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Placental Fatty Acid Transport Across Late Gestation in a Baboon Model of Intrauterine Growth Restriction

Stephanie S. Chassen[1], **Veronique Ferchaud-Roucher**[2,3], **Claire Palmer**[1], **Cun Li**[4,5], **Thomas Jansson**[3], **Peter W. Nathanielsz**[4,5], **Theresa L. Powell**[1,3]

[1]Department of Pediatrics, Section of Neonatology, University of Colorado Anschutz Medical Campus, Aurora, CO, USA

[2]University of Nantes, CHU Nantes, INRA, UMR 1280 Physiology of Nutritional Adaptations, F-44000 Nantes, France

[3]Department of Obstetrics & Gynecology, Division of Reproductive Sciences, University of Colorado Anschutz Medical Campus, Aurora, CO, USA

[4]Department of Animal Science, University of Wyoming, Laramie, WY, USA

[5]Southwest National Primate Research Center, San Antonio, TX, USA

Abstract

Intrauterine growth restriction (IUGR) is associated with specific changes in placental transport of amino acids, folate, and ions. However, little is known about placental fatty acid (FA) transport in IUGR. We hypothesized that placental FA transport proteins (FATP) and FA binding proteins (FABP) are up-regulated and fetal plasma FA concentrations are decreased at term in a baboon model of IUGR. Pregnant baboons were fed control or maternal nutrient restricted (MNR) diet (70% of control calories) from gestation day (GD) 30 (term 184 days). Plasma and placental samples were collected at GD120 (control n = 8, MNR n = 9), GD140 (control n = 6, MNR n = 7), and GD170 (control n = 6, MNR n = 6). Placentas were homogenized, and syncytiotrophoblast microvillous plasma membrane (MVM) and basal plasma membranes (BM) were isolated. Protein expression of FABP1, 3, 4, and 5 (homogenate) and FATP2, 4, and 6 (MVM, BM) was determined by Western blot. FA content in maternal and umbilical vein plasma was measured by GC-MS. Placental FABP1 and FABP5 expression was increased in MNR compared to control at GD170, as was MVM FATP2 and FATP6 expression at GD140 and FATP2 expression at GD170. BM FATP4

Correspondence: Stephanie Skuby Chassen, MD, 13121 E. 17th Avenue, Mail Stop 8402, Aurora, CO 80045; stephanie.chassen@cuanschutz.edu.

Author profile:

Stephanie Chassen, MD is an Assistant Professor of Pediatrics in the section of Neonatology at the University of Colorado. Her clinical interests are in neonatal growth and neurodevelopment, with a research focus on placental nutrient transfer and fetal growth. She currently studies placental fatty acid transfer using different models of intrauterine growth restriction.

Author contributions

PWN designed the experimental protocol and both PWN and CL provided the study samples. TJ and TLP designed the research studies. SSC conducted the Western blot and lipid extraction experiments in TJ/TLP lab, analyzed the results, and wrote the manuscript. VFR, TJ, and TLP supervised the experiments. VFR analyzed and quantified the lipid extraction data using GC/MS. CP developed the statistical model for analysis. All authors discussed the results, edited the manuscript and approved the final version.

Additional Information

Competing Interests

The authors report no conflicts of interest in this work.

and FATP6 expression was increased in MNR at GD140. Fetal plasma FA concentrations were similar in control and MNR. These data suggest adaptation of placental transport to maintain delivery of critically needed FAs for fetal growth and brain development.

Keywords

maternal nutrient restriction; maternal-fetal exchange; fetal growth; fatty acid transport proteins; fatty acid binding proteins; long chain polyunsaturated fatty acids

Introduction

Human intrauterine growth restriction (IUGR) is generally defined as failure of the fetus to reach its genetic growth potential and is associated with perinatal morbidity, neurodevelopmental deficits, and increased risk of cardiovascular disease, obesity and diabetes in adulthood (Barker 1998; Ozanne et al. 2004; Fowden et al. 2006; Gluckman et al. 2008). The most common cause of IUGR in developed countries is placental insufficiency, characterized by a lack of normal gestational increase in uteroplacental blood flow, altered placental function, and decreased umbilical blood flow. The activity of several critical nutrient transport systems is decreased in placentas of human IUGR, including the activity of Systems A and L (amino acid transporters), Na^+/proton exchanger, and Na^+K^+ATPase (Mahendran et al. 1993; Glazier et al. 1997; Jansson et al. 2002; Johansson et al. 2002; Johansson et al. 2003). In contrast, unchanged transporter expression and activity of glucose (Jansson et al. 1993) and increased placental Ca^{2+}ATPase expression and activity (Strid et al. 2003) have been reported in IUGR placentas. However, placental fatty acid (FA) transport has not been studied in detail in IUGR pregnancies.

Long chain polyunsaturated fatty acids (LCPUFA) such as docosahexaenoic acid (DHA) and arachidonic acid (AA) are critical for normal brain development. IUGR infants are at risk for the development of impaired cognitive function in childhood and as young adults (Naeye & Peters, 1987; Berg 1989; Ley et al. 1996), but whether these deficits are related to decreased transplacental supply of LCPUFAs is unknown. In addition, IUGR infants have markedly decreased subcutaneous fat depots, which adversely influences thermoregulation in the neonatal period and could impair postnatal brain development that is dependent on a supply of DHA and AA from adipose tissue reserves (Larciprete et al. 2005). One critical factor determining fetal fat deposition is placental transport of FA. The activity of desaturation and elongation enzymes necessary for LCPUFA formation is low or absent in the fetus and placenta (Haggarty et al. 1997; Ferchaud-Roucher et al. 2019); therefore, LCPUFA must be transferred from the mother across the syncytiotrophoblast, the transport epithelium of the placenta, and the fetal capillary endothelium.

The mechanisms mediating transplacental transport of FA in normal pregnancy are poorly understood and little is known about placental FA transport in IUGR. During normal human pregnancy, there is a pronounced increase throughout gestation in the concentration of maternal circulating lipids, composed of triglycerides, phospholipids, cholesterol ester and non-esterified FA (Haggarty 2010). These lipids serve as the primary FA source for placental transfer to the growing fetus. Maternal triglycerides are hydrolyzed into non-esterified or

"free" FA by specific lipases including lipoprotein lipase (LPL) and endothelial lipase (EL) expressed in the syncytiotrophoblast microvillous plasma membrane (MVM), which is bathed in maternal blood (Lager & Powell, 2012). Although some FA may be transferred across the MVM by simple diffusion, most long chain FA are believed to be taken up into the syncytiotrophoblast by membrane-bound FATPs and fatty acid translocase (FAT/CD36). Once in the syncytiotrophoblast cytoplasm, FA are bound to FABPs and transferred to mitochondria for oxidation or endoplasmic reticulum for re-esterification and lipid droplet formation. Alternatively, these FA are transferred to the fetal circulation across the fetal-facing syncytiotrophoblast basal plasma membrane (BM), likely mediated by FATPs (Haggarty 2010; Brett et al. 2014).

Magnusson and co-workers reported a decreased LPL activity in syncytiotrophoblast microvillous plasma membraes isolated from preterm IUGR placentas (Magnusson et al. 2004). Recently, we found increased protein expression of two FATPs-FATP6 and CD36- in MVM isolated from human IUGR placentas compared to gestational age-matched placentas of appropriately grown for gestational age (AGA) infants (Chassen et al. 2018). Moreover, IUGR was associated with preferential placental accumulation of LCPUFAs as triglycerides, a cellular storage form (Chassen et al. 2018). These findings suggest that IUGR fetuses have abnormal placental lipid metabolism resulting in increased LCPUFA storage compared to placentas of AGA fetuses. Therefore, even with increased transporter expression, FA levels in the fetus may be compromised.

Given the striking similarities in placental structure and the close evolutionary relationship with humans (Graves et al. 1995; Perelygin et al. 1996; Rogers & Hixson, 1997; Rogers et al. 2000), studies in the non-human primate are highly relevant for understanding placental function in women. The human placenta is largely inaccessible prior to delivery and there are currently no approaches to measure placental functions such as nutrient transport across gestation in women. Importantly, our well-established baboon model of 30% global maternal nutrient restriction (MNR) is associated with moderate IUGR close to term, reduced fetal circulating levels of essential amino acids, inhibition of placental mTOR signaling, down-regulation of placental amino acid transport (Kavitha et al. 2014) and peripheral insulin resistance in the offspring (Choi et al. 2011). Thus, this model replicates key features of placental insufficiency in the human. In the current study, we determined the changes in placental expression of FATPs and FABPs across late gestation as well as changes in maternal and cord venous plasma FA content in the MNR baboon model of IUGR. Similarly to our human data, we hypothesized that placental FATPs and FABPs are up-regulated and fetal plasma FA concentrations are decreased in MNR.

Materials and Methods

Ethical Approval

All animal procedures were approved by the Texas Biomedical Research Institute Institutional Animal Care and Use Committee (#1134 PC) and conducted in facilities approved by the Association for the Assessment and Accreditation of Laboratory Animal Care. All procedures conducted in this study comply with the principles and policies outlined by Grundy (2015), under which *The Journal of Physiology* operates.

Animal Housing and Care

Baboons (*Papio* species) were part of a baboon colony maintained by the Southwest National Primate Research Center at the Southwest Foundation for Biomedical Research (SFBR) and were housed in groups of 10–16 females with one male in outdoor metal and concrete cages. Details of housing and environmental enrichment have been previously described, along with the feeding system (Schlabritz-Loutsevitch et al. 2004). In brief, each outdoor social group cage was connected to a chute leading to individual feeding cages. Baboons left their group cage once daily and weights were obtained as they passed along the chute over an electronic scale (GSE 665; GSE Scale Systems, Livonia, MI, USA) prior to entering an individual feeding cage where they were fed over 2-h. Training the baboons to run from their group cages to the individual cage took about two weeks. Once trained, it took about 20 minutes for all baboons from a social group to be run into the individual feeding cages. Baboons spent two hours per day in the individual feeding cages, where their food was provided; the rest of their time was spent in the social group cages. Water was continuously available in both the social group cages and the individual cages. Environmental enrichment consisted of structural (perches and swings) and manipulatable enrichment (balls and chew toys). No feed enrichment was provided since it was necessary to exactly quantify and control each animal's diet.

Study Design & Animal Feeding System

Female baboons were selected on the basis of reproductive age (8–15yr), body weight (10–15kg), and absence of genital and extragenital pathologic signs and mated as described previously (Schlabritz-Loutsevitch et al. 2004). Baboons were observed twice daily for wellbeing and 3 times weekly for turgescence (swelling), color of sex skin, and signs of vaginal bleeding to determine timing of ovulation and conception. Pregnancy was dated by timing of ovulation and sex skin color changes. Ultrasonography was used in only a few instances of the very first animals on the maternal nutrient restriction study (not the animals in this study), and then stopped as it was determined that sex skin color changes were reliable. Female baboon sex skin changes from pink to purple during pregnancy. A single experienced technician observed sex skin tumescence and color changes throughout the study.

The experimental feeding protocol was initiated at gestation day (GD) 30. In their individual feeding cages, baboons were fed Purina Monkey Diet 5038 (Purina, St. Louis, MO, USA). Each biscuit contained crude protein ≥ 15%, crude fat ≥ 5%, crude fiber ≤ 6%, ash ≤ 5%, added minerals ≤ 3% and stabilized vitamin C as well as all other required vitamins. Each control baboon was initially given 60 biscuits in the feeding tray to eat *ad libitum* and at the end of the 2-h feeding period baboons were returned to the group cage and leftover biscuits in the tray, on the floor of the cage, and the pan beneath the cage were counted. Baboons in the MNR group were fed 70% of the total intake of corresponding controls across gestation on a per-kilogram body weight basis. Food consumption, weights, and health status of each animal were recorded daily.

Caesarean section

Baboons were trained to run into a chute attached to the social group cage, and then into a transfer cage. They were transported unsedated to the nearby SNPRC hospital where they were held until procedure time in individual cages. Prior to Cesarean section, baboons were premedicated with ketamine hydrochloride (10 mg/kg, IM). Following intubation, isoflurane (2%, inhaled within carrier gas mixture of compressed air at 2.5 liters/min and oxygen at 0.5 liters/min) was used to maintain a surgical plane of anesthesia throughout surgery. To ensure that an adequate depth of anesthesia was achieved, the nail bed was regularly pinched to create a pain response, and the animal observed for movement of the limbs and blinking of the eyes. Cesarean section was perfomed at GD120 (0.65 of gestation, term = 184 days), GD140 (0.75 of gestation), GD165 (0.9 of gestation) and GD175 (0.92 of gestation) using standard sterile techniques as previously described (Schlabritz-Loutsevitch et al. 2004; Kavitha et al. 2014). Following hysterotomy, the umbilical cord was identified and used for fetal exsanguination with both maternal and fetal baboon under general anesthesia as approved by the American Veterinary Medical Association Panel on Euthanasia (Li *et al.* 2013). While still on the surgical table, ketorolac (1 mg/kg IM) was administered as well as ceftriaxone (50 mg/kg IM). Each was administered one time. Postoperatively, maternal analgesia was administered subcutaneously for 3 days (buprenorphine hydrochloride injection; Hospira, Inc., Lake Forest, IL, USA; 0.015 mg/kg/day). Cephalexin (25 mg/kg oral) was also administered twice daily for 5 days. Mothers were placed in individual cages postoperatively and watched until they were upright under their own power. Twice per day they were observed for signs of discomfort or pain, normal postures, movement and interaction with staff. The incision was also examined for redness, swelling and discharge at these checks, and appetite and stool were also observed. There was no change to maternal diet postoperatively and they were returned to their group cage two weeks after surgery. The mother baboons in this study were research naïve when first assigned to the study and were returned to the primate center colony at study end.

