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A photograph of a hospital hallway. A nurse in white scrubs is pushing a gurney with a patient on it. The hallway is long and brightly lit, with large windows on the left and a polished floor that reflects the lights. The right side of the image is partially obscured by a blue diagonal overlay.

Isabelle Dehaene / Vrouwenkliniek

Hyperemesis gravidarum Urineweginfecties bij zwangeren

Alumni, 09/02/22



Hyperemesis gravidarum


- ▶ Definitie
- ▶ Evidentie
- ▶ Prevalentie
- ▶ Risicofactoren
- ▶ Pathogenese
- ▶ Diagnostiek
- ▶ Complicaties
- ▶ Preventie en aanpak
- ▶ Besluit

WHY GOD IS A MAN (reason 32)

you can't drink any alcohol
and you still get a hangover
every morning



Definitie

- ▶ Exclusiediagnose
 - ▶ Langdurig en ernstig
 - ▶ Nausea en vomitus
 - ▶ Dehydratatie
 - ▶ > 5% lichaamsgewichtverlies
 - ▶ Ketonurie
- 

Prevalentie

- ▶ 0,3-3% van de zwangerschappen
- ▶ 50% nausea + overgeven
- ▶ 25% nausea –
- ▶ 25% klachtenvrij
- ▶ Recidief: 15-80%

Hyperemesis Gravidarum is such a party. I just love being sick for months at a time. I'll bring the IV bags, you bring the barf buckets.



Risicofactoren

- ▶ Etniciteit (> Aziaten en Afrikanen)
- ▶ Lage BMI
- ▶ Jongere maternele leeftijd
- ▶ Nullipariteit
- ▶ Vrouwelijke foetus
- ▶ Meerling
- ▶ Voorgeschiedenis of positieve familiale anamnese
- ▶ Gestationale trofoblastziekte
- ▶ Comorbiditeiten (hyperthyroïdie, psychisch, diabetes,...)
- ▶ Psychologische factoren (stress, ongeplande zwangerschap)
- ▶ Minder vaak bij rooksters

Pathogenese

- ▶ Psyche

- ▶ conversie / somatisatie
- ▶ inadequate respons op stress

- ▶ Evolutionair

- ▶ bescherming tegen potentieel gevaarlijke voedingsstoffen
- ▶ aversie geur/smaak

- ▶ Hormonaal

- ▶ hCG, oestrogeen, progesteron

Diagnostiek

Uitsluiten andere oorzaken!

- ▶ Klinisch onderzoek: koorts, pijn,...?
- ▶ Labo: elektrolytenstoornissen, infectieus,...?
- ▶ Echografie: meerling? mola?

Laboafwijkingen

- ▶ Hypokaliëmie
- ▶ Hyponatriëmie
- ▶ Gestoorde leverfunctie
 - ▶ AST/ALT, klassiek < 300 U/L
 - ▶ bilirubine, klassiek < 4 mg/dL
 - ▶ amylase/lipase, tot 5 keer bovengrens
- ▶ Hyperthyroïdie

Differentiaal diagnose

- ▶ **Gastro-intestinale afwijkingen:** pancreatitis, hepatitis, cholecystitis, appendicitis, ...
- ▶ **Urogenitale afwijkingen:** pyelonefritis, nefrolithiasis, ovariële torsie, ...
- ▶ **Metabole aandoeningen:** Addison, keto-acidose, hyperthyroïdie,...
- ▶ **Neurologische afwijkingen:** migraine, RIP cerebraal, vestibulaire afwijkingen
- ▶ **Psychologisch**
- ▶ **Complicatie bariatrische chirurgie**


Denk er vooral aan als hyperemesis optreedt na 9w amenorreeduur

Complicaties

- ▶ Wernicke encephalopathie
 - ▶ Maternele sterfte
 - ▶ Permanente neurologische schade

- ▶ Psychosociale morbiditeit
 - ▶ Vraag naar TOP

Invloed op zwangerschap

- ▶ Laag geboortegewicht?
 - ▶ Vroeggeboorte?
 - ▶ Cognitieve, gedrags- en emotionele dysfunctie in de zwangerschap?
- 

Preventie

Vroegtijdige aanpak van nausea en vomitus

- ▶ Vitaminepreparaat preconceptioneel
- ▶ Rust
- ▶ Vermijden van stimuli (geur, hitte, vochtigheid, geluid, lichtflitsen)
- ▶ Frequentie maaltijden, start eten voor opstaan
- ▶ Vermijden kruidig/vettig/geurend eten
- ▶ Gember: max 4dd 250 mg; praktisch: 2dd 1co Antimetil



