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Pengarah Hospital Tunku Azizah
(Hospital Wanita dan Kanak-Kanak Kuala Lumpur)

YBhg Dato'/Datin/Tuan/Puan,

CONSENSUS STATEMENT ON MANAGEMENT OF HYPEREMESIS GRAVIDARUM

Adalah dengan segala hormatnya saya merujuk kepada perkara di atas.

2. *Hyperemesis gravidarum* merupakan salah satu gejala yang dialami oleh ibu-ibu hamil terutamanya di peringkat awal kehamilan. Pada kebiasaannya rawatan akan diberikan kepada pesakit yang mengalami *hyperemesis gravidarum* samada sebagai rawatan pesakit luar atau dimasukkan ke wad jika keadaan pesakit memerlukan rawatan lanjut. Namun begitu, terdapat beberapa kes kematian yang berlaku ke atas ibu hamil akibat *hyperemesis gravidarum* ini.

3. *Consensus Statement On Management Of Hyperemesis Gravidarum* telah disediakan oleh Dato' Dr Soon Ruey, Ketua Jabatan O&G Hospital Wanita Dan Kanak-Kanak Likas bersama dengan pakar-pakar O&G. Bersama-sama ini disertakan *Consensus Statement On Management Of Hyperemesis Gravidarum* untuk digunapakai oleh hospital-hospital di bawah jagaan Jabatan Kesihatan Negeri masing-masing.

Sekian, terima kasih.

"BERKHIDMAT UNTUK NEGARA"

Saya yang menjalankan amanah,

(DATUK DR. NOOR HISHAM BIN ABDULLAH)

s.k - Timbalan Ketua Pengarah Kesihatan (Perubatan)

- Timbalan Pengarah Kesihatan (Kesihatan Awam)

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CONSENSUS STATEMENT ON MANAGEMENT OF HYPEREMESIS GRAVIDARUM

1. Introduction

Nausea and vomiting in pregnancy is defined as the symptom of nausea and/or vomiting during early pregnancy where there are no other causes and hence it is a diagnosis of exclusion. Vomiting in pregnancy is a common phenomenon affecting up to 80% of pregnant women.

Hyperemesis gravidarum is the severe form of nausea and vomiting in pregnancy which affects 0.3-3.6% of pregnant women[1]. In severe cases it may result in significant morbidity and even mortality. Hyperemesis gravidarum is diagnosed when there is protracted nausea and vomiting in pregnancy associated with a triad of weight loss of more than 5% of pre pregnancy weight, dehydration and electrolyte imbalance.

Complications of hyperemesis gravidarum are as follows:

Maternal Complications[2]	Fetal complications[3]
1. Nutritional deficiencies 2. Electrolyte imbalances 3. Venous thromboembolism 4. Wernicke encephalopathy 5. Esophageal rupture or Mallory Weis tear 6. Depression and social isolation	1. Low birth weight 2. Small for gestational age

Peak incidence is around 12 weeks of pregnancy[4]; and symptoms usually resolve by 20 weeks in 90% of patients.[5]

2. Risk factors

The following factors predispose to hyperemesis gravidarum:

1. Multiple pregnancy[6,7]
2. Molar pregnancy[6]
3. Previous hyperemesis/previous molar[10]
4. Depression[6] or anxiety[8]
5. Pre pregnancy underweight[9]
6. Younger age[8]
7. Allergies eg. Asthma [8,10]
8. Gastrointestinal disorders[10]
9. Female fetus [11]
10. Higher BMI [8]

Consider the following as differential diagnosis for vomiting in pregnancy

1. Benign intracranial hypertension/raised intracranial pressure/space occupying lesion
2. Infection (appendicitis, hepatitis, urinary tract infection, enteric infections)
3. Gastroesophageal reflux disease
4. Hyperthyroidism
5. Pancreatitis
6. Addison's disease
7. Hypercalcemia/dehydration
8. Intestinal obstruction
9. Ovarian hyperstimulation syndrome/torsion of ovarian cyst
10. Eating disorders/psychological disorders

