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CONDIÇÕES ANTROPOMÉTRICAS E METABÓLICAS MATERNAS E SUA RELAÇÃO COM A GLICEMIA DE RECÉM-NASCIDOS PREMATUROS

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Esta dissertação foi julgada adequada para a obtenção do título de Mestre em Biociências e Saúde e aprovada em sua forma final pelo Orientador e pela Banca Examinadora.

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RESUMO GERAL

O estado nutricional, hormonal e metabólico materno tem implicações diretas sobre o desenvolvimento do bebê intra-utero e influencia o estado de saúde da criança ao longo da infância e na vida adulta, um evento definido como programação metabólica. Considerando que Recém-nascidos Prematuros (RNPT) apresentam maiores chances de desenvolver diversas doenças ao longo da vida, surgem as seguintes questões: São as condições metabólicas e antropométricas maternas determinantes para a glicemia (Gli) do RNPT ao nascimento e aos seis meses de idade corrigida (6m IC)? A condição metabólica em mães com parto prematuro (PP) e seus respectivos RNPT difere de mães com parto a Termo (AT) e seus respectivos Recém-Nascidos a Termo (RNAT). Para tanto, teve-se como objetivos: i) Estabelecer se há diferença entre o estado metabólico materno e do bebê, entre RNAT e RNPT; ii) Identificar se o estado metabólico e antropométrico materno estavam correlacionados ao perfil glicêmico, lipídico e insulinêmico em RNPT ao nascimento e aos 6m IC. Para tal foi realizado estudo quantitativo do tipo observacional, longitudinal, prospectivo. A amostra foi constituída de mães e seus respectivos RNPT que permanecerem na Unidade de Terapia Intensiva Neonatal (UTIN) do Hospital Universitário do Oeste do Paraná (HUOP) os quais foram comparados ao grupo controle, composto por RNAT e suas respectivas mães. Foram avaliados parâmetros antropométricos (peso corporal, estatura e Índice de massa Corporea (IMC) e plasmáticos bioquímicos como: Gli, Triglicerídeos (TG), Colesterol (CT) e Insulina (Ins). Amostras maternas foram coletadas na internação no pré-parto e dos bebês entre as 24-72h após o nascimento e também no retorno aos 6m de IC. Mães de RNPT apresentaram menor média de idade, ganho de peso e de IMC, acompanhado de menor CT em relação a Mães de RNAT ($p<0,05$). RNPT apresentaram maior Ins e Gli, acompanhado de menor CT e TG ao nascer comparado aos RNAT ($p<0,05$). Aos 6 m de IC apenas a Gli dos RNPT continuou maior que em RNAT ($p<0,05$). Usando modelo de regressão linear, foi demonstrado que o ganho de peso corporal e o metabolismo materno influenciaram a Gli dos RNPT ao nascer e aos 6 m de CA. Enquanto o maior ganho de peso materno isoladamente está relacionado à menor Gli do RNPT, a associação de maior ganho de peso materno com maior Gli ou TG materno resultam em aumentos da Gli no RNPT. Aos 6m de IC a maior Gli ou maior TG materno estão relacionados a maiores níveis plasmáticos de gli no RNPT, sugerindo que a condição de saúde materna no momento do parto tem efeitos sobre a Gli do RNPT ao nascer e na infância precoce. Estes achados reforçam o conceito de programação metabólica servindo de subsídios para novas condutas clínicas e o monitoramento apropriado da gestante e do RNPT no intuito de evitar a instalação de quadros patológicos, em especial doenças que rompem a homeostase glicêmica, como é o caso do diabetes.

Palavras-chave: Programação metabólica. Prematuridade. Glicemia.

GENERAL ABSTRACT

Maternal nutritional, hormonal and metabolic status has direct implications on the development of the intrauterine infant and influence the child's health status throughout childhood and adulthood, an event defined as metabolic programming. Considering that preterm newborns (NBs) are more likely to develop several diseases throughout their life, the following questions arise: Are the maternal metabolic and anthropometric conditions determinant for the blood glucose (Glu) of the preterm newborn at birth and at six months of corrected age (6m CA)? The metabolic condition in mothers with preterm birth (PP) and their respective PTNB differ from mothers with term delivery (TA) and their respective term newborns (TNB)? Therefore, the objectives are: i) To establish whether there is a difference between maternal and infant metabolic status, between TNB and PTNB. ii) Identify whether the maternal metabolic and anthropometric status are correlated to the glycemic, lipidic and insulinemic profile in preterm birth and 6m CA. For that, a quantitative study of observational, longitudinal, prospective type was performed. The sample consisted of mothers and their respective PTNB who remained in the Neonatal Intensive Care Unit (NICU) of the Hospital Universitário do Oeste do Paraná (HUOP), which were compared to the control group, composed of newborns and their respective mothers. Anthropometric parameters (body weight, height and Body Mass Index (BMI) and biochemical plasma levels (Gli, triglycerides (TG), cholesterol (CT) and insulin (INS)) were evaluated. Maternal samples were collected between 24 and 48 hours after delivery and of the babies between 24 and 72 hours after, which was associated with a lower mean age, weight gain and BMI, accompanied by lower plasma levels of CT in relation to TNB mothers ($p < 0.05$). PTNB presented higher Ins and Glu, accompanied by lower CT and TG at birth compared to TNB ($p < 0.05$). At 6 months of CA only the TNB Glu remained higher than in TNB ($p < 0.05$). Linear regression, it was demonstrated that body weight gain and maternal metabolism influenced the blood Glu of the preterm infants at birth and at 6m CA. While the greater maternal weight gain alone is related to lower blood glucose in the PTNB, the association of higher maternal weight gain with higher maternal Glu or TG results in increases in blood Glu in PTNB. At 6 m CA greater Glu or higher maternal TG are related to higher plasma Glu levels in PTNB suggesting that the maternal health condition at the time of delivery has effects on the Glu of premature at birth and early childhood. These findings reinforce the concept of metabolic programming by providing subsidies for new clinical behaviors and appropriate monitoring of pregnant and PTNB in order to avoid the installation of pathological conditions, especially diseases that break glycemic homeostasis, such as diabetes.

Keywords: Metabolic programming.Prematurity.Glycemia.

SUMÁRIO

LISTA DE ABREVIATURAS

AIG	Adequados para a Idade Gestacional
AT	A termo
CT	Colesterol Total
DCV	Doenças Cardiovasculares
DNA	Ácido desoxirribonucléico
DM	Diabetes Mellitus
DM2	Diabetes Mellitus tipo 2
DMG	Diabetes Mellitus Gestacional
IC	Idade Corrigida
IG	Idade Gestacional
IMC	Índice de Massa Corpórea
GLI	Glicose
GIG	Grandes para a Idade Gestacional
HAS	HipertensãoArterial Sistêmica
HDL	High Density Lipoprotein
LDL-	Low DensityLipoprotein
HPL	Hormônio Lactogênio Placentário
PA	Pressão arterial
PIG	Pequenos para a Idade Gestacional
PP	Parto Prematuro
PT	Prematuro
RCIU	Restrição do Crescimento Intrauterino
RN	Recém-Nascido
RNPT	Recém-Nascido Prematuro
RI	Resistência à Insulina
RNAT	Recém-Nascido a Termo
SM	Síndrome Metabólica
6 m IC	Seis Meses de Idade Corrigida
SNC	Sistema Nervoso Central
TG	Triglicerídeos
UTIN	Unidade de Tratamento Intensivo Neonatal
VLDL	Very Low Density Lipoprotein (Lipoproteína de muito baixa densidade)

INTRODUÇÃO GERAL

A prematuridade é considerada um problema relevante de saúde pública mundial, em particular devido ao grande impacto exercido sobre a morbidade e mortalidade infantil (WHO, 2012; SANTOS; OLIVEIRA, 2011). Adicionalmente o tratamento adequado do Recém-Nascido Prematuro (RNPT), somada as complicações de saúde ao longo do seu desenvolvimento resulta em elevados custos econômicos para o sistema público de saúde (KHASHU et al., 2009).

Diversos estudos têm demonstrado que o RNPT tem maior chance de desenvolver doenças na infância, tais como, atraso no desenvolvimento cognitivo e motor, dificuldades respiratórias, cegueira e surdez (LIMA et al., 2014; HACK et al., 2009). Adicionalmente dados recentes também indicam que RNPT, apresentam maior predisposição à instalação de doenças crônicas na vida adulta, em especial obesidade, Diabetes Mellitus tipo 2 (DM2), Hipertensão Arterial Sistêmica (HAS) e dislipidemias (De JONG et al., 2012).

Dentro deste contexto especial atenção tem sido destinada à obesidade e suas complicações metabólicas, uma vez que esta condição afeta indivíduos de ambos os sexos, em todas as faixas etárias, tendo assim atingido proporções epidêmicas no mundo todo (WHO, 2011). Neste sentido, a obesidade tornou-se uma das principais questões de saúde pública em diversos países, incluindo o Brasil, em particular, por sua íntima associação a uma disfunção metabólica conhecida como Síndrome Metabólica (SM) (SINAIKO, 2012). A SM é definida como a reunião de alterações metabólicas e hormonais intimamente associadas ao excesso de tecido adiposo, promovendo Resistência à insulína (RI), intolerância a glicose, HAS, e dislipidemia, caracterizada por baixas concentrações de colesterol HDL (High Density Lipoprotein), e níveis elevados de triglicerídeos (TG) (SBC, 2013).

Embora a obesidade possa ser desencadeada por diferentes fatores, dados epidemiológicos indicam que os hábitos alimentares e o sedentarismo são dois

elementos centrais na epidemia mundial de obesidade, particularmente quando afetam etapas precoces do desenvolvimento dos indivíduos (WHO, 2011). Deste modo, o estado nutricional, hormonal e metabólico materno tem implicações diretas sobre o desenvolvimento do bebê e mais importante, repercussões para o estado de saúde na infância e também ao longo da vida adulta (HOFFMAN, 2014; MCARDLE et al., 2006). Por exemplo, o baixo peso materno e as deficiências de micronutrientes específicos durante a gestação podem resultar em baixo peso do bebê ao nascer. Similarmente, o sobrepeso e a obesidade materna, associados com o desenvolvimento do Diabetes Mellitus Gestacional (DMG) e/ou síndromes hipertensivas tem consequências deletérias para a saúde da mãe e do concepto (ABENHAIM et al., 2007). Sendo assim, ambas as condições maternas tem repercussões diretas para a saúde futura destes indivíduos, pois elevam o risco para desenvolvimento de Doenças Cardiovasculares (DCV) e Diabetes Mellitus (DM) (RAVELLI et al., 1998; ROSENBOOM et al., 2000).

A primeira evidência de correlação entre estado materno e impacto no estado de saúde dos filhos ao longo da vida foi feita por Barker et al. (1986), que propuseram a hipótese de “programação” segundo a qual, eventos nutricionais ocorridos durante a vida intrauterina e infância precoce poderiam influenciar o estado de saúde daquele indivíduo na vida adulta (BARKER et al., 1986). Os efeitos da programação fetal, são decorrentes do período do desenvolvimento, sendo, inclusive, benéfica ao feto durante períodos em ambiente gestacional adverso. Por exemplo, em situações de desnutrição gestacional, o concepto pode responder com alterações permanentes em seu metabolismo e estrutura, as quais terão o efeito imediato de garantir a sua sobrevivência (STOCKER et al., 2005). Todavia, a longo prazo, essa programação inicial (metabólica, hormonal e/ou morfológica) aumenta a susceptibilidade a instalação de doenças que podem repercutir na vida adulta, em especial quando o indivíduo é exposto a um ambiente adverso ou desfavorável (BARKER; CLARCK, 1997).

Tendo em vista que vários estudos vem demonstrando a relação do estado de saúde materna, o peso corporal do bebê ao nascimento e idade gestacional (IG) com o desenvolvimento da obesidade na infância, bem como na vida adulta, identificar precocemente os efeitos da programação metabólica promovido pelo nascimento prematuro poderá auxiliar no tratamento e prevenção de doenças a longo prazo, particularmente aquelas que rompem a homeostase energética. Dentro

deste contexto, já existem evidências demonstrando que a prematuridade pode estar associada à alterações no controle da glicêmia e do perfil lipídico (HOVI et al., 2013; PARKINSON et al.,2013; PERNG et al., 2015) ambos marcadores metabólicos de doenças crônicas, como o DM2 e a HAS. A maioria dos estudos, investigando condições ao nascimento e a instalação de doenças na vida adulta, foram realizados em crianças nascidas a termo que apresentam baixo peso ao nascer ou em prematuros tardios, havendo uma lacuna no que se refere especificamente as peculiaridades metabólicas dos RNPT, e sua relação com a condição materna.

Conhecendo a relação entre o estado metabólico materno e a prematuridade nosso projeto levanta as seguintes questões: são as condições metabólicas e antropométricas maternas determinantes para a glicemia e lipidemia do RNPT ao nascimento e aos seis meses de idade corrigida (6m IC)? A condição metabólica em mães com parto prematuro (PP) e seus respectivos RNPT difere de mães com parto a Termo (AT) e seus respectivos Recém Nascidos a Termo (RNAT)? Sendo a gestação, bem como, o nascimento prematuro condições especiais por modularem janelas críticas do desenvolvimento tendo impacto no estado de saúde futura do indivíduo, nossa hipótese é que o estado metabólico e hormonal materno e do RNPT ao nascimento influenciam o controle homeostático glicêmico e lipídico na infância precoce (6 m de IC) destes indivíduos.

REVISÃO GERAL DA LITERATURA

2.1 Programação Metabólica e Estados Patológicos

A nutrição tem grande influência sobre o desenvolvimento dos mamíferos, em particular em períodos críticos do desenvolvimento, os quais incluem a gestação, lactação e os primeiros meses de vida (SILVEIRA et al., 2007). Conforme demonstram diferentes estudos em humanos, a característica do ambiente nutricional nestas denominadas “janelas críticas do desenvolvimento” é o principal fator determinante para o crescimento da criança com repercussões para o seu estado de saúde na vida adulta (SUN et al., 2013; HOFFMAN, 2014; DESAI et al., 2013). As primeiras evidências mostrando que alterações nutricionais fetais na gestação podem ter repercussão para o estado de saúde dos indivíduos na vida adulta foram feitas por estudos realizados em uma coorte de homens nascidos entre janeiro de 1944 a dezembro de 1947 nos país baixos ao final da Segunda Guerra Mundial (1944-1945), período este conhecido como “fome holandesa”. Nesta época, o governo alemão restringiu a oferta de alimentos passando de 1500 quilocalorias por pessoa (Kcal/pessoa) para 1000 e depois para apenas 500 Kcal/pessoa. Essa restrição alimentar durou cerca de seis meses e os homens adultos nascidos de gestações que ocorreram neste período foram estudados aos 19 anos de idade. A maioria destes indivíduos apresentava alterações de peso corporal e metabólicas, incluindo maior incidência de estados patológicos na vida adulta, em especial obesidade. Adicionalmente este estudo demonstrou que o período gestacional afetado tinha repercussões distintas nos eventos patológicos que acometeriam o indivíduo na vida adulta. Quando a desnutrição ocorria no final da gestação, a incidência de obesidade era baixa, e se, no início da gestação, a incidência de obesidade era maior (RAVELLI et al., 1976).

Estudos posteriores também confirmaram que a etapa do desenvolvimento onde o insulto hormonal e ou nutricional acontece pode determinar o tipo de patologia que irá acometer o indivíduo na vida adulta. Por exemplo, insultos nutricionais durante o início da gestação, aumentam a chance de desenvolver DCV na vida adulta. Por outro lado, insultos nutricionais que ocorrem no fim da gestação, promovendo baixo peso ao nascer, elevam o risco de desenvolver obesidade e DM2 na vida adulta (BARKER; FALL, 1993; RAVELLI et al., 1998; RINAUDO; WANG, 2014; ROSENBOOM et al., 2000).

Posteriormente na década de 80 Barker e Osmond (1986) propuseram a hipótese de "programação". Nestes estudos os autores mostraram que eventos nutricionais ocorridos durante a vida intrauterina e na infância precoce contribuem para o desenvolvimento de doenças no adulto. Lucas (1991) definiu o conceito de programação metabólica ou "*metabolic programming*"[1] como qualquer indução, deleção ou alterações no desenvolvimento de uma estrutura somática permanente, que presente em um período crítico ou sensível do desenvolvimento, pode resultar em modificações e até mesmo dano irreversível em estruturas funcionais tendo impacto no futuro. Considerando o estado nutricional e sua relação com o desenvolvimento, Hales e Barker (2001) propuseram a teoria do "*fenótipo econômico*"[2] sugerindo que o desenvolvimento fetal é sensível ao ambiente nutricional. Portanto, o metabolismo de um indivíduo apresenta uma grande capacidade de se adequar a diversos fatores ambientais, gerando uma grande variabilidade genética e uma grande capacidade de sobrevivência a condições adversas (SCHEINER, 1993).

