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Breastfeeding and Allergies

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INTRODUCTION

Vegan diets are free of all flesh foods, eggs, dairy products, and sometimes honey. In the last decade, the prevalence of a vegan diet in Europe has increased by 350% (Ferrara et al., 2017). In Great Britain, the number of vegans quadrupled between 2014 and 2018 (Nils-Gerritt, 2020) in spite of recommendations from several organizations within Europe against adhering to a vegan diet in pregnancy, infancy, and childhood (Lemale et al., 2019; Fewtrell et al., 2017; Richter et al., 2016). These recommendations are based on a high risk of nutrient deficiencies, including B12, iron and docosahexaenoic acid (DHA), among vegans.

B12 is the biggest concern (Pawlak & Bell, 2017; Richter et al., 2016; Sanders, 2009). Foods of plant origin do not contain B12 unless they are fortified (Herbert, 1988) and the requirement for B12 is higher both in pregnancy and lactation, compared to other stages of the lifecycle (European Food Safety Authority, EFSA, 2015). Studies with vegans, mainly non-pregnant and non-lactating adults, show a high prevalence of B12 deficiency (Pawlak et al., 2013) and dozens of case reports have been published describing B12 deficiency symptoms among children breastfed by vegan mothers and/or receiving a vegan diet (Daphna et al., 2010).

Yet there are benefits as well of a vegan diet in both adulthood and childhood. These include a lower risk of developing type 2 diabetes, some cancers, ischemic heart disease and of becoming obese (Tong et al., 2019; Pawlak, 2017; Turner-McGrievy et al., 2017; Tantamango-Bartley et al, 2013). Plant protein intake decreases, while animal protein increases the risk of ovulatory infertility (Chavarro et al., 2008). Beef intake by pregnant women has been associated with lower testosterone concentration in male children (Swan et al., 2007) and barbecued meat in pregnancy has been associated with a significant deficit in birth weight (Jedrychowski et al., 2012). Vegan diets do not require killing animals for food, are friendlier to the environment, and have less impact on global warming.

Therefore, although a vegan diet carries a high risk of nutrient deficiencies, in light of its many benefits, it is appropriate that health professionals should support vegans, rather than discouraging them, and provide education in how to optimize nutrient intake. The goal of this paper is to review information about B12 among vegans and offer guidelines for practitioners supporting vegan pregnant and lactating women and their children.

Keywords: vegan, vitamin B12, pregnancy, lactation, infancy

(A glossary is provided at the end of the article.)

B12, or cobalamin, has a chemical structure more complex than that of any other vitamin and is made only by microorganisms, such as bacteria (Pawlak et al., 2012). It is essential for:

- the synthesis of nucleic acids (DNA) and therefore for growth and development, especially during pregnancy, infancy and childhood; - the synthesis of myelin which provides a protective sheath around nerve cell axons; deficiency may result in the malfunction of both the peripheral and the central nervous systems;
- the synthesis of all blood cells.

B12 deficiency may lead to profound short and long-term health complications, especially in children (Daphna et al., 2010) who may experience blood abnormalities, developmental delays and neurological complications (Chavarro et al., 2008). Deficiency occurs mainly for three reasons:

- inadequate intake of the vitamin
- malabsorption
- genetic defect.

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Inadequate intake is generally the reason for deficiency among vegetarians and especially vegans (Pawlak, 2015).

Malabsorption of B12 occurs among people who have undergone gastro-intestinal surgery, those with certain health conditions such as pernicious anemia, coeliac disease and Crohn's disease, and among people who take medication that affects B12 absorption such as metformin, aspirin and antacids (Pawlak, 2017; 2016).

B12 IN VEGAN PREGNANT WOMEN

Studies of B12 among vegan pregnant women are almost non-existent. However, there are several reasons to suspect that B12 deficiency in these women is common. Findings from two nationally representative cohorts of women of child-bearing age from the United Kingdom (UK), based on participants following various diets, showed that approximately one in eight had low levels of B12 and about one in five had elevated homocysteine, a biomarker of B12 deficiency (Sukumar et al., 2016). Over a third of the vegetarian/vegan participants were deficient in B12 (Sukumar et al., 2016). Another UK study with pregnant women found that 26.2% had B12 deficiency (defined as serum B12 <150 pmol/L) (Sanders, 2009). In various studies, B12 deficiency among vegans often exceeded 50% of the participants, and in more than one study, reached over 80% (Pawlak, 2015; Pawlak et al., 2012).

B12 AMONG LACTATING VEGAN WOMEN

A handful of studies have assessed B12 status in breastmilk from vegan women. Specker et al. (1990) reported B12 levels in 13 vegan lactating mothers. The majority had a B12 concentration amounting to biochemical deficiency. B12 milk concentration was inversely correlated with the length of the mothers' adherence to a vegan diet. My own team has reported a very different outcome from a study (Pawlak et al., 2018) based on breastmilk samples from 26 vegan women, 22 lacto-ovo-vegetarian women, and 26 non-vegetarian women. Breastmilk samples from vegan participants had the highest mean and median B12 of all three groups. However, in this study, almost 80% of participants used B12-containing supplements. These findings suggest that vegan lactating women who do not take B12 supplements are at a high risk of having inadequate B12 in their breastmilk.

WHY IS B12 STATUS IMPORTANT?

Inadequate B12 status has been associated with a number of health complications for both pregnant and lactating women and their offspring (Carter et al., 1987). In pregnancy, B12 deficiency is associated with spontaneous abortion followed by periods of infertility, depression, pre-term delivery, obesity, pre-eclampsia and gestational diabetes (Kouroglou et al., 2019; Lora Peppard et al., 2019; Carmichael et al., 2009; Candito et al., 2003; Bennett, 2001) although it should be acknowledged that many women with sub-optimal B12 status have uneventful pregnancies. However, low maternal B12 results in inadequate stores of this nutrient in newborn babies along with low concentration in breastmilk.

