INTEGRATED HEALTHCARE
PRACTITIONERS
Integrated Healthcare Practitioners' Dietary and Nutritional Supplement, and Herbal Remedies Management Program

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SUCCESSFUL COMPLETION OF THE QUESTIONS AT THE END OF THIS PAPER HAS BEEN APPROVED FOR CONTINUING EDUCATION BY THE BDDT-N; 1.0 CREDIT NUTRITIONAL MEDICINE, 0.5 CREDIT PHARMACOLOGY AND BY THE CNPBC; ONE CE HOUR.

Natural Health Product Recommendations in Pregnancy

Interventions that impact disease risk in offspring.

INTRODUCTION

An emerging research front has thrust the concept of prevention into the academic limelight over the past few years. Investigating the "developmental origins of health and disease" offers opportunities for interventions aimed at disease prevention. The health status of the mother during pregnancy (in utero environment) powerfully influences the phenotype, ie. expression of disease in the offspring during postnatal life, and can be affected by many inputs including nutrient status. Use of folic acid is well recognized for its ability to prevent neural tube defects (NTD), for example. There are, however, several additional natural health products (NHPs) that have been shown to reduce pediatric disease when administered during pregnancy. This article focuses on a selection of NHPs that have been shown to reduce risk of a variety of childhood conditions including atopy, congenital malformations, and pediatric cancers, among others.

FISH OIL

Observational evidence has established an inverse relationship between fish consumption during pregnancy and risk of atopy in the offspring. A systematic review of observational data found that all five studies of fish intake during pregnancy showed positive effects from fish consumption: "fish oil during pregnancy may reduce sensitization to common food allergens and reduce prevalence and severity of atopic dermatitis in the first year of life, with a possible persistence until adolescence with a reduction in eczema, hay fever, and asthma" (Kremmyda 2009).

This has been confirmed in intervention trials. See Table 1. Fish oil administration of between 2.7-3.7g EPA+DHA per day to the mother during pregnancy has been shown to:

- increase neonatal N-3 PUFA levels (Dunstan 2003)
- decrease cytokine response to allergens and production of Th2 promoting cytokines (Dunstan 2003)
- increase numbers of T regulatory cells (Denburg 2005)
- reduce incidence of food allergy and eczema (Furuhjelm 2009)
- reduce risk of asthma at up to 16 years of age by up to 68% (Olsen 1992)

An added benefit to supplementation with fish oil during pregnancy is improvements in measures of intelligence and childhood development, including mental processing (Helland 2003), problem solving (Judge 2007), and hand and eye coordination (Dunstan 2008). See Table 2.

PROBIOTICS

Probiotics have been demonstrated to protect against development of atopy when given to the pregnant mother. A meta analysis of six studies supported probiotics' prevention of pediatric atopic disease (PAD) (Lee 2009). A recent Pubmed search identified eight clinical trials investigating the effects of probiotics in pregnancy on prevention of atopy in offspring; of these, seven showed benefit on outcomes of eczema and allergen sensitization by skin prick test. Half of the studies used combinations of Bifidobacteria and Lactobacillus, while the other half used single stains. See Table 3.