3. Assessment

History:

1. History of persistent vomiting
2. History of nausea and vomiting in previous pregnancy
3. History to exclude other causes - abdominal pain, infection, urinary symptoms, hyperthyroid symptoms
4. Ptyalism
5. Assessment of mood, mental health and impact of Quality Of Life
6. Modified Pregnancy-Unique Quantification of Emesis/Nausea (PUQE) score

Table 1: Modified PUQE score[13]

1. On average in a day, for how long do you feel nauseated or sick to your stomach?				
Not at all (1)	≤1 hour (2)	2-3 hours (3)	4-6 hours (4)	≥6 hours (5)
2. On average in a day, how many times have you vomited or thrown up?				
≥7times (5)	5-6 times (4)	3-4 times (3)	1-2 times (2)	I did not throw up (1)
3. On average in a day, how many times do you have retching or dry heaves without bringing anything up?				
None (1)	1-2 times (2)	3-4 times (3)	5-6 times (4)	≥7 times (5)

Total score (sum of replies to 1,2 and 3): mild NVP ≤6, moderate NVP 7-12, severe NVP ≥13

4. Examination

1. Weight
2. Blood pressure, pulse, temperature, respiratory rate, oxygen saturation
3. General systemic examination including fundoscopy and thyroid
4. Hydration status - look for signs of dehydration (dry mucous membrane, tachycardia, furry tongue, ketotic breath, concentrated urine, loss of skin turgor, symptoms of postural hypotension)
5. Muscle wasting, weakness
6. Abdominal palpation

5. Investigation

Biochemical[12]

1. Urinalysis
    a. To look for evidence of UTI
    b. MSU for culture and sensitivity if positive for nitrites, leucocytes or protein.
    c. For ketonuria
    d. Consider diabetes and measure a blood glucose if concurrent glycosuria and ketonuria present.
2. Full blood count (FBC)
    a. Haematocrit.
    b. White cell count
3. Urea and electrolytes (U&E)
    a. Hyponatraemia
    b. Hypokalaemia
    c. Raised serum urea/creatinine may be seen.
    d. Magnesium/Phosphate
        i. If abnormal electrolytes.

e. Calcium

i. Hypocalcaemia as a result of severe hypomagnesemia causing PTH resistance.

ii. Hypercalcaemia is a rare but potentially treatable cause of vomiting. If left untreated it can progress to severe early onset pre-eclampsia like illness with substantial maternal and neonatal morbidity and mortality.

4. Liver function tests (LFT)

a. Up to 40% have moderately increased transaminases and may resolve in time.

b. They require surveillance by performing LFTs every 2 weeks.

5. Thyroid function tests (TFT) – only if there are pre-pregnancy symptoms.

a. Biochemical hyperthyroidism

i. Clinically euthyroid with a raised free thyroxine, suppressed TSH but absence of thyroid antibodies.

ii. Resolves with improvement in hyperemesis gravidarum.

6. Serum human chorionic gonadotrophin (HCG) level

a. Baseline if molar pregnancy suspected on USS

7. Amylase

a. In suspected pancreatitis

8. Blood glucose monitoring - exclude diabetic ketoacidosis if diabetic[54]

Imaging

1. Pelvic Ultrasound (USS) to rule out multiple pregnancy / molar pregnancy

6. Management

Treatment of hyperemesis is mainly supportive as the condition itself is self-limiting.

