revision Date." Specialist reviewed.	02/22	02/22

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Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members/enrollees. This clinical policy is not intended to recommend treatment for members/enrollees. Members/enrollees should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members/enrollees and their representatives agree to be bound by such terms and conditions by providing services to members/enrollees and/or submitting claims for payment for such services.

Note: For Medicaid members/enrollees, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Note: For Medicare members/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at http://www.cms.gov for additional information.