

Investigation and Management
of
Vitamin B₁₂ and Folate Deficiency

Date: January 2019

Policy Profile	
Policy Reference Number	CoCH 1
Version	9
Status	Final
Trust Lead	Dr S Tueger, Mr Martin Langan
Implementation Date	January 2019
Last Review Date	January 2019
Next Formal Review	January 2020
Approval Record	

• Introduction

Vitamin B₁₂ (or serum cobalamin) and folate levels are amongst the more commonly requested haematological assays but are often used inappropriately. These guidelines are intended to ensure appropriate use and interpretation of these investigations, together with giving brief guidance on the management of patients with documented deficiency.

Normal Ranges:

- Vitamin B₁₂ (150-750 ng/l). However, vitamin B₁₂ levels just within the normal range can lead to symptoms so results between 150-200 ng/l should be assessed on an individual basis.
- Folate (>4 µg/L)

Causes of vitamin B12 deficiency

- Inadequate vitamin B12 in diet (Strict vegan)
- Vitamin B12 malabsorption:
 - Gastric causes: pernicious anaemia, total or partial gastrectomy, coeliac disease
 - Intestinal causes: chronic tropical sprue, crohn's disease and ileal resection, congenital selective malabsorption with proteinuria (AR megaloblastic anaemia), fish tapeworm
 - Pancreatic failure
- Pernicious anaemia (PA)
 - Caused by loss of gastric parietal cells due to autoimmune atrophic gastritis resulting in reduced IF production
 - Commonly associated with other autoimmune conditions (esp. vitiligo and thyroid disease) and slightly increased risk of gastric carcinoma.
 - Familial tendency
- Chronic alcoholism
- Drugs
 - Oral contraceptive pill
The reduced serum B12 level is thought to be due to a reduction in the level of the vitamin B12-carrying protein (transcobalamin) rather than a deficiency of vitamin B12 *per se*.
 - Biguanide (e.g. Metformin) therapy (inhibits vitamin B12 absorption)
 - Cholestyramine
 - Slow K
 - Long term use of PPI or H2-antagonist drugs

• Criteria for requesting Vitamin B₁₂ and / or folate levels:

Absolute indications for measuring vitamin B₁₂:

- Haematological (in increasing order of severity)
 - Isolated red cell macrocytosis
 - Macrocytic anaemia (esp. if MCV >110fl)
 - Pancytopenia (esp. if MCV >120fl)
- Neurological or psychiatric
 - Peripheral neuropathy
 - Cognitive change e.g. dementia
 - Optic neuritis
- Gastrointestinal
 - Investigation of possible malabsorptive process
- Other (rare)
 - Angular cheilosis
 - Sore beefy red tongue

Investigations to help define the cause of the vitamin B12 deficiency

- FBC High MCV >110 fl . 25% of patient will have normal MCV
- Film: hyper segmented neutrophils of >5% of neutrophils with >5 or more lobes
- Anti-intrinsic factor (anti-IF) antibodies. Should be done before starting treatment
- Thyroid function tests and anti-thyroid antibodies
- Test for celiac disease (Tissue transglutaminase (tTG))
- Tests for generalised malabsorption (if symptoms are suggestive) . Please discuss with gastroenterologist

Anti-gastric parietal cell antibodies are present in 85% of cases, but are very non-specific, also being found in autoimmune type A gastritis, thyroid disease, iron deficiency anaemia and 3-10% of healthy population.

Therefore, anti-gastric parietal cell antibody testing for diagnosing pernicious anaemia is not recommended.

- **Interpretation of results**

Vitamin B₁₂

Clinically significant vitamin B₁₂ deficiency may be present even with vitamin B₁₂ levels in the low normal range, especially in elderly people. In difficult cases, further investigations may be appropriate – please discuss with a consultant haematologist. Where there is a neurological or haematological abnormality and low or borderline vitamin B₁₂, giving a course of treatment (see below) is unlikely to do harm. If no clinical response, treatment should be discontinued.

Folate

If there is clinical suspicion of folate deficiency but serum folate levels are within normal limits, it would be advisable to check red cell folate. Please discuss these cases with a consultant haematologist.