A programação fetal tem inicialmente um caráter adaptativo e protetor, por exemplo, em períodos onde os fetos humanos ou de outros mamíferos vivem, em um ambiente gestacional adverso, estes respondem à falta de nutrientes, com alterações permanentes em seu metabolismo e estrutura. Nesta fase inicial de adaptação, a estrutura de alguns órgãos é priorizada, em especial o Sistema Nervoso Central (SNC), em detrimento a outros órgãos e sistemas, possibilitando assim aumentar as chances de sobrevivência fetal (GOTTILIEB et al., 2008). Todavia, considerando que estas alterações tenham sido permanentes, após esse

[1] Processo onde um estímulo ou insulto em janelas críticas do desenvolvimento (gestação, lactação) podem levar a danos irreversíveis no feto tendo repercussões futuras predispondo estes indivíduos a doenças (BARKER e OSMOND, 1986).
[2]Teoria que propõe que o feto seja capaz de se adaptar a situações adversas no útero materno, garantindo sua sobrevivência, com alterações em sua estrutura e metabolismo (HALES; BARKER, 1991).

período crítico, este organismo poderá responder de maneira não adequada às variações da ingesta alimentar na vida adulta. Neste sentido, quando este indivíduo é exposto à maior disponibilidade de nutrientes na vida adulta, o organismo pode apresentar maior predisposição ao acúmulo de energia, apresentando hiperfagia e aumentado conteúdo de tecido adiposo, favorecendo a instalação de doenças metabólicas em especial o DM2 (BARKER, 2007).

Para compreender os efeitos deletérios da programação metabólica sobre a saúde, diferentes modelos experimentais têm sido estudados, em particular explorando o impacto de alterações nutricionais nestas fases. Modelos de obesidade induzidas por dieta em animais são eficazes para avaliação da fisiopatologia das morbidades relacionadas com a obesidade (ROSINI et al., 2012). Essas dietas podem ser ofertadas à mãe durante a gestação e lactação, e após são avaliados sua prole quanto à programação metabólica.

Outros modelos de estudos podem ser utilizados durante a gestação e lactação para avaliar os efeitos da programação na prole, como é o caso dos modelos de desnutrição protéica. Usando este modelo experimental Ozanne et al. (2003) demonstraram que a desnutrição proteica fetal durante a gestação e lactação resulta em déficit de crescimento intra-uterino e eleva a incidência de SM e DM2 na vida adulta. Alterações promovidas pela restrição alimentar na gestação e programação da prole também foram observadas em outras espécies de mamíferos. George et al. (2012) fizeram uma restrição alimentar de 50% em ovelhas a qual durou metade da gestação retornando a dieta normal após este período. Esta manipulação nutricional gestacional promoveu diminuição da sensibilidade à insulina, hiperfagia, e ganho de peso na prole (DEL PRADO et al., 1997; GUILLOTEAU et al., 2009).

Achados moleculares recentes têm demonstrado quais são os mecanismos celulares provavelmente envolvidos nos eventos de programação metabólica, os quais mostram como a interação entre o fenótipo e genótipo pode repercutir no funcionamento do organismo, sendo conhecidos como *epigenética*[3] (BURDGE et al., 2007; DESAI et al., 2015).

Em humanos, condições particulares que afetam o período gestacional também têm sido usadas como modelos para estudo de programação metabólica,

3O conceito de epigenética foi introduzido por Waddington em 1939, e mais tarde, foi relacionado com alterações na expressão genética hereditária, onde não há alterações na sequência do DNA, (ácido desoxirribonucléico) mantendo assim, a identidade celular e integridade do genoma (ESTELLER, 2008).

em especial fatores que afetam o desenvolvimento fetal. Dentro deste contexto, a Restrição do Crescimento Intrauterino (RCIU) caracterizada por falha ou retardo do crescimento fetal, frequentemente, induz ao nascimento de bebês com baixo peso, um evento que impacta a saúde da criança a longo prazo (YANNEY; MARLOW, 2004). Adicionalmente, o baixo peso ao nascer é um fator predisponente de mortalidade e morbidade perinatal sendo um marcador para a instalação de doenças na vida adulta (PADILHA et al., 2007; RIBEIRO et al., 2015; STORME et al., 2016). Usando análise do peso corporal ao nascer Hales et al. (1991), revelaram que 45% das crianças nascidas abaixo de 2.500 g, foram diagnosticados com DM2, obesidade e algum tipo de doença coronária aos 64 anos de idade.

Similarmente obesidade gestacional, acompanhada de DMG e hipertensão gestacional também afetam a saúde do bebê ao nascimento e repercutem sobre a condição de saúde, um efeito que pode aparecer precocemente (DAMM, 2009). Mães com DMG ou DM já existente além de correr maior risco de terem filhos com má-formação, principalmente se houver uma hiperglicemia no primeiro trimestre gestacional, podem ter recém-nascido (RN) macrossômicos (≥ 4.000 kg) (BENER et al., 2011; BRASIL, 2010). Adicionalmente, o DMG também aumenta em até 50% a chance de se desenvolver pré-eclampsia durante a gestação (BAZ et al., 2016). Do mesmo modo, filhos de mães hipertensas na gestação ou com pré-eclampsia apresentam maiores níveis de pressão sanguínea na infância se estendendo ao longo da vida (GEELHOED et al., 2010; OGLAEND et al., 2009), além de apresentarem maior risco cardiovascular quando adultos (KAJANTIE et al., 2009). Evidente exemplo desta associação foi demonstrado em um estudo realizado na China, onde avaliou-se o ganho de peso durante a gestação relacionando-se ao peso dos filhos aos 3 e 6 anos de idade. Filhos de mulheres que tiveram um aumento de peso durante a gestação apresentaram um risco elevado (21%) de excesso de peso e obesidade na infância. Já naquelas mães com excesso de peso ou obesidade pré-gestacional e que tiveram um ganho de peso excessivo na gestação, foram responsáveis por duplicar este risco em seus filhos (GUO et al., 2015).

Em conjunto os estudos usando modelos animais (GEORGE et al., 2012; DEL PRADO et al., 1997; GUILLOTEAU et al., 2009) bem como, estudos em humanos (YANNEY; MARLOW, 2004; HALES et al.,1991; GUO et al., 2015) claramente demonstram os efeitos de alterações nutricionais ou hormonais em períodos críticos

do desenvolvimento, com repercussões para o estado de saúde no futuro. Dentro deste contexto, as condições metabólicas maternas durante a gestação, bem como, o estado metabólico do bebê ao nascimento são marcadores precoces para prever condições que podem favorecer a instalação de doenças na infância ou na vida adulta particularmente as patologias que resultam em rompimento da homeostase energética, resultando em alterações do peso corporal e do controle glicêmico e lipídico (DAMM, 2009).

Dentro deste contexto, a programação metabólica está frequentemente associada à instalação da SM na vida adulta (MIERZYNSKI et al., 2016; STORME et al., 2016; ZAMBRANO et al., 2016). Na década de 80, Reaven (1998) observou que muitos indivíduos frequentemente reuniam uma série de anormalidades metabólicas, dentre as quais destacavam a hiperglicemia, HAS e dislipidemias; um perfil que foi inicialmente denominado de Síndrome X, que mais tarde passou a ser chamada de SM. Segundo o National Cholesterol Education Program – Adult Treatment Panel III (2001) a SM é um conjunto de fatores que associados levam a um risco de desenvolver doenças, dentre as quais as mais frequentes são a disfunções cardiovasculares e o DM. Esta condição está relacionada à presença RI, elevada glicemia de jejum, HAS, concentrações baixas de HDL, excessivo acúmulo de gordura abdominal e altas concentrações de triglicerídeos (TG). A presença de três ou mais critérios destes fatores num mesmo indivíduo, são necessários para confirmar diagnóstico da SM (BALCI et al., 2010; GOLDENBERG; PUNTHAKEE, 2013; SANTOS; OLIVEIRA, 2011). A RI é considerada a base fisiopatológica para o desenvolvimento da SM, uma vez que é o principal hormônio responsável pelo controle da homeostase glicêmica e lipídica, cuja disfunção é um evento chave no DM2 e também tem importante correlação com alterações cardiovasculares (LOTTENBERG et al., 2007; GALLAGHER et al., 2011; BALARINI; BRAGA, 2016).

O DM2 é uma doença multifatorial com estreita relação com obesidade. Essa doença se tornou uma epidemia mundial, anualmente cerca de 4 milhões de pessoas no mundo morrem devido ao DM2 e suas complicações. Adicionalmente o tratamento do DM2 tem impacto direto sobre a economia. Em 2011 o Brasil gastou 65 milhões de reais com internações devido a complicações pelo DM (BRASIL, 2011). Estima-se que em 2030, uma em cada dez pessoas no mundo terão DM2, resultando em mais de 552 milhões de pessoas (IDF, 2012). Fisiologicamente o DM2 está relacionado à falhas na ação e ou secreção do hormônio insulina e a

consequente hiperglicemia decorrente do rompimento da homeostase glicêmica. Deste modo a RI definida pela redução da captação de glicose pelos tecidos sensíveis à insulina (músculo esquelético e tecido adiposo) é o fenômeno central do DM2 (COSTANZO, 2014; GUYTON; HALL, 2011; SUN et al., 2016). Quando o desajuste da homeostase glicêmica ocorre durante o período gestacional desenvolve-se o quadro de DMG. Interessantemente filhos de mães com DMG apresentam 8 vezes mais chances de desenvolver DM2 quando adultos (DAMM, 2009).

Conforme já comentado anteriormente a programação metabólica que induz a SM também está associada a DCV. Similarmente ao DM2, as DCV também geram grande impacto econômico e morbidades sendo responsáveis por 20% das mortes no Brasil (MANSUR; FAVARATO, 2012). Estudo realizado por Barker et al. (2002) com crianças de 3 a 11 anos demonstraram uma relação positiva entre o baixo peso ao nascer associado ao rápido ganho de peso na infância, e a maior incidência de doenças metabólicas e cardiovasculares na vida adulta. Similarmente, Davis et al. (2012) demonstraram em sua revisão sistemática e meta-análise que filhos nascidos de mães com pré-eclampsia durante a gestação tem maiores níveis de Pressão Arterial (PA) do que crianças nascidas de mães que não apresentaram o quadro de pré-eclampsia. Segundo Xie et al. (2014) prole de ratas hipercolesterolêmicas são mais susceptíveis à aterosclerose quando adultos. Deste modo parecem evidentes os efeitos da programação metabólica sobre a saúde.

2.2 Prematuridade: Conceitos e Epidemiologia

A prematuridade é um problema relevante de saúde pública cujos índices vêm aumentando consideravelmente no mundo. Segundo estimativas da Organização Mundial da Saúde (OMS) nascem cerca de 15 milhões de Prematuros (PT) por ano no mundo todo (WHO, 2012). O Brasil é o décimo país do mundo onde mais nasce PT. Os nascimentos PT no Brasil representam 11,7 % do total de partos realizados (WHO, 2012). A prematuridade é responsável pela maior causa de mortalidade na primeira semana de vida de RN representando 28% desses óbitos (BRASIL, 2013). No Paraná em 2011 foram registrados 155.758 nascimentos, dos quais 10,5% eram de PT (BRASIL, 2015). Já no ano de 2013 só na cidade de Cascavel-PR foram

4.646 nascimentos, sendo que destes, 565 (12,2%) correspondiam aos PT (BRASIL, 2013; CASCAVEL, 2015).

É considerado RNPT o bebê que nasce com menos de 37 semanas de IG completa e peso igual ou inferior a 2.500g (WHO, 2012). Todavia, outras faixas de prematuridade podem ser estabelecidas. Deste modo, considerando a IG ao nascimento, Myatt et al. (2012) classificam os RNPTs em 3 faixas distintas: 1 - extremamente prematuro nascidos com menos de 28 semanas; 2 – muito prematuro, nascido entre 28 – 31 semanas; 3 - prematuro tardio nascido entre 32 – 36 semanas e 6 dias (MYATT et al., 2012; WHO, 2012).

O RNPT é considerado um importante problema social, em especial porque indivíduos deste grupo são mais suscetíveis a problemas de saúde do nascimento até a vida adulta resultando em elevado custo econômico para o sistema de saúde pública (KHASHU et al., 2009). A sobrevida do RNPT depende de um tratamento especializado, com equipe multidisciplinar, formada de profissionais capacitados, exigindo equipamentos que muitas vezes não estão disponíveis nas Unidades de Terapia Intensiva Neonatal (UTIN) (RAMOS; CUMAN, 2009).

Neste sentido, estudos das últimas décadas indicam que há uma estreita relação entre as condições metabólicas e nutricionais gestacionais e o estado de saúde ao nascimento, com repercussões para a saúde futura do indivíduo (BARKER et al., 2002; SANTOS; OLIVEIRA, 2011).

A prematuridade pode exercer vários efeitos adversos sobre o bebê, entre eles o risco de desenvolver doenças crônicas na vida adulta, evidência que vem sendo confirmada por diferentes estudos. Por exemplo, estudo de coorte realizado com adultos jovens nascidos PT no norte da Finlândia, demonstrou que estes apresentam uma maior predisposição a doenças cardiometabólicas do que crianças AT (LEPPÃNEN et al., 2015). Adicionalmente ao rápido ganho de peso até os seis primeiros meses de vida do bebê, está intimamente relacionada ao aumento da adiposidade central e obesidade aos 7 anos de idade (STETTLER et al., 2002) e na vida adulta (CHOMTHO et al., 2008). Vasylyeva et al. (2013) confirmaram que crianças nascidas prematuras apresentavam excesso de peso já aos 2 anos de idade, um quadro que persistiu na adolescência. Controverso, em uma meta-análise realizada por Parkinson et al. (2013) demostaram não haver relação de RI ou aumento da glicose (GLI) de jejum em adultos nascidos PT comparados a adultos nascidos AT.

2.3 Crescimento e metabolismo do recém-nascido prematuro

Períodos iniciais da vida, compreendendo desde a concepção até o nascimento, caracterizam-se por acelerado crescimento e desenvolvimento de órgãos e tecidos (BROCK; FALCÃO, 2008). Durante o desenvolvimento intra-uterino o bebê é totalmente dependente de sua mãe para manter as funções vitais constantes, em especial, da circulação placentária. A apropriada comunicação via placenta, garante os níveis adequados de oxigênio e nutrientes, incluindo a GLI (WHO, 1997; WILKER, 2005). O nascimento exige do bebê adaptações à vida extra-uterina a fim de permitir sua sobrevivência. Essa fase de transição ocorre nas primeiras 24 horas de vida (KENNER, 2001), sendo especialmente constituída de adaptações fisiológicas para controle de temperatura, reorganização da hemodinâmica vascular, ajustes respiratórios bem como, metabólicos (TEIXEIRA et al., 2007).

As adaptações funcionais após o nascimento são diferentes nos RNPT, uma vez que o seu desenvolvimento intrauterino foi interrompido em um determinado momento. Deste modo, o RNPT necessita crescer a partir do seu grau de imaturidade, submetendo-se aos mesmos mecanismos de transição da criança AT (WILSON; HOCKENBERRY, 2014). Umas das principais dificuldades para o RNPT é o ajuste da homeostase glicêmica neste período. Assim sendo, nas primeiras horas de vida tantos os RNPT quanto os RNAT são acometidos por uma hipoglicemia de transição, mas no RNPT esta alteração metabólica é uma das mais prevalentes nesta fase devido a sua imaturidade fisiológica, atingindo seus níveis mais baixos na primeira hora de vida (CLOHERTY et al., 2009; WHO, 1997; WILKER, 2005).

As complicações funcionais e metabólicas frequentemente observadas na prematuridade repercutem também sobre crescimento desta criança, bem como, na regulação do seu peso corporal (BARKER, 2004). Do nascimento até os dois anos de idade, ocorrem grandes mudanças nos padrões de crescimento infantil, sendo que o perfil de crescimento nesta fase é diferente no RNPT comparado ao RNAT. Para avaliar o desenvolvimento e crescimento do RNPT, é necessária a utilização da Idade Corrigida (IC), que é definida como o ajuste da idade cronológica em relação ao grau de prematuridade. Como o RNPT tem seu desenvolvimento diferenciado,

este parâmetro permite avaliar o RNPT mais precisamente, sem desconsiderá-lo em relação aos RNAT (BRASIL, 2011; KOSINSKA, 2006; RUGOLO, 2005).

A avaliação adequada da taxa de crescimento do RNPT exige o monitoramento frequente devendo ser realizada através de medidas antropométricas de peso corporal, estatura e perímetro cefálico, usando curvas de crescimento padrão, onde o crescimento é avaliado segundo o sexo e a faixa etária (CDCP, 2000; KUCZMARSKI et al., 2000). Essas curvas de crescimento são muito importantes, pois auxiliam no entendimento do crescimento pós-natal, e podem ser muito úteis na detecção de problemas neste período (BROCK; FALCÃO, 2008). Através da IG e do peso ao nascimento é possível avaliar o crescimento do bebê conforme classificação: Adequados para a Idade Gestacional (AIG); Grande para a Idade Gestacional (GIG) e Pequeno para a Idade Gestacional (PIG) (FENTON; KIM, 2013).

Estudos recentes indicam que além do monitoramento do peso corporal do RNPT, é importante avaliar a velocidade com que esse crescimento ocorre. O crescimento acelerado *(catch-up growth)* é considerado como sendo uma fase rápida de recuperação do crescimento (RUGOLO, 2005; VAAG, 2009) maior do que a média para a idade cronológica e sexo do indivíduo. O crescimento acelerado é, frequentemente, acompanhado por desequilíbrio na composição corporal, com desproporcional ganho de massa adiposa em relação ao aumento do ganho de massa muscular (SAENGER et al., 2007). Este período, de maior aceleração do crescimento, ocorre logo após o nascimento do bebê ainda nas primeiras semanas de vida, em específico, do zero aos seis meses, e, normalmente, vão até os dois anos de idade (EICKMANN et al., 2006; ONG et al., 2000). Estudos demonstram que RNPT que apresentam acelerada velocidade de crescimento, tem maior chance de desenvolver doenças crônicas, tais como a SM quando adultos. Contrariamente, a ausência deste fenômeno em RNPT pode levar a uma baixa estatura (MURPHY et al., 2006). Sendo assim, é de extrema importância a avaliação constante das taxas de crescimento dos RNPT, nos seus primeiros anos de vida. Assim, o monitoramento do peso corporal ao nascimento e, ao longo do crescimento, é fator importante para a programação metabólica e a condição de saúde futura da criança.

