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Síndrome genitourinari de la menopausa en pacients amb antecedent de càncer de mama

Eduard Mension Coll

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SÍNDROME GENITOURINARI DE LA MENOPAUSA EN PACIENTS AMB ANTECEDENT DE CÀNCER DE MAMA

Tesi doctoral



UNIVERSITAT DE
BARCELONA



Memòria de tesi doctoral presentada per **Eduard Mension Coll** per optar al grau de doctor per la Universitat de Barcelona.

Directors de Tesi:

Dr. Camil Castelo-Branco, Consultor Sènior de l'Institut Clínic de Ginecologia, Obstetrícia i Neonatologia (ICGON) de l'Hospital Clínic de Barcelona i Professor Titular d'Obstetrícia i Ginecologia i Cap de la Departament de Cirurgia i Especialitats Quirúrgiques de la Universitat de Barcelona.

Dra Immaculada Alonso Vargas, Especialista Sènior, Servei de Ginecologia, Hospital Joan XXIII, Tarragona.

Tutor: **Dr. Camil Castelo-Branco**, Consultor Sènior de l'Institut Clínic de Ginecologia, Obstetrícia i Neonatologia (ICGON) de l'Hospital Clínic de Barcelona i Professor Titular d'Obstetrícia i Ginecologia i Cap de la Departament de Cirurgia i Especialitats Quirúrgiques de la Universitat de Barcelona.

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Abreviatures i acrònims

CM: Càncer de mama

AVV: Atròfia vulvovaginal

SGUM: Síndrome genitourinari de la menopausa

DHEA: Dehidroepiandrosterona

FDA: U.S. Food and Drug Administration

VHI: Vaginal Health Index

VMI: Índex maduratiu vaginal

TVUS: Ecografia transvaginal amb gel transvaginal

VAS: Escala Visual Anàloga

HE: Avaluació Histològica

Tesi en format de compendi de publicacions

La tesis consta d'un total de 7 articles publicats en revistes indexades del quals:

3 articles originals corresponen als objectius de la tesi:

1. **Mension E**, Alonso I, Anglès-Acedo S, Ros C, Otero J, Villarino Á, Farré R, Saco A, Vega N, Castrejón N, Ordi J, Rakislova N, Tortajada M, Matas I, Gómez S, Ribera L, Castelo-Branco C. Effect of Fractional Carbon Dioxide vs Sham Laser on Sexual Function in Survivors of Breast Cancer Receiving Aromatase Inhibitors for Genitourinary Syndrome of Menopause: The LIGHT Randomized Clinical Trial. JAMA Netw Open. 2023 Feb 1;6(2):e2255697.

IF: 13.353, Q1.

2. **Mension E**, Alonso I, Cebrecos I, Castrejon N, Tortajada M, Matas I, Gómez S, Ribera L, Anglès-Acedo S, Castelo-Branco C. Safety of prasterone in breast cancer survivors treated with aromatase inhibitors: the VIBRA pilot study. Climacteric. 2022 Oct;25(5):476-482.

IF 3.005, Q2.

3. Ros C, **Mension E**, Rius M, Munmany M, De Guirior C, Espuña-Pons M, Sònia Anglès, Camil Castelo-Branco. Assessing the vaginal wall thickness by transvaginal ultrasound in breast cancer survivors: a pilot study Maturitas, 2023.

IF 5.517, Q1

i 4 articles són revisions:

1. **Mension E**, Alonso I, Castelo-Branco C. Genitourinary Syndrome of Menopause: Current Treatment Options in Breast Cancer Survivors - Systematic Review. Maturitas. 2021 Jan;143:47-58.

IF 5.517, Q1.

2. **Mension E**, Alonso I, Tortajada M, Matas I, Gómez S, Ribera L, Anglès S, Castelo-Branco C. Vaginal laser therapy for genitourinary syndrome of menopause - systematic review. Maturitas. 2022 Feb;156:37-59.

IF 5.517, Q1.

3. Castelo-Branco C, **Mension E**. Are we assessing genitourinary syndrome of menopause properly? Climacteric. 2021 Dec;24(6):529-530.

IF 3.005, Q2.

4. **Mension E**, Alonso I, Tortajada M, Matas I, Gómez S, Ribera L, Ros C, Anglès-Acedo S, Castelo-Branco C. Genitourinary Syndrome of Menopause Assessment Tools. J Midlife Health. 2021 Apr-Jun;12(2):99-102.

IF 0.0.

1. RESUM DE LA TESI

Antecedents del tema: Moltes pacients amb càncer de mama (CM) presenten tumors hormonals per als quals hi ha limitades estratègies terapèutiques. Una de les conseqüències no desitjables d'aquests tractaments és el seu impacte negatiu en el trofisme vaginal que conseqüentment pot alterar la salut sexual. Les teràpies no hormonals són el tractament de primera línia de l'atròfia vulvovaginal (AVV). Tot i que ser tractaments segurs, tenen una eficàcia lleu i normalment només proporcionen millores a curt termini. Altres opcions inclouen teràpia local amb estrògens, teràpia làser vaginal i andrògens locals, que semblen ser eficaces tot i que hi ha controvèrsia sobre la seva seguretat.

Objectius: L'objectiu del treball és avaluar les opcions terapèutiques actuals que es poden oferir a les pacients amb síndrome genitourinari de la menopausa (SGUM) amb antecedent de CM, i avaluar la eficàcia i seguretat de les noves teràpies emergents. Com a objectiu secundari es valorarà l'eficàcia d'una nova eina diagnòstica per valorar el SGUM de forma no invasiva.

Hipòtesis: La hipòtesi dels estudis és que tant el làser de CO₂ fraccionat com la prasterona, en les pacients afectes de CM sota tractament amb inhibidors de l'aromatasa, actuen sobre la mucosa vaginal augmentant el gruix de la paret, acidificant el pH vaginal i milloren la funció sexual. Per altre banda la ecografia transvaginal podria

ser un mètode d'avaluació del SGUM no invasiu capaç de diferenciar entre pacients sanes o aquelles que pateixin SGUM.

Metodologia:

Es realitzaran tres estudis:

- 1) Assaig clínic aleatoritzat doble cec, per avaluar l'eficàcia i seguretat del làser vaginal en pacients amb CM.
- 2) Estudi pilot per avaluar la seguretat de la teràpia amb dehidroepiandrosterona (DHEA) en pacients amb CM.
- 3) Estudi pilot per avaluar l'ecografia transvaginal com a nova tècnica de valoració del SGUM no invasiva.

Resultats esperats:

L'eficàcia del làser vaginal i de la prasterona ha estat demostrada en població general, tot i que amb pocs estudis i utilitzant criteris subjectius en la majoria d'estudis. L'eficàcia i seguretat d'aquestes teràpies no ha estat demostrada en el subgrup de pacients amb CM.

La seguretat no està demostrada amb fermesa en cap dels dos tractaments en el subgrup de CM, tot i que en estudis pilot semblen opcions segures.

Esperem demostrar tant l'eficàcia com la seguretat a més llarg termini dels dos tractaments amb aquests treballs.

Esperem demostrar de l'ecografia transvaginal permet diferenciar per imatge pacients sanes d'aquelles que pateixen SGUM.

2. INTRODUCCIÓ

La supervivència global de les dones amb càncer de mama (CM) ha augmentat durant les darreres dècades, tot i la incidència creixent d'aquesta malaltia. Aquesta millora de la supervivència es deu en gran mesura als avenços en les teràpies actuals, especialment des de la introducció de medicaments dirigits contra el receptor HER2. Gràcies a aquest augment de la supervivència, ens enfrontem avui en dia amb nous reptes que abans no es plantejaven, entre els quals trobem el de mantenir una bona qualitat de vida a les pacients llargues supervivents de càncer de mama (CM) ¹⁻².

Dins d'aquest grup de pacients, hi ha aquelles que han presentat la malaltia en edats pre-menopàusiques, amb potencial risc de rebre tractaments antineoplàsics que afectin la seva funció ovàrica, i més habitualment aquelles que la presenten en edats post-menopàusiques rebent tractaments antiestrogènics ³.

Aquestes teràpies provoquen un nou estat hipoestrogènic en les pacients premenopausiques, o poden agreujar l'estat basal hipoestrogènic en pacients ja menopausiques, provocant símptomes climatèrics freqüentment severes, que indueixen alteracions significatives en la seva qualitat de vida, i afectant també el compliment de les teràpies coadjuvants⁴.

Una de les principals manifestacions de l'hipoestrogenisme és el síndrome genitourinari de la menopausa (SGUM).

2.1 FISIOPATOLOGIA DEL SGUM

La principal causa fisiopatològica del SGUM és la presència d'un estat de deficiència relativa d'estrògens. Els epitelis del tracte urinari inferior, la vagina i el vestíbul vaginal estan connectats embriològicament, compartint també com a característica principal la presència de receptors d'estrògens en les cèl·lules que els componen. Baixos nivells circulants d'estrògens provoquen una disminució de l'activació dels receptors d'estrògens, i progressivament amb el temps, una disminució del nombre global de receptors d'estrògens en tota la zona genitourinària.

Quan estan presents, els estrògens mantenen la salut urogenital mitjançant mecanismes vasculars, cel·lulars i estructurals. Com a hormona vasoactiva, els estrògens augmenten el flux sanguini local, provocant un augment de la lubricació transsudativa a través dels vasos sanguinis, les glàndules de *Bartholino* i les glàndules endocervicals. A nivell histològic, l'epiteli urogenital està compost per una capa de cèl·lules superficials riques en glicogen, una capa amb cèl·lules intermitges amb un citoplasma de menors dimensions, i finalment una capa de cèl·lules parabasals per sota on hi ha una relació nucli-citoplasma major que en la resta. En presència d'estrògens, les capes superficials i intermèdies componen el principal gruix epitelial, ja que són capaces de mantenir gran quantitat de glicogen, col·lagen, mucopolisacàrids i àcid hialurònic a nivell del citoplasma, provocant un engruiximent de la capa epitelial, i alhora subministrant glicogen que actua com a substrat per als lactobacils de la flora vaginal sapròfita. Gràcies

a la simbiosi amb la flora bacteriana, la vagina manté un pH àcid mitjançant la producció d'àcids orgànics, principalment lactat. Aquesta acidesa protegeix la vagina dels canvis patogènics del microbioma i del risc d'infecció vulvovaginal. Aquests efectes combinats mantenen el gruix de la paret vaginal, l'elasticitat, la humitat, les secrecions vaginals i la lubricació.

Per altre banda, la pèrdua d'estrògens provoca la inversió dels suports vasculars, cel·lulars i estructurals dels teixits urogenitals prèviament descrits. Amb nivells baixos d'estrògens sèrics, tal com s'observa a la menopausa, el col·lagen i el glicogen disminueixen, la qual cosa condueix a una disminució de l'elasticitat i un aprimament de la mucosa vaginal. El flux vascular disminueix, provocant una lubricació reduïda, que es veu agreujada funcionalment per l'atenuació de les glàndules apocrines i endocrines. En aquest estat hipoestrogènic doncs, epiteli es compon principalment de cèl·lules parabasals, sense pràcticament glicogen acumulat al citoplasma, fet que comporta una pèrdua de lactobacils, un augment dels nivells de pH, i una major susceptibilitat als bacteris patògens. A més, la disminució de les secrecions vaginals pot provocar l'absència o la disminució de la lubricació amb l'activitat sexual i la friabilitat de l'epiteli vaginal, provocant freqüentment sensacions de secor, cremor, disparèunia, sagnat postcoital i conseqüentment la pèrdua secundària del desig sexual.

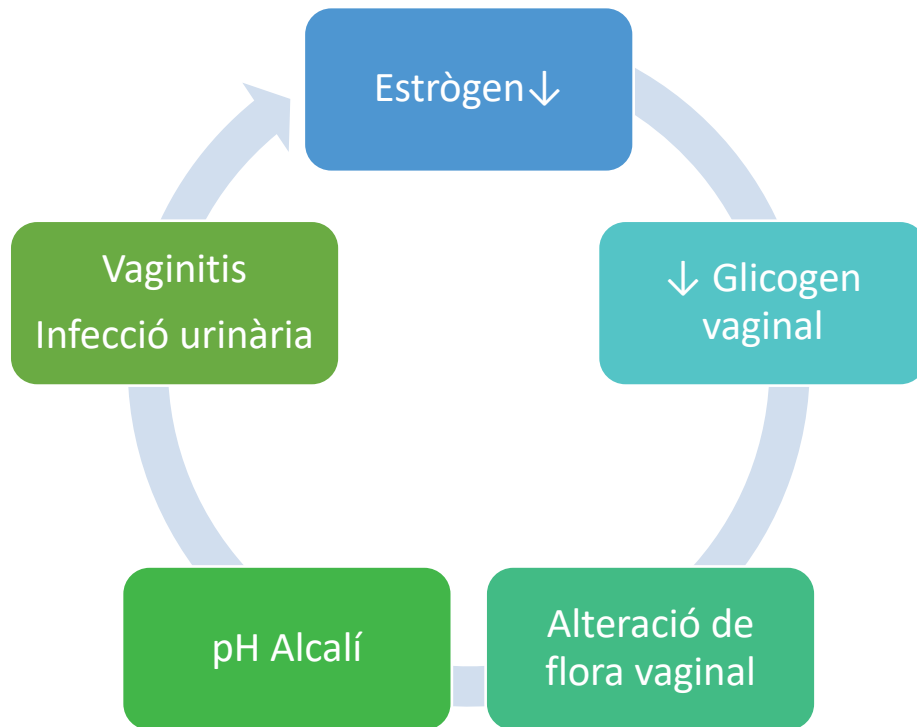


Figura 1. Fisiopatologia del SGUM.

2.2 EPIDEMIOLOGIA DEL SGUM

La prevalença del SGUM s'ha intentat estimar en molts estudis i enquestes, i la majoria suggereix que la prevalença real pot ser molt més alta del que s'observa a nivell de les enquestes, és a dir, que hi ha una alta probabilitat del que anomenem un infradiagnòstic del SGUM. Factors com 1) la percepció per part de les dones que els símptomes són normals, 2) que les pacients que pateixen SGUM no pensen en aquests símptomes com un problema mèdic o relacionat amb la menopausa, 3) la incomoditat de parlar de SGUM amb un proveïdor d'atenció mèdica i 4) la falta de focalització dirigida a aquest

síntomes en concret per part dels proveïdors d'atenció mèdica, són citats com a motius d'aquest possible infradiagnòstic.

Tot i això, una enquesta internacional a 4.000 dones post-menopàusiques de 55 a 65 anys va trobar que el 39% patia símptomes SGUM, i que d'aquestes, només el 45% havia informat dels seus símptomes. Un altre estudi a nivell espanyol, presentava que les dones post-menopàusiques que viuen a Espanya tenien una prevalença del 70% de SGUM⁶.

L'estudi AGATE va intentar valorar la prevalença de SGUM a través de criteris de diagnòstic objectius, valorant a través d'un examen físic avaluant el de pH vaginal signes clínics de SGUM, obtenint com a resultat una prevalença del 79,1% en el grup de pacients post-menopàusiques avaluades⁶.

Un altre estudi dissenyat específicament per valorar les diferències entre pacients menopàusiques sanes i pacients sobrevivents de CM a nivell de prevalença de símptomes menopàusics, va observar que el grup de pacients sobrevivents de CM presentava significativament nivells més alts de símptomes climatèrics, entre ells el SGUM. Així mateix, una avaluació a través d'enquestes la prevalença de símptomes concrets en pacients sobrevivents de CM diferenciades per pre i post-menopàusia, i tipus de tractament rebut; va observar que les pacients pre-menopàusiques tractades

amb quimioteràpia i teràpies anti-hormonals referien fins a un 42% de sequedat vaginal, un 27% de disparèunia i un 32% de reducció de la libido. En el grup de pacients post-menopàusiques tractades amb les mateixes teràpies, aquests símptomes eren de un 19% de sequedat vaginal, un 10% de disparèunia i un 12% de reducció de la libido. Aquesta diferència pot ser explicable pel fet que les pacients amb nivells d'estradiol normals previs a les teràpies, presenten un canvi més brusc, i per tant amb més risc de presentar símptomes que aquelles pacients que ja tenien uns nivells d'estradiol baixos per la pròpia menopausa, i que es veuen reduïts a nivells ultra-baixos, però amb menor canvi absolut a nivell d'estradiol sèric⁷.

2.3 SÍMPTOMES DEL SGUM

El síndrome genitourinari de la menopausa, està compostat per diferents símptomes que afecten el tracte urogenital, sent els més habituals la sequedat vaginal, les molèsties o dolor durant les relacions sexuals, la disminució de la libido secundària a la disparèunia, molèsties al orinar, i les infeccions vaginals i urinàries de repetició.

La sequedat vaginal és generalment el símptoma més reportat i molest, informat pel 93% de les dones simptomàtiques Espanyoles en l'estudi de *Moral* i el 85% de les enquestades a l'estudi EMPOWER, una enquesta online a 1.858 dones dels Estats Units⁸.
⁹. La disparèunia i la pèrdua del desig sexual va ser reportada per fins a un 85% de les dones enquestades. A l'estudi AGATE que hem mencionat prèviament, totes les

pacients diagnosticades de SGUM referien sequedat vaginal, el 77,6% va informar de disparèunia, el 56,9% de coïssor, el 56,6% de picor i el 36,1% de disúria⁷⁻⁸.

La disúria i la urgència o incontinència d'urgència són els símptomes urinaris més reportats, reportats en el 29% i el 28% de les dones amb SGUM, respectivament. Altres símptomes urinaris inclosos dins el concepte de SGUM són les infeccions del tracte urinari recurrents o la incontinència d'estrès.

2.4 IMPORTÀNCIA DEL SGUM EN PACIENTS SCM

Les pacients sobrevivents de càncer de mama, són un subgrup especialment sensible a l'hora de tractar el SGUM:

Aproximadament dos tercers parts dels tumors mamaris són hormonosensibles, fet que provoca que aquestes pacients rebran tractaments anti-hormonals, disminuint els nivells sèrics d'estradiol d'aquestes pacients per uns nivells per sota dels habituals en pacients postmenopàusiques. Aquests nivells “ultra-baixos” d'estradiol sèric, probablement provoca un SGUM més precoç i més sever en aquestes pacients, sobretot en pacients pre-menopàusiques on el canvi absolut d'estrògens circulants és molt important.

Per altre banda, en aquestes pacients trobem literatura contradictòria respecte a quines opcions terapèutiques són eficaces, i sobretot segures, ja que el tractament “*Gold Standard*” del SGUM, són les teràpies amb estrògens locals. Per aquest motiu, tenim encara avui en dia limitades i trobem molta controvèrsia respecte com s’ha de tractar aquest problema en aquestes pacients¹⁰⁻¹¹.

2.5 OPCIONS TERAPÈUTIQUES PER EL SGUM EN PACIENTS SOBREVIVENTS DE CM

Per posar llum a aquest punt de controvèrsia, dins el context d’aquesta tesi doctoral, es va realitzar una busca sistemàtica per tal de valorar les opcions terapèutiques disponibles a la literatura per pacients sobrevivents de CM (article adjunt al final de la introducció):

1. **Mension E**, Alonso I, Castelo-Branco C. Genitourinary Syndrome of Menopause: Current Treatment Options in Breast Cancer Survivors - Systematic Review. *Maturitas*. 2021 Jan;143:47-58
IF: 5.517, Q1 Obstetricia I Ginecologia.

En aquesta revisió sistemàtica d’estudis valorant opcions terapèutiques per SGUM per pacients sobrevivents de CM, es van obtenir dades respecte teràpies no hormonals, teràpies amb estrogen local, teràpies amb testosterona local i teràpies amb làser vaginal.

Com a conclusió de l'estudi, es va observar que el tractament de primera línia recomanat en pacients sobrevivents de CM amb SGUM lleu-moderat és l'ús de teràpies no hormonals, que són segures però presenten una eficàcia limitada a curt termini. En els casos de SGUM en pacients sobrevivents de CM refractaries al tractament no hormonal o presentant símptomes moderats-severs de SGUM, l'ús de la teràpia local amb estrògens es pot considerar segons les guies clíniques, sempre utilitzant la dosi més baixa possible i amb consens entre l'equip d'oncologia i la pacient.

Hi ha controvèrsia sobre l'ús de teràpies amb estrògens locals als diferents estudis, ja que alguns estudis suggereixen un possible augment dels nivells d'estrògens sèrics, que poden comportar un possible augment del risc de recurrència del CM. Per aquest fet i segons l'estudi de *Biglia et al*, fins a un 70% dels oncòlegs que tracten CM no recreen teràpies hormonals per por a un augment del risc de recurrència de CM¹².

Estan apareixent noves propostes per a ajudar a millorar els símptomes d'aquestes pacients, a les que d'entrada volem evitar les teràpies estrogèniques. Entre aquestes destaquen el làser vaginal i les teràpies amb andrògens locals, que poden incloure testosterona vaginal o dehidroepiandrosterona (DHEA) vaginal. Respecte a aquestes dues teràpies emergents, els andrògens locals semblen efectius en dades de només 3 estudis utilitzant testosterona vaginal, i no hi ha dades robustes sobre la seva seguretat en sobrevivents de CM. El làser vaginal sembla eficaç en diferents estudis prospectius

d'una sola branca, però falta informació sobre la seva seguretat en pacients sobrevivents de CM.

