UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

FACULDADE DE MEDICINA

PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS MÉDICAS: ENDOCRINOLOGIA

# O uso da espironolactona em mulheres com a Síndrome dos ovários policísticos: efeitos sobre as concentrações séricas de potássio.

**Thais Areias de Oliveira**

Porto Alegre, maio de 2023

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**Thais Areias de Oliveira**

**Dissertação apresentada ao Programa de Pós- Graduação em Ciências Médicas: Endocrinologia, como requisito parcial para obtenção do título de Mestre.**

**Orientadora:** Profª. Drª. Poli Mara Spritzer

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Esta dissertação de Mestrado segue o formato proposto pelo Programa de Pós-Graduação em Ciências Médicas: Endocrinologia, Faculdade de Medicina, Universidade Federal do Rio Grande do Sul, sendo apresentada na forma de uma revisão geral e um manuscrito sobre o tema da dissertação:

- Revisão: Síndrome dos Ovários Policísticos e Hiperandrogenismo
- Artigo Original: Potassium levels in women with Polycystic Ovary Syndrome using spironolactone for long-term.

**SUMÁRIO**

**Resumo:**

A Síndrome dos Ovários Policísticos (PCOS) é o distúrbio endócrino mais comum entre mulheres em idade reprodutiva, caracterizada por hiperandrogenismo clínico ou laboratorial, oligoanovulação, morfologia policística na ecografia ovariana e anormalidades metabólicas, sendo o hiperandrogenismo uma das manifestações clínicas mais significativas. A síndrome está relacionada a uma piora global da qualidade de vida da mulher e o tratamento envolve medidas farmacológicas e não farmacológicas que incluem tratar, de maneira variável e pessoal, os sintomas do excesso de androgênios, os relacionados à infertilidade e/ou as alterações cardiometabólicas como obesidade, diabetes e hipertensão arterial.

Para controle dos sintomas cosméticos causados pelo hiperandrogenismo, pode-se utilizar o antiandrogênio espironolactona, combinado com anticoncepcionais orais ou como monoterapia. A espironolactona é normalmente bem tolerada, sendo efetiva e segura no tratamento do hirsutismo em pacientes com PCOS. A hipercalemia é o efeito adverso mais temido e as dosagens séricas de potássio são ainda preconizadas pelas diretrizes atuais, embora poucos estudos avaliando os efeitos adversos da espironolactona estejam disponíveis em mulheres com PCOS. O objetivo deste trabalho foi avaliar o efeito da terapia com espironolactona, como antiandrogênio, sobre os níveis de potássio sérico e determinar a incidência de hipercalemia em mulheres com PCOS durante o uso da medicação.

Conduzimos um estudo retrospectivo unicêntrico com dados coletados dos prontuários eletrônicos de 98 avaliações de pacientes com PCOS em uso de espironolactona para hirsutismo, pelo tempo mínimo de 12 meses, com acompanhamento dos níveis séricos de potássio em pelo menos 3 momentos distintos durante o uso. Modelos de equação de estimativa generalizada (GEE) foram usados para avaliar as diferenças nos níveis de potássio e outras variáveis entre pré-exposição e pós-exposição, bem como sua relação com a dose de espironolactona em diferentes momentos (linha de base, 6 meses e 12 meses). Os dados foram considerados significativos em $P < 0,05$.

Um total de 327 medições de potássio sérico foram obtidas (84 pré-exposição e 243 pós-exposição) e nenhuma diferença foi encontrada nos níveis de potássio comparando os pontos de tempo específicos (linha de base, 6 meses e 12 meses), demostrando um perfil seguro com baixa incidência de hipercalemia leve (< 5,6 mEq/L). Este estudo aumenta o corpo de evidências da segurança do uso de espironolactona em populações de baixo risco, indicando que o monitoramento frequente de potássio durante o acompanhamento em mulheres jovens com PCOS com função renal e cardíaca normal pode não ser necessário.

## Síndrome dos Ovários Policísticos e o uso da Espironolactona no controle dos sintomas do hiperandrogenismo

A Síndrome dos Ovários Policísticos (PCOS) é uma doença complexa e heterogênea. É o distúrbio endócrino mais comum entre mulheres em idade reprodutiva, com uma prevalência de 8-13% (1). É caracterizada por hiperandrogenismo clínico ou laboratorial, oligoanovulação, morfologia policística na ecografia ovariana e anormalidades metabólicas, sendo o hiperandrogenismo uma das manifestações clínicas mais significativas (1,2, 3,4,5).

