Maternal dietary omega-3 fatty acids and placental function

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Abstract

The developing fetus requires substantial amounts of fatty acids to support rapid cellular growth and activity. Although the fatty acid composition delivered to the fetus is largely determined by maternal circulating levels, the placenta preferentially transfers physiologically important long-chain polyunsaturated fatty acids (LC-PUFAs), particularly omega-3 (n-3) PUFAs. Maternal dietary supplementation with n-3 PUFAs during pregnancy has been shown to increase gestation length, enhance fetal growth, and reduce the risk of pregnancy complications, although the precise mechanisms governing these effects remain uncertain. Omega-3 PUFAs are involved in several physiological pathways which could account for these effects, including anti-inflammatory, pro-resolving, and anti-oxidative pathways. Recent studies have shown that maternal dietary n-3 PUFA supplementation during rat pregnancy can reduce placental oxidative damage and increase placental levels of pro-resolving mediators, effects associated with enhanced fetal and placental growth. Because several placental disorders, such as intrauterine growth restriction, preeclampsia, and gestational diabetes mellitus, are associated with heightened placental inflammation and oxidative stress, there is considerable interest in the potential for dietary n-3 PUFAs as a therapeutic intervention for these disorders. In this study, we review the impact of dietary n-3 PUFAs on placental function, with particular focus on placental inflammation, inflammatory resolution, and oxidative stress.

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Introduction

Fatty acids are important biological constituents with metabolic, structural, and signaling roles. The developing fetus requires substantial amounts of fatty acids to support rapid cellular growth and activity, and among these the omega-3 (n-3) and omega-6 (n-6) polyunsaturated fatty acids (PUFAs) are crucial (Haggarty 2010). The most biologically important n-3 and n-6 PUFAs are eicosapentaenoic acid (EPA; 20:5n-3), docosahexaenoic acid (DHA; 22:6n-3), dihomogamma linolenic acid (20:3n-6), and arachidonic acid (AA; 20:4n-6) (Haggarty 2010). While these long-chain PUFAs (LC-PUFAs) are metabolic derivatives of the essential fatty acids, α -linolenic acid, and linoleic acid (LA), their formation from these precursors is energetically demanding and so they are most readily obtained from the diet (McCowen & Bistran 2005).

Anthropological, nutritional, and genetic studies suggest that humans evolved on a diet consisting of n-6 and n-3 PUFAs in a ratio of around 1:1 (Simopoulos 2011). In contrast, modern dietary trends have led to a relative deficiency in n-3 PUFA consumption, and an n-6 PUFA intake which far exceeds nutritional requirements. Consequently, the n-6:n-3 PUFA ratio of the current

Western diet is ~ 10 – 20 :1, and this is thought to promote the pathogenesis of many prevalent human diseases (Simopoulos 2011). The n-3 PUFA, DHA, appears to be of particular importance to human health, with this fatty acid considered essential to the cerebral expansion in human evolution (Crawford & Broadhurst 2012). Accordingly, DHA is particularly crucial to fetal and infant neural development (see review, Rogers *et al.* (2013)).

Placenta-related disorders affect around one-third of pregnancies world-wide (Jauniaux *et al.* 2006); examples include intrauterine growth restriction (IUGR), preeclampsia (PE), gestational diabetes mellitus (GDM), and many cases of spontaneous miscarriage. Despite the differing pathologies of these disorders, each is associated with placental inflammation and oxidative stress (Burton & Jauniaux 2011), and possibly disturbed LC-PUFA delivery (Magnusson *et al.* 2004). Given that n-3 PUFAs exhibit both anti-oxidative and anti-inflammatory properties, maternal dietary n-3 PUFA supplementation has been proposed as a potential therapeutic intervention for placenta-related disorders. Indeed, maternal dietary supplementation with n-3 PUFAs during pregnancy can exert beneficial effects including increased gestation length and increased fetal growth (Imhoff-Kunsch *et al.* 2012, Larqué *et al.* 2012,

Jones *et al.* 2013a), and a reduced risk of pregnancy complications (Oken *et al.* 2007). In this study, we review the impact of dietary n-3 PUFAs on placental function, with particular focus on placental fatty acid transport, inflammation, inflammatory resolution, oxidative status, and angiogenesis.

