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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Agency for Healthcare Research and Quality

Scientific Information Request on Omega 3 Fatty Acids and Maternal and Child Health

AGENCY: Agency for Healthcare Research and Quality (AHRQ), HHS.

ACTION: Request for Scientific Information Submissions

SUMMARY: The Agency for Healthcare Research and Quality (AHRQ) is seeking scientific information submissions from the public. Scientific information is being solicited to inform our review of Omega 3 Fatty Acids and Maternal and Child Health, which is currently being conducted by the AHRQ's Evidence-based Practice Centers (EPC) Programs. Access to published and unpublished pertinent scientific information will improve the quality of this review. AHRQ is conducting this systematic review pursuant to Section 902(a) of the Public Health Service Act, 42 U.S.C. 299a(a).

DATES: Submission Deadline on or before [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

ADDRESSES:

Online submissions: http://effectivehealthcare.AHRQ.gov/index.cfm/submit-scientific-information-packets/. Please select the study for which you are submitting information from the list to upload your documents.
E-mail submissions: SIPS@epc-src.org.
Print submissions:
Mailing Address:
Portland VA Research Foundation
Scientific Resource Center
ATTN: Scientific Information Packet Coordinator
PO Box 69539
Portland, OR 97239

Shipping Address (FedEx, UPS, etc.):
Portland VA Research Foundation
Scientific Resource Center
ATTN: Scientific Information Packet Coordinator
3710 SW U.S. Veterans Hospital Road
Mail Code: R&D 71
Portland, OR 97239

FOR FURTHER INFORMATION CONTACT:

Ryan McKenna, Telephone: 503-220-8262 ext. 58653 or Email: SIPS@epc-src.org.

SUPPLEMENTARY INFORMATION:

The Agency for Healthcare Research and Quality has commissioned the Evidence-based Practice Centers (EPC) Programs to complete a review of the evidence for Omega 3 Fatty Acids and Maternal and Child Health.

The EPC Program is dedicated to identifying as many studies as possible that are relevant to the questions for each of its reviews. In order to do so, we are supplementing the usual manual and electronic database searches of the literature by requesting information from the public (e.g., details of studies conducted). We are looking for studies that report on Omega 3 Fatty Acids and Maternal and Child Health, including those that describe adverse events. The entire research protocol, including the key questions, is also available online at: http://effectivehealthcare.AHRQ.gov/search-for-guides-reviews-and-reports/?pageaction=displayProduct&productID=2083

This notice is to notify the public that the EPC Program would find the following information on Omega 3 Fatty Acids and Maternal and Child Health helpful:

- A list of completed studies that your organization has sponsored for this indication. In the list, please indicate whether results are available on ClinicalTrials.gov along with the ClinicalTrials.gov trial number.
    - For completed studies that do not have results on ClinicalTrials.gov, please provide a summary, including the following elements: study number, study period, design, methodology, indication and diagnosis, proper use instructions, inclusion and exclusion criteria, primary and secondary outcomes, baseline characteristics, number of patients screened /eligible /enrolled /lost to follow-up /withdrawn /analyzed, effectiveness/efficacy, and safety results.

- A list of ongoing studies that your organization has sponsored for this indication. In the list, please provide the ClinicalTrials.gov trial number or, if the trial is not registered, the protocol for the study including a study number, the study period, design, methodology, indication and diagnosis, proper use instructions, inclusion and exclusion criteria, and primary and secondary outcomes.
- Description of whether the above studies constitute all Phase II and above clinical trials sponsored by your organization for this indication and an index outlining the relevant information in each submitted file.

Your contribution will be very beneficial to the EPC Program. The contents of all submissions will be made available to the public upon request. Materials submitted must be publicly available or can be made public. Materials that are considered confidential; marketing materials; study types not included in the review; or information on indications not included in the review cannot be used by the EPC Program. This is a voluntary request for information, and all costs for complying with this request must be borne by the submitter.

The draft of this review will be posted on AHRQ's EPC Program website and available for public comment for a period of 4 weeks. If you would like to be notified when the draft is posted, please sign up for the e-mail list at: http://effectivehealthcare.AHRQ.gov/index.cfm/join-the-email-list1/.

The systematic review will answer the following questions. This information is provided as background. AHRQ is not requesting that the public provide answers to these questions. The entire research protocol, is available online at: http://effectivehealthcare.AHRQ.gov/search-for-

guides-reviews-and-reports/?pageaction=displayProduct&productID=2083

The Key Questions

KQ 1. Maternal Exposure

- What is the efficacy of maternal interventions involving—or association of maternal exposures to—n-3 Fatty Acids (FA) (eicosapentaenoic acid [EPA], docosahexaenoic acid [DHA], EPA+DHA [long-chain n-3 FA], docosapentaenoic acid [DPA], alpha-linolenic acid [ALA], stearidonic acid [SDA] or total n-3 FA) on the following:
  - Duration of gestation in women with or without a history of preterm birth (less than 37 weeks gestation)
  - Incidence of preeclampsia/eclampsia/gestational hypertension in women with or without a history of preeclampsia/ eclampsia/ gestational hypertension
  - Incidence of birth of small-for-gestational age human infants
  - Incidence of ante- and/or postnatal depression in women with or without a history of major depression or postpartum depression
- What are the associations of maternal biomarkers of n-3 intake during pregnancy and the outcomes identified above?
- What are the effects of potential confounders or interacting factors (such as other nutrients or use of other supplements, or smoking status)?

