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# Aim 2: Examine the effect of early time-restricted feeding in the perinatal period on maternal health.

## Background:

### Time-restricted feeding

Time-restricted feeding is a feeding approach that is gaining interest. Time restricted feeding is a feeding strategy that is known to affect insulin sensitivity, 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). Furthermore, many rodent models of TRF demonstrate metabolic improvements in insulin resistance without weight loss (Hatori et al., 2012; Liu et al., 2019; Sherman et al., 2012; Woodie et al., 2018), suggesting it may be a uniquely appropriate strategy for use in insulin resistant pregnant women. Although many things affected during pregnancy are also affected by TRF, to date, no study has evaluated time-restricted feeding of normal chow in mouse pregnancy. Only one study of time restricted feeding during gestation was completed, which utilized 60% high fat diet (HFD) and Wistar rats (Upadhyay et al., 2019). This work demonstrated that HFD-TRF feeding led to a similar number of kcals consumed by both HFD-TRF and HFD-AL counterparts. With similar pre-pregnancy body weight gain between these groups. They failed to look at compartmentalization of the body weight before and during pregnancy, and did not asses maternal insulin sensitivity or glycemia. For this reason, I propose to study the effect of TRF in mice before and during pregnancy.

### Pregnancy is a critical time for maternal health and physiological adaptation

Nutrient composition and nutrient restriction have been well studied in the physiological state of pregnancy (Will add the right citations over the weekend). There is sufficient evidence to support that diet can modulate not only offspring health, but also the health of the mother during, and long after gestation (Walter, 2014; Donnelly, 2019). There have been studies that investigate maternal food restriction in both human and animal models. One such study that is largely credited with the burgeoning of the DOHaD field is that of nigel barker, wherein he describes the effects of severe nutrient restriction during pregnancy on offspring insulin signaling later in life, through the narrative of the Dutch hunger winter (CITE). Other, less severe instance of food restriction have also been investigated during pregnancy. One of the most well-studied would be that of Ramadan fasting. However, as Ramadan fasting is not only time restriction of feeding, but also chronodisruption in sleep/wake patterns, I propose that time-restricted feeding is a different model of restrictive feeding practice, and therefore would have distinct effects from Ramadan fasting.

Pregnancy is a time of profound physiological change for expectant mothers; including the onset of insulin resistance without hyperglycemia and increases in body weight and food intake. This suggests there is a molecular driver to reassign the desired set point, making the study of pregnancy a relevant and important implication for not only overweight and obese women of childbearing age, but also obese adults in general. The physiological adaptations to pregnancy are thought to maximize nutrient availability for the fetus.



### Insulin Resistance

The induction of insulin resistance in the mother during mid and late gestation has evolved to make available extra glucose and free fatty acids in maternal circulation and further prevent maternal storage of these substrates, allowing consistent nutrient flux toward the developing fetus. 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. 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). Furthermore, a meta-analysis of incidence of type 2 diabetes found that women with a history of gestational diabetes are at 7.43 times the risk than women who were normoglycemic during their pregnancies (Bellamy, Casas, Hingorani, & Williams, 2009). This makes insulin resistance during gestation a critical public health problem that deserves research attention.

### Gestational weight gain and Food intake

Weight gain is expected for a healthful pregnancy. The IOM recommended amount of weight to gain is based on pre-pregnancy body mass index (BMI) (Rasmussen et al., 2010). Since these recommendations were published, many studies have evaluated the prevalence of excessive gestational weight gain. This excessive gain of weight during gestation appears to be highly prevalent, with rates from 47% of sampled women (Goldstein et al., 2017). Therefore, the prevalent and problematic excessive weight gain in pregnancy is an urgent public health problems that needs to be addressed to improve health indices of not only child health, but also maternal cardiometabolic health.

