

Role of omega-3 fatty acids as a treatment for depression in the perinatal period

Anne-Marie Rees, Marie-Paule Austin, Gordon Parker

Objectives: To consider the possible rationale and utility of omega-3 fatty acids as a treatment for depression in the perinatal period.

Method: A review of published and unpublished research was undertaken, using electronic databases, conferences proceedings and expert informants.

Results: Relevant bodies of evidence include an epidemiological link between low fish intake and depression. Laboratory studies show correlations between low omega-3 fatty acid levels and depression, as well as reduced levels of omega-3 in non-depressed women during the perinatal period. Treatment studies using omega-3 in patients with mood disorders further support an omega-3 contribution, as do neuroscientific theories. Research into omega-3 and infant development also highlights potential effects of depletion in the perinatal period and supports infant safety and benefits of supplementation.

Conclusions: There is a relative lack of knowledge about the safety of standard antidepressants in the perinatal period. There is a clear need for more research into alternative treatments, such as omega-3 fatty acids, in the management of depression in the perinatal period.

Key words: docosahexaenoic acid, omega-3 fatty acids, postnatal depression, pregnancy.

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Omega-3 fatty acids have been promoted in the lay press for treatment of various medical disorders. There is increasing research evidence indicating their possible value in the treatment of mood disorders, including depression in the perinatal period.

Evidence supporting this theory include, first, an epidemiological link between fish intake and depressive mood states, including postnatal depression. Second, laboratory studies show correlations between low omega-3 fatty acid blood levels and depression, and also depletion

of omega-3 during the perinatal period in non-depressed women. Third, there are a number of intervention studies showing the benefit of omega-3 for the treatment of mood disorders.

What is omega-3?

Omega-3 is a polyunsaturated fatty acid (PUFA), as is omega-6, both of which are essential fatty acids. Dietary intake is therefore our only access to PUFAs and unlike saturated fats, PUFAs have been associated with many health benefits. They are divided into the linoleic acid and alpha-linolenic acid series. Linoleic acid is found in vegetable and seed oils (very abundant in the Western diet), while alpha-linolenic acid is found in flaxseed oil, canola oil and walnuts. These are substrates from which higher omega-3 and omega-6 PUFAs are synthesized, such as: eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and arachidonic acid (AA) [1]. However, oily fish are a primary source of omega-3 long-chain

Anne-Marie Rees, Psychiatrist and Senior Research Fellow (Correspondence); Gordon Parker, Scientia Professor, Executive Director

School of Psychiatry, University of New South Wales, Black Dog Institute, Hospital Road, Prince of Wales Hospital, Randwick, New South Wales, 2031, Australia. Email: a.rees@unsw.edu.au

Marie-Paule Austin, Associate Professor and Consultant Psychiatrist

School of Psychiatry, University of New South Wales, Black Dog Institute and Royal Hospital for Women, Sydney, Australia

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PUFAs, such as DHA and EPA, and are most abundant in swordfish, salmon, perch and tuna. Direct intake of DHA and EPA via fish oil is important since the human enzyme pathway required to metabolize these long-chain PUFAs from alpha-linoleic acid is relatively inefficient. This relates to the lack of evolutionary adaptation of these enzymes needed to cope with environmental changes to our diet [2]. Breast milk also provides a direct source of DHA for the infant [3] and the amount of DHA available from that source depends on the maternal diet. The median DHA intake of Australians is 15 mg/day. Australian women have low blood DHA levels compared with women from high fish-eating nations, such as Japan, Korea and Norway, where dietary intakes are approximately 1000 mg/day [4].

