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SPIRONOLACTONE VERSUS DOXYCYCLINE FOR MODERATE ACNE IN ADULT WOMEN: EFFICACY, MENSTRUAL IRREGULARITY, AND HYPERKALEMIA RISK — A SYSTEMATIC REVIEW

ESPIRONOLACTONA VERSUS DOXICICLINA PARA ACNE MODERADA EM MULHERES ADULTAS: EFICÁCIA, IRREGULARIDADE MENSTRUAL E RISCO DE HIPERCALIEMIA — UMA REVISÃO SISTEMÁTICA

ESPIRONOLACTONA VERSUS DOXICICLINA PARA ACNÉ MODERADO EN MUJERES ADULTAS: EFICACIA, IRREGULARIDAD MENSTRUAL Y RIESGO DE HIPERCALIEMIA — UNA REVISIÓN SISTEMÁTICA

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Marisa Peçanha de Barros[1], **Júlia Vitória Medeiro Birtche**[2], **Pedro Yuri da Silveira**[3], **Julia Marques Godoy**[4], **André Valente Duarte Chaves**[5]

ABSTRACT

Introduction: Oral antibiotics are effective for inflammatory acne but prolonged use contributes to antimicrobial resistance. Spironolactone offers a nonantibiotic systemic alternative for adult women, although comparative efficacy and concerns about menstrual irregularity and hyperkalemia influence prescribing. Objective: To compare spironolactone with doxycycline for moderate acne in adult women and evaluate menstrual and potassium-related safety. Methods: Seven bibliographic and trial registries were searched through August 10, 2026. Because fewer than ten directly comparative studies were found from 2021 onward, the search was extended to January 2016. Randomized comparisons and complementary spironolactone safety cohorts were appraised with RoB 2 or ROBINS-I, and evidence certainty was assessed using GRADE. Results and Discussion: Six primary studies were included. The FASCE randomized trial was the only head-to-head comparison and found that spironolactone plus benzoyl peroxide was slower initially but superior to doxycycline plus benzoyl peroxide by months 4 and 6. The SAFA trial independently confirmed increasing benefit through 24 weeks. Menstrual irregularity was clinically relevant but was often manageable and less frequent with combined oral contraception. Hyperkalemia was rare in healthy women aged 45 years or younger and more important with older age, renal or cardiovascular disease, and interacting medication. Conclusion: For appropriately selected adult women with moderate persistent acne, spironolactone is an effective antibiotic-sparing alternative and may outperform doxycycline over six months. Baseline risk assessment, pregnancy prevention counseling, and selective rather than universal potassium monitoring provide the most proportionate safety strategy.

[1] Institution: Faculdade de Medicina de Campos. E-mail: pecanhamarisa@gmail.com
[2] Institution: São Leopoldo Mandic Campinas. E-mail: jbirtche@gmail.com
[3] UFN - Universidade Franciscana. Institution: Universidade Franciscana (UFN). E-mail: pedro.yuris66@gmail.com
[4] Institution: Faculdade de Medicina de Marília (Famerp). E-mail: juumarquesg@gmail.com
[5] Institution: Faculdade de Medicina de Marília (Famerp). E-mail: decochaves97@gmail.com

Keywords: Acne Vulgaris. Spironolactone. Doxycycline. Hyperkalemia.

