UNIVERSIDADE FEDERAL DE UBERLÂNDIA

FACULDADE DE MEDICINA

PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS DA SAÚDE

ASSOCIAÇÃO DO *JETLAG* SOCIAL E DO CRONOTIPO COM O CONSUMO ALIMENTAR E GANHO DE PESO DURANTE A GESTAÇÃO: ESTUDO DE COORTE PROSPECTIVO

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Uberlândia

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Tese apresentada ao Programa de Pós-Graduação em Ciências da Saúde da Faculdade de Medicina da Universidade Federal de Uberlândia, como requisito parcial para a obtenção do Título de Doutor em Ciências da Saúde.

Área de concentração: Ciências da Saúde

Orientadora: Profa. Dra. Cibele Aparecida Crispim

Coorientadora: Profa. Dra. Yara Cristina de Paiva Maia

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UNIVERSIDADE FEDERAL DE UBERLÂNDIA
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ATA

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Anita Maria Tibiletti.

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RESUMO

Introdução: A incompatibilidade entre os relógios circadianos e sociais leva ao desalinhamento circadiano, o qual tem sido amplamente avaliado pelo *jetlag* social (JLS). Estudos têm associado o JLS às doenças nutricionais como a obesidade, mas tal temática ainda não foi estudada em gestantes. O cronotipo, que diz respeito às diferenças inter individuais de alocação de fase dos ritmos circadianos, é um dos fatores que vem sendo associado ao desalinhamento circadiano e também às doenças nutricionais. Entretanto, os efeitos do cronotipo sobre a ingestão alimentar e ganho de peso durante a gestação também não foram abordados pela literatura. **Objetivo:** Esta tese teve dois objetivos principais: 1) identificar a ocorrência de JLS ao longo da gestação e descrever o efeito do peso corporal pré-gestacional sobre o JLS ao longo da gestação; 2) estudar a associação do cronotipo com o consumo alimentar e o ganho de peso durante a gestação. **Material e Métodos:** A primeira fase do estudo foi realizada com 205 gestantes no primeiro trimestre. Posteriormente, 100 gestantes foram acompanhadas por meio de um estudo de coorte prospectivo no segundo e terceiro trimestres gestacionais. O JLS foi calculado com base na diferença absoluta entre o ponto médio do sono nos dias de trabalho e dias livres. A ingestão alimentar foi avaliada por três recordatórios alimentares de 24 horas em cada trimestre, totalizando nove recordatórios. A ingestão e distribuição de energia e macronutrientes foram avaliadas nas refeições ao longo do dia e a qualidade da dieta foi avaliada pelo Índice de Qualidade da Dieta Revisado (IQD-R). O cronotipo foi derivado do ponto médio do sono em dias livres (MSF) corrigido para o débito de sono e as pontuações obtidas foram categorizadas em tercis. Foram calculados o índice de massa corporal (IMC) pré-gestacional (kg/ m²) e o IMC atual (kg/ m²). As recomendações do *Institute of Medicine* foram utilizadas para avaliar a adequação do ganho de peso. A regressão linear e logística e as Equações de Estimações Generalizadas (GEE) ajustadas para fatores de confusão foram utilizadas para determinar a associação entre JLS e os trimestres gestacionais (tempo) e variáveis antropométricas. Além disso, GEE foram utilizadas usadas para determinar os efeitos do cronotipo e dos trimestres gestacionais nos padrões alimentares, energia diária, distribuição de macronutrientes e ganho de peso. **Resultados:** A maioria das gestantes (54,5%) apresentou JLS > 1h no primeiro trimestre gestacional. Foi encontrada associação positiva entre JLS e IMC pré-gestacional no terceiro trimestre ($\beta = 0,200$, $p = 0,046$). Além disso, as análises de GEE mostraram que

as gestantes com peso pré-gestacional normal apresentaram diminuição no JLS do segundo para o terceiro trimestre (1,29 ± 0,11 e 0,93 ± 0,08, respectivamente, p = 0,032), mas isso não foi encontrado nos outros grupos do estado nutricional (baixo peso, sobrepeso e obesidade). Em adição, encontramos um efeito isolado do tem (trimestre de gestação) na média do JLS. Nesse sentido, as gestantes apresentaram diminuição do JLS do segundo para o terceiro trimestre (1,33 ± 0,08 *versus* 1,12 ± 0,07, respectivamente; p = 0,012). Em relação aos resultados relacionados ao cronotipo, gestantes com valores de MSF com tendência à vespertinidade faziam o café da manhã mais tarde e também tinham maior ingestão de energia e carboidratos no jantar, em comparação àquelas com tendência à matutinidade. Gestantes com tendência à matutinidade mostraram uma dieta de melhor qualidade no grupo de leite e derivados e gordura saturada avaliados pelo IQD-R. Além disso, apesar da tendência das gestantes de todos os tercis ganharem peso excessivamente durante a gestação, observou-se que as gestantes com tendência à vespertinidade apresentaram uma pior adequação do ganho de peso gestacional no terceiro trimestre quando comparadas às gestantes com tendência à matutinidade (2,24 ± 0,25 kg *versus* 1,22 ± 0,14 kg, p <0,001). **Conclusão:** O JLS > 1h é bastante prevalente durante a gestação e o excesso de peso pré-gestacional parece levar ao maior risco de apresentar JLS > 1h ao longo da gestação. Além disso, gestantes com tendência à vespertinidade realizam o café da manhã mais tarde e também têm maior ingestão de energia e carboidratos à noite, além de apresentarem um pior padrão de ganho de peso gestacional no terceiro trimestre. Nossos resultados enfatizam a importância de considerar as variáveis cronobiológicas nas diretrizes nutricionais do pré-natal para promover a saúde materno-fetal.

Palavras-chave: Gestantes; *Jetlag* social; Cronotipo; Índice de Massa Corporal; Ganho de peso gestacional.

ABSTRACT

Introduction: The incompatibility between circadian and social clocks leads to circadian misalignment, which has been widely measured by social jetlag (SJL). Studies have associated SJL with nutritional diseases such as obesity, but this topic has not yet been studied in pregnant women. The chronotype, which concerns the inter-individual differences in phase allocation of circadian rhythms, is one of the factors that has been associated with circadian misalignment and also with nutritional diseases. However, the effects of the chronotype on food intake and weight gain during pregnancy were also not addressed in the literature. **Objective:** This thesis had two main objectives: 1) to identify the occurrence of SJL during pregnancy and to describe the effect of pre-pregnancy body weight on SJL throughout pregnancy; 2) to analyse the association of the chronotype with food consumption and weight gain during pregnancy. **Material and Methods:** The first phase of the study was carried out with 205 pregnant women in the first trimester. Thereafter, 100 pregnant women were followed up through a prospective cohort study in the second and third gestational trimesters. The SJL was calculated based on the absolute difference between the midpoint of sleep on working days and free days. Food intake was assessed by three 24-hour food records in each trimesters, totaling nine records. The intake and distribution of energy and macronutrients were assessed at meals throughout the day and the quality of the diet was assessed by the Revised Diet Quality Index (IQD-R). The chronotype was derived from the midpoint of sleep on free days (MSF) corrected for sleep output and the scores obtained were categorized into tertiles. The pre-gestational body mass index (BMI) (kg/ m²) and the current BMI (kg/ m²) were calculated. The Institute of Medicine recommendations were used to assess the adequacy of weight gain. Linear and logistic regression and the Generalized Estimation Equations (GEE) adjusted for confounding factors were used to determine the association between SJL and gestational trimesters (time) and anthropometric variables. In addition, GEE were used to determine the effects of chronotype and gestational trimesters on dietary patterns, daily energy, macronutrient distribution and weight gain. **Results:** Most pregnant women (54.5%) had SJL > 1h in the first trimester of pregnancy. A positive association was found between SJL and pre-pregnancy BMI in the third trimester ($\beta = 0.200$, p = 0.046). In addition, GEE analyzes showed that pregnant women with normal pre-gestational weight showed a decrease in SJL from the second to the third trimester (1.29 $\pm$ 0.11 and 0.93 $\pm$

0.08, respectively, p = 0.032), but this was not found in the other groups of nutritional status (underweight, overweight and obesity). In addition, we found an isolated effect of the trimester of gestation on the SJL average. In this sense, pregnant women showed a decrease in SJL from the second to the third trimester (1.33 ± 0.08 versus 1.12 ± 0.07, respectively; p = 0.012). Regarding the results related to the chronotype, pregnant women with MSF values with a tendency to evening had breakfast later and also had a higher intake of energy and carbohydrates at dinner, compared to those with a tendency to morning. Pregnant women with a tendency to maturity showed a better quality diet in the group of milk and derivatives and saturated fat evaluated by the IQD-R. In addition, despite the tendency of pregnant women of all tertiles to gain excess weight during pregnancy, it was observed that pregnant women with a tendency to evening had a worse adequacy of gestational weight gain in the third trimester when compared to pregnant women with a tendency to maturity (2.24 ± 0.25 kg versus 1.22 ± 0.14 kg, p <0.001).

Conclusion: SJL > 1h is quite prevalent during pregnancy and pre-gestational excess weight seems to lead to a greater risk of having SJL > 1h during pregnancy. In addition, pregnant women with a tendency to evening eat breakfast later and also have a higher intake of energy and carbohydrates at night, in addition to having a worse pattern of gestational weight gain in the third trimester. Our results emphasize the importance of considering chronobiological variables in prenatal nutritional guidelines to promote maternal and fetal health.

Figure 2. Effect of chronotype in the gestational trimesters on adequacy of weight gain during pregnancy (n = 100/ each trimester).

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Table 3. Effect of chronotype on total energy and macronutrients intakes, meal and snack times and time-related eating patterns during pregnancy (Total gestational data's values - represent the average of the three trimesters-, n=100/ each trimester).

Table 4. Effect of chronotype on scores of the total Brazilian Healthy Eating Index-Revised (BHEI-R) and its components during pregnancy (Total gestational data's values -represent the average of the three trimesters-, n=100/ each trimester).

LISTA DE ABREVIATURAS E SIGLAS

FUNDAMENTAÇÃO TEÓRICA

AI	*Adequate Intake*
AMDR	*Acceptable Macronutrient Distribution Range*
DCNT	Doenças crônicas não transmissíveis
DRIs	*Dietary Reference Intakes*
g	Grama
GPG	Ganho de peso gestacional
IBGE	Instituto Brasileiro de Geografia e Estatística
IC	Intervalo de confiança
IMC	Índice de massa corporal
INTERGROWTH-21st	*International Fetal and Newborn Growth Consortium for the 21st Century*
IOM	Instituto de Medicina
JLS	*Jetlag* social
kcal	Caloria
kg	Quilogramas
L	Litros
mg	Miligramas
MSF	Ponto médio do sono nos dias de fim de semana
MSFsc	Ponto médio do sono em dias livres corrigido para débito de sono
MSW	Ponto médio do sono nos dias de semana
NSQ	Núcleo supraquiasmático
OMS	Organização Mundial da Saúde
OR	Odds ratio
RDA	*Recommended Dietary Allowance*
STC	Sistema de temporização circadiana
µg	Microgramas
VET	Valor energético total

ARTIGOS

ANOVA	Análise de variância
BHEI-R	*Brazilian Healthy Eating Index-Revised*
BMI	*Body mass index*
CI	*Confidence interval*
CNPq	Conselho Nacional de Desenvolvimento Científico e Tecnológico
FAPEMIG	Fundação de Amparo à Pesquisa do Estado de Minas Gerais
GEE	*Generalized Estimating Equation*
GzLM	*Generalized Linear Models*
Gord-AA	Calorias provenientes de gordura sólida, álcool e açúcar de adição.
h	Horas
HIV	Human Immuno-Deficiency Virus
kg	Quilogramas
m	Metros
Min	Minutos
MSF	*Mid-sleep time on free days*
MSFsc	*Mid-sleep time on free days corrected for calculated sleep debt*
OR	*Odds ratio*
PSQI	*Pittsburgh Sleep Quality Index*
SD	*Standard deviation*
SE	*Standard error*
SJL	*Social jetlag*
SoFAAS	*Calories from Solid Fats, Alcoholic beverages, and Added Sugars*
SPSS	*Statistical Package for the Social Sciences*
USDA	*United States Department of Agriculture*
WHO	*World Health Organization*
y	*Year*
24HR	*24-Hour Dietary Recall*
%EI	*Energy consumed during a period divided by the total daily energy intake.*

ANEXOS

CEP   Comitê de ética em pesquisa
CAAE   Certificado de Apresentação de Apreciação Ética

APÊNDICES

TCLE   Termo de consentimento livre e esclarecido

SUMÁRIO

INTRODUÇÃO

Os relógios circadianos central e periféricos têm como principal função sincronizar o sistema endógeno ao longo de um período de 24 horas e controlar diversos processos biológicos, como o ciclo vigília-sono (VOIGT; FORSYTH; KESHAVARZIAN, 2013). O desalinhamento circadiano ocorre quando os ritmos circadianos endógenos não são adequadamente sincronizados por pistas ambientais - ou *zeitgebers* - como o ciclo claro-escuro (ROENNEBERG; WIRZ-JUSTICE; MERROW, 2003), a ingestão de alimentos (DE GOEDE et al., 2018; MIEDA et al., 2006; YOO et al., 2004; BRANDSTAET*7*ER, 2004) e a atividade física (ATKINSON et al., 2007; DE GOEDE et al., 2018). Diversas variáveis têm sido propostas para avaliar as diferenças inter individuais de alocação de fase dos ritmos circadianos e também o desalinhamento circadiano. Dentre elas, podemos elencar o cronotipo e o *jetlag* social (JLS), respectivamente.

O JLS descreve e quantifica a discrepância crônica entre o relógio biológico de um indivíduo e o relógio social, ou seja, o conflito entre os horários de sono com e sem as restrições impostas por obrigações sociais (WITTMANN et al., 2006). Proposta por Wittmann e colaboradores em 2006, essa variável é calculada pela diferença absoluta entre o ponto médio do sono nos dias de trabalho e o ponto médio do sono nos dias livres (WITTMANN et al., 2006). Estudos anteriores mostraram que o JLS está associado a problemas de saúde como obesidade (PARSONS et al., 2015; ROENNEBERG et al., 2012), distúrbios metabólicos (PARSONS et al., 2015), diabetes tipo 2 (KOOPMAN et al., 2017), doença cardiovascular aterosclerótica (KANTERMANN et al., 2013; RUTTERS et al., 2014; WONG et al., 2015), bem como com níveis mais elevados de cortisol em indivíduos saudáveis (RUTTERS et al., 2014) e níveis mais elevados de hemoglobina glicada em pacientes com diabetes tipo 2 (REUTRAKUL et al., 2013).

O cronotipo foi definido por Roenneberg (2012) como a fase individual de arrastamento (ROENNEBERG, 2012), ou seja, a fase em que um indivíduo sincroniza com o dia de 24 horas. Essa variável é também descrita como o aspecto biológico que dita a preferência individual para a realização das atividades ao longo do dia e que pode ser percebido pelo nível de concentração e pico de sono no período de 24 horas, dentre outros fatores (MARQUES; MENNA-BARRETO, 1999). Essa preferência usualmente classifica os indivíduos como "matutinos", "intermediários" e "vespertinos" (HORNE; OSTBERG, 1976). Nesse sentido, estudos anteriores demonstraram que certos

cronotipos, particularmente o vespertino, estão associados à má qualidade do sono (BARCLAY et al., 2013), obesidade (CULNAN; KLOSS; GRANDNER, 2013; LUCASSEN et al., 2013; TÜRKOĞLU; CETIN, 2019), aumento do risco de doença cardiovascular (KANTERMANN et al., 2014; MERIKANTO et al., 2013) e distúrbios metabólicos, incluindo diabetes tipo 2 (MERIKANTO et al., 2013). Essas evidências também demonstram que o consumo alimentar parece sofrer interferências do cronotipo, em especial no que fiz respeito aos horários das refeições (NAKADE et al., 2009; REUTRAKUL et al., 2013; SATO-MITO et al, 2011; SILVA et al., 2016; VERA et al., 2018) e qualidade alimentar (CRISPIM; MOTA, 2018). Porém, tais estudos são limitados a poucas faixas etárias e ciclos da vida. Na gestação, por exemplo, pesquisas que relacionam aspectos cronobiológicos aos desfechos nutricionais são extremamente limitadas.

A gestação é um período de intensas mudanças e adaptações fisiológicas e metabólicas (NEWBERN; FREEMARK, 2011), levando ao aumento das necessidades energéticas e nutricionais (PLEĆAS; PLESINAC; KONTIĆ VUCINIĆ, 2014). Entretanto, apesar das evidências que apoiam a importância da nutrição materna como uma medida eficaz para evitar resultados nutricionais gestacionais inadequados - como ganho de peso excessivo (STUEBE; OKEN; GILLMAN, 2009) -, as mulheres grávidas no Brasil consomem uma dieta pobre (MELERE et al., 2013; GOMES et al., 2015) e 51% ganham peso excessivamente (STUEBE; OKEN; GILLMAN, 2009). A inadequação alimentar durante este período pode ser ainda considerada fator de risco para a ocorrência de outros desfechos gestacionais desfavoráveis, incluindo complicações gestacionais como diabetes mellitus gestacional, aumento das taxas de prematuridade, restrição do crescimento fetal e morbimortalidade materno-infantil (KING, 2003; RIFAS-SHIMAN et al., 2009).

Diante do exposto, a identificação de novos fatores associados à evolução nutricional durante a gestação, bem como o conhecimento de suas interações com outros aspectos que sabidamente interferem no estado nutricional materno, são de grande importância na proteção do estado nutricional da gestante. Dessa maneira, aspectos cronobiológicos como o JLS e o cronotipo tornam-se variáveis potenciais nessa área de pesquisa, tendo em vista suas possíveis influências sobre o consumo alimentar (MAZRI et al., 2019) e o estado nutricional (ARORA; TAHERI, 2015; DE PUNDER; HEIM; ENTRINGER, 2019) de outras populações. Entretanto, de acordo com o nosso conhecimento nenhum estudo até o momento examinou o impacto do JLS sobre a

gestação e o efeito do peso corporal pré-gestacional sobre JLS ao longo da gestação e tampouco a influência do cronotipo sobre o consumo alimentar e ganho de peso gestacional ao longo de todo o período gestacional.

Espera-se que este estudo longitudinal demonstre a prevalência de JLS, seu impacto sobre a gestação e o efeito do peso corporal pré-gestacional sobre JLS ao longo da mesma, e também demonstre a associação do cronotipo com o consumo alimentar e ganho de peso durante a gestação. A presente tese tem como finalidade pesquisar novos fatores de risco modificáveis para o consumo alimentar inadequado e ganho de peso excessivo durante a gestação, visando repensar as estratégicas atuais de intervenção nutricional gestacional com o intuito de promover a saúde materno-infantil.

1.1. Considerações iniciais

A formatação desta tese segue o modelo alternativo estabelecido pelo Programa de Pós Graduação e Pesquisa em Ciências Saúde da Faculdade de Medicina da Universidade Federal de Uberlândia, o qual determina que os resultados da tese sejam apresentados em formato de artigos científicos.

A tese foi organizada nas seguintes seções: inicialmente, uma **Fundamentação Teórica** será apresentada como forma de revisão da literatura sobre os temas abordados na tese. Serão então elencados os **Objetivos** em que são expostos os propósitos do estudo; os **Resultados**, que contemplam dois artigos elaborados; a **Conclusão**, que discorre sobre a síntese dos principais resultados do estudo; as **Perspectivas**, nas quais são apresentadas as expectativas para estudos futuros; e o **Pós-texto**, no qual estão incluídos referências bibliográficas, anexos e apêndices.

O primeiro artigo intitulado ***"Changes in circadian misalignment measured by social jetlag from early to late pregnancy and its association with nutritional status: a longitudinal study"*** teve como objetivo identificar a ocorrência de *jetlag* social ao longo da gestação e descrever o efeito do peso corporal pré-gestacional sobre *jetlag* social ao longo do período gestacional. Este artigo está submetido para o periódico *American Journal of Clinical Nutrition* (Fator de impacto = 6.766).

O segundo artigo intitulado ***"Is chronotype associated with dietary intake and weight gain during pregnancy? A prospective and longitudinal study"*** teve como objetivo analisar o efeito do cronotipo nos padrões alimentares, ingestão e distribuição de energia e macronutrientes e ganho de peso durante a gestação. Este artigo está submetido para o periódico *Clinical Nutrition* (Fator de impacto = 6.360).

FUNDAMENTAÇÃO TEÓRICA

2.1. Cronobiologia

A cronobiologia é a ciência que estuda a organização temporal dos seres vivos, ou seja, a capacidade dos seres vivos em expressar de forma recorrente e periódica seu comportamento e sua fisiologia (ARAUJO; MARQUES, 2002; MARQUES; MENNA-BARRETO, 2003). A esta organização temporal dá-se o nome de ritmo biológico (ARAUJO; MARQUES, 2002).

Essa área de conhecimento tem sua história com início no século XVIII, quando o cientista francês Jean-Jacques Dortous de Mairan (1678-1771) observou que os movimentos periódicos de abrir e fechar das folhas de uma planta sensitiva, a *Mimosa pudica*, combinavam com o ciclo ambiental de claro/ escuro. O experimento consistiu em colocar a planta em um baú para que ela ficasse em escuro constante e o pesquisador pôde observar que, mesmo nessa condição, o ritmo espontâneo de abertura e fechamento das folhas foi mantido (MENNA-BARRETO; MARQUES, 2002). Em 1835, De Candolle publicou outra importante observação: as plantas, quando isoladas do ambiente externo, apresentavam um ciclo de 22 a 23 horas, e quando expostas aos estímulos ambientais, eram forçadas a um ciclo de 24 horas exatas (MARQUES; MENNA-BARRETO, 1999). Porém, a cronobiologia como ciência é bem recente e seu reconhecimento pela comunidade científica internacional teve início em 1960 com a realização do *Cold Spring Harbor Symposia on Quantitative Biology: Biological Clocks,* sendo esse uma das primeiras reuniões científicas internacionais na área de cronobiologia e decisivo para o seu desenvolvimento (CHOVNICK, 1960; ROTENBERG; MARQUES; MENNA-BARRETO, 2003). Desde então, a cronobiologia vem crescendo enquanto área consolidada da ciência, estudada por profissionais de diversas áreas que têm analisado diferentes aspectos reconhecidamente relevantes para a saúde e qualidade de vida dos indivíduos, como o cronotipo, o padrão vigília-sono e a regularidade do estilo de vida (ARAUJO; MARQUES, 2002).