Since omega-6 dietary intake is high and omega-3 intake low, the ratio of omega-6 to omega-3 in Western diets is currently very high compared to the past. Man has evolved on a diet with an omega-6 : 3 ratio of 1 : 1 whereas today this ratio is greater than 10 : 1 [2,5,6]. As omega-6 fatty acids become more prevalent in the diet, membrane levels of the omega-3 fatty acids are reduced and production of long-chain PUFAs, such as DHA and EPA (from short-chain PUFAs such as alpha-linolenic acid), decrease, due to competition for the same metabolic enzymes. In general, it is suggested that benefits from omega-3 fatty acids are based on an appropriate balance between omega-3 and omega-6 fatty acids [5].

Evidence for the role of omega-3 in depression

There are several lines of evidence suggesting that omega-3 fatty acids may have an important role to play in the treatment of depression, especially during the perinatal period.

Epidemiological evidence

Epidemiological data suggest that societies consuming large amounts of fish and omega-3 fatty acids have lower rates of major depression. In cross-national collaborative studies, North American and European populations showed much higher rates of depression than Taiwanese populations (10-fold higher) [7]. Hong Kong [8], Chinese regions [9] and Japan [10,11] also have much higher fish consumption rates and lower rates of depression than Western countries. These studies used culturally specific, well-verified rating scales. Cultural factors are thought to be significant confounders [12], but do not completely explain such findings.

Particularly relating to the perinatal period, cross-national analyses have demonstrated that lower concentrations of omega-3 fats in the mother's milk (mainly

DHA), as well as lower natural rates of seafood consumption, are robustly correlated with high rates of postnatal depression (correlations in the order of 0.8) [13]. The preferential diversion of omega-3 fats to the baby during gestation and breast-feeding makes women more vulnerable to depression at this stage of life.

Other supporting evidence for this dietary hypothesis includes the suggestion that low plasma concentrations of DHA predict low concentrations of cerebrospinal fluid 5-hydroxyindolacetic acid (5-HIAA) [13]. Low concentrations of 5-HIAA, the main metabolite of serotonin, have been widely reported to be associated with depression and suicide. A large Finnish cross-sectional study [14] and a large cohort of Japanese subjects, followed for 17 years [15], have both found a decrease in depression and risk of suicide among subjects with higher rates of fish consumption.

Studies of omega-3 levels

Fatty acid analysis can be undertaken by thin layer chromatography to give levels of omega-3 in the plasma and red blood cells, as well as in breast milk. Studies have reported a reduced level of omega-3 fatty acids [1,16] and an increase in the omega-6/omega-3 ratio in depressed patients [6]. They were all case-controlled studies, and despite small numbers, results were significant.

Blood levels of DHA and other fatty acids have been shown to be depleted during the perinatal period, particularly by the third trimester, and with significant depletion during lactation and the postnatal period [17–19]. Depletion appears independent of breastfeeding [20]. Metabolic and postmortem studies indicate that the fetus accumulates an average of 67 mg of DHA per day during the third trimester which exceeds the intake of many Australian women [20].

The Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC) provides important data relating to omega-3. The relationship between postnatal depression and dietary DHA highlighted a reduction in the prevalence of depressive symptoms with increasing omega-3 long-chain PUFA intake. The result remained highly significant after adjustment for social and perinatal variables [21]. In another smaller study, where women had also been part of the Adelaide Mothers' and Babies' Iron Trial, analysis indicated that a 1% higher plasma DHA status was associated with a 59% reduction in the likelihood of reporting depressive symptoms in the postnatal period [22].

Omega-3 supplementation studies have been conducted in non-depressed women. Studies report that neonatal PUFA levels are increased via maternal dietary

supplementation with fish oils [19,23]. A study of maternal omega-3 supplementation in the postnatal period has also shown a strong, specific and dose-dependent effect on the breast milk and maternal plasma DHA levels [24,25].

In view of the above studies it has been hypothesized that, if low omega-3 levels correlate with depression, this may be one explanation as to why the perinatal period is a time of increased vulnerability to depression, since women generally become depleted of omega-3 at this time.

