



## Case Report

# Concentrated Gelatinized Proprietary Phenotype Formulation of *Lepidium peruvianum* (maca) Positively Impacts Polycystic Ovarian Syndrome (PCOS), Premenstrual Syndrome (PMS), Dysmenorrhea, and Hormone Levels for Fertility Optimization: A Case Report

Stefani Kovacovsky Hayes<sup>1</sup>, Susan Manongi<sup>2</sup>, Kim Ross<sup>3-5\*</sup>

<sup>1</sup>Kwan Yin Healing Arts Center, Northwest Portland, OR, United States

<sup>2</sup>The Heartwood Clinic, Northwest Portland, OR, United States

<sup>3</sup>Sonoran University of Health Sciences, College of Nutrition, Tempe, AZ, United States

<sup>4</sup>Symphony Natural Health, West Lake City, UT, United States

<sup>5</sup>Symphony Natural Health Institute, West Lake City, UT, United States

**\*Corresponding author:** Kim Ross, Sonoran University of Health Sciences, College of Nutrition, Tempe, AZ, United States

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### Abstract

Polycystic Ovarian Syndrome (PCOS) is considered one of the most common endocrine and metabolic issues in premenopausal (fertile/reproductive age) women. Women with PCOS can experience multiple signs and symptoms, including but not limited to unexplained weight gain or the inability to lose weight, obesity, pelvic pain, virilism, hirsutism, acne, menstrual irregularities, insulin resistance, infertility, decreased follicle-stimulating hormone (FSH), increased luteinizing hormone (LH), imbalanced LH/FSH ratio, and increased anti-Mullerian hormone (AMH). Multiple root causes of PCOS have been identified, which may present challenges in determining the best clinical care for women. Further, because the diagnostic criterion for PCOS has changed over time, some confusion within the medical community regarding the best therapies for care exists. Additionally, treatment options can vary based on the criterion each patient meets. It is reported that over two-thirds of women with PCOS are seeking alternative care, such as herbal and supplement options. The purpose of this case report is to share the experience of one woman with PCOS using a concentrated gelatinized proprietary phenotype formulation of *Lepidium peruvianum* (maca), commercially known as MacaHarmony<sup>®</sup>, as the primary therapy to address menstrual irregularities, ovulatory dysfunction, premenstrual syndrome (PMS), dysmenorrhea, and imbalanced hormones (altered LH/FSH ratio, functionally elevated estradiol, and elevated AMH). In three months, the patient experienced dramatic improvements, including menstrual regularity, enhanced ovulation (improved cervical mucous and libido, decreased ovulatory pain), and decreased length and severity of dysmenorrhea and PMS symptoms (breast tenderness, mood changes). The patient maintained these positive outcomes for over two years. A two-year comparative analysis of labs showed improved LH/FSH ratio and estradiol levels, providing optimized hormonal balance and thereby enhanced fertility potential. In addition, several cardiometabolic markers (glucose, HDL cholesterol, triglycerides) were improved. These improvements may serve as the basis for future research into how specific maca phenotypes or combinations of maca phenotypes, when gelatinized and concentrated, can assist women with PCOS and enhance fertility outcomes.

**Keywords:** PCOS; Irregular menses; Dysmenorrhea; PMS; LH/FSH ratio; fertility; *Lepidium peruvianum*; Maca; Case report

**Abbreviations:** ADHD: attention-deficit hyperactivity disorder; AMH: Anti-Mullerian Hormone; bid: twice daily; cap: capsule; caps: capsules; CBC: complete blood count; CMP: comprehensive metabolic panel; E2: estradiol; FSH: follicle-stimulating hormone; H: high; HPA: hypothalamus-pituitary-adrenal; IV: intravenous; LH: luteinizing hormone; LN: low-normal; mcg/L: micrograms per liter; mIU/mL: milli-international units per milliliter; mg: milligrams; mg/mL: milligrams per milliliter; mm: millimeter; NA: not applicable; nmol/L: nanomoles per liter; ng/mL: nanograms per milliliter; PCOS: polycystic ovarian syndrome; pg/mL: picograms per milliliter; PMS: premenstrual syndrome; prn: as needed; qd: once daily; TSH: thyroid stimulating hormone; uIU/mL: micro-international units per milliliter.

## Introduction

Polycystic Ovarian Syndrome (PCOS) is considered one of the most common endocrine and metabolic issues in premenopausal women. It is estimated that up to 22% of women from all ethnicities and backgrounds in their reproductive years contend with this disruptor of hormones and metabolism, depending on the diagnostic criteria used [1-3].

Multiple root causes have been identified, including insulin resistance, obesity, mitochondrial dysfunction, chronic inflammation, genetic variants, oxidative stress, environmental toxin exposure, poor diet and lifestyle, and mental and emotional stressors [4-7].

The clinical approach to care for women with PCOS can be challenging because the diagnostic criterion has changed over time, creating some confusion within the medical community [3]. Additionally, treatment options can vary based on the criterion each patient meets.

According to the most recent diagnostic criteria, known as the modified Rotterdam criteria, if two or more of the following are present, a diagnosis of PCOS can be made by a qualified healthcare provider: [8]

- 1. Clinical and/or biochemical hyperandrogenism:** Elevated androgens (total or free testosterone levels, elevated DHEA levels) and/or symptoms of hyperandrogenism, including hirsutism, acne, and hair loss.
- 2. Oligo-anovulation:** Menstrual cycles occurring greater than 35 days apart or less than eight (8) menses per year.
- 3. Changes in ovary morphology:** Polycystic appearance on ultrasound (20 or more follicles per ovary or 10 cm<sup>3</sup> or greater ovarian volume).

Beyond the diagnostic criterion, women with PCOS can experience multiple signs and symptoms, including but not limited to unexplained weight gain or the inability to lose weight, obesity, pelvic pain, virilism, insulin resistance, infertility, decreased follicle-stimulating hormone (FSH), increased luteinizing hormone (LH), altered LH/FSH ratio, and increased anti-Mullerian hormone (AMH) [4,9].

While conventional medical therapies may be required for the management of PCOS, it is reported that 70% of women seek complementary and alternative medicine (CAM), which includes herbal therapies and dietary supplements, as an option for care, with 65.5% of those women reporting improvements in multiple aspects of their health as a result [10].

The purpose of this case report is to share the experience of one woman with PCOS using a concentrated gelatinized proprietary phenotype formulation of *Lepidium peruvianum* (maca), commercially known as MacaHarmony<sup>®</sup>, as the primary therapy to address menstrual irregularities, ovulatory dysfunction, premenstrual syndrome (PMS), dysmenorrhea, and imbalanced hormones (altered LH/FSH ratio, functionally elevated estradiol, and elevated AMH). In three months, the patient experienced dramatic improvements, including menstrual regularity, enhanced ovulation (improved cervical mucous and libido and decreased ovulatory pain), and decreased length and severity of dysmenorrhea and PMS symptoms (breast tenderness, mood changes). The patient maintained these positive outcomes for over two years. A two-year comparative analysis of labs showed improved LH/FSH ratio and estradiol levels, providing optimized hormonal balance and thereby enhanced fertility potential. In addition, several cardiometabolic markers (glucose, HDL cholesterol, triglycerides) were improved. The case report was written following the CARE guidelines [11].

As described in the discussion, up to 17 phenotypes of maca are known, displaying different biological responses in the body. Therefore, this case report refers to a concentrated gelatinized proprietary phenotype formulation known as MacaHarmony<sup>®</sup> and will be referred to as such in this case report.