Table 2 Suggested dietary guidelines to improve oral tolerance

When fixing meals

Avoid cooking if possible. Ask for help from friends or family

Prepare foods that do not require cooking, like sandwiches

Avoid smell of hot food—try having cold food instead

Drink chilled beverages—flat lemonade, diluted fruit juice, weak tea or clear soup as they are tolerated better than water

Avoid eating in a place that is stuffy, too warm, or has cooking odors

Have someone else to remove covers from cooked foods

When eating

Eat small frequent meals—nibble on light snacks between meals

Drink fewer liquids with meals. Drink liquids half to 1 h after meals

Drinking liquids can cause a full, bloated feeling

Avoid food that is fatty, fried, spicy, very sweet, such as candy, cake or cookies, or foods with strong odors, like cooked broccoli, cabbage, fish, etc

Choose bland foods. Try toast, crackers, pretzels, rice, oatmeal, skinned chicken (baked or broiled, not fried), and fruits and vegetables that are soft or bland

Eat easily digested starches, like rice, potatoes, noodles, cereal and bread

Choose low-fat protein foods like skinless chicken and boiled beans

Try eating salty, sweet food combinations, like potato chips or pretzels before meals

Other tips

Eat best when you feel best or hungry

Rest after meals. Sit up in a chair for about an hour after meals

Avoid sudden movements. Rise slowly from the bed

Eat crackers, toast, pretzels, or rice cakes before getting out of bed

When feeling nauseated, slowly sip on carbonated beverages

Wear loose clothes

Taking a multivitamin at the time of conception may decrease the severity of nausea and vomiting during pregnancy

Avoid stress—constant threat of nausea or vomiting is itself a stressor

Multivitamine

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The effect of periconceptional multivitamin-mineral supplementation on vertigo, nausea and vomiting in the first trimester of pregnancy

A. E. Czeizel, I. Dudas, G. Fritz, A. Técsői, A. Hanck, and G. Kunovits

The finding that periconceptional multivitamin-mineral supplementation significantly lowered the incidence of pregnancy-induced vertigo, nausea and vomiting, is surprising. Although high dose vitamin B6 and vitamin B complex therapy has been suggested as a treatment for hyperemesis gravidarum (Gant et al. 1975), our study is the first randomized placebo-controlled prospective trial to demonstrate this effect with a multivitamin-mineral preparation. It is unlikely that such a low dose (Table 1) of the vitamin B complex alone could achieve this beneficial effect. It seems much more likely that it is due to a general optimization of nutritional status and metabolism.

Gember

- ▶ Ginger treatment of hyperemesis gravidarum. Eur J Obstet Gynecol Reprod Biol. 1991 Jan 4;38(1):19-24.
- ▶ Thirty women participated in a **double-blind randomized cross-over trial** of the efficacy of a natural product, the powdered root of ginger (*Zingiber officinale*), and placebo in hyperemesis gravidarum. Three patients had to be withdrawn. Each woman swallowed capsules containing either 250 mg ginger or lactose q.i.d. during the first 4 days of the treatment period. Interrupted by a 2 days wash-out period the alternative medication was given in the second 4-day period. The severity and relief of symptoms before and after each period were evaluated by two scoring systems. The scores were used for statistical analyses of possible differences. Subjectively assessed, **19 women (70.4%) stated preference to the period in which ginger**, as was later disclosed, had been given (**P = 0.003**). More objectively assessed by relief scores a **significantly greater relief of the symptoms was found after ginger treatment compared to placebo (P = 0.035)**. No side effects were observed. The possible mutagenic and antimutagenic characters of ginger reported in a study of *E. coli* have not been evaluated with respect to any significance in humans. **Powdered root of ginger in daily doses of 1 g during 4 days was better than placebo in diminishing or eliminating the symptoms of hyperemesis gravidarum.**

Gember

Ginger for Nausea and Vomiting in Pregnancy: Randomized, Double-Masked, Placebo-Controlled Trial. *Obstet Gynecol* 2001;97: 577–82

Methods: Women with nausea and vomiting of pregnancy, who first attended an antenatal clinic at or before 17 weeks' gestation, were invited to participate in the study. During a 5-month period, 70 eligible women gave consent and were randomized in a double-masked design to receive either oral ginger 1 g per day or an identical placebo for 4 days. Subjects graded the severity of their nausea using visual analog scales and recorded the number of vomiting episodes in the previous 24 hours before treatment, and again during 4 consecutive days while taking treatment. At a follow-up visit 7 days later, five-item Likert scales were used to assess the severity of their symptoms.