Uma das metas principais da cronobiologia é estudar as características relativas ao tempo da matéria viva, ou seja, a variabilidade das funções biológicas ao longo das 24 horas do dia (ALMONDES et al., 2006), como os eventos bioquímicos, fisiológicos ou comportamentais importantes para sobrevivência. Dois conceitos fundamentais dessa área são a organização temporal interna e a organização temporal externa (MOORE-EDE;

SULZMAN; FULLER, 1982). A organização temporal interna diz respeito a uma ordem sequencial das fases dos ritmos biológicos de diversas variáveis fisiológicas ao longo do dia de um organismo, como por exemplo a temperatura corporal, a secreção de melatonina, de cortisol, insulina, a glicemia, a pressão arterial, a frequência cardíaca, entre outras. Essa ritmicidade endógena na ausência do ambiente também é chamada de livre-curso (MARQUES; MENNA-BARRETO, 2003). A organização temporal externa, por sua vez, se caracteriza pelas relações temporais entre eventos fisiológicos e eventos ambientais que são reconhecidos pela sua capacidade de sincronizar os ritmos biológicos, como o caso do ciclo claro/ escuro (MENNA-BARRETO; WEY, 2007).

2.2. Ritmos biológicos

Os ritmos biológicos são gerados endogenamente em todos os níveis de organização (desde a célula até os sistemas mais elaborados do organismo), tendo como expressão as mudanças de acordo com o período do dia. Tais ritmos são modulados por variações temporais, como o ciclo claro/ escuro, atividade/ repouso, jejum/ alimentação e por outras condições ambientais e sociais (ARAUJO; MARQUES, 2002), mas também podem persistir sem estas variáveis ambientais, o que os caracterizam como ritmos gerados endogenamente (MARTINS, 2010). Esses fatores que imprimem nos organismos marcas temporais, impondo periodicidade aos ritmos biológicos, são conhecidos como *zeitgebergs* (termo alemão para "fornecedor de tempo") ou sincronizadores (arrastadores) de tempo.

Nas espécies vivas observam-se ritmos biológicos que se caracterizam como estados funcionais que variam periodicamente no tempo, podendo ser classificados em: circadianos, ultradianos ou infradianos, classificação inicialmente proposta por Franz Halberg (1969) e bastante usada e aceita atualmente (ARAÚJO; MARQUES, 2002). O ritmo biológico mais central na cronobiologia é o ritmo circadiano, que é caracterizado como um ciclo de aproximadamente 24 horas (MARTINEZ-CARPIO; COROMINAS, 2004) e é demonstrado por processos fisiológicos rítmicos que se aproximam de um dia, como, por exemplo, o ciclo sono/ vigília, a temperatura corporal, as secreções hormonais, a função renal, os parâmetros cardiovasculares, a função respiratória, entre outras. Os ritmos ultradianos são aqueles que possuem um período menor que 20 horas, em geral, minutos, como o ritmo de liberação de alguns hormônios e os batimentos do coração; e os ritmos infradianos são aqueles cujo período de repetição é maior que 28 horas, como,

por exemplo, o ciclo menstrual (ARAUJO; MARQUES, 2002; MARQUES; MENNA-BARRETO, 2003).

Os ritmos circadianos são os mais conhecidos por serem facilmente observados, podendo ser eventos bioquímicos, fisiológicos ou comportamentais controlados por um sistema de temporização circadiana (STC). Assim, pela oscilação regular de seus estímulos, o STC é caracterizado por uma resposta molecular, promovendo a ritmicidade circadiana a fim de antecipar uma ação e preparar o organismo para a possibilidade de uma determinada mudança sistemática ambiental ou interna (ARAUJO; MARQUES, 2002; MARQUES; MENNA-BARRETO, 2003).

Nos mamíferos, o núcleo supraquiasmático (NSQ) presente no hipotálamo (WELSH et al., 2010) foi por muito tempo considerado a mais importante estrutura do STC. Conhecido didaticamente como relógio central, esta estrutura é regida (sincronizada) pela luz em um período de 24 horas. Isto ocorre porque a luz estimula células específicas localizadas na retina que enviam projeções neurais via trato retino-hipotalâmico diretamente para o NSQ. Posteriormente, o NSQ pode sincronizar os diferentes relógios de tecidos periféricos do corpo por meio de várias cascatas de sinalização. Tais relógios periféricos foram descobertos no final da década de 90 (BALSALOBRE; DAMIOLA; SCHIBLER, 1998; YAMAZAKI et al., 2000; YOO et al., 2004) e, desde então, já foi descrita sua presença em órgãos como pâncreas, fígado, trato gastrointestinal, músculo esquelético e tecido adiposo (POGGIOGALLE; JAMSHED; PETERSON, 2018) (Figura 1). Os relógios dos tecidos periféricos recebem entradas de sincronização de várias outras pistas, como temperatura corporal, atividade locomotora, comportamento alimentar e a composição alimentar dos alimentos (DE GOEDE et al., 2018). Além disso, os relógios de tecido central e periférico podem ser arrastados para sinais de tempo específicos (*zeitgebers*), como luz para o NSQ, alimentação para o fígado e atividade física para o músculo esquelético.
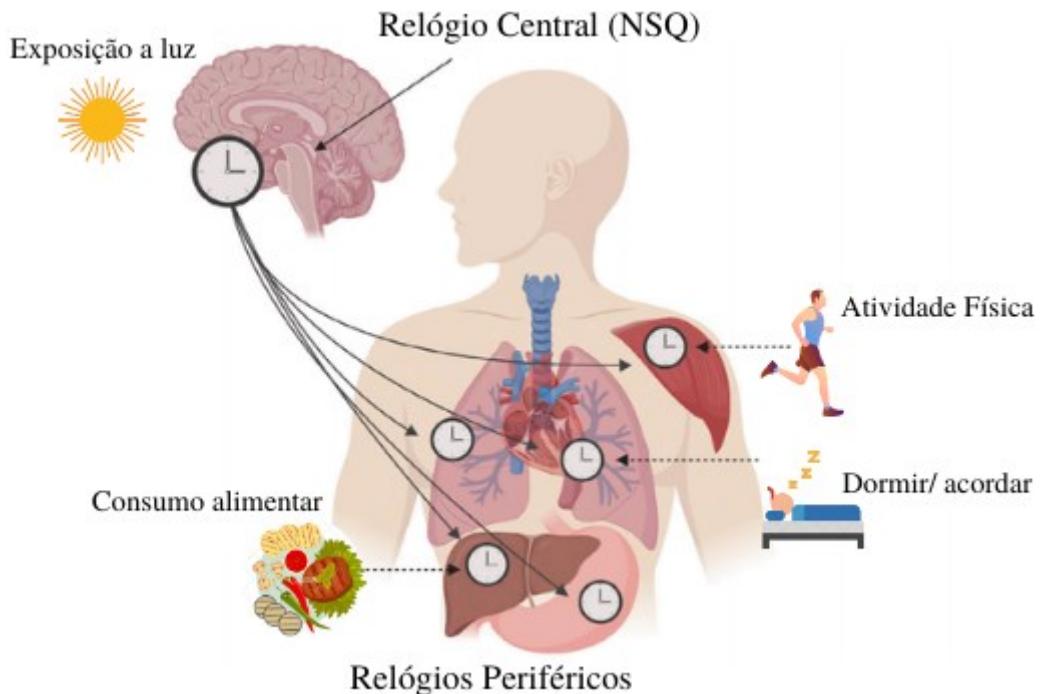
Figura 1: Mecanismo de sincronização dos ritmos circadianos envolvendo o relógio central e relógios periféricos.

Fonte: Adaptado e traduzido de Greco & Sassone-Corsi (GRECO; SASSONE-CORSI, 2020). O relógio central localizado no núcleo supraquiasmático (NSQ) hipotalâmico se conecta a relógios periféricos para garantir a sincronia e a fisiologia. O NSQ é arrastado pela luz, enquanto os osciladores periféricos podem ser redefinidos por sinais ambientais (*zeitgebers*), como os horários de dormir/ acordar, o consumo alimentar ou a atividade física. Uma variedade de fatores ambientais pode alterar os ritmos específicos dos tecidos, levando à perda de coerência temporal entre os relógios dos tecidos.

2.2.1. Ritmos biológicos e tipologia circadiana

A espécie humana é diurna, com uma tendência em concentrar os episódios de atividade/ vigília durante o dia e o repouso/ sono durante a noite. Porém, os indivíduos apresentam diferenças/ preferências individuais relacionadas as atividades de rotina e sono, seja em relação a sua duração ou horários (HORNE; OSTBERG, 1976).

O termo cronotipo foi definido por Roenneberg (2012) como a fase individual de arrastamento, ou seja, a fase em que um indivíduo sincroniza com o dia 24h (ROENNEBERG, 2012) ou ainda o comportamento em relação às diferenças inter individuais de alocação de fase dos ritmos circadianos (DUARTE, 2018). Nesse contexto,

as preferências individuais pelos horários de realização das atividades são utilizadas para identificar os cronotipos, os quais podem ser classificados em matutino, intermediário e vespertino (HORNE; OSTBERG, 1976). Os indivíduos matutinos apresentam marcada preferência por acordar e dormir cedo, se sentem mais dispostos e apresentam melhores níveis de alerta ao acordar e encontram dificuldades em manter-se acordados além do seu horário habitual de dormir. Por outro lado, os indivíduos vespertinos apresentam uma preferência por horários mais tardios para dormir e acordar, especialmente nos finais de semana. Além disso, vespertinos cochilam mais durante o dia e tende a se alimentar em horários irregulares ao longo do dia. Os indivíduos que não possuem hábitos e/ ou preferências tão definidas são classificados como intermediários, representando a maioria da população (HORNE; OSTBERG, 1976).

O cronotipo individual pode ser avaliado pelo ponto médio do sono nos dias livres (do inglês, *mid-sleep on free days* - MSF) (ROENNEBERG et al. 2007). Essa variável é calculada como o ponto médio entre o início e o fim do sono. Por exemplo, assumindo uma duração de sono de oito horas, um cronotipo de 4:00 adormece à meia-noite e acorda às 8:00 do dia seguinte. Os dias livres são utilizados, ao invés de dias de trabalho, para reduzir a influência das demandas sociais no comportamento sono-vigília. O ponto médio do sono nos dias de trabalho tende a ser mais cedo do que aqueles em dias de folga, pois muitos indivíduos acordam mais cedo devido ao uso de despertadores a fim de levantar a tempo para o trabalho (ROENNEBERG et al. 2007). O ponto médio do sono nos dias livres, ou seja, dias sem trabalho é, portanto, visto como um indicador mais preciso, determinando os horários que o sono ocorre naturalmente, preferencialmente, sem uso de despertadores.

No entanto, Roenneberg e colaboradores (2007) encontraram uma relação significativa entre a duração do sono nos dias de trabalho e dias livres e cronotipo avaliado pelo MSF. Quanto mais tardio o cronotipo, menor é o sono nos dias de trabalho e mais longo o sono nos livre. Esse resultado sugeriu aos pesquisadores que tanto a duração quanto o horário de sono nos dias livres são influenciados pelo possível déficit de sono acumulado ao longo da semana de trabalho. Portanto, o cronotipo deve ser corrigido para a influência do débito de sono (MSFsc). Essa correção adicional para débito de sono é calculada como a diferença entre a duração média do sono nos dias livres e a média do sono nos dias de trabalho, quando a duração do sono dos dias livres é maior que nos dias de trabalho.

Roenneberg (2015) descreveu que os tempos de MSFsc são uma característica contínua e que sua distribuição não é apenas específica por idade e sexo, mas também por população e que classificações em grupos podem ser apenas significativas dentro de uma determinada população cultural e/ ou geográfica. Além disso, foi apontado que, enquanto não é possível determinar essas categorizações, devemos ter cuidado ao compartimentar a distribuição de MSFsc em categorias que separam o indivíduo do normal (ROENNEBERG, 2015). Nesse sentido, Roenneberg (2015) sugere que para análises estatísticas seja utilizada uma comparação entre o terço inicial, intermediário e final da distribuição do MSFsc.

2.3. Sincronização e dessincronização dos ritmos circadianos

Nosso NSQ se sincroniza com a duração do dia, ou seja, com a presença de luz (ou ausência dela), funcionando como um relógio que regula esses processos (REFINETTI, 2005) e sincronizando os ritmos circadianos com o ciclo claro-escuro (COOMANS; RAMKISOENSING; MEIJER, 2015). Assim, a luz do dia é a principal pista ambiental para sincronizar o STC, mas na ausência de luz os ritmos podem ser modulados por outras pistas também importantes, desde que haja regularidade, ou seja, ocorram sempre em torno do mesmo horário. Estas pistas podem ser sociais, como a hora do início do trabalho e a hora das principais refeições (ALOÉ; AZEVEDO; HASAN, 2005; CHALLET et al., 2003; MENDOZA et al., 2010).

O alinhamento dos ritmos circadianos se refere às condições em que nossos relógios central e periféricos permanecem sincronizadas entre si e com o ambiente, ou seja, sob condições fisiológicas, nosso NSQ - o qual é sensível à luz -, sincroniza nossos relógios periféricos espalhados pelo organismo. Por sua vez, os relógios periféricos, exibem sensibilidade diferencial para outros *zeitgebers* ambientais, tais como a alimentação e atividade física. É importante destacar ainda que o NSQ também orienta a ingestão de alimentos e a prática de atividade física, bem como as respostas fisiológicas a esses comportamentos, mantendo todos os relógios em sincronia (GAMBLE; YOUNG, 2013). No entanto, condições de desalinhamento circadiano ocorrem quando o ciclo sono-vigília, a ingestão de alimentos e/ ou esforço físico ocorrem fora dos períodos programados no NSQ. Nesse caso, estes *zeitgebers* colocam os relógios periféricos funcionando anormalmente, alinhados com períodos diferentes do relógio central no NSQ (QIAN; SCHEER, 2016).

Vários fatores ambientais exercem influência sobre nossos relógios biológicos, levando a uma relativa flexibilidade que nos permite, por exemplo, alterar nossa rotina de trabalho ou nos adaptarmos às mudanças de fuso horário. No entanto, há limites para essa flexibilidade, que impedem, por exemplo, a adaptação completa de nossos ritmos biológicos (MORENO; FISCHER; ROTENBERG, 2003). Isso pode levar à dessincronização do ritmo circadiano, o que por sua vez pode levar o organismo a esforços de adaptação que conduzirão a situações de desgaste, conhecida por ter impactos negativos na saúde (COVASSIN; SINGH; SOMERS, 2016; MAURY; RAMSEY; BASS, 2010; REA et al., 2008). Esses prejuízos têm-se manifestado em humanos como condições crônicas de saúde, como síndrome metabólica, diabetes tipo 1, doenças cardiovasculares, câncer e distúrbios intestinais (CARUSO; LUSK; GILLESPIE, 2004; KARLSSON; KNUTSSON; LINDAHL, 2001; MORIKAWA et al., 2005; MOTA et al., 2016; PENEV et al. 1998; SCHERNHAMMER et al., 2003; SILVA et al., 2016).

Alguns fatores são reconhecidos pela literatura por usualmente levarem à dessincronização do ritmo circadiano, como é caso do trabalho em turnos, das extensas jornadas de trabalho, do *jetlag* ocasionado por viagens transmeridionais e, mais recentemente, o JLS, considerado uma nova categoria de dessincronização do ritmo circadiano (WITTMANN et al., 2006; LIMA; VARGAS, 2014).

2.3.1. *Jetlag* social

JLS é uma medida de desalinhamento circadiano que descreve a discrepância entre as preferências biológicas dos horários e do tempo de dormir de um indivíduo (relógios biológicos) e as demandas sociais e horários estabelecidos para estudo, trabalho e eventos, que exigem um tempo de sono específico (relógio social) (WITTMANN et al., 2006). Essa medida parte da premissa que os indivíduos respeitam suas preferências biológicas pelo tempo de sono nos dias livres e/ ou dias de folga, mas que durante dias úteis optam por alternativas que lhes permitam cumprir as demandas sociais (ROENNEBERG et al. 2012). A ocorrência semanal em determinado grau deste padrão coloca o indivíduo em desalinhamento circadiano crônico.

Há relatos que corroboram com a disparidade entre o tempo biológico e o tempo social. Um estudo epidemiológico realizado com mais de 65000 participantes da Europa Central encontrou que um terço da população sofria de 2 horas ou mais de JLS e 69% relataram pelo menos 1 hora de JLS (ROENNEBERG et al., 2012). Um recente estudo

do nosso grupo realizado com 792 indivíduos (73% mulheres; idade 55.9 ± 12.4 anos) encontrou uma prevalência de 24% de JLS > 1h (MOTA et al. 2017) entre pessoas com doenças crônicas não transmissíveis (DCNT). Além disso, outros autores encontraram prevalências de JLS > 1h entre 31% e 39% (KOOPMAN et al., 2017; LANG et al., 2018) e estimativas mais altas, entre 69-70% (WITTMANN et al., 2006; RANDLER et al., 2013). No entanto, essas altas estimativas podem ser influenciadas pela participação de populações mais jovens (idade entre 14 e 94 anos no estudo de Witmann et al., 2006, e média de 23,8 ± 3,7 anos no estudo de Randler et al., 2013).

A variável JLS proposta por Wittmann e colaboradores em 2006 é calculada pela diferença absoluta entre o ponto médio do sono nos dias de livres/ final de semana (do inglês, *mid-sleep on free days* - MSF) e o ponto médio do sono nos dias de trabalho/ semana (do inglês, *mid-sleep on workdays* - MSW) (WITTMANN et al., 2006; ROENNEBERG et al., 2012). Por exemplo, quando uma pessoa dorme das 22:00h às 06:00h nos dias de trabalho/ semana, o ponto médio é às 02:00h, e quando dorme das 00:00h às 10:00h nos dias livres/ finais de semana, o ponto médio é às 05:00h, o que resulta em um JLS de 3h (05:00h – 02:00h).

O JLS pode ser analisado de maneira contínua, de forma a demonstrar o grau de desalinhamento, ou de forma categórica, quando utiliza-se pontos de corte pré estabelecidos pela literatura. Usualmente o valor > 1h indica que o indivíduo possui JLS (WITTMANN et al., 2006), mas pesquisadores têm utilizado outros valores para determinar essa discrepância, como maior do que meia hora (REUTRAKUL et al., 2013), maior que 2h (RUTTERS et al., 2014); que 3h (PARSONS et al., 2015) ou também pela exposição ao JLS (grande ou pequena exposição) (CARVALHO et al., 2020).

2.3.1.1. *Jetlag* social, saúde e estado nutricional

O excesso de peso é um problema crítico de saúde pública que afeta 96 milhões de pessoas, ou, mais especificamente, 60,3% da população adulta do Brasil (IBGE, 2020). Vários fatores etiológicos estão intimamente relacionados ao aumento da obesidade, sendo os hábitos alimentares e a prática de atividade física os principais fatores que convergem para essa ocorrência. Porém, atualmente outras variáveis– como o JLS – vêm sendo apontados como fatores de risco para o desenvolvimento da obesidade e suas doenças associadas (PARSONS et al., 2015; WONG et al., 2015).

Roenneberg e colaboradores (2012) foram os primeiros pesquisadores a investigar a relação entre o JLS e o excesso de peso. Em um estudo epidemiológico com 64.043 indivíduos com idade entre 16 e 65 anos, esses autores encontraram que indivíduos com > 1h de JLS apresentaram maior risco para sobrepeso, mesmo após ajustes para variáveis de confusão (sexo, idade, duração do sono e cronotipo) (ROENNEBERG et al., 2012). Um recente estudo transversal também investigou essa relação numa análise que incluiu 534 adultos jovens (18-25 anos), e os resultados revelaram que indivíduos com maior JLS apresentaram maior índice de massa corporal (IMC). Seguindo essa linha de investigação, outros estudos realizados em adultos (ISLAM et al., 2018; PARSONS et al. 2015; ZERÓN-RUGERIO et al., 2019; WONG et al 2015) e adolescentes (MALONE et al. 2016; MATHEW; HALE; CHANG, 2020) também mostraram esse efeito negativo do JLS sobre o peso corporal.

Estudos do nosso grupo também investigaram a relação entre o JLS e o excesso de peso. Mota et al., (2019) examinaram a associação entre o JLS e o status de obesidade em 792 pacientes (581 mulheres [73%], idade: 55,9 + 12,4 anos) com DCNT como obesidade, hipertensão arterial sistêmica, diabetes mellitus tipo 2 ou dislipidemia. Após ajustes para variáveis de confusão, indivíduos com JLS >1h apresentaram maior razão de chance (odds ratio: OR) de apresentar sobrepeso (IMC > 25kg/ m²) (OR=2,0; intervalo de confiança [IC]=1,2- 3,6; p=0,006) e ser obeso não saudável (OR=1,8; IC=1,1-2,8; p=0,01) quando comparado aos indivíduos com JLS < 1h (MOTA et al., 2019). Carvalho et al., (2020) avaliaram a evolução de perda de peso ao longo de seis meses após cirurgia bariátrica (n=122 pacientes, 77% mulheres, idade entre 28 – 41 anos) e sua relação entre a exposição ao JLS. A interação entre JLS e o tempo de seguimento influenciou negativamente a evolução do peso (p = 0,01) e o IMC (p = 0,04), ou seja, indivíduos com mais JLS perderam menos peso quando comparados aos com menos JLS. Além disso, a regressão linear mostrou uma associação negativa entre a exposição JLS média ao longo dos seis meses e a porcentagem de perda de peso (coeficiente = -0,30, p = 0,006), perda de peso corporal (kg) (coeficiente = -0,17, p = 0,03) e a redução de IMC (coeficiente = -0,24, p = 0,007) (CARVALHO et al., 2020). Entretanto, Alves et al. (2016), ao avaliar 423 trabalhadores em turnos (idade: 33,0 [25-42], 73,3% mulheres), não encontraram associação entre o JLS e o IMC (0=0,01; p=0,69) ou risco de sobrepeso ou obesidade (OR=0,79; IC=0,46-1,34, p=0,39) (ALVES et al., 2016).

Cabe ressaltar que as pesquisas dessa área desenvolvidas até o momento foram realizadas com populações não gestantes. Diante dos resultados supracitados, é

importante que o JLS seja investigado durante o período gestacional como um possível fator de risco para o ganho de peso gestacional (GPG) inadequado, tendo em vista que esse é um momento de diversas modificações fisiológicas e nutricionais que, muitas vezes, podem levar a mulher ao ganho de peso excessivo e obesidade futura (GILMORE; KLEMPEL-DONCHENKO; REDMAN, 20015; STUEBE; OKEN; GILLMAN, 2009).

2.2. Gestação

2.2.1. Nutrição gestacional, ganho de peso e desfechos materno-fetais

Na gestação ocorrem importantes e intensos ajustes morfofisiológicos que visam proporcionar um ambiente ideal para o desenvolvimento do feto (HOPKINS et al., 2010). É marcada ainda por inúmeras alterações metabólicas, com demanda calórica adicional para sustentar o aumento de tecidos maternos e dos produtos da concepção (IOM, 2009).