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Table 1. Fish Oil and Atopy

Reference	Design	Outcomes
Kremmyda 2009	Systematic review of observational and interventional evidence around intake of n-3 PUFAs and protection against atopic sensitization and against the clinical manifestations of atopy.	All five epidemiological studies investigating the effect of maternal fish intake during pregnancy on atopic or allergic outcomes in infants/children of those pregnancies concluded protective associations. "Fish oil during pregnancy may reduce sensitization to common food allergens and reduce prevalence and severity of atopic dermatitis in the first year of life, with a possible persistence until adolescence with a reduction in eczema, hay fever, and asthma."
Dunstan 2003	RCT: 98 atopic, pregnant women were given fish oil (3.7g N-3 PUFAs per day) or placebo from 20 weeks' gestation until delivery. Neonatal PUFA levels and immunologic response to allergens were measured at birth. At age 1 y, infants were clinically assessed for atopic symptoms and skin tests.	Fish oil supplementation achieved significantly higher proportions of N-3 PUFAs in neonatal erythrocyte membranes compared with the control group (P<.001). All neonatal cytokine (IL-5, IL-13, IL-10, and IFN-gamma) responses to all allergens tended to be lower in the fish oil group. Infants in the fish oil group were 3 times less likely to have a positive skin prick test to egg at 1 year of age, OR 0.34 (95% CI 0.11-1.02). Although there was no difference in the frequency of atopic dermatitis at 1 year of age, infants in the fish oil group also had significantly less severe disease, OR 0.09 (95% CI 0.01-0.94).
Denburg 2005	At birth, CB CD34+ cells (regulatory T cells) were isolated and analyzed.	Percentages of CB CD34+ cell numbers (regulatory T cells) were higher after N-3 PUFA than placebo.
Furuhjelm 2009	RCT: 145 pregnant women carrying high-risk children were given 1.6g EPA and 1.1g DHA, or placebo from gestational week 25 to 3-4 months of breastfeeding. Skin prick tests, IgE antibodies were assessed.	The period prevalence of food allergy was lower in the fish oil group (1/52, 2%) compared to the placebo group (10/65, 15%, p < 0.05). Incidence of IgE-associated eczema was also lower, fish oil group: 4/52, 8%; placebo group: 15/63, 24%, (P< 0.05).
Olsen 1992 Olsen 2008	RCT: 533 women with normal pregnancies were assigned to receive fish oil delivering 2.7g N-3 PUFAs; olive oil placebo; or no treatment. Follow up at 16 years analyzed endpoints related to atopy.	At 16 years, the hazard rate of asthma was reduced by 63% (95% CI: 8%, 85%; P=0.03), whereas the hazard rate of allergic asthma was reduced by 87% (95% CI: 40%, 97%; P=0.01) in the fish oil compared with the olive oil group.
Krauss-Etschmann 2008	RCT surrogate study: 311 pregnant women received daily either 1) fish oil with 0.5g DHA + 0.15g of EPA; 400mug of methyl-tetra-hydrofolic acid, both, or placebo from the 22nd gestational week. Th1/Th2-related molecules were quantified in a subset of maternal and cord blood samples.	Fish oil supplementation was associated with increased TGF-beta mRNA in maternal and cord blood compared to placebo. Fish oil decreased cord blood mRNA levels of IL-4, IL-13, and CCR4 (all P<0.001), natural killer cells (P<0.001), and CCR3+CD8+ T cells (P<0.04) compared to placebo. Fish oil decreased expression of Th2 promoting cytokines in the infant.
Warstedt 2009	Surrogate Study: 145 pregnant women with allergic disease in their immediate family were supplemented daily with 2.7g omega-3 LCPUFA or 2.8g soybean oil as placebo from the 25th gestational week.	Lipopolysaccharide-induced prostaglandin E2 secretion from whole blood culture supernatants decreased in a majority of the omega-3-supplemented mothers (P=0.002).

No clinical trials exist investigating vitamin D supplementation during pregnancy for outcomes related to atopy. Observational evidence suggests that higher vitamin D levels during pregnancy may be associated with reduced risk of childhood wheeze and better bronchodilator response (Devereux 2007). One study found that supplementation with cod liver oil during pregnancy reduced risk of type 1 diabetes in offspring by 70%, however the causal agent (N-3 PUFAs or vitamin D or both) cannot be inferred from this study alone (Stene 2000). Other studies have failed to produce such positive results, and further study is required to elucidate the relationship between vitamin D and atopy; however, given that significant clinical benefits have been found from vitamin D supplementation in post-natal life, it is possible that this might hold true in prenatal life as well (Sidbury 2008). See Table 4.

