

Chapter 5 Vitamin B12 in pregnancy – preparing for a healthy child

To shame what is strong, God has chosen what the world counts as weakness. He has chosen things low and contemptible, near nothings, to overthrow the existing order.

1 Corinthians 1:27b to 30

Figure 5-1 Preventive programme summary

4 to 6 months before pregnancy:

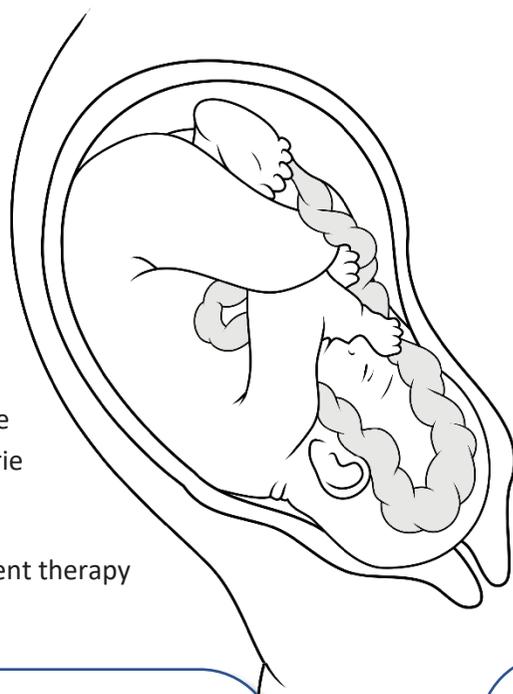
Routine blood test for: FBC + B12 + folic acid, serum ferritin, fasting blood sugar, TSH - T3 - T4, LFT + U+E, Lipid/Vitamin D/AM Cortisol (if indicated).

Follow up one- to three-monthly as required.

Newborn:

Routine B12 and folic acid screening test in the newborn, along with current practice of Guthrie and phenylketonuria.

Commence without delay optimum replacement therapy for any of the above deficiencies diagnosed.



Mother and Father should:

Stop smoking (CO + CN poisoning).

Reduce alcohol consumption.

Follow a healthy balanced diet.

Withdraw and stop any harmful or unneeded prescription medication.

Avoid stress and have adequate rest and leisure activities.

Identify vegetarian and vegan would-be mothers, advise appropriately and follow them up monthly.

Achieve these beneficial results:

Baby advanced neurologically and physically (milestones);

Avoids many neurological and psychiatric diseases in later life: impact on dementia and cancer;

Mother enjoys pregnancy and breast-feeding without fatigue or depression;

Baby continues to receive B12 and folic acid via breast milk – and maternal bonding achieved.

Avoid these potential problems:

Hypotonia (floppy baby syndrome);

cleft lip; cleft palate; Down Syndrome;

Neural tube defects (NTDs); Spina Bifida;

Attention Deficit Hyperactivity Disorder (ADHD); foetal alcohol spectrum disorder (FASD); Meningocele.

Mother avoids miscarriages, haemorrhage, postnatal depression, hair loss, fainting, eclampsia and morning sickness during pregnancy.

5.1 Advance preparation for a healthy pregnancy

In this chapter we explain that women contemplating pregnancy should be tested for vitamin B12 deficiency and supplemented if necessary just as they are currently for folate (folic acid). Vitamin B12 is completely safe for adults, for pregnant women, for foetuses and babies, for small children, for any age in fact. Lack of vitamin B12 presents a serious risk for the health of both mother and child.

It is vital to provide an optimum vitamin and nutritional status in the mother to achieve gene expression correctly in the neonate. Couples preparing to conceive should consider all factors illustrated in the Preventive Programme Summary (Figure 5-1). Vitamin B12 is needed for folate metabolism in the body which leads in various steps to compounds necessary for the synthesis of DNA (which contains the instructions for all life processes) and the correct functioning of every cell in the human body (see Figure 9-1). It is also needed to convert homocysteine to methionine, which in turn leads to production of S-adenosyl methionine (SAME) used in building thousands of compounds and proteins needed for healthy cells, tissues and organs. Vitamin B12 has wide-ranging effects on fertility, the health of the mother during pregnancy, the health of the child as embryo, neonate, infant and into later life. Low vitamin B12 levels in pregnant women have been linked to increased risk of early and recurrent miscarriage, premature births and low birth weight (Obeid et al., 2017). They have also been linked to increased risk of having a child with congenital heart defects and hyperhomocysteinaemia in the mother, leading to risk of cardiovascular problems in both mother and child in later life (Verkleij-Hagoort et al., 2006). Most importantly, vitamin B12 deficiency can lead to functional folic acid deficiency (because of the interaction between the two vitamins) which is well known to cause neural tube defects (NTDs).

The following summarises some key points regarding vitamin B12 in pregnancy:

1. “Both folate and cobalamin [B12] deficiency have been implicated in recurrent fetal loss and fetal neural tube defects” at birth (Hoffbrand, 2018, pp. 701-702). Folate deficiency is now rare due to dietary supplementation, but B12 deficiency is largely ignored.
2. Vitamin B12 and folic acid (together) lower homocysteine in both mother and baby, and prevent future cardiovascular disease risk.
3. “Long-term nutritional cobalamin deficiency in infancy leads to poor brain development and impaired intellectual development. In infancy there may be feeding difficulties, lethargy, and coma” (Hoffbrand, 2018, p. 701). Continued vitamin B12 deficiency, if left untreated, may predispose a person to dementia in later life.
4. The nutritional status in mother, foetus and neonate has a substantial impact on all aspects of development at this critical time. Vitamin B12 is a methyl donor for DNA and gene expression. Providing a methyl donor in the diet, before and during pregnancy, alters the state of methylation of the offspring's DNA. This means that genes either express correctly or incorrectly.
5. Mononuclear DNA damage is increased in children and their mothers as a result of vitamin B12 deficiency (Minnet et al., 2011). As well as the importance of vitamin B12 in enabling genes to turn on and off (vital for correct development of the child), the donated methyl groups appear to be important in preventing damage to DNA. (The importance of nutrition in epigenetic alterations in the embryo is discussed in Wu et al. (2004)).

6. Vitamin B12 is needed for folate metabolism, and interaction of the two vitamins is essential for the conversion of homocysteine to methionine, for the synthesis of purines and pyrimidine, for methylation reactions, and for the maintenance of cellular levels of folate. One consequence of vitamin B12 deficiency is raised homocysteine which may lead to pregnancy complications. Research has suggested that maintaining optimal vitamin B12 status may be crucial to lowering homocysteine levels in the mother (Molloy et al., 2002).

5.2 Birth defect preventive programme: vitamin B12 supplementation

A couple planning to conceive should consider healthy lifestyle choices and have blood test checks for deficiencies and then appropriate supplementation. It is well understood that pregnant mothers usually need nutritional supplements, because of the high nutritional demands of pregnancy. We recommend that mothers-to-be should have vitamin B12 supplementation to ensure optimal health of the foetus and baby.

There are many different causes of B12 deficiency (see Chapter 2) but the most common are limited dietary intake and problems with absorption (Hoffbrand, 2012). If the mother is not getting enough vitamin B12, then the foetus will not get enough vitamin B12 through the placenta and umbilical cord.

Case 5-1 Teenage female: delayed periods

In an unusual case, the mother of a fifteen-year-old girl requested a home visit. Her concern was that although her daughter had the normal breast development of a teenager, so far there had been no sign of her starting a monthly period. The hospital performed a vaginal examination and identified that she had only a rudimentary vagina. There was no visible or palpable cervix or uterus. An ultrasound scan confirmed the above abnormality.

This mother and several members of her family had been diagnosed with vitamin B12 deficiency in previous years. Sadly, compliance to regular B12-replacement therapy had been very poor. We suggest that non-compliance with both folic acid oral supplements and B12 injections by the mother during pregnancy resulted in this birth defect (mononuclear DNA damage) which would have been totally preventable, since the treatment was preventive rather than reactive medicine.

