Ketones: A barrier to treatment

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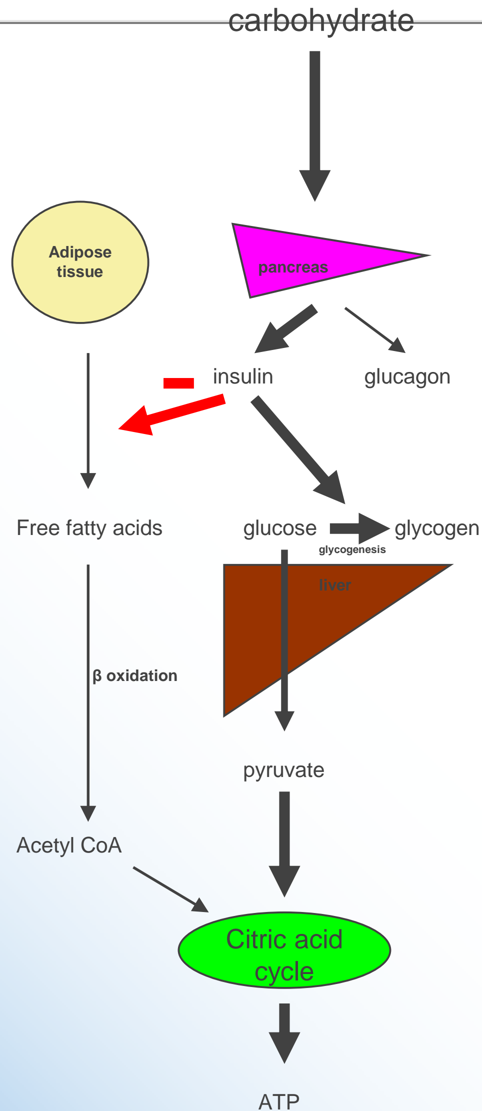
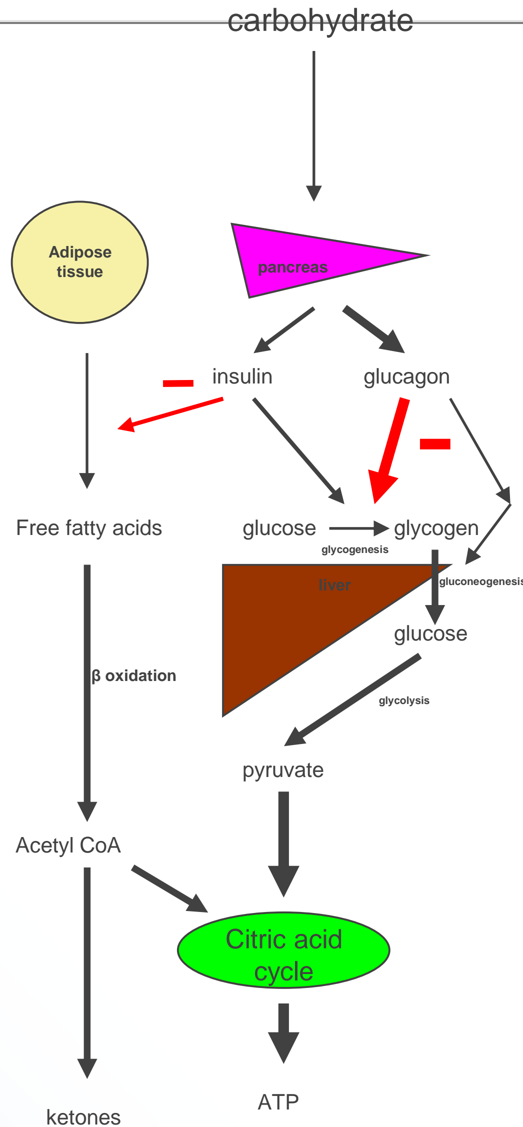
Ketones / ketonuria

