Strategic Hormonal Evaluation in Keto-AdaptatioN (SHEKAN)

The Ohio State University

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Protocol Title: Strategic Hormonal Evaluation in Keto-AdaptatioN (SHEKAN)

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Drug/Device Manufacturer: Mira Fertility Monitoring Kit: Quanovate Tech. Femometer Ring: Co-Innovation Biotech Co., Ltd.

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1. Abbreviations and Definitions

BOHB (Beta-hydroxybutyrate) – The primary ketone body produced via ketogenesis that serves as fuel.

DXA (Dual-Energy X-ray Absorptiometry) - DXA is a non-invasive imaging technique used to measure bone mineral density and body composition, including fat and lean mass.

KD (Ketogenic Diet) – A high-fat, low-carbohydrate, and moderate-protein diets that increase ketone bodies' production.

RMR (Resting Metabolic Rate)- A key component of your overall energy expenditure. This value represents the amount of calories your body burns while at rest to maintain basic life sustaining functions.

2. Background and Rationale

Summarize and synthesize the available research, including published data, to provide justification for the study.

Ketogenic diets (KDs)—characterized by high fat, low carbohydrate, and moderate protein intake—induce a metabolic shift from glucose to fat as the primary energy substrate, resulting in the production of ketone bodies: beta-hydroxybutyrate (BHB), acetoacetate, and acetone. This physiological state, known as nutritional ketosis, promotes enhanced fat oxidation, decreased glucose utilization, and improved metabolic flexibility. KDs have been associated with a range of beneficial health outcomes, including increased insulin sensitivity, improved lipid profiles, reduced visceral adiposity, and preservation of lean body mass during weight loss interventions (Gershuni et al., 2018).

Initially employed for managing refractory epilepsy, KDs have since gained broad application in clinical research targeting obesity, type 2 diabetes, polycystic ovary syndrome (PCOS), cancer, and neurodegenerative disorders such as Alzheimer's disease. In these contexts, KDs have demonstrated efficacy in reversing insulin resistance, reducing systemic inflammation, and modifying hormonal profiles, all of which are central to women's metabolic health.

Despite the growing body of research supporting the therapeutic potential of ketogenic diets, there is a marked gap in understanding their sex-specific effects. Most ketogenic diet studies either underrepresent women or fail to account for the hormonal fluctuations unique to the menstrual cycle, which can influence metabolism, mood, energy levels, and body composition. Preliminary data suggest that men and women respond differently to dietary interventions, including KDs, due in part to variations in sex hormones, fat distribution, and substrate metabolism (Clegg et al., 2006; Mauvais-Jarvis, 2015). However, these differences remain poorly characterized in the context of long-term ketogenic adaptation.

Emerging research has begun to explore how ketogenic diets may benefit women with endocrine disorders such as PCOS—where improvements in insulin sensitivity, menstrual regularity, and reproductive hormone profiles have been observed, often independent of weight loss (Rossetti et al., 2024; Magagnini et al., 2022). Yet, few studies have examined these outcomes in healthy, regularly menstruating women, leaving a critical gap in understanding how a eucaloric ketogenic diet interacts with normative reproductive hormonal cycling.

Moreover, women are disproportionately affected by metabolic and neurodegenerative diseases, with data suggesting that fluctuating estrogen levels across the lifespan—particularly during reproductive transitions—may exacerbate vulnerability to insulin resistance and cognitive decline. Reduced cerebral glucose metabolism, a consistent finding in Alzheimer's disease, appears earlier and more severely in women. In contrast, ketone metabolism remains stable with aging and neurodegeneration, suggesting that ketones may serve as an alternative brain fuel to preserve cognitive function and delay disease onset (Cunnane et al., 2016; Kackley et al., 2024).

Finally, psychological and behavioral responses to dietary changes—including mood, sleep quality, energy levels, and appetite regulation—are influenced by both metabolic state and hormonal

context. Nutritional ketosis may offer a unique avenue for improving psychological well-being, yet these outcomes are underexplored in women undergoing keto-adaptation.

Taken together, these gaps underscore the urgent need for a dedicated study that examines the physiological, hormonal, metabolic, and behavioral responses to ketogenic diets in premenopausal women. By capturing data across multiple menstrual cycles with structured metabolic and psychological assessments, the SHEKAN study will address a critical void in the literature and provide evidence to inform sex-specific dietary guidelines and therapeutic strategies for women's health.

3. Objectives

Describe the purpose of the study.

To investigate the physiological, hormonal, metabolic, and behavioral adaptations that occur in healthy, premenopausal women undergoing keto-adaptation over the course of three consecutive menstrual cycles. The study aims to characterize changes in reproductive hormones and evaluate the broader health effects—including insulin sensitivity, lipid markers, body composition, mood, sleep, and energy—associated with a well-formulated ketogenic diet.

Primary Objectives and Outcome Measures

Describe the study objectives and outcomes.

1. Evaluate Hormonal Adaptations to Ketoadaptation -
   Outcome Measures: Changes in serum levels of estradiol, progesterone, LH, and FSH across menstrual phases
2. Assess Metabolic and Lipid Marker Responses –
   Outcome Measures: blood β-hydroxybutyrate (BHB) and Lipid profile
3. Analyze Body Composition –
   Outcome Measures: Percent body fat, lean mass, and visceral adiposity (via DXA) changes

Secondary Objectives and Outcome Measures

Describe any secondary objectives and outcomes.