5.3 Vitamin B12 and fertility

It is well known that severe vitamin B12 deficiency (as in pernicious anaemia, for example) leads to temporary infertility (NHS, 2016a). Research has shown that prolonged B12 deficiency results in infertility by causing changes in ovulation or development of the ovum or changes leading to defective implantation (Bennett, 2001). Vitamin B12 is necessary for the proper functioning of the endocrine system, which is necessary both for preparing a woman's body for pregnancy, and for maintaining the pregnancy. A significant number of women diagnosed with vitamin B12 deficiency in our Practice also suffered from hormonal disturbances (see, for example, Cases 7-5 and 7-6 in Chapter 7).

Case 5-2 Cardiomyopathy and mitral-aortic defect in pregnant mother

Hayley Matthews (born 1979) presented in February 2011 with cardiomyopathy/mitral-aortic regurgitation and closure of the ventricular tunnel. She was concerned about getting pregnant because of her own frailty and likely heart defects in the baby. Her blood serum level was found to be 283 ng/L (normal range 350-900 ng/L) and replacement therapy commenced. She rapidly gained strength, and when she wanted a baby folic acid supplements were added. Hospital cardiology clinics were surprised that she had a healthy pregnancy and no post-natal problems. Her baby was born in July 2013 healthy and with no heart defect.



Case 5-3 Vital role of vitamin B12 and folic acid in fertility



Donna Dyson already had an 11-year-old daughter. For the previous three years or so she had been trying for a baby but unfortunately had been having irregular periods, or no periods for months. She suspected some early miscarriages, and experienced extreme fatigue, headaches, mood swings and depression, and fainting attacks. She was losing hope of becoming pregnant again.

A routine blood test confirmed vitamin B12 deficiency, and we commenced her on B12-replacement therapy. Following the initial loading doses, she was given weekly (and subsequently monthly) injections as part of ongoing treatment programmes.

Her regular periods returned; her fatigue symptoms diminished, and she became energetic. Folic acid was commenced and given alongside vitamin B12 as she was very keen to have another child. She became pregnant and had a healthy child.

An interview with Donna Dyson is available on the B12d.org website: www.b12d.org/testimonials

Hormones, particularly cyclical hormones, are controlled by the pituitary (which is itself controlled by the hypothalamus from the brain). The pituitary protrudes out into the bloodstream and samples the blood, determining levels of hormones going around the body and comparing these levels to the levels that the pituitary expects. If blood levels are lower than expected, then the pituitary sends a

signal to the hormone-producing gland (endocrine gland) to increase production, and if the levels are higher than expected then the pituitary either stops stimulating the endocrine gland, or may in a few cases send a suppressing signal.

The female sex hormones (oestrogen and progesterone) are no exception. The levels and relative proportions of these two vary over a lunar month cycle (28 days) when a woman is not pregnant, and the endocrine glands (the ovaries and uterus) that produce them, need to be finely tuned to secrete them in the correct proportions. This cycles the thickening of the uterus wall, release of an ovum, and subsequent refreshing and expulsion of the ovum.

During pregnancy, a number of hormones need to act together to ensure that the usual cycle of uterus wall breakdown and subsequent release of another ovum does not happen. The uterus needs to support the growing child, including formation of placenta, and the stretching and repositioning of muscles and bones of the mother to accommodate the size of the child.

5.4 Considerations during pregnancy: the myth of haemodilution

“I also have another query. I am a midwife and so interested to know the normal B12 levels in pregnancy during each trimester. A client with symptoms was tested and it was 63 in her first trimester. Her GP prescribed 1 injection and her consultant obstetrician has said that 63 is normal in pregnancy and she should not be treated. Her only symptom is excessive tiredness which does keep her in bed. She did get improvement from the injection. She is now nearing the end of her pregnancy. I’d be interested to know your opinion on B12 in pregnancy. Thank-you.”

Erika Thompson – Beautiful Births, *Wessex Independent Midwives* (Thompson, 2017)

The level of vitamin B12 in the blood has been found to decrease during pregnancy. This was noted by Chanarin (1990, p. 141). A more recent longitudinal study on the effect of pregnancy on maternal and foetal cobalamin status showed that the mother’s vitamin B12 levels (measured both as cobalamin and as holoTranscobalamin) dropped from the 8th to 32nd weeks of pregnancy compared with the levels at preconception (which were in the “normal” range), but were higher in umbilical cord blood. In this study, levels were measured in 92 women, showing an average of 293 pmol/L at preconception to 198 pmol/L at the 32nd week, but the average level in the cord was 325 pmol/L. The researchers’ interpretation of these figures was that “there is a strain on cobalamin status during pregnancy” (Murphy et al., 2007).

We would interpret these findings as indicating that the mother’s body stores of vitamin B12 are being used up. This natural drop makes it all the more important to monitor vitamin B12 levels in pregnant women because any unusually low serum vitamin B12 (which a GP might mistakenly attribute to haemodilution during pregnancy as in the example quoted above) could lead to severe consequences. Haemodilution of any of the important markers should be an immediate flag to a doctor that something is deficient.

We suggest that pregnant women mobilise their body stores of B12 to increase the blood serum B12 level to meet the needs of the growing embryo and foetus. Vitamin B12 is a key component for healthy cell growth and division, so this makes sense. Researchers have shown that during

pregnancy the placenta “actively concentrates cobalamin [vitamin B12] in the foetus, resulting in foetal serum levels twice those of maternal serum” (Smith & Coman, 2014). If the mother’s levels are healthy, this gives the newborn enough stores of vitamin B12 to last for 6-12 months.

However, for a vitamin B12-deficient mother, the drop in maternal vitamin B12 levels has important consequences: her vitamin B12 status will worsen during pregnancy and, depending on her degree of deficiency, the foetus may also become deficient. It has also been shown that mothers with low vitamin B12 levels have raised homocysteine (Hct) and methylmalone (MMA) levels and, predictably, low cobalamin and high Hct/MMA levels in their newborns (Li et al., 2017; Smith & Coman, 2014).

5.5 Identifying the non-anaemic B12-deficient mother

An important clinical problem which is often overlooked is the non-anaemic mother-to-be who does not typically present with obvious vitamin B12 deficiency. She (the patient) may have neurological and psychiatric abnormalities and, if tested, typically have a low or borderline serum vitamin B12 level. Psychiatric disturbance is common in both folate and vitamin B12 deficiency.

In such people, it would be useful to confirm a diagnosis by a trial of vitamin B12-replacement therapy for at least three months (therapeutic trial). Vitamin B12 is completely safe and beneficial for adults, children and people preparing to be parents, and is inexpensive. A trial will assess whether the symptoms improve.

If the mother is under-diagnosed, untreated or only given folic acid supplement, there is a higher likelihood that she would deliver a child with neuromuscular damage, Subacute Combined Degeneration of the spinal cord (SACD), congenital abnormalities, tumours (including brain damage) and NTDs. It is a straightforward matter to ensure that the mother is not vitamin B12 deficient by giving vitamin B12-replacement therapy before and during pregnancy, at the time that the mother is often already prescribed mandatory folic acid supplementation (see Table 5-3).

5.6 Vegetarian/vegan mothers and vitamin B12 deficiency

Because of the high demands on the body during pregnancy, vegetarian/vegan mothers may well have subclinical vitamin B12 deficiency. Infants born to vitamin B12-deficient mothers, including those with subclinical deficiency, may be predisposed to develop disease or disabilities, particularly so when they are exclusively breast-fed. Some may develop haematological diseases such as anaemia and pancytopenia. Breast-fed infants born to vegetarian/vegan mothers have been observed to experience substantial neurological damage manifested by developmental delay, irritability, tremor and convulsions. Furthermore, these conditions may persist as long-term cognitive and developmental delay, despite adequate therapy.

Case 5-4 Vegetarian mother from London

A young couple moved up from London to manage a shop they bought in the north-east. The lady was in her twenties, 10 weeks’ pregnant with her first child and had been receiving antenatal care from the GP and the midwifery team in London. She was already receiving mandatory folic acid 400 µg daily. She transferred her care to our surgery and complained of fatigue and other symptoms which she associated with the pregnancy. On enquiry, she said she had been a lifelong vegetarian. Blood serum B12 and folic acid levels had not been done in London.

A blood test we carried out reported an extremely low serum B12 level of 28 ng/L. We commenced her immediately on an intensive B12-replacement programme while continuing her on folic acid. She enjoyed her pregnancy from this point on, and remained exceptionally well. She gave birth to a healthy baby who was breast-fed during the ensuing months. Although she remained a vegetarian, she continued monthly vitamin B12 injections and as a result the baby continued to receive sufficient B12 from the breast milk.