Most cases of B12 deficiency in infants are a result of maternal depletion (Daphna et al., 2010). Symptoms usually occur within four to ten months of birth, although sometimes appear earlier in life and quite often are seen in older children (Honzik et al., 2010). Health problems caused by B12 deficiency in infants and children are listed in Table 1. Infant death has also been reported in more than one country (Allen, 2011; ABC News, 2005; Grinberg, 2005; Stickley, 2002; BBC News, 2001).

TABLE 1.
DOCUMENTED SYMPTOMS OF VITAMIN B12 DEFICIENCY IN INFANTS AND CHILDREN

Anthropometric/ developmental	Low birthweight, developmental delays, fall in growth curves (weight < 10th percentile, height < 10th percentile, head circumference < 10th percentile), unable to sit alone, unable to walk, abnormal fine and gross motor function, delays in speech development
Neurological	Involuntary movements, lack of responses to stimuli/interaction with people, mood swings, irritability, apathy, tremors, convulsions, brain atrophy
Hematologic	Low serum/plasma B12, elevated methylmalonic acid, elevated homocysteine, low hemoglobin and hematocrit, pancytopenia, megaloblastic anemia (elevated MCV), lymphoblastic leukemia
Dermatological	Hyperpigmentation, pallor
Other	Anorexia, refusal to eat solid foods, vomiting, not smiling, low bone density, brain atrophy, respiratory failure

It is important to mention that the average time from the onset of B12 deficiency symptoms until diagnosis is about three months and, in many cases, considerably longer (Honzik et al., 2010) when the diagnosis is not made until a child is referred for evaluation to a hematologist and/or neurologist. The response of deficient infants to B12 treatment depends on the infants' symptoms. Hematologic symptoms, lethargy and social lack of responsiveness may subside almost overnight (Honzik et al., 2010). Anemia may be gone within two weeks and anthropometric growth improves steadily. However, it takes several months to years for neurological symptoms to disappear and in some cases, they may be irreversible. Some infants may develop secondary complications of B12, such as epilepsy (Honzik et al., 2010).

CASE STUDY: Long-term complications of B12 deficiency in childhood

Emma was diagnosed with B12 deficiency at 15 months of age, although she had experienced symptoms such as poor appetite and frequent vomiting since she was eight months. Her mother had adhered to a vegan diet for seven years and reportedly took 'nutritional and vitamin' supplements. In spite of this, the child developed lethargy, developmental delays, severe macrocytic anemia and global cerebral atrophy. Her weight at 15 months was just 6.34 kg; her iron status was also impaired. In spite of B12 replacement therapy, at 28 months of age, her fine motor skills were the equivalent of 9 months, her gross motor skills the equivalent of 18 months, her expressive language the equivalent of 10 months, and her receptive language the equivalent of 12 months (Centers for Disease Control and Prevention, 2003).

Cognitive manifestations of vitamin B12 deficiency in infants and young children, as is the case with neurological symptoms, may not always be easily reversible. A Dutch study (Louwman et al., 2000) reported on a group of adolescents who, until six years of age, had consumed a vegan type of macrobiotic diet. At six, they had been diagnosed with B12 deficiency and changed their diet to either lacto-ovo-vegetarian or omnivorous. The results of tests of short-term memory, divergent thinking, information processing time and psychomotor development were compared with those of a control group who had no history of B12 deficiency. The authors concluded that 'a shortage of cobalamin, without the typical hematologic signs of cobalamin deficiency, was associated with an impairment of cognitive performance that has consequences for daily life. These findings have implications not only for subjects consuming or previously consuming a macrobiotic diet, but for all subjects who avoid animal products, whether because of medical reasons, beliefs, or poverty' (Louwman et al., 2000:767).

ADEQUATE VITAMIN B12 INTAKE

Recommended intake of B12 in the UK is 1.5 µg/day for all adults, regardless of pregnancy or lactation status (British Nutrition Foundation, 2016, revised 2019). The European Food Safety Authority (EFSA) calls for an intake of 4.0 µg/day by adults, 4.5 µg/day by pregnant women, and 5.0 µg/day by lactating women (EFSA, 2015).

In the UK, one study (Sukumar et al., 2016) found inadequate B12 intake in one out of every eight women capable of childbearing, while one in five had elevated homocysteine in spite of the fact that 96% of study participants met the UK reference intake for B12. In the most recent UK study (Fallon & Dillon, 2020), the mean intake of B12 among 20 vegan women (mean age 27.6 years) was just 1.3 µg, indicating a high likelihood of deficiency. Koebnick and colleagues (2004) in Germany reported that 39% of 27 pregnant lacto-ovo-vegetarian women had low B12 status during at least one trimester of pregnancy and concluded that, 'although further studies will be needed to confirm our results, the present data do strongly suggest that the requirement for vitamin B12 during pregnancy has been underestimated and that (…) the recommended dietary allowances (2.6 µg/d) need re-evaluation' (p3324).

Inadequate B12 is the cause of elevated homocysteine, a biomarker of B12 status. Sukumar et al. (2016) have shown that among women capable of childbearing, intake of 5 µg/day or higher was associated with the lowest homocysteine concentration. The study by Bae et al. (2015) of B12 status in pregnant women in the United States concluded that adequate intake in pregnancy is approximately three times as high as the Institute of Medicine's 2.6 µg/day recommendation.

According to EFSA, adequate intake for children seven months to six years of age is 1.4 µg/day. In the United States, baby cereal products contain 0.12-0.15 µg of B12 per serving (EFSA, 2015). Therefore, the easiest and most reliable way to prevent B12 deficiency in infants and children who are given a vegan diet is to use a B12 supplement.

