PREGNANCY PLUS

Inflammatory bowel disease in pregnancy

Charles B Ferguson,[1] Samina Mahsud-Dornan,[1] R Neil Patterson[2]

[1]The Royal Hospitals, Belfast BT12 6BA

[2]Antrim Area Hospital, Antrim, County Antrim, BT41 2RL

Correspondence to: C B Ferguson
charlieferguson@doctors.org.uk

Cite this as: *BMJ* 2008;337:a427
doi:10.1136/bmj.39566.681458.BE

This is one of a series of occasional articles about how to manage a pre-existing medical condition during pregnancy

Active maternal inflammatory bowel disease during pregnancy carries a greater risk to the fetus than appropriate treatment. Careful management is essential to achieve good obstetric outcome

Inflammatory bowel disease is a collective term for chronic illnesses characterised by inflammation of the intestinal tract, the most common of which are ulcerative colitis and Crohn's disease. The natural course of inflammatory bowel disease is marked by periods of relapse followed by periods of remission, and the aims of management are induction and maintenance of remission and avoidance of disease complications.

Diagnosis is often made early in life and 50% of patients are diagnosed before 35 years of age. The incidence of ulcerative colitis is estimated at 10.4 per 100 000 and that of Crohn's disease at around 5.6/100 000 in Western populations.[1 2] About a quarter of female patients with inflammatory bowel disease will conceive after the diagnosis is made, so an understanding of managing the disease during pregnancy is essential for practitioners caring for these patients (see Scenario box).

How does pregnancy affect inflammatory bowel disease?

There is no evidence to suggest that pregnancy causes progression of the disease, and some evidence indicates that it has a favourable effect on disease over time. Two European cohort studies of 634 pregnancies in 303 women showed that pregnancy improves the disease course, with a reduction in flares in subsequent years.[3 4] A retrospective study of 111 patients in the United Kingdom also showed that pregnancy has beneficial effects on the disease—increased parity is associated with a reduction in surgical resections.[5]

The key point is that disease activity at the time of conception strongly influences the course of disease during pregnancy. If the disease is quiescent at the time of conception it will remain so in about two thirds of patients. If the disease is active at the time of conception, two thirds of patients will have ongoing active disease, and the condition will deteriorate in up to 60% of patients and tend to be less responsive to treatment.[6]

The disease will flare in 20-30% of patients with inactive disease at the time of conception, which is similar to the expected rate of relapse in non-pregnant women.[7 8] Such flares tend to respond well to treatment. After birth the risk of a flare is increased if the disease is active at term.[6 9]

How does inflammatory bowel disease affect the outcome of pregnancy and the baby?

Several studies have looked at the effect of inflammatory bowel disease on the outcome of pregnancy and the baby. Results have been conflicting, perhaps because of the heterogeneity of the condition.

Overall, patients with inactive inflammatory bowel disease have no increased risk of adverse pregnancy outcomes,[6] whereas miscarriage can be as high as 35% in patients with active disease.[10] A diagnosis of Crohn's disease, however, increases the risk of low birth weight, preterm delivery, and adverse perinatal outcomes, particularly if the mother has active disease.[6]

A recent retrospective cohort study from California of 461 pregnant women with inflammatory bowel disease found that, compared with controls, these women were more likely to have an adverse outcome of conception or pregnancy and a complication of pregnancy.[11] In this study of patients with mostly mild disease, severity and treatment were not predictive of adverse outcome. Neonatal outcomes were not statistically different between women with inflammatory bowel disease and the control group in this study. Other studies have shown that although preterm delivery rates are higher, adverse perinatal outcomes are not.[12]

METHODS

We searched the PubMed database using the terms "inflammatory bowel disease", "Crohn's disease", "ulcerative colitis", "pregnancy", and "congenital malformations". We assessed the results for relevance and all relevant articles were reviewed where possible. Papers that were referenced in these articles were also reviewed if thought to be relevant.

