# Translational Aim 3: Characterize the prevalence and associations of restricted feeding with maternal and child health in humans.

## Background:

### Intermittent fasting and time-restricted feeding

Time-restricted feeding (TRF), meaning a designated and condensed period in which one consumes their daily calories (usually between 6-10 hours in length).This method is a modality to implement intermittent fasting, which is distinct from two other modalities, alternate day fasting (ADF) where an individual alternates full days of fasting and *ad libitum (AL)* feeding, and periodic fasting, encompassing a fast of 24 hours or more periodically throughout the month or year, followed by *AL*  feeding for the rest of the time (Stockman, Thomas, Burke, & Apovian, 2018). Studies in adult humans show improvements in insulin sensitivity, hypertension, as well as other molecular markers of health (Halberg et al., 2005; Hatori et al., 2012; Kahleova, Lloren, Mashchak, Hill, & Fraser, 2017; Liu et al., 2019; n.d.; Ravussin, Beyl, Poggiogalle, Hsia, & Peterson, 2019; Sherman et al., 2012; Sutton et al., 2018; Woodie et al., 2018). There is evidence that these metabolic improvements can be achieved without weight loss or caloric restriction in both humans (Sutton et al., 2018), and animals (Hatori et al., 2012). This suggests that time-restricted feeding may be an appropriate strategy for use in insulin resistant pregnant women. Although it should be said that IF is a controversial dietary practice, which could contribute to the lack of research of this practice in pregnant women. The goal of this portion of the proposed dissertation work is to observe eating practices without assigning an intervention, be begin the lengthy process of understanding whether or not this could be applied to expectant female humans.

### Fasting and in pregnancy

Intermittent fasting during pregnancy has not been examined in humans, even at the observational level. The closest analogue to the TRF paradigm of IF would be fasting in Ramadan. Ramadan fasting takes place over the course of a month in the Islam calendar. During Ramadan, all food and water consumption if confined to after sunset and before morning prayer (1 hour before sunrise). The length of the fast depends on location and time of year when Ramadan takes place in the Islamic calendar. In the United States, this translates to 16 hours of fasting. In most cultures who practice Islam, there are two meals, one larger meal after sundown that breaks the fast, and one before sunrise that is smaller. These studies show that gestational age is often similar between those who fasted and those who did not fast during pregnancy (Awwad et al., 2012; Daley et al., 2017; Hizli et al., 2012; Savitri et al., 2014). Furthermore, there may be a greater incidence in low birth weight babies (Awwad et al., 2012; Savitri et al., 2018), especially if the Ramadan fasting took place in the first trimester of pregnancy (Ziaee et al., 2010). Ramadan fasting is an imperfect proxy for the TRF paradigm of IF, as it often is accompanied by changes in sleep patterns and food choices, both of which could independently affect disease risk and health.

### Nutrient Restriction in Gestation

Studies of nutrient restriction in gestation in animal models have demonstrated that caloric restriction increases incidence of low birthweight, and may initiate unhealthful catch up growth upon weaning, resulting in excess body weight, body fat, and leptin resistance upon reaching adulthood. Experiments with restrictive feeding in pregnancy have mostly been accomplished using mild to moderate caloric restriction, not time-related restriction. In animals, caloric restriction during pregnancy results in lower birth weights than *ad libitum* feeding (Cunha et al., 2015; Govic, Penman, Tammer, & Paolini, 2016). Having a lower birth weight has been independently associated with greater incidence of metabolic disease. Notably, infants born small for gestational age (SGA) are at increased risk for hypertension, type II diabetes, obesity, heart disease, stroke, renal failure, and even precocious pubertal development (Metrustry et al., 2018; Seckl & Holmes, 2007). This is thought to be related to programming *in utero* for a nutrient-restricted environment whereas the post-natal environment is not one that is restricted, making those programmed adaptations from gestation inappropriate for the outside food environment.

### Neonatal Health Outcomes

Preterm birth is a significant health risk for neonates. It has been demonstrated that infants born before term (37 weeks’ gestation), are at greater lifetime risks for higher total cholesterol, triglycerides, glucose and insulin as well as high blood pressure (Suzuki, 2018)(Lewandowski Adam J. et al., 2015). Because pregnancy is a complex period of rapid adaptation for the mother, the etiological drivers of pre-term birth have been difficult to isolate and study. Mothers with short stature, lower educational attainment, who smoke, or have diabetes are more likely to deliver before term (Kramer, McLean, Eason, & Usher, 1992). Some of these risk factors can directly be tied to nutritional status, such as diabetes. However, many cannot be directly corrected by nutrition, but would likely have consequences for maternal nutritional status, such as increased need for water soluble vitamins in those who smoke, lower fruit and vegetable intakes in those with lower incomes, and lower food security for women who have lower educational attainment. This can be difficult to disentangle from other conditions that are associated with pre-term birth, such as infant birth weight.

