Reproductive System and Sexual Disorders: Current Research

Quinlivan and Pakmehr, Reprod Sys Sexual Disorders 2013, 2:1
DOI: 10.4172/2161-038X.1000116

Review Article Open Access

Fish Oils as a Population Based Strategy to Reduce Early Preterm Birth

Julie A. Quinlivan[1-3]* and Sahar Pakmehr[1]

[1]Ramsay Health Care, Joondalup, WA 6027, Australia
[2]Women's and Children's Medical Research Institute, University of Adelaide, Adelaide, SA, Australia
[3]University of Notre Dame Australia, Fremantle, WA Australia

Abstract

Preterm birth remains the leading challenge in perinatal mortality and morbidity in the developing world. Existing strategies to reduce preterm birth target at risk women and are not suitable as a population strategy because of their expense. However, more than 50% of preterm births are to women with no pre-existing risk factors. Therefore, population based strategies are desirable.

We present the evidence for fish oil supplements as a population based strategy to reduce early preterm birth.

Fish oils act as competitive antagonists of series two prostaglandins and can target premature cervical ripening as a cause of early preterm birth. These oils are safe and well tolerated by pregnant women. Analyses from randomised trials show that fish oils may be promising as a population based strategy for the prevention of early preterm birth.

Keywords: EPTB; Fish oils; Cervical cerclage; Iatrogenic factors

Introduction

Preterm birth is the leading cause of perinatal mortality and morbidity accounting for more than 85% of all perinatal complications and deaths [1]. The prevention of preterm birth remains the most challenging issue in obstetric and neonatal care.

Existing strategies to prevent preterm birth including management of at risk women in high-risk pregnancy clinics, ultrasound based cervical surveillance, with cervical cerclage or progesterone therapy as a targeted intervention when cervical length shortens or where there is another identified risk for preterm birth [2-4].

However, these surveillance and intervention therapies may not be a suitable strategy for a population based primary prevention campaign because of their expense and/or need for clinical expertise. Yet population based strategies are urgently required as more than 50% of Early Preterm Births (EPTB) occur spontaneously without identifiable risk factors [5].

Idiopathic preterm birth, without obvious precipitating factors such as infection, or iatrogenic factors such as delivery initiated due to a secondary factor such as pre eclampsia, is thought to have its basis in premature ripening of the uterine cervix [1,5,6]. An imbalance between Omega 3 (ω-3) and Omega 6 (ω-6) fatty acid intakes may be associated with disturbances in the production of prostaglandins, a critical element in cervical ripening and the initiation of labour, which may in turn lead to idiopathic preterm birth.

Improving ω−3 long chain polyunsaturated fatty acid (ω−3 LCPUFA) nutrition in pregnancy could represent a potential population based strategy to reduce preterm birth due to the role that ω−3 LCPUFA play in the maintenance of normal gestation length and the initiation of labour.

Impact of Preterm Birth on the Community

Preterm birth is defined as birth before 37 completed weeks of pregnancy. Approximately 8%-10% of births worldwide each year are preterm. Nearly 20% of all preterm births occur before 34 completed weeks of pregnancy and are called Early Preterm Birth (EPTB) [1,5,6]. It is EPTB that is the major cause of perinatal mortality, serious neonatal morbidity and moderate to severe childhood disability in developed countries [1,5-8].

There is a lack of the data on economic cost associated with preterm birth. However, a 2005 US study reported the annual cost to be 26 billion [1]. The cost of care for infants born following EPTB is substantially higher and is estimated at US $100,000 to $150,000 per infant [9]. These costing estimates do not include the ongoing costs of lifelong care of individuals affected by intracranial haemorrhage, necrotising enterocolitis, chronic lung disease, retinopathy, cerebral palsy and developmental delay [7-10].

Furthermore, EPTB children may have learning disabilities, abnormal behaviours, motor and cognitive developmental delay that lead to long-term disabilities and loss of opportunity in life [9]. There are yet further costs of ongoing care with social security expenditure on disability pensions, as well as the emotional stress and loss of income from the care giving parent. These factors combine to impose an enormous financial and social burden on families and society.