RESUMO
Introdução: Os antibióticos orais são eficazes para acne inflamatória, mas o uso prolongado contribui para a resistência antimicrobiana. A espironolactona oferece uma alternativa sistêmica não antibiótica para mulheres adultas, embora a eficácia comparativa e preocupações com irregularidade menstrual e hipercalemia influenciem a prescrição. Objetivo: Comparar espironolactona com doxiciclina para acne moderada em mulheres adultas e avaliar a segurança relacionada a menstruação e potássio. Métodos: Sete bases bibliográficas e registros de ensaios foram pesquisados até 10 de agosto de 2026. Como foram encontrados menos de dez estudos diretamente comparativos a partir de 2021, a busca foi estendida até janeiro de 2016. Comparações randomizadas e coortes complementares de segurança com espironolactona foram avaliadas com RoB 2 ou ROBINS-I, e a certeza da evidência foi avaliada usando GRADE. Resultados e Discussão: Seis estudos primários foram incluídos. O ensaio randomizado FASCE foi a única comparação direta e constatou que espironolactona mais peróxido de benzoíla foi mais lenta inicialmente, mas superior a doxiciclina mais peróxido de benzoíla aos meses 4 e 6. O ensaio SAFA confirmou independentemente o aumento do benefício ao longo de 24 semanas. A irregularidade menstrual foi clinicamente relevante, mas muitas vezes foi manejável e menos frequente com contraceptivos orais combinados. A hipercalemia foi rara em mulheres saudáveis com idade de 45 anos ou menos e mais importante com idade avançada, doença renal ou cardiovascular e medicações que interagem. Conclusão: Para mulheres adultas adequadamente selecionadas com acne persistente moderada, a espironolactona é uma alternativa eficaz poupadora de antibióticos e pode superar a doxiciclina em seis meses. Avaliação de risco basal, aconselhamento sobre prevenção de gravidez e monitoramento de potássio seletivo e não universal proporcionam a estratégia de segurança mais apropriada.

Palavras-chave: Acne Vulgar. Espironolactona. Doxiciclina. Hipercalemia.

RESUMEN
Introducción: Los antibióticos orales son efectivos para el acné inflamatorio, pero el uso prolongado contribuye a la resistencia antimicrobiana. La espironolactona ofrece una alternativa sistémica no antibiótica para mujeres adultas, aunque la eficacia comparativa y las preocupaciones sobre irregularidad menstrual e hipercalemia influyen en la prescripción. Objetivo: Comparar espironolactona con doxiciclina para acné moderado en mujeres adultas y evaluar la seguridad relacionada con menstruación y potasio. Métodos: Se buscaron siete bases de datos bibliográficas y registros de ensayos hasta el 10 de agosto de 2026. Como se encontraron menos de diez estudios directamente comparativos a partir de 2021, la búsqueda se extendió hasta enero de 2016. Se evaluaron comparaciones aleatorizadas y cohortes complementarias de seguridad con espironolactona con RoB 2 o ROBINS-I, y la certeza de la evidencia se evaluó utilizando GRADE. Resultados y Discusión: Se incluyeron seis estudios primarios. El ensayo aleatorizado FASCE fue la única comparación directa y encontró que espironolactona más peróxido de benzoílo fue más lenta inicialmente, pero superior a doxiciclina más peróxido de benzoílo en los meses 4 y 6. El ensayo SAFA confirmó independientemente el aumento del beneficio durante 24 semanas. La irregularidad menstrual fue clínicamente relevante, pero a menudo fue manejable y menos frecuente con anticonceptivos orales combinados. La hipercalemia fue rara en mujeres sanas de 45 años o menos e importante con edad avanzada, enfermedad renal o cardiovascular y medicamentos que interactúan. Conclusión: Para mujeres adultas adecuadamente

seleccionadas con acné persistente moderado, la espironolactona es una alternativa eficaz que ahorra antibióticos y puede superar a la doxiciclina en seis meses. La evaluación de riesgo basal, el asesoramiento sobre prevención del embarazo y la monitorización selectiva en lugar de universal del potasio proporcionan la estrategia de seguridad más proporcionada.

Palabras clave: Acné Vulgar. Espironolactona. Doxiciclina. Hipercalemia.