1. Explore Mood and Behavioral Effects of Ketoadaptation -
   Outcome Measures: Mood and psychological status (via PROMIS surveys)
2. Contribute to the Evidence Base on Ketogenic Interventions in Women’s Health
   Outcome Measures: Comprehensive summary statistics and patterns of adaptation, recommendations for future studies based on observed physiological and psychological trends.

4. Study Design & Procedures

		Y	N	Comments
1.	Is this a multi-site study?	☐	☒	If yes, complete the Multi-Site Research appendix.
2.	Does the research involve the use of an approved drug or biologic, use of an unapproved drug or biologic, or use a food or dietary supplement intended to diagnose, cure, treat, or mitigate a disease or condition?	☐	☒	If yes, complete the Drug appendix.
3.	Does the research involve the use of a device to evaluate its safety or effectiveness or use a humanitarian use device (HUD)?	☐	☒	If yes, complete the Device appendix.

Provide information about all research interventions and activities that are to be performed.

Participants in the SHEKAN study will undergo several assessments that are performed solely for the purpose of research. These activities are designed to evaluate the hormonal, metabolic, behavioral, and body composition changes associated with a ketogenic diet across three consecutive menstrual cycles.

1. **Dietary Intervention**
    - Participants will follow a 12-week, well-formulated ketogenic diet designed to maintain nutritional ketosis (≥0.5 mmol/L BHB).
    - During the first 4 weeks, participants will receive: Controlled feeding support via grocery provision or meal services (e.g., Factor, Pangea Keto) based on each individual's caloric requirements.
    - Weeks 5–12 will shift to a self-guided ketogenic diet with continued access to educational materials and dietitian consultations.
    - Dietary adherence will be monitored via daily ketone and glucose levels using finger-stick testing (KetoMojo) and uploaded via a secure app.
2. **Daily Monitoring**
    - **Finger-stick testing**: Participants will measure fasting glucose and ketones each morning using KetoMojo devices. Data will be shared with the research team for adherence tracking.
    - **FemTech devices**: Participants will wear the Femometer smart ring nightly to track basal body temperature and use the Mira urine hormone analyzer as instructed to monitor ovulatory hormone trends. These data will be used to align weekly study visits with menstrual cycle phases and hormonal fluctuations.
3. **Weekly Research Assessments**
    - **Blood draws**: Weekly venipuncture for serum collection (~96 mL total) to assess estradiol, progesterone, luteinizing hormone, and follicular-stimulating hormone levels.
    - **Resting Metabolic Rate (RMR)**: Weekly fasted RMR testing using indirect calorimetry and a metabolic cart.
    - **Body composition**:

        - DXA scans at baseline and week 16 to measure body fat, lean mass, and visceral adiposity.
        - Weekly InBody scans for body composition tracking.
    - **Urine testing**: Weekly hydration assessment via urine-specific gravity (<1.025) and pregnancy testing prior to blood collection.
4. **Survey Instruments**
    - Participants will complete validated PROMIS surveys assessing mood, sleep, anxiety, depression, and cognitive function.
    - Menstrual cycle tracking and symptom reporting will also be collected through REDCap surveys at scheduled testing visits.

Research Design

Identify the research design appropriate to answer the question(s) under study.

Diet intervention study

Detailed Study Procedures

	Y	N	Comments
1. Are you requesting expedited IRB review? Note: The federal regulations establish two main criteria for an expedited review: **a.** The research may not involve more than "minimal risk" (refer to appendix). **b.** The entire research project must be consistent with one or more of the federally defined categories (refer to appendix).	☐	☒	If yes, complete the Expedited Review appendix.
2. Does the research involve genetic testing?	☐	☒	If yes, complete the Genetic Testing appendix.

Describe the selected procedures sufficiently to justify their use in answering the defined research question(s).

N/A

Describe procedures for data collection. Be sure to specify the source records that will be used to collect data about participants. Upload all surveys, scripts, and data collection forms/spreadsheets to the Other Attachments section of the SmartForm.