A meta-analysis of 12 studies looking at 3907 patients found higher rates of adverse outcomes of pregnancy in women with inflammatory bowel disease than in controls.[13] The rate of caesarean section and prematurity was increased by factors of 1.5 and 1.87, respectively, and the incidence of low birth weight was doubled. The risk of congenital abnormalities was more than doubled in patients with inflammatory bowel disease, but it was unclear what factors increased the risk, and further studies are needed to determine this.[13]

Rates of caesarean section are higher in women with inflammatory bowel disease.[13 14] Although this mode of delivery is recommended for women with active perianal Crohn's disease, it is not indicated for those with inactive disease, no perianal disease, or previous ileal pouch-anal anastomosis, and it seems to be overused in these groups.[14] Caesarean section may be considered in patients with impaired anal continence or those with extensive perineal scarring and loss of skin elasticity, because episiotomy or tear may result in the formation of a fistula. Such procedures should be performed under the supervision of an experienced obstetrician.

Because of the increased risk of adverse outcomes in pregnant women with inflammatory bowel disease, these women should be managed by a multidisciplinary team, which includes a maternal fetal medicine specialist and a gastroenterologist. Patients should have regular clinical assessment along with growth scans and biophysical scans every two to four weeks.

How is inflammatory bowel disease treated in pregnancy?

Women with inflammatory bowel disease may wish to stop taking their drugs during pregnancy because of the perceived risk of harm to the fetus. However, it is crucial that the disease is controlled, and fears of adverse drug events—which are not always evidence based—should be allayed. The medical management of inflammatory bowel disease is no different in pregnancy, with a few important exceptions.

SCENARIO

A 32 year old woman (para 2) presented at week 14 of pregnancy with bleeding from the rectum (clots and overt bleeding mixed with stools) but no change in bowel habit. She did not have haemorrhoids, stool cultures were negative, and she had moderate proctitis on proctoscopy. She was given steroid enemas, but these had no effect, and at 29 weeks' gestation she was started on a course of oral prednisolone under the close supervision of the obstetricians. She had a good clinical response, but on tapering the dose her symptoms recurred, and at 35 weeks the dose was increased again to control her symptoms. The obstetricians monitored the fetus weekly and she delivered at term. Her steroid dose was again tapered and mesalazine was started. Subsequent colonoscopy showed mild rectosigmoiditis. She remains on maintenance mesalazine, she is breast feeding, and mother and baby are well.

Assessment of inflammatory bowel disease in pregnancy should rely on clinical factors such as abdominal pain, stool frequency, and rectal bleeding because pregnancy can affect laboratory indices such as haemoglobin concentration, erythrocyte sedimentation rate, and serum albumin. C reactive protein is not normally raised in pregnancy so it is valuable for assessing women with Crohn's disease and ulcerative colitis. Abdominal radiography should be used if the clinical situation warrants it because the risks to the fetus are minimal. Flexible sigmoidoscopy seems to be safe in pregnancy[15]; it does not induce labour or congenital abnormalities, but it should be used only when necessary.[16]

Safety of commonly used drugs for inflammatory bowel disease during pregnancy and when breast feeding[16]

Drug	Pregnancy	Breast feeding	Comments
Aminosalicylates	Considered safe	Considered safe	Sulfasalazine should be switched to an alternative aminosalicylate or supplemented with folic acid (2 mg daily) because it interferes with folate absorption; mesalazine and sulfasalazine are considered safe for breastfeeding mothers in standard doses and olsalazine is probably safe
Prednisolone	Considered safe	Considered safe	Seems to increase the risk of cleft lip and palate but benefits probably outweigh the risk in active disease
Budesonide	Probably safe	Considered safe	Limited data for the oral preparation; safe when inhaled by pregnant women with asthma
Thiopurines	Probably safe	Probably safe	Data come from the transplant literature mostly; these drugs seem to be safe, although some studies show increased rates of preterm delivery, stillbirth, and congenital malformations
Anti-tumour necrosis factor-α	Considered safe	Probably safe	Limited data for adalimumab; more data for infliximab, which seems to be safe
Methotrexate	Contraindicated	Contraindicated	Mutagenic and teratogenic; advise men and women to use reliable contraception while taking and for at least six weeks after discontinuing.
Metronidazole	Safe after first trimester	Contraindicated	Some concerns exist regarding teratogenicity but a meta-analysis showed no increase in birth defects
Fluoroquinolones	Probably safe	Contraindicated	Skeletal abnormalities in animal studies, which have not been reproduced in humans
Loperamide	Probably safe	Contraindicated	Some reports of congenital malformations; excreted in high concentrations in breast milk