O estado nutricional materno antes e durante a gestação apresenta elevado impacto sobre o crescimento e desenvolvimento fetal e do recém-nascido e o consumo alimentar é considerado um fator importante para o melhor desenvolvimento gestacional (PICCIANO, 2003). Nesse tema, o efeito da qualidade da alimentação sobre os desfechos da gestação tem sido relatado em diversos estudos (KOMINIAREK; PEACEMAN, 2017; NICODEMUS, 2018; RAMAKRISHNAN et al., 2012; SAMURA et al., 2016).

No decorrer da gestação o metabolismo energético muda, tendo em vista que a mulher necessita de uma quantidade maior de energia para suprir o aumento da taxa de metabolismo basal e para formar as reservas energéticas maternas e fetais (PICCIANO, 2003). Baseado nisso, o *Institute of Medicine* (IOM) dos Estados Unidos (IOM, 2006) recomenda um acréscimo diário de 340 kcal no segundo trimestre de gestação e de 452 kcal no terceiro trimestre de gestação, o que diferencia as necessidades energéticas de gestantes em relação às mulheres não gestantes (>19 anos). O IOM (2009) recomenda ainda que a ingestão energética de gestantes não seja inferior a 1.800kcal (IOM, 2009). Em se tratando de macronutrientes, o IOM (2006) recomenda que uma "faixa aceitável de distribuição de macronutrientes" (*Acceptable Macronutrient Distribution Range* - AMDR) para a dieta materna (> 19 anos). Essa dieta deve variar entre 10-35% do valor energético total (VET) de proteínas, 20-35% de lipídios e 45-65% de carboidratos, sendo estes valores iguais aos das mulheres não gestantes (>19 anos) (IOM, 2006).

Em relação aos micronutrientes, as recomendações de ingestão durante a gestação também estão aumentadas, destacando-se o ferro e o ácido fólico (IOM, 2006) (Tabela 1). Além disso, o consumo de ácido graxo poli-insaturado ômega-3 na gestação parece relacionar-se com o prolongamento da gestação (CRIVELLENTI, ZUCCOLOTTO, SARTORELLI, 2018). O IOM (2006) recomenda que o consumo diário de ácidos graxos poli-insaturados ômega-3 seja entre 5 a 10% do total do VET.

Tabela 1. Valores da Ingestão Dietética de Referência (*Dietary Reference Intakes* - DRIs): Ingestão Dietética Recomendada (*Recommended Dietary Allowance* - RDA) e Ingestão Adequada (*Adequate Intake* - AI) para mulheres não gestantes e gestantes.

RDA ou AI*	Mulheres não gestantes		Gestantes		Alteração dos valores de RDA ou AI na gestação**
	19 a 30 anos	31 a 50 anos	19 a 30 anos	31 a 50 anos	
Carboidratos (g/dia)	130	130	175	175	↑↑↑
Fibras Totais	25*	25*	28*	28*	↑
Ômega 6 (g/dia)	12*	12*	13*	13*	↑
Ômega 3 (g/dia)	1,1*	1,1*	1,4*	1,4*	↑↑↑
Proteína (g/kg/dia)	0,8	0,8	1,1	1,1	↑↑↑↑
Vitamina A (µg/dia)	700	700	770	770	↑
Vitamina C (mg/dia)	75	75	85	85	↑
Vitamina D (µg/dia)	15	15	15	15	=
Vitamina E (mg/dia)	15	15	15	15	=
Vitamina K (µg/dia)	90*	90*	90*	90*	=
Tiamina (mg/dia)	1,1	1,1	1,4	1,4	↑↑↑
Riboflavina (mg/dia)	1,1	1,1	1,4	1,4	↑↑↑
Niacina (mg/dia)	14	14	18	18	↑↑↑
Vitamina B6 (mg/dia)	1,3	1,3	1,9	1,9	↑↑↑↑↑
Folato (µg/dia)	400	400	600	600	↑↑↑↑↑
Vit.B12 (µg/dia)	2,4	2,4	2,6	2,6	↑
Ác.Pantotênico (mg/dia)	5*	5*	6*	6*	↑↑
Biotina (µg/dia)	30*	30*	30*	30*	=
Colina (mg/dia)	425*	425*	450*	450*	↑

Cálcio (mg/dia)	1000	1000	1000	1000	=
Cromo (µg/dia)	25*	25*	30*	30*	↑↑
Cobre (µg/dia)	900	900	1000	1000	↑
Flúor (mg/dia)	3*	3*	3*	3*	=
Iodo (µg/dia)	150	150	220	220	↑↑↑↑↑
Ferro (mg/dia)	18	18	27	27	↑↑↑↑↑
Magnésio (mg/dia)	310	320	350	360	↑
Manganês (mg/dia)	1,8*	1,8*	2,0*	2,0*	↑
Molibdênio (µg/dia)	45	45	50	50	↑
Fósforo (mg/dia)	700	700	700	700	=
Selênio (µg/dia)	55	55	60	60	↑
Zinco (mg/dia)	8	8	11	11	↑↑↑↑
Potássio (mg/dia)	4700*	4700*	4700*	4700*	=
Sódio (mg/dia)	1500*	1500*	1500*	1500*	=
Cloro (mg/dia)	2300*	2300*	2300*	2300*	=
Água Total (L/dia)[a]	2,7*	2,7*	3,0*	3,0*	↑

[a]Água Total: inclui água presente nos alimentos, bebidas e água. *Valores de *Adequate Intake* – AI. **Refere-se ao aumento dos valores de RDA ou AI para gestantes quando comparada com as recomendações para mulheres não gestantes na mesma faixa etária, ↑: aumento em torno de 10%; ↑↑: aumento em torno de 20%; ↑↑↑: aumento em torno de 30%; ↑↑↑↑: aumento em torno de 40%; ↑↑↑↑↑: aumento em torno de 50%; =: não altera o valor. Fonte: adaptado de IOM, 2006.

Aproximadamente metade do ganho de peso durante a gestação é atribuído diretamente à unidade fetoplacentária (feto, placenta, líquido amniótico, útero grávido) e os outros 25% estão associados ao aumento do volume sanguíneo, volume extravascular e tecido mamário (Figura 2). O restante do ganho de peso pode ser atribuído às alterações metabólicas que ocorrem para aumentar o acúmulo materno de água, gordura e proteína celular (HYTTEN, 1991). O ganho de peso que ocorre além desses fatores leva ao aumento da gordura materna (MCGRAW, 2018).
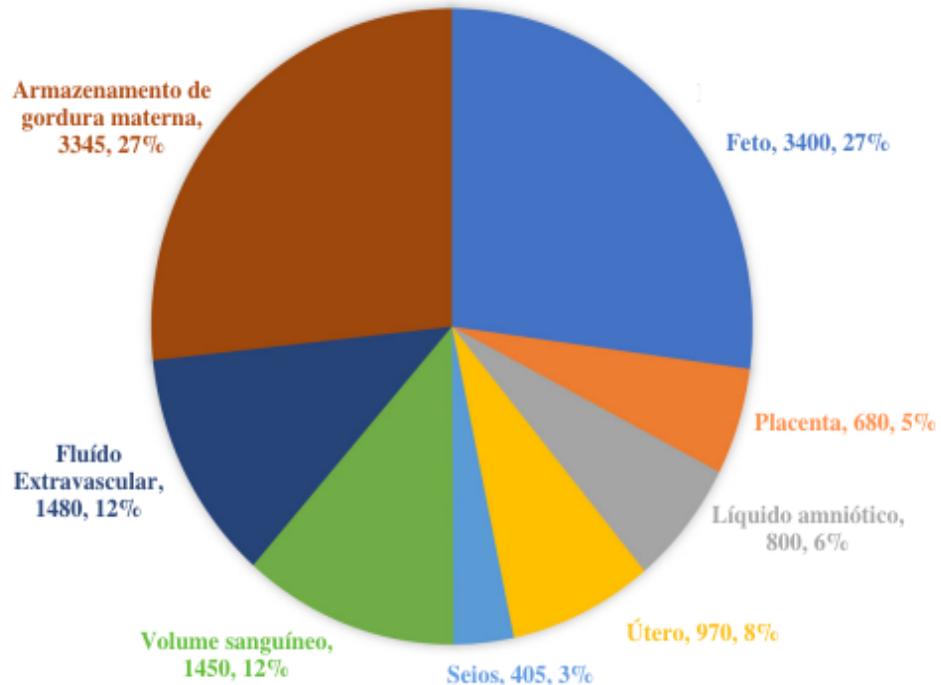
Figura 2. Ganho de peso (g) com base em componentes relacionados à gestação.
Fonte: Adaptado e traduzido de Champion & Harper (CHAMPION; HARPER, 2020)

Em 2009, o IOM publicou diretrizes revisadas para GPG com atualizações das recomendações devido às mudanças nos aspectos da saúde das mulheres em idade fértil. Um importante foco dessa revisão foi baseado nas elevadas taxas de sobrepeso, obesidade, postergação da concepção e, ainda, no aparecimento de doenças crônicas, como diabetes e hipertensão arterial durante esse período da vida da mulher, o que coloca em risco a saúde da mãe e do feto. O Ministério da Saúde (BRASIL, 2012) recomenda a utilização dessas diretrizes que fazem recomendações do ganho de peso total e por trimestre gestacional, específicas para cada classe de IMC pré-gestacional, com base nas definições da Organização Mundial da Saúde (OMS) (RASMUSSEN, 2009) (Tabela 2). Ao criar essas diretrizes, o IOM se concentrou na associação do GPG com os principais resultados maternos e infantis, incluindo parto cesáreo, diabetes gestacional, hipertensão induzida pela gestação, retenção de peso pós-parto, tamanho do bebê, parto prematuro e obesidade infantil (IOM, 2009). Além disso, essas recomendações são baseadas em evidências que apoiam a associação entre ganho de peso gestacional, peso ao nascer e retenção de peso pós-parto (GYNECOLOGY ACOOA, 2013; RASMUSSEN, 2009).

A estratificação das recomendações de GPG com base no IMC pré-gestacional é baseada nas mudanças no consumo de energia que ocorrem em pacientes com obesidade

(CUNNINGHAM et al., 2015). Mulheres com obesidade requerem menos ganho de peso devido ao aumento da deposição de gordura, o que faz com que o gasto de energia da gestação seja muito menor do que o de mulheres sem obesidade (BUTTE et al., 2004).

Tabela 2. Novas recomendações para ganho de peso total e ganho de peso por semana durante a gestação de acordo com o índice de massa corporal (IMC) pré-gestacional (*Institute of Medicine, 2009*).

IMC pré-gestacional (kg/m²)	Categoria de peso pré-gestacional	Ganho de peso no primeiro trimestres (kg)	Taxas de ganho de peso no segundo e terceiro trimestres (kg)**	Faixa de ganho de peso total (kg)
< 18,5	Baixo peso	2,3	0,51 (0,44 – 0,58)	12,5 – 18,0
18,5 – 24,9	Eutrofia	1,6	0,42 (0,35 – 0,50)	11,5 – 16,0
25,0 – 29,9	Sobrepeso	0,9	0,28 (0,23 – 0,33)	7,0 – 11,5
≥ 30	Obesidade*	-	0,22 (0,17 – 0,27)	5,0 – 9,0

* Inclui todas as classes de obesidade.

**Os cálculos assumem ganho de peso de 0,5-2 kg no primeiro trimestre (IOM, 2009).

Apesar das contribuições das recomendações atuais no monitoramento do ganho de peso gestacional e também na prevenção de agravos maternos e fetais relacionados ao GPG inadequado, novas propostas têm surgido ao longo dos últimos anos devido às limitações dos estudos existentes, como por exemplo a seletividade amostral derivada de um país específico, o que ocorreu no método proposto pelo estudo de Atalah et al., (1997) (ATALAH; CASTILLO; GOMEZ, 1997; ISMAIL et al., 2016). Entre as novas propostas está o *International Fetal and Newborn Growth Consortium for the 21st* (INTERGROWTH-21st) (ISMAIL et al., 2016).

O projeto INTERGROWTH-21st é um estudo multicêntrico, multi-étnico, de base populacional, realizado entre 2009 e 2014 em oito áreas urbanas: Pelotas, Brazil; Shunyi, China; Nagpur, India; Turim, Italia; Parklands, Nairobi, Quênia; Muscat, Oman; Oxford, Reino Unido e Seattle, Estados Unidos; excluindo, assim, o principal viés de estudos anteriores. Em 2016 o INTERGROWTH-21st, lançou novas recomendações de ganho de peso de acordo com a semana gestacional, além de uma curva para monitoramento do GPG segundo a idade gestacional para mulheres com IMC pré-gestacional de eutrofia

(INTERGROWTH-21st, 2016), com o intuito de prevenir os milhões de casos evitáveis de morte neonatal que ainda acontecem em âmbito mundial em decorrência de complicações no processo gestacional, dentre outras o GPG inadequado (IOM, 2009).

As causas de GPG excessivo costumam ser multifatoriais e complexas e têm sido alvo de importante investigação, uma vez que as taxas de sobrepeso e obesidade em mulheres em idade fértil são crescentes (YEH; SHELTON, 2005; DAVIS et al., 2012). Nesse tema, estima-se que 50% das mulheres em idade fértil estejam com sobrepeso ou obesidade e 18% iniciam a gestação com IMC acima do normal (THANGARATINAM et al., 2012). Segundo a OMS, a prevalência de obesidade na gestação varia de 1,8% a 25,3% (WHO, 2012). No Brasil, a maioria das gestantes atendidas em serviços de saúde pública apresenta GPG excessivo (ASSUNÇÃO et al., 2009; NASCIMENTO et al., 2011).

Diversas complicações maternas podem ocorrer relacionadas ao sobrepeso e obesidade, dentre elas o diabetes gestacional (HUNG et al., 2015), a intolerância à glicose (HERRING et al. 2009), a hipertensão gestacional (FORTNER et al. 2009), a pré-eclâmpsia (XIA et al. 2016), altos índices de cesarianas, (CHU et al. 2007), complicações anestésicas e cirúrgicas, hemorragia pós-parto, anemia, infecção do trato urinário e endometrite (GUELINCKX et al., 2007; ROUSE; NUTHALAPATY, 2008). Também são descritas incontinência urinária de esforço, depressão, baixas taxas de amamentação e disfunções musculoesqueléticas, como dor lombar e dor pélvicas posterior, sensação de peso e formigamento nos membros, o que pode resultar em limitações nas atividades diárias (BARACHO et al., 2007; GUELINCKX et al., 2007; LI; JEWELL; GRUMMER-STRAWN, 2003 ROUSE; NUTHALAPATY, 2008). Para o feto, os riscos da obesidade ou sobrepeso materno variam desde macrossomia fetal até natimortos, morte neonatal, internação em unidade neonatal, prematuridade, anormalidades congênitas (defeitos no tubo neural, gastrosquise) e obesidade infantil com riscos associados a longo prazo (THANGARATINAM et al., 2012). Ainda pode ocorrer hipoglicemia, síndrome da angústia respiratória e convulsões neonatais (CORREA; GILBOA; BESSER, 2008; YANG et al., 2012).

Diante de todas as evidências que consideram a gestação uma fase da vida muito importante em termos de cuidados à saúde, têm-se sugerido mudanças no estilo de vida, adequação da dieta e programas de atividade física na tentativa de adequar o GPG, prevenir a inadequação de ganho ponderal, retenção de peso pós-gestacional e possíveis resultados adversos relacionados (COHEN; KOSKI, 2013; JERIC; ROJE; MEDIC,

2013). Intervenções que associam o exercício físico e controle dietético reduzem de forma significativa o ganho de peso durante a gestação, assim como estratégias para aumentar os níveis de atividade física são ferramentas fundamentais e de extrema importância para controlar o ganho ponderal na gestação, além de melhorar a saúde da mulher a longo prazo (BROEKHUIZEN et al., 2012; BUSCHUR; KIM, 2012; COHEN; KOSKI, 2013; KNUDSEN et al., 2012; JERIC; ROJE; MEDIC, 2013; POLLEY; WING; SIMS, 2002).

Uma meta-análise que avaliou o GPG e retenção de peso pós-parto descobriu que mulheres com GPG excessivo retiveram uma média adicional de 3,06 kg de peso pós-parto (IC 95%, 1,50-4,63 kg) em três anos pós-parto e 4,72 kg (IC 95%, 2,94-6,50 kg) 15 anos após o parto (NEHRING et al., 2015). Em adição, já se sabe que o GPG excessivo pode levar a um ciclo de aumento do IMC (GILMORE; KLEMPEL-DONCHENKO; REDMAN, 20015). Por exemplo, mulheres que iniciaram sua primeira gestação com um IMC normal, mas experimentaram GPG excessivo e retenção de peso pós-parto, podem entrar em uma gestação subsequente com um IMC mais alto, um ciclo que tem o potencial de se repetir em gestações subsequentes. Essas mulheres estão, dessa maneira, em risco de obesidade e doenças relacionadas à obesidade nos anos após a gestação.

2.2.2. Estado nutricional gestacional e desalinhamento circadiano

Nas últimas duas décadas a identificação de comportamentos que podem promover ganho de peso e obesidade tornaram-se o primeiro plano da saúde pública e do interesse científico. Embora a maioria das pesquisas e esforços de saúde pública tenham se concentrado na alimentação excessiva, escolhas de dietas não saudáveis e inatividade física como causas de saúde metabólica adversa, esses fatores podem não ser os únicos responsáveis pela elevada incidência de ganho de peso indesejado e obesidade na sociedade moderna (STENVINKEL, 2015). Portanto, outros fatores de risco potenciais devem ser identificados a fim de desenvolver contramedidas eficazes para promover a saúde e combater as doenças metabólicas. Um desses novos fatores de risco pode ser o desalinhamento circadiano (ARBLE et al., 2015; MARKWALD; WRIGHT; 2014).

Diversas e convincentes evidências indicam que existe uma profunda conexão entre os sistemas circadiano e reprodutivo em vários níveis de organização e estágios do ciclo reprodutivo em mamíferos (BISANTI et al., 1996; GOODMAN, 1999; KENNAWAY, 2005; LABYAK et al., 2002; SUMMA; VITATERNA; TUREK, 2012). Além disso, o GPG é um fenômeno biológico único e complexo, e evidências emergentes

sugerem que a interrupção do ritmo circadiano normal pode ser um fator contribuinte para a obesidade (TUREK et al., 2005; OGDEN et al., 2013).

O sistema circadiano e o metabolismo energético estão intimamente ligados e evoluíram para promover certas atividades energeticamente dispendiosas durante o dia ou durante a noite. Porém, na sociedade moderna de 24 horas, as pessoas muitas vezes optam por participar desses comportamentos em momentos biológicos inadequados (ARAUJO; MARQUES, 2002; MARQUES; MENNA-BARRETO, 2003).

Em humanos, a dessincronização das funções do sistema de temporização está ligada a consequências circadianas e metabólicas, incluindo distúrbios do sono (KOHYAMA, 2008), IMC elevado (PARKES, 2002; VAN AMELSVOORT; SCHOUTEN; KOK, 1999), metabolismo lipídico plasmático alterado (KARLSSON, 2003) e risco aumentado de doença cardiovascular (HA; PARK, 2005). Estudos da área básica mostraram que a exposição de camundongos à luz constante ao longo de 24h resultou em um aumento da massa corporal (FONKEN et al., 2010). Coomans e colaboradores (2013) relataram que manter camundongos em uma luz brilhante constante e alimentá-los com ração normal ou rica em gordura resultou em ganho de peso mais rápido em comparação com camundongos comendo dietas ricas em gordura ou ração normal em um ambiente ciclo claro/ escuro (COOMANS et al., 2013). Sabe-se que o trabalho em turnos e o JLS (formas de dessincronização circadiana) estão associados à obesidade e doenças metabólicas (WANG et al., 2011) em humanos, porém os efeitos destas formas de desalinhamento circadiano sobre o ganho de peso gestacional não têm sido explorados na literatura.

2.2.2. Estado nutricional gestacional e cronotipo

Um fator de ordem cronobiológica que vêm sendo mencionado na literatura como capaz de levar a alterações metabólicas e nutricionais nos seres humanos, com possível impacto sobre o estado nutricional, é o cronotipo. Em geral, as evidências sugerem que indivíduos com um cronotipo tardio, ou vespertino, apresentam menor adesão a dietas saudáveis (MAUKONEN et al. 2016), maior ingestão calórica noturna (Roßbach et al., 2018), atraso no horário das refeições (MAUKONEN et al., 2017), hábito de pular o café da manhã (REUTRAKUL et al. 2014), menor consumo de frutas e vegetais (PATTERSON et al. 2016), maior preferência para alimentos/ bebidas açucarados e álcool (KANERVA et al. 2012), além de possuírem uma pior qualidade dietética,

provavelmente devido a dessincronização dos ritmos biológicos (MUÑOZ et al., 2017). Por outro lado, os indivíduos matutinos apresentam maior consumo de fibras (MAUKONEN et al., 2017), vegetais verde/ amarelo, vegetais brancos e algas (YOSHIZAKI et al. 2018), ácidos graxos monosaturados e poliinsaturados no café da manhã (MUÑOZ et al., 2017) e frutas (GONTIJO et al. 2018, YOSHIZAKI et al. 2018, MUÑOZ et al. 2017, KANERVA et al. 2012). Isso parece estar associado a um maior número de refeições durante o dia, em especial o café da manhã.

Uma das associações mais relatadas entre cronotipo e ingestão alimentar é em relação ao horário das refeições. Nesse sentido, o cronotipo vespertino vem sendo significativamente associado ao atraso no horário das refeições em comparação com os do tipo matinal (GARAULET et al. 2013; LUCASSEN et al. 2013; RUIZ - LOZANO et al. 2016; MAUKONEN et al. 2017; NIMITPHONG et al. 2018; TEIXEIRA et al. 2018; GANGWAR et al. 2018). Isso pode ser considerado preocupante, tendo em vista que estudos recentes sugeriram que não apenas "o que" e "quanto" é ingerido, mas também "quando" é ingerido desempenha um papel na regulação do peso (GARAULET et al. 2013; WANG et al. 2014; MCHILL et al. 2017) e metabolismo de glicose e lipídios (MORGAN et al. 2012; LEUNG et al. 2017).