Results: All participants except three in the placebo group remained in the study. The visual analog scores of post-therapy minus baseline nausea decreased significantly in the ginger group (2.1 ± 1.9) compared with the placebo group (0.9 ± 2.2 , $P = .014$). The number of vomiting episodes also decreased significantly in the ginger group (1.4 ± 1.3) compared with the placebo group (0.3 ± 1.1 , $P < .001$). Likert scales showed that 28 of 32 in the ginger group had improvement in nausea symptoms compared with 10 of 35 in the placebo group ($P < .001$). No adverse effect of ginger on pregnancy outcome was detected.

Gember

Table 4. Symptoms Assessed by Likert Scales

Symptom rating	Placebo ($n = 35$)	Ginger ($n = 32$)
Much worse	0	0
Worse	9 (25.7%)	0
Same	16 (45.7%)	4 (12.5%)
Better	9 (25.7%)	8 (25%)
Much better	1 (2.9%)	20 (62.5%)

Data are presented as n (%); Fisher exact test, $P < .001$.

Gember

Effect of ginger on relieving nausea and vomiting in pregnancy: a randomized placebo-controlled trial. Nurs Midwifery Stud 2014;3(1):e11841

Patients and Methods: This seven-day clinical trial was performed on 120 eligible pregnant women with symptoms of mild to moderate nausea and vomiting before 16 weeks gestation. They were divided into; ginger, placebo and control groups, by block randomization. Women were asked to record their nausea and vomiting for three days, and then participants received either ginger capsules, or a placebo for four days. No intervention was done with the control group. Data measure was self-recorded symptoms according to the

“In conclusion, ginger is effective in reducing nausea and vomiting in pregnancy in mild to moderate symptomatic women before 16 weeks gestation. Since this study was performed on mild to moderate nausea and vomiting, the results are not generalized to severe nausea and vomiting.”



Aanpak nausea en vomitus

- ▶ Continueren gember
- ▶ **Meclozine** (Agyrax): 1dd 25 mg, max 1dd 50 mg (2 co)
- ▶ **Metoclopramide** (Primperan): 3dd 10 mg
- ▶ Doxylamine/**Pyridoxine** (Navalit): tot 4 co, 1 – 1 – 2 co

Meclozine

- Lepley, D., Smith, M. B. (1957) *Arch. Surg.* **70**, 511.
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Shapiro, P. B., Bronsther, B., Frank, E. D., Fine, J. (1958) *Proc. Soc. ex*

random series of 100 pregnant women, 88 experienced these symptoms and 73 had taken some form of medication: a large proportion had treated themselves without

Meclozine

- ▶ Anti-emetische werking: chemosensorische regio van de medulla oblongata
- ▶ Anticholinerg effect: voorzichtig bij urinaire retentie, glaucoom, digestieve of urinaire obstructie, verminderde darmmotiliteit
- ▶ Bijwerkingen: slaperigheid of sedatie, gevoel van droge mond, *zelden*: gezichtsstoornissen, misselijkheid en brak en, artralgie
- ▶ Max 50 mg


Metoclopramide

- ▶ Geen enkele placebo-gecontroleerde RCT!
- ▶ Evenwel langdurige ervaring

Metoclopramide

- ▶ Effect: verhoogt contracties van antrum maag, ontspant pylorussfincter en verhoogt peristaltiek dunne darm + anti-emetisch
- ▶ Bijwerkingen: slaperigheid ++, depressie, hypotensie (IV), diarree, asthenie
- ▶ Extrapyramidale stoornissen: vnl in begin, kan na één toediening, stop, spontane resolutie, zelden R noodzakelijk, min 6u tussen 2 giften
- ▶ Tardieve dyskinesie: langdurige behandeling, mogelijk onomkeerbaar, max 3 maanden
- ▶ Dosisaanpassing bij ernstige nier/leverfunctiestoornissen
- ▶ Contra-indicatie: epilepsie

Doxylamine/pyridoxine

- ▶ Effectief
 - ▶ Veilig
 - ▶ Geen evidentie voor teratogeniciteit
 - ▶ Bijwerkingen: cfr meclozine
- 

