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Project Title - Phase II 6-month Cyclic Progesterone/Spironolactone pilot Therapy Trial in Polycystic Ovary Syndrome—pre-post, single-arm feasibility study

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Abstract:

Androgenic Polycystic Ovary Syndrome (PCOS) creates physical/emotional burdens in 4-20% of premenopausal women living with PCOS (WLWP) including: few menstruations per year, subfertility, hirsutism/acne and low quality of life by validated PCOS Questionnaire (PCOSQ). Combined hormonal contraceptives (CHC), the current standard-of-care, improve PCOSQ only 16%; with stopping CHC, benefits disappear within 6-months. We hypothesize too-fast brain/luteinizing hormone (LH) pulses cause PCOS. Progesterone (P4) slows LH when testosterone (FreeT) is normal. Combining two approved medications, Cyclic P4 with anti-androgen, Spironolactone (Sp), will likely provide effective, durable benefits. WLWP lit-review suggested significant P4 7-14-day benefits. A 6-month prospective feasibility study of CyclicP4/Sp is necessary.

Overall purpose: Perform a pilot study in 40 WLWP on Cyclic P4 (300 mg/bedtime, 14 days/month) plus Spironolactone (Sp, 200 mg/d).

Feasibility: Assess longitudinal within-WLWP 6-month changes in: 1) PCOSQ; 2) FreeT, HbA1c, and LH; plus 3) WLWP's acceptance of CyclicP4/Sp.

Methods: Single-centre, prospective, longitudinal single cohort study. Recruit ~7-8 WLWP/month over 4-6 months; 85% retention. Eligible WLWP have physician-diagnosed PCOS, are 1-month off CHC/metformin, ages 19-35 (avoiding adolescence/perimenopause), HbA1c <6.4% (no diabetes) and commit to non-hormonal contraception, if needed.

Recruitment uses online, internet, strategic ads and tear-tab posters. Measures at 0 and 6 months: as above plus K+ (safety assessment). Menstrual Cycle Diary monitoring (flow, adherence), 2 visits, monthly telephone/emails for support and assessment of any adverse effects. Statistical analysis: changes by paired T-test.

Summary: A feasibility 6-month study of CyclicP4/Sp will facilitate a CIHR-funded RCT of CHC versus this innovative and likely beneficial treatment for WLWP.

Overall Objectives—to answer this

Research question: *Does 6-months Cyclic Progesterone (CyclicP4) and Spironolactone (Sp) treatment of women living with androgenic PCOS improve their PCOS-specific quality of life?*

To assess, in women ages 19-35 with physician-diagnosed androgenic polycystic ovary syndrome (PCOS) taking open-label cyclic progesterone (CyclicP4, 300 mg at bedtime [hs]) and daily spironolactone (Sp 200 mg at hs) for six months/cycles, ***the within-woman* changes *in*:**

1. **Primary Objective**--Health-Related Quality of Life (HRQoL) by the PCOS-specific (PCOSQ) instrument
2. ***Secondary Objectives*:**

i. Changes in early follicular phase a.m. salivary free testosterone (FreeT) and serum luteinizing hormone (LH) absolute levels, and relative to initial BMI, and months (m) since last combined hormonal contraception (The Pill, CHC) or metformin use.

ii. Menstrual cycle lengths, predictability and Menstrual Cycle Diary© (Diary) experiences related to mo since last (CHC/metformin) use, regularity of physical activity and initial BMI.

iii. Women's Perceived Change in acne and sleep (-5 to 0 to +5) at studyend.

iv. Changes in SF-36 generic HRQoL instrument; plus, difference from values in age- and BMI range-similar local population-based women from the BC CaMos cohort.

v. Changes in weight, waist circumference, blood pressure, BMI, HbA1c, tobacco and alcohol use, and exercise.

vi. Changes in early follicular phase a.m. salivary estradiol, cortisol and DHEA.

vii. Changes in leukocyte telomere length, C-reactive protein (hsCRP),serum albumen, Anti-Mullerian Hormone and mitochondrial DNA

viii. Menstrual Cycle Diary final cycle records versus a normative Diary database of ovulatory cycles using principal components analysis.

