Management of Nausea and Vomiting of Pregnancy

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Introduction

Nausea and vomiting of pregnancy (NVP) affects 70-85% of women in the first trimester. It is defined as nausea and vomiting during early pregnancy where there are no other causes (RCOG 2016). The severity of this symptom, however, varies greatly between women and can occur at all times of the day. In most cases nausea and vomiting is associated with a reduced risk of miscarriage and does not lead to increased perinatal mortality. NVP should only be diagnosed when onset is in the first trimester of pregnancy and other causes of nausea and vomiting have been excluded.

Hyperemesis Gravidarum (HG) is defined as triad of a severe protracted nausea and vomiting associated with 5% pregnancy loss, dehydration, and electrolyte imbalance.
It is diagnosed by the following triad of symptoms, on a background of protracted NVP:
- **Weight loss of more than 5%**
- **Dehydration**
- **Electrolyte imbalance**

Severe cases of hyperemesis gravidarum associated with repeated admissions and weight loss should be differentiated and carefully monitored for growth restriction in pregnancy. The infants of mothers with HG may be born prematurely, be small for gestational age, have significantly lower birth weights, or have 5-minute Apgar scores of < 7.8.

Nausea and vomiting usually 4-7 weeks of pregnancy and peaks at 9 weeks resolving in 90% of cases by 20 weeks.

Vomiting, either persisting or of new onset beyond 20 weeks is uncommon and should prompt a search for other causes.

Initial Assessment

This should include a detailed history and physical examination with time of onset and duration of symptoms being noted.

Findings which may suggest alternative diagnosis include:

- Abdominal pain or tenderness
- Urinary symptoms
- Fever/infective symptoms
- Headache or abnormal neurological examination
- Goitre

History

- Previous history of NVP/HG
- Quantify severity using PUQE score: nausea, vomiting, hypersalivation, spitting, loss of weight, inability to tolerate food and fluids, effect on quality of life
- History to exclude other causes:
  - abdominal pain
  - urinary symptoms
  - infection
  - drug history
  - chronic Helicobacter pylori infection

Examination

- Temperature
- Pulse
- Blood pressure
- Oxygen saturations
- Respiratory rate
- Abdominal examination
- Weight
- Signs of dehydration
- Signs of muscle wasting
- Other examination as guided by history

Investigation

- Urine dipstick:
  - quantify ketonuria as 1+ ketones or more
- MSU
- Urea and electrolytes:
  - hypokalaemia/hyperkalaemia
  - hyponatraemia
  - dehydration
  - renal disease
- Full blood count:
  - infection
  - anaemia
  - haematocrit
- Blood glucose monitoring:
  - exclude diabetic ketoacidosis if diabetic
- Ultrasound scan:
  - confirm viable intrauterine pregnancy
  - exclude multiple pregnancy and trophoblastic disease
- In refractory cases or history of previous admissions, check:
  - TFTs: hypothyroid/hyperthyroid

– LFTs: exclude other liver disease such as hepatitis or gallstones, monitor malnutrition
– calcium and phosphate
– amylase: exclude pancreatitis
– ABG: exclude metabolic disturbances to monitor severity

ABG arterial blood gas; LFTs liver function tests; MSU midstream urine; TFTs thyroid function test

Classification of severity of nausea and vomiting

The classification should be done based on the PUQE score.
PUQE score can be used for classification of NVP as mild, moderate or severe and can be used to assess progress with the treatment.

Chart 1: PUQE score assessment

Motherisk PUQE-24 scoring system					
In the last 24 hours, for how long have you felt nauseated or sick to your stomach?	Not at all (1)	1 hour or less (2)	2–3 hours (3)	4–6 hours (4)	More than 6 hours (5)
In the last 24 hours have you vomited or thrown up?	7 or more times (5)	5–6 times (4)	3–4 times (3)	1–2 times (2)	I did not throw up (1)
In the last 24 hours how many times have you had retching or dry heaves without bringing anything up?	No time (1)	1–2 times (2)	3–4 times (3)	5–6 times (4)	7 or more times (5)

PUQE-24 score: Mild ≤ 6; Moderate = 7–12; Severe = 13–15.

