Hormonal Changes Associated with Reproduction in Females with Type 2 Diabetes Mellitus and Prediabetes: Protocol for A Systematic Review and Meta-Analysis

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Hormonal Changes Associated with Reproduction in Females with Type 2 Diabetes Mellitus and Prediabetes: Protocol for A Systematic Review and Meta-Analysis

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Abstract

Background: ABSTRACT
Introduction
Reproductive hormones play a crucial role in regulating the menstrual cycle, ovulation, and fertility in females. Hormonal imbalances, particularly involving estradiol, progesterone, luteinizing hormone LH, FSH, and testosterone, can significantly affect reproductive health. T2DM is a chronic metabolic disorder characterized by insulin resistance and hyperglycemia, both of which have been associated with disruptions in the HPO axis and altered ovarian steroidogenesis. Prediabetes is an intermediate metabolic state between normoglycemia and diabetes, with a high risk of progression to T2DM. Emerging evidence suggests that even in the prediabetic state, changes in reproductive hormone concentrations may occur, potentially leading to menstrual irregularities, anovulation, and infertility. This systematic review protocol outlines the planned synthesis and analysis of existing literature investigating hormonal changes associated with reproduction in females with T2DM and prediabetes.

Methods and Analysis
This protocol is prepared in accordance with the PRISMA-P 2020 guidelines. Electronic databases including PubMed, Google Scholar, Scopus, and EBSCO will be systematically searched for published observational, case-control, and cross-sectional studies reporting on reproductive hormone changes in females with T2DM and/or prediabetes. Eligible participants will be females in their reproductive age diagnosed with T2DM or prediabetes. Studies involving pregnant women, those with type 1 diabetes mellitus, known endocrine disorders unrelated to diabetes, or those receiving hormonal therapy will be excluded. The control group will consist of non-diabetic females without known reproductive endocrine disorders. Data on changes in estradiol, progesterone, LH, FSH, and testosterone will be extracted. A second reviewer will verify extracted data, with disagreements resolved by a third reviewer. The risk of bias will be assessed using the Downs and Black checklist. Where sufficient data are available, Review Manager (RevMan) v5.4 will be used to perform a meta-analysis, and the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach will be used to assess evidence quality.

Results and Conclusion
This review will use only publicly available published data, which will be collected after protocol publication. The findings will provide a comprehensive synthesis of current evidence regarding reproductive hormonal changes in females with T2DM and prediabetes, highlighting knowledge gaps and informing future clinical and epidemiological research. These results may guide early detection and intervention strategies to preserve reproductive health in at-risk women.

Objective: • To determine the prevalence of hormonal imbalances in females with type 2 diabetes mellitus and prediabetes globally.

Objectives: • To determine the changes in reproductive hormone concentrations; specifically, estradiol, progesterone, testosterone, FSH, and LH in females with T2DM and prediabetes.
• To identify the patterns of reproductive hormone dysregulation associated with metabolic dysfunction in females with T2DM and prediabetes.
Secondary

Methods: METHODOLOGY
This systematic review protocol has been prepared following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) 2020 guidelines (Page et al., 2021).
Systematic Review Registration
The protocol has been registered with the International Prospective Registry of Systematic Reviews (PROSPERO) CRD420251078685.
Ethics Approval and Consent to Participate
No new data will be collected from individuals; only previously published data will be examined. Therefore, ethics approval is not required for this systematic review and meta-analysis, and no informed consent will be necessary.
Eligibility Criteria for the Study
This review will include cross-sectional, prospective, and retrospective observational studies investigating variations in reproductive hormone concentrations; specifically, estradiol, testosterone, progesterone, FSH, and LH in females with prediabetes or T2DM. The inclusion criteria will also include all T2DM and prediabetic patients according to the diagnostic criteria below in their reproductive age. patients undergoing any form of diabetes treatment, such as insulin therapy or oral hypoglycemic agents will be excluded in this study. Additionally, patients with a history of liver and kidney disease, those who have severe infectious disease, menopausal women, as well as Pregnant women and individuals undergoing hormone replacement therapy or using hormonal contraceptives will not be eligible for this study.
Diagnostic Criteria
Prediabetes will be diagnosed according to the American Diabetes Association (American Diabetes Association, 2021) criteria, defined as one or more of the following: impaired fasting glucose (IFG) defined as fasting plasma glucose 5.6–6.9 mmol/L (100–125 mg/dL); impaired glucose tolerance (IGT) defined as 2-hour plasma glucose 7.8–11.0 mmol/L (140–199 mg/dL) after a 75 g oral glucose tolerance test; HbA1c defined as with 5.7–6.4%.
Type 2 Diabetes Mellitus will be diagnosed according to the ADA criteria as: fasting plasma glucose ?7.0 mmol/L (126 mg/dL); 2-hour plasma glucose ?11.1 mmol/L (200 mg/dL) during OGTT; HbA1c ?6.5%.