Collection of tissue samples

Placentas were collected and trophoblast chorionic villous tissue pieces (1 cm^3) were immediately dissected from 8 different placental locations according to standardized protocol, washed in saline, and homogenized in 250 mM sucrose, 10 mM HEPES-Tris, and 1mM ethylenediaminetetraacetic acid, pH 7.4 at 4°C with protease and phosphatase inhibitors. Samples were then snap-frozen in liquid nitrogen and stored at −80°C until further processing. Heparanized blood samples from fetal umbilical vein and maternal uterine vein were obtained at cesarean section. Fetal brain weights were obtained at necropsy.

Isolation of syncytiotrophoblast plasma membranes

Syncytiotrophoblast microvillous plasma membrane (MVM) and basal plasma membrane (BM) were prepared simultaneously from each placenta according to a well-established protocol with some modifications (Illsley et al. 1990; Johansson et al. 2000). Briefly, after initial centrifugation steps, MVM was separated by differential centrifugation and Mg^{2+} precipitation and BM was purified further on a sucrose gradient. Samples were snap frozen

in liquid N_2 and stored at −80°C. MVM enrichment was determined as the ratio of alkaline phosphatase activity in MVM over homogenate measured by standard assays. MVM vesicle enrichment was not significantly different between control and MNR groups (control, 3.06 ± 0.3, n = 19 total; MNR, 3.68 ± 0.3, n = 21 total; $P = 0.2$), with no differences across gestation and in general agreement with previous studies (Kavitha et al. 2014). BM enrichment was determined by BM/homogenate ratio of VDAC1 protein expression by Western blot. VDAC1 is a major component of the outer mitochondrial membrane, regulating transfer of Ca^{2+} but is also exclusively localized to the syncytiotrophoblast BM (Schein *et al.* 1976; Oh *et al.* 2016). Mean BM enrichments of VDAC1 were not significantly different between control and MNR groups (control, 11.8 ± 1.7, n = 16 total; MNR, 8.5 ± 0.9, n = 22 total; $P = 0.1$), with no differences across gestation. Protein concentration of MVM and BM was assessed using Bradford BCA assay (Bradford, 1976).

Western blot analysis

Protein expression of FATP and FABP isoforms was determined by Western blotting, as previously described (Kavitha et al. 2014). Protein expression of FABP isoforms in placental homogenate (FABP1, FABP3, FABP4, FABP5) as well as FATP isoforms in MVM and BM (FATP2, FATP4, FATP6) was measured. Monoclonal antibodies to FABP1 (Cell Signaling Technology Cat# 13368, RRID:AB_2798192) and FABP4 (Cell Signaling Technology Cat# 3544, RRID:AB_2278257) produced in rabbit were purchased from Cell Signaling (Danvers, MA). Monoclonal antibody to FATP4 (Abcam Cat# ab199719, Lot#GR211435-1, RRID:AB_2716563) and polyclonal antibodies to FABP3 (Abcam Cat# ab45966, Lot#GR128276-1, RRID:AB_2102301), FABP5 (Abcam Cat# ab128650, Lot#GR198582-1, RRID:AB_11143773), FATP2 (Abcam Cat# ab85801, Lot#GR7246-2, RRID:AB_10696530), and FATP6 (Abcam Cat# ab84183, Lot#GR64605-5, RRID:AB_1925441) produced in rabbit were obtained from Abcam (Cambridge, MA).

Samples were prepared with Laemmli (homogenate) or 3X urea + DTT (MVM, BM) sample buffer and 15 μg total protein (22.5 μg for FATP2) was loaded onto Biorad any-kD precast polyacrylamide 15-well gels. Electrophoresis was performed at 120 volts for 20 minutes followed by 150 volts for 30 (homogenate) or 100 (MVM, BM) minutes. Proteins were transferred onto polyvinylidene fluoride (PVDF) membranes at 4°C overnight at constant voltage of 30 volts. Membranes were blocked with 5% milk for 1-hr at room temperature (RT), then washed with TBST and incubated overnight at 4°C with the appropriate primary antibody (all FABPs, 1:1000 in 5% BSA/TBST; CD36, 1:500 in 3% BSA/TBST; FATP2, 1:300 in 3% BSA/TBST; FATP4, FATP6, 1:1000 in 1% BSA/TBST). Membranes were washed and incubated for 1-hr at RT with HRP-linked secondary antibody. After washing, bands were visualized using enhanced chemiluminescence detection reagents (Pierce Biotechnology) and images obtained using G:Box Chemi system (Syngene, Frederick, MD) or film exposure. Target protein expression was adjusted for amount of total protein loaded and any variations in transfer by staining membranes for total protein with Amido Black. Band densitometries were analyzed using ImageJ software v1.49.

Fatty acid extraction

Lipid extraction—Venous plasma from maternal (uterine vein) and fetal (umbilical vein) circulations was collected at each gestation time point and stored at −80°C until analysis. Samples were then thawed and 30 μL per sample was used for lipid extraction to quantify FA in total plasma lipid and in major lipid fractions as previously described (Ferchaud-Roucher et al. 2017). Procedural blank of 0.9% sodium chloride was processed in the same analytical conditions. Samples were vortexed after addition of each solvent and all solvents used were HPLC grade. Conditions for all drying steps were under N_2 at 40°C. In short, 1 mL methanol (MeOH, Sigma-Aldrich) was added to each sample and centrifuged at 500 *g* for 15 min at RT with subsequent removal of top MeOH layer and discarding of pellet. Next, 370 μL water and 1 mL dichloromethane (DCM, Sigma-Aldrich) were added to the MeOH layer and centrifuged at 500 *g* for 10 min at RT. The bottom DCM layer was then removed, transferred to a new glass tube, and dried. Lipids were then resuspended in 300 μL isooctane/ethyl acetate (3:1 v/v; Sigma-Aldrich) and aliquoted into glass tubes for measuring total lipid composition (100 μL) and FA composition in four cellular lipid classes (200 μL). Prior to hydrolysis of total lipids, samples were dried and resuspended in 500 μL ethanol (EtOH, Sigma-Aldrich).

Lipid class solid phase extraction (SPE) and separation—The 200 μL aliquot of lipids resuspended in isooctane/ethyl acetate were spiked with a SPE mixture of four internal standards representative of the four lipid classes studied. Samples were then dried and resuspended in 200 μL hexane/chloroform ($CHCl_3$)/MeOH (95:3:2 v/v/v; Sigma-Aldrich). Each lipid sample was then loaded onto solid phase extraction (SPE) columns and lipid class fractions were collected into new glass tubes by eluting the SPE NH_2 cartridges with 3 mL hexane (cholesterol ester, CE, fraction), 3 mL 1% diethyl ether/10% DCM in hexane (triglyceride, TG, fraction), 3 mL diethyl ether/acetic acid (95/5 v/v; nonesterified FA, NEFA, fraction), and 1.5 mL MeOH/$CHCl_3$ (6:1 v/v) pooled with 1.5 mL MeOH (phospholipid, PL, fraction). Each eluted fraction was dried, resuspended in 500 μL EtOH, and vortexed.

Lipid hydrolysis and derivatization of fatty acids—Each lipid class fraction in EtOH was spiked with FA internal standard solution as previously described (Ferchaud-Roucher et al. 2017), followed by addition of 500 μL 1N NaOH and incubation for 1h at 90°C. Following cooling to RT, 525 μL 1N HCl was added to achieve pH < 2. Saponified FAs were extracted twice by 2 mL isooctane, combined top layers were dried, and 25 μL each of 1% pentafluorobenzyl bromide in acetonitrile and 1% N,N-diisopropylethalamine in acetonitrile were added followed by incubation at RT for 20 minutes. Samples were then dried, resuspended in 100 μL isooctane and diluted 1:20 in isooctane for gas chromatogrphay-mass spectrometry injection (GC-MS). GC-MS instrument, methods, and absolute quantification have been previously described (Rudolph et al. 2014; Rudolph et al. 2012).

Data presentation and statistical analysis

For each target in the western blotting, the mean density of all control samples was arbitrarily assigned a value of 1.0, and individual density values were expressed relative to this. Protein expression was summarized with means ± SD and compared between MNR and

control groups using student's *t* test (GraphPad Prism, v6.0). Due to the low number of samples in the GD165 and GD175 groups, the groups were analyzed as one "term" group with average gestation days of 170, leaving three gestational age groups for analysis: 120, 140 and 170 days. Linear mixed models were used to assess for differences in plasma lipid concentration across gestation between sample types and study groups. All models included a random intercept to account for correlation between maternal and fetal samples. R version 3.4.1 software (R Foundation for Statistical Computing, Vienna, Austria, http:www.R-project.org) was used for mixed model analysis. Statistical significance was set at 0.05.

Results

Animal weights

As shown in Table 1, fetal and placental weights were not significantly different between the control and MNR groups at any of the three gestational ages. At term, GD170 MNR fetal weights were 7% smaller ($P = 0.1$) than fetal weights in the control group. These animals are a subset of a larger sample size with an overall significant 10–15% fetal weight difference by GD165 (Kavitha et al. 2014; Pantham et al. 2015). There were no sex differences amongst the groups in terms of placental weights. At GD170 there was a similar degree of weight reduction in males (8%) and females (6%) in the MNR group. There were no differences (including sex differences) in relative fetal brain weights (brain:body weight ratio) between control and MNR at any gestational age.

Fatty acid binding protein (FABP) expression in placental homogenate

At GD120 and GD140 protein expression of FABP1, FABP3, FABP4, and FABP5 was unchanged in placental homogenate of baboons fed a MNR diet compared to controls (Figure 1). However, at GD170 expression of FABP1 (+329%, $P = 0.007$) and FABP5 (+58%, $P = 0.02$) was significantly increased in MNR baboons compared to control.

Fatty acid transport protein (FATP) expression in MVM

Protein expression of FATP2, FATP4 and FATP6 at GD120 was similar in MVM isolated from placentas of MNR baboons compared to controls (Figure 2). However, at GD140, FATP2 (+151%, $P = 0.007$) and FATP6 (+236%, $P = 0.003$) expression was significantly increased in MVM isolated from MNR compared to controls, with no observed differences between groups in FATP4 expression. FATP4 and FATP6 expression was unchanged at GD170, but FATP2 (+277%, $P = 0.04$) expression was significantly increased in MNR MVM at this time point.

Fatty acid transport protein (FATP) expression in BM

FATP2 and FATP4 expression in BM at GD120 did not differ between groups, but FATP6 expression was significantly decreased in MNR compared to control (−44%, $P = 0.047$, Figure 3). At GD140 there was a significant increase in expression of FATP4 (+64%, $P = 0.02$) and FATP6 (+143%, $P = 0.008$) in BM isolated from MNR compared to control, but no difference between groups in BM expression of any of the FATPs at GD170. There were also no significant differences in expression of FATP isoforms between MVM and BM in control or MNR at any of the gestational time points (Figure 4).

Fatty acid levels in fetal plasma

We found no statistically significant differences between MNR and control groups in umbilical venous FA concentrations in total plasma lipids (Table 2) at any gestational age. When analyzing lipid classes in umbilical vein plasma a few differences between the MNR and control groups emerged. Only the low abundance FA dihomo-γ-linolenic acid was decreased in MNR compared to control in TG (Table 3) and NEFA (Table 4) at GD120. There were no differences between groups in FA concentrations in phospholipid (Table 5) at any time point. There were relatively few differences between MNR and control in FA in CE (Table 6), at the GD120 and 140 time points, demonstrating increased concentrations in MNR compared to control.

Fatty acid levels in maternal plasma

Differences between MNR and control maternal plasma FA concentrations in total lipids were found (Table 2), demonstrating overall lower FA content in MNR compared to control at each gestational age, with significant differences in concentrations of stearic, linoleic and α-linolenic at multiple time points, and γ-linolenic and palmitic acids at GD170. The sum of all FAs in total lipid was also significantly lower in MNR at GD120 and 170. Similarly, maternal FA concentrations in lipid classes were mostly lower in the MNR group (Tables 3–6). The significant differences were largely in the NEFA fraction (Table 4) where we demonstrated lower concentrations of myristic, stearic and arachidonic acids in MNR compared to control at GD120. Additionally, nearly all of the FA in this fraction were lower in MNR at GD140. Significantly lower concentrations of several FA were also demonstrated in phospholipid fraction (Table 5) at multiple time points in MNR. There were minimal differences between groups in maternal plasma concentrations of FA in TG (Table 3) and CE fractions (Table 6).

Control maternal - fetal differences in total lipids

Stearic, linoleic and α-linolenic FA concentrations were significantly greater in total lipids from maternal compared to fetal plasma at all gestational ages studied (Table 2, **denoted by asterisk**); however, an interesting overall pattern of total lipid concentrations emerged across gestation. At GD120 half of the measured FAs were significantly lower in maternal plasma compared to the cord plasma including most of the LCPUFAs and saturated FA; however, at GD170 this relationship was reversed, demonstrating higher maternal plasma concentrations compared to fetal plasma for 10 of the 15 FA measured.

Control maternal - fetal differences in lipid classes

Most FAs in the TG fraction (Table 3) were significantly lower in the mother compared to the fetus at GD120 but this was not sustained throughout gestation. Non-esterified fatty acids (Table 4) were also lower in maternal plasma compared to cord plasma for a few low abundance LCPUFA species (dihomo-γ-linolenic, adrenic, DHA and n-6 docosapentaenoic acids) at GD120, but at GD140 essentially all NEFAs were higher in the maternal circulation compared to the fetus. Nearly half of the FAs in the PL fractions (Table 5) demonstrated lower maternal levels at GD120 but at GD170 this finding was reversed, with significantly greater maternal concentrations of the majority of FA in this fraction. Many FA species in

the CE fraction were lower in the maternal compared to fetal plasma at all gestational ages studied (Table 6).