Table 2. Fish Oil and Intelligence

Reference	Design	Outcomes
Helland 2003, 2008	RCT: 341 pregnant women took cod liver oil (1,183mg DHA + 803 mg EPA) or placebo from 18 wks gestation until 3 mo after delivery. At 4 years of age, 90 children underwent intelligence testing using the Kauffman Assessment Battery for Children scale.	Children born to mothers who had taken cod liver oil during pregnancy and lactation scored significantly higher on the Mental Processing Composite of the K-ABC (P=0.49). There was also a tendency to higher scores on the other three subscales among children who were born to mothers taking cod liver oil. At 7 years, there was a correlation between maternal plasma phospholipids concentrations of ALA and DHA and sequential processing.
Judge 2007	RCT: 98 atopic, pregnant women were given fish oil (3.7g N-3 PUFAs per day) or placebo from 20 weeks' gestation until delivery. Neonatal PUFA levels and immunologic response to allergens were measured at birth. At age 1 y, infants were clinically assessed for atopic symptoms and skin tests. At birth, CB CD34+ cells (regulatory T cells) were isolated and analyzed.	Infants whose mothers had received DHA had significantly better performance of problem-solving tasks, P<0.05 for all subscales of the Planning test. No significant differences between groups on the Fagan Test.
Dunstan 2008	RCT: 98 pregnant women were given fish oil (2.2g DHA + 1.1g EPA daily) or placebo from gestation week 20 until delivery.	At 2.5 years of age, children whose mothers had received fish oil had a significantly higher score for eye and hand coordination (P=0.008 vs placebo). This was also correlated with N-3 PUFA levels in cord blood RBCs, and inversely correlated with n-6 PUFA.
Hibbeln 2007	Prospective cohort: 11,875 pregnant women were followed for associations between seafood consumption at 32 weeks' gestation and developmental, behavioral, and cognitive outcomes of the children from age 6 months to 8 yr.	Maternal seafood intake during pregnancy <340g per wk associated with increased risk of children being in lowest quartile for verbal intelligence quotient (IQ): OR 1.48, 95% CI 1.16-1.90 for those with no seafood consumption. Low maternal seafood intake was associated with increased risk of suboptimum outcomes for prosocial behaviour, fine motor, communication, and social development scores.

Table 3. Probioitcs During Pregnancy and Atopy

Reference	Design	Outcomes
Lee 2008	Meta-Analysis of clinical trials related to the efficacy of probiotics for pediatric atopic disease (PAD). Data from the 6 prevention studies (N=1,581) and 4 treatment trials (N=299) were pooled.	Prevention corresponded with summary effect sizes of 0.69 (0.57, 0.83) and 0.66 (0.49, 0.89), respectively, supporting probiotics' PAD prevention potential, which decreased further to 0.61 after exclusion of the 1 trial of postnatal-only probiotics.
Niers 2009	DB PC RCT: probiotic mixture was prenatally administered to 156 mothers of high-risk children, and to their offspring for the first 12 months of life. Bifidobacterium bifidum, Bifidobacterium lactis, and Lactococcus lactis, 1x109 CFU each daily	Parental-reported eczema during the first 3 months of life was significantly lower in the intervention group compared with placebo, 6/50 vs 15/52 (P=0.035). At 3 mo, incidence was comparable. Cumulative incidence of parental-reported eczema at 1 and 2 years was 23/50 (intervention) vs 31/48 (placebo) and 27 (intervention) vs 34 (placebo), respectively.
Wickens 2008	DB PC RCT in 474 pregnant women were randomized to take one of two probiotics or placebo daily from 35 weeks gestation until 6 months if breast-feeding; infants received probiotic until 2 years. Incidence of eczema and atopy assessed at 2 years. Lactobacillus rhamnosus HN001 6x109 CFU or Bifidobacterium animalis subsp lactis strain HN019 9x109 CFU.	Infants receiving L rhamnosus had a significantly (P=0.01) reduced risk of eczema (HR 0.51, 95% CI 0.30-0.85) compared with placebo, but this was not the case for B animalis subsp lactis (HR, 0.90; 95% CI, 0.58-1.41). L rhamnosus (71.5%) was more likely than B animalis subsp lactis (22.6%) to be present in the feces at 3 months, although detection rates were similar by 24 months.