How many hours have you slept out of 24 hours? _____ Why? _____

On a scale of 0 to 10, how would you rate your wellbeing? _____

0 (worst possible) → 10 (the best you felt before pregnancy)

Can you tell me what causes you to feel that way? _____

Differential diagnoses

Differential Diagnosis of Vomiting During Pregnancy

- Genitourinary - UTI, ectopic pregnancy, uraemia, pyelonephritis, ovarian torsion.
- Metabolic and endocrine disorders- hypercalcaemia, thyrotoxicosis, Diabetic ketoacidosis, Addison's disease.
- Gastrointestinal conditions-Gastritis, peptic ulcer, pancreatitis, bowel obstruction, hepatitis, cholecystitis, appendicitis, gastric malignancy.
- Neurological disorders- vestibular disease, migraine.
- Drug-induced vomiting- iron, opioids.
- Psychological- eating disorders.

Adverse Effects

Wernicke's encephalopathy
Secondary to Vitamin B^1 (thiamine) deficiency.
Characterised by Diplopia, abnormal ocular movements, ataxia and confusion.
Typical ocular signs are a 6^{th} nerve palsy, gaze palsy or nystagmus.
This type of encephalopathy can be precipitated by IV fluids containing dextrose (glucose).
Wernicke's encephalopathy is associated with 40% incidence of fetal death.

Hyponatraemia
Plasma sodium (less than120 mmols/l) produces lethargy, seizures and respiratory arrest.

Other vitamin deficiencies
Cyanocobalamin (Vitamin B_{12})
Pyridoxine (Vitamin B_6)
These deficiencies produce anaemia and peripheral neuropathy.

Mallory – Weiss tears
Prolonged vomiting may lead to tears of the oesophagus with hematemesis.

Malnutrition
With prolonged protein and calorie malnutrition weight loss and muscle wasting can occur.

Deep venous thrombosis
If a patient is dehydrated and immobilised because of bed rest, the risk of thromboembolism is increased.

Fetal complications
Incidence of fetal death associated with Wernicke's encephalopathy (40%).
Risk of lower birth weight.

Observations and Investigations

• Baseline weight – this should be repeated daily for women on IV fluid therapy.

• Urinalysis – for ketonuria and indicators of UTI.

• MSU – to be sent for MC&S.

• BM – exclude DKA if diabetic

• FBC – the haematocrit is often raised if dehydrated.

• U&E/Creatinine - there may be hyponatraemia and hypokalaemia. Serum urea is usually low but creatinine levels may be raised if dehydrated.

• Faecal sample for MC&S if patient has diarrhoea.

• Ultrasound scan - to confirm gestational age and exclude molar or twin pregnancy. This can be scheduled for the next available outpatient appointment, as long as the NVP resolves with treatment and in the absence of other indications for an urgent scan.

In refractory cases check:

• LFT's - mild elevations in bilirubin and transaminases are not uncommon but should resolve as the hyperemesis improves. Significant elevations of transaminases particularly in the presence of jaundice should prompt a search for viral hepatitis.

• TFT's - abnormal TFT's are common in women with hyperemesis with a biochemical thyrotoxicosis shown by a raised free thyroxine level and/or a suppressed TSH level. However, the women are usually clinically euthyroid and the abnormalities usually resolve as the hyperemesis improves. Treatment with anti-thyroid drugs is not usually necessary.

• Plasma $Ca2+$ and $PO4^{2}$ - hyperparathyroidism is a rare cause of persistent vomiting.