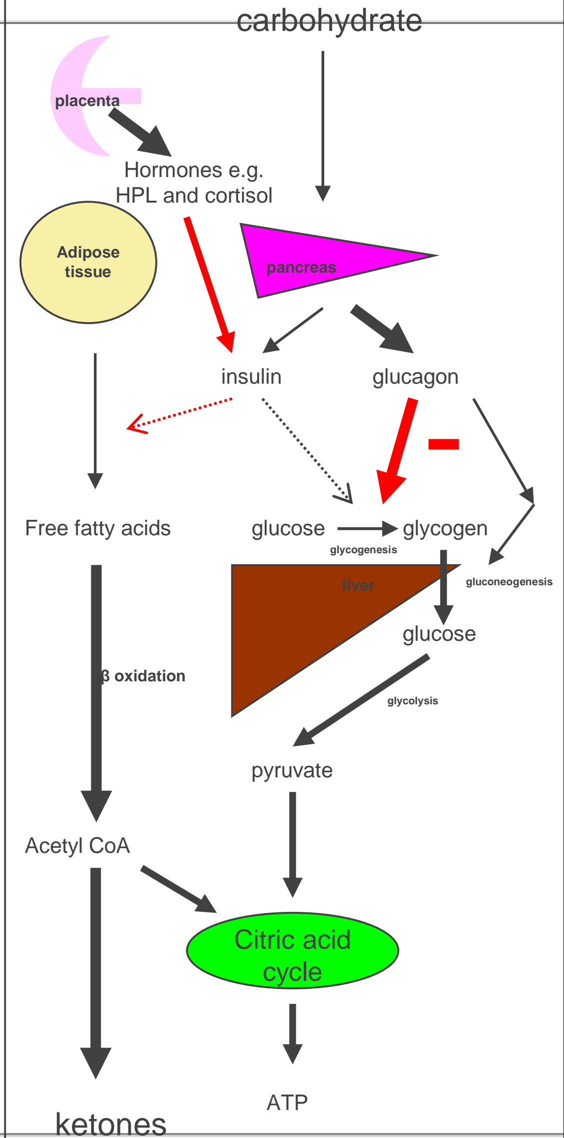
The presence and quantity of ketones in the urine – ketonuria - has traditionally been used as a measure of the severity of hyperemesis.

When the body is deprived of glucose as a fuel (for example if someone is not eating or drinking) then the body breaks down fat and ketones are one product generated when the body uses fat as a fuel.

However – it is possible to treat hyperemesis with intravenous fluids or to be able to drink enough or eat minimal amounts such that there are no ketones in the urine but still have severe incapacitating nausea and vomiting.







KING'S HEALTH PARTNERS

Frise CJ et al. 'Starvation ketoacidosis in pregnancy' Eur J Obstet Gynecol (2012)

Ketones – non diabetic ketosis

Ketones in urine are a common finding particularly in late pregnancy

Starvation ketoacidosis is a condition characterised by a metabolic acidosis with a high anion gap and ketonaemia, in the absence of hyperglycaemia.

It occurs to a mild degree in non-pregnant individuals after fasting for 14 days or more, but can occur more severely and rapidly in pregnant women.

Hyperemesis Gravidarum (HG)

- **0.3-1% of pregnancies[1]**
- **Peak occurrence 8-12 weeks gestation**
- **Severe end of NVP spectrum[2]**
  - intractable nausea, vomiting, dehydration
  - ketosis, electrolyte imbalance
  - weight loss (> 5% of body weight)

1. Niebyl JR. Clinical practice. Nausea and vomiting in pregnancy. *N Engl J Med.* Oct 14 2010;363(16):1544-1550.
2. Jarvis S, Nelson-Piercy C. Management of nausea and vomiting in pregnancy. *BMJ.* 2011;342:d3606.

Decision making approach to outpatient or inpatient admission
Assess symptoms of nausea and vomiting in pregnancy
Check fluid status of patient
Check urine for ketones

Mild nausea and vomiting in pregnancy
Urine ketones negative

Community based care
Encourage oral fluid intake
Small frequent meals with bland foods and avoid spicy, fatty, odorous foods
If persistent sickness
Consider antiemetics (for example, cyclizine 50 mg orally, three times daily; prochlorperazine 5 mg orally, sublingually, or rectally, three times daily; metoclopramide 10 mg orally, three three times daily)
(Consider antiemetics listed in box 3)

Moderate dehydration
Urine ketones +1-2

Short admission (4-6 hours) with outpatient based care
Intravenous fluids
Normal saline 1 L + 20 mmol/L KCl
Infuse 2 L (over 4 hours)
Multivitamin supplementation
Oral or intravenous (if available) thiamine 25-50 mg daily or intravenous Pabrinex
Antiemetic drugs
For example, one dose of cyclizine 50 mg intravenously or metoclopramide 10 mg intramuscularly, or both

After 4-6 hours: reassess
Continue with outpatient based management once hydrated
Encourage oral fluids and oral antiemetics