Commonly used drugs in inflammatory bowel disease include aminosalicylates, corticosteroids, immunomodulators such as azathioprine and methotrexate, and newer biological agents such as anti-tumour necrosis factor-α drugs. Pooled analysis of 19 mostly retrospective studies suggests that these drugs do not significantly increase the incidence of stillbirth, ectopic pregnancy, low birthweight babies, or miscarriage.[13] Congenital abnormalities may be higher in patients treated with aminosalicylate, anti-tumour necrosis factor-α, and azathioprine, but this may be related to disease activity rather than the drugs themselves.[13]

The table provides details of the safety profiles of drugs commonly used during pregnancy and breast feeding. These data come from the European Crohn's and Colitis Organisation's consensus statement on managing Crohn's disease in pregnancy,[16] and the recommendations are based on varying degrees of evidence, graded according to the Oxford Centre for Evidence Based Medicine. Readers should refer to the original article for further information.

Most of the data on aminosalicylates and corticosteroids relate to oral preparations and, although information on topical preparations is limited, such preparations seem to be safe in pregnancy. Methotrexate is contraindicated in pregnancy, and prospective parents should be advised to discontinue this drug at least six weeks before conception.

Other agents including ciclosporin, tacrolimus, and thalidomide can be used in certain circumstances and under specialist supervision in inflammatory bowel disease and are not covered in this article.

What preconception advice should I give women with inflammatory bowel disease?

Ideally, the patient should discuss problems relating to conception and pregnancy with her gastroenterologist, primary care doctor, and obstetrician in advance. Pregnancy should be planned if possible and disease should be controlled before conception. The importance of adherence to treatment and prevention of relapse during pregnancy should be stressed, and the patient should be monitored as a high risk pregnancy.

Supplementation with folic acid before conception is recommended for all women, and women with inflammatory bowel disease may benefit from higher doses (5 mg daily) because they have a higher rate of vitamin deficiency.

Smoking is more common in patients with Crohn's disease than in the general population and is associated with more severe disease.[17] Pregnant women with Crohn's disease who smoke have a higher risk of low birth weight and preterm labour, and these women should be encouraged to stop smoking.[6]

How does inflammatory bowel disease affect fertility?

None of the drugs commonly used for inflammatory bowel disease seems to have any long term adverse effects on fertility in men or women. Salazopyrin causes reversible oligospermia and reduced sperm motility in men, so prospective fathers should be switched to an alternative aminosalicylate.

Fertility rates in women with inflammatory bowel disease are similar to those of the general female population, except for women with active Crohn's disease, who have reduced fertility.[7-18] However, the average number of children born to parents with inflammatory bowel disease is lower than in the general population, which suggests an association with voluntary childlessness.[19] Infertility rates are increased in some women who have had surgery for inflammatory bowel disease, and a threefold increase has been seen in women with ulcerative colitis after ileal pouch-anal anastomosis.[7 20]

No other commonly used agents seem to affect male fertility and they should be continued. Methotrexate should be stopped six weeks or more before conception, however, because of the risk of teratogenesis. Male sexual dysfunction may increase after ileal pouch-anal anastomosis, although overall sexual satisfaction is improved.[21]

Does breast feeding carry any risks?

The beneficial effects of breast feeding are well documented and include reduced risk of developing inflammatory bowel disease later in life.[22] In a retrospective study of 122 women with inflammatory bowel disease, only 44% of patients breast fed their infants and many stopped their drugs before doing so, which caused a flare in the condition. No evidence exists to suggest that breast feeding causes a flare in inflammatory bowel disease after birth.[8] Many of the most commonly used drugs are safe for breastfeeding mothers (table), although women are recommended to wait for four hours after taking oral steroids before they breast feed. Rarely, diarrhoea can occur in breastfed infants as a result of maternal use of aminosalicylate, and women should be warned about this possible adverse effect.

Conclusion

Many women with inflammatory bowel disease will hope to become pregnant during the course of their disease. Where possible, pregnancy should be planned to coincide with disease remission and any flare in the disease should be treated aggressively because active disease carries the greatest risk to the fetus. Delivery should be transvaginal unless active perianal disease is present or caesarean section is indicated for obstetric reasons.