2.4 Regulação do peso corporal do RNPT

Diversos estudos demonstram a relação do peso ao nascer com o estado de saúde do indivíduo na vida adulta. Neste sentido, tanto o elevado peso corporal, como o baixo peso corporal ao nascimento, são condições que podem ser consideradas marcadores de estados patológicos a médio e longo prazo (BALCI et al., 2010). O RN com peso inferior a 2.500g é denominado baixo peso, e dependendo da IG, é considerado ou não RNPT (MARCONDES, 2003).

Estudos com RNAT PIG mostram que estes apresentam maior chance de desenvolver DM2, HAS na vida adulta (BARKER, 2004). As consequências do baixo peso ao nascer associadas ao excesso de peso durante a infância incidem 25 a 63% sobre o risco de doenças metabólicas na pessoa adulta (BARKER et al., 2002). Ainda nas fases iniciais da vida, o baixo peso ao nascer e o acelerado crescimento pós-natal, também são fatores de risco para o surgimento de doenças na vida adulta (SINGHAL; LUCAS, 2004). Para Neitzke et al. (2011) o peso ao nascer não é a causa da SM e sim um marcador de risco para esta síndrome.

Similarmente, alterações de peso em crianças nascidas GIG levam a um aumento da massa de tecido adiposo corporal, bem como, maiores chances de desenvolver obesidade e DM2 futuramente (ARMITAGE et al., 2005). Adicionalmente, crianças que nasceram acima de 4.000 g, apresentaram duas vezes e meia mais chances de serem obesos na adolescência do que aqueles que nasceram com peso normal, bem como, três vezes mais chances de desenvolver HAS e SM na adolescência (SOUZA et al., 2013). Esta relação também foi demonstrada em estudo realizado na Itália por Chiavaroli et al. (2014), no qual foram avaliadas, durante a infância e adolescência, crianças nascidas a termo PIG, AIG e GIG. O estudo demonstrou que os nascidos PIG e GIG apresentaram maior RI, e também um perfil cardiometabólico desfavorável já na infância, piorando na adolescência quando comparados com crianças nascidas AIG.

Dentro deste contexto, a prematuridade exerce um efeito marcante sobre o peso corporal e as taxas de crescimento, tornando-se assim importante evento que pode favorecer a instalação precoce de doenças. Como na fase final da gestação ocorre um grande aumento na velocidade de fornecimento de nutrientes para o bebê, os depósitos de gordura são formados neste período (último trimestre

gestacional). Um RNAT tem aproximadamente de 15% a 16% de gordura corporal, enquanto um RNPT apenas 2% (ALARADI; MAINOUS, 2012). Após o nascimento, entre o 4º e o 7º dia de vida pós-natal frequentemente ocorre perda de peso corporal (EUSER et al., 2008). No RNPT esta perda é de até 15% do seu peso de nascimento, enquanto em uma criança AT esta queda varia de 3 a 10%. Se o RNPT teve uma nutrição adequada, bem como, o mesmo não seja portador de qualquer doença ou malformação, terá uma recuperação de seu peso até os dois anos de idade. Nestas mesmas condições a altura será recuperada até os três anos de idade. Crianças nascidas prematuras ou PIG apresentam menor sensibilidade a insulina e um elevado risco de DM2 (HOFMAN et al., 2004). Desta forma o nascimento prematuro, acompanhado de alterações do peso corporal irão modular o crescimento e o metabolismo corporal tendo efeitos sobre a saúde na infância, adolescência e vida adulta (BARKER; FALL, 1993).

2.5 Homeostase Glicêmica e Lipídica do RNPT

A homeostase é considerada um processo fisiológico responsável por manter relativamente constante as condições do meio interno incluindo a manutenção dos níveis dos diferentes substratos energéticos (GUYTON; HALL, 2011; GAVRIELLI; MANTZOROS, 2016). Neste sentido, a homeostase glicêmica é afetada por diversos fatores metabólicos ou hormônios, todavia o hormônio insulina é considerado um regulador central da glicemia (SCHUIT, 2015). O rompimento da homeostase glicêmica é evidenciado na hiperglicemia (aumento das concentrações de GLI plasmática) ou hipoglicemia (diminuição das concentrações de GLI plasmática) e, frequentemente, está envolvida em falhas de secreção e/ou a ação do hormônio insulina (FRONZO; FERRANINI, 1991). Considerando a GLI a principal fonte de energia para as células, a manutenção de concentrações glicêmicas adequadas é fundamental para o bom funcionamento do organismo; um evento regulado pela ação periférica da insulina (COSTANZO, 2014; MONTEIRO et al., 2015).

A insulina é considerada um hormônio peptídico formado por duas cadeias lineares A e B ligadas por pontes de dissulfeto (COSTANZO, 2014). A insulina fetal é detectada no plasma por volta das 12 semanas de gestação, e é responsável, por promover o crescimento bem como estimular a captação celular de aminoácidos e a

síntese de proteínas, além de elevar os depósitos de glicogênio e lipídios nos tecidos como fígado, tecido adiposo e músculo (FANAROFF; FANAROFF, 2014).

A hipoglicemia neonatal é comum após o nascimento nas primeiras 24 horas de vida e no RNPT dentro dos três primeiros dias, as taxas de glicose são menores do que no RNAT (PLATT, 2005). A dificuldade em preservar a glicemia em RNPT parece estar relacionada as reservas metabólicas de glicogênio hepático, frequentemente diminuídas nestes RN devido a incapacidade fetal de realizar a gliconeogênese (HUME et al., 2005).

A insulina é um hormônio com impacto direto também no perfil lipídico, pois tem a função de estimular a lipogênese, elevar o armazenamento de gordura, bem como inibir a oxidação de ácidos graxos (COSTANZO, 2014; SOBREVIA et al., 2016). Os lipídios exercem importantes funções no organismo sendo essenciais para o desenvolvimento fetal. O Colesterol Total (CT), TG, ácidos graxos e os fosfolípides são os lipídios mais importantes biologicamente. O CT é considerado um precursor de hormônios esteróides, da vitamina D e dos ácidos biliares, além de ser encontrado nas membranas celulares, com o papel de ativar enzimas e fluidez das membranas. Já os TG são considerados formas de armazenamento energético encontrados no tecido adiposo e muscular (SBC, 2013; WOOLLETT, 2011).

A homeostase lipídica é dependente da função hepática, um processo diretamente afetado pelo hormônio insulina. No metabolismo lipídico o fígado faz a oxidação dos ácidos graxos, sintetizando lipoproteínas, CT e fosfolipídios. As dislipidemias são consideradas alterações no metabolismo lipídico, podendo ser de origem primária (hereditária) ou secundária (consequente a doenças de base ou uso de medicamentos) (COSTANZO, 2014). O perfil lipídico é definido pelas dosagens de CT, TG, HDL e LDL (Low Density Protein) (SBC, 2013).

Segundo estudos, as concentrações de CT estão diminuídas, enquanto os TG apresentam-se elevados em RNAT. Esta relação parece estar invertida, em RNPT (DONEGÁ et al., 2006; RADUNOVIC et al., 2000). Adicionalmente, observa-se que adultos nascidos prematuros apresentam concentrações elevadas de LDL, aumento nas concentrações de CT e diminuição do HDL quando comparados à adultos nascidos AT (HOVI et al., 2013; KAJANTIE et al., 2004; PARKINSON et al., 2013). Este perfil lipídico desfavorável pode ter relação direta com a maior incidência de DCV e aterogênicas em adultos nascidos prematuros, conforme demonstra estudo realizado recentemente na Finlândia. Neste estudo, adultos jovens (entre 19 e 27

anos) nascidos prematuros, apresentaram alteração no perfil lipídico em relação a adultos jovens nascidos AT (HOVI et al., 2013). Estes dados são clara evidência de que a condição metabólica ao nascimento pode influenciar o estado de saúde ao longo da vida. Porém, existem dados controversos mostrando não haver relação entre a IG e alterações nas concentrações de CT ou TG ao longo da vida (IRVING et al., 2000; MORTAZ et al., 2003).

2.6 Gestação e o parto prematuro

A interrupção da gestação pode estar associada a alterações fetais, maternas e placentárias (BROCK; FALCÃO, 2008). A etiologia do parto prematuro geralmente é multifatorial ou idiopática (BITTAR; ZUGAIB, 2009) podendo ser afetada por vários fatores socioambientais como o estilo de vida. Entre as principais causas conhecidas estão as múltiplas gestações, inflamação ou infecção do trato urinário, o uso de substâncias indevidas, hipertensão, níveis elevados de alguns fatores de coagulação, exposição a agentes químicos, e o baixo nível socioeconômico (EUSER et al., 2008; MYATT et al., 2012; SWAGGART et al., 2015).

Considerando que os eventos ocorridos durante a gestação podem ter impacto sobre o desenvolvimento no metabolismo futuro do embrião, conhecer a condição metabólica materna e sua relação com o estado de saúde do bebê é fundamental. Neste sentido, o estudo de Lunde et al. (2007) demonstra que, aproximadamente 14% da variação da IG esta relacionado com fatores genéticos maternos e 11% por fatores genéticos do feto. A nutrição materna e a oxigenação da placenta têm efeitos predominantes sobre o peso corporal do bebê ao nascer. O crescimento de órgãos e tecidos em mamíferos, referente à divisão celular, ocorre, na maior parte, durante o desenvolvimento intrauterino e envolve a proliferação, diferenciação e a migração de células em estruturas organizadas, enfatizando que o ambiente do útero deve ser o melhor possível (DESAI et al., 2013). Dentro deste contexto, a alimentação materna inadequada, no período gestacional, tem repercussões diretas à longo prazo sobre o estado de saúde de seus filhos entre

eles a maior incidência de obesidade, DM2 e SM (VELKOSKA et al., 2008; NÜSKEN et al., 2011; VICKERS et al., 2000).

As alterações no metabolismo glicêmico e lipídico na fase gestacional são geralmente fisiológicas no intuito de fornecer energia suficiente para manter o feto nutrido, bem como, preparar o metabolismo materno para o momento do parto e, em seguida, para a amamentação (MELO et al., 2007). No início da gestação ocorre grande acúmulo de nutrientes, especialmente o de gordura, após a metade da gestação estes nutrientes são transferidos para o feto. As intensas alterações fisiológicas ocorridas na gestação são, em parte, controladas pela placenta a qual tem a função primordial de redistribuir oxigênio e nutrientes para o feto em desenvolvimento. Assim frequentemente observa-se que complicações do fluxo sanguíneo placentário culminam em RCIU e baixo peso ao nascer (DIAZ et al., 2014).

Conforme comentado anteriormente os distúrbios nutricionais da mãe durante a gestação, têm repercussões para o bebê. Neste caso tanto o baixo peso materno e deficiências de micronutrientes específicos, podem resultar em baixo peso corporal do bebê ao nascer, assim como, o sobrepeso e a obesidade materna podem predispor a instalação do DMG e síndromes hipertensivas, com consequências deletérias para a saúde da mãe e do concepto (TRIUNFO; LANZONE, 2015). Alteração materna gestacional de qualquer natureza tem impacto sobre a saúde fetal ao nascimento e repercutem sobre a condição de saúde futura desta criança (ABENHAIM et al., 2007; McARDLE et al., 2006). Por exemplo, estudo em roedores tem demonstrado que a restrição protéica materna durante a gravidez provoca déficit de crescimento intrauterino do bebê e aumento da incidência de DM2 e SM ao longo da vida resultando na prole obesa quando adultos. Adicionalmente, animais oriundos desta nutrição gestacional apresentam aumento na expressão de receptores de insulina do músculo, assim como, adipócitos hipertróficos (GUAN et al., 2005; OZANNE et al., 2003).

2.7 Regulação do Peso Corporal da Gestante

O diagnóstico nutricional precoce da gestante deve ser propiciado durante a assistência pré-natal, e, se necessário, fazer a recuperação deste quadro e garantir um ganho de peso adequado durante a gestação, para que sejam evitados desvios do crescimento no feto (FUJIMORE et al., 2001). O Índice de Massa Corpórea (IMC) é o mais utilizado para classificar o peso na população, por ser de baixo custo e fácil aplicabilidade. É obtido do produto entre o peso corporal (Kg) dividido pela altura (m^2) ao quadrado (Kg/m^2). Este índice pode variar em diferentes populações (WHO, 2011). Antes da gestação se utiliza o IMC normal para mulheres considerado IMC pré-gestacional, e a partir deste índice é avaliado o estado nutricional durante a gestação. O IMC materno durante a gravidez deve se encontrar adequado para favorecer o bem-estar da mãe e da criança (BRASIL, 2005). Conforme preconizado pelo Ministério da Saúde (2005), o estado nutricional materno deve ser verificado na primeira semana de pré-natal, para poder assim estabelecer uma previsão de quantos Kg a mãe deverá ganhar durante a gestação. Conforme a situação nutricional inicial há uma faixa de ganho de peso considerada adequada. Recomenda-se que mães com IMC baixo ganhe entre 12,5 e 18,0 Kg; Já uma mãe que está com um IMC adequado entre 15,5 a 16,0 Kg; A mulher que apresenta sobrepeso deve ganhar em 7,0 e 11,5 Kg enquanto que uma mulher obesa deve ganharentre 5,0 a 9,0 Kg (BRASIL, 2005).

Alterações de peso corporal materno afetam o peso corporal do bebê ao nascer e tem relação com o estado de saúde da criança. Neste sentido, estudos de Yogev e Catalano (2009) demonstraram que filhos de mães com IMC elevado tem maior chance de desenvolver obesidade infantil e SM no futuro. Na Malásia um grupo de pesquisadores avaliou o IMC de mães antes e durante a gestação, e também o IMC de seus filhos após o nascimento até um ano de idade. Neste estudo foi demonstrada uma relação positiva entre o IMC materno e perfil de IMC da criança (ZALBAHAR et al., 2015).

Similarmente um estudo de coorte realizado por Reynolds et al. (2010), avaliou os efeitos da composição corpórea e do ganho de peso durante a gestação em mães escocesas, em relação à adiposidade no início da vida adulta em seus filhos. Este estudo verificou, então, um aumento na gordura corpórea dos filhos

cujas mães apresentavam um IMC aumentado no início da gravidez, observando, também, uma relação favorável entre gordura nos filhos adultos e o ganho de peso da mãe durante a fase gestacional.

Adicionalmente, o excesso de nutrientes maternos, devido à obesidade e a presença do DMG são responsáveis pela hiperinsulinemia fetal, uma alteração que promove também um aumento de peso corporal nesta criança. Bebês macrossômicos (≥ 4.000 g ao nascer) geralmente são filhos de mães diabéticas, e apresentam um elevado risco de morbidade neonatal em particular pela hipoglicemia (KERCHE et al., 2005).

Os achados descritos anteriormente (YOGEV; CATALANO, 2009; ZALBAHAR et al., 2015; REYNOLDS et al., 2010; KERCHE et al., 2005) claramente demonstram a importância de acompanhar a evolução do peso corporal da gestante, bem como, caracterizar seu estado metabólico, particularmente quando estas alterações podem estar relacionadas à prematuridade. Diversos estudos demonstram que mulheres obesas ou com ganho excessivo de peso durante a gestação, apresentam elevada incidência de PP (CNATTINGIUS et al., 2013; FAUCHER et al., 2016), além de que, a desnutrição materna também pode levar a esse quadro (TRIUNFO; LANZONE, 2015).

2.7.1 Homeostase Glicêmica e Lipídica da Gestante

Durante a gestação ocorre uma RI fisiológica, principalmente no último trimestre, quando ocorre uma diminuição do acúmulo de gordura, devido a um aumento da lipólise (FERRIOLS et al., 2015) disponibilizando assim GLI e lipídios para o feto (DIAZ et al., 2014). A secreção de insulina durante a gestação se eleva em torno de 60%. Ela é responsável por estimular a lipogênese e reduzir a oxidação de ácidos graxos, promovendo aumento nas concentrações lipídicas na gestante (FERRIOLS et al., 2015).

O hormônio lactogênio placentário (HPL) é o principal hormônio relacionado a RI, por aumentar as concentrações glicêmicas sanguíneas. Mas, também, estão envolvidos outros hormônios hiperglicemiantes como o estrógeno, progesterona e a prolactina. Estes hormônios hiperglicemiantes aumentam a RI para que o bebê

possa receber nutrientes a fim de satisfazer suas necessidades nutricionais. Na gestação, um aumento na produção de estrogênio e progesterona leva a uma hiperplasia nas células beta pancreáticas e, consequentemente, secreção aumentada de insulina (COSTANZO, 2014). Segundo Catalano et al. (2009) há uma diminuição de 44% na sensibilidade à insulina durante a gestação normal comparada a 56% da diminuição em gestações com DMG.