### Digestive efficiency and chronodisruption

Although we often read energy taken in and perceive it to mean that all of that energy is utilized or absorbed at similar levels in all people, it is likely not true. Digestive efficiency many change as a function of genotype (clock KO’s, (Pan & Hussain, 2009), physiological state, or diet). Furthermore, it has been demonstrated that perturbation of the circadian system can lead to preferential absorption of certain macronutrients; such as preferred carbohydrate to protein metabolism and overall increased fatty acid absorption with disruption of Clock done by pan and colleagues(Pan & Hussain, 2009). It has also been demonstrated that timing of food is sufficient to entrain the circadian system (Sherman et al., 2012).

### Mechanisms linking time-restricted feeding to metabolic health

Needs some details here, this is where you could introduce cortisol/GDF15 *etc* The specific mechanism of insulin sensitivity after treatment with eTRF in adult humans and animals is incompletely understood. One candidate mechanism could be the growth and differentiation factor, GDF15. The effects of GDF15 are known to be mediated through the GFRAL receptor (Hsu et al., 2017) in the brainstem, and plays a role in weight and appetite regulation () Furthermore, it has been demonstrated to promote ketogenesis and fatty acid catabolism(Hsu et al., 2017). GDF15 is produced in response to stressors (namely), and works to reduce food intake. ADD MORE ABOUT ORIGIN AND PROPOSED MECH OF GDF15. It is known to increase during gestation, and is associated with reduced food intake, and leanness, and improvements in glucose tolerance (Macia et al., 2012). Sugulle and colleagues demonstrated that GDF15 is elevated in human pregnancies that are complicated by pre-eclampsia and diabetes (Sugulle et al., 2009). It has also been demonstrated that overexpression of GDF15 in adult mice fed both chow or high fat diet was able to reduce glycemic response to IPGTT challenge and had greater insulin sensitivity compared to wildtype controls (Macia et al., 2012).

Another candidate hormone to investigate is corticosterone. Corticosterone concentration in the blood is known to increase steadily over rodent pregnancies until late term(Barlow, Morrison, & Sullivan, 1974; Jafari, Mehla, Afrashteh, Kolb, & Mohajerani, 2017). This rise in corticosterone is also known to overlap with the steady rise in insulin resistance of pregnancy in mice(Musial et al., 2016). Therefore, it may be that levels of corticosterone in the circulation could be affected by feeding strategy and may therefore affect insulin resistance of pregnancy. INCLUDE MY DATA HERE FROM IRPREG STUDY

MODEL

eTRF – to explain the groups before we get to the subaims

## Specific aim 2.1 Contributions of eTRF on maternal energy expenditure and metabolic flexibility

Works in TRF of humans and animals have demonstrated mixed results with respect to energy expenditure. In some, energy expenditure is increased using this feeding strategy (Halberg, 2005; Gabel, 2018 ), while many more fail to detect any significant increase in daily energy expenditure (Ravussin et al., 2019). Based on preliminary results, the food intake and body composition levels are unchanged; however,, these are only proxy measurements of actual energy expenditure. It is possible that while food intake and body weight do not have detectable differences, that there is an increase in energy expenditure to balance food intake and body weight. This may manifest itself in many ways. It could be through physical activity, thermogenesis, or even by differences in absorptive capacity of food.

Although significant differences in total daily energy expenditure is not often seen, there are often periods where RER is distinct from ad lib controls. Namely, during the night, the RER/RQ lowers, resulting in greater fat utilization, and during the day, a high RER?RQ predominates – demonstrating greater metabolic capacity for flexibility in those exposed to TRF(. 2016; 14: 290.

* Increase in the postprandial period which compensates for the extra absorption and does not manifest as additional weight gain

## Specific aim 2.2 Determine effect of eTRF on maternal feeding patterns

Food intake increases during pregnancy to allow facilitate sufficient nutrient levels to continue maternal healthful living and to provide energy and essential nutrients for the developing fetuses (S. R. Ladyman, Carter, & Grattan, 2018). This increase in food intake is usually transient, and most pronounced during the last two weeks of gestation in mice(S. R. Ladyman et al., 2018); followed by a sharp uptick during lactation, with up to 254% more food taken in by lactating mice than age-matched, non- lactating controls(Sharon Rachel Ladyman, Khant Aung, & Grattan, 2018).

