Protocol #: 21-3969
Project Title: The Influence of Combined Oral Contraceptives on Weight, Body Composition, Eating Behaviors, and Appetite in Pre-menopausal Women with Overweight or Obesity
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HYPOTHESIS AND SPECIFIC AIMS

The overall objective of this feasibility pilot study is to prospectively evaluate the effects of initiating a combined estrogen and progestin oral contraceptive (**COC**) compared to non-hormonal contraceptives (**NHCs**) on body weight, body composition, eating behaviors, and appetite in pre-menopausal women with overweight or obesity.

Our overall hypothesis is that initiation of COCs in women with overweight or obesity will be associated with greater weight gain and increases in cardiometabolic health risks than use of NHCs over 6 months. We will recruit pre-menopausal women with overweight or obesity who have already elected to initiate COCs through the Comprehensive Women's Health Center (CWHC) as well as a control group comprised of age and BMI matched NHC users. We will evaluate the feasibility of recruiting women initiating a COC and women using NHCs from both the CWHC and the general population into a prospective, observational study as well as the feasibility of evaluating changes in weight, body composition, eating behaviors, and appetite over 6 months from COC initiation. I propose the following specific aims:

Aim 1: Assess the feasibility of recruiting and retaining a racially/ethnically diverse group of pre-menopausal women with overweight or obesity initiating COCs compared to age- and BMI-matched NHC users. We aim to recruit ~10 women per month for 6 months (N=64; n=32 COCs, n=32 NHCs; >20% in each group of African American or Hispanic race/ethnicity) and assess feasibility of completion of outcome measures. We hypothesize that at least 80% of participants will continue their chosen contraceptive method and complete outcome measures within a 2-week window at 6 months.

Exploratory Aim 2: Explore the influence of COC vs. NHC use on body weight, body composition, and cardiometabolic risk factors. We hypothesize that women with overweight or obesity initiating COCs will exhibit greater increases in body weight, fat mass, homeostatic model assessment for insulin resistance (HOMA-IR), triglycerides, and blood pressure compared to age- and BMI-matched NHC users.

Exploratory Aim 3: Explore the influence of COC vs. NHC use on energy intake (EI), eating behaviors, and appetite. We hypothesize that women with overweight or obesity initiating COCs will have greater increases in dietary energy and fat/carbohydrate intake, hunger, disinhibition, reward-based eating, emotional eating, binge eating, and food cravings at 6 months compared to age- and BMI-matched NHC users.

RESEARCH METHODS

A. Outcome Measure(s):

Feasibility Outcomes: *Feasibility of recruitment/enrollment* will be assessed by evaluating the number of patients who express interest, eligibility rate, and enrollment rate. *Retention* will be assessed as number of participants who remain on their contraceptive method and who complete the study divided by number enrolled. *Feasibility of completion of outcome measures* will be assessed as the number of participants completing the study outcome measures at each time point within a 2-week window divided by number of active participants.

Anthropometrics: Anthropometrics will be collected at 0, 3, and 6 months. Gowned body weight will be measured in the morning in a fasted state using a digital scale accurate to ±0.1 kg. Height will be measured to the nearest 1 mm with a stadiometer at baseline to calculate BMI. Blood pressure will be measured with a manual sphygmomanometer. Fat mass (FM) and lean mass (LM) will be measured with DXA (Hologic Horizon W, version Apex 5.6.04). A review of the electronic medical record (EMR) for clinic weights over the previous 12 months before starting contraception will also be performed.

Outcome Questionnaires: Questionnaires will be administered at 0, 3, and 6 months. Cognitive restraint, unrestrained eating, and emotional eating will be assessed with the Three Factor Eating Questionnaire-Revised 18v2[37,38]. The Reward-Based Eating Drive Scale will be utilized to assess preoccupation with food, loss of control over eating, and lack of satiety[39]. The Palatable Eating Motives Scale will be administered to measure tendency to use palatable foods to cope with negative feelings[40]. The Trait Food Craving Questionnaire will measure behavioral, cognitive, and physical aspects of craving for different foods[41]. The Binge Eating Scale will be used to identify the presence and severity of binge eating behaviors[42]. The Perceived Stress Scale will be used to measure levels of stress on the participant within the past month[43,44]. The Life Events Questionnaire will be used to assess number of life stressors and the level of effect of these stressors[45,46]. Interval History questionnaires will be administered at months 3 and 6 to capture any changes in birth control method, medical history, and health and exercise history during the intervention.