- How is the efficacy or association of n-3 FA on the outcomes of interest affected by the ratio of different n-3 FAs, as components of dietary supplements or biomarkers?
- How does the ratio of n-6 FA to n-3 FA intakes or biomarker concentrations affect the efficacy or association of n-3 FA on the outcomes of interest?
- Is there a threshold or dose-response relationship between n-3 FA exposures and the outcomes of interest or adverse events?
- How does the duration of the intervention or exposure influence the effect of n-3 FA on the outcomes of interest?

KQ 2. Fetal/childhood exposures

- What is the influence of maternal intakes of n-3 fatty acids or the n-3 fatty acid content of maternal breast milk (with or without knowledge of maternal intake of n-3 FA) or n-3 FA-supplemented infant formula or intakes of n-3 FA from sources other than maternal breast milk or supplemented infant formula on the following outcomes in term or preterm human infants?
  - Growth patterns
  - Neurological development
  - Visual function
  - Cognitive development
  - Autism
  - Learning disorders
  - Attention Deficit Hyperactivity Disorder (ADHD)
  - Atopic dermatitis
  - Allergies
  - Respiratory illness

- What are the associations of the n-3 FA content or the n-6/n-3 FA ratio of maternal or fetal or child biomarkers with each of the outcomes identified above?

KQ 3. Maternal or childhood adverse events:

- What are the short and long term risks related to maternal intake of n-3 FA during pregnancy or breastfeeding on:
  - Pregnant women
  - Breastfeeding women
  - Term or preterm human infants at or after birth
- What are the short and long term risks associated with intakes of n-3 FA by human infants (as maternal breast milk or infant formula supplemented with n-3 FA)?
- Are adverse events associated with specific sources or doses?

PICOTS (Population, Intervention, Comparator, Outcome, Timing, Setting)

Population(s)

- KQ 1 (Maternal exposures and outcomes)
  - Healthy pregnant women (for outcomes of birth weight, intrauterine growth restriction/small for gestational age, duration of gestation, risk of pre-eclampsia, eclampsia, or pregnancy hypertension)
  - Pregnant women with a history of pre-eclampsia, eclampsia, or pregnancy hypertension (only for outcome of risk of pre-eclampsia, eclampsia, or pregnancy hypertension)
  - Pregnant women with a history of major depressive disorder or postpartum depression (only for the outcome of risk for peripartum depression)

- KQ 2 (In utero and postnatal (through the first year of life) exposures and outcomes)
    - Healthy preterm or full term infants of healthy women/mothers whose n-3 fatty acid exposures were monitored during pregnancy
    - Breastfed infants of healthy mothers whose n-3 fatty acid exposure was monitored and/or who participated in an n-3 fatty acid intervention during breastfeeding beginning at birth
    - Healthy preterm or full term infants with and without family history of respiratory conditions (for outcomes related to atopic dermatitis, allergy, respiratory conditions) of mothers whose n-3 exposures were monitored during pregnancy and/or breastfeeding
    - Healthy children or children with a family history of a respiratory disorder, a cognitive or visual development disorder, autism spectrum disorder, ADHD, or learning disabilities, age 0 to 18 years who participated in an n-3 fatty acid-supplemented infant formula intervention or an n-3 supplementation trial during infancy
- KQ 3 (Adverse events associated with n-3 interventions)
    - Healthy pregnant women or pregnant women in the other categories described above
    - Offspring of women enrolled in an n-3 fatty acid intervention during pregnancy
    - Offspring of women whose exposure to n 3 fatty acids was assessed during pregnancy
    - Children whose exposure to n-3 fatty acids (through breast milk, infant formula, or supplementation) was monitored during the first year of life