Reference	Design	Outcomes
Hurree 2008	DB PC RCT in 171 mother-infant pairs from an ongoing trial of nutrition modulation by dietary counseling and probiotic supplementation. Lactobacillus rhamnous GG and Bifidobacterium lactis Bb12 1x1,010 CFU each daily.	The risk of sensitization assessed by skin prick testing increased in infants with allergic mothers breastfeeding over 6 months (OR=4.83, P=0.005), or exclusively breastfeeding over 2.5 months (OR=3.4, P=0.018). Probiotic supplementation had a protective effect against sensitization in infants with a high hereditary risk due to maternal sensitization (OR=0.3, P=0.023).
Abrahamsson 2007	DB PC RCT in 232 pregnant women with allergic disease and their infants. The mothers received probiotic daily from gestational week 36 until delivery. Their babies then continued with the same product from birth until 12 months of age and were followed up for another year. L reuteri ATCC 55730 1 x 108 CFU daily.	The cumulative incidence of eczema was similar, 36% in the treated versus 34% in the placebo group. The L reuteri group had less IgE-associated eczema during the second year, 8% versus 20% (P=0.02), however. Skin prick test reactivity was also less common in the treated than in the placebo group, significantly so for infants with mothers with allergies, 14% versus 31% (P=0.02).
Kukkonen 2007	DB PC RCT in 1223 pregnant women carrying high-risk children were given a probiotic mixture or a placebo for 2 to 4 weeks before delivery. Their infants received the same probiotics plus GOS or placebo for 6 months. Cumulative incidence of allergic diseases and IgE sensitization was assessed at 2 and 5 years.	At 2 years, probiotic treatment no effect on the cumulative incidence of allergic diseases but tended to reduce IgE-associated (atopic) diseases: OR 0.71; 95% CI, 0.50-1.00). Probiotic treatment reduced eczema (OR, 0.74; 95% CI, 0.55-0.98) and atopic eczema (OR, 0.66; 95% CI, 0.46-0.95).
Kuitunen 2009	Lactobacillus rhamosus GG 5x109 CFU, Lactobacillus rhamnosus LC705 5x109 CFU, Bifidobacterium breve Bb99 2x108 CFU, and Propionibacterium freudenreichii spp. shermanii JS 2x109 CFU daily.	At 5 years, there was no significant difference in other outcomes, but there was less IgE-associated allergic disease in cesarean-delivered children receiving probiotics (24.3% vs 40.5%; OR 0.47; 95% CI, 0.23% to 0.96%).
Kalliomäki 2001	DB PC RCT: 159 pregnant mothers carrying high-risk children were given probiotic prenatally, and post-natally to the infants for 6 months. Lactobacillus GG 1x1010 CFU daily.	The frequency of atopic eczema in the probiotic group was half that of the placebo group (15/64 23% vs 46%, RR 0.51, 95% CI 0.32-0.84).
Rautava 2002	Subanalysis in 62 mother-infant pairs who were breastfeeding and used the probiotic until 3 months of age.	The risk of eczema during the first 2 years of life in infants whose mothers received probiotics was significantly reduced (15% vs 47%, relative risk, 0.32 (95% CI, 0.12-0.85); P .0098).
Böttcher 2008	RCT. 109 women were treated with L. reuteri or placebo from gestational week 36 until delivery. Skin prick test and/or circulating allergen-specific IgE antibodies were tested at 6, 12, and 24 months of age. Lactobacillus reuteri, CFU not specified.	Treatment was associated with low levels of TGF-beta2 and slightly increased levels of IL-10 in colostrum. Infants receiving breast milk with low levels of TGF-beta2 were less likely to become sensitized during their first 2 yr of life. A similar trend was observed for development of IgE-associated eczema.
Kopp 2008	DB PC RCT: 105 pregnant women from families ≥1 member with an atopic disease received either the probiotic or placebo from 4-6 wks before delivery to 6 mo postnatally. Lactobacillus GG 5 x 109 CFU twice daily.	There was no difference in incidence or severity of atiopic dermatitis. More children in the probiotic group had recurrent episodes of wheezing bronchitis, 26 vs 9.1%.