Dietary Energy Intake and Macronutrient Intake: Dietary EI and macronutrient intake will be quantified using a written 3-day diet record at baseline and 6 months. Dietary intake data will be collected and analyzed using Nutrition Data System for Research (NDS-R) software (version 2019), developed by the Nutrition Coordinating Center (NCC), University of Minnesota, Minneapolis, MN[47] to determine kilocalorie and macronutrient content of EI.

Visual Analog Scale: Pre- and post-meal hunger and satiety will be measured using visual analog scales (VAS) before and after each meal for the 3-day time period coinciding with the 3-day diet records[48-51]. Data will be collected using smartphone technology with text messaging reminders (linked to the REDCap study database).

Laboratory Assessments: A 12-hour fasting AM blood sample will be obtained at baseline and 6 months and to assess fasting insulin and glucose (to calculate HOMA-IR) as well as lipids. Baseline samples will also be used to analyze for SNVs in genetic loci of estrogen and progesterone receptor genes.

All measures will be assessed as specified below (Table 1).

Table 1. Outcome Measures by Study Month

	Screening	Baseline	3 month	6 month
Consent	x			
H&P	x			
Screening Questionnaires	x			
Anthropometrics (BMI [kg/m^2], WC [cm]) and Vitals (BP)	x	x	x	x
Body Composition (DXA)		x		x
Lab Collection: Glucose, Insulin, Lipids		x		x
Lab Collection: SNV Analysis		x		
Outcome Questionnaires		x	x	x
3-day Diet Diaries		x		x
Dietary Adherence with VAS		x	x	x

B. Description of Population to be Enrolled:

The study will be performed in a cohort of up to 64 females of reproductive age, age 18-40 years, with overweight or class I and II obesity (BMI 25-39.9 kg/m^2) who are seen at the Comprehensive Women's Health Center (CWHC) or a University of Colorado Hospital Anschutz Outpatient Pavilion (UCH AOP) contraception clinic to initiate COCs and women from the CWHC or general population who are using NHCs. Participant inclusion age will be capped at 40 years old to avoid including women in the peri-menopausal phase. Pre-menopausal status will be confirmed by an MD. To be eligible to participate in this observational, feasibility pilot study, volunteers must meet the following inclusion and exclusion criteria:

Inclusion Criteria

- Females
- Age 18-40 years
- Overweight or class I and II obesity (BMI 25-39.9kg/m^2)
- Free of major psychiatric illnesses
- Electing to start the Sprintec (norgestimate/ethinyl estradiol 0.25mg/35mcg) COC
- Using non-hormonal forms of contraception: copper intrauterine device (Cu-IUD), male condoms, tubal ligation, partner vasectomy, withdrawal/natural family planning, spermicide, abstinence, or other NHCs as determined by PI

Exclusion Criteria

- Diabetes
- Use of medications thought to affect body weight, energy intake, glycemic parameters, or estrogen (i.e. systemic glucocorticoids, stimulants, weight loss pharmacotherapy, metformin)
- History of weight loss surgery
- History of polycystic ovarian syndrome
- History of congenital adrenal hyperplasia
- Use of a different COC or hormonal contraception method within the past 3 months
- Planning pregnancy
- Planning to stop contraceptive within the next 6 months
- Planning to change diet or join a weight loss program or research study within the next 6 months
- Recent therapeutic abortion or miscarriage in the past 1 month if fetal gestational age <10 weeks, or 3 months if fetal gestational age >10 weeks
- Pregnancy with delivery in the past 6 months
- Currently lactating
- Transmen who were assigned female at birth and either currently using or planning to use gender-affirming hormone therapy in the next 6 months
- Use of other forms of reproductive hormones such as testosterone or dehydroepiandrosterone (DHEA)
- Current tobacco use