5.7 Neural tube defects: the roles of folic acid and vitamin B12

In the 1970s researchers discovered a connection between the occurrence of neural tube defects (NTDs) and folate (vitamin B9) status in pregnant women. Because the roles of vitamin B12 and folate are interlinked, lack of vitamin B12 similarly puts the growing foetus at significant risk of NTDs (see Case 5-5). These are among the most common birth defects reported worldwide. NTDs are extremely serious and include spina bifida, anencephaly, and encephalocele. They result from failure of closure of the neural tube after the third or fourth week of gestation – that is, very early in the pregnancy (Thompson et al., 2009).

5.7.1 Food fortification with folic acid

As a result of the discovery of the importance of folate, in the 1990s several countries, including the US, introduced mandatory folic acid fortification of food. Since then, the incidence of NTDs in these countries has dropped but not been eliminated entirely so ways of minimising the risk further are being sought (O'Leary & Samman, 2010). At the same time, questions have been raised about the desirability of food fortification with folic acid since high levels of folic acid in the blood have been linked to various unsatisfactory outcomes, such as insulin-resistance and obesity in children born to pregnant women with this status. High folic acid levels have also been linked to reduced response to antifolate drugs used against malaria, rheumatoid arthritis, psoriasis, and cancer (Smith et al., 2008). A further concern is that supplementation with folic acid to ensure all mothers receive enough folate during pregnancy may mask vitamin B12 deficiency because high levels of folic acid can correct some of the effects of B12 deficiency, such as macrocytosis, but not others – so neurological damage could progress undetected.

5.7.2 Vitamin B12 and folate/folic acid interlinked metabolisms

As described in Chapters 1 and 4, adequate vitamin B12 is vital for the proper functioning of the folate cycle. Therefore, lack of vitamin B12 can lead to a functional lack of folate even if there is sufficient folate in the diet. The action of vitamin B12 on the folate cycle is through the coenzyme methionine synthase (MS) which is needed to convert a folate compound, 5-methyltetrahydrofolate, to tetrahydrofolate which can then be used in a series of biochemical reactions leading to the production of nucleotides for DNA synthesis (that is, for cell replication). If vitamin B12 is deficient, the role of methionine synthase is reduced and, according to the “methyl-folate trap” hypothesis, methyl folate accumulates in cells and cannot be further metabolised. This compromises folate-dependent DNA synthesis (Molloy, 2018).

At the same time, this coenzyme plays a key role in converting homocysteine to methionine in the methionine cycle, leading to another chain of reactions necessary for DNA methylation. “The continuous recycling of homocysteine to methionine through this enzyme is an essential cellular

reaction wherein folate-derived methyl groups are transferred to a multitude of products, including methyl-DNA and methylated proteins that contribute to gene expression and gene silencing mechanisms (i.e., epigenetic control of cellular functions). One current hypothesis for the role of folate in neural tube formation relates to the importance of such epigenetic processes in orchestrating the flow of molecular processes that must be achieved during neural tube closure” (Molloy, 2018).

It is not known whether impairment of one of these cycles alone is responsible for NTDs or whether they result from a combination of these effects. High-dose synthetic folic acid supplementation can override the effects of lack of methionine synthase on the folate cycle, but they cannot substitute for the homocysteine-methionine reaction. So a vitamin B12-deficient mother would, at the very least, suffer from impaired DNA methylation.

A great deal of research has been done into the effects of folate/folic acid deficiency on NTD occurrence but considerably less into the role of vitamin B12 deficiency in these defects. As a result, vitamin B12 supplementation is rarely considered (Obeid et al., 2017). This general lack of awareness of the impact of vitamin B12 deficiency on pregnancy has been attributed to the assumption that vitamin B12-deficient women could not conceive because pernicious anaemia – previously considered the main cause of vitamin B12 deficiency - was known to lead to infertility (Molloy et al., 2008). However, it is now known that there are many other causes, and stages, of vitamin B12 deficiency which do not rule out pregnancy.

It is interesting to note, for example, in the clinical guidance listed in Table 5-1, the recommendations for folic acid/folate supplements, considering that folic acid deficiency is rarely encountered due to food fortification, and that folic acid is available in a far wider range of foodstuffs (both vegetarian and non-vegetarian) than vitamin B12. Supplementation with vitamin B12 is much less emphasised although deficiency may be far more common.

Additionally, absorption and utilisation of folic acid may be much reduced if vitamin B12 levels are lower. In contrast, folic acid absorption and utilisation are guaranteed if the vitamin B12 level in the circulation and amniotic fluid are maintained normal before, during and after pregnancy, especially if the mother is breast-feeding. We conclude that careful consideration needs to be given to vitamin B12 supplementation alongside folate supplementation during pregnancy.

5.7.3 Impact of vitamin B12 deficiency on occurrence of Neural Tube Defects

Nevertheless, some studies on the impact of vitamin B12 status on the occurrence of NTDs have been undertaken. A survey of such research in different population groups showed that studies consistently reported a two-to-fourfold increased risk of NTDs in mothers with low vitamin B12 status (O'Leary & Samman, 2010). Research in Canada, for example, on the impact of food fortification with folic acid, found a threefold increase in the risk of NTDs in mothers who had low vitamin B12 levels (Thompson et al., 2009). The researchers concluded that vitamin B-12 fortification of foods might reduce NTDs more than fortification with folic acid alone.

Several studies have reported that births with NTDs correspond with low B vitamins in the amniotic fluid. In one study, low vitamin B12 occurred more frequently than low folate in amniotic fluid associated with NTD pregnancies at between 15 and 20 weeks' gestation (Dawson et al., 1998). Folate supplementation reduces the risk of recurrent NTDs, but the research shows that both folate

and vitamin B12 deficiencies may be independent risk factors. An overview of current research has called for a wider observational study of the impact of vitamin B12 status on NTDs (Ray & Blom, 2003).

Case 5-5 Neural tube defect in severe vitamin B12 deficiency

A few years ago, one late evening I received a phone call from a very distressed lady, requesting an urgent home visit to her 30-year-old daughter. The daughter was discharged from hospital following her first confinement. Her mother was weeping; the father stood silent but handed over the hospital discharge letter to me: "full-term baby born with NTD/anencephaly (absence of cerebral cortex and skull vault); heartbeat and breathing stopped 20 minutes from the time of birth". I remained speechless for a while and departed saying that I would revisit in a few days' time which I did.

Three generations of this family, including this mother, had been diagnosed with severe vitamin B12 deficiency and had been receiving regular parenteral B12 replacement. Unfortunately, she had stopped the one-monthly repeat injections. She was aware of the importance of continuing the injections before and during the pregnancy. She therefore only received mandatory folic acid during the pregnancy.

I reassured her she would have a healthy baby if she recommenced vitamin B12 injections and that, when pregnant, she should continue with B12 injections and daily folic acid. She followed my advice and became pregnant again and was blessed with two healthy and alert babies, a boy and a girl, both without any birth defects whatsoever. The whole family is thankful for this miracle.

In a recent discussion of whether foods should be fortified with vitamin B12 as well as folic acid, one researcher (Molloy, 2018) makes the following observations:

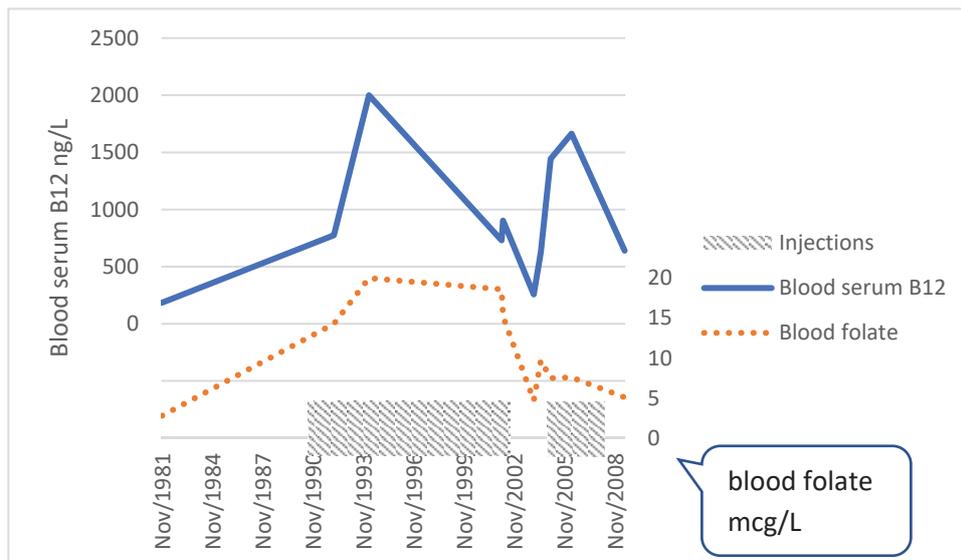
1. Folate/folic acid status does not appear to be the sole determinant of NTD susceptibility;
2. NTDs have been found still to occur particularly in women with low vitamin B12 levels;
3. The neural tube closes in the first 20-28 days of pregnancy, so the pre-pregnancy folate/vitamin B12 status of the mother is crucial;
4. Factors influencing the folate/vitamin B12 status of the mother may include a combination of genetic variants affecting vitamin B12 metabolism and poor dietary intake of these vitamins.