### Maternal Health Outcomes

The appropriate amount of weight that is to be gained for a healthful pregnancy is drawing attention from both clinicians and researchers in recent years, and recommendations have been tailored to pre-pregnancy BMI to optimize offspring health outcomes (Rasmussen et al., 2010). Gestational weight gain has been associated with offspring body mass index and risk of obesity from infancy all the way through adulthood (Schack-Nielsen, Michaelsen, Gamborg, Mortensen, & Sørensen, 2010). Although insulin resistance and weight gain are considered normal adaptations to pregnancy, there are many women who experience excessive, pathological insulin resistance and gestational weight gain; which manifests as gestational diabetes. Cho and colleagues estimate that globally, gestational diabetes affects 9.8% of pregnancies in women aged 20-24 years; the prevalence dramatically increases for women of advanced age during pregnancy (45-49 years) to 45.1% (Cho et al., 2018).

## Main exposure and outcome variables:

Because the insulin-resistance is a well-document association for both maternal fasting in Ramadan and intermittent fasting, the primary outcome of interest for this study for mothers will be the development of gestational diabetes. Other analyses for preeclampsia, hyperemesis gravidarum will also be conducted.

In terms of the offspring, because birth weight is seen in women who observe Ramadan fasting and because intermittent fasting is may affect body weight, the main outcome variable for this study will be child birth weight. The exposure that will be evaluated in relation to these outcomes is the duration of the feeding window in expectant mothers.

## Translational Aim 3.1: Examine the baseline characteristics of the BUMP cohort

Because no previous study has utilized BUMP cohort data, there must be some descriptive statistics done in order to understand what confounding variables and collinearities exist in the cohort.

### Study Population:

In brief, recruitment is done in the Vonn Voigtlander Women’s clinic, with special focus on the maternal and fetal medicine clinic days, who serve high risk obstetric patients. As of August 2019, this sample consists of roughly 800 women enrolled at different stages in their pregnancies. Eligible women are those who are 18 years or older, who van read and understand the consent form in English, and receive their prenatal care at the VVWH and plan to deliver at VVWH. Research assistants are told by physicians during prenatal care visits if patients are interested in enrolling in the BUMP study. The study is explained, a pamphlet is given, and if a patient is interested, the research assistant obtains written informed consent and gives the participant the questionnaire (appendix 1). Inclusion criteria will be women with live, singleton births. Pregnancies complicated by fetal anomaly, congenital birth defects, or poor placentation/placental defects, or multiple gestation will be excluded. This will result in a population of women that could be quite heterogeneous; who may or may not have obesity, may or may not have experienced gestational hypertension, gestational diabetes, preterm birth, cesarean delivery, or taken glucocorticoid drugs during the course of their pregnancy.

### Power analysis:

A power analysis was conducted for linear regression models using G\*power (Faul, Erdfelder, Lang, & Buchner, 2007). Analyses were conducted by calculating Cohen’s D using mean data from maternal Ramadan fasting studies of the main outcomes (gestational diabetes and low birth weight), a power of 0.80, and a significance level of 0.5. As both effect sizes (Cohen’s D) were quite large, >0.50, additional power analyses were conducted using a medium effect size (arbitrary, 0.3), and small effect size (arbitrary 0.15). As the true effect size of maternal feeding window has not been calculated before and hasn’t been characterized yet in this study population, it is uncertain whether or not the calculated effect sizes will be replicable in this study. The multiple power analyses provide a range of sample sizes, with as few as 31 participants and as many as 203 participants. As the BUMP recruitment has been active for one year and >800 participants have been recruited, I propose to recruit the full 203 participants required to identify a small effect size.

Table 1: Gestational Diabetes

|  |  |  |  |
| --- | --- | --- | --- |
| **Effect size** | **Sample size for each group** | **Seeking to recruit** | **Source of Cohen’s D** |
| 0.621 (large) | 27 | 54+10% | (Baynouna Al Ketbi, Niglekerke, Zein Al Deen, & Mirghani, 2014) |
| 0.3 (medium) | 49 | 98+10% | arbitrary |
| 0.15 (small) | 92 | 184 +10% | arbitrary |

Table 2: Low Birth Weight

|  |  |  |  |
| --- | --- | --- | --- |
| **Effect size** | **Sample size for each group** | **Seeking to recruit** | **Source of Cohen’s D** |
| 0.5864 | 14 | 28+10% | (Savitri et al., 2014) |
| 0.3  (medium) | 49 | 98+10% | arbitrary |
| 0.15 (small) | 92 | 184 +10% | arbitrary |

### Ethical Approval, Data Acquisition, and Data management:

The recruitment of participants and collection of medical information and biospecimens has been approved by the University of Michigan Institutional Review Board (HUM00118179). I will prepare, submit, and be approved for a secondary use permit before beginning any analysis described below. I will submit requests for the full medical information I seek from charts and will be supplied with de-identified participant data. This data will be held on a secure server, with access only to those who are part of the study team and named in the secondary use IRB application. Participant data will not be downloaded on personal computers, and will be backed up on MBOX. As biological assays are conducted on biorepository tissues, they will be merged with the original dataset to maintain a single, de-identified dataset available for statistical analysis.