Study Design
This systematic review will include clinical observational studies such as prospective observational studies, case-control studies, cohort studies, and cross-sectional studies that investigate hormonal changes associated with reproduction in females diagnosed with T2DM or prediabetes. Eligible studies must report changes in reproductive hormones, including but not limited to estradiol, progesterone, LH, FSH, and testosterone. Both human studies and relevant clinical observational research that provide quantitative hormonal measurements will be considered.
Population
The target population for inclusion will be females of reproductive age diagnosed with either T2DM or prediabetes. Studies including both normal (non-diabetic) and prediabetic/T2DM populations will be considered eligible, provided they report on reproductive hormonal outcomes for the female participants separately.
Comparators
In this systematic review, the eligible comparator group will be females of reproductive age with normal glucose metabolism (non-diabetic controls).
Outcomes
This review aims to assess changes in reproductive hormonal concentrations in females with T2DM and prediabetes compared to healthy controls. Outcomes of interest will include differences in concentrations of estradiol, progesterone, LH, FSH, and testosterone (reported as odds ratios with 95% confidence intervals).
Search Strategy
All data sources published on the association between reproductive hormonal changes and T2DM or prediabetes from 2000–2025 will be obtained. Screening of articles will be performed independently by two reviewers (DT and AS). The databases to be searched include PubMed, Google Scholar, Scopus, and EBSCO. Boolean operators will be applied, with ‘AND’ used to combine T2DM/prediabetes terms and reproductive hormone terms, and ‘OR’ used between related terms within these categories. The keywords will include: “type 2 diabetes mellitus”, “prediabetes”, “impaired fasting glucose”, “insulin resistance”, “reproductive hormones”, “estradiol”, “progesterone”, “luteinizing hormone”, “follicle-stimulating hormone”, “testosterone”, and “menstrual irregularities”. Additionally, bibliographies of related articles and relevant review papers will be manually screened for potentially eligible studies.

Duplicate records will be removed from all search results. Publications that are clearly irrelevant will be excluded after reviewing titles and abstracts. The remaining articles will be assessed through full-text screening according to predefined inclusion and exclusion criteria.

Data Extraction

Two reviewers (DT and AS) will independently extract data and relevant information from the selected articles into a Microsoft Excel spreadsheet. Extracted content will include: first author's name, year of publication, country, and study setting. Study characteristics such as number of participants, gender distribution, age range, and measured reproductive hormone markers (estradiol, progesterone, LH, FSH and testosterone) will be recorded. The quality of the extracted data will be checked by a second reviewer, and any disagreements will be resolved with the assistance of a third reviewer (AK).

Risk of Bias

The potential risk of bias will be assessed independently by two reviewers (DT and AS) in the selected studies using the modified Downs and Black Checklist which is designed for cross-sectional and observational studies. This checklist is designed to evaluate the methodological quality of both randomized and non-randomized comparative studies. Scores will be rated as follows: excellent (12–13), good (10–11), moderate (7–9), poor (5–6), and very poor (<5). Any disagreements will be resolved through discussion, and if necessary, a third reviewer (AK) will be consulted to reach consensus. In cases where reported data are unclear, the primary study authors will be contacted up to three times. If no response is obtained, the unclear data will be excluded from the analysis.

Data Synthesis and Analysis

Data will be synthesized and analysed using Review Manager (RevMan) software, version 5.4. The characteristics of each included study will be summarized in tabular form. Where studies report comparable data (i.e., similar populations, comparators, and hormonal outcomes), a meta-analysis will be conducted and displayed in a forest plot. The relative weight of each study, automatically generated by RevMan, will be included in the plots.