TREATMENT OF B12 DEFICIENCY

Two effective B12 deficiency treatment options exist:

- intramuscular injection

and

- B12 supplementation.

Nasal B12 sprays and toothpaste fortified with B12 are also available in some European countries; however, the efficacy of these has not been extensively evaluated. For adults, a B12 supplement of 1000 µg/day seems as effective as therapy with intramuscular injection although supplements are needed for a longer period of time, perhaps several weeks, than when injections are utilized.

MAINTENANCE

Monthly B12 injections can be utilized as a maintenance therapy or regular use of a B12 supplement is an alternative option. Anecdotal evidence suggests that the benefits of monthly B12 injections wear off with some patients feeling progressively worse in the days prior to their next injection. Regular use of B12 supplements avoids this happening. Findings by Sukuma et al. (2016) showed that the incidence of B12 supplement use among women of childbearing age dropped from 8.7% in 2000-2001 to 4.2% in a 2008-2012. It is unclear how commonly B12 supplements are used among vegans in the UK or elsewhere in Europe.

ALGAE AS A SOURCE OF VITAMIN B12

Many vegans use algae, such as spirulina, nori, or kombu, to supply B12. However, some studies show that these only contain analogues of B12 that are inactive in humans and not the true B12, while other research shows that they contain some active B12. The analogues, also known as pseudo-B12 compounds, interfere with absorption and metabolism of the true B12. Practically speaking, algae should not be relied upon as a source of B12 (Pawlak, 2016).

B12 AND FOLIC ACID INTERACTION

Recent evidence suggests that high maternal folate coupled with low maternal B12 adversely impacts intrauterine growth. In India, a country with a high prevalence of B12 deficiency, high maternal folate-to-B12 ratio during pregnancy has been associated with reduced birth weight, length and head circumference and also with neonatal abdominal adiposity and childhood insulin resistance (Gadgil et al., 2014; Yajnik et al., 2008).

Among vegans using prenatal dietary supplements and/or multivitamins, a high folate-to-B12 ratio has become increasingly likely to occur. This is because many prenatal dietary supplements contain higher-than-recommended folic acid doses (e.g. 800µg) but may or may not contain B12. A multivitamin usually contains 400µg of folic acid.

B12-OMEGA-3 INTERACTION

Latest evidence (van Wijk et al., 2012) shows an interesting interaction between B vitamins, including B12, and long-chain omega-3 fatty acids (eicosapentaenoic acid - EPA, and docosahexaenoic acid - DHA). Animal studies indicate that adequate B12 along with adequate DHA are associated with neurogenesis (Rathod et al., 2016). Human studies show similar benefits regarding preservation of both grey and white brain matter in the elderly (Jernerén et al., 2015). Because of the benefits of EPA and DHA for fetal development, health authorities recommend that pregnant women ingest fish twice per week, not exceeding 12oz. Most studies on vegans show poor EPA and DHA intake and status (Sanders, 2009). Intake can be improved by using algae-derived (vegan) EPA and DHA supplements along with B12 supplements. It is important to understand that plant sources of omega-3 fatty acids only contain alpha-linolenic acid (ALA) but not EPA or DHA. Conversion of ALA to EPA is limited and there is virtually no conversion to DHA. Thus, using vegan EPA and DHA supplements is the only way to ensure adequate status.

PRACTICE POINTS

1. Among vegans who do not supplement, developing B12 deficiency is not a matter of if but when.
2. Regular use of B12 supplements constitutes an easy way to remedy this problem.
3. Health professionals who advise vegans should arm themselves with convincing arguments regarding the efficacy of B12 supplements since many vegans are resistant to the idea of using supplements (Antony, 2003).
4. Supplements are especially important during pregnancy and lactation because inadequate B12 status during this period can have a profound impact on the health of offspring.
5. If B12 supplements are not available, alternative reliable sources (e.g. B12 injections, nasal sprays, or fortified toothpaste) should be used.

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GLOSSARY

Anthropometric	Relating to the study of the measurements and proportions of the human body
Cobalamin	Vitamin B12; important for the normal formation of red blood cells and nerve tissues. B12 deficiency can cause anaemia and nerve and brain damage.
Docosahexaenoic acid	An omega-3 fatty acid that is important for the brain, skin and eyes.
Hematocrit	The volume percentage of red blood cells in blood
Homocysteine	An amino acid synthesized in the body that is vital for a number of physiological functions
Hyperpigmentation	A medical term used to describe darker patches of skin.
Lymphoblastic leukaemia	A type of cancer that affects white blood cells.
Mean corpuscular volume (MCV)	A measure of the average volume of a red blood corpuscle; a high MCV indicates macrocytic anaemia which can be caused by B12 deficiency.
Megaloblastic leukaemia	A condition in which the bone marrow produces very large, abnormal, immature red blood cells .
Methylmalonic acid (MMA)	A substance synthesized by the body that is essential for normal cellular function
Neurogenesis	The process by which new neurons are formed in the brain – of critical importance during the period when the unborn baby is developing.
Pancytopenia	Deficiency of red and white blood cells, and platelets.

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Breastfeeding and Allergies

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INTRODUCTION
There is evidence that allergens can be transmitted via breast milk. However, allergens are usually transmitted in a highly processed form which is tolerated well by the vast majority of infants. Occasionally, exclusively breastfed babies can present with signs of allergies, more commonly 'delayed type' allergies. Such delayed manifestations may be an 'allergic proctocolitis', presenting with blood and mucus in the stool of an otherwise well baby, or an 'enteropathy' or 'colitis', in which symptoms may include diarrhoea, blood in the stools, failure to thrive, vomiting or crampy colicky pains.