Existing Strategies to Prevent Preterm Birth and EPTB

Currently there is no population-based strategy for the prevention of PTB or EPTB apart from generic attendance at antenatal care. A broad applicable safe and effective prevention strategy for preterm birth is required.

Specific strategies in high-risk women have been identified. Several cohort studies have now provided evidence that women with a short cervix, detected by transvaginal ultrasound in midtrimester of pregnancy (18-24 weeks of gestation) are at risk of preterm delivery [11]. For population purposes, women with a cervix of 15 mm or less at 18 to 24 weeks gestation, have a 50% chance of having a preterm delivery at less than 33 weeks of gestation [11-13]. Cervical length measurements are predictive for PTB and EPTB in both nulliparous and parous women [13,14]. Women identified with a short cervix

***Corresponding author:** Julie Quinlivan, Professor, Suite-106 Private Consulting Rooms, Joondalup Health Campus, Shenton Avenue Joondalup WA 6027 Australia, Tel: 61-8-93409631; E-mail: quinlivanj@ramsayhealth.com.au

Received December 19, 2012; **Accepted** February 18, 2013; **Published** February 28, 2013

Citation: Quinlivan JA, Pakmehr S (2013) Fish Oils as a Population Based Strategy to Reduce Early Preterm Birth. Reprod Sys Sexual Disorders 2: 116. doi:10.4172/2161-038X.1000116

on ultrasound, may then be offered intervention with progesterone therapy or cerclage.

The evidence for progesterone therapy is promising. Several trials have reported a reduction in PTB in at-risk women [2,14-16]. The trial by Meis et al. enrolled women with a documented history of a previous spontaneous preterm labour or preterm premature rupture of membranes [2]. The intervention consisted of a weekly injection of 250 mg of progesterone commencing between 16 and 20 weeks of gestation and continuing until delivery or 37 weeks of gestation. PTB was reduced from 54.9 % in the placebo group to 36.3% in the treatment group [2].

The de Fonseca et al. trial enrolled women at high risk for preterm delivery who had a cervical length of 15 mm or less on ultrasound at 20 to 24 weeks [16]. The intervention was progesterone 200 mg daily per vagina from 24 weeks till 34 weeks gestation. In women with a shortened cervix there was a small significant reduction in PTB but no significant change in perinatal morbidity or mortality [16].

The largest trial was the PREGNANT trial, where 30,000 women were screened for cervical length between 10-20 mm in midtrimester of pregnancy. Patients allocated to vaginal progesterone gel (90 mg) had a 45% reduction in the rate of EPTB [17].

Cervical cerclage has also been reported to be effective in treating women with short cervical length on screening ultrasound and women with a history of previous early preterm birth [4,18,19].

The concept of offering universal cervical length screening followed by progesterone therapy or surgical cerclage is promising for the developed world. Cost effectiveness analysis evaluating universal cervical length screening in singleton gestations to identify those with short cervical length followed by vaginal progesterone have been published and report that such a strategy may be cost effective [14,15,20].

However, not all centres in the developed world, let alone the developing world, can afford to implement routine cervical length screening. Cervical length screening requires operator skill, access to ultrasound, and preferably access to transvaginal ultrasound, in order to achieve reliable results.

Where all patients already undergo as the standard of care a mid second trimester anatomy scan at a facility that has the equipment and trained staff capable of doing transvaginal scanning, then a policy of universal transvaginal cervical length screening followed by treatment with progesterone or cerclage may be cost effective in reducing the risk of PTB [14]. However, these facilities are not reliably present in the developed world, let alone the developing world.

Low Cost Options

Addressing the imbalance between ω-3 and ω-6 fatty acid may reduce disturbances in the production of prostaglandins and may in turn lead to reductions in EPTB and PTB [21]. Interventions achieved through the optimisation of maternal nutritional status to prevent PTB was identified as an area of research priority at the Preventing Preterm Birth Initiative at the Annual Grand Challenges in Global Health meeting in India in November 2011. Improving ω−3 LCPUFA nutrition in pregnancy shows promise due to the role of series-3 prostaglandins in the maintenance of normal gestation length and the initiation of labour.