C. Study Design and Research Methods

Overview: This study will be performed at the CWHC, the University of Colorado Anschutz Medical Campus (CU-AMC), and the University of Colorado Hospital Anschutz Outpatient Pavilion (UCH AOP). The primary outcome of this pilot and feasibility study is to determine the feasibility of recruiting and retaining a racially/ethnically diverse group of pre-menopausal women with overweight or obesity initiating COCs from the CWHC as well as age- and BMI-match NHC control from the general population. We aim to recruit ~9-10 women per month for 6 months (N=64; evenly distributed as n=32 COCs and n=32 NHCs). We will do a nested subject selection based on race/ethnicity in a 1:1 ratio per group with the goal of including >20% women in each group of African American or Hispanic race/ethnicity. Outcome measures will be performed at the Clinical and Translational Research Center (CTRC) Core Lab and the Colorado Clinical Translation Science Institute (CCTSI) Bionutrition Core located at CU-AMC.

Rationale and Justification for Study Design: Contraceptive decision-making is a highly personal process and women often have strong preferences on their contraceptive choice based on contraceptive attributes[52]. It would be unethical to counsel against or withhold contraception from women seeking birth control or deliver a COC placebo. Since NHCs do not contain any synthetic reproductive hormones, NHCs serve as the ideal control for this study. To avoid large drop-out rates in this study, participants in the COC arm will only be enrolled in this study if they elect to initiate COCs (or remain on NHCs) after consultation and thorough contraceptive-counseling with a medical provider at CWHC; they will not be randomized to COC vs. NHCs. We recognize there may be differences in baseline characteristics between women electing to initiate COC versus those who use NHCs. If present, we will adjust for these differences in our analyses.

Study Participants: Participants will be recruited into this *observational* study after they have elected to initiate contraception and selected their contraception method via standard of care. Females of reproductive age (18-40 years old), with overweight or class I and II obesity (BMI 25-39.9 kg/m^2) who are using NHCs or who have an established clinical relationship with providers at the CWHC or UCH AOP and have elected to initiate contraception with COCs will be included in the study. Dr. Lazorwitz (co-mentor) and his research team have extensive experience conducting clinical trials with contraception, including recruiting and enrolling current contraceptive users and new contraceptive users. The CWHC is the primary site for Dr. Lazorwitz's research activities through the NICHD Contraceptive Clinical Trials Network and the recruitment methods described for this study are similar to how this team recruits for novel contraceptive method trials and extension trials of current contraceptive users. As CWHC is a family planning focused clinic, it is an ideal recruitment site for a study of contraceptive method initiators. Dr. Lazorwitz also has two partners with contraception clinics in the UCH AOP who can offer help recruiting potential participants by distributing fliers with information about the study. Women electing to start Sprintec (norgestimate/ethinyl estradiol 0.25mg/35mcg) will be included in the COC group. Sprintec is the most commonly prescribed monophasic COC at the CWHC and includes a 3rd generation progestin of lower androgenicity[53]; approximately 80 women are prescribed Sprintec per month. In comparison, women using NHCs (including Cu-IUD, male condoms, tubal ligation, partner vasectomy, withdrawal, and abstinence) will be included in the NHC group. The use of NHCs in the general population of reproductive-aged women who are sexually active is estimated to be 40%[6].

Recruitment and Screening: Women who are seen for a standard-of-care in-person or telehealth clinical visit for contraception counseling and initiation at the CWHC or UCH AOP who elect to start Sprintec and meet study age and BMI criteria will be asked about interest in participating in this observational study. Women who are seen for routine care in other University of Colorado outpatient clinics and who elect to start Sprintec and who meet age/BMI criteria will be given study fliers and study staff contact information to participate in this observational study. Both potential COC users and NHC users will be recruited from the general population through a combination of e-mail bulletins, printed fliers, and social media. If a woman from the general population meeting age/BMI criteria expresses interest in initiating a COC, she will still be referred to the CWHC or UCH AOP for a standard-of-care in-person or telehealth contraceptive counseling visit and medical examination. After shared-decision making with a provider, if she still elects to start Sprintec, then study staff will reach out to the potential participant for enrollment into this observational study. If women using NHCs meet age and BMI criteria when presenting to CWHC or UCH AOP and elect to remain on NHCs, they will also be asked about interest in participation in this study. Women who are interested in enrolling in this observational study will then undergo an in-person, telephone, or telehealth screen by the study PRA or PI to confirm eligibility and provide an overview of the study. Participants will be asked to sign an eConsent if they agree to participate in the study either in-person on a computer or tablet with a member of the study team present, or on their home device (computer, laptop, tablet, etc.) if study and consent is reviewed via phone or Zoom. If a participant declines eConsent, they will be given the option to sign a paper consent in-person or remotely and email their signed consent to the study team. After providing informed eConsent, participants will be brought to the CTRC for baseline measures and blood draw. A review of the electronic medical record (EMR) for clinic weights