O rompimento da homeostase glicêmica durante o período gestacional caracteriza o DMG o que leva a uma hiperglicemia podendo ser de gravidade variável, e que pode persistir ou não após o parto (SBD, 2007). Frequentemente os hormônios contra-reguladores da insulina também estão elevados no DMG. Abreu (2014) em seu estudo com mães com DMG, conclui que os filhos dessas mães apresentavam maior massa adiposa corporal e circunferência abdominal aumentada, quando comparados à crianças nascidas de mães sem DMG. Adicionalmente, estudos em adultos nascidos de mães com RI mostra que estes são mais propensos a desenvolverem doenças como HAS, dislipidemias, obesidade, DM2, independente de serem macrossômicos ou não (GUNDERSON et al., 2014; YAN; YANG, 2013).

No período gestacional as concentrações lipídicas apresentam um papel importante na manutenção da gravidez, ocasionando mudanças complexas na homeostase lipídica. O início da gestação constitui-se de uma fase do metabolismo anabólico, no qual há maior disponibilidade de TG devido à elevada produção hepática, permitindo assim, o armazenamento de energia pela gestante. Já no último trimestre gestacional, ocorre a fase catabólica na qual há um aumento da RI, devido a ação do HPL estimulando a lipólise e reduzindo o acúmulo de gorduras (BENÍTEZ et al., 2010; FERRIOLS et al., 2015; LAIN; CATALANO, 2007). A hipertrigliceridemia materna durante a gestação é considerada fisiológica até certo ponto. Um excesso de TG (>181 mg/dL) pode levar ao risco de pré-eclampsia materna (FERRIOLS et al., 2015). Segundo estudos, os TG aumentam gradativamente durante a gestação, especialmente no terceiro trimestre (PARCHWANIL; PATEL, 2011; PUSUKURU et al., 2016), podendo este aumento ser de até 3 vezes comparado às concentrações de TG normais (PARCHWANIL; PATEL, 2011; PHUSE, 2012; HODSON et al., 2013).

A associação entre a RI característica da gestação, mais o aumento das VLDL (very low density lipoprotein) resultado do aumento nas concentrações de

estrógeno, é o principal mecanismo envolvido no aumento dos TG gestacional (FERRIOLS et al, 2015). O perfil lipídico da gestante pode afetar o feto em desenvolvimento. Por exemplo, a diminuição do CT materno no segundo trimestre gestacional está relacionado à fetos microcéfalos (EDISON, 2007).

Conforme Emet et al. (2013) em seu estudo com gestantes normais (sem histórico de doenças crônicas, ou complicações na gravidez), houve um aumento significativo nas concentrações de CT, TG, HDL, LDL ao longo da gestação. Estudos mostram também que o CT pode aumentar em até 43% durante a gestação e diminuir rapidamente após o parto. Os TG também se elevam significativamente, podendo se elevar em 50% a 200% neste período (LANDÁZURI et al., 2006). No último trimestre gestacional o CT pode aumentar até 65%. Os TG também se encontram elevados, voltando ao normal após o parto (FERRIOLS et al., 2015)

O perfil lipídico da mãe pode alterar as condições de nascimento Li et al. (2015) avaliaram mulheres chinesas e verificaram uma diminuição nas concentrações de CT, TG, HDL e LDL nas mulheres que tiveram filhos prematuros em relação à mulheres com gestação normal. Já em um estudo de coorte realizado em Amsterdã, com 4008 gestantes, verificou-se que, concentrações elevadas de TG no primeiro trimestre gestacional, contribuem para pré-eclampsia, PP e nascimento de crianças GIG (VRIJKOTTE et al., 2012).

O perfil glicêmico e lipídico materno está intimamente relacionado com a prematuridade. Estudo como de Catov et al. (2007) demonstraram a presença de hipercolesterolemia, trigliceridemia e aumento de LDL em mulheres com PP. Similarmente Chatzi et al. (2009) demonstraram que mães de RNPT apresentam elevadas concentrações circulantes de CT assim como a diminuição do HDL materno associado com o RCIU. Neste mesmo estudo foi demonstrado que o estresse oxidativo no feto causado pela hiperlipidemia materna pode resultar em danos à parede vascular e também rupturas na placenta, levando ao PP. Deste modo, as alterações metabólicas maternas podem estar associadas ao estado de saúde do bebê e ter implicações para a saúde da criança.

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ARTIGO CIENTÍFICO

PREMATURITY AND MATERNAL HEALTH CONDITIONS INFLUENCE PLASMA GLUCOSE AND TRIGLYCERIDE LEVELS IN NEWBORNS AT SIX MONTHS OF CORRECTED AGE

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Abbreviations: 6 m of CA, 6 months of corrected age; PT-infants, preterm-infants; FT-infants, full-term; CC, cephalic circumference; GLM, generalized linear model; PT, preterm; GA, gestational age; T2D, type 2 diabetes; CVD, cardiovascular diseases; ITU, intensive therapy unit; AGA, Adequate for GA; SGA, small for GA; LGA, larger for GA; CA, corrected age; VLBW, very low birth weight;

The running title: Prematurity and Maternal Health Conditions

Keywords: preterm, pregnancy, metabolic programming, newborn.

ABSTRACT

We here in evaluated whether maternal health conditions and prematurity demonstrate correlation with plasmatic metabolic parameters at 6 months of corrected age (6 m of CA). This was a cross- sectional and prospective study conducted from May 2015 to March 2017 in a public maternity hospital in Brazil that evaluated 71 preterm-infants (PT-infants) and 82 full-term (FT-infants) and their respective mothers. At birth, PT-infants presented a lower body weight, height and cephalic circumference (CC), in association with high glucose, insulin and reduced plasma triglyceride levels, compared to FT-infants. At 6 m of CA, PT-infants had recovered their body weight, but not height and CC and still had augmented plasma glucose levels, in relation to FT-infants. Using a generalized linear model (GLM), we demonstrated that greater maternal body weight gain or high degree of prematurity are correlated with augmented plasma glucose levels in PT-infants at 6 m of CA. In contrast, high maternal plasma insulin level is correlated with reduced glycemia in PT- infants at 6 m of CA. A greater maternal body weight gain, associated with high maternal glycemia, insulinemia, plasma cholesterol levels and increased degree of prematurity are correlated with high plasma triglyceride levels in PT-infants at 6 m of CA. In conclusion, maternal body weight gain and prematurity are elements that affects glycemia and triglyceridemia at 6 m of CA. Thus, to characterize maternal and infant health conditions in premature newborns is necessary to preserve glucose and lipids homeostasis at long of life avoiding installation of chronic diseases

Keywords: preterm, pregnancy, metabolic programming, newborn.

INTRODUCTION

Preterm (PT) birth is classically defined as the birth of an infant before 37 completed weeks of gestation[1]. However, gestational age (GA) has been used to subdivide premature newborns, according the degree of prematurity, as: extremely PT (<28 weeks), very PT (28 to <32 weeks) and moderate PT (32 to <37 weeks)[1-2]. Premature birth constitutes a worldwide health problem and has a significant impact on infant mortality and morbidity during infancy[1]. Moreover, an infant born at PT presents a major risk for the development of neurological, sensory, respiratory and motor disabilities later on in life[3-4], resulting in elevated society and economic costs to the public health system[5].

Over the last decades, advances in perinatal care have promoted rises in the survival rates of infants born PT, with many reaching adulthood[6]. However, prematurity is an event that alters a critical period of development, resulting in metabolic, hormonal and nutritional changes at birth with implications for health state over the long term[7]. For example, infants born PT frequently present a small size at birth, in association with rapid growth rates (catch-up) during childhood; both events are directly related to risks for the development of obesity and diabetes later in life[8]. Similarly, maternal health conditions have a clear impact on prematurity[9]. In this context, changes in the maternal anthropometric and metabolic conditions, such as excessive or inadequate body weight gain[10], hyperglycemia[11], dyslipidemia[12-13], hypertension[14] or urinary tract infection[2] during gestation contributes to cause premature birth. Interestingly, maternal metabolic and anthropometric alterations did not have just an immediate impact on the PT infant, but also contribute to disease risk in the long term[15]. Taken together, these findings reinforce the concept of the fetal origins hypothesis proposed by Barker and Fall[16], denominated "metabolic programming". This hypothesis proposes that exposure to adverse nutritional or hormonal conditions during critical stages of early development, such as gestation, lactation and the first years of infancy might contribute to pathological states later on in life[17-18].

In this context, disturbances in blood glucose and lipid homeostasis are a common disorder observed during the adulthood of individuals exposed to programming fetal agents early in life, including prematurity[19]. According to epidemiological studies, adults that were born premature present a major risk for the development of type 2 diabetes (T2D); a disease characterized by hyperglycemia and insulin resistance[20]. Unfortunately, T2D is a grave metabolic condition that also affects children during the early years of

infancy[21]. The infant born at PT has a greater difficulty in preserving glucose homeostasis during the first few days of life, in particular due to limited glycogen stores, lower gluconeogenic hormone activities, and decreased hormonal responses, particularly of cortisol and insulin[22]. In this context, several studies have shown that plasma glucose and insulin levels were higher in PT than in FT-infants[23] and presented associations with disease conditions at 2 years of age[24]. Studies in humans and rodents have demonstrated that insulin resistance and consequent glucose intolerance, hallmarks of metabolic syndrome, are consistently programmed by maternal and newborn metabolic or nutritional imbalances[25-26-27]. Although hiperinsulinemia and insulin resistance have been reported in very PT newborns[28-29], contradictory results showing the link between prematurity and insulin resistance in adulthood have been reported[30]. In addition, low birth weight is associated with PT birth and correlates with increased risk of cardiovascular diseases (CVD) in adulthood. Thus, premature newborns frequently present alterations in various lipid fractions such as reduced triglycerides and high LDL-cholesterol; events that could be related to the origins of atherosclerosis during early life[31].

The programming effect that is induced by prematurity, as well as its relationship with maternal health conditions, is a complex event and the exact mechanisms coupling premature birth with diseases later on in life remain unclear. Thus, the characterization of maternal and infant metabolic profiles in this group of vulnerable newborns could avoid or attenuate metabolic programming consequences induced by prematurity, in particular disturbances in glucose and lipids homeostasis and T2D disease. Thus, the aim of the present study was to characterize the relationship between maternal health conditions and glucose and lipid levels in PT-infants, at birth and at 6 months of corrected age (CA).

MATERIALS AND METHODS

This is a cross-sectional and prospective study conducted from May 2015 to February 2017 in a public maternity hospital in the city of Cascavel-PR, Brazil. The study was approved by the Institutional Human Ethics Committee of the University of Western Parana n. 1.134.712, Parana, Brazil. A total of 3123 FT-infants and 314 PT-infants were initially included in the study and distributed into two groups, according to delivery type: PT-infants, n= 116 and FT-infants, n= 161 and their respective mothers. The PT births were defined as newborns born at less than 37 weeks of gestational age (GA), while

141 newborns born at ≥37 weeks of GA were considered FT, according to the WHO[1].
142 Informed consent was obtained from mothers and mothers who refused to participate in
143 the study were excluded from the study. The experimental groups were formed using the
144 following exclusion criteria:

145 - Mothers-FT and FT-infants: Pregnant women who did not live in the region and those
146 younger than 18 years old, presenting diabetes and/or hypertension diseases or those that
147 died were excluded. Newborns with congenital anomalies, exposed to phototherapy or
148 with any pathological conditions were excluded. In addition, mothers and newborns who
149 did not return for the follow-up appointment or who did not undergo blood sample
150 collection (or insufficient blood collection) were also excluded from this study.

151 -Mothers-PT and PT-infants: Those PT-infants that were born with congenital anomalies,
152 those that remained for less than 7 days in the Intensive Therapy Unit (ITU), those that
153 died during the hospitalization period or were lost to follow-up were excluded from this
154 study. Mothers or newborns who did not undergo blood sample collection, or for whom
155 there was insufficient blood collected for biochemical analysis, were also excluded.

156 Thus, after the exclusion criteria, 67 mothers-PT and 82 mothers-FT were included
157 in the study, according to the Flowchart shown in Figure 1. Data were collected via a
158 single, pre-coded, semi-open questionnaire by interviewers during hospitalization within
159 the first 72 hours after birth. This questionnaire was especially prepared for the study
160 covering the following domains: maternal age (years), ethnicity (white and nonwhite);
161 maternal schooling (years); Family income (minimum salary-MS); marital state and type of
162 delivery. Anthropometric maternal data collected were; pre - pregnancy (pp) and at last
163 query (lq) body weight (BW) in kilograms (Kg). The total body weight gain (Δ) was
164 obtained from the difference between ppBW –lqBW and expressed by Gestational Age
165 (GA). The GA was based on the first day of the last menstrual period[31]. Heights (m^2) of
166 mothers were also recorded, and the maternal body mass index (BMI) was calculated
167 (weight /height in kg/m^2) at pre-pregnancy (ppBMI) and at last query (lqBMI), according to
168 the curve of Atalah[32]. When necessary, data were also collected from the hospital files. At
169 birth, anthropometric data for newborns were obtained; body weight (g), height (cm) and
170 cephalic circumference (CC). These data and the respective GA of newborns were used to
171 classify them as: Adequate for GA (AGA); Small for GA (SGA) and Larger for GA (LGA),
172 according Fenton and Kim[33]. Mothers' blood samples were collected at the time of
173 hospitalization while the infants' blood samples were collected between 24-72 hours after

delivery and submitted to biochemical analysis, according to the description in the next section. At six months of age for the FT-infants or corrected age (CA) for the PT-infants, anthropometric variables (body weight, height and CC) were reevaluated and another blood sample was collected for biochemical analysis. The delta (Δ) was calculated for anthropometric and metabolic variables to calculate the difference between the conditions at birth - the conditions at 6 m of CA.

Plasma biochemical analysis. In order to determine the plasma metabolic profile of the mothers and their respective infants, blood samples were collected, centrifuged and plasma separated and glucose, triglycerides, total cholesterol determined by the dry chemistry method in an automated VITROS 4600 by Ortho Clinical Diagnosis. Insulin (µUI/mL) was analyzed by the Electrochemiluminescence in an automated UniCelDxI 800, Beckman Coulter, using an Access Ultrasensitive Insulin immunoassays system (Beckman Coulter).

Statistical Analysis. Data are expressed as mean ± standard deviation (SD) and the difference between groups (FT and PT) evaluated by unpaired t test or Mann-Whitney U test, according to the previously performed normality (Shapiro-Wilk) analysis. Sociodemographic characteristics were expressed as frequencies (percentages) and submitted to independent Chi-square test for the association between categorical variables, with-permutational Monte-Carlo methods applied when necessary. Finally, we also used a Generalized Linear Models (GLM) to describe a potentially nonlinear relationship between predictor terms and a plasma biochemical variable. The R version 3.3.2 (Since Pumpkin Patch) was used for statistical analyses and a level of significance $p < 0.05$ was used for all analyses.

RESULTS

Table 1 lists the maternal sociodemographic characteristics of study participants. Maternal age was significantly lower in Mothers-PT (26±7 years), in relation to Mothers-FT (29±8 years; $p<0.05$). In both maternal groups, there was larger frequency of white ethnicity; however the frequency of non-white individuals was lower in Mothers-PT, compared with Mothers-FT ($p<0.05$). The frequency of maternal schooling, occupation and family income were similar between groups of mothers. Married or stable partnership

was the most frequent marital status in both maternal groups. In addition, cesarean delivery was more frequent in Mother-PT, while normal delivery was more frequent in Mothers-FT ($p<0.05$). Despite a greater frequency of a single gestation in both groups of mothers, twin births were more frequent in the Mothers-PT group, in relation to the Mothers-FT ($p<0.05$). The maternal anthropometric and metabolic blood biomarkers are shown in Table 2. Although the pre-pregnancy body weight was been similar between maternal groups, there was significant difference in body weights at last query and, consequently, in weight gain. The body weight at last query and weight gain were lower in Mothers-PT (72±14 and 8±6Kg, respectively) in relation to Mothers-FT (80±14 and 13±7Kg, respectively) ($p<0.05$). Accordingly, the body weight gain by GA was different between maternal groups (Mothers-PT= 0.262/Kg/weeks and Mothers-FT = 0.336/Kg/weeks); $p<0.05$. Similarly, maternal pre-pregnancy BMI and height were similar in both groups of mothers. However the BMI at last query and BMI gain were significantly lower in Mothers-PT when compared to Mothers-FT ($p<0.05$). The plasma levels of glucose, triglycerides and insulin were similar in Mothers-FT and Mothers-PT. However, Mothers-PT presented reduced total plasma cholesterol levels (202±50 mg/dL) in relation to Mothers-FT (233±52 mg/dL); $p<0.05$.

The anthropometric characteristics of newborns at birth and at 6 m of CA are shown in Table 3. The PT-infants presented significant reductions in body weight (1609±62g), height (40±4cm) and CP (29±3cm) at birth, in relation to the same variables in FT-infants (body weight: 3240±44g; height: 48±2cm; CP: 34±2cm); $p<0.05$. Although the body weights were similar between PT-infants and FT-infants at 6m of CA, height and CC remained significantly lower in PT-infants, compared to FT-infants ($p<0.05$). Considering these differences between anthropometric conditions at birth and at 6 m of CA, we calculated the variation or delta (Δ) in the period. As such, the gains in body weight, height and CC were significantly higher in PT-infants than in FT-infants ($p<0.05$).