O consumo noturno também é outro comportamento frequentemente avaliado em estudos que relacionam o consumo alimentar ao cronotipo. Indivíduos com tendência à vespertinidade tendem a realizar refeições noturnas regulares (ISHIHARA et al., 1985) e a consumir mais calorias durante o jantar (MUÑOZ et al., 2017) e antes de dormir (SUH et al., 2017) em comparação aos matutinos. Lucassen et al., (2013) encontraram uma associação significativa entre cronotipo e alimentação noturna, no qual o cronotipo vespertino foi relacionado à maior ingestão calórica após às 20:00h (LUCASSEN et al., 2013). Esses achados corroboram com os dados de Reutrakul et al., (2013), que identificaram que vespertinos consumiam significativamente mais calorias durante o jantar (REUTRAKUL et al., 2013). Entre os principais problemas relatados pela literatura pela ingestão alimentar excessiva no período noturno estão tolerância à glicose reduzida e resistência à insulina (KALSBEEK; LA FLEUR; FLIERS, 2017; LEUNG et al., 2020; SHARMA et al., 2017), a redução da oxidação de gordura (GLUCK et al., 2011), maior risco de excesso de peso (ALJURAIBAN et al., 2015; BARON et al., 2011; BO et al., 2014; MAUKONEN et al., 2019; WANG et al., 2014) e uma menor termogênese induzida pela dieta (ROMON et al., 1993).

Também é importante ressaltar que o cronotipo é considerado um importante fator determinante para a realização - ou não - do café da manhã e o hábito de pular essa refeição é muito encontrado entre os vespertinos (SATO-MITO et al. 2011; REUTRAKUL et al. 2014; SILVA et al. 2016). Em contrapartida, a realização do café da manhã é uma forte característica entre matutinos, sendo esse hábito considerado um importante indicador de saúde (CAHILL et al. 2013; BETTS et al. 2014). Um recente estudo do nosso grupo encontrou que indivíduos vespertinos tinham 1,7 vezes maior probabilidade de pular o café da manhã do que os matutinos (IC 95%: 1,1–2,9, p = 0,02) (TEIXEIRA et al. 2018). Evidências da área sugerem que o café da manhã é considerado uma refeição extremamente importante do dia, atuando como um componente central nas necessidades nutricionais diárias e contribuindo significativamente para a ingestão energética e qualidade nutricional (MATTHYS et al., 2006; CLAYTON, JAMES, 2016). Os possíveis mecanismos para a associação entre café da manhã e proteção à saúde estão relacionados ao fato de que a ingestão de alimentos pela manhã tem maior poder de saciedade e é capaz de reduzir a quantidade total de energia ingerida durante o dia, enquanto a ingestão de alimentos tarde da noite não tem as mesmas propriedades em termos de saciedade e pode levar à maior ingestão total de energia (DE CASTRO 2004). Além disso, não realizar o café da manhã tem sido consistentemente associado à baixa ingestão de micronutrientes (NICKLAS et al. 1998; WILLIAMS 2005; DESHMUKH-TASKAR et al. 2010) e uma prevalência maior de não atingir a ingestão recomendada de cálcio (NICKLAS et al. 1998; WILLIAMS et al. 2005), folato (NICKLAS et al. 1998; WILLIAMS et al. 2005), magnésio (DESHMUKH-TASKAR et al. 2010), vitamina C (NICKLAS et al. 1998; WILLIAMS et al. 2005) e vitamina A (NICKLAS et al. 1998; WILLIAMS et al. 2005; DESHMUKH-TASKAR et al. 2010). Além disso, o comportamento de pular o café da manhã entre os vespertinos pode ser devido a um atraso em seus ritmos circadianos. Assim, indivíduos vespertinos podem não consumir essa refeição por falta de sinalização dos relógios biológicos referentes ao horário em que a refeição deve ser consumida (SILVA et al. 2016).

Além disso, estudos com animais demonstraram que comer em horários circadianos inadequados pode contribuir para um pior controle de peso e saúde metabólica (ARBLE et al. 2009; HATORI et al. 2012; LONGO; PANDA 2016). Estudos transversais (ALJURAIBAN et al. 2015; WANG et al. 2013) e longitudinais (BO et al. 2014; PURSLOW et al. 2008) em humanos encontraram associações entre ingestão energética matinal e menor risco de obesidade, enquanto ingestão energética noturna foi

associado a um maior risco de obesidade. No entanto, o papel do cronotipo na associação entre o tempo de ingestão de energia e a obesidade não está claro. Um estudo transversal de pequena escala nos Estados Unidos encontrou uma associação entre a ingestão de energia à noite e maior IMC independente do tempo de sono (BARON et al. 2011), enquanto dois estudos transversais recentes indicaram que a ingestão de energia sincronizada com ritmos circadianos intrínsecos pode ser mais benéfica em termos de melhor controle de peso (MCHILL et al. 2017; MUNOZ et al. 2017).

A relação entre cronotipo e consumo alimentar durante o período gestacional ainda é pouco explorada. Estudos recentes de nosso grupo identificaram essa associação, como o estudo de Gontijo et al., (2019), que investigaram as associações entre cronotipo e qualidade da dieta de 100 mulheres no primeiro trimestre gestacional (≤12 semanas de gestação) com idade média de 27,3 ± 5,7. Os resultados mostraram que gestantes com tendência a matutinidade apresentaram melhor qualidade da dieta identificada pelo Índice de Qualidade da Dieta Revisado (IQD-R) para população brasileira, com escores mais elevados para a pontuação total e para o componente frutas totais (GONTIJO et al., 2019). Os autores também afirmaram que outros componentes do IQD-R - como "carnes, ovos e leguminosas", "vegetais totais", "vegetais verdes-escuros e alaranjados e leguminosas" - provavelmente não foram associados ao cronotipo porque são grupos alimentares que incluem tipos de alimentos geralmente consumidos durante grandes refeições – como almoço e jantar – (que não são negligenciadas independente do cronotipo) pela maioria dos brasileiros (DE OLIVEIRA SANTOS et al. 2015). Além disso, também encontramos que durante a gestação mulheres com uma maior alimentação noturna eram mais propensas a ter um cronotipo noturno (GONTIJO et al. 2020).

Também podemos encontrar reflexos das características alimentares de pessoas com tendência à vespertinidade mencionadas acima sobre o GPG. Estudos recentes do nosso grupo demonstraram um ganho excessivo de peso durante a gestação relacionado ao cronotipo noturno (GONTIJO et al. 2019; TEIXEIRA et al., 2019). Teixeira et al., (2019) investigaram a associação entre o cronotipo e o ganho de peso no início do período gestacional e descobriram que gestantes com tendência à vespertinidade eram mais propensas a ganhar peso neste período. Gontijo et al., (2019) também constataram que gestantes com maior ingestão energética noturna apresentaram maior ganho de peso excessivo do que gestantes com menor ingestão energética noturna, o que supostamente poderia ser justificado pela variabilidade cronotípica entre o grupo.

Esses resultados devem encorajar estudos futuros que possam estudar um possível efeito deletério da alimentação noturna por gestantes com tendência à vespertinidade sobre o ganho de peso durante a gestação.

OBJETIVOS

Objetivo Geral

Esta tese teve dois objetivos principais: 1) identificar a ocorrência de JLS ao longo da gestação e descrever o efeito do peso corporal pré-gestacional sobre o JLS ao longo da gestação; 2) estudar a associação do cronotipo com o consumo alimentar e o ganho de peso durante a gestação.

Objetivo Específico

Identificar a ocorrência de JLS ao longo do período gestacional (Artigo 1).

Descrever o efeito do peso corporal pré-gestacional sobre o JLS ao longo da gestação (Artigo 1).

Analisar o efeito do cronotipo sobre os padrões alimentares, ingestão e distribuição de energia e macronutrientes (Artigo 2).

Analisar o efeito do cronotipo sobre o ganho de peso gestacional (Artigo 2).

RESULTADOS

Artigo 1

Artigo intitulado "Changes in circadian misalignment measured by social jetlag from early to late pregnancy and its association with nutritional status: a longitudinal study", submetido para o periódico *American Journal of Clinical Nutrition* (Fator de impacto = 6.766).

Changes in circadian misalignment measured by social jetlag from early to late pregnancy and its association with nutritional status: a longitudinal study

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Abstract

Background: A mismatch between circadian and social clocks leads to a circadian misalignment, which has been widely measured by social jetlag (SJL). Studies have associated SJL with nutritional diseases such as obesity, but it has not been studied in pregnant women. Therefore, this study aimed to identify the occurrence of SJL throughout pregnancy and to describe the effect of pre-pregnancy body weight on SJL throughout pregnancy. **Methods:** The baseline of the present study was conducted with 205 1st trimester pregnant women of whom 100 were followed in their 2nd and 3rd trimester. SJL was calculated based on the absolute difference between mid-sleep time on workdays versus work-free days. The pre-pregnancy BMI and current BMI (kg/ m²) were calculated. Linear regression and Generalised Estimating Equation (GEE) adjusted for confounders were used to determine the association between SJL and the gestational trimesters (time), and anthropometric variables. **Results:** Most of the pregnant women (54.5%) presented SJL > 1h in the first gestational trimester. A positive association between SJL and pre-gestational BMI in the third trimester (β= 0.200, p = 0.046) was found. In addition, GEE analyzes showed that pregnant women of a normal weight showed a decrease in SJL from the second to the third trimester (1.29 ± 0.11 and 0.93 ± 0.08, respectively, p = 0.032), but this was not found in the other groups of nutritional status (underweight, overweight and obesity). We also found an isolated effect of the gestation trimester on the SJL mean. In this sense, pregnant women had a decrease in SJL from the second to the third trimester (1.33 ± 0.08 versus 1.12 ± 0.07, respectively; p = 0.012). **Conclusions:** SJL is quite prevalent during the gestational period and excessive pre-gestational weight seems to lead to a higher risk of having SJL over the pregnancy.

Keywords: Social jetlag, Pregnant women, Body Mass Index, Excessive Weight.

Introduction

The central and peripheral circadian clocks have the main function of synchronizing the endogenous system over a 24-hour period and controlling several biological processes, such as the sleep-wake cycle (Voigt et al., 2013). Circadian misalignment occurs when endogenous circadian rhythms are not synchronized by environmental clues – or *zeitgebers* – such as light-dark cycle (Roenneberg et al., 2003), food intake (De Goede et al., 2018; Mieda et al., 2006; Yoo et al., 2004; Brandstaetter, 2004) and physical activity (De Goede et al., 2018, Atkinson et al., 2007).

Social jetlag (SJL) is a measure of the discrepancy between biological and social time resulting from a conflict between a sleep timing with and without the constraints imposed by social obligations (Wittmann et al., 2006). Proposed by Wittmann and colleagues in 2006, this variable is calculated by the mean difference between the time of sleep on workdays versus work-free days (Wittmann et al., 2006) and has been used as a measure of circadian misalignment. Previous studies have shown that SJL is associated with health problems, such as obesity (Roenneberg et al., 2012; Parsons et al., 2015), metabolic disorders (Parsons et al., 2015), type 2 diabetes (Koopman et al., 2017), atherosclerotic cardiovascular disease (Rutters et al., 2004, Kantermann et al., 2013, Wong et al., 2015), as well as with higher levels of cortisol in healthy individuals (Rutters et al., 2004) and higher levels of glycated hemoglobin in patients with type 2 diabetes (Reutrakul et al., 2013). Recent studies conducted by our group demonstrated that SJL is associated with an increased risk of overweight, metabolic complications (Mota et al., 2017) and a poor diet (Mota et al., 2019) in individuals with chronic non-communicable diseases. Thus, the aforementioned evidence suggest that chronic SJL has implications for human health.

The physical and physiological changes resulting from the gestational process to support fetal development and adapt to the stress imposed on the body can significantly impact the sleep-wake pattern (Tsai et al., 2016; Ko et al., 2010), resulting in decreased hours of sleep (Facco et al., 2010), poor sleep quality (Ko et al., 2010; Hung et al., 2013), diurnal sleepiness (Pien et al., 2005) and insomnia (Sivertsen et al., 2015). Moreover, pregnancy requires coordination of several physiological systems, including metabolic, endocrine, and circadian (Boden et al., 2013). It is believed that such changes could alter biological rhythms, but little is known about the effects of pregnancy evolution on the circadian alignment/ misalignment of pregnant women. Current studies have already described negative consequences of circadian misalignment on the outcome of pregnancy

in animal models (Miller et al., 2004; Dolatshad et al., 2006; Summa et al., 2012; Chen et al., 2015), such as the decrease in the number of live births (Dolatshad et al., 2006; Chen et al., 2015), prolonged the stage of labor, but not the duration of pregnancy (Chen et al., 2015), an elevated rate of full-term pregnancy failure (Miller et al., 2004; Dolatshad et al., 2006; Summa et al., 2012) and disturbed the fetal intrauterine growth and the growth of neonatal rats (Chen et al., 2015). However, little is known about the effect of gestational physiological time on the circadian alignment of these women.

The aim of this study was to identify the occurrence of SJL throughout the three gestational trimesters and to describe the effect of pre-pregnancy body weight on SJL throughout pregnancy. We hypothesized that SJL increases throughout the gestational period and that women with a higher than normal pre-gestational BMI present a higher risk of having SJL higher than 1h throughout the pregnancy.

Materials and methods

Participants and Ethics

This is a two phases study (baseline and longitudinal) conducted between October 2015 and February 2017 at the prenatal service of the Integrated Care Units and Clinical Hospital of the Federal University of Uberlândia, located in Uberlândia, Minas Gerais, Brazil.

Pregnant women in the first gestational trimester were invited to participate when they were waiting for prenatal consultation in the waiting room. Before the invitation, a brief explanation of the research and procedures was given. Pregnant women were recruited according to the following eligibility criteria: being older than 18 years old, not being a shift worker (including pregnant women who worked between 7am and 19pm), not using illegal substances, not being pregnant with twins, not being Human Immuno-Deficiency Virus (HIV) positive and not having diseases such as syphilis, toxoplasmosis, rubella, cytomegalovirus, varicella or having fetal malformation or anomalies in the current pregnancy, as well as those who did not provide all necessary information for the development of the study and reported using the alarm clock on weekends.

A total of 252 pregnant women at the first gestational trimester were invited to participate in the baseline of the study. Seventeen did not accept to participate. Thirty participants were excluded because they did not provide all necessary information (n = 25), or presented previous diseases (n = 3), or had twin pregnancy (n = 2) (Figure 1).

After the initial characterization, one hundred pregnant women were invited to participate in the second phase of the study (longitudinal phase), which involved being evaluated during the whole pregnancy during the (second and third trimester).
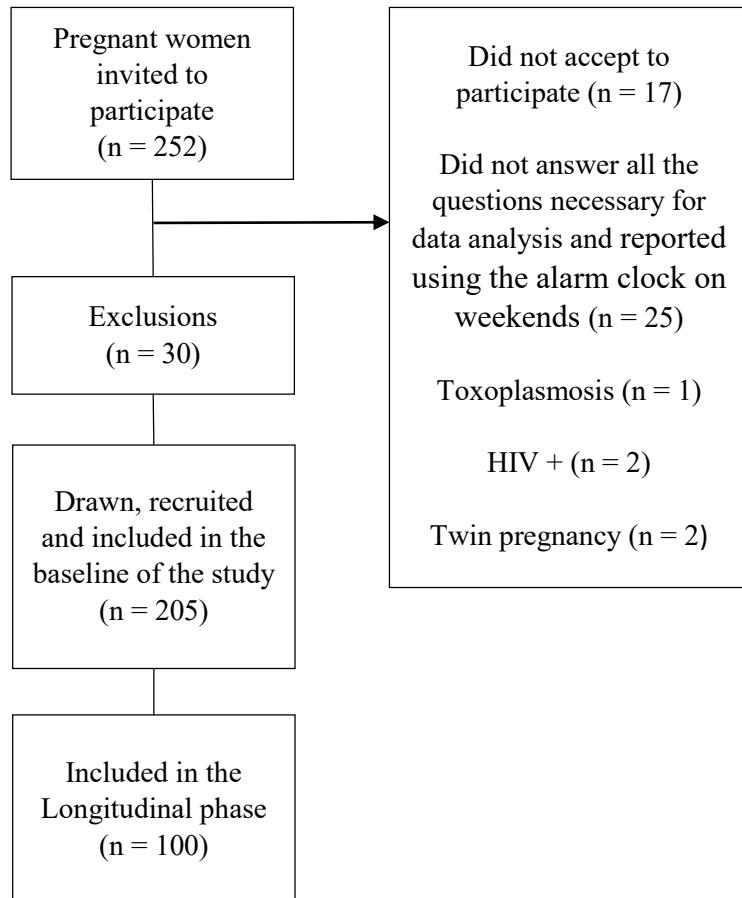
Figure 1: Study flowchart.
Note: HIV - Human Immuno-Deficiency Virus

This study was approved by the Human Research Ethics Committee (protocol number 1.199.829/ 2015) of the Federal University of Uberlândia. Research was conducted according to the guidelines in the Declaration of Helsinki. All participants signed a free and informed consent form.

Methods

A total of 205 pregnant women were evaluated in the first trimester (4th to 12th gestational weeks). A questionnaire was applied by the researchers in order to evaluate socio-demographic aspects such as age, years of education, marital status and family

income. Interviews and measurements were conducted by trained researchers while the pregnant women were waiting for medical appointments in the public service units.

A subsample of 100 pregnant women that were assessed in the first trimester were included in a longitudinal study and assessed over the next two gestational trimesters, evaluated between the 20th and 26th week and again between the 30th and 37th week.

Data on morning sickness (vomiting, nausea) and heartburn, physical activity, employment status, workload, medication use and sleep pattern were self-reported in all three phases.

Anthropometric variables

The height and current weight were measured, and body mass index (BMI) was calculated. The current BMI was classified according to the gestational week suggested by Atalah et al. (1997) for the gestational age, as recommended by World Health Organization (WHO) (2000). Their current weight was measured over the three evaluations. The pre-pregnancy weight was self-reported and the pre-pregnancy BMI (kg/m²) was calculated and classified according to the WHO classification (2000). The weight gain was evaluated in each trimester by the following described steps: first, the recommended weight gain (Institute of Medicine 2009) in each trimester was calculated considering the number of gestational weeks corresponding to the interval between the evaluations, except for the first trimester, which the recommended weight gain was considered in the range of 0.5 to 2 kg per month. Then, the weight gain in each trimester was evaluated using the difference between the value of the current measured weight and the value of the previous trimester weight, or pre-gestational weight in the first trimester.

Sleep data, social jetlag and chronotype

Pregnant women were asked to report their usual bedtimes and waking times on workdays and work-free days, adapted from Munich Chronotype Questionnaire (Roenneberg et al., 2003). Sleep duration was computed using the weighted average of self-reported sleep duration, which considers both, weekdays and weekends, using the formula: [(Reported current weekday sleep duration × 5) + (Reported current weekend sleep duration × 2)]/ 7 (Reutrakul, et al. 2013).

SJLwas calculated as the absolute difference between the time of mid-sleep on weekdays and weekends (Wittmann et al., 2006). We classified the data into two groups: without SJL (≤ 1h) and with SJL (>1h) (Roenneberg et al., 2012).

Chronotype was derived from the mid-sleep time on free days on weekend (MSF), with a further correction for calculated sleep debt (MSFsc) - calculated as the difference between average sleep duration on weekends and the average sleep during the week (Roenneberg et al., 2007).

Sleep quality was assessed by Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989) translated into Portuguese (Bertolazi et al., 2011), which has been used by other researchers in studies with Brazilian population sample (Bertolazi et al., 2011; Mota et al., 2014). The PSQI is an instrument widely used to measure the subjective sleep quality of sleep during the last month of pregnancy and has been validated in populations of pregnant women in previous studies (Qiu et al., 2016; Zhong et al., 2015).

At each of the three evaluations sleep data were evaluated and SJL and chronotype were calculated.

Statistical analysis

All statistical analyses were performed using the SPSS version 20.0 (SPSS Inc., Chicago, IL, USA), and $p<0.05$ was considered statistically significant. Initially, the data normality was tested by Kolmogorov–Smirnov test. Categorical variables were summarized using frequencies and percentages, and continuous variables were summarized using means and standard error or median and interquartile intervals. Descriptive statistics were used to summarize participant sociodemographic, lifestyle, anthropometrics, sleep patterns and circadian data.

The Generalized Linear Models (GzLM) with linear distributions adjusted for age, marital status, schooling, work (yes or no) and gestational age (current BMI), were used to determine the association between SJL (dependent variable) and BMI categories in the baseline (n= 205) (independent variables; baseline of the study). Generalized Estimating Equation (GEE) models using linear distributions were used in the longitudinal phase to determine the effects of the gestational time [first (n=100), second (n=100) and third trimester (n=100)], nutritional status and their interaction on SJL. Analyses were adjusted for age, marital status, schooling, work (yes or no), gestational age, parity, body mass index and PSQI global sleep quality score. Pairwise comparisons were performed using the Sidak sequential test in both tests (GzLM and GEE).

Linear regression analysis adjusted for confounders (age, marital status, schooling, work (yes or no), gestational age and parity) were performed to associate SJL (dependent variable) with anthropometric variables (independent) in the baseline (n=205)

and also in the analysis of the three trimesters (n=100). Logistic regression models were used to predict the odds ratio (OR) for categories of anthropometric variables (appropriate: normal weight; inappropriate: underweight, overweight and obesity) according to having JSL >1h presence (>1h) or absence of SJL (≤1h) in each gestational trimester. All analyses were adjusted for confounders and the results were expressed as the odds ratio with 95% confidence interval (CI).

Results

Socio-demographic data, lifestyle, anthropometry, sleep patterns and circadian-related data are presented on Table 1. Most women were married or lived with a partner (64.8% of all women in baseline; 79.0% of the women followed during the longitudinal phase). Regarding the pre-gestational BMI, 53.7% who participated only in the baseline and 57.0% who were followed the longitudinal phase had normal weight at the beginning of pregnancy.

Table 1: Socio-demographic data, lifestyle, anthropometry, sleep patterns and circadian-related data of all pregnant women in the baseline and the women followed in the longitudinal phase.