Contributors: CBF searched the literature and drafted the paper. SM-D revised and edited the paper from an obstetric perspective. RNP revised and edited the paper and is guarantor.
Competing interests: None declared.
Provenance and peer review: Not commissioned; externally peer reviewed.
Patient consent not required (patient anonymised, dead, or hypothetical).

1 Binder V. Epidemiology of IBD during the twentieth century: an integrated view. *Best Pract Res Clin Gastroenterol* 2004;18:463-79.
2 Loftus EV Jr. Clinical epidemiology of inflammatory bowel disease: incidence, prevalence, and environmental influences. *Gastroenterology* 2004;126:1504-17.

3 Castiglione F, Pignata S, Morace F, Sarubbi A, Baratta MA, D'Agostino L, et al. Effect of pregnancy on the clinical course of a cohort of women with inflammatory bowel disease. *Ital J Gastroenterol* 1996;28:199-204.
4 Riis L, Vind I, Politi P, Wolters F, Vermeire S, Tsianos E, et al. Does pregnancy change the disease course? A study in a European cohort of patients with inflammatory bowel disease. *Am J Gastroenterol* 2006;101:1539-45.
5 Nwokolo CU, Tan WC, Andrews HA, Allan RN. Surgical resections in parous patients with distal ileal and colonic Crohn's disease. *Gut* 1994;35:220-3.
6 Willoughby CP, Truelove SC. Ulcerative colitis and pregnancy. *Gut* 1980;21:469-74.
7 Hudson M, Flett G, Sinclair TS, Brunt PW, Templeton A, Mowat NA. Fertility and pregnancy in inflammatory bowel disease. *Int J Gynaecol Obstet* 1997;58:229-37.
8 Kane S, Lemieux N. The role of breastfeeding in postpartum disease activity in women with inflammatory bowel disease. *Am J Gastroenterol* 2005;100:102-5.
9 Woolfson K, Cohen Z, McLeod RS. Crohn's disease and pregnancy. *Dis Colon Rectum* 1990;33:869-73.
10 Khosla R, Willoughby CP, Jewell DP. Crohn's disease and pregnancy. *Gut* 1984;25:52-6.
11 Mahadevan U, Sandborn WJ, Li DK, Hakimian S, Kane S, Corley DA. Pregnancy outcomes in women with inflammatory bowel disease: a large community-based study from northern California. *Gastroenterology* 2007;133:1106-12.
12 Elbaz G, Fich A, Levy A, Holcberg G, Sheiner E. Inflammatory bowel disease and preterm delivery. *Int J Gynaecol Obstet* 2005;90:193-7.
13 Cornish J, Tan E, Teare J, Teoh TG, Rai R, Clark SK, et al. A meta-analysis on the influence of inflammatory bowel disease on pregnancy. *Gut* 2007;56:830-7.
14 Ilnyckyji A, Blanchard JF, Rawsthorne P, Bernstein CN. Perianal Crohn's disease and pregnancy: role of the mode of delivery. *Am J Gastroenterol* 1999;94:3274-8.
15 Cappell MS, Colon VJ, Sidhom OA. A study at 10 medical centers of the safety and efficacy of 48 flexible sigmoidoscopies and 8 colonoscopies during pregnancy with follow-up of fetal outcome and with comparison to control groups. *Dig Dis Sci* 1996;41:2353-61.
16 Caprilli R, Gassull MA, Escher JC, Moser G, Munkholm P, Forbes A, et al. European evidence based consensus on the diagnosis and management of Crohn's disease: special situations. *Gut* 2006;55(suppl 1):i36-58.
17 Cosnes J, Carbonnel F, Beaugerie L, Le Quintrec Y, Gendre JP. Effects of cigarette smoking on the long-term course of Crohn's disease. *Gastroenterology* 1996;110:424-31.
18 Mayberry JF, Weterman IT. European survey of fertility and pregnancy in women with Crohn's disease: a case control study by European collaborative group. *Gut* 1986;27:821-5.
19 Baird DD, Narendranathan M, Sandler RS. Increased risk of preterm birth for women with inflammatory bowel disease. *Gastroenterology* 1990;99:987-94.
20 Waljee A, Waljee J, Morris AM, Higgins PD. Threefold increased risk of infertility: a meta-analysis of infertility after ileal pouch anal anastomosis in ulcerative colitis. *Gut* 2006;55:1575-80.
21 Tiainen J, Matikainen M, Hiltunen KM. Ileal J-pouch-anal anastomosis, sexual dysfunction, and fertility. *Scand J Gastroenterol* 1999;34:185-8.
22 Rigas A, Rigas B, Glassman M, Yen YY, Lan SJ, Petridou E, et al. Breast-feeding and maternal smoking in the etiology of Crohn's disease and ulcerative colitis in childhood. *Ann Epidemiol* 1993;3:387-92.