MNR maternal – fetal differences in total lipid

Similar to the control group finding, the essential FAs linoleic and α-linolenic acids were higher in maternal compared to fetal plasma at every time point across gestation (Table 2). Conversely, most of the measured FA at GD120 were significantly lower in the maternal circulation compared to fetal. However, at GD170 these differences no longer persisted, with several of the FAs being found in greater concentrations in maternal plasma, including stearic, linoleic, α-linolenic, eicosapentaenoic, and n-3 docosapentaenoic acids.

MNR maternal – fetal differences in lipid classes

Patterns of FA concentration differences in lipid classes (Tables 3–6) were similar to those observed in the control group. At GD120 most of the measured FAs were lower in maternal compared to fetal circulation in TG (Table 3) and CE fractions (Table 6). Several of these differences persisted to GD170 in CE fraction but not in TG. FA species myristic, adrenic, DHA, and n6 docosapentaenoic acids were also lower in maternal plasma at GD120 in NEFA fraction (Table 4) but not by GD170. Similarly, in the PL fraction (Table 5) myristric, palmitic, palmitoleic, and arachidonic acids were lower in maternal plasma at the earliest gestation time point, and differences which were largely absent by GD170. In fact, at this time point many of the FAs in PL fraction were higher in maternal plasma compared to fetal (stearic, linoleic, α-linolenic, eicosapentaenoic, n3- and n6 docosapentaenoic acids).

Fatty acid concentration changes across gestation

The association between gestational age and total FA concentration was significantly different between maternal and fetal samples in the MNR ($P < 0.01$) and control ($P < 0.01$) groups (Figure 5). In the control (Figure 5a) and MNR (Figure 5b) groups, total maternal FA concentration increased on average, by 19.77 and 15.44 units each day, respectively, whereas fetal concentrations decreased by 17.67 and 14.39 each day, respectively. These plasma changes were largely attributable to significant changes in specific lipid class levels over time (Figure 6). Maternal FA in PL increased on average by 13.13 and 9.41 units per day in control (Figure 6a; $P < 0.01$) and MNR (Figure 6b; $P < 0.01$), respectively. Conversely, fetal FA in PL decreased on average by 7.72 units per day (Figure 6c; $P < 0.01$) in control. Fetal FA in TG also decreased on average by 10.41 and 10.06 units per day in control (Figure 6c; $P < 0.01$) and MNR (Figure 6d; $P < 0.01$), respectively.

Discussion

Maternal nutrient restriction in the baboon is a well-established model of IUGR with extensive similarities to human IUGR due to placental insufficiency (Schlabritz-Loutsevitch et al. 2004; Schlabritz-Loutsevitch et al. 2005; Carter, 2007; McDonald et al. 2013; Kavitha et al. 2014; Pantham et al. 2015). This non-human primate model allows us to obtain critical information on placental lipid transport and fetal FA levels across late gestation in normal and IUGR pregnancies, which is difficult to generate in pregnant women. In this study we demonstrated for the first time that MNR in the baboon is associated with increased

expression of FA binding and transport proteins in late gestation. Specifically, we found increased expression of FATP2 and FATP6 in MNR MVM at GD140, increased FATP2 expression in MNR MVM at GD170, and increased FABP1 and FABP5 in MNR homogenate at GD170. These data are consistent with our recent report demonstrating increased FATP expression in placental MVM isolated from human term pregnancies with IUGR (Chassen et al. 2018). These findings have important implications for our understanding of placental FA transport in growth restricted fetuses.

This study demonstrates for the first time a profile of fetal and maternal plasma FA concentrations in a baboon IUGR model involving maternal nutrient restriction. As expected with reduced global caloric intake, the maternal MNR FA concentrations are lower than control. Importantly, in both control and MNR groups there is an increase in circulating FA across gestation consistent with the maternal hyperlipidemia that develops in the second half of pregnancy in women. Interestingly, the circulating FA increase in the baboon is largely attributable to increasing phospholipids rather than the marked increase in triglycerides characteristic of human pregnancies.

While we found MNR to be associated with increased placental FABP and FATP expression, the umbilical vein plasma FA concentrations were largely unaltered in the MNR fetus compared to control. These findings are consistent with an appropriate adaptation in the baboon placenta to maintain FA transfer when maternal FA levels are low. We therefore propose that a compensatory upregulation of placental transport proteins that are responsible for FA transfer from the mother to the fetus occurs when maternal nutrients are limited.

Another interesting pattern we found in both control and MNR fetal FA profiles was that fetal concentrations decreased across the last third of pregnancy. This was evident both in total plasma FA and in TG and PL classes. We speculate that the decreasing circulating FA concentrations in the fetus across late gestation may reflect preferential shuttling of FA to and incorporation in the fetal brain, which grows rapidly in this period of gestation in both control and MNR fetuses. Baboon fetuses are born with much less adipose tissue but some FA is likely deposited in fat stores. We assume that in human fetuses exposed to nutrient restriction a similar preferential fat incorporation in the brain over the adipose tissue also occurs to support continued brain growth at the expense of fat deposition in adipose tissue. Indeed, a relatively normal brain size and reduced adipose tissue mass is a common feature of human IUGR infants.

Baboons have been used extensively in studies of placentation because of their similarities to humans in villous structure, syncytiotrophoblast barrier, pattern of circulation in the intervillous space, and remodeling of spiral arteries following trophoblast invasion (Carter 2007). Thus, the baboon is a valuable model for understanding placental dysfunction associated with conditions such as IUGR and preeclampsia. Human IUGR has many potential etiologies, including poor nutrient delivery secondary to insufficient maternal nutrition, which can affect placental structure and function (Bloomfield & Harding, 1998). Studies of the MNR model of IUGR have previously demonstrated both morphological and physiological placental changes. At mid-gestation (GD90), the MNR placental volumetric structure is unchanged (Schlabritz-Loutsevitch et al. 2007). However, by the end of gestation

(GD165-175) placental weight, villous volume and surface area, capillary surface area, and villous isomorphic coefficient are all decreased in MNR, changes which are likely to limit total placental nutrient transport capacity (Schlabritz-Loutsevitch et al. 2007).

MNR in the baboon is also associated with inhibition of placental mTOR and insulin/IGF-1 signaling pathways, decreased expression of amino acid transporter isoforms, decreased transplacental transport of essential amino acids and lower fetal levels of essential amino acids (Kavitha et al. 2014). These characteristics replicate established findings in human IUGR that are secondary to placental insufficiency (Mahendran et al. 1993; Glazier et al. 1997; Jansson et al. 1998; Norberg et al. 1998; Paolini et al. 2001; Jansson et al. 2002; Maulik et al. 2006). Importantly, the downregulation of placental amino acid transporters occurs six weeks before a significant reduction in fetal weight is observed, suggesting that changes in placental nutrient transport may be directly contributing to fetal growth restriction (Pantham et al. 2016). We have reported previously that our protocol for MNR in baboons results in a moderate (~10–15%), statistically significant, decrease in fetal weight by GD165 (Kavitha et al. 2014; Pantham et al. 2015) with typically somewhat larger groups than we were able to study at GD170 in the current report. Given these considerations, we strongly argue that the findings in the current study are directly relevant for IUGR due to placental insufficiency, despite the fact that the reduction of fetal weights at GD170 did not reach statistical significance. Similar to the human, little is known about FA transport in fetal growth restriction, nor its impact on fetal growth in the baboon nutrient restriction model. The similarities between baboon and human in reproductive physiology, placental structure, and localization of nutrient transporters suggest similar mechanisms of nutrient delivery, contributing to the relevance of this IUGR model for studying human disease.

Our findings of increased FATP and FABP expression in the MNR baboon placenta at the end of pregnancy is in general agreement with recent findings using *in vitro* experimental systems and in other animal models of IUGR. Biron-Shental *et al.* determined FABP expression and lipid droplet formation in primary human trophoblast cell culture in hypoxic versus standard conditions and reported that the hypoxic cells had increased FABP1, FABP3 and FABP4 expression as well as increased lipid droplet number (Biron-Shental et al. 2007). Nüsken and collaborators evaluated placental FA transporter expression in pregnant rats with acute utero-placental insufficiency secondary to bilateral uterine artery and vein ligation and found increased FABP3 and CD36/fatty acid translocase expression (Nüsken et al. 2015). Placental expression of CD36/fatty acid translocase was also reported to be up-regulated in a mouse model of IUGR resulting from placental overexpression of the human anti-angiogenic molecule sFlt-1 (Kühnel et al. 2017).

Fetal fat deposition in the human increases exponentially with gestational age, with the highest accretion rate at term when placental surface area, blood flow, and maturity of placental villi are maximal (Haggarty et al. 1997). Despite differences in the degree of adiposity in the term baboon (5%) and human fetus (15%) (Widdowson & Spray, 1951; Catalano et al. 1992) it is likely that fetal fat deposition in the baboon occurs predominantly in late gestation. Fatty acid transfer across the placenta is believed to be mediated by facilitated diffusion down a maternal-fetal diffusion gradient (Haggarty 2010). Lower FA concentrations in the fetal circulation than in maternal plasma have been reported for term

human healthy pregnancy (Haggarty 2010) which is consistent with this model. In contrast, our finding of greater concentrations of several FA species in the fetus compared to maternal plasma earlier in gestation at GD120 and 140 in the current study is at odds with this concept of diffusion gradients driving lipid transfer across the placenta. Possible explanations include fetal production of a subset of FA in the baboon fetal liver or release of FAs incorporated into more complex lipid forms (TG, CE and PL) in the fetal circulation which are not contributing to the diffusion gradient. Resolving this issue would require additional samples that are not available and makes studies of lipid profiles across human gestation particularly interesting.

Though we did not find significant differences between control and MNR fetal FA concentrations, there were several interesting differences in the maternal-fetal concentration gradient. Of great interest is the neurodevelopmental sequelae of IUGR in the human, and the importance of LCPUFAs, particularly DHA and arachidonic acid, for brain growth. Previous studies in the fetus and preterm infant have demonstrated that LCPUFA are transported in the circulation predominantly as phosphatidylcholine (Bernhard *et al.* 2017) and evidence exists that the placenta may secrete FAs in a PL form to the fetus (Larqué et al. 2011). We also found evidence in humans that DHA is released from the placenta as a lyso-phosphatidyl choline, which is higher in the fetal circulation (Ferchaud-Roucher et al. 2019). Interestingly, in baboon pregnancy at GD170 the fetal plasma DHA-PL concentrations in MNR are not different compared to control, despite lower maternal levels of DHA-PL in the MNR group. One possible explanation is that placental lipid transfer is more efficient in MNR, a speculation indirectly supported by the upregulation of fatty acid transporters and fatty acid binding proteins in MNR.

Because the specific roles of different FABP and FATP isoforms are poorly understood, the significance of the differential regulation of placental FABP and FATP isoforms in MNR remains to be fully established. FABP5 is known as keratinocyte-type FABP (KFABP) as it binds retinoic acid with a similar binding affinity as it does FA and is involved in either inhibition or promotion of cell growth based on activation of different receptors (Storch & McDermott, 2008). Additionally, it has been suggested that KFABP functions as an antioxidant protein by scavenging reactive lipids (Storch & McDermott, 2008). FABP1 is also known as liver-type FABP and is believed to be involved in enterocyte lipid absorption in addition to hepatocyte lipid transport and lipoprotein metabolism and binds unsaturated FAs with higher affinity than saturated FA (Storch & McDermott, 2008). Given the importance of LCPUFA delivery to the developing fetal brain, upregulation of placental FABP1 in MNR in our study may serve to maintain placental LCPUFA delivery in a nutrient deficient state. FATP2 is expressed primarily in the liver and kidney and plays a prominent role in hepatocyte uptake of long chain FA (Anderson & Stahl, 2013). Thus, it is possible that the higher MVM FATP2 expression in MNR at GD140 and 170 as compared to controls contributes to enhance the placental capacity to transfer DHA.

Although the weights of MNR fetuses near term in the current study were not statistically significantly lower than control fetuses, other studies with a larger number of animals support that this model is associated with a significantly decreased fetal weight (~10–15%) at GD165 (Kavitha et al. 2014; Pantham et al. 2015), representing moderate IUGR prior to

term. Importantly, because this non-human primate model allows studies of placentas and fetuses across the second half of pregnancy, we have established that a wide range of changes reflective of developing IUGR precede a statistically significant reduction in fetal growth. For example, Cox *et al.* demonstrated decreased renal tubule density within the renal cortex of MNR fetal kidneys compared to control, as well as an acceleration in fetal renal differentiation by GD90 (0.5 gestation), therefore shortening critical phases of renal growth (Cox et al. 2006). The authors speculate these findings may result in decreased functional capacity in later life and contribute to the increased predisposition to hypertension and renal disease that exists in offspring of nutrient restricted mothers (Cox et al. 2006).

MNR in the baboon has also been shown to induce major cerebral developmental disturbances, a known complication of IUGR, as early as 0.5 gestation as evidenced by imbalances in cell proliferation and cell death and impaired glial maturation and neuronal process formation, among others (Antonow-Schlorke et al. 2011). There is also a fetal hepatic response to reduced nutrient availability in MNR involving alterations in the function of the insulin-like growth factor (IGF) axis including increased hepatic glycogen at 0.5 gestation without changes in overall fetal or liver weights (Li et al. 2009). Additionally, Kamat *et al.* found alterations in hepatic beta-adrenergic receptors potentially leading to alterations in glucose homeostasis in the setting of nutrient deprivation (Kamat et al. 2011). Finally, Pantham *et al.* established that there is a decrease in placental MVM system A amino acid transporter activity in MNR at GD120 (0.65 gestation), prior to the onset of impairments in fetal growth trajectory, suggestive that reduced amino acid transport is a cause rather than consequence of IUGR in the setting of inadequate maternal nutrition (Pantham et al. 2016). Thus, we argue that the current report is a study of IUGR, despite the lack of significant difference in fetal weight. The findings of lower lipid content in the maternal circulation of MNR compared to the control fed animals allows us to examine how the placenta responds to reduced nutrient availability that is highly relevant to women with food insecurity, low fat diets, or failed trophoblast invasion, all of which reduce nutrient delivery to the placenta.