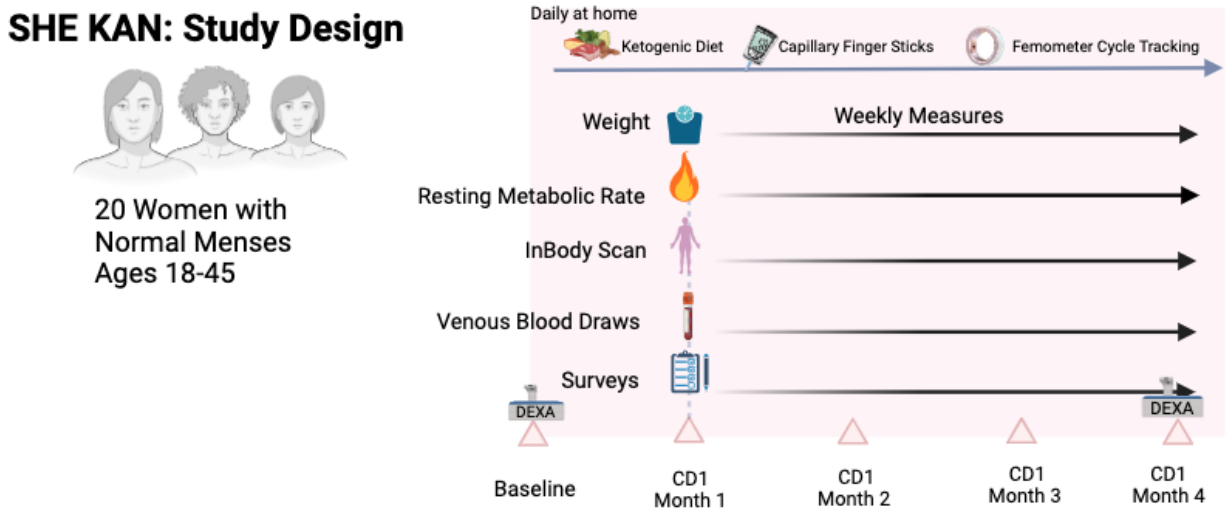


Fig 1 | Study Schematic

Data will be collected at specific time points throughout the 12-week study. Research assessments begin at screening and continue weekly throughout the 12-week dietary intervention and follow-up period. Data sources include physical measurements, biospecimens, device outputs, and validated survey instruments, as described below:

Screening and Baseline (Week 0)

1. **Medical and Diet History Questionnaires**
   Participants will complete a medical history, menstrual history questionnaire and a dietary history questionnaire (ASA24 & DHQ-III). These forms provide baseline information on health status and dietary habits.
2. **Anthropometric Measurements**
   At the baseline visit, height, weight, BMI, waist, and hip circumference will be recorded by study staff.
3. **DXA Scan**
   A full-body DXA scan will be conducted to assess baseline body composition, including lean mass, fat mass, and visceral adiposity. The scan report will serve as the source document.
4. **Resting Metabolic Rate (RMR)**
   Participants will undergo fasted RMR testing using a metabolic cart and ventilated hood system. Gas exchange will be measured to determine baseline resting energy expenditure. Test output will be stored as part of source data.
5. **InBody Scan**
   A baseline body composition scan will be performed using the InBody device.
6. **FemTech Device Setup**
   Participants will be issued a Femometer ring and Mira test kit. Instructions will be provided on how to wear the ring nightly and when to use urine hormone strips to track ovulatory trends.
7. **KetoMojo Setup**
   Participants will be trained on the use of the KetoMojo device for daily finger-stick

measurement of fasting glucose and ketones. Device syncing and data-sharing procedures will be explained.

8. **Initial Blood Draw and Urine Testing**
   A fasting blood sample will be collected to assess baseline reproductive hormones. Urine will be collected to confirm negative pregnancy status and assess hydration via urine-specific gravity (<1.025).

Weeks 1–12 (During Ketogenic Diet Intervention)

1. **Daily Data Collection**
   - **Glucose and Ketones**: Participants will perform a daily finger-stick test each morning while fasting using the KetoMojo device. Data will be automatically stored and later uploaded for review by the research team.
   - **FemTech Devices**: The Femometer ring will be worn nightly to track core body temperature. Mira strips will be used as instructed to monitor urinary LH and E3G levels during the peri-ovulatory window.
2. **Weekly Study Visits (In-Person)**
   At each visit, the following procedures will be performed:
   - **Urine Testing**: Participants will provide a urine sample to test for hydration status (urine-specific gravity) and pregnancy.
   - **Blood Draw**: Fasting venous blood will be collected to assess reproductive hormones (estradiol, progesterone, LH, FSH).
   - **RMR Testing**: Resting metabolic rate will be measured after a 30-minute rest period using indirect calorimetry with a ventilated hood.
   - **InBody Scan**: Body composition will be measured weekly via the InBody device.
   - **Surveys**: Participants will complete a battery of validated PROMIS instruments evaluating sleep, depression, anxiety, and cognitive function via REDCap.

Week 16 (Final Assessments Post-Intervention)

1. **Final DXA Scan**
   A second DXA scan will be performed to assess changes in fat and lean mass compared to baseline.
2. **Final Survey and Device Return**
   Participants will complete a final set of REDCap-based surveys and return all study devices (Femometer, Mira, and KetoMojo).

Source Records

Data will be collected from:

- Case report forms (height, weight, anthropometrics)
- REDCap (PROMIS surveys, menstrual tracking)

- Laboratory reports (blood and urine testing)
- DXA and InBody scan reports
- Device-generated logs (KetoMojo, Femometer, Mira)
  All data will be de-identified using participant IDs and securely stored in compliance with institutional and IRB policies.

Describe the timeline for participant evaluations and the duration of project participation, for both individual study activities and total study participation, when applicable.

Timeline for Participant Evaluations and Duration of Participation

Each participant will be enrolled in the study for a total of approximately **12 weeks**, which roughly translates to 3 menstrual cycles. This includes:

- **1 screening/baseline visit (Week 0)**
- **12 weeks of ketogenic diet intervention with weekly study visits (Weeks 1–12)**
- **1 final follow-up visit (Week 16)**

The total time commitment for the participant across all visits is approximately **15–20 hours** over 16 weeks. Below is a detailed breakdown of all study activities and their timing, duration, and procedures.

