Pregnancy and Postpartum Observational Dietary Study (PPODS):

Percent Dietary Saturated Fat Composition in Pregnancy & Postpartum Weight Loss

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PERSONAL STATEMENT

Approximately 7 years ago, I sat in my former chairman’s office as a chief Ob/Gyn resident ready to negotiate my first faculty position. I confidently sat there seeking ‘protected time for research’ and walked away naively thrilled at being granted a half day a week. In retrospect what I knew then was ‘I love asking questions and pursuing answers’ – what I did not appreciate were the details of the conduct of rigorous research methods, the need to publish and pursue funding and the critical role of experienced mentorship for my development.

After receiving the protected time I requested and committing to a research career, I decided to pursue additional degrees to deepen my knowledge and capabilities. In the first 4 years following residency, I obtained a MPH from Harvard’s School of Public Health and a MEd from UMass. In addition to attending classes, my early attending years were focused on solidifying clinical skills, building a practice, attaining board certification and having my first child. With the aforementioned activities, research was relegated to mostly nights and weekends with the notable exception that I assisted nearly all residents with required research projects and ultimately became the Director of Resident Research. This position allowed me to utilize and hone my newly acquired skills on a wide breadth of topics and methodologies. The benefits of this work for the Department included more robust research products as reflected by a significant increase in presentations at local and national conferences and resident competitiveness for fellowships.

Since then my personal focus, growth, and impact have continued. First, I led and/or collaborated on several projects regarding weight gain and obesity in pregnancy and biomarker evaluation of obstetric-related diseases; hence solidifying my interest in pregnancy as a ‘crystal ball’ into which future maternal and offspring cardiometabolic health can be viewed and potentially even altered/optimized. Second, I reached outside of my Department and took advantage of many opportunities to network, to attend research skill development sessions, and to find highly valued mentors, Advisors and collaborators. Third, my current chair, Dr. Julia Johnson, recognized my efforts and potential by creating a new research division and appointed me as the founding Director in July 2009. As Director, my responsibilities include developing my own research agenda and funding pipeline and developing the people and Department processes and infrastructure required to scale Department research capabilities and expertise.

Since creating the division, there have been many successes including its most recent being the organization and hosting of UMMS’ first Community of Scholars event. I am optimistic about its future and our ability to make an even greater impact while furthering UMMS’ mission. One particular area of opportunity is the ‘Pregnancy & Postpartum Observational Dietary Study’ (PPODS) as presented in this application. PPODS is an exciting translational project that is housed in Ob/Gyn, on which I am co-principal investigator. Its funding through the CCTS is enabling collaboration among faculty from the school and clinical systems representing 6 departments and spanning clinical to basic sciences. Information from this cohort will provide critical data for future extramural funding applications and for interventions.

I am applying for this award to ensure that we capitalize on, and maintain, momentum and productivity for this foundational study as I am expecting our second child in September and will have the added responsibilities associated with infant care over the subsequent year. I have identified a well matched candidate who could start immediately to cover essential project tasks and add capacity to our team. Hiring an entry level technician would allow my more seasoned team members to delegate less complex work to this person allowing them to function more optimally in their roles and to perform some of the work I typically complete as part of my hands-on approach to cultivating and maintaining projects. This domino delegation would allow me to focus on higher-level strategic functions, such as continued divisional growth and collaboration solidification, efforts to prepare grants and manuscripts and personal development. In addition to supporting PPODS, this candidate would create capacity for other team members to assist me in covering responsibilities related to my research Division Director role where here too, a gap in my availability runs the risk of stalling personal, professional, and divisional growth along with research efforts of students, residents, fellows and other faculty both within and outside of our Department. In addition to other tasks, this person would take over the daily logistics of biologic specimen collections critical to planned experiments and funded projects for multiple basic science labs (e.g. collection of cord blood, umbilical cords, placentas and cervical explants for Doctors Greiner, Lawson, Clapham, Duenas DeCamp, Peters and the Stem Cell Bank). In addition to near term support, given that we’re a young growing division, building a pipeline of young talent is an essential part of our continuity and growth strategy. This award would provide 80% support for a research technician position. Dr. Johnson has agreed to augment its impact by committing to another 20% support for said position and by continuing my protected research time and support.
PROJECT PLAN

SPECIFIC AIMS: Weight gain in young adults increases risks for cardio-metabolic and other health conditions throughout adulthood (Carnethon, 2004; Norman, 2003; Daviglus, 2004; Truesdale, 2006) and weight loss decreases these risks (Kowler, 2002; Ratner, 2005; Orchard, 2005). Pregnancy weight gain and postpartum weight retention (PPWR) contribute to increases in BMI among women of childbearing age (Walker, 2005). On average, women retain approximately 3 kg/pregnancy at 10 years (Gore, 2003), and failure to lose pregnancy weight within 6 months post-partum predicts long-term obesity (Rooney, 2002; Linne, 2003). Thus, post-partum weight loss is key to women’s long-term health.