Variables	Baseline	Longitudinal phase		
	1st trimester (n = 205) Mean ± SD or Median [interquartile range] or n (%)	1st trimester (n = 100) Mean ± SD or Median [interquartile range] or n (%)	2nd trimester (n = 100) Mean ± SD or Median [interquartile range] or n (%)	3rd trimester (n = 100) Mean ± SD or Median [interquartile range] or n (%)
Age, years	27.66 ± 9.79	27.70 ± 5.61		
Gestational age, weeks	9.79 ± 2.45	10.12 ± 2.40	24.00 ± 3.12	34.14 ± 2.61
Work (yes)	102 (49.7%)	56 (56.0%)	44 (44.0%)	43 (43.0%)
Physical activity (no)				
Participated in physical activity	17 (8.2%)	17 (17.0%)	21 (21.0%)	20 (20.0%)
Marital status				
Married or live with a partner	133 (64.8%)	79 (79.0%)		
Single	71 (35.2%)	21 (21.0%)		
Schooling				
Basic education complete/ not complete	20 (9.8%)	5 (5.0%)		
High school education complete/ not complete	159 (77.5%)	68 (68.0%)		
Higher education complete/ not complete	26 (12.7%)	27 (27.0%)		
Anthropometric variables:				
Height (m)	1.65 ± 0.08	1.64 ± 0.06		
Pre-pregnancy weight (kg)	65.77 ± 14.32	65.49 ± 12.83		
Pre-gestational BMI (kg/ m²)	24.46 ± 4.95	24.25 ± 4.30		
Underweight	18 (8.8%)	6 (6.0%)		
Normal weight	110 (53.7%)	57 (57.0%)		
Overweight	42 (20.4%)	24 (24.0%)		
Obesity	35 (17.1%)	13 (13.0%)		
Weight – current (kg)	67.57 ± 17.28	66.90 ± 13.44	72.02 ± 13.35	78.34 ± 13.52
BMI - current (kg/ m²)	25.07 ± 5.19	24.80 ± 4.51	26.65 ± 4.47	28.98 ± 4.40
Underweight	20 (9.5%)	13 (13.0%)	13 (13.0%)	11 (11.0%)
Normal weight	108 (52.7%)	46 (46.0%)	42 (42.0%)	36 (36.0%)
Overweight	50 (24.5%)	27 (27.0%)	29 (29.0%)	32 (32.0%)

Obesity	27 (13.3%)	14 (14.0%)	16 (16.0%)	21 (21.0%)
Sleep patterns				
Week sleep time (h:min)*	22:51 ± 01:25	22:48 ± 01:18	22:42 ± 00:54	22:57 ± 01:07
Weekend sleep time (h:min)*	23:40 ± 01:56	23:51 ± 01:12	23:53 ± 01:01	23:49 ± 01:07
Week awake time (h:min)*	7:33 ± 01:50	7:31 ± 01:39	7:17 ± 01:30	7:22 ± 01:21
Weekend awake time (h:min)*	8:56 ± 01:38	8:48 ± 01:27	8:54 ± 01:28	8:37 ± 01:16
Mean week sleep duration (h)	8.67 ± 1.76	8.71 ± 1.53	8.58 ± 1.56	8.41 ± 1.43
Mean weekend sleep duration (h)	9.17 ± 1.58	8.93 ± 1.33	9.02 ± 1.55	8.80 ± 1.30
Circadian-related data				
Social jetlag (h)	1.17 [0.00 – 5.50]	0.95 [0.00 – 4.83]	1.27 [0.00 – 3.79]	1.00 [0.00 – 3.08]
Chronotype (MSF) (h:min)	4:16 ± 1:21	4:08 ± 1:23	4:13 ± 1:17	4:18 ± 1:12

Note: BMI: Body mass index; MSF = Midsleep phase on free days. *Time is presented in 24-h clock time. Values are presented as mean and SD (standard deviation) for normally distributed data or as median [interquartile range] for not normal distributed data or n (%).

Figure 2 shows the distribution of SJL of all pregnant women in the first phase analysis (n = 205). The majority (54.5%) presented SJL higher than 1h in the first trimester of pregnancy.
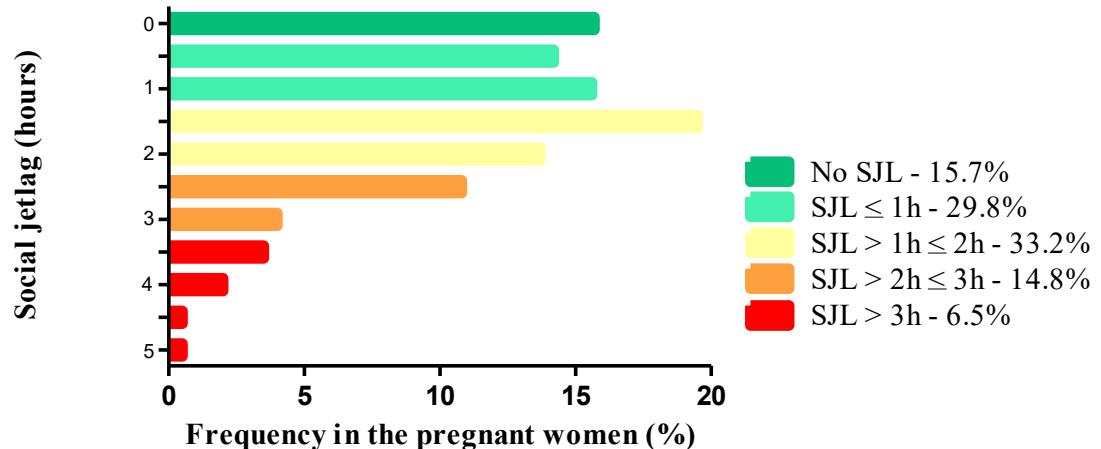
Figure 2. Distribution of social jetlag (SJL) of all pregnant women in the baseline (n=205). The distribution is based on half-hourly bins. Color-coding is arbitrary and classifies the population into the five SJL groups indicated in the legends.

The distribution of SJL of the pregnant women of the longitudinal phase over the three gestational trimesters is presented in Figure 3.
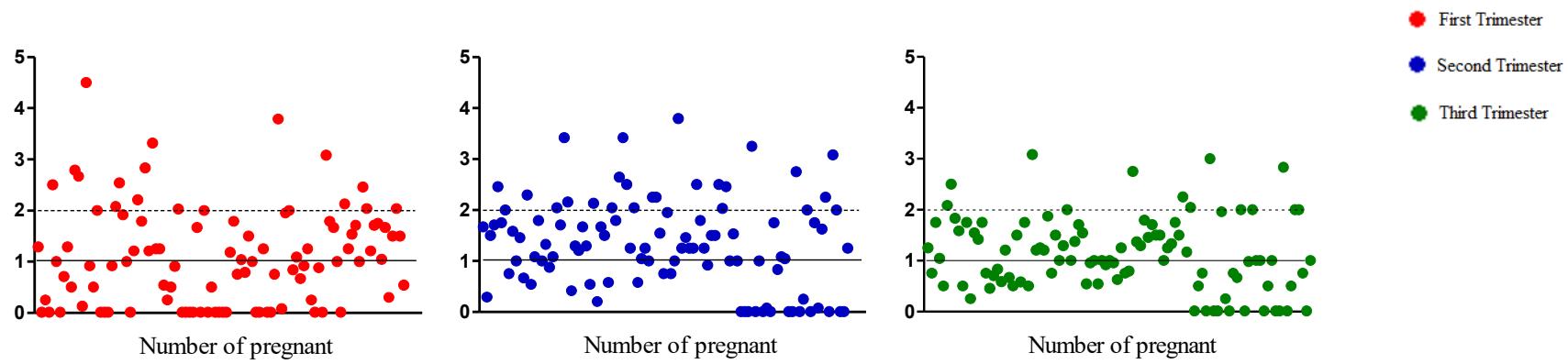
Figure 3. Distribution of social jetlag (SJL) (h:min) throughout each gestational trimester in the longitudinal phase. The value of SJL in hours is shown for each pregnant woman according to the gestational trimester (n = 100).

Figure 4 shows the trajectory of the categories of SJL (> 1h) over the three gestational trimesters in the longitudinal phase. A total of 77 (77.0%) pregnant women had no SJL higher than 1h during at least one trimester, 22 (22.0%) had no SJL higher than 1h in all three trimesters and 23 consistently had SJL higher than 1h in all three trimesters (23.0%).
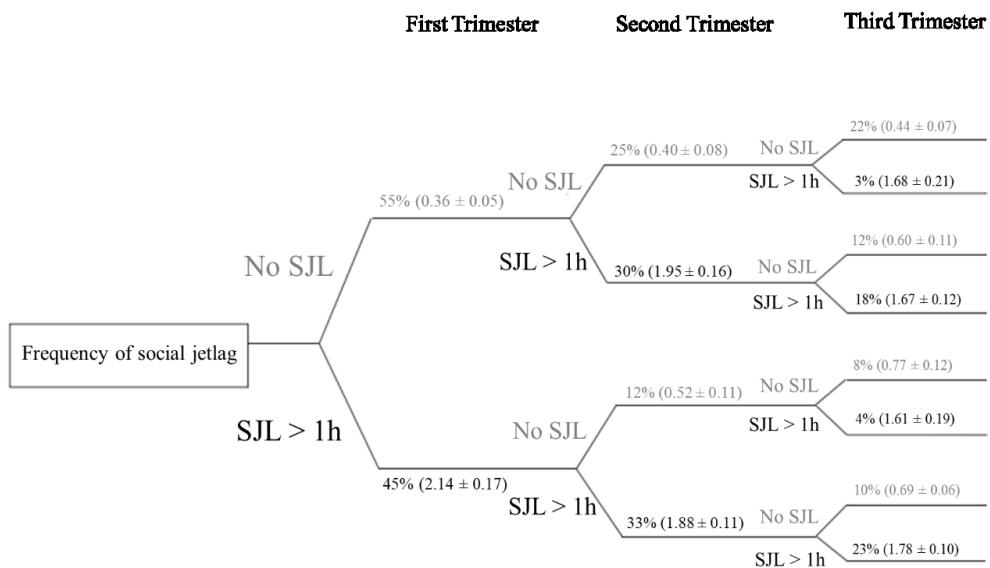
Figure 4. Trajectory of social jetlag (SJL) (No ≤1h or >1h) category across three trimesters in the pregnant women in longitudinal phase (n = 100). The categories were summarized using frequencies (%). Means ± standard error (SE) of each category are presented in parentheses.

Figure 5 presents the frequency of SJL higher than 1h of pregnant women over the three gestational trimesters. The second gestational trimester showed the higher number of pregnant women with SJL higher than 1h (63.0%) when compared to the first and third trimester (44.0% and 48.0%, respectively).
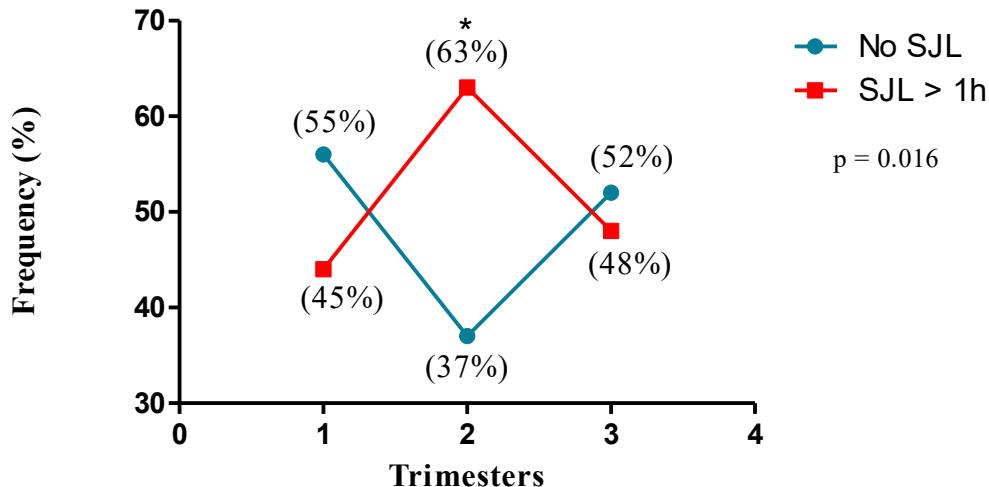
Figure 5. Frequency of social jetlag (SJL) by time category in pregnant participants over the three gestational trimesters in longitudinal phase. The number of participants in each category is shown in brackets (n=100; n=100 first trimester; 100 second trimester; and 100 third trimester).

Note: P values were calculated using the Pearson's chi-square test (p <0.05) and are comparative between the trimester of the longitudinal phase.

Table 2 presents the results of the linear regression that tested the associations between SJL and anthropometric variables. We found a positive association between SJL and pre-gestational BMI in the third trimester (β= 0.200, p = 0.046). No other significant associations were found.

Table 2. Linear regression analysis associating social jetlag (dependent variable) with anthropometric variables (independent variable) in the baseline (n=205) and over the trimesters in the longitudinal phase (n=100).

Anthropometric variables	Baseline		Longitudinal phase					
	1st trimester (n = 205)		1st trimester (n = 100)		2nd trimester (n = 100)		3rd trimester (n = 100)	
	β	p-valor	β	p-valor	β	p-valor	β	p-valor
Pre-gestational BMI (kg/ m²)	0.130	0.083	0.072	0.479	0.115	0.254	0.200	**0.046**
Current BMI (kg/ m²)	0.115	0.128	0.115	0.255	0.137	0.189	0.128	0.209
Weight gain (kg)	-0.127	0.070	-0.021	0.833	0.064	0.543	0.020	0.850

Note: Linear regression analysis adjusted model for age, marital status, schooling, work (yes or no), gestational age and parity. Bold value is statistically significant at p < 0.05. BMI = body mass index.

Table 3 presents the association between SJL and anthropometric variables in the first phase, as well as throughout the trimesters. Analysis were adjusted for confounding variables. We did not found differences in SJL (dependent variable) between BMI categories (independent variable) in the baseline (pre-gestational: p=0.071; current: p=0.165). However, in the longitudinal phase, we found a significant effect of the interaction between gestation time (first, second and third trimester) and the categories of pre-gestational BMI (independent variables) on SJL (dependent variable). This indicates that normal weight pregnant women decreased the SJL from the second to the third trimester (1.29 ± 0.11 and 0.93 ± 0.08, respectively, $p = 0.032$), which did not happen with the three other groups of nutritional states. We also found an isolated significant effect of the gestation time on the mean of SJL; in this sense, pregnant women decreased the SJL from the second to the third trimester (1.33 ± 0.08 versus 1.12 ± 0.07, $p = 0.012$, respectively).

Table 3. Association of social jetlag with anthropometric variables in the baseline (n=205) and throughout the trimesters in the longitudinal phase (n=100).

Anthropometric variables	Baseline		Longitudinal phase					
	1st trimester (n = 205)		Overall (n = 100)		1st trimester (n = 100)	2nd trimester (n = 100)	3rd trimester (n = 100)	
	(N) Mean ± SE	*p-valor	Mean ± SE	**p-valor	Mean ± SE	Mean ± SE	Mean ± SE	**p-valor
Social jetlag†			1.19 ± 0.88		1.10 ± 0.10^{ab}	1.33 ± 0.08^{a}	1.12 ± 0.07^{b}	**0.012**
Pre-gestational BMI‡								
Underweight	(18) 1.35 ± 0.28		1.17 ± 0.09		1.33 ± 0.28^{ab}	1.04 ± 0.15^{ab}	1.13 ± 0.23^{ab}	
Normal weight	(110) 1.27 ± 0.11	0.071	1.08 ± 0.08	0.216	1.02 ± 0.13^{ab}	1.29 ± 0.11^{a}	0.93 ± 0.08^{b}	**0.032**
Overweight	(42) 1.41 ± 0.16		1.30 ± 0.13		1.00 ± 0.19^{ab}	1.48 ± 0.22^{ab}	1.41 ± 0.14^{ab}	
Obesity	(35) 1.94 ± 0.22		1.43 ± 0.15		1.50 ± 0.31^{ab}	1.37 ± 0.19^{ab}	1.41 ± 0.16^{ab}	
BMI - current‡								
Underweight	(20) 1.42 ± 0.22		1.15 ± 0.14		1.05 ± 0.27	1.40 ± 0.15	1.00 ± 0.20	
Normal weight	(108) 1.22 ± 0.13	0.165	1.02 ± 0.09	0.121	1.06 ± 0.14	1.08 ± 0.13	0.93 ± 0.10	0.478
Overweight	(50) 1.49 ± 0.16		1.30 ± 0.10		1.05 ± 0.18	1.64 ± 0.16	1.21 ± 0.13	
Obesity	(27) 1.77 ± 0.21		1.38 ± 0.16		1.37 ± 0.30	1.39 ± 0.22	1.38 ± 0.14	

Note: SE = Standard error. BMI = body mass index. *p values calculated by - Generalised linear models (GzLM) (mean ± standard deviation) in the baseline. Adjusted to age, marital status, schooling, work (yes or no), gestational age and parity. Sidak post-hoc test, p-value < 0.05 was considered significant. **p values calculated by Generalized Estimating Equation (GEE) (mean ± standard deviation) in the longitudinal phase. Significant results of the models were shown in bold. †Adjusted to age, marital status, schooling, work (yes or no), parity, body mass index and Pittsburgh Sleep Quality Index Global Sleep Quality Score. ‡Adjusted to age, marital status, schooling, work (yes or no), parity and gestational age. Sidak post-hoc test, letters differents represent statistical difference in pairwise comparisons, p-value < 0.05.Total gestational data's values represent the average of the three trimesters.

       Table 4 shows the odds ratio (OR) for having >1h of SJL according to adequacy of pre-gestational BMI, current BMI and weight gain in each gestational trimester. Results indicated a higher risk of having SJL higher than 1h in the third trimester when pregnant women had inadequate pre-gestational BMI (OR = 3.059, IC 95% = 1.343-6.964), and also in second trimester when pregnant women had inadequate current BMI (OR = 3.470, IC 95% = 1.490-8.081).

Table 4. Odds ratio (OR) for having >1h of social jetlag according to anthropometric variables categories in the gestational trimesters (reference group: ≤1h of social jetlag).

| | Baseline | | Longitudinal phase | | | | | |
| | 1st trimester | | 1st trimester | | 2nd trimester | | 3rd trimester | |
	OR (IC 95%)	p-valor	OR (IC 95%)	p-valor	OR (IC 95%)	p-valor	OR (IC 95%)	p-valor
Pre-gestational BMI								
Adequate (reference group)	1.0	0.938	1.00	0.898	1.00	0.577	1.00	**0.008**
Inadequate	1.024 (0.568-1.847)		1.113 (0.502-2.466)		1.263 (0.556-2.869)		3.059 (1.343-6.964)	
Current BMI								
Adequate (reference group)	1.00	1.000	1.00	0.904	1.00	**0.004**	1.00	0.182
Inadequate	1.000 (0.550 - 1.820)		0.952 (0.432-2.099)		3.470 (1.490-8.081)		1.769 (0.765-4.091)	
Weight gain								
Adequate (reference group)	1.00	0.431	1.00	0.389	1.00	0.361	1.00	0.389
Inadequate	1.554 (0.97 - 4.87)		0.683 (0.287-1.626)		0.652 (0.260-1.632)		0.683 (0.287-1.626)	

Note: Logistic regressions analysis adjusted model for age, marital status, schooling, work (yes or no), parity and gestational age. Bold value is statistically significant at $p < 0.05$. IC: confidence interval.

Figure 6 illustrates the possible effect of pre-gestational and current BMI on the SJL according to the previously analyses presented. We found a relationship between pre-pregnancy BMI and SJL, in which pregnant women classified as normal weight in the pre-gestational BMI decreased the SJL from the second to the third trimester (Table 3). A relationship between the current BMI and SJL was also observed, in which pregnant women classified was inadequate in current BMI (underweight, overweight and obesity) presented a higher chance of having SJL higher than 1h when compared to those with normal weight (Table 4).
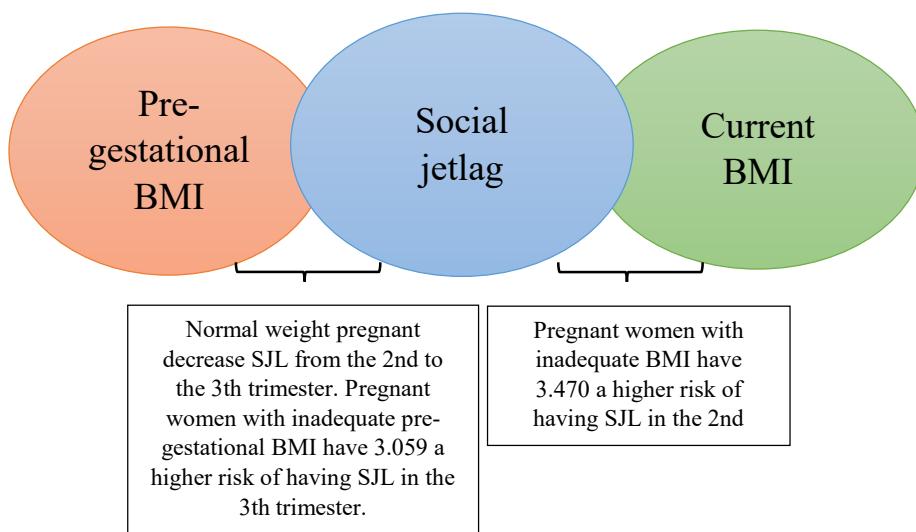
Figure 6. Relationship between social jetlag, pre-gestational BMI and BMI current.

Discussion

The present study aimed to identify the prevalence of SJL and to describe the effect of pre-pregnancy body weight status on SJL throughout pregnancy. In our best knowledge, this is the first cohort study to describe SJL over the gestational period. Our results indicated a high prevalence of circadian misalignment measured by SJL, with most part of pregnant women (54.5%) presenting SJL higher than 1h in the first gestational trimester and 77.0% of the pregnant women having SJL higher than 1h during at least one trimester. In the longitudinal phase, we found that normal weight pregnant women tend to decrease the SJL from the second to the third trimester, which was not found in underweight, overweight and obese ones. Our results also indicated a higher risk of

having SJL higher than 1h in the second and third trimester when pregnant women had inadequate BMI. These results partially confirm our hypothesis that SJL changes throughout the gestational period. Regarding our initial hypothesis that relates the occurrence of SJL higher than 1h to body weight status, we found that pregnant women with excessive weight tend to maintain the degree of pre-gestational circadian misalignment, while pregnant women with normal weight decrease SJL over the gestation.

Studies in animal models have demonstrated that genetic disruption of the circadian clock negatively influences pregnancy outcomes (Miller et al., 2004; Kennaway et al., 2005; Dolatshad et al., 2006; Kennaway et al., 2011). The effects of circadian system environmentally-imposed disturbances on mammalian model pregnancy seems to dramatically reduce the pregnancy success (Summa et al., 2012), decrease the number of births (Chen et al., 2015) and disturbed the fetal intrauterine growth and the growth of neonatal rats (Chen et al., 2015). Epidemiological studies have also showed an association between gestational chronodisruption – as usual in shift work (Bonzini et al., 2011; Chau et al., 2014; Strohmaier et al., 2019), travel across time zones (Cone et al., 1998; Aspholm et al., 1999), or light exposure at night (Begtrup et al., 2019) - and adverse pregnancy outcomes in humans, as fetal loss and spontaneous abortion (Zhu et al., 2004), duration of pregnancy (including preterm or postterm birth) (Zhu et al., 2004; Pompeii et al., 2005) and low birth weight and/ or small for gestational age (Xu et al., 1995; Bodin et al., 1999). Also, studies suggest that pregnant night workers might have an increased risk of miscarriage (Begtrup et al., 2019), hypertensive disorders during pregnancy (Suzumori et al., 2019) and preterm delivery (Davari et al., 2018). Thus, the high prevalence of SJL higher than 1h in pregnant women should be considered very worrying.