over the previous 12 months before starting contraception will also be performed after consent. Selected contraceptive method will be initiated after baseline measures are collected.

Compensation: Subjects will be compensated for their time and effort in the study. Subjects will receive $100 for completing all assessment measures at baseline, 3-month, and 6-month follow-up visits.

D. Description, Risks and Justification of Procedures and Data Collection Tools:

Overview of Risks: Risks of study-related complications will be reduced by carefully selecting participants for inclusion in this study. We have clearly defined the contraindications to participation. Every effort will be made to minimize risks including a review of participants' health before study initiation. The study physician will contact the primary care physician of a participant, as needed, to clarify any issues that arise. The risk of finding a previously undiagnosed medical condition will be explained clearly as part of the informed consent, with the possibility that the condition(s) might require follow-up evaluation and treatment. This study will be scheduled to minimize time lost from work or studies, and subjects will receive some compensation for the time involved in completing the outcome measures detailed herein. Members of the research team, including the nursing staff at the CTRC, are trained and experienced in all of the methods and measures that will be performed. These measures will be performed in a controlled clinical environment (the CTRC) with access to a full completement of hospital services. Patients without significant co-morbidities will be recruited for this study to minimize the risks of serious adverse events, as discussed in the *Data and Safety Monitoring Plan*.

Risks of DXA Scan: All participants will undergo two DXA scans to assess body composition. The DXA procedure involves exposure to ionizing radiation. During the DXA, the effective radiation exposure is approximately 0.3 mrems per total body scan. The radiation exposure for the total study will be 0.6 mrems, which is below the annual body radiation exposure of 5,000 mrems permitted for radiation workers by federal regulation. It is possible that the study team will incidentally identify potential bone disorders (i.e., osteoporosis) and follow up testing will be recommended by the study MD.

Minimizing Risks Associated with DXA: To minimize the risk of radiation exposure from the DXA scan trained technicians conduct will conduct all scans, thus, reducing the likelihood of repeat assessments. If non-diagnostic evidence of osteoporosis is identified during the whole-body scan, the study physician will notify the participant and recommend further testing.

Risks of Screening: The primary risk from screening measures is diagnosis of a previously unknown disease. If a previously undiagnosed disease is found during screening or during any of the procedures, the study doctor will discuss the diagnosis with the participant and refer the participant to their primary care provider.

Minimizing Risks Associated with Screening: Every effort will be made to minimize risks including a review of participants' health before the testing. The study physician will contact the family physician, as needed, to clarify any issues that arise. The risk of finding a previously undiagnosed medical condition will be explained clearly as part of the informed consent, with the possibility that the condition(s) might require follow-up evaluation and treatment. This study will be scheduled to minimize time lost from work or studies, and subjects will receive some compensation for the time involved in completing the studies detailed herein.

Risks of Venipuncture: Each time blood is drawn about 1 tablespoon will be removed by putting a needle into the vein. This is the standard medical method used to obtain blood for tests. Subjects will feel pain when the needle goes into the vein but should not feel any after it is in the vein. A bruise may form at the site after the needle is removed. There is also a slight chance you may become light-headed or faint during this procedure.

Minimizing Risks Associated with Venipuncture: To minimize the risks associated with venipuncture, all procedures will be conducted by trained personnel.

Risks of Anthropometric Measures: There are no risks associated with these procedures.

Outcome Questionnaires: Some questionnaires include questions that may make some participants uncomfortable but would not be expected to pose any risk to subjects.