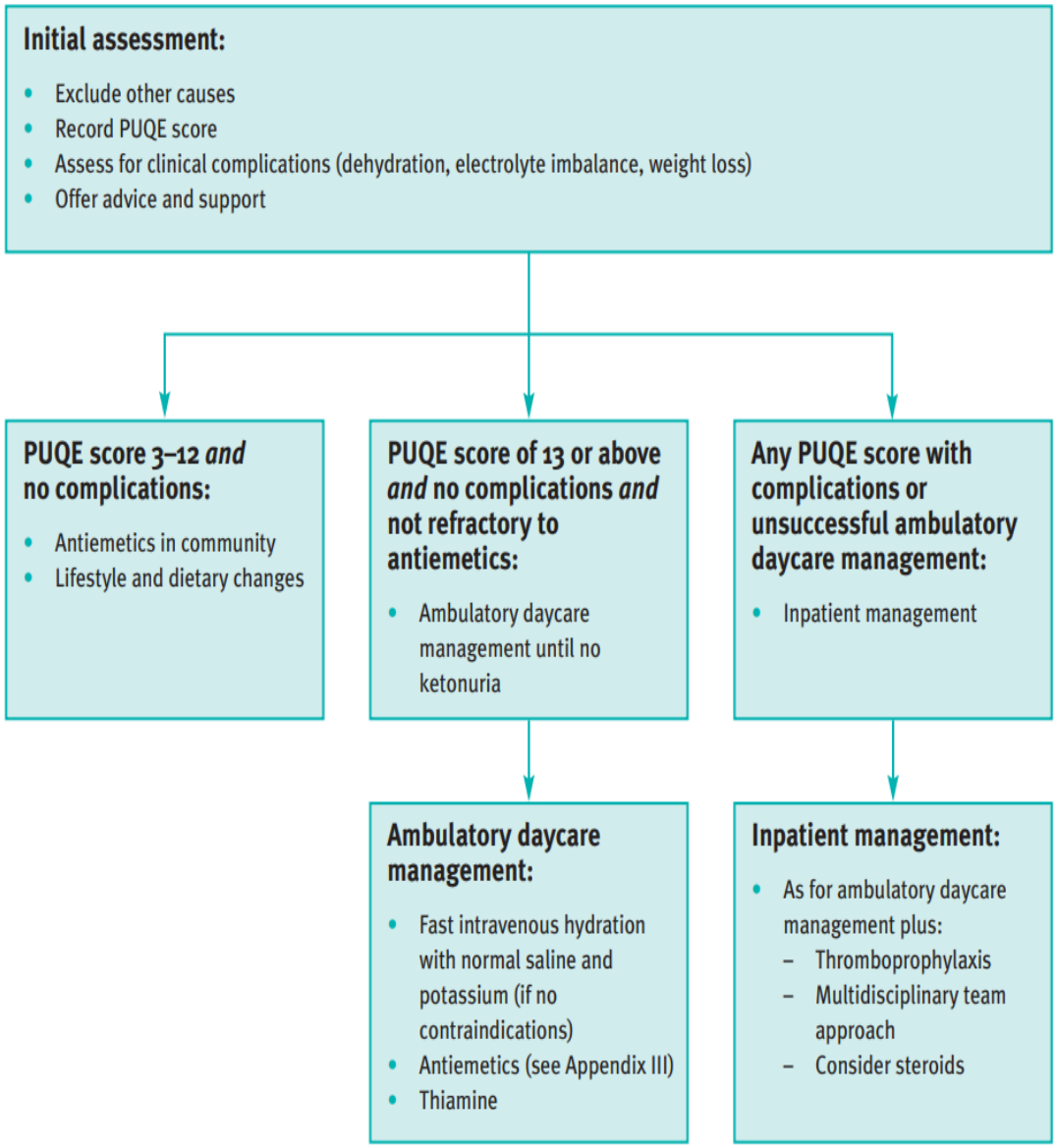
Management

- Women with **mild** NVP should be managed in the community with antiemetics.

- Ambulatory day care management should be used in patients with PUQE score of <13 where community/primary care measures have failed.