## Case Presentation-June 17, 2021

A 31-year-old Caucasian female was referred by her acupuncturist for naturopathic care to explore options for preconception planning and for symptoms that include irregular periods, PMS, and hirsutism. The patient's medical history includes ADHD, anxiety, and depression, which a psychiatrist is treating, and migraine headaches, which are being treated by her primary care physician (PCP). She takes Adderall XR 20 mg daily, Fluoxetine 20 mg daily for ADHD, anxiety, and depression, Ondansetron 5 mg, and Sumatriptan 50 mg, as needed for migraines. Vitamin D, 1000 IU per day, was taken in supplemental form. Her family medical history includes depression, anxiety, allergies, asthma, stroke, dementia, and cancer.

The patient’s menstrual health history includes an average menstrual cycle frequency of 35-45 days, with the longest being 70 days, which occurred earlier in 2021. This frequency meets one of the diagnostic criteria for PCOS. The patient reports five days of bleeding, with 18-24 hours of heavy bleeding and menstrual cramps, rated on a pain scale as 5-7 out of 10 (with 10 being the most severe pain). This pain was diffuse in her thighs and lower back, lasting about one (1) hour each day of a five (5) day menstrual cycle. She also has PMS, with symptoms of breast tenderness five to seven days prior to menses, mood changes (anger/emotional sensitivity) two to three days before menses, and hirsutism that began in adolescence. Hirsutism was assessed using the Ferriman-Gallwey score, in which a total score of  $\geq 8$  is diagnostic [12]. The patient’s score was 16, meeting a second criterion for PCOS. The treating clinician made a diagnosis of PCOS. Further, the patient reports pain at ovulation, though an ultrasound had not been completed to see if ovarian cysts were present by the treating physician or other healthcare providers. She reports a history of normal pap smears.

A physical exam assessed hirsutism with findings of moderate and diffuse dark hair growth on the chin, upper lip, upper abdomen, lower abdomen, lower back, thighs, and legs. The patient reported hair growth on the nipples, but this was not evaluated by

the provider. The patient’s body weight was 220 pounds and body mass index (BMI) was 37.8 (Class 2 obesity).

Based on these clinical findings, recommendations were provided as detailed in the Case Recommendations (Table 1). This included increasing the dose of the vitamin D supplement, beginning a prenatal vitamin, and adding MacaHarmony® due to hormonal imbalance symptoms and PCOS diagnosis. Additionally, she was encouraged to begin tracking her menstrual cycle with regularity, including PMS symptoms and details of menses, along with ovulation symptoms, including cervical mucous and libido.

Further, a lab request was made for a fasting complete blood count (CBC), comprehensive metabolic panel (CMP), lipid panel, thyroid hormone panel, androgen hormone and fertility hormone testing. The fertility hormone testing was to be conducted on day two or three of the menstrual cycle for estradiol (E2), FSH, LH, and AMH and seven days before menstruation (typically on day twenty-one of the cycle) for progesterone (Table 2). Based on these results, additional recommendations would be provided. The patient was referred for Arvigo Techniques of Maya Abdominal Therapy™. Monthly follow-up visits were suggested for continuity of care, symptom monitoring, and fertility decision support. A timeline of all consultations reported on can be viewed in Image 1.

**Table 1:** Case Recommendations.

<b>Relevant History:</b> A 31-year-old Caucasian female sought care for preconception planning and menstrual symptoms that include irregular periods (35-45 days on average), PMS, and hirsutism. She has a medical history of ADHD, anxiety, depression, and migraine headaches. She takes Adderall XR 20 mg qd, Fluoxetine 20 mg qd, Ondansetron 5 mg prn, Sumatriptan 50 mg prn, and 1,000 IU vitamin D as prescribed by other providers. The treating clinician made a diagnosis of PCOS.						
	June 2021	July 2021	August 2021-March 2022	April 2022	August -December 2022	January-November 2023
<b>Dietary Recommendations</b>						
A Mediterranean diet (focused on vegetables, healthy fats, proteins, and iron-rich foods) and decreased sugar intake were recommended starting in July 2021 and reinforced throughout care. In July 2023, an increased focus on blood sugar-balancing foods was emphasized.						
FemmenessencePRO HARMONY (MacaHarmony®) ( <i>Lepidium peruvianum</i> -maca) Symphony Natural Health	1cap bid	1 cap bid <sup>a</sup>	1 cap bid	2 caps bid	1 cap bid <sup>b</sup>	2 caps qd <sup>c</sup>
Prenatal SAP <sup>d</sup> Nutritional Fundamentals for Health	3 caps qd	3 caps qd	3 caps qd	3 caps qd	3 caps qd	3 caps qd
Vitamin D3 <sup>e</sup> Thorne	2,000 IU (unknown brand)	5,000 IU	5,000 IU	5,000 IU	5,000 IU	5,000 IU

Trident SAP 66:33 <sup>csf</sup> Nutritional Fundamentals for Health	N/A	2 soft gels qd	2 soft gels qd	2 soft gels qd	2 soft gels qd	2 soft gels qd
<b>Lab Recommendations</b>						
See Table 2 for laboratory details	Yes	No	Yes March 2022	No	No	Yes June 2023
<b>Lifestyle Recommendations</b>						
<ol style="list-style-type: none"> <li>Beginning in June 2021, it was recommended that the patient track her menstrual cycle and symptoms, including ovulation symptoms.</li> <li>Intentional, continuous movement for at least 15 minutes daily was initiated in July 2021 and continually reinforced throughout care.</li> </ol>						
<b>Referrals</b>						
<ol style="list-style-type: none"> <li>Arvigo Techniques of Maya Abdominal Therapy™: In July 2021</li> <li>IV iron series: In July 2021 and July 2023, based on lab values</li> </ol>						
<b>Key:</b>						
<sup>a</sup> Began on July 14, 2021						
<sup>b</sup> December 2022: The client revealed this supplement was being taken as two caps qd in the morning						
<sup>c</sup> January and April 2023: MacaHarmony® was not taken						
<sup>d</sup> Take with food						
<sup>e</sup> Take with fish oil for improved absorption.						
<sup>f</sup> The patient was not compliant with daily dosing; instead, this was taken a few times weekly.						
<b>Abbreviations:</b> ADHD: attention-deficit hyperactivity disorder; bid: twice daily; cap: capsule; caps: capsules; IV: intravenous; PMS: premenstrual syndrome; PCOS: polycystic ovarian syndrome; prn: as needed; qd: once daily						
<b>Summary of Results Achieved:</b>						
<ol style="list-style-type: none"> <li>Normalization of menstrual frequency (28-32 days)</li> <li>Resolution of ovulation pain and cramping</li> <li>Improved ovulation as evidenced by increased cervical mucus and libido</li> <li>Decreased/resolved PMS duration and intensity of symptoms</li> <li>Decreased menstrual blood flow and improved quality of menstrual blood (bright red vs. brown)</li> <li>Decreased menstrual cramping (intensity, duration, and location)</li> <li>Hormone balancing as evidenced by a reduction of LH, normalization of LH/FSH ratio, and a reduction in E2 to optimal levels for fertility.</li> </ol>						

**Table 2: Laboratory Results.**

Biomarker	Reference Range	07/03/21 <sup>a</sup>	08/09/21 <sup>b</sup> Day 3 of menstrual cycle	09/18/21 <sup>^</sup>	04/09/22 <sup>a</sup> Day 20 of a 32-day cycle	07/07/23 <sup>a</sup> Day 21 of a 33-day cycle	08/16/23 <sup>a</sup> Day 2 of menstrual cycle	11/13/23 <sup>c</sup>
<b>CBC, CMP, Lipids, nutrients, inflammatory markers*</b>								
RBC	[4-5.2] 10*12/L	4.40		4.61	4.56	4.33		
HGB	[12-16] g/dL	11.5 (L)		12.7	13.4	12.7		
HCT	[36-46] %	37.9		41.1	42.0	39.4		