Screening and Baseline Visit (Week 0) – Approx. 1.5 to 2 hours

- **Informed consent and eligibility confirmation**
- **Medical history, menstrual history and dietary questionnaires (ASA24 & DHQ-III)**
- **Anthropometric measurements**: Height, weight, BMI, waist, and hip circumference (~10 min)
- **DXA scan**: To assess body composition (~30 min)
- **InBody scan**: Baseline lean/fat mass (~10 min)
- **Resting Metabolic Rate (RMR) test**: Using indirect calorimetry after a 30-min rest (~45 min total)
- **Urine testing**: Pregnancy and urine specific gravity (USG) <1.025 (~10 min)
- **Fasting blood draw**: 1 draw (~8 mL)
- **Device setup**: Instruction on KetoMojo, Femometer, and Mira use (~15 min)

Intervention Phase (Weeks 1–12) – Weekly Visits (~1 hour/visit)

At Each Weekly Visit (12 Total)

- **Fasting blood draw**
  - Volume: ~8 mL per visit
  - Frequency: Once per week for 12 weeks

  - Total volume during intervention: **96 mL**
- **Urine collection**
  - Pregnancy test and USG
- **Resting Metabolic Rate (RMR) test** (~45 min)
- **InBody body composition scan** (~10 min)
- **PROMIS surveys** on sleep, anxiety, depression, and cognitive function (~10–15 min)

At-Home Daily Activities During Weeks 1–12

- **Finger-stick testing for ketones and glucose** using KetoMojo (daily; ~5 min/day)
- **Use of Femometer ring** (nightly during sleep)
- **Use of Mira luteinizing hormone test strips** first thing in the morning (~5 min)

Final Follow-Up Visit (Week 16) – Approx. 45 minutes

- **DXA scan** for post-intervention body composition (~30 min)
- **PROMIS surveys** (final battery; ~10–15 min)
- **Device return and study debriefing**

Describe plans for long-term follow-up once all research related procedures are complete, if any, and specify what data will be collected during this period.

N/A

Alternatives to Participation

Indicate any alternatives to participating in the research, if applicable, including available procedures or treatments outside the research that may be advantageous to the participant.

N/A

5. Institutional Approvals

1. Check all institutional approvals that apply to research being conducted at Ohio State.
☐ Comprehensive Cancer Center (CCC) Clinical Scientific Review Committee (CSRC): Approval or exemption required prior to IRB review for all cancer-related research. Upload a copy of the approval letter to the Other Attachments section of the SmartForm.
☐ Institutional Biosafety Committee (IBC): Approval required prior to IRB review for research involving biohazards (recombinant DNA, infectious or select agents, viruses, toxins), gene transfer, or xenotransplantation.

Upload a copy of the approval letter to the Other Attachments section of the SmartForm.

☒ Human Subject Radiation Committee (HSRC):
Approval required for research involving radiologic procedures for research purposes (e.g., non-clinical care X-rays, DEXA or CT scans, nuclear medicine procedures).
Complete the Radiation appendix and upload a copy of the HSRC approval letter to the Other Attachments section of the SmartForm.

6. Participant Population

1. Specify the participant population(s). Check all participant groups that apply. For any population other than adults, complete the applicable appendix.

☒ Adults
☐ Adults with impaired decision-making capacity
☐ Children
☐ Neonates of uncertain viability
☐ Nonviable neonates
☐ Non-English-speaking individuals
☐ Pregnant women/fetuses (only if pregnant women will be intentionally recruited and/or studied)
☐ Prisoners

Describe the sample population from which the study team plans to either recruit or access private, identifiable information for the research.

This study aims to recruit 24 female participants between the ages of 18 - 40 years, who report regular menstrual cycles. Each participant must meet all the inclusion criteria and none of the exclusion criteria at the screening visit to participate.

Create a numbered list of the eligibility criteria that define who will be included in the final study sample (e.g., age, gender, condition).

1. Healthy women aged 18-40 years.
2. Self-reported, 27–32-day menstrual cycles.
3. Must have access to a smartphone, computer or tablet to access the diet survey and resources.
4. Must be willing to self-report menstrual cycles

If appropriate, describe why certain populations may be excluded (e.g., non-English speaking individuals for studies involving informed consent).

1. History of reproductive disorders.
2. Pregnancy or lactation during the study period.
3. Recurring disordered eating behaviors or other food insecurity concerns.
4. Suffered a lower body injury in the last 6 months
5. Other major health concerns

Number of Participants

The number of participants is defined as the number of individuals who agree to participate (i.e., those who provide consent or whose records are accessed) even if all do not prove eligible or complete the study. The total number of research participants may be increased only with prior IRB approval.	
1. Indicate the number of participants to be enrolled locally.	20
2. For multi-site studies, indicate the total number of participants to be enrolled across all sites.	N/A

Explain how this number was derived (e.g., meets statistical power, limited population). If applicable, explain how many individuals are expected to agree to participate and how many evaluable participants are needed to conduct the study (excluding screen failures).

- SHE KAN is a pilot study designed to assess feasibility and estimate effect sizes rather than to detect small differences between groups.
- A post hoc power analysis will be performed based on observed data to guide the design of subsequent larger-scale studies.

Participant Identification

Describe how potential participants will be identified (e.g., advertising, individuals known to the investigators, record review).

A cohort of eligible participants will be identified through a multi-faceted recruitment strategy including community outreach, physical flyers distributed in local neighborhoods and relevant public venues, and targeted digital advertisements on platforms such as Instagram, and Facebook. The study team will also utilize word-of-mouth strategies and partnerships with local organizations to reach underrepresented groups.

Explain how the investigator(s) will gain access to this population, as applicable, and provide evidence that you will be able to recruit the necessary number of participants to complete the study.

Investigators will gain access to the target population through strategic collaborations with community-based organizations and leveraging the research team's ongoing presence and reputation in the community through the SHE IS Lab. In addition, undergraduate researchers will conduct in-person recruitment efforts (e.g., flyering and tabling), which will enhance reach and visibility. Based on prior recruitment success using similar outreach methods during pilot phases of SHEKAN and the study team's embeddedness within the community, we are confident in our ability to recruit the target sample size. Weekly recruitment benchmarks (e.g., at least 2 participants screened per student per week) have been established to ensure adequate enrollment.