Collection of Biological Samples  
By participating in the study, women consent to collection of urine, blood, placenta, and cord blood. During each trimester, women who consent to be part of the study are given urine containers and asked to provide up to 100 mL of urine. Urine is then frozen and kept at the Michigan Medicine Central Biorepository under a unique study ID. Blood samples that are drawn for research purposes are coordinated to occur at the same time as prenatal lab draws to minimize participant burden. Present in the research kit are vacutainers for blood draw, which usually takes place at a Michigan Medicine laboratory. Trained phlebotomists collect 40 mL of whole blood each trimester. Blood samples are then picked up by research assistants, aliquoted, and stored Because blood samples are in coordination with prenatal labs, there may be inconsistency in fasting state of these samples. The mid-gestation blood draw is usually done in combination with the oral glucose tolerance test screen for gestational diabetes, which is recommended to occur between 24 and 28 weeks gestation (Randel, 2014). Therefore, indices like insulin will need to be interpreted with caution. After delivery and cutting of the umbilical cord, cord blood will be collected by labor and delivery nurses for clinical and research purposes, up to 40 mL of which can be used for research purposes. Upon delivery of both the infant and the placenta, a labor and delivery nurse will collect two (each sized 1x1x3 cm) placental samples. One sample will be stored in RNAlater, and another will be fixed and embedded in paraffin for histological analysis. All biological samples are stored in the Michigan Medicine Central Biorepository under a unique study ID/barcode. Study samples will not be stored with identifying information.

### Medical Chart Data

Medical chart data is accessible to the research team and can be compiled at the request of the secondary use IRB protocol. This process allows this to access diagnosis codes for the pregnancy and child health in the subsequent infant’s chart. The proposed medical data to be retrieved from the medical chart will include: last measured pre-pregnancy height and weight, maternal age at conception, last measured gestational weight and height, maternal medication use (glucocorticoid, insulin, metformin, progesterone, aspirin, statins, ADHD medications), maternal smoking and drug use history, pre-existing diabetes or hypertension, gestational diabetes, hyperemesis gravidarum, hypertensive disorders of pregnancy, intrauterine fetal demise, birth weight of offspring in grams, gestational age at birth, and APGAR score. These medical data will then be compiled for each participant and added to the demographic and feeding window data compiled from the intake questionnaire.

### Assessment of Feeding Window

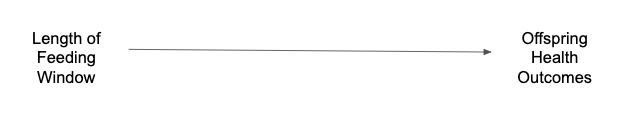
In order to ascertain the window within each participant consumes their meals each day, the following questions were added to the intake questionnaire, “On a typical day during your pregnancy, when was the first time in the day you had something to eat?” to determine the beginning of the feeding period, and “On a typical day during your pregnancy, when was the last time you had something to eat before going to bed?” to assess the closing of the feeding period. Ideally, the responses will be grouped into a categorical variable consisting of 2-hour differences in length of the feeding window:

* >12 hours
* 10-12 hours
* 8-10 hours
* 6-8 hours,
* <6 hours.

These feeding windows are all reflected in the TRF literature (Rothschild, Hoddy, Jambazian, & Varady, 2014).

## Translational Aim 3.2. Investigate the associations of feeding window length on maternal and child health outcomes

No studies to date have evaluated the effects of time-restricted feeding on the incidence of maternal and child outcomes in human populations. There have been studies on the effects of Ramadan fasting during pregnancy on these outcomes. As stated previously, Ramadan fasting is inconsistent in its findings. Some studies associated fasting with lower birth weight, whereas others see no effect. Studies on gestational age are somewhat more consistent in that there is no apparent relationship between Ramadan fasting and preterm birth. Although imperfect, one such cross-sectional study evaluated a consistent exposure to Ramadan fasting and categorized participants based on the level of fasting completed (1-10d, 11-20d, 21-29 days in the 2017 month of Ramadan). They found that Ramadan fasting only affected two of their nine outcomes. The odds of gestational diabetes were lower in expectant mothers who participated in the Ramadan fast (2.6% vs 8.3%)(Safari, Piro, & Ahmad, 2019). The strength of the association remained after adjusting for maternal education, maternal age, maternal occupation, parity, and pre-pregnancy BMI (OR = 1.51 (0.06+/-1.74)). There were no observed differences in rates of preterm labor, preeclampsia, low birth weight, fetal height, fetal head circumference, or APGAR score at 5 minutes. Based on the work done during Ramadan fasting in pregnancy and other TRF literature, *I anticipate that women who have shorter eating windows are less likely to develop pregnancy related maternal health issues (diabetes, preeclampsia, hyperemesis gravidarum) and that there will be no effect on child birthweight.* (Figures 1 and 2)

