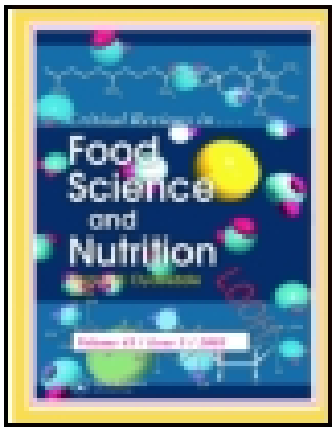


Critical Reviews in Food Science and Nutrition
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/bfsn20

Pregnancy and infants' outcome: nutritional and metabolic implications.

C Berti [a], I Cetin [a], C Agostoni [b], G Desoye [c], R Devlieger [d], P M Emmett [e], R Ensenauer [f], H Hauner [g], E Herrera [h], I Hoesli [i], S Krauss-Etschmann [j], S F Olsen [k], U Schaefer-Graf [l], B Schiessl [m], M E Symonds [n] & B Koletzko [o]

[a] Unit of Obstetrics & Gynecology and Center for Fetal Research Giorgio Pardi , University of Milan , Italy

[b] Dept of Maternal & Pediatric Sciences , University of Milan, and Fondazione IRCCS Ca' Granda-Ospedale Maggiore Policlinico , Milan , Italy

[c] Dept of Obstetrics & Gynaecology , Medical University of Graz , Austria

[d] Dept of Obstetrics & Gynaecology , University Hospitals K.U , Leuven , Belgium

[e] Centre for Child & Adolescent Health, School of Social & Community Medicine , University of Bristol , United Kingdom

[f] Research Center, Dr. von Hauner Children's Hospital , Klinikum der Ludwig-Maximilians-Universität , München , Germany

[g] Else Kroener-Fresenius-Centre for Nutritional Medicine, Klinikum rechts der Isar , Technical University of Munich , Germany

[h] Unit of Biochemistry & Molecular Biology , Universidad San Pablo CEU , Madrid , Spain

[i] Dept of Obstetrics and Gynaecology , University Hospital of Basel , Switzerland

[j] Comprehensive Pneumology Center , Ludwig Maximilians University Hospital and Helmholtz Zentrum Munich , Germany

[k] Centre for Fetal Programming, Statens Serum Institut , Copenhagen , Denmark

[l] Berlin Center for Diabetes & Pregnancy, St. Joseph Hospital, Dept. Obstetrics & Gynecology , Berlin

[m] Fetal Maternal Unit, Dept of Obstetrics & Gynecology , University of Munich

[n] The Early Life Nutrition Research Unit, Academic Child Health, School of Clinical Sciences , University Hospital of Nottingham , United Kingdom

[o] Dr. von Hauner Children's Hospital , University of Munich Medical Centre , Germany

Accepted author version posted online: 14 Mar 2014.

Pregnancy and infants' outcome: nutritional and metabolic implications.

Berti C[1], Cetin I[1], Agostoni C[2], Desoye G[3], Devlieger R[4], Emmett PM[5], Ensenauer R[6], Hauner H[7], Herrera E[8], Hoesli I[9], Krauss-Etschmann S[10], Olsen SF[11], Schaefer-Graf U[12], Schiessl B[13], Symonds ME[14], Koletzko B[15]

[1]Unit of Obstetrics & Gynecology and Center for Fetal Research Giorgio Pardi, University of Milan, Italy

[2]Dept of Maternal & Pediatric Sciences, University of Milan, and Fondazione IRCCS Ca' Granda-Ospedale Maggiore Policlinico, Milan, Italy

[3]Dept of Obstetrics & Gynaecology, Medical University of Graz, Austria

[4]Dept of Obstetrics & Gynaecology, University Hospitals K.U. Leuven, Belgium

[5]Centre for Child & Adolescent Health, School of Social & Community Medicine, University of Bristol, United Kingdom

[6]Research Center, Dr. von Hauner Children's Hospital, Klinikum der Ludwig-Maximilians-Universität München, Germany

[7]Else Kroener-Fresenius-Centre for Nutritional Medicine, Klinikum rechts der Isar, Technical University of Munich, Germany

[8]Unit of Biochemistry & Molecular Biology, Universidad San Pablo CEU, Madrid, Spain

[9]Dept of Obstetrics and Gynaecology, University Hospital of Basel, Switzerland

[10]Comprehensive Pneumology Center, Ludwig Maximilians University Hospital and Helmholtz Zentrum Munich, Germany

[11]Centre for Fetal Programming, Statens Serum Institut, Copenhagen, Denmark

[12]Berlin Center for Diabetes & Pregnancy, St. Joseph Hospital, Dept. Obstetrics & Gynecology, Berlin

[13]Fetal Maternal Unit, Dept of Obstetrics & Gynecology, University of Munich

[14]The Early Life Nutrition Research Unit, Academic Child Health, School of Clinical Sciences, University Hospital of Nottingham, United Kingdom

[15]Dr. von Hauner Children's Hospital, University of Munich Medical Centre, Germany.

Running title: nutrition, physiology and pregnancy

Corresponding author: Irene Cetin, Unit of Obstetrics & Gynecology, Dept Clinical Sciences, Hospital 'L. Sacco', and Center for Fetal Research Giorgio Pardi, University of Milan, Via G. B. Grassi, 74, 20157 Milano, Italy; Tel: +3902 50319804, fax: +3902 50319806; E-mail: irene.cetin@unimi.it

Abstract

Pregnancy is a complex period of human growth, development and imprinting. Nutrition and metabolism play a crucial role for the health and wellbeing of both mother and fetus, as well as for the long-term health of the offspring. Nevertheless, several biological and physiological mechanisms related to nutritive requirements together with their transfer and utilization across the placenta are still poorly understood. In February 2009, the Child Health Foundation invited leading experts of this field to a workshop to critically review and discuss current knowledge, with the aim to highlight priorities for future research. This paper summarizes our main conclusions with regards to maternal pre-conceptional body mass index, gestational weight gain, placental and fetal requirements in relation to adverse pregnancy and long-term outcomes of the fetus (nutritional programming). We conclude that there is an urgent need to develop further human investigations aimed at better understanding of the basis of biochemical mechanisms and pathophysiological events related to maternal-fetal nutrition and offspring health. An improved knowledge would help to optimize nutritional recommendations for pregnancy.

Key Words: fetal nutrition, fatty acids, placental transport, maternal body mass index, maternal diabetes.

INTRODUCTION

The central role of nutrition and metabolism in pregnancy for health and wellbeing of pregnant women, pregnancy outcomes, and long-term health and development of the offspring has been generally recognised.

The key features of pregnancy to be highlighted from the nutritional perspective are as follows:

- Pregnancy can be described by a three compartment model comprising mother, placenta and fetus. Each of these compartments has different physiological, metabolic and genetic characteristics with placental transport function prominent in determining fetal supply and the composition of umbilical cord blood (Pardi and Cetin, 2006; Cetin and Alvino, 2009);

- Pregnancy is a dynamic state, during which the mother switches from an anabolic condition during early pregnancy to a catabolic state during late pregnancy, with qualitative differences in dietary requirements during early and late pregnancy (Fraser and Rutter, 1999). Interestingly, energetic adaptations seem to be also a function of maternal body mass index (BMI), with gestational weight gain (GWG) being the major determinant of incremental energy needs (Butte et al., 2004);

- Maternal pre-pregnancy BMI and total GWG can affect the immediate and long-term health of the child, and may predispose the mother to health concerns such as gestational diabetes (Thorsdottir *et al.*, 2002; Cedergren, 2006). Among its effects on the pregnancy outcome, gestational diabetes may induce structural and functional changes in placenta (Desoye and Hauguel-de Mouzon, 2007) altering the composition of fetal nutrients with consequences for the growing fetus (Jansson *et al*., 2006).

Hence, imbalances in both nutritional intakes and status during pregnancy might have long-lasting effects both on maternal health outcomes, as well as on the long-term health and development of the offspring, for example through fetal programming of later obesity, diabetes and cardiovascular disease risks (Alfaradhi and Ozanne, 2011).

Since maternal nutrition and metabolic adaptations need to be monitored and interpreted together with the evaluation of placental function and fetal nutrition, growth and morphology, we aim to critically discuss current available knowledge on maternal nutritional status, fetal requirements, and placenta physiology and functionality in relation to adverse pregnancy and long-term outcomes. In particular, as lipids seem to play a key role as an emerging nutrient to ensure a proper development and growth to the fetus, we will discuss the metabolic model of *n-3* fatty acids to partly explain the programming of the offspring health.

MATERNAL NUTRITIONAL STATUS DURING PREGNANCY: RELEVANCE FOR ADVERSE PREGNANCY AND LONG TERM OUTCOMES

Nutritional status at the beginning of pregnancy is an important determinant of pregnancy outcome.