One such concern about the use of TRF in gestation is that the narrow eating window would provide too little time to consume sufficient calories to support maternal needs and fetal growth. This is especially a concern based on data available from human trials of TRF. In adult humans, when TRF/IF is employed, there is often a reduction in total kcal intake which then leads to weight loss. However, this is often not seen in animal studies even in studies of HFD feeding with TRF, food intake is similar. ().Furthermore, Upadhyay and colleagues found that TRF of a high fat diet in gestation yielded offspring growth similar to AL chow fed control pups(Upadhyay et al., 2019). For this reason, I do not expect that dams assigned to eTRF treatment to be unable to consume necessary calories to continue a healthful pregnancy. Preliminary data suggests that with the eating window of 6 hours, there are no differences in total 24-hour energy intake in the preliminary cohort.

In our preliminary data, we observe no differences in overall food intake between AL and eTRF mice, even though we detect a 126% increase in energy intake during the restricted window.

## Specific aim 2.3 Evaluate effects of eTRF on gestational weight gain and maternal body composition

Although only one study has been done in TRF in pregnancy, there have been many studies in non-pregnant adults in humans and in mice that evaluate body weight, body composition, and BMI after treatment with eTRF. The literature is divergent in humans and animals. In most studies with humans employing different models of intermittent fasting, there is a moderate reduction of body weight when isocaloric/eucaloric feeding is not employed as part of the study (stote, 2017; Gabel 2018). In rodent models; however, TRF of chow diet usually does not impart weight loss (Liu et al., 2019; Woodie et al., 2018). When High fat diet is given, TRF stimulates body weight loss (Hatori et al., 2012; Liu et al., 2019; Sherman et al., 2012). We will monitor body composition (Fat mass, lean mass, free water) indirectly by EchoMRI and we predict to observe no differences in fat, lean, or water content compared to gestational-age matched, *ad libitum* fed control.

## Specific aim 2.4 Assess the effect of eTRF on maternal digestive efficiency

Although digestion and nutrient utilization are active areas of research in both pregnant animals and humans, the physical and physiological changes of the alimentary canal in pregnancy are not well characterized. The vast majority of work that has been done in both humans and in animals focuses on micronutrient transport and utilization during gestation; especially of iron and calcium(Fisher & Nemeth, 2017; Kovacs, 2000).These studies have demonstrated in animal models that there is hypertrophy of the absorptive surfaces in pregnant animals compared to their non-pregnant counterparts (Kovacs, 2000). Still, no measurement of absorptive capacity have evaluated the effect of 6-hour eTRF on the digestive tract, especially not during pregnancy. This is a critical gap in the literature as circadian rhythms and food restriction have been found to entrain enterocyte nutrient transporters to anticipate caloric intake in animals with intact CLOCK (Pan, 2009). In the case of macronutrient transport, timing of food delivery was found to be a more potent entrainment tool than even light/dark cycle manipulation in mice (Pan & Hussain, 2009). For this reason, I believe that macronutrient and energy absorption will be more complete in dams fed eTRF. of These changes may be especially useful in shift working pregnant mothers as shift workers are heavy GI complainers ().

* Fasting is also known to induce remodeling of GI nerve activity (doi 1007/s10237-019-01185-7.)

Fasting may therefore be one of the ways we can aid women with GI symptoms in pregnancy experience relief highly prevalent – may not go down this route.