In summary, in this study we report that MNR in the baboon is associated with increased placental expression of FA binding and transport proteins in late gestation. We have also demonstrated for the first time a profile of fetal and maternal plasma FA concentrations in the experimental baboon model of growth restriction. This profile includes gestational age-related changes in maternal FAs (increase across gestation) and fetal FAs (decrease across gestation) in both control and MNR groups. We also demonstrated reduced maternal MNR FA concentrations compared to control following reduced global caloric intake and largely unaltered umbilical vein plasma FA concentrations in the MNR fetus. These findings suggest an appropriate adaptation to maintain placental FA transfer to the fetus when maternal FA levels are low.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

- Intrauterine growth restriction (IUGR) is associated with perinatal morbidity and increased risk of lifelong disease, including neurodevelopmental impairment.
- Fatty acids (FA) are critical for normal brain development, but their transport across the placenta in IUGR pregnancies is poorly understood.
- This study used a baboon model of IUGR (maternal nutrient restriction, MNR) to investigate placental expression of FA transport and binding proteins, and to determine gestational age-related changes in maternal and fetal plasma FA concentrations.
- We found MNR to be associated with increased placental expression of FA binding and transport proteins in late gestation, with fetal plasma FA concentrations that were similar to those of control animals.
- This study is the first to report a profile of fetal and maternal plasma FA concentrations in a baboon model of growth restriction with data that suggest adaptation of placental transport to maintain delivery of critically needed FA.

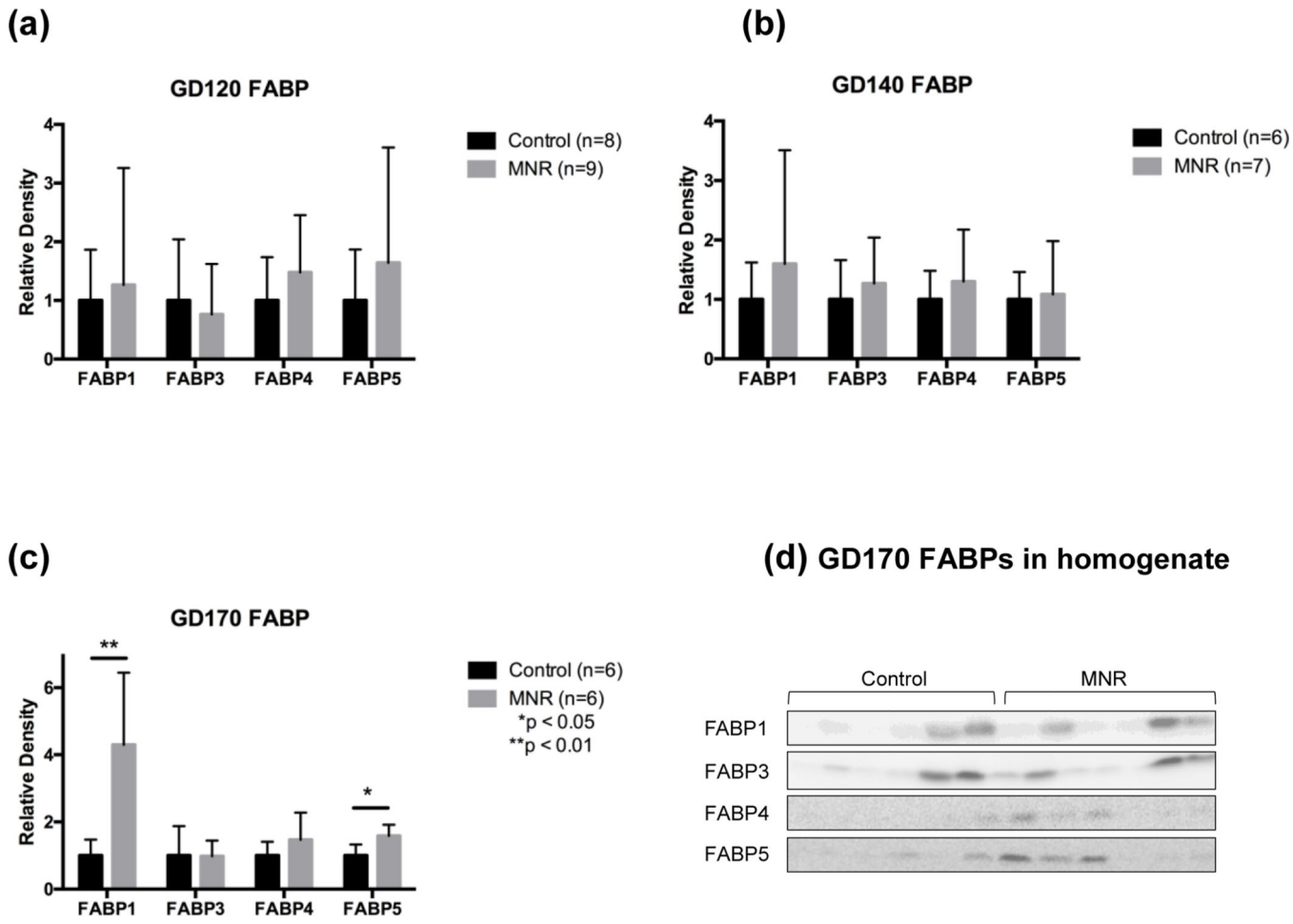

Figure 1. Protein expression of fatty acid binding proteins (FABPs) in placental homogenate.

Histograms demonstrating protein expression of FABP1, FABP3, FABP4, and FABP5 in placental homogenate of maternal nutrient restricted (MNR) and control baboons at gestation day (GD)120 (**a**), GD140 (**b**), and GD170 (**c**) depicted as mean relative densities ± SD. Representative western blot shown (**d**).

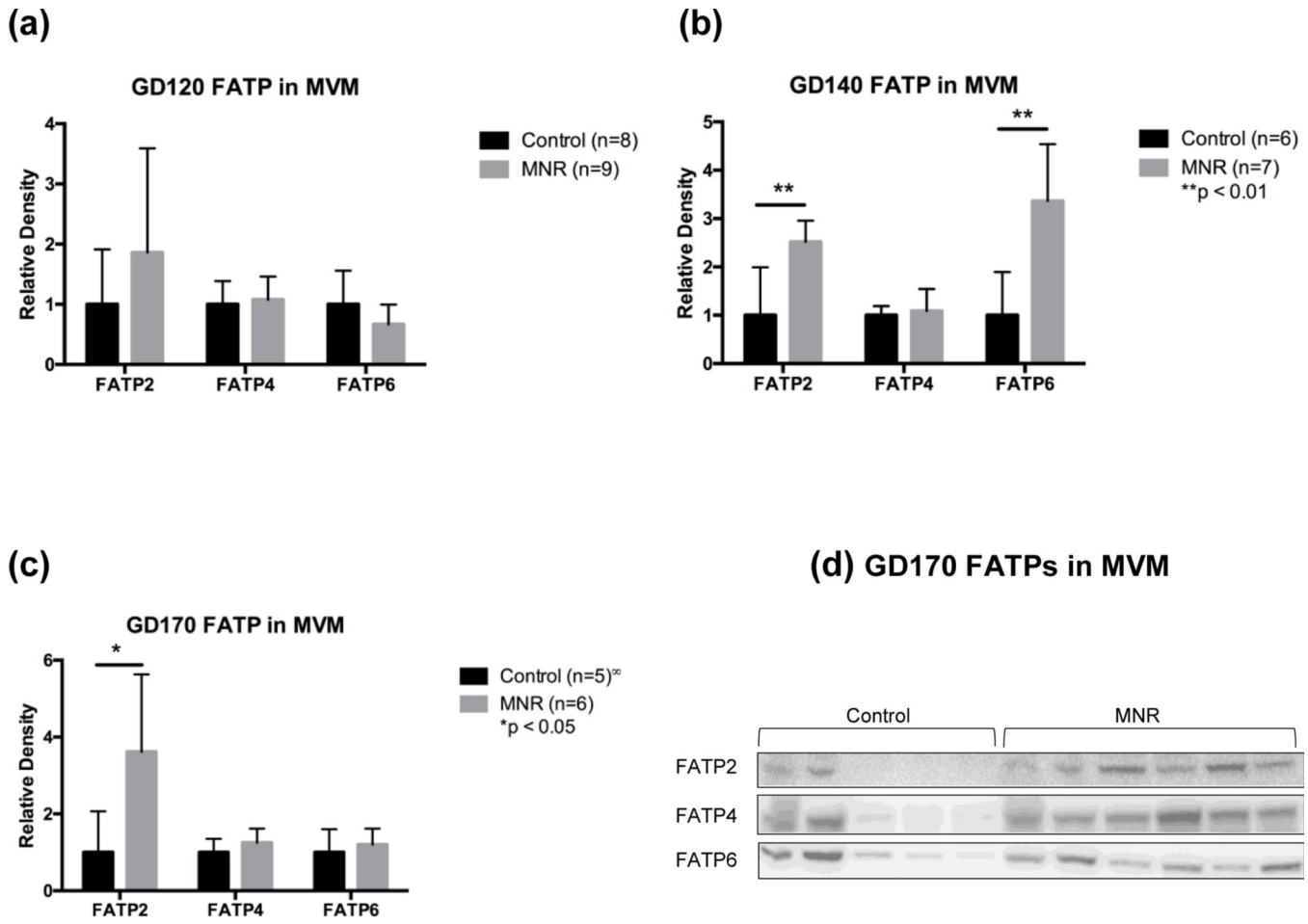

Figure 2. Protein expression of fatty acid transport proteins (FATPs) in syncytiotrophoblast microvillous plasma membrane (MVM).

Histograms demonstrating protein expression of FATP2, FATP4, and FATP6 in MVM of maternal nutrient restricted (MNR) and control baboons at gestation day (GD) 120 (**a**), GD140 (**b**), and GD170 (**c**) depicted as mean relative densities ± SD. ∞ indicates smaller control sample size at GD170 (5 instead of 6) due to insufficient MVM isolation of one sample. Representative western blot depicting MVM expression of FATP2, FATP4 and FATP6 at GD170 is also shown (**d**).

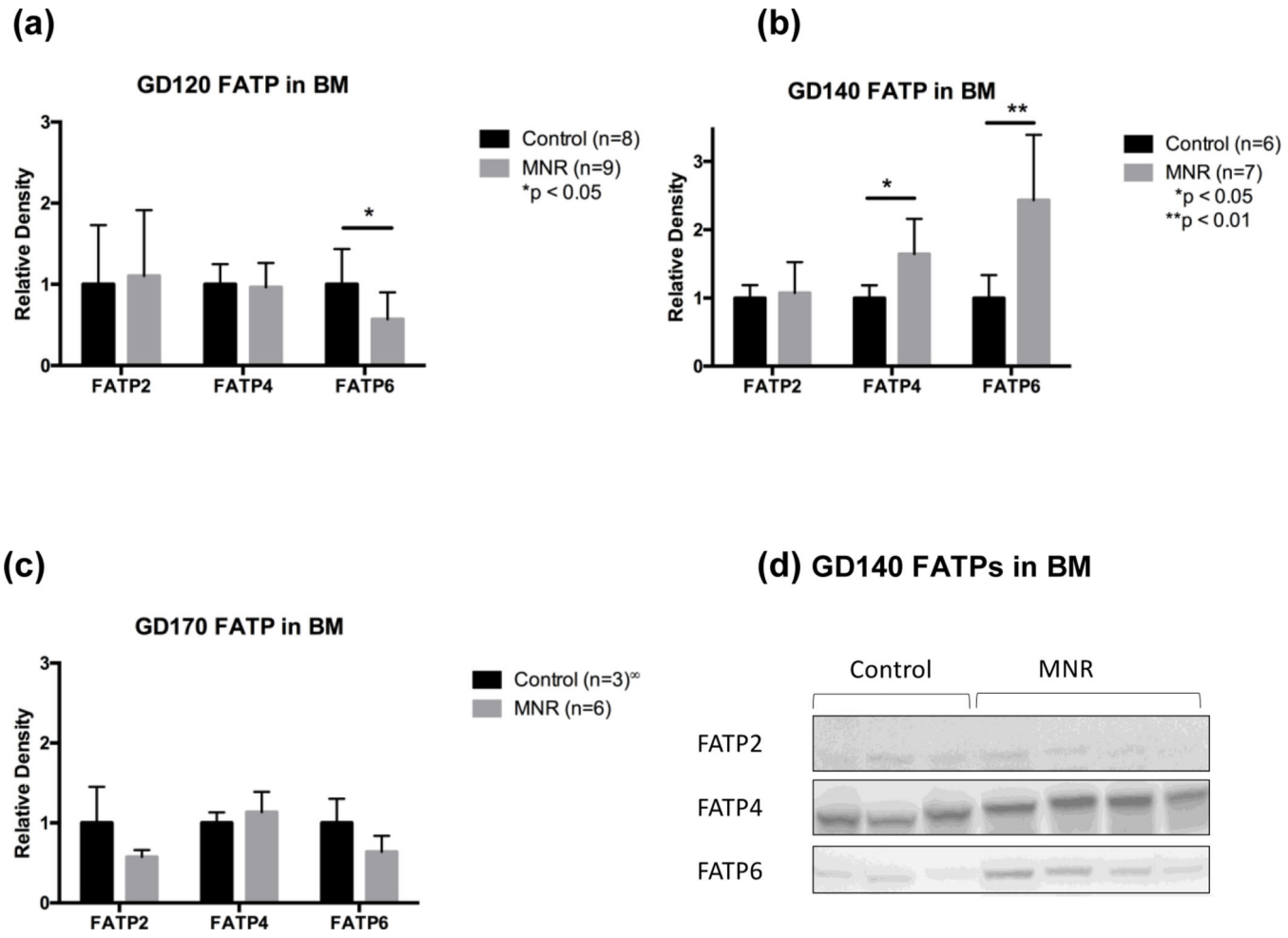

Figure 3. Protein expression of fatty acid transport proteins (FATPs) in syncytiotrophoblast basal plasma membrane (BM).