Maternal dietary supply

The enzymes responsible for the synthesis of LC-PUFA from essential fatty acid precursors ($\Delta 5$ - and $\Delta 6$ -desaturases) are undetectable (Hanebutt *et al.* 2008) or expressed at very low levels in the placental tissue (Wadhvani *et al.* 2013). As such, placental synthesis of LC-PUFAs is unlikely to meet fetal demand, and the fetus must rely on maternal dietary supply and fatty acid stores to access physiologically important LC-PUFAs. We have recently shown that maternal, placental, and fetal fatty acid compositions are highly dependent on maternal dietary fatty acids in rat (Jones *et al.* 2013a). We also demonstrated that placental and fetal tissue levels of LC-PUFAs are positively correlated with their respective levels in maternal plasma during late gestation (Jones *et al.* 2013a), similar to observations in human pregnancy near term (Elias & Innis 2001). These studies highlight the capacity of maternal dietary fatty acids to effectively alter placental and fetal lipid environments.

Placental fatty acid transport

Adequate LC-PUFA delivery is critical for optimal fetal development. In particular, fetal accretion of DHA is essential for early development of the brain and the visual system (Rogers *et al.* 2013), and overall demand peaks during the final trimester of human pregnancy to accommodate rapid growth of the fetal brain (Duttaroy 2009). The placenta normally mediates adequate delivery of physiologically important PUFAs to the fetus by extracting and transporting fatty acids in a directional, preferential, and timely manner (Haggarty 2010). In pathological pregnancies (e.g. IUGR and GDM), however, disturbances in the molecular mechanisms governing placental fatty acid transport have been reported (Magnusson *et al.* 2004).

Placental regulation of fatty acid supply

The placenta may play a key role in the regulation of fatty acid availability via the release of placental-derived leptin, a potent stimulator of lipolysis (Haggarty 2004). Human placental BeWo trophoblast cells synthesise leptin and secrete it at both the apical and basal surfaces (Wyrwoll *et al.* 2005). Accordingly, the human placenta secretes leptin into both maternal and fetal circulations, although >95% of total leptin is released into the maternal compartment (Linnemann *et al.* 2000,

Lepercq *et al.* 2001), potentially acting to mobilize maternal fat stores. A study by Hoggard *et al.* (2001) has shown that placental leptin secretion increases as fetal:placental weight ratio increases, which as the authors suggest may enhance fatty acid availability as fetal requirement increases during late gestation.

Preferential placental fatty acid uptake and delivery

Comparisons between maternal and fetal plasma fatty acid levels demonstrate that transport of physiologically important LC-PUFAs occurs in a directional and preferential manner, closely correlating with fetal requirement (Haggarty 2010). This has been demonstrated following oral ingestion of stable isotope-labeled fatty acids by pregnant women 12 h before elective caesarean, where placental transfer of DHA was preferential to that of palmitic acid (16:0), oleic acid (OA; 18:1n-9), and LA (Gil-Sánchez *et al.* 2010).

Maternal circulating total fatty acid concentrations increase during late pregnancy (Gil-Sánchez *et al.* 2011), an effect driven by a shift from lipid storage in early pregnancy to lipid catabolism in late pregnancy, in part due to rising estrogen levels (Duttaroy 2009). This gestational hyperlipidemia enhances placental access to fatty acids. Placental lipoprotein lipase (LPL) and epithelial lipase, which are present in the maternal-facing microvillous membrane of the syncytiotrophoblast (Fig. 1), release fatty acids from maternal circulating triglyceride (TG)-rich lipoproteins to allow

Figure 1 Schematic representation of placental fatty acid transport mechanisms and potential metabolic fates within the placental tissue (modified from Hanebutt *et al.* (2008)). TGs, triglycerides; LPL, lipoprotein lipase; EL, epithelial lipase; NEFA, non-esterified fatty acid; FAT/CD36, fatty acid translocase; FATPs, fatty acid transport proteins; FABP, fatty acid-binding protein; FABPpm, plasma membrane FABP; p-FABPpm, placental plasma membrane FABP; PG, prostaglandin; LT, leukotriene; PC, prostacyclin; TX, thromboxane; PPAR, peroxisome proliferator-activated receptor; RXR, retinoic acid X receptor.

placental uptake of non-esterified fatty acids (NEFAs) (Gil-Sánchez *et al.* 2011). Concentrations of two NEFAs, DHA, and AA are three- to four-fold higher in the placental intervillous space than in the maternal circulation, at least around the time of delivery (Benassayag *et al.* 1997), suggesting placental lipases selectively release LC-PUFAs from TGs. Indeed, LPL is known to preferentially hydrolyse fatty acids in the second position of TGs, which tend to be less saturated (Christensen *et al.* 1995). Placental lipase activity increases during the final trimester of pregnancy, probably serving to enhance placental fatty acid delivery during the period of maximal fetal fatty acid requirement (Duttaroy 2009).