Apesar do grande número de estudos, a etiopatogenia da SOP não é totalmente compreendida. O excesso de androgênios induz ao aumento de pelos terminais, acne e alopécia.(1,5,6). Mulheres com PCOS apresentam maior prevalência de obesidade e sobrepeso, câncer endometrial, fatores de risco cardiovascular, dislipidemia, diabetes mellitus tipo 2 e infertilidade (4,5,7,8). A obesidade e a resistência à insulina, por sua vez, agravam os sintomas do hiperandrogenismo, formando um círculo vicioso (1,9, 10).

Somado aos fatores cosméticos, a síndrome modifica a qualidade de vida global da mulher, estudos demonstram prevalência aumentada de ansiedade e depressão nessa população. (1,11,12).

### Tratamento da Síndrome dos Ovários Policísticos

O manejo deve ser realizado de maneira multidisciplinar e individualizado, variando de acordo com os sintomas dermatológicos da paciente, o desejo de gestar, e a presença de patologias associadas que agregam mobimortalidade. (1,2,4,13,14,15)

Para as pacientes que não desejam gestar em curto-prazo, o tratamento envolve medidas farmacológicas e não farmacológicas. Mudanças no estilo de vida como dieta, exercício físico e redução de peso corporal nas que apresentam sobrepeso/obesidade são benéficas no controle dos sintomas de hiperandrogenismo, na regularização dos ciclos menstruais e ovulação e devem ser sempre incentivadas em associação com o tratamento farmacológico. (1,4,13,16). Diversos estudos apontam que uma redução de 5-10% do peso pode melhorar significativamente os parâmetros clínicos, reprodutivos e metabólicos (2,16,17).

**Tratamento dos sintomas do hiperandrogenismo**

As estratégias farmacológicas disponíveis que visam o controle do hiperandrogenismo agem na diminuição dos androgênios séricos circulantes e seus efeitos em nível tecidual. A escolha da terapia anti-androgênica deve ser guiada conforme a gravidade dos sintomas e do desconforto da paciente (2,6,18). As candidatas ao tratamento devem estar cientes de que o uso crônico dos medicamentos provavelmente será necessário e que a melhora clínica ocorre após alguns meses do inicio do tratamento. (6)

Os contraceptivos orais combinados (COCPs) são medicamentos de primeira linha para mulheres que não desejam engravidar, agindo na regulação dos períodos menstruais e também no controle do hirsutismo, acne e da perda de cabelos de padrão feminino.(2,13,19). Isso ocorre através da ação antigonadotrófica do componente estrogênico, reduzindo a secreção ovariana de androgênios e pelo aumento da produção hepática da globulina ligadora de hormônios sexuais (SHBG), a qual reduz a fração androgênica livre (2,13,19). Os COCPs contem uma combinação de estrogênio e de progestogênio, sendo que o componente progestogênico também apresenta uma ação inibitória sobre a biossíntese de androgênios (13) e reduzem consideravelmente o risco de hiperplasia e câncer endometrial (7,14).

Em casos de hirsutismo moderado a severo ou resposta inefetiva aos COCPs, após seis meses de uso, pode-se associar um antiandrogênio (1,6,14,19). Opções como a espironolactona, acetato de ciproterona (CPA), finasterida e flutamida são eficazes na redução dos sintomas dermatológicos, sendo a flutamida não mais recomendada pelo risco de toxicidade hepática (19). Em mulheres com PCOS, são em geral prescritas em combinação com os COCPs, conferindo maior potência, ou em monoterapia, caso haja contraindicações ao uso destes. (6,14). Entretanto, são proscritas na gestação e deve-se garantir que métodos contraceptivos efetivos sejam utilizados, pelo risco de virilização incompleta de fetos do sexo masculino (1,5,6,14,19,20).

**A espironolactona como opção antidrogênica**

Entre os antindrogênios, a espironolactona é amplamente utilizada pelo seu bom perfil de segurança e pelo baixo custo. É um esteroide sintético e atua como antagonista não seletivo do receptor mineralocorticóide com afinidade moderada para receptores de progesterona e androgênios. (21).