MCHC	[31-37] g/dL	30.3 (L)		30.9 (L)	31.9	32.2		
Glucose	[65-99] mg/dL	91				79		
Insulin Level	[5-23] uIU/mL	12			11	13		
HB A1c, %	<=6.4 %	5.3				5.2		
Total Cholesterol	<=199 mg/dL	149			154	161		
Triglycerides	<=149 mg/dL	158 (H)			130	104		
HDL Cholesterol	>=40 mg/dL	32 (L)			33 (L)	45		
LDL Cholesterol	<=99 mg/dL	85			95	95		
Chol/HDL ratio		4.7			4.7	3.6		
Hs-CRP	[0.2-3] mg/L	4.2 (H)			2.3			
Ferritin	[10-291] ng/mL	11		135	51	29		
Homocysteine	[3.7-13.9] umol/L	9.9			8.5			
MMA	<= 400 nmol/L	<200			<200			
Vitamin D 25OH	[30-100] ng/mL	29.1 (L)			37.9			
<b>Hormones</b>								
Testosterone, Total	[0-48] ng/dL	27				27		
Testosterone, Free	[0-14] pg/mL	5				4		
Testosterone, % Free	[0.5-3] %	1.9				1.5		
SHBG	[11-180] nmol/L	28				48		
DHEA-S	[35-430] ug/dL	92						
Estradiol	[20-144] pg/mL <sup>d</sup>		41.3				26	
Luteinizing Hormone (LH)	[1.9-12.5] mIU/mL <sup>d</sup>		8.2				4.5	

Follicle Stimulating Hormone (FSH)	[2.5-10.2] mIU/mL <sup>d</sup>		5.4				5.8	
LH/FSH ratio	N/A <sup>e</sup>		Abnormal				Normal	
Anti-Mullerian Hormone (AMH)	[0.66-8.75] ng/mL Median 3.00 or [0.7-3.50] <sup>f</sup>		7.09 (H or N)				8.34 (H or N)	
Progesterone	[3.3-28.0] ng/mL <sup>g</sup>				8.4 <sup>h</sup>	Not Received: Lab Error		Not Received: Lab Error
Prolactin	[2.8-29.2] ng/mL				6.9			
Thyroid Stimulating Hormone (TSH)	[0.33-4.7] uIU/mL	0.8			0.71	0.8		
Free T3	[2.3-4.2] pg/mL	3.4			3.1	3.7		
Free T4	[0.89-1.76] ng/dL	1.06			1.19	1.02		
Thyroglobulin Ab	[</= 4.0] IU/mL					<0.9		
Thyroid Peroxidase Antibody	[0.3-9.0] IU/mL					0.9		

**Key:**

<sup>a</sup>= Providence Lab

<sup>b</sup>= Zoom Care Lab (sent to LabCorp and Esoterix, Inc)

<sup>c</sup>= LabCorp

<sup>d</sup>=follicular phase

<sup>e</sup>= The lab does not provide a reference range. Saadia Z. Follicle Stimulating Hormone (LH: FSH) Ratio in Polycystic Ovary Syndrome (PCOS) - Obese vs. Non- Obese Women. *Med Arch.* 2020;74(4):289-293. doi:10.5455/medarch.2020.74.289-293

<sup>f</sup>= Lab provided the following information: "AMH concentrations of  $\geq 1.06$  ng/mL is correlated with a better response to ovarian stimulation, produced more retrievable oocytes and higher odds of live birth according to Gleicher et al. *Fertility and Sterility*, 2010; 94:2824-2827. The current AMH test method correlates with the study method with a slope of 0.94. Females at risk of ovarian hyperstimulation syndrome or polycystic ovarian syndrome (PCOS) may exhibit elevated serum AMH concentrations. AMH levels from PCOS patients may be 2 to 5 fold higher than age-appropriate reference interval values. Granulosa cell tumors of the ovary may secrete AMH along with other tumor markers. Elevated AMH is not specific for malignancy, and the assay should not be used exclusively to diagnose or exclude an AMH-secreting ovarian tumor." Additionally, OHSU Core Lab (ReproSource, 200 Forest St, Marlborough, MA) that can evaluate the hormone lists the AMH reference range as 0.7-3.50.

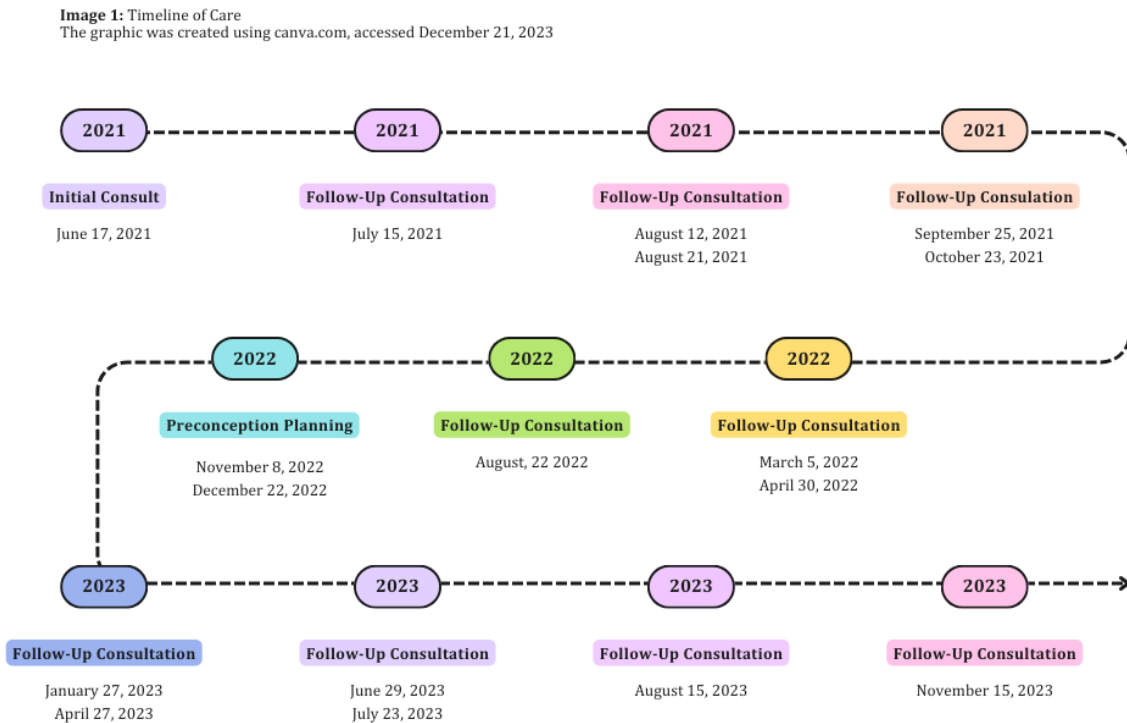
<sup>g</sup>= luteal phase

<sup>h</sup>=progesterone was evaluated on day 20 of a 32-day (rather than a typical 28-day) menstrual cycle. Ranges reported are based on testing during the luteal phase, typically done on days 20-21 out of a 28-day cycle.

<sup>^</sup>= to assess iron status after iron infusion

\*Other laboratory findings from the CBC, CMP, and Lipid panel were within normal range.