NEFAs may enter the placental syncytium by passive diffusion or via several membrane-bound carrier proteins (Fig. 1) including fatty acid translocase (FAT/CD36), fatty acid transport proteins (FATP1–6), plasma membrane fatty acid-binding protein (FABPpm), or placental plasma membrane FABP (p-FABPpm) (Hanebutt *et al.* 2008). Although the specific mechanisms of these proteins in placental fatty acid uptake, metabolism, and transfer are not fully understood, directional and preferential transfer of fatty acids across the placenta could be attributable to differences in the affinity of NEFAs for these proteins. For example, p-FABPpm exhibits higher affinity and binding capacity for DHA and AA compared with OA and LA (Campbell *et al.* 1998a). This carrier protein is also exclusively found in the microvillous membrane of the syncytiotrophoblast, potentially driving uni-directional transfer of LC-PUFAs from maternal to fetal compartments (Campbell *et al.* 1998b).

Once within the cell, NEFAs bind to cytosolic FABPs which facilitate intracellular fatty acid movement and interactions with subcellular organelles (Hanebutt *et al.* 2008, Gil-Sánchez *et al.* 2011). FABPs have increasing affinity for fatty acids with increasing chain length; however, binding affinity is tissue specific (Richieri *et al.* 2000) and FABP's binding specificity in placental tissue is currently unknown.

Regulation of placental fatty acid transport

Placental LC-PUFAs appear to act in an autocrine fashion to regulate their own uptake, transport, and metabolism. This is supported by reports showing that n-3 PUFA supplementation increases placental *FATP1* and *FATP4* mRNA expression in both human and rat (Larque *et al.* 2006, Wadhwani *et al.* 2013), presumably to further enhance LC-PUFA uptake. In addition, incubation of placental BeWo cells with LC-PUFAs (DHA, EPA, and AA) stimulates further cellular LC-PUFA uptake (Johnsen *et al.* 2009). Accordingly, we have recently reported that n-3 PUFA levels in rat placental labyrinth zone (LZ) are proportionally higher in n-3 PUFA-supplemented pregnancies than would be predicted based on control levels (Fig. 2; Jones *et al.* 2013a),

Figure 2 Linear regression analyses for n-3 PUFA composition (% of total fatty acids) of maternal plasma and placental LZ at (a) day 17 and (b) day 22 of rat pregnancy. This figure was originally published in Jones *et al.* (2013a). Mothers were fed either a standard (Std) or high n-3 PUFA (Hn3) diet from day 1 of pregnancy. There was no significant difference in the slope of the regression lines between the two diet groups. * $P < 0.05$ compared with elevation of regression line for the Std group (ANCOVA).

suggesting placental LZ uptake and retention of n-3 PUFAs is enhanced in response to heightened n-3 PUFA availability.

This autocrine effect may be mediated via a number of molecular regulators, including the peroxisome proliferator-activated receptors (PPARs). PPARs are ligand-activated nuclear transcription factors which play critical roles in metabolic, developmental, and inflammatory processes. Many PUFAs, including DHA, EPA, AA, and LA, are natural ligands for PPARs (Jawerbaum & Capobianco 2011), and all three PPAR isoforms (α , β/δ , and γ) are present in the placenta (Hewitt *et al.* 2006a). Knockout studies indicate that PPAR γ and β/δ are particularly important for placental development and vascularization (Jawerbaum & Capobianco 2011). Once activated, PPARs form heterodimers with retinoic acid X receptor; this complex then binds to the PPAR-response element (PPRE) in the promoter region of target genes to drive their expression. PPREs have been identified in the promoter regions of genes encoding fatty acid transport proteins (Frohnert *et al.* 1999, Schachtrup *et al.* 2004). Accordingly, oral supplementation of a PPAR γ agonist, rosiglitazone, has been shown to increase placental mRNA expression of *Fabppm*, *Fat* (*Cd36*), *Fatp1*, and *Fatp4* in mice, although *Fatp2*, *Fatp3*, and *Fatp6* were reduced (Schaiff *et al.* 2007). Interestingly, placental labyrinthine mRNA expression of *Ppara* and *Pparg* increased towards term in rat (Hewitt *et al.* 2006a), suggesting increased fatty acid trafficking at this time.