A random-effects model will be applied, under the assumption that effect sizes across studies are not identical and that data follow a normal distribution. Heterogeneity will be evaluated by visual inspection of forest plot confidence interval (CI) overlap and quantified using the I^2 statistic. I^2 values will be interpreted as follows: <25% = low heterogeneity, ~50% = moderate heterogeneity, and >75% = high heterogeneity. If substantial heterogeneity is detected, subgroup analyses will be performed to identify potential sources (e.g., population characteristics, diagnostic criteria, or geographic location).

If applicable, additional synthesis of prevalence data on reproductive hormone changes in females with T2DM and prediabetes will be conducted using Meta-XL (an add-in for Microsoft Excel). The Freeman–Tukey double arcsine transformation will be used to stabilize variance, and the D'Agostino & Pearson omnibus normality test will assess the normal distribution of data. Pooled prevalence estimates with 95% CIs will be calculated, and heterogeneity will be reassessed as described above. Where data allow, subgroup comparisons (e.g., by age group or hormonal profile) will be conducted.

Assessment of Strength of Evidence

The strength and quality of the evidence will be evaluated using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) system (Ryan and Hill, 2016). GRADE provides a transparent framework for rating the quality of evidence and grading the strength of recommendations, particularly for intervention effectiveness and observational findings.

Results: RESULTS

No participants have been sought as of June 2025, as this review will rely solely on publicly accessible published data. Data extraction will commence once this protocol is published. Ethical approval will not be required, as the review is based on secondary data from existing studies. However, corresponding authors of included studies will be contacted if clarification of reported data is necessary.

Conclusions: Principal Findings

Reproductive hormone alterations in females with T2DM and prediabetes represent an important intersection between metabolic and reproductive health. This systematic review and meta-analysis will synthesise existing evidence on how T2DM and prediabetes affect key reproductive hormones, including estradiol, progesterone, LH, FSH, and testosterone. The review will also summarise the hormonal mechanisms underlying menstrual irregularities, anovulation, infertility, and related reproductive disorders in these populations.

In recent years, increasing global prevalence of T2DM and prediabetes, driven by lifestyle and dietary changes, has intensified concern about their effects beyond glucose metabolism. Hormonal dysregulation linked to insulin resistance and chronic hyperglycemia may impair the HPO axis, disturb steroidogenesis, and accelerate reproductive aging. By pooling and critically appraising previous studies, this review aims to provide a comprehensive understanding of the interplay between metabolic dysfunction and reproductive hormone alterations, informing strategies for prevention and early intervention in at-risk women.

Limitations

This review will exclude studies focusing exclusively on male reproductive hormones or on reproductive hormones in contexts unrelated to T2DM or prediabetes. In addition, non-human studies and those without explicit hormone measurements; only

clinical symptom reporting without biochemical data will not be considered.

Acknowledgements
The authors would like to express their gratitude to the College of Health Sciences (UKZN) for academic and institutional support.

Authors' Contributions
DT and AK were responsible for brainstorming, designing the study and drafting the protocol. DT, AS, and AK were responsible for reviewing the eligible study and final draft of the manuscript. Funders had no role in developing the protocol.

Funding
The College of Health Sciences funded this study; however, the funders had no role in study design and manuscript preparation.

Conflicts of Interest
None declared. Clinical Trial: International Prospective Register of Systematic Reviews (PROSPERO) CRD420251078685, https://www.crd.york.ac.uk/PROSPERO/view/CRD420251078685.

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Hormonal Changes Associated with Reproduction in Females with Type 2 Diabetes Mellitus and Prediabetes: Protocol for A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction

Reproductive hormones play a crucial role in regulating the menstrual cycle, ovulation, and fertility in females. Hormonal imbalances, particularly involving estradiol, progesterone, luteinizing hormone LH, FSH, and testosterone, can significantly affect reproductive health. T2DM is a chronic metabolic disorder characterized by insulin resistance and hyperglycemia, both of which have been associated with disruptions in the HPO axis and altered ovarian steroidogenesis. Prediabetes is an intermediate metabolic state between normoglycemia and diabetes, with a high risk of progression to T2DM. Emerging evidence suggests that even in the prediabetic state, changes in reproductive hormone concentrations may occur, potentially leading to menstrual irregularities, anovulation, and infertility. This systematic review protocol outlines the planned synthesis and analysis of existing literature investigating hormonal changes associated with reproduction in females with T2DM and prediabetes.