5.7.4 Our finding: serum folate levels mirror vitamin B12 levels

We would like to add to this debate observations from our own clinical experience. As described in the Introduction, we first came across a case of vitamin B12 deficiency without macrocytosis in the 1980s (Case 5-7). At that time, the importance of folic acid was not well known so although we instituted vitamin B12 replacement, we did not think of supplementing the patient with folic acid. She received vitamin B12 injections between 1992 and 2001, and again between 2003 and early 2007, but continued to eat broadly the same diet. In reviewing the effects of the B12 therapy in subsequent blood tests, we were surprised to note that, despite non-supplementation with folic acid and no change in the patient's diet, her serum folate levels had risen and continued to mirror closely those of vitamin B12. The same pattern was observed in a second patient (see Charts 5-1 and 5-2).

We monitored our first patient over a long time and were thus able to observe that this pattern persisted. This is to us clear evidence that adequate vitamin B12 can restore and maintain folic acid levels; in other words it appears to optimise folic acid absorption. We suggest, therefore, that maintaining adequate vitamin B12 status may be just as important as maintaining adequate folic acid status in preventing NTDs. It might also reduce the need for very high-dose folic acid, so avoiding the known detrimental effects of such high doses.

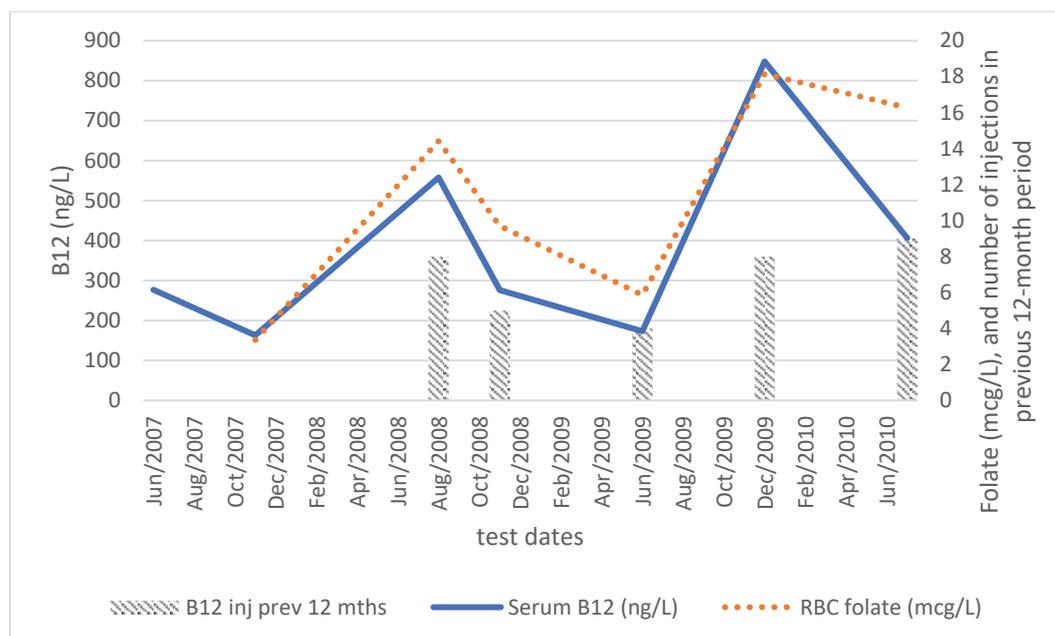
Chart 5-1 Glenise Mason, blood vitamin B12 and folate levels (note B12 supplementation only, folate follows B12 even without folate supplements)



Source: Patient records

Note how blood folate levels (the dotted lower line, units 0 – 20 mg/L) follow blood serum B12 (upper solid line, units 100 – 2000 ng/L). The grey boxes at the bottom show periods when vitamin B12-replacement injections were being administered; the white areas indicate when no vitamin B12 was being administered. The same effect was observed in another patient:

Chart 5-2 Patient A, blood vitamin B12 and folate levels (note B12 supplementation only, folate level follows B12 level)



Source: Patient records

See also table Table i-2 on page 7.

UK guidance (see Table 5-1) recommends supplementing the mother’s diet with folate or folic acid to ensure the child’s proper neurological development. We suggest that a pregnant or pre-pregnant woman diagnosed as folate deficient on the basis of blood serum folate levels may benefit more from vitamin B12 supplements raising her blood serum folate and available folate by mobilising body stores, than from dietary or mandatory folate supplements. It is also important to consider whether the diet of both vegetarians and non-vegetarians contains adequate amounts of folic acid.

5.8 Embryo and neonate B12-deficiency manifestation

Vitamin B12 deficiency has been described in infants born to severely B12-deficient mothers. These infants develop megaloblastic anaemia at about three to six months of age, presumably because they are born with low stores of vitamin B12 and because they are fed breast milk with low B12 content. The vitamin B12 content of breast milk is largely determined by the mother’s recent vitamin B12 intake. Supplementation with vitamin B12 during pregnancy and breast-feeding can prevent depletion of the mother’s stores and deficiency in infants (Obeid et al., 2017).

Babies born to vitamin B12-deficient mothers have also shown growth retardation, impaired psychomotor development, and other neurological sequelae.

We are surprised that newborns are not already screened for vitamin B12 deficiency during a Guthrie test²⁴ which already screens to identify the much less common (but easily treated) condition of phenylketonuria.

Paediatricians in Australia have reported:

“On average, the cobalamin concentration in breast milk is 0.42 mcg/L (Allen, 2002). Breast milk B12 concentrations have been found to be lower in women consuming a strict vegetarian diet compared to omnivorous women (0.23 ± 0.09 mcg/L vs. 0.38 ± 0.08 mcg/L). Infants fed breast milk containing less than 0.36 mcg/L had elevated methylmalonate levels. Additionally the milk B12 concentration was inversely proportional to the length of time the vegetarian diet was consumed (Specker et al., 1990). Exclusively breast fed infants of deficient mothers are most at risk as most commercially available infant formulas are fortified with cobalamin” (Smith & Coman, 2014).

A recent study of maternal supplementation (with 50 µg of daily oral vitamin B12) during pregnancy and early lactation in a resource-poor area of India showed that this measure significantly improved maternal plasma and breast milk measures of vitamin B12 status, as well as multiple measures of infant vitamin B12 status. The researchers noted that this was the first such study of the effects of supplementation and the results could be of global interest because of the potential benefits of such a programme to poor communities worldwide (Duggan et al., 2014).

5.9 Clinical symptoms of vitamin B12 deficiency in infants and children

Vitamin B12 deficiency in infancy may manifest in many different ways, making it difficult to diagnose. In 2007 I wrote to the British National Formulary (BNF) Editorial Board to say that there should be a guidance on vitamin B12 deficiency for babies and young children. At the same time, I wrote to the parliamentary Health Select Committee and to the editor of *The Times*. Thankfully, we now have patient-safe BNF Guidelines on vitamin B12 deficiency for children (BNFC, 2008) which appeared shortly after my letter.