Histograms demonstrating protein expression of FATP2, FATP4, and FATP6 in BM of maternal nutrient restricted (MNR) and control baboons at gestation day (GD) 120 (**a**), GD140 (**b**), and GD170 (**c**) depicted as mean relative densities ± SD. ∞ indicates smaller control sample size at GD170 (3 instead of 6) due to insufficient BM isolation of three samples. Representative western blot depicting BM expression of FATP2, FATP4 and FATP6 at GD140 is also shown (**d**).

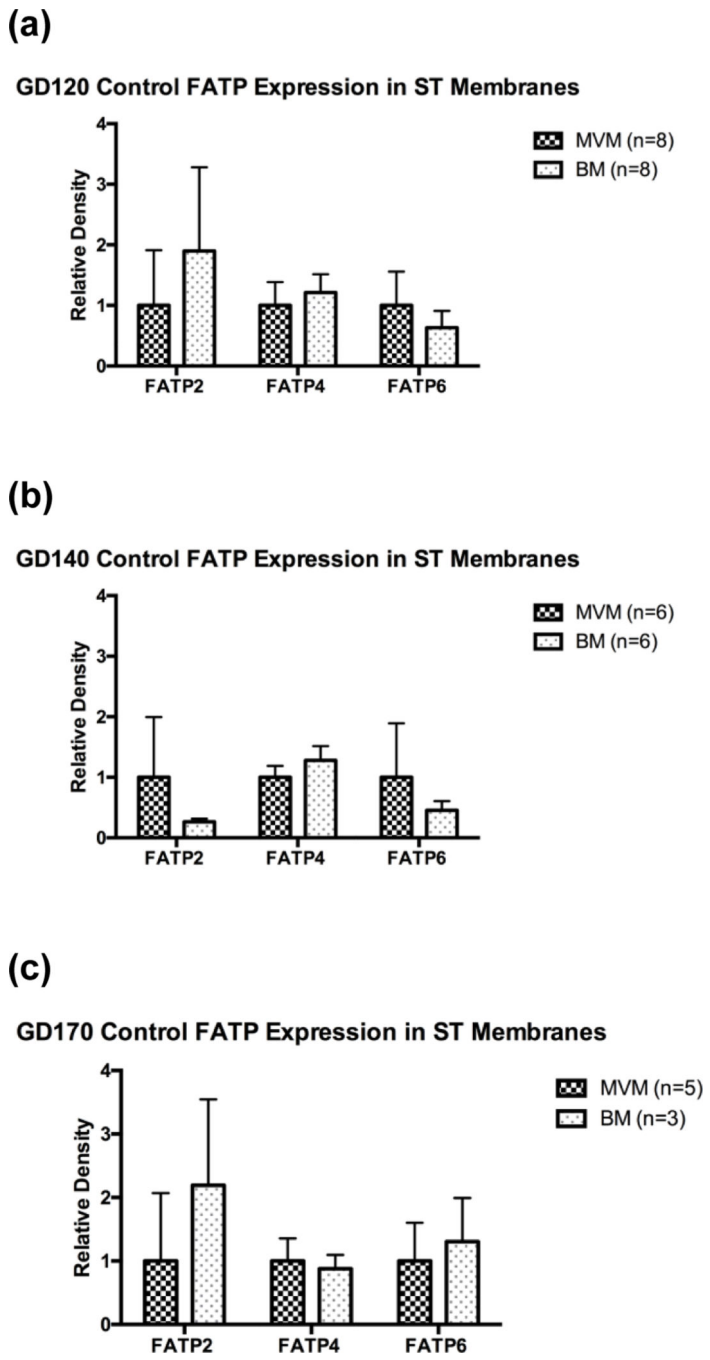

Figure 4. Polarization of fatty acid transport protein (FATP) expression between syncytiotrophoblast (ST) microvillous plasma membrane (MVM) and basal plasma membrane (BM).

Histograms demonstrating protein expression of FATP2, FATP4, and FATP6 in MVM compared to BM of control baboons at gestation day (GD) 120 (**a**), 140 (**b**), and 170 (**c**) depicted as mean relative densities ± SD.

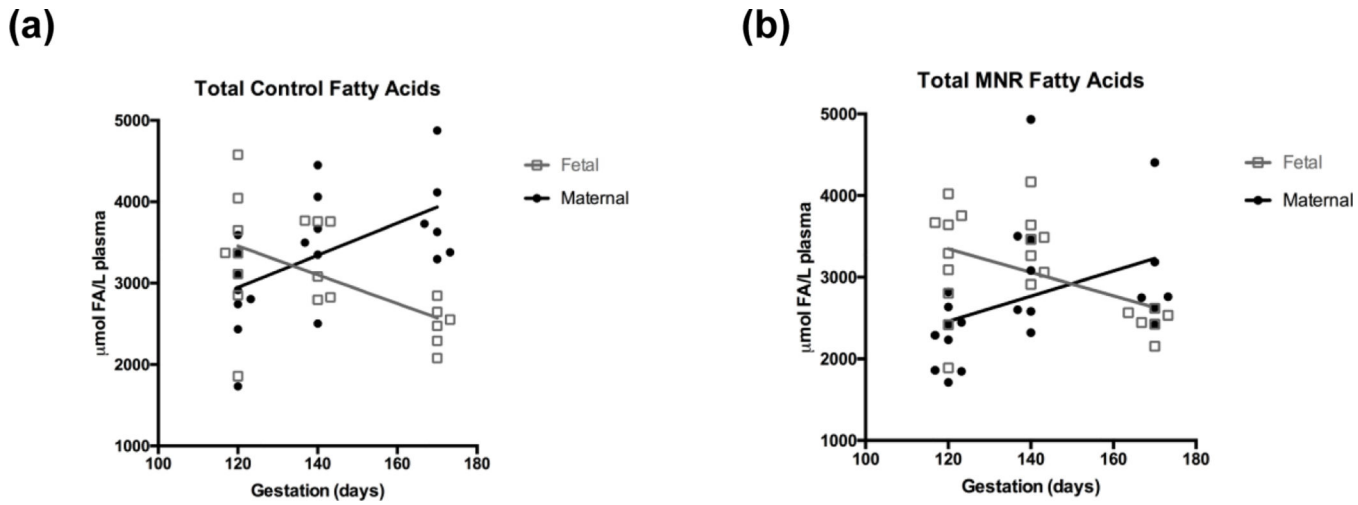

Figure 5. Total plasma fatty acid (FA) concentrations across gestation, based on linear mixed models.

Scatterplots demonstrating control and maternal nutrient restriction (MNR) total FA concentrations across gestation in maternal and fetal plasma. Values plotted are individual plasma concentrations in μmol FA/L plasma. Abbreviation: MNR, maternal nutrient restriction.

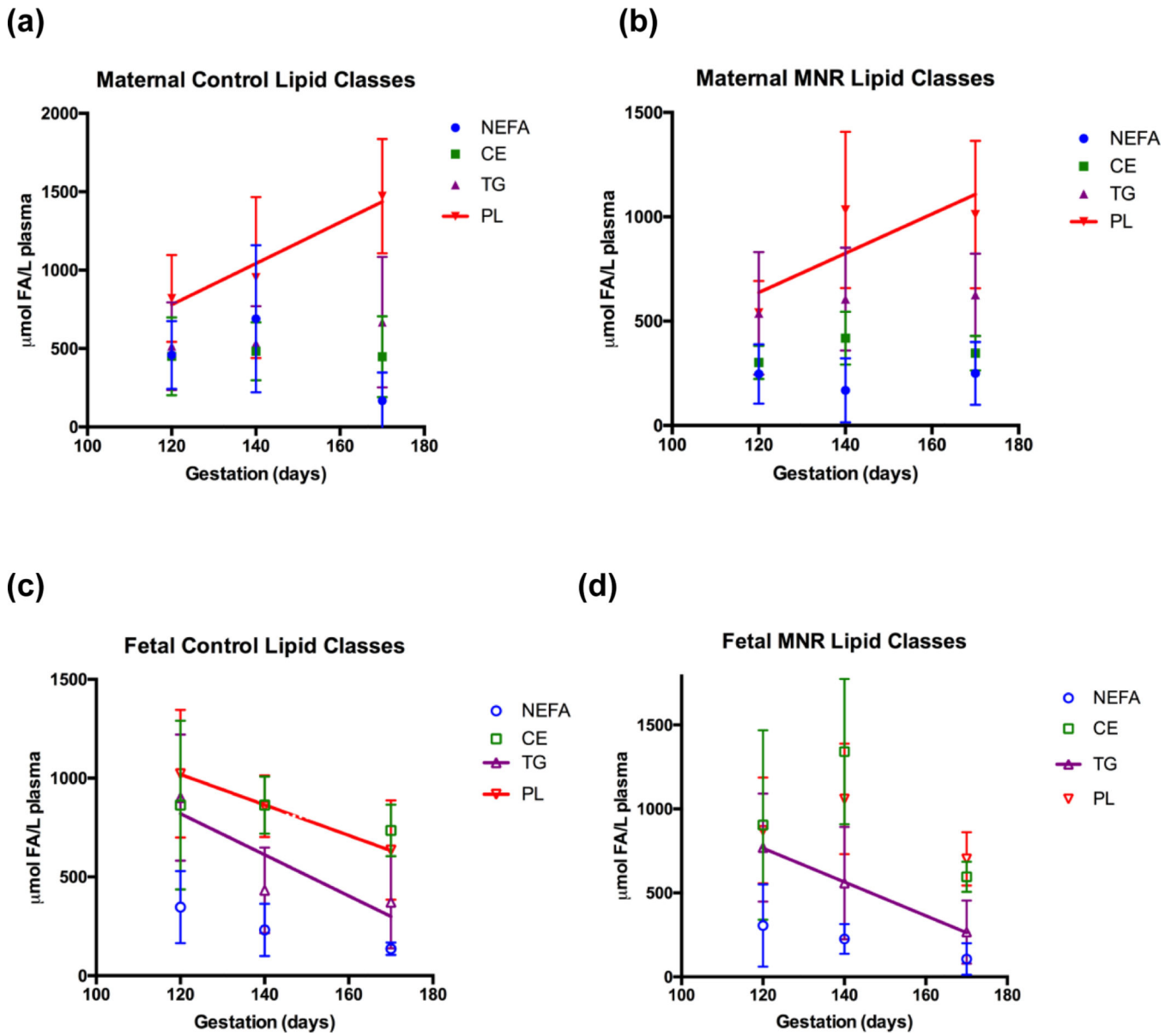

Figure 6. Maternal (a,b) and fetal (c,d) plasma fatty acid (FA) concentrations in lipid classes across gestation, based on linear mixed models.

Scatterplots demonstrating maternal and fetal FA concentrations in lipid classes across gestation in control and maternal nutrient restriction (MNR) animals. Values plotted are mean concentrations in μmol FA/L plasma with SD bars. Abbreviations: MNR, maternal nutrient restriction; FA, fatty acids; NEFA, non-esterified fatty acids; CE, cholesterol ester; TG, triglyceride; PL, phospholipid.

Table 1.

Mean fetal, placental, and brain weights in control and MNR baboons at different gestational ages.

	GD120			GD140			GD170		
Parameter	**Control**	**MNR**	**p value**	**Control**	**MNR**	**p value**	**Control**	**MNR**	**p value**
Number of animals	8	9		6	7		6	6	
Male	6	7		2	6		4	4	
Female	2	2		4	1		2	2	
Fetal weight (g)	328 ± 59	322 ± 35	0.8	477 ± 54	499 ± 32	0.4	804 ± 59	748 ± 53	0.1
Placental weight (g)	139 ± 25	136 ± 20	0.8	152 ± 17	159 ± 18	0.5	219 ± 32	206 ± 20	0.4
Brain weight (g)	40 ± 5	38 ± 5	0.4	61 ± 1.7	64 ± 7	0.2	84±10	80 ± 4	0.3
Brain:body weight ratio	0.122 ± 0.009	0.117 ± 0.007	0.2	0.131 ± 0.01	0.129 ± 0.01	0.9	0.105 ± 0.01	0.107 ± 0.01	0.9

Data are presented as mean ± SD. Abbreviations: MNR, maternal nutrient restriction; GD, gestational day; g, grams

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Table 2.

Mean plasma total lipid fatty acid concentrations (μmol fatty acid/L plasma) in control and maternal nutrient restriction (MNR) pregnancies, based on linear mixed models.