Cow's milk is the most common trigger for early manifestations of food allergy in breastfed babies. However, 95% of cow's milk allergic infants will respond to strict cow's milk elimination from the mother's diet, and can thus continue to breastfeed. In allergic proctocolitis, the response to maternal elimination occurs within 48-72 hours. In enteropathy, the response may take two to three weeks; hence the trial of maternal elimination needs to be longer to look for improvement in symptoms.

In all cases of maternal dietary elimination, a dietitian should be involved to help identify hidden sources of milk protein (or other identified allergens) in the diet, and to ensure that the mother's diet is adequate. A good pre-natal vitamin and a calcium supplement (1000 mg calcium daily) are recommended for the breastfeeding mother if she is eliminating dairy from her diet. Blanket elimination of foods during breastfeeding is discouraged and potentially harmful to both mother and infant. If there is a suspicion of food allergy presenting during breastfeeding, an assessment by a specialist to determine the exact causative allergens is encouraged. The vast majority (95%) of infants who present with allergies during the breastfeeding period can continue to breastfeed with targeted dietary exclusions by the mother.

The pathogenesis, manifestations and management of allergies in breastfed infants are described in this article, as well as the role of breastfeeding in allergy prevention.
KEYWORDS: breastfeeding, food allergies, cow's milk protein allergy, IgE mediated allergies, delayed-type food allergies, elimination diets
(A glossary is provided at the end of the article.)

Human milk is the 'gold standard' for infant nutrition and a nutritionally complete diet in the first six months of a baby's life (Commins, 2020; Minniti et al., 2014). In addition, colostrum and breast milk provide multiple factors that are required to support the infant's immunity and promote the establishment of a healthy gut microbial population.

The composition of breast milk changes throughout the lactation period as it adapts to the changing needs of the infant. Foods and proteins are already highly 'filtered' and processed by the time they pass through into breast milk, and the vast majority of babies tolerate breast milk extremely well.

However, there is evidence that recognisable food proteins can pass into breast milk. In addition to the processed allergen, breast milk contains a number of substances which usually make the transmitted allergens well tolerated (Järvinen-Seppo et al., 2014; Minniti et al., 2014). Secretion in the breastmilk of secretory IgA, specific IgG, lactoferrin and complement C3 and several interleukins (IL-4,10 and 12) act as anti-microbials and immune-modulators and allow breast milk to be mostly 'tolerogenic', in other words - they promote oral tolerance to most transmitted allergens. Despite such a protective environment, occasionally, transmitted allergens can evoke allergic reactions in infants. These can manifest either as IgE-mediated (immediate-type) allergies, or more commonly as non IgE-mediated food allergies, including eczema and gut symptoms (Järvinen-Seppo et al., 2014).

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TABLE I: Allergen availability in breast milk after maternal consumption

Allergen	Duration of allergen availability in breast milk after maternal consumption
Cow's milk protein (Restani et al., 1999; Sorva et al., 1994; Host et al., 1990; Machtinger & Moss, 1986)	1-12 hours
Egg: Ovalbumin (Metcalfe et al., 2016; Palmer et al., 2005; Fukushima et al., 1997)	2-6 hours
Peanut protein (Vadas et al., 2001)	1-3 hours
Wheat protein: Gliadin (Chirdo et al., 1998; Troncone et al., 1987)	2-4 hours

TRANSMISSION OF ALLERGENS VIA BREAST MILK

Maternal dietary macromolecules are absorbed in the gut and can be transmitted in human milk. The amount of allergen transmitted via breast milk is allergen-dependent, varies from one mother to another and from feed to feed. Peanut proteins, for example, have been shown to be transmitted in only 48% of lactating women after peanut ingestion (Vadas et al., 2001). This may depend on the permeability of the mammary epithelium (Benn et al., 2004).

Although evidence regarding specific allergen availability in breast milk is rather scarce, some allergens have been studied and are summarised in Table I. For cow's milk protein, it has been found that the whey component (beta lactoglobulin) passes into breast milk in small but variable amounts: usually equivalent to the amount in an extensively hydrolysed formula. In addition, in rare cases there may be some cross reactivity between human milk proteins and cow's milk proteins (Restani et al., 1999; Sorva et al., 1994; Host et al., 1990; Machtinger & Moss, 1986).

For egg protein, a recent randomised controlled trial found that increasing maternal dietary egg intake during early lactation was associated with higher breast milk ovalbumin concentrations (Metcalfe et al., 2016).

MANIFESTATIONS OF FOOD ALLERGIES DURING BREASTFEEDING

(a) IgE-mediated allergies during breastfeeding

IgE-mediated allergies most commonly manifest when supplementary feeds or solids are introduced. Sometimes an IgE-mediated allergy may manifest during exclusive breastfeeding. In the latter case, the allergen is transmitted into the breast milk within 1-12 hours after maternal ingestion of the offending food, and then causes symptoms in the infant any time from minutes to two hours after the breastfeed during which the allergen is transmitted.

Manifestations of IgE-mediated allergies in breast-fed infants can be urticaria (hives), lethargy (floppiness) or respiratory symptoms; rarely, anaphylaxis may occur and cyanosis/low blood pressure (Monti et al., 2006; Lifschitz et al., 1988). Because of the delay in the transmission of the allergen into the breast milk, the offending agent may not be immediately obvious, and will need to be determined by standard screening methods for IgE-mediated allergies, namely skin prick tests, specific serum IgE test or in equivocal cases, food challenge (Muraro et al., 2014).

Diagnosis and follow-up of a baby with immediate type food allergy during breastfeeding should ideally be handled by a paediatric allergist.