ω−3 LCPUFA and Preterm Birth

Prostaglandins and other eicosanoids derived from ω-6 and ω-3 fatty acids play essential roles in normal and pathologic initiation of labour [22,23]. The feto-placental unit is supplied with ω-3 LCPUFA from the maternal circulation. Circulating levels of ω-3 LCPUFA are directly linked to maternal intake [24]. The rises in ω-3 LCPUFA within the utero-placental unit in normal pregnancy are countered by rises in local production of 2-series prostaglandins within the same tissues, a critical element in cervical ripening and the initiation of labour. This balance plays an important role in the maintenance of normal gestation length [24]. If local production of prostaglandins within the feto-placental unit is too high, or local accumulation of ω-3 LCPUFA is too low, the cervix may prematurely ripen and uterine contractions increase, which may in turn lead to PTB or EPTB [21].

Many pregnant women have diets that are low in ω-3 LCPUFA and high in ω-6 fatty acid leading to a predominance 0020-series prostaglandins. In contrast, ω-3 LCPUFA antagonise the production of 2-series prostaglandins. AA directly competes with ω-3 LCPUFA for incorporation into cells. Diets those are high in ω-3 LCPUFA result in preferential incorporation of the series 3 prostaglandins into cellular phospholipids and the displacement of AA and series 2 prostaglandins [25,26]. Therefore optimising ω-3 LCPUFA intake in pregnancy may reduce the accumulation of local prostaglandins that prematurely ripen the uterine cervix and thus lead to a lower risk of PTB.

Dietary Intakes of ω-3 LCPUFA in Pregnant Women are Inadequate

Metabolic and post-mortem studies indicate that the fetus accumulates 70 mg of ω-3 LCPUFA per Kg per day, mainly as docosahexaenoic acid (DHA, 22:6 ω-3), during the second half of pregnancy [26]. To achieve this, the World Health Organisation recommends that pregnant women have an intake 300 mg/d of ω-3 LCPUFA. However, surveys of pregnant women indicate daily intakes are considerably lower than this recommended figure. An Australian study reported the median ω-3 LCPUFA intake was only 15 mg/day [27] with the intake in pregnant women being even lower due to the conflicting advice provided to pregnant women to reduce intake of high mercury containing fish [27].

Given the level of ω-3 LCPUFA intake required to achieve normal rises in the feto-placental unit for the maintenance of normal pregnancy are well above the intake of many pregnant women, this highlights a potential dietary deficiency that may contribute towards dietary related PTB and EPTB.

Epidemiological Association between ω-3 LCPUFA Intake in Pregnancy and Gestational Length

The epidemiological associations between the dietary intake of ω-3 LCPUFA intake and pregnancy duration were first made twenty years ago. In a population based study the duration of gestation comparing the genetically similar populations of Denmark and the Faroe Islands it was observed that the Faroe Islanders ate more marine fat (ω-3 LCPUFA) and had longer gestations than the Danish women [28]. Subsequent studies demonstrated a positive association between ω-3 LCPUFA intake and the duration of gestation [29-31]. Although promising, randomised trials were required to ensure that confounders did not explain the associations observed in the epidemiological studies.

RCTs of ω-3 LCPUFA Supplementations in Pregnancy to Prevent Preterm Birth

The strongest evidence to support the efficacy of the ω-3 LCPUFA supplementation in pregnancy to reduce EPTB comes from our

DOMInO trial [32]. DOMInO was a large-scale RCT that was originally designed to assess the effect of ω-3 LCPUFA supplementation during the last half of pregnancy on the prevalence of postnatal depression in women and on early childhood neurodevelopmental outcomes. The secondary outcome of the trial was the incidence of PTB and EPTB. The trial enrolled 2399 women from five perinatal centres around Australia who were randomly assigned to receive identical looking capsules containing either fish oil concentrate (900 mg ω-3 LCPUFA/day) or a blend of vegetable oils (no ω-3 LCPUFA) from 20 weeks gestation until birth.