Unfortunately, the prevalence of SJL in pregnant women is currently unknown, which makes it impossible to compare our findings with previous studies. However, studies conducted with other groups have found that SJL has been highly prevalent among young people, adults and the elderly (Wittmaan et al., 2006; Randler et al., 2013; Roenneberg et al., 2012). Two studies developed with Germany population (age: 14 to 94y) found a SJL prevalence among 69-70% (Wittmann et al., 2006; Randler et al., 2013). Roenneberg et al. (2012), in an epidemiologic study developed with 65,000 Europe participants, found that 33% of them have SJL ≥ 2 hours and 69% have, at least, 1 hour of SJL. Also, a Netherlander study (n = 1585, 60,8 ± 6y), found that 31% of the sample reported SJL between 1 and 2 hours and 8% reported SJL > 2 hours (Koopman et al.,

2017). In addition, Lang et al. (2018) found that 31,1% of Australian people have SJL > 1h (n=837; 18-75y). In Brazil, studies from our group with shift workers (Alves et al., 2016), university students (Silva et al., 2016; Tavares et al., 2020) and patients with chronic diseases (Mota et al., 2017; Mota et al., 2019) have followed the same pattern as in the other countries previously mentioned.

Among factors that can influence the SJL, we can emphasize age range. Roenneberg et al. (2012) identified that younger individuals (15-25y) have a higher degree of SJL and that after 30 years old they seem to have a progressive reduction in the hours of SJL. This finding corroborates with other studies, which also found higher prevalence of SJL (> 1h) in younger individuals: 80% (337/423) (Alves et al., 2016); 83% (661/796) (Parsons et al., 2015) when compared the prevalence identified in to studies with older populations; 25% (111/437) (Wong et al., 2015). These data can explain the high SJL prevalence found in the present study since our sample is young. Another factor that frequently is associated with SJL is the chronotype. This variability in the sleep-wake cycle is especially evident among late types, who generally report a greater accumulated sleep debt during the week (Roenneberg et al., 2012). Taillard et al. (1999) found that around 72.5% of evening types changed their bedtime and wake up time in, at least, two hours between the workdays and the weekend, compared to 49.8% of morning types (circadian preference defined by Horne and Ostberg, 1976). In fact, individuals with eveningness tendency are more susceptible to SJL than those with morningness tendency (Levandovski et al., 2011; Collado Mateo et al., 2012; Wittmann et al., 2006; Tavernier et al., 2015), since this sleep-wake cycle irregularity during the week and on weekend was considered a compensatory strategy for the evening types, who are generally more susceptible to asynchrony in their "biological" and "social" clocks (Zimmermann, 2011). In the present study, we found a positive association between chronotype and the SJL only in the first trimester ($\beta = 0.393$; $p = 0.006$; data not shown).

Our results also show that pregnant women decreased the SJL from the second to the third trimester. Such results demonstrate that the degree of SJL tends to change during pregnancy, which can be justified by the fact that each gestational trimester have specific characteristics that could influence the sleep quality. There is, for example, an increase in sleep duration, daytime sleepiness and insomnia in the first trimester of pregnancy, while sleep quality tends to decrease (Schweiger, 1972; Suzuki et al., 1994) due to nocturnal urinary frequency and heartburn (Facco et al., 2010). In the second trimester, in addition to the facts already mentioned, fetal movement and frequent heartburn can disturb sleep

(Leung et al., 2005). Lastly, in the third trimester sleep pattern can be altered due to abdominal increase and anxiety (Guilleminault et al., 2000; Jomeen, 2007; Neau et al., 2009). As many pregnant women in our sample (57%) weren't working in the third trimester, this may have reduced social demand and minimized the effects of sleep problems, impacting in the SJL in this trimester. However, studies in the literature that assessed the SJL in a longitudinal context are still limited (Tavernier et al., 2015; McMahon et al., 2018) and have not been conducted with pregnant women, which makes it impossible to compare with our findings.

SJL has been identified as a possible risk factor for the development of excess weight in non-pregnant populations. The first study that showed the relationship between SJL and overweight was carried out by Roenneberg et al. (2012). The authors found that individuals (n = 64,039; age: 16 – 65y) with SJL > 1h had a higher risk to be overweight (OR = 3.3, CI = 2.5-4.3; p = 0.001), even after adjustment for confounders. Parsons et al. (2015) found that individuals with greater SJL scores had higher average BMI (p = 0.012) and more fat mass (p = 0.031), were more likely to be obese (OR = 1.2; 95%, p = 0.045) and to meet criteria for the metabolic syndrome (OR = 1.3; 95%, p = 0.031). A recent study developed by our group found that chronic diseases patients (n = 792; age: 55.9y) with SJL (>1 h) presented a higher odds ratio (OR) of being overweight (OR = 2.0; p = 0.006) and metabolically unhealthy obese (OR = 1.8; p = 0.01) (Mota et al. 2017). Also, another study developed by our group evaluated the evolution of weight loss over six months after bariatric surgery and its association with SJL, showing that patients who were more exposed to SJL had less fat loss and less BMI reduction over six-month (Carvalho et al., 2020). It is still possible that there is a bidirectional relationship between SJL and body weight, given that that excess weight also seems to predispose a SJL increase (Zhang et al., 2019), as found by a Chinese population study that found that BMI seems to be a positive predictor for SJL (p = 0.017) (Zhang et al., 2019). This result corroborates ours, which indicate a higher risk to have SJL higher than 1h in the second and third gestational trimester when pregnant women had inadequate BMI. Although the mechanisms are not completely elucidated, humoral, genetic, feeding habits and behavioral factors are can identified as possible responsible for the association between excess weight and the development of circadian misalignment (Salgado-Delgado et al., 2010). Additional studies are needed to understand the causality relationship between body weight and SJL.

As a strong point of our study, we highlight the SJL analysis at the beginning and also during pregnancy, which allowed us to evaluate SJL changes over time. We emphasize as a limitation the use of subjective questionnaires, which, although validated in other studies, are dependent on the memory and motivation of the participants. Another limitation in our study is that we followed-up pregnant women who had regular appointments in the public health system, and the generalization of the results for all pregnant women cannot be done, especially in high-risk pregnant women. Also, the selection of pregnant women who were followed throughout the pregnancy was not random, which may have led to selection bias. Despite these limitations, we expect that the results of the present study can improve the understanding of the association between SJL and anthropometrics variables during pregnancy. However, the need for further studies on this subject is evident.

We conclude that SJL higher than 1h is very prevalent during all gestational trimesters. We also found a positive association between SJL and pre-gestational BMI in the third trimester. Normal weight pregnant women decreased the SJL from the second to the third trimester, reinforcing that SJL is related with excessive pre-gestational weight. Thus, new studies that include these variables may lead to a better understanding the dynamics of SJL and factors that contribute to increased SJL risk may be important. An examination of how these factors relate to each other both in the short term and long-term will undoubtedly make important contributions to our understanding of how SJL relate to pregnancy. If our findings are confirmed in the future studies, monitoring chronobiological variables such as SJL in promoting maternal and fetal health may emerge as a strategy to improve the effectiveness of prenatal care.

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Artigo 2

Artigo intitulado "Is chronotype associated with dietary intake and weight gain during pregnancy? A prospective and longitudinal study", submetido para o periódico *Clinical Nutrition* (Fator de impacto = 6.360).

Is chronotype associated with dietary intake and weight gain during pregnancy? A prospective and longitudinal study

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ABSTRACT

Background: The effects of chronotype on dietary intake and weight gain over the pregnancy has not been addressed by the literature. The aim of this study was to analyse the effect of chronotype on eating patterns, energy and macronutrient intakes and distribution and weight gain during pregnancy. **Methods:** Prospective cohort study carried out with 100 pregnant women in the first, second and third gestational trimester. The dietary intake was assessed by three 24-hour dietary recalls in each trimester. Energy and macronutrient intakes and distribution were evaluated at meals throughout the day. Chronotype was derived from the time of mid-sleep time on free days and the obtained scores were categorized by tertiles. Recommendations from the Institute of Medicine were used to assess the adequacy of weight gain. Generalized Estimating Equation models were used to determine the effects of chronotype and gestational trimesters on eating patterns, daily energy, macronutrients distribution and weight gain. **Results:** Pregnant women with MSF values indicative of eveningness have breakfast later and also have a higher energy and carbohydrate intake at dinner when compared to those 'morning' women. Pregnant women 'morning' showed a better diet quality in terms of milk and dairy and saturated fat. Also, despite the tendency for all tertiles to gain excess weight during pregnancy, we found that pregnant women with a tendency to eveningness had a worse adequacy of gestational weight gain in the third trimester when compared to those pregnant women with a tendency to 'morning' (2.24 ± 0.25 versus 1.22 ± 0.14, p <0.001). **Conclusions:** Pregnant women with a tendency to evening consume breakfast later in the day and present a greater consumption of energy and carbohydrates in the evening, as well as a worse standard of gestational weight gain in the third trimester. Our results emphasize the importance of considering chrononutrition variables in the nutritional antenatal guidelines to promote maternal-foetal health.

Keywords: Pregnant women; Chronotype; Chrono-nutrition; Meal timing; Time of energy intake; Gestational weight gain.

INTRODUCION

Individual preference for waking and sleeping times is named chronotype (Roenneberg et al., 2003). This variable reflects how the circadian system fits into the 24-hour day with respect to the rhythms of physiology, cognition and behaviors (Roenneberg et al., 2003). Therefore, the individuals' chronotype reflects the daytime preferences in so-called "early birds", or morning types, or nighttime "night owls", or evening types. Individuals with sleep patterns between the two types are classified as intermediate (Horne and Östberg, 1976). Chronotype is a biologically determined preference but can be modified and suffer interference from numerous environmental factors (Koskenvuo et al., 2007). In this sense, some studies have shown that chronotype is associated with sex (Roenneberg et al., 2015), age (Roenneberg et al., 2007), area of residence (urban or rural) (Hida et al., 2012) and physical activity (Schaal et al., 2010).

Previous reports have also demonstrated that certain chronotypes, particularly the evening type, are associated with poor sleep quality (Barclay et al., 2013), obesity (Culnan et al., 2013; Lucassen et al., 2013; Türkoğlu et al., 2019), increased risk of cardiovascular disease (Merikanto et al., 2013; Kantermann et al., 2014) and metabolic disorders including type 2 diabetes (Merikanto et al., 2013). In the nutritional perspective, eveningness has been associanted with unhealthy dietary habits (Kanerva et al., 2012; Maukonen et al., 2016; Silva et al., 2016; Teixeira et al., 2018), such as an increased unhealthy snacks consumption (Arora and Taheri 2015), lower fruit and vegetable consumption (Arora and Taheri 2015, Patterson et al., 2016), a higher preference for sugary food/ beverages and alcohol (Kanerva et al., 2012; Mota et al., 2016) and frequently overeating (Sato-Mito et al., 2011a; Arora and Taheri, 2015). In addition, the most reported association between eating behaviour and chronotype is on meal timing, given that evening individuals usually delay the meal timing during the day (Sato-Mito et al., 2011b; Garaulet et al., 2013; Muñoz et al., 2017; Silva et al., 2016), with a consumption of more calories during dinner (Muñoz et al., 2017; Teixeira et al., 2018) and before bedtime (Suh et al., 2017). Also, evening people are more likely to skip breakfast (Reutrakul et al., 2013; Teixeira et al., 2018)

Although this theme is little explored in pregnant women, a study by our group investigated the associations between chronotype and diet quality of pregnant women in the first gestational trimester (≤12 weeks of gestation), and found that morningness tendency was associated with better diet quality, which was identified by higher scores

of the total Brazilian Healthy Eating Index-Revised (BHEI-R) and/ or fruit components (Gontijo et al., 2018). Another study by our group investigated the association between chronotype and weight gain in the early gestational period, and found that pregnant women who tend to eveningness are more likely to gain weight during the gestational period (Teixeira et al., 2019). However, the effects of chronotype on dietary intake and weight gain over the pregnancy is still poorly evaluated in the literature.

Despite the evidence that supports the importance of maternal nutrition as an effective measure to avoid inadequate nutritional outcomes - such as excessive weight gain (Stuebe et al., 2009) -, pregnant women in Brazil consume a poor diet (Melere et al., 2013; Gomes et al., 2015) and 51% gain excess weight (Stuebe et al., 2009). Therefore, the identification of new factors associated with nutritional evolution during pregnancy, as well as the knowledge about their interactions with other aspects that are known to interfere with maternal nutritional status, are of great importance in protecting the nutritional status of pregnant women. Therefore, chronobiological aspects such as the chronotype become potential variables in the research area, in view of their potential to influence food consumption (Mazri et al., 2019) and nutritional status (Arora and Taheri 2015; de Punder et al., 2019) from other populations.

The aim of this study was to analyse the effect of chronotype on time-related eating patterns, energy and macronutrient intakes and distribution and weight gain during pregnancy. We hypothesised that pregnant woman with an indicative of eveningness present an inadequate distribution of energy intake throughout the day, i.e., a lower intake in the morning meals and a greater intake in the evening meals, as well as an excessive weight gain during pregnancy.

MATERIALS AND METHODS

Subjects and ethics

A longitudinal study was carried out with one hundred pregnant women evaluated in the first, second and third trimesters of the pregnancy. The study was conducted at the prenatal service of the Integrated Care Units of Uberlândia and Clinical Hospital of the Federal University of Uberlândia, located in Uberlândia, Minas Gerais, Brazil, between October 2015 and February 2017. Before the invitation, a brief explanation of the research and procedures was made. Data collection was conducted by trained personnel with

detailed interviews and measurements occurred in the moment that pregnant women were waiting for their medical appointment.

Ethics approval was obtained from the coordinating Ethics Committee (protocol number 1.199.829/ 2015) of the Federal University of Uberlândia. Research was conducted according to the guidelines in the Declaration of Helsinki. All participants signed a free and informed consent form.

Eligibility criteria

Pregnant women were recruited according to the following eligibility criteria: being older than 18 years and healthy, having a single fetus pregacy, had performed the first prenatal visit within up to the 12th week of gestation, not being shift worker, and not using illegal substances. Pregnant women with a positive test for human immunodeficiency virus, syphilis, toxoplasmosis, rubella, cytomegalovirus and varicella were excluded, as well as those who did not provide all necessary information for the development of the study and reported using the alarm clock on weekends.

Sample size

The sample size calculation were based on ANOVA, within-between interaction, with an effect size of 0.25, an alpha level of 0.05, 95% power, 3 groups, 3 measurements, a correlation between repeated measures of 0.5, and a non-sphericity correction ϵ of 1. Given these specifications, a total sample of 94 women was required. During the time of the study, 130 women in the first trimester of pregnancy were invited to participate. Thirty participants were excluded because they did not provide all necessary information (n = 25), or presented previous diseases (n = 3), or twin pregnancy (n = 2), obtaining a final sample of 100 pregnant women participants. The sample size required for this study was determined using the G*Power software version 3.1 (Faul et al., 2007).

Sociodemographic and health behaviors

An experienced team in sleep and nutrition studies applied a structured questionnaire regarding demographic characteristics such as age, occupation, level of education, previous pregnancy, gestational age and physical activity, resulting in three evaluations, in the first (≤13 weeks of pregnancy), second (20th to 26th week) and third trimester (30th to 37th week).

Sleep patterns

To determine sleep habits, the participants were asked to report usual bedtime, wake-up time, sleep-onset latency and usual sleep duration on weekdays and weekends during the pregnancy. The questions used in the survey were "What time have you been going to sleep on weekdays?"; "How many minutes on average do you stay awake in bed before you fall asleep after lights are turned off on weekdays?", "Did you use wake up with the help of someone or an alarm clock on weekdays?", "What time have you been waking up on weekdays?"; "What time have you been going to sleep on weekends?", "How many minutes on average do you stay awake in bed before you fall asleep after lights are turned off on the weekends?", "What time have you been waking up on weekends?" and "Did you use wake up with the help of someone or an alarm clock on weekends?".

To assess the sleep duration, the average of self-reported sleep duration, which considers weekdays and weekends, was computed using: [(Reported current weekday sleep duration x 5) + (Reported current weekend sleep duration x 2)]/7 (Reutrakul et al., 2014).

Social jetlag is defined as a behavioral indicator of circadian misalignment and was calculated based on the absolute difference between midsleep time – moment that individual reaches 50% of total sleep time – on weekdays and weekends (Wittmann et al., 2006).

Chronotype

Chronotype was derived using mid-sleep time on free days at the weekend (MSF) with a further correction for calculated sleep debt, which as calculated as the difference between average sleep duration on weekends and weekdays (Roenneberg et al., 2007). Participants who reported using the alarm clock on weekends were excluded.

Food intake evaluation

Dietary intake was assessed by three 24-Hour Dietary Recall (24HR) and evaluated in the first, second and third trimesters using the 5-stage multiple-pass interviewing technique (Conway et al., 2003). The first one was collected in the moment of the interview and the others two were carried out by telephone interviews, according to the technique used in the Vigitel Study (Brasil 2015). We instructed the volunteers to provide as much detail as possible on the food and drinks consumed the day before the

assessment, from the first to the last meal, including recipes for home-cooked foods and brand names. The three 24HR recalls were applied on nonconsecutive days, including one on the weekend. Portion sizes were estimated using food pictures of various portion sizes and common household measurements such as cups, glasses, bowls, teaspoons and tablespoons, in addition to individual food items/ units.

The 24HRs that showed implausible data with energy intakes of less than 500 kcal/ day or more than 3500 kcal/ day (Loy et al., 2017) were excluded and were not included in the calculations of average consumption. In this case, the plausible data of the other 24HRs of the participant were included in the analysis. The average consumption of the 3 days was used for analysis.

The software Dietpro®, version 5i, was used to calculate the nutrients of food intake and a Brazilian database (Brasil 2011) was preferentially used as a reference, followed by nutrients information from food labels and the United States Department of Agriculture (USDA) international nutrients database (United States Dietetic Association 2005).

The qualitative dietary assessment was performed using the BHEI-R (Previdelli et al., 2011), validated for the Brazilian population (Andrade et al., 2013). BHEI-R is based on the Healthy Eating Index 2005 (HEI-2005) developed for the American population (Guenther et al., 2008), with some adjustments (Previdelli et al., 2011). The BHEI-R is composed of 12 components: Total Fruit; Whole Fruit; Total Vegetables; Dark Green and Orange Vegetables and Legumes; Total Grains; Whole Grains; Milk and Dairy; Meat, Eggs and Legumes; Oils; Saturated Fat; Sodium; and SoFAAS (calories from solid fats, alcohol and added sugars) (Previdelli et al., 2011).

The number of daily servings was adjusted by the energy density (1000 cal/day). Depending on the component, scores can range from 0 (minimum) to 5, 10 or 20 (maximum) points. The maximum score is given for intake greater or equal to the portions recommended for the food groups, and zero for no intake. However, the proportion for the components Saturated Fat, Sodium and SoFAAS is inverse, that is., the higher the consumption the lower the score will be. The intermediary scores were calculated in accordance with the quantity consumed. The Total BHEIR is the sum of the scores of the components and can reach up to 100 points (Previdelli et al., 2011).

Time-related eating patterns

Time-related eating patterns were evaluated through the number of meals, eating duration and nightly fasting. The number of meals was determined by the number of caloric events ≥50 kcal/day with time intervals between meals of ≥15 min (Gibney and Wolever, 1997), reported in the 24HR. The time of the first and last meal was assessed through the 24HR. Eating duration was determined by the length, in hours, between the first and last caloric event in the 24HR (Gill and Panda, 2015). Night-fasting interval was determined by calculating the longest fasting interval between eating episodes from 19:00h to 06:59h (Loy et al., 2017). These variables were calculated from the average of the 24HR.

The distribution of energy and macronutrients throughout the day was evaluated by the percentage of total daily energy intake and the percentage of energy intake from protein, fat and carbohydrates segregated in four meal times: Morning (breakfast and mid-morning snacks), Lunch, Afternoon (afternoon snacks), and Evening (dinner and night-time snacks). To classify the types of meals or snacks (breakfast, mid-morning snacks, lunch, afternoon snacks, dinner and night-time snacks), we considered participants perceptions of the type of meal and/or snacks (Trancoso et al., 2010), and also analysed the type of food often consumed by the Brazilian population at every meal (Sato et al., 2010).

Meal-sleep relationships were assessed by the interval between the time of waking up and the time of the first food episode and the interval between the time of the last food episode and bedtime.

Anthropometric variables and adequacy of weight gain assessment

Weight was measured with a scale to an accuracy of 0.1 kg (Welmy®, São Paulo, Brazil). Height was measured to an accuracy of 0.1 cm using a stadiometer fixed to the wall (Welmy®). The height of the pregnant woman was measured only in the first evaluation and used over all other trimesters. Pre-pregnancy BMI (kg/ m²) was calculated and the pregnant was classified according to the BMI classification by the World Health Organization (WHO 2000): underweight (< 18.50 kg/ m²), normal weight (18.50 - 24.99 kg/ m²), overweight (25.00 - 29.99 kg/ m²) and obese (30.00 - 39.99 kg/ m²).

The current weight was measured over the three evaluations and the BMI was classified in accordance with the curve from Atalah et al., (1997) for the gestational age, according to the recommendations by WHO. The Institute of Medicine recommendation was used to assess weight gain during pregnancy (Institute of Medicine 2009): In the first

trimester the adequate weight gain range of 0.5 to 2 kg and mean 0.51; 0.42; 0.28 and 0.22 kg per week in the 2nd and 3rd trimester, for women who had pre-gestational BMI classified as underweight, normal weight, overweight and obese, respectively.

The adequacy of the weight gain was evaluated in each trimester by the following described steps: first, the recommended weight gain (Institute of Medicine 2009) in each trimester was calculated considering the number of gestational weeks corresponding to the interval between evaluations, except for the first trimester in which the recommended weight gain was considered in the range of 0.5 to 2 kg. Second, the weight gain in each trimester was evaluated using the current measured weight value subtracted from the value of the weight in the previous trimester, or pre-gestational weight in the case of the first trimester. Third, to evaluate the adequacy of the weight gain in the trimesters, the value of the weight gain in each trimester was divided by the value of the recommended weight gain. Values equal to 1 represent a weight gain equal to the recommended weight gain (Adequate), values greater than 1 represent a weight gain above the recommended amount (Excessive), and values lower than 1 represent a weight gain below the recommended amount (Insufficient).

Statistical analyses

Statistical analyses were performed using SPSS version 21.0 (SPSS Inc., Chicago, IL). Categorical data were shown as frequencies and percentages, while continuous data were shown as means and standard error. Significance level was set at 5%.

Generalized estimating equations (GEE) and generalized linear model (GzLM) analysis were performed for the different approaches of this study, which will be described separately below. In both tests, Gamma distribution was chosen considering the smaller Quasi Likelihood under Independence Model Criterion for GEE or Akaike Information Criterion for GzLM. All pairwise comparisons were performed by Sidak sequential test.

