

**Annex 2**

**DHA requirements in pregnancy and lactation.  
Background Paper for Discussion: SACN**

**S A Wootton and A A Jackson  
Institute of Human Nutrition  
University of Southampton  
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## **Introduction**

It is clear that there is a requirement for long chain polyunsaturated fatty acids (LCPUFA) for the normal development of the mammalian brain. For the human the extent of accumulation of LCPUFA during fetal life and early infancy has attracted attention and some controversy. It has been suggested that preformed LCPUFAs, particularly docosahexaenoic acid (DHA, 22:6n-3) and eicosapentaenoic acid (EPA, 20:5n-3), have to be provided preformed in the diets of infants to meet the high demands of rapidly growing tissues and organs. The mother is the primary source of these essential fatty acids for the fetus and breast-fed infant. Relatively little consideration has been given to the ability of the mother to provide adequate amounts of EPA and DHA and the effect this is likely to have upon her own dietary requirements.

The current dietary intakes of DHA in the UK can be estimated to be around 100mg/d for adult women. For those individuals who do not consume fish, or are consuming a low-fat diet the intake is likely to be substantially less [1]. There is evidence that the capacity for DHA synthesis from  $\alpha$ LNA may be limited. Therefore, it has been recommended by some that DHA itself should be considered to be an essential dietary constituent [2] and that pregnant women have the need to consume as much as 300 mg/d DHA [3]. We have reviewed evidence which provides information on the maternal requirement for LCPUFA, with a special emphasis on DHA and EPA. We sought to address the question: whether there is sufficient evidence based on biochemical and functional outcomes to identify a specific dietary requirement during pregnancy and lactation. In particular we have looked for evidence of the existence of a depleted state during pregnancy and/or lactation that would support the proposal of the need for a dietary recommendation for individual LCPUFA in women of child bearing age.

### **Measuring the demands for LCPUFA during in pregnancy and lactation**

There is very little information either on the LCPUFA requirements of non-pregnant women, or the extent to which the current dietary intakes are sufficient to meet their needs. In part this may be attributed to a lack of satisfactory, agreed markers which are suitable, sensitive and specific for defining LCPUFA status, or measures which can be taken to characterise an inadequacy.

Those markers of status that are usually reported relate to concentrations of fatty acids within the circulation. These may be expressed as total fatty acids or related to their concentrations in different circulating pools. The functional significance of these measures in characterising any aspect of functional status is uncertain. Similar measures have been measured during pregnancy and taken to mark LCPUFA status, such as concentrations of fatty acids in maternal or umbilical blood. These measures may have been related to dietary intake in the mother or associated with measures of the outcome for the pregnancy, such as the duration of pregnancy, infant size at birth, or measures of growth and functional development.

During pregnancy, in addition to meeting her own usual needs for EPA and DHA, a woman must also meet the additional demands associated with the accretion of maternal, placental

and fetal tissues. The timing of the changed demands may vary at different stages of the pregnancy. The evidence suggests that the mother may accumulate increased adipose tissue as a reserve from very early in pregnancy, which can then be drawn on at later stages. For the fetus the demands are likely to be particularly high during the last trimester of pregnancy. The additional demands for LCPUFA or specific fatty acids during a normal pregnancy have not been adequately defined.

Estimates of LUCPFA accretion in fetal and placental tissues during a normal pregnancy have been made, based upon information from postmortem material. It has been estimated that the fetus accumulates about 60 to 70 mg n-3 LCPUFA/d during the last trimester of pregnancy, mostly in the form of DHA [4,5]. This may be a significant under-estimate as it does not take into account the LCPUFA associated with placental tissue, nor the extent to which LCPUFA accumulate in fetal adipose tissue as a reserve for early postnatal life. A more reasonable estimate for the net accretion by the fetus during the pregnancy would be at least 10 g DHA. Of this about 6 to 7g would represent fetal accretion over the last trimester mainly for brain development. A further 2 g DHA would be deposited within about 1 kg of fetal adipose tissue.

The delivery of nutrients to the infant through human milk draws upon nutrients taken in the diet, and also the maternal reserves deposited during pregnancy. It is recommended that infants should be fed on human milk exclusively, for the first six months of life. It has been estimated that during lactation the mother has to make available about 70 to -80 mg DHA/d for milk formation, in addition to her own basal requirements [6,7]. There may be some saving of DHA through a reduction in losses associated with menstruation during lactational amenorrhea, but these are likely to be small. Thus, if a woman is to have sufficient DHA available in reserves to cover the requirements of 6 months of lactation, she would need to accumulate about 12 g DHA during pregnancy as an integral part of her adipose tissue reserves.