	GD120			GD140			GD170		
FETAL PLASMA	**Control**	**MNR**	**p value**	**Control**	**MNR**	**p value**	**Control**	**MNR**	**p value**
myristic (14:0)	31.51 ± 12.41 *	30.78 ± 10.77 †	0.837	32.85 ± 8.46 *	30.01 ± 7.37 †	0.489	22.01 ± 4.18	20.61 ± 4.3	0.742
palmitic (16:0)	983.07 ± 223.85 *	919.99 ± 229.12 †	0.404	933.48 ± 99.23	922.39 ± 138.72	0.898	734.13 ± 105.45	730.8 ± 73.3	0.97
palmitoleic (16:1 n-7)	0.09 ± 0.06	0.02 ± 0.03	0.994	69.65 ± 41.6 *	75.35 ± 63.08 †	0.621	29.16 ± 11.27	31.14 ± 7.6	0.868
stearic (18:0)	535.59 ± 149.78	536.63 ± 90.89	0.987	583.1 ± 52.11	613.23 ± 72.38	0.681	543.16 ± 59.55	494.02 ± 58.	0.518
oleic (18:1 n-9)	930.24 ± 301.68 *	882.21 ± 272.82 †	0.602	892.76 ± 244.17	957.14 ± 150.58 †	0.541	572.49 ± 97.28	614.02 ± 66.	0.704
linoleic (18:2 n-6)	187.03 ± 60.27	182.76 ± 48.57	0.881	202.21 ± 47.53	231.7 ± 30.42	0.368	166.73 ± 36.92	151.89 ± 14.	0.662
α-linolenic (18:3 n-3)	18.98 ± 7.07	16.76 ± 4.97	0.492	12.83 ± 5.27	17.07 ± 3.9	0.253	18.5 ± 3.41	16.9 ± 4.23	0.678
γ-linolenic (18:3 n-3)	7.66 ± 4.99 *	7.38 ± 2.45 †	0.84	4.82 ± 2.09	6.79 ± 3.72	0.217	4.54 ± 0.94	8.4 ± 2.99	**0.02**
dihomo-γ-linolenic (20:3 n-6)	31.48 ± 8.88	26.8 ± 6.61 †	0.311	31.43 ± 7.85	36.63 ± 10.75	0.326	22.69 ± 4.04	29.56 ± 5.1	0.211
arachidonic (20:4 n-6)	472.36 ± 121.79 *	424.29 ± 139.59 †	0.272	448.08 ± 109.39 *	426.42 ± 110.5 †	0.666	268.37 ± 24.33	246.31 ± 41.	0.672
eicosapentaenoic (20:5 n-3)	5.28 ± 1.51 *	5.05 ± 1.71 †	0.815	3.86 ± 4	3.26 ± 3.72	0.597	4.07 ± 1.46	2.09 ± 0.6	0.089
adrenic (22:4 n-6)	6.1 ± 1.87 *	5.32 ± 1.37 †	0.127	5.79 ± 0.75 *	4.85 ± 0.88 †	0.108	6.36 ± 0.91 *	7.19 ± 1.25	0.175
n3 docosapentaenoic (22:5 n-3)	5.85 ± 1.4	5.19 ± 1.02	0.451	6.21 ± 1.82	5.74 ± 1.7	0.633	6.63 ± 1.76	5.38 ± 1.06	0.223
docosahexaenoic (22:6 n-3)	128.57 ± 34.41 *	123.32 ± 35.87 †	0.688	96.22 ± 13.46	92.66 ± 18.07	0.812	75.56 ± 18.36	92.37 ± 26.	0.279
n6 docosapentaenoic (22:5 n-6)	10.22 ± 4.04	10.04 ± 2.25	0.912	7.52 ± 2.34	5.61 ± 1.31	0.297	7.46 ± 2.31	6.54 ± 1.29	0.628
Total	3354.04 ± 811.89	3176.56 ± 697.95 †	0.51	3330.79 ± 481.15	3428.85 ± 412.78	0.751	2481.85 ± 269.63	2457.24 ± 165	0.939

	GD120			GD140			GD170		
MATERNAL PLASMA	**Control**	**MNR**	**p value**	**Control**	**MNR**	**p value**	**Control**	**MNR**	**p value**
myristic (14:0)	13.29 ± 6.76	14.25 ± 7.62	0.789	14.99 ± 3.7	16.65 ± 6.35	0.686	19.48 ± 3.19	16.8 ± 10.3	0.529
palmitic (16:0)	673.5 ± 136.52	556.5 ± 103.9	0.122	872.9 ± 166.27	807.47 ± 231.98	0.45	1036.81 ± 159.06 *	816.14 ± 206.	**0.014**
palmitoleic (16:1 n-7)	0.03 ± 0.03	0.04 ± 0.04	0.999	20.43 ± 13.57	15.19 ± 12.67	0.649	20.25 ± 8.98	14.11 ± 7.7	0.608
stearic (18:0)	768.23 ± 167.21 *	583.06 ± 85.18	**0.004**	891.73 ± 240.85 *	815.88 ± 238.54 †	0.3	1020.68 ± 119.18 *	820.14 ± 197.	**0.008**

	GD120			GD140			GD170		
MATERNAL PLASMA	**Control**	**MNR**	**p value**	**Control**	**MNR**	**p value**	**Control**	**MNR**	**p value**
oleic (18:1 n-9)	568.86 ± 171.99	460.92 ± 115.77	0.241	740.45 ± 150.3	631.05 ± 191.67	0.299	713.51 ± 310.25	576.31 ± 172.	0.21
linoleic (18:2 n-6)	338.05 ± 58.38 *	262.68 ± 46.28 †	**0.008**	477.29 ± 111.2 *	452.99 ± 85.44 †	0.458	503.23 ± 91.52 *	369.97 ± 81.6	**<0.001**
α-linolenic (18:3 n-3)	29.34 ± 7.44 *	26.92 ± 6.63 †	0.455	38.21 ± 9.87 *	26.72 ± 11.52 †	**0.002**	41.95 ± 7.38 *	30.44 ± 10.1	**0.003**
γ-linolenic (18:3 n-3)	2.72 ± 1.01	3.26 ± 2.05	0.694	5.15 ± 2.58	3.72 ± 3.45	0.37	9.28 ± 4.79 *	5.73 ± 3.32	**0.032**
dihomo-γ-linolenic (20:3 n-6)	23.07 ± 8.31	17.65 ± 4.98	0.241	35.29 ± 13.66	26.66 ± 19.97	0.103	38.8 ± 7.38 *	33.9 ± 15.5	0.371
arachidonic (20:4 n-6)	293.52 ± 86.99	214.97 ± 58.55	0.073	346.48 ± 103.98	287.77 ± 137.04	0.242	280.8 ± 55.13	211 ± 55.32	0.18
eicosapentaenoic (20:5 n-3)	3.19 ± 1.11	2.23 ± 0.7	0.325	3.71 ± 3.76	2.21 ± 2.31	0.18	6.76 ± 0.7 *	5.09 ± 1.2 †	0.151
adrenic (22:4 n-6)	3.37 ± 0.77	3.12 ± 0.84	0.631	3.37 ± 1.24	3.58 ± 1.11	0.715	4.84 ± 0.95	4.13 ± 0.96	0.241
n3 docosapentaenoic (22:5 n-3)	5.87 ± 1.35	5.36 ± 1.78	0.555	8.77 ± 3.03 *	7.89 ± 3.98 †	0.376	8.16 ± 0.93	6.94 ± 1.02	0.232
docosahexaenoic (22:6 n-3)	101.98 ± 29.98	91.27 ± 28.8	0.412	118.43 ± 33.38	103.7 ± 38.72	0.325	120.1 ± 27.07 *	105.36 ± 24.	0.343
n6 docosapentaenoic (22:5 n-6)	10.69 ± 5.67	10.52 ± 3.6	0.912	11.2 ± 3.74	9.46 ± 6.04 †	0.341	11.8 ± 3.25 *	8.44 ± 1.25	0.076
Total	2835.69 ± 574.51	2252.74 ± 378.47	**0.031**	3588.39 ± 665.62	3210.94 ± 884.13	0.222	3836.46 ± 584.98 *	3024.49 ± 721	**0.011**

Values expressed as mean ± SD

* p value < 0.05 maternal vs fetal in control group

† p value < 0.05 maternal vs fetal in MNR group

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Table 3.

Mean plasma fatty acid concentrations (μmol fatty acid/L plasma) in triglyceride fraction in control and maternal nutrient restriction (MNR) baboons, based on linear mixed models.

	GD120			GD140			GD170		
FETAL PLASMA	**Control**	**MNR**	**p value**	**Control**	**MNR**	**p value**	**Control**	**MNR**	**p value**
myristic (14:0)	11.57 ± 5.32 *	9.65 ± 4.55	0.345	6.31 ± 3.17	6.55 ± 2.5	0.92	7.58 ± 8.92	3.52 ± 1.71	0.093
palmitic (16:0)	225 ± 93.95 *	195.54 ± 78.66 †	0.328	103.95 ± 43.26	123.54 ± 61.95	0.57	95.45 ± 70	69.02 ± 33.54	0.46
palmitoleic (16:1 n-7)	20.91 ± 19.15 *	19.35 ± 14.08 †	0.687	5.52 ± 2.96	5.95 ± 4.12	0.923	3.04 ± 2.08	3.03 ± 1.4	0.999
stearic (18:0)	52.52 ± 26.14	41.95 ± 23.7	0.401	41.73 ± 19.02	46.69 ± 40.5	0.731	38.13 ± 53.39	20.81 ± 10.36	0.247
oleic (18:1 n-9)	481.02 ± 182.26 *	405.54 ± 183.29	0.319	228.54 ± 131.6	302.42 ± 174.47	0.394	173.65 ± 116.5	128.92 ± 117.19	0.619
linoleic (18:2 n-6)	63.57 ± 35.44	53.68 ± 33.99	0.559	31.04 ± 22.25	55.87 ± 51.59	0.2	41 ± 40.43	28.83 ± 30.58	0.545
α-linolenic (18:3 n-3)	3.13 ± 1.84	2.94 ± 2.49	0.885	1.85 ± 2.7	3.07 ± 2.3	0.417	3.37 ± 3.63	1.32 ± 1.38	0.189
γ-linolenic (18:3 n-3)	4.21 ± 3.06 *	3.55 ± 0.84 †	0.237	0.92 ± 0.37	1.17 ± 0.42	0.69	0.64 ± 0.34	1.52 ± 0.89	0.185
dihomo-γ-linolenic (20:3 n-6)	3.92 ± 2.38 *	2.49 ± 1.5 †	**0.008**	0.72 ± 0.27	0.87 ± 0.36	0.812	1.5 ± 2.77	0.67 ± 0.17	0.192
arachidonic (20:4 n-6)	15.95 ± 6.44 *	15.83 ± 9.01 †	0.948	5.02 ± 1.06	5 ± 1.73	0.99	3.75 ± 2.11	4.43 ± 1.82	0.744
eicosapentaenoic (20:5 n-3)	1.41 ± 0.75 *	1.38 ± 1.13 †	0.894	0.05 ± 0.04	0.17 ± 0.22	0.642	0.28 ± 0.37	0.22 ± 0.06	0.833
adrenic (22:4 n-6)	1.9 ± 0.4 *	1.68 ± 0.67 †	0.176	0.68 ± 0.22	0.83 ± 0.33 †	0.4	0.5 ± 0.36	0.67 ± 0.3	0.366
n3 docosapentaenoic (22:5 n-3)	1.65 ± 0.47 *	1.43 ± 0.65 †	0.292	0.71 ± 0.33	0.79 ± 0.37	0.728	0.47 ± 0.28	0.42 ± 0.15	0.847
docosahexaenoic (22:6 n-3)	11.74 ± 4.38 *	11.69 ± 7.3 †	0.972	4.73 ± 1.11	4.3 ± 1.41	0.792	2.18 ± 0.95	2.37 ± 0.67	0.913
n6 docosapentaenoic (22:5 n-6)	3.1 ± 0.84 *	3.14 ± 1.46 †	0.902	0.74 ± 0.85	0.57 ± 0.74	0.646	0.56 ± 0.37	0.89 ± 0.23	0.417
Total	901.59 ± 319.3 *	769.83 ± 321.68 †	0.304	432.52 ± 216.43	557.79 ± 334.31	0.393	372.09 ± 233.84	266.65 ± 187.56	0.489

	GD120			GD140			GD170		
MATERNAL PLASMA	**Control**	**MNR**	**p value**	**Control**	**MNR**	**p value**	**Control**	**MNR**	**p value**
myristic (14:0)	4.34 ± 2.87	7.87 ± 4.94	0.083	5.24 ± 2.87	9.62 ± 5.02	0.06	9.09 ± 4	7.22 ± 4.11	0.44
palmitic (16:0)	122.96 ± 51.39	128.33 ± 49.46	0.858	120.27 ± 42.36	155.61 ± 73.05	0.305	194.91 ± 107.07 *	179.32 ± 49.36 †	0.663
palmitoleic (16:1 n-7)	3.11 ± 1.72	4.25 ± 3.11	0.767	3.22 ± 1.52	6.16 ± 4.98	0.506	12.15 ± 11.53 *	4.83 ± 2.54	0.11
stearic (18:0)	33.81 ± 21.01	43.88 ± 26.78	0.424	39.12 ± 15.38	46.46 ± 31.52	0.61	46.86 ± 28.15	41.34 ± 12.26	0.712