In particular, obesity is a major health concern among women of reproductive age sinceit represents a major risk factor for obstetric complications including gestational hypertension, gestational diabetes, cesarean delivery, macrosomia, as well as birth defects such as neural tube defects, congenital heart disease and multiple other congenital anomalies (Prentice, 2004; ESHRE Capri Workshop Group, 2006). Both animal and epidemiological studies indicate that maternal obesity increase the risk for later obesity, cardio-metabolic disease and type 2 diabetes

in the offspring (Drake and Reynolds, 2010; Rooney and Ozanne, 2011). Of growing interest are investigations on the impact of maternal overweight and obesity on asthma symptoms in children. At present, only one cohort study (Patel *et al.*, 2011) showed a link between maternal pre-pregnancy overweight/obesity and risk of asthma symptoms in adolescent offspring. The increase in risk was seen only among adolescents without parental predisposition to atopy. Moreover, an association was recently described between obesity as well as other maternal metabolic conditions and neurodevelopment problems in children (Krakowiak *et al*, 2012).

Maternal weight gain in pregnancy

Improper GWGs has been associated with a range of potentially adverse outcomes including preterm birth, small or large for gestational age infants, increased rates of cesarean delivery and post-partum weight retention (Viswanathan *et al.*, 2008; Kiel *et al.*, 2007). Specifically, excessive maternal GWG is a risk factor for gestational hypertension and preeclampsia as well as fetal macrosomia. Of major concern is the association between excessive GWG and offspring overweight, not previously considered by the IOM but currently confirmed by several studies (Oken *et al.*, 2007; Wrotniak *et al.*, 2008; Oken *et al.*, 2008; von Kries *et al.*, 2011). This relationship seems to be modified by maternal pre-pregnancy BMI (Oken *et al.*, 2007; Wrotniak *et al.*, 2008).

Weight gain below recommendations might be accompanied by preterm birth, small for gestational age neonates, and failure to initiate breastfeeding (Villamor and Cnattingius, 2006). Associations have therefore been suggested to be linearly related to maternal weight change during pregnancy and even noted in women with a normal pre-pregnancy BMI (Villamor and

Cnattingius, 2006). Although the physiological mechanism by which obesity and excessive GWG may cause gestational diabetes and hypertensive disorders of pregnancy is still under investigation, plausible explanationsinclude adverse effects of insulin resistance, elevated plasma cholesterol and leptin i (Hauguel-de Mouzon *et al.*, 2006). In pregnancy, the placenta is the primary source of leptin. Plasma concentration of leptin can be increased by proinflammatory cytokines or in response to insulin stimulation, whereas it decreases in response to low plasma insulin (Hauguel-de Mouzon *et al.*, 2006). Raised fetal and placental leptin are associated with diabetes and preeclampsia, and umbilical cord blood leptin levels are higher in diabetic pregnancies associated with fetal macrosomia and increased fat mass (Cetin *et al.*, 2000). Increased leptin synthesis may result in a "chronic" inflammatory status which may be responsible (Grimble, 1998) for structural and vascular insults during diabetic pregnancy, mainly in obese women, as well as hypertension or placenta insufficiency (Hauguel-de Mouzon *et al.*, 2006). The desirable degree of pregnancy weight gain remains a matter of debate, despite a recent revision of the 1990 Institute of Medicine (IOM) recommendations for weight gain during pregnancy (Rasmussen *et al.*, 2009) in which ranges for the increase in body mass have been recommended by pre-pregnancy BMI. Lower gestational increases in body mass of 2-10 kg in women with a pre-pregnancy BMI between 20-24.9 kg/m^2 (Cedergren, 2007) and even moderate losses of body mass in overweight (0.03 kg/week) and obese (0.019 kg/week) women (Oken et a., 2009) have also been associated with optimal maternal and fetal outcomes.

Recent data (Bavarian Perinatal Statistics) suggest that additional factors such as maternal smoking during pregnancy and parity may modify the risks of adverse pregnancy outcomes between and within groups of maternal BMI (Beyerlein *et al.*, 2009). Interestingly, GWG of

obese pregnant women frequently exceeds the IOM range. This may partially be explained by an unbalanced diet and lack of daily physical activity (Guelinckx *et al.*, 2008; Streuling *et al.*, 2010; Tanentsapf *et al.*, 2011). Even if the optimal approach to reduce GWG in obese patients is not known, in a recent RCT nutritional advice improved dietary habits of obese women (reduced energy and fat intake), but had no significant effect on GWG or birth weight (Guelinckx *et al.*, 2010).

Additionally, research so far has focussed only on GWG as a continuous and linear increase during pregnancy, while it is reasonable that the pattern of GWG on its own might have a considerable influence on fetal growth . Insight in patterns of GWG associated with adverse outcome and effective interventions to increase the proportion of mothers gaining weight within current recommendations are also needed. To be effective, these interventions should include psychosocial education besides dietary and lifestyle counselling (Amianto *et al.*, 2011).

Gestational diabetes

Diabetes, both before and during pregnancy, is associated with fetal and maternal risks. Fetuses show greater incidence of congenital anomalies (Schaefer-Graf *et al.*, 2000), disturbances of intrauterine growth (Schaefer-Graf *et al.*, 2003) and postnatal anthropometric development during their first years of life (Schaefer-Graf *et al.*, 2005). Fetuses of diabetic women may experience cardiomyopathy with poorer diastolic function in early pregnancy, followed by a thickened interventricular septum towards the end of pregnancy (Abu-Sulaiman and Subaih, 2004; Russell *et al.*, 2008; Nizard and Ville, 2009). Malformations of the central nervous system

like spina bifida, hydrocephaly and the caudal regression syndrome are "typical" fetal malformations found in pregnancies with maternal diabetes (Kaissi *et al.*, 2008).

In obese diabetic patients, the possibility to reduce the high frequency of fetal macrosomia by glucose control is quite limited. Langer *et al.* (2005) showed that only the addition of insulin is able to achieve normal fetal growth in this population. Besides hyperglycemia, this may be due to further metabolic disturbances that should be prevented. Comparison of lipid profiles in maternal serum near delivery and in cord blood demonstrated that high maternal free fatty acid (FFA) concentrations are found in both the mother and infant (Schaefer-Graf *et al.*, 2008). Although the association of high maternal glucose and macrosomia has been well documented, excess fetal growth can occur even despite satisfactory glycemic control (Evers *et al.*, 2002; Schwartz *et al.*, 1994). Recently, it has been proposed that altered maternal lipid metabolism rather than hyperglycemia constitutes a risk for macrosomia in GDM (Schaefer-Graf *et al.*, 2008; Herrera and Ortega-Senovilla, 2010a). Moreover, placental function and transport may be affected in diabetic pregnancies, leading to increased nutrient transfer particularly for fatty acids (Jansson *et al.*, 2006; Cetin *et al*, 2012).

NUTRITION IN PREGNANCY AND PROGRAMMING OF OFFSPRING HEALTH

Each stage in embryonic and fetal development is dependent on and influenced by appropriate maternal nutrient supply, and the timing of nutritional insults seems to impact differently on the nature of adult diseases by programming postnatal pathophysiology (Symonds *et al.*, 2007). The concept of early programming of lifelong health has been well established (Godfrey and Barker, 2001; Koletzko *et al.*, 2011) Accordingly, nutrient restriction occurring in the 1st trimester of

pregnancy seems to be linked to increased prevalence of coronary heart disease, raised lipids and obesity; in mid pregnancy with kidney diseases, and during late gestation with decreased glucose tolerance in adult life (Ravelli *et al.*, 1998; Ravelli *et al.*, 1999; Roseboom *et al.*, 2000; Roseboom *et al.*, 2001).Moreover, evidence has accumulated to show that nutrition in early life can program lifelong health also with respect to risks for infection, allergy and autoimmune diseases such as diabetes T1, inflammatory bowel disease, and celiac disease, bone health, neural and brain function, and obesity (Koletzko *et al.*, 2009).

Although it is clear from animal studies that changes in macro- or micronutrient intake can have significant effects on fetal growth and development, the extent to which these findings translate to the human situation are far from clear (Symonds and Budge, 2009; Cetin et al., 2010).

Metabolic and physiological adaptations occur during pregnancy to ensure optimal substrate supply to the fetus (Fraser and Rutter, 1999). The first trimester of pregnancy is characterized by fat storage in adipose tissue, resulting in increased maternal net body weight. This may lead to adequate maternal lipid availability not only later in gestation, but even in lactation, when the increased lipolytic activity increases the circulating lipids to sustain neonatal growth (Herrera, 2002). Finally, a complex relationship between dietary composition and changes in food intake occur in women also around the perinatal period. In fact it is not uncommon for maternal food intake to decrease at some stage in the 1st trimester, which may be an important adaptation that enables changes in maternal body composition to occur through pregnancy thus ensuring nutrient flux to the fetus is maintained, particularly the supply of glucose (Symonds, 2009).