Intervention studies

There are several studies of omega-3 in the treatment of depression. In one small study 2 g/day of EPA was added to maintenance medication in patients with recurrent unipolar depressive disorder and who had not responded to an adequate trial of an antidepressant. Results showed highly significant benefits of omega-3 compared to placebo by 3 weeks of treatment [26]. The authors queried whether omega-3 treatment augments standard antidepressant action in a manner similar to lithium or has independent antidepressant properties of its own.

A similar placebo-controlled treatment study, using omega-3 fatty acids in addition to antidepressant treatment in patients with ongoing depression (despite adequate antidepressant treatment), demonstrated a significant benefit with 1 g EPA, but not for doses of 2 g and 4 g. The authors suggested that this finding could be explained by low participant numbers. DHA was not used in the treatment (but is a metabolite of EPA) and the subjects were of both genders [27].

Another placebo-controlled trial involved treating patients with ongoing major depression with 4.4 g EPA and 2.2 g DHA per day. Treatment was adjunctive to usual antidepressant medication and there were significant reductions in depression rating scale scores after 6 weeks of omega-3 treatment [28].

A double blind, placebo-controlled treatment study has been conducted using 2 g/day of DHA as monotherapy for the treatment of depression over 6 weeks but the results were not statistically significant [29]. Limitations of the study included the fish aftertaste problem, use of a pure DHA product (when perhaps a combination of DHA and EPA is needed), and problems with the length of the study and dose of DHA.

In terms of perinatal studies, a randomised double blind trial [30] has examined the effect of maternal DHA supplementation on the emergence of postnatal depression and plasma phospholipid levels. Breast-feeding mothers received either DHA or placebo for 4 months.

The results showed increased plasma phospholipid levels of DHA with supplementation of DHA, as compared to placebo. There was no difference within the groups on either self-rating or clinician-rated measures of depression. It should be noted that women in this study were not depressed at recruitment and the aim of the study was to assess whether DHA supplementation prevented women from becoming depressed postnatally. Much larger numbers would have been needed to show a significant result in such a preventative study. The dose of DHA was also lower than in other studies.

A small open label trial (Marlene P. Freeman: personal communication, 2004) followed 12 pregnant women with major depression who received a combination of EPA and DHA as monotherapy. Subjects averaged reductions of around 40% on the Edinburgh Postnatal Depression Scale and on the Hamilton Depression Rating Scale.

There are no randomised controlled studies in the literature assessing the efficacy of omega-3 as a treatment for depression in the perinatal period.

Neuroscientific theories

Several neuroscientific theories relating to omega-3 and depression will now be outlined.

First, there is an abundance of the omega-3 long-chain PUFA, DHA, in the non-myelin cell membranes of the central nervous system [20]. The particularly high concentrations of DHA in synaptic membranes indicate a critical role in synaptic transmission [31] and membrane fluidity.

Phospholipids (which have fatty acids in their structure) cause membrane fluidity alterations depending on the ratio of different fats present and their chemical positioning. Membrane fluidity affects the function of enzymes (e.g. adenylate cyclase) and ion channels (e.g. calcium, sodium and potassium channels), and has signal transduction effects via mechanisms involving G-proteins [32]. These effects lead to changes in receptor numbers and functioning as well as alterations to neurotransmitter levels (e.g. serotonin), resulting in neurotransmission effects [16]. Therefore, for normal neuronal function to occur, the right balance of fatty acids must be present and this is largely environmentally determined [31]. Animal studies also support omega-3 involvement in receptor function, neurotransmitter levels (particularly dopamine), and monoamine metabolism related to depression [12,33].

An associated theory relates to the immune and inflammatory systems and the well known association between depression and the acute-phase immunological response, demonstrated by alterations in certain eicosanoid and cytokine blood levels in depressed patients.