Methods and Analysis

This protocol is prepared in accordance with the PRISMA-P 2020 guidelines. Electronic databases including PubMed, Google Scholar, Scopus, and EBSCO will be systematically searched for published observational, case-control, and cross-sectional studies reporting on reproductive hormone changes in females with T2DM and/or prediabetes. Eligible participants will be females in their reproductive age diagnosed with T2DM or prediabetes. Studies involving pregnant women, those with type 1 diabetes mellitus, known endocrine disorders unrelated to diabetes, or those receiving hormonal therapy will be excluded. The control group will consist of non-diabetic females without known reproductive endocrine disorders. Data on changes in estradiol, progesterone, LH, FSH, and testosterone will be extracted. A second reviewer will verify extracted data, with disagreements resolved by a third reviewer. The risk of bias will be assessed using the Downs and Black checklist. Where sufficient data are available, Review Manager (RevMan) v5.4 will be used to perform a meta-analysis, and the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach will be used to assess evidence quality.

Results and Conclusion

This review will use only publicly available published data, which will be collected after protocol publication. The findings will provide a comprehensive synthesis of current evidence regarding reproductive hormonal changes in females with T2DM and prediabetes, highlighting knowledge gaps and informing future clinical and epidemiological research. These results may guide early detection and intervention strategies to preserve reproductive health in at-risk women.

Ethics and Dissemination

As the review will be based solely on published literature, ethical approval is not required.

Registration Details

International Prospective Register of Systematic Reviews (PROSPERO) CRD420251078685, https://www.crd.york.ac.uk/PROSPERO/view/CRD420251078685.

Keywords

systematic review, meta-analysis, reproductive hormones, type 2 diabetes mellitus, prediabetes, estradiol, progesterone, luteinizing hormone, follicle-stimulating hormone, testosterone, fertility

INTRODUCTION

Reproductive hormones play vital roles in regulating menstrual cycles, ovulation, and fertility in females(Tandon and Chintala, 2001; Das, Mukherjee and Banerjee, 2023). Estradiol, the main estrogen, is crucial for follicular development, endometrial proliferation, and triggering the mid-cycle luteinizing hormone (LH) surge required for ovulation (Christensen *et al.*, 2012; Barbieri, 2014). Progesterone, secreted by the corpus luteum after ovulation, supports endometrial receptivity for implantation and maintains early pregnancy (Cable and Grider, 2023). Follicle-stimulating hormone (FSH) and LH, produced by the anterior pituitary, coordinate ovarian follicular growth and ovulation, respectively (Durnerin *et al.*, 2008). Testosterone, although present at lower levels in females, contributes to libido and follicular maturation (Rojas-Zambrano *et al.*, 2025). The balance of these hormones is essential for normal reproductive function, and disturbances can significantly impair fertility.

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance and persistent hyperglycemia (Celik *et al.*, 2021). According to the International Diabetes Federation, over 500 million adults globally are living with diabetes, with a substantial proportion in low- and middle-income countries (Ong *et al.*, 2023). In South Africa, about 4.5 million adults are affected, with many cases undiagnosed (Pheiffer *et al.*, 2021). T2DM can disrupt the hypothalamic-pituitary-ovarian (HPO) axis through chronic hyperglycemia, hyperinsulinemia, and oxidative stress, leading to altered FSH and LH secretion, hyperandrogenism, diminished estradiol and progesterone production, and accelerated ovarian aging (Unluhizarci, Karaca and Kelestimur, 2021; Wang and Wang, 2022; Yan *et al.*, 2022). These alterations increase the risk of reproductive complications such as menstrual irregularities, infertility, and polycystic ovary syndrome (PCOS) (Bogari, 2020; Creţu *et al.*, 2020). However, before the onset of T2DM, individuals often experience a transitional phase of prediabetes.

Prediabetes is an intermediate metabolic state characterized by impaired fasting glucose, impaired glucose tolerance, or HbA1c levels above normal but below diabetic thresholds (Zhang, Shen and Wang, 2022). It affects over 400 million people worldwide, with prevalence rising rapidly, especially in urban South African populations (Rooney *et al.*, 2023; Sosibo *et al.*, 2023). Even before progression to T2DM, insulin resistance in prediabetes can impair reproductive hormone balance, leading to mild hyperandrogenism, altered estradiol and progesterone secretion, and ovulatory dysfunction (Yeung *et al.*, 2010; Sosibo *et al.*, 2024). Since prediabetes is reversible, early detection

of hormonal changes offers an opportunity to prevent long-term reproductive and metabolic complications.