Division of the group into chronotype tertiles

Initially, the MSF of each trimester was calculated and GEE were used to analyze the effect of gestational trimester (independent variable) on MSF (dependent variable). The model was adjusted for age, marital status, schooling, work and body mass index. As the MSF did not change significantly over the pregnancy (first trimester (h:min): 04:14 ± 00:13; second trimester (h:min): 04:23 ± 00:12; and third trimestrer (h:min): 04:31 ±

00:12; p = 0.673), the mean of the three trimesters was determined and used to categorise the participants in tertils: first tertil (h:min): < 3:54; second tertil (h:min): ≥ 3:54 ≤ 4:36; and third tertil (h:min): > 4:36. The classification of chronotype using tertiles has been proposed by some authors (Vetter et al., 2011; Vetter et al., 2012; Juda et al., 2013; Felden et al., 2016; Oliveira et al., 2020), since there may be particularities inherent to the different sample studied and the cutoff points previously defined in the literature may not be adequate for the study sample.

Maternal characteristics

GzLM was performed to analyze the mean differences on age, pre-pregnancy weight, pre-pregnancy BMI and current BMI (dependent variables) according to chrontype groups (independent variable) for continuous variables. All analyses were adjusted for age. Pearson chi-square test was used for categorical variables.

Effect of chronotype and gestational trimester on chronobiological, nutritional and anthropometric variables

GEE were used to analyze the effect of chronotype groups and gestational trimester (independent variables) and its interaction on sleep patterns, social jetlag, energy and macronutrient intakes and distribution (total of the day and at each meal), meal time, number of eating episodes, eating duration, night-fasting, scores of the total BHEI-R and weight gain during pregnancy (dependent variables). A GEE model was performed for each dependent variable. All models were adjusted for age, marital status, schooling, work, physical activity and body mass index.

RESULTS

Maternal characteristics according to the groups are presented in Table 1. The pregnant women in the first and second tertile group were older compared to the third tercile. For the other variables analysed, no differences were found between the groups (Table 1).

Table 1: Socio-demographic data, lifestyle and anthropometry of pregnant women during pregnancy (n = 100/ each trimester).

Variables	All women (n=100) Mean ± SD or n (%)	Chronotype 1st Tertile (n =32) Mean ± SD or n (%)	2nd Tertile (n =35) Mean ± SD or n (%)	3rd Tertile (n =33) Mean ± SD or n (%)	p-value
Age, years	27.72 ± 5.61	29.05 ± 5.65[a]	28.10 ± 5.35[ac]	26.02 ± 5.46[b]	**<0.001**
Work					
1st trimester	56% (56.0%)	21 (6.72%)	19 (6.65%)	16 (5.28%)	0.368
2nd trimester	44% (44.0%)	17 (5.44%)	15 (5.25%)	12 (3.96%)	0.251
3rd trimester	43% (43.0%)	17 (5.44%)	16 (5.60%)	10 (3.30%)	0.192
Marital status					
Married or live with a partner	79 (79.0%)	26 (8.32%)	30 (10.5%)	23 (7.59%)	0.272
Single	21 (21.0%)	6 (1.92%)	5 (1.75%)	10 (3.30%)	
Schooling					
Basic education complete/ not complete	5 (5.0%)	3 (0.96%)	2 (0.70%)	0 (0.0%)	0.308
High school education complete/ not complete	68 (68.0%)	18 (5.76%)	24 (8.40%)	26 (8.58%)	
Higher education complete/ not complete	27 (27.0%)	11 (3.52%)	9 (3.15%)	7 (2.31%)	
Physical activity (no)					
1st trimester	83 (83.0%)	25 (8.00%)	32 (11.2%)	26 (8.58%)	0.257
2nd trimester	79 (79.0%)	23 (7.36%)	29 (10.15%)	27 (8.91%)	0.484
3rd trimester	80 (80.0%)	24 (7.68%)	29 (10.15%)	27 (8.91%)	0.688

Anthropometric variables:

Pre-pregnancy weight (kg)	65.49 ± 12.83	66.12 ± 1.27	65.77 ± 1.20	64.59 ± 1.22	0.660
Pre-gestational BMI (kg/ m²)	24.25 ± 4.30	24.77 ± 0.43	24.22 ± 0.41	23.77 ± 0.42	0.260
Underweight	6 (6.0%)	1 (0.32%)	0 (0.00%)	5 (1.65%)	0.211
Normal weight	57 (57.0%)	19 (6.08%)	21 (7.35%)	17 (5.61%)	
Overweight	24 (24.0%)	6 (1.92%)	12 (4.20%)	6 (1.98%)	
Obesity	13 (13.0%)	6 (1.92%)	2 (0.70%)	5 (1.65%)	
Current BMI (kg/m2)					
1st trimester	24.80 ± 0.44	25.29 ± 0.82	24.60 ± 0.61	24.53 ± 0.87	0.138
2nd trimester	26.65 ± 0.45	26.94 ± 0.81	26.70 ± 0.68	26.34 ± 0.87	
3rd trimester	28.98 ± 0.44	28.82 ± 0.80	29.28 ± 0.67	28.82 ± 0.82	

Note: Pearson chi-square test was used to compare proportion variables. Generalized Linear Models (GLzM) and Generalized Estimating Equations model. Adjusted to age, marital status, schooling and work. Significant associations shown in bold. Sidak test: different letters represent statistical difference in pairwise comparisons, p-value < 0.05. Values are presented as mean and SE (standard error) or n (%). BMI= body mass index. Physical activity (no): shows pregnant women who did not perform physical activity.

The effect of the chronotype on gestational averages of variables related to sleep patterns and social jetlag are shown in Table 2. Pregnant women in the first tertile slept earlier both during the week and on weekends when compared to second and third tertile. Also, first tertile pregnant women woke up earlier than second and third tertile during the week and woke up earlier than third tertil on weekends. Pregnant women in the first tertile group slept less than pregnant women in the third tertile during the week and slept more than pregnant women in the second tertile during the weekend (Table 2). In addition, a lower SJL was found among first tertile pregnant women when compared to the second tertil pregnant women (Table 2).

Table 2. Effect of chronotype on sleep patterns and social jetlag during pregnancy (Total gestational data's values -represent the average of the three trimesters-, n=100/ each trimester).

Dependents variables	Chronotype			Tests of Model Effects		
	1st Tertile (n =32)	**2nd Tertile (n =35)**	**3rd Tertile (n =33)**			
	Mean ± Std. Error	Mean ± Std. Error	Mean ± Std. Error	Wald chi-square	Df	Sig.
Sleep patterns and circadian data						
Week sleep time (h:min)	22:23 ± 00:08[a]	22:55 ± 00:09[bc]	23:07 ± 00:09[c]	12.564	2	**0.002**
Week awake time (h:min)	06:36 ± 00:06[a]	07:07 ± 00:08[b]	08:24 ± 00:13[c]	56.228	2	**<0.001**
Mean week sleep duration (h)	08.21 ± 0.18[a]	8.19 ± 0.17[a]	9.29 ± 0.18[b]	23.849	2	**<0.001**
Weekend sleep time (h:min)	23:00 ± 00:09[a]	24:07 ± 00:05[bc]	24:21 ± 00:06[c]	45.671	2	**<0.001**
Weekend awake time (h:min)	08:10 ± 00:12[a]	08:30 ± 00:04[a]	09:37 ± 00:09[b]	49.487	2	**<0.001**
Mean weekend sleep duration (h)	9.16 ± 0.22[a]	8.36 ± 0.11[b]	9.26 ± 0.13[ac]	27.714	2	**<0.001**
Social jetlag (h)	0.95 ± 0.10[a]	1.19 ± 0.09[ab]	1.46 ± 0.12[b]	9.213	2	**0.010**

Note: Generalized Estimating Equations model. Adjusted to age, marital status, schooling, work, physical activity and body mass index. Significant associations shown in bold. Sidak test: different letters represent statistical difference in pairwise comparisons, p-value < 0.05.

Table 3 shows the effect of chronotype on total energy and macronutrients intakes, meal and snack times and time-related eating patterns during pregnancy. The pregnant women in the first and second tertile consumed breakfast earlier when compared to the third tertile. Also, pregnant women and first tertil pregnant women had a higher eating duration compared to second and third tertile. Pregnant women of the first tertile presented a smaller interval (hours) between the last meal and sleep onset than third tertil pregnant women (Table 3).

Table 3. Effect of chronotype on total energy and macronutrients intakes, meal and snack times and time-related eating patterns during pregnancy (Total gestational data's values -represent the average of the three trimesters-, n=100/ each trimester).

Dependents variables	Chronotype			Tests of Model Effects		
	1st Tertile (n =32)	2nd Tertile (n =35)	3rd Tertile (n =33)			
	Mean ± Std. Error or n (%)	Mean ± Std. Error or n (%)	Mean ± Std. Error or n (%)	Wald chi-square	Df	Sig.
Total energy and macronutrients intake						
Total Energy (kcal)	1676.50 ± 61.60	1628.89 ± 68.79	1648.94 ± 60.01	0.275	2	0.871
Protein (g)	69.41 ± 3.29	65.96 ± 3.03	68.58 ± 2.72	0.684	2	0.710
Fat (g)	66.06 ± 2.95	61.16 ± 2.94	62.77 ± 2.93	1.453	2	0.484
Carbohydrate (g)	200.39 ± 7.25	203.80 ± 8.9	202.33 ± 7.55	0.093	2	0.955
Meal and snack times						
Breakfast (h:min)	08:02 ± 00:06[a]	08:21 ± 00:06[a]	08:52 ± 00:07[b]	23.077	2	**<0.001**
Mid-morning snacks (h:min)	09:58 ± 00:06	10:00 ± 00:04	10:08 ± 00:06	1.463	2	0.481
Lunch (h:min)	12:17 ± 00:04	12:09 ± 00:03	12:24 ± 00:04	5.881	2	0.053
Afternoon snacks (h:min)	16:14 ± 00:04	16:04 ± 00:05	16:18 ± 00:06	3.187	2	0.203
Dinner (h:min)	20:09 ± 00:06	19:49 ± 00:05	20:00 ± 00:07	5.409	2	0.067
Night-time snacks (h:min)	21:52 ± 00:09	22:13 ± 00:07	22:27 ± 00:18	3.926	2	0.140
Time-related eating patterns						
Number of eating episodes	4.79 ± 0.12	4.73 ± 0.09	4.61 ± 0.12	1.006	2	0.605
Eating Duration (h)	12.12 ± 0.15[a]	11.31 ± 0.21[bc]	11.24 ± 0.27[c]	12.841	2	**0.002**

Night-fasting (h)	10.29 ± 0.15	10.36 ± 0.15	9.94 ± 0.18	3.226	2	0.183
Midpoint caloric (h:min)	14:06 ± 00:13	14:31 ± 00:15	14:28 ± 00:14	1.907	2	0.385
Interval sleep end - first meal (h:min)	01:37 ± 00:09	01:59 ± 00:12	01:28 ± 00:10	4.145	2	0.126
Interval last meal - sleep onset (h:min)	02:12 ± 00:08[a]	02:43 ± 00:08[ab]	02:33 ± 00:09[b]	6.026	2	**0.049**
Pregnant women skipping breakfast						
1st trimester	1 (0.32%)	3 (1.05%)	2 (0.66%)	-	-	0.625
2nd trimester	0 (0.0%)	3 (1.05%)	3 (0.99%)	-	-	0.223
3rd trimester	0 (0.0%)	5 (1.05%)	2 (0.66%)	-	-	0.070
Pregnant women eating after dinner						
1st trimester	10 (3.20%)	13 (4.55%)	9 (2.97%)	-	-	0.623
2nd trimester	7 (2.24%)	11 (3.85%)	15 (4.95%)	-	-	0.154
3rd trimester	8 (2.56%)	6 (2.10%)	14 (4.62%)	-	-	0.061

Note: Pearson chi-square test was used to compare proportion variables. Generalized Estimating Equations model. Adjusted to age, marital status, schooling, work, physical activity and body mass index. Significant associations shown in bold. Sidak test: different letters represent statistical difference in pairwise comparisons, p-value < 0.05.

Table 4 shows the effect of chronotype on scores of the total BHEI-R and its components during the pregnancy. The first tertile showed a better diet quality in terms of milk and dairy (first tertile > second tertile) and saturated fat (first tertile < second tertile). No differences were found between groups for the scores of the total BHEI-R and other components (Table 4).

Table 4. Effect of chronotype on scores of the total Brazilian Healthy Eating Index-Revised (BHEI-R) and its components during pregnancy (Total gestational data's values -represent the average of the three trimesters-, n=100/ each trimester).

Dependents variables	Chronotype			Tests of Model Effects		
	1st Tertile (n =32)	2nd Tertile (n =35)	3rd Tertile (n =33)			
	Mean ± Std. Error	Mean ± Std. Error	Mean ± Std. Error	Wald chi-square	Df	Sig.
Components of the BHEI-R (min.− max.)						
Total Fruit* (0–5)	3.17 ± 0.19	2.77 ± 0.17	2.84 ± 0.17	2.706	2	0.259
Whole Fruit† (0–5)	3.14 ± 0.19	3.11 ± 0.20	3.10 ± 0.22	0019	2	0.991
Total Vegetables‡ (0–5)	2.96 ± 0.14	3.17 ± 0.17	3.02 ± 0.15	0.881	2	0.644
Dark Green and Orange Vegetables and Legumes‡ (0–5)	2.29 ± 0.14	2.30 ± 0.19	2.27 ± 0.14	0.016	2	0.992
Total Grains§ (0–5)	4.36 ± 0.09	4.44 ± 0.07	4.35 ± 0.09	0.638	2	0.727
Whole Grains (0–5)	0.38 ± 0.07	0.25 ± 0.08	0.40 ± 0.10	1.334	2	0.513
Milk and Dairy‖ (0–10)	5.01 ± 0.27[a]	3.88 ± 0.034[b]	4.52 ± 0.31[ab]	6.116	2	**0.047**
Meat, Eggs and Legumes (0–10)	7.95 ± 0.24	7.64 ± 0.21	7.54 ± 0.27	1.408	2	0.495
Oils¶ (0–10)	9.81 ± 0.10	9.76 ± 0.10	9.68 ± 0.12	0.586	2	0.746
Saturated Fat (0–10)	5.68 ± 0.27[a]	6.92 ± 0.21[b]	6.63 ± 0.32[ab]	12.042	2	**0.002**
Sodium (0–10)	5.91 ± 0.21	5.25 ± 0.23	5.42 ± 0.24	4.834	2	0.089
Calories from SoFAAS (0–20)	10.39 ± 0.51	10.59 ± 0.49	11.05 ± 0.55	0.787	2	0.675
Total BHEI-R (0–100)	61.28 ± 0.82	60.26 ± 0.86	61.02 ± 1.10	0.766	2	0.682

Note: BHEI-R: Brazilian Healthy Eating Index-Revised. SoFAAS: Solid Fats, Alcoholic beverages, and Added Sugars. *All fruit including fruits and fruit juice; †All fruit excluding fruit juice; ‡Legumes counted as vegetables only after Meat, Eggs and Legumes standard is met; §Total grain: cereals, roots, and tubers; ‖Includes milk and other dairy products and soy-based beverages; ¶Includes monounsaturated and polyunsaturated fats, oils from oilseeds, and fat in fish. Generalized Estimating Equations model. Adjusted to age, marital status, schooling, work, physical activity and

body mass index. Significant associations shown in bold. Sidak test: different letters represent statistical difference in pairwise comparisons, p-value < 0.05.

We also analyzed the effect of the chronotype on the energy and macronutrients distribution throughout the day. Pregnant women in the first tertile consumed more energy in the afternoon snack than those in the second tertile, and less energy at dinner than those in the second and third tertile. In addition, pregnant women in the first tertile consumed more carbohydrate in the afternoon snack when than those in the second tertile and less carbohydrates at dinner than those in the second and third tertile. No differences were found in the distribution throughout the day for protein and fat (Figure 1).
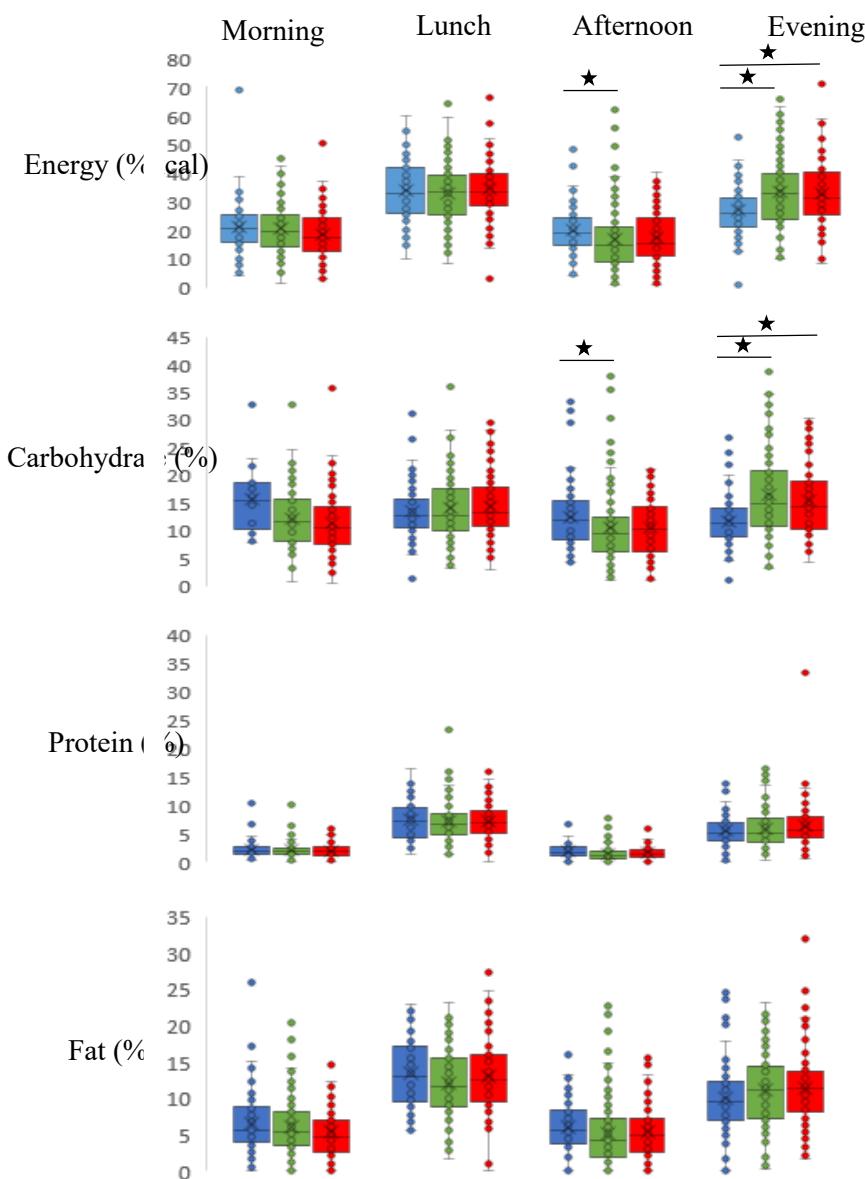

Figure 1. Effect of chronotype on distribution of energy and macronutrients throughout the day (total gestational data's values represent the average of the three trimesters; n=100/ each trimester).

Note: Generalised Estimating Equations model. Adjusted to age, marital status, schooling, work, physical activity and body mass index. Significant Tests of Model Effects showed in bold. Significant associations shown in bold. Sidak test: same symbols represent statistical difference in pairwise comparisons, p-value < 0.05.
Number of pregnant women who had a meal n (%): Morning: first tertile = 94; second tertile: 91; third tertile: 92; Lunch: first tertile = 94; second tertile: 99; third tertile: 98; Afternoon: first tertile = 89; second tertile: 97; third tertile: 89; Night: first tertile = 92; second tertile: 101; third tertile: 99. *Statistical significance, p<0.05

Figure 2 shows the effect of chronotype in the gestational trimesters on adequacy of weight gain during pregnancy. Despite the tendency for all tertiles to gain excess weight during pregnancy, we found differences on this variable between each chronotype tertile. Comparisons between tertiles show that pregnant women in the second and third tertiles gained more excessive weight in the third trimester when compared to those in the first tertile (2.03 ± 0.15 and 2.24 ± 0.25, respectively, versus 1.22 ± 0.14, $p < 0.001$). In addition, pregnant women from the second tertile gained more excessive weight from the first to the third trimester (1.17 ± 0.10 versus 2.03 ± 0.15, respectively) and pregnant women from the third tertile gained more excessive weight from the second to third trimester (1.20 ± 0.10 versus 2.24 ± 0.25, respectively).
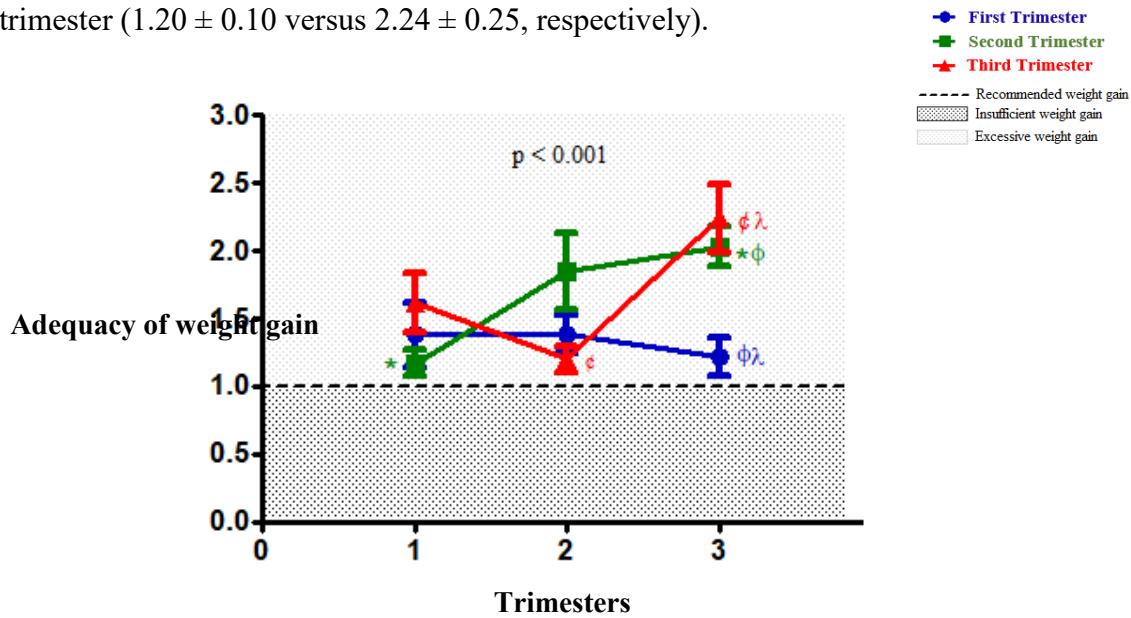

Figura 2. Effect of chronotype in the gestational trimesters on adequacy of weight gain during pregnancy (n = 100/ each trimester).