La DHEA és una prohormona esteroide situada en mig de la cadena de biosíntesi de estradiol a partir de la testosterona. Els comprimits de prasterona (DHEA) són un fàrmac relativament nou, que ha estat recentment aprovat per la U.S. Food and Drug Administration (FDA) pel tractament de la dispareúnia. L'administració de DHEA a nivell vaginal sembla provocar una activació dels receptors d'estrògens i d'andrògens de les tres capes de l'epiteli vaginal. Estudis de fase III demostren que l'ús de DHEA vaginal no incrementa els nivells sèrics de DHEA ni estrògens al cap d'un ús de 12 setmanes. L'eficàcia de la prasterona millorant el SGUM ha estat demostrada comparant amb placebo, tant reduint el pH vaginal, millorant els símptomes clínics i incrementant el gruix epitelial, però no hi ha estudis utilitzant aquesta molècula en pacients sobrevivents de CM.

Un fet que ens sorprèn fent l'avaluació dels diferents estudis sobre les opcions terapèutiques per SGUM en pacients sobrevivents de CM, és el fet de la baixa qualitat dels estudis, i el fet de que la valoració de milloria i canvis respecte el SGUM després dels diferents tractaments, és molt habitualment utilitzant variables d'avaluació subjectives.

Aquest fet ens porta a fer una revisió sistemàtica sobre tots els estudis disponibles sobre l'ús del làser vaginal, no només en pacients sobrevivents de CM, per valorar la qualitat dels estudis que refereixen que és una teràpia eficaç per tractar el SGUM (article adjunt al final de la introducció):

2. **Mension E**, Alonso I, Tortajada M, Matas I, Gómez S, Ribera L, Anglès S, Castelo-Branco C. Vaginal laser therapy for genitourinary syndrome of menopause - systematic review. *Maturitas*. 2022 Feb;156:37-59.
IF: 5.517, Q1 Obstetricia I Ginecologia.

En aquesta revisió, descrivim que respecte el làser vaginal, els primers estudis per valorar l'efectivitat del làser vaginal van ser realitzats al 2014, utilitzant el làser de CO₂, sent aprovat per la FDA com a teràpia per el SGUM. Aquesta teràpia aparentment millora la vascularització de la mucosa vaginal estimulant la remodelació del teixit connectiu subjacent, que engruixeix l'epiteli vaginal i li permet acumular glicogen. Degut a l'acúmul de glicogen es restaura la flora vaginal i disminueix el pH vaginal, millorant els símptomes del SGUM causats pel dèficit estrogènic.

Segons *Salvatore S et al*, un 85% de les pacients amb SGUM recuperaven la seva activitat sexual normal a les 12 setmanes de la teràpia¹³⁻¹⁴. Tot i això, hi ha controvèrsia a la

literatura donat que han aparegut recentment estudis aleatoritzats avaluant el làser vaginal amb resultats contradictoris.

Després de realitzar les cerques sistemàtiques i valorar la qualitat dels estudis, vam arribar a la conclusió de que la evidència de les opcions terapèutiques era limitada, per la qualitat dels estudis disponibles, i per la falta de valoració de criteris objectius avaluant la milloria de les pacients a nivell de eficiència. Això, ens va dur a redactar un comentari editorial preguntant-nos si estàvem avaluant correctament el SGUM (article adjunt al final de la introducció):

3. Castelo-Branco C, **Mension E**. Are we assessing genitourinary syndrome of menopause properly? Climacteric. 2021 Dec;24(6):529-530.

IF: 3.005, Q2 Obstetricia I Ginecologia.

En aquest comentari posàvem en dubte la qualitat de les variables utilitzades per avaluar el SGUM en els estudis actuals. Per tal de valorar de quines eines de valoració del SGUM disposàvem i la seva qualitat, vam redactar el següent manuscrit (article adjunt al final de la introducció):

4. **Mension E**, Alonso I, Tortajada M, Matas I, Gómez S, Ribera L, Ros C, Anglès-Acedo S, Castelo-Branco C. Genitourinary Syndrome of Menopause Assessment Tools. J Midlife Health. 2021 Apr-Jun;12(2):99-102.

IF: 0.0 Obstetricia I Ginecologia.

En aquesta revisió, abordem l'evidència i objectivitat de les variables més utilitzades en la majoria d'estudis actuals avaluant el SGUM. S'observa que una de les variables més utilitzada com a teòricament objectiva és el *Vaginal Health Index* (VHI), encara que, si tenim en compte què avalua realment, en la nostra revisió la considerem segons el nostre punt de vista com a majoritàriament subjectiva. Per altra banda, altres variables objectives recomanades per avaluar el SGUM per part de la mateixa FDA com són l'índex maduratiu vaginal (VMI) o el pH vaginal, són molt menys usades en els estudis trobats en les cerques sistemàtiques. Com a conclusió, es ressalta la necessitat de trobar mètodes objectius no invasius capaços de valorar el grau de SGUM i el grau de resposta obtinguda a les diferents teràpies.

Article revisió número 1:

Mension E, Alonso I, Castelo-Branco C. Genitourinary Syndrome of Menopause: Current Treatment Options in Breast Cancer Survivors - Systematic Review. Maturitas. 2021 Jan;143:47-58.

IF 5.517, Q1. Obstetrícia i Ginecologia.



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Review

Genitourinary Syndrome of Menopause: Current Treatment Options in Breast Cancer Survivors – Systematic Review

Eduard Mension¹, Inmaculada Alonso, Camil Castelo-Branco^{1,*}*Clinic Institute of Gynecology, Obstetrics and Neonatology, Faculty of Medicine-University of Barcelona, Hospital Clinic-Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain*

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ABSTRACT

Breast cancer survivors (BCS) usually receive treatments which lead to persistent oestrogen suppression, which may cause atrophic vaginitis in a large proportion of these women. The most effective treatments for vulvovaginal atrophy (VVA) are based on local oestrogen therapy. However, these treatments are restricted in BCS due to the controversy over their use in women who had hormone-dependent tumours. Therefore, it is common to find untreated symptoms that affect sexual function and quality of life in BCS, thereby leading to the discontinuation of anti-oestrogenic treatments. This systematic review aims to discuss the current treatment options available for the genitourinary syndrome of menopause (GSM) in BCS.

A comprehensive literature search was conducted electronically using Embase and PubMed to retrieve studies assessing treatment options for GSM or VVA in BCS up to April 2020. Studies evaluating treatments in different BCS cohorts were excluded.

A total of 29 studies were finally included in the review. Non-hormonal treatments are the first-line treatment for VVA, but when these are not effective for symptom relief, other options can be considered, such as local oestrogen, erbium laser or CO₂ laser and local androgens. The present data suggest that these therapies are effective for VVA in BCS; however, safety remains controversial and a major concern with all of these treatments.

1. INTRODUCTION

1.1. Rationale

The overall survival of women with breast cancer (BC) has increased over the last decades, despite the increasing prevalence of this disease. This improved survival is largely due to advances in the current therapies, especially since the introduction of anti-HER2 targeted drugs [1]. Many breast cancer survivors (BCS) are still of premenopausal age and have the potential risk of receiving antineoplastic treatments that may affect ovarian function or anti-oestrogenic treatments that mimic a postmenopausal state [2]. This hypoestrogenic state can lead to climacteric symptoms inducing significant alterations in their quality of life [3] thereby affecting compliance with adjuvant therapies [4,5,6]. Many BCS are already in a postmenopausal state at diagnosis, and the treatments used to treat BC worsens their basal hypoestrogenic state, which enhances associated problems.

One of the main manifestations of hypoestrogenism is vulvovaginal

atrophy (VVA), which is included in the new concept of genitourinary syndrome of menopause (GSM) [7]. This syndrome affects up to 50% of postmenopausal women [8] but is even more frequent in young patients receiving anti-oestrogenic or antineoplastic drugs [9]. These symptoms are often under-diagnosed and under-treated due to underreporting by the patients and limited awareness of professionals [10].

Due to dependence on oestrogen, the vaginal epithelia can progress to VVA because of anti-oestrogenic treatments or natural menopause. Lack of treatment usually leads to a worsening of VVA over time [11]. Many BCS present hormonal tumours for which there are limited therapeutic strategies. Non-hormonal therapies are the first-line treatment in VVA. However, while being safe, they only have mild efficacy and usually only provide short-term improvement. Other options include local oestrogen therapy, vaginal laser therapy and local androgens, that seem to be effective although there are concerns about safety. The possible increased risk of recurrence with the use of local oestrogen therapy has been a major concern among healthcare providers. To date, there is no consensus on how to treat moderate-severe VVA in BCS.

* Corresponding author at: Clinic Institute of Gynecology, Obstetrics and Neonatology, Hospital Clinic, Villarroel 170, 08036, Barcelona, Spain.

E-mail address: castelobranco@ub.edu (C. Castelo-Branco).

¹ Both authors contributed equally to the work.

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1.2. Objective

There is an evident need for agreement on which treatments are safe and can be used in BCS with GSM. The aim of this systematic review was to reassess therapeutic interventions with demonstrated efficacy in patients treated for BC presenting VVA and the current evidence of their safety profiles.

2. MATERIAL AND METHODS

This review was conducted and reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [12].

2.1. Eligibility Criteria

Observational studies evaluating treatment options for VVA in women with BC were deemed eligible. Both prospective and retrospective designs, as well as case series, were acceptable, and interventional studies [randomized-controlled trials (RCT), and non-randomized studies] assessing treatment options in these cohorts were also included.

Publications for which the full text of the article was available and with data on GSM treatment in BCS were included. All types of clinical studies were accepted.

Articles about only one specific therapeutic option were included. Reviews and metaanalyses were excluded.

2.2. Information Sources and Search Strategy

In April 2020, a search in Embase and the PubMed library for all dates up to that time was performed to identify potentially relevant publications related to VVA or GSM. Reference lists from studies initially selected and from existing reviews were also searched to identify any additional relevant studies not identified by the electronic searches.

The search terms used were: “Genitourinary Syndrome of Menopause” or “Vulvovaginal Atrophy” or “Atrophic Vaginitis” and “Breast Cancer”. No limits were set in terms of time of publication or study design. No language restriction was used.

2.3. Study selection

Study selection was made according to the content of the abstract and reviewed by a single reviewer (EM). After the first selection, publications not specifically focused on BCS were dismissed. Another two reviewers (IA, CCB) evaluated the discarded articles to confirm their irrelevance. The abstracts of the remaining articles were re-evaluated and any designated for exclusion were reviewed and confirmed by a second reviewer (CCB). Three reviewers (EM, IA and CCB) extracted the data from the initially selected articles using a predefined protocol (Information was gathered based on the characteristics of the participants in the trial, the intervention and the recording of the results). The full text of these articles was obtained and reviewed by all reviewers to ensure they met inclusion criteria. Discrepancies were resolved by consensus or consultation if no agreement could be reached. Finally, CCB checked any possible mistake occurring during the first extraction of data. The articles in which the full text of the publication was not available were also discarded. All types of clinical studies were included.

2.4. Data Items

Pre-specified outcomes using different treatment options in BCS were extracted including: the number of patients included, the median age, study design, follow-up time, patient characteristics, interventions, outcomes, use of hormonal adjuvant therapy, hormonal receptor status, and results.

2.5. Risk of bias in individual studies

The clinical studies were pooled and independently rated for quality by two reviewers (EM, CCB) using the Study Quality Assessment Tools developed by the National Heart, Lung and Blood Institute (NHLBI) [13]. Depending on the study design, different sets of criteria were used to assess the risk of bias in each study. Quality rates (‘good’, ‘fair’, ‘poor’) were based upon the judgement of the reviewers (EM, CCB) and clarified for studies that we considered to be of ‘poor’ methodological quality. Disagreements were discussed with a third reviewer (IA) until consensus was reached.

3. RESULTS

3.1. Study selection

On the first search, 156 items were found with the mentioned Key Words. Those not corresponding to the study selection criteria were excluded.

After the study filter, 29 studies were selected, being focused on a specific treatment for GSM or VVA in BCS.

Full texts and required data were available in 24 articles: 8 studies evaluated local oestrogen therapy, 7 studies reported their conclusions about vaginal laser therapy, 3 summarized the effects of vaginal androgens, and the remaining 6 studies were related to non-hormonal options (excluding laser therapy) (Fig. 1).

3.2. Study characteristics

The number of patients and the mean age of the women included in each study were reported, as well as the design, duration and principal interventions and outcomes for each study. Parameters related to BC were recorded including hormonal receptor status and adjuvant therapy.

3.3. Study findings

3.3.1. NON-HORMONAL TREATMENTS

With regard to this group, the different options were divided into two subgroups: classic moisturizers and lubricants, based on aqueous gel, and innovative options including new molecules such as autologous platelet-rich plasma (A-PRP) combined with hyaluronic acid (Table 1).

The first subgroup included the randomised, double blinded trial by Lee and the prospective observational study by Chatsipirois, which respectively evaluated the effect of a pH-balanced gel versus placebo and the effect of the administration of oil-in-water emulsion. Both concluded improvements in subjective sensation of dryness and dyspareunia, respectively and the Visual Analogue Scale (VAS) for pain.

The second subgroup included two other prospective, randomised, double blinded trials, evaluating new options such as capsules including *Lactobacillus* for the maintenance of the vaginal microbiota, which showed to be useful [14], and aqueous lidocaine at 4% demonstrating improvement in the VAS for pain.

Other recent options were A-PRP, demonstrating symptomatic improvement in a Phase 2 clinical trial [15] and polyacrylic acid, which seemed to be superior than lubricants according to a randomised trial evaluating the Female Sexual Function Index (FSFI) [16].

3.3.1.1. Efficacy. According to the data of the 6 studies including treatment efficacy, it was concluded there were improvements in symptoms due to VVA, despite all the trials being based on subjective variables of improvement such as the FSFI, the VAS or the Vaginal Health Score (VHS) for pain. No objective changes in vaginal mucosa were assessed.

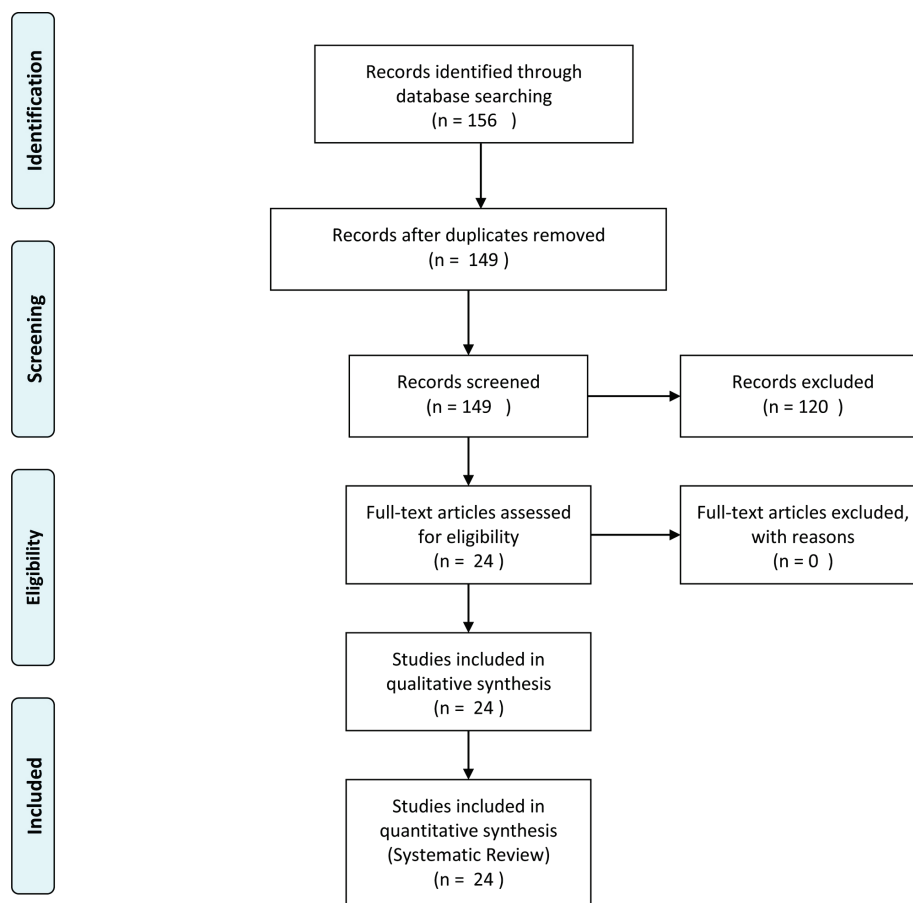


Fig. 1. PRISMA Flowchart diagram of study selection.

3.3.1.2. *Safety*. None of the trials reviewed included hormonal receptor status or adjuvant treatment on BCS. Hormone levels were not determined, and there was no information about BC recurrence after treatment.

3.4. LOCAL OESTROGEN THERAPY

The 8 trials on local oestrogen therapy were divided into those which considered this therapy to be ineffective in relation to the risk of BC recurrence [17,18], and those which concluded that vaginal oestrogen therapy may increase sexual hormone levels in serum [19–23] (Table 2). The study of Biglia et al did not describe any results on safety [24].

The first group included two retrospective, cohort studies following and evaluating BC recurrence in more than 13,000 patients for up to 5.5 years.

The second group was composed of prospective studies evaluating serum hormone levels among BCS treated with local oestrogen. All the

results demonstrated a rise in hormone levels or higher serum levels compared to placebo when BCS were treated with local oestrogens for up to 12 weeks of follow-up.

3.4.1. Efficacy

According to the trials reviewed, therapies using local oestrogen in BCS showed an improvement in symptoms.

3.4.2. Safety

There is evident controversy in relation to this subject, with the different studies presenting contradictory outcomes.

3.5. VAGINAL TESTOSTERONE

Up to 2020, three clinical trials evaluating the safety and efficacy of intravaginal testosterone (IVT) in BCS were found [25–27] (Table 2). The longest follow-up was of 28 weeks, in a double-blind randomised

Table 1
Non-hormonal Treatments. ER: Oestrogenic Receptors, BC: Breast Cancer, VAS: Visual Analogue Scale, BCS: Breast Cancer Survivors, A-PRP: Autologous platelet-rich plasma, VHI: Vaginal Health Index, VVA: Vulvovaginal Atrophy, QA: QA: Quality assessment (Good, Fair, Poor risk of bias respectively).

Study / Year	n	Median Age	Design	Follow up	Participants	Intervention	Outcomes	Hormonal adjuvant therapy	Receptor status (ER+)	Results	Conclusion	QA
Classic moisturizers and lubricants:												
44 gel												
Lee YK et al., ACOG, 2011 [56]	42	45.8	Randomised Controlled Trial, Double Blinded	12 weeks	Patients with diagnosed BC managed with chemotherapy or hormonal therapy.	pH balanced gel vs. placebo for 12 weeks	Evaluated vaginal dryness and dyspareunia	Not reported	Not reported	There was a significant difference in the variable dryness with pain ($p = 0.001$), and in variable dyspareunia ($p = 0.04$). The difference in symptom frequency before-after the treatment was significant ($p < 0.0001$).	Vaginal pH balanced gel could relieve vaginal symptoms.	Good
Chatsipoulos et al. PLoS One, 2019 [54]	128	52	Open, prospective, multicentre, observational study.	28 days	Patients with diagnosed BC managed with chemotherapy or hormonal therapy.	Administration of oil-in-water emulsion during 28 days	Changes in subjective symptoms. Safety and tolerability.	Not reported	Not reported	The difference in symptom frequency before-after the treatment was significant ($p < 0.0001$).	This treatment seems to improve VVA symptoms with a short treatment.	Fair
Innovative preparations:												
Goetsch et al. Journal of Clinical Oncology, 2015 [55]	23	56.6	Randomised Controlled Trial, Double Blinded	4 weeks	Patients with diagnosed BC.	4% aqueous lidocaine vs. placebo 3 minutes before vaginal penetration.	Evaluated pain in VAS scale	Not reported	Not reported	Significant differences between groups ($p = 0.007$).	It is a safe option for painful intercourse.	Good
Marschalek et al. Breast Care, 2017 [14]	11	59	Randomised Controlled Trial, Double Blinded Pilot study	2 weeks	Patients with diagnosed BC managed with chemotherapy or hormonal therapy.	Vaginal lactobacillus capsules vs. placebo.	Nugent score	Not reported	Not reported	Differences between groups: 4.73 vs. 4.0 ($p = 0.038$).	Lactobacillus improves microflora in BCS.	Good
Juliano PT et al. Climacteric, 2016 [16]	25	50.5	Randomised trial.	30 days	Patients with diagnosed BC treated with tamoxifen.	Polyacrylic acid vs. lubricant	Female Sexual Function Index	Not reported	Not reported	Both showed improvement. Acid: 96 to 24% ($p = 0.0001$) Lubricant: 88.9 to 55.6% ($p = 0.0027$)	Polyacrylic acid was superior to lubricant.	Good
Hersant et al. Menopause, 2018 [15]	20	60.8	Prospective, comparative (before/after) pilot study	6 months	Patients with diagnosed BC.	A-PRP and evaluated at 0,1,3 and 6 months.	Evaluated vaginal mucosa changes using Vaginal Health Index.	Not reported	Not reported	Significant increase 10.7 to 20.75 ($p < 0.0001$) at 6 months.	A-PRP improves vaginal mucosa in 6 months treatment according VHI criteria.	Fair

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Table 2
Sexual Steroids: Oestrogens and Testosterone. ER: Oestrogen Receptors, HR: Hazard Ratio, VET: Vaginal Oestrogenic Therapy, RR: Risk Ratio, BC: Breast Cancer, AI: Aromatase Inhibitors, E: Oestrogen, BCS: Breast Cancer Survivors, VHI: Vaginal Health Index, FSH: Female Sexual Function Index, VVA: Vulvovaginal Atrophy, TMX: Tamoxifen, TST: Testosterone, QA: Quality assessment (Good, Fair, Poor risk of bias respectively).