Aims of treatment:

1. Alleviate symptoms of nausea/vomiting
2. Rehydration
3. Correction of electrolyte imbalance
4. Prevention of complications

7.Admission criteria

Hyperemesis gravidarum can be managed as outpatient or inpatient depending on severity and complications of the disease. Outpatient management with daily attendance for intravenous fluids have been introduced and managed in some hospitals.[12]

Ambulatory day care management should be used for suitable patients when primary care measures have failed and where the PUQE score is less than 13.[54]

Patients unsuitable for outpatient management

1. Abnormal urea and electrolytes
2. Loss of 5% body weight
3. Haematemesis
4. Persistent vomiting after day case hydration
5. Persistent ketonuria after day case hydration
6. Second attendance for day case hydration
7. Suspected other cause for vomiting
8. Diabetes mellitus
9. Severe hyperemesis (refer to modified PUQE score)
10. Confirmed or suspected comorbidity (such as urinary tract infection and inability to tolerate oral antibiotics).

8.Non-pharmacological management

1. Change of environment/avoidance of triggers
2. Dietary
    a. eliminate greasy/fried food/ coffee/ spicy/ very sweet food [14,15]
    b. small frequent meals throughout the day[16]
    c. high protein diet/salty/low flat/bland diet/dry toast[16,17,18,19]
    d. peppermint tea[24]
3. Supportive psychotherapy[21]
4. Acupressure applied by wrist band or finger at pericardium 6 (PC6) located 2.5 finger breaths up from the wrist crease on the inside of forearm, between the tendons of palmaris longus and flexor carpi radialis.
5. Ginger capsule at least 1-1.5g/day orally in divided doses[23]

9.Fluid therapy

Correction of dehydration and electrolyte abnormalities

1. Normal saline with additional potassium chloride with administration guided by daily monitoring of electrolytes, is the most appropriate intravenous hydration
2. Fluids required = maintenance fluids (25-30mls/kg/day) + replacement fluids (based on clinical and laboratory monitoring)

    *Consider adding potassium chloride to fluids – tailor according to potassium deficit (high doses should be used with caution in view of risks of hyperkalaemia and cardiac arrhythmias)
3. Avoid dextrose containing fluids as these can precipitate Wernicke's encephalopathy in a woman who is thiamine deficient[25]
4. Dextrose infusions are not appropriate unless the serum sodium levels are normal and thiamine has been administered[54]
5. Avoid rapid administration of normal saline as can result in too rapid a correction in sodium levels and may cause central pontine myelinolysis[26,27]

6. Fluid replacement can be tailored to ketonuria/electrolytes and discontinued once normalised and a normal diet has resumed.
7. Consider correcting for other electrolyte imbalances if present.

10. Pharmacological

1. Antiemetics
    a. Antihistamines
        i. Meclozine 25mg/Pyridoxine 50mg PO 1-2 tabs 2-3 times daily[28].
        ii. Promethazine IM/PO/IV/PR 12.5-25 mg 4-8 hourly (maximum 100 mg)[37]
    b. Dopamine antagonist
        i. Phenothiazines
            1. Prochlorperazine (PO 5-10mg 6-8 hourly; deep IM 12.5 mg 8 hourly)[38]
            2. Chlorpromazine (10-25mg 4-6 hourly PO/IV/IM or 50-100mg 6-8hourly PR)[37,38]
        ii. Metoclopramide (5-10 mg 8hourlyPO/IV/IM maximum for 5 days)[38] - Metoclopramideis safe and effective, but because of the risk of extrapyramidal effects it should be used as second-line therapy[54]
        iii. Domperidone 10 mg 8 hourly PO; 30–60 mg 8 hourly PR[54]
    c. Serotonin inhibitors / 5-HT_3 antagonist (use only if no other alternatives and benefits outweigh risks)
        i. Ondansetron (slow IV 8 mg over 15 minutes then PO 4-8 mg 6-8 hourly) can cause cardiac defect if given in early pregnancy[36]