The role of d*ietary *fat: long chain polyunsatured fatty acids (LC-PUFA)

The most relevant fats for organ and tissue function are represented by long-chain polyunsaturated fatty acids (LC-PUFA). Diet-induced changes in arachidonic acid (ARA, 20:4n-6), eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3) have the potential to modulate cellular functions on many levels. PUFA-enriched diets have been shown to lead to significant changes in expression of several genes in the central nervous tissue, and these effects appear to be mainly independent of their effects on membrane composition. The direct effects of PUFA on transcriptional modulators, the downstream developmentally and tissue-specifically activated elements – on the whole, an epigenetic mechanism (Innis, 2005) - might be one of the clues to understanding the beneficial effects of the *n-3* PUFA on the nervous system (Kitajka *et al.*, 2004). It is therefore biologically plausible to hypothesize that maternal *n-3* fatty acid intakes might have significant effects on several pregnancy outcomes as well as on subsequent growth, development and health of the offspring (Koletzko *et al.*, 2008; Cetin *et al.*, 2009). For example, *n-3* fatty acids exert a vasodilator effect by means of modulation of prostaglandin secretion that is by improving the prostacyclin/thromboxane ratio through the reduction of thromboxane (TXA2) production. *N-3* fatty acids increase the level of prostacyclin, which relaxes the uterine muscles, resulting in delay of onset of labour and reduce the activity of eicosanoid promoters of the parturition process, particular prostaglandins F and E2 (Saldeen and Saldeen, 2004).

Effect on pregnancy outcomes

Based on the results of two randomised controlled studies (RCTs), a meta-analysis found that supplementation with *n-3* LC-PUFA in high-risk pregnancies was associated only with a significantly lower rate of early preterm birth (before 34 weeks of gestation) (Horvath *et al.*, 2007). In their meta-analysis of RCTs including pregnant women regardless of their risk for preterm delivery, Makrides *et al.* (2009) concluded that not clear difference in the relative risk of preterm birth existed between women supplemented or not with marine oil, even if women supplemented had a lower risk of early preterm birth. A more recent meta-analysis, including low and high risk women for preterm birth, demonstrated that supplementation with marine *n-3* fatty acids reduced the rate of preterm birth both before 34 and 37 weeks of gestation, and significantly increased the mean birth weight (Salvig and Lamont, 2011). No effect of *n–3* LC-PUFA supplementation was found in women with low-risk pregnancies in the meta-analysis of 6 RCTs by Szajewska *et al.* (2006). Interestingly, moderate fish intake (up to three servings per week) from the beginning of the pregnancy compared to low intake (less than once a month) was reported to reduce the probability of repeated preterm birth. There was no further reduction in preterm birth among women who consumed more than three servings of fish per week (Klebanoff *et al.*, 2011). These results support recommendations advising fish consumption twice weekly (Koletzko *et al.*, 2008). Available data, even if highly heterogeneous, suggest that *n-3* LC-PUFA may increase the length of gestation (Jensen, 2007), and that marine oil supplementation may be of most benefit in prolonging gestation in women with high-risk pregnancies.

Conclusive evidence on the benefit of supplementation of *n-3* fatty acids for preventing preeclampsia is lacking. Makrides *et al.* (2009) analysing data from 6 RCTs including 2783 pregnant women, randomised to fish oil/supplementation or placebo, found no clear difference in the relative risk of preeclampsia between the two groups. Similarly, no evidence was found that supplementation with *n–3* LC-PUFA influenced the rate of preeclampsia (Szajewska *et al.*, 2006), and some data even suggest a risk increasing effect of *n-3* fatty acids on this outcome (Olafsdottir *et al.*, 2006). Further larger RCTs are likely needed to investigate the clinical benefits of the routine use of n-3 fatty acid supplements during pregnancy in reducing the risk of preeclampsia.

Effects on offspring's outcomes

Only few large intervention trials are available assessing the effects of maternal LC-PUFA supplementations during pregnancy on long-term outcomes. They show that high intakes of DHA (i.e., 0.8 and 2.2 g/day starting around the 19th wk of pregnancy and prolonged until delivery or until three months post partum have been associated with higher eye and hand coordination scores at two years (Dunstan et al., 2008) and cognitive function at four (Helland *et al.*, 2003) and seven (Helland *et al.*, 2008) years of age, respectively. Since outcome function measurements have been performed with different developmental scales and tests through these studies, comparability and predictability are difficult to assess. Lower DHA dosages (200 mg/d) have been reported to result in associations of visual performance with the infants' DHA status, irrespective of the maternal allotment in the trial (Malcolm *et al.*, 2003). Similarly, DHA supplementation of breastfeeding mothers for 4 months resulted in higher infant plasma DHA contents during supplementation and a higher Bayley Psychomotor Development Index only at

30 months of age (Jensen *et al.*, 2005). A benefit for problem solving has also been found at age 9 months in infants of mothers who consumed DHA-containing functional food during pregnancy (300 mg/d starting at 24 wks gestation to term) (Judge *et al.*, 2007a), whilst differences in visual acuity were found only at 4 months of age (Judge *et al.*, 2007b). When supplementation with 400 mg DHA/d from the 18th week of pregnancy up to term was studied, a lower risk of poor visual acuity was found in infants of supplemented women as compared to control infants, raising the question of possible benefits of DHA for pregnancies of women who are DHA deficient at baseline (Innis and Friesen, 2008). A 1.3 g fish oil supplementation trial in lactating mothers showed an association between visual acuity at 4 months and the infant DHA status, irrespective of the maternal diet (Lauritzen *et al.*, 2004). In contrast, in the DOMInO trial, DHA supplementation in pregnancy did not result in improved cognitive and language development at 18 months (Makrides *et al.*, 2010). Since comparability and predictability are difficult to assess as outcome function measurements have been performed with different developmental scales and visual assessments through these studies, besides different dose supplements, available evidence does not allow for any supportive conclusion on the role of maternal supplementation. Accordingly, dose, duration and period of supplementation may exert different effects. Genetic variants of the control of fatty acid pathways on LC-PUFA synthesis add a relevant variability, either in infants (Caspi et al, 2007) and mothers (Morales et al, 2011). The dietary source of DHA represents another independent and yet underscored variable. In this regard, the Avon Longitudinal Study of Parents and Children investigating the relationship between fish intake in pregnancy and child neurodevelopment pointed out the superiority of whole fish, compared to fish-derived oils, in positively affecting offspring outcome, in spite of

the possible pollutant content (Oken and Belfort, 2010). A better development of stereovision at age 3 was found to be associated with eating fish in both pregnancy and lactation period, and this association was still present at 7 and 12 years of age. Moreover, fish consumption in pregnancy was associated with better scores on verbal Intelligence Quotient in children aged 8 years (Oken and Belfort, 2010). Fish eating in pregnancy and lactation period are therefore likely important factors in relation to neurodevelopment in children.

Fatty acids in the maternal diet may have an impact on adipose tissue development during the fetal period. Both *in vitro* and animal studies have shown that *n-6* fatty acids stimulate the differentiation of immature preadipocytes to mature adipocytes, whereas *n-3* fatty acids (have the contrary effect. These studies further demonstrated that a reduction of ARA intake, a higher intake of *n-3* LC-PUFAs (i.e. DHA, EPA) and a resulting lower *n-6/n-3* fatty acid ratio was associated with less expansive adipose tissue development in the first year of life (Ailhaud and Guesnet, 2004; Aihaud, 2006). Recently, a prospective observational cohort study indicated that higher *n-3* PUFA levels (and lower *n-6/n-3* ratios) in the maternal diet and in umbilical cord were associated with lower adiposity in children at age 3 years and lower relative risk of obesity, and that the concentration of leptin was directly correlated with adiposity (Donahue *et al.*, 2011). A RCT is currently being performed to investigate the effect of lowering the *n-6/n-3* fatty acid ratio from the 15th week of gestation until 4 months after delivery on adipose tissue development in the offspring (Hauner *et al.*, 2009).