Characterizing a premature condition, the mean GA in PT-infants was 31±3 weeks, compared with the mean GA of 39±1 weeks in FT-infants (Table 4). The frequencies of females or males, as well as the distribution of AGA, LGA and SGA were similar between both groups of newborns (Table 4). The metabolic biochemical profiles of newborns at birth and at 6 m of CA are shown in Figure 2 (A-L). At birth, plasma levels of glucose (80±5mg/dL) and insulin (11±3mg/dL) were significantly greater in PT-infants compared to FT-infants (glucose: 63±1mg/dL; insulin: 2±1mg/dL) (Figure 2A and 1J; $p<0.05$). In contrast, the plasma triglyceride levels were lower in PT-infants (48±4mg/dL) in relation to

FT-infants (123±6mg/dL) at birth (Figures 2D and 2G $p<0.05$). Interestingly, only the plasma levels of glucose remained significantly higher in PT-infants (83±1) in relation to FT-infants (79 ±1) at 6 m of CA ($p<0.05$). Again, because of the difference between the "at birth" and "6 m of CA" conditions, we calculated the variation or delta for all biochemical variables. Thus, while the delta for triglycerides was higher, the deltas for plasma glucose and insulin levels were lower in PT-infants compared with respective the deltas in FT-infants (Figures 2C, 2F, 2I, 2L; $p<0.05$).

Using GLM analysis, we evaluated the effects of maternal or neonate conditions on the metabolic state at 6 m of CA (Tables 5 and 6). In FT-infants, the maternal metabolic or anthropometric conditions did not influence metabolic blood biomarkers at 6 m of CA (data not shown). However, the degree of prematurity as well as maternal anthropometric and metabolic state was correlated with metabolic conditions in PT-infants at 6 m of CA. Thus, a higher degree of prematurity correlated with higher plasma glucose levels in PT-infants at 6 m of CA (line F; Table 5). Similarly, when maternal body weight gain was greater during gestation, glycemia was higher in PT-infants at 6 m of CA (line A; Table 5). In contrast, when maternal plasma insulin levels were greater at delivery, glycemia was lower in PT-infants at 6 m of CA (line E; Table 5). In addition, maternal conditions, such as elevated maternal body weight gain, glycemia, insulinemia and plasma cholesterol levels at delivery, associated with a greater degree of prematurity, resulted in increased plasma triglyceride levels at 6 m of CA (line C; Table 6).

DISCUSSION

The relationship between mother and fetus during gestation involves metabolic and hormonal aspects that go beyond intrauterine development, and have immediate effects at birth, with consequences on health states over the long term [24]. This event is known as "developmental programming" or "fetal origins of adult disease" [16]. Considering that premature birth is a cause of child mortality and morbidity, a better understanding of this process is a relevant subject of research in terms of public health, in particular because precocious interventions could avoid the metabolic programming consequences of prematurity in adulthood[1]. In this context, the disruption of glucose and lipid homeostasis is a metabolic condition that is frequently associated with metabolic programming diseases

later on in life[35-19]. Thus, we here in evaluated maternal conditions that could affect the plasma glucose and triglyceride levels of PT infants at 6 m of CA, compared with these same parameters in mothers and infants born FT.

Its well recognized that anthropometric maternal conditions, such as body weight, height and BMI, before, during and after gestation, are variables that can affect newborns at birth hand have implications on their health in the long term[15]. In our study, both maternal groups presented overweight (BMI>25-29.9<) at prepregnancy and at last query. Epidemiological studies have demonstrated that the presence of underweight or obesity are factors that increase the risk for delivery PT[36-37]. Excessive fat mass during pregnancy is also one of the most established risk factors for negative long-term programming[38], including PT birth[15]. Weight gain during pregnancy reflects, in part, on the duration of gestation (longer pregnancies allow more weight gain), which must be considered by calculating week-specific weight gain[39]. Using body weight gain by weeks, we demonstrated that despite being overweight Mothers-PT presented less body weight gain, in relation to Mothers-FT, during gestation. Several authors have suggested that reduced body weight gain during gestation is a risk factor for PT delivery, as well as for the birth of babies SGA[10-15]. However, we found no difference in the frequency of SGA and LGA infants between the groups. In contrast, a study conducted in 97,157 women with singleton pregnancies by Enomoto *et al.*[40], demonstrated that a gestational weight gain above the optimal range was associated with a higher incidence of LGA newborns, while a weight gain of below the optimal range correlated with a higher incidence of SGA and PT birth.

Maternal metabolic conditions, particularly disruptions in glucose and lipids homeostasis, can affect neonate health at birth with repercussions a long life[41-42]. In our study, Mothers-PT presented adequate plasma concentrations of glucose, insulin and triglycerides, but reduced plasma cholesterol levels in relation to Mothers-FT. Inadequate total cholesterol in mothers have been related to PT birth[12-43]. In a case-control study, Catov *et al.*[12] included only spontaneous PT and found an association between high maternal total cholesterol and very early PT. However, total cholesterol during early gestation was not associated with any of the outcome measures, including PT birth in a study carried out by Vrijkote *et al.*[44]. In addition, is important to recognize that, during normal pregnancy, women show an increase in lipid levels, including levels of triglycerides and total cholesterol as GA progresses[45-46].

Premature birth is related to several metabolic anormalities, in particular premature neonates have difficulty in preserving glucose homeostasis[47]. There is growing evidence that PT infants have an increased risk of T2D and CVD in adult life[48]. Thus, we evaluated the newborns and their anthropometric and metabolic conditions, comparing PT infants and AT infants at birth and at 6 m of CA. The infants born prematurely had impaired growth in early postnatal life, in a period comparable to the third trimester of pregnancy[49]. In confirmation of this, PT infants in our study presented reduced body weight, CP and height at birth in relation to AT infants. However, at 6 m of CA, these premature neonates had recovered their body weight, suggesting accelerated postnatal growth an event known as catch-up growth[49]. Catch- up growth begins during the first months of life and can be slow and progressive in PT-infants[50] and it is an independent risk factor for adverse health outcomes. Importantly, accelerated catch-up is closely related to diseases later in life[49], including T2D[50] and therefore, alterations in glucose regulation have been proposed as a candidate for explaining this mechanism[51]. Adults born premature have higher fasting glucose levels, lower insulin sensitivity and higher blood pressure than adults born FT[29-48-52]. The reduction in insulin sensitivity, as a result of premature birth, is already present in children between the ages of 4 and 10 years[29]. Our study found that PT infants present higher glucose and insulin levels at birth, accompanied by reduced plasma levels of triglycerides in relation to FT-infants. Hyperglycemia was common and most severe among those born earliest and smallest[39]. Interestingly, Scheurer e*t al.*[53] demonstrated a relationship between hyperglycemia at birth and later slow growth at 4 m of CA in premature newborns. Using cord blood analysis in PT-infants, Ahamad *et al.*[23] demonstrated that more premature neonates present greater plasma insulin levels. Kwon *et al.*[54] also found reduced triglyceride levels in PT-infants, compared to FT-infants, although they did not observe differences in glucose or insulin levels between FT-infants and PT-infants.

According to a review by Hume *et al.*[47], at post-delivery, blood glucose levels fall in newborns, and thereafter, stabilization of glycemia is dependent on the activation of hepatic glycogenolysis and gluconeogenesis. Transient disturbances in neonatal glucose homeostasis are common during this time, especially when metabolic reserves are low, as occurs in prematurity. PT-infants have lower hepatic glycogen reserves, lower activities of key gluconeogenic enzymes, and inadequate hormonal responses[55-56-47]. Unfortunately, we did not measure insulin sensitivity, but our data show higher glucose and insulin in PT-infants at birth, suggesting insulin resistance. Corroborating this hypothesis, higher insulin and insulin resistance, measured by the HOMA index, was found in very PT-infants by

Ahmad *et al.*[23]. According to several studies, hyperinsulinemia in PT-infants is related to immature beta cell insulin secretion that is induced by glucose[57].

For the first time, we demonstrated that plasma glucose levels remained augmented at 6 m of CA, in prematurely born babies, suggesting difficultly in the preservation of glucose homeostasis during the precocious phase of infancy. Insulin resistance is a hallmark of T2D and is frequently observed in PT-infants that present catch-up during growth[49]. Data indicate that the PT-infants of our study also appear to present growth catch-up. Weight gain during the first 6 months of life was more strongly related to the risk of insulin resistance in adulthood, compared with weight gain later on in infancy[57]. Jong *et al*[7] demonstrated that very low birth weight (VLBW) infants already have one or more components of metabolic syndrome at 2 years of CA, such as hypertriglyceridemia and low HDL levels. In our study, the metabolic parameters of PT-infants at 6 m of CA show that they already present changes in insulin sensibility and, consequently disruption in glucose homeostasis. Importantly, by calculating the variation (Δ) in metabolic blood biomarkers, it is possible to characterize the differences between PT and FT-infants during the early phases of infancy. Thus, in premature newborns, from birth to 6 m of CA, a gradual reduction in glycaemia and plasma insulin levels occurs, while the plasma triglyceride levels increase, in contrast to observations in FT-infants. We believe that this shift in metabolism maybe considered as a metabolic marker for diseases later on in life in premature neonates. Further studies are necessary to evaluate this affirmation.

The PT birth is therefore a common, complex condition that results from multiple interactions between the maternal and the fetal health states and their external environments, resulting in programming effects over the long term. Thus, using GLM analysis, we evaluated whether maternal or infant conditions could be correlated with changes in plasma metabolic parameters at 6 m of CA. According to our findings, the degree of prematurity per se and maternal body weight gain during gestation correlated with higher plasma glucose levels in PT-infants already by 6 m of CA, reinforcing the concept of prematurity, maternal conditions and metabolic programming[16-53]. In addition, maternal conditions such as greater body weight gain, high cholesterol, insulin, and plasma glucose levels are associated with a higher degree of prematurity and result in increased plasma triglyceride levels in PT- infants at 6 m of CA. Despite limited information regarding the relationship between the lipid metabolism of the mother and the newborn, it is evident that this association determines the incidence of CDV in adulthood[42]. Using an experimental design that was similar to that of our study, Sales *et al.*[58] demonstrated that

maternal biochemical variables (total cholesterol, HDL-c and triglycerides) and body weight gain alone are not significantly associated with the lipid profile of the FT-infants. According to results obtained by Sreekarthik *et al.*[31], PT infants present altered cord blood lipid profiles and high atherogenic indices at birth, suggesting a greater cardiovascular risk. To our knowledge, this is the first study to demonstrate a relationship between maternal metabolic conditions and triglyceride levels in PT-infants at 6 m of CA; reinforcing the importance of preserving an adequate nutritional and metabolic status in mothers during gestation to avoid diseases later on.

This study is limited by its small sample size and the fact that parturients and infant were not fasting when blood was collected, which may have overestimated the values obtained. However, despite this, we were able to find significant differences between FT and PT-infants in the growth, body weight and plasma parameters at birth and at 6 m of CA. More importantly, we show the maternal influences on PT-infant at 6 m of CA. A better understanding of these mechanisms may contribute to developing better practices for the clinical management of mothers and their babies, in particular those born premature. In conclusion, maternal body weight gain during gestation and prematurity are elements that can determines plasmatic glucose and triglycerides levels at 6 m of CA in premature newborns. Thus, to characterize maternal conditions at delivery as well as establish the metabolic profile of premature babies at birth it is essential to understand glucose and lipid homeostasis in PT-infants to avoid diseases later on in life, particularly T2D and CDV.

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Conflict of Interest

The authors declared no interest conflict.

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535

TABLES

Table 1.Maternal sociodemographic characteristics.

	Mothers-PT (n=67)	Mothers-FT (n=82)	p-value
Age (years)[1]	26±7	29±8	<0.0001
	n (%)	**n (%)**	
Ethnicity			
White	57 (85%)	58 (79%)	0.386
Non White	10 (15%)	15 (21%)	
Maternal Schooling (years)			
Zero – 4	4 (6%)	1 (1%)	0.213*
Five- 9	17 (25%)	15 (21%)	
Ten or more	46 (69%)	57 (78%)	
Marital status			
Married or stable partnership	60 (90%)[a]	52 (71%)[b]	0.010*
Single	7 (10%)[b]	17 (23%)[a]	
Other	0 (0%)	7 (5%)	
Occupation			
Household	26 (39%)	26 (36%)	0.255*
Formal/informal	37 (55%)	46 (63%)	
Other	4 (6%)	1 (1%)	
Family income			
<1 MS	3 (4%)	8 (11%)	0.065
1 to 2 MS	36 (54%)	24 (33%)	
3 to 4 MS	22 (33%)	28 (38%)	
>5 MS	6 (9%)	12 (16%)	
Delivery			
Normal	29 (43%)[b]	46 (63%)[a]	0.019
Cesarean	38 (57%)[a]	27 (37%)[b]	
Gestation			
Single	63 (94%)[b]	73 (100%)[a]	0.034
Twin	4 (6%)[a]	0 (0%)[b]	

[1]mean±SD, n: number; % percentage; MS: minimum salary; [a,b]different letters represent significant differences;

*Chi-square with permutational Monte-Carlo method.

Table 2. Maternal anthropometric and metabolic characteristics.

	Mothers-PT (n=67)	**Mothers-FT (n=82)**	**p- value**
$_{pp}$Body Weight (Kg)	65±14	67±14	0.257*
I_qBody Weight (Kg)	72±14	80±14	0.003
Δ Weight gain (Kg)	8±6	13±7	<0.0001*
Height (cm)	160±7	161±6	0.336
$_{pp}$BMI	25±5	26±5	0.501*
$_{lq}$BMI	28±5	31±5	0.008*
Δ BMI	3±2	5±3	<0.0001*
Glucose (mg/dL)	102±40	96±32	0.568*
Triglycerides (mg/dL)	207±89	233±103	0.165*
Total Cholesterol (mg/dL)	202±50	233±52	<0.0001
Insulin (µUl/mL)	23±33	21±25	0.643*

Data are mean±SD. pp= pre-pregnancy; lq=last query; BMI= body mass index; Δ= delta

* Mann-Whitney-U

Table 3. Anthropometric characteristics of PT and FT-infants.

		PT-infants (n=71)	**AT-infants (n=82)**	p-value
At birth	**Body Weight (g)**	1609±623	3240±442	<0.0001*
	Height (cm)	40±4	48±2	<0.0001
	CC (cm)	29±3	34±2	<0.0001*
At 6 m of CA	**Body Weight (g)**	7074	7892	<0.0001
	Height (cm)	65	67	0.005*
	CC (cm)	42	44	<0.0001*
Δ	**Body Weight (g)**	5464±953	4651±705	<0.0001
	Height (cm)	25±3	18±2	<0.0001
	CC (cm)	14±3	10±2	<0.0001

Data are mean±SD; CC= cephalic circumference

* Mann-Whitney-U Test

Table 4. Gestational Age, Sex and Classification in newborns at birth

	PT-infants (n=71)	FT- infants (n=82)	p-value
GA (weeks)	31±3	39±1	<0.0001
Gender			
Female	31	37	0.399
Male	40	36	
Classification[1]			
SGA	4	4	0.179
LGA	2	8	
AGA	65	61	

[1] SGA = Small for gestational age; LGA=Large for gestational age and AGA= Adequate for Gestational age (FENTON; KIM, 2013).

❖Mann-Whitney-U Test

Table 5 – Analyses of maternal variable influences on plasma glycemia levels in PT-Infants at 6 m of CA using GML.

Line	Coefficient	Parameters	Standard Errors	t	p-value
	Intercepto	67.52794	4.92887	13.700	<2e-16***
A	Weight Gain	11.67753	4.95300	2.358	0.01980***
B	Glucose	0.05053	0.02711	1.864	0.06446
C	Triglycerides	-0.01206	0.01092	-1.104	0.27147
D	Cholesterol	0.02960	0.02064	1.434	0.15389
E	Insulin	-0.06736	0.03126	-2.155	0.03291*
F	Prematurity	5.83183	1.89013	3.085	0.00246 **

Table 6 – Analyses of maternal variable influences on plasma triglyceride levels in PT-Infants at 6 m of CA using GML.

Line	Coefficients	Parameters	Standard Error	t	p-value
	Intercept	-1.390e+03	1.802e+030	-0.771	0.4429
A	WG.Glu.Ins.PT	-3.909e-01	2.131e-01	-1.859	0.0703
B	WG.Chol.Ins.PT	-2.105e-01	1.145e-01	-1.839	0.0698
C	WG.Glu.Chol.Ins.PT	2.134e-03	1.1054e-03	2.024	0.0464*
D	WG.Glu.Tg.Chol.Ins.PT	-1.118e-05	6.123e-06	-1.827	0.0716

WG= Weight Gain, Glu= Glucose, Chol= Cholesterol, Tg= Triglycerides, Ins= Insulin, PT= PT-Infant.

FIGURES

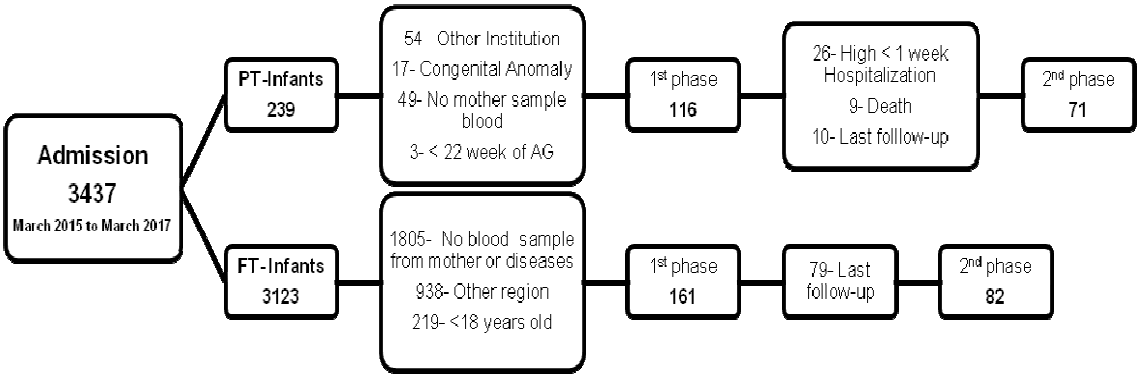

Fig.1. Flowchart of experimental design.