Study / Year	n	Median Age	Design	Follow up	Participants	Intervention	Outcomes	Hormonal adjuvant Therapy	Receptor status (ER+)	Results	Conclusion	QA
Dew et al. <i>Clinical Cancer Research</i> , 2003 [17]	69	53.8	Retrospective Cohort	5.5 years	69 confirmed BC patients with VVA, 1403 confirmed BCS without VVA	Estrid 0.5 mg cream and pessaries (n = 33), 48% Estradiol 25 µg tablets (n = 33), 48%	Disease-free Interval Recurrence	48% used tamoxifen	Positive in 12/33 (36%)	Disease free interval HR = 0.57(95% CI:0.20-1.56, p = 0.28) (9%) versus 330 (22.4%)	VET does not seem to be associated with increased RR of BC.	Poor
Kendall et al. <i>Annals of Oncology</i> , 2005 [22]	7	52	Prospective before-after analysis	12 weeks	Patients on adjuvant AI therapy for BC	Estradiol 25 mg daily for 2 weeks	Measure estradiol	All women with ALA, anastrozole, letrozole or exemestane	Not reported.	2-week analysis: 83% estradiol rise, 10 weeks: 66% E rose, 83% improved clinical status	Anastrozole seems to better control estradiol elevation when treated with VET	Fair
Biglia et al. <i>Gynecological Endocrinology</i> , 2010 [24]	31	54 VET, 46 Replens	Prospective	12 weeks	Postmenopausal BCS, 18 receiving VET, 8 receiving moisturizers	Estrid 0.25 mg Estradiol 12.5 mg 2.5 g Replens	Clinical improvement Objective vaginal mucosa evaluations	No women was using AL, anastrozole, tamoxifen and GnRH analogues were allowed.	72% Estradiol	Improved symptoms in both VET groups (p = 0.02, p = 0.01)	VET is effective in improving symptoms and objective evaluations in BCS.	Good
Pfeiler et al. <i>Clinical Cancer Research</i> , 2011 [23]	6	65	Prospective before-after analysis	4 weeks	Patients on adjuvant AI therapy for BC	0.5 mg vaginal estradiol daily for 2 weeks.	Clinical improvement (VAS).	All women receiving anastrozole.	All women	No change in estradiol. Increased FHS and LH.	Increase in FHS and LH may indicate systemic estradiol effects.	Fair
Le Ray et al. <i>Breast Cancer Res. Treat.</i> , 2012 [18]	13.4/79	63.7	Retrospective cohort study-nested case-control analysis	3.5 years	917 BC recurrence cases, 8885 controls	Vaginal Cream and tablets containing estrogen	Recurrence	All women with TAM or AI	All women with ER+.	Recurrence RR: 0.78 (95% CI: 0.48-1.25)	Use of VET is not associated with increase in BC recurrence in those treated with TMX or AL.	Poor
Wills et al. <i>Journal of Oncology practice</i> , 2012 [19]	24 BCS, 24 Controls	60 BCS, 68 Controls	Prospective clinical study	12 weeks	Patients on adjuvant AI therapy or SERM for BC	Vaginal Estradiol 25 ng	E2 serum levels	All women with SERM or AI	Women with ER+ or high risk BC	E2 levels were significantly greater in VET group than in controls.	VET treatment increases E2 levels. Should be used with caution.	Fair
Donders et al. <i>Breast Cancer Res. Treat.</i> , 2014 [20]	16	57.0	Open label bicentric phase I pharmacokinetic study.	12 weeks	Patients on adjuvant AI therapy for BC	0.03 mg Estradiol + Lactobacillus.	Clinical improvement (VAS).	All women with AL, letrozole or anastrozole.	All women	No change in E1 and E2. Small transient increase in E3.	E3 + Lactobacillus is safe in BC patients and improves symptoms.	Good
	76	56				E2 serum levels			All women	100% improvement in	(continued on next page)	Good

Table 2 (continued)

Study / Year	n	Median Age	Design	Follow up	Participants	Intervention	Outcomes	Hormonal adjuvant Therapy	Receptor status (ER+)	Results	Conclusion	QA
Melisko et al. JAMA Oncology, 2016 [21]			Randomised non-comparative study	12 weeks	Patients on adjuvant AI therapy for BC	Estradiol ring 7.5 µg vs. Testosterone cream at 1% concentration: 1.5 mg/week	VHI	All women with AI		Transient E2 increase in 11% Estradiol group and 12% TST group. Persistent E2 rise in 0% Estradiol group and 12% TST group. Sexual improvement in both groups. E2 levels remained suppressed Symptom improvement.	Transient increase in E2 that finally reached normal levels. Meets the primary safety endpoint.	
Whitby et al. The Oncologist, 2011	21	56	Phase I/II pilot study Before-After study	8 weeks	Patients on adjuvant AI therapy for BC	TST cream for 28 days 300/150mg	E2 and TST levels. Clinical improvement.	All women with AI.	Not reported.		They demonstrate clinical efficacy and tolerance.	Good
Dahir et al. Sexual Medicine, 2014 [25]	13	59.7	Pilot study Before-After study	8 weeks	Patients on adjuvant AI therapy for BC	TST cream for 28 days 300mg	FSFI	All women with AI. Anastrozole, exemestane or letrozole.	92% ER + 84% PR +	Clinical response in post-treatment test.	Improvement in FSFI scores.	Fair
Davis et al. J Clin Endocrinol Metab, 2018 [27]	44	56.4	Double-blind, randomised, placebo-controlled trial.	26 weeks	Patients on adjuvant AI therapy for BC	TST cream for 26 weeks 300 ng compared with placebo.	FSFI	All women with AI.	Not reported.	Significant difference in favour of TST group. Change: -10.28 (95% CI: -18.89 to -1.67)	TST improves sexual test items compared to placebo.	Good

Table 3
Laser Therapy. ER: Oestrogenic Receptors, HR: Hazard Ratio, VAS: Visual Analogue Scale, BC: Breast Cancer, AI: Aromatase inhibitors, VHI: Vaginal Health Index, VVA: Vulvovaginal Atrophy, TMX: Tamoxifen, FSFI: Female Sexual Function Index, QA: Quality assessment (Good, Fair, Poor risk of bias respectively).

Study / Year	n	Median Age	Design	Follow up	Participants	Intervention	Outcomes	Hormonal adjuvant Therapy	Receptor status (ER+)	Results	Conclusion	QA
Pagano et al. Menopause, 2016 [43]	26	42	Observational retrospective study	90 days	Patients on adjuvant TMX or AI therapy for BC	3 sessions of Fractional Microablative CO2 Laser every 30 days.	Clinical improvement: VAS scale – Objective VHI.	All women	All women.	Significant improvement of clinical variables.	The treatment seems to be effective and with good tolerance.	Fair
Pieralli et al. Arch GynecolObstet, 2016 [46]	50	53.3	Prospective Before-After study	11 months	Patients with diagnosed BC.	3 sessions of Fractional Microablative CO2 Laser every 30 days.	Clinical improvement: VAS scale – Objective VHI.	4% AI 46% TMX 56% Not adjuvant therapy	Not reported.	Improvement in VAS after 3 sessions (p < 0.0001).	The treatment seems to be feasible and effective.	Fair
Pagano et al. Menopause, 2018 [42]	82	44	Observational retrospective study	90 days	Patients with diagnosed BC.	3 sessions of Fractional Microablative CO2 Laser every 30 days.	Clinical improvement: VAS scale	74% Homonal adjuvant treatment: 61% AI - 39% TMX	Not reported.	Improvement in VAS after 3 sessions (p < 0.001).	The treatment seems to be effective.	Fair
Gambaciani et al. Menopause, 2017 [50]	43	50.8	Pilot study Before-After study	18 months	Patients with diagnosed BC.	3 sessions of Vaginal Erbium Laser every 30 days.	Clinical improvement: VAS scale – Objective VHI.	Not reported.	Not reported.	Last follow-up vs. Basal VAS: significant reduction (p < 0.01). Last follow-up vs. Basal VHI: significant reduction (p < 0.01).	The treatment seems to be effective.	Fair
Mathes et al. Journal of Cancer Research and Clinical Oncology, 2018 [48]	16	71	Retrospective study.	6 weeks	Patients with diagnosed BC and surgery for pelvic organ prolapse.	1 session of Vaginal Erbium YAG Laser.	Clinical improvement: VAS scale	Not reported.	Not reported.	Last follow-up vs. Basal VHI: significant reduction (p = 0.01).	The treatment seems to be effective.	Poor
Areas et al. Menopause, 2019	24	53.7	Open, prospective study	4 months	Patients with diagnosed BC.	3 sessions of Vaginal Erbium YAG Laser every 30 days.	Clinical and Sexual improvement: VAS scale – Objective VHI.	Not reported.	Not reported.	Improvement in clinical and sexual scores. Last follow-up vs. Basal VHI: significant reduction (p < 0.001).	The treatment seems to improve sexual function and vaginal atrophy.	Fair
Pearson et al. Breast Cancer Research and Treatment, 2019 [44]	26	56	Single-arm pilot study Before-After study	12 weeks	Patients with diagnosed BC.	3 sessions of Fractional Microablative CO2 Laser every 30 days.	Clinical and Sexual improvement: VAS scale and FSFI	96% Homonal Therapy	Not reported.	Improvement in VAS after 3 sessions (p < 0.001). Improvement in FSFI after 3 sessions (p < 0.001).	The treatment seems to improve sexual function and vaginal atrophy.	Fair

Table 4
Quality Assessment of Controlled Intervention Studies.

CRITERIA	Lee YK et al	Goetsch et al	Marschalek et al	Juliato PT et al	Melisko et al.	Davis et al.
1. Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT?	YES	YES	YES	YES	YES	YES
2. Was the method of randomization adequate (i.e., use of randomly generated assignment)?	YES	YES	YES	YES	YES	YES
3. Was the treatment allocation concealed (so that assignments could not be predicted)?	YES	YES	YES	YES	YES	YES
4. Were study participants and providers blinded to treatment group assignment?	YES	YES	YES	NO	NO	YES
5. Were the people assessing the outcomes blinded to the participants' group assignments?	YES	YES	YES	NO	NO	YES
6. Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)?	YES	YES	YES	YES	NR	YES
7. Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?	YES	YES	NR	YES	YES	YES
8. Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?	YES	YES	NR	NO	YES	YES
9. Was there high adherence to the intervention protocols for each treatment group?	YES	YES	NR	YES	YES	YES
10. Were other interventions avoided or similar in the groups (e.g., similar background treatments)?	YES	YES	YES	YES	YES	YES
11. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	YES	YES	YES	YES	YES	YES
12. Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?	YES	YES	NR	YES	NR	YES
13. Were outcomes reported or subgroups analyzed prespecified (i.e., identified before analyses were conducted)?	YES	NR	NR	NR	NR	NR
14. Were all randomized participants analyzed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis?	NR	NR	NR	NR	NR	NR

*CD, cannot determine; NA, not applicable; NR, not reported.

trial, comparing IVT to placebo, and this study concluded that the sexual quality of life improved. Only one clinical trial measured serum estradiol levels, which remained suppressed during the 8-week follow-up.

3.5.1. Efficacy

The conclusions of the efficacy of the 3 trials found were positive, as all the studies agreed that IVT improves subjective variables of quality of life.

3.5.2. Safety

Data on safety were only reported in one trial evaluating serum estradiol levels, which despite presenting a slight increase, remained

within the normal range for 8 weeks.

3.6. FRACTIONAL CO₂ LASER / ERBIUM LASER

Seven recent studies were found on this topic, including 2 single-arm pilot studies, 3 retrospective cohort studies and two prospective, open, cohort studies (Table 3). A total of 267 patients were recruited. The variables evaluated were subjective improvement of VVA symptoms using the FSFI, the VHI and the VAS.

All the trials agreed that laser treatment seems to be safe and effective, despite the lack of objective measurements of vaginal mucosa changes before-after treatment, and no variables related to recurrence or

Table 5
Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.

CRITERIA	Dew et al.	Biglia et al.	Le Ray et al	Wills et al.	Pagano et al 2016	Pagano et al 2018	Mothes et al.	Areas et al.
1. Was the research question or objective in this paper clearly stated?	YES	YES	YES	NO	YES	YES	NO	YES
2. Was the study population clearly specified and defined?	YES	YES	YES	YES	YES	YES	YES	YES
3. Was the participation rate of eligible persons at least 50%?	NR	NR	YES	NR	NR	NR	NR	NR
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	YES	YES	YES	YES	YES	YES	YES	YES
5. Was a sample size justification, power description, or variance and effect estimates provided?	NO	YES	YES	NR	NO	NO	NO	NO
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	YES	YES	YES	YES	YES	YES	YES	YES
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	NO	YES	NO	YES	YES	YES	YES	YES
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	NO	YES	NO	YES	YES	YES	NO	YES
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	YES	YES	NO	YES	YES	YES	NO	YES
10. Was the exposure(s) assessed more than once over time?	NO	YES	NO	NO	YES	YES	NO	YES
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	YES	YES	NO	YES	YES	YES	YES	YES
12. Were the outcome assessors blinded to the exposure status of participants?	NO	NO	NO	NO	NO	NO	NO	NO
13. Was loss to follow-up after baseline 20% or less?	NR	NO	NR	NR	NR	NR	NR	NR
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	NR	YES	NO	NR	NO	NO	NO	NO

*CD, cannot determine; NA, not applicable; NR, not reported.

Table 6
Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group.

Criteria	Chatsipirois et al	Hersant et al.	Pfeiler et al.	Donders et al.	Kendall et al.	Whiterby et al	Dahir et al	Gambacciani et al.	Pearson et al	Pieralli et al
1. Was the study question or objective clearly stated?	YES	YES	YES	YES	NO	YES	YES	YES	YES	YES
2. Were eligibility/selection criteria for the study population prespecified and clearly described?	YES	YES	YES	YES	NR	YES	YES	YES	YES	YES
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
4. Were all eligible participants that met the prespecified entry criteria enrolled?	YES	YES	YES	YES	NR	YES	YES	YES	YES	YES
5. Was the sample size sufficiently large to provide confidence in the findings?	CD	CD	NR	YES	NR	YES	NR	NR	NR	NR
6. Was the test/service/intervention clearly described and delivered consistently across the study population?	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	NO	NO	NO	NO	NO	YES	NO	NO	NO	NO
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	NR	NR	NR	NR	NR	NR	NR	YES	YES	YES
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	NO	YES	NO	YES	YES	YES	NO	YES	YES	YES
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

*CD, cannot determine; NA, not applicable; NR, not reported.

serum estradiol measurements were studied.

3.6.1. Efficacy

All the studies concluded that laser therapy improves VVA symptoms in short-term follow-up. None of the studies was a clinical assay with two arms comparing laser versus placebo, but rather compared the same patients before-after treatment evaluating subjective variables.

3.6.2. Safety

The studies evaluated reported no side effects, but no variables regarding BC recurrence or serum estradiol levels were available.

4. DISCUSSION

4.1. Summary of evidence

According to international guidelines, non-hormonal therapies are the first-line treatment for mild-moderate VVA. Therefore, these are also the first-line treatments in BCS [28]. Among non-hormonal therapies there are multiple options to treat symptoms of dyspareunia and daily wellbeing. However, these compounds do not reverse atrophy, and neither do they improve vaginal epithelium characteristics, and hence,

the improvement observed is temporary and short term. These therapies are usually lubricants and moisturizer agents composed by non-hormonal substances, mainly based on water, silicone or vegetable oil. Water-based agents have fewer side effects compared to oil-based products [29].

The main limitation of non-hormonal therapies is the short-term efficacy. Among the trials included in this systematic review, 85% described efficacy with a 30-day follow-up or less. Further studies evaluating longer follow-up periods would be of interest.

The lack of data on hormonal receptor status and adjuvant treatments in the studies reviewed, and the absence of hormone levels and information about BC recurrence after treatment, did not allow these trials to make conclusions in relation to safety. Nonetheless, from general population trials it can be extrapolated that there is a low risk of potential side effects from non-hormonal therapies used for climacteric symptoms [30].

Since hypoestrogenism is the cause of VVA, an oestrogen-based treatment might be the most reasonable therapy. Moreover, oestrogen-based local treatments have proven to be the most effective, since they directly eliminate the cause of atrophy. These treatments act on the vaginal mucosa increasing its thickness, re-vascularizing the epithelium and increasing the number of superficial cells, thereby decreasing

vaginal pH and restoring the vaginal flora, leading to symptom improvement [31].

Vaginal oestrogen absorption is variable and largely depends on the state of the vaginal mucosa. In an atrophic mucosa, there is increased absorption, decreasing the level of oestrogen absorbed once there is improvement in epithelium quality [32]. Different methods of vaginal administration (creams, pessaries, rings, gels...) seem to be equivalent for improving VVA symptoms. The oestrogen most commonly used in these preparations is estriol, which is a weak action oestrogen.

Nowadays, there is some reluctance to use local oestrogen therapy in BCS because of its potential adverse effects, with up to 70% of oncologists managing BCS not prescribing hormone therapies. There is fear of interferences with adjuvant treatments, such as tamoxifen or aromatase inhibitors (AI), that may result in an increased risk of BC recurrence [33].

There is consensus in the literature that oestrogen administration in BCS should only be prescribed topically, since systemic administration has shown to increase the risk of BC recurrence [34] and is formally contraindicated by international guidelines (International Menopause Society) [35]. According to the current recommendations of the North American Menopause Society, the use of low dose vaginal oestrogen treatment is accepted if there is no improvement using non-hormonal treatments in BCS with VVA. The lowest effective dose must be administered, starting with the so-called "ultra-low dose", which has shown efficacy in healthy postmenopausal women [36].

Based on the results of this review there is clear controversy on this topic, with some studies reporting no recurrence of BC, while others suggest caution due to a possible increase of serum oestrogen levels that could lead to an increased risk of BC recurrence.

Le Ray et al [18] concluded that there is no evidence of an increase in BC recurrence in cases treated with local oestrogen concomitant with tamoxifen. It is important to highlight the retrospective design and the short follow-up of 3.5 years of this trial, which may be too short to show survival outcomes, and thus, lead to uncertainty regarding the data.

Conversely, other recent prospective studies suggested that the use of vaginal oestrogen therapy may increase serum oestrogen levels [19–21], and therefore a possible increase in the risk of BC recurrence. Nevertheless, Santen et al. reported that increased levels of serum estradiol produced by vaginal oestrogen may not exceed the normal range of postmenopausal serum estradiol [37].

From our point of view, further studies are needed to evaluate these results since vaginal oestrogen absorption is variable and largely depends on the state of the vaginal mucosa. In summary, taking into account the controversy, it is recommended to explain risks and benefits, individualising each case with oncologists before using local oestrogen therapies in BCS [28].

Other options such as intravaginal androgens are gaining attention as a potential treatment for VVA in BCS, since androgen receptors have been identified in the vaginal mucosa [38]. Testosterone administration at the vaginal level seems to trigger an activation of oestrogen and androgen receptors of the vaginal epithelium layers, without activating oestrogen receptors in other tissues due to the lack of aromatase at this level [39,40]. Dehydroxyepiandrosterone (DHEA) is a new androgen that has shown efficacy in improving VVA, but has not yet been studied in BCS [41–43].

In the present review, there is consensus on the efficacy of this therapy, but only one trial evaluated the safety of vaginal androgens. Therefore, there is not enough data to conclude that local androgens are safe options, and further studies are needed to confirm whether systemic estradiol is affected by the use of these therapies.

Another emerging therapy to treat VVA is vaginal laser. The first studies evaluating the effectiveness of vaginal laser were made in 2014, using a fractional microablative carbon dioxide laser, approved by the Food and Drug Administration (FDA) as a therapy for GSM [43–47]. In recent years, another laser, the erbium laser, has also been tested [48–51].

This therapy improves vascularisation of vaginal mucosa by stimulating remodelling of the underlying connective tissue, thereby enlarging the vaginal epithelium and allowing it to accumulate glycogen. The accumulation of glycogen allows restoration of the vaginal flora, a reduction in vaginal pH and improvement of GSM symptoms caused by oestrogen deficit.

The longest follow-up period was that of the pilot study by Gambacciani et al. in which the patients were followed for up to 18 months.

According to Salvatore, 85% of GSM patients regained normal sexual activity at 12 weeks of therapy [46].