There is evidence that the risk to develop asthma is determined in part by the intrauterine environment and that intake of marine *n-3* PUFA in pregnancy may further have immuno-modulatory effects on the child. One small trial randomised atopic pregnant women to receive

3.7 g *n-3* PUFA/d from the 20th week of gestation until delivery. Neonatal cytokines tended to be lower in the fish oil group that was 3 times less likely to have positive skin prick test to egg (Dunstan *et al.*, 2003). The authors also reported lower numbers of infants at one year with recurrent wheeze in the fish oil group (Denburg *et al.*, 2005). In a larger trial with a longer follow-up, 533 women with normal pregnancies were randomly assigned around 30 weeks of gestation to receive fish oil providing 2.7 g *n-3* PUFA, olive oil, or no oils until delivery (Olsen *et al.*, 1992). Fish oil supplementation prolonged pregnancy (Olsen *et al.*, 1992), was associated with thromboxane and prostacyclin production (Sorensen et al., 1993) and raised concentrations of *n-3* fatty acids in umbilical cord blood and vessel walls (van Houwelingen *et al.*, 1995). A registry-based follow-up of the children (Olsen *et al.*, 2008) at 16 years of age showed that the hazard rate of both asthma and allergic asthma was significantly reduced in the fish oil compared with the olive oil group. The results from this trial support that increasing *n-3* PUFA in late pregnancy may carry an important prophylactic potential in relation to offspring asthma (Olsen *et al.*, 2008). Another multicenter, double-blind, RCT sought to investigate how supplementation of pregnant women with a fish oil preparation modulates allergy-related immune parameters in mothers and offspring. To this end 311 pregnant women received daily either fish oil methyl-tetra-hydrofolic acid, both, or placebo from the 22nd gestational week. Fish oil supplementation was associated with increased TGF-beta mRNA in maternal and cord blood while IL-1 and IFN-gamma were decreased in mothers only ($p < 0.001$). Cord blood mRNA levels of IL-4, IL-13, CCR4 and further natural killer cells and $CCR3^{+}CD8^{+}$ T cells were decreased in the fish oil group. These data indicate that maternal and fetal immunity are differentially affected (Krauss-Etschmann *et al.*, 2008).

PLACENTAL NUTRIENT TRANSFER: FATTY ACIDS

Mediating maternal-to-fetal transfer of nutrients and oxygen is one of the key functions of the placenta that is exposed to metabolites and hormones of the mother and the fetus. Any impairment may have consequences for the growing fetus and has been implicated as one reason for fetal growth restriction (Cetin and Alvino, 2009). Despite this significance, surprisingly little is known about the mechanism, regulation and derangement of lipid transfer processes in aberrant fetal growth.

Since dietary essential fatty acids and LC-PUFA are mainly transported in the maternal circulation in the form of either TG or phospholipids associated with lipoproteins, the maternal hyperlipidemia occurring during the last half of gestation increases the availability of those PUFA for placental transfer (Herrera and Lasuncion, 2011; Herrera and Ortega-Senovilla, 2010b). The presence of lipoprotein receptors in the placenta allows their uptake. In addition, placental tissue expresses lipoprotein lipase, phospholipase A2 and intracellular lipase activities. Esterified fatty acids in maternal lipoproteins are therefore hydrolyzed and taken up by the placenta, where their re-esterification and intracellular hydrolysis facilitate the released of fatty acids to the fetus (Herrera *et al.*, 2006).

LC-PUFA percentages in the lipids of cord plasma are higher than in maternal plasma at the time of birth (Herrera et al., 2004). Given the limited ability of the fetus and the human placenta to desaturate and elongate fatty acids, presumably associated also to individual genetic patterns (Morales et al., 2011), a preferential materno-fetal transfer of LC-PUFA has been suggested.

Figure 1 shows the placental handling of fatty acids. Fatty acids are released from maternal TG by endothelian lipase on the maternal surface of the placenta. The placental transfer of fatty acids is a complex process that involves their binding to membrane proteins and cytoplasmatic transport proteins. Fatty acids may be esterified in the placenta and cross the tissue in either direction. Recently, *in vitro* studies have identified placental plasma membrane fatty acid binding proteins (FABPs), which show a higher affinity and binding capacity for DHA and AA compared with linoleic acid (LA, C18:2n-6) and oleic acid (OA,C18:1n-9). Interestingly, a double blind RCT (European NUHEAL Study), in which healthy pregnant women received 500 mg DHA+150 mg EPA, 400µg 5-methyl-tetrahydrofolic acid, 500 mg DHA+400 µg 5-methyl-tetrahydrofolic acid, or placebo, showed a correlation of the mRNA expression of the membrane placental proteins FATP-1 and especially of FATP-4 with maternal and cord DHA, leading to the conclusion that these lipid carriers are involved in placental transfer of LC-PUFA (Larqué *et al.*, 2006). Importantly, whereas DHA or 5-methyl-tetrahydrofolic acid given singly had no effect, their combined administration resulted in signs of increased trophoblast proliferation (Klingler et al., 2006). Changes in fatty acid transport proteins are considered key mediators of cellular fatty acid uptake as demonstrated by transgenic and knockout animal models (Dodge and Stahl, 2006). Under *in vivo* conditions, the maternal administration of FFA labeled with stable isotopes before cesarean delivery, led to significantly higher placental uptake of [^{13}C]DHA suggesting that the placenta shows a preferential accretion of DHA relative to the other fatty acids (Larqué *et al.*, 2003).

Placental transfer of fatty acids has been investigated in maternal obesity and diabetes as well as in conditions of intrauterine growth restriction and a number of changes have been reported in

placental lipoprotein and endothelial lipases (Tabano *et al.*, 2006; Gauster *et al.*, 2007; Gauster *et al.*, 2011) as well as in lipoprotein receptors (Wadsack *et al.*, 2007), FATP and perilipins (Scifres *et al.*, 2011), confirming the role of the placenta in altering the composition of fetal nutrients in these pathologies of pregnancy (Cetin *et al*, 2012).

CONCLUSIONS

Many important nutritional matters need to be taken into account to achieve a successful pregnancy with optimal outcome for mother and child. Collectively, the role of macronutrients needs to be better understood in relation to recommendations for maternal diet. Both maternal DHA status and intake in pregnancy and DHA status of infants at birth, hampered by the genetic pattern, may be associated with the offspring's developmental performance, but the evidence is till not conclusive. A standardization of developmental tests performed on infants is needed, as well as long-term surveys to clarify the associations between early DHA-related developmental patterns and later cognitive ability, following adjustment for variant haplotypes involving e.g. the FADS 2 genes.

A call for adaptation of the recommendations of optimal gestational weight gain is also required in several subgroups of women, particularly in relation to lifestyle factors to develop reliable recommendations of energy intakes during pregnancy. Since the pre-conceptional nutritional status seems to play a key role in reproductive health, prenatal counselling starting from adolescence may represent an important intervention for controlling several potential risk factors for poor pregnancy outcome. This may increase general awareness of the importance of a healthy diet and lifestyle not only throughout pregnancy but also before through all the life-span.

Conflict of interest

The authors do not report a potential conflict of interest.

ACKNOWLEDGMENTS

The workshop on which this manuscript is based was funded by the charitable Child Health Foundation, Munich, Germany (Stiftung Kindergesundheit, www.kindergesundheit.de). BK is the recipient of a Freedom to discover Award of the Bristol Myers Squibb Foundation, New York, NY, USA. The work report herein has been carried out within the EURRECA Network of Excellence (www.eurreca.org) which is financially supported by the Commission of the European Communities, specific Research Technology and Development (RTD) Programme Quality of Life and Management of Living Resources, within the Sixth Framework Programme, contract no. 036196.

REFERENCES

- Abu-Sulaiman, R. M., and Subaih, B. (2004). Congenital heart disease in infants of diabetic mothers: echocardiographic study. *Pediatr Cardiol.* **25**: 137-140.
- Ahima, R. S., and Flier, J. S. (2000). Leptin. *Annu Rev Physiol.* **62**: 413–437.
- Alfaradhi, M. Z., and Ozanne, S. E. (2011). Developmental programming in response to maternal overnutrition. *Front Gene.* **2**: 27. doi:10.3389/fgene.2011.00027.
- Amianto, F., Lavagnino, L., Abbate-Daga, G., and Fassino, S. (2011). The forgotten psychosocial dimension of the obesity epidemic. *Lancet* **378**: e8.
- Ben-Haroush, A., Yogev, Y., Mashiach, R., and Meizner I. (2003). Pregnancy outcome of threatened abortion with subchorionic hematoma: possible benefit of bed-rest? *Isr Med Assoc J.* **5**: 422-424.
- Beyerlein, A., Schiessl, B., Lack, N., and von Kries, R. (2009). Optimal gestational weight gain ranges for the avoidance of adverse birth weight outcomes: a novel approach. *Am J Clin Nutr.* **90**: 1552-8.
- Butte, N. F., Wong, W. W., Treuth, M. S., Ellis, K. J., and O'Brian, Smith. E. (2004). Energy requirements during pregnancy based on total energy expenditure and energy deposition. *Am J Clin Nutr.* **79**: 1078–87.
- • Caspi, A., Williams, B., Kim-Cohen, J., Craig, I.W., Milne, B.J., Poulton, R., Schalkwyk, L.C., Taylor, A., Werts, H., and Moffitt, T.E. (2007). Moderation of breastfeeding effects on the IQ by genetic variation in fatty acid metabolism. *Proc Natl Acad Sci USA* **104**:18860-5.Cedergren, M. (2006). Effects of gestational weight gain and body mass index on obstetric outcome in Sweden. *Int J Gynaecol Obstet.* **93**: 269-74.Cetin, I. (2001). Amino acid

interconversions in the fetal-placental unit: the animal model and human studies in vivo. *Pediatr Res*. **49**: 148-154.

