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

I will first characterize the prevalence of pregnancy-associated complications in the biorepository for understanding maternal and pediatric health (BUMP) cohort, then will further investigate the associations of the length of feeding window with perinatal health outcomes including: preterm birth, small for gestational age, intrauterine fetal demise, gestational diabetes, gestational weight gain, and pre-eclampsia.

**Background:**

Fasting in pregnancy

Intermittent fasting during pregnancy has not been thoroughly examined in humans. The closest analogue to the TRF paradigm of IF would be fasting in Ramadan. [Insert Ramadan graphic here]. In general, Ramadan fasting is not a good mimetic for the TRF paradigm of IF, as it often is accompanied by changes in sleep patterns and food quality, both of which could independently affect disease risk and health.

Preterm birth

Pre term 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.

SGA/low birthweight

Infant birth weight is associated with \_\_\_\_\_.

Pre-ecclampsia

Gestational diabetes

Gestational weight gain

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 (INSERT REPORT). 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) .

**Method:**

Study population  
Assessment of the eating window  
Data Analysis

* Uni – understand distributions of the exposures and outcomes – will I need to change for normality assumptions
* Bivariate – outcomes against things we expect to be confounders or effect modifiers
* Multi – what method will I use?
  + Should I use Logistic regression

What do we know

What is missing

What we want to do

What we expect to see

The impact it will have

**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 who 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 seen in appendix 1.

Inclusion criteria will be women with live, singleton births who completed at least 2 of the 3 collections during pregnancy. 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.

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 \_\_\_\_\_\_\_\_\_\_\_\_.  
  
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 is then \_\_\_\_\_\_\_\_\_\_. Blood samples are then picked up by research assistants and processed by \_\_\_\_\_ and stored and aliquoted at \_\_\_\_\_\_. 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 a grain of salt.   
  
After delivery and cutting of the umbilical 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 is accessible to the research team. This information will provide

**Outcomes:**

After gaining access to this study material, we will have the ability to search in medical charts for the following maternal outcomes:

2nd use IRB

Data scraping with the following variables

In order to correct for confounding variables, I will first conduct a univariate analysis to identify variables associated with the listed outcomes above ().

**Predicted confounders for bivariate analysis:**

Maternal gest age at enrollment  
Maternal race/ethnicity  
Household Income  
pre-pregnancy BMI  
Gestational Weight Gain

Smoking Status

Sleep quality

Offspring Sex

Aim 3.2. Investigate the relationships between

* Categorical variable of feeding windows

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 find 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 eating period. 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, and <6 hours. These feeding windows are all reflected in the TRF literature (Rothschild, Hoddy, Jambazian, & Varady, 2014).

**Aim 3.3 Compare to hard birth outcomes**

The BUMP cohort not only has chart data available, but also has a series of biological samples for use that will help us to derive more mechanistic answers to our questions about the associations with shorter feeding periods and maternal and child health outcomes. Among the chart information that we would like to assess the association of feeding with are: preterm birth, small for gestational age, intrauterine fetal demise, gestational diabetes, gestational weight gain, and pre-eclampsia.

ID biomarkers I’d like to address in urine/blood of these mamas – should reflect animal portion

**Potential Pitfalls and alternative approaches:**

Low recruitment/underpowered in the feeding windows

Could evaluate as a continuous vs categorical variable.

Limited amount of repeat samples

Use multiple linear regression instead of MLMs

Lower or unrepresentative incidence of disease states

Be cautious in interpretations

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.

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

**Works Consulted**

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