3. ***Safety Objectives*:** Sp use and risk of abnormal flow when started after one P4 cycle; potassium (K+) increase and whether it rises too unsafe levels given Sp dosing of ≤ 200 mg/d
4. ***Feasibility* Objectives:** Willingness to continue to take CyclicP4/Sp therapy (7-part Likert scale); preference (if past CHC therapy) for CHC versus (vs) CyclicP4/Sp (7-part Likert)

Rationale and Background

The **rationale** for this pilot[1], single arm, single centre, prospective 6-month (6-mo) open-label interventional study is the *need to provide therapy choices for women with androgenic **PCOS*.**

As a **background**, women with PCOS comprise 4-20% of menstruating women[2] and ~10% of adult women in population-based data have *androgenic* PCOS[3]. Healthcare providers (HCP) diagnose PCOS in adult women (>2 years [y] since menarche[4]) who meet ≥2 of 3 criteria[5]:

1) Oligomenorrhea;
2) Clinical (hirsutism/acne) or biochemical (high Free Testosterone, FreeT) Androgen Excess;
3) Typical cysts and larger ovary by ultrasound; other causes must also be eliminated[5,6].

Living with androgenic PCOS is distressing[7]; its facial hair, acne and infertility issues challenge a women's gender image[8]. Women with PCOS often have decreased HRQoL[9], depression and/or anxiety[10]. CeMCOR has documented importantly (>5-unit lower domain score[11]), universally, lower generic HRQoL (via SF-36) in 93 local participants with PCOS despite their greater education than the 56 population-based, age-similar local controls[12]. SF-36 domain scores ranged from -5.8- -19.9 (mean -11.6) lower[12] **(*Appendix Fig 1*).**

Combined hormonal contraceptives (CHC)[13] are current PCOS standard-of-care, that improve menstrual

regularity, androgen excess (hirsutism/acne) plus PCOS-Q health related quality of life (HRQoL) by 16% for fertility-seeking women with PCOS[14]. An internet survey (2015-16) of >1300 European/N American women with PCOS found the following ***top concerns*:**

1) difficulty losing weight;
2) subfertility;
3) abnormal menstrual cycles, and
4) hirsutism/acne[15].

However, continuous CHC in an RCT was only effective for concerns 3 and 4[14]; it did not aid in important weight loss nor in increased live birth rate post-clomiphene[16]. Also, based on prospective data, within 6-months of stopping CHC, its clinical benefits for women with PCOS, except less acne, had virtually disappeared[17]. CHC are convenient, readily available and women and healthcare providers (HCP) are comfortable with them. However, not all women with PCOS find CHC acceptable or tolerable. ***Women with PCOS need effective non-CHC treatment options***.

Our 2019, similar *unfunded* WHRI Catalyst application was positively assessed. Reviewers wrote: "a very innovative proposal that is highly relevant to women's health" since "current treatment does not meet 2 of top 4 concerns, including infertility"; and that it promised "women with androgenic PCOS will benefit." Since then, we have gained more pertinent knowledge. We conducted a review of the literature on PCOS and micronized P4 therapy[18] that showed cyclic P4 caused predictable flow with lower LH and T levels; vaginal P4 in letrozole ovulation induction also improved live birth rates[18]. We further documented the 6- months within-woman daily Menstrual Cycle Diary[19] (Diary) change in a woman living with androgenic PCOS volunteer taking cyclic P4 her physician had prescribed; she had significantly decreased fluid retention, breast tenderness and cervical mucus **(*Appendix Fig 2*)**[20].

We have also just launched (July 15, 2020) a PCOS treatment survey to assess WLWP's preferences and willingness to volunteer for research (www.cemcor.ubc.ca). Finally, Besins© have now committed to provide an arms-length donation of the oral micronized progesterone needed for Cyclic P4 for this 6-month, single-arm interventional trial. In addition to these recent data, Dr. Prior has past 20-year, 200-woman strong clinical experience effectively treating women with androgenic PCOS with *Cyclic P4* ("luteal phase replacement" since ovulatory disturbances are very common) *plus Spironolactone* (Sp, anti-androgen therapy that is effective, safe and cheap).

Women with PCOS on these two therapies, in Prior's clinical experience, developed ovulatory normal-length cycles, lost acne and former beard hair, felt better so they exercised more and ate better with resultant weight loss; they could eventually stop all therapy. They were also able to spontaneously (when off spironolactone) become pregnant. Prior learned the key role of P4; women with PCOS would briefly "relapse" with increased stress or weight change disrupting ovulation that was readily reversed by re-treated with Cyclic P4.