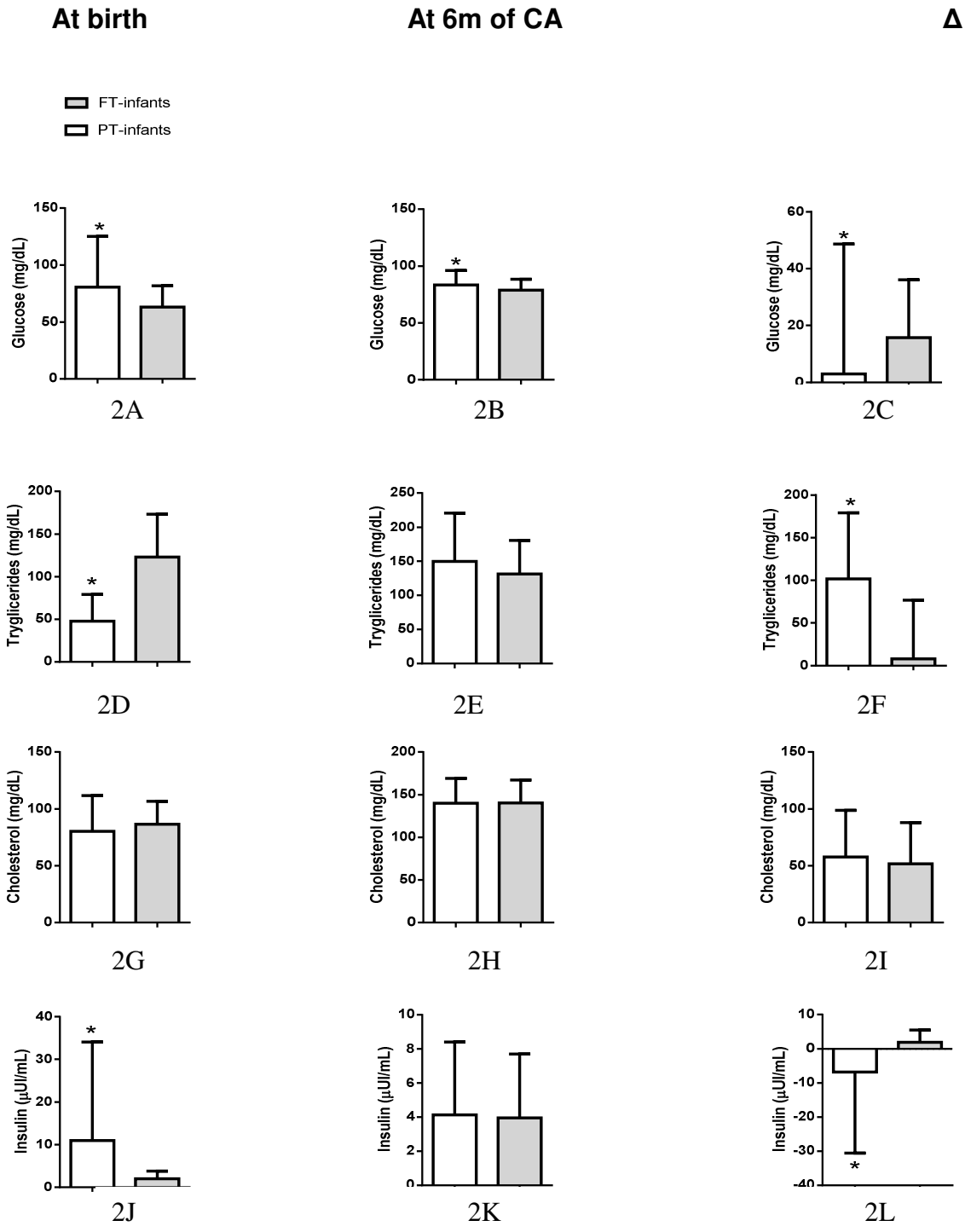

Fig. 2. Plasma metabolic parameters in newborns at birth and at 6 m of CA. Data are mean±SD; PT-infants, n=71 and FT-infants, n=82. The plasma values for each biochemical variable at birth are shown in Figures 2A, 2D, 2G, 1J and at 6 m of CA in Figures 2B, 2F, 2H, 2K. The delta (Δ) was obtained as the difference between values at birth minus the values at 6 m of CA and are shown in Figures 2C, 2F, 2I, 2L. *p<0.05.

ANEXO A

Certificado do Comitê de Ética em Pesquisa com Seres Humanos da UNIOESTE

UNIVERSIDADE ESTADUAL DO OESTE DO PARANÁ/

Plataforma Brasil

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: REPERCUSSÕES DA PREMATURIDADE:ESTRESSE MATERNO E PROGRAMAÇÃO METABÓLICA APÓS A ALTA HOSPITALAR/Estresse e papel materno apos uma intervenção educativa

Pesquisador: cláudia silveira viera

Área Temática:

Versão: 3

CAAE: 16348813.7.1001.0107

Instituição Proponente: Centro de Ciências Biológicas e da Saúde CCBS - UNIOESTE

Patrocinador Principal: Financiamento Próprio
MINISTERIO DA CIENCIA, TECNOLOGIA E INOVACAO

DADOS DO PARECER

Número do Parecer: 1.134.712

Data da Relatoria: 25/06/2015

Apresentação do Projeto:

Projeto bem apresentado e respeita todos os princípios teóricos, metodológicos e éticos.

Objetivo da Pesquisa:

Pertinentes ao estudo com o intuito de implantar um laboratório de estudos/práticas educativas aos sujeitos envolvidos.

Avaliação dos Riscos e Benefícios:

Os sujeitos participantes não serão expostos a riscos biológicos ou constrangimentos, apenas os riscos mínimos de abordagem educativa. Os benefícios serão a longo prazo, apos os resultados obtidos, em que se espera que o grupo de intervenção tenha melhores indices acerca do conhecimento do cuidado de saude ao filho e consequentemente, reduzir o estresse.

Comentários e Considerações sobre a Pesquisa:

Relevante para a área materna infantil e neonatologia.

Considerações sobre os Termos de apresentação obrigatória:

Todos apresentados.

Endereço: UNIVERSITARIA
Bairro: UNIVERSITARIO **CEP:** 85.819-110
UF: PR **Município:** CASCAVEL
Telefone: (45)3220-3272 **E-mail:** cep.prppg@unioeste.br

UNIVERSIDADE ESTADUAL DO OESTE DO PARANÁ/

Plataforma Brasil

Continuação do Parecer: 1.134.712

Recomendações:

Não há recomendações.

Conclusões ou Pendências e Lista de Inadequações:

Não há pendências.

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

Considerações Finais a critério do CEP:

Emenda aprovada. O projeto não necessita adequações.

CASCAVEL, 01 de Julho de 2015

Assinado por:
João Fernando Christofoletti
(Coordenador)

Prof. Dr. João Fernando Christofoletti
Coordenador do Comitê de Ética em
Pesquisa com Seres Humanos
Portaria nº 5387/2012 - GRE

Endereço: UNIVERSITARIA
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ANEXO B

Normas da revista científica

Directions to Contributors
British Journal of Nutrition
(Revised September 2014)

British Journal of Nutrition **(BJN) is an international peer-reviewed journal that publishes original papers and review articles in all branches of nutritional science. The underlying aim of all work should be to develop nutritional concepts.**

SUBMISSION
This journal uses ScholarOne Manuscripts for online submission and peer review. Complete guidelines for preparing and submitting your manuscript to this journal are provided below.

SCOPE

The British Journal of Nutrition encompasses the full spectrum of nutritional science and reports of studies in the following areas will be considered for publication: Epidemiology, dietary surveys, nutritional requirements and behaviour, metabolic studies, body composition, energetics, appetite, obesity, ageing, endocrinology, immunology, neuroscience, microbiology, genetics, and molecular and cell biology. The focus of all manuscripts submitted to the journal must be to increase knowledge in nutritional science.
The journal does NOT publish papers on the following topics: **Case studies; papers on food technology, food science or food chemistry; studies of primarily local interest; complementary medicine; studies on pharmaceutical agents or that compare the effects of nutrients to those of medicines; substances that are considered primarily as medicinal agents; studies in which a nutrient or extract is administered by a route other than orally (unless the specific aim of the study is to investigate parenteral nutrition) nor studies using non-physiological amounts of nutrients (unless the specific aim of the study is to investigate toxic effects).**

In vivo and in vitro models

Studies involving animal models of human nutrition and health or disease will only be considered for publication **if the amount of a nutrient or combination of nutrients used could reasonably be expected to be achieved in the human population.**
Studies involving *in vitro* models will only be considered for publication **if the amount of a nutrient or combination of nutrients is demonstrated to be within the range that could reasonably be expected to be encountered in vivo, and that the molecular form of the nutrient or nutrients is the same as that which the cell type used in the model would encounter in vivo.**

Extracts

Studies involving extracts will only be considered for publication **if the source of starting material is readily accessible to other researchers and that there are appropriate measures for quality control, that the method of extraction is described in sufficient detail with appropriate quality control measures, that the nutrient composition of the extract is characterised in detail and that there are measures to control the quality of the composition of the extract between preparations, and that the amount of extract used could reasonably be expected to be achieved in in the human population (or in animals if they are the specific target of an intervention). Studies involving extracts in *in vitro* models** will only be considered for publication **if the above guidelines for studies involving extracts are followed, and that the amount and molecular form of the extract is the same as that which would be encountered by the cell type used in the model in vivo.**

Manuscripts submitted to BJN that are outside of the journal's scope or do not meet the above requirements will be rejected immediately.

REVIEW PROCESS

British Journal of Nutrition **uses a single blind review process.**

As part of the online submission process, authors are asked to affirm that the submission represents original work that has not been published previously, and that it is not currently being considered by another journal. Authors must also confirm that each author has seen and approved the contents of the submitted manuscript. Finally, authors should confirm that permission for all appropriate uses has been obtained from the copyright holder for any figures or other material not in his/her copyright, and that the appropriate acknowledgement has been made to the original source.

At submission, authors are asked to nominate at least four potential referees who may then be asked by the Editorial Board to help review the work. Manuscripts are normally reviewed by two external peer reviewers and a member of the Editorial Board.

When substantial revisions are required to manuscripts after review, authors are normally given the opportunity to do this once only; the need for any further changes should at most reflect only minor issues. If a paper requiring revision is not resubmitted within 2 months, it may, on resubmission, be deemed a new paper and the date of receipt altered accordingly.

PUBLISHING ETHICS

British Journal of Nutrition **considers all manuscripts on the strict condition that:**

1) The manuscript is your own original work, and does not duplicate any other previously published work;

2) The manuscript has been submitted only to the journal - it is not under consideration or peer review or accepted for publication or in press or published elsewhere;

3) All listed authors know of and agree to the manuscript being submitted to the journal; and
4) The manuscript contains nothing that is abusive, defamatory, fraudulent, illegal, libellous, or obscene.

The Journal adheres to the Committee on Publication Ethics (COPE) guidelines on research and publications ethics.

Text taken directly or closely paraphrased from earlier published work that has not been acknowledged or referenced will be considered plagiarism. Submitted manuscripts in which such text is identified will be withdrawn from the editorial process. If a concern is raised about possible plagiarism in an article published in British Journal of Nutrition, this will be investigated fully and dealt with in accordance with the COPE guidelines.

ARTICLE TYPES

British Journal of Nutrition **publishes the following: Research Articles, Review Articles, Systematic Reviews, Horizons in Nutritional Science, Workshop Reports, Invited Commentaries, Letters to the Editor, Obituaries, and Editorials. Research Articles, Reviews, Systematic Reviews, Horizons Articles, Letters to the Editor and Workshop Reports should be submitted to http://mc.manuscriptcentral.com/bjn. Please contact the Editorial Office on bjn.edoffice@cambridge.org regarding any other types of article.**

Review Articles
BJN is willing to accept critical reviews that are designed to advance knowledge, policy and practice in nutritional science. Current knowledge should be appropriately contextualised and presented such that knowledge gaps and research needs can be characterised and prioritised, or so that changes in policy and practice can be proposed along with suggestions as to how any changes can be monitored. The purpose or objective of a review should be clearly expressed, perhaps as question in the Introduction, and the review's conclusions should be congruent with the initial objective or question. Reviews will be handled by specialist Reviews Editors. Please contact the Editorial Office with any queries regarding the submission of potential review articles. All reviews, including systematic reviews and meta-analyses, should present the uncertainties and variabilities associated with the papers and data being reviewed; in particular BJN cautions against uncritical acceptance of definitions and non-specific global terminologia, the advice of advisory bodies, and reference ranges for example.
Reviews: **These articles are written in a narrative style, and aim to critically evaluate a specific topic in nutritional science.]**
Horizons in Nutritional Science: **These are shorter than Review articles and aim to critically evaluate recent novel developments that are likely to produce substantial advances in nutritional science. These articles should be thought-provoking and possibly controversial.**
Systematic Reviews and meta-analyses: **The journal endorses the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement, a guideline to help authors report a systematic review and meta-**

analysis (see British Medical Journal (2009) 339, b2535). A systematic review or meta-analysis of randomised trials and other evaluation studies should follow the PRISMA guidelines.

Letters to the Editor

Letters are invited that discuss, criticise or develop themes put forward in papers published in BJN. They should not, however, be used as a means of publishing new work. Acceptance will be at the discretion of the Editorial Board, and editorial changes may be required. Wherever possible, letters from responding authors will be included in the same issue as the original article.

DETAILED MANUSCRIPT PREPARATION INSTRUCTIONS

Language

Papers submitted for publication must be written in English and should be as concise as possible. We recommend that authors have their manuscript checked by someone whose first language is English before submission, to ensure that submissions are judged at peer review exclusively on academic merit.

We list a number of third-party services specialising in language editing and / or translation, and suggest that authors contact as appropriate. Use of any of these services is voluntary, and at the author's own expense.

Spelling should generally be that of the *Concise Oxford Dictionary* (1995), 9th ed. Oxford: Clarendon Press. Authors are advised to consult a current issue in order to make themselves familiar with BJN as to typographical and other conventions, layout of tables etc. Sufficient information should be given to permit repetition of the published work by any competent reader of BJN.

Published examples of BJN article types can be found below:

Research Article
Review Article
Horizons Article
Letter to the Editor

Authorship

The Journal conforms to the International Committee of Medical Journal Editors (ICMJE) definition of authorship, as described by P.C. Calder *(Br J Nutr (2009) 101, 775).*

The contribution of individuals who were involved in the study but do not meet these criteria should be described in the Acknowledgments section.

Ethical standards

The required standards for reporting studies involving humans and experimental animals are detailed in an Editorial by G.C. Burdge (Br J Nutr (2014) 112**).**

Experiments involving human subjects

The notice of contributors is drawn to the guidelines in the World Medical Association (2000) Declaration of Helsinki: ethical principles for medical research involving human subjects, with notes of clarification of 2002 and 2004

(http://www.wma.net/en/30publications/10policies/b3/), the *Guidelines on the Practice of Ethics Committees Involved in Medical Research Involving Human Subjects* (3rd ed., 1996; London: The Royal College of Physicians) and the Guidelines for the ethical conduct of medical research involving children, revised in 2000 by the Royal College of Paediatrics and Child Health: Ethics Advisory Committee (Arch Dis Child (2000) 82, 177–182). Articles reporting randomised trials must conform to the standards set by the Consolidated Standards of Reporting Trials (CONSORT) consortium.

Required disclosures: **A paper describing any experimental work on human subjects must include the following statement in the Experimental Methods section: "This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects/patients were approved by the [insert name of the ethics committee; a specific ethics number may be inserted if you wish]. Written [or Verbal] informed consent was obtained from all subjects/patients. [Where verbal consent was obtained this must be followed by a statement such as: Verbal consent was witnessed and formally recorded]." For clinical trials, the trial registry name, registration identification number, and the URL for the registry should be included.**
PLEASE NOTE: **From 1 October 2014, as a condition for publication, all randomised controlled trials that involve human subjects submitted to BJN for review must be registered in a public trials registry. A clinical trial is defined by the ICMJE (in accordance with the definition of the World Health Organisation) as any research project that prospectively assigns human participants or groups of humans to one or more healthrelated interventions to evaluate the effects on health outcomes. Registration information must be provided at the time of submission, including the trial registry name, registration identification number, and the URL for the registry.**

Experiments involving the use of other vertebrate animals
Papers that report studies involving vertebrate animals must conform to the 'ARRIVE Guidelines for Reporting Animal Research' detailed in Kilkenny et al. (J Pharmacol Pharmacother (2010) 1,94-99) and summarised at www.nc3rs.org.uk. Authors must ensure that their manuscript conforms to the checklist that is available from the nc3Rs website. The attention of authors is drawn particularly to the ARRIVE guidelines point 3b ('Explain how and why the animal species and model being used can address the scientific objectives and, where appropriate, the study's relevance to human biology', point 9c ('Welfare-related assessments and interventions that were carried out prior to, during, or after the experiment') and point 17a ('Give details of all important adverse events in each experimental group'). The Editors will not accept papers reporting work carried out involving procedures that cause or are considered likely to cause distress or suffering which would confound the outcomes of the experiments, or experiments that have not been reviewed and approved by an animal experimentation ethics committee or regulatory organisation.