- Cedergren, M. I. (2007). Optimal gestational weight gain for body mass index categories. *Obstet Gynecol*. **110**: 759-764.
- Cetin, I., and Alvino, G. (2009). Intrauterine growth restriction: implications for placental metabolism and transport. A review. *Placenta* **30**: S77-S82.
- Cetin, I., Berti, C., and Calabrese, S. (2010). Role of micronutrients in the periconceptional period. *Hum Reprod Update* **16**: 80-95.
- Cetin, I., Morpurgo, P. S., Radaelli, T., Taricco, E., Cortelazzi, D., Bellotti, M., and Pardi, G. (2000). Fetal plasma leptin concentrations: relationship with different intrauterine growth patterns from 19 weeks to term. *Pediatr Res.* **48**:646-451.
- Cetin, I., Parisi, F., Berti, C., Mandò, C., and Desoye, G. (2012). Pplacental fatty acid transport in maternal obesity. *J DOHaD*: doi:10.1017/S2040174412000414.
- Denburg, J. A., Hatfield, H. M., Cyr, M. M.., Hayes, L., Holt, P. G., Sehmi, R., Dunstan, J. A., and Prescott, S. L. (2005). Fish oil supplementation in pregnancy modifies neonatal progenitors at birth in infants at risk of atopy. *Pediatr Res*. **57**: 276-81.
- Desoye, G., and Hauguel-de Mouzon, S. (2007). The human placenta in gestational diabetes mellitus. *Diab Care* **30**: S120-S126.
- Desoye, G., and Shafrir, E. (1994). Placental metabolism and its regulation in health and diabetes. *Mol Aspects Med*.**15**: 505-682.

- Devlieger, R., Casteels, K., and Van Assche, F. (2008). Reduced adaptation of the pancreatic B cells during pregnancy is the major causal factor for gestational diabetes: current knowledge and metabolic effects on the offspring. *Acta Obstet Gyn Scan.* **87**: 1266-70.
- Devlieger, R., Guelinckx, I., and Vansant, G. (2008). The impact of obesity on female reproductive function. *Obes Rev.* **9**: 181-2.
- Devlieger, R., Guelinckx, I., and Vansant, M. (2008). Follow-up in obese pregnant women to prevent stillbirth. *Am J Obstet Gynecol.* **99**: e17-8.
- Dodge, H., and Stahl, A. (2006). Protein-mediated fatty acid uptake: novel insights from in vivo models. *Physiology* **21**: 259-268.
- Donahue, S. M. A., Rifas-Shiman, S. L., Gold, D. R., Jouni, Z. E., Gillman, M. W., and Oken, E. (2011). Prenatal fatty acid status and child adiposity at age 3 y: results from a US pregnancy cohort. *Am J Clin Nutr.* **93**: 780–8.
- Drake, A. J, and Reynolds, R. M. (2010). Impact of maternal obesity on offspring obesity and cardiometabolic disease risk. *Reproduction* **140**: 387-98.
- Dunstan, J. A., Mori, T. A., Barden, A., Beilin, L. J., Taylor, A. L., Holt, P. G., and Prescott, S. L. (2003). Fish oil supplementation in pregnancy modifies neonatal allergen-specific immune responses and clinical outcomes in infants at high risk of atopy: a randomized, controlled trial. *J Allergy Clin Immunol.* **112**: 1178-84.
- Dunstan, J. A., Simmer, K., Dixon, G., and Prescott, S. L. (2008). Cognitive assessment of children at age 2(1/2) years after maternal fish oil supplementation in pregnancy: a randomised controlled trial. *Arch Dis Child Fetal Neonatal Ed.* 93: F45-50.

- Evers, I. M., de Valk, H. W., Mol, B. W., ter Braak, E. W., and Visser, G. H. (2002). Macrosomia despite good glycaemic control in type 1 diabetic pregnancy; results of a nationwide study in The Netherlands. *Diabetologia* **45**: 1484-1489.
- Fraser, R. B., and Rutter, S. (1999). Maternal diet and fetal substrate provision. *Curr Obstet Gynaecol.* **9**: 145 152.
- Gauster, M., Hiden, U., Blaschitz, A., Frank, S., Lang, U., Alvino, G., Cetin, I., Desoye, G., and Wadsack, C. (2007). Dysregulation of placental endothelial lipase and lipoprotein lipase in intrauterine growth-restricted pregnancies. *J Clin Endocrinol Metab.* **92**: 2256–2263.
- Gauster, M., Hiden, U., van Poppel, M., Frank, S., Wadsack, C., Hauguel-de Mouzon, S., and Desoye, G. (2011). Dysregulation of placental endothelial lipase in obese women with gestational diabetes mellitus. *Diabetes* **Doi***: 10.2337/db10-1434.*
- Godfrey, K. M., and Barker, D. J. P. (2001). Fetal programming and adult health. *Public Health Nutr.* **4**: 611-624.
- Grimble, R. F. (1998). Nutritional modulation of cytokine biology. *Nutr.* **14**: 634-640.
- Guelinckx, I., Devlieger, R., and Vansant, G. (2009). Reproductive outcome after bariatric surgery: a critical review. *Hum Reprod Update* **15**: 189-201.
- Guelinckx, I., Devlieger, R., Beckers, K., and Vansant, G. (2008). Maternal obesity: pregnancy complications, gestational weight gain and nutrition. *Obes Rev.* **9**: 140-50.
- Guelinckx, I., Devlieger, R., Mullie, P., and Vansant, G. (2010). Effect of lifestyle intervention on dietary habits, physical activity, and gestational weight gain in obese pregnant women: a randomized controlled trial. *Am J Clin Nutr.* **91**: 373-80.

- Hauguel-de Mouzon, S., Lepercq, J., and Catalano, P. (2006). The known and unknown of leptin in pregnancy. *Am J Obstet Gynecol.* **194**: 1537-45.
- Hauner, H., Vollhardt, C., Schneider, K. T. M., Zimmermann, A., Schuster, T., and Amann-Gassner, U. (2009). The impact of butritional fatty acids during pregnancy and lactation on early human adipose tissue development: rationale and design of the INFAT study. *Ann Nutr Metab.* **54**: 97-103.
- Helland, I. B., Smith, L., Blomen, B., Saarem, K., Saugstad, O. D., and Drevon, C. A. (2008). Effect of supplementing pregnant and lactating mothers with n-3 very-long-chain fatty acids on children's IQ and body mass index at 7 years of age. *Pediatrics* **122**: pe 472-9.
- Helland, I. B., Smith, L., Saarem, K., Saugstad, O. D., and Drevon, C. A. (2003). Maternal supplementation with very-long-chain n-3 fatty acids during pregnancy and lactation augments children's IQ at 4 years of age. *Pediatrics* **111**: pe39-44.
- Herrera, E. (2002). Implications of dietary fatty acids during pregnancy on placental, fetal and postnatal development—A review. *Placenta* **23**: S9–S19.
- Herrera, E., Ortega, H., Alvino, G., Giovannini, N., Amusquivar, E., and Cetin, I. (2004). Relationship between plasma fatty acid profile and antioxidant vitamins during normal pregnancy. *Eur J Clin Nutr.* **58**: 1231-8.
- Herrera, E., and Ortega-Senovilla, H. (2010a). Disturbances in lipid metabolism in diabetic pregnancy – Are these the cause of the problem? *Best Pract Res Clin Endocrinol Metabol.* **24**: 515-525.Herrera, E. and Ortega-Senovilla, H. (2010b). Maternal lipid metabolism during normal pregnancy and its implications to fetal development. *Clin Lipidol.* **5**: 899-911.