(b) Non IgE-mediated allergies during breastfeeding

In non IgE-mediated allergies, symptoms are delayed by hours to days after ingestion of the offending allergen, which in the vast majority of cases is cow's milk and/or soya. Some examples of gut or skin manifestations are as follows.

Protein-induced allergic proctitis/proctocolitis

This condition usually presents by six months of age (typically between two and eight weeks of age) with fresh blood-streaked mucous stools, and occasionally, loose or frequent stools in breastfed or formula-fed infants who otherwise appear well and thriving (Nowak-Wegrzyn et al., 2015; Lake, 2000). About 60% of proctocolitis occurs in exclusively breastfed infants (Ohtsuka et al., 2012). Exclusion of cow's milk from maternal diet results in resolution of symptoms within 72-96 hours in most cases. Research has found that up to 5% of these infants do not show the desired improvement on a strict maternal elimination diet and benefit from an amino acid formula. Most infants outgrow this disorder by one year of age (Nowak-Wegrzyn et al., 2015; Lake, 2000).

Dietary protein enteropathy

Food allergy leads to flattening of the lining of the gut and consequent absorption disturbances leading to symptoms such as protracted diarrhoea, vomiting, bloating and failure to thrive. In contrast to infants with allergic proctocolitis, allergic enteropathy usually manifests in a miserable, colicky infant with possible (but not inevitable) growth faltering (Nowak-Wegrzyn et al., 2015).

Food Protein Induced Enterocolitis Syndrome (FPIES)
FPIES is a potentially severe, non-IgE, cell-mediated food hypersensitivity. FPIES typically presents with severe, repetitive, projectile vomiting one to three hours after ingestion of an offending allergen, leading to lethargy and sometimes profound dehydration or even shock. Some infants may have diarrhoea, usually starting five to ten hours after food ingestion (Jarvinen & Nowak-Wegrzyn, 2013; Sicherer, 2005).

FPIES in relation to maternal dietary cow's milk and soy in exclusively breastfed infants is extremely rare, although it has been reported (Tan et al., 2012; Monti et al., 2011).

The acute phase can be the first manifestation of FPIES, or it can occur when the allergen is removed from the diet and then reintroduced. Chronic exposure (such as from a cow's milk or soy-based formula) to the offending allergen may cause vomiting and diarrhoea, failure to thrive, and protein deficiency.

Allergic eosinophilic oesophagitis (EoE)
Eosinophilic oesophagitis is characterised by chronic, relapsing, eosinophilic inflammation of the oesophagus. The most common trigger is cow's milk, and this disorder has also been described in exclusively breastfed infants (Papadopoulou et al., 2014; Greenhawt et al., 2013).

Children with allergic EoE have symptoms suggestive of gastro-oesophageal reflux disease (GORD), such as vomiting, dysphagia, irritability and feeding difficulties. However, they tend not to respond to conventional GORD therapies. Endoscopy and biopsy show an increased number of eosinophils (more than 15 per high power field under the microscope) in the lower and middle oesophagus (Papadopoulou et al., 2014; Greenhawt et al., 2013).

Motility disturbances
Cells which are involved in allergic reactions, such as mast cells and eosinophils, can interact with the enteric nervous system (so-called 'neuro-immune' interactions) to cause motility (movement) disturbances. This can lead to food allergies manifesting as vomiting, constipation, treatment resistant reflux or colic (Nowak-Wegrzyn et al., 2015).

DIAGNOSIS

The diagnosis of delayed-type gastrointestinal syndromes is not straightforward because a typical baby has undetectable food-specific IgE antibodies by skin prick or blood test. The cornerstone of diagnosis is a typical history (e.g. blood in the stool in proctocolitis, recurrent vomiting in FPIES) followed by an elimination-reintroduction diet. Disappearance of symptoms during maternal avoidance of trigger foods and reappearance during reintroduction of trigger foods is diagnostic of food allergy.

MIMIC OF COW'S MILK ALLERGY – LACTOSE INTOLERANCE (Gray & du Toit, 2018)

Lactose is the sugar in milk of all mammals including humans. Breastfed babies can therefore experience symptoms of lactose intolerance if there is a relative lactose overload or a deficiency in lactase enzyme. An abundance of foremilk can worsen the problem. Symptoms such as diarrhoea, excessive gas, fussiness and failure to thrive may occur and mimic cow's milk allergy. A trial of block feeding (using only one breast at a time per feed or even for two feeds in a row) and a trial of lactase enzyme drops may be considered. This condition often resolves by three months of age as lactase levels in the gut increase.

MANAGEMENT OF FOOD ALLERGY DURING BREASTFEEDING (Gray & du Toit, 2018; Levin et al., 2015; Järvinen-Seppo, 2014; Muraro et al., 2014; Sicherer & Sampson, 2014; Fiocchi et al., 2010)

If an infant is symptomatic owing to the presence of dietary food triggers in breast milk, the cornerstone of management is maternal avoidance of these foods, coupled with choice of an appropriate formula milk if supplementary feeding is necessary or the mother is weaning, and avoidance of the offending food when solids are being introduced.

Infants with IgE-mediated allergy require a written emergency anaphylaxis plan and access to an adrenaline autoinjector in severe cases.

In the case of infants who have manifest allergies during breastfeeding, once the allergen has been identified, strict avoidance of that allergen in the maternal diet is usually advocated. This is because it is difficult to identify the threshold for reactivity in an infant, and also the threshold dose can become smaller with repeated episodes. Some infants reacting to milk and egg via the breast milk may tolerate maternal ingestion of these foods in the baked form. This is not routinely recommended without assessment by an allergist.

Cow's milk is the most common trigger for early manifestations of food allergy, regardless of clinical presentation. Strict avoidance of cow's milk from the mother's and infant's diet is needed in cow's milk protein allergy, unless otherwise suggested on the basis of allergy testing.