Participant Recruitment and Selection

Describe how potential participants will be screened or otherwise determined to be eligible.

Potential participants will first complete a brief screening questionnaire either via a QR code linked to an online screener or in-person using a tablet provided by the research team. The screener will assess basic eligibility criteria such as age, biological sex at birth, menstrual cycle status, and general health information. Participants who meet eligibility criteria will then be contacted by the study team to schedule an initial visit and obtain consent.

Describe the recruitment process, including the setting in which recruitment will take place.

Recruitment will take place in both physical and virtual settings. Undergraduate researchers will conduct in-person recruitment at community centers, universities, grocery stores, clinics, and other accessible locations. Flyers with QR codes will be placed in women's restrooms, community bulletin boards, and other high-traffic areas. Social media campaigns will run continuously, directing interested individuals to the screening form.

Explain how the recruitment process respects potential participants' privacy.

Recruitment activities will be designed to protect participant privacy. Physical flyers will include general study descriptions and direct interested individuals to private digital platforms for further information. In-person recruitment will be conducted respectfully in public areas without pressuring individuals, and all identifiable data collected will be stored securely with access limited to authorized study personnel. All data collection and participant communications will occur in private or password-protected environments.

7. Cost to Participants and Incentives to Participate

Potential Costs/Reimbursements

Describe any potential costs participants or their insurer will incur as a result of study participation (e.g., parking, study drugs, diagnostic tests). Indicate here which costs, if any, will be reimbursed or covered by the study.

N/A

Incentives

Describe any compensation or other incentives (e.g., free services, cash payments, gift cards, classroom credit) that will be offered to potential participants. Include the amount and timing of all incentives or compensation, the form of compensation (e.g., cash, check, gift card), and how the compensation will be received (e.g., mailed, in person, online). This information must also be included in the consent form.

Participants will be paid $50 for each full cycle they complete in the form of a check in person. The first month may not be a full cycle, thus participants will be paid $50 upon completion of their FIRST full cycle in the study (from onset of period to onset of period). They will be paid another $50 dollars after the second complete cycle and the remaining $50 after the last. In total, participants could receive $150 in compensation.

8. Compensation for Research-Related Injury

If the research involves greater than minimal risk to participants, describe the available compensation in the event of research related injury or explain why no compensation is available.

In the event of a research-related injury resulting from participation in this study, medical treatment will be made available to the injured participant. However, there is no formal program for financial compensation or payment for medical costs or other expenses incurred due to such an injury. Treatment may be provided at the participant's own expense, or billed to their insurance company if applicable.

The lack of compensation is due to institutional policy and the nature of research funding. Participants will be informed that they are not waiving any legal rights by agreeing to participate, and they retain the right to seek legal remedies as permitted by law.

9. Informed Consent Process

1. Specify the consent process(es) to be used for the study. Check all processes that apply. For any waivers or alterations, complete the applicable appendix.

☒ Informed Consent with Written Signature (e.g., on paper)
☐ Informed Consent with Electronic Signature
Note: If the method used to obtain electronic signatures does not qualify as a legally valid signature, also check "Waiver of Consent Documentation." See guidance provided by the Office of Technology and Digital Innovation.
☐ Waiver of Consent/Parental Permission Documentation
☐ Deception (i.e., procedure in which investigators deliberately mislead participants during research by withholding information or providing false information).
Note: If this is selected, also check "Waiver or Alteration of the Consent Process."
☐ Waiver or Alteration of the Consent Process
☐ Waiver of the Parental Permission Process

Describe the consent process. Explain when and where consent will be obtained and how participants or their legally authorized representatives will be provided sufficient opportunity to consider participation.

Participants that meet the initial qualifying criteria will visit the study center for a screening meeting. The participant and a member of the research team will meet in a private office to discuss the informed consent form. The informed consent form will be provided to the participant for their review, the study will be described in full detail and any questions the interested participant has will be encouraged and responded to. If they choose to participate in the study, they will be asked to sign the consent form providing written consent. If the participant provides consent, they will be provided with a few questionnaires including medical history, diet history and menstrual history questionnaire.

Specify who will provide consent or permission (i.e., participant, legally authorized representative, parent and/or guardian).

The participant will provide consent.

Explain how the possibility of coercion or undue influence will be minimized in the consent process.

Any possibility of coercion or undue influence related to the consent process will be minimized as throughout. Special care and time will be taken to fully explain the protocol and alternatives to each participant. At any point in time participants are welcome to leave the study. There is no significant benefit, financial or otherwise, that might coerce or influence these participants to consent against

their better judgement. It will be made clear to participants that they must be willingly volunteering for this research study.

10. Privacy of Participants

Describe the steps that will be taken to protect participants' privacy and make them feel at ease with the research situation in terms of the questions being asked and the procedures being performed.

Participant privacy will be respected at all times throughout the study. Privacy concerns expressed by participants will be taken very seriously. Similar to ensuring safety of our participants is prioritized the privacy of our participants will be monitored and protected. Additional steps will be taken to minimize/eliminate any activities that might stigmatize participants including visits to the PAES buiiding. Privacy accommodations during changing clothes, using the restroom, screening, testing, and data collection processes will be explained to participant prior to their implementation.