Interventions to promote weight loss among post-partum women (Kuhlmann, 2008) have been minimally effective. An underlying assumption in these studies is that excess adipose tissue responds to weight loss strategies independent of the manner in which the weight was accrued. Recent studies from our group (Corvera laboratory) question this assumption having found that while different obesogenic diets induce very similar degrees of fat mass accumulation in mice, the rate and extent of fat loss varied significantly following the transition to a normal (non-obesogenic) rodent diet. These differences correlated with differential deposition of fat amongst the visceral and subcutaneous (SQ) depots of the mice in response to diet composition, and with differential effects on energy expenditure upon transition to normal chow. Thus, these results show that the composition of the diet that led to the accumulation of excess adipose tissue has an important effect on subsequent weight loss. While the diets used in these studies varied in several parameters, only the percent saturated fat correlated with the preferential increase in SQ adiposity, decreased energy expenditure and persistence of fat mass. The overall goal of this translational research project is to evaluate whether associations among consumption of saturated fat, fat deposition and weight loss observed in mice, can be observed in human subjects during pregnancy and the postpartum period focusing on both maternal and offspring effects.

Specific aims of the project are to:

1. Investigate whether dietary composition during pregnancy, specifically percent saturated fat content, is associated with early (i.e., six month) postpartum weight loss (primary aim).
2. Investigate whether dietary composition during pregnancy, specifically percent saturated fat content, differentially affects ratio of subcutaneous (SQ) to visceral fat deposition during gestational weight gain (secondary aim).
3. Investigate whether dietary composition during pregnancy, specifically percent saturated fat content, is associated with hypertrophic versus hyperplastic SQ and visceral adipose tissue growth, and alteration of SQ and visceral adipose vascular architecture (secondary aim).
4. Investigate whether dietary composition during pregnancy, specifically percent saturated fat content, and maternal weight gain during pregnancy, is associated with differences in epigenetic profiles of metabolic pathway genes in the neonatal and maternal tissues (exploratory aim).

SIGNIFICANCE

This project addresses the topic of PPWR and weight loss, an under-studied area of enormous public health importance. Weight gain during the childbearing years places women at increased risk for numerous health consequences throughout the lifespan (i.e., hypertension, dyslipidemia, metabolic syndrome, insulin resistance, diabetes, vascular inflammation, cardiovascular disease, stroke and some cancers) (Carnethon, 2004; Norman, 2003; Daviglus, 2004). However, many women gain excessively during pregnancy and do not lose this weight in the post-partum period.

The significance of the work proposed in this study is that it will test the hypothesis that, controlling for the number of total calories consumed, the dietary composition during pregnancy will significantly influence weight loss postpartum. There are very limited studies to date addressing weight-management interventions for postpartum women (Kulmann, 2008; Keller, 2008; Leermakers, 1998; O’Toole, 2003), and studies are beginning to examine dietary components which may assist with weight loss postpartum. For example, a 2009 Brazilian study (de Castro, 2009) found that a high protein diet (>1.2g/kg) in the postpartum period leads to greater weight loss among postpartum women, though fat composition was not examined separately (de Castro, 2009; Lyu, 2009). However, if the proposed project reveals differential adipose deposition and weight loss as a function of dietary pattern during pregnancy, it would provide support for rolling back the timeline and intervening for PPWR not in the postpartum period, but rather during pregnancy. In addition, our work will test the hypothesis that, controlling for covariates mentioned above, dietary composition will influence the mode (hypertrophy or hyperplasia) by which adipose tissue expands to accommodate calorie storage, and
the adipose tissue depot that preferentially expands. There is virtually no available information on the effects of diet composition on these parameters, despite overwhelming evidence for the associations between visceral adiposity and higher risk of metabolic disease, and of obesity-associated inflammation and adipocyte hypertrophy. This line of inquiry has the potential to translate findings in animal models to the human condition and if correlated would allow for (1) return to animal models for elucidation of underlying mechanisms and (2) development of human clinical interventions that have the possibility of directly optimizing weight outcomes for mothers and their offspring and indirectly affecting other immediate and long-term cardiometabolic risks and conditions.