- **Inpatient** management should be considered if:
    - Continued nausea and vomiting and inability to keep down oral antiemetics.
    - Continued nausea and vomiting associated with ketonuria and/or weight loss (>5% body weight) despite oral antiemetics.
    - Confirmed or suspected comorbidity (such as UTI with inability to tolerate oral therapy)
    - Electrolyte imbalances and nutritional deficiencies
    - Sodium Chloride 0.9% with added potassium Chloride, guided by daily electrolyte review is the recommended fluid replacement for hydration.

Since most women with NVP require only oral antiemetics, management in the community/ primary care is appropriate to avoid unnecessary hospital admissions and disruption to the woman's life. Women who have vomiting but are not dehydrated can be managed in the community with antiemetics, support, reassurance, oral hydration and dietary advice



Rapid Hydration fluid prescription

- Normal saline 1L over 2 hours
- 0.9% Normal saline 1L with 20 mmol of K over 2 hours after careful monitoring of electrolytes. This can be repeated if required symptomatically and in consideration of bloods results.

Dextrose containing fluid inappropriate and can cause Wernicke's encephalopathy in Thiamine deficient states and should be given with high dose (100mg) of parenteral thiamine.

Medications

Ambulatory management: Initial TTO for

- Cyclizine 50 mg TDS or promethazine 20 mg p.o.TDS as first line
- See appendix 2 for anti-emetics.
- Thiamine 50 mg po TDS

Different drug classes may have different mechanisms of action and therefore synergistic effects, therefore combinations of drugs from different classes should be used in women who do not respond to a single antiemetic. Persistent vomiting may mean that oral antiemetics are not absorbed therefore IV, PR, subcutaneous or IM routes may be necessary and more effective.

Thiamine – this should be given routinely to women with prolonged vomiting, (i.e. requiring IV fluids for longer than 24 hours), to prevent Wernicke's encephalopathy.

Treating reflux and decreasing acid production can significantly decrease nausea and vomiting. In cases resistant to Ranitidine, Omeprazole 20-40 mg can be used once daily.

Teratogenicity: There is no clear evidence to suggest that therapeutic doses of antihistamines, prochlorperazine or metoclopramide are associated with an increased rate of congenital abnormalities above the background rate for the population.

In a US retrospective cohort study including 1.8 million pregnancies, first trimester ondansetron use was associated with an increased risk of cleft lip and palate, from 11 in 10,000 to 14 in 10,000 pregnancies. (3 additional cases per 10 000 women treated; adjusted relative risk, 1.24, (95% CI 1.03-1.48)). **Use of ondansetron in the first trimester should therefore be reserved for cases where other management has failed, following counselling of the above risks with the patient.**

Patients requiring admission

- **IV fluids**
- **Daily monitoring of electrolytes**
- **Enoxaparin**
- **Anti-emetics,** as per Appendix 2
- **Women with intractable vomiting may have gastro-oesophageal reflux disease, gastritis, and oesophagitis. Proton pump inhibitor should be considered and has been found safe in pregnancy.**
- **Thiamine/Pabrinex:** In severe or prolonged vomiting, including all readmissions, IV Pabrinex should be considered (see appendix 3)
- **Steroids**: Corticosteroids have been used in cases of resistant hyperemesis although data is conflicting regarding efficacy. They should not be prescribed except under close consultant supervision.
- **Referral** – for dietary advice or psychological assessment may be necessary in some women.
- **MDT:** Consider multidisciplinary input for severe and refractory cases, considering inclusion of obstetrician, gastroenterologist, dietician, nurses, pharmacists, and mental health.
- **Women with history of severe nausea and vomiting and hyperemesis gravidarum should avoid iron containing preparation as this can exacerbate the symptoms.**

- **Nausea and vomiting requiring repeated admissions and lasting beyond 5 months is associated with SGA and serial scan should be considered to monitor fetal growth.**

Corticosteroids

Corticosteroids should not be used until conventional treatment with intravenous fluid replacement and regular antiemetics has failed. The suggested dose is intravenous hydrocortisone 100 mg twice daily, and once clinical improvement occurs convert to oral prednisolone 40–50 mg daily, with the dose gradually tapered until the lowest maintenance dose that controls the symptoms is reached. In most cases prednisolone needs to be continued until the gestational age at which HG would have typically resolved and in some extreme cases this occurs at delivery.