Why would Cyclic Progesterone and Spironolactone be effective for androgenic PCOS? Because scientific evidence suggests that *deficient progesterone* is the key to resolving the fundamental physiological and metabolic imbalances in PCOS. Although the origin of PCOS is multifactorial with contributions from genetic, *in utero* androgen exposure, inflammation and environmental variables[21], it appears to begin with ***abnormally fast pulsing hypothalamic GnRH***[22]. The GnRH quick pulses (stimulated by afferents from GABA-A and Kisspeptin) lead to similarly pulsing LH that increases ovarian thecal testosterone (T) production, suppresses FSH, and prevents ovulation. The result is abnormally high FreeT production[22], tonic or elevated estrogens, and few cycles with most having ovulatory disturbances; these changes in turn lead to insulin resistance, obesity[23], decreased fertility and increased risk for endometrial cancer. Higher insulin levels/resistance also increase FreeT production[24], with inflammation[25] and obesity both contributing[21]. Once begun, androgenic PCOS creates a self-

perpetuating, ‘vicious cycle’.

Since progesterone normally slows GnRH and LH pulsing at the menstrual midcycle[26], **treatment with CyclicP4 may be effective PCOS therapy.** However, the higher FreeT levels in PCOS appear to interfere with P4's LH pulse-slowing actions[22]. In women with PCOS on CyclicP4, adding an anti-androgen such as spironolactone (Sp), allowed luteal phase P4 levels to effectively slow LH pulses to normal[27] with resulting lower LH and FreeT levels. P4 itself also lowers androgen *activity* by competing for the 5- alpha reductase enzyme that converts T to its active skin metabolite, dihydrotestosterone (DHT)[28].

Despite the promising new information, none of the PCOS studies we recently reviewed gave oral micronized P4 for longer than a single (usually 7-12) day cycle[18]; it is not yet known whether 200 mg of Sp will be effective for women with PCOS having body mass index (BMI) values >30; if Sp given after a 14-day cycle of P4 followed by withdrawal flow will prevent abnormal bleeding patterns[29], and how high K+ will be elevated, and whether it, as in treatment of acne[30], will be without serious risk. We previously studied quality of life in women with PCOS on no, or no specific, therapy, using the appropriate generic SF-36 HRQoL tool for population comparison[12]. Data are still needed for androgenic PCOS on this innovative Cyclic P4/Sp therapy using the PCOS-Specific HRQoL instrument[7]. In addition, it is not clear whether the recent use of CHC or metformin will interfere with or potentiate potential beneficial effects of CyclicP4 and Sp. Thus, there are important data that are needed before it will be possible to plan an appropriately powered ***RCT comparing this new PCOS therapy versus (vs) CHC*.** As Dr. Helena Teede, leader of a PCOS international stakeholder consortium[13] wrote (2018/09/01): "*I. . .strongly state the need for a study such as Prior and colleagues are proposing."*

Study hypothesis and aims

Our ***hypothesis*** is that CyclicP4/Sp will effectively increase the total PCOSQ score during 6-mo of therapy (Primary objective). We also *hypothesize* that women will elect to continue Cyclic P4/Sp and prefer it to CHC (Feasibility objective). Clinical experience suggests that Sp started after one cycle of P4 treatment will not cause flow problems, and will not dangerously increase K+ (Safety objectives).

Our ***aims*** (as outlined in **Objectives**) are to obtain open-label, prospective 6-mo interventional data on CyclicP4/Sp in 40 women, of all BMI values, with healthcare provider (HCP)-diagnosed androgenic PCOS, to track changes in the PCOS-Questionnaire (1º outcome), FreeT and LH levels as well as changes in weight, waist circumference, blood pressure, estradiol, cortisol, and DHEAS levels and self-perceived acne and sleep. We are also adding science-based objectives to document changes in leukocyte telomere length (LTL) which is a genetic marker of cellular aging and has been shown to be in women with PCOS than controls. In addition, because of the strong role of inflammation we are assessing changes in C-reactive protein (hsCRP) and albumen and the ratio of the two which was diagnostic for PCOS in a large community sample.

Our *primary overall purpose* is to assess the effectiveness of 6-mo CyclicP4/Sp in improving the lives of women living with PCOS by the PCOSQ to provide essential data for planning an adequately powered RCT that will formally compare CHC vs CyclicP4/Sp. We will also learn changes in key hormonal values (FreeT, LH and HbA1c), assess its safety by K+ levels and flow and experience changes by daily Diaries [***Appendix Fig 3***].

Study design, methodology and analysis plan

Design: this is a pre-post, pilot (Phase II) prospective 6-mo, single arm, open-label interventional study
Methods: Our *primary outcome* is the 6-mo validated PCOS-specific HRQoL tool, PCOSQ[7], that is sensitive to change and comprehensively covers all primary issues for women with PCOS WLWP except acne[31,32].

Interventions: oral micronized progesterone (P4) 300 mg taken at bedtime (a dose that keeps the serum P4 at/above the luteal phase level for 24 hours)[33] and is sufficient to decrease LH pulsatility[22]. We will prescribe P4 cyclically 14 days/month or for cycle days 14-27 of a normal-length menstrual cycle (***CyclicP4***). In addition, all women with androgenic PCOS will start spironolactone (**Sp**) 200 mg/bedtime *in the* ***second cycle***.