In allergic proctocolitis, the response to maternal elimination occurs within 48-72 hours. In enteropathy, the response may take two to three weeks; hence the trial of maternal elimination needs to be longer to look for improvement in symptoms.

If there is no response to a cow's milk elimination diet, it may be that:

- The maternal elimination diet is not complete and there is still ingestion of hidden sources of allergen;
- Rarely, that additional foods need to be eliminated (such as egg, peanut, or wheat);
- Symptoms are not related to food allergy (as

is commonly the case in atopic dermatitis);
- The infant is actually reacting to breast milk proteins that are cross reacting with cow's milk protein. This is very rare (less than 5% of allergic cases) but will necessitate discontinuation of breastfeeding and use of an amino acid formula.

In all cases of maternal dietary elimination, a dietitian should be involved to help identify hidden sources of milk protein (or other identified allergens) in the diet, and to ensure nutritional adequacy of the maternal diet. A good pre-natal vitamin and a calcium supplement (1000 mg calcium daily) are needed for the mother who is avoiding cow's milk protein strictly.

> 95% of cow's milk allergic infants will respond to strict maternal elimination of cow's milk protein during lactation and can thus continue to breastfeed safely.

INTRODUCTION OF FORMULA MILK

If breast milk is inadequate or the mother is choosing to wean off the breast in a cow's milk protein allergic infant, alternatives include hypoallergenic formulas (extensively hydrolysed cow's milk-based formulas and amino acid-based formulas). Partially hydrolysed cow's milk formulas are not hypoallergenic and thus not appropriate. Extensively hydrolysed formulas are tolerated by about 90% of infants with cow's milk allergy. Breast milk, in theory because of the filtration process, is already 'equivalent' to an extensively hydrolysed formula; hence, strictly speaking, infants reacting to cow's milk transmitted via breast milk will do better on an amino acid formula if the mother needs to wean/supplement. Certainly an amino acid-based formula is recommended over extensively hydrolysed formulas in:

- Infants with IgE-mediated cow's milk allergy who are at high-risk for anaphylaxis
- EoE
- Infants who continue to exhibit symptoms on extensively hydrolysed formulas
- Infants who continue to exhibit symptoms after maternal elimination of cow's milk.

In non IgE-mediated cow's milk allergy, there is a significant overlap with soya allergy; hence a soya formula is not recommended. In IgE-mediated cow's milk allergy, use of a soya-based formula is an affordable and palatable alternative to hydrolysed formulas if the baby has tested negative to soya during allergy testing. Milks of other mammalian origin such as goat's milk should be avoided owing to high degrees of cross-reactivity with cow's milk.

TIMING OF REINTRODUCTION OF ALLERGENS IN THE ALLERGIC BREAST-FED BABY (Nowak-Wegrzyn et al., 2015; Fiocchi et al., 2010)

In a child with an immediate-type allergic reaction during breastfeeding, it is recommended to wait until one year after the last reaction occurred before reintroducing allergens and in addition to be guided by skin tests/specific IgE trends. Reintroduction should take place under physician supervision in infants with IgE-mediated allergy.

For non-IgE-mediated allergic manifestations which are evident in breast-fed babies, introduction of cow's milk and soy into the diet of lactating mothers should be attempted at the discretion of the physician/allergist, often at around nine to twelve months of age. Milder cases may tolerate maternal reintroduction at an earlier stage, and certainly baked milk products may be attempted in a lactating mother at around six months of age. Introduction of cow's milk products into the infant's diet may be attempted after one year of age. This is often done in a step wise fashion – starting with baked milk products, progressing to an extensively hydrolysed formula in infants supplemented with amino acid formula, yoghurt, cheese and then cow's milk. If at any stage the child shows symptoms of allergy, the reintroduction should be halted and resumed again two to three months later. In proctocolitis, introduction can be attempted at nine to twelve months, but in FPIES, it is usually recommended to wait until 12-18 months after the last reaction. The age at introduction of cow's milk or soy in the case of EoE is at the discretion of the clinician taking care of the infant and is often delayed until later (Papadopoulou et al., 2014; Greenhawt et al., 2013).

In case of proctocolitis and dietary protein enteropathies, the trigger food may be reintroduced at home, if there is no history of an immediate reaction. Reintroduction should take place under physician supervision in infants with FPIES.

It is wise to repeat a skin prick test or specific IgE before such reintroduction in non IgE-mediated allergies to detect the occasional case in which an IgE mechanism has evolved.

FOOD ALLERGIES MANIFESTING UPON WEANING

If the breast-fed baby presents for the first time with symptoms during supplementary feeds with a cow's milk containing formula milk, or when solids are introduced, then they should be investigated and the offending allergen eliminated from the infant's diet. However, if they are asymptomatic during breastfeeding, even if the mother is consuming the offending allergen, then insufficient amounts of intact allergen are passing into the breast milk to cause symptoms and the mother can continue to consume the offending foods during lactation. All too often, strict elimination diets are prescribed for lactating mothers when in fact, breast milk is not triggering symptoms.

ECZEMA IN THE BREAST-FED BABY

(a) Mild eczema

Atopic eczema is common in infancy. In an exclusively breastfed infant with mild eczema, it is reasonable to initially prescribe a skin-care regimen, and if the eczema does not respond, referral to a specialist may be warranted. A significant elimination diet is unnecessary. It can compromise the well-being of the mother and infant and should not be implemented without a proper diagnosis of food allergy.