Omega-3 fatty acids and placental inflammation

Inflammation is the immediate response of the innate immune system, which serves to remove invading pathogens and promote regeneration of damaged tissues (Calder 2003). Pregnancy is often described as a state of controlled, mild, maternal, systemic inflammation, as evidenced by higher circulating levels of pro-inflammatory mediators in pregnant women compared

with non-pregnant women (Rusterholz *et al.* 2007). Pregnancy-related inflammation is proposed to play a key role in maternal tolerance of the semi-allogenic fetus (Paulesu *et al.* 2010), and induce maternal insulin resistance thereby enhancing glucose passage to the developing fetus (Parsons *et al.* 1992). Although pregnancy-related inflammation is considered adaptive, excessive placental inflammation is associated with a number of pregnancy disorders including preterm birth (Kemp *et al.* 2010), PE (Rusterholz *et al.* 2007), miscarriage (Kwak-Kim *et al.* 2009), IUGR (Amarilyo *et al.* 2011), and GDM (Kuzmicki *et al.* 2009).

Differential eicosanoid synthesis

Eicosanoids are important immunological messengers, which include prostaglandins (PGs), prostacyclins, thromboxanes (TX), and leukotrienes (LT). PGs are important regulators of parturition, with an involvement in promotion of cervical ripening, uterine contractility, regulation of placental blood flow, and fetal adaptations to labor (Keelan *et al.* 2003, Hertelendy & Zakár 2004). Eicosanoids, however, are also central to inflammatory activation, and excessive levels are associated with cellular damage.

In response to an inflammatory stimulus, phospholipase enzymes, primarily phospholipase A₂, release a 20-carbon PUFA (AA or EPA) from the cellular membrane, which is then metabolised either by cyclooxygenase (COX) enzymes to become a PG or TX, or by lipoxygenase-5 (LOX5) to become an LT (Fig. 3). COX1 is generally considered constitutive, whereas COX2 is rapidly induced by inflammatory stimuli (Calder 2003). Depending on the specific fatty acid derivative, eicosanoids can be either pro- or anti-inflammatory. As cellular membranes contain relatively high amounts of the n-6 PUFA, AA, this is the principle eicosanoid precursor (Calder 2003). AA-derived eicosanoids are primarily pro-inflammatory; acting to enhance local blood flow; increase pro-inflammatory cytokine; and reactive oxygen species (ROS) production, and bring about fever, erythema, pain, and edema (Calder 2003).

Dietary intake of n-3 PUFAs results in the partial replacement of AA by EPA in cellular membranes (Calder 2003). Thus, EPA acts as a competitive inhibitor of AA eicosanoid synthesis by decreasing AA availability in cellular membranes. In addition, EPA competes with AA for COX- and LOX5-active sites, the resultant eicosanoids which differ in structure and are far less biologically potent (Calder 2011). In contrast to the pro-inflammatory AA-derived eicosanoids, those derived from EPA are either directly anti-inflammatory or pro-inflammatory, but synthesis occurs at low efficiency or not at all (Calder 2003). Consequently, dietary n-3 PUFA supplementation can reduce inflammation by either disrupting pro-inflammatory eicosanoid generation or promoting the generation of anti-inflammatory forms.

Figure 3 Eicosanoid generation from LC-PUFAs, AA, and EPA. AA-derived eicosanoids are of the 2- or 4-series, and typically promote pro-inflammatory mechanisms. EPA-derived eicosanoids are of the 3- or 5-series, and either exert anti-inflammatory actions, are pro-inflammatory but relatively less potent, or disrupt pro-inflammatory eicosanoid generation by competitively inhibiting production.

During pregnancy, dietary n-3 PUFA supplementation from gestational week 20 has been shown to reduce LT production in neonatal neutrophils by gestational week 37 (Prescott *et al.* 2007). Similarly, pre-treatment of decidual cells with n-3 PUFAs *in vitro* decreased PG production, whereas production was enhanced with AA treatment (Arntzen *et al.* 1998).