We recommend that a child born to a mother with known vitamin B12 deficiency, a child who presents with delayed development, hyperactivity, dyspraxia, behavioural problems, learning disabilities, autistic spectrum disorder-like symptoms, should initially be screened by a blood test. This is to exclude a number of common conditions, including vitamin B12 deficiency, underactive thyroid and inborn errors of metabolism. Treatment should then follow the BNF guidelines. Regardless of the cause, babies and toddlers found to be anaemic due to low ferritin (hypoferritinaemia), should have iron supplementation instituted.

The Australian team referred to above also noted the urgency of being alert to possible vitamin B12 deficiency in infants. They state: “Vitamin B12 deficiency is an important and possibly under recognised cause of neurological morbidity in infants. The causes of infantile vitamin B12 deficiency are heterogeneous, ranging from dietary deficiency in a breast feeding mother to specific inborn errors of metabolism”. They noted that the infant brain appears to be “particularly susceptible to the myelination based mechanisms of B12 deficiency as myelination occurs mostly in the first 2 years of

²⁴ For description of the Guthrie test, see NHS: ‘Your pregnancy and baby guide: Newborn blood spot test’ at <https://www.nhs.uk/conditions/pregnancy-and-baby/newborn-blood-spot-test/>

life, but is at its peak in the first 6 months of life". Neurological symptoms are common: infants might show "Hypotonia [low muscle tone], developmental delay, developmental regression, eye movement abnormalities, irritability, chorea, tremor and seizures" but at the same time have no unusual haematological signs (Smith & Coman, 2014).

They observe that in older children the symptoms commonly include: paraesthesia, ataxia, abnormal movements, glossitis and personality change. Abnormal pigmentation of the dorsum of the fingers, toes and in the axillae, arms and medial thighs; hypotonia, hyperreflexia and choreoathetoid movements are also found.

Evidence from other research confirms this severe impact of vitamin B12 deficiency on infants. For example, Casella et al. (2005) report a case of a 6-month-old infant (born to a strict vegetarian mother) who showed insidious developmental regression and brain atrophy but who recovered after vitamin B12 therapy. Another case report (Glaser et al., 2015) describes an infant (born to a mother suffering from undiagnosed pernicious anaemia and exclusively breast-fed) whose MRI scan showed cerebral atrophy and delayed myelination: the infant was treated with vitamin B12 and on follow-up at 8 years' old was symptom-free. A study of 40 breast-fed infants (aged around 4.5 months) suffering from vitamin B12 deficiency showed a range of consequences. These included failure to thrive (48% of children), hypotonia (40%), developmental delay (38%) and microcephaly (23%). Two-thirds of children had anaemia (megaloblastic in 28% of all children). The majority had methylmalonic aciduria, hyperhomocysteinemia and increased aminotransferases (Honzik et al., 2010). A study of neurological symptoms in infants with vitamin B12 deficiency aged about one year in Turkey showed principally hypotonia (100%), anorexia (92.8%), neurodevelopmental (85.7%), and social retardation symptoms (80.9%)(Taşkesen et al., 2011).

If untreated, the vitamin B12 deficiency will persist into later life. The condition Juvenile Pernicious Anaemia/B12 deficiency resembles PA/B12 deficiency in adults. Children with this condition suffer from the expected associated glandular disorders, particularly those most relevant to their stage of life, such as autoimmune thyroiditis, Addison's disease, or hypoparathyroidism. Some have mucocutaneous candidiasis (Hoffbrand, 2018, p. 704):

Case 5-6 Child treated and mother diagnosed

The child in the photo (born 2006) was lacking energy, becoming withdrawn and not going out to play; on testing he had low levels of serum B12 (133 ng/L compared with the normal range 350-900 ng/L), folic acid 4.9 mg/L (normal range 5-20 mg/L) and ferritin 18 mg/L (normal 25-280 mg/l). Treatment for deficiency of all three resulted in the happy child who can be observed in the photo.

A genetic link was suspected so the mother (Sallyann Phillips) was tested. Her vitamin B12 level was found to be very low at 112 ng/L, with folic acid 3.7 mg/L and ferritin 25 mg/L. She is much better now she is receiving treatment. She had previously thought tiredness was due to having her young son.



5.10 Inheriting the genes for vitamin B12 deficiency

One of the known causes of vitamin B12 deficiency is inherited genetic conditions which impair vitamin B12 metabolism. Genetic variants (polymorphisms) can influence the amount of vitamin B12 in tissues by affecting the proteins involved in vitamin B12 absorption, cellular uptake and intracellular metabolism (Surendran et al., 2018). A number of such genes have been identified. Interestingly and encouragingly, researchers also found that high doses of vitamin B12 could override these disorders: “The remarkable feature of vitamin B12 utilisation disorders has been their potential for treatment. The discovery that high-dose vitamin B12 can overcome pathway deficits in some patients has given new life to individuals with an otherwise potentially severe or fatal disease” (Froese & Gravel, 2010). These researchers have recommended screening of newborns for homocysteine and methylmalonate (markers of vitamin B12 deficiency) so that any disorders can be identified and treated before serious stages of deficiency develop.

In a study of twins by Swedish researchers, the heritability of vitamin B12 levels was found to be 59%, indicating that the genetic influence on vitamin B12 levels is high (Nilsson et al., 2009). These genetic effects are not properly understood but researchers suggest that they result from a combination of factors, including environmental influences (which include diet).

This means that if a person has these genes in their genome (DNA), then in conditions where their metabolism is stressed (for example by lack of vitamin B12 in the diet), they are more likely than others to exhibit the symptoms of, and suffer from, vitamin B12 deficiency.

Folate metabolism is known to be affected by polymorphisms of six genes in Caucasians (MTHFR, MTRR, FOLH1, C β S, RFC1, SHMT) (McKay et al., 2012). Some of the same genes (MTHFR) and others (TCbIR, BHMT, TCN2, CUBN, AMN, FUT2) affect vitamin B12 metabolism (Beech et al., 2011; Mills et al., 2012; Tanaka et al., 2009; Zittan et al., 2007). The polymorphisms may be different, or certainly have different prevalences, in Asians (Sukla & Raman, 2012).

In our Practice we encountered a number of instances in which vitamin B12 deficiency was inherited, as illustrated in the cases described below.

Case 5-7 Vitamin B12 deficiency in the Mason family

In our Practice, we observed that vitamin B12 deficiency seems to run in families. Our landmark case – the one that started us on our journey of discovery of the widespread effects of vitamin B12 deficiency – is an example. Both the mother, Glenise Mason, and her daughter, Nicola Lonsdale, presented with similar symptoms.



Glenise Mason presented with recurrent anaemia and neuropsychiatric symptoms which did not respond to iron supplement. However, she had no macrocytosis or anti-IF antibodies so initially I did not think of vitamin B12 deficiency. As described in the Introduction, in 1981, after ten years of treating her, it suddenly struck me that her symptoms resembled those of the Brahmin women I had treated in India many years previously. I persuaded the laboratory to run a serum B12 test which gave a result of 185 ng/L. I then diagnosed vitamin B12 deficiency and instituted vitamin B12-replacement

therapy by injection. She recovered and her anaemia cleared up.

In 1996, her daughter attended with similar symptoms and a blood B12 level of 137 ng/L. She was also treated with vitamin B12-replacement therapy and recovered.

This example illustrated **three ground-breaking discoveries**:

- (1) B12 deficiency can occur without macrocytosis (previously considered a necessary symptom) but with neuropsychiatric signs and symptoms.
- (2) Genetic inheritance of vitamin B12 deficiency - the transcription defect is passed down from one generation to the next: mother's B12 deficiency – 185 ng/L (low with significant signs and symptoms); daughter's B12 deficiency – 137 ng/L (low with significant signs and symptoms).
- (3) Folic acid availability to the body is very dependent on the vitamin B12 status. Both mother and daughter had dietary folate intake which was considered adequate, but the folate was not available to the body without sufficient vitamin B12 (see Chart 5-1).

Case 5-8 Mother champions the case for her daughters

This is another example of predisposition to vitamin B12 deficiency being inherited. Hilda Wiffen (born 1931) came to the surgery with neuropathy in December 2005. Her vitamin B12 level at the time was 211 ng/L, and she was commenced on oral B12 tablets.