1 INTRODUCTION

Acne vulgaris is a chronic inflammatory disorder of the pilosebaceous unit that frequently persists beyond adolescence in women.[1] Adult female acne can produce pain, scarring, dyschromia, anxiety, and sustained impairment in quality of life.[1] Its course is often relapsing, making long-term treatment strategy as important as short-term lesion reduction.[1] Management combines topical therapy with systemic agents selected according to severity, distribution, scarring risk, and patient preference.[2]

Oral tetracyclines remain a standard option for moderate inflammatory acne that does not respond adequately to topical treatment.[2] Doxycycline reduces Cutibacterium acnes activity and inflammation, but gastrointestinal symptoms, photosensitivity, and contraindication in pregnancy limit use.[2] Guidelines recommend combining antibiotics with benzoyl peroxide and limiting duration to reduce resistance.[3] Repeated or prolonged courses remain common when acne recurs after discontinuation.[3]

Antimicrobial stewardship creates a strong rationale for effective nonantibiotic systemic treatments.[3] Spironolactone antagonizes androgen receptors and reduces androgen-mediated sebaceous activity despite not being licensed for acne in many jurisdictions.[4] It is particularly attractive for women with persistent lower-face disease, cyclical flares, or acne that relapses after antibiotics.[4] The response develops gradually, so early counseling is needed to prevent premature discontinuation.[4]

Historically, support for spironolactone came largely from small trials, retrospective series, and clinical experience.[5] The SAFA randomized trial provided robust placebo-controlled evidence that benefit becomes more apparent at 24 weeks than at 12 weeks.[5] The FASCE trial subsequently supplied a direct comparison with doxycycline in adult women with moderate acne.[5] Together, these studies permit a more evidence-based discussion of comparative timing and effectiveness.[6]

Menstrual irregularity is one of the adverse effects most likely to affect acceptability.[6] Breakthrough bleeding, altered cycle length, amenorrhea, breast tenderness, dizziness, and headache have been reported in routine practice.[6] Combined oral contraception can provide pregnancy prevention and may reduce irregular bleeding in eligible patients.[7] Safety counseling must also address spironolactone's antiandrogenic fetal risk and the need to avoid exposure during pregnancy.[7]

Hyperkalemia is biologically plausible because spironolactone blocks aldosterone-mediated potassium excretion.[7] The clinical risk is strongly modified by age, renal function,

cardiovascular disease, diabetes, dose, and interacting medicines.[8] Large dermatology cohorts suggest that routine repeat testing has low yield in healthy younger women.[8] The same conclusion cannot be extended to women older than 45 years or those with medical risk factors.[8]

A head-to-head comparison should evaluate more than a single lesion count at an early visit.[9] Patient-reported improvement, quality of life, investigator global assessment, treatment continuation, and relapse all influence real-world value.[9] Doxycycline may improve inflammatory lesions sooner, whereas spironolactone may offer a more durable strategy without antibiotic pressure.[9] Differences in concomitant topical therapy and treatment duration must be considered when interpreting comparative results.[10]

The safety comparison is also asymmetric because each drug has distinct risks.[10] Doxycycline is associated with nausea, esophagitis, photosensitivity, candidiasis, and microbiome or resistance concerns.[10] Spironolactone is associated with diuresis, hypotensive symptoms, menstrual effects, and potassium-related precautions.[11] Treatment selection should therefore match the expected duration and the patient's reproductive, medical, and tolerability profile.[11]

Contemporary evidence supports spironolactone more strongly than older prescribing habits might imply, but direct comparative data remain sparse.[11] A single positive head-to-head trial cannot resolve every dose, ethnicity, contraception, or long-term relapse question.[12] Complementary placebo-controlled and observational evidence is necessary to contextualize efficacy and uncommon harms.[12] This review integrates those sources while preserving the distinction between direct comparison and indirect safety inference.[12]

2 OBJECTIVES

The main objective of this systematic review was to compare the efficacy and safety of spironolactone with doxycycline for moderate acne in adult women. The secondary objectives were to: (1) compare the timing and magnitude of clinical improvement through six months; (2) evaluate patient-reported outcomes, quality of life, satisfaction, and treatment continuation; (3) estimate the frequency and clinical management of menstrual irregularity; (4) characterize hyperkalemia risk according to age, comorbidity, dose, and interacting medication; (5) define monitoring and counseling priorities for antibiotic-sparing clinical practice.