Key: CFU colony forming units; DB double blind; GOS galacto-oligosaccharides; PC placebo controlled; RCT randomized controlled trial

MULTIVITAMIN

Two meta analyses of observational and interventional evidence have been conducted examining the effect of multivitamins in pregnancy on risk of several congenital anomalies as well as pediatric cancers (Goh 2007, 2006). Both found significantly reduced risk associated with multivitamin use. See Table 5.

Incidentally, and of interest when advising mothers about prenatal vitamin use, Gill found that in women with nausea and vomiting of pregnancy, discontinuing iron-containing prenatal multivitamins reduced the severity of nausea in two thirds of women (P<0.001) (2009). These women were instead instructed to take folic acid plus an adult multivitamin.

Table 4. Vitamin D in Pregnancy

Reference	Design	Outcomes
Stene 2000	Cohort study with 85 diabetic subjects + 1,071 controls in Norway. Subjects were studied for the intake of cod liver oil (contains N-3 fatty acids and vitamin D)	When mothers took cod liver oil during pregnancy their offspring had a significantly lower risk of diabetes, OR 0.30, 95% CI: (0.12 to 0.75), P=0.01.
Erkkola 2009	Cohort study following 1,669 children for the association between maternal intake of vitamin D during pregnancy on the emergence of asthma, allergic rhinitis (AR), and atopic eczema by the age of 5 years in children with HLA-DQB1-conferred susceptibility for type 1 diabetes.	When adjusted for potential confounders, maternal intake of vitamin D from food was negatively related to risk of asthma, HR 0.80; 95% CI 0.64-0.99, and allergic rhinitis HR 0.85; 95% CI 0.75-0.97. Vitamin D supplements alone were not associated with any outcome.
Devereux 2007	Cohort Study conducted in 2,000 healthy pregnant women in Scotland from 12 wk gestation. Maternal vitamin D intake was studied for associations with wheezing symptoms, spirometry, bronchodilator response, atopic sensitization, and exhaled nitric oxide in offspring at 5 y.	There was lower risk of ever wheeze (OR 0.48, 95% CI 0.25-0.91), wheeze in the previous year (OR 0.35, 95% CI 0.15-0.83), and persistent wheeze (OR 0.33, 95% CI 0.11-0.98) in children whose mothers were in the highest vs the lowest quintile of vitD intake. Lower maternal total vitamin D intake was associated with decreased bronchodilator response (P=0.04).

Table 5. Multivitamin Use in Pregnancy and Fetal Outcomes

Reference	Design	Outcomes
Goh 2007	Meta analysis of 7 observational studies examining the protective effect of multivitamin use in pregnancy on pediatric cancers.	Use of multivitamins reduced risk of the following cancers: leukemia 39% (OR 0.61, 95%CI 0.50-0.74); pediatric brain tumors 27% (OR 0.73, 0.60-0.88); and neuroblastoma 47% (OR 0.53, 0.42-0.68).
Goh 2006	Meta analysis of 41 RCTs and observational data examining the protective effect of multivitamin use in pregnancy on congenital anomalies.	Use of multivitamins significantly reduced risk of the following anomalies: neural tube defects (OR 0.52, 95%CI 0.39-0.69 in prospective studies), cardiovascular defects (OR 0.61, 0.40-0.92), and limb defects (OR 0.57, 0.38-0.85). There was also weaker evidence of a protective effect against cleft palate, urinary tract anomalies, and congenital hydrocephalus.

