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Postpartum changes in maternal and infant erythrocyte fatty acids are likely to be driven by restoring insulin sensitivity and DHA status

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ABSTRACT

Introduction: Perinatal changes in maternal glucose and lipid fluxes and *de novo* lipogenesis (DNL) are driven by hormones and nutrients. Docosahexaenoic acid (DHA) reduces, whereas insulin augments, nuclear abundance of sterol-regulatory-element-binding-protein-1 (SREBP-1), which promotes DNL, stearoyl-CoA-desaturase (SCD, also Δ9-desaturase), fatty acid-(FA)-elongation (Elovl) and FA-desaturation (FADS). Decreasing maternal insulin sensitivity with advancing gestation and compensatory hyperinsulinemia cause augmented postprandial glucose levels, adipose tissue lipolysis and hepatic glucose- and VLDL-production. Hepatic VLDL is composed of dietary, body store and DNL derived FA. Decreasing insulin sensitivity increases the contribution of FA from hepatic-DNL in VLDL-triacylglycerols, and consequently saturated-FA and monounsaturated-FA (MUFA) in maternal serum lipids increase during pregnancy. Although other authors described changes in maternal serum and RBC essential-FA (EFA) after delivery, none went into detail about the changes in non-EFA and the mechanisms behind -and/or functions of- the observed changes.

Hypothesis: Postpartum FA-changes result from changing enzymatic activities that are influenced by the changing hormonal milieu after delivery and DHA-status.

Empirical data: We studied FA-profiles and FA-ratios (as indices for enzymatic activities) of maternal and infant RBC at delivery and after 3 months exclusive breastfeeding in three populations with increasing freshwater-fish intakes. DNL-, SCD- and FADS2-activities decreased after delivery. Elongation-6 (Elovl-6)- and FADS1-activities increased. The most pronounced postpartum changes for mothers were increases in 18:0, linoleic (LA), arachidonic acid (AA) and decreases in 16:0, 18:1ω9 and DHA; and for infants increases in 18:1ω9, 22:5ω3, LA and decreases in 16:0 and AA. Changes were in line with the literature.

Discussion: Postpartum increases in 18:0, and decreases in 16:0 and 18:1ω9, might derive from reduced insulin-promoted DNL-activity, with more reduced SCD- than Elovl-activity that leaves more 16:0 to be converted to 18:0 (Elovl-activity) than to MUFA (SCD-activity). Postpartum changes in ΣDNL, saturated-FA and MUFA related negatively to RBC-DHA. This concurs with suppression of both SCD- and Elovl-6 activities by DHA, through its influence on SREBP. Infant MUFA and LA increased at expense of their mothers. Sustained transport might be important for myelination (MUFA) and skin barrier development (LA). Maternal postpartum decreases in FADS2-, and apparent increases in FADS1-activity, together with increases in LA, AA, and

Abbreviations: AA, arachidonic acid; ACC, acetyl-Coenzyme A carboxylase; ALA, α-linolenic acid; ChREBP, carbohydrate responsive element binding protein; DHA, docosahexaenoic acid; DNL, *de novo* lipid synthesis or *de novo* lipogenesis; EFA, essential fatty acids; Elovl-6, elongation of very long chained fatty acids family member 6; EPA, eicosapentaenoic acid; FA, fatty acids; FADS, fatty acid desaturase; FAS, fatty acid synthase; LA, linoleic acid; LXR, liver-X-receptor; MUFA, monounsaturated fatty acids; RBC, erythrocyte; PP, postpartum; PUFA, polyunsaturated fatty acids; SAFA, saturated fatty acids; SCD-1, stearoyl-Coenzyme A desaturase family member 1; SREBP-1, sterol regulatory element binding protein-1; VLDL, very low density lipoprotein.

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fer to the incorporation into milk lipids and discontinued placental AA-utilization.
Implications: Perinatal changes in maternal and infant FA status may be strongly driven by changing insulin sensitivity and DHA status.

Introduction

Long chain polyunsaturated fatty acids (LCP-FA) of the ω3 (LCPω3) and ω6 series (LCPω6) are important across the entire life cycle [1], but notably during infant development. LCP can be derived from (fatty) fish (docosahexaenoic acid; DHA, 22:6ω3) and from meat and eggs (arachidonic acid, AA, 20:4ω6) or derive from endogenous synthesis from the parent essential FA (EFA; linoleic acid, LA, 18:2ω6 and alpha-linolenic acid, ALA, 18:3ω3) by consecutive steps of desaturation and elongation, in which FADS1 (Δ5-desaturase) and especially FADS2 (Δ6-desaturase) are rate limiting [2–5]. LCP are abundant in brain [6] and the absolute content of infant brain AA and DHA increase rapidly from the last trimester of pregnancy up to 2 years postpartum [7]. Insufficient LCPω3 intakes have been implicated in suboptimal (neuro)development, cardiovascular disease and (neuro)psychiatric disease [1]. Obstetric complications such as pregnancy-induced hypertension, gestational diabetes, preeclampsia and type 2 diabetes mellitus in pregnancy are characterized by a relative LCP deficiency, that is likely to be caused by the dilution of LCP by fatty acids that derive from glucose by hepatic *de novo* lipogenesis (DNL) [8,9].