Figure 1: Directed acyclic graph for aim 3.2

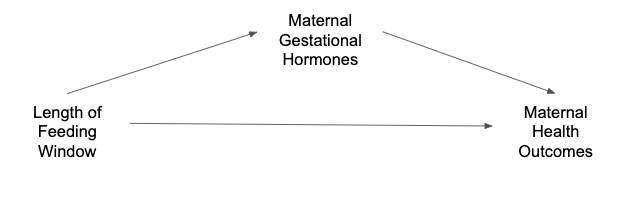
****

Figure 2: Directed acyclic graph for aim 3.3

To assess the associations of feeding window length with maternal and child health outcomes, multiple linear regression analysis will be used for the categorical and continuous outcomes; such as offspring birth weight, gestational age, and APGAR score. For dichotomous outcomes, such as gestational diabetes, hypertensive disorders of pregnancy, and hyperemesis gravidarum logistic regression will be employed.

## Translational Aim 3.3 Examine the molecular basis for feeding window association with maternal and child health in biological samples

The metabolic and biochemical effects of fasting during pregnancy are critically understudied. It is known that a large proportion of the Islamic world chooses to fast when pregnancy, for many reasons (Safari et al., 2019). However, as pregnant mothers are a particularly difficult group to enroll and study, there is very little data on what fasting does to maternal and child hormonal and nutritional signals. Of those few studies, the majority exist as case studies or observational studies of women with existing diabetes during pregnancy (CITE). Observational studies of pregnant, normo-glycemic women who observed Ramadan fast noticed that women had higher post-prandial glucose responses after breaking the fast than pregnant controls (measured one hour after first meal in the morning) (Baynouna Al Ketbi et al., 2014). This sample is imperfect in a few ways. The two samples were taken at different times of day, which is known to affect glycemia and insulinemia in humans. Furthermore, the measurement of fasting and post-prandial glucose alone is insufficient to begin to understand the mechanisms that may be activated by maternal fasting. A baseline understanding of the associations of habitual dietary fasting and markers of metabolic health in the blood of pregnant women is a critical need. The BUMP cohort biological samples (blood, and urine) can help to fill that gap. The hormones to be assayed in the blood samples is largely to be determined by the results of the model organism aims of this proposed dissertation work. The initial list will be comprised of blood insulin, glucose, GDF15, and cortisol provide the strongest candidates. Each will require 50uL of plasma, totaling 200uL minimum of each sample. To provide translatability to the animal study, human maternal blood samples may be tested for other contributing hormones that demonstrate effect in the animal cohort.

Univariate and Bivariate Analyses

In order to assess the distributions of the maternal feeding window data and gestational and infant outcomes, I will conduct a univariate analysis of each variable independently. This will determine whether or not these variables need to be normalized for use in multiple regression and will determine cutoffs for the categorical variables. Bivariate analyses will then be conducted by examining the distributions of the outcome variables across socio-demographic and maternal health indices. This will identify variables that should be considered confounders in the relationship between the feeding window during pregnancy and maternal and child health outcomes. As seen in table 3, these are the current proposed variables to be considered in the bivariate analyses.

Table 3: Potential confounders:

|  |  |
| --- | --- |
| **Proposed confounder** | **Source of variable** |
| Maternal gestational age at enrollment | Medical chart |
| Maternal race/ethnicity | Enrollment questionnaire |
| Household income | Enrollment questionnaire |
| Maternal pre-pregnancy BMI | Medical chart |
| Gestational weight gain | Medical chart |
| Maternal smoking status | Enrollment questionnaire |
| Maternal sleep quality | Enrollment questionnaire |
| Offspring sex | Medical chart |

Multivariate Analyses

To assess the associations of feeding window length with maternal and child health outcomes, multiple linear regression analysis will be used for the categorical and continuous outcomes; such as offspring birth weight, gestational age, and APGAR score. For dichotomous outcomes, such as gestational diabetes, hypertensive disorders of pregnancy, and hyperemesis gravidarum logistic regression will be employed.

Proposed models:

Logistic Regression Models:

**Exposure:** Maternal length of the feeding window **Outcome:** Gestational Diabetes

Model 1: Logit(Pr(Y=1)) = maternal feeding window + maternal education

Model 2: Logit(Pr(Y=1)) = Model 1 + maternal pre-pregnancy BMI  
Model 3: Logit(Pr(Y=1)) = Model 2 + Sleep quality

Model 1, the most simplistic will consider only the exposure variable and a well-recognized measure of socioeconomic status, maternal education. Models 2 and 3 will consider Model 1’s covariates as well as inclusion of maternal pre-pregnancy BMI, which can be an indicator of baseline risk of developing diabetes (Torloni et al., 2009), independent of pregnancy and sleep quality, which is known to be associated with risk of developing gestational diabetes (Facco et al., 2017). Models may be subject to change after univariate and bivariate analysis of cohort data.