- Herrera, E., Amusquivar, E., López-Soldado, I., and Ortega, H. (2006). Maternal lipid metabolism and placental lipid transfer. *Horm Res.* **65**: S59-S64.
- Herrera, E., and Lasunción, M. A. (2011). Maternal-fetal transfer of lipid metabolites. **In**: Fetal and neonatal Physiology, 4th edition. pp. 441-454. Polin, R. A, Fox, W. W., and Abman, S. H., Eds., Elsevier, Saunders, Philadelphia.
- Hibbeln, J. R., Davis, J. M., Steer, C., Emmett, P., Rogers, I., Williams, C., and Golding, J. (2007). Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study): an observational cohort study. *Lancet* **369**: 578-85.
- Horvath, A., Koletzko, B., and Szajewska, H. (2007). Effect of supplementation of women in high-risk pregnancies with long-chain polyunsaturated fatty acids on pregnancy outcomes and growth measures at birth: a meta-analysis of randomized controlled trials. *Br J Nutr.* **98**: 253-9.
- Innis, S. M, and Friesen, R. W. (2008). Essential n-3 fatty acids in pregnant women and early visual acuity maturation in term infants. *Am J Clin Nutr.* **87**: 548-557.
- Innis, S. M. (2003). Perinatal biochemistry and physiology of long-chain polyunsaturated fatty acids. *J Pediatr.* **143**: S1-S8.
- Innis, S. M. (2005). Essential fatty acid transfer and fetal development. *Placenta* **26**: S70-S75.
- Innis, S. M. (2007). Fatty acids and early human development. *Early Human Devel.* **83**: 761–766.
- Jansson, T., Cetin, I., Powell, T. L., Desoye, G., Radaelli, T., Ericsson, A., and Sibley, C. P. (2006). Placental transport and metabolism in fetal overgrowth – a workshop report. *Placenta* **27**: S109-13.

- Jensen, C. L. (2007). Effects of n-3 fatty acids during pregnancy and lactation. *Am J Clin Nutr.* **83**: 1452S–7S.
- Jensen, C. L., Voigt, R. G., Prager, T. C., Zou, Y. L., Fraley, J. K., Rozelle, J. C., Turcich, M. R., Llorente, A. M., Anderson, R. E., and Heird, W. C. (2005). Effects of maternal docosahexaenoic acid intake on visual function and neurodevelopment in breastfed term infants. *Am J Clin Nutr.* **82**: 125-32.
- Judge, M. P., Harel, O., and Lammi-Keefe, C. J. (2007a). Maternal consumption of a docosahexaenoic acid-containing functional food during pregnancy: benefit for infant performance on problem-solving but not on recognition memory tasks at age 9 mo. *Am J Clin Nutr.* **85**: 1572-7.
- Judge, M. P., Harel, O., and Lammi-Keefe, C. J. (2007b). A docosahexaenoic acid-functional food during pregnancy benefits infant visual acuity at four but not six months of age. *Lipids* **42**:117-22.
- Kaissi, K. A., Klaushofer, K., and Grill, F. (2008). Caudal regression syndrome and popliteal webbing in connection with maternal diabetes mellitus: a case report and literature review. *Cases J.* **1**: 407.
- Kiel, D. W., Dodson, E. A., Artal, R., Boehmer, T. K., and Leet, T. L. (2007). Gestational weight gain and pregnancy outcomes in obese women: how much is enough? *Obstet Gynecol.* **110**: 752-8.
- Kitajka, K., Sinclair, A. J., Weisinger, R. S., Weisinger, H. S., Mathai, M., Jayasooriya, A. P., Halver, J. E., and, Puskás L. G. (2004). Effects of dietary omega-3 polyunsaturated fatty acids on brain gene expression. *Proc Natl Acad Sci USA* **101**:10931-6.

- Klebanoff, M. A., Harper, M., Lai, Y., Thorp, J. Jr, Sorokin, Y., Varner, M. W., Wapner, R. J., Caritis, S. N., Iams, J. D., Carpenter, M. W., Peaceman, A. M., Mercer, B. M., Sciscione, A., Rouse, D. J., Ramin, S. M., Anderson, G. D.; and Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units Network (MFMU) (2011). Fish consumption, erythrocyte fatty acids, and preterm birth. *Obstet Gynecol.* **117**: 1071-7.
- Klingler M, Blaschitz A, Campoy C, Caño A, Molloy AM, Scott JM, Dohr G, Demmelmair H, Koletzko B, Desoye G. The effect of docosahexaenoic acid and folic acid supplementation on placental apoptosis and proliferation. Br J Nutr. 2006;96:182-90.
- Koletzko, B., Lien, E., Agostoni, C., Böhles, H., Campoy, C., Cetin, I., Decsi, T., Dudenhausen, J. W., Dupont, C., Forsyth, S., Hoesli, I., Holzgreve, W., Lapillonne, A., Putet, G., Secher, N. J., Symonds, M., Szajewska, H., Willatts, P., Uauy, R.; and World Association of Perinatal Medicine Dietary Guidelines Working Group (2008). The roles of long-chain polyunsaturated fatty acids in pregnancy, lactation and infancy: review of current knowledge and consensus recommendations. *J Perinat Med.* **36**: 5-14.
- Koletzko, B., Symonds, M.E., and Olsen, S. F. for The Early Nutrition Programming Project and The Early Nutrition Academy (2011). Programming research: where are we and where do we go from here? *Am J Clin Nutr* **94**: 2036S-43S.
- Koletzko, B., von Kries, R., Monasterolo, R. C., Subías, J. E., Scaglioni, S., Giovannini, M., Beyer, J., Demmelmair, H., Anton, B., Gruszfeld, D., Dobrzanska, A., Sengier, A., Langhendries, J. P., Cachera, M. F., Grote, V.; and European Childhood Obesity Trial Study Group (2009). Infant feeding and later obesity risk. *Adv Exp Med Biol.* **646**: 15-29.

- Krakowiak, P., Walker, C. K., Bremer, A. A., Baker, A. S., Ozonoff, S., Hansen, R. L., and Hertz-Picciotto (2012). Maternal metabolic conditions and risk for autism and other neurodevelopmental disorders. *Pediatrics* **129**: e1121-8.
- Krauss-Etschmann, S., Hartl, D., Rzehak, P., Heinrich, J., Shadid, R., Del Carmen Ramírez-Tortosa, M., Campoy, C., Pardillo, S., Schendel, D. J., Decsi, T., Demmelmair, H., Koletzko, B. V.; and Nutraceuticals for Healthier Life Study Group (2008). Decreased cord blood IL-4, IL-13, and CCR4 and increased TGF-beta levels after fish oil supplementation of pregnant women. *J Allergy Clin Immunol.* **121**: 464-470.e6.
- Langer, O., Yogev, Y., Xenakis, E. M., and Brustman, L. (2005). Overweight and obese in gestational diabetes: the impact on pregnancy outcome. *Am J Obstet Gynecol.* **192**:1768-76.
- Larqué, E., Demmelmair, H., Berger, B., Hasbargen, U., and Koletzko, B. (2003). In vivo investigation of the placental transfer of ^{13C}-labeled fatty acids in humans. *J Lipid Res.* **44**: 49–55.
- Larqué, E., Krauss-Etschmann, S., Campoy, C., Hartl, D., Linde, J., Klingler, M., Demmelmair, H., Caño, A., Gil, A., Bondy, B., and Koletzko, B. (2006). Docosahexaenoic acid supply in pregnancy affects placental expression of fatty acid transport proteins. *Am J Clin Nutr.* **84**: 853– 61.
- Lauritzen, L., Jorgensen, M. H., Mikkelsen, T. B., Skovgaard, I. M., Straarup, E-M., Olsen, SF., Høy, C-E., and Michaelsen, K. F. (2004). Maternal fish oil supplementation in lactation: effect on visual acuity and n-3 fatty acid content of infant erythrocytes. *Lipids* **39**: 195-206

- Llorente, A. M., Jensen, C. L., Voigt, R. G., Fraley, J. K., Berretta, M. C., and Heird, W. C. (2003). Effect of maternal docosahexaenoic acid supplementation on postpartum depression and information processing. *Am J Obstet Gynecol.* **188**: 1348-53.
- Makrides, M., Duley, L., and Olsen, S. F. (2009). Marine oil, and other prostaglandin precursor, supplementation for pregnancy uncomplicated by preeclampsia or intrauterine growth restriction. *Cochrane Database Syst Rev.* **Doi**: 10.1002/14651858.CD003402.pub2.
- Makrides, M., Gibson, R., McPhee, A., Yelland, L., Quinlivan, J., Ryan, P., and the DOMInO Investigative Team. (2010). Effect of DHA supplementation during pregnancy on maternal depression and neurodevelopment of young children. *JAMA* **304**:1675-1683.
- Malcolm, C. A., McCulloch, D. L., Montgomery, C., Shepherd, A., and Weaver, L. (2003). Maternal docosahexaenoic acid supplementation during pregnancy and visual evoked potential development in term infants: a double blind, prospective, randomised trial. *Arch Dis Child Fetal Neonatal Ed.* **88**: F383-90.
- Morales, E., Bustamante, M., Gonzalez, J.R., Guxens, M., Torrent, M., Mendez, M., Garcia-Esteban, R., Julvez, J., Forns, J., Vrijheid, M., Molto-Puigmarti, C., Lopez-Sabater, C., Estivill, X., and Sunyer, J. (2011). Genetic variants of the FADS gene cluster and ELOVL gene family, colostrums LC-PUFA levels, breastfeeding, and child cognition. *PLoS One* **6**:pe17181
- Newnham, J. P., Moss, T. J. M., Nitsos, I., Sloboda, D. M., and Challis, J. R. G. (2002). Nutrition and the early origins of adult disease. *Asia Pacific J Clin Nutr.* **11**: S537-S542.
- Nizard, J., and Ville, Y. (2009). The fetus of a diabetic mother: Sonographic evaluation. *Semin Fetal Neonatal Med.* **14**: 101-5.