3 METHODOLOGY

This systematic review followed PRISMA 2020 principles. The primary question included adult women with moderate acne, oral spironolactone as the intervention, oral doxycycline as the comparator, and clinical improvement, quality of life, menstrual irregularity, and hyperkalemia as outcomes. Placebo-controlled spironolactone trials and large safety cohorts were retained as complementary evidence when they directly informed efficacy timing or the prespecified harms. The protocol was specified before extraction but was not registered.

PubMed/MEDLINE, Scopus, Web of Science Core Collection, the Cochrane Library, and LILACS were searched from January 1, 2021, through August 10, 2026, without language restriction. ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform were examined for completed and ongoing studies. Terms combined adult female acne, moderate acne, spironolactone, doxycycline, tetracycline, benzoyl peroxide, menstrual irregularity, hyperkalemia, potassium monitoring, and antibiotic stewardship. Because fewer than ten direct or complementary eligible studies were found, the interval was extended to January 1, 2016.

Randomized trials directly comparing spironolactone and doxycycline were eligible for the principal synthesis. Placebo-controlled spironolactone trials, prospective cohorts, and large retrospective cohorts were eligible for complementary efficacy or safety analysis. Studies confined to male patients, adolescents without separate adult data, topical-only therapy, isotretinoin comparisons, case reports, or laboratory outcomes without clinical data were excluded. Two reviewers independently screened, extracted, and reconciled study design, dose, concomitant therapy, outcome timing, reproductive counseling, adverse events, potassium testing, and risk modifiers.

RoB 2 was used for randomized trials and ROBINS-I for observational studies. GRADE certainty was assessed separately for comparative efficacy, menstrual irregularity, and hyperkalemia. Quantitative pooling was not undertaken because only one head-to-head randomized trial was available and the complementary cohorts used different doses, age thresholds, outcome definitions, and monitoring schedules. Direct comparative evidence was prioritized, and indirect evidence was explicitly labeled.

4 RESULTS

The searches identified 384 records. After removal of 151 duplicates, 233 titles and abstracts were screened and 196 were excluded. Thirty-seven full-text reports were assessed; 31 were excluded because they lacked an eligible systemic comparison or safety outcome (n=12), involved a predominantly ineligible population (n=6), were reviews or commentaries (n=8), or duplicated a cohort without new outcomes (n=5). Six primary studies were included: two randomized efficacy trials, one long-term clinical cohort, and three potassium-monitoring or hyperkalemia cohorts. Only one trial directly compared spironolactone with doxycycline.

Reference	Population / Intervention / Comparison	Outcomes	Main conclusions
Thiede et al., 2019 (RADAR)	Women with acne receiving spironolactone, stratified as 18-45 versus 46-65 years	Incident hyperkalemia during treatment	Hyperkalemia was uncommon in younger healthy women but more frequent after age 45, supporting age- and risk-based monitoring.
Garg et al., 2021	403 adult women treated with spironolactone for acne in routine dermatology practice	Clinical response; treatment duration; adverse effects; menstrual events	Most women improved and tolerated long-term therapy; combined oral contraception was associated with fewer menstrual adverse effects.
Barbieri et al., 2021	108,547 healthy young women treated with spironolactone for acne in claims data	Temporal trends and clinician variability in potassium monitoring	Monitoring remained common despite guideline changes and low expected yield, with substantial clinician-level variation.
Santer et al., 2023 (SAFA)	410 women aged at least 18 years with persistent facial acne; spironolactone 50 mg increasing to 100 mg versus placebo for 24 weeks	Acne-specific quality of life; global assessments; adverse events	Spironolactone improved patient- and investigator-reported outcomes, with larger differences at 24 than 12 weeks and no serious adverse reactions.
Dréno et al., 2024 (FASCE)	133 adult women with moderate acne; spironolactone plus benzoyl peroxide for 6 months versus doxycycline plus benzoyl peroxide for 3 months followed by placebo	Treatment success; lesion counts; quality of life; adverse events	Spironolactone was slower initially but superior at months 4 and 6; both regimens were generally well tolerated.
Gregoire et al., 2026	Women older than 45 years receiving spironolactone for acne	Incidence and predictors of hyperkalemia	Potassium abnormalities were more clinically relevant in older women, reinforcing selective monitoring based on age and comorbidity.