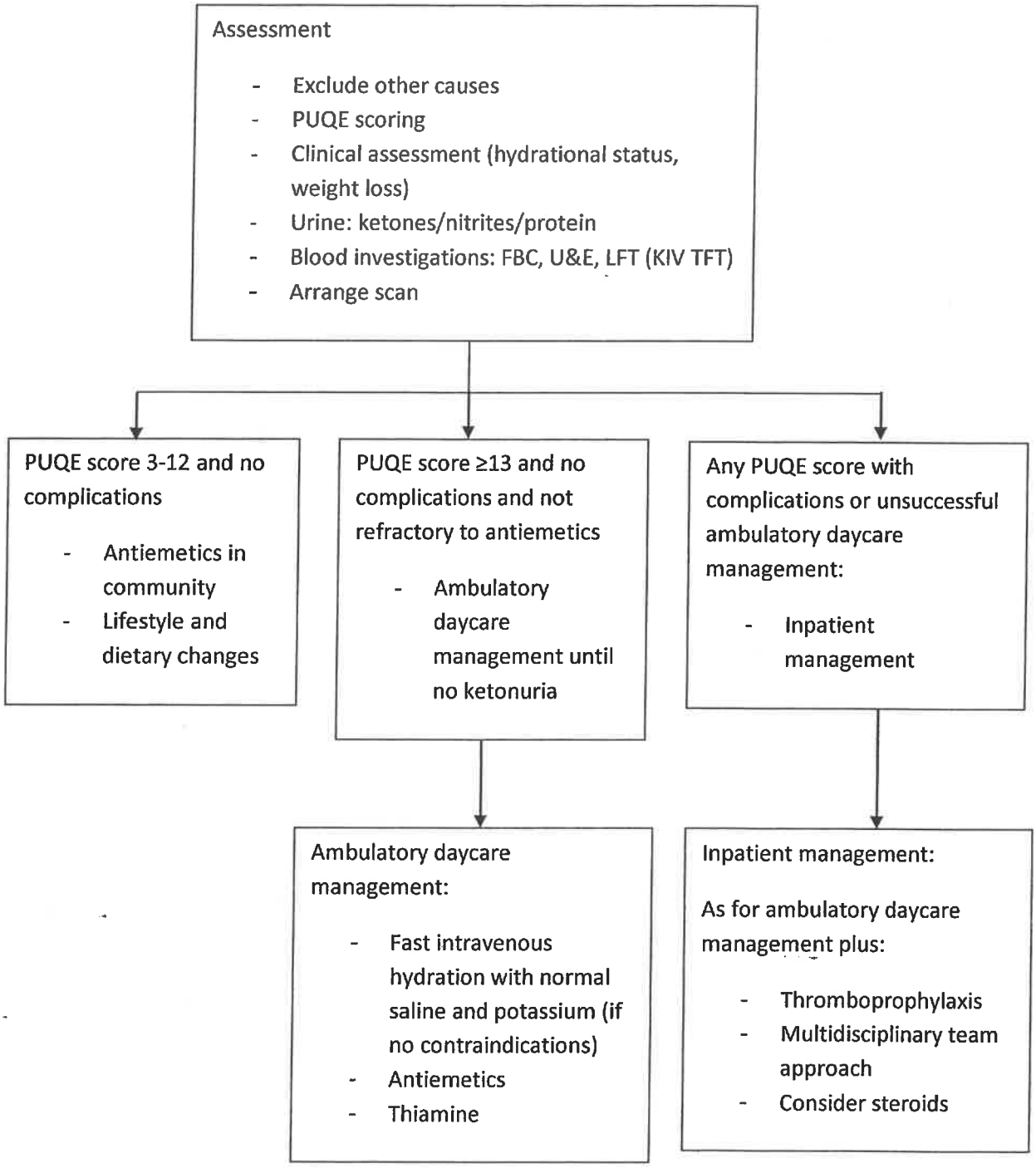
            There is evidence that ondansetron is safe and effective, but because data are limited it should be used as second-line therapy[54]
    d. Corticosteroids (reserved for refractory cases) - may cause oral cleft in fetus if given less than 10 weeks gestation[30-34]
        i. IV hydrocortisone 100mg twice daily, and once clinical improvement occurs convert to oral prednisolone 40-50mg

daily, with the dose gradually tapered until the lowest maintenance dose that controls the symptoms is reached. In most cases, continue until the gestational age at which HG would have typically resolved and in some extreme cases this occurs at delivery.