## Specific aim 2.5 Determining how eTRF affects insulin sensitivity and glycemia in pregnant mice

Studies of time restricted feeding have demonstrated improvements in insulin sensitivity in both animals () and humans (Halberg et al., 2005; Sutton et al., 2018). However, this is usually not accompanied by drastic changes in glycemia (Halberg et al., 2005; Hatori et al., 2012; Liu et al., 2019; Sherman et al., 2012; Sutton et al., 2018; Woodie et al., 2018). In fact, reduction in glycemia was only apparent in 1 human study, and only detectable by the use of continuous glucose monitoring, where they found that night-time glucose was reduced whereas daytime glycemia was unchanged (Jamshed et al., 2019). For this reason, I hypothesize that insulin sensitivity will be improved during gestation and that glycemia will not be affected. To test insulin sensitivity, an insulin tolerance test (ITT) will be conducted, as it assesses both glycemic control and insulin production and is therefore more sensitive than a glucose tolerance test (GTT) (Kim, 2009) , and previous work has demonstrated that in pregnancy, insulin tolerance is affected, whereas glycemia is not (Musial et al., 2016). If the ITT demonstrates improved insulin sensitivity, I propose to conduct a hyperinsulinemic-euglycemic clamp during the mid- pregnancy, when insulin resistance is known to be greatest in mice (Musial et al., 2016). This will provide more information to further evaluate the mechanisms that underlie insulin sensitivity; such as contribution from hepatic glucose production, peripheral glucose disposal, and whole organ glucose utilization. We will also determine NEFA levels, as fatty acids are a major contributor to gluconeogenesis.

Based on these results, we will hypothesize a mechanism by which eTRF may improve insulin sensitivity. We propose that GDF15 may be a key moderator of eTRF responses because of its known activity increasing from and will measure its levels in serum from AL and eTRF mice at E17.5. If GDF15 is elevated in concert with improvements in insulin sensitivity, future experiments will investigate eTRF on GDF15 knockout mice. GDF15 may be induced in response to high volume meals of eTRF, leading to reduced desire to eat-normalizing food intake, and inducing insulin sensitivity (GDF15 paper I’m reading now).

According to Peterson and colleagues, non-pathological excursions in glycemia may be evident in participants undergoing TRF, and the only way to catch these MAGE events, described in (Service et al., 1970), is through constant transmission of blood or interstitial glucose(Jamshed et al., 2019). This demonstrated that the mean amplitude of glycemic excursions, was lower in eTRF compared to the control group. They also demonstrated that 24-hour glucose was One of the few fairly consistent findings of time-restricted feeding trials in both humans and animals is an improvement of insulin resistance. This is usually accompanied by a reduction in insulin levels, and no changes in glycemia. However, based on Peterson and colleagues’ recent findings about eTRF reducing nocturnal glucose excursions, static fasting blood glucose during the light cycle is likely insufficient to fully capture the effects to eTRF on glycemia(Jamshed et al., 2019).

## Methods:

### Animals:

C57BL6/J mice were previously used in the insulin resistance of pregnancy experiment were used in this experiment. At 134 days of age, age matched females were randomized to either *ad libitum* (AL) or early time-restricted eating (eTRF). Dams randomized to AL feeding had 24-hour access to chow (5% fat, 24% protein, 3.7% sucrose, 32% starch). Dams randomized to eTRF feeding were allowed *ad libitum* access to chow during 6 hours of the dark cycle (8pm-2am). At 2 am, all dams were moved to clean cages to standardize stress and handling between feeding regimens (Hatori, 2012). Animals were held in a 12:12 light dark cycle, in a temperature and humidity-controlled facility. Food intake was monitored daily, with 6 hour and 24-hour intake calculated as total grams of food consumed per day multiplied by utilizable energy in the provided diet. Dams were switched to AL feeding upon parturition.

### Mating:

Dams were singly housed for the course of the experiment. After a one-week acclimation period, males were added to the cages in monogamous pairs. Males were allowed to remain in cages until copulatory plug appeared, which was noted as day 0.5 of pregnancy. At gestation day 19, males were removed to prevent second pregnancies after delivering. During the course of the birth and post-natal period until PND 21, dams were singly housed with their litters.

### Body Composition:

Once a week, Dams weight was measured weekly using an electronic scale (Mettler Toledo). Body composition including fat mass, lean mass, and free water was assessed indirectly via magnetic resonance imaging (EchoMRI).