Multiple Linear Regression Models:

**Exposure:** Maternal length of the feeding window **Outcome:** child birth weight

Model 1: maternal feeding window + maternal education

Model 2: Model 1 + gestational weight gain  
Model 3: Model 2 + Offspring sex

Model 1 comprises the most simplistic model and will account only for the exposure variable and socioeconomic status. Model 2 will account for the same covariates as model 1, but will also take include gestational weight gain, which has been proven to be associated with larger birth weights and child fat mass (Schack-Nielsen et al., 2010). Model 3 will include child sex, as differences of sex-specific intrauterine growth and adaptation to numerous environmental stimuli (Alwasel et al., 2011; Clifton, 2010) have been seen in human pregnancy. Models proposed are subject to change based on initial analyses of cohort data.

**Potential Pitfalls and alternative approaches:**

### Low recruitment/underpowered in the feeding windows

Because recruitment is part of an observational instead of interventional study, we will not know the length of the feeding window until after the recruitment process. Because of this, there may not be an even distribution of women in each of the designated feeding window groups. If this is the case, there are two alternative approaches. The first is to continue recruitment, which may introduce selection bias and for that reason is not recommended. The second is to analyze the distributions of the feeding window variable collected and to use more iterative cut offs that are apparent in the data.

### Lower or unrepresentative incidence of disease states

As this study proposes to use participant data that is recruited in an untargeted manner, it is possible that recruitment could result in lower than expected incidence of the maternal outcomes investigated. It is also possible that because of the prestige in neonatal care associated with this hospital could attract a greater than expected incidence in maternal health outcomes. Either situation could affect the generalizability of the results of this study.

### Confounding of feeding variable by dietary quality

While the purpose of this proposed dissertation work is to further the understanding of the relationship between length of time fasting and maternal and child health, using only the length of the fast as the only dietary measure is a limitation. There are many components to consider when attempting to understand dietary adequacy, and timing of meals is only one. Others such as dietary quality, macro- and micronutrient adequacy, macronutrient distribution, energy intake, and food safety are all concerns that may affect the relationship. Because dietary quality data is not collected for this sample, we cannot say that associations determined are exclusively because of the feeding window. However, the literature on TRF has shown some robust effects in models that utilize Western, high-fat dietary exposures, meaning there could still be some relationship of the feeding window to outcomes independent of diet quality and calorie intake.

### Poor reliability of fasting state in blood samples

The BUMP cohort design makes it reasonable and easy for participants to enroll in the study, and one fantastic example is in the drawing of neonatal labs. It may be unreliable to assume a similar level of feeding or fasting in these samples. For that reason, insulin and glycemic health data sensitive to fasting/refeeding cycles will be interpreted with caution. It may be of benefit to specifically choose the mid-gestation collection point, as this is done in concert with the oral glucose tolerance test, and therefore is likely to be more uniform in the feeding level (75g of glucose within 1 hour of blood draw).

### Residual Confounding

As is the case with any observational study, the inclusion of any confounding variables is a best attempt at reducing the relationship between the outcome and the exposure through the causal pathway, but there is also potential for residual confounding. Furthermore, as the intake questionnaire is both quite simplistic and could simply not measure a confounding variable that could occlude the relationships we are looking for.

## Methods:

### Human blood hormone determination: ELISA

Human blood insulin concentration will be determined by ELISA (Crystal Chem catalog #90095). This highly reactive and non-cross reactive assay for C-peptide will be done in duplicate for each sample. Insulin concentration will be calculated using a standard curve fit to known concentrations of a set solution. Individual observations will be reported as the mean concentration (pg/mL) of the two replicates.

### Statistical Analysis

Statistical analysis will be conducted in R. Logistic regression analyses will result in odds ratios (OR) and 95% confidence intervals (CI). Multiple linear regression analyses will be expressed as beta coefficients (β) and 95% confidence intervals.