Enteral/Parenteral Nutrition

- There are no defined criteria for the initiation of enteral or parenteral nutrition. These options should be considered with the involvement of the full MDT and after the failure of all other medical options.
- Close monitoring of metabolic and electrolyte balance, related complications and nutritional requirements is required.
- Enteral nutrition: nasogastric, nasoduodenal or nasojejunal tubes, or percutaneous gastrostomy or jejunostomy feeding. Lower complication rate than parenteral nutrition. In some cases, can exacerbate nausea and vomiting.
- Total parenteral nutrition (TPN): Consider as a last resort and under careful supervision of pharmacist/dietician. Complications include thrombosis, vascular perforation, infection, and metabolic disturbance.

When should termination of pregnancy (TOP) be considered?

This should only be considered when all other treatment options have failed. Up to 10% of pregnancies with HG may end in TOP, in women who would not otherwise have chosen this (RCOG 2016). Initiation of a prompt and responsive management plan may reduce this.

Occasionally, HG or its complications may lead to life-threatening illness where TOP is seen as the only option. Treatment options of antiemetics, corticosteroids, enteral and parenteral feeding, and correction of electrolyte or metabolic disturbances should be considered before deciding that the only option is termination of the pregnancy. A psychiatric opinion should also be sought, and the decision for termination needs to be multidisciplinary, with documentation of therapeutic failure if this is the reason for the termination. Women should be offered counselling before and after a decision of pregnancy termination is made.

Postnatal counselling

Recurrence risk of nausea and vomiting and HG in subsequent pregnancy is reported to be 15.2% in a Norwegian study to 81% using self-reported diagnosis.
Early dietary modification in subsequent pregnancy and pre-emptive treatment with antiemetics reduced the symptom of nausea and vomiting.

Monitor

- Blood glucose on admission.
- Daily U&E's.
- Routine urinalysis for ketones

Senior medical review should be arranged in patients where the diagnosis is not clear and appropriate medical/ surgical review arranged.

Patients who have improved after initial severe hyperemesis can be discharged to the GAU rapid hydration pathway for future treatment if necessary.

Follow-up after discharge from GAU

Women should be encouraged to self-refer to GAU if required. The IV cannula would be removed and re-sited on any further readmission. If a patient requires repeated readmissions senior review is indicated, with consideration of admission.
.
Women will be assessed by the team in GAU on the suitability for discharge. A prescription for medication for discharge and a discharge summary will be completed by the on-call doctor for gynaecology.

Women will be given a patient information leaflet about hyperemesis in pregnancy and about the support available in GAU. A telephone support number will be included in this leaflet.

Alternative therapy

• Seabands
A number of systematic reviews have shown that P6 Neiguan point acupressure (located on the volar aspect of the forearm 3 fingerbreadths proximal to the wrist) appear to improve nausea and vomiting symptoms. Other systematic reviews 4 do not demonstrate equivocal evidence on the efficacy of P6 acupressure. However, as no adverse effects on pregnancy were shown and it may be of benefit, the use of acupressure wristbands should be considered for patients. See appendix 4 for instructions for the patient how to apply pressure.

• Ginger
There is some evidence to suggest that ginger may be of benefit to some patients in reducing the severity of nausea and vomiting. This can be used in women who have mild to moderate symptoms and would like to avoid antiemetics. A systematic review also reported on woman hospitalised for hyperemesis and ginger was shown to significantly reduce the degree of nausea and number of attacks of vomiting. There was no evidence of adverse effects on pregnancy outcome. However, one review reported stomach irritation, anticoagulant effect and potential interaction with beta blockers and benzodiazepines.

Avoiding fatigue

Severe nausea and vomiting can be associated with fatigue. Survey conducted by pregnancy sickness support group found that rest and napping was found to be effective in reducing the symptoms. Napping and rest may help by reducing the

sensory trigger associated with nausea and vomiting. Effort should be made to identify and avoid the sensory triggers to minimise symptoms.