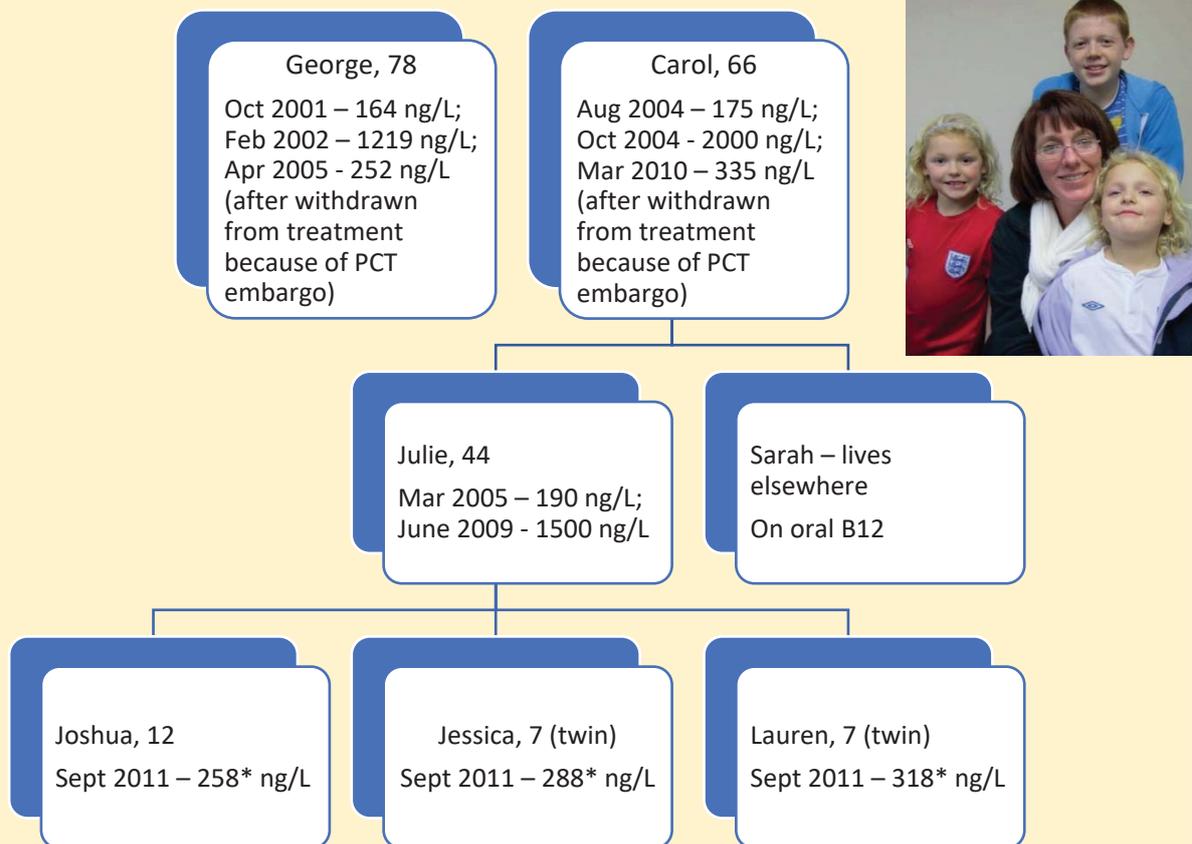
She asked the surgery to check for vitamin B12 deficiency in each of her daughters. One daughter, Brenda, was diagnosed with Multiple Sclerosis (MS) by a neurologist, and since June 2006 she was treated with immuno-suppressants. However, she did not improve, and her general condition and left-sided weakness worsened.

In the light of our knowledge of the effects of vitamin B12 deficiency and treatment (that treatment does not interfere with other medications and there is no risk in taking B12 supplements), Brenda was offered vitamin B12-replacement therapy. Her condition has since improved. This prompted her sisters to consider whether they might have vitamin B12 deficiency. They were subsequently treated and are also improving.

Subsequently, Hilda's granddaughter presented, aged 15, suspecting that she might have inherited B12 deficiency. Our provisional diagnosis, on the basis of signs and symptoms, was in fact B12 deficiency, which was later confirmed by a blood test.

Case 5-9 Inherited vitamin B12 deficiency in the Storey family

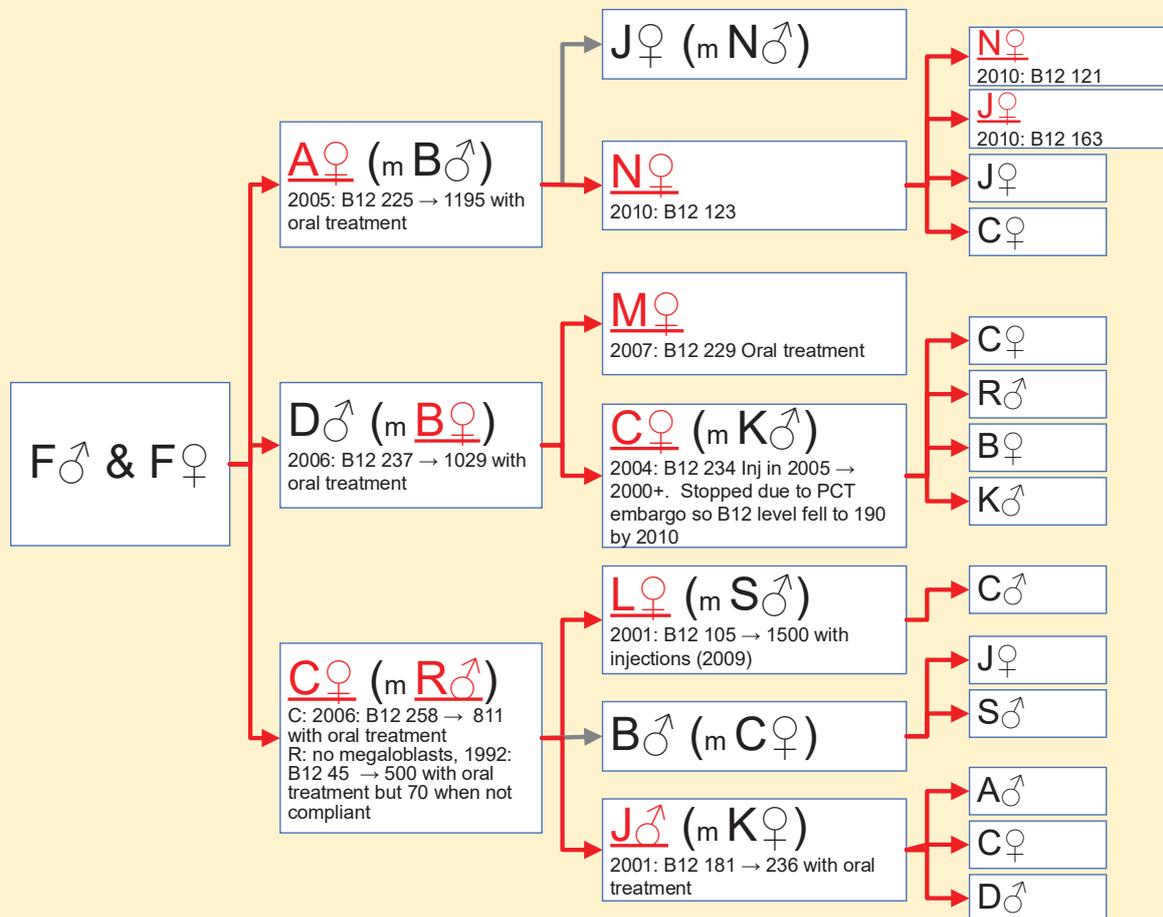
The data below show the vitamin B12 levels of several generations of the same family (ages are given after the names). The first figure shows the vitamin B12 level at diagnosis. The much higher figure is blood serum B12 during treatment. Treatment should not be stopped when the blood level is higher: this shows the treatment is working.



*Clinically low level

Case 5-10 The inheritance of deficiency across four generations

The figure below shows the vitamin B12 level (ng/L) of members of one family across four generations. The first number is the B12 level at diagnosis with date. The second number (following →) is the level after treatment (>200ng/L = not permitted to inject due to clinical guidelines at the time).



