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Predicting the effect of maternal docosahexaenoic acid (DHA) supplementation to reduce early preterm birth in Australia and the United States using results of within country randomized controlled trials ☆

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ABSTRACT

The DHA to Optimize Mother Infant Outcome (DOMInO) and Kansas DHA Outcomes Study (KUDOS) were randomized controlled trials that supplemented mothers with 800 and 600 mg DHA/day, respectively, or a placebo during pregnancy. DOMInO was conducted in Australia and KUDOS in the United States. Both trials found an unanticipated and statistically significant reduction in early preterm birth (ePTB; i.e., birth before 34 weeks gestation). However, in each trial, the number of ePTBs were small. We used a novel Bayesian approach to estimate statistically derived low, moderate or high risk for ePTB, and to test for differences between the DHA and placebo groups. In both trials, the model predicted DHA would significantly reduce the expected proportion of deliveries in the high risk group under the trial conditions of the parent studies. Among the next 300,000 births in Australia we estimated that 1112 ePTB (95% credible interval 51-2189) could be avoided by providing DHA. And in the USA we estimated that 106,030 ePTB (95% credible interval 6400 to 175,700) could be avoided with DHA.

1. Introduction

N-3 long chain polyunsaturated fatty acid (LCPUFA) status in pregnancy was first linked to longer gestation, higher birth weight and less preterm birth (PTB) in early studies by Olsen and collaborators. They observed longer gestation among Faroe Islanders, who consume a diet higher in fish and therefore higher in two n-3 LCPUFA, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), compared to Danes [1,2]. It is now generally understood that n-3 LCPUFA supplementation during pregnancy increases gestation duration; a 2006 Cochrane review included 3 randomized controlled trials (RCT) of n-3 LCPUFA supplementation with 1621 women, revealing a significant 2.6 d increase in gestation duration favoring n-3 LCPUFA supplementation [3]. Two RCT of DHA supplementation reported since 2006 found a significant increase in gestation of 1 and 2.9 days, respectively [4,5].

Although DHA supplementation would likely result in fewer PTBs, the overall increase in gestation of several days may have limited clinical significance. Clinical significance would be enhanced, however, if the relatively small overall increase in gestation was due to a decrease in deliveries at higher risk for PTB. In fact, our RCTs conducted in women with normal risk of PTB found

Abbreviations: ADORE, assessment of DHA on reducing early preterm birth; DHA, docosahexaenoic acid; DOMInO, DHA to Optimize Mother Infant Outcome; EPA, eicosapentaenoic acid: KUDOS, Kansas DHA outcomes study; LCPUFA, long chain polyunsaturated fatty acids; ORIP, omega-3 fats to reduce the incidence of prematurity; PTB, preterm birth; ePTB, early preterm birth; RCT, randomized controlled trials

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a significant reduction in early PTB (ePTB), defined as births before 34 weeks [4,5]. The DHA to Optimize Mother Infant Outcome (DOMInO) trial, conducted in Australia, provided 800 mg DHA and 100 mg EPA daily and reduced ePTB by 51.6% [4], while a smaller trial, the Kansas DHA Outcomes Study (KUDOS), conducted in the Midwestern portion of the United States provided 600 mg DHA daily and reduced ePTB by 87.5% [5].

In the developed world, ePTB results in longer hospitalizations, increased risk of additional hospitalizations in the first year of life, and greater short and long term cost to society relative to PTBs of 34–37 weeks gestation. Although some drugs have been shown to reduce uterine contractions in an attempt to delay labor, their efficacy in preventing PTB is limited and they have undesirable side effects [6]. At present there is no effective method to prevent spontaneous ePTB. Our recent studies suggest that n-3 LCPUFA, particularly DHA, could be a promising agent for reducing ePTB [4,5].

Our present investigation has two primary purposes: 1) to conduct an analysis of both DOMInO and KUDOS to determine if the effects of DHA on gestation and birth weight were due to a particular subset of the birth population; and 2) to use the results of DOMInO and KUDOS to model the predicted effect of DHA supplementation on ePTB within Australia and the United States. The model's utility was demonstrated in a previous report [7] in which we used the mean and variance-covariance of 3 normal distributions for birth weight and gestational age determined by Schwartz et al. [8] from more than 250,000 US births and utilized flexible commensurate priors from Hobbs et al. [9]. In that analysis we determined how many low birth weight (<2.5 kg) and preterm births (<37 wks gestation) could be prevented by providing 20,000 pregnant women 600 mg/day of DHA had they been cared for in centers demographically similar to the one where the KUDOS trial was conducted [7].