### Insulin Sensitivity:

*Insulin tolerance test:*

Insulin sensitivity was assessed by insulin tolerance test 16 days after mating began. Gestational age during ITT was determined using plug data, body weight gain, and date of delivery. As a result, most dams were in the 1st or 3rd week of gestation during this time. After 6-hour fast, blood glucose was taken using a glucometer and tail clip. Females were given insulin injections (0.75 units/kg body weight; Humulin U100 in cold sterile, filtered Phosphate buffered saline (PBS)) and blood glucose was tested using a glucometer at 15-minute intervals for 2 hours. If animals began to exhibit moribund behaviors, 300 units of 10% glucose in cold sterile filtered PBS was administered and subsequent BG measurements were omitted from the ITT.

*Hyperinsulinemic-euglycemic clamp:*

After mating and confirmation of pregnancy by weight gain of 1.75g signaling 7 days of pregnancy (Heyne et al., 2015), animals will be placed singly housed into a special cage unit. Dams will be cannulated and exogenous insulin will be administered, inducing a state of hyperinsulinemia(Kim, 2009) and thereby suppressing hepatic glucose production. Glucose is infused to maintain blood sugar, with the amount infused correlating to the ability of that animal to utilize insulin to dispose of glucose. Greater glucose infusion rates represent more insulin sensitive animals. This method also allows for understanding of tissue-specific glucose disposal. 2-deoxy-glucose is given as a bolus75 minutes after initiation of the clamp. Sample and tissues are taken for analysis of glucose content

Radiolabeled [3H] glucose HGP= whole body glucose turnover – GIR.

This was already done in Musial, as well as hepatic vs adipose vs skeletal muscle insulin signaling and then also fetal vs placental vs maternal tissue use of radiolabeled glucose.

### Glycemia:

As Jamshed and colleagues have previously demonstrated, the use of continuous glucose monitoring may demonstrate more significant trends in glycemia that static blood glucose and terminal blood glucose measurement are able to capture(Jamshed et al., 2019). For this reason, I propose to use continuous glucose telemetry during pregnancy to collect 24-hours of continuous glucose measurements without the need for serial sampling. With the collaboration and expertise provided from the animal phenotyping core, implantable glucose telemetry units will be implanted into dams during early pregnancy. The telemetry units collect glucose data can collect data anywhere from 28 to 45 days; therefore, glycemia during the entire pregnancy can be captured with this implantable device.

### Energy Expenditure:

CLAMS

### Digestive Physiology:

*Energy Absorption*

To determine if there exist any differences in the amounts of energy consumed from food consumed between eTRF dams and ad libitum fed dams, fecal calorimetry will be performed. Full 24-hour fecal samples will be collected from dams individually and then dried. Dried fecal matter will be assessed by a bomb calorimeter to determine total energy content in the stool as described by Murphy and colleagues (Murphy et al., 2010). Results will be expressed as total energy intake for that day – energy found in stool.

*Macronutrient absorption into portal circulation*

macronutrient absorption should be assessed in vivo. This can be accomplished through the use of *in situ* looping of the intestinal tract. Anaesthetized dams at day 17.5 will have two small incisions made on the abdomen, and peritoneal cavity will be flushed with PBS. A proximal jejeunal loop will be made and a mixture of PBS/radiolabeled macronutrient solution (PBS/ [3H] Triolein/[14C] Cholesterol and cholesterol for lipid absorption, and [14C] alpha Methylglucoside (αMG) for carbohydrates, and [3H]glycylsarcosine (gly-sar) for protein) will be introduced to the lumen of the loop via microsyringe. After 1-hour elapses, loops will be collected as well as blood samples from the portal vein. Blood will then be centrifuged at 4 degrees C at 5000 RCF for 20 minutes to collect serum. Serum will be analyzed by scintillation counter to quantify nutrient absorption into portal circulation.

Pitfalls in general:

Restriction may affect implantation- see that paper from INSS?

May lead to dams being hungry/eating pups- perhaps, but share data

One concern about using eTRF in pregnant dams is that it would lead to growth restriction of the pups.

May be growth restricted pups- evidence against it – Detrick’s pediatrics paper

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