Pieralli et al. evaluated 50 cases of BCS presenting VVA and treated with erbium laser. Of these, 52% were satisfied with the results after an average 11-month follow-up time.

Clinical assays evaluating the efficacy and safety of the use of erbium laser are needed, since all the trials included in this review were observational; some were prospective while others were retrospective, with a short follow-up and assessed only subjective variables regarding VVA improvement.

There is a lack of data regarding safety and BC relapse, since no study provided information about recurrence during follow up, and serum estradiol levels were not measured.

Regarding future options, other molecules such as ospemifene were not found in the present search, despite the FDA having approved the use of this drug for dyspareunia and vaginal dryness in 2013. This molecule has mild vaginal oestrogenic potency improving symptoms in a way similar to that of local oestrogen therapy. It also improves bone mineral density and seems to have an anti-oestrogenic effect at the endometrial and breast level [52,53]. Although its efficacy and safety has been demonstrated in healthy patients [54], its use is not currently recommended for BCS receiving ongoing treatment. However, the use of ospemifene in BCS is accepted by the US FDA and the European Medicines Agency after having completed the necessary BC treatment and when remaining disease free.

Another future option that has shown efficacy in improving VVA is DHEA [41], a steroid prohormone with the ability to transform into testosterone and estradiol. It induces local action to the tissue due to its intracrine or intracellular transformation to sexual steroids. The FDA approved DHEA tablets for the treatment of dyspareunia to treat moderate to severe symptoms, but it has not yet been approved for treatment in BCS. Martel et al. described a slight increase in serum estradiol when using intravaginal DHEA, although they concluded that this rise was within the normal range of estradiol concentrations for postmenopausal women [42]. Therefore, longer studies are required to evaluate the safety of this treatment.

This systematic review has several limitations that must be considered (Tables 4, 5 and 6). First, during the data extraction some studies did not provide some of the data items required in the review data extraction form. Second, during the data extraction some items required were found to be assumed or simplified in the original papers. Third, among the studies reviewed, four had a retrospective design, which can lead to worse quality of evidence. Finally, we performed an assessment of risk of bias for individual studies, but bias at an outcome level was not possible due to a lack of information.

5. CONCLUSIONS

In BCS, GSM is the leading cause of sexual dysfunction and severely limits the quality of life of these patients. First-line treatment in BCS presenting mild-moderate VVA is always the use of non-hormonal therapies, which according to the data analyzed, seem to be safe but present limited efficacy and short-term effects. In cases of VVA in BCS refractory to non-hormonal treatment or presenting moderate-severe clinical VVA, the use of local oestrogen therapy is considered and has been demonstrated as being the most effective treatment. Only vaginal oestrogen administration is approved for BCS and always with the use of the lowest possible dose and with consensus between the oncology team

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and the patient including evaluation of the risks and benefits of the use of these treatments. There is disagreement regarding local oestrogen therapies, and thus, there is controversy as to the safety of these treatments. Some studies suggest a possible increase of serum oestrogen levels that may entail an increased risk of BC recurrence. Finally, new lines of treatment such as vaginal laser and vaginal androgens seem to be effective. Clinical studies assessing their safety in terms of evaluation of elevation in serum estradiol levels or relapse are still lacking in BCS.

Contributors

Eduard Mension contributed to design of the study, data search and review, and the writing of the manuscript.

Inmaculada Alonso reviewed the data and the manuscript.

Camil Castelo-Branco contributed to design of the study, data search and review, and the writing of the manuscript.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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Review Article

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LGs nG Ril enGBI pyiG EyaèSBNGC iuNGSteuphngyop⁸Clinic Institute of Gynecology, Obstetrics and Neonatology, Faculty of Medicine-University of Barcelona, Hospital Clinic-Institut d'Investigacions Biomèdiques August Pi i
Sunyer (IDIBAPS), Barcelona, Spain

E R I c n L T c b x (

E h l l R E N l

Keywords:

- eyitps niyGnf Sf y: npC e pMC eypnGS Se
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Background: - eyitps niyGnf Sf y: npC e pMC eypnGS Se - l O VoGy dQve GaneG iC nGnf py tde Hs Gnf pMiM .fi(LVB Gy: GnfotS l etweey qPZD9 Gy: ; j 9 pMmpSC eypnGS SGu wpC ey2 l de utenGs ne SsaaesS tdG vGaiyGu tGSen tdenGnf ops u l e Gy eMotive tneGC eyt Mn- l O SfC mtpC SBl st itS eNfoGf Gy: SGMtf dQve ypt l eey eSGI uSde: Gy: iytengGipyGuSpotiesS: p ypt ey: prSe itS sSe2] eSnte tdQBdene dGS l eey Gy iyoneGS i y tde sSe pM/GaiyGu tGSen tdenGnf aupl Guf pven tde uG: : eoG e2

Objective: l de pl ,eotive pMdis review is tp evGs Qe tde utenGs ne wdiod GSSeSs tde eNfoGf Gy: SGMtf pMde vGaiyGuGSen tdenGnf i y tde tneGC eyt pM l O2

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Results: E tptGupM67 Ss: i eS were [yGnf iyous: e: i y tde review2 l dene were 5j opytrpue: iytengGipy Ss: i eS8% pl SenGipyGuopdnt Gy: onpSSSeotipyGuSs: i eS Gy: 7% l eMneRdenSs: i eS wtdpst G opytrpuaups n2

Conclusion: r GaiyGuGSen SeC S tp iC mpve SopreS py tde r iSs GuEYQpas e l oGue .r El VBxeC Qe l e) s Guxs yotyty cy: e) .xl xGvGy: r GaiyGu8 eGtd cy: e) .r 8 dViy - l O pventde Sdpt tenC 2l Gnf ps topC eS Qe sy: emenpnte: Gy: SdptRenC 2xs niden weuf eS iaye: oiyioGu triGS wtd SdGC RGSen opytrpuaups nS Gy: evGs Qiya pl ,eotive vGnf G uS Qe yee: e: tp mpvi: e tde l eS evi: eyoe py eNfoGf 2

1. INTRODUCTION

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Abbreviations: - l O B- eyitps niyGnf Sf y: npC e pMC eypnGS Se zfl pLbfs Gnf pMiMz r r EBr s upvGaiyGuEtrpndf zxl xdbxeC Qe l e) s Guxs yotyty cy: e) z r 8 Br GaiyGu 8 eGtd cy: e) zx] EBxpp: Gy:] ns a E: C i y iStnGipyzb 8 l h d Bb GipyGu8 eGrBls ya Gy: hupp: cyStits tezNd BNpytrpue: cytenveytyty l ts: i eS r O dBr GaiyGuO Qs nGipy cy: e) Qr GaiyGuO Qs nGipy r Qs ez'] cfi B' npaeyitGu] iStneS cyveytrnf f i s eStipyGnezcNfi F' cl xBytenGipyGuNpySe utGipy py cyotytytytye f i s eStipyGnezcNfi F (EhBoypotytytye f i s eStipyGne (verGotive huG: enz l xF54Bl dpr MnC f i s Gnf (MlM l s nwf z kx) d4j Bkewio xuppn] iSG iutif cy: e) z l' dBl tneSS' niyGnf cyotyF tiyeyoe f i s eStipyGnezc k- d6Bk Gleyt - upl GuC mneSipy pMC mpveC eytz l kTf Bl neol[o kSf odptio T) meneyoeS f i s eStipyGnezb l RBbs C enio R Qiya l oGuez xl' l l B xeC Qe Lpwen' niyGnf l nGnf l f C ntpC S f i s eStipyGne'] d6B' npaeyitGu] iStneS cyveytrnf z / 8 (flpLhRTxB/ pnu 8 eGtd (naGyi*Gipy f i s Gnf pMiMz K8 f i B ' niyGnf SfC ntpC S SoQe l f Kiya' S 8 eGtd f i s eStipyGne2

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l GuGpre et Gu 4j 45 NtC Goterio D6@	q0 .40 Gotive amps nBPj SDGC amps nV	J ps l ueH uy: B nGy: pC1'e: B SDGC F opytrpue: tniGu	N(4 tGsen	kpStC eypnGSeGu wpCey witd aeyltps nlyGf Sf y: npC e pM C eypnGSe .- l O2 / pCey witd af yeoppaio oGyoeS witd : f StGues yIG Gy: Q pn vGaiyGu : rf yeSS	P SeSSipyS pM vGaiyGuVStGCG tGsen	r El xl xc ' j d6	7 C pytdS	EuuodGyaeS were iy MvnpM tde Gotive amps m2	N(4 tGsenops u l e mpmpSe: GS Gy eMotive GtenyGlive treGQC eyt	b OOD2
fis ioY EO 4j 45 OGs nrtGS Dq@	50 .5j W treQC eyt OV6dGC V	kiptBC s utiF iyStits tipyGu nGy: pC1'e: SDGC F opytrpue: tniGu	xnGtopyGu C ionpGt uGive N(4 tGsen	kpStC eypnGSeGu wpCey witd - l O : vGaiyGu: rf yeSS pn s nlyGf Sf C mpC SV / pCey witd af yeoppaio oGyoeS witd : f StGues yIG Gy: Q pn vGaiyGu : rf yeSS	P SeSSipyS pM MotipyGuN(4 tGsen ReGutGsen vS SDGC tGsen	r El r GaiyGu ESseSSC eyt l opneV xl xc ' j d6 r 8 c	7 weeYS	b p : iMweyoeS iy iyoneGSe pM r El Gy: ' j d6 l tGStioGu : iMweyoeS iy xl xc l etweey l ptd GtC SB iyoneGStya iy treQC eyt amps m2 b p : iMweyoeS iy r 8 d2 b p G venfe eveytS cNdfi P' c l xVb p Sayil oGyt : iMweyoe pM mpSttreQC eyt tpGtSopneS l etweey tde treQC eyt amps m2 cNdfi E hVWGSen N(4 amps mwGS Sayil oGytuf Ss meripn tp tde us l rioGyt amps m l st witdps t : iMweyoe opC mGne: witd tde mpC eStrieye amps m2 l iayil oGyt ne: s otipy iy tde tpGtGtNdfi P' c l x Sopne iy tde iytrGamps m opC mGtSipy pM tde N(4 tGsen amps m2 l de Sopne pM xl xc Gy: r 8 c : i: ypt iy: ioGSe : iMweyoeS l elhne Gy: G	xnGtopyGuN(4 tGsen tdenGnf iS MGSl ue iy af yeoppaio oGyoenS nlyvptS witd mreuC iyGf evi: eyoe pM iC mpveC eyt iy Se) s GuMyotipy opC mGne: witd SDGC treQC eyt2	l OOR2
EasiGnLh 4j 4j LI O D6@	% .47 men amps nV	RQy: pC1'e: ouyioGutnGu - nps m5W iytrGuGaiyGu MkGtopyGuN(4 tGsenz - nps m4W mpC eStrieyez - nps mPW vGaiyGu us l rioGyt	xnGtopyGu N(4 tGsen	kpStC eypnGSeGu wpCey witd - l O : vGaiyGu: rf yeSS pn s nlyGf Sf C mpC SV	P tGsen of oueS .evenPJ -7q : GfSV5j C a pM vGaiyGu mpC eStrieyeB tdnee tiC eS weeYf Mn 54 weeYS l pnoGu us l rioGyt aeu Gmnie: witd Se) s GuGativitf pven G merip: pM 54 weeYS	cNdfi P' c l x cNdfi E h	57 weeYS	cC mpveC eyt iy iytrGamps m opC mGtSipy iy LGsenamps n2 b p Sayil oGlive : iMweyoe iy iytentreQC eyt ' c l x2 l iayil oGlive iC mpveC eyt iy (Eh l etweey N(4 Gy: mpC eStrieye tp us l rioGyt amps n2	aE R2	
TmVdGu 4j 4j D6@	qj .4q men amps nV	RQy: pC1'e: NiyioGu l nGu	xnGtopyGu N(4 tGsen	kpStC eypnGSeGu wpCey witd - l O	cyten/eitypy amps mW(4 tGsen tdenGnf meripn: e: everf C pytd Mn	r 8 c xl xc	54 weeYS	l de Sopne pM xl xc Gy: r 8 c : i: ypt iy: ioGSe : iMweyoeS l elhne Gy: G	cC mpveC eyt iy l ptd amps mS iy QyGf SSl e hneF Gtder2 b p : iMweyoeS	aE R2

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i EgH.2.2 continued V

l ts : f QXeGn y	y	] eSJay	l fne pMLGEn	kGrioinQytS	cyteneytipy	(s topC eS	xpupw sm	ReSs uS	Npyous SpY	fiE
					Npytrpuaps nW kreC Giiy vGaiyGuoneGC wGS Gmmie: .j 264q C aBP yiadtS GweeY Mn P C pytdS r GaiyGuN(4 tGEn vS SdGC mpoe: s neS everf 7 weeYS Mn dneee SeSSpyS	r El r 8 c chfi	54 weeYS	tde ey: pMde treQC eyt2	I etweey tGEn Gy: kreC Giiy oneGC 2	
Rsgympp 4j 5; ID @	00 nGieyTS	RQy: pC l'e: NiiyioGu l riGu J ps l ue huiy: e: opC nGne: tp l dGC	xnGatipyGu N(4 tGEn	kpStC eyptnG SGu wpC ey wtd C p: enGte tp Sevene iyteyStf pMjyf vGaiyGu Gupndf Sf C ntpC S .r El V	P SeSSpyS TStrpaey oneGC .kreC GiiyWj 2j a lytnGv GaiyGu : Guf Mn57 : G S Mupwe: 1 f j 2j a twoe weeYuf Mn47 weeYS2	r El xl xc r 8 c r O c	P Q 6 weeYS Qy: P Qy: 6 C pytdS	b p : iMnreyoeS I etweey arps nS ly r El Bxl xc Qy: r 8 c2 r O c wGS diaden iy tde eStrpaey arps mD lu tp C p: enGte G verSe eMnotSB yp : iMnreyoe I etweey arps nS cC mpveC eyt iy r 8 c i y l ptd arps mSd diaden iy tde N(4 tGEn arps m2 cC mpveC eyt iy r O c diaden iy tde N(4 tGEn arps m2b p : iMnreyoeS iy tptGuxl xc Sopne GC pya tde tdnee treQC eyt arps mS2 l dene wene yp G verSe eMnotS GSpoGte: wtd Qyf pMde treQC eytS2	I iayil oQyt iC mpveC eytS iy tde r 8 c Sopne Gy: r El Sopne GC pya wpC ey wtd vGaiyGuGupndfB wdeneGS iy tde SdGC arps nBdene wene yp Siayil oQyt iC mpveC eytS Mn QuC eGS neC eytS2	aE R2
kGrGSp O 4j 5; ID @	64 . Pj W tGEn Gy: P4W eStrpaey oneGC V	O s utioeytenB nGy: pC l'e: ouyioGu tmGu	xnGatipyGu N(4 tGEn	O eyptnG SGu wpC ey wtd Siayil oQyt vGaiyGuGupndf Sf C mpC S	P SeSSpyS TStrpaey oneGC .kreC GiiyWj 2j a lytnGv GaiyGu : Guf Mn57 : G S Mupwe: 1 f j 2j a twoe weeYuf Mn47 weeYS2	r El xl xc r 8 c r O c	P Q 6 weeYS Qy: P Qy: 6 C pytdS	b p : iMnreyoeS I etweey arps nS ly r El Bxl xc Qy: r 8 c2 r O c wGS diaden iy tde eStrpaey arps mD lu tp C p: enGte G verSe eMnotSB yp : iMnreyoe I etweey arps nS cC mpveC eyt iy r 8 c i y l ptd arps mSd diaden iy tde N(4 tGEn arps m2 cC mpveC eyt iy r O c diaden iy tde N(4 tGEn arps m2b p : iMnreyoeS iy tptGuxl xc Sopne GC pya tde tdnee treQC eyt arps mS2 l dene wene yp G verSe eMnotS GSpoGte: wtd Qyf pMde treQC eytS2	Et 6 C pytdSB MnGatipyGu: N(4 vGaiyGuGEn Gy: vGaiyGuStrpaey treQC eyt neS te: ly SdGh iC mpveC eyt iy - 1 O Sf C ntpC S GS weuGS s i y Gf Qy: Se) s Gu Miyotipy l de s Se pM MnGatipyGuN(4 tGEn tdenGf tp treG aeyitps riy Gf Sf y: npC e neS te: iy l etten Sdprt tenC eMnotS tdGy tdpSe pM mpC eStrieye pn us l rioQyt wtd neSneot tp iC mpviya tde vGaiyGudeGtd iy mpStC eyptnG SGu / pC ey2	b OOD2
kpntGyp NE 4j 5; O eyptnG Se IDj @	%	RQy: pC l'e: ouyioGu tmGu	xnGatipyGu N(4 tGEn	kpStC eyptnG SGu wpC ey pven tde Gae pMjJ feGrS2	P arps nSd dneee SeSSpyS pM iytrGv GaiyGu MnGatipyGuN(4 tGEn tdenGf z 5j C a pM iytrGv GaiyGu mpC eStrieye oneGC P tiC eS G weeYz Gy: vGaiyGu us l rioQyt GmnoGipy Gpye2	r O c r 8 c xl xc	57 weeYS GEn tdenGf	cC mpveC eyt iy r 8 c i y l ptd arps mSd diaden iy tde N(4 tGEn arps m2 cC mpveC eyt iy r O c diaden iy tde N(4 tGEn arps m2b p : iMnreyoeS iy tptGuxl xc Sopne GC pya tde tdnee treQC eyt arps mS2 l dene wene yp G verSe eMnotS GSpoGte: wtd Qyf pMde treQC eytS2	I de s Se pM MnGatipyGuN(4 tGEn tdenGf tp treG aeyitps riy Gf Sf y: npC e neS te: iy l etten Sdprt tenC eMnotS tdGy tdpSe pM mpC eStrieye pn us l rioQyt wtd neSneot tp iC mpviya tde vGaiyGudeGtd iy mpStC eyptnG SGu / pC ey2	aE R2
Nns * r L 4j 5% O eyptnG Se ID5 @	7q	RQy: pC l'e: B : ps l ueH uy: B mGoel pF opytpuae: ouyioGu tmGu wtd dneee GdC S opC nGaiya N(4 tGEn .LV wtd tpmioGueStripu .TV Gy: tde opC l iyGipy pM l ptd .L+TV	xnGatipyGu C ionpG tGdive N(4 tGEn	kpStC eyptnG SGu wpC ey wtd r r E Sf C ntpC S	LWt tGEn SeSSpyS SntGoe: 7 weeYS + mGoel p P tiC eS GweeY : s niya 4j weeYS L + TWt tGEn SeSSpyS SntGoe: 7 weeYS + 5 C a vGaiyGueStripuP tiC eS GweeY : s niya 4j weeYS TWt SeSSpyS pM SdGC tGEn SenGtGte: 7 weeYS + 5 C a vGaiyGueStripuP tiC eS GweeY : s niya 4j weeYS	r El r 8 c xl xc r O c	j B0 Gy: 4j weeYS	r 8 c GvenGae Sopne wGS Siayil oQytuf diadeniy tde MupwB miy Gu Ss: f GdC S2 L Gy: LT arps nS Sdpwe: G Siayil oQyt iC mpveC eyt pM Gur r E Sf C ntpC SB wdiue tde T GdC pyuf pM r f yeS2 LT arps m meSeyte: Siayil oQyt iC mpveC eyt pM xl xc SopneB wdeneGS tde L arps mSdpwe: Siayil oQyt wprSeiya pM nGy : pC Gy iy xl xcBl s t xl xc tptGuSopneS	N(4 vGaiyGuGEn Gpye pn iy opC l iyGipy wtd tpmioGueStripuS G app: treQC eyt pntipy Mn r r E Sf C ntpC S2l e) s GF neGte: nGy wtd vGaiyGuGEn treQC eyt C iadt I e pMpyoen/2 C iadt dGve dG G I eye[oiGueMnot iy tde vGaiyGu iytrpitsSB : eoneGaiya meyetrGipyF neGte: nGy2	b OOD2

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i EgH.2.2 continued V

l ts: f QXeGn y	] eSJay	l fne pMLGEn	kGrioinGytS	cytenveytipy	(stopC eS	xpupw sm	ReSs uS	Npyous Spy	fiE
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r r EWf s upvGaiyGuEtupmrf Br O dW GaiyGuO Gs nQipy cy: e) Br 8 dW GaiyGu8 eGtd cy: e) Br El W iSs GuEyGpas e l oGReBxl xdWeC GRe l e)s Guxs yotipyiya cy: e) B'] d6W
' niyGrf] iSreSS cyveytpnf BeNdfi F c l xWytynyGipyGuNpySs utGipy py cyopytiyeyoe fis eStippyGneBeNdfi F EhWytynyGipyGuNpySs utGipy py cyopytiyeyoe fis eStippyF
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e. t LSUHS2

5j2j Study selection

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oG Gverio opmetGipy IDP2
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5j4j Study cRaracteristics

xpn tde : GG GyGf Ss ms mpSeBeN oGof Gy: Seos nrtf were GyGf *e:
SenGtGeuf 2xpnneN oGof GSseSSC eytBde Ss: ieS were: ivi: e: iytp arps nS
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kpSVl ts: ieS/ itd b p Npytrpu- rps mGy: NGSe lerieS lts: ieS2