- Nohr, E. A., Vaeth, M., Baker, J. L., Sørensen, T. I. A., Olsen, J., and Rasmussen, K. M. (2008). Combined associations of prepregnancy body mass index and gestational weight gain with the outcome of pregnancy. *Am J Clin Nutr.* **87**: 1750 –9.Oken, E., and Belfort, M. B. (2010). Fish, fish oil, and pregnancy. *JAMA* **304**: 1717-8.
- Oken E, Kleinman KP, Belfort MB, Hammitt JK and Gillman MW, (2009). Associations of gestational weight gain with short- and longer-term maternal and child health outcomes. *Am J Epidemiol.* **170**: 173-180.
- Oken, E., Rifas-Shiman, S. L., Field, A. E., Frazier, A. L., and Gillman, M. W. (2008). Maternal gestational weight gain and offspring weight in adolescence. *Obstet Gynecol.* **112**: 999-1006.
- Oken, E., Taveras, E. M., Kleinman, K. P., Rich-Edwards, J. W., and Gillman, M. W. (2007). Gestational weight gain and child adiposity at age 3 years. *Am J Obstet Gynecol.* **196**: 322 e1-8.
- Olafsdottir, A. S., Skuladottir, G. V., Thorsdottir, I., Hauksson, A., Thorgeirsdottir, H., and Steingrimsdottir, L. (2006). Relationship between high consumption of marine fatty acids in early pregnancy and hypertensive disorders in pregnancy. *BJOG.* **113**: 301e9.
- Olsen, S. F., Østerdal, M. L., Salvig, J. D., Mortensen, L. M., Rytter, D., Secher, N. J., and Henriksen, T. B. (2008). Fish oil intake compared with olive oil intake in late pregnancy and asthma in the offspring: 16 y of registry-based follow-up from a randomized controlled trial. *Am J Clin Nutr.* **88**: 167-75.
- Olsen, S. F., Sorensen, J. D., Secher, N. J., Hedegaard, M., Henriksen, T. B., Hansen, H. S., and Grant A. (1992). Randomised controlled trial of effect of fish-oil supplementation on pregnancy duration. *Lancet* **339**: 1003-7.

- Ornoy, A. (2005). Growth and neurodevelopmental outcome of children born to mothers with pregestational and gestational diabetes. *Pediatr Endocrinol Rev.* **3**: 104-113.
- Pardi, G., and Cetin, I. (2006). Human fetal growth and organ development: 50 years of discoveries. *Am J Obstet Gynecol.* **194**: 1088–1099.
- Patel, S. P., Rodriguez, A., Little, M. P., Elliott, P., Pekkanen, J., Hartikainen, A. L., Pouta, A., Laitinen, J., Harju, T., Canoy, D., and Järvelin, M. R. (2011). Associations between pre-pregnancy obesity and asthma symptoms in adolescents. *J Epidemiol Community Health* **Doi**:10.1136/jech.2011.133777.
- Rasmussen, K. M., Catalano, P. M., and Yaktine, A. L. (2009). New guidelines for weight gain during pregnancy: what obstetrician/gynecologists should know. *Curr Opin Obstet Gynecol.* **21**: 521-6.
- Ravelli, A. C. J., van der Meulen, J. H. P., Michels, R. P. J., Osmond, C., Barker, D. J. P., Hales, C. N., and Bleker, O. P. (1998). Glucose tolerance in adults after prenatal exposure to famine. *Lancet* **351**: 173–77.
- Ravelli, A. C. J., van der Meulen, J. H. P., Osmond, C., Barker, D. J. P., and Bleker, O. P. (1999). Obesity at the age of 50 y in men and women exposed to famine prenatally. *Am J Clin Nutr.* **70**: 811–816.
- Rooney, K. and Ozanne, S. E. (2011). Maternal over-nutrition and offspring obesity predisposition: targets for preventative interventions. *Int J Obes.* **35**: 883-90. Roseboom, T. J., van der Meulen, J. H. P., Osmond, C., Barker, D. J. P., Ravelli, A. C. J., Schroeder-Tanka, J. M., van Montfrans, G. A., Michels, R. P. J., and Bleker, O. P. (2000). Coronary heart disease after prenatal exposure to the Dutch famine, 1944-45. *Heart* **84**; 595-598.

- Roseboom, T. J., van der Meulen, J. H. P., Ravelli, A. C. J., Osmond, C., Barker, D. J. P., and Bleker, O. P. (2001). Effects of prenatal exposure to the Dutch famine on adult disease in later life: an overview. *Mol Cell Endocrinol.* **185**: 93–98.
- Russell, N. E., Foley, M., Kinsley, B. T., Firth, R. G., Coffey, M., and McAuliffe, F. M. (2008). Effect of pregestational diabetes mellitus on fetal cardiac function and structure. *Am J Obstet Gynecol.* **199**: 312-317.
- Saldeen, P., and Saldeen, T. (2004). Women and omega-3 fatty acid. *Obstet Gynecol Surv.* **59**: 722-30.
- Salvig, J. D., and Lamont, R. F. (2011). Evidence regarding an effect of marine n-3 fatty acids on preterm birth: a systematic review and meta-analysis *Acta Obstet Gynecol Scand.* **90**: 825-38.
- Schaefer-Graf, U. M., Buchanan, T. A., Xiang, A., Songster, G., Montoro, M., and Kjos, S. L. (2000). Patterns of congenital anomalies and relationship to initial maternal fasting glucose levels in pregnancies complicated by type 2 and gestational diabetes. *Am J Obstet Gynecol.* **182**: 313-20.
- Schaefer-Graf, U. M., Graf, K., Kulbacka, I., Kjos, S. L., Dudenhausen, J., Vetter, K., and Herrera, E. (2008). Maternal lipids as strong determinants of fetal environment and growth in pregnancies with gestational diabetes mellitus. *Diab Care* **31**: 1858-63.
- Schaefer-Graf, U. M., Kjos, S. L., Kilavuz, O., Plagemann, A., Brauer, M., Dudenhausen, J. W., and Vetter, K. (2003). Determinants of fetal growth at different periods of pregnancies complicated by gestational diabetes mellitus or impaired glucose tolerance. *Diab Care* **26**: 193-8.