	GD120			GD140			GD170		
MATERNAL PLASMA	**Control**	**MNR**	**p value**	**Control**	**MNR**	**p value**	**Control**	**MNR**	**p value**
oleic (18:1 n-9)	261.23 ± 183.6	276.57 ± 198.96	0.84	297.23 ± 158.84	312.43 ± 130.45	0.861	325.68 ± 240.01	304.86 ± 115.2 †	0.817
linoleic (18:2 n-6)	71.28 ± 48.83	61.92 ± 41.01	0.581	54.65 ± 26.37	62.59 ± 22.51	0.682	61.78 ± 49.54	72.13 ± 27.05 †	0.607
α-linolenic (18:3 n-3)	4.45 ± 3.7	3.5 ± 3.05	0.469	3.23 ± 1.53	3.6 ± 2.6	0.809	4.67 ± 5.46	3.99 ± 2.24	0.662
γ-linolenic (18:3 n-3)	1.2 ± 0.28	1.67 ± 0.96	0.409	0.86 ± 0.7	0.94 ± 0.46	0.906	2.23 ± 2.01 *	1.59 ± 0.7	0.339
dihomo-γ-linolenic (20:3 n-6)	0.85 ± 0.5	0.77 ± 0.42	0.883	0.54 ± 0.27	0.55 ± 0.31	0.995	0.72 ± 0.31	0.81 ± 0.34	0.886
arachidonic (20:4 n-6)	4.93 ± 0.92	4.47 ± 2.31	0.795	3.52 ± 1.75	3.3 ± 0.88	0.912	4.33 ± 2.21	3.92 ± 1.03	0.846
eicosapentaenoic (20:5 n-3)	0.62 ± 0.73	0.28 ± 0.11	0.142	0.07 ± 0.09	0.09 ± 0.1	0.938	0.2 ± 0.2	0.26 ± 0.07	0.853
adrenic (22:4 n-6)	0.58 ± 0.3	0.45 ± 0.19	0.417	0.42 ± 0.2	0.48 ± 0.2	0.768	0.55 ± 0.4	0.66 ± 0.26	0.591
n3 docosapentaenoic (22:5 n-3)	0.98 ± 0.64	0.56 ± 0.24	**0.046**	0.96 ± 0.64	0.85 ± 0.3	0.653	0.76 ± 0.58	1 ± 0.51 †	0.337
docosahexaenoic (22:6 n-3)	3.13 ± 2	2.05 ± 0.88	0.446	3.86 ± 2.63	2.61 ± 0.8	0.439	4.06 ± 3.12	3.15 ± 1	0.59
n6 docosapentaenoic (22:5 n-6)	1.05 ± 0.57	0.8 ± 0.36	0.453	0.37 ± 0.5	0.41 ± 0.55	0.909	0.94 ± 0.58	1.13 ± 0.59	0.625
Total	514.53 ± 280.12	537.37 ± 292.97	0.859	533.59 ± 236.62	605.7 ± 246.81	0.623	668.93 ± 416.94 *	626.21 ± 197.92 †	0.779

Values expressed as mean ± SD

* *p* value < 0.05 maternal vs fetal in control group

† *p* value < 0.05 maternal vs fetal in MNR group

Table 4.

Mean plasma fatty acid concentrations (μmol fatty acid/L plasma) in non-esterified fatty acid (NEFA) fraction in control and maternal nutrient restriction (MNR) baboons, based on linear mixed models.

	GD120			GD140			GD170		
FETAL PLASMA	**Control**	**MNR**	**p value**	**Control**	**MNR**	**p value**	**Control**	**MNR**	**p value**
myristic (14:0)	20.71 ± 9.68	15.3 ± 14.41 †	0.218	8.71 ± 6.36	7.4 ± 5.59	0.794	2.73 ± 6.9	2.98 ± 6.36	0.962
palmitic (16:0)	138.73 ± 91.11	117.47 ± 130.75	0.619	82.78 ± 49.46	79.21 ± 32.84	0.942	26.22 ± 69.72	3.23 ± 59.82	0.651
palmitoleic (16:1 n-7)	2.13 ± 1.39	1.47 ± 0.55	0.565	4.06 ± 2.18	2.47 ± 1.28	0.226	1.59 ± 0.65	1.46 ± 1.43	0.923
stearic (18:0)	148.44 ± 102	143.65 ± 106.58	0.913	62.75 ± 37.82	76.49 ± 62.07	0.785	66.56 ± 72.75	49.04 ± 139.75	0.737
oleic (18:1 n-9)	21.62 ± 17.39	13.67 ± 8.46	0.65	57.56 ± 43.36	45.16 ± 34.23	0.536	25.99 ± 21.75	37.83 ± 52.6	0.569
linoleic (18:2 n-6)	7.93 ± 5.26	7.95 ± 6.86	0.996	12.15 ± 9.83	11.79 ± 7.87	0.941	10.32 ± 7.94	9.25 ± 8.46	0.829
α-linolenic (18:3 n-3)	0.34 ± 0.36	0.32 ± 0.48	0.974	0.83 ± 0.88	0.77 ± 0.63	0.87	0.61 ± 0.76	0.43 ± 0.49	0.653
γ-linolenic (18:3 n-3)	0.46 ± 0.16	0.41 ± 0.24	0.532	0.19 ± 0.05	0.2 ± 0.11	0.909	0.15 ± 0.06	0.19 ± 0.05	0.722
dihomo-γ-linolenic (20:3 n-6)	0.56 ± 0.25 *	0.36 ± 0.13	**<0.001**	0.16 ± 0.06	0.15 ± 0.06	0.906	0.13 ± 0.02	0.14 ± 0.03	0.855
arachidonic (20:4 n-6)	3.51 ± 1.95	3.08 ± 0.87	0.404	1.36 ± 0.3	1.2 ± 0.1	0.787	1 ± 0.13	0.94 ± 0.18	0.928
eicosapentaenoic (20:5 n-3)	0.33 ± 0.15	0.28 ± 0.1	0.259	0.01 ± 0.01	0.01 ± 0.01	0.989	0.06 ± 0.03	0.06 ± 0.01	0.98
adrenic (22:4 n-6)	0.19 ± 0.08 *	0.15 ± 0.08 †	0.122	0.06 ± 0.03	0.07 ± 0.02	0.631	0.06 ± 0.02	0.08 ± 0.03	0.511
n3 docosapentaenoic (22:5 n-3)	0.14 ± 0.05	0.12 ± 0.05	0.594	0.09 ± 0.03	0.08 ± 0.02	0.665	0.06 ± 0.03	0.06 ± 0.01	0.977
docosahexaenoic (22:6 n-3)	1.99 ± 0.69 *	1.65 ± 0.48 †	0.093	1.27 ± 0.22	1.04 ± 0.18	0.316	0.79 ± 0.25	0.82 ± 0.1	0.913
n6 docosapentaenoic (22:5 n-6)	0.31 ± 0.11 *	0.28 ± 0.14 †	0.573	0.11 ± 0.11	0.08 ± 0.1	0.522	0.09 ± 0.05	0.15 ± 0.04	0.261
Total	347.4 ± 182.3	306.18 ± 245	0.649	232.11 ± 132.33	226.13 ± 89.15	0.954	136.37 ± 31.52	106.67 ± 93.75	0.783

	GD120			GD140			GD170		
MATERNAL PLASMA	**Control**	**MNR**	**p value**	**Control**	**MNR**	**p value**	**Control**	**MNR**	**p value**
myristic (14:0)	16.56 ± 9.66	6.85 ± 6.39	**0.027**	26.17 ± 17.29 *	5.26 ± 8.09	**<0.001**	4.28 ± 10.66	1.59 ± 7.08	0.628
palmitic (16:0)	171.64 ± 89.18	87.64 ± 84.33	0.05	277.68 ± 196.2 *	57.67 ± 52.86	**<0.001**	46.08 ± 98.6	48.95 ± 66.64	0.856
palmitoleic (16:1 n-7)	2.11 ± 1.78	1.22 ± 0.79	0.437	11.32 ± 8.41 *	1.73 ± 0.93	**<0.001**	2.91 ± 1.58	1.3 ± 0.57	0.263
stearic (18:0)	201.21 ± 130.55	107.11 ± 48.04	**0.032**	169.73 ± 151.81 *	53.45 ± 81.66	**0.021**	57.84 ± 88.48	127.22 ± 86.61	0.208
oleic (18:1 n-9)	37.45 ± 19.63	23.32 ± 14.52	0.42	164.45 ± 107.33 *	35.88 ± 27.05	**<0.001**	38.23 ± 19.97	45.89 ± 32.5	0.696

	GD120			GD140			GD170		
MATERNAL PLASMA	**Control**	**MNR**	**p value**	**Control**	**MNR**	**p value**	**Control**	**MNR**	**p value**
linoleic (18:2 n-6)	22.1 ± 12.13 *	14.43 ± 9.57	0.067	33.24 ± 16.2 *	10.97 ± 4.96	**<0.001**	13.63 ± 6.71	19.2 ± 12.21 †	0.261
α-linolenic (18:3 n-3)	1.08 ± 0.85 *	0.83 ± 0.78	0.447	2.27 ± 1.34 *	0.77 ± 0.58	**<0.001**	0.75 ± 0.7	1.1 ± 0.81	0.374
γ-linolenic (18:3 n-3)	0.49 ± 0.15	0.51 ± 0.33	0.792	0.4 ± 0.29 *	0.26 ± 0.13	0.178	0.47 ± 0.21 *	0.48 ± 0.24 †	0.941
dihomo-γ-linolenic (20:3 n-6)	0.38 ± 0.16	0.28 ± 0.12	0.06	0.28 ± 0.13 *	0.14 ± 0.07	**0.024**	0.15 ± 0.07	0.22 ± 0.08	0.379
arachidonic (20:4 n-6)	4.33 ± 2.36	3.24 ± 1.02	**0.032**	2.42 ± 1.13 *	1.48 ± 0.43	0.106	1.69 ± 0.47	2.02 ± 0.62	0.606
eicosapentaenoic (20:5 n-3)	0.34 ± 0.2	0.27 ± 0.07	0.074	0.03 ± 0.03	0.02 ± 0.03	0.845	0.08 ± 0.06	0.12 ± 0.04	0.363
adrenic (22:4 n-6)	0.11 ± 0.04	0.08 ± 0.04	0.212	0.17 ± 0.1 *	0.09 ± 0.04	**0.003**	0.09 ± 0.03	0.1 ± 0.04	0.568
n3 docosapentaenoic (22:5 n-3)	0.16 ± 0.06	0.1 ± 0.04	0.095	0.36 ± 0.23 *	0.15 ± 0.04 †	**<0.001**	0.14 ± 0.05 *	0.16 ± 0.06 †	0.68
docosahexaenoic (22:6 n-3)	1.06 ± 0.33	0.73 ± 0.28	0.108	1.99 ± 1.09 *	0.78 ± 0.24	**<0.001**	0.72 ± 0.34	0.88 ± 0.29	0.534
n6 docosapentaenoic (22:5 n-6)	0.2 ± 0.1	0.13 ± 0.06	0.128	0.15 ± 0.15	0.08 ± 0.1	0.221	0.15 ± 0.08	0.2 ± 0.09	0.343
Total	459.21 ± 216.83	246.73 ± 142.14	**0.019**	690.64 ± 469.72 *	168.72 ± 153.39	**<0.001**	167.2 ± 180.71	249.43 ± 150.25	0.436

Values expressed as mean ± SD

* *p* value < 0.05 maternal vs fetal in control group

† *p* value < 0.05 maternal vs fetal in MNR group

Table 5.

Mean plasma fatty acid concentrations (μmol fatty acid/L plasma) in phospholipid fraction in control and maternal nutrient restriction (MNR) baboons, based on linear mixed models.

	GD120			GD140			GD170		
FETAL PLASMA	**Control**	**MNR**	**p value**	**Control**	**MNR**	**p value**	**Control**	**MNR**	**p value**
myristic (14:0)	11.46 ± 5 *	8.14 ± 3.02 †	0.132	6.04 ± 3.65 *	9.62 ± 8.28 †	0.154	3.81 ± 4.2	6.81 ± 2.86 †	0.252
palmitic (16:0)	324.6 ± 80.73 *	252.54 ± 77.63 †	0.101	322 ± 55.9	398.97 ± 146.72	0.126	216.3 ± 84.54	238.35 ± 59.93	0.673
palmitoleic (16:1 n-7)	7.37 ± 5.35 *	5.48 ± 2.4 †	0.263	10.98 ± 6.26 *	13.14 ± 7.58 †	0.265	3.04 ± 0.94	2.83 ± 0.99	0.915
stearic (18:0)	263.09 ± 90.79	234.25 ± 79.15	0.554	136.17 ± 75.1	194.43 ± 99.95	0.296	158.68 ± 108.47	233.29 ± 59.27	0.197
oleic (18:1 n-9)	40.95 ± 9.38	34.41 ± 11.77	0.661	67.35 ± 27.96	80.53 ± 30.49	0.44	40.86 ± 8.73	39.12 ± 12.37	0.922
linoleic (18:2 n-6)	37.01 ± 14.05	33.68 ± 16.16	0.789	45.44 ± 14.93	58.07 ± 17.58	0.374	35.77 ± 12.07	28.46 ± 7.51	0.62
α-linolenic (18:3 n-3)	1.95 ± 0.88	1.77 ± 1.15	0.849	3.64 ± 1.26	4.42 ± 1.66	0.474	2.32 ± 1.3	1.46 ± 0.39	0.442
γ-linolenic (18:3 n-3)	1.75 ± 2.54 *	0.99 ± 0.5	0.052	0.42 ± 0.21	0.72 ± 0.59	0.492	0.39 ± 0.1	0.64 ± 0.3	0.584
dihomo-γ-linolenic (20:3 n-6)	27.76 ± 14.52 *	23.48 ± 13.94 †	0.336	17.13 ± 6.86	22.68 ± 10.66	0.276	9.89 ± 2.75	12.57 ± 3.62	0.613
arachidonic (20:4 n-6)	251.43 ± 129.85 *	228.43 ± 137.98 †	0.509	188.76 ± 50.57	210.55 ± 60.18 †	0.585	121.03 ± 44.7	91.97 ± 25.62	0.483
eicosapentaenoic (20:5 n-3)	1.37 ± 1.03	1.27 ± 0.78	0.887	4.01 ± 2.04	3.95 ± 2.38	0.938	1.97 ± 1.61	0.46 ± 0.16	0.053
adrenic (22:4 n-6)	2.09 ± 0.97 *	1.58 ± 0.62	0.053	2.32 ± 0.5 *	2.35 ± 0.56 †	0.939	2.19 ± 0.34	2.27 ± 0.79 †	0.797
n3 docosapentaenoic (22:5 n-3)	1.94 ± 0.46	1.67 ± 0.5	0.378	2.13 ± 0.94	2.36 ± 0.43	0.528	2.32 ± 0.77	1.65 ± 0.55	0.072
docosahexaenoic (22:6 n-3)	46.24 ± 13.68	41.35 ± 16.48	0.563	49.11 ± 12.05	54.51 ± 7.76	0.578	35.2 ± 12.96	39.33 ± 16.58	0.681
n6 docosapentaenoic (22:5 n-6)	3.23 ± 1.87	2.68 ± 0.9	0.603	3.09 ± 1.31	2.99 ± 0.61	0.937	1.99 ± 0.48	3.09 ± 1.49	0.382
Total	1022.23 ± 322.87	871.72 ± 315.13 †	0.28	858.58 ± 156.52	1059.28 ± 329.04	0.209	635.77 ± 251.95	702.29 ± 159.35	0.688