Severe dehydration
Urine ketones +3-4

*** Inpatient admission**
Intravenous fluids
Intravenous thiamine
Intravenous antiemetics
Low molecular weight heparin

*If a patient has signs of severe hyperemesis gravidarum, meets the exclusion criteria for outpatient management (see fig 3), or outpatient management is not feasible then admit as inpatient

Fig 2 Treatment options (community, outpatient, or inpatient based management)

Jarvis & Nelson-Piercy. BMJ 2011;342

human reproduction

ORIGINAL ARTICLE *Early pregnancy*

Hospital admission for hyperemesis gravidarum: a nationwide study of occurrence, reoccurrence and risk factors among 8.2 million pregnancies

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Nausea Vomiting in pregnancy: prevalence 80%
Hyperemesis gravidarum: prevalence 1.5%

Fiaschi, Nelson-Piercy, Tata. Human Reproduction, May,2016

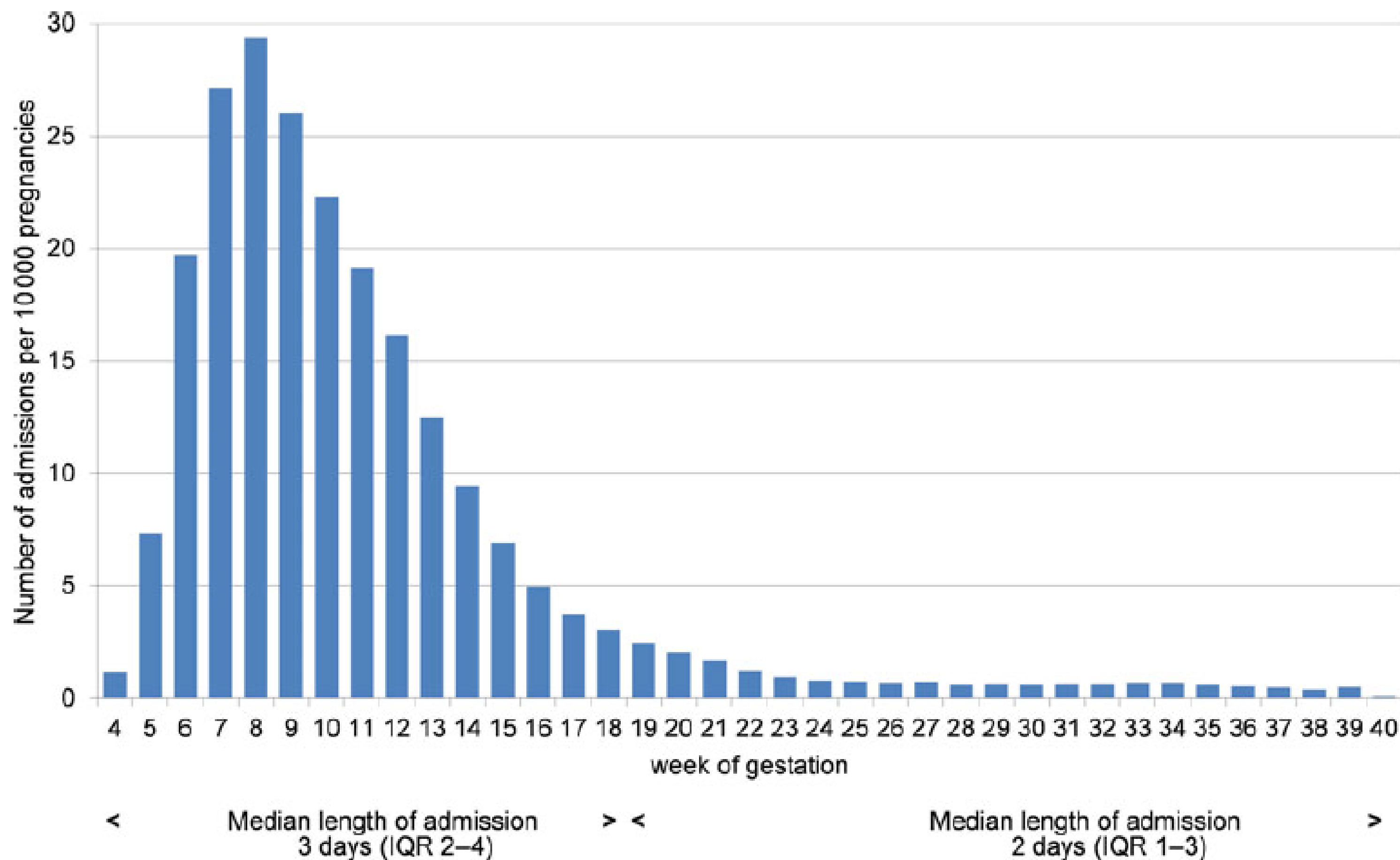


Figure 2 Admissions for hyperemesis gravidarum by gestational week. IQR, interquartile range.