Hypothesis

We hypothesize that the changing hormonal milieu at the end of pregnancy and the maternal LCPω3 status might influence the magnitudes of both DNL and LCP-synthesis.

Our attention towards the possible influence of the changing hormonal milieu at the end of pregnancy and the possible influence of LCPω3 on DNL and LCP-synthesis was drawn after we studied the postpartum changes in the erythrocyte (RBC) non-EFA and EFA composition of mothers, and their exclusively breastfed infants, with increasing LCPω3 intakes [10], as derived from their highly different intakes of tropical freshwater fish [11] and as confirmed by their increasing LCPω3 intakes [12]. At the time we did not measure fasting insulin and glucose levels, nor did we perform oral glucose tolerance tests to verify insulin sensitivity in the pregnancy-end or after 3 months lactation. However, the decreasing insulin sensitivity with advancing gestation [13] and its rapid restoration thereafter are well known [14]. Secondly, after obtaining our results we believe that our data showed several arguments for the influence of both the hormonal milieu at the end of pregnancy and the influence of LCPω3 on DNL and LCP synthesis. In this article we review the literature and discuss the outcomes of our study in the light of the changing insulin sensitivity during pregnancy and with regard to the influence of the concurrent LCPω3 status.

Evaluation of the hypothesis

Glucose transport across the placenta is unrestricted, while FA cross with more difficulty [15]. There is sufficient evidence to state that maternal insulin sensitivity decreases with advancing gestation [13,15–18]. The decreasing maternal insulin sensitivity and compensatory hyperinsulinemia facilitate transplacental nutrient transfer by causing a unique combination of augmented glucose production [13], elevated postprandial glucose levels [13], adipose tissue lipolysis [18] and increased hepatic VLDL production [18] that is likely to result in part from augmented DNL. Interestingly, one study in an East African population described reduced postprandial glucose levels in pregnant compared to non-pregnant women [19], but unfortunately did not investigate concomitant insulin levels to evaluate actual insulin sensitivity.

The liver synthesizes VLDL from FA that are derived from the diet, stores and DNL (which is directed at $\geqslant$16:0 in the liver) [18,20]. Within the liver, saturated-FA (SAFA) may become desaturated by stearoyl-CoA desaturase (SCD) to form mono-unsaturated-FA (MUFA) such as 16:1ω7 and 18:1ω9 [21], while elongation of 16:0, 16:1ω7 and 18:1ω9 by 'elongation of very long chain fatty acids family member 6' (Elovl-6) will form 18:0, 18:1ω7 and 20:1ω9, respectively [22]. High carbohydrate intakes and insulin resistance in humans increase the contribution of FA from hepatic DNL in VLDL-triacylglycerols (TG) [23,24]. Animal studies confirm that insulin positively influences the activities of the enzymes involved in DNL (i.e. FA synthase, FAS and acetyl-Coenzyme A carboxylase, ACC), SCD, Elovl-6, and the desaturase enzymes FADS1 and FADS2 [3,20,22,25]; while glucose also has positive effects on DNL, SCD and Elovl-6 [20], but negative effects on FADS1 and FADS2 activities [3]. In contrast, DHA is a potent suppressor of DNL, SCD, Elovl-6 and also of FADS1 and FADS2 [4,25]. Changes in enzymatic activities have been correlated to their enzyme product/EFA ratios (DNL activity index) and enzyme product/substrate ratios (SCD, Elovl-6, FADS1 and FADS-2 activity indices) in serum lipids [22,26–30] and adipose tissue [31], although no data are available for these indices in RBC.

The increasing insulin resistance towards the pregnancy-end causes the 'hyperlipidemia of pregnancy' that is characterized by consistent increases in maternal plasma phospholipids (PL) and RBC SAFA and MUFA [32–35]. These derive from DNL and adipose tissue lipolysis and cause a relative dilution of PUFA with advancing gestation. Lower PUFA might in addition be explained by the selective transfer of LCP across the placenta ('biomagnification'), which is in contrast to SAFA, MUFA and their parent EFA [36].

After delivery, the rapidly changing hormonal milieu and notably the restoring insulin sensitivity [13,14], may be expected to drive tremendous FA changes that become reflected in the RBC-FA composition. These changes are mostly opposite to those observed during pregnancy. In addition, the nutrient supply becomes rerouted from transplacental transfer to breastfeeding and fat becomes the infant's main energy source. In contrast to the liver, conversion of SAFA to MUFA via SCD or chain-elongation via Elovl-6 [37,38] is limited in the lactating breast, and so is FADS-activity [39]. Humans have little capacity to convert EFA to LCP [40]. Consequently, the developing infant derives its LCP mainly from breast milk that on its turn derives the LCP mainly from maternal long term storage organs (70%) and to a lesser extent from the diet (30%) [39,41].

The FA composition of the maternal stores might become reflected in the course of the maternal plasma PL-FA and RBC-FA. Lactating women show postpartum increases of LA, AA, eicosapentaenoic acid (EPA, 20:5ω3) and 22:5ω3 to, and even beyond, pre-pregnancy values, while DHA decreases below preconceptional values [42]. The infant' demands might be reflected in the courses of the infant plasma PL-FA and RBC-FA that show consistent increases of LA, 18:0 and 18:1ω9, and a decrease of 16:0 after delivery [43–45]. Infants also show a consistent decrease of AA, while DHA