Appendix 1: BUMP Study Intake Questionnaire  
  
Page 1: University of Michigan Pregnancy Biorepository Study ID: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

HUM00118179 Date: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

1. **What is your Ethnicity:**

⃞ Hispanic or Latino or Spanish Origin

⃞ Not Hispanic or Latino or Spanish Origin

⃞ Unknown

⃞ Prefer not to say

1. **What is your Race (check all that apply):**

⃞ American Indian or Alaska Native

⃞ Asian

⃞ Black or African American

⃞ Native Hawaiian or Other Pacific Islander

⃞ White

⃞ Unknown

⃞ Prefer not to say

⃞ Other 🡪 Please describe: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

1. **What is the highest level of education you have completed:**

⃞ Some high school, no diploma

⃞ High school graduate, diploma or equivalent (for example: GED)

⃞ Some college credit, no degree

⃞ Trade/technical/vocational training

⃞ Associate degree

⃞ Bachelor’s degree

⃞ Master’s degree

⃞ Doctorate or Professional degree

⃞ Prefer not to say

1. **What is your annual household income:**

⃞ $11,999 or less

⃞ $12,000 to $24,999

⃞ $25,000 to $49,999

⃞ $50,000 to $99,999

⃞ $100,000 to $149,999

⃞ $150,000 or more

⃞ Prefer not to say

1. **How would you best describe your marital or partnership status:**

⃞ Single, never married

⃞ Married or domestic partnership

⃞ Widowed

⃞ Divorced

⃞ Separated

⃞ Prefer not to say

⃞ Other 🡪 Please describe: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Page 2: University of Michigan Pregnancy Biorepository Study ID: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

HUM00118179 Date: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

1. **How many people are in your household (including yourself):** \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_
2. **Do you currently snore 3 or more nights a week?**  ⃞ Yes ⃞ No ⃞ I don’t know
3. **Before your pregnancy did you snore more than 3 nights a week?**  ⃞ Yes ⃞ No ⃞ I don’t know
4. **Are you currently a smoker?**  ⃞ Yes ⃞ No

9a. If yes, how much do you smoke per day? \_\_\_\_\_\_\_\_\_

1. **Are you a former smoker?**  ⃞ Yes ⃞ No

10a. If yes, when did you quit? \_\_\_\_\_\_\_\_\_\_

1. **Are you regularly exposed (several times/week) to someone else’s smoke during the past 3 months?**

⃞ Yes ⃞ No

1. **Do you live near a landfill (less than 2 miles)?**  ⃞ Yes ⃞ No
2. **Please let us know if you use any of the following personal care products on a regular basis:**

Perfumes and cosmetics  ⃞ Yes ⃞ No

Hair care products ⃞ Yes ⃞ No

1. **Have you had dental fillings in the past 3 months?**  ⃞ Yes ⃞ No
2. **Do you eat canned foods (at least once a week)?**  ⃞ Yes ⃞ No

**15a. If yes, how often do you eat canned food?**

⃞ 1 serving or less/day ⃞ 2-3 servings a day ⃞ 4 servings or more/day

1. **Do you eat at fast food restaurants (at least once a week)?**  ⃞ Yes ⃞ No

16a. **If yes, how often?**

⃞ once a week ⃞ 2-3 times/week ⃞ 4 times or more/week

1. **Do you eat fresh vegetables (at least once a week)?**  ⃞ Yes ⃞ No

17a. **If yes, how often?**

⃞ 1-3 servings/day ⃞ 4-5 servings/day ⃞ 6 or more servings/day

1. **Do you feel stressed?**  ⃞ Yes ⃞ No

**18a. If yes, how often do you feel stressed?**

⃞ Never ⃞ Almost Never ⃞ Some Days ⃞ Most Days ⃞ Every Day

## References

Alwasel, S. H., Abotalib, Z., Aljarallah, J. S., Osmond, C., Alkharaz, S. M., Alhazza, I. M., … Barker, D. J. P. (2011). Sex Differences in birth size and intergenerational effects of intrauterine exposure to Ramadan in Saudi Arabia. *American Journal of Human Biology*, *23*(5), 651–654. https://doi.org/10.1002/ajhb.21193

Awwad, J., Usta, I. M., Succar, J., Musallam, K. M., Ghazeeri, G., & Nassar, A. H. (2012). The effect of maternal fasting during Ramadan on preterm delivery: A prospective cohort study. *BJOG: An International Journal of Obstetrics and Gynaecology*, *119*(11), 1379–1386. https://doi.org/10.1111/j.1471-0528.2012.03438.x

Baynouna Al Ketbi, L. M., Niglekerke, N. J., Zein Al Deen, S. M., & Mirghani, H. (2014). Diet restriction in Ramadan and the effect of fasting on glucose levels in pregnancy. *BMC Research Notes*, *7*, 392. https://doi.org/10.1186/1756-0500-7-392

Cho, N. H., Shaw, J. E., Karuranga, S., Huang, Y., da Rocha Fernandes, J. D., Ohlrogge, A. W., & Malanda, B. (2018). IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Research and Clinical Practice*, *138*, 271–281. https://doi.org/10.1016/j.diabres.2018.02.023

Clifton, V. L. (2010). Review: Sex and the Human Placenta: Mediating Differential Strategies of Fetal Growth and Survival. *Placenta*, *31*, S33–S39. https://doi.org/10.1016/j.placenta.2009.11.010