(b) Moderate to severe eczema
Food allergies contribute to eczema in only about one fifth to one third of children with moderate to severe eczema, and in 90% or more of such cases, an IgE-mediated mechanism is involved. Clues to food allergy include eczema that exacerbates within hours to a day of maternal ingestion of certain foods, such as cow's milk or peanut, and improves with maternal avoidance of the trigger food. Additional clues are early onset eczema in a baby less than three months of age, and in babies with chronic gastro-intestinal symptoms or failure to thrive. Indications for food allergy testing in an infant with eczema are outlined in Table II.

Guidelines from the UK National Institute of Health and Clinical Excellence (NICE) (2007) state that in moderate to severe eczema in a baby of less than six months, a trial of maternal elimination of cow's milk protein (or trial of extensively hydrolysed formula in the case of formula-fed babies) should be attempted for three to four weeks in addition to standard topical eczema therapy.

Food allergy needs to be proven before recommending specific elimination diets. Certainly there is no role for blanket elimination diets in the lactating mother if the child has eczema; targeted avoidance should be advised by the specialist after appropriate assessment. Many children with eczema have positive allergy tests but will tolerate the food; hence, this is best dealt with by an allergist with the capacity to perform food challenges if needed. Generally, if foods seem to be tolerated with no obvious immediate symptoms, and eczema is treatment responsive, then foods do not need to be eliminated regardless of allergy test results.

COLIC AND BREASTFEEDING

Minor gastrointestinal problems are extremely common in the first year of life, and a source of great anxiety for parents. The term 'colic' is used broadly to refer to prolonged excessive crying or unsettled periods for no apparent reason, and which is difficult to soothe. It occurs in breast- and formula-fed babies alike (Deshpande, 2015). A rather old fashioned, but still widely used definition of colic refers to crying which:

- lasts for more than 3 hours a day
- happens more than 3 days per week
- persists for longer than 3 weeks
- in a child with normal growth patterns.

Colic is multifactorial and possible contributing factors are listed in Table III.

Simple colic does not respond to cow's milk exclusion (Evans et al., 1981). A general reduction in caffeine, alcohol and gas-forming foods should be considered in severe colic, but blanket exclusion of multiple allergenic foods is not warranted.

In selected infants with colic, especially those with additional factors such as eczema, failure to thrive or treatment-resistant reflux, a non-IgE-mediated cow's milk protein allergy should be considered. Such cases may warrant a cow's milk free diet during breastfeeding for two to three weeks. If there is no response, the mother should revert to her normal diet, or in rare cases with a high suspicion of an allergic aetiology, the baby should be trialled on an amino acid formula for two to three weeks whilst the mother continues to express to keep up her milk supply.

It should be remembered that colic can affect 20-40% of infants, whereas cow's milk allergy affects two to five per cent, so only a small proportion of colicky babies will have a cow's milk protein allergy. Alternative contributing factors in breast-fed babies, such as overfeeding, a quick let down reflex, or relative lactose overload, should be considered.

ALLERGY PREVENTION AND BREASTFEEDING

The World Health Organization (Eidelman et al., 2012) recommends exclusive human milk feeding for the first six months of life, with continued breastfeeding for one to two years of life or longer. However, data regarding exclusive breastfeeding for allergy prevention is conflicting.

Several studies (Victora et al., 2016; De Silva et al., 2014) have shown benefits of breastfeeding in relation to food allergy and eczema prevention; however, breastfeeding beyond six months does not seem to confer additional benefits pertaining to allergy prevention (Kramer & Kakuma, 2002).

TABLE II: Indications for allergy testing in children with eczema (Gray & Levin, 2014)

1. Moderate to severe eczema, especially if not responding to standard treatment
2. Early onset eczema (< 6 months)
3. A history suggestive of immediate food allergies
4. A history of recurrent worsening of eczema after ingestion of a certain food
5. Associated features suggestive of allergy such as severe colic or failure to thrive

TABLE III: Factors possibly contributing to colic

Immaturity of the gut
Neurological immaturity
Trapped wind causing gut discomfort or pain
Disturbance in the bacteria of the gut
Reflux of gastric acid into the oesophagus
Feeding difficulties such as overfeeding, under-feeding, swallowed air or foremilk abundance
Exposure to tobacco smoke in pregnancy or after birth
Cow's milk protein allergy (plays a role in some babies)
Lactose intolerance
Hypersensitivity to environmental stimuli
Infant temperament, family stress and emotional tension during pregnancy

Maternal breastfeeding for the first three months seems to reduce the incidence of eczema (Gdalevich et al., 2001), possibly via ingestion of soluble IgA (Orivuori et al., 2013). Randomised studies and a systematic review found a reduction in the incidence of cow's milk protein allergy (CMPA) with exclusive breastfeeding for four months compared with feeding with cow's milk based formula, but this cannot be generalised to other food allergies (Liao et al., 2014; Greer et al., 2008). Breastfeeding may also reduce the number of early (mainly viral-related) wheezes (Elliot et al., 2008). Certainly, no formula milk has been found to be more beneficial than breastfeeding as an allergy prevention strategy.

However, the more long-term protective role of breastfeeding is still controversial, especially in relation to eczema and asthma (De Silva et al., 2014). Disappointingly, some studies have shown that extensive exclusive breastfeeding may increase food sensitisation and allergy in high risk infants, and other studies have shown an increase in eczema with breastfeeding amongst children with no parental allergic history (Snijders et al., 2007; Bergmann et al., 2002).

SUMMARY:
Breastfeeding and allergy prevention
Exclusive breastfeeding for the first four to six months of an infant's life is still recommended as an allergy prevention strategy where genetic predisposition poses an increased risk. However, exclusive breastfeeding for six months remains a public health message not relating to allergies. The continuation of breastfeeding after six months should be recommended because of other beneficial health effects even though research shows inconclusive results for allergy prevention.