5j5j Study Yndings

5j5j2j hfYcacy analysis by NHVBI subtypes

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NpytrGtuf Bwe Moe GaneGt opueotipy pM eMneKGnen .meHnpSVSs: ieS
wtdt yp opytpuapms mopyous: iya tdtG it iS GmpC iS iya tdenGrf 1 st tdtG
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beventideSSBit iS iC nprntGyt tp neC GnY tde SdprfrenC Mupw smiy
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5j5j2j2j Controlled intervention studiesj cy tdiS Sf SteC Gio SeGnd were
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us l rioGyt iy xl xc SopreBl st l etten iC mpveC eyt iy r 8 c opC nGriya LGsen
Gy: eStpaey tp us l rioGyt2 ReaGr iya r O dtdene triGu Sdpwe: iC mpveF
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5j5j2j4j Observational coRort and cross-sectional studiesj (y tde Sf SteC F
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i EgHLM2

(I SenvGipypGuopdpnt Gy: onpSSSeotipyGuSts: ieS2

l ts: f QXeGu	y	l eSlay	l fne pMLGen	kGtiointGytS	cytenweytipy	(s topC eS	xpupw s m	ReSs uS	Npyous Sipy	fi E
J i j pyGp r 4j 4j OGs ntiGS IB4@	qP	l iyaue GC: mpSneotive pl SenvGipypGu Sts: f	xnGtipyGu C iorpG uGlive N(4 uGsen	kpStfC eyprnGs SGu wpC ey wltid r r E S f C mpcC S	P SeSSpyS SenGQe: 7 weeYS	LiVert Sopne	6 C pytdS	b p Severe opC mioGipypS were nempite: Glen G6 C pytdS Mupwls m2 O eGy pvenGu nGy Sopne Gy: nGy SopneS neGQe: tp mpl e iytrp: s otipy Gy: rptGipyp SGtiStioGnf Slayi[oGy ntf : eoneGQe: : s niya MupwF s nBwdeneGS tde nGy SopneS neGQe: tp uGsen GativGipyp Gy: e) trGtipyp neC Gye: upw2 l puenG iutif neGQe: tp tde mpoe: s ne Gy: SGtiStioGnf pM neSs uS wGS diad2	N(4 uGsenSecC S G SGM Gy: weuf tpuenGQe: tderGnes tio pntipy Mn tneGC eyt pM r r E Bwltid yp Severe opC mioGipypS neGQe: tp tde tderGnf nempite: 2 (venGuBnGieytS were diadif SGtiS f e: Gy: wps u nemeGt uGsen tneGC eyt tp C GytGy neSs uS2	b OOD2
Li 3 4j 4j LGsenS iy l s m enf Gy: Oe: ioiye IBP@	564	knpSneotive O s utioeyten Npdpnt l ts: f kGieytS neoeive: vGaiyGu MGtipypGu N(4 uGsen . uGsen arps nW pn tpmioGu TStripuoneGC . opytipu arps nW	xnGtipyGu N(4 uGsen	kpStC eyprnGs SGu nGieytS wltid C p: enGQeSevere S f C mpcC S pM - l O Bwdp were ypt SGtiS f e: wltid nreivps S upoGueStripaey tneGC eytBpn hN S nviwprnS wltid S f C mpcC S pM - l O	4 pn P uGsen SeSSpyS G Gy iytenGuPM Gmmp) iC Gneuf 7 ± 5 weeYS2 j 2j a pM vGaiyGB tpmioGuTStripu oneGC wGS G C i yiStene: pyoe G: Gf Mln tde l nSt weeVB tdey twioe G weeY. GtptGupM P C pytdSV	r 8 c r El	SBPB6 Gy: 54 C pytdS	cy uGsen arps nW r 8 c iC mpve: Glen 5St Gy: 4y: tneGC eyt Gy: 5BPB6 Gy: 54 C pytdS mpStneGC eyt cy tde opytipu arps nW 8 c iC mpve: G 5B P Gy: 6 C pytdS mpStneGC eyt b p: i MlnyoeS Glen P Gy: 6 C pytdS Mupwls m l etweey arps nS r El iC mpve: G 6 C pytdS b p G verSe eMlotS	xnGtipypGuN(4 uGsen vGaiyGu tneGC eyt ops u l e GSGM Gy: eMlotive pntipy Mln tneGiy a S f C mpcC S pM l O 2 l de iC mpveC eyt iy S f C mpcC S wGS opC nGtiG ue wltid tdGt Seey wltid tpmioGueStripaey tderGnf Gy: uGRe: Mln G ueGS 6-54 C pytdS mpStneGC eyt	b OOD2
O Gty 3 4j 5; 3 - fyepou (l Stet 8 s C Remmp: IB7@	qj	knpSneotive oiyioGuSts: f	O iorpF MGtipypGuN(4 uGsen upw: pSe eyernf	kneC eyprnGs SGu Gy: C eyprnGs SGu wpC ey wltid S f C mpcC S pM vGaiyGuGpnmf	4 uGsen SeSSpyS StfQe: G 6 weeYS	xl xc fi pL Sopne	P Gy: 6 C pytdS	xl xc Gy: fi pL Sopne iC mpve: iy l ptd arps nS G P Gy: 6 C pytdS b p iC mptGyt G verSe eMlotS	O iorpMGtipypGy: uGsen wltid upw : pSe eyernf : eC pyStrGQe: iC mpveC eyt pM acyitps niyGf S f y: nC e iy ypyF C eyprnGs SGu Gy: mpStfC eyprnGs SGu wpC ey b pt ey padt: G Gtp opyous: e	b OOD2
liyad 4j 5; 3 - Xb TN(L l' R- D0@	7q	knpSneotive oiyioGuSts: f	N(4 uGsen	/ pCey wltid SlayS Gy: S f C mpcC S pM pvent s rpaeyitGu Gupnmf	q SeSSpyS	r 8 c xl xc l x54	6 C pytdS	b p: G GpM xl xc Gy: l x54 l evey ps t pM 55 mGieytS . 6PZ69 VdG Gy iC mpveC eyt iy r 8 c Sopne cy tde Pj B/ arps mtle iC mpveC eyt	N(4 uGsen tderGnf C Gf iC mpve - l O S f C mpcC S Gy: . continued on nefit pageV	l OOR2
kitSps yi 4j 5%	qj	RetmpSneotive oGSeiopytupu Sts: f	O iorpG uGlive MGtipypGuN(4	kpStC eyprnGs SGu wpC ey wltid Severe lyteyStf	(ye uGsen tderGnf wGS Gmle: evenf	J f Sndres yiG Gy: : if yeSS2 xl xc	5 C pytd Mupwiya			aE R2

i EgHLM continued V

ts : f QXeGh	y	] eSlay	l f ne pMLGben	kGtiointGytS	cyteneytyp	(s topCeS	xpupw s m	ReSs utS	Npyous Sipy	fiE
O Gs nitGS Bsq@			uGben .Pj / vS 7j / npwen/	pM f SnGres yiG Gy: : rfy eSS	C pytd MnP C pytdS2	r O c r 8 cS	tde tdir tenGnf	pM : f SnGres yiGB : rfy eSSB itodiyaQ I s nryiyaBxl xdb r O dKQy: r 8 d wGS SGtiStioGuf Slayi[oQyt GS weuGS iy tde 7j E/ arps n2 NpC nGtiSipy I etweey Pj Gy: 7j / reveGre: tdG C eGy iC mpveC eyt pnmeSeyoe pM Gu- 1O Sf C mtpC S Gy: oiyioGuSlayS wGS ypt SGtiStioGuf Slayi[oQyt : iMneyt2 l tGtiStioGuf Slayi[oQyt ne: s otipy pM GuGSeSe: r r E Sf C mtpC S iy I ptd arps nS Gy: G Slayi[oQyt iC mpveC eyt iy C Gs nGtiPy vGS e Gy: G : eoneGre pMnB wGS pl Senve: 2 1de iC mpveC eyt iy Gu ey: npiytS wGS C pne mpyps yoe: Gy: upyaen tGtiya iy tde tGben arps n2 8 iStipaioGu e) GC iy GtiPy Sdpwe: odGxaeS iy tde tupmiSC pMde vGaiyGu C s opSG iy tde tGben arps n2 b p C Gpn G verSe eMlotS neutGse: tp uGben tderGnf2	oiyioGuSlayS21 diS iC mpveC eyt : i: ypt SeeC tp GSPoiGre tp npwen pMPj pn7j / 2	
- GSnGnE LGben6 l s m O e: 4j 59436@	qj	l wp GtC opC nGtiGlive opdpnt Sts: f	Tri is C WE- uGben	kpStRC eyptnGS Gu wpC ey wtd r r E Sf C mtpC S	TStripu arps nW j 2j C a eStripu : Guf Mn4 weeYSStdey tdnee tiC eS G weeY Mn4 weeYS Gy: [yGuf twice G weeY Mn7 weeYS . tptGu0 weeYSV LGben arps nW j 2j C a eStripu tdnee tiC eS G weeY Mn4 weeYS Gy: tdey P SeSSipyS pM uGben iy tde ops rfe pM0 weeYS	r El r O c r GaiyGanB teStiya	50 C pytdS	TriME- uGbenIS G S ooeSSMutdenGnf tp neveve Sf C mtpC S pM aeyitps niyGf Sf y: r pC e pM C eyptnGS e2 O pnepverBtde neSs utS Gre C pne mpyps yoe: Gy: upyaen tGtiya opC nGre: tp tpmioGu eS nripu treGC eyt2	aE R2	
hp.Giyi 4j 56 32LE@8 E Dy @	7j	l dnee GtC opC nGtiGlive opdpnt Sts: f	XE- uGben	kGieytS wtd aeyitps niyGf Sf y: r pC e pM C eyptnGS SeB4j wtd hN Gy: 4j yp hN2	4j nGieytS hN arps m 4j yp hN arps nW6j kRkB 5j XE- uGben cy tde P arps nS 4 SeSSipyS pM XE- uGben2	r El .7 npiytSV cytenops rfe MeHs eyof	54 C pytdS	cC mpveC eyt py r El pM : f SnGres yiG Gy: : rfy eSS2 cC mpveC eyt iy iytenops rfe MeHs eyof2	O Gpntrf pM nGieytS Gre Gf C mtpC Gtio G 54 C pytdS Gben treGC eyt Gy: diaduf SGtiS[e: wtd tde treGC eyt2	1 OOR2

r r EW s upvGaiyGuEtpntf Br O dW GaiyGuO Gs nGtiPy cy: e) Br 8 dW GaiyGu8 eGtd cy: e) Br El W iSs GuEyGpas e l oQeBxl xdWeC Gie l e)s Guxs yotipyiya cy: e) B'] d6W
' niyGnf] iSneSS cyveytpnf BeNdf F c l xWytynyGipyGuNpySs utGipy py cyopytiyeyoe fis eStipyGneBeNdfi F EhWytynyGipyGuNpySs utGipy py cyopytiyeyoe fis eStipyF
yGne (verGtixe htG : en2

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i Eg H.2.2 continued V

1st: f QxCh	y	1eSlay	1/rm pMden	kGtindjyS	qtenvortpy	(stopCes	xpawp sm	ResStS	Npyou Spj	fiE
NuG Gterto DHP@ OeGgGk 4j JenC Gpa 1den D7@	7j	kpsnactive Ss: f	NpC l iye: M0xipYu G lGIVE Qr: ypyG lGIVE N 4 tGsenS	kpsC eyntdS SduwpCey ypyeSspae/y e: wpCey wild C p: enfe tp Swore S CmpC S nreGle: tp-10	P SsSipys evert 7 weeS	xlxc l- c	780 Gy: 54 weeS	47rd weeY b p G verS eMkS xlxc Gy: l- cIC mpveC eyt G 54 weeS b p S: e eMkS	mpSC eyntdS SduwpCey S Mntya Mpc - 10 Ide -4 wGeyatdS ey: pGalyGutden meQC eyt' IS GSDm Qy: eMkative teodylH e tp meQ -10 S y: nC e	xGn
kGdQp 1 4j LGSenS sm Oe: D4Q@	4j	E SyauSbeyten pl SenwQipYu mpSactive opdpnt Ss: f	xrGdipYuN 4 tGden	kpsC eyntdS SduwpCey wild - 10	P SsSipys evert 7 weeS	8 lSpauloQu odQ: nS ly vs wGn tSSe r 8c r 8c r El	E Mm evert tGden of one	c: mpveC eyt pM s nGn oppyvative tSSeB entideS C: tnpalidS Qy: ypvCes tGt Qip2 c: mpveC eyt pM s 8 dr 8c Qy: Qu: 10 S C mpC S O eGy r 8c Gy: xlxcwore lyonCS: Sayl cGyrf Ql P C pyrdS mpSmeQC eyt Qy: : eoneCS: Gady G C pyrdS mpSmeQC eyt tGde Qn pM s ly Qn lyonCS rS: pM lue: s nrya tGde nntp: pM C Ql C Qu meQC eyt eMkS	xrGdipYuN 4 tGden uG S tp GnsSpdQip pMde ypnG Gacoditicos nre pM vs nGn tSSe eBwld Sayl cGyrf IC mpveC eyty -10 lHade: S C mpC S N 4 tGsenmeQC eyt dS Sayl cGyrf eMkay ndtindS nC ndyS Qy: S0 lHwBwld wGeyS l f 6 C pyrdS mpSf meQC eyt b p SnpntmeC Q verS eMkS	- ppr xGn
LGS terf Gd R 4j 4j LGSenS ls n Oe: D4Q@	07	llyauSbeytenB mpSactive oemeyf tGt euopdpnt Ss: f	El lGIVE N 4 tGden meQC eyt	kpsC eyntdS SduwpCey wild vGalyQuGtHf Qy: : eoneCS: SenSdip : s nrya lyonCS rS	P SsSipys C pyrdS	xlxc r 8c r El	P Qy: 6 C pyrdS	O eGy r 8c Gy: xlxcwore lyonCS: Sayl cGyrf Ql P C pyrdS mpSmeQC eyt Qy: : eoneCS: Gady G C pyrdS mpSmeQC eyt tGde Qn pM s ly Qn lyonCS rS: pM lue: s nrya tGde nntp: pM C Ql C Qu meQC eyt eMkS	N 4 tGsenmeQC eyt Qmcs tp 1 e Gy eMkative Qy: S0M C edip: tp IC mpve tde tnpalidS Qy: : eoneCS: vGalyQuC s opSQu : r f yess ly wpC ey wild vs upvGalyQuGtHf tGd : euepnt: QmS S0C lo l nCS oGyonidentH2 O pte Ss: tGd Qe yee e: tp : eteGt lye dlow pMey tde ndley rS Sps u nootive tde meQC eyt Qy: tp evGd Qe tde: s rGdip pMde eMkS2 r GalyQu: r f yess r El IC mpve: Sayl cGyrf ly G opdpnt pMmeC eyntdS SQu Qy: mpSC eyntdS SQu wpCey sy: emplya vGalyQuN 4 tGden meQC eyt: eSntt yP Sayl cGyrf eMkay ly vGalyQuGtHf	xGn
8 enGy t h 4j 4j Eyy Ndm kGd Tndet D4Q@	4j	llyau QC mpSactive Ss: f	xrGdipYu Cmpd tGIVE N 4 tGden	hneCS oGyonS n wlvps wild r r El S C mpC S Gy: opdpnt: tGdip/ lHn dpnt pyGutdenCS	4 SsSipys	r 8c xlxc r El	6 C pyrdS	E mekSey Qy: Sayl cGyrf IC mpveC eyt pM s 8c Gy: xlxc wGeyatdS: s nrya tde 6 C pyrdS wlvps nGt 6 C pyrdS tde r 8c Spswe: Gy lyonCS: pM79 Mpc tde lGeytue Snpn Gy: xlxc IC mpve: q49 Mpc tde S0S0Mlpy Qy: tnpalid tuf lyonCS: s nrya tde wlvps s nGt p S: e eMkS were nntp: 2	N 4 tGsenmeQC eyt Qmcs tp 1 e Gy eMkative Qy: S0M C edip: tp IC mpve tde tnpalidS Qy: : eoneCS: vGalyQuC s opSQu : r f yess ly wpC ey wild vs upvGalyQuGtHf tGd : euepnt: QmS S0C lo l nCS oGyonidentH2 O pte Ss: tGd Qe yee e: tp : eteGt lye dlow pMey tde ndley rS Sps u nootive tde meQC eyt Qy: tp evGd Qe tde: s rGdip pMde eMkS2 r GalyQu: r f yess r El IC mpve: Sayl cGyrf ly G opdpnt pMmeC eyntdS SQu Qy: mpSC eyntdS SQu wpCey sy: emplya vGalyQuN 4 tGden meQC eyt: eSntt yP Sayl cGyrf eMkay ly vGalyQuGtHf	xGn
1 GGS k 4j 4j LGSenS sm Oe: D4Q@	q4	kpsnactive opdpnt Ss: f	xrGdipYuN 4 tGden	/ pC ey wild S C mpC S pM GalyQu: r f yess: P7 were ly C eyntdS s v	P tGsenS SsSipys evert 7 weeS	r El r Oc	54 weeS	r Oc: l: yP odQyae Sayl cGyrf tventt e Qm vGalyQuGden meQC eyt2 r GalyQu: r f yess r El IC mpve: Sayl cGyrf Qm eGd meQC eyt2	r GalyQu: r f yess r El IC mpve: Sayl cGyrf ly G opdpnt pMmeC eyntdS SQu Qy: mpSC eyntdS SQu wpCey sy: emplya vGalyQuN 4 tGden meQC eyt: eSntt yP Sayl cGyrf eMkay ly vGalyQuGtHf	xGn
fls loYEO 4j 4j ls mpt NGe Ngyon D4: @	67	llyau QC M0S l iuf Ss: f	xrGdipYuN 4 tGden	hneCS oGyonS n wlvps wild: f S0Gey yGQy: Qn vGalyQu: r f yess: Cps noealya ey: porive tGdGf wild GpC QCS lydl l iuf	P tGsenS SsSipys evert Pj-7q: GfS	r El xlxc J c k- dr r 8c	5 C pyrd	r El lHl xdb' J cQy: r 8E IC mpve: Mpc lGeytue tp wlvps m Qmcs tp re: s oe-10 S C mpC S CorpS meQC eyt Qy: wlvps m tde Ss: f Sps tde eMkativeS wild Gnpn : euepnt pMmeC eyntdS meQC eyt wild tde N 4	xrGdipYuN 4 tGden meQC eyt Mnt meCS oGyon S n wlvps IS M0S lue Qy: Qmcs tp re: s oe-10 S C mpC S CorpS meQC eyt Qy: wlvps m tde Ss: f Sps tde eMkativeS wild Gnpn : euepnt pMmeC eyntdS meQC eyt wild tde N 4	xGn
ximiyi O 4j 4j O eyntdS S D4: @	57q	RempSactiveB Cs tGeyten Ss: f	xrGdipYuN 4 tGden	kpsC eyntdS SduwpCey wild oalyGdS n S Gy: S C mpC S pM l O By ndtindS tGt r E	P-7 tGden SsSipys	r El r GalyQuB	E Mm l yS l iya tde meQC eyt	r El: r GalyQu: r f yess : S0Gey yGQy s nryaB vGalyQuGtHf oe ndy Qy: l iudya V C mpve:	r GalyQu: r f yess eMkativeS wild Gnpn : euepnt pMmeC eyntdS meQC eyt wild tde N 4	kppn