Conditions associated with folate deficiency include:

- Dietary deficiency
- Alcoholism
- Malabsorption
- Haemolysis
- Malignancy
- Pregnancy

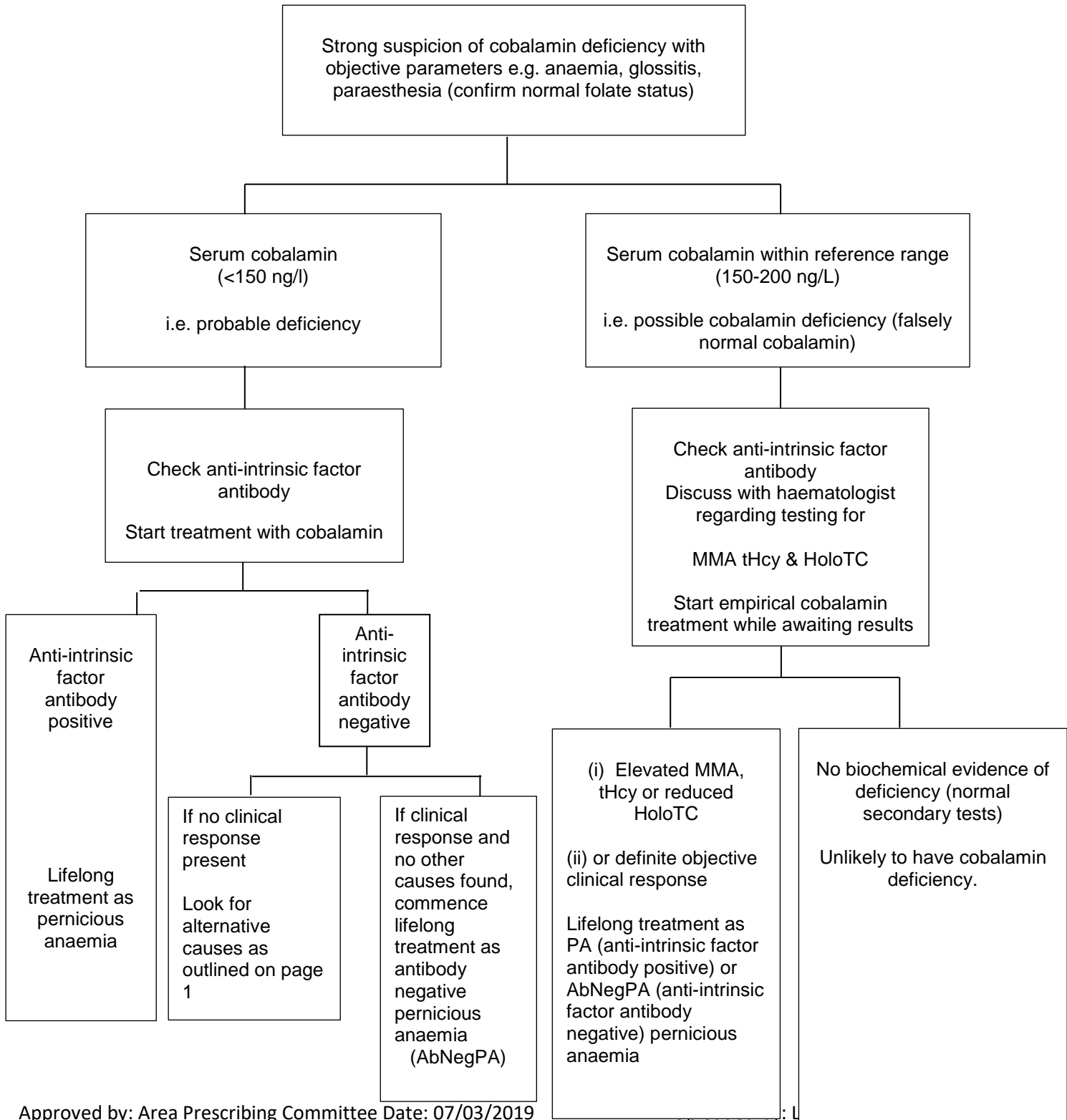
For interpretation of vitamin B₁₂ and folate results, please see the table below:

	Serum folate	RBC folate	Serum vitamin B ₁₂
Negative folate balance	Low	Normal	Normal
Folate deficiency	Low	Low	Normal/low
B12 deficiency	Normal/high	Normal/low	Low
Combined Deficiency	Low	Low	Low

Investigation and management of vitamin B₁₂ deficiency can be divided into two, based on indications for assessment:

- Investigation and management of patients presenting with a strong clinical suspicion of cobalamin deficiency and objective parameters to support this. (Algorithm 1)
- Investigation without objective clinical parameters (Algorithm 2)

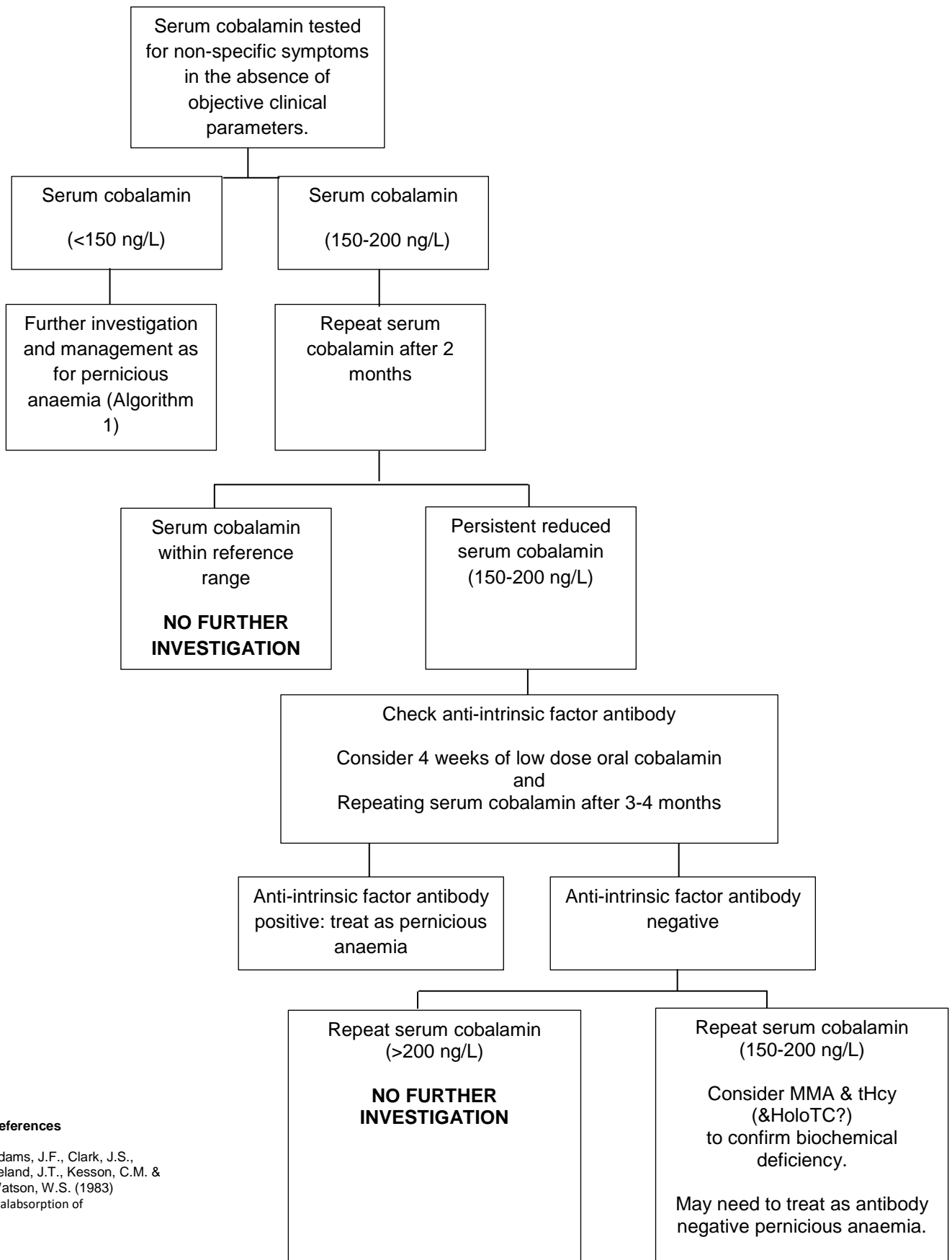
Algorithm 1. Investigation and management of patients presenting with a strong clinical suspicion of cobalamin deficiency and objective parameters to support this.