Given the male fetus teratogenic effects of Sp, to be eligible, all participants at pregnancy risk must agree to conscientiously use some form of ***non-hormonal contraception***: condom/vaginal spermicide or copper IUD. There is evidence that metformin improves cycle regularity and lowers androgen levels even in normal-weight, non-diabetic women with PCOS[24]. We will include women 1-m *off metformin* and, to avoid needing it since it may confuse CyclicP4 & Sp effects on PCOSQ in WLWP[32], we will screen for increased risks for type 2 Diabetes Mellitus (T2DM) and exclude women with HbA1c >6.4%[13] who are at increased diabetes risk.

Participants will be **eligible** if they are women with PCOS diagnosed by a physician and their PCOS is androgenic per PCOS/Androgen Excess Society criteria[4]. *We will enroll 40 eligible women.* (This is feasible for to recruitment in 4-5 months; we anticipate it providing adequate power since an RCT with significant PCOSQ results had similar #/arm[14]). Eligible women must be ages 19-35 to be at or above the BC age of majority, unlikely to be within 2-years of menarche[6] and to avoid perimenopause when PCOS experiences change[34]. Women with previous or recent CHC or metformin treatment are eligible, provided CHC or metformin has been discontinued for ≥1 month (although we will encourage at least three months off, if possible). All will be screened and have a normal HbA1c. Since women having all BMI values are eligible, we will assess it for a potential influence on our objectives.

Women with PCOS will be **ineligible** if seeking fertility, do not commit to using non-hormonal contraception if at risk for pregnancy, are pregnant, currently taking reproductive hormones, or are unwilling to stop CHC, metformin for a month before enrolling or to record daily experiences in the Diary.

We will assign each participant a unique number. No identifying data will leave the PI's locked office in a locked file thus securing name, contact and code data.

Recruitment will be from the Metro Vancouver region by the CeMCOR's proven successful and cost-effective methods[35]. We will emphasize social media recruitment if current COVID-19 restrictions continue into the spring of 2021. CeMCOR has a pandemic safety plan in place for remote or in-person trial conduct.

Tools: To assess these data's generalizability at baseline, elements of the Canadian Multicentre Osteoporosis Study (***CaMos Questionnaire****)* will be interviewer-administered (in person or video-conferenced) for comparison with local population-based CaM*os* controls[12]. If in-person research is allowed, participants at enrolment visit will have weight, height, waist circumference and blood pressure (BP) measured and complete the validated ***PCOSQ***[7] and SF-36; we will repeat these measures at 6-mo. (Note, for consistency, given COVID uncertainties, all women will be provided the PCOSQ and SF-36 and be asked to complete these in their own homes prior to the initial and final visits. If COVID restrictions persist, women with PCOS will measure their own weight, height, and waist circumference at home, and blood pressure [BP] at a pharmacy). Also, at the end of this trial, WLWP will record changes in acne and sleep (graded -5 to +5) by the ***Women's Perceived Change Questionnaire*** (WPCQ)[36] as well to repeat CaM*os* questionnaire diet and physical activity and answer feasibility questions about their preferences.

Laboratory testing will include morning, early follicular phase (cycle days 1-3, or any day if last flow >40 days earlier) assessments at baseline and in the beginning of the 7th cycle:
Serum LH (by standard, monitored Vancouver General Hospital [VGH] laboratory methods)
FreeT obtained from morning saliva and analyzed by the reliable, specific, new liquid chromatography

mass spectrometry (LC/MS-MS) method of Gao[37]. These, obtained at home, will be stored in the home freezer. Given the pulsatility of steroids[26] three saliva samples will be obtained over 3 days and quantitatively pooled into a single analytic sample. At the end of the study we will ship all analytic saliva samples, labelled with ID# and date, to Germany on dry ice for analysis. Returned data will be by coded date-specific hormonal data (***cortisol*, *estradiol* and *DHEA*** as bonus descriptive measures) via password-protected email. Each woman's samples will be analyzed in the same batch.
Venous HbA1c (VGH laboratory—standard methods) during the early follicular phase at screening and in the 7th cycle.
Serum K+ (VGH laboratory—standard methods) after 5 months on Sp in the follicular phase at the trial's end.

Analysis plan: Our pilot study's purpose is to provide treatment-related estimates of changes and variability in key outcomes. The statistical analysis plan will be written by Dr. Joel Singer (biostatistician/epidemiologist) in consultation with the clinical team.