**Image 1: Timeline of care.**



### Follow-Up Consultation- July 15, 2021

This clinician reviewed the results of androgen testing (testosterone and DHEA), CBC, CMP, lipid panel, and thyroid hormone panel testing with the patient. Of note, the androgens were within normal range. High sensitivity-CRP (hs-CRP) and triglycerides were elevated, and ferritin, HDL cholesterol, MCHC, hemoglobin, and vitamin D were low (Table 2).

Based on the lab results and previous clinical findings, recommendations were provided, as detailed in Table 1. These recommendations included beginning a Mediterranean-style food plan that focused on adding more vegetables, healthy fats, and proteins, focusing on iron-rich foods, and decreasing sugar intake to decrease insulin levels and support overall well-being and fertility. The patient was also counseled on increasing activity in her day. Supplement recommendations included another increase in the dose of vitamin D due to deficiency, beginning omega-3 fatty acids to support hs-CRP and HDL levels, general wellness and fertility, and continuing the prenatal vitamins and MacaHarmony®.

The patient reported that she started the prenatal vitamin and increased vitamin D at the beginning of this month. Additionally, she had just started MacaHarmony® the day before this visit (July 14, 2021).

The additional previously provided recommendations remained unchanged. Based on the laboratory findings of low iron, the patient was referred to an infusion pharmacy to begin an IV iron series for five weeks. Further assessment would be conducted after the collection of laboratory tests completed seven days before menses and day two or three of the menstrual cycle.

### Follow-Up Consultations-August-October 2021

Labs were drawn on day three of the menstrual cycle and discussed with the patient during the August 12, 2021, visit. Of note, LH was greater than FSH, causing an increased LH/FSH ratio, which is common with PCOS, though both are within the reference range as stand-alone values. AMH was within the normal reference range provided by the lab; however, it was above the median range and was higher than reported in the literature for the normal range, given the patient’s age, which is also common for PCOS (Table 2).

The patient had gradually improved her dietary intake, with a primary focus on increasing vegetable intake. She had not yet implemented any exercise. The patient started MacaHarmony® on July 14, 2021, three weeks into her menstrual cycle. By her menstrual bleeding three weeks later (August 7, 2021), the patient had already noticed an improvement in the color of the menstrual blood (bright red versus historically darker blood). This cycle was 45 days from the previous one (Table 3). At this point, she also noticed a change in the quality of her menstrual cramps. They changed from more diffuse in the upper thighs and lower back for about one hour each of her menstruating days to more focused pain over the uterus for 30-60 minutes on each of her menstruating days.

At this time, the patient hadn’t yet noticed improvements in hirsutism or PMS. This was not of concern to the clinician since implementing the maca supplement began less than one month ago, and some menstrual cycle changes were already occurring.

Visits were maintained for continuity of care and symptom monitoring (Table 3)

- During the visit on August 21<sup>st</sup>, the patient reported a greater increase in cervical mucous for one mid-cycle day, believing ovulation occurred on or around day 10. She reported the improvement of experiencing no ovulation pain. Menstrual cramping was more localized to cramping around the uterus but still experienced at a higher level (5-7/10) for about one hour each of the five days of bleeding.
- September: The patient reported less blood loss, four days of good cervical mucus mid-cycle, and a menstrual cycle 32 days from the last cycle. Repeat labs for iron status were completed.
- October: The patient experienced a 34-day cycle. She also noticed that her periods were less heavy, describing it as moderate flow with cramping that remained localized to the uterus and decreased in intensity to 3/10, lasting for about an hour on the first cycle day.

During these months, the clinician did not observe any changes in hirsutism.

The patient had complied with supplement recommendations, though she occasionally missed doses of fish oil, and continued to improve her dietary intake as recommended. Engagement in regular exercise had not yet been started.

At the conclusion of these visits, the clinician advised the patient to continue with all previous recommendations (Table 1).

**Table 3: Menstrual Cycle Frequency and Symptoms.**

Date	Menses Frequency (days)	Symptoms
3/15/21	-	Upon presentation for the initial consultation in June 2023, the patient reported symptoms of irregular, prolonged menstrual cycles (average of 35-45 days, longest 70 days), heavy bleeding, PMS that includes breast tenderness five to seven days before menses, mood changes two to three days before menses, ovulation pain, and lack of cervical mucous at ovulation.
5/24/21	70	
6/23/21	31	Breast tenderness, moodiness, darker brown menstrual blood, and cramping described as diffuse in the upper thighs and lower back for about one hour each menstruating day.
8/7/21	45	Bright red menstrual blood, cramping over the uterus for 30-60 minutes on each menstruating day, increase in cervical mucous, no ovulation pain.
9/8/21	32	Less blood loss and cramping; four days of good cervical mucus mid-cycle
10/12/21	34	Moderate blood flow with less intense cramping



11/12/21	31	November 2021-March 2022: Mild or no PMS symptoms; Continued moderate blood flow, mild cramping, and good cervical mucous at ovulation
12/16/21	35	
1/14/22	29	
2/15/22	32	
3/20/22	33	
4/21/22	32	Moderate menstrual cramping; continued with good cervical mucus on day 14 of the menstrual cycle, no ovulation pain or cramping; and a noticeable increase in libido midcycle
8/19/22	Over the last several months, an average of 28	May - August 2022: Less or no cramping during ovulation or menses, less or no PMS, continued good cervical mucus and libido midcycle without midcycle pain.
September – December 2022	Average of 28-32 days	September – December 2022: Continued to experience resolution of pain and good cervical mucus and libido midcycle. Blood flow remains moderate.
January 2023	Average of 28-32 days	Stopped maca for about one month: 1) Increased PMS, including breast tenderness and mood changes lasting five days before menses, 2) Increased cramping through thighs and back, 3) Darker colored blood, suggesting the blood flow is taking longer to travel from the uterus to the vagina and is less efficient at shedding blood from the previous cycle.
April 2023	Average of 28-32 days when taking maca, and 39 days without it	Stopped maca for approximately one month for a second time and experienced the same symptoms reported in January 2023 and a more extended cycle frequency.
June – November 2023	Average of 28-30 days	June- August 2023: Some mild breast tenderness on some months lasting two days before menses. Continued with previous improvements. November 2023: Continued good cervical mucous and libido midcycle, mild PMS (one day of moodiness three days before menses), no menstrual cramping or breast tenderness, no ovulation pain, moderate blood flow.

**Follow-Up Consultations: March-August 2022**

After several months, the patient returned for follow-up consultations to report on progress and have repeat laboratory testing completed.

In **March 2022**, the patient stated that she has been consistent in taking her supplements, and over the past few months, she experienced mild or no PMS symptoms. Her menstrual cycles were reported as “regular” with a frequency of 29-33 days, with one exception, that was 35 days. The menstrual cycle lasted five days with moderate blood flow and less cramping. She noticed more cervical mucous at ovulation (Table 3). By this time, she was doing well with dietary enhancements. The patient was also happy

to report that she exercised intermittently over the past several months but has become more regular as of March. She remained compliant with all supplements except fish oil, which was only taken a few days per week. The clinician did not make changes in recommendations at this time.

In **April 2022**, the patient completed repeat laboratory tests, including progesterone levels. Eleven days prior to menses, the serum progesterone level was 8.4 ng/mL. This result was promising since progesterone is typically the highest about seven days before menses. Other laboratory findings improved to normal ranges except for HDL cholesterol, which remained low (Table 2).

At this time, it was self-reported that good cervical mucus was

present on day 14 of the menstrual cycle, and a noticeable increase in libido mid-cycle was experienced without any ovulation pain or cramping. Her latest menstrual cycle brought moderate cramping, but no other PMS symptoms were present (Table 3). The patient or clinician did not observe changes in hirsutism, and the patient remains compliant with supplements and dietary improvements.