Minimizing Risks Associated with Outcome Questionnaires: Participants will be advised that they do not have to answer any questions that make them uncomfortable.

Risks of Confidentiality and Privacy: The use of questionnaires and collection of personal medical information poses a risk to confidentiality and privacy and may cause embarrassment. However, we foresee no psychological, social, or legal risks beyond those of participating in a health-related research study. There are no alternatives that would permit the acquisition of the information required.

Minimizing Risks Associated with Confidentiality and Privacy: These risks will be minimized by not including personal identifying information on the forms, when possible, and by conducting interviews and collection of personal information in a private setting.

Data Monitoring and Safety Plan: This pilot study aims to evaluate feasibility of recruiting women initiating a COC from the CHWC/UCH AOP or using a NHC into a prospective, observational study as well as the feasibility of evaluating changes in weight, body composition, eating behaviors, and appetite over 6 months from COC initiation (or 6 months of NHC use). The measurement protocols pose minimal risk to patients. Because of this low-risk status, the data safety monitoring plan for this feasibility pilot focuses on close monitoring by the PI (an MD with current board certification in Endocrinology) in conjunction with 3 other MDs who will serve as mentors to the PI and are board certified either in Endocrinology or Obstetrics and Gynecology. All mentors have served as PIs of numerous federally funded projects and are familiar with CU-AMC's safety monitoring protocols.

Measurement and Reporting of Adverse Events: We will collect adverse event data on a case-by-case basis. Adverse events will be reviewed, collated, and evaluated by the PI within 72 hours. All serious adverse events will be evaluated by the PI and mentors within 24 hours. Serious adverse events are defined as: death, life threatening injuries, inpatient hospitalization, persistent or significant disability/incapacity, or congenital anomaly/birth defect. Serious adverse events that are definitely or probably related to the protocol and any unanticipated adverse events that are definitely or probably related to the protocol will be reported to COMIRB and the CTRC within 5 days using the COMIRB Unanticipated Problem Report Form. Any study-related serious adverse events and any deaths (regardless of relatedness) will be reported to COMIRB. All other adverse events will be documented by standard COMIRB procedures.

Monitoring for Out-of-Range Laboratory Values: Laboratory data is collected in this study at two timepoints in this study (baseline and 6-months). Laboratory data (glucose, insulin, and a lipid panel) will be reviewed by the PI and out-of-range values will be reported to the subject. SNV analysis will be run on stored lab samples from baseline blood draws if funding allows. This genetic data will not be reported to the subject and is for hypothesis-generation.

Data and Quality Management: The principal investigator will be responsible for conducting this study, including overseeing participant safety, and complying with all reporting requirements to COMIRB. The investigative team will be trained in accordance with both COMIRB and HIPAA compliance issues and will act to maintain confidentiality and protect health information. Electronic data will be stored on secure servers with a high level of security, controlled access, daily back-up, and long-term retention of back-up files. Clinical data, including adverse events, concomitant medications, comorbidities, laboratory data, and study-specific outcomes will be entered into REDCap. All questionnaires will be collected using REDCap, thus negating the need to enter data from paper questionnaires. REDCap includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Study documents will be retained for a minimum of 7 years as per HIPAA regulations. Any hard copies of study data will be kept in participants' charts in a locked and secured file cabinet in the PI's or Study Coordinator's office. Access to all study data will be restricted to the PI and research personnel. While the study staff and the PI cannot be blinded to participant group assignment and outcome measures,

blinding will occur whenever possible to minimize bias. For example, the CTRC staff collecting labs or performing DXAs will be blinded to participant group assignment. Those scoring questionnaires and the personnel at the CCTSI analyzing diet diaries will also be blinded to group assignment during analysis. Finally, the statistician will be blinded when analyzing outcome measures. Field and range checks will be programmed to minimize data entry errors. Data distribution will be checked periodically, and outliers verified; missing data will be tracked and checked.