Diversos estudos sugerem que a espironolactona é bem tolerada, efetiva e segura no

tratamento de acne e hirsutismo. A prevalência de efeitos adversos é variável, mas a gravidade é geralmente leve e a maioria das mulheres tolera o tratamento. (22,23,24,25,26,27)

O efeito adverso mais comum associado ao tratamento com espironolactona é irregularidade menstrual (amenorréia, aumento ou diminuição do fluxo menstrual, sangramento intermintente e encurtamento do ciclo) (22,26,28,29).

Outros efeitos menos frequentes são sensibilidade ou aumento mamário, cefaleia, fadiga e, mais raramente, diminuição de libido, sonolência, cólicas abdominais, vômitos, náuseas, diarreia, tontura, confusão, anorexia, hipercalemia, hipotensão postural, xerose, melasma e edema facial (6,25,26). O uso de terapia combinada com COCPs minimiza a prevalência de disturbios menstruais quando comparada a monoterapia com SPL.(26) mas pode aumentar a prevalência de hipercalemia, principalmente em COCPs contendo a drosperinona como progestina (30).,sendo uma combinação não indicada como primeira linha de tratamento.

A hipercalemia é o efeito adverso mais temido e a medida de potássio sérico seriada é preconizada pelos guidelines atuais (2). A efetividade, segurança e presença de efeitos colaterais durante o uso de espironolactona na população com Hipertensão Arterial Sistêmica e cardiopatia é bem conhecida desde o estudo Randomized Aldactone Evaluation Study (RALES), de 1999 e seu uso é aprovado pelo FDA para esses fins há décadas. (31). De maneira oposta, apesar do uso da espironolactonca como terapia antiandrogênica na população com PCOS ser realizada há anos e ter sua efetividade e segurança já conhecida, segue sendo usada nas ultimas décadas de maneira *off label*.

Plovanich, em estudo retrospectivo que avaliou 974 mulheres em uso de espironolactona para tratamento de acne demonstrou que essa manifestação é rara, majoritariamente transitória e clinicamente insignificante, ao evidenciar uma prevalência de hipercalemia semelhante nas pacientes em uso de SPL e nas pacientes controle (0,72% x 0,76%) (32).

Portanto, os objetivos deste trabalho foram: 1) Avaliar o efeito da terapia com espironolactona, como antiandrogênio, sobre os níveis de potássio sérico e 2) Determinar a incidência de hipercalemia em mulheres com PCOS durante o uso da medicação.

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# Potassium levels in women with Polycystic Ovary Syndrome using spironolactone for long-term.

Short running title: Spironolactone and potassium levels in PCOS

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**Summary**

**Objective**: Spironolactone (SPL) has been used to manage hyperandrogenic manifestations in women with polycystic ovary syndrome (PCOS), but data on the risk of hyperkalemia in this population are scarce. The aim of this study was to evaluate the incidence of hyperkalemia in women with PCOS using SPL in the long term.

**Design:** Single-center retrospective study.

**Patients:** Inclusion and analysis of 98 women with PCOS (20 of whom were duplicates, returning after treatment interruption for a mean of 38 months) who received SPL for a minimum of 12 months and had at least 3 measurements of potassium levels over time. **Measurements:** Clinical and hormonal profiles before and during SPL treatment.

**Results:** Mean age was 29.1 (SD 9.6) years, and body mass index was 32.2 (SD 8.1) kg/m². Nine patients had diabetes, and 22 had prediabetes. SPL was used in combination with combined oral contraceptive pills in 55 participants and progestin-only pills/LARC in 28; metformin was added in 35, and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers in 15. Median SPL dose was 100 (range, 50-150) mg. A total of 327 serum potassium measurements were obtained (84 pre-exposure and 243 post-exposure). Four potassium measurements were above the reference range before exposure and 19, during exposure. All potassium measurements above the reference range during follow-up were classified as mild hyperkalemia (5.1-5.5 mEq/L).

**Conclusions:** The present findings suggest that women with PCOS, without kidney or heart disease, using SPL combined with hormonal contraception for managing clinical hyperandrogenism have a low incidence of hyperkalemia and well-tolerated minor adverse effects.