Based on the labs, the clinician modified the dose of MacaHarmony® increasing to two capsules twice daily to further support hormonal balance, ovulation, and menstrual regularity (Table 1).

During May-July 2022, no care sessions were conducted.

In **August 2022**, the patient reported much of the same progress she experienced previously. This included regular cycles occurring “right around 28 days” (as stated by the patient), less or no cramping, less or no PMS, good cervical mucus and libido midcycle without midcycle pain. She stated that the prescribed maca (MacaHarmony®) supplement has been “very helpful” for regulating menses. The patient reports good compliance with diet, movement, and supplements, although she only takes fish oil occasionally. Of note, the patient reported that she did not increase the dose of MacaHarmony® as instructed previously. The clinician decided since the patient was experiencing positive improvements in symptoms and was compliant with one capsule twice daily, this dose would be continued.

During September - October 2022, no care sessions were conducted.

#### **Follow-Up Consultations- November – December 2022**

In November, the patient was joined by her wife for the consultation. The focus of this session was on family planning as the couple was exploring a known donor option for pregnancy. Current hormonal labs of both the patient and her wife were encouraged to help determine who would be the ideal woman to carry the first pregnancy.

In December, the patient was again joined by her wife to focus on family planning. The couple mutually decided that the patient’s wife would carry the pregnancy. This decision was based not on labs or age but on personal preference. Therefore, the goal for the patient is to continue to improve her hormonal balance for wellness and future pregnancy, as well as for vitality for parenting and supporting her wife during pregnancy.

While this was not the focus of the consult, the patient provided an update on her progress. She reported good supplement compliance, occasionally missing a dose over the last several months. It was revealed to the clinician that the patient was taking two capsules of MacaHarmony® in the morning rather than, as recommended, one capsule twice daily. She reported that she

continued to experience her menses every 28-32 days for five days with moderate blood flow. She reported pain-free ovulation with good cervical mucous and mid-cycle libido (Table 3).

#### **Follow-Up Consultations - January-April 2023**

In **January 2023**, the patient reported that she independently decided to discontinue the use of MacaHarmony® for “a month” and provided a summary of noticeable changes, which included: 1) Increased PMS, including breast tenderness and mood changes lasting five days prior to menses, 2) Increased cramping through thighs and back as she experienced at the start of care, 3) Darker colored blood, suggesting the blood flow is taking longer to travel from the uterus to the vagina and is less efficient at shedding blood from the previous cycle (Table 3).

The clinician spoke to the patient about resuming MacaHarmony®; however, the patient wanted to take two capsules in the morning for ease and continued compliance. The patient was advised that a dose of one capsule twice daily is routinely recommended. However, the clinician was aware of some colleagues who were successfully dosing this formulation of maca one time per day, in the morning. It was mutually agreed upon that two capsules one time per day could be continued, as the patient had positive outcomes upon taking this dose.

In **April 2023**, the patient reported a moderate level of consistency in taking two capsules of MacaHarmony® daily. However, she stated she “had fallen off maca for about a month.” As a result, she again experienced noticeable, adverse changes, as noted in January 2023, and a more extended frequency between cycles (39 days) (Table 3).

The patient explained that her occasional breaks from the prescribed MacaHarmony® reinforced to her that when she stopped taking it, an increase in symptoms and menses length occurred, so she was motivated to take it consistently. Therefore, at the conclusion of this visit, the clinician encouraged the patient to comply with the prescribed MacaHarmony® supplement and reinforced adherence to the additional supplements, dietary, and exercise plan (Table 1).

#### **Follow-Up Consultations: June – August 2023**

The patient resumed regular follow-up consultations to monitor progress.

In **June 2023**, the patient reported taking two capsules of MacaHarmony® each morning. Her cycles were averaging 28 days with mild PMS (breast tenderness) on some months lasting two days. Labs were ordered at this time.

In **July 2023**, the clinician discussed the recent laboratory results. Of note, insulin levels increased, ferritin levels decreased,

and free testosterone decreased, though all remain in the normal range. Cardiovascular markers, including HDL cholesterol, triglycerides, and glucose, improved.

Based on these findings, the clinician recommended another round of IV iron series, dietary strategies to support glucose and insulin balancing, such as eating vegetables first, and walking within 90 minutes following a meal. The clinician also requested the patient test hormones on day two or three of the next menstrual cycle and day 21 (ideally seven days before menses) for more accurate timing than the previous.

At this time, the patient expressed a commitment to resume her compliance with diet and exercise so she can be supportive of her wife and their future pregnancy.

In **August 2023**, the patient had labs drawn on day two of her menstrual cycle. A decreased LH resulted in normalizing the LH/FSH ratio, and the previously functionally elevated estradiol levels were reduced. AMH remained elevated, which is expected with a history of infrequent menses and ovulation since the initiation of

menses. Day 21 testing was not completed (Table 2). The patient's weight was reduced to 209 pounds, and her body mass index (BMI) was reduced to 35.9.

The clinician followed up with the patient to complete day 21 hormone testing and to check on her progress but did not hear back from the patient until **October**. At that time, she indicated she would complete the previously requested lab for serum progesterone level. The patient also shared the news that her wife was pregnant.

In **November 2023**, at the time of writing this case, the patient had repeated serum progesterone testing, but a lab error occurred again. The patient reports good compliance with the supplements, diet, and regular movement. The menstrual cycle was reported as an average of 28-30 days. She continued to have good cervical mucous and libido midcycle, lasting three days. She reported only mild PMS consisting of low-level moodiness occurring for only one day, three days prior to her cycle, and no longer was experiencing breast tenderness (Table 3).

### Patient Perspective

“Taking MacaHarmony has been the main reason my periods have become more regular. My periods were relatively normal but came at extremely irregular intervals (normally about 45–60-day cycles), but I’ve had 28-32day cycles for quite a while now after being on MacaHarmony for a little more than two years.”

## Results and Discussion

Using a concentrated gelatinized proprietary phenotype formulation of *Lepidium peruvianum* (maca), known as MacaHarmony® as the primary therapy, a 31-year-old female experienced dramatic improvements in her hormone health within three months and she was able to sustain this for over two years. Improvements included 1) positive changes in PMS with the length of symptoms decreased to one day (compared to a previous 5-7 days of symptoms), with breast tenderness resolved and moods drastically improved, 2) decrease in dysmenorrhea described as less intense cramping pain localized to the uterus (rated as 3 out of 10 with ten being the most severe pain) and lasting approximately only one hour of the first day of the menstrual cycle compared to cramping that was diffuse through the thighs and back, rated on a pain scale of 5-7 out of 10, lasting for about an hour on all five days of the cycle, 3) the normalization in the frequency of the menstrual cycle (average of 28-32 days compared to an average of 35-40 days), 4) less blood loss, and 5) improved ovulation characterized by less pain and cramping and increased cervical mucus and libido, lasting three days. Further, a two-year comparative analysis showed improvements in LH/FSH ratio and day two E2 levels. During two separate time frames, when the patient stopped taking MacaHarmony®, she experienced an increase in PMS (breast

tenderness and moodiness), ovulation and menstrual pain, and more extended frequency between menstrual cycles, suggesting a high correlation to the use of MacaHarmony® and the regulation of these outcomes.

Secondary outcomes included improvements in select cardiometabolic markers (HDL cholesterol, triglycerides, and glucose) and weight loss with the combination of supplements, diet, and exercise.