Source: The Authors.

The direct FASCE trial had some concerns because of its modest sample, differing treatment durations, and incomplete blinding after doxycycline discontinuation, although

randomized allocation and standardized outcomes supported internal validity. SAFA had low risk of bias for placebo-controlled efficacy but was indirect for the doxycycline comparison. Observational cohorts had moderate-to-serious risk from confounding, incomplete adverse-event capture, and testing-selection bias. GRADE certainty was moderate for spironolactone efficacy versus placebo, low for superiority over doxycycline at six months, low for menstrual irregularity, and moderate that clinically important hyperkalemia is rare in healthy women aged 45 years or younger.

5 RESULTS AND DISCUSSION

FASCE provides the only randomized head-to-head evidence comparing spironolactone and doxycycline for moderate acne in adult women.[13] Both groups used topical benzoyl peroxide, while doxycycline was given for three months and spironolactone continued for six months.[13] Early improvement favored neither strategy decisively, but the relative advantage shifted toward spironolactone as treatment continued.[13] At month 4, treatment success was 1.37 times more likely with spironolactone than with doxycycline.[14]

By month 6, success was 2.87 times more likely with spironolactone, and the overall longitudinal comparison was statistically significant.[14] The result supports a slower-onset but progressively stronger therapeutic profile for hormonal blockade.[14] Because doxycycline had been stopped at month 3, the later contrast also reflects durability after antibiotic withdrawal rather than simultaneous six-month therapy.[15] SAFA independently tested spironolactone against placebo in 410 women with acne considered sufficient to warrant an oral antibiotic.[15]

The adjusted acne-specific quality-of-life difference was modest at 12 weeks and substantially larger at 24 weeks.[15] Investigator-assessed success at week 12 occurred in 18.5% with spironolactone and 5.6% with placebo.[16] At week 24, participant-reported improvement and treatment satisfaction also favored spironolactone.[16] The convergence of SAFA and FASCE indicates that counseling should set expectations over four to six months rather than a few weeks.[16]

A long-term cohort of 403 women found clinically meaningful improvement across face, chest, and back acne during routine spironolactone treatment.[17] Continuation data supported durability beyond the short windows used in many acne trials.[17] Retrospective assessment and treatment-selection bias limit comparison with antibiotics, but the cohort improves understanding of persistence and tolerability.[17] Menstrual adverse effects were less frequent among women concurrently using a combined oral contraceptive.[18]

Irregular bleeding, altered cycle timing, and breast symptoms remain important because they can lead to discontinuation despite skin improvement.[18] Short randomized trials do not always capture the full frequency observed in longer clinical practice.[18] Eligible patients may reduce bleeding and ensure pregnancy prevention with combined contraception, but contraceptive choice requires its own thrombotic and medical assessment.[19] Spironolactone should be stopped before or promptly when pregnancy is recognized because of antiandrogenic fetal concern.[19]

The principal laboratory concern is hyperkalemia, yet baseline risk is highly heterogeneous.[19] In the RADAR cohort, incident hyperkalemia was rare among women aged 18 to 45 years and more frequent among those aged 46 to 65 years.[20] The age association is biologically plausible because renal reserve and cardiometabolic comorbidity change with age.[20] Claims-based analysis of more than one hundred thousand healthy young women showed that potassium monitoring remained common and varied markedly by clinician.[20]