Stopping Rules, Withdrawals, and Terminations: In this minimal-risk observational pilot and feasibility study, it is unlikely that excessive adverse events will require stopping the study. However, as outline above, we will monitor adverse event rates in all participants and alert COMIRB if a larger than reasonably expect adverse event rate should occur. Safety stopping rules will be determined by the PI and her co-mentors and will relate to the risk-to-benefit ratio. All withdrawals and terminations will be reviewed by the PI and research team involved in this study on a case-by-case basis. The data will be evaluated separately to assess for association of contraceptive choice and specific adverse event outcome. An individual subject may be terminated from the study if the volunteer requests to leave the study, evidence of deliberate non-compliance, if the volunteer discontinues or switches their selected contraceptive method or becomes pregnant during the study. Other causes for termination include development of a chronic condition or acute condition likely to impact upon metabolic variables, require medications likely to impact upon metabolic variables, or impair the ability of the subject to participate.

E. Potential Scientific Problems:

Outcome measures cannot be timed to the menstrual cycle as women on COCs will no longer have true endogenous cycles. However, we will attempt to collect measures within the same monthly 2-week time frame from COC initiation, and ensure measures are obtained during the active pill weeks in COC users. Secondly, we will only be evaluating a single monophasic COC formulation (norgestimate/ethinyl estradiol 0.25mg/35mcg) in this pilot study to minimize confounding on outcomes due to inclusion of other subtypes of COCs such as low estrogen COCs (higher rates of discontinuation/formulation change due to breakthrough bleeding), triphasic COC's (difficult to obtain outcome measures on the same dose), or COCs with androgenic progestins. However, future larger studies could be powered for subgroup analyses to compare the effect of different COC preparations. We will not measure synthetic estrogen or progestins as standard lab assays cannot measure the synthetic reproductive hormones used in COCs; specialized assays will be considered in future studies to evaluate individual-level differences in COC metabolism. We elected to only include women with overweight or obesity in this pilot study as we believe this subgroup for women may be at greater risk for COC-associated weight gain, however future studies can include normal weight women as well to explore this comparison. Issues with recruitment/retention could impact our sample size, however one of our primary aims is to assess the feasibility of enrollment so no early stopping criteria related to low enrollment will be in place. Rather, alternative strategies to be considered in the event of difficulty with enrollment include reassessing the length of washout period needed to enroll women with a history of prior contraceptive use, pregnancy, or fetal loss. In the event of low enrollment, we will also consider changing the age limits (for example, decreasing lower age limit to 16 years), increasing BMI range, recruiting from other women's health clinics, or increasing reimbursement for participation.

F. Data Analysis Plan:

Analytical Plan: The primary objective of this study is to obtain feasibility and retainment data. This feasibility pilot study is more hypothesis-generating than testing. We will obtain preliminary data about the influence of COC on weight, body composition, eating behaviors, and lab data to inform a larger, fully-powered, prospective cohort study. In this study, 32 participants in each group (COC and NHC will be enrolled at baseline and we expect 20% attrition by month 6.

Statistical Analyses: Baseline characteristics will be summarized by COC users vs. NHC users using descriptive statistics. Between-group comparisons will be made using a two-sample t-test or Fisher's exact test for continuous and categorical variables, respectively. For *Aim 2* and *Aim 3*, our analyses will include any participant with one or more data point who does not discontinue chosen

contraception or switch contraceptive methods. A linear mixed effect model (LMM) will be used to fit repeated outcome measures where the independent variables consist of group (COC and NHC) and time (i.e., baseline and follow-up time visits) and group by time interaction terms, each as a classification variable. Under this model, mean change in the outcome value between time points will be estimated for each group and between-group differences in the change score will be tested; the corresponding 95% confidence interval (CI) will also be calculated. Normality of outcome measures will be examined for each outcome using the Shapiro-Wilk test and will also be graphically examined using residual plots of the statistical model. Data transformation (i.e. log or square root) will not be used to reduce the skewedness of data, as appropriate, if normality assumption is violated. Unstructured or heterogenous compound symmetry covariance will be used for the LMM model as appropriate. To minimize confounding, we will control for baseline age and BMI. Any other imbalanced potential confounding variables will be adjusted for as covariates in the statistical model. No interim analysis is planned. A p-value <0.05 will be considered statistically significant.