Fiaschi, Nelson-Piercy, Tata. Human Reproduction, May,2016

HG admission and readmission (surrogate for severity) higher risk if :

- younger (<30)
- more socioeconomically deprived status
- Asian or Black ethnicity,
- carrying a female fetus
- multiple pregnancy

Table 1 Risk of hyperemesis gravidarum according to maternal characteristics (n = 8 215 538 pregnancies).

Maternal and pregnancy characteristics	Pregnancies in women						Risk of HG		Risk of HG readmission[a]	
	Without HG n = 8 093 653		With HG n = 121 885		With HG readmission n = 34 704					
	n	%	n	%	n	%	AOR[b]	95% CI	AOR[b]	95% CI
Ethnicity										
White	5 579 842	68.94	74 376	61.02	20 111	57.95	Reference			
Black and white	98 936	1.22	2304	1.89	668	1.92	1.56	1.49–1.63	1.66	1.53–1.81
Asian	738 389	9.12	20 345	16.69	6741	19.42	1.82	1.79–1.86	2.12	2.05–2.19
Black	384 520	4.75	11 928	9.79	3613	10.41	2.14	2.09–2.19	2.33	2.24–2.43
Chinese	41 296	0.51	313	0.26	85	0.24	0.58	0.52–0.66	0.60	0.48–0.76
Other	168 194	2.08	2730	2.24	810	2.33	1.22	1.17–1.27	1.37	1.27–1.48
Missing	1 082 476	13.37	9889	8.11	2676	7.71	0.79	0.77–0.81	0.80	0.76–0.83
Birth plurality[c]										
Singleton	7 932 988	98.01	117 866	96.70	33 398	96.24	Reference			
Twins	121 083	1.50	3383	2.78	1111	3.20	2.09	2.02–2.16	2.43	2.29–2.59
Triplets and more	5613	0.07	163	0.13	62	0.18	2.33	1.99–2.72	3.17	2.46–4.09
Unknown	33 969	0.42	473	0.39	133	0.38	0.97	0.89–1.07	0.95	0.79–1.14
Sex of the baby										
Male	3 868 562	47.80	51 899	42.58	14 314	41.25	Reference			
Female	3 814 614	47.13	62 459	51.24	18 202	52.45	1.23	1.22–1.25	1.30	1.27–1.33

Fiaschi, Nelson-Piercy, Tata. Human Reproduction, May,2016

Comorbidities most strongly associated with HG were:

- parathyroid dysfunction (aOR 3.83, 95% CI 2.28–6.44),
- Hypercholesterolemia (aOR 2.54, 1.88–3.44),
- Type 1 diabetes (aOR 1.95, 1.82–2.09),
- thyroid dysfunction (aOR 1.85, 1.74–1.96).

History of HG was the strongest independent risk factor (aOR . 4.74, 4.46–5.05).

Women with higher parity had a lower risk of HG compared with nulliparous women (aOR . 0.90, 0.89–0.91), which was not explained by women with HG curtailing further pregnancies

