Project Title	**Dietary omega-3 and omega-6 fatty acids supplementation in pregnant women with diabetes: Randomised, double-blind, placebo-controlled trial**
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Background	The long-chain polyunsaturated fatty acids, arachidonic (AA) and docosahexenoic (DHA) acids are structural components of cell and sub-cellular membranes. They are particularly vital for the function of neuro-visual, vascular and immune systems. During pregnancy there is a higher demand for DHA and AA. It is estimated that the foetus accumulates about 70 mg/day of omega-3 fatty acids, mainly DHA, and at least a comparable amount of AA. Since the foetus has a very limited ability of synthesising AA and DHA, the mother must meet most of the foetal requirement for the two fatty acids. Indeed, both AA and DHA are selectively transferred from the mother to the foetus by the placenta. There is evidence that both type 1 and type 2 diabetes impair the activity of delta-6 and delta-5 desaturases, enzymes necessary for the synthesis of AA and DHA. This impairment is ameliorated by insulin therapy. In a prospective study of type 1, type 2 and gestational diabetic women and their babies, we have investigated if diabetes during pregnancy affects adversely maternal and foetal AA and DHA status. The investigation revealed that the levels of both fatty acids were significantly reduced in red cell choline phosphoglycerides of the mothers, and in red cell and plasma choline phosphoglycerides of their neonates, at birth. Although not as remarkable, a similar effect was also apparent in red cell ethanolamine phosphoglycerides. Choline- and ethanolamine-phosphoglycerides are the major phospholipids of the outer and inner leaflet of plasma membrane lipid bilayer, respectively. Intriguingly, in spite of intensive insulin therapy, both the type 1 and type 2 diabetic women and their neonates had highly compromised AA and DHA. The fact that the abnormality is more pronounced in the outer leaflet, choline phosphoglycerides, which is intimately associated with receptors, might provide an

	explanation for the impaired insulin receptor function and insulin resistance in the women with type 2 and gestational diabetes. The low AA and DHA in the diabetic mothers could be due to impaired accretion and/or synthesis. Low maternal status and/or placental dysfunction and the consequential reduction of the transfer of the fatty acids from the mother, may explain the abnormality in the neonates. In a pilot study of Korean women with gestational diabetes and their babies, we found that the mothers with gestational diabetes, similar to their British counterparts, had compromised red cell AA and DHA. In contrast, their neonates had normal levels of plasma and red cell DHA. Since foetal DHA status is enhanced by increased maternal intake of DHA in pregnancy, it is plausible that the normal DHA level in the neonates of the Korean gestational diabetics could be a reflection of high intake of DHA from fish in Korean women (75g/day vs 13-34g/day in European).
Aims	To investigate if the membrane lipid abnormality in diabetic women and their neonates could be rectified by nutritional (DHA and AA) supplementation during pregnancy.
Patients (Subjects)	Women with singleton pregnancy with diabetes (type 2 or gestational) and without any medical condition (healthy controls)
Inclusion and exclusion criteria	• Inclusion – Pregnant women aged 17-45 years old without any medical condition and pregnant women with diabetes (type 2 diabetes or gestational diabetes) • Exclusion - Smokers; History of stillbirth or foetal death; Pregnancy with more than one foetus; Known major foetal anomaly; Current or planned corticosteroid therapy; Asthma requiring medication; Current or planned beta adrenergic therapy; Chronic hypertension requiring medication within 6 months of or during pregnancy; Chronic medical conditions such as HIV/AIDS, kidney disease, or congenital heart disease; Hematologic or autoimmune disease such as sickle cell disease, other hemoglobinopathies, lupus, or antiphospholipid syndrome; Maternal or foetal conditions likely to require preterm delivery, such as pre-eclampsia, preterm labour, or intrauterine growth retardation; Previous or planned tocolytic therapy to induce labour or increase contraction strength.
Intervention	Subsequent to recruitment the diabetics (type 2 and gestational) and healthy non-diabetic controls will be randomly assigned to the treatment or the placebo group. The treatment groups will receive two gelatine capsules a day providing 600 mg DHA and 17 mg AA until delivery. The capsule also contains 2.8mg of vitamin E per gram polyunsaturated fatty acids to prevent oxidation. The control (placebo) groups will receive one gelatine capsule per day containing an inert placebo (high oleic acid sunflower oil) and vitamin E per day until delivery.
Compliance	Blood cell DHA status will be used as objective measure to assess compliance.
Endpoints	• Primary - Maternal and foetal (cord) membrane lipid fatty acids levels at delivery • Secondary - Placental lipid fatty acids composition and expression of placental fatty acid binding and transporter proteins
Data analyses	The data will be presented as mean± standard deviation (sd), median and percentile or median. Statistical differences of continuous variables of the two groups will be examined with Mann–Whitney–Wilcoxon or t-test depending on the homogeneity of variance (data distribution). All patients who started the treatment regardless of the duration of supplementation or follow-up period will be analysed. Statistical analysis will be performed with the use of SPSS for Windows, version 17 (SPSS Ltd., Woking, Surrey, UK) and other pertinent data analyses software.

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