**Keywords:** Antiandrogens; clinical hyperandrogenism; hirsutism; PCOS; potassium; side effects; spironolactone

## Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder among women of reproductive age, with an approximately 13% prevalence [1]. It is a complex condition characterized by hyperandrogenism, oligo-anovulation, polycystic ovarian morphology, and associated cardiometabolic abnormalities. [2, 3, 4, 5, 6]

PCOS management usually includes non-pharmacological measures, such as weight control and lifestyle changes, together with pharmacological therapy [7, 8, 9, 10.] While combined oral contraceptive pills (COCPs) are the mainstay of pharmacological treatment, many patients will have an antiandrogen drug added to their regimen to control hyperandrogenic manifestations. [3, 11]

Spironolactone (SPL) is a synthetic steroid that acts as a non-selective mineralocorticoid receptor antagonist. Originally used as an antihypertensive drug, SPL has been used off-label to manage hirsutism and female pattern hair loss in women with PCOS. [11, 12]. SPL has moderate affinity for the androgen receptor, acting as an androgen antagonist and significantly improving the signs of hyperandrogenism. [13, 14, 15]

Few studies assessing the adverse effects of SPL in women with PCOS are available. However, as SPL is an aldosterone antagonist, monitoring serum potassium levels is recommended due to the possibility of hyperkalemia during its use [16], and recent studies have shown that the occurrence of this event in women with acne is infrequent and usually mild.[17, 18, 19]

Therefore, the present study aimed to evaluate the effect of SPL on the incidence of hyperkalemia in women with PCOS. Secondary endpoints included the frequency of hyperkalemia according to SPL dose and SPL use in combination with other medications.

## Materials and Methods

### *Study design and participants*

We conducted a single-center, retrospective study with data collected from the electronic medical records of patients with PCOS receiving care at the outpatient clinic of the Gynecological Endocrinology Unit, Division of Endocrinology of the Hospital de Clínicas de Porto Alegre, Brazil, between March 2010 and January 2020. PCOS was defined according to the Rotterdam criteria [20.]

Seventy-eight women with PCOS aged 18 to 50 years taking SPL for hirsutism for a minimum of 12 months and having at least 3 potassium measurements were included. Of these 78 patients, 20 women who used SPL intermittently, having stopped the medication for a mean of 37.7 months (range, 12-91 months) for multiple reasons (pregnancy desire, participation in another research project, or poor adherence) and then resuming treatment, were included in our sample twice, totaling 98 evaluations. Pregnant women, patients with chronic kidney and/or heart disease, and those with hyperandrogenic disorders other than PCOS were not included in the study. The study protocol was approved by the local Research Ethics Committee.

*Data collection*

The following data were collected through an individual and comprehensive review of medical records: weight, height, blood pressure, hirsutism (modified Ferriman-Gallwey [mFG] score), presence of comorbidities (previous diagnosis of diabetes, prediabetes, or systemic arterial hypertension), SPL dose, and use of other medications (COCPs, progestin-only pills [POPs], levonorgestrel-releasing intrauterine system [LNG-IUS], etonogestrel implant metformin, angiotensin-converting enzyme inhibitors [ACEis], and angiotensin receptor blockers [ARBs]). Potassium levels were assessed before and during SPL use. The serum potassium reference range was defined as 3.5 to 5.0 mEq/L, according to the reference kit.
Hyperkalemia was classified as mild (5.1 to 5.5 mEq/L), moderate (5.6 to 6.0 mEq/L), or severe ($\geq$ 6.0 mEq/L).[21.]

The prevalence of postural hypotension and other adverse effects was assessed by a description of the complaint in the medical records throughout the follow-up period. Hirsutism was defined as mFG score $\geq 6$.[3]

Total testosterone was obtained by chemiluminescence immunoassay. Measurements were performed at baseline and at 6- and 12-month follow-up, with 2 additional assessments at 18 and 24 months when information was available.

*Statistical analysis*

The Shapiro-Wilk normality test and descriptive statistics were used to evaluate the distribution of data. Results are presented as mean (SD). Generalized estimating equation (GEE) models were used to assess differences in potassium levels and other variables between pre-exposure and post-exposure as well as their relationship to SPL dose at different time points (baseline, 6 months, and 12 months). A GEE model of normal distribution with identity link function was used for continuous variables, whereas a model of binomial distribution with logit link function was used for binary outcomes.