We will assess all changes from baseline within-woman by paired T test; multiple regression will be used to assess the association of the final PCOSQ with baseline PCOSQ, BMI and physical activity, and recent CHC/metformin use at baseline. We will describe the PCOSQ overall percentage change (for comparison with CHC[14])[7]. As previously[12], we will describe baseline demographic and anthropometric variables for women with androgenic PCOS vs population-based regional similar-aged CaM*os* controls. We will describe cycle lengths and variability changes. We will analyze ordinal Diary variables with non-parametric statistics and can compare with initially normally ovulatory women[38],[39] using SPSS for all analyses. Statistics will be performed by Drs. Shirin/Goshtasebi with direction from and support by Dr. Singer.

Anticipated results

Based on past retention and the eagerness with which women with PCOS seem to desire a new therapy, we anticipate that ≥36 women will complete this study. We will replace any losses to follow-up to ensure this number completes. Their data will provide an estimate of the expected changes in PCOSQ score/domains to enable an adequately powered comparative RCT with CHC (see below). Keeping the Diary may improve women's self-efficacy; as women with PCOS feel better, they also may improve lifestyle habits and exercise (assessed by a few repeat CaM*os* questions at the final visit). In addition to quality of life measures, we also anticipate improvements in cycle length and regularity, acne, sleep[40], weight[23], waist circumference, HbA1c and BP[41].

Safety related results and amelioration

Although there is no specific Health Canada PCOS indication for Cyclic Progesterone nor for Spironolactone, the standard, BC College of Physicians and Surgeon's approved (2020) drug monographs for "Progesterone" and "Spironolactone" https://www.cpsbc.ca/library (accessed Nov 10, 2020) specifically describe progesterone as commonly used for irregular cycles, or luteal phase insufficiency that are present in most women with PCOS, in similar doses, and as cyclic therapy. In addition, spironolactone is commonly used for acne vulgaris and hirsutism as well as PCOS in usual clinical practice.
The dose ranges recommended for both progesterone and spironolactone includes the doses for this study. For these reasons, Health Canada instructions and the Chair of the Clinical Research Ethics board both indicate we do not need to obtain Health Canada, Clinical Trials Administration approval for this

study.
We will (with signed permission from each participant) write to their primary healthcare provider informing her/him of the study, the purpose, rationale, the medications being prescribed, their doses and durations for each. We will invite them to ask any questions or relate any concerns to Dr. J. C. Prior, PI, providing her contact information.

We anticipate no difficulties for women taking Cyclic Progesterone (P4). However, if a woman might be sleep deprived, we will re-enforce the importance of starting CyclicP4 on an evening following which it is possible to sleep in the next morning. Also, they should take the progesterone just as they are ready to fall asleep to avoid dizziness. We will also tell them that occasionally women my experience increased estrogen-related effects (breast tenderness, cervical mucus, fluid retention) for the first cycle of progesterone. All of these transient issues are resolved by the second cycle.
When starting spironolactone (Sp), we will warn women to increase their fluid intakes to compensate for initial, mild ~1-week-long Sp-related diuretic effects. Although abnormal vaginal bleeding is a side-effect of Sp, since we will start it only after they have experienced withdrawal flow following one cycle of P4, based on extensive previous clinical experience we expect Sp to cause no abnormal flow. Sp, because of its mineralocorticoid-blocking effects, raises serum potassium (K+) values. We expect only mild increases to the upper limit of normal K+ values and will monitor for this at study end. The most serious adverse effect with spironolactone is potential feminization of a male fetus should the woman become pregnant. All women who are sexually active with a man in this study are required to agree to conscientious use of a non-hormonal contraceptive method. We are providing condoms and vaginal spermicide for those women needing pregnancy protection. If women are unable or unwilling to use the barrier/spermicide, they will be required to get a copper IUD inserted before they are eligible.

Study timeline

In mid-July 2020, we posted (www.cemcor.ubc.ca) an ethics-approved androgenic PCOS therapy survey. Women will indicate where they live—local, potentially interested women will thus become aware of this up-coming study.
Our ethics applications and other administrative requirements will be completed by December, 2020. We will order needed supplies, recruit and train a research assistant to aid Dr. Shirin between December and early January. Recruitment will begin in the spring of 2021.

Each interested woman will contact us by email or telephone. We will email them the consent form. If they agree to consent we will telephone-screen for eligibility and obtain a HbA1c. If eligible and >1 month off CHC and/or metformin, we will teach them accurate and convenient Diary-keeping (http://www.cemcor.ca/resources/daily- menstrual-cycle-diary).