For feasibility *Aim 1*, we hypothesize that at least 80% of participants will continue their chosen contraceptive method and complete outcome measures within a 2-week window at 6 months. Enrollment rate will be calculated as the number of enrolled patients divided by the number of screened and eligible prospects. Retention rates and rates of completing outcome measures at baseline and follow-up visits will be tabulated using the number of enrolled participants as the denominator. A 95% confidence interval (CI) for these rate estimates will be calculated using Copper-Pearson exact method. These analyses will be conducted globally and by study groups.

Precision of Estimates: With a total sample size of 60, 50, and 25, the error margins (i.e. half of the width of a 95% CI for a proportion) will be at most 0.14, 0.15, and 0.2, respectively. These error margins are estimated assuming the observed proportion to be 0.5 (i.e. the most variable case).

For *Aim 2*, we hypothesize that women with overweight or obesity initiating COCs will exhibit greater increases in body weight, fat mass, HOMA-IR, triglycerides, and blood pressure compared to women using NHCs. Each exploratory outcome (body weight, body composition, blood pressure, lipids, and HOMA-IR) will be analyzed using the LMM. The contrast of the change score between baseline and 6 months is of primary interest. For body composition data, the above LMM analysis will be applied after isometric log ratio (iLR) transformation of the outcome (i.e. CoDA analysis). We will also use any weights retrieved from the EMR to assess weight trajectory prior to COC start and compare this to weight gain trajectory after COC initiation or continued NHC use from study start.

Power and Sample Size Calculations: Thirty-two participants in each group will be enrolled at baseline. Accounting for 20% attrition by month 6, a sample size of n=25 per group will provide 80% power at 5% significance to detect a between-group difference of 0.81 standard deviation (SD) of the individual change score. In the 2001 Coney et al.[7] study that followed weight changes with COC use out to 6 months, the SD of weight change at 6 months was 2.6 kg. Assuming a similar SD in our study, we will have sufficient power to detect a 2.4 kg between-group difference in weight change at 6 months, which is of clinical significance.

For *Aim 3*, we hypothesize that women with overweight or obesity initiating COCs will have greater increases in dietary energy and fat/carbohydrate intake, hunger, disinhibition, reward-based eating, emotional eating, binge eating, and food cravings at 6 months compared to NHC users. Analyses for these exploratory outcomes are conducted identically as in Aim 1 using the LMM model. The EI data may be analyzed using the CoDA technique as discussed for body composition data above.

Power Consideration: The minimum detectable effect size for between-group difference in the change score is 0.81 standard deviations of the individual change score.

Other Analyses: If significant results are found from Aim 2 for weight and body composition, we will conduct exploratory mediation analysis to assess to what degree the between-group differences in weigh tor DXA variable can be explained by the change score of the behavioral variables (i.e. potential mediator) in Aim 3. Product-of-two-coefficient method will be used to estimate the indirect effect and the bootstrap method will be used to estimate the 95% CI for the indirect effect. We are

collecting serum blood from participants and storing it for future analysis, should funding become available. One such analysis would be to assess baseline blood samples from participants for the SNV in the estrogen receptor (ESR1 rs9340799). No formal analysis plan has been formulated for SNV analysis as this is a purely exploratory endeavor to gather relevant data for a larger trial as we are significantly under-powered for any detectable differences.

G. Summarize Knowledge to be Gained:

The goal of this study is to understand the impact of reproductive hormones on weight in women and to ultimately develop more effective obesity prevention and treatment strategies for reproductive age women. As weight management is an important goal for reproductive-aged women with overweight or obesity, and COCs are a commonly used method of contraception, this study will help provide insight on the extent to which COCs are associated with weight gain and will begin to explore potential underlying mechanisms that may contribute to weight changes with COC use in women with overweight or obesity. Data collected from this study will support feasibility of enrollment and retention of the target study population and will be used to optimize the design of a fully powered, K-level, prospective cohort study evaluating weight gain with COC vs. NHC use. Finally, data collected from this study will also serve to generate hypotheses to direct selection of outcome measures in a larger prospective cohort trial, as well as to explore future smaller mechanistic studies of the short-term impact of COC on weight, body composition, eating behaviors, and appetite. Ultimately, we hope to help guide medical providers in identifying individuals who are at-risk of weight gain and counsel women with overweight or obesity on the most appropriate contraception method.