### Background and strength of primary therapy

Maca is the commonly known name of two species of plants belonging to the *Brassicaceae* family- *Lepidium peruvianum* and *Lepidium meyenii*. These two species are often referred to as the same; however, research dates back to the 1960s when distinctions between the species were first reported [13]. In this case report, a concentrated gelatinized proprietary phenotype formulation of *Lepidium peruvianum* known as MacaHarmony® was the primary treatment. The treating clinicians have used this botanical therapy extensively in clinical practice with a high success rate for various hormonal health concerns, including PMS, PCOS, infertility, and menstrual health support. Of importance, the literature shows that there are up to 17 colors of maca, with distinctions in their physiological responses within the human body and varying results

in clinical outcomes [14-16]. The clinicians recognize this vital distinction for clinical care and attribute the specific formulation to the outcomes noted. The clinicians have a history of using other maca supplements (unknown or improper phenotypes) that did not result in the positive outcomes noted in this case report and, therefore, discontinued their use.

The benefits of maca have been reported in many animal models, with limited studies conducted in humans. However, maca has traditionally been used by the Peruvian people for energy, fertility, and libido [17]. In recent years, its clinical use for women has expanded to support energy, menstrual health, mood, bone health, menopausal symptoms, healthy hormone levels (estradiol, LH, FSH, progesterone, cortisol), and fertility [18-28]. At present, the literature on maca's impact on hormone levels is limited despite its reported mechanism of action through the hypothalamus-pituitary-adrenal (HPA) axis. Most significantly, using the formulation of maca phenotypes known as Maca-GO<sup>®</sup>, four clinical trials have demonstrated a statistically significant decrease in LH and FSH and an increase in estradiol levels in peri and post-menopausal women [21-23,29].

In alignment with those findings, this case report demonstrated improvements using MacaHarmony<sup>®</sup> in day two LH/FSH ratio and estradiol levels to support ovulatory function and fertility in premenopausal (fertile/reproductive age) women. To date, only one other case report has reported improvements in LH levels using the same formulation (MacaHarmony<sup>®</sup>) [28]. To the author's knowledge, this is the first published case using maca to demonstrate improvements in estradiol levels for optimizing fertility. Studies have shown lower day-three estradiol levels increase pregnancy rates [30,31]. The positive changes in LH/FSH ratio and E2 levels are of high significance to the treating clinicians since normalization of hormones can be challenging, if not impossible, in women with PCOS and often require conventional fertility medications to achieve this shift.

Additionally, the use of maca in cardiometabolic outcomes is emerging in the literature. Clinical trials have shown reductions in glucose levels [32], blood pressure [23,33], and IL-6 levels [26,33] with increases in HDL cholesterol [21,23]. Within this case report, some cardiovascular markers, including HDL cholesterol, triglycerides, and glucose, improved. However, it cannot be inferred that this was due to maca alone, as the patient was consistent with diet and exercise at the time of lab draw.

Of importance, the patient had no side effects from using maca, which is consistent with the available literature to date. Conversely, conventional treatments used to manage PCOS and improve ovulation, such as oral birth control pills, Clomid, and Letrozole, are reported to have side effects including, but not limited to, hot flashes, fatigue, dizziness, abdominal pain and bloating, breast tenderness, headache, breakthrough bleeding/

spotting, blurred vision, mood disturbances, anxiety, weight gain, and deficiencies in B vitamins [34-37]. Further long-term use of these conventional treatments can increase the risk for other health concerns [38,39].

In this case, the authors believe that using MacaHarmony<sup>®</sup> containing a specific formulation of phenotypes for a premenopausal (fertile/reproductive age) woman, resulted in improvements in menstrual cycle regularity, dysmenorrhea, ovulation, PMS symptoms, and select hormone levels.

### **Background and Strengths of Adjunctive Therapies**

The recommendations for this patient included prenatal vitamins, vitamin D, and omega-3 fatty acids for overall wellness, nutritional insufficiency, and fertility support.

Prenatal vitamins are well-accepted as a therapy for women in the preconception phase of their life. The nutritional status of the mother before, during, and after pregnancy can significantly impact the health of the fetus and baby. Some essential nutrients needed during this time include folate (B9), iron, iodine, calcium, choline, vitamin D, B6, and B12 [40-43]. Most nutrients' Recommended Daily Allowance (RDA) increases during pregnancy and through lactation [40]. For these reasons, the treating clinicians recommend prenatal vitamins to all women in the preconception planning stage.

Low levels of vitamin D are often associated with a "sunlight deficiency"; however, as an antioxidant, anti-inflammatory, immune, and mitochondrial regulator, as well as a hormone, vitamin D serves many crucial roles for health [44]. Supplementation of vitamin D is best determined on laboratory findings using 25-hydroxyvitamin D [25(OH)D] [45]. Though a wide range exists for what is considered normal (25-80 ng/mL), higher vitamin D levels (>50 ng/mL) have been associated with better health, including improved pregnancy outcomes [45-47]. The dose of vitamin D was increased from 1,000 IU per day to 5,000 IU per day to address this patient's insufficiency.

Like vitamin D, omega-3 fatty acids have shown benefits to many aspects of health despite its controversy in the literature. The recommendation for fish oil was made primarily to help reduce hs-CRP and support her overall wellness and conception goals. Reported benefits of fish oil include lowering inflammatory markers (hs-CRP) [48], improving cardiometabolic markers in women with PCOS [49], and increasing fertility rates [50]. Specifically, DHA has also been shown to improve gestation/reduce preterm birth [51,52], improve infant size [51], decrease adiposity in children of obese mothers [53], and provide benefits for supporting fetal brain development [54]. While the patient was semi-compliant with fish oil, the clinician continuously reinforced the recommendation for its many health benefits.

### Additional case strengths

Additional strengths of this clinical case include 1) An extensive timeline of care (2021-2023) was reported 2) A limited number of supplements/interventions were recommended making it easier to infer the improvements in the menstrual cycle and symptoms as a direct response to using MacaHarmony® based on the available literature and extensive clinical experience of the clinicians 3) There was a noticeable decrease in symptoms when the patient was using maca compared to when she stopped using it on two separate occasions 4) Routine labs were ordered to monitor progress 5) The patient had excellent compliance with vitamin D and prenatal multivitamin-mineral, and excellent/very good compliance with maca (reporting only a two-month break in the more than two years of care)

### Limitations

The clinicians acknowledged several limitations of this case report. First, as with all case reports (N=1), the outcomes of this case cannot be translated to the general population of women with PCOS. Second, minor compliance concerns with using the recommended supplements were noted in this case. Of note, on two separate occasions, a lack of compliance with the primary therapy occurred due to the patient's volition. Additionally, the supplement was taken, at times, in a single dose rather than divided doses during the day as recommended. While this is not desired for clinical care, it was also a strength of the case since the absence of the primary therapy (MacaHarmony®) reinforced to the patient how helpful this supplement was, and the alteration in the dosing did not negatively impact the outcomes. Third, there were prolonged periods of time without follow-up to monitor progress and adjust care or recommendations if needed. Missed or a lack of follow-up can occur for various reasons, including a low sense of urgency, cost, fear or anxiety around the appointment, and forgetfulness, among others [55]. However, the treating clinicians noted that the extended periods of time were not detrimental to care and were due to life events, including a busy time of her employment, getting married, travel, and the holiday season. Fourth, some limitations existed with laboratory results, including 1) some labs were not completed in a timely manner 2) a progesterone lab draw was not obtained at the appropriate time of the menstrual cycle. The clinician requested seven days before menses, and it was completed 11 days prior, creating inconsistent timing to compare against the normal ranges 3) The July progesterone lab draw resulted in a lab error and the repeat progesterone lab was not obtained in August 2023 due to lack of patient compliance. This test was finally completed in November 2023 but incurred another lab error. 4) Day 2-3 hormonal labs from 2021 and 2023

were analyzed using different lab equipment and, therefore, have the potential to provide slight variability in the results.