EPA is the PUFA that affects the function of eicosanoids (e.g. prostaglandins, leukotrienes and thromboxanes) and cytokines (e.g. interleukins). This occurs because the enzymes used for metabolism of short-chain omega-3 and omega-6 fatty acids to form long-chain EPA (omega-3) and AA (omega-6) are the same. AA is a precursor for eicosanoids and therefore if EPA is increased, AA decreases and eicosanoid formation is affected. Prostaglandin E2 and Thromboxane B2, which are known to play a role in depression and antidepressant treatment, are involved in this process. Eicosanoids have been linked to neurotransmission and have second messenger effects. Proinflammatory cytokines, which are increased in depression, are similarly affected by the ratio of omega-3 to omega-6 fatty acids [1,34,35].

Research suggests that depression may inhibit neurogenesis in the hippocampus [36] and promoting nerve growth factors (e.g. brain-derived neurotrophic factor) can improve depression [37]. Research has also shown that omega-3 fatty acids (particularly DHA) can have an effect on this process [38].

Another theory relates to gene expression. EPA, DHA and eicosanoids directly activate receptors in the DNA. Depletion of PUFAs in early life (e.g. *in utero* and neonatally) may affect expression of certain genes which play a role in synaptic plasticity [39]. This depletion may predispose to diseases associated with DHA and EPA depletion later in life (e.g. Alzheimer's disease, depression and cardiac disease). This theory suggests that early detection and treatment of omega-3 depletion is crucial.

Omega-3 infant research

As well as research into mood disorders, other important research into omega-3 in the perinatal period relates to infant development.

Neurodevelopment

PUFAs such as DHA are major structural components of neural membranes and are involved in neurological development, cognitive function, learning and behaviour [18]. Some randomised controlled trials in newborns have suggested improved cognitive development with omega-3 supplementation [40] and also possible effects on IQ and neurological abnormalities later in childhood [41–44]. These studies showed superior neurodevelopment for breast-fed infants (DHA being abundant in breast milk) compared to formula-fed infants and that formula fortified with omega-3 is superior to classic infant formula. Although these are important trials, there is still much controversy in this area. A systematic review of 21 randomised controlled trials comparing the

effects of breast milk and formula feeding on neurodevelopmental parameters in term and preterm infants has been reported [45]. It suggested that the beneficial effects of breast-feeding and PUFA supplementation of formula are more prominent for preterm than term infants. The authors concluded that there were few safety concerns regarding PUFA supplementation of formula but medium and long-term effects are still inconclusive.

Infant formulae have not traditionally contained DHA, since their fat is derived from vegetable oils, which do not contain long-chain PUFAs. In light of the emerging literature looking at fortifying infant formulas, several authorities (including the Food and Drugs Administration, Therapeutic Goods Administration and the World Health Organization) are already recommending that infant formulae be fortified with DHA [46,47].

Safety

As highlighted above, studies are reassuring in terms of the safety of omega-3 use in the perinatal period. There have also been animal safety studies indicating that omega-3 fats have no adverse effects on the fetus and infant [46,47].

Obstetric studies are also reassuring regarding safety. In addition, they indicate other obstetric advantages with omega-3 supplementation, including longer gestational times, reduced rate of premature labour and greater birth weight [48]. Studies have also shown no increase in gestational diabetes, pre-eclampsia or bleeding times [49].

It is therefore suggested that the use of omega-3 supplementation in the perinatal period has benefits not only for maternal depression but also for the fetus and newborn.

It should be noted that it may be safer for a pregnant woman to increase her omega-3 intake via a supplement rather than by increasing her fish intake as methylmercury and other contaminants are present in fish from certain areas of the world. There is debate about the damaging effects on fetal neurodevelopment, but placental transfer of these contaminants does occur [44]. Quality controlled omega-3 supplements may be a safer option.

Importance of treating depression in the perinatal period

Women's mental health in the perinatal period is an important public health issue [50], with around 13% of women expected to suffer from depression in the postnatal period and similar numbers in pregnancy [51]. The impact on the mother, infant and family of prolonged

and untreated depression is well documented, with increased rates of chronic depression and impaired socio-occupational functioning in the mother [52,53]. Maternal depression is associated with less secure attachment in the infant [53,54] and an increased risk of mental health problems in adolescence [55]. There are developmental effects on the infant, involving subtle cognitive and behavioural impairments [54], when assessed in the early primary school years [56].