Cytokine production

Cytokines are signaling molecules involved in a wide range of physiological processes, including inflammatory, immunosuppressive, cellular differentiation, and apoptotic pathways (Paulesu *et al.* 2010). Cytokines also play a central role in reproduction, allowing the maternal–fetal crosstalk required to coordinate the events of a successful pregnancy (Paulesu *et al.* 2010). During the early stages of pregnancy, the uterine inflammatory environment is characterized by increased pro-inflammatory cytokine production, which is important for embryo receptivity and implantation. Near term, levels of pro-inflammatory cytokines again increase rapidly, which is thought to stimulate the PG synthesis associated with parturition. Besides these two developmental stages, the majority of gestation is characterized by a predominance of anti-inflammatory cytokines allowing for uterine quiescence, and fetal growth and development (Paulesu *et al.* 2010). Excessive generation of pro-inflammatory cytokines throughout pregnancy is apparent in placental disorders, including recurrent spontaneous abortion and PE (Paulesu *et al.* 2010).

The ability of n-3 PUFAs to reduce pro-inflammatory cytokine levels has been demonstrated in rodent and human studies (see review, [Calder \(2011\)](#)). Despite this, surprisingly little is known regarding the impact of n-3 PUFAs on placental pro-inflammatory cytokine levels. [Stark et al. \(2013\)](#) recently demonstrated that DHA reduces lipopolysaccharide (LPS)-induced tumor necrosis factor α levels in term, but not in preterm, placental explants. In contrast, we found that maternal dietary n-3 PUFA supplementation in rat pregnancy did not suppress placental mRNA expression of key pro-inflammatory cytokines near term ([Jones et al. 2013b](#)). Interestingly, we also recently demonstrated that glucocorticoids, steroid hormones well recognized for their potent anti-inflammatory effects ([Vandevyver et al. 2013](#)), were similarly unable to suppress placental expression of pro-inflammatory cytokines in late gestation in rat ([Mark et al. 2013](#)). Collectively, these data suggest that placental inflammatory regulation during late gestation may be unconventional, possibly complicated by signaling pathways that promote parturition.

Fatty acid-activated transcription factors and receptors

The precise molecular mechanisms governing the anti-inflammatory effects of n-3 PUFAs are uncertain, although it has been proposed that they act to modulate the activity of key transcription factors (PPARs and/or nuclear factor κ B (NF κ B)) and receptors (i.e. G-protein-coupled receptor (GPR120)) involved in inflammatory signaling.

In addition to the involvement of PPARs in placental fatty acid trafficking described previously, they also mediate the expression of inflammatory genes. For example, activation of PPAR γ and/or PPAR β/δ can reduce the expression of COX2, inducible nitric oxide synthase (iNOS), cellular adhesion molecules, pro-inflammatory cytokines, and NF κ B target genes ([Bensinger & Tontonoz 2008](#), [Jawerbaum & Capobianco 2011](#)). Many PUFAs including DHA, EPA, AA, and LA are natural ligands to PPARs ([Jawerbaum & Capobianco 2011](#)), and therefore the anti-inflammatory effects of n-3 PUFAs may be mediated via PPAR activity. Perhaps surprisingly, the effect of dietary n-3 PUFA supplementation on placental PPAR activity is currently unknown.

Recently, membrane-associated GPR120, has been identified and implicated in anti-inflammatory signaling ([Oh et al. 2010](#)). Importantly, DHA and EPA, but not AA, palmitic, or myristic acids, promote GPR120-mediated gene activation ([Oh et al. 2010](#)). This suggests a unique role of this receptor in the mediation of n-3 PUFA-driven anti-inflammatory effects, but the specific role of GPR120 in the placenta has not yet been elucidated.

NF κ B is a nuclear transcription factor involved in a range of cellular functions, but is particularly

well characterized for its role in inflammation. Upon activation, NF κ B is able to translocate to the nucleus where it promotes the expression of pro-inflammatory cytokines, adhesion molecules, and iNOS and COX2 genes ([Calder 2011](#)). Dietary supplementation with n-3 PUFAs (EPA and DHA) has been shown to suppress NF κ B activity in several *in vivo* and *in vitro* studies (see review, [Calder \(2011\)](#)).