### Conclusion

This case report (N=1) demonstrated the effective use of a concentrated gelatinized proprietary phenotype formulation of *Lepidium peruvianum* (maca), commercially known as MacaHarmony®, to decrease the intensity and duration of PMS, improve menstrual regularity and dysmenorrhea, decrease ovulation pain and cramping, improve mid-cycle cervical mucous, restore LH/FSH ratio balance, and optimize estradiol levels for fertility in a woman diagnosed with PCOS. This therapy, combined with general nutrient support (multivitamins, vitamin D, and omega-3 fatty acids), diet, and exercise, also contributed to improvements in cardiovascular markers and weight loss. A case report cannot provide a definitive association between therapies and outcomes. However, the positive outcomes of this case may provide clinicians with guidance for a clinical approach for women with PCOS to balance hormones and optimize fertility. The authors believe additional research should be explored into how specific maca phenotypes or combinations of maca phenotypes, when gelatinized and concentrated, can assist women with PCOS and enhance fertility outcomes.

### Declarations

### Informed Consent

The patient presented in this case report provided written informed consent to publish patient information in the present manuscript. The patient also received a copy of the manuscript to read and review.

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### Conflict of Interest

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## References

1. Jabeen A, Yamini V, Rahman Amberina A, Dinesh Eshwar M, Vadakedath S, et al., (2022) Polycystic Ovarian Syndrome: Prevalence, Predisposing Factors, and Awareness Among Adolescent and Young Girls of South India. *Cureus* 14: e27943.
2. Deswal R, Narwal V, Dang A, Pundir CS (2020) The Prevalence of Polycystic Ovary Syndrome: A Brief Systematic Review. *J Hum Reprod Sci* 13:261-271.
3. Copp T, Muscat DM, Hersch J, McCaffery KJ, Doust J, et al., (2020) Clinicians' perspectives on diagnosing polycystic ovary syndrome in Australia: A qualitative study. *Hum Reprod* 35:660-668.
4. Szukiewicz D, Trojanowski S, Kociszewska A, Szewczyk G (2022) Modulation of the Inflammatory Response in Polycystic Ovary Syndrome (PCOS)—Searching for Epigenetic Factors. *Int J Mol Sci* 23:14663.
5. Abraham Gnanadass S, Divakar Prabhu Y, Valsala Gopalakrishnan A (2021) Association of metabolic and inflammatory markers with polycystic ovarian syndrome (PCOS): an update. *Arch Gynecol Obstet* 303:631-643.
6. Aboeldalyl S, James C, Seyam E, Ibrahim EM, Shawki HED, et al., (2021) The role of chronic inflammation in polycystic ovarian syndrome—a systematic review and meta-analysis. *Int J Mol Sci* 22:2734.
7. Zeng LH, Rana S, Hussain L, Asif M, Mehmood MH, et al., (2022) Polycystic Ovary Syndrome: A Disorder of Reproductive Age, Its Pathogenesis, and a Discussion on the Emerging Role of Herbal Remedies. *Front Pharmacol* 13:874914.
8. Christ JP, Cedars MI (2023) Current Guidelines for Diagnosing PCOS. *Diagnostics (Basel)* 13:1113.
9. Morshed MS, Banu H, Akhtar N, Sultana T, Begum A, et al., (2021) Luteinizing hormone to follicle-stimulating hormone ratio significantly correlates with androgen level and manifestations are more frequent with hyperandrogenemia in women with polycystic ovary syndrome. *J Endocrinol Metab* 11:14-21.
10. Alesi S, Ee C, Moran LJ, Rao V, Mousa A (2022) Nutritional Supplements and Complementary Therapies in Polycystic Ovary Syndrome. *Adv Nutr* 13:1243-1266.
11. Riley DS, Barber MS, Kienle GS, Aronson JK, von Schoen-Angerer T, et al., (2017) CARE guidelines for case reports: explanation and elaboration document. *J Clin Epidemiol* 89:218-235.
12. Lumezi BG, Berisha VL, Pupovci HL, Goçi A, Hajrushu AB (2018) Grading of hirsutism based on the Ferriman-Gallwey scoring system in Kosovar women. *Postepy Dermatol Alergol* 35:631-635.
13. Meissner HO, Mscisz A, Kedzia B, Pisulewski P, Piatkowska E (2015) Peruvian maca: Two scientific names *Lepidium Meyenii* Walpers and *Lepidium Peruvianum* Chacon – Are they phytochemically synonymous? *International Journal of Biomedical Science* 1-15.
14. Obregon L (2001) "Maca" *Planta Medicinal y Nutritiva del Peru*. 1st ed. Lima: Instituto de Fitoterapia Americano. 1-182.
15. Tarabasz D, Szczeblewski P, Laskowski T, Płaziński W, Baranowska-Wójcik E, et al., (2022) The Distribution of Glucosinolates in Different Phenotypes of *Lepidium peruvianum* and Their Role as Acetyl- and Butyrylcholinesterase Inhibitors—In Silico and In Vitro Studies. *Int J Mol Sci* 23:4858.
16. Geng P, Sun J, Chen P, Brand E, Frame J, et al., (2020) Characterization of Maca (*Lepidium meyenii*/*Lepidium peruvianum*) Using a Mass Spectral Fingerprinting, Metabolomic Analysis, and Genetic Sequencing Approach. *Planta Med* 86:674-685.
17. Gonzales GF, Gonzales C, Gonzales-Castañeda C (2009) *Lepidium meyenii* (Maca): A Plant from the Highlands of Peru – from Tradition to Science. *Forschende Komplementärmedizin* 16:373-380.
18. Friedman J, Sheeder J, Lazorwitz A, Polotsky AJ (2022) Herbal supplement use among reproductive-aged women in an academic infertility practice. *F S Rep* 4:104-111.
19. Ross K (2023) Improvements in Premenstrual Syndrome, Primary Dysmenorrhea, and Menorrhagia with Natural Therapies: A Case Report. *Curr Res Cmpl Alt Med* 7: 207.
20. Ross K (2021) Nutritional management of surgically induced menopause: A case report. *Womens Health (Lond)*. 17:17455065211031492.
21. Meissner HO, Mscisz A, Bilinska-Reich H, Kapczynski W, Mrozikiewicz P, et al., (2006) Hormone-Balancing Effect of Pre-Gelatinized Organic Maca (*Lepidium peruvianum* Chacon): (II) Physiological and Symptomatic Responses of Early-Postmenopausal Women to Standardized doses of Maca in Double Blind, Randomized, Placebo-Controlled, Multi-Centre C. *Int J Biomed Sci* 2:360-374.
22. Meissner HO, Kapczynski W, Mscisz A, Lutomski J (2005) Use of gelatinized maca (*lepidium peruvianum*) in early postmenopausal women. *Int J Biomed Sci* 1:33-45.
23. Meissner HO, Reich-Bilinska H, Mscisz A, Kedzia B (2006) Therapeutic Effects of Pre-Gelatinized Maca (*Lepidium Peruvianum* Chacon) used as a Non-Hormonal Alternative to HRT in Perimenopausal Women - Clinical Pilot Study. *Int J Biomed Sci* 2:143-159.
24. Meissner HO, Mscisz A, Reich-Bilinska H, Mrozikiewicz P, Bobkiewicz-Kozłowska T, et al., (2006) Hormone-Balancing Effect of Pre-Gelatinized Organic Maca (*Lepidium peruvianum* Chacon): (III) Clinical responses of early-postmenopausal women to Maca in double blind, randomized, Placebo-controlled, crossover configuration, outpatient study. *Int J Biomed Sci* 2:375-394.
25. Meissner HO, Reich-Bilinska H, Mrozikiewicz P, Mscisz A, Lowicka Ms, et al., (2005) Hormone-balancing and Pharmacological Effects of Therapeutic Doses of *Lepidium peruvianum* (Maca-GO) in postmenopausal women. *Menopause*.
26. Stojanovska L, Law C, Lai B, Chung T, Nelson K, et al., (2015) Maca reduces blood pressure and depression, in a pilot study in postmenopausal women. *Climacteric* 18:69-78.
27. Honma A, Fujiwara Y, Takei S, Kino T (2022) The improvement of daily fatigue in women following the intake of maca (*Lepidium meyenii*) extract containing benzyl glucosinolate. *Functional Foods in Health and Disease*. 12.
28. Fahoum M, Ross K (2023) An Integrative Approach for Improving and Managing Premenstrual Syndrome (PMS) and Premenstrual Dysphoric Disorder (PMDD): A Case Report. *Curr Res Cmpl Alt Med* 7:211.
29. Takewaka T, Hara K (2019) Clinical Effect of Oral Administration of Maca (*Lepidium meyenii*) Extract on Japanese Peri-Menopausal Women Subjects: A Randomized, Double-Blind, Placebo-Controlled Study. *International Journal of Biomedical Science* 15:11-18.