**RESEARCH DESIGN & METHODS**

1. **Study setting:** Ambulatory OB practices of faculty & residents of the Dept of Ob/Gyn at UMMHC, which have 1,550 new prenatal visits and 1,200 deliveries/yr. The population is 20% Latina, 12.5% Black and 55% non-Latina white women.

2. **Eligibility:** All English-speaking pregnant women with singleton gestations and negative gestational diabetes screen (~28 weeks) will be considered for enrollment. Exclusions: (1) age <20 or ≥ 40 years, (2) tobacco, alcohol and/or illicit drugs, (3) using medications that affect weight, (4) selected medical conditions: HIV, hepatitis, autoimmune disease, gastric bypass history, eating disorder history, (5) initiated prenatal care after completion of first trimester (13 weeks) and (8) plans to move within the study period.

3. **Recruitment and retention procedures:** RC will review schedules, lab results and medical records to generate daily list of eligible women to whom informative letters mailed. Women approached and consented at next prenatal visit. In our prior studies we have attained 85% recruitment and 90% retention rates (Moore Simas, 2008; Maynard, 2008; Maynard, 2010).

4. **Measurements & Assessments** will include clinical, behavioral, psychosocial and biologic measures as indicated in table.

4a. 1° Exposure – Dietary Intake/Composition: 24 Hr Recalls are considered gold standard for diet assessment in clinical studies and will be utilized per protocol.

4b. 1° Outcome Variables: (1) Postpartum Weight Loss: Measured weight at 6 months postpartum subtracted from measured weight following delivery (i.e. after loss of weight attributable to neonate, placenta and amniotic fluid). (2) SQ & Visceral Fat Deposition: Limited MRI studies capturing 4-6 axial images will allow quantification of SQ & visceral adipose tissue volume (Machann, 2010) in the immediate in-patient postpartum period. Serial skin fold thickness (SFT) measurements will additionally be performed at seven body sites. (3) Adipose Tissue Biopsies: Subset of subjects undergoing Cesarean delivery will have SQ (within surgical incision) and visceral (omental) adipose tissue biopsies. Size and number of adipocytes determined after fixation, section and analysis by light microscopy in 10 fields/specimen along with capillary density (number cell profiles stained with endothelial specific markers (e.g. vWF) in 10-20 fields/specimen).

4c. **Potential Covariates to be Assessed** include but are not limited to prepregnancy BMI, gestational weight gain, physical activity, lactation status, demographic factors and psychosocial parameters.

5. **Sample Size, Power Calculation & Analyses (Aim 1):** To test our aims, we will recruit a sample of 100 eligible pregnant women, conservatively assuming retention of 80 subjects by study end. To compare post-partum weight change in a high saturated fat with a low saturated fat group, we will use a standard t-test (vs Wilcoxon test depending on normality) with a two-sided alpha=0.05 and power=0.80. With these assumptions and cohort split into the two fat content groups at the median, we will be able to detect a difference of 0.65 standard deviation units. We expect that we will be able to detect even smaller differences through the use of regression models that control for potential covariates as previously indicated.

**IRB & FUNDING:** This study has been approved by the IRB (Docket #14187) – screening and recruitment have commenced. This study is predominantly funded as of Jan 1, 2011 by the UMMS CCTS Pilot Project Program.
REFERENCES:


## PROPOSED BUDGET

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<td>Dr. Tiffany Moore Simas</td>
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### Other Costs

All other costs for this study including patient stipends, MRI, telephone-administered 24 hour diet and exercise recalls, adipose tissue biopsy processing supplies are either covered by the funded CCTS proposal or being provided in kind by the highly invested investigator team.