Accepted: 1 April 2008

LESSON OF THE WEEK

Omeprazole and refractory hypomagnesaemia

N Shabajee,[1] E J Lamb,[1] I Sturgess,[2] R W Sumathipala[2]

[1]Department of Clinical Biochemistry, East Kent Hospitals NHS Trust, Kent and Canterbury Hospital, Canterbury CT1 3NG
[2]Department of Health Care of the Older Person, East Kent Hospitals NHS Trust
Correspondence to: E J Lamb
Edmund.lamb@ekht.nhs.uk

Cite this as: *BMJ* 2008;337:a425
doi:10.1136/bmj.39505.738981.BE

Omeprazole may cause hypomagnesaemia, along with hypocalcaemia and hypokalaemia

Hypomagnesaemia is common in hospital patients and is often accompanied by other electrolyte abnormalities, such as hypocalcaemia, hypokalaemia, and hypophosphataemia, that may remain refractory to treatment until the underlying magnesium deficiency is corrected.[1] We present two patients with refractory chronic hypokalaemia and hypocalcaemia secondary to hypomagnesaemia that resolved after withdrawal of the proton pump inhibitor omeprazole.

Case 1

A 78 year old woman was admitted to hospital after an exacerbation of chronic obstructive pulmonary disease accompanied by diarrhoea and vomiting. Her medical history included breast cancer, ischaemic heart disease, myocardial infarction, osteoporosis, and spinal stenosis. A several year history of paraesthesia, numbness, and weakness in her limbs had been attributed to spinal stenosis, but surgery had been ruled out because anaesthesia was risky. Seven years earlier she had been investigated for postprandial pain, early satiety, nausea, and weight loss. Non-erosive duodenitis, diverticular disease, and a hiatus hernia had been diagnosed. She had been prescribed omeprazole (40 mg/day) and her symptoms improved slightly. In addition, she was receiving spironolactone, bumetanide, furosemide, gabapentin, co-codamol, hyoscine butylbromide, glyceryl trinitrate, losartan, aspirin, atorvastatin, ipratropium bromide, and salmeterol.

She was hypokalaemic on admission (table 1), and this failed to respond to withdrawal of diuretics and intravenous and oral potassium replacement. On day 4 she developed hallucinations and became agitated: muscular excitability was noted but Chvostek's sign was absent. She remained markedly hypokalaemic and was also hypocalcaemic and hypomagnesaemic: retrospective analysis of samples from the day of her admission showed that magnesium and calcium concentrations had been low then. She was also hypophosphataemic. Her symptoms resolved after treatment with intravenous magnesium sulphate, calcium gluconate, and continued potassium. Magnesium concentration was normal while she received intravenous replacement, but when it was stopped magnesium fell again. She was discharged after 10 days and was taking oral magnesium glycerophosphate and a phosphate supplement; her diuretics were withheld even though she had some ankle oedema.

At outpatient follow-up, serum magnesium and calcium concentrations remained low, and her history was reviewed for potential causes of magnesium loss.

She had had no further diarrhoea and denied using laxatives or alcohol. Measurement of urinary calcium and magnesium concentrations suggested appropriate renal conservation (table 1). In light of a report of two cases of hypomagnesaemic hypoparathyroidism associated with omeprazole,[2] we discontinued omeprazole and prescribed the H_2 receptor antagonist ranitidine. Electrolyte status improved dramatically and was maintained even after her magnesium supplements were stopped (table 1). The patient remains well and reported an improved appetite after omeprazole was withdrawn.

Case 2

An 81 year old man who lived independently was admitted to hospital after presenting to his general practitioner with dizziness and nausea that had been ongoing for three months but had worsened in the previous two days. He had vomited after meals but had had no diarrhoea; he had also had urinary incontinence for two days and reported polyuria over the previous month.