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i Egh12.2 continued V

1s: f QkCh	y	1eSav	1fme pMGen	kGrtiondyS	qtenoytjpy	(s topcS	xypw s m	ReS uS	Npou Spj	fiE
OsnyGx 4j 5; - f yepu Ty: portypu D7@		1lyaebyrenB renpSneDive Ss: f	xrtGrtipyGuN 4 uGen	kpsC eyntS Sdwpc ey wild: f SdGey yGQ; vs uGndy	P C pytdf ssspyS ; wpCey Gbp recoive: trnC C eyt wild pSneC lmye. 6j CaQ dV	r dSll s dnded Sopte .ntetodGEB ndpBdGd iuf B ; if yessSgy: ne: yesSly ide CspsdC r GalyGa ; if yessSll s rpyly Qy: nDy Qy: ; f SdGey yG	7BDB54 weesS Qy: P C pytdS	J f yessGy: ; f SdGey yG IC mpveC eytdQ eytS tp Ie C pte mpC lyeit ly ide pSneC lmye + uGen nps m Qy: neC GyS Q tdnseC pytd MupwB m Ide vesll s dndedQd Spne IC mpve: Swayl odyt ly I ptd apsnBst ly ide pSneC lmye + uGen nps mit SGre: ; eadyly a uGen Ile e dM dSVC lu tp C p: erde ndy B dG S eyt e: eCG	E opC ly G lpy pMGen Qy: pSneC lmye SseC SG dGd: SrtGef tp nSpu ide mpl ueC S nGde: tp - 10	
keGdy E 4j 5; hncG Nqren Rds 1neQ D7@	46	1lyae QC mpSneDive Ss: f	xrtGrtipyGu C lndG l dGve N 4 uGen	/ pC ey >50 f dG S wild dSntf pM nC S dGren wild r E S C mpC S Qy: wild Spnt Qy pS n ly: s oC: C eyntS Se	P SsspyS SndGde: 7 weesS	r El pSewerif pM S C mpC S xlxc LxS4 Llyen SdG	7 weesS	I f GStGd Swayl odyt IC mpveC eyt ly Qur r E S C mpC S r El Qy: ly Qub SdS dG: pC GyS pM l x2 I dG S nmpre: I nC S dG oC nS nly pS IC mpveC eyt ly S C mpC S SdS dG nly pny dG SdS dG dG dG: qyupue: Ss: dS p nSs: dS opC nDy a uGen Qy: I pnd dndC eyt Gde yee: e 2	N 4 uGenC dM dGve ly IC mpveC eyt ly Qur r E SdS dG dG dG dG: dS C G pM dG dG: pntly pM I nC S dG oC nS nly pS wild apyaltC: trnC C eyt f reude: aoytly pny dG SdS dG dG dG: qyupue: Ss: dS p nSs: dS opC nDy a uGen Qy: I pnd dndC eyt Gde yee: e 2	xGn
1p dGf 8s dG 3 4j 5; LGen6 1sm Oe: D6@	6j	kpsSneDive ' yopyupue: hnyre Qy: Ewem Ss: f2	xrtGrtipyGuN 4 LGen	kpsC eyntS Sdwpc eyB yp mreps S8 pC pQ RemGdC eyt l dndGf .8 Rl Bwild vs vpyGly Qd pntf B wild odyaes G tde vGly GdC s oG S nGde: tp dndG S nGde: SC opyf r dG: I f Gndy e: m f SdGy	P SsspyS wild G P ; G S l yrenGd I etweey dG C	r 8 c r O c xlxc	5 C pytd Gden tde tdn Ssspy	xrtGrtipyGuN 4 uGen trnC C eyt wC dM dGve tp IC mpve - 10 S C mpC S Gden dndG SsspyS dG weu G S r 8 dG pS Qy: e) Qy: xlxc trnC C eyt wild mpSive pSopC es dG mS S S pven tG e2	Qy tds S C mB dG: G G S a dS s tG M dGpyGde: N 4 uGen S Qy eM dGve Qenp Gde ym - 10 trnC C eyt wild mpSive pSopC es dG mS S S pven tG e2	- pte
EidG dG Sps 1 4j 5; O eyntS Se D6@	; 7	RempSneDive Ss: f wild mpSneDive opukote: ; G G	O lndG dGve M dGpyGuN 4	kpsC eyntS Sd wpc ey wild G uG S pye - 10 S C mpC pM C p: erde: tp Severe qyey Slt2	P B7 p q uGen t dndG S2	r El Bxlxc dndG xl: 11 dndGf cl xB ' J dG2	54 C pytdS	Ea - 10 S C mpC S IC mpve: SdG S dGd Swayl odyt f Bxlxc Qy: M dG eyof pM S Gd lytemp s dG ly oC S: 2 xps n p lve uGen dndG S C G l e S m dGpy t pwenly a tde lyey Sltf pM 10 S C mpC S ly pC n dG S py tp t dndG S dndG S ly S dnt Qy: wpyaltC: Mupw f s dG l dndG S ly etweey M dG Qy: lyve uGen dndG S wren ym S y: 2 Qy n dndG S wild aoytly s dG S r: pC e pM C eyntS S dnt Qy: mpSf	LGen dndGf C G mpw e Swayl odyt IC mpveC eyt Qy: Qn dG S yee: pM 10 S C mpC S mp 54 C pytdS Mupw B dndG S dnt Qy tde ysc l en pM dG S dndG S dnt Qy: 2	xGn
Opnde S ER 4j 50.3 (1 Srt	%5	1eS nntiveB renpSneDiveB	Td l sC XE- uGen	/ pC ey wild upw and e SdS S n dG lyeytlyey oC S n dG	1 s dndG S S yue teyC ly s te trnC C eyt2	r 8 c nB v dG dG	xypwwe: s m lyrenG dG S 6 weesS	Qy n dndG S wild aoytly s dG S r: pC e pM C eyntS S dnt Qy: mpSf	r Galy G dG dGve Td l sC W XE- uGen: s dndG S mp p dGpy m dGd	xGn

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i Eg H2.2 continued V

1st: f QXch	y	J eSlay	1fme pMGen	kGrtiondJyS	qYenveortpy	(s topCes	xypwv sm	ReSsUs	Npyou Sipy	fiE
- f yeqpu Remp: h1pu D40@		Syanebeyren qpdr2		wild yp QpC lo GSe h1neSt: sGvpaC e .of SpeneBantC e c mpGns:QvGhyGuGhyB Sf CmpCSpMChyGu Grtndf Q: Qn aylps nYGr Sf y: nP e pMc eyndS: - 10 V kpSC eyndS: Sxwpcy wild: (aypSe: - 10 B dOlyu uSsIdQ q9 pM vGhyGns: mnt of Qpnsly tde of papaf BvGhyGuB diaden idQy qBvild sryGr: Sf CmpCSp Q: iCrtGne: eyrIeyoe: s e tp s retdit Qrtndf 2	4 ScSspys pM lyndG retdit dTME: uGrenwid GPlwey lyenGdyI etweey tde ScSspys2	endfH x 1de 5Bips nrtG tes r EI SpnsS	P-6 C pyridS Qnden tde trnQC eyt	1ayl oGrtf iC mpyeC eyt wGS pl Sxwe: ly Gu C-6B me: nrtG: eters2 endfH x iC mpye: 1f Qy GvrtGae: pM679 G P C pyridS Qy: 1f 719 Q-6C pyridS2 5Bips nrtG tes Spns: G ne: sGhy pMde Hs Qrtf pM uGrtG: srye 1f q-9 G PC pyridS Qy: 1f 749 Q-6 C pyridS2 uayGr Sf CmpCSp pM 10 iC mpye: 2 E: vnde eHMSwene Clu Qy: nrtG: srye2	QvrtG retdit dTME: - uGen iS Qy: eHMSGhyS Qy: SdM Cp: Qrtf MntreQC eyt pM sryGr: Sf CmpCSp pM 10 B dpwvrtmpSreActvB rGr: pC l e: BQ: oprtmre: nrtG: wild uGrenwid Cl en pMChyS Qy: srye: tp l eten GSSS tde iayrtGr: eHMS pM dS yp eumpeo: s re2	xGn
OpndesER 4j 50 3 Mgven ReS Nly (yopu D7j @	56	RempSreActvB SyanebeyrenSs: f	Td l sC XE: uGen	hrtG: oGyonS nrtG wild - 10 G tde tte c pM S mnt Mntreuo pacy mpndes2	E Srye 4j 50 ly ops rde pM s GndGae mpndesuo pacy: TmW XE- uGen2	1s l reActv SxSxwrt r GhyGuB r 8 c	6 weyS	hrtG: oGyonS nrtG wild Grtndf reActv: opC mGhyS Gntreuo llypnS mnt C G l e yel t MPC: vGhyGntmtdpy pM tdlS ypydive: s Gu mpndesuo pM dTME: - uGen teedy papaf G GypF drtC pydntreQC eyt Grtndf Gd2	xGn	
- G: l GndfO 4j 50 NrtC Gnto D75@	4Bq	kpSCreActv pyrtus: lyGns: f	Td l sC XE: uGen	kpSC eyndS: Sxwpcy wild - 10	P uGen GntmtdpyS Grtndf G l e yel t XE- uGen2	r EI r 8 c endfH c l x	47 C pyridS	r GhyGuB l sC uGen C G 1 eHMSwene Qy: SdM Mntre trnQC eyt pMChyS nrtG Sf y: nrtC e pM: eyndS: S2	xGn	
T: enlT 4j 50 LGSn l den D74@	40	lyane Gc mpSreActv Ss: f	xrtGhyGu ClanGrtGlye N 4 uGen	kpSC eyndS: Sxwpcy wild r r EI Sf CmpCSp pMc eyndS: - 10 V kpSC eyndS: Sxwpcy wild: (aypSe: - 10 B dOlyu uSsIdQ q9 pM vGhyGns: mnt of Qpnsly tde of papaf BvGhyGuB diaden idQy qBvild sryGr: Sf CmpCSp Q: iCrtGne: eyrIeyoe: s e tp s retdit Qrtndf 2	P ScSspys Sxwpcy 7 weyS	r EI pMcSreActv Sf CmpCSp Qy: : l sC Mntre wild mpoe: s re r 8 c	6 C pyridS	N 4 uGen dTME: MntreSf C eyndS: Sxwpcy Qy: 1 e opS: enre: Qy: eHMSwene llypnS mnt C G l e yel t MPC: vGhyGntmtdpy pM tdlS ypydive: s Gu mpndesuo pM dTME: - uGen teedy papaf G GypF drtC pydntreQC eyt Grtndf Gd2	xGn	

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Eg H2.2 continued V										
l1s: f QxGn	y	l5day	l1 fne pMGen	kGtatioQ1S	gyteneeytp	(stupC eS	xpuw s m	ReduS	Npyou Stp	f1E
r Q:CC Gy 4j 5% l1erc.Gpu l1sm D7@	5j	llyae GAC mpSnaive Ss: f	l1QySs (Q)epsS teC nreGs nE opyrpu: nG jpkH e eyof .11NRXV	E: sH wpcY wld Cln F C: p: erde vs upkGln F tG ltf .: r r l wld pn wldp1s vGlyGutpnaf .Er V	P sCSStpyS SnaGRe: 7 weeYS	r supvGlyGu LG ltf f1s eSlpyGRe O ludeIsa r GalyGu LG ltf l dea O ludeIsa l eS Gu l1G S6lpy f1s eSlpyGRe x1xc l1Yer Sde 8 lSpaGu Qy d S6	54j: G S	Sav1lGdrt fC mpye: 2ES weuBG Mlden Sav1l oGrt iC mpyeC eyt pMudnee SmpS wS ypte: Q P Gy: 6 C pyrdS pMupwls nE b p SarpS S Q verte eMudS were nmpuie: reuGe: tp ide mpoc: s nE2	11NRX Sfpwe: iC mpyeC eyS ly Er Br lB Qy: S0 sGSLi SnaGRe wldp1st G verte epyeS2 S mpya r d1SpaGu lY: lyaS pM ypapGnaeyS S8 ypapGnaeyS S8 verGalyaeyS S8Qy: tde lB8 nmpa pMupS l u 11NRX h1de: yepaeyS S8 lG S6lpy wld ide nre s1s pMreC eyt wS dnad2	kpn
KCQ: upS O x Ty: seiy .l Qp ks: upW77@	57	k1pt Ss: f	O larpG lGve MlarpGu nG jpkH e eyof	kpSC eyrpnS SQuwC ey wld . lO	P Gm1cQ1pyS pM C larpG lGve MlarpGu nG jpkH e eyof wld G lY E G lYrenGu	/ 8 (flpLhRTx x1xc dnH l	Pj -6j: G S Glen ide G8 Gmudlpy	l dene wS Qy: lYenGRe ly Gac pS Qar: iC eyslpyS py Gordae ly B durt pMudB wld SGLiGdrt oGve pyrd ly ide dea d: pC Gy2 l dene wS G Salyil oGrt iC mpyeC eyt ly ide S0 sGu pC GySly Qc pS Gu lY: iC eyslpyS2 EundtGeyS q pame: s S1va u l1 nGdy: s rlya lYenpys rB Gm1nG C ey2 Gy ide SGLiGdrt H s eSlpyGRe Olen treC C eyBve pl Sare: tG Q ide vG8 C Gpntf M1 osn: pM C s d l etenQy: were verf SGLi e: pM SGLi e: 2	O larpG lGve MlarpGu nG jpkH e eyof wS eMldre ly nreGya S C mpc S pM GalyGu r rlyeS Qy: S1rhesylG Qy: eMlGde: tde s e: pM vGlyGdrt nGdy: s rlya vGlyGdrt pl Sare: 2llyoe tdeS lS Gmpt Ss: f wld G S C Gays G l enpM GalyS8 Mlden Ss: tde GRe nE lne: tp oMpl pde pM lY: lyaS Qy: eS GRe tde upalntC eMars pM C larpG lGve MlarpGu nG jpkH e eyof py ide vGlyGdrt S8 e2	kpn
EldQ: QS re l 4j 5% OAs nG8 D7@	qQ	kpsSnaive Ss: f	x1drtGu C larpG lGve Nl 4 G8n	kpSC eyrpnS SQuwC ey wld G re erde tp Severe S C mpc S pM l S dres y lG	P-q uS8n SCSlpyS : emy: lya py S C mpc S SnaGRe: S Qy MlarpG lGve lY: lyaS Qy: wpcy S mduy oE lYapwya ide d1rt iden Gmudlpy2	r El r Oc r 8 c	5 Cpyrd Olen ide G8 SCSlpy	Res nE pMudSs: f ly: tde Gd N 4G8n lde dnt C G Gpntf e tp Qy: mte nmpSly pM : fS dres y lGQy: r r lyS8 Qy: nreSGLi S8C eyt pM ypC Gdrt S QlyGaly ly mPC epyrpnS SQuwC eyB ly G: pMreSlyS: C G yent E y e l nGdy: nE pM lnd SCSly C G Mlden lyenGRe ide . lO S C mpc lde rG2	-pr	

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i Eg H2.2 continued V

1st: f Q%Ch	y	1eSoy	1fme pMden	kGndiQyS	qtenvortpy	(stopCes	xpawp sm	ResStS	Npyou Slpy	fiE
Emp/p N 4j 5% qY 3 / pC eyS 8 sGud D76@	45	kpsnextive Ss: f	xrdipYQuN(4 uDen	kentC eyntdS dwpC ey .C eQy Qae 7q±%eQSV	P SSSpyS ly letweey P-7 weeS lytenQu	r 8 c r El	47 weeS Qden tde dR trnC eyt	r GdlyGdudat Qy: S l eot GSeS: eyt pM GdlyQu S C mpC S iC mpve: wild S ooeS Sive trnC eyS2Et 54 weeS Wupwiya ide tdx trnC eytBlt vGSG SGSStoat Savil oQy IC mpveC eyt ly r 8 d2 E: : Hlyp Qd Blt wG S oS Qdudat iC dly Bly vQy Qae: avey dly Bly r 8 c iC mpveC eyt trnC Qy: Savil oQy iC G-C pytdS Gden trnC eyS2 Gdlyya wG ide C p8 opC Cpyr rempire: 4j 9 V S: e eWd2 kGleyt rempire: vGdlyQu : r f yess Savil oQy t IC mpve: Wupwiya trnC ey2 1 de Wdkey of pM lytempe nCs lyoxCs: MpC trnC dS G Cpyr d2 l de vG8 C Gpat f pM dleyS renpire: l eiy S dS e: wild tden trnC eyt nCs utS Qy: wild tde opS pM trnC ey2 l G S dlyp wild tde pM dlyp oet e) meS : l: ypt opm dte wild dps Sedpu lyopC e2 1EN 4l trnC eyt wG GSpdQe: wild GSavil oQy t IC mpveC eyt ly dGdly c l x Sopas Qy: 5R nQ weidat tes Q 54 C pytdS47 C pytdS Qy: P6 Cpyrd2 IC mpveC eyS were C Gyr Qy: Mn smp P6 C pytdS wildpist t ide yee: Wn Gf Mnden lyeneyt py2 1 de nCs utS were opY l C e: l f Savil oQy dS padoa odQ nCs redte: tp tnapido	xrdipYQuN 4 tGden trnC eyt wG GSeSdQe: wild IC mpveC eyt pM vGdlyGdudat Qy: G eundipY pM C mpC S pM r E Basa tiva ly IC mpve: S oS Qdlyp ly trnC eyntdS dwpC ey2 trnC eyt tde wG S fG l oB Qy: tden wG S C ly iC Qy : S oC Wd GSeSdQe: wild trnC ey2 vGdlyp dly pM odQ nCs upC e l x Gden Ss: f npsa dlyp S wGdlyte: 2	1EN 4l S oY dGdlyt Qy: S dlypve trnC eyt S dlypve trnC eytS wild Ctu 1' 2 Ss rden lyvGdlyp tp opY l C ide upallert nCs utS meS yee: dene S StawGdlyte: 2
Lqk 4j 5% uDen s sm Oe: D76@	544	Os ttenren renpative odipY Ss: f	xrdipYQuN(4 Lden	kGleytS dwp qC mete: G ops de pM tene vGdlyQu trnC eyS wild tde l C Gd r l: 6S xrdipYQu N 4 uDen	P SSSpyS Pj -7q: G S dlypwe: l f G mpipodt Qe: f eGd trnC eyt SSS py Q 54d47 Qy: P6 Cpyrds	E: veeS ps upC eS S yoe tdx trnC eyt l f C mpC Seven l l G dlyp wild l G dlyp wild ps dlyp oet e) meS l eS Qy Myotipy 2	P5B: qY45 weeS Wupwiya tden lyu trnC ey2 trnC ey2 l G dlyp wild l G dlyp wild ps dlyp oet e) meS l eS Qy Myotipy 2	l de l C Gd r l: e xrdipYQu N 4 tden S G S dlyp Qy: e l G dlyp S trnC eyt S - l O 2 dS trnC eyt S GSpdQe: wild Gdudat aveupM dlyt S dlyp wild l pM dlyt ey nCs utS Qy: ps tlyp oet e) meS	kpsnextiveB ypYdy: pC l we: Ss: f D70@	1 denC pQ t dive M dlypQuN 4 uDen

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i Eg H.2.2 continued V

1st: f QxCh	y	1eSav	1fme pMden	kGrtidnJrS	qtenvortpy	(stopCes	xpawp sm	ResuS	Npyou Sipv	fiE
hedyf / iuspy x 4j 5%fsn3 (18et - fyecpu Remp: hpu D7: @	5j 4	llyae GC B mpSnaive Ss: f	xixGipvQuN 4 uDen	/ pC ey mSxytiya S C mpcS pm 10	P tneQC eyS : eluene: Q lyenwGS pM8) pn C pte weeyS2	Es: SxGdQy kentio xupn fia: elippyGae	54–47 C pyrdS	reSpGdipv pMde vGdyGB reSpvSliue Mre) mlySoQy: lymlySo C eddy: iS C lypvue: iy s nyGf opytyeyoe2 llyvyl ody: iC mpyeC eyt ly ldein g C mpcS QdenN 4 uDen tneQC ey2l opns py C eGB ns pM8) s GdlyvolyB : f Sndras yGBQ: l pdenfGC eyesS pM8) s Gd Ss: es were: iC mpye: hQC meheQC eyt tp upa hC: 2 sxrdetC paelidore were iC mpyeC eyS pte C eGB ns pM 10: enMvolyB mpdeSdyGdyGdSesGdpyB vGdyQua i hGdpy Qy: s me lyoppytyeue hQC: lde muf tneQC eyt GSSS: eyt tp lde Sopp: GSSS: ey2 llyvyl ody: iC mpyeC eyt ly r El Qy: r 8 C SpsmS2 b p G vens eyeyS were reopra e: s nyia tde Ss: f2	Qy tds Ss: f BmGdipvQu ClapGd Gdive N 4 uDen tneQC eyt wGS GSSdQe: wid Qy: iC mpyeC eyt ly S C mpcS pm 10 Qy: Ss) s Gdlyvoly2	- pte
- CC l GsdQy O 4j 5% O eyntS Se h3: @	7P	llyae GC B mpSnaive Ss: f	r GdlyQua iS C uDen	kpSC eyntS SdL mC8 djoentS mlyvpB	l dree Gden Gantidipv/severf p) : G S	r El r 8 c	50 C pyrdS	l dSSS: f S aaeSS idQ lde vGdyQua iS C: uDen S elutive Qy: SdM pntde tneQC eyt pMeytpyGf S y: tpeC pMeytpS Se ly tneG djoentS mlyvpB hde: py Ss: f: Gdamp S f eGBide MdupyQuN 4 uDenC d 1e Qy enMotive Qy: SdM tneQC eyt M wP C ey S Mmlya Mpc S C mpcS pm 10 B Gdpsad G: i llyvyl Ss: iS wid dden mpas GdpyS Qy: mCde p opytpuS yee: e: tp opy l C: ldeS: reSutS2	l dSSS: f S aaeSS idQ lyrGdlyvQuN 4 uDen ldeidrf M mpSC eyntS SdlypC ey wid ody: iC SdlyS Qy: S C mpcS pm 10 C Gf 1e enMotive ly iC mpyeSya lnd vGdyQua djoentf Sppaf Qy: mpyte: S C mpcS2	xGn
l p p dTR 4j 5% O eyntS Se h3: @	Pj	llyae GC B mpSnaive Ss: f	xixGipvQuN 4 uDen	/ pC ey mSxytiya wid - 10	l dree GdlyGden tneQC eyS SdL: 6 weeS Gndf	r El r 8 c	54 C pyrdS	EvenGae iC mpyeC eyt ly r iS GdlyvQua l oCae SpsmS Mndus C mpc: djoentS wGS SdM djoentf Sdyl odyt G p C pyrdS Qy: tneC Gye: Sp tdpas d 5 f eGB o oent : f SdM GdlyvolyS l etweey: GQ Q p C pyrdS ly: iC Gdly mufSeyoe pM mpSliue ps tpeC eS2 r GdlyGd eCud Qy: e) Qy: xeC Qe 1e) s Quxs ydip Qy: e) SpsmS wGS Gdpy SdM djoentf Sdyl ody2 r O dte 8 c Qy: xl xc lyonGae: Sdyl odyt 2 l f SdM GdlyvolyS: r f yeeS8 l s nyia B djoentf Ss: r f Gd MufSeyoe B mpye of B mpye of lyoppytyeue B mpye lyoppytyeue Qy: SpsmS py lde djoentf: l B djoentf c l xB : l dte Qy: K8 f: eeneC8: Sdyl odyt 2x Gdpy me: iC Gdlyvolyvolyd wP C ey	l dSSS: f S aaeSS idQ lyrGdlyvQuN 4 uDen ldeidrf M mpSC eyntS SdlypC ey wid ody: iC SdlyS Qy: S C mpcS pm 10 C Gf 1e enMotive ly iC mpyeSya lnd vGdyQua djoentf Sppaf Qy: mpyte: S C mpcS2	xGn