Cunha, F. da S., Dalle Molle, R., Portella, A. K., Benetti, C. da S., Noschang, C., Goldani, M. Z., & Silveira, P. P. (2015). Both food restriction and high-fat diet during gestation induce low birth weight and altered physical activity in adult rat offspring: The “Similarities in the Inequalities” model. *PloS One*, *10*(3), e0118586. https://doi.org/10.1371/journal.pone.0118586

Daley, A., Pallan, M., Clifford, S., Jolly, K., Bryant, M., Adab, P., … Roalfe, A. (2017). Are babies conceived during Ramadan born smaller and sooner than babies conceived at other times of the year? A Born in Bradford Cohort Study. *Journal of Epidemiology and Community Health*, *71*(7), 722–728. https://doi.org/10.1136/jech-2016-208800

Facco, F. L., Grobman, W. A., Reid, K. J., Parker, C. B., Hunter, S. M., Silver, R. M., … Zee, P. C. (2017). Objectively measured short sleep duration and later sleep midpoint in pregnancy are associated with a higher risk of gestational diabetes. *American Journal of Obstetrics and Gynecology*, *217*(4), 447.e1-447.e13. https://doi.org/10.1016/j.ajog.2017.05.066

Faul, F., Erdfelder, E., Lang, A.-G., & Buchner, A. (2007). G\*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*, *39*(2), 175–191. https://doi.org/10.3758/BF03193146

Govic, A., Penman, J., Tammer, A. H., & Paolini, A. G. (2016). Paternal calorie restriction prior to conception alters anxiety-like behavior of the adult rat progeny. *Psychoneuroendocrinology*, *64*, 1–11. https://doi.org/10.1016/j.psyneuen.2015.10.020

Halberg, N., Henriksen, M., Söderhamn, N., Stallknecht, B., Ploug, T., Schjerling, P., & Dela, F. (2005). Effect of intermittent fasting and refeeding on insulin action in healthy men. *Journal of Applied Physiology*, *99*(6), 2128–2136. https://doi.org/10.1152/japplphysiol.00683.2005

Hatori, M., Vollmers, C., Zarrinpar, A., DiTacchio, L., Bushong, E. A., Gill, S., … Panda, S. (2012). Time-Restricted Feeding without Reducing Caloric Intake Prevents Metabolic Diseases in Mice Fed a High-Fat Diet. *Cell Metabolism*, *15*(6), 848–860. https://doi.org/10.1016/j.cmet.2012.04.019

Hizli, D., Yilmaz, S. S., Onaran, Y., Kafali, H., Danişman, N., & Mollamahmutoğlu, L. (2012). Impact of maternal fasting during Ramadan on fetal Doppler parameters, maternal lipid levels and neonatal outcomes. *The Journal of Maternal-Fetal & Neonatal Medicine: The Official Journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians*, *25*(7), 975–977. https://doi.org/10.3109/14767058.2011.602142

Kahleova, H., Lloren, J. I., Mashchak, A., Hill, M., & Fraser, G. E. (2017). Meal Frequency and Timing Are Associated with Changes in Body Mass Index in Adventist Health Study 2. *The Journal of Nutrition*, *147*(9), 1722–1728. https://doi.org/10.3945/jn.116.244749

Kramer, M. S., McLean, F. H., Eason, E. L., & Usher, R. H. (1992). Maternal Nutrition and Spontaneous Preterm Birth. *American Journal of Epidemiology*, *136*(5), 574–583. https://doi.org/10.1093/oxfordjournals.aje.a116535

Lewandowski Adam J., Davis Esther F., Yu Grace, Digby Janet E., Boardman Henry, Whitworth Polly, … Leeson Paul. (2015). Elevated Blood Pressure in Preterm-Born Offspring Associates With a Distinct Antiangiogenic State and Microvascular Abnormalities in Adult Life. *Hypertension*, *65*(3), 607–614. https://doi.org/10.1161/HYPERTENSIONAHA.114.04662

Liu, B., Page, A. J., Hatzinikolas, G., Chen, M., Wittert, G. A., & Heilbronn, L. K. (2019). Intermittent Fasting Improves Glucose Tolerance and Promotes Adipose Tissue Remodeling in Male Mice Fed a High-Fat Diet. *Endocrinology*, *160*(1), 169–180. https://doi.org/10.1210/en.2018-00701

Meal Frequency and Timing Are Associated with Changes in Body Mass Index in Adventist Health Study 2 | The Journal of Nutrition | Oxford Academic. (n.d.). Retrieved August 16, 2019, from https://academic-oup-com.proxy.lib.umich.edu/jn/article/147/9/1722/4743530

Metrustry, S. J., Karhunen, V., Edwards, M. H., Menni, C., Geisendorfer, T., Huber, A., … Valdes, A. M. (2018). Metabolomic signatures of low birthweight: Pathways to insulin resistance and oxidative stress. *PloS One*, *13*(3), e0194316. https://doi.org/10.1371/journal.pone.0194316

Randel, A. (2014). ACOG Releases Guideline on Gestational Diabetes. *American Family Physician*, *90*(6), 416–417.