Using physical distancing and masks, enrolled women will have initial and final in-person visits (UBC-CeMCOR space 4th floor 2775 Laurel St.). They will also usually have a visit at 3-mo for refill of medicines and review of diaries and general support as well as providing their original HbA1c and LH results. We will make monthly email/telephone contact (“how are you?”), provide any needed support and ask them to bring completed diaries in-person or by mail before receiving (in person or couriered) their medication refills at 3-months.

Women with PCOS will have a final visit in the early 7th cycle bringing completed PCOSQ and SF-36 forms, be asked a couple of short CaM*os* questions (about habits and exercise), report their perceived changes in acne and sleep, have weight, waist circumference, BP measured, have laboratory testing (LH, HbA1c and K+) and bring the final completed Diaries. We will also ask a final questionnaire, if they

have previously used CHC, that assesses women's preferences, on a 7-point Likert scale[42], for CyclicP4/Sp vs CHC. We will similarly assess their likelihood of continuing CyclicP4/Sp therapy.

We should know the primary **study results** by spring of 2022 so we can re-apply for CIHR in 3/2022 for our long- planned one-year comparative RCT of CHC vs CyclicP4/Sp followed by a 6 months post trial no-drug documentation.

Once analyzed, we will immediately communicate study results with participants with PCOS via an email notification and link to password-protected articles on www.cemcor.ubc.ca. Online articles will be posted on the CeMCOR for general women's knowledge about PCOS after data are officially presented and/or published.

Relevance to the health of women in British Columbia

Women with androgenic PCOS have had no major innovation in therapy for at least 3 decades. We believe results of this trial will allow them to opt for something other than CHC and the need for expensive and often difficult fertility interventions. This 6-mo, open-label interventional study using a within-woman pre-post design is piloting one of two arms of a proposed future CIHR-funded RCT comparing CHC, the standard-of-care therapy for PCOS, with Cyclic Oral Micronized Progesterone and Spironolactone.

Encouraging data from science and clinical experience support CyclicP4/Sp. Should this pilot study show what we expect—better PCOSQ quality of life including emotional, weight, hirsutism, cycles and fertility domains, it will have provided the first evidence supporting a potentially important new therapy for PCOS. This new therapy might be life-changing for the majority of women now living with androgenic PCOS in B.C.

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APPENDIX

Dissemination plan for the results

This pilot includes embedded knowledge translation since we have co-investigators who are trained in family medicine (AG), obstetrics and gynecology (SS), public health (JS) and endocrinology (MD and JCP) as well as a community partner who is a woman living with PCOS (FM).

We will initially privately share pilot study results with participating women using a password-protected section of the popular CeMCOR website (www.cemcor.ubc.ca) that received 3,500-5,000 page-views a day from over 180 countries world-wide. We will upload a number of short reports, notifying each via email of new postings as we have successfully done following a CIHR-funded RCT of progesterone for perimenopausal hot flushes.

We will submit the results to the annual international Endocrine Society conference; we expect a podium or plenary poster presentation. We will present the new data to UBC and BC academic medical lectures, in particular, for Women's Health Research Institute rounds, VCHRI's C2E2 and family practice monthly or weekly "rounds."

We will submit the results of this phase II pilot study for publication: *J. Clin Endocrinol Metab, Human Reproduction, Clinical Endocrinol or Fertility Sterility.*

As soon as the data are in press, we will seek public media (newspapers/CBC's *The National* and other Canadian and worldwide (*The Conversation*) reporting as well as creating social media posts highlighting the results of this innovative new therapy for women living with androgenic PCOS.

We will create new CeMCOR online articles about PCOS describing the new therapy, how it works and

what to expect. This website garners 3,500-5,000 page-views/day from >180 countries. Finally, we will post CeMCOR articles for Healthcare Providers to aid them in understanding Cyclic Progesterone/ Spironolactone therapy for PCOS, detailing how to prescribe it, what to expect in the responses for women with androgenic PCOS and what evidence suggests that the potential benefits and risks may be.

Future goals outlining how the catalyst grant will facilitate funding and research

The purpose of this pilot is to provide estimates of the baseline PCOS-Q and its 6-month change and standard deviation of change in 36 women taking Cyclic Progesterone (CyclicP4) and Spironolactone (Sp). This will provide data necessary to design an adequately powered randomized comparative trial versus combined hormonal contraceptives (CHC), the standard of care for PCOS. Our intent, once we have these data is to again apply to the Canadian Institutes for Health Research to do a planned 1:1 randomized, 1.5-year prospective comparative study with a final six months' observational phase off all therapy for all participants so we can assess the relative and absolute durability of improvements on each therapy. The data from this pilot are also essential for assessing: 1) Sp response by BMI; 2) effects of previously discontinued CHC or metformin; 3) adverse effects; 4) women's preferences and willingness to continue Cyclic P4/Sp therapy. We anticipate re-applying to CIHR in March 2022.