11. Confidentiality and Management of Study Materials

	Y	N	Comments
1. Does the research involve obtaining and storing participants' data and/or biospecimens for future, unspecified, research?	☐	☒	If yes, complete the Repositories appendix.

Describe the steps that will be taken to secure study data.

Each participant (i.e., biological samples and questionnaires) will receive a unique subject identifier (e.g., SHEKAN #01) to replace personal names. The only document linking participant names to study IDs will be the signed informed consent form and the corresponding master linking file. These will be stored separately from research data—either in a locked file cabinet in the Kinesiology file storage room (PAES A4) or in password-protected, encrypted digital files on secure OSU servers.

All other study files will contain only the coded study ID and will be stored either in the same locked file storage room or on secure, password-protected institutional servers. Access to identifiable information will be restricted to the PI and designated study staff who require it for study operations.

Data and identifiers will be maintained until study data are published and for up to **10 years** after completion of the study, after which the master linking file will be destroyed.

Describe any procedures that will be used for quality control of collected data.

All data will be reviewed in real-time and at least bi-weekly by study staff for completeness, accuracy, and consistency.

Describe how data (and if applicable, biospecimens) will be handled study wide.

Data will be collected via a secure, password-protected electronic data capture (EDC) platform. Standard operating procedures will guide data entry, monitoring, and reporting. Biospecimens, if applicable, will be labeled with study IDs only and stored under temperature-controlled conditions until analysis. All procedures will comply with IRB-approved protocols and HIPAA requirements..

Specify the identifiable information that will be included in the data or associated with the biospecimens.

Participant name on the signed informed consent form and the master linking file connecting names to study IDs. No other direct identifiers will be included in the research dataset.

Specify where and how data or biospecimens will be stored and for how long.

All study data will be stored on secure, encrypted servers maintained by the lead research institution. Biospecimens (if collected) will be stored in locked, access-controlled laboratory freezers. Both data and biospecimens will be retained for up to **10 years** following study completion, unless required longer by sponsor or regulatory guidelines.

Specify who will have access to the data or biospecimens.

Only study investigators, designated research staff, and authorized institutional data analysts will have access to coded research data. Access to the consent forms and master linking file will be limited to the PI and designated study staff.

Specify who will be responsible for receipt or transmission/transport of the data or biospecimens and how will transmission/transport will occur.

Any biospecimen shipments will be conducted by designated laboratory or study coordinators via certified carriers with temperature control, tracking, and chain-of-custody documentation. Electronic data transfers will occur only over encrypted, secure platforms (e.g., SFTP, OSU institutional repositories).

Indicate what will happen to identifiable data at the end of the study (e.g., kept identifiable, coded, deidentified). If identifiers will be maintained, provide the rationale supporting this request. If the data will be deidentified, describe the process.

At the conclusion of the study and following the required retention period, all identifiers will be permanently destroyed. The master linking file will be deleted, leaving only fully deidentified datasets.

If data or biospecimens will be shared broadly with outside groups (i.e. dbGaP), specify what will be shared, with whom, in what form (e.g., identifiable, coded, deidentified/anonymized).

Deidentified datasets may be shared with qualified external collaborators or institutional repositories under appropriate data use agreements. Shared data will not contain direct identifiers, and no genetic or genomic data will be generated or submitted to dbGaP as part of this study.

If data or biospecimens will be shared broadly with outside groups or databases (i.e. dbGaP), specify whether participants will have the ability to opt-in or remove the data/biospecimens from these outside groups later if they choose. Generally, if the materials are identifiable, a participant should be able to withdraw them unless retention is required under federal regulation (e.g., FDA).

Not applicable. This study will not generate genetic or genomic data for submission to dbGaP. If any deidentified study data are shared with qualified collaborators or secure institutional repositories, these datasets will not contain direct identifiers, and once deidentified, they cannot be withdrawn.

12. HIPAA Research Authorization

1. Is individually identifiable Protected Health Information (PHI) subject to the HIPAA Privacy Rule requirements to be accessed, used, or disclosed in the study?
   - ☒ No
   - ☐ Yes

Note: The PHI obtained as part of this research must not be reused or disclosed to any other person or entity other than those with IRB approval, except as required by law or for authorized oversight of the research project, without additional approval. IRB approval must be obtained for other research involving the use or disclosure of this PHI.

2. If PHI is accessed, used, or disclosed, specify how authorization requirements will be met (check all that apply). For any waivers or alterations, complete the applicable appendix.
   - ☐ Written Authorization
   - ☐ Partial Waiver (for identification and recruitment purposes only)
   - ☐ Full Waiver (authorization will not be obtained)
   - ☐ Alteration (written authorization will not be obtained or all required elements will not be included)

Explain how the requested PHI (i.e., HIPAA identifiers and associated health information) are the minimum necessary information to accomplish the research objectives.

The study will not access, use, or disclose Protected Health Information (PHI) as defined under the HIPAA Privacy Rule. Identifiable information collected (e.g., name on the consent form, contact information for scheduling) will not be linked to or obtained from a covered entity's medical record. Therefore, a HIPAA authorization is not required. The HIPAA authorization language will be removed from the consent form to ensure consistency.

13. Reasonably Anticipated Benefits

Potential Direct Benefits:

List the potential benefits that participants may expect as a result of this research study. If there are no direct benefits to individual participants, indicate so.

Benefits of this study include body composition analysis from DXA Scans and greater insights in regard to their menstrual cycle. Otherwise there are no direct benefits of the study.