Required disclosures: **Where a paper reports studies involving vertebrate animals, authors must state in the Experimental Methods section the**

institutional and national guidelines for the care and use of animals that were followed and that all experimental procedures involving animals were approved by the [insert name of the ethics committee or other approving body; wherever possible authors should also insert a specific ethics/approval number].

Manuscript Format
The requirements of BJN are in accordance with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals produced by the ICMJE.

Typescripts should be prepared with 1.5 line spacing and wide margins (2 cm), the preferred font being Times New Roman size 12. At the ends of lines, words should not be hyphenated unless hyphens are to be printed. Line numbering and page numbering are required.

Manuscripts should be organised as follows:

Cover Letter
Papers should be accompanied by a cover letter including a brief summary of the work and a short explanation of how it advances nutritional science. The text for the cover letter should be entered in the appropriate box as part of the online submission process.

Title Page
The title page should include:
1. The title of the article;
2. Authors' names;
3. Name and address of department(s) and institution(s) to which the work should be attributed for each author;
4. Name, mailing address, email address, telephone and fax numbers of the author responsible for correspondence about the manuscript;
5. A shortened version of the title, not exceeding 45 characters (including letters and spaces) in length;
6. At least four keywords or phrases (each containing up to three words).

Authors' names should be given without titles or degrees and one forename may be given in full. Identify each author's institution by a superscript number (e.g. A.B. Smith1) and list the institutions underneath and after the final author.

If the paper is one of a series of papers that have a common main title followed by a subtitle specific to the individual paper, numbering should not be used to indicate the sequence of papers. The format should be 'common title: specific subtitle', with a short common title, e.g. 'Partitioning of limiting protein and energy in the growing pig: testing quantitative rules against experimental data'.

Abstract
Each paper must open with an unstructured abstract of not more than 250 words**. The abstract should be a single paragraph of continuous text without subheadings outlining the aims of the work, the experimental approach taken, the principal results (including effect size and the results of statistical analysis) and the conclusions and their relevance to nutritional science.**

Introduction

It is not necessary to introduce a paper with a full account of the relevant literature, but the introduction should indicate briefly the nature of the question asked and the reasons for asking it. It should be no longer than two manuscript pages**.**

Experimental methods

The methods section must include a subsection that describes the methods used for statistical analysis (see the section on statistical analysis in the appendix below) and the sample size must be justified by the results of appropriate calculations and related to the study outcomes. For studies involving humans subjects or experimental animals, the Methods section must include a subsection that reports the appropriate ethical approvals for the study (see Ethical Standards above). All analytical procedures must be accompanied by a statement of within and between assay precision.

PCR analysis: **Where experiments involve measurement of mRNA including microarray analysis, for analysis of individual genes, mRNA should be measured by quantitative RTPCR. A statement about the quality and integrity of the RNA must be provided together with the results of eletrophoretic analysis of the purity of the PCR products. Unless published elsewhere, full details of the oligonuceoltide primers and of the PCR protocol must be stated either in the text or in Supplementary Material. The stability of reference genes used for normalisation of PCR data must be reported for the experimental conditions described. Where possible, analysis of mRNA levels should be accompanied by assessment of either protein levels or activities.**

Microarray analysis: **Studies involving microarray analysis of mRNA must conform to the "Minimum Information about a Microarray Experiment" (MIAME) guidelines including deposition of the raw data in an appropriate repository (the Access Code must be state din the Methods). All microarray experiments must be accompanied by appropriate validation by quantitative RTPCR.**

Results

These should be given as concisely as possible, using figures or tables as appropriate. Data must not be duplicated in tables and figures.

Discussion

While it is generally desirable that the presentation of the results and the discussion of their significance should be presented separately, there may be occasions when combining these sections may be beneficial. Authors may also find that additional or alternative sections such as 'conclusions' may be useful. The discussion should be no longer than five manuscript pages**.**

Acknowledgments

Here you may acknowledge individuals or organizations that provided advice and/or support (non-financial). Formal financial support and funding should be listed in the following section.

Financial Support

Please provide details of the sources of financial support for all authors, including grant numbers. For example, "This work was supported by the Medical research Council (grant number XXXXXXX)". Multiple grant numbers should be separated by a comma and space, and where research was funded by more than one agency the different agencies should be separated by a semi-colon, with "and" before the final funder. Grants held by different authors should be identified as belonging to individual authors by the authors' initials. For example, "This work was supported by the Wellcome Trust (A.B., grant numbers XXXX, YYYY), (C.D., grant number ZZZZ); the Natural Environment Research Council (E.F., grant number FFFF); and the National Institutes of Health (A.B., grant number GGGG), (E.F., grant number HHHH)". This disclosure is particularly important in the case of research that is supported by industry. Support from industry not only includes direct financial support for the study but also support in kind such as provision of medications, equipment, kits or reagents without charge or at reduced cost and provision of services such as statistical analysis; all such support must be disclosed here and if no such support was received this must be stated. Where no specific funding has been provided for research, please provide the following statement: "This research received no specific grant from any funding agency, commercial or not-for-profit sectors." In addition to the source of financial support, please state whether the funder contributed to the study design, conduct of the study, analysis of samples or data, interpretation of findings or the preparation of the manuscript. If the funder made no such contribution, please provide the following statement: "[Funder's name] had no role in the design, analysis or writing of this article."

Conflict of Interest

Please provide details of all known financial, professional and personal relationships with the potential to bias the work. Where no known conflicts of interest exist, please include the following statement: "None." For more information on what constitutes a conflict of interest, please see the International Committee of Medical Journal Editors (ICMJE) guidelines.

Authorship

Please provide a very brief description of the contribution of each author to the research. Their roles in formulating the research question(s), designing the study, carrying it out, analysing the data and writing the article should be made plain.

References

Number references consecutively in the order in which they first appear in the text using superscript Arabic numerals in parentheses, e.g. 'The conceptual difficulty of this approach has recently been highlighted(1,2–4)'. If a reference

is cited more than once the same number should be used each time. References cited only in tables and figure legends should be numbered in sequence from the last number used in the text and in the order of mention of the individual tables and figures in the text. Names and initials of authors of unpublished work should be given in the text as 'unpublished results' and not included in the References. At the end of the paper, on a page(s) separate from the text, references should be listed in numerical order using the Vancouver system. When an article has more than three authors only the names of the first three authors should be given followed by 'et al.' The issue number should be omitted if there is continuous pagination throughout a volume. Titles of journals should appear in their abbreviated form using the NCBI LinkOut page. References to books and monographs should include the town of publication and the number of the edition to which reference is made. References to material available on websites should include the full Internet address, and the date of the version cited.

Examples of correct forms of references are given below.

Journal articles

1. Setchell KD, Faughnan MS, Avades T et al. (2003) Comparing the pharmacokinetics of daidzein and genistein with the use of 13C-labeled tracers in premenopausal women. Am J Clin Nutr 77**, 411–419.**

2. Barker DJ, Winter PD, Osmond C et al. (1989) Weight in infancy and death from ischaemic heart disease. Lancet ii**, 577–580.**

3. Forchielli ML & Walker WA (2005) The role of gut-associated lymphoid tissues and mucosal defence. Br J Nutr 93**, Suppl. 1, S41–S48.**

4. Skurk T, Herder C, Kraft I et al. (2004) Production and release of macrophage migration inhibitory factor from human adipocytes. Endocrinology (Epublication ahead of print version).

Books and monographs

5. Bradbury J (2002) Dietary intervention in edentulous patients. PhD Thesis, University of Newcastle.

6. Ailhaud G & Hauner H (2004) Development of white adipose tissue. *In Handbook of Obesity. Etiology and Pathophysiology*, 2nd ed., pp. 481–514 [GA Bray and C Bouchard, editors]. New York: Marcel Dekker.

7. Bruinsma J (editor) (2003) *World Agriculture towards 2015/2030*: *An FAO Perspective*. London: Earthscan Publications.

8. World Health Organization (2003) *Diet, Nutrition and the Prevention of Chronic Diseases. Joint WHO/FAO Expert Consultation. WHO Technical Report Series* no. 916. Geneva: WHO.

9. Keiding L (1997) *Astma, Allergi og Anden Overfølsomhed i Danmark – Og Udviklingen 1987–199I (Asthma, Allergy and Other Hypersensitivities in Denmark, 1987–1991)*. Copenhagen, Denmark: Dansk Institut for Klinisk Epidemiologi.

Sources from the internet

10. Nationmaster (2005) HIV AIDS – Adult prevalence rate. http://www.nationmaster.com/graphT/hea_hiv_aid_adu_pre_rat (accessed June 2013).

Figures

Figures should be supplied as separate electronic files. Figure legends should be grouped in a section at the end of the manuscript text. Each figure should be clearly marked with its number and separate panels within figures should be clearly marked (a), (b), (c) etc. so that they are easily identifiable when the article and figure files are merged for review. Each figure, with its legend, should be comprehensible without reference to the text and should include definitions of abbreviations. The nature of the information displayed in the figures (e.g. mean (SEM)) and the statistical test used must be stated. We recommend that only TIFF, EPS or PDF formats are used for electronic artwork. Other non-preferred but usable formats are JPG, PPT and GIF files and images created in Microsoft Word. Note that these nonpreferred formats are generally NOT suitable for conversion to print reproduction. For further information about how to prepare your figures, including sizing and resolution requirements, please see our artwork guide. In curves presenting experimental results the determined points should be clearly shown, the symbols used being, in order of preference, ○, ●, △, ▲, □, ■, ×, +. Curves and symbols should not extend beyond the experimental points. Scale-marks on the axes should be on the inner side of each axis and should extend beyond the last experimental point. Ensure that lines and symbols used in graphs and shading used in histograms are large enough to be easily identified when the figure size is reduced to fit the printed page. Statistically significant effects should be indicated with symbols or letters. Colour figures will be published online free of charge, and there is a fee of £350 per figure for colour figures in the printed version. If you request colour figures in the printed version, you will be contacted by CCCRightslink who are acting on our behalf to collect colour charges. Please follow their instructions in order to avoid any delay in the publication of your article. Images submitted with a manuscript should be minimally processed; some image processing is acceptable (and may be unavoidable), but the final image must accurately represent the original data. Grouping or cropping of images must be identified in the legend and indicated by clear demarcation. Please refer to the Office of Research Integrity guidelines on image processing in scientific publication. Authors should provide sufficient detail of image-gathering procedures and process manipulation in the Methods sections to enable the accuracy of image presentation to be assessed. Authors should retain their original data, as Editors may request them for comparison during manuscript review.

Tables

Tables should be placed in the main manuscript file at the end of the document, not within the main text. Be sure that each table is cited in the text. Tables should carry headings describing their content and should be comprehensible without reference to the text. Tables should not be subdivided by ruled lines.

The dimensions of the values, e.g. mg/kg, should be given at the top of each column. Separate columns should be used for measures of variance (SD, SE etc.), the ± sign should not be used. The number of decimal places used should be standardized; for whole numbers 1.0, 2.0 etc. should be used. Shortened forms of the words weight (wt) height (ht) and experiment (Expt) may be used to save space in tables, but only Expt (when referring to a specified experiment, e.g. Expt 1) is acceptable in the heading.

Footnotes for table legends are given in the following order: (1) abbreviations, (2) superscript letters, (3) symbols. Abbreviations are given in the format: RS, resistant starch. Abbreviations in tables must be defined in footnotes in the order that they appear in the table (reading from left to right across the table, then down each column). Symbols for footnotes should be used in the sequence: *†‡§||¶, then ** etc. (omit * or †, or both, from the sequence if they are used to indicate levels of significance). For indicating statistical significance, superscript letters or symbols may be used. Superscript letters are useful where comparisons are within a row or column and the level of significance is uniform, e.g. 'a,b,cMean values within a column with unlike superscript letters were significantly different (P<0·05)'. Symbols are useful for indicating significant differences between rows or columns, especially where different levels of significance are found, e.g. 'Mean values were significantly different from those of the control group: *P<0·05, **P<0·01, ***P<0·001'. The symbols used for P values in the tables must be consistent.

Supplementary material

Additional data (e.g. data sets, large tables) relevant to the paper can be submitted for publication online only, where they are made available via a link from the paper. The paper should stand alone without these data. Supplementary Material must be cited in a relevant place in the text of the paper. Although Supplementary Material is peer reviewed, it is not checked, copyedited or typeset after acceptance and it is loaded onto the journal's website exactly as supplied. You should check your Supplementary Material carefully to ensure that it adheres to journal styles. Corrections cannot be made to the Supplementary Material after acceptance of the manuscript. Please bear this in mind when deciding what content to include as Supplementary Material.

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APPENDIX: MATHEMATICAL MODELLING, STATISTICS AND NOMENCLATURE

Mathematical modelling of nutritional processes

Papers in which mathematical modelling of nutritional processes forms the principal element will be considered for publication provided: (a) they are based on sound biological and mathematical principles; (b) they advance nutritional concepts or identify new avenues likely to lead to such advances; (c) assumptions used in their construction are fully described and supported by appropriate argument; (d) they are described in such a way that the nutritional purpose is clearly apparent; (e) the contribution of the model to the design of future experimentation is clearly defined.

Units

Results should be presented in metric units according to the International System of Units (see Quantities, Units and Symbols in Physical Chemistry, 3rd ed. (2007) Cambridge: RSC Publishing), and Metric Units, Conversion Factors and Nomenclature in Nutritional and Food Sciences (1972) London: The Royal Society – as reproduced in *Proceedings of the Nutrition Society* (1972) 31**, 239–247). SI units should be used throughout the paper. The author will be asked to convert any values that are given in any other form. The only exception is where there is a unique way of expressing a particular variable that is in widespread use. Energy values must be given in Joules (MJ or kJ) using the conversion factor 1 kcal = 4.184 kJ. If required by the author, the value in kcal can be given afterwards in parentheses. Temperature is given in degrees Celsius (ºC). Vitamins should be given as mg or µg, not as IU. For substances of known molecular mass (Da) or relative molecular mass, e.g. glucose, urea, Ca, Na, Fe, K, P, values should be expressed as mol/l; for substances of indeterminate molecular mass (Da) or relative molecular mass, e.g. phospholipids, proteins, and for trace elements, e.g. Cu, Zn, then g/l should be used. The 24 h clock should be used, e.g. 15.00 hours. Units are: year, month, week, d, h, min, s, kg, g, mg, µg, litre, ml, µl, fl. To avoid misunderstandings, the word litre should be used in full, except in terms like g/l. Radioactivity should be given in becquerels (Bq or GBq) not in Ci. 1 MBq = 27·03 µCi (1Bq = 1 disintegration/s).**

Statistical treatment of results

Data from individual replicates should not be given for large experiments, but may be given for small studies. The methods of statistical analysis used should be described, and references to statistical analysis packages included in the text, for example: Statistical Analysis Systems statistical software package version 6.11 (SAS Institute, Cary, NC, USA). The description should provide enough information for a statistician with access to the data to reproduce the results presented. Information such as analysis of variance

tables should be given in the paper only if they are relevant to the discussion. A statement of the number of replicates, their average value and some appropriate measure of variability is usually sufficient. Authors must state whether their data follow a Gaussian distribution or not, and the choice of statistical tests must be consistent with the distribution of the data.

Justification for the sample size must be given. **If the study is based on a power calculation, details of this should be provided including the desired effect size and power as well as the estimate of variability that was used. Comparisons between means can be made by using either confidence intervals (CI) or significance tests. The most appropriate of such measures is usually the standard error of a difference between means (SED) or the standard errors of the means (SEM). The SEM represents the uncertainty associated with the estimation of a given mean and is not directly related to the SED or comparisons among means in mixed models as it is in fixed effects models. The SED estimates the uncertainty associated with the difference between two means; because it is used in various mean comparisons tests, SED can be implied within the tests per se. The standard deviation (SD) is more useful only when there is specific interest in the variability of individual values and no treatment means are being compared. The sample size (n per treatment) should also be stated in text or in the table. Standard analysis of variance assumes homogeneous variance. Unless there is heterogeneous variance, as tested by an appropriate statistic, or there is unequal n, a pooled SEM or SED simplifies tables and is preferred. The number of decimal places quoted should be sufficient but not excessive. If data transformations are being used, text should clearly state which variables have been transformed in which way and how that was decision was reached (e.g., tests for normality, diagnostic plots).**
Authors should consider whether their study is rather of explorative (hypothesis-generating) or confirmative (hypothesis-testing) nature. This is particularly important when results from multiple tests are being presented, which can be the case when various treatments are being compared, multiple endpoints are considered, or different subgroups are being analysed. Such multiple testing issues occur often in exploratory studies, and authors should take care not to overstate findings in these situations. At least the number of significant results should be compared to the number of tests compared, where 1 in 20 findings would be expected by chance alone. Methods that control certain error rates (experiment-wise error rate, false discovery rate, etc…) such as post-hoc tests can be used in this context, but are not obligatory, as long as the exploratory nature of the results is made clear. In confirmative studies, pre-planned comparisons or primary endpoints should be stated upfront and analysed by appropriate tools such as contrast testing for pre-planned comparisons. Unnecessary multiple testing corrections with respect to secondary comparisons or endpoints should be avoided to not compromise the power of the study. Measurements on the same experimental unit over time or in different sections of tissue generally are not independent. If the repeated measures are taken from the same animal or human subject, which are expected to be randomly chosen to represent a population, an appropriate mixed model should be fitted while investigating the best covariance of error structures. All major statistical software packages offer a wide variety of structures; the one chosen should be stated.

