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Cyclic progesterone and spironolactone treatment for androgenic polycystic ovary syndrome

Submission date
29/08/2021

Recruitment status
No longer recruiting

Registration date
07/09/2021

Overall study status
Completed

Last Edited
27/01/2025

Condition category
Nutritional, Metabolic, Endocrine

[X] Prospectively registered

[X] Protocol

[_] Statistical analysis plan

[X] Results

[_] Individual participant data

Plain English summary of protocol

Background and study aims
Polycystic ovary syndrome with higher than normal men's type hormone (called androgenic PCOS) occurs in 10% of women in the population. There are many potential causes. There is no durable treatment that deals with women's four main concerns: weight loss, regular cycles, fertility and hirsutism/acne and signs of high men's type hormones. The current treatment is combined hormonal contraception (The Pill) which results in some improvement but not all can take it and the benefits wear off after 6 months from stopping. The aim of this study is to perform a feasibility study of cyclic progesterone (given for 14 days to be similar to following egg release in a normal cycle) and spironolactone (a hormone that blocks men's hormone actions) over six cycles.

Who can participate?
Women or non-binary born female with physician-diagnosed androgenic PCOS, aged 19-40 years, living in Metro Vancouver, who do not have diabetes

What does the study involve?
Participants are treated with cyclic progesterone and spironolactone for 6 months. The primary outcome of the study is a change in the PCOS-specific quality of life. The researchers will assess safety with potassium measurements at the end of the study, and observe whether cyclic progesterone prevents spironolactone-related abnormal bleeding. The researchers will obtain women's reactions to taking these medicines. Participants will have two blood tests, collect first-morning saliva on 9 different days (stored in a home freezer), keep a daily menstrual cycle diary for 2 weeks on no treatment and for about 6 months on treatment, and answer questionnaires.

What are the possible benefits and risks of participating?
The benefits of participating are helping discover new treatments for PCOS, free access to cyclic progesterone (that is costly in Canada) and spironolactone, learning about yourself through diary-keeping, learning your own lab results, learning the results of the whole study (eventually). The researchers will also provide a free menstrual cup if interested (DivaCup), and the Prior book, Estrogen's Storm Season - stories of perimenopause. The risks of participating are a

possible adverse reaction to either study medicine, an elevated potassium value from spironolactone, and abnormal bleeding from spironolactone. The researchers will avoid the risk of pregnancy on spironolactone by providing condoms and vaginal spermicide for women sexually active with a man.

Where is the study run from?
The Centre for Menstrual Cycle and Ovulation Research of the University of British Columbia (Canada)

When is the study starting and how long is it expected to run for?
January 2020 to November 2023

Who is funding the study?
1. Women's Health Research Institute (Canada)
2. Besins Healthcare International (Monaco)
3. Pure Integrative Pharmacy (Canada)

Who is the main contact?
1. Katie Nelson, kaitlin.nelson@ubc.ca
2. Dhani Kalidasan, dhani.kalidasan@ubc.ca
3. Dr Jerilynn C. Prior, jerilynn.prior@ubc.ca

Contact information

Type(s)
Scientific

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Type(s)
Public

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
H20-02824

Study information

Scientific Title
Phase II 6-month cyclic progesterone/spironolactone pilot therapy trial in polycystic ovary syndrome: pre-post, single-arm feasibility study

Acronym
Cyclic P4/Sp in PCOS

Study objectives
Cyclic progesterone and spironolactone treatment over 6 months in women with androgenic polycystic ovary syndrome will significantly improve within-woman quality of life measured using the specific, validated PCOS-Q Health-Related Quality of Life instrument.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 25/01/2020, Clinical Research Ethics Board of the University of British Columbia (UBC CREB Office, Room 210, Research Pavilion, 828 West 10th Avenue, Vancouver, BC V5Z 1L8, Canada; Tel: not available; pia.ganz@ors.ubc.ca), ref: H20-02824

Study design
Single-centre single-arm interventional open-label 6-month therapy trial

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Other

Study type(s)
Treatment

Participant information sheet
See study outputs table

Health condition(s) or problem(s) studied
Polycystic ovary syndrome (PCOS)

Interventions
This is a prospective, open-label, single-arm, pragmatic interventional feasibility study in premenopausal women without type 2 diabetes mellitus (off combined hormonal contraceptives and/or metformin for 1 month) with physician-diagnosed androgenic PCOS treated with oral micronized progesterone (biochemically the same as endogenous ovarian progesterone) for 14 days/month or menstrual cycle, at a dose of 300 mg at bedtime (CyclicP4).