The current systematic review aims to identify, evaluate, and synthesise the literature examining changes in reproductive hormones among females with T2DM and prediabetes. Where applicable, a meta-analysis will be performed to combine data on the association between these metabolic states and alterations in hormones such as estradiol, progesterone, LH, FSH, and testosterone. This review will improve understanding of the reproductive endocrine disturbances associated with these conditions and may guide strategies to preserve fertility, prevent progression to more severe endocrine dysfunction, and improve women's reproductive health outcomes.

RESEARCH QUESTION

What variations occur in the concentrations of reproductive hormones (estradiol, progesterone, testosterone, FSH, and LH) in females with T2DM and prediabetes in their reproductive age globally?

OBJECTIVES

Primary Objectives:

- To determine the changes in reproductive hormone concentrations; specifically, estradiol, progesterone, testosterone, FSH, and LH in females with T2DM and prediabetes.
- To identify the patterns of reproductive hormone dysregulation associated with metabolic dysfunction in females with T2DM and prediabetes.

Secondary Objective:

- To determine the prevalence of hormonal imbalances in females with type 2 diabetes mellitus and prediabetes globally.

METHODOLOGY

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No new data will be collected from individuals; only previously published data will be examined. Therefore, ethics approval is not required for this systematic review and meta-analysis, and no informed consent will be necessary.

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Study Design

This systematic review will include clinical observational studies such as prospective observational studies, case-control studies, cohort studies, and cross-sectional studies that investigate hormonal changes associated with reproduction in females diagnosed with T2DM or prediabetes. Eligible studies must report changes in reproductive hormones, including but not limited to estradiol, progesterone, LH, FSH, and testosterone. Both human studies and relevant clinical observational research that provide quantitative hormonal measurements will be considered.

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Outcomes

This review aims to assess changes in reproductive hormonal concentrations in females with T2DM and prediabetes compared to healthy controls. Outcomes of interest will include differences in concentrations of estradiol, progesterone, LH, FSH, and testosterone (reported as odds ratios with 95% confidence intervals).

Search Strategy

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RESULTS

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DISCUSSION

Principal Findings

Reproductive hormone alterations in females with T2DM and prediabetes represent an important intersection between metabolic and reproductive health. This systematic review and meta-analysis will synthesise existing evidence on how T2DM and prediabetes affect key reproductive hormones, including estradiol, progesterone, LH, FSH, and testosterone. The review will also summarise the hormonal mechanisms underlying menstrual irregularities, anovulation, infertility, and related reproductive disorders in these populations.

In recent years, increasing global prevalence of T2DM and prediabetes, driven by lifestyle and dietary changes, has intensified concern about their effects beyond glucose metabolism. Hormonal dysregulation linked to insulin resistance and chronic hyperglycemia may impair the HPO axis, disturb steroidogenesis, and accelerate reproductive aging. By pooling and critically appraising previous studies, this review aims to provide a comprehensive understanding of the interplay between metabolic dysfunction and reproductive hormone alterations, informing strategies for prevention and early intervention in at-risk women.

Limitations

This review will exclude studies focusing exclusively on male reproductive hormones or on reproductive hormones in contexts unrelated to T2DM or prediabetes. In addition, non-human studies and those without explicit hormone measurements; only clinical symptom reporting without biochemical data will not be considered.

Acknowledgements

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Authors’ Contributions

DT and AK were responsible for brainstorming, designing the study and drafting the protocol. DT, AS, and AK were responsible for reviewing the eligible study and final draft of the manuscript. Funders had no role in developing the protocol.

Funding

The College of Health Sciences funded this study; however, the funders had no role in study design and manuscript preparation.

Conflicts of Interest

None declared.

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Abbreviations

T2DM:	Type 2 Diabetes Mellitus
HPO:	Hypothalamic-Pituitary-Ovarian
PCOS:	Polycystic Ovary Syndrome
LH:	Luteinizing Hormones
FSH:	Follicle-Stimulating Hormone
PRISMA:	Prepared Reporting Items for Systematic Reviews and Meta-Analyses
ADA:	American Diabetes Association
IFG:	Impaired Fasting Glucose
IGT:	Impaired Glucose Tolerance
HbA1c:	Glycated Haemoglobin
CI:	Confidence Interval
RevMan:	Review Manager Program
GRADE:	Grading of Recommendations Assessment, Development, and Evaluation