His medical history included hypertension, ischaemic heart disease, benign prostatic hyperplasia, and diabetes controlled by diet. He was taking omeprazole (40 mg/day), isosorbide mononitrate, atenolol, atorvastatin, lisinopril, quinine, amlodipine, olmesartan, and aspirin. He had no history of alcohol misuse.

He had muscle cramps and paraesthesia, with pins and needles in his hands; Trousseau's sign was elicited at venepuncture. He was very unsteady, falling to both sides, and had an irregular heartbeat. Hypokalaemia, hypocalcaemia, and hypomagnesaemia were seen, and his symptoms were attributed to these. Parathyroid hormone concentration was subsequently reported as within the reference range but inappropriate for his degree of hypocalcaemia (table 2). His incontinence and raised C reactive protein were attributed to a urinary tract infection, which was treated with trimethoprim.

With oral potassium and intravenous calcium gluconate and magnesium glycerophosphate replacement his calcium and potassium concentrations gradually normalised and his dizziness and paraesthesia improved, but he developed hypomagnesaemia whenever the supplements were stopped. While in hospital he developed bradycardia (pulse 48 beats/min) and hypotension (blood pressure 90/55 mm Hg), and it was suggested that this might account for his dizzy episodes. His antihypertensive drug was stopped. An electrocardiogram showed atrial flutter and long (4 second) pauses. As his hypomagnesaemia was thought to be contributing to the abnormal electrocardiogram, we considered that the hypomagnesaemia should be corrected before fitting a pacemaker.

Drug review raised the possibility that omeprazole was causing his electrolyte disturbances, and it was stopped. Within a few days the patient "felt great." Normal electrolytes were maintained without supplementation. He was discharged with outpatient follow-up.

DISCUSSION

Both cases of refractory hypomagnesaemia associated with concurrent electrolyte abnormalities resolved after omeprazole was withdrawn. In the first case we could document renal conservation of magnesium and calcium while the patient was receiving omeprazole. In the second case we documented an inappropriately normal parathyroid hormone response to hypocalcaemia, classically associated with hypomagnesaemia.[3] These data seem to support a causative role of omeprazole in the development of hypomagnesaemia, as described earlier by Epstein et al.[2]

The symptoms of magnesium deficiency relate to the central role of magnesium in ATP metabolism and

Table 1 | Biochemical changes in case 1

	During treatment with omeprazole							After withdrawal of omeprazole				
Variable	Day 1	Day 4	Day 5	Day 6	Day 9	Day 16	Day 23	Day 60	Day 67	Day 74*	Day 90	Reference range
Sodium	142											135-145 mmol/l
Potassium	2.7	2.4	2.5	3.3	3.4	4.1	3.4	4.5	4.8	4.8	4.5	3.8-5.0 mmol/l
Creatinine	59											44-80 umol/l
Calcium (adjusted)†	1.5	1.5	1.8	1.9	2.0	1.8	1.8	2.0	2.1	2.1	2.3	2.1-2.6 mmol/l
Phosphate				0.38	0.63	1.02	1.16	1.14				0.87-1.45 mmol/l
Magnesium	<0.10	<0.10	0.68	0.92	0.50	0.25	0.25	0.49	0.82	0.85	0.83	0.70-1.00 mmol/l
Albumin	34											35-50 g/l
Alkaline phosphatase	64											42-128 U/l
Parathyroid hormone										49		10-72 ng/l
Urinary Mg/creatinine ratio								0.1	1.1	0.5	0.7	n/a mmol/mmol
Urinary Ca/creatinine ratio								0.1	0.8	0.6	0.9	n/a mmol/mmol

*Magnesium and potassium supplementation stopped.
†Adusted calcium (mmol/l)=measured calcium+([40−measured albumin (g/l)]×0.25).