Clinical Features

Nausea

Vomiting

Ptyalism

Dehydration

Weight Loss

Protein-calorie malnutrition

Ketonuria

Hyponatraemia

Hypokalaemia

Low urea

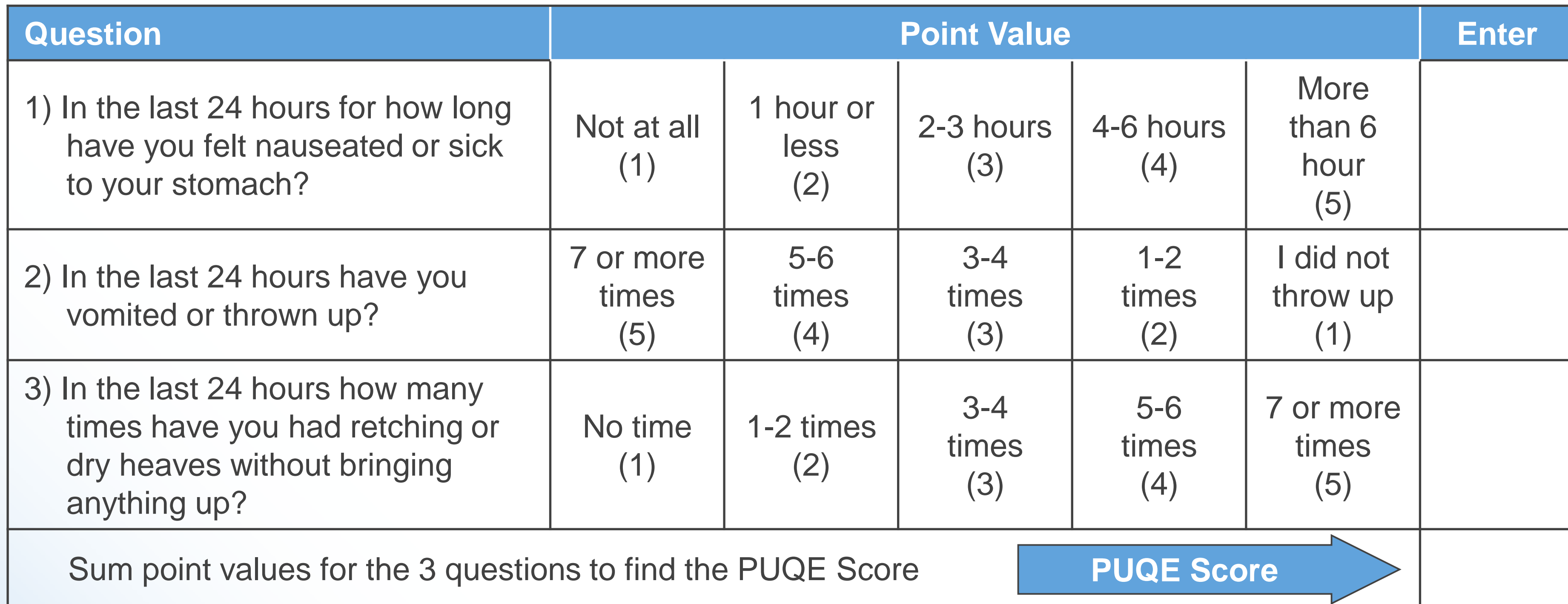
Hypochloraemic alkylosis

Vitamin deficiency

Validated measures of severity

- The Rhodes Index
- Pregnancy-Unique Quantification of Emesis/Nausea (PUQE) index.
- 3 questions, correlate with Rhodes
- Moderate – severe NVP = PUQE ≥ 7

PUQE: Validated Scoring System for NVP



Question	Point Value					Enter
1) 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 hour (5)	
2) 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)	
3) 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)	
Sum point values for the 3 questions to find the PUQE Score				PUQE Score		

PUQE-24 Score	≤6	7-12	13-15
NVP Severity	Mild	Moderate	Severe

Hospital Management

- **Intravenous fluid and electrolytes**
- **Emotional support**
- **Nutritional support - Thiamine**
- **Antiemetic therapy**
- **Thromboprophylaxis**

Royal College of Obstetricians & Gynaecologists

The Management of Nausea and Vomiting of Pregnancy and Hyperemesis Gravidarum

Green-top Guideline No. 69

June 2016

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

D

Ambulatory daycare management should be used for suitable patients when community/primary care measures have failed and where the PUQE score is less than 13.

C

Inpatient management should be considered if there is at least one of the following:

✓

- continued nausea and vomiting and inability to keep down oral antiemetics
- continued nausea and vomiting associated with ketonuria and/or weight loss (greater than 5% of body weight), despite oral antiemetics
- confirmed or suspected comorbidity (such as urinary tract infection and inability to tolerate oral antibiotics).

I visited my GP who said he would prescribe the ondansetron on repeat only because you had authorised it 'because GPs aren't allowed to prescribe high risk medications during pregnancy.'

I politely mentioned that the UK guidelines recommend ondansetron for HG. He was of the view that NVP is very normal so I should 'keep eating and keep vomiting' because something will stay down eventually!

Thank you once again for seeing me at short notice and for making the nausea and vomiting bearable!

I feel so much better and it's all thanks to you! I have been able to eat small meals after weeks of surviving on 2 crackers a day.

Of course you could use my GPs quote - whatever it takes to get GPs to understand that HG is more than a touch of morning sickness!