Taken together, an estimate of the DHA which a woman would have to accumulate during pregnancy, to meet the increased needs of her pregnancy and lactation, would be of the order of 22 – 25 g. This would be in addition to that required by the woman to satisfy her own intrinsic requirements for DHA. A typical diet for a non-pregnant woman would provide about 100 mg/d DHA, that is about 9 g DHA over the last trimester of the pregnancy and about 18 g DHA during the 6 months of lactation. If the pattern and amount of DHA in the diet was unchanged over pregnancy and lactation, and if the woman had been in balance while consuming 100mg DHA/d prior to pregnancy, then to meet the increased needs by changing consumption would require a doubling of maternal intake during the last trimester of pregnancy and a 60-70% increase in maternal intake during lactation. There is no evidence that women selectively increase their consumption of DHA during pregnancy or lactation.

### **Meeting increased demands in pregnancy.**

If the dietary supply of DHA is marginally adequate, and the intake is not changed during pregnancy and lactation, then the extent to which the increased requirement can be met will depend on:

- i) the extent to which LCPUFA may be conserved by reducing its rate of oxidised or loss through other routes,

- ii) the amount of pre-formed EPA and DHA present in adipose tissue stores reserves that can be effectively mobilised when needed,
- iii) the ability to increase the formation of DHA from precursors such as  $\alpha$ LNA.

Amenorrhoea during pregnancy will conserve some nutrients and there will be a decrease in the loss of LCPUFA through this route, however, the impact on DHA requirements is likely to be modest. The usual diet consumed in the UK may be relatively rich in n-6 fatty acids such as linoleic acid, but is likely to be poor in n-3 fatty acids such as  $\alpha$ LNA, EPA or DHA. Thus, most women are likely to enter pregnancy with marginal or poor n-3 PUFA status [8,9]. The dietary supply of preformed DHA is generally low at any time, and a woman's ability to access n-3 PUFA contained in adipose tissue might be critical when demands are increased. For n-3 PUFA derived from the diet, or mobilised from adipose reserves, the predominant fatty acid is likely to be  $\alpha$ LNA and a woman's ability to effectively convert this into other fatty acids, such as DHA is likely to play an increasingly important role in satisfying the fetal demands for DHA. In circumstances where the maternal reserves are low, poorly mobilised or synthesis constrained, then it is likely that the effective supply of DHA to the fetus may be compromised unless the dietary intake of DHA during pregnancy is adequate.

There is direct evidence, for adults, term and preterm infants, to show that there is conversion of  $\alpha$ LNA to DHA. However, the conversion appears tightly regulated with a limited capacity under many situations and in amounts which are so limited that it is unlikely to be sufficient to meet a substantial increase in the demands for DHA [10-13]. However, for non-pregnant women of reproductive age, the capacity is several orders of magnitude greater [14], possibly due to oestrogen-mediated up-regulation of the second  $\Delta$ 6-desaturation and final peroxisomal  $\beta$ -oxidation reaction [15]. There is the possibility that the fetus contributed to its own needs by synthesising DHA from LCPUFA.

There are no measurements of the magnitude of maternal DHA synthesis in pregnancy. Based, on information from tracer studies it is unlikely that more than 5% of available  $\alpha$ LNA would be converted to DHA. It remains to be determined whether conversion at this rate is adequate to meet the increased needs of pregnancy and lactation, although the indications are that it is unlikely to be sufficient. Large dietary supplements  $\alpha$ LNA to pregnant women do not appear to improve either their DHA status or that of their offspring [16]. An important consideration is that even when diets rich in  $\alpha$ LNA are consumed, the ability to synthesise adequate amounts of DHA may be constrained by excess intake of the n-6 PUFA competing for the same synthetic pathway [17] or a limited availability of micronutrients which serve as co-factors in the synthesis of DHA. Diets limiting in iron [18], magnesium [19], zinc [20], calcium [21], riboflavin [22], pyridoxine [23] and B12 [24] have each been associated with constraint in LCPUFA desaturation and chain elongation. Furthermore, animal studies show that the consumption of imbalanced diets, low in protein [25] or high in sucrose [26], or modest consumption of ethanol [27] impairs LCPUFA status whilst acute or chronic inflammation may also increase demands on LCPUFA metabolism, altering the availability of circulating fatty acids [28].

In theory a poor dietary supply or limited synthesis may be ameliorated by mobilisation of body reserves. The DHA in adipose tissue reserves of a woman as she enters pregnancy or accumulates during her pregnancy are potentially available if they can be mobilised. Crude estimates would suggest that for every 10kg of body fat that could be mobilised, might yield about 15-18 g of DHA. This assumes that within the adipose tissue DHA comprises about 0.2% of total fatty acids, the same as observed in adult men [29] as there is no information on

the fatty acid composition of adipose tissue in pregnant or non-pregnant women of child bearing age. The net accumulation of adipose tissue during pregnancy, makes it unlikely that mobilisation of adipose tissue can make a substantial contribution to meeting the needs of the pregnancy itself, but may be an potential source of DHA during lactation. Maternal obesity is associated with insulin resistance, impairing mobilisation of LCPUFA from adipose tissue reserves, whereas thin mothers with little body fat reserve may well have less to mobilise. In either case, there would be a greater need for endogenous DHA synthesis or a greater dependency on dietary DHA to satisfy the demands. There are no studies which have specifically examined the effect of maternal fatness on LCPUFA status during pregnancy.