2. Vitamin supplementation
    a. Thiamine (PO 25-50mg TDS if tolerating orally) – For all women with prolonged vomiting especially before administration of dextrose or parenteral nutrition.
    b. Folic Acid (PO 5mg OD once tolerating orally as empirical supplement in pregnancy)
3. Anti-reflux medication – used for women developing gastro-oesophageal reflux disease, oesophagitis or gastritis
    a. Alginate (PO 10-20 mls TDS – maximum 80 mls/day)[45]
    b. Ranitidine (IV 50mg TDS; PO 150 mg BD)[46]
    c. Omeprazole (IV/PO 40 mg BD)[47]
4. Thromboprophylaxis
    a. VTE risk scoring as per Malaysian Ministry of Health CPG-Prevention and Treatment of Venous Thromboembolism-MOH/P/PAK/264.13(GU)
    b. TED stocking
    c. Pharmacological anticoagulants if VTE score dictates

5. Enteral/parenteral nutrition- Women who are refractory to all pharmacological and non-pharmacological treatment need to be supported with either enteral or parenteral nutrition as long as deemed necessary

Treatment algorithm[5]



11. Inpatient Care

Fluid replacement (intravenous)	Maintenance (25-30mls/kg/day) + replacement (based on clinical and laboratory monitoring)[54] *Appropriate electrolyte (potassium) replacement according to serum potassium result *Consider Insulin Sliding Scale with patient with Diabetes Mellitus
Antiemetics	**First Line:** 1-Meclozine 25mg/Pyridoxine 50mg PO 1-2 tabs 2-3 times daily 2- Prochlorperazine (PO 5-10 mg 6-8 hourly; deep IM/IV 12.5 mg 8 hourly) 3- Promethazine Deep IV/IM/PO 12.5-25 mg 4-8 hourly (maximum 100 mg) 4- Chlorpromazine (10-25mg 4-6 hourly PO/IV/IM or 50-100mg 6-8hourly PR) **Second Line:** 1- Metoclopramide 10mg IM/IV/PO TDS (maximum 5 days' duration) 2- Ondansetron 4–8 mg 6–8 hourly PO; 8 mg over 15 minutes 12 hourly IV 3- Domperidone 10 mg 8 hourly PO; 30–60 mg 8 hourly PR **Third Line(refractory cases):** 1- Steroids IV hydrocortisone 100mg twice daily, and once clinical improvement occurs convert to oral prednisolone 40-50mg daily, with the dose gradually tapered until the lowest maintenance dose that controls the symptoms is reached
Vitamins	1- Thiamine (IV 100 mg bolus in 100 mls Normal Saline then 100 mg OD for 2-3 days; PO 25-50mg TDS if tolerating orally)

	2- Folic Acid (PO 5mg OD once tolerating orally)
Gastric prophylaxis	1- Alginate (PO 10-20 mls TDS – maximum 80 mls/day) 2- Ranitidine (IV 50mg TDS; PO 150 mg BD) 3- Omeprazole (IV/PO 40 mg BD)
Thromboprophylaxis	Refer to Malaysian Ministry of Health CPG- Prevention and Treatment of Venous Thromboembolism- MOH/P/PAK/264.13(GU)
Dietary Advice	1- Stop Iron therapy (resumes once nausea settles) 2- Dietary changes: a. eliminate greasy/fried food/ coffee/ spicy/ very sweet food [14,15] b. small frequent meals throughout the day[16] c. high protein diet/salty/low flat/bland diet/dry toast[16,17,18,19] d. peppermint tea[24]
In ward assessment (daily)	1- Vomiting History (PUQE score- refer appendix) 2- Vital sign and hydration status 3- Fluid Input output chart 4- Urine ketone 5- Daily electrolytes level (renal profile) if on intravenous hydration 6- LFT if severe Hyperemesis 7- Weigh twice weekly