Note: Generalized Estimating Equations model. Adjusted to age, marital status, schooling, work, physical activity and body mass index. Sidak test: same symbols represent statistical difference in pairwise comparisons, p-value < 0.05.

DISCUSSION

In our best knowledge this is the first cohort study to analyze the effect of chronotype on dietary patterns during pregnancy. Our results indicate that pregnant women with MSF values indicative of eveningness have breakfast later and have a poorer diet quality obtained by BHEI-R. These 'evening' pregnant also have a higher energy and carbohydrate intake at dinner when compared to those 'morning' women. Also, we found that pregnant women with a tendency to eveningness had a worse adequacy of gestational weight gain in the third trimester. These results partially confirm our hypothesis that pregnant women with a tendency to eveningness present a higher energy intake at night and an excessive weight gain during pregnancy compared to pregnant woman with tendency to morningness.

Evidence have suggested that eveningness is associated with metabolic diseases (Reutrakul et al., 2013), particularly obesity (Culnan et al., 2013; Lucassen et al., 2013; Yu et al., 2015; Türkoğlu et al., 2019). According to studies from the chrononutrition area, some unhealthy eating behavior are more common among evening types, such as regularly skip breakfast (Sato-Mito et al., 2011b; Reutrakul et al., 2014; Roßbach et al., 2017; Teixeira et al., 2018), present a higher consumption of sugar (Yu et al., 2020; Xiao et al., 2019), meat (Maukonen et al., 2016; Fleig et al., 2009), sweet beverage (Li et al., 2018; Yoshizaki et al., 2018), noodles (Sato-Mito et al., 2011a), caffein (Arora et al., 2014; Fleig et al., 2011), fast food (Yu et al., 2020; Fleig et al., 2011), chocolate (Kanerva et al., 2012) and a higher energy intake at later time of the day and at night and (Lucassen et al., 2013; Teixeira et al., 2018; Xiao et al., 2018; Teixeira et al., 2018). These habits have been pointed as an important route for the association between chronotype and excessive weight (Mota et al., 2016; Teixeira et al., 2018). Interestingly, a recent review proposed by Mazri et al., (2020) on this topic found that the most reported association between eating behaviour and chronotype in the studies was in terms of meal timing. This is because evening individuals, although usually perform fewer meals, have postpone the mealtime throughout the day, which culminates in a high nocturnal food intake (Muñoz et al., 2017; Suh et al., 2017).

Our study found a greater energy and carbohydrate distribution in the evening meals among pregnant women with a tendency to evening compared to pregnant women with a tendency to morning, which corroborates with Reutrakul et al., (2013). It is already known that a lower energy distribution (Loy et al., 2016) and, more specifically, a

reduction in the distribution of carbohydrates at night during pregnancy could benefit glycemic control during this period (Chandler-Laney et al., 2016; Loy et al., 2016). Studies on this topic conducted with non pregnant women have showed that nocturnal eating may result in metabolic disruption (Knutsson et al., 2002; Holmbäck et al., 2003; Fonken et al., 2010), obesity (Wang et al., 2014) and an increased risk of type 2 diabetes (Park et al., 2013). A possible explanation to these unfovarables factors is that meals can work as a *zeitgeber*, synchronizing peripheral clocks (Vieira et al., 2014; Schibler et al., 2015; Froy et al., 2018). Thus, the eating meals during night periods could impact the circadian alignment (Wehrens et al., 2017). Moreover, the fasting period during the night seems to have an important role on circadian rhythms, besides stimulating fat metabolism and the metabolic switch between glucose and fat oxidation (Paoli et al., 2019). In summary, the fat oxidation is lower at night compared to morning (Gluck et al., 2011; Hibi et al., 2013), since energy metabolism is less efficient at night (Romon et al., 1993; Fong et al., 2017). In this way, the thermogenesis induced by the morning diet is significantly higher when compared to the evening ones (Romon et al., 1993; Morris et al., 2015). In addition, there is a reduced sensitivity to nighttime insulin (Reutrakul and Van Cauter 2014), which can lead to metabolic overload if food intake occurs overnight.

Another explanation for the relationship between eating at night, as usual by evening types individuals, and metabolic damage, is that eating at night can also lead to increased intake, partly due to an insufficient satiety function (Oike et al., 2014). In this sense, evidence suggests that eating late at night can have adverse effects on body weight and health (Thompson et al. 2006; Park et al. 2013; Wang et al. 2014; Fong et al. 2017). Studies have also pointed that eating at night tends to delay bedtime, reducing sleep time, which is considered a risk factor for obesity (Hasler et al., 2004; Gangwisch et al., 2005; Patel et al., 2006). In this sense, it is already well documented that eveningness is associated with sleep deprivation (Merikanto et al., 2012; Roepke and Duffy 2010). In addition, other studies (Garaulet et al. 2013; Lucassen et al., 2013; Ruiz-Lozano et al., 2016a; Gangwar et al., 2018; Nimitphong et al., 2018; Teixeira et al., 2018) found that individuals with a tendency to eveningness present the habit to consume breakfast later when compared to individuals with a morningness tendency. This behavior may be due to the habit of going to bed later, which leads to morning awakening and breakfast time later, which could also favor the redistribution of energy and macronutrient intake to the end of the day and for the night, even leading to a greater omission of breakfast, which is

more frequent among late chronotypes (Meule et al., 2012; Dashti et al., 2015; Crispim e Mota, 2018).

Interestingly, not only eat late has been seen a risk factor for health, but also eat early has been shown to be a protective factor (Murakami et al., 2018; Sato-Mito et al., 2011a). A study carried out with non-pregnant populations showed that individuals who have their first food episode earlier may feel less rushed and, therefore, probably consume a more adequate meal in terms of quality and quantity (Murakami et al., 2018). This morning eating pattern can lead to better satiety and hunger control throughout the day (Jakubowicz et al., 2012), resulting in less food consumption at night. Our study found a better diet quality for the milk and dairy components among pregnant women with a greater tendency to morningness than those classified in the second tertile, which was also observed by Sato-Mito et al., (2011a). This result was probably due to the higher intake of dairy products in this group, which are commonly eaten for breakfast in the Brazilian dietary pattern (Brasil, 2014; Pereira et al., 2017). Due to the fact that breakfast is considered protective habit to prevent obesity (Garaulet et al., 2013; Jakubowicz et al., 2013; Ruiz-Lozano et al., 2016b), optimizing metabolic and endocrine regulation (Astbury et al., 2011; Reutrakul et al., 2014) and promote better diet quality (Matthys et al., 2006), it is important that evening types should be educated about the importance of this meal.

All of the aforementioned factors capable of leading to metabolic and nutritional changes as a result of nocturnal intake may supposedly justify the results of that study in which pregnant women with a tendency to eveningness had excessive weight gain in the third trimester when compared to pregnant women with a tendency to morningness. These results corroborate with our previous study that demostrated an excessive weight gain during pregnancy related to evening chronotype (Teixeira et al., 2019). Gontijo et al., (2019) also found that pregnant women with higher energy intake at night had higher excessive weight gain than pregnant with a lower night energy intake, which could be justified by the chronotype variability between the group. Also, Teixeira et al., (2019) found that pregnant women who tend to eveningness are more likely to gain weight in the early gestational period. These results should encourage future studies that can prove the harmful effect of nighttime eating on weight gain during pregnancy.

Our study also found that pregnant women with tendency to mornigness had a longer eating duration. Although a long eating duration has been associated with negative health aspects such as to higher risks of metabolic diseases (Gill and Panda, 2015) and an

impact at homeostasis, and consequently lead to mistimed responses of food anticipatory activities (Johnston, 2014), there is a limited evidence regarding the relationship between chronotype and eating duration (Mazri et al., 2020). In the present study, longer eating duration is related to eat breakfast earlier, since the time of the last meal did not differ between groups. Our study also analized the hour interval between last meal and sleep onset and founded that pregnant women with tendency to morningness had a smaller hour interval between these two variables compared to pregnant women with eveningness tendency. We believe that this result is a consequence of bedtime of pregnant women with morningness tendency, since their bedtime during the week and on weekend was earlier compared to the pregnant women with eveningness tendency. Although the sleep/ wake, fasting/ eating and dark/ light cycles occur in parallel and influence each other, it is expected that eating and sleeping behavior occur at different moments, aligned with light and dark periods, respectively. When such overlap does occur, it typically takes the form of night eating (Veronda et al., 2020).

As a strong point of our study we have the longitudinal design, allowing us to evaluate the intra-individual variation and the response behavior over time. Nevertheless, it is also essential to highlight the limitations of this study. Some evaluations were done using questionnaires, which despite being validated instruments and widely used in literature studies, may be influenced by the memory and cooperation of volunteers and lead to erros. However, to obtain accurate data, respondents were trained before participating in the survey and our team has been highly trained to aplicar os validated questionnaires. Another limitation of our study is that our analysis was performed with only 100 pregnant women who had regular appointments in the public health system, and the generalization of the results for all pregnant women cannot be done, especially in high-risk pregnant women. Despite these limitations, we expect that the results of the present study can improve the understanding of the association between eating behaviour and chronobiological variables during pregnancy. However, the need for further studies on this subject is evident.

In conclusion, pregnant women with a tendency to evening consume breakfast later in the day and present a greater consumption of energy and carbohydrates in the evening, as well as a worse standard of gestational weight gain in the third trimester. These data showed that chronotype is strongly related to eating patterns during pregnancy. Further studies are needed to understand whether chronotype significantly mediates an influence of eating timing and patterns on weight gain during pregnancy. If

the results of the present study are confirmed, it may improve the effectiveness of nutritional interventions in prenatal care for promoting maternal-fetal health.

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AUTHORSHIP: The authors' responsibilities were as follows: L.C.T.B., C.A.G., W.M.F., C.A.C., and Y.C.P.M. conceptualized and designed the study; L.C.T.B., C.A.G., G.P.T., Y.C.P.M. and W.M.F. collected the data; L.C.T.B., C.A.G., L.P.M., C.A.C., and Y.C.P.M. analysed and interpreted the data; L.C.T.B. wrote the initial manuscript; L.C.T.B., C.A.G., L.P.M., G.P.T., W.M.F., C.A.C., and Y.C.P.M. reviewed the manuscript and approved the final manuscript.

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CONCLUSÕES

A partir das análises longitudinais conduzidas pelo presente estudo foi possível concluir que o JLS é prevalente durante todos os trimestres gestacionais. Também encontramos uma associação positiva entre JLS e IMC pré-gestacional no terceiro trimestre. Gestantes com peso normal diminuíram o JLS do segundo para o terceiro trimestre, reforçando que o JLS está relacionado ao excesso de peso pré-gestacional (Artigo 1). Além disso, gestantes com tendência à vespertinidade apresentaram um consumo do café da manhã mais tardio e um maior consumo de energia e carboidratos à noite, além de um pior padrão de ganho de peso gestacional no terceiro trimestre (Artigo 2).

Estes resultados, se forem confirmados em estudos futuros, poderão melhorar a eficácia das intervenções nutricionais no pré-natal, o que enfatiza a importância de se considerar as variáveis cronobiológicas nas diretrizes nutricionais do pré-natal para promover a saúde materno-fetal.

PERSPECTIVAS

Como perspectiva, pretende-se realizar análises adicionais e elaborar artigos com os seguintes objetivos:

- Estudar as associações entre JLS e os padrões alimentares, ingestão e distribuição de energia e macronutrientes durante o período gestacional.

- Estudar a associação entre *jetlag* alimentar e ganho de peso ao longo da gestação.

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ANEXOS

ANEXO A - Comprovante de aprovação do projeto de pesquisa pelo Comitê de Ética em Pesquisa (CEP).

UFU — Comitê de Ética em Pesquisa

UNIVERSIDADE FEDERAL DE UBERLÂNDIA/MG

Plataforma Brasil

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: INFLUÊNCIA DO TRABALHO EM TURNOS E DA QUALIDADE DA DIETA NO PERÍODO GESTACIONAL SOBRE OS DESFECHOS GRAVÍDICOS

Pesquisador: Yara Cristina de Paiva Maia

Área Temática:

Versão: 2

CAAE: 43473015.4.0000.5152

Instituição Proponente: Faculdade de Medicina

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 1.199.829

Situação do Parecer:
Aprovado

Endereço: Av. João Naves de Ávila 2121- Bloco "1A", sala 224 - Campus Sta. Mônica
Bairro: Santa Mônica   **CEP:** 38.408-144
UF: MG   **Município:** UBERLANDIA
Telefone: (34)3239-4131   **Fax:** (34)3239-4335   **E-mail:** cep@propp.ufu.br

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APÊNDICES

APÊNDICE A – Termo de consentimento livre e esclarecido (TCLE).

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Você está sendo convidado (a) para participar da pesquisa intitulada **"Influência do trabalho em turnos e da qualidade da dieta no período gestacional sobre os desfechos gravídicos"**, sob a responsabilidade dos pesquisadores: Yara Cristina de Paiva Maia, Cristiana Araújo Gontijo e Laura Cristina Tibiletti Balieiro. Nesta pesquisa nós pretendemos descreve a influência do trabalho em turnos e da qualidade da dieta no período gestacional sobre os desfechos gravídicos em gestantes atendidas na rede pública de saúde da cidade de Uberlândia, MG. O Termo de Consentimento Livre e Esclarecido (TCLE) será obtido pela pesquisadora Cristiana Araújo Gontijo, Laura Cristina Tibiletti Balieiro e Bruna Borges Macedo no momento da apresentação do estudo que será realizado no momento da consulta pré-natal, no primeiro, segundo e terceiro trimestre gestacional.

Na sua participação você fornecerá informações sobre: Condição socioeconômica; Trabalho em Turno; Identificação do Cronotipo; Avaliação Antropométrica (peso, estatura, índice de massa corporal, ganho de peso); Recordatório Alimentar de 24 horas; Questionário de Frequência Alimentar; Nível de atividade física habitual; Intercorrências Durante a Gestação; Avaliação Clínica durante a Gestação; Escala de Sonolência de Epworth; Índice de Qualidade do Sono de Pittsburgh; e dados do prontuário médico, como: cistite, presença de doenças crônicas, hipotireoidismo gestacional, prematuridade, restrição de crescimento intrauterino, abortamento, sangramentos, descolamento prematuro de placenta, alteração do líquido amniótico, edema gestacional, idade gestacional da ocorrência do parto, tipo de parto, exames bioquímicos (dosagem de hemoglobina e hematócrito, glicemia em jejum, teste de tolerância oral de glicose) e pressão arterial. Além das seguintes informações sobre os bebês: peso e comprimento ao nascer, Apgar, má-formações e aleitamento materno na alta hospitalar.

Em nenhum momento você será identificado. Os resultados da pesquisa serão publicados e ainda assim a sua identidade será preservada. Você não terá nenhum gasto e ganho financeiro por participar na pesquisa. Os riscos consistem em constrangimento ("vergonha") para medição de peso e estatura e responder aos questionários, mas serão tomados todos os cuidados para se evitar qualquer ocorrência deste tipo. Existindo ainda, a possibilidade remota de sua identificação, porém todos os procedimentos serão tomados para preservar seu anonimato, sendo os nomes substituídos por códigos. Além disso, por necessitar de uma disponibilidade do tempo do indivíduo, pode causar desconforto. O benefício será a descrição da influência do trabalho em turnos e da qualidade da dieta no

período gestacional sobre os desfechos gravídicos em gestantes atendidas na rede pública de saúde da cidade de Uberlândia, MG.

Você é livre para deixar de participar da pesquisa a qualquer momento sem nenhum prejuízo ou coação. Uma cópia deste TCLE ficará com você. Qualquer dúvida a respeito da pesquisa, você poderá entrar em contato com:

Yara Cristina de Paiva Maia. Professor Adjunto I, Curso de Nutrição, Faculdade de Medicina, Universidade Federal de Uberlândia. Endereço: Avenida Pará, 1720- Bloco 2U, Sala 20, *Campus* Umuarama. Fones: 3218-2084. Cristiana Araújo Gontijo. Curso de Nutrição, Faculdade de Medicina, Universidade Federal de Uberlândia/ Laura Cristina Tibiletti Balieiro. Curso de Nutrição, Faculdade de Medicina, Universidade Federal de Uberlândia.

Poderá também entrar em contato com o Comitê de Ética na Pesquisa com Seres-Humanos – Universidade Federal de Uberlândia: Av. João Naves de Ávila, nº 2121, bloco 1A, sala 224, Campus Santa Mônica – Uberlândia –MG, CEP: 38408-100; fone: 34-32394131.

Uberlândia,_____de_____de 201__.

_____
Prof. Dr(a) Yara Cristina de Paiva Maia
Coordenadora

_____
Cristiana Araújo Gontijo
Nutricionista/ Doutoranda

_____
Laura C. Tibiletti Balieiro
Nutricionista/ Mestranda

Eu aceito participar do projeto citado acima, voluntariamente, após ter sido devidamente esclarecido.

_____
Participante da pesquisa

APÊNDICE B – Instrumento de coleta de dados, Questionário de avaliação.

Questionário de Avaliação

Data nascimento: ___/___/___   Idade: _____
Idade da menarca:_____   Apresenta ciclos menstruais regulares:_____
DUM: ___/___/___   DPP: ___/___/___
IG DUM: _____   IG 1ª USG: _____

Gestações anteriores: (   ) Não   (   ) Sim, quantas: _____
Intercorrências obstétricas ou gestacionais anteriores:
_____
Intercorrências gestacionais atuais:
_____

Antecedentes pessoais:

Você tem ou teve alguma destas doenças citadas abaixo:

DOENÇA	SIM	Tempo	
Diabetes (Tipo)			
Dislipidemias			
Hipertensão arterial			
Doença Cardiovascular			
Câncer			
Doença da Tireóide - Especificar:			
Outras			

Condição socioeconômica
Estado civil: Você é:
___Casada ___Mora com companheiro   ___Solteira   ___Viúva
___Separada/ divorciada

Escolaridade: Até que ano da escola você completou? _____

Núcleo familiar: Quantas pessoas moram na sua casa, incluindo você?
Quantos são crianças, menores de 5 anos? _____

Das pessoas que moram em casa, quantas trabalham? _____

Estilo de Vida

Você <u>fuma ou já fumou</u>?

_____Sim (ler as alternativas)   _____Não, nunca fumou (Pular para questão x)

Situação da fumante:

___Você fumava antes da gestação e continua fumando. Quantos cigarro(s) por dia?___

___Você fumava antes da gestação e parou. Quantos cigarro(s) por dia?____

___Você não fumava antes da gestação e passou a fumar na gestação. Quantos cigarro(s) por dia? _____

Você consume ou consumia <u>bebida alcoólica</u>:

_____Sim (ler as alternativas) _____Não, nunca bebeu (Pular para próxima questão)

Situação do consumo:

___Você bebia antes da gestação e continua bebendo.

___Você bebia antes da gestação e parou.

___Você não bebia antes da gestação e passou a beber na gestação.

Quantidade, frequência e qual bebida:

Você teve algum desses sintomas nesta gestação?

Azia __sim __não. Se sim, quantas vezes você apresentou azia no último mês? _____

Enjoo/Náusea __sim __não. Se sim, quantas vezes você apresentou náusea no último mês? _____

Vômito __sim __não. Se sim, quantas vezes você apresentou vômito no último mês? _____

Desejo de alimento especial __sim __não. Se sim, quantas vezes ocorreu no último mês? _____

Desejo de comer coisas que não são alimentos, como giz, terra? ___sim ___não

Se sim, quantas vezes você ocorreu no último mês? _____

<u>Uso de suplementos:</u>

Você está fazendo uso de suplementos:(   ) Não   (   ) Sim:

Se sim, qual:_____Dosagem: _____Frequência:

<u>Uso de medicamentos:</u>

Você está fazendo uso de medicamento:(   ) Não   (   ) Sim:

Se sim, qual:_____Dosagem: _____Frequência:

<u>Atividade</u>:

Atividade Profissional: _____   Horário de Trabalho: _____

Trabalho em turno: (   )Sim   (   )Não

Turno que trabalha: _____   Há quanto tempo?_____

Já trabalhou em turnos: (   )Sim   (   )Não   Horários:_____   Há quanto tempo?_____

Presença de esforço físico intenso, exposição a ruídos, agentes químicos e físicos potencialmente nocivos, estresse, postura predominante no trabalho atual?

_____

Atividade Física

Pratica atividade física: (   )Sim   (   )Não

Qual: _____ Há quanto tempo? _____

Frequência: _____Duração: _____

Avaliação Antropométrica

Peso pré-gestacional: _____ Altura: _____

IMC pré-gestacional: _____

Medida	1º trimestre	2º trimestre	3º trimestre
Altura			
Semana gestacional			
Peso atual			
IMC atual			

Hábitos de sono

A que horas normalmente você vai dormir durante a semana? _____:_____horas

Quanto tempo você leva para dormir a noite durante a semana? _____ minutos.

A que horas normalmente você acorda durante a semana? _____:_____horas

Você acorda com auxílio de um despertador ou de alguém durante a semana?

(   ) sim   (   ) não

_____

A que horas normalmente você vai dormir nos dias livres (fins de semana ou folga)?

_____:_____horas

Quanto tempo você leva para dormir a noite nos dias livres (fins de semana ou folga)?

_____ minutos.

A que horas normalmente você acorda nos dias livres (fins de semana ou folga)?

_____:_____horas

Você acorda com auxílio de um despertador ou de alguém nos dias livres (fins de semana/ folga)? (   ) sim   (   ) não

_____

Quanto tempo você gostaria de dormir a noite? _____ horas _____ minutos.

Como você considera a qualidade do seu sono de 0 a 10?

     0 1 2 3 4 5 6 7 8 9 10

Muito ruim_____.____Muito Boa

Uso de medicamento para dormir ou antidepressivos? (   ) Sim   (   ) Não

Quais:

1)_____ Freq: _____x D S M   Consome há _____ A   M

Dose: _____ g mg

2)_____ Freq: _____x D S M   Consome há _____ A   M

Dose: _____ g mg

3)_____ Freq: _____x D S M   Consome há _____ A   M

Dose: _____ g mg

4)_____ Freq: _____x D S M   Consome há _____ A   M

Dose: _____ g mg

5)_____ Freq: _____x D S M   Consome há _____ A   M

Dose: _____ g mg

D: Diária; S: Semanal; M: Mensal.

A: Anos. M: Meses.

APÊNDICE C – Formulário para aplicação de Recordatório Alimentar 24 horas.

Recordatório Alimentar 24 Horas

Código: _____Data Avaliação: ___/___/___

Refeição	Alimentos/ Preparações	Medida Caseira
Horário:		
Horário:		
Horário:		
Horário:		
Horário:		
Horário:		