Approved by: Area Prescribing Committee Date: 07/03/2019

Review by: January 2020

Algorithm 2. Investigation of low serum cobalamin in patients without objective clinical parameters.



References

Adams, J.F., Clark, J.S., Ireland, J.T., Kesson, C.M. & Watson, W.S. (1983) Malabsorption of

When to refer:

- Uncomplicated vitamin B12 or folate deficiency does NOT require routine referral for Haematology outpatient assessment.
- Consider referring to Haematology:
 - The cause of vitamin B12 or folate deficiency is uncertain following investigations, or other blood disorder is suspected.
 - Failure to respond to therapy i.e. there is not a prompt rise in Hb (Note: Vitamin B12 levels do not require re-checking if the patient is already on replacement therapy). The FBC can be used to monitor response.
- Refer to gastroenterologist urgently if there is a suspicion of gastric cancer (eg, because of co-existing iron deficiency).

Consider referral to a dietitian

- If vitamin B12 or folate deficiency is thought to be due to a poor diet.

Treatment and monitoring of vitamin B₁₂ and Folate Deficiency

INAPPROPRIATE TREATMENT OF VITAMIN B₁₂ DEFICIENCY WITH FOLIC ACID CAN CAUSE IRREVERSIBLE NERVE DAMAGE. IF IN DOUBT PLEASE DISCUSS WITH A CONSULTANT HAEMATOLOGIST BEFORE COMMENCING TREATMENT.

IN CASES PRESENTING WITH SEVERE ANAEMIA, BLOOD TRANSFUSION MAY BE HAZARDOUS BY PRECIPITATING HIGH OUTPUT CARDIAC FAILURE – AGAIN PLEASE DISCUSS WITH A HAEMATOLOGIST.

For people with neurological involvement:

- Ideally, management should be guided by a specialist, but if specialist advice is not immediately available, consider the following:

Initially administer hydroxocobalamin 1 mg intramuscularly on alternate days until there is no further improvement, and then administer hydroxocobalamin 1 mg intramuscularly every 2 months.

For people with no neurological involvement:

- Initially administer hydroxocobalamin 1 mg intramuscularly on alternate days for 2 weeks.
- Maintenance dose (where the vitamin B₁₂ deficiency is not thought to be diet related): administer hydroxocobalamin 1 mg intramuscularly every 3 months for life (standard dose). Note that the manufacturers' licence is for every 2–3 months.
- Maintenance dose (where vitamin B12 deficiency is thought to be diet related): advise people either to take oral cyanocobalamin tablets 50–150 micrograms daily between meals or have a twice-yearly hydroxocobalamin 1 mg injection. The injection regimen may be preferred in the elderly (who are more likely to have malabsorption), and vegans (as currently available brands of oral cyanocobalamin may not be suitable for vegans).
- In vegans, this treatment may need to be life-long, whereas in other people with dietary deficiency replacement treatment can be stopped once the vitamin B₁₂ levels have been corrected and the diet has improved.
- Advise people to eat foods rich in vitamin B₁₂. Foods which have been fortified with vitamin B₁₂ (for example some soya products, and some breakfast cereals and breads) are good alternative sources to meat, eggs, and dairy products. (See British Dietetic Association Guidelines for Supplementation of Vegetarian Diets – attached)
- Add folic acid 5mg PO daily for 4 weeks for patients with anaemia due to vitamin B12 deficiency. This avoids the possibility of inducing folate deficiency consequent upon the increased normoblastic red cell production that should follow after providing a source of the previously deficient vitamin B12.

Folate

Patients with documented folate deficiency should be treated with oral folic acid. Standard dosing is 5mg/day orally for 1-4 months, or until complete haematological recovery occurs. The oral route is sufficient even in those with malabsorption.