References

The management of nausea and vomiting of pregnancy and hyperemesis gravidarum (Greentop Guideline 69), RCOG 2016

Huybrechts KF, et al. Association of maternal first-trimester ondansetron use with cardiac malformations and oral clefts in offspring. JAMA 2018; 320: 2429–37

Ondansetron: small increased risk of oral clefts following use in the first 12 weeks of pregnancy. Drug Safety Update volume 13, issue 6: January 2020: 2
https://www.gov.uk/drug-safety-update/ondansetron-small-increased-risk-of-oral-clefts-following-use-in-the-first-12-weeks-of-pregnancy

Management of Nausea and Vomiting in Pregnancy – use the PUQE score chart.

Appendix 1
Admission Proforma

Patient details
Telephone

Date	**……/……/……..**
Arrival time	
Assessment time	
Referred by	
Discharge time	

Age	LMP	Gravidity	Parity

Vomiting Yes How many times in last 24 hours **……..**

PUQE score (see chart 1)

Blood in vomit Yes / **No If Yes, refer to doctor.**

Last tolerated fluids …… Last tolerated food ……

Abdominal pain / diarrhoea / urinary symptoms If yes, refer to doctor.

Scan in this pregnancy? Yes/ No

If yes scan findings:

Hx of diabetes? Yes If Yes, refer to doctor

Hx of thyroid disease? Yes If Yes ask doctor to review TFTs

Medical History Drug History

Surgical History Allergies

Examination

Blood pressure		Urinalysis	
Pulse			
Temperature		Weight	

Clinically suitable for rapid hydration and GAU management

No
Patients not suitable require medical review and appropriate investigations.

Yes
Patients suitable for Rapid hydration take following actions:

FBC
U & E
TFT and LFT if necessary on clinical grounds
Medications prescribed
VTE

Ward Leave

Patients can have ward leave once if they still have ketones in their urine. If they require ward leave more than three times during the same admission, please refer to senior medical team.

Date		Date to return	
Time		Time to return	
Urinalysis		Signature	

Hyperemesis Day Centre Discharge Protocol

Blood results (If abnormal results should be reviewed by the medical team)

Date	Na	K	Urea	Creat.	HB	Hct	Platelets	LFT	WCC	TFT

USS result if available…….

Able to tolerate fluids? Yes

Urinalysis NAD? Yes

Observations normal? (please document)

Blood Pressure		Urinalysis	
Pulse			
Temperature		Weight	

Any other symptoms?	Yes (If yes refer to doctor)	No
TTOs prescribed?	Yes	
Follow up/ re-referral instructions	Yes	
Information leaflet given	Yes	
Support telephone number given	Yes	

Person discharging……..

(Name, designation, signature) …….....

Date of discharge……../……../……

ANTI-EMETIC DRUGS TO USE IN HYPEREMESIS
Appendix 2

Class of drug	Drug	Dosage	Route	Main side-effects Safety data	Comments
First line antihistamines H1 Receptor antagonist	Cyclizine Promethazine	50 mg TDS 10-20 mg TDS	PO/IV/IM PO	Drowsiness, dry mouth, blurred vision. Extensively used during pregnancy. No increase in rate of major congenital malformations observed	
First line Phenothiazines	Prochlorperazine (stemetil, buccastem)	10 mg po TDS 12.5 mg IM 3-6 mg buccal BD	PO IM BUCCAL	Extra-pyramidal reactions in some young patients. No evidence of increased risk of congenital malformations.	Can be used PRN in addition to regular antihistamines
Second Line Centrally acting	Metoclopromide	10 mg TDS 10 mg TDS 10 mg TDS	PO IM IV	Use in younger adults has been associated with dystonias and should therefore not be routinely used as first-line treatment and for longer than 5 days	Can be used PRN in addition to regular antihistamines
Third Line Serotonin receptor (5HT3) antagonists	Ondansetron	4-8 mg BD 4-8 mg BD 16mg OD	PO IV/IM PR	A 2018 study has suggested an increased risk of isolated cleft palate following first trimester exposure to ondansetron. Can be used following counselling if other treatments fail.	**Avoid in first trimester if possible**
Fourth Line Corticosteroids	Prednisolone Hydrocortisone	Reducing course starting at 40mg/day 100mg bd	PO IV	Glycosuria Psychosis fetal growth restriction	**Use in rare circumstances after review by gastro. Prescribed only by a consultant**
Proton pump inhibitors	**Omeprazole**	20-40mg daily	PO/IV	Consider in cases of GERD	Safety data on Omeprazole shows no harmful effects on pregnancy