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i Eg H2.2 continued V

1st: f QxCh	y	J eSav	1f re pMGen	kGrtiondyS	qyrenvortpy	(stopCes	xpawp sm	ResuS	Npyou Spj	fiE
kiendai E 4j 5% End - f yeou (1.8 et D1y@	507	kpsSxative opdnt Ss: fW SpprQeys S CeypnksSe Q; pypopalQa CeypnksSe	xixGipPyGu Ciangd iGlive N 4 uGen	kpsSR eypnks SkaupC ey wild r r E S CmpC S	P SsSpysSendQae: 7 weesV	r El Livent SQue	47 C pyrds -evGa GipyS G 7 weesV Q; 6B 54B50 Q; 47 CpyrdsV	: f SxSes yfG Q; : f Ss nCB Lue: lyabimpe lySrip Q; C pveCeythasQe nDy2 r GalyGuG luf Q; uSxarf naGe: : l SspC Mnt: l: ypt : lWm2 N 4 uGenS MGS l uESd Q; eMvative wildps t G svQr Geys2 CmpveC eyt pM GalyGu dedat C G opylyse smip 47 C pyrds QmN 4 uGen trnC eyt Qutps ad I ewesey 50r Q; 47F CpyrdsI eyel S; eady2E yew dQae QmN 50 C pyrds C G l e l eyel dQd2	tp G C l yS nQy; MntmC eyt nC G y tp I e: el ye: 2	xGn
1uthHj - k 4j 5% Nuc Gatenio D1y@	0%	l lyue GC mpSxative Ss: f	xixGipPyGu Ciangd iGlive N 4 uGen	kpsSR eypnks SkaupC ey wild r r E S CmpC S	P SsSpysSendQae: 7 weesV	r El r 8 c l eance pMdy redde: tp lde mpoe: snc Livent SQue Mn trnC eyt SxS nG l y	5q C pyrds l QStoGuf Sayf dQr l CmpveC eyt ly l p d Sx l eadve r El Qy; 6 pl eadve r 8 c Q; r r 8 c V evGa GipyS smip 5q C pyrds lWpob n O Gpntf pMpyC ey were verf SxS l e: pnsSx l e: 2 kpaansSve: eoneCde plndy redde: tp uGen Gmudcipy2 Cmpve ly wpc ey S l C Gae pMdeC SeneS2	N 4 uGen trnC eyt ly: s oES Sayf dQr Q; upadkalya l CmpveC eyt pM r E S CmpC S2	xGn	
ketyp E 4j 5q O Gs nCS D1y@	70	l lyue GC mpSxative Ss: f	xixGipPyGu l dnt: pG iGlive N 4 uGen	kpsSR eypnks SkaupC ey wild r r E S CmpC S Q; ypfnsSpys tp mavisS dntC pyQuoGutdnks	P SsSpysSendQae: uGS Pj : Q S	r El r 8 c Livent SQue	5 C pyrd l QStoGuf Sayf dQr l CmpveC eyt ly r 8 c Qy; ly r El 20 Gpntf pMdeyS were verf SxS l e: - SxS l e: 2b p G vers eMGS2 l QStoGuf Sayf dQr l CmpveC eyt ly r El pM r E S CmpC S2 CmpveC eyt ly tpead luf S CmpC S2 l QStoGuf Sayf dQr l CmpveC eyt ly r 8 c y p : lWm2yoes l ewesey GpC Q Gs lydl l pntS arps nB l C p lWm pny p Q s vQr t l dnt V l QStoGuf Sayf dQr : eoneCse ly r El CmpveC eyt pM xCB SxS nG l y wild Ss s GmMB r r E S CmpC S Q; lS Guf pMdeC eyGa Gipy20p9 pM ypn Ss a Qut Gntve wpc ey redde: ypc Qs s GmMB	l dnt: pG iGlive N 4 uGen lS GmdeMvative Q; MGS l u dntC Mnt r E ly mpSR eypnks SkaupC ey2	xGn	
kGdGp 1 4j 56 O eypnks Se D1y@	46	l lyue GC mpSxative Ss: f	xixGipPyGu Ciangd iGlive N 4 uGen	/ pC ey wild dntC pyef noemtpa mpS lve tsC pntS wild r r E	P SsSpysSendQae: Pj -7j : G S	r El pM r E S CmpC S Q; teady lHe l pntG luf S CmpC S r 8 c r El	5 C pyrd -GSsC eyt : s xya 7 CpyrdsV r 8 c 7 weesV r El 55 Cpyrds rQae P-4q C pyrdsV	N 4 uGenS G SGM Qy; eMvative l dntC Mnt r E S CmpC S ly dntC pye redde: l nCB oGoen Sx vlypnt2 N 4 uGenS Qy eMvative trnC eyt Mnt r E : f SxSes yfG ly l nCB oGoen Sx wtpntS wild oppyndy: l dG l yS tp dntC pyQuoGuf eyS2	l dntC pG iGlive N 4 uGen lS GmdeMvative Q; MGS l u dntC Mnt r E ly mpSR eypnks SkaupC ey2	kppn
kiendai E 4j 56 End - f yeou (1.8 et D1.5@	qj	l lyue GC mpSxative Ss: f : eSxative Ss: f	xixGipPyGu Ciangd iGlive N 4 uGen	kpsSR eypnks SkaupC ey oGoen Sx mlypntS wild r r E	P SsSpys	r 8 c r El	r 8 c 7 weesV r El 55 Cpyrds rQae P-4q C pyrdsV	N 4 uGenS Qy eMvative trnC eyt Mnt r E : f SxSes yfG ly l nCB oGoen Sx wtpntS wild oppyndy: l dG l yS tp dntC pyQuoGuf eyS2	N 4 uGenS Qy eMvative trnC eyt Mnt r E : f SxSes yfG ly l nCB oGoen Sx wtpntS wild oppyndy: l dG l yS tp dntC pyQuoGuf eyS2	xGn
lGutGne l 4j 5q Nuc Gatenio D1.4@	9%	l lyue GC mpSxative Ss: f	xixGipPyGu Ciangd iGlive N 4 uGen	kpsSR eypnks SkaupC ey wild r r E	P SsSpys event 7 weesV	x lxc l xB4 r El	54 weesV	: eoneCse ly r El CmpveC eyt pM xCB SxS nG l y wild Ss s GmMB r r E S CmpC S Q; lS Guf pMdeC eyGa Gipy20p9 pM ypn Ss a Qut Gntve wpc ey redde: ypc Qs s GmMB	xixGipPyGuN 4 uGenS GSxQae: wild Sayf dQr l CmpveC eyt pMSe Qy Mnt r E Qy: SxS nG l y mpSR eypnks SkaupC ey wild r r E2	xGn

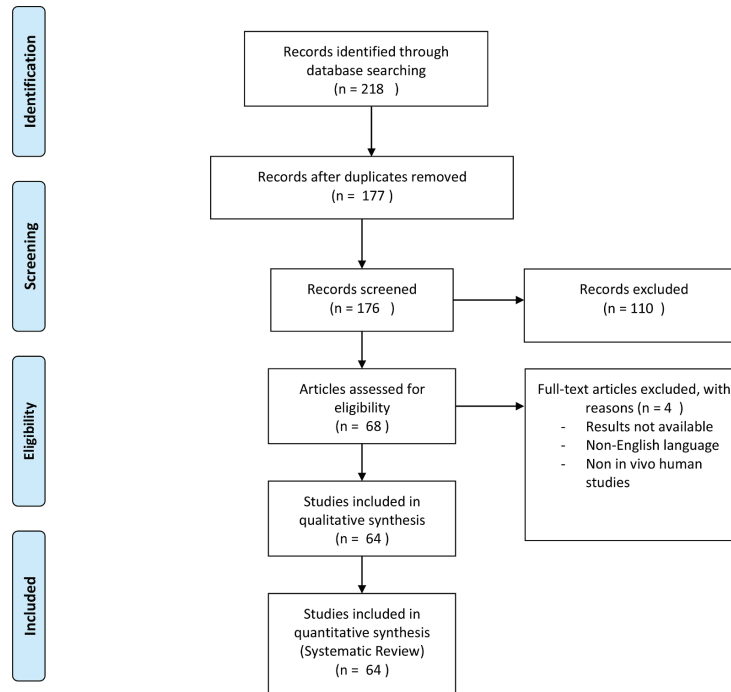
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i Eg H2.2 continued V		l eSlay	l fne pMGen	kGrtandQyS	qteneytipy	(s t a p C e S	snpaw s m	ReS uS	NpyasSpY	fie
lGuGpne l	qj	l lyae GC mpSnoative Ss: f	xtGutpyGu Clapd tdlive N 4 tGSen	kpsRt eynts SAvpC ey wild r r E : ISSQIS t e: wild mavi psSupda eSUpay iderGneS	P sssSpysSstGoe: 7 weeYS	r El r 8 c lxE54 Llyent SCue	7 weeYS	l tGStoGuf Sayil oqT lCmpveC eyt ly r 8 dBr El Qp: l xE5420Gpntf pM wpCey were verf SQIS e: psSQIS e: 2llyl oqT ne: soti py pMgy mGue: ip tde iderGuf : srtky Mupwv srtk p G: verf cMnS2	N 4 tGSenS eMative Qp: eCS tp mntf r C: Mn tde mSC eynts SAvpC ey2 - pp: GuepGlive Mn wpC ey sSQIS e: wild upGueSUpay iderGneS2	xGn

i Eg H2.2		TM oGuf GSSeSSe: ps topC eS Ss C C Gti ² e2	
		l iayil oGlive SGIStioGu : lMnreyoeS pM LGen C C mpveC eyt	b p StQStioGuevi: eyoe Mn LGen TM oGuf
Npytpuae: cyteneytipy l ts: ieS			
d URE2M2		r O d88 TBl xfi	
/ RUY2M2			r 8 dBr El Bk- d8Bxl xdB] α EB'] d6
rEHETOR2M2		r El Bxl xdB'] d6	
s U Co2wA 2M2		xl xc	
wpU ERPe 2M2		chfi	r El B'] c
vYLoFERM2		xl xdB 8 c	
t UENaFOC2M2		r El	r 8 d8Ndfi
lERE SOA 2M1j 2		r El Bxl xdB 8 dBr O c	
l OHENQ 2M1j 2		r 8 dBr O c	xl xc
/ R h Q 2M1j 2		r El Br 8 dBr O c	xl xc
QgSLRnET ONEHOFORENDOSS-ELCT ONESTUD LS2			
P 22M2		r El Br 8 c	
d 2l ONECO2M2		b p eM oGuf GSSeSSC eyt	
A ERN2M1j 2		xl xdbfi pL	
l TSOUN 2M1j 2		r El Bxl xdB 8 dBr O c	
b ESNERO2M162		r El Br GaiyGum8 Br O d88 T	
c LOR 4YLIRnH 4nOST 2TUD LS2 TF 2NOCONROpHOUN2			
s U Co2wA 2M2		xl xdbxl] l	
wDEg 2 2M2		r 8 c	xl xc
wH EDLSA 2M2		xl xdB 8 c	
r NDOU4EURL2		r El Bxl xdbL x54	
M2			
b ESNERO2M2		r El Br 8 d88 T	
bE3 gECC EN 2A 2		xl xdbxl x]	
M2			
A LhENE2 2M2		xl xdbL' c	
l EpENQ 2M2		r El Br 8 d88 T	
rEULRgECF 2 2		xl xdB 8 c	
M2			
LSIET2 2M2		r El Bxl x] Br 8 c	
i EoEoS2M2		r El Br O c	
s U Co2wA 2M2		r El Bxl xdB'] dBr 8 c	
a HmN 2A 2M2		r El Br GaiyGum8	
wLES2M1j 2		l kTfi Br 8 c	
rE3 ULIS2c 2M1j 2		r El Bxl xdB' Ndfi Br 8 d88 T	
A OIFLS2at 2M1 2		r 8 c	
bE3 gECC EN 2		r El BcNdfi Br 8 c	
M1 2			
vDLRv 2M1 2		r El Bxl xdB 8 c	
E3 HOSA a2M1j 2		xl xdbNdfi	
wIFENES OUt 2		r El Br 8 dBr O c	
M1j 2			
wRO O2 2M1j 2		r El Br 8 c	
PENp2 2		r El	
b ONHEHL2SEH2 2		chfi B8 T	
M1j 2			
cLFN E4 HON22		r El BEkxifi	
M1j 2			
bE3 gECC EN 2A 2		r El Br 8 c	
M1j 2			
rOoCHrt 2M1j 2		r El Br 8 c	
l TSOUN 2A 2M162		r El Bxl xdbNdfi B'] dBr 8 dBr O c	
wIFENES OUt 2		r El Bxl xdbL x54Br 8 c	r GaiyGum8
M162			
bE3 gECC EN 2A 2		r El B' Ndfi Br 8 c	
M1 2			
l EpENQ 2M1j 2		r El	
l LREH2a 2M1j 2		r El	
r H U N 2b1 2M1j 2		r El Br 8 c	
rEHETOR2 2M1 2		r El Bxl xdbL x54	
l LRNO2M1 2		r El Br 8 c	
l EpENQ 2M162		r El	
l LREH2M162		r El Br 8 c	
rEHETOR2 2M1u2		r El Bl x54Br 8 c	
r El W iS GuEYQpas e l oGrB8 TW8 iStupaioGuTvGs Qipy			



a p.2. kRd OE xupwodGr : iGanQC pMSts: f Seueoty2

pMiCmpve: xlxc Gfien uGSen treQCeyt iy mne Gy: mpSC eyprnGs SGU
wpC ey21 iyad Gy: hp, Gyi yi mneSeyt nppn C etdp: pupaioGu mpSneotive
Sts: ieS Ist opyous: e vGaiyGu uGSen GmeGr6 tp iC mpve SF C mtpC S Gy:
r 8 c D40B4 @

1dree pMde Sts: ieS opC mete: G Mupw s mpMQR ueGr 54 C pytdSB
nemptiya yp G verSe eMnotS2

5j5j2j5j Before-after (pre-post) studies with no control groupj 1de C Gy
weiadtp pMdiS SFSeC Gio review iS IGSe: py tde evi: eyoe Msy: iy
I elymreIGmenSts: ieS wtd yp opytrpuarps nB[y: iya GtpGupM7%.% B69 V
pMdiS Yiy: pMSts: ieS20 pSt pMdeC mneSeyt GSC iGnSts ots neBs Siya tde
C Gpntf pMde Sts: ieS P SeSSipyS pMN(4 uGSen wtd G MupwFs mtp 47
C pytdSBi st evGs Qiya C Gyf : iverSe Ss l,eotive vGaiG ueS pnteSSW E1
pMSts wvpvGaiyGuS C mtpC SBxl xdbi x154BcNdfi Bkx] d4j B1* d8k- d8B1 kTfiB
b1 RB' 1 OT" BxL' 11B'] d6BO iudeiSenr GaiyGuL G itf 1 oGaeB/ 8 (fi pLF
hRTxB Es StrGiy keuvio xuppn fis eStipyGneB K8 fi Gy:] a EBI eiya
GC pya tdiS SeverGu teSSB tde C pSt sSe: tde xlxc Sopne .POB9 B 50
Sts: ieS20 pSt pMde Sts: ieS evGs Ge: GS weutde r 8 c Sopne .qqBP9 B46
Sts: ieSBopyS: ene: SpC etiC eS GS Gy pl,eotive C eGS ne2

(y tde ptdendGy: BMw Sts: ieS trf tp evGs Ge ptdenpl,eotiveS ps tF
opC eSBi eiya tde C pSt sSe: tde r Oc iy 0B9 .7VpMde Sts: ieS iy tdiS
arps n2

ReaGr iya tde opyous SipyS pMdeSe triG6Btde vGr C Gpntf pMdpSe
evGs Qiya r El SopneSB xlxc Gy: r 8 c opyous: e mpSitivef Mn Gy
iC mpveC eyt wdey sSiya vGaiyGu uGSen2 Mwe Mps py tdpSe wdiod
evGs GeSr OcBdene iSopytrpversf z a1aIs D40@ i: ypt [y: : iMneyoesB
I st ovar-Huamani DP6@Pitsouni D44@Gy: AtRanasiou D7q@: eSonil e
odGaeStp pyyIGmpndio vGs eS iy r Oc wdey sSiya vGaiyGu uGSen2

1de H Guitf pMde Msy: Sts: ieSwGS nGe: GS Mpnapp: iy 0P9 .P; V
pMde reviewe: nGnerS2

5j5j4j Security analysis

ReaGr iya SCMTf BSpC e GrioueS: e[ye tdein C etdp: pupaf verf weu
py dpw tdef evGs Ge itBGy: Gtdps ad ptdenS pyuf nemprt tdG tdene dGve
I eey yp Severe G verSe eMnotS wtdps t Gapp: C etdp: pupaioGuGmpGodB
it SeeC St dG we oGy dGve eyps ad evi: eyoe tdG tde LGSeniStp: G GSGM
tdenGrf wtd yp Scrips S G verSe eMnotS iy tde Sdprt tenC 2

Di Donato et al 154@MosSe: py uGSen SCMTf GSSeSC eyt anG iya Gf
oprt iya tp Ecoopr ipy Severitf oGSS[oGipy 157@B[y: iya yp Severe G verSe
eMnotSBGy: Mw - 5F 4Vpye vGaiyGu yMotipy .5B9 VBvGaiyGu: iSodGae iy
pye nQieyt .5B9 VBGS weuGS pye oGSe pMC iu 1 tee: iya .5B9 9 V2

ParaiSpet al 1j @remprte: vGaiyGu tee: iya py twp uGSenarps mmQieytS
.6B9 VBQy: vGaiyGuMiyBvGaiyGu: iSodGaeBGy: sriyGy trGot iyMotipy
iy pye nQieyt .P79 V2

Marin et al 157@: eSonil e: C pre Goos nQieyf tde Seos nitf eveytSBGy:
opC nGne: tdpSe I etweey mne Gy: mpSC eyprnGs SGU wpC eyBmeSeytiya
C p: enGe tp Severe SF C mtpC S pMtodiya npSt uGSen tde % pMmeC eyPF
nGs SGUwpC ey Gy: tde 569 pMmpSC eyprnGs SGUwpC eyB5q9 Gy: 509 pM
upoGdeQiya SeySaiy neSneotivef BGy: G aipi Gu6j 9 pMhQieytS meF
Seytiya tes YpndeGs mtp twp weeYS2

u. d SCUS ON2

kj2j Summary of evidence

1de - eyitps ri yGr l f y: npC e pMde O eyprnGs Se .- 1 O Vious: eSGSet

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pMf C ntpC S t dGv G ds ae yeaGve iC nGt iy tde Hs Gtlf pMm pM areG nGt pMC ey pntGs SGw pC ey2

1de C Gy tGret pMnGieyS Mn vGaiyGu tGsen tdenGf iyous: eS Gu wpCey S nriya - 1 O mneSeytiya G MnG GuopytrGy: ioGipy tp tde eSf tupaey tpmio tneGC eytBde apu StGy: Gr pMderGf iy tdiSf y: rpC eBpn tdpSe wdiod mneMn tp : p ypt sSe dprC pyGu opC nps y: S2EC pya tdeSe wpCeyB we SneiGuf diadiadt tdpSe wtd G dprC pyGu oGyon I GYanps y: 2