A sensitivity analysis was performed by excluding patients using ACEis/ARBs to evaluate the impact of other antihypertensive drugs, combined with SPL, on potassium concentrations. All analyses were performed using SPSS, version 18.0 (IBM Corp.). Data were considered significant at $P < 0.05$.

**Results**

The records of 98 women were included and analyzed (20 of whom were duplicates, returning after treatment interruption for a mean of 38 months). Mean patient age was 29.12 (SD, 9.57) years, and body mass index (BMI) was 32.2 (SD, 8.1) kg/m². Nine patients had diabetes, 22 had prediabetes, 19 had systemic arterial hypertension, and 50 had BMI > 30 kg/m². SPL was used in combination with COCPs in 55 participants and with POPs/ LNG- IUS/etonogestrel implant in 28; metformin was added in 35, and ACEis/ARBs in 15. Fourteen women were using non-hormonal contraceptive methods and one had no need for contraception.

Median SPL dose was 100 (range, 50-150) mg. Table 1 shows the characteristics of patients before SPL treatment.

A total of 327 serum potassium measurements were obtained (84 pre-exposure and 243 post-exposure). No differences were observed between the distinct time points (baseline, 6 months, and 12 months) or between SPL doses (50, 100, and 150 mg) (Table 2).

Regarding the incidence of hyperkalemia, four potassium measurements were above the reference range (4.7%) before exposure and 19 (7.8%), during exposure (4 to 6 at each time point). No difference was found in potassium levels between specific time points (baseline, 6 months, and 12 months), P=0.218.

Of the 19 samples, 6 (31.6%) were from patients with previous hypertension and using ACEis or ARBs. A sensitivity analysis excluding these patients did not change the results. Four patients had mild hyperkalemia more than once during follow-up, accounting for 13 of these 19 measurements.

Table 3 shows weight, BMI, total testosterone levels, and mFG score before and during follow-up, stratified by treatments combined with SPL: COCP (n=55); POP, LNG-IUS, etonogestrel implant, or other non-hormonal contraceptive method (n=42); and metformin (n=35). Weight and BMI did not change significantly over time, regardless of the treatment added to SPL. Total testosterone levels decreased significantly at 6 and 12 months when a COCP was combined with SPL. Hirsutism (mFG score $\geq$ 6) decreased significantly after 12 months of SPL use in all groups.

The most common minor adverse effect observed in this sample of women with PCOS was irregular menstrual bleeding in 8 patients (8.2%), 5 of them using POPs irregularly and the other 3 using COCPs, followed by dizziness in 6 (6.1%) and postural hypotension in 3 (3.1%), reported as lightheadedness when standing, blurred vision, and syncope sensation. SPL was discontinued in only 2 cases (2.1%) due to poor tolerance, one due to breast tenderness and the other due to cramps (Table 4).

## Discussion

This retrospective study of women with PCOS evaluating the effect of SPL combined with other therapies on potassium levels showed a safe profile with a low incidence of mild hyperkalemia (< 5.6 mEq/L). Other minor adverse effects, such as unscheduled vaginal bleeding and self-reported postural hypotension, were also uncommon and well tolerated, and SPL was discontinued in only 2 patients (2.1%) for reasons other than hyperkalemia.

SPL is a potassium-sparing diuretic that acts on distal nephron tubules promoting diuresis and potassium reabsorption.[22.] A secondary effect is exerted by antagonism of the androgen receptor[13,14] accounting for the antiandrogen effects of SPL. Its efficacy as an antiandrogen agent has been recognized in hyperandrogenic conditions. [3, 12, 23, 24] SPL is an inexpensive, widely available medication, but data are sparse on the frequency and severity of

hyperkalemia with the long-term use of SPL in women with PCOS without kidney or heart disease.

Frequent monitoring of potassium is often recommended when SPL is used for indications such as heart failure.[25, 26.] These populations consist mostly of older persons under polypharmacy who may have diminished renal perfusion, which predisposes them to fluid and electrolyte disturbances. However, women with PCOS using SPL due to its antiandrogenic properties are usually younger and healthier than them, as observed in the present study, in which only few patients were > 45 years old.

Studies of transgender women using SPL in the context of the gender-affirming hormone therapy have been recently published. Two retrospective studies [27, 28] with SPL doses ranging from 25 to 400 mg found a very low incidence of hyperkalemia. Age > 45 years in the first study and serum creatinine ≥ 2 mg/dL in the second study were the predisposing factors for potassium elevation.