Appendix 3: Use of Pabrinex

One pair of Pabrinex ampoules (contains 250mg Thiamine) IV:

Draw the contents of ampoule 1 and 2 into a syringe and mix. Add to 100mls Sodium Chloride 0.9% and infuse over 15-30 minutes (given x1 weekly and repeated if vomiting persists).

Monitor closely – risk of anaphylaxis. NOTE also contains 1g of glucose. Consider changing back to oral thiamine when patient able to tolerate. Women with deranged biochemistry are at higher risk of Wernicke's encephalopathy.

Since potentially serious allergic adverse reactions may occur during or shortly after, administration it is recommended that:

- Use is restricted to patients in whom parenteral treatment is essential
- Intravenous injections should be administered slowly (over 10 minutes)
- Facilities for treating anaphylaxis must be available when administered

Appendix 3 Instructions for acupressure point P6 for women with mild symptoms and who would like to avoid medication.

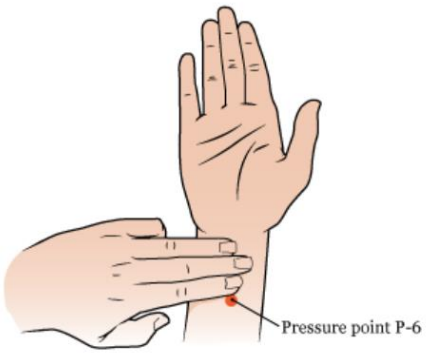


Figure 1. Placing 3 fingers across wrist to measure where to put thumb

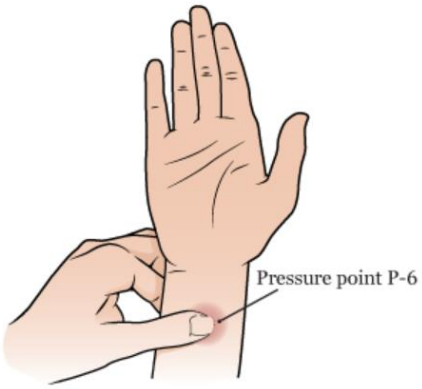


Figure 2. Placing thumb on point below index finger

1. Position your hand so that your fingers are pointing up and your palm is facing you.
2. Place the first 3 fingers of your other hand across your wrist (see Figure 1). Your fingers should be placed just below your wrist crease (where your wrist bends).
3. Place your thumb just below your index (pointer) finger. Remove the 3 fingers from your wrist but keep your thumb on that spot (see Figure 2). Use your thumb to press down on the spot. You should be able to feel 2 large tendons

(tissue that connects muscles to bones) in between your thumb. This spot in between the 2 tendons is pressure point P-6.
    - Once you have found the pressure point, you can relax your hand and keep it in a comfortable position.
4. Press down on this point with your thumb. Move your thumb in a circle while applying pressure. You can move it in clockwise (to the right) or counterclockwise (to the left) circles. Do this for 2 to 3 minutes.
    - Some people may find it hard to use their thumb. You can use your index finger instead.
    - Be firm when applying pressure, but do not press so hard that it hurts. You may feel some aching or tenderness, but it should not be painful. If you feel any pain, you're pressing down too hard.
5. Repeat steps 1 to 4 on your other wrist.