Omega-3 fatty acids and placental inflammatory resolution

Until recently, it was thought that the resolution of inflammation was a passive process, simply due to the eventual dissipation of pro-inflammatory signals. It is now clear, however, that inflammatory resolution is a highly active and coordinated process, largely driven by specialized pro-resolving lipid mediators (SPMs; [Recchiuti & Serhan 2012](#)). These SPMs, namely resolvins, protectins, maresins, and lipoxins, are directly derived from LC-PUFAs and are often regarded as specialized forms of eicosanoids due to their common generation by COX and LOX enzymes. Resolvins, protectins, and maresins are derived from n-3 PUFAs; resolvins can be generated from either EPA (E-series resolvins; RvE) or DHA (D-series resolvins; RvD), whereas protectins and maresins are derived only from DHA ([Recchiuti & Serhan 2012](#)). Maresins were only recently identified, and so evidence to confirm their anti-inflammatory and pro-resolving effects are limited. In contrast, the potential biological activity of resolvins and protectins has been confirmed by many *in vivo* and *in vitro* studies (for review see, [Recchiuti & Serhan \(2012\)](#)).

We have recently reported, for the first time, the presence of resolvins, protectins, and their precursors in the rat placental LZ ([Jones et al. 2013b](#)). Levels of these SPMs were relatively high in placental tissue, and the level of protectins increased toward term, suggesting an involvement in the maintenance of a healthy inflammatory balance, because pro-inflammatory signals rise markedly leading up to, and during, parturition ([Keelan et al. 2003](#)). Maternal dietary n-3 PUFA supplementation effectively increased placental levels of these pro-resolving mediators ([Jones et al. 2013b](#)), potentially enhancing the placental capacity to resolve inflammation. These findings highlight the therapeutic potential of n-3 PUFAs to limit placental inflammation associated with pregnancy disorders, although further functional studies in placental tissues are required.

Lipoxins are derived from the n-6 PUFA, AA, and have shown clear pro-resolving and anti-inflammatory activities in various *in vitro* and *in vivo* studies (for review see [Ryan & Godson \(2010\)](#)). With regard to the placenta, *in vitro* administration of lipoxin A₄ (LXA₄) reduced LPS-induced apoptosis, pro-inflammatory cytokine secretion, and NF κ B activity in human extravillous trophoblast

cells, and *in vivo* administration of the synthetic LXA₄ analog, BML111, during mid-gestation reduced low-dose LPS-induced placental pro-inflammatory cytokine mRNA expression in rat (Lin *et al.* 2012). Although these findings signify a potential for AA to promote pro-resolving effects via lipoxin generation, a balance must be met between these pro-resolving mediators and the potentially damaging effects of AA-derived pro-inflammatory eicosanoids.

Omega-3 fatty acids and placental oxidative stress

There is mounting evidence that excessive oxidative stress in utero-placental tissues plays a pivotal role in the development of pregnancy complications (Jauniaux *et al.* 2006, Burton & Jauniaux 2011). Oxidative stress occurs when cellular production of ROS, by-products of cellular respiration, exceeds the protective capacity of local antioxidant defences and thus causes damage to cellular components. ROS levels are limited by a range of antioxidant enzymes including the superoxide dismutase, catalase, glutathione peroxidase, and/or the thioredoxin system (Burton & Jauniaux 2011). Alternatively, oxidative damage may be limited by reduced ROS production. For example, it has been proposed that uncoupling proteins (UCPs) limit ROS generation by uncoupling oxidative phosphorylation (Mailloux & Harper 2011), a primary metabolic source of ROS. Oxidative stress can be exacerbated by inflammation and *vice versa*, as pro-inflammatory cytokines are produced in response to ROS and subsequently stimulate further ROS production by target cells (Burton & Jauniaux 2011).

The importance of limiting placental and fetal ROS exposure is highlighted during early pregnancy, while the earliest stages of embryonic and fetal development (approximately the first 10 weeks of human gestation) take place in a low oxygen environment (<20 mmHg) (Jauniaux *et al.* 2006). This hypoxia is thought to protect the rapidly dividing embryonic and fetal cells from ROS-mediated damage, and is achieved by the presence of trophoblastic 'plugs' preventing blood flow into the intervillous space. At ~11–14 weeks human gestation, these trophoblastic plugs detach, thus increasing blood flow and oxygen tension (>50 mmHg) as required to facilitate rapid growth of the fetus (Jauniaux *et al.* 2006). The onset of placental perfusion is accompanied by a rapid influx of ROS (Jauniaux *et al.* 2006) and an increased synthesis of enzymatic antioxidants to limit ROS-induced cellular damage (Jauniaux *et al.* 2000). Accordingly, the premature onset of full maternal–fetal circulation is associated with many miscarriages (Burton & Jauniaux 2011).