In women using SPL for acne treatment, no difference was found in the rate of hyperkalemia between similar populations taking and not taking SPL (0.72% in SPL users vs 0.76% baseline rate in non-users).[18] The guideline of the American Academy of Dermatology, updated in 2016, recommends against routine monitoring of serum potassium during acne treatment in patients at low risk of hyperkalemia [23], although there is no clear consensus on this issue. [29] Finally, a retrospective analysis of adverse events in women using SPL for any indication, reported to the United States Food and Drug Administration between 1969 and 2018, found that hyperkalemia was the most frequent adverse effect but extremely uncommon in patients aged ≤ 45 years (1.9% of all hyperkalemia cases).[30] Taken together, data from the literature and the present results seem to support a recommendation against frequent potassium monitoring in patients at low risk of hyperkalemia.

Limitations of our study include the retrospective design and the use of recorded data, as minor adverse effects might have been missed due to lack of recording in the patient's records. Also, the small sample size and lack of a larger number of patients aged > 45 years prevented us from stratifying our results by age group. Our study has strengths. First, all patients attended routine medical appointments and were asked about adverse effects. Also, a total of 327 serum potassium measurements were obtained, which corresponds to a mean of 4 measurements for each single patient. We did not exclude patients with diabetes or prediabetes, hypertension, or obesity and could assess potassium levels according to other medications used in combination with SPL, such as COCPs, POPs, metformin, ACEis, and ARBs. The long follow-up period, up to 18-24 months, for more than two-thirds of the sample ensured the evaluation of adverse effects even in the long term.

In conclusion, the results of this retrospective study of women with PCOS, without kidney or heart disease, taking SPL for hyperandrogenic manifestations found no life-threatening episodes of hyperkalemia, a low incidence of mild hyperkalemia, and only well-tolerated other minor adverse effects, with a low rate of drug discontinuation. Our study adds to the body of evidence of the safety of SPL use in low-risk populations and could indicate that frequent monitoring of potassium during follow-up in young women with PCOS with normal kidney and heart function may not be needed.

**Conflict of interest statement**

The authors declare that they have no conflict of interest.

**Data availability statement**

The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Author Contributions**

Thais Areias de Oliveira contributed to study design, was involved with data collection and analysis, drafted the article and participated in the final review of the manuscript. Lucas Bandeira Marchesan contributed to data analysis, drafted the article and participated in the final review of the manuscript. Poli Mara Spritzer was involved with the conception and design of the study, data analysis, drafted the article and participated in the final review of the manuscript. All authors contributed to the article and approved the submitted version.

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**Table 1. Characteristics of participants with PCOS before spironolactone treatment**

| Variable | Mean ± SD or n (%) |
|---|---|
| Age (y) | 29.12 ± 9.57 |
| BMI (kg/m²) | 32.2 ± 8.1 |
| mFG score | 14.27 ± 6.3 |
| Medications combined with SPL | |
| COCP | 55 (56.1%) |
| POP/LARC | 28 (28.5%) |
| Metformin | 35 (35.7%) |
| ACEi/ARB | 15 (15.3%) |
| SPL dose | |
| 50 mg | 14 (14.3%) |
| 100 mg | 71 (72.4%) |
| 150 mg | 13 (13.3%) |
| Testosterone (nmol/L) | 2.18 ± 1.28 |
| Potassium (mEq/L) | 4.43 ± 0.35 |

Values are expressed as mean ± SD or n (%). PCOS: polycystic ovary syndrome; BMI: body mass index; mFG: modified Ferriman-Gallwey score; SPL: spironolactone; COCP: combined oral contraceptive pill; POP: progestin-only pill; LARC, long-acting reversible contraception: levonorgestrel intrauterine system, etonogestrel implant; ACEi/ARB: angiotensin-converting enzyme inhibitor/angiotensin receptor blocker.