Potential Societal Benefits:

List the potential benefits that society and/or others may expect as a result of this study.

The Strategic Hormonal Evaluation and Instrument-Reliability Study Keto-Adaptation and Nutrition (SHEKAN) holds the promise of substantial societal benefits. If successful, the validation of non-invasive fertility tracking devices could revolutionize family planning, offering accessible and user-friendly tools for individuals and couples to make informed decisions about conception or contraception. The study's insights into the correlation between hormonal markers and tracking technologies may empower women with a deeper understanding of their reproductive health, potentially reducing dependence on invasive procedures for fertility monitoring. This, in turn, could alleviate the physical and emotional burdens associated with certain testing methods. Additionally, the findings may pave the way for personalized health strategies based on hormonal patterns, fostering more informed choices for optimizing reproductive health. The study's contribution to public education about menstrual cycles and hormonal variations could dispel myths and

misconceptions, promoting a supportive societal perspective on women's health. If non-invasive tracking devices prove reliable, they could offer more cost-effective and accessible methods for monitoring reproductive health, potentially reducing healthcare costs. Positive outcomes may also stimulate further innovations in fertility tracking technology, driving advancements that benefit both individuals and healthcare professionals.

14. Risks, Harms, & Discomforts

Potential Risks, Harms, and/or Discomforts

Describe all reasonably expected risks, harms, and/or discomforts that may apply to the research. At a minimum, include the risk of breach of data confidentiality. Discuss severity and likelihood of occurrence. As applicable, include potential risks to an embryo or fetus if a woman is or may become pregnant. Consider the range of risks, including physical, psychological, social, legal, economic, and any other potential risk to the study population.

As with all studies, this study poses certain risks to the participant. The investigator and research team will practice utmost caution and adherence to the policies to mitigate any risks possible. Risks may arise in the following areas:

- Femometer Ring

Ill-fitted Femometer Rings pose a risk of restricting blood flow which can cause swelling, oxygen restriction, and tissue death if left untreated.

- InBody

There are no known risks or side effects to completing an InBody assessment.

- Blood Draws

Blood draws will take place via a butterfly needle. 96 mL of blood will be drawn throughout the entire study. The needle may cause discomfort and bruising at puncture site and bruising may persist for several weeks. There is also risk of infection.

Risks are minimized by using sterile disposable needles and gauze and the practice of aseptic (sterile) techniques during the blood draw.

- Body Composition-DEXA

This study involves exposure to radiation from a DEXA EXPERT spine, femur or whole-body scan. This radiation exposure is used for research purposes only. The total amount of radiation that the participant will receive in this study is around 0.78 mSv or 78 mrem and is approximately equivalent to a uniform whole-body exposure of 47 days of exposure to natural background radiation. This use involves minimal risk and is necessary to obtain the research information desired. DEXA risks include exposure to as much radiation as a flight from New York to Los Angeles which may elevate cancer risk. DEXA risks are minimized as the measures are only performed twice on each participant.

- Cycle Tracking

Using electronic cycle tracking apps such as being implemented in this study do run the risk of data breaches. Precautions have been taken to secure HIPPA protected health information as well as deidentifying participant information. However, in the event of a data breach compromising participant privacy all parties will be notified.

- Surveys

The participant will be asked to complete certain medical history questionnaires which may pose risk of causing emotional distress due to their sensitive nature. The participant will be informed of the nature of the surveys beforehand and can be referred to a clinician in the event they find it necessary.

Risk Mitigation

Describe how risks, harms, and/or discomforts will be minimized. Address all risks described in the section above.

DEXA risks are minimized as the measures are only performed twice on each participant. The extra lifetime risk of dying of a fatal cancer due to the radiation exposure from this research may range from about one in 500,000 to about one in 200,000. At such low radiation exposures, scientists disagree about the amount of risk. These estimates are very uncertain, and there may be no extra risk at all. This amount is less than a participant would receive from one year of natural exposure in the San Diego area, which is approximately 0.78 mSv. Cumulative exposure from radiation may increase your risk of developing certain types of cancer in the future. All blood draws will be taken by trained phlebotomists. Risk Mitigation Measures: To minimize the risk of breach of data confidentiality, several safeguards will be implemented: Secure Data Storage: All participant data, including medical records and contact information, will be stored securely in password-protected, encrypted databases. Access to this data will be restricted to authorized research team members

only. Anonymization: Identifiable information such as names and contact details will be replaced with unique study identifiers in the research database to ensure participant anonymity. Data Encryption: Any data transmitted electronically, such as during data collection or when sharing information within the research team, will be encrypted to prevent unauthorized access during transmission. Access Control: Access to research data will be limited to the core research team, and all members will be required to sign data confidentiality agreements. Data will be accessible only on a need-to-know basis.

If testing will be performed to identify individuals who may be at increased risk (e.g., pregnant women, individuals with HIV/AIDS, depressive disorders), address the timing and method of testing; include how positive test results will be handled.

Weekly urine pregnancy tests will be performed prior to blood collection to ensure participant safety due to the study's dietary intervention and DEXA scans. These tests are for research safety purposes only and are not diagnostic. Participants will be informed of the results immediately. A positive pregnancy test will result in withdrawal from the study, and the participant will be referred to their healthcare provider for appropriate follow-up. Test results will be recorded under the participant's study ID and maintained as part of the research record.