Aanpak hyperemesis gravidarum

- ▶ Opname-indicatie: ‘echte” hyperemesis gravidarum: dehydratatie en/of $> 5\%$ lichaamsgewichtverlies (tov voor/begin zwangerschap)
 - ▶ IV- vocht
 - ▶ thiamine 100 mg IV/d indien > 3 weken emesis
 - ▶ anti-emetica IV: metoclopramide
 - ▶ corrigeren elektrolyten
 - ▶ eten volgens aanvoelen
 - ▶ psychosociale ondersteuning op indicatie

Ondansetron

- ▶ Geen placebo-gecontroleerde RCT
- ▶ Vergelijkende studie met metoclopramide: gelijkaardig anti-emetisch en anti-nausea effect, minder bijwerkingen bij ondansetron, metoclopramide goedkoper
- ▶ Vergelijkende studie met doxylamine/pyridoxine: superieur effect van ondansetron

Ondansetron

- ▶ Bijwerkingen: hoofdpijn, duizeligheid, moeheid, constipatie, warmtegevoel/flush
- ▶ Verlenging QT-interval
 - ▶ vnl bij hypokaliëmie, hypomagnesiëmie, hartlijden
 - ▶ cave concomitante medicatie met invloed op QT
 - ▶ elektrolyten- en EKG-monitoring (hypokaliëmie/-magnesiëmie corrigeren)
- ▶ Teratogeen?

Ondansetron

- ▶ Cheilognatopalatoschizis en cardiale afwijkingen
- ▶ Huybrechts et al., 2018
- ▶ 88.000 blootgestelden (1^e trim), 1.727.000 niet blootgestelden
- ▶ Propensity score adjusted risks:
 - ▶ een afwijking: RR 1,01; 95%CI 0,98 - 1,05
 - ▶ cardiale afwijking: RR 0,99; 95%CI 0,93 - 1,06
 - ▶ CLP: RR 1,24; 95%CI 1,03 - 1,48
- ▶ Liveborn!

Ondansetron

- ▶ Zambelli-Weiner et al, 2019
- ▶ 82.000 blootgesteld (1^e trim), 780.000 niet blootgesteld
- ▶ adjusted OR:
 - ▶ cardiac defects: aOR 1,04; 95%CI 1,00 - 1.08
 - ▶ CLP: aOR 1,12; 95% CI 0,95 - 1,33
- ▶ Liveborn!
- ▶ Methodologische issues

Ondansetron

- ▶ ” It is the position of the European Network of Teratology Information Services Scientific Committee that the Zambelli-Weiner study is methodologically and ethically compromised to an extent that the results thereof cannot be considered when assessing the totality of evidence on the safety of ondansetron in pregnancy”

Ondansetron

- ▶ Damkier et al. Ondansetron in pregnancy revisited: Assessment and pregnancy labelling by the European Medicine Agency (EMA) & Pharmacovigilance Risk Assessment Committee (PRAC). Basic Clin Pharmacol Toxicol 2021;128:579-582
- ▶ “We believe that the **methodologically sound data on congenital cardiovascular malformations** from first-trimester exposure to ondansetron are substantial and **reassuring**. These data do not suggest an increased risk. **Even if a small excess risk of congenital oral cleft may still be present**, ondansetron in the first trimester should **remain an option for pregnant women with severe NPV**”.
- ▶ “We are of the opinion that specific wording against the use of ondansetron in first trimester is not justifiable and not substantiated by underlying scientific evidence.”


Aanpak ernstige hyperemesis

- ▶ Ondansetron
- ▶ Nasogastrische tube als medicamenteuze behandeling onvoldoende en verdere gewichtsafname
- ▶ Refractaire hyperemesis gravidarum: overweeg methylprednisolone: 3dd 16mg Medrol gedurende 3 dagen, afbouw over 2 weken


Alternatieve behandelingen

- ▶ Acupunctuur of acupressure?
- ▶ Very low level of evidence

Besluit

- ▶ Aloude problematiek
 - ▶ Desondanks weinig evidentie
 - ▶ Exclusiediagnose
 - ▶ Preventie
- 

Alarmsymptomen

- ▶ Recidiverend/refractair/laattijdig
 - ▶ Geassocieerde symptomatologie: abdominale pijn, koorts, dysurie, neurologische symptomen, diarree,...
 - ▶ Opname indicatie: 'echte' hyperemesis gravidarum
- 

Urineweginfecties bij zwangeren

Verwekkers

- ▶ 85% E. coli
- ▶ Andere gram-neg: Klebsiella, Enterobacter, Proteus.
- ▶ Minder frequent gram-pos: Enterococcus faecalis, GBS