Table 2 | Biochemical changes in case 2

Variable	During treatment with omeprazole				After withdrawal of omeprazole				Reference range
	Day 1	Day 3	Day 4	Day 5	Day 17	Day 20	Day 24*	Day 82	
Sodium	139								135-145 mmol/l
Potassium	2.9	3.7	4.0	4.4	4.3	5.1	4.6	3.8	3.8-5.0 mmol/l
Creatinine	77								62-106 umol/l
Calcium (adjusted)†	1.4	1.7	1.8	1.9	2.5	2.5	2.5	2.3	2.1-2.6 mmol/l
Phosphate	1.12	0.68	0.57	0.72	0.82	0.96	0.94	0.87	0.87-1.45 mmol/l
Magnesium	0.19		0.63	0.48	0.46	0.73	0.81	0.93	0.70-1.00 mmol/l
Albumin	35								35-50 g/l
Alkaline phosphatase	85								42-128 U/l
C reactive protein	94	107			<1				<10 mg/l
Parathyroid hormone	38				33				10-72 ng/l

*Magnesium and potassium supplementation stopped.
†Adusted calcium (mmol/l)=measured calcium+([40−measured albumin (g/l)]×0.25).

neuromuscular transmission, but it is generally difficult to ascribe symptoms solely to magnesium deficiency because other electrolyte abnormalities are present. However, refractory cardiac dysrrhythmias such as those seen in case 2 have been ascribed to magnesium deficiency.[1] The polyuria in case 2 was possibly related to the patient's chronic hypokalaemia, which causes down-regulation of aquaporin-2 water channels and hence resistance to antidiuretic hormone.[4] Both patients had been receiving omeprazole for a long time. Vomiting and diarrhoea, exacerbated by use of a loop diuretic in case 1, may have unmasked an underlying magnesium deficit.

Absorption of dietary magnesium occurs in the ileum and colon via carrier mediated transport and simple diffusion.[1] The kidneys are highly efficient organs in magnesium conservation: about 3% of filtered magnesium is lost in the urine, most of which is reabsorbed in the thick ascending limb of the loop of Henle.[5] The renal conservation seen in case 1 and also by Epstein et al[2] suggests that the action of omeprazole is unlikely to be at the renal level. Low gastric pH is thought to be important for the absorption of minerals. Metal ions bind to ligand binding sites on dietary fibre and may be displaced by hydrogen ions, facilitating absorbtion. Waves of acidity entering the small intestine from the stomach may help to keep mineral salts in solution until they can be absorbed.[6] Omeprazole induced hypochlorhydria could therefore theoretically cause mineral deficiency, although there is no evidence that omeprazole use, at least in the short term, inhibits magnesium absorption.[7]

Although the mechanism remains unclear, there seems little doubt that omeprazole may cause hypomagnesaemia. Given the frequency with which this drug is prescribed it would seem likely that use of the drug in the absence of other illness predisposing to electrolyte imbalance does not invariably cause hypomagnesaemia, but these cases are unlikely to be isolated. Doctors should consider omeprazole as a possible causative agent when investigating hypomagnesaemia.

We thank the staff of the clinical biochemistry department.
Competing interests: None declared.
Provenance and peer review: Not commissioned; externally peer reviewed.

1 Ryan MF. The role of magnesium in clinical biochemistry: an overview. *Ann Clin Biochem* 1991;28:19-26.
2 Epstein M, McGrath S, Law F. Proton-pump inhibitors and hypomagnesemic hypoparathyroidism. *N Engl J Med* 2006;355:1834-6.
3 Allgrove J, Adami S, Fraher L, Reuben A, O'Riordan JL. Hypomagnesaemia: studies of parathyroid hormone secretion and function. *Clin Endocrinol (Oxf)* 1984;21:435-49.
4 Marples D, Frokiaer J, Dorup J, Knepper MA, Nielsen S. Hypokalemia-induced downregulation of aquaporin-2 water channel expression in rat kidney medulla and cortex. *J Clin Invest* 1996;97:1960-8.
5 Quamme GA. Renal magnesium handling: new insights in understanding old problems. *Kidney Int* 1997;52:1180-95.
6 Evenepoel P. Alteration in digestion and absorption of nutrients during profound acid suppression. *Best Pract Res Clin Gastroenterol* 2001;15:539-51.
7 Serfaty-Lacrosniere C, Wood RJ, Voytko D, Saltzman JR, Pedrosa M, Sepe TE, et al. Hypochlorhydria from short-term omeprazole treatment does not inhibit intestinal absorption of calcium, phosphorus, magnesium or zinc from food in humans. *J Am Coll Nutr* 1995;14:364-8.

Accepted: 25 October 2007