15. Monitoring

	Y	N	Comments
1. Does the research involve greater than minimal risk (i.e., the harms or discomforts described are beyond those ordinarily encountered in daily life or during the performance of routine physical or psychological tests)?	☒	☐	If yes, describe a data and safety monitoring plan below.

Describe the plan to oversee and monitor data collected to ensure participant safety and data integrity. If the plan is outlined in a separate document, upload it to the documents page of the application SmartForm. If not, describe it below and include the following:

- The information that will be evaluated (e.g., incidence and severity of actual harm compared to that expected)
- Who will perform the monitoring (e.g., investigator, sponsor, or independent monitoring committee/board)
- Timing of monitoring (e.g., at specific points in time, after a specific number of participants have been enrolled/treated) and
- Decisions to be made as a result of the monitoring process (e.g., provisions to stop the study early for unanticipated problems)

Accurate and detailed research data and records will be kept for the research project. The PI has the right and authority to control the appropriate use-of and access- to the research data, including the use of data in scholarly publications and presentations. The PI or a designee will inspect all data and research records for compliance with the Institutional Review Board (IRB) and The Ohio State University's policies and procedures every four months or 25%, 50%, 75%, 100% completion of the study, whichever is sooner. In the unlikely event that this occurs the PI along with the Ohio State ORRP will be in contact and all decisions will be made in accordance with policies and procedures detailed by the ORRP. If an adverse event should occur, the PI, with consultation from the research team, will evaluate if the study should continue. The severity and actual harm compared to that expected for the current adverse event and all previous adverse events will be used in the determination to continue.

16. Data Analysis

Internal/External Validity

Describe measures that have been taken to avoid study bias (consider the threats to internal/external validity).

To minimize internal bias, the SHEKAN study employs standardized protocols across all participants, including scheduled weekly assessments (e.g., resting metabolic rate, DXA, blood draws), controlled dietary guidance with ongoing dietitian support, and validated instruments for hormonal and behavioral assessments (e.g., Femometer, Mira, PROMIS surveys). Strict inclusion/exclusion criteria reduce confounding factors (e.g., excluding those with reproductive disorders). Device calibration, consistent testing environments, and fasting state protocols further reduce procedural variability.

To strengthen external validity, the study targets a demographically defined, yet generalizable population (healthy women aged 18–40 with regular cycles), and incorporates real-world elements such as self-guided dietary adherence after initial support. De-identification, participant education, and secure data capture (via REDCap) ensure data integrity and reproducibility.

Data Analysis Techniques

Specify the analytic techniques the researcher will use to answer the study questions. Indicate the statistical procedures (e.g. specific descriptive or inferential tests) that will be used and why the procedures are appropriate. Note: The IRB does not need the actual formulas to be used, just a description of them. If applicable, specify the proposed analytic approaches for qualitative data.

Potential pitfalls and alternatives: These include participant variability, technical malfunctions, data synchronization and privacy issues, and incomplete data sets. Mitigation strategies include conducting regular equipment calibration, establishing alternative data validation methods, utilization of OSU's RedCap portal for secure data collection, employing standardized time synchronization protocols, providing participant education for uniform and consistent device usage, and enhancing participant engagement. The study's significance lies in its potential to reshape methodologies in women's health research, offering more accessible, practical, and reliable alternatives to traditional blood-based monitoring.

Descriptive Statistics

- Continuous variables (e.g., metabolic markers, hormonal levels, symptom severity) will be summarized as means and standard deviations or medians and interquartile ranges, depending on their distribution.
- Categorical variables (e.g., menopausal status, dietary adherence) will be summarized as frequencies and percentages.

Baseline Comparisons

- Baseline continuous variables will be compared between study groups (e.g., ketogenic diet [KD] vs. control group) using independent samples t-tests. For non-normally distributed data, Mann-Whitney U tests will be used.
- Categorical variables will be compared using Chi-square tests or Fisher's exact tests, as appropriate.

Primary Analysis

- The primary outcome is the change in symptom severity related to perimenopause over time.
- A **linear mixed-effects model** will evaluate these changes, accounting for repeated measures within participants. The model will include:
    - Fixed effects: intervention group (KD), time, and group-by-time interaction.
    - Random effects: participant-level variability.
- The key focus will be the **group-by-time interaction term**, which will assess the differential effect of the ketogenic diet on symptom severity compared to the control group.

Secondary Analyses

- Changes in metabolic (e.g., fasting glucose, ketone levels) and hormonal (e.g., estrogen, progesterone) outcomes will also be analyzed using linear mixed-effects models.

Exploratory Analyses

- Subgroup analyses will explore potential moderators of the intervention's effectiveness, such as:

  - Age (early vs. late perimenopause).
  - Baseline ketone levels.
  - Degree of dietary adherence.
- Correlations between changes in metabolic markers, hormonal outcomes, and symptom severity will be assessed using Pearson or Spearman correlation coefficients, depending on data distribution.

Handling Missing Data

- Missing data will be addressed using multiple imputation or mixed-effects modeling techniques, which are robust to data that are missing at random (MAR).
- Sensitivity analyses will evaluate the robustness of results to alternative assumptions about the nature of missing data.

Power and Sample Size

- SHE KAN is a pilot study designed to explore trends and preliminary outcomes of a ketogenic diet intervention in healthy women with regular menstrual cycles.
- A **post hoc power analysis** will be performed based on observed data to guide the design of subsequent larger-scale studies.

Significance Level

- All statistical tests will be two-tailed, with a significance level set at $\alpha = 0.05$.

17. Bibliography

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