Placental ROS generation is high due to the high inherent metabolic activity of the placental cells; therefore all major antioxidant systems are present within the placenta (Perkins 2006, Jones *et al.* 2010).

The beneficial effect of limiting placental ROS levels has recently been shown by two separate studies. First, Umekawa *et al.* (2008) demonstrated that global over-expression of the antioxidant enzyme, thioredoxin-1, in mouse pregnancy reduced placental oxidative status and increased fetal growth. Similarly, we have recently demonstrated that maternal n-3 PUFA dietary supplementation reduced placental levels of F₂-isoprostanes, a highly reliable marker of oxidative damage (Fig. 4), which was associated with enhanced fetal and placental growth (Jones *et al.* 2013a). Collectively, these studies suggest that during normal pregnancy, placental ROS may tonically suppress fetal growth.

Omega-3 PUFAs could potentially limit oxidative damage by enhancing ROS scavenging capacity and/or by limiting ROS generation. We recently demonstrated that maternal n-3 PUFA supplementation enhanced mRNA expression and activity of major antioxidant enzymes in the placental LZ across the final third of rat pregnancy (Jones *et al.* 2013c), coincident with reduced placental oxidative damage (Jones *et al.* 2013a). These findings are consistent with an *in vitro* study, in which treatment of placental BeWo cells with modest levels of DHA reduced oxidative DNA damage and increased cell survival when challenged by an oxidative insult (Shoji *et al.* 2009). Similarly, in human placental explants, DHA administration reduced LPS-induced oxidative damage and restored antioxidant capacity (Stark *et al.* 2013). Dietary n-3 PUFAs may also reduce ROS generation, given that they increase *Ucp2* mRNA expression in mouse white adipose tissue (Hun *et al.* 1999) and rat myocytes (Hatakeyama & Scarpace 2001). Importantly, *UCP2* has been localized to human

Figure 4 Levels of F₂-isoprostanes (pg/mg tissue) in the female placental labyrinth and junctional zones at days 17 and 22 of rat pregnancy. This figure was originally published in Jones *et al.* (2013a). Mothers were fed either a standard (Std) or high omega-3 (Hn3) diet from day 1 of pregnancy. Values are mean $\pm$ S.E.M. ($n=4-8$ per group). * $P<0.05$ and ** $P<0.01$ overall compared with corresponding Std diet group in the same zone (two-way ANOVA; *post hoc* LSD); § $P<0.001$ compared with day 17 in the same zone (two-way ANOVA).

placental tissue, being predominantly expressed by the syncytiotrophoblast (Stark *et al.* 2012), although maternal dietary n-3 PUFA supplementation in the rat did not affect placental *Ucp2* mRNA expression in our recent study (Jones *et al.* 2013c). The effect of maternal n-3 PUFA supplementation on oxidative status of the early gestation placenta, and of particular interest during the onset of placental perfusion, is unknown.

Omega-3 fatty acids and placental angiogenesis

Omega-3 PUFAs typically inhibit angiogenic pathways, whereas n-6 PUFAs promote angiogenesis. This is supported by several *in vitro* studies, where n-3 PUFA administration has been shown to reduce formation of capillary-like structures (tubes) in a number of endothelial cell models (reviewed in Massaro *et al.* (2008)). *In vivo* evidence is currently limited to tumor-associated angiogenesis, whereby n-3 PUFA administration limits angiogenesis via reduced synthesis of pro-angiogenic AA-derived eicosanoids and transcriptional down-regulation of several growth factors (for review see Kang & Lui (2013)). In the placenta, however, n-3 PUFAs appear to promote rather than inhibit vascular development. This has been demonstrated by *in vitro* studies, where n-3 PUFA administration in the first trimester placental extravillous trophoblast cell line, HTR8/SVneo, upregulated angiogenic growth factors such as vascular endothelial growth factor-A (VEGF-A) and angiopoietin-like 4, which was associated with enhanced tubular network formation (Johnsen *et al.* 2011, Basak & Duttaroy 2013a,b). Interestingly, recent studies have suggested that in first trimester trophoblastic cells, n-3 PUFA-stimulated tube formation was associated with increased expression of *FABP4* associated with enhanced tube formation (Basak & Duttaroy 2013a,b). Whether *FABP4* directly mediates the placental pro-angiogenic response or simply reflects n-3 PUFA-driven fatty acid trafficking is unclear. Regardless, pro-angiogenic effects of n-3 PUFAs in the placenta may in part facilitate the enhanced fetal and placental growth observed in dietary n-3 PUFA-supplemented pregnant rats (Jones *et al.* 2013a). It is important to note, however, that possible angiogenic effects of n-3 PUFAs on the placenta are yet to be investigated in an *in vivo* model.