Asymptomatische bacteriurie

- ▶ Asymptomatische patiënte met bacteriurie zonder pyurie
- ▶ Midstream/gekatheteriseerd staal met groei $> 10^5$ cfu/mL
- ▶ Incidentie vergelijkbaar met niet-zwangeren, 2 à 10% van de zwangeren
- ▶ Verhoogd risico op pyelonefritis en sepsis
- ▶ Verhoogd risico op vroeggeboorte
- ▶ Screening rond 16 weken (midstream urinekweek)

Cystitis

- ▶ Symptomatische patiënte met bacteriurie en pyurie
- ▶ Midstream/gekatheteriseerd staal met groei $> 10^3$ cfu/mL

Behandelingsopties

- ▶ **Penicilline:** veilig
- ▶ **Cefalosporine:** veilig
- ▶ **Nitrofurantoin:** veilig mits voorzorgen: niet in het 3e trimester of bij dreigende vroeggeboorte wegens risico op hemolytische anemie neonaat, vooral igv G6PD-deficiëntie (favisme)
- ▶ **Sulfonamide en trimetoprim:** geen eerste keuze gezien toenemende resistentie en risico's voor de foetus (neurale buis defecten en cardiale afwijkingen (1^e trim), neonatale hyperbilirubinemie en icterus (3^e trim))
- ▶ **Fluoroquinolones:** relatieve contra-indicatie (theoretische aantasting foetale gewrichtskraakbeen)
- ▶ **Glucosaminosiden:** relatieve contra-indicatie (theoretische nefrotoxiciteit en ototoxiciteit)
- ▶ **Macroliden:** veilig, indicatie: GBS bacteriurie en penicilline-allergie
- ▶ **Tetracyclines:** gecontra-indiceerd wegens negatief effect op tand- en botontwikkeling
- ▶ **Fosfomycine:** veilig, effectief, lage E.coli resistentie, hoge compliantie, weinig gegevens 1^e trimester

- ▶ Controlestaal 1 à 2 weken na beëindigen therapie

Behandeling - beleid UZG

- ▶ Nitrofurantoïne: 3dd 100mg 5d
- ▶ Fosfomycine: 3g
- ▶ Cefuroxime (Zinnat): 3dd 500mg 5d

Pyelonefritis

- ▶ Infectie ter hoogte van de nier, gepaard gaande met tekenen van weefselinvasie: koorts, koude rillingen, nausea, flankpijn
- ▶ Verhoogd risico op sepsis en vroeggeboorte
- ▶ Opname
- ▶ Op indicatie echo nieren (recidief, trage respons)
- ▶ Hydratatie en antipyretica
- ▶ Antibiotherapie

Pyelonefritis - beleid UZG

- ▶ Empirisch tot kweek gekend, rekening houdend met eventueel eerdere kweekresultaten
- ▶ **Ceftriaxone IV 2g, 1dd**
- ▶ Peni-allergie, risicofactoren voor complicaties of resistentie, hemodynamisch instabiel en/of tekenen van orgaanfalen: Meropenem IV 1g oplaad, gevolgd door 500mg 6dd
 - ▶ Risicofactoren complicaties = urologische voorgeschiedenis/anatomische afwijkingen, recidiverende urineweginfecties, diabetes mellitus
 - ▶ Risicofactoren resistentie = recente antibiotherapie (<6m), gehospitaliseerd (>48u), recente hospitalisatie (<3m)
- ▶ 14 dagen

Postpartum

▶ Borstvoeding

▶ **Penicilline:** veilig

▶ **Cefalosporine:** veilig

▶ **Nitrofurantoinen:** veilig

▶ **Sulfonamide en trimetoprim:** te vermijden bij vroeggeboorte, hyperbilirubinemie, G6PD-deficiëntie

▶ **Fluoroquinolones:** risico onbekend

▶ **Glucosaminosiden:** alleen op strikte indicatie

▶ **Macroliden:** veilig

▶ **Tetracyclines:** kortdurig gebruik (<3w) veilig

▶ **Fosfomycine:** veilig

Postpartum - beleid UZG

- ▶ Cystitis: fosfomycine of nitrofurantoïne
- ▶ Pyelonefritis:
 - ▶ borstvoeding: ceftriaxone IV 1dd 2g
 - ▶ kunstvoeding: levofloxacin po 1dd 500mg
- ▶ Urosepsis: Meropenem IV 1g oplaad, 6dd 500mg + Amikacine éénmalig 25 mg/kg

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