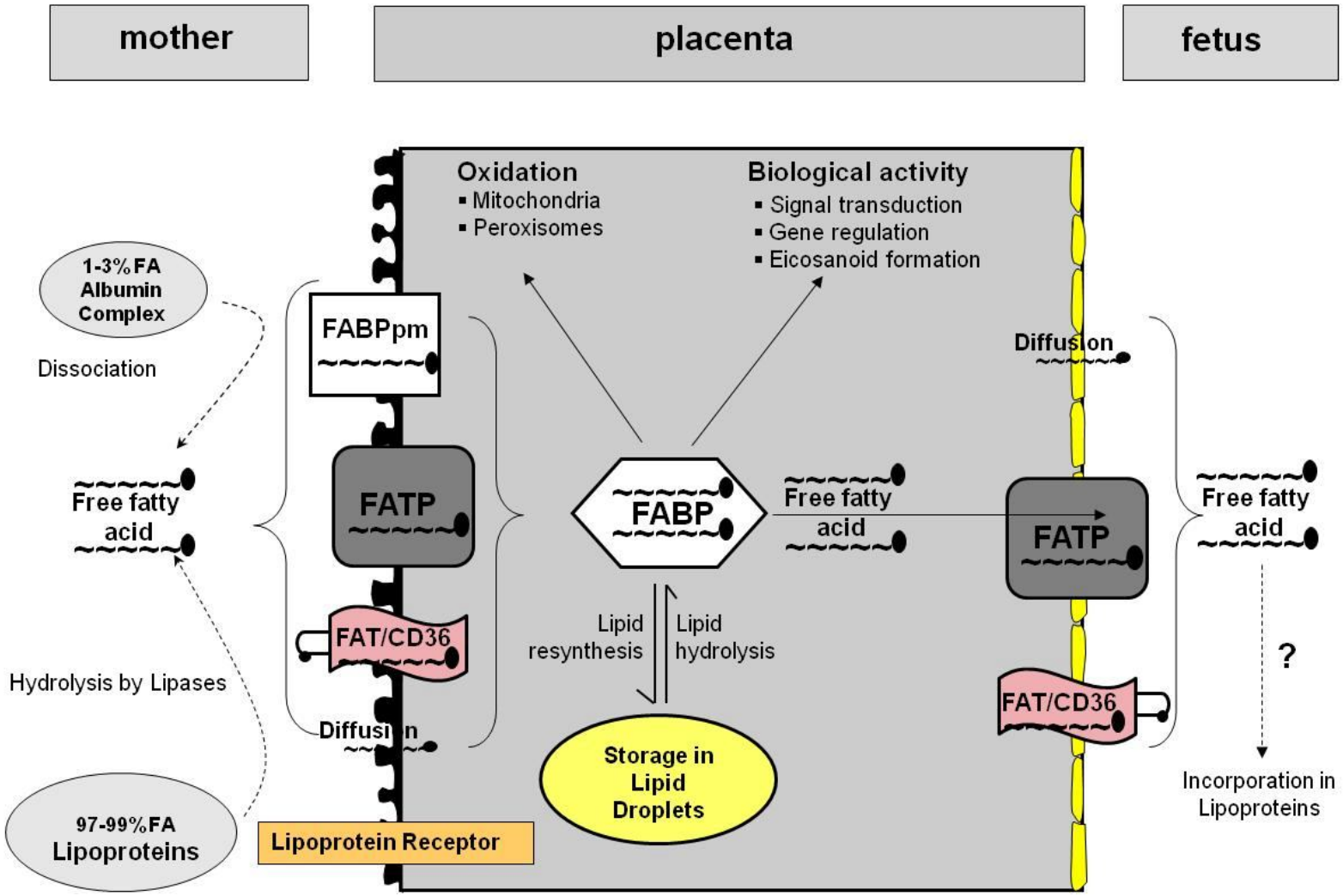
- Schaefer-Graf, U. M., Pawliczak, J., Passow, D., Hartmann, R., Rossi, R., Bührer, C., Harder, T., Plagemann, A., Vetter, K., and Kordonouri, O. (2005). Birth weight and parental BMI predict overweight in children from mothers with gestational diabetes. *Diab Care* **28**: 1745-50.
- Schwartz, R., Gruppuso, P. A., Petzold, K., Brambilla, D., Hillesmaa, V., and Teramo, K. A. (1994). Hyperinsulinemia and macrosomia in the fetus of the diabetic mother. *Diab Care* **17**: 640-648.
- Scifres, C. M., Chen, B., Nelson, D. M., and Sadovsky, Y. (2011). Fatty acid binding protein 4 regulates intracellular lipid accumulation in human trophoblasts. *J Clin Endocrinol Metab*. **96**: E1083–E1091.
- Sharkey, D., Fainberg, H. P., Wilson, V., Sebert, S., Bos, P., Bell, R., Gardner, D. S., Symonds, M. E., and Budge, H. (2009). Maternal nutrient restriction during pregnancy differentially alters the unfolded protein response in adipose and renal tissue of obese juvenile offspring. *FASEB J.* **23**: 1314-1324.
- Sibley, C. P., Turner, M. A., Cetin, I., Ayuk, P., Boyd, C. A., D'Souza, S. W., Glazier, J. D., Greenwood, S. L., Jansson, T., and Powell, T. (2005). Placental phenotypes of intrauterine growth. *Pediatr Res.* **58**: 827-832.
- Sorensen, J. D., Olsen, S. F., Pedersen, A. K., Boris, J., Secher, N. J., and FitzGerald, G. A. (1993). Effects of fish oil supplementation in the third trimester of pregnancy on prostacyclin and thromboxane production. *Am J Obstet Gynecol.* **168**: 915-22.
- Streuling I, Beyerlein A, von Kries R. (2010). Can gestational weight gain be modified by increasing physical activity and diet counselling? A meta-analysis of intervention trials. Am J Clin Nutr 92: 678-87.

- Symonds, M. E. (2009). Nutrition and its contribution to obesity and diabetes: a life-course approach to disease prevention? *Proc Nutr Soc.* **68**: 71–77.
- Symonds, M. E., and Budge, H. (2009). Nutritional models of the developmental programming of adult health and disease. *Proc Nutr Soc.* **68**: 173-8.
- Symonds, M. E., Stephenson, T., Gardner, D. S., and Budge, H. (2007). Long term effects of nutritional programming of the embryo and fetus: mechanisms and critical windows. *Reprod Fertil Dev.* **19**: 53–63.
- Tabano, S., Alvino, G., Antonazzo, P., Grati, F. R., Miozzo, M., and Cetin, I. (2006). Placental LPL gene expression is increased in severe intrauterine growth-restricted pregnancies. *Pediatr Res.* **59**: 250-3.
- Tanentsapf, I., Heitmann, B. L., and Adegboye, A. R. (2011). Systematic review of clinical trials on dietary interventions to prevent excessive weight gain during pregnancy among normal weight, overweight and obese women. *BMC Pregnancy Childbirth*. **11**: 81.
- The ESHRE Capri Workshop Group (2006). Nutrition and reproduction in women. *Hum Reprod Update* **12**: 193–207.
- Thorsdottir, I., Torfadottir, J. E., Birgisdottir, B. E., and Geirsson, R. T. (2002). Weight gain in women of normal weight before pregnancy: complications in pregnancy or delivery and birth outcome. *Obstet Gynecol.* **99**: 799-806.
- van Houwelingen, A. C., Sorensen, J. D., Hornstra, G.,and Simonis, M. M. G., Boris, J., Olsen, S. F., and Secher, N. J. (1995). Essential fatty acid status in neonates after fish-oil supplementation during late pregnancy. *Br J Nutr.* **74**: 723-31.

- Villamor, E., and Cnattingius, S. (2006). Interpregnancy weight change and risk of adverse pregnancy outcomes: a population-based study. *Lancet* **368**: 1164–70.
- Viswanathan, M., Siega-Riz, A. M., Moos, M. K., Deierlein, A., Mumford, S., Knaack, J., Thieda, P., Lux, L. J., and Lohr, K. N. (2008). Outcomes of maternal weight gain. *Evid Rep Technol Assess*. **168**: 1-223.
- von Kries, R., Ensenauer, R., Beyerlein, A., Amann-Gassner, U., Hauner, H., and Rosario, A. S. (2011). Gestational weight gain and overweight in children: Results from the cross-sectional German KiGGS study. *Int J Pediatr Obes.* **6**: 45-52.
- Wadsack, C., Tabano, S., Maier, A., Hiden, U., Alvino, G., Cozzi, V., Hüttinger, M., Schneider, W. J., Lang, U., Cetin, I., and Desoye, G. (2007). Intrauterine growth restriction is associated with alterations in placental lipoprotein receptors and maternal lipoprotein composition. *Am J Physiol Endocrinol Metab.* **292**: E476-84.
- Williams, C., Birch, E. E., Emmett, P., North, K. and the ALSPAC Study Team (2001). Stereoacuity at 3.5 years of age in children born full-term is associated with prenatal and postnatal dietary factors; a report from a population based cohort study. *Am J Clin Nutr*. **73**: 316-322.
- Wrotniak, B. H., Shults, J., Butts, S., and Stettler, N. (2008). Gestational weight gain and risk of overweight in the offspring at age 7 y in a multicenter, multiethnic cohort study. *Am J Clin Nutr*. **87**: 1818-24.
- Xu, Y., Cook, T. J., and Knipp, G. T. (2006). Methods for investigating placental fatty acid transport. *Methods Mol Med.* **122**: 265-84.
- Yogev, Y., and Visser, G. H. (2009). Obesity, gestational diabetes and pregnancy outcome. *Semin Fetal Neonatal Med.* **14**: 77–84.

Figure Legends

Figure 1. Fatty acids are released from maternal triacylglycerols and/or phospholipids by lipolytic activity (LP) on the maternal surface of the placenta. They are then taken up into the syncytiotrophoblast by various transporters and translocases. In the cytoplasm they are bound to fatty acid binding proteins. Several pathways of their subsequent utilization can be followed: (i) re-esterification and *de novo* formation of triglycerides, phospholipids and cholesterol esters. These components can then be stored in lipid droplets surrounded by proteins, which may be involved in subsequent mobilization of the stored lipids by hydrolysis. (ii) fatty acid oxidation in mitochondria and peroxisomes, (iii) activating peroxisome-proliferator activator receptors (PPARs) and (iv) conversion into eicosanoids, and participation in blood flow regulation. The mechanisms of fatty acid release from the syncytiotrophoblast into the fetal circulation are unclear as is the mechanism by which they become incorporated into fetal lipoproteins (Adapted from Xu *et al*., 2006).



ACCEPTED MANUSCRIPT