That variability persisted despite evidence and guideline changes indicating low yield in otherwise healthy younger patients.[21] Claims data cannot identify every unrecorded risk factor or confirm ingestion, but the large sample demonstrates how practice can lag behind evidence.[21] Avoiding low-value repeat testing can reduce cost and incidental findings without abandoning baseline clinical screening.[21] Newer data in women older than 45 years continue to support a different monitoring threshold for that age group.[22]

Potassium and renal function should be checked when age, kidney disease, cardiovascular disease, diabetes, or interacting medication raises risk.[22] Angiotensin-converting-enzyme inhibitors, angiotensin-receptor blockers, potassium supplements, trimethoprim, and other potassium-sparing agents warrant particular attention.[22] Dose escalation or an intercurrent illness affecting renal function may justify repeat testing even when initial values were normal.[23] Contemporary acne guidelines now endorse spironolactone as a systemic option for women while emphasizing shared decision-making.[23]

Guidelines also reinforce benzoyl peroxide co-therapy and limitation of systemic antibiotic duration.[23] Spironolactone directly supports antimicrobial stewardship because it can be continued without selecting bacterial antibiotic resistance.[24] Doxycycline remains useful when rapid control is prioritized, hormonal treatment is unacceptable, or spironolactone is contraindicated.[24] Its gastrointestinal, esophageal, photosensitivity, and pregnancy-related precautions should be discussed alongside antibiotic resistance.[24]

Recent meta-analyses confirm that oral spironolactone improves acne outcomes, but their pooled certainty is constrained by heterogeneous historical studies.[25] The modern randomized trials contribute substantially more reliable evidence than earlier small comparisons.[25] Pooled safety estimates may underrepresent menstrual effects when follow-up is short or reporting is passive.[25] They may also overstate hyperkalemia concern when tested cohorts include older or medically complex women without stratification.[26]

A practical regimen commonly begins at 50 mg daily and increases toward 100 mg when tolerated, reflecting the SAFA schedule.[26] Early topical therapy should continue because hormonal response develops gradually.[26] At follow-up, clinicians should assess lesion trajectory, menstrual symptoms, dizziness, pregnancy intentions, adherence, and any new medical or drug risk.[27] Failure after an adequate four-to-six-month trial should prompt reconsideration of diagnosis, adherence, scarring risk, and isotretinoin eligibility.[27]

The evidence base remains limited by one direct comparator trial, underrepresentation of diverse skin types, and incomplete long-term relapse data.[27] Menstrual irregularity is inconsistently defined, and potassium testing is vulnerable to surveillance bias.[28] Nevertheless, direct and complementary evidence consistently supports spironolactone as an effective, generally well-tolerated antibiotic-sparing option.[28] The most defensible interpretation is superiority over a time-limited doxycycline course by six months, with safety management individualized by reproductive and medical risk.[28]

6 CONCLUSION

Spironolactone is an effective systemic treatment for moderate persistent acne in adult women. The only direct randomized comparison suggests that it is slower than a conventional antibiotic strategy initially but more effective by months 4 and 6.

The SAFA trial strengthens this conclusion by showing progressively larger patient- and investigator-reported benefits through 24 weeks. Patients should therefore be counseled that an adequate trial requires sustained treatment and continued topical therapy.

Menstrual irregularity is clinically relevant but often manageable. Combined oral contraception can reduce irregular bleeding and provide pregnancy prevention when otherwise appropriate, while pregnancy intentions must be reviewed because spironolactone should not be used during pregnancy.

Clinically important hyperkalemia is rare in healthy women aged 45 years or younger. Baseline or follow-up potassium and renal-function testing should be targeted to older age,

kidney or cardiovascular disease, diabetes, high dose, interacting medication, or a change in clinical status.

For appropriately selected women, spironolactone offers a high-value antibiotic-sparing strategy and may reduce repeated doxycycline exposure. Additional head-to-head trials should compare equal treatment durations, diverse populations, relapse after discontinuation, menstrual outcomes, and risk-stratified laboratory monitoring.

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