Initial underlined and highlighted in red indicates known B12 deficiency. All others have not been tested.
 Oral = oral administration of B12; inj = administration of B12 by injection
 Many young children (right-hand side) have not been tested
 Upper case letters are initials of first name

Table 5-1 Supplementation with vitamin B12: current UK guidance

Doctors in the UK rely on a number of sources for guidance and for keeping their clinical practice up to date. Official sources are the National Institute for Health and Care Excellence (NICE) and NHS [online]. The British National Formulary (BNF) and BMJ “Best Practice” are important professional guides. Aside from this last (the BMJ), at January 2019 there is little information about vitamin B12 supplementation from these official sources.

VITAMIN	NICE UK	BNF	NHS	Good Medical Practice ¹
B12	<p>NICE acknowledges that there is a significant gap, with no NICE guideline made available for vitamin B12 deficiency, but has not at the time of writing addressed it.</p> <p>Dr Chandy wrote to NICE (4/9/14) about the “Urgent need for a patient-safe Vitamin B12 deficiency NICE Guideline”.</p>	<p>2006 – BNF for Children recommended vitamin B12 injections for pregnant women and toddlers with B12 deficiency.</p> <p>Some variation in the length of time between injections has been noted in the different official sources.</p> <p>However, the BNF (2019) states:</p> <p>“There is no justification for prescribing multiple ingredient vitamin</p>	<p>Yes, if mother is vegetarian then they may have some trouble with their iron and B12 levels and will need to talk to their midwife or GP.</p> <p>The website states, with reference to eating well: “Vegetarian and vegan mums-to-be need to make sure they get enough iron and vitamin B12, which are mainly found in meat and fish, and vitamin D” (NHS, 2018).</p>	<p>If vitamin B12 deficiency is suspected (whether by signs and symptoms, or blood serum level), then begin replacement therapy. The blood serum test for B12 is known to give false negatives (say that someone is replete when they are actually deficient).</p> <p>For people planning pregnancy and parenthood, blood tests should direct supplementation from 3 months before pregnancy onwards. Ranges (based on our experience):</p> <p>Normal B12 level: 550 ng/L and above</p> <p>Subnormal with Signs and Symptoms</p> <p>< 500 ng/L < 400 ng/L < 300 ng/L < 200 ng/L</p>

¹ BMJ Best Practice [online] is used by many healthcare professionals to update their Continuous Professional Development (CPD). We sent a detailed academic paper highlighting our recommendations, and shortly afterwards they produced a “Good Medical Practice” section on Vitamin B12 which closely agrees with our recommendations.

VITAMIN	NICE UK	BNF	NHS	Good Medical Practice ¹
		preparations containing B12 or Folic Acid.”		Low - below 200 ng/L Normal Folic Acid 6-20 ng/ml Normal Ferritin >50-200 µg/L
Folic Acid	400 mcg daily from planning the pregnancy until 12 weeks’ pregnant, and postnatal, if deficient.	Yes , for prevention of the occurrence of neural tube defects (NTDs). Up to 5 mg daily for women who are in the high-risk group who want to conceive.	400 mcg daily from planning the pregnancy until 12 th week of pregnancy.	Screening and treatment as described.
Vitamin D	No official guidance.	No; see above statement regarding vitamin preparations.	Healthy Start Vitamins* (containing vitamins C, D and folic acid) are available free of charge to women on the Healthy Start Scheme during pregnancy and until the baby is one-year old.	Screening and treatment as described.

* “Healthy Start” drops: if the neonate needs help with vitamin supplements then they need: vitamin A 223 mcg; vitamin C 20 mg; vitamin D 7.5 mcg. We would also suggest, for a child, methyl B12 500 mcg (sublingual lozenges) daily for four weeks.

Table 5-2 Characteristics of vitamin B12 and folate (vitamin B9) deficiency

CHARACTERISTICS	VITAMIN B12 (COBALAMIN)	VITAMIN B9 (FOLATE/FOLIC ACID)
Symptoms of deficiency (basic biochemistry)	<p>Failure to remove toxins/radicals from cell and body fluids.</p> <p>Impaired energy production (failure to produce NADPH – an energy carrier in metabolic pathways - and Adenosine Triphosphate (ATP), an organic chemical involved in energy transfer).</p> <p>Impaired DNA synthesis and lipid metabolism leading to:</p> <ul style="list-style-type: none"> • Neuropathy • Autoimmune complications • Imbalance of endocrine system • Digestive impairments and related conditions • Impaired DNA transcription and replication • Megaloblastic or immature red blood cells • Failure to switch genes off or on at appropriate points in cell development 	<p>DNA transcription: the folate cycle leads to production of thymidine necessary for DNA synthesis. Folate is also needed in the conversion of homocysteine to methionine. The folate cycle can be disrupted by lack of vitamin B12.</p> <p>Deficiency of folate can lead to impaired cell and foetal development.</p>
Dietary source of vitamin	<p>Meat, fish, milk and milk products, poultry.</p> <p>Not available from vegetables.</p>	Both plant and animal foods, including fruit and vegetables.
Daily requirement	For non-deficient humans: recommended dietary intake for adults is set at 2.4 mcg per day in the US; 2.5 mcg per day in the European Union; 1.5 mcg per day in the UK. Impairment of entero-hepatic recycling mechanism can lead to much greater requirements.	Adults and children over 11 years old in the UK = 200 mcg per day; 400 mcg per day in pregnancy.

CHARACTERISTICS	VITAMIN B12 (COBALAMIN)	VITAMIN B9 (FOLATE/FOLIC ACID)
Enhanced metabolic demand during pregnancy	Yes – for all body functions.	Yes – typically for neural tube development (both folate and vitamin B12 needed).
Deficiency symptoms before and during pregnancy	<p>MOTHER: fatigue, depression, dizziness, eclampsia, bleeding, frequent miscarriages, morning sickness; could be a major cause of postnatal depression; may be associated with hair loss.</p> <p>FOETUS/NEWBORN: retarded development of all vital parts or vital parts missing in the newborn, e.g. kidney, ureter, vagina, uterus. Prone to NTD; encephaly; cleft lip/palate; Down syndrome; autistic spectrum disorder. Newborn with moderate to severe CNS/PNS and mild-to-moderate neuromuscular damage of the growing child.</p>	Due to folate food fortification, moderate to severe folic acid deficiency is not often seen. Also, mandatory supplementation before pregnancy and up to 12 weeks of pregnancy minimises the possibility of folic acid deficiency causing similar damage to the mother, foetus and newborn child to the same extent as vitamin B12 deficiency.
<p>Making it available:</p> <ul style="list-style-type: none"> • Absorption • Transportation • Utilisation by the cell receptors 	<p>The absorption process of vitamin B12 is complex and delicate. Disruption at any point (whether through autoimmune attack on gastric parietal cells or other cause) results in deficiency and multisystem disease manifestations, such as neurological, neuropsychiatric, haematopoetic or polyglandular conditions (often irreversible if not treated promptly).</p> <p>Normally, about 2 mg cobalamin is stored in the liver and another 2 mg is stored elsewhere in the body.</p> <p>The steps of the absorption route are:</p>	<p>Folate is easily absorbed through the proximal jejunum and transported to the cell by a carrier.</p> <p>Normal individuals have 5-25 mg of folic acid in various body stores, half in the liver.</p> <p>Deficiency will occur in months if the dietary intake is curtailed.</p> <p>Our clinical evidence/finding is that: if there is not an adequate amount of vitamin B12 in the circulation, folic acid will not be absorbed or utilised to provide the crucial methyl donor for perfect DNA transcription.</p>

CHARACTERISTICS	VITAMIN B12 (COBALAMIN)	VITAMIN B9 (FOLATE/FOLIC ACID)
	<p>Saliva – transcobalamin I combines with vitamin B12 to aid subsequent absorption.</p> <p>Stomach – stomach acids and proteases digest whey protein around vitamin B12. True B12 (i.e. not pseudo-vitamins) bind with R-binder. Intrinsic factor (IF) is released in the stomach by the crypt cells.</p> <p>Duodenum – IF combines with usable vitamin B12 to aid absorption.</p> <p>Terminal ileum – vitamin B12 binds to receptors in the intestinal wall and is absorbed and transferred into the blood. This happens preferentially to B12 combined with IF.</p> <p>Blood – “active B12” (approximately 20% of total blood serum B12) is a combination of transcobalamin II (TCII) and vitamin B12. The form of the rest of vitamin B12 in blood is not understood, although cells cannot absorb non-active B12.</p>	
Active form	<p>There are two active forms of vitamin B12 in the cell:</p> <p>Methylcobalamin: is the cofactor in the enzyme methionine synthase (MS) which participates in the homocysteine-methionine cycle in the cytosol of cells. This cycle is crucial for the regeneration of S-adenosyl methionine (SAME) required for lipid metabolism and methylation of DNA. MS also plays a</p>	<p>Folate is the name for a group of related compounds. Folic acid is the synthetic form.</p> <p>The active form is Tetrahydrofolate.</p>