**Total Support Requested:** $29,993.60 for 1 year

**Tiffany A. Moore Simas, MD, MPH, MEd**, Co-Principal Investigator, is Assistant Professor in the Departments of Obstetrics & Gynecology and Pediatrics. Dr. Moore Simas is a board-certified generalist Ob/Gyn and director of the Ob/Gyn research division. She will oversee all aspects of this project in conjunction with co-PIs including recruitment, implementation, specimen collection, analysis, interpretation of results, manuscript and grant preparation. Dr. Moore Simas has recruited from a similar patient population for studies involving collection of biologic specimens in the pregnancy, delivery and postpartum period. Her efforts and division provide the day to day logistical support that is integral to this study.

**Milagros C. Rosal, PhD**, is Co-Principal Investigator and Associate Professor in the Department of Medicine’s Division of Preventive and Behavioral Medicine. Dr. Rosal will oversee all aspects of this project with co-PIs as indicated above.
Silvia Corvera, MD, Co-Principal Investigator, is Professor in the Department of Molecular Medicine. She will oversee all aspects of this project in conjunction with co-PIs as indicated above. Dr. Corvera will directly oversee the laboratory technician processing and analyzing adipose tissue biopsies.

Sarwat Hussain, MD, Co-Investigator, is Professor and Vice-Chair of Radiology. Dr Hussain’s expertise will be utilized for quantification of subcutaneous versus visceral adipose tissue deposition as per magnetic-resonance imaging in subjects in the postpartum period. He will personally read and interpret all study-specific imaging studies.

Bruce Barton, PhD, Co-Investigator, is Professor of Biostatistics and Health Services Research in the Department of Quantitative Health Sciences. Dr. Barton’s expertise and experience in management, design, and analysis of longitudinal data especially as it relates to growth and development in children, including measures of anthropometry and cardiovascular disease risk factors, and the relationship of nutrition, physical activity, and psychosocial factors to anthropometry will be utilized extensively in this study. He will assist in outcome and risk factor measurement and study design issues; design statistical models to test major project hypotheses; and supervise the execution of planned analyses.

Barbara Olendzki, RD, MPH, LDN, Co-Investigator. Ms. Olendzki is a clinical and research nutritionist in the Division of Preventive and Behavioral Medicine. She has considerable expertise in dietary and physical activity assessments in randomized controlled trials using 24-hour recall methodology. She will be responsible for directly overseeing the implementation of the diet and physical activity assessments in the proposed study, specifically she will train and supervise the nutritionists administering the 24-hour recalls.

Laura Robidoux, BS, will be a research coordinator for the project. Ms. Robidoux will have a key role in the project, including but not limited to execution of and/or supervision of research assistant for execution of: (1) the day-to-day operations of the proposed project, ensuring adherence to protocols and high quality control, (2) screening, identifying and recruiting study participants, (3) Implementing informed consent procedures, (4) completing baseline in-clinic assessments including skin fold thickness, blood pressure, weight and survey measurements, (5) monitoring of inpatient obstetrics census for admission of study participants, (6) completing chart reviews and case-report forms, (7) contacting participants at delivery, 6 weeks, 3 months and 6 months post delivery for completion of in-clinic assessments (i.e., skin fold thickness, blood pressure, weight and survey measurements), (8) scheduling MRI visits and (9) communicating with study subjects regularly and as needed to optimize subject retention.

Adipose Tissue Biopsy Technician (TBN) will be responsible for processing and analysis of fat biopsies including assessment of size and number of adipocytes after fixation via light microscopy in 10 fields per biopsy specimen. Additionally, the technician will measure capillary density by counting the number of cell profiles stained with endothelial specific markers in 10-20 fields per biopsy specimen.

Xun Liao, MS will be the data analyst for the project. She will clean data, monitor data integrity and conduct statistical analysis under the direction of Dr. Bruce Barton. She will additionally participate in analysis specific discussions and decisions; and participate in summarization of results for presentation at scientific meetings and in manuscripts. Her effort will be .60 calendar months (5%) in budget period 2.
Research Technician (TBH), under the direction of the research coordinator, will execute (1) screening, identifying and recruiting study participants, (2) Implementing informed consent procedures, (3) completing baseline in-clinic assessments including skin fold thickness, blood pressure, weight and survey measurements, (4) monitoring of inpatient obstetrics census for admission of study participants, (5) completing chart reviews, case-report forms and data entry, (6) contacting participants at delivery, 6 weeks, 3 months and 6 months post delivery for completion of in-clinic assessments and (7) scheduling MRI visits. (Temporary, non-benefited, grade 15 position at $17.50/hr and 3% fringe).