Appropriate interventions are therefore needed for the early detection and treatment of depression at this time of life [50].

Are we satisfied with existing antidepressant treatments for this population group?

Pharmacological treatment for depression is often required and beneficial in the perinatal period [57]. However, many women with depression will refuse medication due to concerns about exposing their infant to psychotropic drugs, either through placental transfer in pregnancy, or through breast milk. Placental transfer of selective serotonin reuptake inhibitors (SSRIs) is confirmed by sampling of umbilical cord blood; transfer of fluoxetine is up to 70% through the placenta compared to 5% transfer via breast milk to the newborn [58].

Research data on the safety of antidepressant use during pregnancy and lactation is limited by research methodology [59]. However, we now have a few controlled but non-randomised studies with respect to SSRIs and tricyclic antidepressants (TCAs). They have not identified any increased risk of major structural anomalies with first trimester exposure [59,60]. Toxicity and withdrawal in the newborn however, may be more prevalent than previously thought [60–62].

Longer term neurodevelopmental studies are limited. A well controlled study of 60 children exposed to fluoxetine in utero showed no increase in neurobehavioural deficits or developmental delays at the age of 5–6 years [63].

In the lactation period, studies involving small subject numbers suggest that SSRIs are likely to be safe [64]. However, occasional cases of toxicity in the infant have been reported with fluoxetine, sertraline and paroxetine, characterized by irritability, sleep disturbances and feeding difficulties [58].

While antidepressant use in the perinatal period is not associated with increased rates of teratogenicity, data examining the potential for toxicity and withdrawal in the short term remain sparse, as do longer-term neurobehavioural data.

Omega-3 research is needed

Given the many issues outlined above, there is a pressing need not only for more research into antidepressants treatments in the perinatal period, but also for alternate treatments such as omega-3 fatty acids.

The stigma of taking an antidepressant and concerns regarding safety are likely to affect a woman's decision to take such medication. Natural remedies have greater patient acceptability and mothers appear more confident about the safety of omega-3 treatment during pregnancy and breast feeding. In addition, the advantages of omega-3 supplementation on infant neurodevelopment are appealing to mothers. The role of omega-3 in the treatment of mental illness is currently being promoted in the lay press as well as the psychiatric community; therefore further research is necessary to establish whether such benefits can be demonstrated.

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References

1. Maes M, Christophe A, Delanghe J, Altamura C, Neels H, Meltzer H. Lowered omega-3 polyunsaturated fatty acids in serum phospholipids and cholesteryl esters of depressed patients. *Psychiatry Research* 1999; 85:275–291.
2. Simopoulos AP. Evolutionary aspects of diet and essential fatty acids. *World Review of Nutrition and Dietetics* 2001; 88:18–27.
3. Hibbeln JR. Seafood consumption, the DHA content of mothers' milk and prevalence rates of postpartum depression. *Journal of Affective Disorders* 2002; 69:15–29.
4. Meyer B, Mann N, Lewis J *et al.* Dietary intakes and food sources of omega-6 and omega-3 polyunsaturated fatty acids. *Lipids* 2003; 38:391–398.
5. Keller JR. Omega-3 fatty acids may be effective in the treatment of depression. *Topics in Clinical Nutrition* 2000; 17:21–27.
6. Adams PB, Lawson S, Sanigorski A, Sinclair AJ. Arachidonic acid to eicopentaenoic acid ratio in blood correlates positively with clinical symptoms of depression. *Lipids* 1996; 31:S157–S161.