MATERNAL DIET DURING LACTATION

Mothers may inadvertently sensitise their children to certain foods through breast milk; however, changing maternal diets during breastfeeding has not been found to influence food allergy in the infant (De Silva et al., 2014; Kramer & Kakuma, 2014).

In fact, a recent cohort found that maternal elimination diets during lactation resulted in lower levels of breast milk–specific IgA, which was associated with the development of cow's milk allergy in infants (Järvinen et al., 2013). However, the participants included in this study had a significant atopic family history, affecting the applicability of the results to the general public.

SUMMARY:
Maternal diet and allergy prevention
Maternal avoidance of highly allergenic food is not recommended as an allergy prevention strategy. Note: this recommendation does not apply to infants who already show signs of allergic disease from an early age, in whom maternal avoidance of certain foods may form part of the management.

MATERNAL/INFANT SUPPLEMENTATION DURING LACTATION

There is increasing evidence that gut microbial composition plays an important role in local and systemic maturation of the immune system, and thus plays a potential role in allergy pathophysiology. To this effect, probiotics (beneficial bacteria) and prebiotics (non- digestible oligosaccharides which stimulate selectively the growth of beneficial bacteria) have been investigated during the perinatal period for their potential modification of postnatal gut colonisation. Breastmilk is naturally rich in prebiotics, thus potentially contributing towards optimising gut microbiota in the infant. Maternal probiotic supplementation during pregnancy and lactation, whilst showing potential benefit in eczema reduction in the offspring, has led to inconclusive results for food allergy prevention (Kalliomäki et al., 2003). Finding the optimal doses and strains of probiotics and the optimal timing of supplementation for potential allergy prevention remains in the realm of active research.

Maternal fish oil supplementation and vitamin D during lactation has not been consistently shown to reduce infant food allergy (Klemens et al., 2011).

SUMMARY:
Probiotic supplementation of maternal diet and allergy prevention
Routine supplementation of the maternal (or infant) diet during lactation as an allergy prevention strategy has not produced consistent results and is currently not recommended.

BREASTFEEDING AND THE INTRODUCTION OF SOLIDS

From an allergy prevention point of view, studies have shown that delaying solids beyond four months of age does not seem to confer additional allergy protection benefits (Tromp et al., 2011; Zutavern et al., 2008). There is a growing body of evidence that excessive avoidance of natural exposure to allergens, which was the main food allergy prevention strategy in the past, can lead to impaired immunological tolerance. Therefore, the current recommendation of the European Academy of Allergy and Clinical Immunology (EAACI) and of the American Academy of Paediatrics (AAP) is the introduction of complementary foods between four to six months according to local standard practice and the needs of the infant, irrespective of atopic heredity. However, looking beyond allergy prevention, care should be taken in advising early solids introduction in resource-constrained settings, in which enforced partial breastfeeding may lead to an overall reduction in the duration of breastfeeding (Levin et al., 2017). Moreover, early introduction of solids and a shortened duration of exclusive breastfeeding has been associated with risk for childhood obesity, adult-onset coeliac disease, eczema, anaemia, diarrhoeal disease and non-communicable diseases (Joneja, 2012).

There is no benefit in withholding exposure to potentially allergenic solids once weaning has commenced, irrespective of atopic heredity. Current studies are showing a trend towards an advantage of earlier introduction of allergenic foods such as peanut (Perkins et al., 2016; du Toit et al., 2015). However, if the infant already shows signs of atopy or allergy, further evaluations need to be pursued to aid in the prudent introduction of solids.

SUMMARY:
Introduction of solids and allergy prevention
Introducing potential food allergens whilst continuing to breastfeed may provide a reduced risk for development of food allergy (Gray et al., 2018).

CONCLUSION

Food allergens do get transmitted via breast milk, but generally in a protective form. Rarely, exclusively breastfed babies can present with food allergies - either immediate reactions (such as hives or maculopapular rash) or, more commonly, delayed-onset reactions (such as eczema, proctocolitis, FPIES, and eosinophilic gastroenteropathies).

The most common allergens transmitted via breast milk and causing symptoms are cow's milk and soya. Investigations to elicit the offending allergen should ideally be done in the specialist setting

The vast majority of infants with allergies during breastfeeding can continue to breastfeed with targeted exclusions by the mother. Involvement of a dietitian in overseeing exclusion diets and appropriate nutritional supplementation is vital. Around five per cent of infants will not improve adequately on a maternal elimination diet and will need an amino acid formula. Breastfeeding still has a role to play in allergy prevention, mostly in the first four to six months of life. Exclusion diets during lactation do not prevent allergies.

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GLOSSARY

atopic dermatitis	eczema
complement C	protein that is part of the immune system
enteric	relating to the intestines
enteropathy	disease of the intestine
eosinophilic oesophagitis	inflammation of the oesophagus owing to the build-up of a type of white blood cell (eosinophil)
hydrolysed	broken down
IgA	an antibody that is important for the immune functioning of mucous membranes
IgE-mediated (immediate-type) allergies	a type of allergy in which the reaction occurs very quickly, within seconds to 2 hours of eating the food
IgG	most common antibody found in the human circulation
interleukin	small protein important for cell signalling
lactoferrin	protein found in milk
macromolecule	a very large molecule such as protein
macropapular rash	rash characterized by a flat, red (in light-skinned people) area on the skin and small bumps
non IgE-mediated food allergies	a type of allergy in which the reaction is delayed by hours to days after a particular food is ingested
ovalbumin	protein found in egg white
pathogenesis	the way in which a disease develops
proctitis	inflammation of the lining of the rectum
proctocolitis	inflammation of the rectum and colon
serum IgE test	a test to measure the level of IgE antibodies that are made by the body in response to certain allergens

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