CHARACTERISTICS	VITAMIN B12 (COBALAMIN)	VITAMIN B9 (FOLATE/FOLIC ACID)
	<p>key role in the metabolism of folate/folic acid which leads through a series of steps to products needed in DNA synthesis.</p> <p>Adenosylcobalamin: is the cofactor in the enzyme MethylMalonylCoA mutase which works in the mitochondria of cells. It is used in the Krebs cycle for energy production.</p> <p>In blood, free (not bound to TCII) vitamin B12 can combine with a number of radicals to protect the body, e.g. heavy metals, organic toxins, free radicals.</p> <p>Other forms of vitamin B12, including cyanocobalamin and hydroxocobalamin, are inactive biologically and need to have the radical group changed to one of the active forms to become useful.</p> <p>Cobalamin analogues (e.g. phytocobalamins) are typically inactive and cannot be converted to an active form.</p>	
Biological role	<p>Vitamin B12 is required for biochemical pathways in both the cytosol and mitochondria of cells.</p> <p>The B12-dependent enzyme methionine synthase catalyses the conversion of homocysteine to methionine. At the same time, in an interlinked reaction, it converts the folate compound 5-methyl-tetrahydrofolate to tetrahydrofolate, a form needed for other reactions, leading to DNA synthesis.</p>	<p>Folate performs several crucial metabolic roles in the body. It is vital for cell division and DNA synthesis, regeneration of methionine from homocysteine and for accepting and donating one-carbon units for normal metabolism and regulation.</p> <p>The first step in its metabolism is conversion of Tetrahydrofolate (THF) to 5,10-methylene-THF. Some of the 5,10-methylene-THF is then reduced to 5-methyl THF by the enzyme methylene tetrahydrofolate reductase</p>

CHARACTERISTICS	VITAMIN B12 (COBALAMIN)	VITAMIN B9 (FOLATE/FOLIC ACID)
	<p>When this reaction is impaired, the folate cycle is deranged, leading to lack of products for DNA synthesis which affects the formation of red blood cells (causing megaloblastic haematopoiesis). Large doses of folic acid can overcome this block and produce a partial haematological remission in patients with vitamin B12 deficiency which may therefore “mask” the vitamin B12 deficiency. As a result, vitamin B12 deficiency may advance to a severe stage before it is recognised.</p> <p>Tissue folate stores in vitamin B12 deficiency are substantially reduced despite normal or supernormal serum folate levels.</p> <p>Vitamin B12 in the form of adenosylcobalamin is required for the enzyme MethylMalonylCoA mutase which is involved in catabolism of some fats and amino acids (Molloy, 2018). Deficiency of vitamin B12 impairs this reaction and may be another route leading to the neurological complications of vitamin B12 deficiency.</p>	<p>(MTHFR). The N5 group of 5-methyl-THF is used to donate a one-carbon group to homocysteine, thereby converting it to methionine, via the action of the B12-dependent enzyme methionine synthase. If vitamin B12 is deficient, this reaction cannot take place, even when folate levels are high. This is the “methyl-folate trap” hypothesis.</p> <p>Tissue folate deficiency therefore develops which results in megaloblastic haematopoiesis.</p> <p>The methionine synthase reaction also regenerates THF required for the formation of 5,10-methylene-THF and 10-formyl-THF used directly in synthesis of thymidylate and purines, precursors of DNA.</p> <p>Methionine is required for protein synthesis and, through its conversion to S-adenosyl methionine (SAME), is a key methyl donor involved in more than 100 methyltransferase reactions with a wide variety of acceptor molecules, including methylation of DNA, RNA, proteins, and phospholipids. Methylation of DNA affects gene expression and specialisation.</p>
The homocysteine connection	One chemical (and blood) characteristic of vitamin B12 deficiency is the build-up of homocysteine because this amino acid cannot be converted to methionine in the absence of vitamin B12. High levels of homocysteine are a risk factor for venous and arterial thrombosis.	Homocysteine elevated risk factor for arterial and venous thrombosis. Due to folate food fortification, combined deficiencies of B12 and folic acid are not common.

CHARACTERISTICS	VITAMIN B12 (COBALAMIN)	VITAMIN B9 (FOLATE/FOLIC ACID)
	<p>Impairment of conversion of homocysteine to methionine may also contribute to neurological complications of vitamin B12 deficiency because it leads to reduced production of S-adenosyl methionine (S-AdoMet) which has consequences for fatty acid synthesis and the integrity of the myelin nerve sheath.</p>	<p>Deficiency of vitamin B12 can lead to functional folic acid deficiency.</p>

Table 5-3 Suggested specific vitamin B12 replacement for the pregnant mother

Vitamin B12 status of the mother	During pregnancy	Recommended treatment for the mother	Recommended treatment for the child
Non-vegetarian woman with normal blood serum B12 level.	Anticipate that blood serum vitamin B12 levels may fall, indicating that the mother is using her stores of vitamin B12 to supply the growing baby. If vitamin B12 levels decrease during pregnancy, then the mother has exhausted her stores of vitamin B12.	<p>If vitamin B12 levels fall sharply during pregnancy, the mother should receive B12-replacement therapy during pregnancy and especially during the first three months.</p> <p>If vitamin B12 levels in the blood rise or remain normal during pregnancy, then this is a normal physiological state and no replacement is required (usual pregnancy supplement containing B12 is fine).</p>	<p>If the mother's B12 levels rise or remain normal during pregnancy, whether naturally or through vitamin B12 supplementation, then the child should be born normal and have no requirement for vitamin B12 supplementation.</p> <p>Providing a methyl donor¹ (B12) before and during pregnancy may permanently alter the state of methylation of the offspring's DNA, restoring normal gene expression, and development throughout life.</p>
B12-deficient woman on normal diet who may not be diagnosed as B12 deficient.	Vitamin B12 deficiency will worsen due to high demand from the growing baby. The mother's signs and symptoms will worsen, including fatigue and low mood (tearful and depressed). We now know that this is NOT	<p>Symptoms</p> <ul style="list-style-type: none"> • Post-natal depression (“baby blues”) • Hair loss • Extreme lethargy 	Risk that the baby will be born vitamin B12 deficient – “floppy” and with neuromuscular damage. This requires urgent treatment with vitamin B12 injections – 1000µg hydroxocobalamin daily for 10 days. Review clinically and continue replacement therapy accordingly.

¹ A methyl donor is any substance that can transfer a methyl group (a molecular group composed of one carbon atom bonded to three hydrogen atoms — CH₃) to another substance. Methylation is important for gene expression. Vitamin B12 is an important methyl donor in the complex chain of reactions which lead to DNA methylation. The importance of B12 in proper function of DNA is discussed in Chapter 9.

Vitamin B12 status of the mother	During pregnancy	Recommended treatment for the mother	Recommended treatment for the child
	"just being pregnant", and the mother can have a happier pregnancy.	<ul style="list-style-type: none"> • Dizziness/fainting Vitamin B12-replacement therapy should alleviate this.	In severe cases the infant may require hospital admission for vitamin B12-replacement therapy.
Vegetarian/vegan woman with B12 deficiency; diagnosed B12-deficient woman with Signs and Symptoms. Always requires treatment, which should commence three months prior to pregnancy.	Continue the already established replacement therapy as both mother and baby require vitamin B12 (the baby for its neuromuscular development).	Continue vitamin B12-replacement therapy for the woman during nursing and afterwards.	With sufficient vitamin B12-replacement therapy for the mother, the baby is expected to be born normal and require no vitamin B12-replacement therapy. Vitamin B12-replacement therapy for the mother should ensure sufficient vitamin B12 in the mother's breast milk. If vegetarian milk (soya milk) is used as an alternative then vitamin B12 supplementation for the child will be needed.