7. Cross National Collaborative Group. The changing rate of major depression: cross national comparisons. *Journal of American Medical Association* 1992; 268:3098–3105.
8. Chen C, Wong J, Lee N, Chan-Ho M, Lau JT, Fung M. The Shatin community mental health survey in Hong Kong II. *Archives of General Psychiatry* 1993; 50:125–133.
9. Varriainen E, Dianjun D, Marks JS. Mortality, cardiovascular risk factors, and diet in China, Finland and the United States. *Public Health Report* 1991; 106:41–46.
10. Hirayasu A. An epidemiological and sociopsychiatric study on the mental and neurologic disorders in an isolated island in Otinawa. *Psychiatry Neurology Japan* 1969; 71:301–311.
11. Haruki A. A psychiatric epidemiological and sociopsychiatric survey on mental disorders in Tsuma-mura, Okinoshima Island, Shimane prefecture. *Psychiatry Neurology Japan* 1972; 74:301–311.
12. Hibbeln JR, Salem N. Dietary polyunsaturated fatty acids and depression. *American Journal of Clinical Nutrition* 1995; 62:1–9.
13. Hibbeln JR. Seafood consumption, the DHA content of mothers' milk and prevalence rates of postpartum depression. *Journal of Affective Disorders* 2002; 69:15–29.
14. Tanskanen A, Hibbeln J, Hintikka J, Haatainen K, Honkalampi K, Viinamaki H. Fish consumption, depression and suicidality in a general population. *Archives of General Psychiatry* 2001; 58:512–513.
15. Hirayama T. *Life-style and mortality: a large census-based cohort study in Japan*. Basel, Switzerland: Karger, 1990.
16. Peet M, Murphy B, Shay J, Horrobin D. Depletion of omega-3 fatty acid levels in red blood cell membranes of depressive patients. *Society of Biology Psychiatry* 1998; 43:315–319.
17. Al MDM, van Houwelingen AC, Kester ADM, Hasaart THM, de Jong AEP, Hornstra G. Maternal essential fatty acid patterns during normal pregnancy and its relationship with the neonatal essential fatty acid status. *British Journal of Nutrition* 1994; 74:55–68.
18. Holman RT, Johnson SB. Deficiency of essential fats and membrane fluidity during pregnancy and lactation. *Proceedings of the National Academy of Science of the USA* 1991; 88:4835–4839.
19. Hornstra G. Essential fatty acids in mothers and their neonates. *American Journal of Clinical Nutrition* 2000; 71:1262S–9S.
20. Innis S. Perinatal biochemistry and physiology of long chain PUFA. *Journal of Pediatrics* 2003; 143:S1–S8.
21. Hibbeln J, Davis J, Heron J *et al*. Low dietary omega-3s and increased depression risk in 14,541 pregnancies. *Paper presented at American Psychiatric Annual Meeting; San Francisco, CA*. 2003.
22. Makrides M, Crowther C, Gibson R *et al*. Low DHA, not iron, status is associated with symptoms of post-partum depression. *Paper presented at 8th Annual Congress of Perinatal Society of Australia and New Zealand, Sydney, Australia*. 2004.
23. Harris WS, Connor WE, Lindsey S. Will dietary omega-3 fatty acids change the composition of human milk? *American Journal of Clinical Nutrition* 1984; 40:780–785.
24. Makrides M, Neumann MA, Gibson RA. Effect of maternal docoheaxaenoic acid (DHA) supplementation on breast milk composition. *European Journal of Clinical Nutrition* 1996; 50:352–357.
25. Makrides M, Gibson RA. Long-chain polyunsaturated fatty acid requirements during pregnancy and lactation. *American Journal of Clinical Nutrition* 2000; 71:307–311.
26. Nemets B, Stahl Z, Belmaker R. Addition of omega-3 fatty acid to maintenance medication treatment for recurrent unipolar depressive disorder. *The American Journal of Psychiatry* 2002; 159:447–479.