After the first full menstrual cycle on CyclicP4 (to avoid abnormal vaginal bleeding) the researchers will begin treating with the androgen- and mineralocorticoid-receptor blocker, spironolactone, at a dose of 200 mg at bedtime taken daily for 5 months.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Progesterone, spironolactone

Primary outcome measure
Health-related quality of life (HRQoL) change is measured within-woman with androgenic PCOS by the PCOS-Questionnaire© (PCOS-Q) instrument comparing the total score, and domain-specific scores between Phase 0 (screening, random cycle day) and the early follicular phase of Cycle 7 (study end) after 6-months' treatment with cyclic progesterone (CyclicP4) and 5-months' treatment with spironolactone (Sp) therapies

Secondary outcome measures
Current secondary outcome measures as of 29/12/2021:
1. Serum luteinizing hormone (LH) measured by conventional laboratory methods and salivary free testosterone (FreeT) measured by liquid chromatography/mass spectroscopy (LC/MS-MS) in a quantitative aliquot (derived from three separate mornings' samples) given the pulsatility of hormones in saliva) changes are compared within-woman between Phase 0 and Cycle 7
2. Salivary FreeT change measured by liquid chromatography/mass spectroscopy (LC/MS-MS) is compared within-woman between Phase 0 and Cycle 1 early follicular phase after 14 days of

CyclicP4 taken in late Phase 0 to bring on menstruation
3. Weight (kg, measured using balance beam), height (m, measured using weight scale stadiometer), waist circumference (cm, measured using NIH method), blood pressure (seated, automated mean of three readings), body mass index (kg/m²), blood HbA1c (measured using standard laboratory methods), tobacco and alcohol use measured using CaMos questionnaire, and physical activity changes within-woman assessed between Cycle 1 and Cycle 7
4. Menstrual cycle lengths, variability (predictability), flow (assessed by counts of soaked standard-sized pad/tampons or by menstrual cup semi-quantitative measures) and Menstrual Cycle Diary© (Diary) experience changes recorded within-woman are compared between Phase 0 data and the mean of experiences from Cycles 1-6, and also compared between Phase 0 and Cycle 6
5. Estradiol, progesterone, cortisol and DHEA saliva data within-woman changes measured using high-throughput liquid chromatography-tandem mass spectrometry from Phase 0 to Cycle 1 (after one 14-day CyclicP4 exposure) and from Phase 0 to Cycle 7
6. Women's Perceived Change questionnaire on acne and sleep quality, scored on a Likert Scale (-5 to 0 to +5), assessed in the follicular phase of Cycle 7
7. Generic HRQoL changes assessed within-woman using the SF-36 instrument domain scores and mental and physical summary scores from Phase 0 to Cycle 7
8. SF-36 HRQoL domain and summary scores at Phase 0, and also at Cycle 7, are compared with most recent SF-36 data in age- and BMI range-similar local population-based women from the regional population-based BC Canadian Multicentre Osteoporosis Study (CaMos) cohort.
9. Serum C-reactive protein (hsCRP) and albumin (assessing inflammation) by local laboratory methods, Leukocyte Telomere Length (LTL) and mitochondrial DNA copy number (assessments of genetic aging, by UBC Cote lab-specific methods), and Anti-Mullerian Hormone (AMH, assessment of reproductive reserve) by the best method available (in archived serum stored at -70°C) in 2022-2023 changes will be measured and compared within-woman from Phase 0 to Cycle 7
10. Diary Phase 0, and also Cycle 6 records will be compared with similar-aged normative premenopausal data (archived from the 1-year Prospective Ovulation Cohort, n=53, Prior NEJM 1990) using non-parametric methods and principal components analysis
11. Changes within-woman in all measures between Phase 0 and Cycle 7 will be assessed using regression methods for an influence related to how long (in months, up to 1-year) since women in this trial stopped taking combined hormonal contraceptives (CHC) or metformin treatments
12. Serum potassium (K+) measured by standard laboratory methods at Cycle 7 and determined to be, or not be, within or less than 10% above the local laboratory reference range
13. Potential adverse effects of Sp assessed using the presence/absence of abnormal /unpredictable menstrual timing and flow in Cycle 2
14. Women's willingness to continue taking CyclicP4/Sp therapy assessed using a 7-part Likert scale at Cycle 7; women's preference assessed on a 7-part Likert scale for CHC vs CyclicP4/Sp therapy in women who had previously taken CHC as a PCOS treatment