In a pre-planned secondary analysis, we observed fewer EPTB in the ω-3 LCPUFA supplemented group compared with control (1.09% vs. 2.25%, adjusted RR 0.49, 95% CI 0.25 to 0.94, p=0.03). The impact of ω-3 LCPUFA supplementation on gestational length was most marked at the extremes of gestation where the highest levels of mortality and morbidity are observed in clinical practice. Our finding was consistent with the Cochrane systematic review of the two prior smaller RCT that reported that women allocated to marine oil had a lower risk of EPTB compared with control (RR 0.69, 95% CI 0.49 to 0.99, 2 trials, n=860) (25).

In our DOMInO trial there were also potential cost benefits identified. There were significantly fewer admissions to level three intensive care in the ω-3 LCPUFA group compared with control (RR 0.57, 95% CI 0.34 to 0.97, p=0.04). This last outcome was driven almost entirely by the lower rates of EPTB in the ω-3 LCPUFA group (32).

The key factor was that the DOMInO trial and the other RCT comparing the efficacy of marine oils were unselected patient populations and therefore this intervention represented a potential public health strategy for the reduction in EPTB and its consequent mortality and morbidity.

ω-3 LCPUFA Supplementation in Pregnancy is Safe

The doses of ω-3 LCPUFA in the RCTs have not been associated with an increased risk of adverse side effects. The systematic reviews reported no differences in the incidence of antepartum hospitalisation, caesarean section, eclampsia or other serious maternal morbidity [25,33-35]. The relative risk of miscarriage, stillbirth or neonatal death did not differ between treatment and control groups [25,33,34]. The DOMInO trial also supports the safety data from the systematic reviews. Women allocated to ω-3 LCPUFA supplements had similar rates of haemorrhage and antenatal hospitalizations compared to the placebo group. Similarly, there were no differences between the groups in maternal report of nose bleeds, vaginal blood loss, constipation, nausea or vomiting at 28 and 36 weeks' gestation [32].

However, an increased in the incidence of post-term inductions or post-term pre-labour caesarean sections was observed in the ω-3 LCPUFA supplemented group compared with control (17.59% vs. 13.72%, adjusted RR 1.28, 95% CI 1.06 to 1.54, p=0.01). This is consistent with the underlying hypothesis that dietary supplementation prolongs pregnancy.

From Here to Where?

It is imperative that any effective intervention strategy is also safe. Although the DOMInO trial has provided evidence to support the hypothesis that maternal ω-3 LCPUFA supplementation in pregnancy reduces the incidence of EPTB, there is a need to address the safety issue of increased risk of post-term birth.

Animal studies demonstrate that ω-3 LCPUFA supplementation in mid gestation is associated with significant elevations in ω-3 LCPUFA in the uterus, membranes and fetus, with the most marked elevations seen in the uterus itself [24]. As the duration, dose and timing of supplement administration are altered, the levels accumulated within the feto-placental unit change in timed dose response relationship. This means that supplement administration needs to be timed to achieve optimal ω-3 LCPUFA concentrations in the uterus at times when it can impact upon clinical outcomes.

We need to time supplement administration to achieve the required levels of ω-3 LCPUFA within the materno-fetal unit to prevent EPTB and PTB and yet have levels return to baseline by 40 weeks gestation to avoid post term birth. It has been shown that within six weeks, people who stop taking fish oil capsules have their plasma and red cell ω-3 LCPUFA return to levels which are similar to the general population of low fish consumers [36,37]. By stopping ω-3 LCPUFA supplementation at 34 weeks gestation, this innovative intervention strategy might reduce the risk of early preterm birth without increasing the risk of post-term birth. We have now commenced a trial to investigate this hypothesis.

Summary

Population based strategies to reduce PTB and EPTB are being sought. Dietary supplements with ω-3 LCPUFA offer an exciting avenue for future research. Supplements are safe and appear to be effective in reducing the incidence of EPTB but this is achieved at the expense of an increase in post dates pregnancy. Refinement in the timing and dosage of supplements is required to develop a protocol for routine clinical practice. We are commencing the ORIP trial (Omega-3 to reduce the Incidence of Preterm birth). This randomised trial of 4700 women will help clarify the timing and dose of Omega-3 oils to optimise pregnancy outcomes.

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