Rasmussen, K. M., Abrams, B., Bodnar, L. M., Butte, N. F., Catalano, P. M., & Siega-Riz, A. M. (2010). Recommendations for Weight Gain During Pregnancy in the Context of the Obesity Epidemic. *Obstetrics and Gynecology*, *116*(5), 1191–1195. https://doi.org/10.1097/AOG.0b013e3181f60da7

Ravussin, E., Beyl, R. A., Poggiogalle, E., Hsia, D. S., & Peterson, C. M. (2019). Early Time-Restricted Feeding Reduces Appetite and Increases Fat Oxidation But Does Not Affect Energy Expenditure in Humans. *Obesity*, *27*(8), 1244–1254. https://doi.org/10.1002/oby.22518

Rothschild, J., Hoddy, K. K., Jambazian, P., & Varady, K. A. (2014). Time-restricted feeding and risk of metabolic disease: A review of human and animal studies. *Nutrition Reviews*, *72*(5), 308–318. https://doi.org/10.1111/nure.12104

Safari, K., Piro, T. J., & Ahmad, H. M. (2019). Perspectives and pregnancy outcomes of maternal Ramadan fasting in the second trimester of pregnancy. *BMC Pregnancy and Childbirth*, *19*. https://doi.org/10.1186/s12884-019-2275-x

Savitri, A. I., Amelia, D., Painter, R. C., Baharuddin, M., Roseboom, T. J., Grobbee, D. E., & Uiterwaal, C. S. P. M. (2018). Ramadan during pregnancy and birth weight of newborns. *Journal of Nutritional Science*, *7*. https://doi.org/10.1017/jns.2017.70

Savitri, A. I., Yadegari, N., Bakker, J., van Ewijk, R. J. G., Grobbee, D. E., Painter, R. C., … Roseboom, T. J. (2014). Ramadan fasting and newborn’s birth weight in pregnant Muslim women in The Netherlands. *The British Journal of Nutrition*, *112*(9), 1503–1509. https://doi.org/10.1017/S0007114514002219

Schack-Nielsen, L., Michaelsen, K. F., Gamborg, M., Mortensen, E. L., & Sørensen, T. I. A. (2010). Gestational weight gain in relation to offspring body mass index and obesity from infancy through adulthood. *International Journal of Obesity*, *34*(1), 67–74. https://doi.org/10.1038/ijo.2009.206

Seckl, J. R., & Holmes, M. C. (2007). Mechanisms of disease: Glucocorticoids, their placental metabolism and fetal “programming” of adult pathophysiology. *Nature Clinical Practice. Endocrinology & Metabolism*, *3*(6), 479–488. https://doi.org/10.1038/ncpendmet0515

Sherman, H., Genzer, Y., Cohen, R., Chapnik, N., Madar, Z., & Froy, O. (2012). Timed high-fat diet resets circadian metabolism and prevents obesity. *FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology*, *26*(8), 3493–3502. https://doi.org/10.1096/fj.12-208868

Stockman, M.-C., Thomas, D., Burke, J., & Apovian, C. M. (2018). Intermittent Fasting: Is the Wait Worth the Weight? *Current Obesity Reports*, *7*(2), 172–185. https://doi.org/10.1007/s13679-018-0308-9

Sutton, E. F., Beyl, R., Early, K. S., Cefalu, W. T., Ravussin, E., & Peterson, C. M. (2018). Early Time-Restricted Feeding Improves Insulin Sensitivity, Blood Pressure, and Oxidative Stress Even without Weight Loss in Men with Prediabetes. *Cell Metabolism*, *27*(6), 1212-1221.e3. https://doi.org/10.1016/j.cmet.2018.04.010

Torloni, M. R., Betrán, A. P., Horta, B. L., Nakamura, M. U., Atallah, A. N., Moron, A. F., & Valente, O. (2009). Prepregnancy BMI and the risk of gestational diabetes: A systematic review of the literature with meta-analysis. *Obesity Reviews*, *10*(2), 194–203. https://doi.org/10.1111/j.1467-789X.2008.00541.x

Woodie, L. N., Luo, Y., Wayne, M. J., Graff, E. C., Ahmed, B., O’Neill, A. M., & Greene, M. W. (2018). Restricted feeding for 9h in the active period partially abrogates the detrimental metabolic effects of a Western diet with liquid sugar consumption in mice. *Metabolism*, *82*, 1–13. https://doi.org/10.1016/j.metabol.2017.12.004

Ziaee, V., Kihanidoost, Z., Younesian, M., Akhavirad, M.-B., Bateni, F., Kazemianfar, Z., & Hantoushzadeh, S. (2010). The Effect of Ramadan Fasting on Outcome of Pregnancy. *Iranian Journal of Pediatrics*, *20*(2), 181–186.