Vitamin B₁₂ deficiency must be excluded before giving folic acid to a patient with megaloblastic anaemia since administration of folic acid may worsen neurological complications of untreated vitamin B₁₂ deficiency.

Monitoring

How should vitamin B₁₂ or folate deficiency be monitored in patients who have or are receiving replacement?

Initially: FBC after 10–14 days to document the response and after 8 weeks to confirm a normal blood count.

Long term:

Folate: not necessary unless the cause persists

Vitamin B₁₂: not necessary in replaced patients

Patients with PA have an increased risk of developing gastric or colorectal adenocarcinoma, with the risk appearing greatest in the first two years after diagnosis, so patients should be monitored for signs or symptoms of these malignancies during this period.

Patients presenting with severe anaemia may develop a transient hypokalaemia following treatment, the clinical significance of which is unknown, and potassium replacement therapy may be considered.

No further testing for cobalamin levels is required.

Pitfalls of vitamin B₁₂ measurement

There are many pitfalls for the assessment of vitamin B₁₂:

Drug use:

Metformin

Metformin paradoxically reduces the serum cobalamin level but improves intracellular metabolism. Reduced vitamin B₁₂ levels in those on metformin are rarely clinically significant and usually improve with dietary improvement of vitamin B₁₂ intake. Vitamin B₁₂ should only be assessed in patients with diabetes if objective evidence of deficiency is present including peripheral neuropathy or macrocytic anaemia. Low levels of vitamin b12 should be investigated with anti-intrinsic factor antibodies and should be treated with a short course of vitamin B₁₂ (50-150 micrograms orally for 4 weeks). Response should be assessed clinically and continued if benefit is shown. There is no need for prophylactic vitamin B₁₂ administration. It has been suggested that an increased intake of calcium reverses the vitamin B₁₂ malabsorption induced by metformin. Bauman WA et al, *Diabetes Care* 2000 (23) 1227-31.

Proton pump inhibitors and H2 antagonists

Prolonged use of proton pump inhibitors causes gastric hypochlorhydria leading to reduced separation of vitamin B₁₂ from food. This usually causes a subclinical deficiency but oral replacement (50-150 micrograms orally) may be appropriate if objective evidence of deficiency is found.

Gastrointestinal surgery

Both gastrectomy and bariatric surgery can lead to vitamin B₁₂ deficiency and require regular monitoring and replacement If levels are falling despite good dietary intake. Oral replacement is often inadequate in these patients.

Pregnancy

Pregnancy causes a physiological lowering of plasma cobalamin levels by up to 30% by the third trimester. Vitamin B₁₂ levels should not routinely be measured during pregnancy. Empirical treatment of cobalamin deficiency should be given if paraesthesia, neuropathy or megaloblastic anaemia occurs.

Vegetarian and vegan diets

Vegetarians and vegans are at increased risk of vitamin B₁₂ deficiency especially during pregnancy and when breastfeeding. Monitoring should be considered, especially at high-risk times, and oral supplementation may be required.

REVIEW OF PATIENTS ON LONG TERM VITAMIN B₁₂

Check Intrinsic Factor (IF) antibodies and if negative and no original macrocytic anaemia, STOP vitamin B₁₂ injections and recheck vitamin B₁₂ levels at 6 months and then 12 months. If still in normal range, only recheck if symptomatic or develop new anaemia.

If patients are asymptomatic and no cause for vitamin B₁₂ deficiency was found, then stopping vitamin B₁₂ injection or reducing frequency to twice/year in first instance and then stopping would be very reasonable if patients remain asymptomatic.

For those with a dietary cause, dietary advice should be offered and a switch to vitamin B₁₂ tablets considered.

References

- NICE guideline on Anaemia - and vitamin B₁₂ folate deficiency: <http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency>
- Devalia, V. et al. (2014). Guidelines for the diagnosis and treatment of cobalamin and folate disorders. British Journal of Haematology, 496-513.
- Remacha, A. et al. (2003). Vitamin B₁₂ metabolism in HIV-infected patients in the age of highly active antiretroviral therapy: role of homocysteine in assessing vitamin B₁₂ status. American Journal of Clinical Nutrition, pp 420–4.