**Table 2. Potassium levels in women with PCOS according to spironolactone doses**

| Variable | Baseline | 6 months | 12 months | p-value |
|---|---|---|---|---|
| Potassium (mEq/L) | 4.43 (4.33 - 4.53) | 4.52 (4.42 - 4.62) | 4.50 (4.42 - 4.58) | 0.311 [a] |
| SPL dose | | | | 0.305 [b] |
| 50 mg | 4.54 (4.35 - 4.73) | 4.62 (4.38 - 4.85) | 4.57 (4.39 - 4.74) | |
| 100 mg | 4.43 (4.35 - 4.52) | 4.48 (4.40 - 4.57) | 4.43 ( 4.34 - 4.51) | |
| 150 mg | 4.3 (4.10 - 4.53) | 4.47 (4.31 - 4.63) | 4.50 (4.38 - 4.64) | |
| | | | | 0.589 [c] |

Values are expressed as estimated mean (CI). PCOS: polycystic ovary syndrome; SPL, spironolactone. [a] Generalized estimating equations (GEE) comparing potassium levels between time points; [b] GEE comparing potassium levels between SPL doses; [c] GEE comparing potassium levels between time points and SPL doses (interaction term).

**Table 3. Weight, BMI, hirsutism score and testosterone over time in women with PCOS using spironolactone**

| Variable | Baseline | 6 months | 12 months | p-value |
|---|---|---|---|---|
| **SPL all** [a] | | | | |
| Weight (kg) | 83.8 (24.1) | 83.7 (24.1) | 82.8 (23.2) | 0.941 |
| BMI (kg/m²) | 32.2 (8.23) | 32.1 (8.32) | 31.9 (8.02) | 0.875 |
| TT (nmol/L) | 2.18 (1.28) | 1.84 (1.07) | 1.66 (1.04) | **0.001** |
| mFG score | 14.27 (6.3) | ___ | 9.63 (4.8) | **0.000** |
| **SPL + COCP** | | | | |
| Weight (kg) | 75.5 (19.4) | 74.5 (18.7) | 74.1 (18.4) | 0.737 |
| BMI (kg/m²) | 29.4 (6.93) | 29.2 (6.68) | 29.12 (6.62) | 0.558 |
| TT (nmol/L) | 2.18 (1.07) | 1.66 (0.9) | 2.04 (1.07) | **0.006** |
| mFG score | 15.92 (6.9) | ___ | 9.96 (5.1) | **0.000** |
| **SPL + non-COCP** | | | | |
| Weight (kg) | 95.2 (21.6) | 96.9 (21.2) | 92.3 (19.1) | 0.760 |
| BMI (kg/m²) | 36.3 (7.04) | 36.2 (7.75) | 35.03 (6.82) | 0.511 |
| TT (nmol/L) | 1.63 (0.83) | 1.59 (0.66) | 1.25 (0.66) | 0.192 |
| mFG | 12.38 (5.97) | ___ | 8.50 (4.59) | **0.000** |
| **SPL + MTF** [a] | | | | |
| Weight (kg) | 96.3 (25.5) | 96.2 (25.2) | 93.9 (23.7) | 0.752 |
| BMI (kg/m²) | 36.3 (7.79) | 36.3 (7.74) | 35.5 (7.20) | 0.845 |
| TT (nmol/L) | 2.39 (1.59) | 2.01 (1.32) | 1.8 (1.14) | 0.163 |
| mFG score | 13.18 (6.35) | ___ | 8.88 (4.48) | **0.001** |

Values are expressed as mean (SD). BMI: body mass index; PCOS: polycystic ovary syndrome; SPL: spironolactone; TT: total testosterone; mFG: modified Ferriman-Gallwey score; COCP: combined oral contraceptive pill; non-COCP: progestin-only pill, levonorgestrel intrauterine system, etonogestrel implant, copper intrauterine device, or condom; MTF: metformin. [a] Participants using any contraceptive method combined with SPL.

**Table 4. Other adverse effects in women with PCOS during spironolactone treatment**

| Adverse effect | N | % |
|---|---|---|
| No adverse effect | 68 | 69.3% |
| Irregular menstrual bleeding | 8 | 8.16% |
| Postural hypotension | 3 | 3.06% |
| Dizziness | 6 | 6.12% |
| Nausea | 4 | 4.08% |
| Headache | 3 | 3.06% |
| Cramps | 2 | 2.04% |
| Sleepiness | 1 | 1.02% |
| Abdominal pain | 1 | 1.02% |
| Breast pain | 1 | 1.02% |
| Low libido | 1 | 1.02% |
| Total 98 | 100% | PCOS: polycystic ovary syndrome. |