### **Pregnancy and Lactation and Maternal DHA Depletion.**

In cross-sectional and prospective studies it has been demonstrated that pregnancy is associated with an increase in circulating concentrations of DHA in plasma phospholipids, by about 50% at 10 weeks compared with non-pregnant values. Some studies indicate that DHA remains elevated until term [8], whereas others report lower values at term than at 28 weeks [30]. The extent to which these changes reflect a general increase in phospholipid concentration associated with an increase in circulating lipoproteins (pregnancy-related hypertriglyceridaemia) or a specific mobilisation of DHA from adipose tissue is unclear. There is some indication that women may track for plasma DHA concentration throughout pregnancy [Burdge unpublished]. Greater increases in the concentration of Mead acid (assumed to be a general marker of LCPUFA status) and Osbond acid (assumed to be a specific marker of DHA status) in plasma phospholipids during pregnancy have been seen by Hornstra and colleagues and taken to be indicative of a reduction in the functional LCPUFA status [31].

The magnitude of the increase in plasma DHA, and decline in 'functional DHA status' reported by Hornstra, differs markedly between women, but the basis of these differences have not been explored in detail. There is conflicting evidence on the effect of parity on the changes in DHA. If repeated pregnancies were to lead to poorer DHA status because of progressive depletion and incomplete recovery between pregnancies, it would be expected that there would be an inverse relationship between the DHA status of pregnant women and the number of completed pregnancies. Although an inverse relationship for plasma phospholipids DHA has been reported [32], the same group were unable to identify any relationship in a later study of non-pregnant women from the same population [33]. They concluded that this might in part be related to the interpregnancy interval, whereby if the interval was too short then there would incomplete replenishment of maternal DHA stores.

Maternal DHA concentration decreases by about 30% during the post-partum period [6], but is not necessarily immediate after parturition, but may be prolonged in duration. The decrease is observed in all mothers irrespective of whether they chooses to breast feed or not, suggesting that this may be related to changes in endocrine status or increased utilisation of maternal DHA reserves, independent of lactation. However, the change in plasma phospholipids DHA concentration appears greater in lactating women and may be enhanced when the period of lactation is extended [34]. These observations would support the view that prolonged and extensive lactation may be causally related to maternal DHA depletion particularly when associated with multiple pregnancies. Numerous factors affect the DHA content of breast milk, but maternal DHA intake appears to be a major determinant. Whilst DHA supplementation has been shown to increase plasma and breast milk DHA concentration of lactating women [7], it remains is not known whether increased DHA intake would ameliorate maternal DHA depletion over successive pregnancies and periods of lactation.

### **Effects of supplementation on maternal status and outcome.**

The maternal supply of LCPUFA may be derived preformed from the diet or from body reserves, or synthesised within the body either from dietary constituents or from body reserves. For n-3 PUFA, diets rich in cold water fish (or fish oils or marine lipids) can provide large amounts of EPA and DHA. Maternal PUFA status varies with fish and/or n-3 PUFA consumption in both the non-pregnant and pregnant state [9, 35]. Regular consumption of oily fish is associated with higher circulating DHA levels [36, 37], and supplementation with EPA and DHA increases circulating DHA levels during pregnancy and at term [38]. During a pregnancy in which the mother consumes fish or suitable supplements, there are higher concentrations of DHA and lower concentrations of n-6 PUFA in cord blood samples which in turn correlate with maternal blood DHA, and also maternal dietary n-3 PUFA intake [40]. The evidence linking n-3 PUFA intakes and changes in maternal n-3 PUFA status with alterations in duration of pregnancy length and fetal development is strong although the mechanisms underlying these relationships is unclear. In general, higher intakes during pregnancy of n-3 PUFA, in the form of oily fish, are associated with longer gestational length, greater birth length and weight and lower risks of intra-uterine growth retardation, small size for gestation age and premature birth [6, 40]. Some studies in which the dietary intervention has been EPA/DHA have shown such similar effects, whereas others have not demonstrated any change in the outcomes of pregnancy although there has been an increase in the circulating concentrations of DHA in the mother [31]. It may be that in part this difference in outcome reflects a difference in the background pattern of habitual fish consumption in the diet before and during pregnancy which would alter the background pattern and balance of LCPUFA that a mother brings to her pregnancy. Any effect of an increase in EPA/DHA consumption during pregnancy needs to be assessed against the background condition.

### **Conclusion.**

There is some evidence that for many women there is a marginal status for n-3 PUFA during pregnancy and lactation. Although, the formation of DHA and DHA status appear tightly regulated, a marginal state for many women during pregnancy and lactation can not be excluded. The extent of dietary dependence on increased levels of consumption of n-3 PUFA, or specifically of DHA, to improve pregnancy outcome needs to be demonstrated. The possible effects of the status for other nutrients, or stressful conditions in modulating DHA status needs to be determined.

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