Interventions/Exposures

- Interventions (KQ1, 2, 3 unless specified):
    - N-3 fatty acid supplements (e.g., EPA, DHA, ALA, singly or in combination
    - N-3 fatty acid supplemented foods (e.g., eggs) with quantified n-3 content
    - High-dose pharmaceutical grade n-3 fatty acids, e.g., Omacor®, Ropufa®, MaxEPA®, Efamed, Res-Q®, Epagis, Almarin, Coromega, Lovaza®, Vascepa® (icosapent ethyl)
        - Exclude doses of more than 6g/d, except for trials that report adverse events
    - N-3 fatty acid enriched infant formulae (KQ2,3)
        - E.g., Enfamil® Lipil®; Gerber® Good Start DHA & ARA®; Similac® Advance®
        - N-3 enriched follow-up formulae
        - Exclude parenterally administered sources
    - Marine oils, including fish oil, cod liver oil, and menhaden oil with quantified n-3 content
    - Algal or other marine sources of omega-3 fatty acids with quantified n-3 content
- Exposures (KQ1,2)
    - Dietary n-3 fatty acids from foods if concentrations are quantified in food frequency questionnaires
    - Breast milk n-3 fatty acids (KQ2)
    - Biomarkers (EPA, DHA, ALA, DPA, SDA), including but not limited to the following:
        - Plasma fatty acids
        - Erythrocyte fatty acids

        - Adipocyte fatty acids

Comparators

- Inactive comparators:
    - Placebo (KQ1, 2, 3)
    - Non-fortified infant formula (KQ2)
- Active comparators
    - Different n-3 sources
    - Different n-3 concentrations (KQ1, 2, 3)
    - Alternative n-3 enriched infant formulae (KQ2)
    - Soy-based infant formula (KQ2)
    - Diet with different level of Vitamin E exposure

Outcomes

- Maternal outcomes (KQ1)
    - Blood pressure control
        - Incidence of gestational hypertension
        - Maternal blood pressure
        - Incidence of pre-eclampsia, eclampsia
    - Peripartum depression
        - Incidence of antepartum depression[10]
        - Incidence of postpartum depression, e.g.
            - Edinburgh Postnatal Depression scale
            - Structured Clinical Interview (SCI)
    - Gestational length
        - Duration of gestation
        - Incidence of preterm birth
    - Birth weight

        - Mean birth weight
        - Incidence of low birth weight/small for gestational age
- Pediatric Outcomes (KQ2)
    - Neurological/visual/cognitive development
        - Visual development, e.g.
            - Visual evoked potential acuity
            - Visual acuity testing
                - Teller's Acuity Card test
            - Electroretinography
        - Cognitive/neurological development, e.g.
            - EEGs as measure of maturity
            - Psychomotor developmental index from Bayley's scales
            - Bayley's mental development index
            - Knobloch, Passamanick, and Sherrard's developmental Screening Inventory scores
            - Neurological impairment assessment
            - Active sleep, quiet sleep, sleep-wake transition, wakefulness
            - Fagan Test of Infant Intelligence
            - Stanford-Binet IQ
            - Receptive Vocabulary
                - Peabody Picture Vocabulary Test-Revised
        - Auditory development
            - Nerve conduction test
            - Latency Auditory evoked potential
    - Risk for ADHD
        - Studies will be included only if they employ a validated evaluation procedure

        - E.g., Wechsler Intelligence Scale for Children
        - Behavioral rating scales, e.g., Connors, Vanderbilt, and Barkley scales
    - Risk for Autism spectrum disorders
        - Studies will be included only if they employ a validated evaluation procedure
            - E.g., Modified Checklist of Autism in Toddlers
    - Risk for learning disabilities
        - Studies will be included only if they employ a validated evaluation procedure
    - Risk for atopic dermatitis
    - Risk for allergies
        - Studies will be included only if they employ a validated allergy assessment procedure, preferably challenge
    - Incidence of respiratory disorders
        - Spirometry in children 5 and over (peak expiratory flow rate [PEFR] and forced expiratory volume in 1 second [FEV1])
- KQ 3: Adverse effects of intervention(s)
    - Incidence of specific adverse events reported in trials by study arm

Timing

- Duration of intervention or follow-up
    - Key Question 1,3 (maternal interventions/exposures):
        - Interventions implemented anytime during pregnancy but preferably during the first or second trimester
        - Followup duration is anytime during pregnancy (for maternal outcomes of pre/eclampsia or maternal

hypertension); term (for outcomes related to birth weight, duration of pregnancy); or within the first 6 months postpartum (for the outcome of postpartum depression)

- Key Question 2, 3 (infant exposures):
  - Interventions implemented within one month of birth or exposures measured within 1 month of birth
  - Followup duration is 0 to 18 years

Settings

- Community-dwelling individuals seen by primary care physicians or obstetricians in private or academic medical practices (KQ1, 3)
- Community dwelling children seen in outpatient health care or educational settings (KQ2, 3)

Study designs will be limited to Randomized Controlled Trials, prospective cohort studies, and nested case control studies (cross-sectional, retrospective cohort, and case study designs will be excluded; studies must have measure of intake/exposure prior to outcome). Language will be restricted to English. Only peer-reviewed studies will be included; unpublished studies will not be included.

Sharon B. Arnold, Ph.D.
Deputy Director

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