Figures

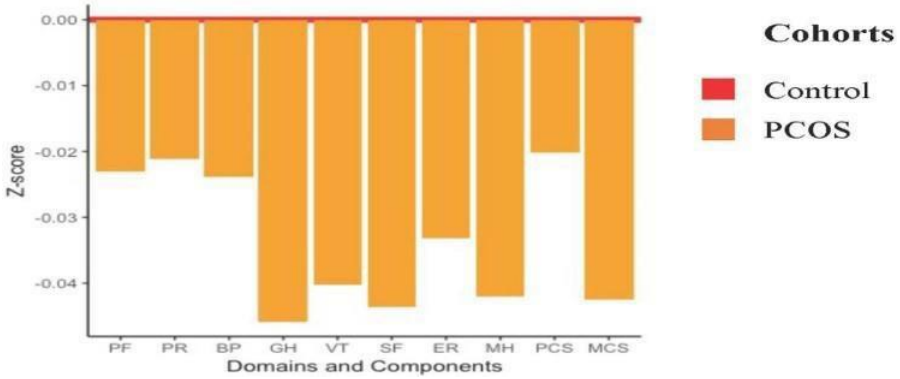


Figure 1. The Z-scores (showing portions of a standard deviation) of SF-36 HRQoL domain and component scores of 93 local premenopausal women with PCOS versus 56 age-similar women from the randomly sampled BC Canadian Multicentre Osteoporosis Study population-based regional controls.