27. Peet M, Horrobin D. A dose ranging study of the effects of ethyl-eicopentaenoate in patients with ongoing depression despite apparently adequate treatment with standard drugs. *Archives of General Psychiatry* 2002; 59:913–919.
28. Su KP, Huang SY, Chiu CC, Shen WW. Omega-3 fatty acids in major depressive disorder. A preliminary double blind placebo-controlled trial. *European Neuropsychopharmacology* 2003; 13:267–271.
29. Marangell LB, Martinez JM, Zboyan HA, Kertz B, Kim HF, Puryear LJ. A double-blind, placebo-controlled study of the omega-3 fatty acid docosahexaenoic acid in the treatment of major depression. *American Journal of Psychiatry* 2003; 160:996–998.
30. Llorente AM, Jensen CL, Voigt RG *et al*. Effect of maternal docoheaxaenoic acid supplementation on postpartum depression and information processing. *American Journal of Obstetrics and Gynaecology* 2003; 188:1348–1353.
31. Horrobin DF. Essential fatty acids, psychiatric disorders and neuropathies. In: DF Horrobin, ed. *Omega-6 essential fatty acids: pathophysiology and roles in clinical medicine*. New York: Wiley-Liss, 1990; 305–320.
32. Lee CR, Hamm MW. Effect of dietary fat and cholesterol supplements on glucagon receptor binding and adenylate cyclase activity of rat liver plasma membrane. *Journal of Nutrition* 1989; 119:539–546.
33. Logan AC. Neurobehavioural aspects of omega-3 fatty acids: possible mechanisms and therapeutic value in major depression. *Alternative Medicine Review* 2003; 4:410–424.
34. Maes M. Fatty acids, cytokines, major depression. *Society of Biology Psychiatry* 1998; 43:313–314.
35. Lieb J. Lithium and antidepressants: inhibiting eicosanoids, stimulating immunity, and defeating microorganisms. *Medical Hypotheses* 2002; 59:429–432.
36. Sapolsky RM. The possibility of neurotoxicity in the hippocampus in major depression: a primer on neuron death. *Biology Psychiatry* 2000; 48:755–765.
37. Shimizu E, Hashimoto K, Okamura N *et al*. Alterations of serum levels of brain-derived neurotrophic factor (BDNF) in depressed patients with or without antidepressants. *Biology Psychiatry* 2003; 54:70–75.
38. Ikemoto A, Nitta A, Furukawa S *et al*. Dietary omega-3 fatty acid deficiency decreases nerve growth factor content in rat hippocampus. *Neuroscience Letters* 2000; 285:99–102.
39. Kitajka K, Sinclair AJ, Weisinger RS *et al*. Effects of omega-3 polyunsaturated fatty acids on brain expression. *Proceeding of the National Academy of Sciences of the USA* 2004; 101:10931–10936.
40. Willatts P, Forsyth JS, DiModugno MK, Varma S, Colvin M. Effect of long chain polyunsaturated fatty acids in infant formula on problem solving at 10 months of age. *Lancet* 1998; 352:688–691.
41. Lucas A, Morley R, Cole TJ, Lister G, Leeson-Payne C. Breast milk and subsequent intelligence quotient in children born preterm. *Lancet* 1992; 339:261–264.
42. Lanting CI, Fidler V, Huisman M, Touwen BCL, Boersma ER. Neurological differences between 9 year old children fed breast-milk or formula-milk as babies. *Lancet* 1994; 344:1319–1322.
43. Horwood LJ, Ferguson DM. Breastfeeding and later cognitive and academic outcomes. *Pediatrics* 1998; 101:e9.
44. Daniels JL, Longnecker MP, Rowland AS, Golding J and the ALSPAC Study Team. *Epidemiology* 2004; 15:394–402.
45. Gibson RA, Chen W, Makrides M. Randomized trials with polyunsaturated fatty acid interventions in preterm and term infants: functional and clinical outcomes. *Lipids* 2001; 36:873–883.