2. Methods

2.1. DOMInO trial

The DOMInO trial was a double-blind RCT conducted in five Australian perinatal centers between 2005 and 2009 (ACTRN12605000569606; anzctr.org.au). The methods and primary results for the trial are published elsewhere [4]. Briefly, English speaking women who had a singleton pregnancy between 18 and 21 weeks gestation and who were not participating in another fatty acid trial were eligible. Women who had a known fetal abnormality or a bleeding disorder in which tuna oil was contraindicated were excluded. Women who were already taking a supplement containing DHA or anticoagulant therapy, or had a documented history of drug or alcohol abuse were also excluded. Participants randomized to the DHA group were asked to consume three DHA-rich fish oil capsules, providing a total of 800 mg of DHA and 100 mg of EPA, daily from trial entry until delivery. Participants randomized to the placebo group received three vegetable oil capsules without LCPUFA. Demographic characteristics were collected from participants at baseline and birth details, including infant birth weight and gestational age at delivery, were obtained from medical records.

2.2. KUDOS trial

KUDOS was a double-blind RCT conducted in the United States between 2006 and 2009 (NCT00266825; www.clinicaltrials.gov). The trial methodology and pregnancy outcomes have been reported [5]. Women were eligible if they were English-speaking, aged 16–35 years, between 8 and 20 weeks' gestation and planning to deliver at a hospital in the Kansas City metropolitan area. Women carrying more than one fetus or who had diabetes mellitus, systolic blood pressure ≥ 140 mm Hg, any serious health condition likely to affect the growth and development of their offspring, or a body mass index ≥ 40 were excluded. Participants assigned to the DHA group received three DHA-rich marine algae-oil capsules containing a total of 600 mg DHA/day from trial entry until delivery. Participants assigned to the placebo group received the same number of capsules containing vegetable oil (half soybean and half corn oil) without DHA. Demographic characteristics were obtained from participants or their medical record at baseline, along with a blood sample for measuring red blood cell phospholipid DHA as a percentage of total fatty acids by weight. Gestational age was determined from the expected date of delivery based on a late first trimester or early second trimester ultrasound and infant birth weight was collected from medical records.

2.3. Statistical methods

Exploratory analyses were conducted to determine the effect of the DHA intervention on infant birth weight and gestational age at delivery. These outcomes were jointly modeled using a mixture of three normal distributions that represented subgroups of women at low, moderate and high risk for PTB. The mixture of these three subgroups was estimated in the DHA and placebo groups separately [7]. This novel Bayesian approach was used to estimate the percentage of pregnancies at statistically derived low, moderate or high risk for PTB, and to test for differences in these outcomes between the DHA and placebo groups. Each analysis was based on a prediction of the number of high risk PTBs that could be avoided among the next 4,000,000 births in the USA and 300,000 births in Australia assuming their mothers received the same amount and source of DHA as in KUDOS or DOMInO, respectively. These numbers are an approximation of the total annual births in the United States and Australia. . Demographic and clinical characteristics were compared descriptively among women who were classified as low, moderate or high risk for PTB using the mixture distribution. All participants who provided birth data were included in the analysis in their randomized groups. The analysis was performed separately on data from the DOMInO and KUDOS trials using SPSS 22.0 (www.ibm.com) and Matlab (www.mathworks.com).

3. Results

Baseline characteristics were well balanced between women randomized to the DHA and placebo groups, as reported previously [4,5]. Infant weight and gestational age at birth were available for 2363 (98.5%) of the 2399 women recruited to the DOMInO trial and 299 (85.4%) of the 350 women recruited to the KUDOS trial. Birth weight increased with gestational age in both treatment groups for each trial as expected (Fig. 1).

Using the Bayesian model, DHA supplementation altered the gestational age profile at birth in both the DOMInO and KUDOS trials. Specifically, the distribution of women across the statistically derived low, moderate and high risk subgroups for PTB was altered by the DHA intervention, but this was significant only in the high risk subgroup (Table 1, and Fig. 2 for DOMInO trial). In the DOMInO trial, 2.15% of women assigned to the DHA group compared with 3.76% of women assigned to the placebo group were high risk ($p=0.02$), while in the KUDOS trial 2.69% and 7.09% of women were high risk in the DHA and placebo groups, respectively ($p=0.02$).

The model from DOMInO predicted DHA would reduce ePTB by