Table 6. Calcium and Blood Pressure

Reference	Design	Outcomes
Hatton 2003	RCT: pregnant women were given 2g calcium or placebo daily from weeks 13 to 21 of gestation until delivery. Blood pressure was measured at 3 mo and 2 yr postpartum.	Systolic BP in the calcium-supplemented infants was 2.2mmHg lower than in the placebo group (P>0.05). At 2 years of age, systolic BP was 4.8mmHg lower in the calcium supplemented group (P<0.05), whereas diastolic BP was 3mmHg lower (P>0.05).
Belizan 1997	RCT: 591 children of mothers who were randomly assigned during pregnancy to receive 2g/day of elemental calcium or placebo had blood pressure (BP) assessed at 7 yrs.	Systolic BP was lower in the calcium group (mean difference -1.4mmHg; 95% CI -3.2 to 0.5) than in the placebo group. The effect was found predominantly among children whose BMI at assessment was >median for this population: mean difference -5.8mmHg (-9.8 to -1.7mmHg) for children with an BMI >17.5, and -3.2mmHg (-6.3 to -0.1mmHg) for those with an index of >15.7 to 17.5).

CALCIUM

There is some evidence to suggest that children of women given calcium during pregnancy have lower blood pressure during childhood. Studies have not examined how long this effect persists, though it is possible that it may persist to adulthood if mediated by central "programming" or modeling. See Table 6.

CONCLUSION

There are several NHPs with evidence in support of their ability to reduce risk of childhood disease and improve cognitive health: fish oil, probioitics, vitamin D, multivitamins, and calcium. These interventions demonstrate the powerful ability of natural medicines to positively influence the epigenetic/ developmental origins of disease.

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Questions

1. Fish oil consumption during pregnancy may reduce sensitization to common food allergens and reduce prevalence and severity of atopic dermatitis in the first year of life, with a possible persistence until adolescence with a reduction in eczema, hay fever, and asthma.
   A) True
   B) False

2. Fish oil during pregnancy has been shown to do which of the following: a) decrease cytokine response to allergens, b) increase production of Th1 dominant cytokines, c) increase numbers of T regulatory cells, d) increase incidence of food allergy, e) reduce risk of asthma at up to 16 years of age.
   A) a, b & d
   B) a, b & e
   C) a, c & e
   D) all of the above

3. Evidence for use of probiotics during pregnancy for outcomes related to atopy consists of:
   A) Observational evidence only
   B) Randomized, placebo controlled trials
   C) Meta analyses
   D) B and C

4. Trials of probiotics using single strains and trials using combinations of strains have both shown benefit on outcomes related to atopy when given during pregnancy.
   A) True
   B) False

5. Seven of eight controlled clinical trials reviewed here showed positive outcomes for use of probiotics during pregnancy on outcomes related to atopy.
   A) True
   B) False

6. Observational evidence shows that higher vitamin D levels during pregnancy may be associated with reduced risk of childhood wheeze and better bronchodilator response, but there are no clinical trials of vitamin D in pregnancy and atopy to date.
   A) True
   B) False

7. Use of multivitamins during pregnancy have been found to significantly reduce risk of asthma in offspring.
   A) True
   B) False

8. Multivitamins during pregnancy reduce risk of the following conditions in the offspring: a) leukemia, b) pediatric brain tumors, c) Down's syndrome, d) cardiovascular defects, e) neural tube defects:
   A) a & e
   B) a, c & e
   C) a, b, d & e
   D) all of the above

9. Evidence from human trials suggest that administration of probiotics may be especially beneficial for:
   A) infants delivered by Cesarean section
   B) infants of mother's with depression
   C) infants of mother's with lactose intolerance
   D) all of the above

10) Hibbeln et al (2007) showed that decreased fish intake during pregnancy increased risk of a) lower IQ in offspring, b) lower incidence of fish allergy, c) suboptimal prosocial development, d) suboptimal fine motor development, e) depression in offspring
   A) a & b
   B) a, b & c
   C) a, c, d & e
   D) all of the above

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