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stadiometer), waist circumference (cm, measured using NIH method), blood pressure (seated, automated mean of three readings), body mass index (kg/m²), blood HbA1c (measured using standard laboratory methods), tobacco and alcohol use measured using CaMos questionnaire, and physical activity changes within-woman assessed between Cycle 1 and Cycle 7
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Overall study start date
25/01/2020

Completion date
31/12/2023

Eligibility

Key inclusion criteria
Current inclusion criteria as of 08/12/2022:
1. Community dwelling
2. Physician diagnosed with androgenic PCOS
3. Ages 19-40 years (we will screen those between the ages of 35-40 for very early

perimenopause (Prior JC. (2005). Clearing confusion about perimenopause. BC Medical Journal 47(10): 534-538)
4. If applicable, 1 month off combined hormonal contraceptives
5. If applicable, 1 month off metformin therapy
6. Not at high risk for type 2 diabetes mellitus (T2DM) (based on HbA1c >6.4%)
7. Not seeking fertility in the next 6-7 months
8. Willing to use a barrier (condoms, provided) and an applicator full of vaginal spermicide if at risk for pregnancy (sexually active with a man)

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Participant type(s)
Patient

Age group
Adult

Lower age limit
19 Years

Upper age limit
40 Years

Sex
Female

Target number of participants
40

Total final enrolment
41

Key exclusion criteria
Current exclusion criteria as of 18/03/2022:
1. PCOS based only on oligomenorrhea and polycystic ovary morphology without androgen excess.
2. High risk for type 2 diabetes mellitus based on HbA1c of 6.4 or higher
3. Younger than 19 years or older than age 35 years
4. Unwilling to stop combined hormonal contraceptives (for 1 month before joining) or other hormonal contraception (such as DepoMPA for 6 months) and during the study
5. Unwilling to stop metformin (for 1 month before joining) and during the study
4. Unwilling to stop working toward fertility for 7 months

5. Unwilling to use a barrier method (condom) and a whole applicator of vaginal spermicide with each intercourse (if at risk for pregnancy)
6. Currently breastfeeding and have been for less than 6 months
7. History of migraines with aura and/or neurological signs and symptoms since this brain sensitivity may mean starting or stopping progesterone could trigger a migraine

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1. PCOS based only on oligomenorrhea and polycystic ovary morphology without androgen excess.
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5. Unwilling to stop metformin (for 1 month before joining) and during the study
4. Unwilling to stop working toward fertility for 7 months
5. Unwilling to use a barrier method (condom) and a whole applicator of vaginal spermicide with each intercourse (if at risk for pregnancy)

Date of first enrolment
29/10/2021

Date of final enrolment
02/03/2023

Locations

Countries of recruitment
Canada

Study participating centre
University of British Columbia Centre for Menstrual Cycle and Ovulation Research
2775 Laurel Street, Suite 4111
CeMCOR, UBC Division of Endocrinology
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Sponsor information

Organisation
Women's Health Research Institute

Sponsor details

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Sponsor type
Research organisation

Website
https://whri.org/research/

ROR
https://ror.org/0455vfz21

Funder(s)

Funder type
Research organisation

Funder Name
Women's Health Research Institute

Funder Name
Besins Healthcare International

Funder Name
Pure Integrative Pharmacy

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact, open-access, peer-reviewed journal. The protocol is currently posted on an open-access University website (http://hdl.handle.net/2429/77625). The researchers have also written a protocol for submission for publication.

Intention to publish date
31/05/2025

Individual participant data (IPD) sharing plan

The researchers will share results privately with all participants as they become available through a password-protected section of the CeMCOR website (https://www.cemcor.ubc.ca). They will share the results more widely once the main paper has been published. The data officer for the Centre for Menstrual Cycle and Ovulation Research (currently Jerilynn C. Prior [Jerilynn.prior@ubc.ca]) is the contact for use of the data (alternate email Dharani Kalidasan [dhani.kalidasan@ubc.ca]). Per ethics regulations, all data will be de-identified before any sharing. The requesting, qualified scientists will be asked to provide a hypothesis and a primary objective for use of the data and will be required to work with CeMCOR scientists in further evaluation of these data.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version 1	28/09/2021	29/12/2021	No	Yes
Protocol (other)		03/02/2022	08/09/2022	No	No
Thesis results		06/01/2025	27/01/2025	No	No