Interestingly, as placental *Pparg* expression increases over late gestation in rat (Hewitt *et al.* 2006a), expression of the angiogenic factor *Vegfa* similarly increases (Hewitt *et al.* 2006b). Accordingly, downregulation of placental *Pparg* expression by dexamethasone treatment (Hewitt *et al.* 2006a) is associated with reduced *Vegfa* expression and fetal capillary density in the placenta, indicating reduced placental angiogenesis (Hewitt *et al.* 2006b). Therefore, n-3 PUFA-stimulated activation of PPAR γ may be a key mediator of placental angiogenesis.

Potential risks of omega-3 dietary supplementation

Although there are potential benefits associated with dietary n-3 PUFA supplementation during pregnancy, it is also important to ascertain the potential risks, especially given that many women currently increase n-3 PUFA intake during gestation. It has been suggested that excessive dietary n-3 PUFA intake may exacerbate cellular damage caused by an oxidative insult. This is based on the susceptibility of n-3 PUFAs to lipid peroxidation, the by-products of which can damage cellular components (Al-Gubory 2012). An *in vitro* study on placental cells by Shoji *et al.* (2009) demonstrated enhanced lipid peroxidation and reduced cell survival in response to high levels of DHA administration (100 μ M), although modest levels (1 or 10 μ M) reduced DNA oxidative damage and enhanced cell survival rate. This was recently supported by Stark *et al.* (2013), who found high doses of DHA administration (100 μ M) in term placental explants enhanced lipid peroxidation and DNA oxidative damage, while more modest doses (1 or 10 μ M) reduced LPS-induced oxidative damage and restored antioxidant capacity. Our *in vivo* research has found that despite relatively high dietary n-3 PUFA supplementation in pregnant rats, placental levels of the ROS-induced lipid peroxidation marker, F₂-isoprostanes, were reduced (Fig. 4; Jones *et al.* 2013a). In contrast, Franke *et al.* (2010) have recently shown marginally higher plasma lipid peroxidation with n-3 PUFA supplementation in pregnant women, although the placental contribution to these enhanced levels is unknown. Further research is required to clarify the potential risks associated with enhanced dietary n-3 PUFA supplementation.

Concluding remarks

Overall, results from our research and others suggest that maternal dietary n-3 PUFA supplementation may provide a therapeutic intervention to limit placental inflammation and oxidative stress associated with several pregnancy disorders. Despite this, clinical trials of n-3 PUFA supplementation demonstrate conflicting results regarding pregnancy outcome (Imhoff-Kunsch *et al.* 2012, Larqué *et al.* 2012). It has been suggested that this is because supplementation is often begun during mid to late gestation (~22 weeks; Larqué *et al.* 2012). Maternal adipose tissue composition contributes significantly to fetal fatty acid accretion during late gestation. Therefore, small changes in the composition of habitual maternal diet before pregnancy, or during early pregnancy, are likely to have a large effect on LC-PUFA delivery to the fetus during late gestation (Haggarty 2004). Importantly, where our group has seen enhanced placental levels of pro-resolving mediators and reduced placental oxidative damage associated with maternal dietary n-3 PUFAs, supplementation began on day 1 of

rat pregnancy (Jones *et al.* 2013a,b). Perhaps surprisingly, the possible beneficial effects of early dietary n-3 PUFA supplementation on placental function in humans are unknown. Although recognizing the potential benefits of n-3 PUFA intake during pregnancy, the World Health Organization states that evidence is as yet insufficient to support routine supplementation with fish oil during pregnancy (World Health Organization 12.13.2011). The studies reviewed here provide a strong basis for investigation into the effects of n-3 PUFA supplementation from early pregnancy on placental function, with particular regard to inflammatory and oxidative status, in a clinical setting. It is also important to note that the large majority of studies in this area have each considered only one time period, generally in the second half of gestation, and so there is a clear need for additional studies on the effects of n-3 PUFAs on placental function at earlier stages of pregnancy.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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