	GD120			GD140			GD170		
MATERNAL PLASMA	**Control**	**MNR**	**p value**	**Control**	**MNR**	**p value**	**Control**	**MNR**	**p value**
myristic (14:0)	5.14 ± 4.41	3.01 ± 3.16	0.333	1.01 ± 3.78	4.62 ± 8.18	0.152	5.09 ± 5.32	3.31 ± 2.69	0.496
palmitic (16:0)	210.77 ± 77.47	131.19 ± 43.16	0.07	290.98 ± 170.74	327.1 ± 120.05	0.472	437.33 ± 103.05 *	272.22 ± 100.97	**0.002**
palmitoleic (16:1 n-7)	1.3 ± 0.5	1.18 ± 0.87	0.945	3.92 ± 2.68	5.2 ± 5.24	0.508	4.76 ± 1.49	1.99 ± 1	0.169
stearic (18:0)	298.15 ± 124.1	188.36 ± 60.7	**0.024**	221.47 ± 125.85 *	249.02 ± 84.69	0.621	436.68 ± 200.59 *	392.54 ± 148.72 †	0.445

	GD120			GD140			GD170		
MATERNAL PLASMA	**Control**	**MNR**	**p value**	**Control**	**MNR**	**p value**	**Control**	**MNR**	**p value**
oleic (18:1 n-9)	34.61 ± 15.12	23.99 ± 5.81	0.476	81.06 ± 56.77	107.43 ± 75.66	0.122	127.03 ± 47.22 *	56.49 ± 25.29	**<0.001**
linoleic (18:2 n-6)	80.1 ± 38.55 *	56.04 ± 16.95 †	0.053	109.22 ± 57.75 *	116.52 ± 30.55 †	0.608	153.37 ± 31.94 *	95.45 ± 38.32 †	**<0.001**
α-linolenic (18:3 n-3)	4.32 ± 1.91 *	2.89 ± 0.79	0.134	6.64 ± 2.7 *	8.86 ± 3.09 †	**0.041**	11.88 ± 4.73 *	5.43 ± 2.67 †	**<0.001**
γ-linolenic (18:3 n-3)	0.32 ± 0.14	0.34 ± 0.15	0.968	0.34 ± 0.25	0.33 ± 0.42	0.989	0.88 ± 0.58	0.44 ± 0.33	0.346
dihomo-γ-linolenic (20:3 n-6)	15.81 ± 4.69	12.62 ± 7.26	0.473	17.09 ± 10.48	14.67 ± 15.84	0.635	22.72 ± 2.61 *	16.35 ± 8.09	0.228
arachidonic (20:4 n-6)	116.33 ± 38.34	82.09 ± 33.66	0.326	146.64 ± 93.86	127.27 ± 76.51	0.627	176.75 ± 47.42	96.55 ± 29.45	0.053
eicosapentaenoic (20:5 n-3)	2.3 ± 0.88	1.59 ± 0.56	0.284	3.33 ± 2.54	2.93 ± 2.06	0.59	3.83 ± 1.14 *	1.98 ± 0.68 †	**0.018**
adrenic (22:4 n-6)	1.34 ± 0.33	1.1 ± 0.25	0.362	1.34 ± 0.85	1.46 ± 0.49	0.707	2.12 ± 0.52	1.53 ± 0.39	0.065
n3 docosapentaenoic (22:5 n-3)	2.33 ± 0.65	1.76 ± 0.46	0.069	2.79 ± 1.39	2.88 ± 0.53	0.803	3.74 ± 0.79 *	2.7 ± 0.66 †	**0.005**
docosahexaenoic (22:6 n-3)	41.13 ± 12.42	29.37 ± 7.71	0.165	62.32 ± 35.64	60.14 ± 31.37	0.823	77.9 ± 27.98 *	55.84 ± 14.11	**0.028**
n6 docosapentaenoic (22:5 n-6)	5.83 ± 1.89 *	4.31 ± 2.23	0.152	5.08 ± 2.95	4.78 ± 4.01	0.803	7.63 ± 3.41 *	7.42 ± 4.07 †	0.864
Total	819.78 ± 277.45	539.85 ± 152.76	**0.045**	953.23 ± 513.24	1033.21 ± 375.29	0.616	1471.71 ± 364.72 *	1010.26 ± 353.46 †	**0.005**

Values expressed as mean ± SD

* p value < 0.05 maternal vs fetal in control group

† p value < 0.05 maternal vs fetal in MNR group

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Table 6.

Mean plasma fatty acid concentrations (μmol fatty acid/L plasma) in cholesterol ester fraction in control and maternal nutrient restriction (MNR) baboons, based on linear mixed models.

	GD120			GD140			GD170		
FETAL PLASMA	**Control**	**MNR**	**p value**	**Control**	**MNR**	**p value**	**Control**	**MNR**	**p value**
myristic (14:0)	8.93 ± 4.85 *	9.21 ± 5.46 †	0.836	11.5 ± 3.73 *	10.17 ± 2.43 †	0.386	6.13 ± 1.31 *	6.62 ± 1.61 †	0.757
palmitic (16:0)	140.75 ± 44.5 *	157.58 ± 95.99 †	0.377	160.16 ± 33.09 *	166.66 ± 43.86 †	0.766	110.27 ± 13.49 *	117.83 ± 16.73 †	0.739
palmitoleic (16:1 n-7)	32.99 ± 10.25 *	37.13 ± 23.7 †	0.525	46.58 ± 36.44 *	45.83 ± 21.63 †	0.92	18.16 ± 7.12	19.24 ± 3.39 †	0.889
stearic (18:0)	45.55 ± 22.13 *	37.99 ± 19.54 †	0.353	65.79 ± 19.91 *	80.57 ± 34.47 †	0.113	51 ± 10.68 *	36.54 ± 8.67 †	0.135
oleic (18:1 n-9)	467.85 ± 275.32 *	460.48 ± 329.81 †	0.929	442.15 ± 66.68 *	862.92 ± 330.23 †	**<0.001**	440.76 ± 117.29 *	307.45 ± 70.97 †	0.176
linoleic (18:2 n-6)	66.18 ± 41.8	75.43 ± 40.29	0.583	59.55 ± 20.34	93.07 ± 27.78	0.083	57.22 ± 9.13	52.7 ± 10.6	0.822
α-linolenic (18:3 n-3)	3.81 ± 2.63	4.22 ± 2.33	0.764	5.2 ± 1.86	8.2 ± 2.59	0.058	3.8 ± 1.74	2.45 ± 0.84	0.409
γ-linolenic (18:3 n-3)	4.85 ± 2.89 *	4.85 ± 3.34 †	0.997	2.4 ± 0.87	3.34 ± 1.77 †	0.365	1.51 ± 0.54	3.32 ± 0.83	0.093
dihomo-γ-linolenic (20:3 n-6)	3.08 ± 1.59	3.32 ± 2.1 †	0.61	1.66 ± 0.6	2.1 ± 0.67 †	0.427	1.36 ± 0.4	1.89 ± 0.28	0.357
arachidonic (20:4 n-6)	82.51 ± 45.93 *	104.29 ± 65.93 †	0.124	62.96 ± 28.9 *	61.86 ± 23.9 †	0.946	40.42 ± 7.72	42.53 ± 4.73	0.9
eicosapentaenoic (20:5 n-3)	0.94 ± 0.62	1.27 ± 1.19	0.229	1.34 ± 0.74 *	1.22 ± 0.52 †	0.707	0.66 ± 0.21	0.37 ± 0.06	0.391
adrenic (22:4 n-6)	0.16 ± 0.09	0.32 ± 0.49 †	**0.031**	0.09 ± 0.06	0.07 ± 0.05	0.813	0.11 ± 0.02	0.13 ± 0.05	0.834
n3 docosapentaenoic (22:5 n-3)	0.13 ± 0.12	0.21 ± 0.27 †	0.067	0.07 ± 0.05	0.05 ± 0.04	0.686	0.08 ± 0.03	0.08 ± 0.02	0.984
docosahexaenoic (22:6 n-3)	5.6 ± 2.86	6.81 ± 4.42 †	0.24	3.75 ± 1.54	4.32 ± 1.07	0.627	3.34 ± 1.15	4.35 ± 1.15	0.409
n6 docosapentaenoic (22:5 n-6)	0.52 ± 0.28	0.89 ± 0.98 †	**0.049**	0.2 ± 0.25	0.19 ± 0.24	0.96	0.25 ± 0.15	0.44 ± 0.13	0.398
Total	863.84 ± 427.22 *	904.01 ± 564.83 †	0.763	863.41 ± 144.49 *	1340.58 ± 432.65 †	**0.002**	735.06 ± 130.24 *	595.94 ± 89.14	0.379

	GD120			GD140			GD170		
MATERNAL PLASMA	**Control**	**MNR**	**p value**	**Control**	**MNR**	**p value**	**Control**	**MNR**	**p value**
myristic (14:0)	1.26 ± 0.93	1.14 ± 0.64	0.933	3.01 ± 4.15	1.68 ± 0.92	0.383	2.28 ± 0.9	2.09 ± 1.05	0.908
palmitic (16:0)	55.74 ± 29.68	40.9 ± 9.78	0.436	60.33 ± 36.97	51.85 ± 16.78	0.698	63.17 ± 36.04	51.97 ± 9.43	0.621
palmitoleic (16:1 n-7)	1.99 ± 0.78	1.89 ± 1.2	0.987	2.84 ± 1.2	2.06 ± 1.33	0.917	3.64 ± 3.12	1.82 ± 1.87	0.814
stearic (18:0)	10.06 ± 5.83	8.33 ± 5.47	0.831	21.1 ± 31.9	10.24 ± 10.66	0.244	7.31 ± 12.03	6.43 ± 4.19	0.928

	GD120			GD140			GD170		
MATERNAL PLASMA	**Control**	**MNR**	**p value**	**Control**	**MNR**	**p value**	**Control**	**MNR**	**p value**
oleic (18:1 n-9)	163.14 ± 131.02	91.84 ± 42.39	0.39	217.03 ± 82.21	175.32 ± 70.47	0.661	179.78 ± 113.69	131.12 ± 58.74	0.622
linoleic (18:2 n-6)	146.9 ± 61 *	108.2 ± 27.76 †	**0.022**	127.56 ± 37.68 *	131.68 ± 22.62 †	0.831	127.11 ± 70.5 *	107.89 ± 14.42 †	0.337
α-linolenic (18:3 n-3)	8.86 ± 4.09 *	6.43 ± 2.37	0.079	8.43 ± 5.19 *	8.35 ± 3.78	0.956	6.65 ± 4.97	6.39 ± 1.26 †	0.878
γ-linolenic (18:3 n-3)	1.81 ± 0.9	1.73 ± 0.89	0.936	2.52 ± 2.14	1.35 ± 1.62	0.259	4.42 ± 3.16 *	2.4 ± 1.93	0.062
dihomo-γ-linolenic (20:3 n-6)	2.24 ± 1.06	1.66 ± 0.85	0.232	1.71 ± 0.91	0.9 ± 0.55	0.142	1.58 ± 0.95	1.39 ± 0.55	0.748
arachidonic (20:4 n-6)	51.24 ± 24.73	34.34 ± 12.84	0.232	32.98 ± 7.63	29.65 ± 19.05	0.837	45.39 ± 31.68	28.62 ± 10.35	0.319
eicosapentaenoic (20:5 n-3)	1.41 ± 0.79	1.01 ± 0.43	0.152	0.71 ± 0.41	0.62 ± 0.36	0.796	0.92 ± 0.6	0.79 ± 0.12	0.698
adrenic (22:4 n-6)	0.06 ± 0.04	0.05 ± 0.02	0.907	0.03 ± 0.02	0.03 ± 0.02	0.973	0.06 ± 0.02	0.04 ± 0.01	0.859
n3 docosapentaenoic (22:5 n-3)	0.1 ± 0.07	0.06 ± 0.03	0.449	0.07 ± 0.03	0.08 ± 0.04	0.771	0.09 ± 0.04	0.07 ± 0.02	0.632
docosahexaenoic (22:6 n-3)	5.11 ± 1.94	4.23 ± 1.5	0.395	4.29 ± 1.21	3.99 ± 1.78	0.799	4.97 ± 3.24	4.49 ± 1.55	0.698
n6 docosapentaenoic (22:5 n-6)	0.59 ± 0.2	0.5 ± 0.18	0.616	0.11 ± 0.19	0.27 ± 0.4	0.444	0.54 ± 0.49	0.53 ± 0.24	0.938
Total	450.5 ± 248.51	302.32 ± 79.9	0.265	482.72 ± 184.22	418.07 ± 127.01	0.671	447.9 ± 257.79	346.05 ± 83.55	0.519

Values expressed as mean ± SD

* *p* value < 0.05 maternal vs fetal in control group

† *p* value < 0.05 maternal vs fetal in MNR group

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