12. Discharge advice and follow up plan

Individualised management plan

- Advise women to continue anti-emetics where appropriate
- Advise on when to seek further medical attention if symptoms recur
- Arrange follow up appointment under Health Clinic (duration based on patient's symptoms)
- Women with severe nausea and vomiting in pregnancy or hyperemesis gravidarum who continue to have symptoms into the late second or third trimester should be offered serial growth scan.

13. Management and prevention of complications of hyperemesis gravidarum

1. **Wernicke's encephalopathy**

    a. Wernicke's encephalopathy is a potentially reversible yet serious neurological complication caused by vitamin B1 deficiency.

    b. It is precipitated by glucose containing fluids before thiamine supplementation.

    c. Mean maternal age occurrence 26.7 +/- 4.9 years old and mean gestational age of 14.3 +/- 3.4 weeks[48]

    d. The fetal loss rate is 37% (excluding termination of pregnancy)[48]

    e. Clinical presentation:

        i. Classical triad (47%)[48]

            a. Confusion

            b. Ocular abnormalities (nystagmus, ophthalmoplegia, 6th nerve palsy)

            c. Ataxia (gait, finger nose ataxia)

i. Memory loss

ii. Apathy

iii. Decreased level of consciousness

iv. Blurred vision

f. Diagnosis:

i. No specific laboratory test

ii. MRI is highly specific and comparatively safer then CT scan[49,50]

iii. Serum thiamine level not helpful

g. Treatment:

i. Thiamine IV 100 mg bolus in 100 mls Normal Saline then 100 mg OD for 2-3 days[44]

ii. Rapid clinical improvement helps confirm the diagnosis.

iii. Subsequently treat with oral thiamine 50 mg OD until normal diet intake

iv. Administration of IV thiamine should preceed total parenteral nutrition (TPN) as the dextrose load in TPN can precipitate encephalopathy.

2. Malory Weiss Tear

a. It is caused by laceration of esophageal mucosa resulting in hematemesis

b. It must be differentiated from other serious causes of hematemesis

c. Usually occurs after repeated bouts of vomiting

d. To consider endoscopic procedure if symptoms persist after vomiting subsided, significant drop in haemoglobin level and suspicion of any other sinister causes.

e. Empirical administration of anti-reflux medication

3. Venous thromboembolism

a. Obstetric embolism is the leading cause of maternal death in Malaysia[51]

b. The combination of pregnancy, immobility and dehydration confer significant risk of thrombosis in patients with hyperemesis gravidarum.

c. LMWH is the pharmacological treatment of choice[52]

d. Management as per CPG MOH Prevention and Treatment of Venous Thromboembolism

4. Termination of pregnancy

a. Women suffering from hyperemesis gravidarum have increased likelihood for termination of pregnancy[53].

b. Termination of pregnancy may be considered in women with severe hyperemesis gravidarum complicated with life threatening physical and mental conditions.

c. A multidisciplinary approach in a consultant led unit should be the goal in managing these patients.

14. Summary

1. Hyperemesis gravidarum is a potentiallylife-threatening condition with severe and disabling complications.
2. Hyperemesis gravidarum is a diagnosis of exclusion.
3. Treatment is mainly supportive, aiming to alleviate symptoms and prevent complications.
4. Adequate and appropriate fluid and electrolyte replacement is the most important component of the management.
5. It is likely that a multifactorial aetiology contributes to the difficulty in treatment of hyperemesis gravidarum.
6. The commonly used medications are generally not teratogenic.
7. Wernicke's encephalopathy can be prevented by administering thiamine.
8. Thromboprophylaxis should be given to all women admitted for hyperemesis.

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