30. Smotrich DB, Levy MJ, Widra EA, Hall JL, Gindoff PR, et al., (1995) Prognostic value of day 3 estradiol on in vitro fertilization outcome. *Fertil Steril* 64:1136-1140.
31. Licciardi FL, Liu HC, Rosenwaks Z (1995) Day 3 estradiol serum concentrations as prognosticators of ovarian stimulation response and pregnancy outcome in patients undergoing in vitro fertilization. *Fertil Steril* 64:991-994.
32. Gonzales-Arimborgo C, Yupanqui I, Montero E, Alarcón-Yaquetto DE, Zevallos-Concha A, et al., (2016) Acceptability, Safety, and Efficacy of Oral Administration of Extracts of Black or Red Maca (*Lepidium meyenii*) in Adult Human Subjects: A Randomized, Double-Blind, Placebo-Controlled Study. *Pharmaceuticals (Basel)*. 9:49.
33. Gonzales GF, Gasco M, Lozada-Requena I (2013) Role of Maca (*Lepidium meyenii*) Consumption on Serum Interleukin-6 Levels and Health Status in Populations Living in the Peruvian Central Andes over 4000 m of Altitude. *Plant Foods Hum Nutr* 68:347-351.
34. Nutrient Depletion Checker [Internet]. *NatMed Database*. Therapeutic Research Center; 2023 [cited 2023 Nov 30].
35. Yang AM, Cui N, Sun YF, Hao GM (2021) Letrozole for Female Infertility. *Front Endocrinol (Lausanne)* 12: 676133.
36. Cosette Pharmaceuticals, Inc [Internet]. 2023 [cited 2023 Nov 30]. Clomid.
37. Legro RS, Brzyski RG, Diamond MP, Coutifaris C, Schlaff WD, et al., (2014) Letrozole versus Clomiphene for Infertility in the Polycystic Ovary Syndrome. *N Engl J Med* 371:119-129.
38. Yilmaz S, Yilmaz Sezer N, Gönenç İM, İlhan SE, Yilmaz E (2018) Safety of clomiphene citrate: a literature review. *Cytotechnology* 70:489-495.
39. Qiu Y, Hu Y, Xing Z, Fu Q, Zhu J, et al., (2021) Birth control pills and risk of hypothyroidism: A cross-sectional study of the National Health and Nutrition Examination Survey, 2007-2012. *BMJ Open* 11: e046607.
40. Li M, Francis E, Hinkle SN, Ajjarapu AS, Zhang C (2019) Preconception and prenatal nutrition and neurodevelopmental disorders: A systematic review and meta-analysis. *Nutrients* 11:1628.
41. Suzuki T, Nishigori T, Obara T, Masumoto T, Mori M, et al., (2022) Maternal folic acid supplement use/dietary folate intake from preconception to early pregnancy and neurodevelopment in 2-year-old offspring: the Japan Environment and Children's Study. *Br J Nutr* 128:2480-2489.
42. Nishigori H, Obara T, Nishigori T, Ishikuro M, Tatsuta N, et al., (2022) Prenatal folic acid supplementation and autism spectrum disorder in 3-year-old offspring: the Japan environment and children's study. *J Matern Fetal Neonatal Med* 35:8919-8928.
43. Avram C, Bucur OM, Zazgyva A, Avram L, Ruta F (2022) Vitamin Supplementation in Pre-Pregnancy and Pregnancy among Women—Effects and Influencing Factors in Romania. *Int J Environ Res Public Health* 19:8503.
44. Minich DM, Henning M, Darley C, Fahoum M, Schuler CB, et al., (2022) Is Melatonin the “Next Vitamin D”? A Review of Emerging Science, Clinical Uses, Safety, and Dietary Supplements. *Nutrients* 14:3934.
45. Kennel KA, Drake MT, Hurley DL (2010) Vitamin D deficiency in adults: When to test and how to treat. *Mayo Clin Proc* 85:752-757.
46. Hynes C, Jesurasa A, Evans P, Mitchell C (2017) Vitamin D supplementation for women before and during pregnancy: An update of the guidelines, evidence, and role of GPs and practice nurses. *Br J Gen Pract* 67:423-424.
47. Meng X, Zhang J, Wan Q, Huang J, Han T, et al., (2023) Influence of Vitamin D supplementation on reproductive outcomes of infertile patients: a systematic review and meta-analysis. *Reproductive Biology and Endocrinology* 21.
48. Raygan F, Taghizadeh M, Mirhosseini N, Akbari E, Bahmani F, et al., (2019) A comparison between the effects of flaxseed oil and fish oil supplementation on cardiovascular health in type 2 diabetic patients with coronary heart disease: A randomized, double-blinded, placebo-controlled trial. *Phytother Res* 33:1943-1951.
49. Melo V, Silva T, Silva T, Freitas J, Sacramento J, et al., (2022) Omega-3 supplementation in the treatment of polycystic ovary syndrome (PCOS) - A review of clinical trials and cohort. *Endocr Regul* 56:66-79.
50. Stanhiser J, Jukic AMZ, McConnaughey DR, Steiner AZ (2022) Omega-3 fatty acid supplementation and fecundability. *Hum Reprod* 37:1037-1046.
51. Shireman TI, Kerling EH, Gajewski BJ, Colombo J, Carlson SE (2016) Docosahexaenoic acid supplementation (DHA) and the return on investment for pregnancy outcomes. *Prostaglandins Leukot Essent Fatty Acids* 111:8-10.
52. Carlson SE, Colombo J, Gajewski BJ, Gustafson KM, Mundy D, et al., (2013) DHA supplementation and pregnancy outcomes. *Am J Clin Nutr* 97:808-815.
53. Foster BA, Escaname E, Powell TL, Larsen B, Siddiqui SK, et al., (2017) Randomized controlled trial of DHA supplementation during pregnancy: Child adiposity outcomes. *Nutrients* 9:566.
54. Massari M, Novielli C, Mandò C, Di Francesco S, Porta MD, et al., (2020) Multiple micronutrients and docosahexaenoic acid supplementation during pregnancy: A randomized controlled study. *Nutrients* 12:2432.
55. Adepoju OE, Chae M, Liaw W, Angelocci T, Millard P, et al., (2022) Transition to telemedicine and its impact on missed appointments in community-based clinics. *Ann Med* 54:98-107.