46. Arterburn LM, Boswell KD, Koskelo E, Kassner SL, Kelly C, Kyle DJ. A combined subchronic toxicity and neurotoxicity study of a single-cell source of docosahexaenoic acid triglyceride (DHASCO oil). *Food and Toxicology* 2000; 38:35–49.
47. Burns RA, Wibert GJ, Diersen-Schade DA, Kelly CM. Evaluation of single-cell sources of docosahexaenoic acid and arachidonic acid: 3-month rat oral safety study with an in utero phase. *Food and Toxicology* 1999; 37:23–26.
48. Olsen SF, Secher NJ, Tabor A, Weber T, Walker JJ, Glud C. Randomized clinical trials of fish oil supplementation in high risk pregnancies. *British Journal of Obstetrics and Gynaecology* 2000; 107:382–395.
49. Onwude JL, Lilford RJ, Hjartardattir H, Staines A, Tuffnell D. A randomised double blind placebo controlled trial of fish oil in high risk pregnancy. *British Journal of Obstetrics and Gynaecology* 1995; 102:95–100.
50. Austin M-P. Antenatal psychosocial screening, assessment and prevention for ‘perinatal’ distress, depression & anxiety: where to from here? *Archives of Women’s Mental Health* 2004; 7:1–6.
51. Evans J, Heron J, Francomb H, Oke S, Golding J. Cohort study (ALSPAC) of depressed mood during pregnancy and after childbirth. *British Medical Journal* 2001; 323:257–260.
52. Kumar R, Robson K. A prospective study of emotional disorders in child bearing women. *British Journal of Psychiatry* 1984; 144:35–47.
53. NICHD Early Child Care Research Network. Chronicity of maternal depressive symptoms, maternal sensitivity, and child functioning at 36 months. *Developmental Psychology* 1999; 5:1297–1310.
54. Murray L, Cooper P. Postpartum depression and child development. *Psychological Medicine* 1997; 27:253–260.
55. Hammen C, Brennan P. Severity, chronicity and timing of maternal depression and risk for adolescent offspring diagnoses in a community sample. *Archives of General Psychiatry* 2003; 60:253–258.
56. Williams H, Carmichael A. Depression in mothers and behavioural problems with their preschool children. *Journal of Paediatric Child Health* 1991; 27:76–82.
57. Appleby L, Warner R, Whitton A, Faragher B. A controlled study of fluoxetine and cognitive behavioural counselling in the treatment of postnatal depression. *British Medical Journal* 1997; 314:932–936.
58. Heikkinen T, Ekblad U, Palo P, Laine K. Pharmacokinetics of fluoxetine and norfluoxetine in pregnancy and lactation. *Clinical Pharmacology and Therapeutics* 2003; 73:330–337.
59. Austin M-P, Mitchell P. The use of psychotropic medications in pregnant women. *Medical Journal of Australia* 1998; 169:428–431.
60. Hendrick V, Stowe ZN, Altshuler L, Hwang S, Lee E, Haynes D. Placental passage of antidepressant medication. *American Journal of Psychiatry* 2003; 160:993–996.
61. Laine K, Heikkinen T, Ekblad U, Kero P. Effects of exposure to selective serotonin reuptake inhibitors during pregnancy on serotonergic symptoms in newborns and cord blood monoamine and prolactin concentrations. *Archives of General Psychiatry* 2003; 60:720–726.
62. Costei A, Kozer E, Ho T, Ito S, Koren G. Perinatal outcome following third trimester exposure to paroxetine. *Archives of Pediatrics and Adolescent Medicine* 2002; 156:1129–1132.
63. Nulman I, Rovet J, Stewart DE. Neurodevelopment of children exposed in utero to antidepressant drugs. *New England Journal of Medicine* 1997; 320:19–23.
64. Austin M-P, Mitchell P. The use of psychotropic medications in breast-feeding women: acute and prophylactic treatment. *Australian and New Zealand Journal of Psychiatry* 1998; 32:778–784.