If comparisons between means are made using CI, the format for presentation is, e.g. 'difference between means 0·73 (95 % CI 0·314, 1·36) g'. If significance tests are used, a statement that the difference between the means for two groups of values is (or is not) statistically significant should include the level of significance attained, preferably as an explicit P value (e.g. P=0·016 or P=0·32) rather than as a range (e.g. P<0·05 or P>0·05). It should be stated whether the significance levels quoted are one-sided or two-sided (when relevant). Where a multiple comparison procedure is used, a description or explicit reference should be given. Where appropriate, a superscript notation may be used in tables to denote levels of significance; similar superscripts should denote lack of a significant difference. When the method of analysis is unusual, or if the experimental design is at all complex, further details (e.g., experimental plan, raw data, confirmation of assumptions, analysis of variance tables, etc.) should be included. Adequate detail should be provided for a subsequent reader to interpret and potentially repeat the approach used. For example, the statistical model should be provided or described in adequate detail, and all blocking factors and criteria should be provided. Regressions should provide appropriate estimates of parameter uncertainty (not necessarily provided by graphing software).

Chemical formulas

These should be written as far as possible on a single horizontal line. With inorganic substances, formulas may be used from first mention. With salts, it must be stated whether or not the anhydrous material is used, e.g. anhydrous CuSO4, or which of the different crystalline forms is meant, e.g. CuSO4.5H2O, CuSO4.H2O.

Descriptions of solutions, compositions and concentrations

Solutions of common acids, bases and salts should be defined in terms of molarity (M), e.g. 0.1 M-NaH2PO4. Compositions expressed as mass per unit mass (w/w) should have values expressed as ng, µg, mg or g per kg; similarly for concentrations expressed as mass per unit volume (w/v), the denominator being the litre. If concentrations or compositions are expressed as a percentage, the basis for the composition should be specified (e.g. % (w/w) or % (w/v) etc.). The common measurements used in nutritional studies, e.g. digestibility, biological value and net protein utilization, should be expressed as decimals rather than as percentages, so that amounts of available nutrients can be obtained from analytical results by direct multiplication. *See Metric Units, Conversion Factors and Nomenclature in Nutritional and Food Sciences*. London: The Royal Society, 1972 (para. 8).

Cell lines

The Journal expects authors to deposit cell lines (including microbial strains) used in any study to be published in publicly accessible culture collections, for example, the European Collection of Cell Cultures (ECACC) or the American Type Culture Collection (ATCC) and to refer to the collection and line or strain numbers in the text (e.g. ATCC 53103). Since the authenticity of subcultures of culture collection specimens that are distributed by individuals cannot be

ensured, authors should indicate laboratory line or strain designations and donor sources as well as original culture collection identification numbers.

Gene nomenclature and symbols

The use of symbols and nomenclature recommended by the HUGO Gene Nomenclature Committee is encouraged. Information on human genes is also available from Entrez Gene, on mouse genes from the Mouse Genome Database and on rat genes from the Rat Genome Database.

Nomenclature of vitamins

Most of the names for vitamins and related compounds that are accepted by the Editors are those recommended by the IUNS Committee on Nomenclature. See Nutrition Abstracts and Reviews (1978) 48**A, 831–835.**

Acceptable name	*Other names**
Vitamin A	
Retinol	Vitamin A_1
Retinaldehyde, retinal	Retinene
Retinoic acid (all-trans or 13-cis)	Vitamin A1 acid
3-Dehydroretinol	Vitamin A_2
Vitamin D	
Ergocalciferol, ercalciol	Vitamin D2 calciferol
Cholecalciferol, calciol	Vitamin D3
Vitamin E	
α-, β- and γ-tocopherols plus tocotrienols	
Vitamin K	
Phylloquinone	Vitamin K_1
Menaquinone-n (MK-n)†	Vitamin K_2
Menadione	Vitamin K_3, menaquinone, menaphthone
Vitamin B1	
Thiamin	Aneurin(e), thiamine
Vitamin B_2	
Riboflavin	Vitamin G, riboflavine,
Lactoflavin	
Niacin	
Nicotinamide	Vitamin PP
Nicotinic acid	
Folic Acid	
Pteroyl(mono)glutamic acid	Folacin, vitamin Bc or M
Vitamin B_6	
Pyridoxine	Pyridoxol
Pyridoxal	
Pyridoxamine	
Vitamin B_{12}	
Cyanocobalamin	
Hydroxocobalamin	Vitamin B_{12a} or B_{12b}
Aquocobalamin	
Methylcobalamin	
Adenosylcobalamin	

Inositol
Myo-inositol *Meso*-inositol
Choline
Pantothenic acid
Biotin Vitamin H
Vitamin C
Ascorbic acid
Dehydroascorbic acid

***Including some names that are still in use elsewhere, but are not used by BJN. †Details of the nomenclature for these and other naturally-occurring quinones should follow the Tentative Rules of the IUPAC-IUB Commission on Biochemical Nomenclature (see European Journal of Biochemistry (1975) 53, 15–18). 11**
The terms vitamin A, vitamin C **and** vitamin D **may still be used where appropriate, for example in phrases such as 'vitamin A deficiency', 'vitamin D activity'.**
The term vitamin E **should be used as the descriptor for all tocol and tocotrienol derivatives exhibiting qualitatively the biological activity of α-tocopherol. The term** tocopherols **should be used as the generic descriptor for all methyl tocols. Thus, the term** tocopherol **is not synonymous with the term** vitamin E**.**
The term vitamin K **should be used as the generic descriptor for 2-methyl-1,4-naphthoquinone (menaphthone) and all derivatives exhibiting qualitatively the biological activity of phylloquinone (phytylmenaquinone).**
The term niacin **should be used as the generic descriptor for pyridine 3-carboxylic acid and derivatives exhibiting qualitatively the biological activity of nicotinamide.**
The term vitamin B_6 **should be used as the generic descriptor for all 2-methylpyridine derivatives exhibiting qualitatively the biological activity of pyridoxine.**
Regarding folate**, due to the wide range of C-substituted, unsubstituted, oxidized, reduced and mono- or polyglutamyl side-chain derivatives of pteroylmonoglutamic acid that exist in nature, it is not possible to provide a complete list. Authors are encouraged to use either the generic name or the correct scientific name(s) of the derivative(s), as appropriate for each circumstance.**
The term vitamin B_{12} **should be used as the generic descriptor for all corrinoids exhibiting qualitatively the biological activity of cyanocobalamin. The term** corrinoids **should be used as the generic descriptor for all compounds containing the corrin nucleus and thus chemically related to cyanocobalamin. The term** corrinoid **is not synonymous with the term** vitamin B_{12}.
The terms ascorbic acid **and** dehydroascorbic acid **will normally be taken as referring to the naturallyoccurring L-forms. If the subject matter includes other optical isomers, authors are encouraged to include the L- or D- prefixes, as appropriate. The same is true for all those vitamins which can exist in both natural and alternative isomeric forms. Weight units are acceptable for the amounts of vitamins in foods and diets. For concentrations in biological tissues, SI units should be used; however, the authors may, if they wish, also include other units, such as weights or international units, in parentheses*. *See***

Metric Units, Conversion Factors and Nomenclature in Nutritional and Food Sciences **(1972) paras 8 and 14–20. London: The Royal Society.**

Nomenclature of fatty acids and lipids

In the description of results obtained for the analysis of fatty acids by conventional GLC, the shorthand designation proposed by Farquhar JW, Insull W, Rosen P, Stoffel W & Ahrens EH (*Nutrition Reviews* (1959), 17**, Suppl.) for individual fatty acids should be used in the text, tables and figures. Thus, 18 : 1 should be used to represent a fatty acid with eighteen carbon atoms and one double bond; if the position and configuration of the double bond is unknown. The shorthand designation should also be used in the abstract. If the positions and configurations of the double bonds are known, and these are important to the discussion, then a fatty acid such as linoleic acid may be referred to as cis-9,cis-12-18 : 2 (positions of double bonds related to the carboxyl carbon atom 1). However, to illustrate the metabolic relationship between different unsaturated fatty acid families, it is sometimes more helpful to number the double bonds in relation to the terminal methyl carbon atom, n. The preferred nomenclature is then: 18 : 3n-3 and 18 : 3n-6 for α-linolenic and γ-linolenic acids respectively; 18 : 2n-6 and 20 : 4n-6 for linoleic and arachidonic acids respectively and 18 : 1n-9 for oleic acid. Positional isomers such as α- and γ-linolenic acid should always be clearly distinguished. It is assumed that the double bonds are methylene-interrupted and are of the cis-configuration (see Holman RT in Progress in the Chemistry of Fats and Other Lipids (1966) vol. 9, part 1, p. 3. Oxford: Pergamon Press). Groups of fatty acids that have a common chain length but vary in their double bond content or double bond position should be referred to, for example, as C20 fatty acids or C20 PUFA. The modern nomenclature for glycerol esters should be used, i.e. triacylglycerol, diacylglycerol, monoacylglycerol not triglyceride, diglyceride, monoglyceride. The form of fatty acids used in diets should be clearly stated, i.e. whether ethyl esters, natural or refined fats or oils. The composition of the fatty acids in the dietary fat and tissue fats should be stated clearly, expressed as mol/100 mol or g/100 g total fatty acids.**

Nomenclature of micro-organisms

The correct name of the organism, conforming with international rules of nomenclature, should be used. If desired, synonyms may be added in parentheses when the name is first mentioned. Names of bacteria should conform to the current Bacteriological Code and the opinions issued by the International Committee on Systematic Bacteriology. Names of algae and fungi must conform to the current International Code of Botanical Nomenclature. Names of protozoa should conform to the current International Code of Zoological Nomenclature.

Nomenclature of plants

For plant species where a common name is used that may not be universally intelligible, the Latin name in italics should follow the first mention of the common name. The cultivar should be given where appropriate.

Other nomenclature, symbols and abbreviations

Authors should consult recent issues of BJN for guidance. The IUPAC rules on chemical nomenclature should be followed, and the recommendations of the Nomenclature Committee of IUBMB and the IUPACIUBMB Joint Commission on *Biochemical Nomenclature and Nomenclature Commission of IUBMB in Biochemical Nomenclature and Related Documents* (1992), 2nd ed., London: Portland Press (*http://www.chem.qmul.ac.uk/iupac/bibliog/white.html*). The symbols and abbreviations, other than units, *are essentially those listed in British Standard* 5775 (1979–1982), *Specifications for Quantities*, *Units and Symbols*, parts 0–13. Day should be abbreviated to d, for example 7 d, except for 'each day', '7th day' and 'day 1'. Elements and simple chemicals (e.g. Fe and CO2) can be referred to by their chemical symbol (with the exception of arsenic and iodine, which should be written in full) or formula from the first mention in the text; the title, text and table headings, and figure legends can be taken as exceptions,. Well-known abbreviations for chemical substances may be used without explanation, thus: RNA for ribonucleic acid and DNA for deoxyribonucleic acid. Other substances that are mentioned frequently (five or more times) may also be abbreviated, the abbreviation being placed in parentheses at the first mention, thus: lipoprotein lipase (LPL), after that, LPL, and an alphabetical list of abbreviations used should be included. Only accepted abbreviations may be used in the title and text headings. If an author's initials are mentioned in the text, they should be distinguished from other abbreviations by the use of stops, e.g. 'one of us (P. J. H.)…'. For UK counties the official names given in the *Concise Oxford Dictionary* (1995) should be used and for states of the USA two-letter abbreviations should be used, e.g. MA (not Mass.) and IL (not Ill.). Terms such as 'bioavailability' or 'available' may be used providing that the use of the term is adequately defined. Spectrophotometric terms and symbols are those proposed in *IUPAC Manual of Symbols and Terminology for Physicochemical Quantities and Units* (1979) London: Butterworths. The attention of authors is particularly drawn to the following symbols: m (milli, 10□3), μ (micro, 10□6), n (nano, 10□9) and p (pico, 10□12). Note also that ml (millilitre) should be used instead of cc, μm (micrometre) instead of μ (micron) and μg (microgram) instead of γ. Numerals should be used with units, for example, 10 g, 7 d, 4 years (except when beginning a sentence, thus: 'Four years ago...'); otherwise, words (except when 100 or more), thus: one man, ten ewes, ninety-nine flasks, three times (but with decimal, 2.5 times), 100 patients, 120 cows, 136 samples.

Abbreviations

The following abbreviations are accepted without definition by BJN:

ADP (GDP)	**adenosine (guanosine) 5'-disphosphate**
AIDS	**acquired immune deficiency syndrome**
AMP (GMP)	**adenosine (guanosine) 5'-monophosphate**
ANCOVA	**analysis of covariance**
ANOVA	**analysis of variance**
apo	**apolipoprotein**
ATP (GTP)	**adenosine (guanosine) 5'-triphosphate**
AUC	**area under the curve**
BMI	**body mass index**
BMR	**basal metabolic rate**

bp	**base pair**
BSE	**bovine spongiform encephalopathy**
CHD	**coronary heart disease**
CI	**confidence interval**
CJD	**Creutzfeldt-Jacob disease**
CoA and acyl-CoA	**co-enzyme A and its acyl derivatives**
CV	**coefficient of variation**
CVD	**cardiovascular disease**
Df	**degrees of freedom**
DHA	**docosahexaenoic acid**
DM	**dry matter**
DNA	**deoxyribonucleic acid**
dpm	**disintegrations per minute**
EDTA	**ethylenediaminetetra-acetic acid**
ELISA	**enzyme-linked immunosorbent assay**
EPA	**eicosapentaenoic acid**
Expt	**experiment (for specified experiment, e.g. Expt 1)**
FAD	**flavin-adenine dinucleotide**
FAO	**Food and Agriculture Organization (except when used as an author)**
FFQ	**food-frequency questionnaire**
FMN	**flavin mononucleotide**
GC	**gas chromatography**
GLC	**gas–liquid chromatography**
GLUT	**glucose transporter**
GM	**genetically modified**
Hb	**haemoglobin**
HDL	**high-density lipoprotein**
HEPES	**4-(2-hydroxyethyl)-1-piperazine-ethanesulfonic acid**
HIV	**human immunodeficiency virus**
HPLC	**high-performance liquid chromatography**
Ig	**immunoglobulin**
IHD	**ischaemic heart disease**
IL	**interleukin**
IR	**infra red**
Kb	**kilobases**
Km	**Michaelis constant**
LDL	**low-density lipoprotein**
MHC	**major histocompatibility complex**
MRI	**magnetic resonance imaging**
MS	**mass spectrometry**
MUFA	**monounsaturated fatty acids**
NAD+, NADH	**oxidized and reduced nicotinamide-adenine dinucleotide**
NADP+, NADPH	**oxidized and reduced nicotinamide-adenine dinucleotide phosphate**
NEFA	**non-esterified fatty acids**
NF-κB	**nuclear factor kappa B**
NMR	**nuclear magnetic resonance**
NS	**not significant**

NSP	**non-starch polysaccharide**
OR	**odds ratio**
PAGE	**polyacrylamide gel electrophoresis**
PBS	**phosphate-buffered saline**
PCR	**polymerase chain reaction**
PG	**prostaglandin**
PPAR	**peroxisome proliferator-activated receptor**
PUFA	**polyunsaturated fatty acids**
RDA	**recommended dietary allowance**
RER	**respiratory exchange ratio**
RIA	**radioimmunoassay**
RMR	**resting metabolic rate**
RNA, mRNA etc.	**ribonucleic acid, messenger RNA etc.**
rpm	**revolutions per minute**
RT	**reverse transcriptase**
SCFA	**short-chain fatty acids**
SDS	**sodium dodecyl sulphate**
SED	**standard error of the difference between means**
SFA	**saturated fatty acids**
SNP	**single nucleotide polymorphism**
TAG	**triacylglycerol**
TCA	**trichloroacetic acid**
TLC	**thin-layer chromatography**
TNF	**tumour necrosis factor**
UN	**United Nations (except when used as an author)**
UNICEF	**United Nations International Children's Emergency**
Fund UV	**ultra violet**
VLDL	**very-low-density lipoprotein**
V_{O2}	**O_2 consumption**
V_{O2max}	**maximum O2 consumption**
WHO	**World Health Organization (except when used as an author)**

Use of three-letter versions of amino acids in tables: Leu, His, etc.
CTP, UTP, GTP, ITP, as we already use ATP, AMP etc.

Disallowed words and phrases

The following are disallowed by BJN:

deuterium or tritium (use ^2H and ^3H)
c.a. or around (use approximately or about)
canola (use rapeseed)
ether (use diethyl ether)
free fatty acids (use NEFA)
isocalorific/calorie (use isoenergetic/energy)
quantitate (use quantify)
unpublished data or observations (use unpublished results)

ANEXO C

Comprovante de submissão

British Journal of Nutrition

Home

Author

Review

Submission Confirmation

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Title
PREMATURITY AND MATERNAL HEALTH CONDITIONS INFLUENCE PLASMA GLUCOSE AND TRIGLYCERIDE LEVELS IN NEWBORNS AT SIX MONTHS OF CORRECTED AGE

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