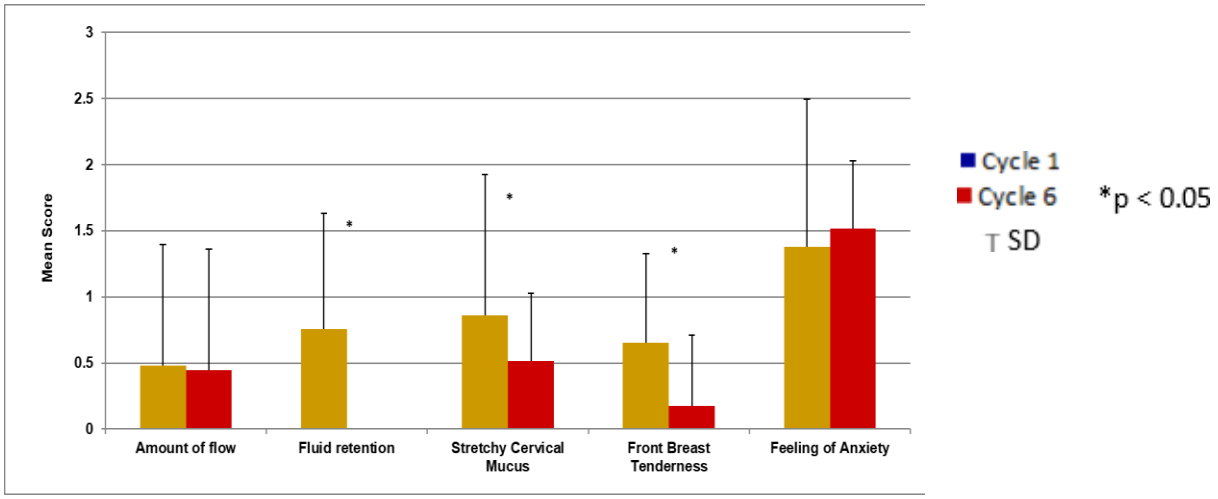
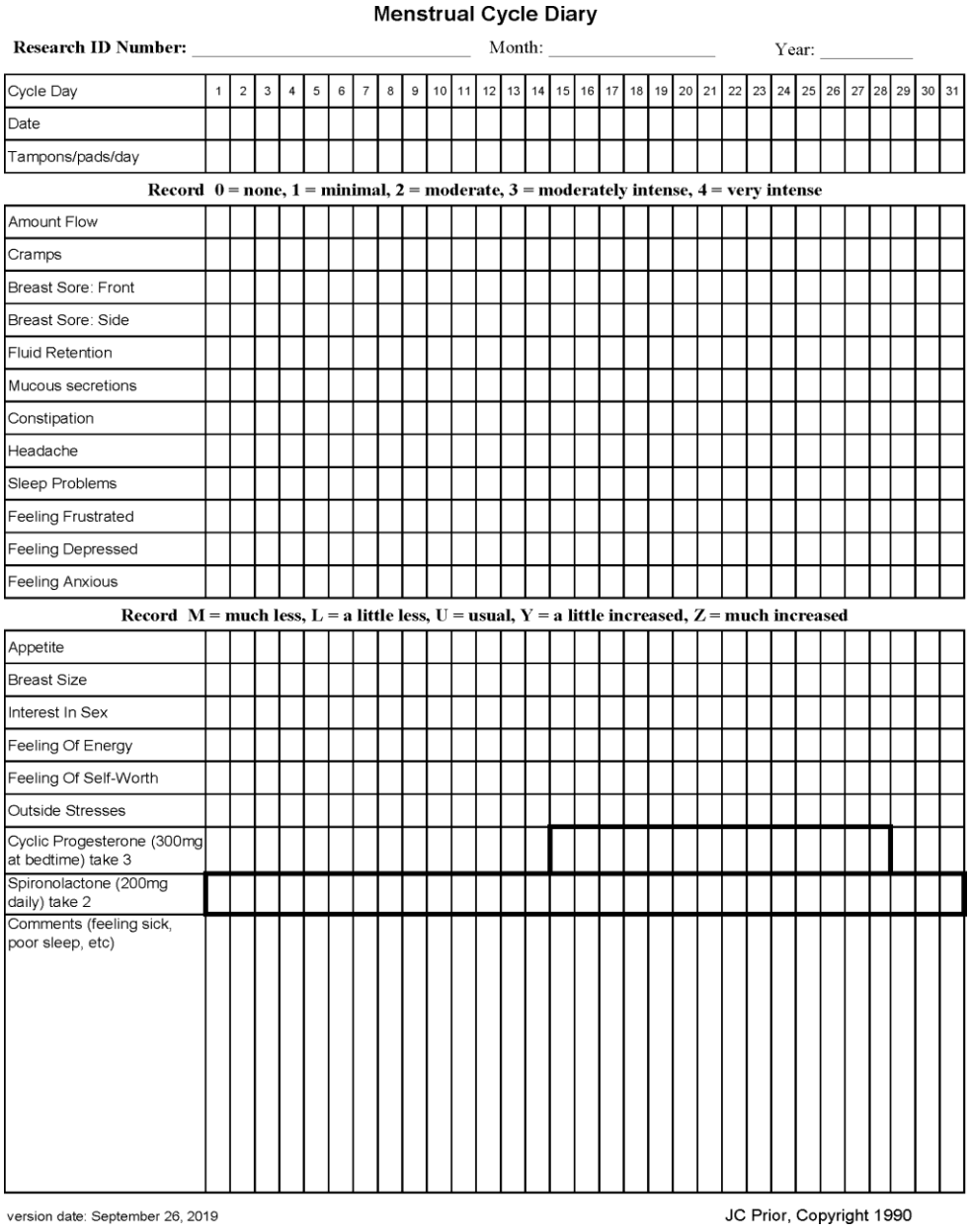


Figure 2. Within-woman PCOS's Diary Experiences Changes on Cyclic Oral Micronized Progesterone Over Six Cycles. Mean (SD) (reported for all cycle days) of the selected Menstrual Cycle Diary© experiences during cycles 1 and 6 in a single, within-woman analysis using Wilcoxon Signed Ranks Test.



Menstrual Cycle Diary

Research ID Number: _____ Month: _____ Year: _____

Cycle Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Date																															
Tampons/pads/day																															

Record 0 = none, 1 = minimal, 2 = moderate, 3 = moderately intense, 4 = very intense

Amount Flow																															
Cramps																															
Breast Sore: Front																															
Breast Sore: Side																															
Fluid Retention																															
Mucous secretions																															
Constipation																															
Headache																															
Sleep Problems																															
Feeling Frustrated																															
Feeling Depressed																															
Feeling Anxious																															

Record M = much less, L = a little less, U = usual, Y = a little increased, Z = much increased

Appetite																															
Breast Size																															
Interest In Sex																															
Feeling Of Energy																															
Feeling Of Self-Worth																															
Outside Stresses																															
Cyclic Progesterone (300mg at bedtime) take 3																															
Spironolactone (200mg daily) take 2																															
Comments (feeling sick, poor sleep, etc)																															

version date: September 26, 2019

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Figure 3 The Menstrual Cycle Diary© adapted for Cycles 2-6 of this PCOS Pilot Study to also show the days of the month or cycle days of taking each of this study's medications. This record will also allow us to record pill counts that, with returned medications, will assess adherence. (Note, Cycle 1 will only show the cycle days on which Cyclic Progesterone therapy should be taken.)