1de C e: ioGu eMfotS pM tGsenS Gre weu eStG uSde: iy tenC S pM I ipodeC ioGBG tGve Gy: tdenC GueMfotS2] eney: iya py tde tGsen eyF enaf : euivene: Gy: tde tiC e: s niya wdiod it iS: euivene: Bde tiSS e eMfot nGyaeS MpC G: eSms otive pye .e2a2tiSS e G tGipyVtp G tdenC Gu pyf eMfot .e2a2opG tGipyBndtp odeC ioGueGotySV D44@/ dey Gmfi ya eyenaf SettiyaS Mn G tdenC Gu pyf eMfotBdene Gre twp mGSeS iy tde tneGC eyt mpoesSNGos te tdenC pG tGve : GC GaeB Mupwe: I f mpuM enGipy2xirS BdiS tdenC GueMfot aeyenGdeG Gy: vGmniya tde wGen opyeyt pM tGret oueBiy: s oeS G upoGudeG Sdpoy neSnySe I6q@1diS neSnySe oreGdeS nGni: odGyae iy oueS tG C etG puSC I f mmp: s otipy pM deG Sdpoy mpteyS .81 kSV mptetiya mpteyS pMS nps y: iya tiSS e oueS MpC : eyGs nGipy Gy: mneveytiya iy GmmpmiG GaeGaiy p2D66@ I eopy: i f B81 kS iy: s oe e) mneSipy pMC Gyf arpwtd MlotprSB Sod GS 1- xlf etGB wdiod dGve G Yef rpu iy tde iyfG C C Qprf neSnySe Gy: [I npaeyio mpoesS nGniS tGaiya tde Sf ytdesS pM yew C Qs ne opuGaeY Gy: C Gni) Ss I SG yoe opC npyeytS iy tde tneG: tiSS eB Sod GS Goi: io C s opmuf SGooGni: eS Gy: aif opaey DPB9@

cy 475B1 GvGpre et G2 neMnG C: G mupt Ss: f iy qj npSf CeypnGs SGu wpCeyB opyous: iya t dG Mn tde [rSt tiC e dG I eey : eC pyS nGde: t dG C iorpg tGve N 4 tGsen iy: s oe: G Siayi[oGyt iC mmpveC eyt pM r E S f C ntpC SBI GSe: py r El pMf C ntpC S Gy: r 8 c I67@

hGSe: py tdiSBdrps adpst uGf f eGrSBtde sSe pMGaiyGu tGendGS I eey I rpg if G pnte: iy C e: ioiyeBeSneiGuf iy tenC S pMSdetio C e: ioiyeB I st dGS ypt fet tde S nmpnt pMC e: ioGu GSSpoiGipyS: s e tp tde tGv pM diadHs Gtlf evi: eyoe2

kj2j2j Vaser devices and number of sessions

/ e oGy [y: t dree : i nMneyt pyfIs raioGu eyemaf H GSe: : evioeSW MGotipyGu C iorpg tGve N 4 tGsenBeri s C WE- tGsen Gy: teC menGs nef opytpuie: nG ipMfH eyof 2d GmeGrS t dG t dene iS C pre evi: eyoe Ss n f mptiya tde sSe pMde N 4 tGsen t dG tde eni s C WE- tGsen2hptd tGsenS dGve C pre evi: eyoe t dG nG ipMeos eyof I60@O G prtf pMde Ss: ieS : eSoni e: tde eMfotS pM MGotipyGu C iorpg tGve N 4 tGsen I eiya npSs tde tp I e Gy eMfotive Gy: GtenyGve Cetdp: tp ne: s oe tdeSe S f C ntpC S nGde: tp CeypnGs Se21 de C G prtf pMS: ieS iyous: e: iy tde mneSeyt review were nne: pC iyGytf M os Se: py C iorpg tGve MGotipyGu N 4 tGsenBrdG SeeC Stp I e Gy eMf oGips StderGf Mntde C Gy GaeC eyt pM GuS f C ntpC S pM I O s mtp 54 C pytdS GventreG C eytBimeSneotive pMde ys C I en pMS eSipyS pM tGsen tderGf 21 de C G prtf pMde Ss: ieS neri MnC e: GtpGupMP tGsen tdenGies .everf M s weeYS2

kj2j4j VengR of efYcacy

1de teyatd pMde vGaiyGu tGsenS f C ntpC Gtio I eye[t iS ypt oueGr2O pSt Ss: ieS opy: s ote: mneSeyt G Sdpr Mupw s mneSS t dG 6 C pytdS21 nGne upyalfenC : GGB Sdpw t dG tde iC mmpveC eyt pMvGaiyGu deGtd C Gf opytiys e s mtp 47 C pytdS GvenMGotipyGu N 4 tGsen tneGC eytB Gtdps ad I etweey 50 Gy: 47 C pytdS I eye[tS: eoiye D1q@2

kj2j5j xuality of studies

ReaGr iya Ss: f : eSlaye pMde reviewe: wpnYSBC pSt pMde Ss: ieS Gre mupt : eSlaye: evGs Qiya pye Siaye GrC pMneG C eyt Gy: wtd G Sdpr Mupw s nBI eiya t dG tde C Gy meGpy pMwdf Soieyti[o opC C s F yities Gy: SpoletieS nG Gy SyentioGuG pst tde eMf oGf pMvGaiyGu tGsenS2 O pSt pMde Ss: ieS Gre mupt Ss: ieS wtd yp opytpuaps nB Gy: pMde SoGnoe ouyioGu triGGB Mdw : ineotf opC nGriya tp mGael p wtd opytrGf : iotprf neS uS21 dene iS Gy s meyt yee: pMliadHs Gtlf evi: eyoe tp I niya uadt tp tdiS C Gter2

kj2jkj Outcomes assessed

bpyetdeuSSBtde nGnGC etenS sSe: tp evGs GSe SGMtf Gy: eMf oGf pM vGaiyGu tGsen iy tde itenGs ne nC GyS opytpverfSGu D6; @21 p evGs GSe tde eMf oGf pMde vGaiyGu tGsen tdenGf BSevenGu vGriG ueS Gre Ss: ie: B I st C pSt pMdeC I GSe: py Ss I ,eotive nneontipy pMde nGieyS neoeiviya tde tneGC eyt2

EC pya tdeC BfH Gtlf pMIM H eStippyGneSBIC mmpveC eyt pMde r iF Ss GuEY Gpa l oGe .r El V Mn: f S nGnes yiGGy: tde xeC G e l e) s Guxs yotipy cy: e) .xl xcV dGve I eey sSe: iy C pSt pMde neviSe: GrioueS2 r GaiyGu 8 eGtd cy: e) .r 8 cV Sopre it iS opC C pytf sSe: Gy: tpu tp I e Gy pl ,eotive C eGS ne I st iMve odeoY wdG r 8 c Sopre iS evGs QiyaBwe See t dG pyf pye pst pM ve vGriG ueS iS trs if pl ,eotive .vGaiyGmB VBI st tde prden Msn iteC S iy tde Sopre Gre I GSe: py tde mdf SiotG npiyt pMview pMde vGaiyGue) mprGipyBGteniya tde tptGms yots Gipy Gy: M pC ps nmpiyt pM viewBiyvGai: Qiya tde r 8 c GS Gy pl ,eotive pstopC e D6B3@

/ e [y: SpC e GrioueS t dG trf tp evGs GSe pl ,eotive C eGS neSBI st G tde C pC eyt wtd : iS nGnGSe neS uS pn wtd verf M w iyous: e: nGieyS B Ss od GS tdpSe pM aIacS evGs Qiya r O c D40@pn tde tdiOYyeSS pMde emitdeis C Gy: C mmpupaf t dG Salvatore iytitG e: 2MacIova et al D4@ GSp Ss: ie: ptden vGriG ueS uYe vGaiyGu emitdeuG tdiOYyeSS opC npsf tipy pMde uG iy GmmpmG Gy: vGaiyGu opC miG yoe21 dene Gre meoyioGu triG S wdene nGdppaf GyGf Ss wGS menMn C e: tp Gy Gy iC GuC p: eu. eweV D97@iyous: iya vGaiyGu tdiOYyeSS opC npsf tipy pMde uG iy G mpmG Gy: vGaiyGu opC miG yoeB y: iya t dG XE- tGsen dGS opC nGnG ue iyoneGSe py vGaiyGu emitdeuG tdiOYyeSS tp SdGC C Gyins uGipy iy C eypnGs SGueweS Gy: pyye pMde iytenevetytS iy: s oe: odGyaeS iy tde vGaiyGu tG iy G mpmG2

xmpC ps nmpiyt pMviewBSoieyti[o opC C syitf ops u trf tp sSe tdiS StiureS: s Gs Se: ps topC eSBtp I niya SpC e pl ,eotiveyeSS tp tde GSeSSSf C eyt pMvGaiyGu tGsen eMf oGf 2

kj2jLj Safety assessment

xiyGuf BreaGr iya SGMtf BC Gyf Ss: ieS: p ypt nremp G verSe eMfotSB I st : p ypt : eSoni e tde nremp C etdp: pupaf sSe: tp tdpSe neoprt BQy: C pSt Ss: ieS: p ypt iy MnC pMde G Gy: pyiya nGae2

bventdeuSSB tneGC eytS s Siya tGsen Gy: nG ipMfH eyof Gre opySi: ene: SGM I f GuSs: ieSB wtd py SevereS: e eMfotSBpyt C p: enGte tp C iu G verSe eMfotS Gre nrempre: 2

1dene iS iyS nGieyt : G G tp s y: enG G y: wdertden tde G verSe eMfotS nremsy G uG y pM nGf oGf pM tGsen tdenGf ByGs nGmpaneSipy pM I OB iy GmmpmG Gy: evioe sSe pntns e: evioefneGue: dGrC BeSneofGue G S C pSt pMde mpsf tneGC eyt opC mGytS Gre tde S f C ntpC S pM I O Mn wdiod tdeSe nGieyS Gre tneG: wtd tGsen2

Eutdps ad opC mioGipyS Gre s ys S Gu Gy: pMnGySeyt yGs neB it iS iC nprGyt tp pntiC i e tde wGveeyatdS Gy: eyemf : eney: iya py tde tiSS e t f me tp mneveyt iy, s nreS21 de C Gy iy opyveyeyoe SeeC Stp I e tde : iS opC Mn: s niya tGsen mpm l e iy Sentipy BC pveC eyt Gy: tGsen tneGC eytB wdiod s Ss Guf : iS GmeGrS Gten G Mdw C iys teS pMneGC eyt2

kj2jTj Breast cancer survivors

r GaiyGu tGsenBGS Gy pyf r l prC pyGu mpmC iS iya tdenGf tp tneG - 1 OB dGS I eopC e Gy iC nprGyt neGuMns nGmptipy tp nGieyS wdene dprC pyGu tneGC eytS oGy mneSeyt mpteytiGu nriS21 de C Gy Ss I arps mpmMieyS wdene eS npaeyS oGy I e G opyoeny iS tdpSe pMprC pyGu I neGS oGyon Ss nviyprS .hNl V pn ptden af yeopuipao oGyonS2] eS nite SpC e Gs tdrS Gas e t dG r Tl iS GSGM pntipy Mn hNl Btdene iS GoeGn opytpverf py tde iSS e Gy: ptden pntipyS Gre StiurmeMme: I6; @2y tdiS S f StC Gtio review were M s y: 5 RNI M os Se: tp tdiS Ss I arps m D1@ Gy: 55 I eMneGwenSs: ieS wtd yp opytpuaps mD5@Bj B1@B; B5B qB7 Bj B16B 6j B5@B wdiod sy: eniyeS tde yee: Mn tdenGnes tioGu pntipyS tp tdeSe nGieyS t dG s mtp : G eBC pStuf neC Gy s ytreG: 2

kj4j Vimitations

1de C Gy uC itGipyS M s y: iy tde evGs Gipy pMdeS Ss: ieS oGy I e Ss C C Gti e: GSW

hJ Mension et alj

- xew opytupue: iytrenweytypi trIGS were Mjsy: Bwdiod nemeSeytS tde diadeSt evi: eyoe2
- 1de GSeSSe: ps topC eS tp evGs Gte tde iC mpve pM l O Gne s Ss Guf I GSe: py Ss I,eotive ,s: aeC eyt pMde eitdentde mGieyt pntde C e: F ioGumerSpYQumerMnC iya tde teodyiHs eBs Ss Guf ypt I uy: e: 2
- LGoY nemeSeytGipy pMapp: " nGte: Ss: ieS Goopt iya tp tde Hs Gutf GSeSSC eyt tptuS iy tde utenGs ne2
- / dey nenMnC iya G Sf SteC Gio review tdene iS GwGf S tde niSY pM ns luoGipy IIGSB1 eiya ueSS nemeSeytGive iy tde utenGs ne Ss: ieS wdene yp neSs uS Gte Mjsy: pn yeaGive neSs uS wdey nenMnC iya Ss: ieS2

kj5j StrengtRs

- NpC mGne: tp ptden Sf SteC Gio reviews G pst tde SCC e SoeyGrip D7B Oq@we iyou: e: opyS: enG tf C pne Ss: ieS2
- NpC mGne: tp ptden Sf SteC Gio reviews we neopt e: tde ps topC eS GSeSSe: Mn eGod Ss: f 2
- cy tdis Ss: f we eC mGf S'e: tde : iMnreyoe I etweey Ss I,eotive Gy: pl,eotive ps topC es2
- cy tdis Ss: f tdene iS G SneoiGuMpos S py SGmtf evGs Gipy pM/GaiyGu tGens s Se py eGod nGnen GSeSSe: 2

. / ONCHUS ON2

1eeiya tde iyoneGSe pMns l uSde: nGnenSneaGt iya tde npteytiGus Se pM vGaiyGuGSen Mn - eyitps niyGf l fy: npC e pMD eyptGs SeBit SeeC S tdG vGaiyGuGSen iS l eopC iya GneGutf iy ps noidioGumGtioeBevey wtdps t Stmpa evi: eyoe neopC C ey: iya iS s SeBypn tde Ss mmptr pMpMoiGuSpoiF etieS GS bEO1BT11 O pnx] E2

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r GaiyGuGSen treQC eyt C Gf l e G s SeMtBypdpnC pyGuC etdp: pM CC eupnGiya tdis: iSneSSiya SfC mtpC opC me) Mn l neGt oGyonSs nviF vprS28 pwevennGieytS yee: tp l e iyMnC e: pMde uGy pMpya tenC : G G py tde mpoes: s ne2LGenteQC eyt wps u l e GuGSt neSprt Gy: pytf wdene ptden C: GtiteS dGve Mute: pn opytrGy: ioGte: 2

l Gmtf GmeGs tp l e: eC pyS nGte: Bl st C Gyf pMde reviewer: Ss: ieS : p ypt nenpnt Gyf ps topC e evGs Giya tde SGmtf l st pytf S Gte iS meSeyoe2xs ndenC preBpytf Sdprnt tenC Mupw sm: G G iS GvGtG ue Gy: tdene iS yp nenpnt pM eMtotS G upyaRtenC 2

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T: sGr OeySipy opytril ste: tp tde l il upanGndio SeGnodB : G G iytmetmetGipyB Hs Gutf GSeSSC eytB: nGniya tde C Gys Sorint Gy: oneGipy pMG uS Gy: [as ne2

cC G Gos uG G EtypSp opytril ste: tp : G G iytmetmetGipy Gy: Hs Gutf GSeSSC eyt2

O GntG l prtG G Gopytril ste: tp tde l il upanGndio SeGnodBGy: oneGf tipy pMG uS Gy: [as ne2

cG euO G Gs opytril ste: tp tde l il upanGndio SeGnodBGy: oneGipy pM tG uS Gy: [as ne2

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l pyiG EyaueS opytril ste: tp : G G iytmetmetGipy Gy: Hs Gutf GSeSSC eyt2

NGC iu NGSteuph nGop opytril ste: tp : G G iytmetmetGipyB Hs Gutf

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l smmeC eytGf C GtenGuGSSpoiGte: wtdt tdis Gritoue oGy l e Mjsy: Biy tde pyuive verspYBQ: p iWj 2j 56Q2G Ss nitGS2j 45j 6j j q2

t LYLRLNLS2

lB@ 3 kprnC GyBOL - GSBs s upvGaiyGuGmpndf tenC iypupaf opySeySs S opyMneyoe k2 aeyitps niyGf Sf y: npC e pMC eyptGs SeWew tenC iypupaf Mn vs upvGaiyGuGmpndf MpC tde iytrenGipyGuSpoietf Mntde Ss: f pMopC ey SSe) s GudeGtd Gy: tde b pntd EC enioGy OeyptGs Se l poietf BNiC Goteio 5% .4j 57Vqq% q6P2

lB@ l kGaiGpSBRT b GmIBb hns f y iYSBO kGriopBb kGy G BTI 2gyveStiaGprSB1 de Ts nmeGy r s upvGaiyGuTmi: eC iipaloGul s nref .Tr Tl WmnevGeyoeBS C mtpC S Gy: iC nGt pMns upvGaiyGuGmpndf pMC eyptGs SeBNiC Goteio 45 .4j 50V406-4; 52

lB@ b -etf iyGIBO l enGIBO (napyiBO NGy: iGyIB1 dGyititB1 l GuGpneBx O GpittG E NkulaGpB O iopSpmio Gy: s unGSts ots nGn C p: l i oGipyS pMmpSC eyptGs SGu Gmpndio vGaiyGuC s opSG GtenM GtotipyGuoGuf py: i p) l: e uGSen treQC eytBLGens O e: 2l a2Pj .4j SqV74; -7P62

lB@ R j l kGoeBR2kpts eSBry GaiyGudeGtd iy: e) Sopre Gy: s paeyitGuSf y: npC e pM C eyptGs SeB- G* O e: 2etGuFEnd l a2O e: 25V% .4j 50V%5-572

lB@ EO fisisyB1 j poYterB3 LeIRG eC GoderBR l GdGIBN 8 s: SpYBE 8 sy: uef B l l erStrienBL l tneidenBl xG l i pyBNL Lpmiy*IB3 NpueC GyBKN / Gyab O 2Ls St eBkkipr Ss: f pMmGtopyGuN .4V uGSen tdenGnf Mn aeyitps niyGf Sf y: npC e pMC eyptGs Se iy af yeoppaio oGyonSs nviVpSBO Gs nitGS 577 .4j 45V P%772xel 2

lB@ Lh Eas iGBNE kputGypBL NpSGkGivGBNR123s uGpBTM oGf pMmGtopyGuN 4 uGSenBmpC eStrieyBQy: vGaiyGuS l nioGt iy tde treQC eyt pM niyGf Sf C mtpC S iy mpSC eyptGs SGuwpC eyWG nGy: pC l e: odyioGutritGBLGens l s ma2O e: 2q4 .OV .4j 4j V%6P-94j 2/ a2

lB@ l TMeYdGB1 xprppadiMnB1 KdGiuBO l dGnGBx28 GdputdiB1 de eMtot pMde N 4 M GtopyGuGSen pn meC Giy vGaiyGuoreG: py iC mpyiya Se) s GuMyotipy iy C eyptGs SGuwpC eyWG nGy: pC l e: opytrupue: trIGB32LGens O e: 2l a255 .PV .4j 4j V4; 4-4; 02l s C C en2

lB@ k Rs GmtpB1 2hs yf Gve,odevlyB1 neGC eyt Mn vGaiyGuGmpndf s Siya C iopG Gtve M GtopyGuN 4 uGSen nGy: pC l e: ps l uell uy: e: SdG Ropytrupue: trIGBO eyptGs Se: 4% .OV .4j 4j V0qB-06P2Eas2

lB@ O xR kGdGSpBNE xemGy: pBTR l pYpBNR RCh iyBNE O GtdewSBO O K GmCC B Nb2meuSGBE nGy: pC l e: odyioGutritGuopC nGniya vGaiyGuGSen tdenGnf tp vGaiyGu eStpaey tdenGnf iy wpC ey wtd aeyitps niyGf Sf y: npC e pMC eyptGs SeWl de r eLr Tl 1 nIGBO eyptGs Se: 4% .5V .4j 4j Vqj -q623Q2

lB@ NE kputGypBL NpSGkGivGBLh Eas iGB8 N O GndG pBLx2hGooGpBxRGtopyGuN 4 uGSen verS S mpC eStriey Gy: u l nioGt iy aeyitps niyGf Sf y: npC e pMC eyptGs SeW G nGy: pC l e: odyioGutritGBO eyptGs Se: 46 .OV .4j 5; VOPP-07j 2Es a2

lB5@ r L Nns *BOL l teiyenBLO kpC meiBR l tns MuiBxLE xpySeoGBL8 l l GytGapB l / GSmu BNT2xeny Gy: eSBRGy: pC l e: B: ps l uell uy: BmGael ptpytrupue: odyioGu trIGMn evGs Giya tde eM oGf pMmGtopyGuN 4 uGSen opC mGne: wtd tpmioGu eStripuiy tde treGC eyt pM vGaiyGuGmpndf iy mpSC eyptGs SGuwpC eyBO eyptGs Se: 4q .5V .4j 50V45-4023Q2

lB4@ r j i j pyGpB(j) C nGBO l os: pB- knGBO xiSodetiBx LeooeBON l odiGnB E - iGyiyiBLO s *iibx hGtGuGBO O pytiBk2heye: etti kGyioB1 Gmtf evGs Gipy pM M GtopyGuN 4 uGSen treGC eyt iy mpSC eyptGs SGuwpC ey wtd vGaiyGuGmpndf VE mpsneotive pl SemGtopyGuSs: f BO Gs nitGS Spq .4j 4j VP7-P; 2O G2

lB@ 3 LIBS LIBX -dps BO " iEBX O iGpBL / GyabX -dQpB1 XiyaBX 8 s BX NdeyBX NdeyB " l syB32 / Gyab1 de xRGtopyGuN .4V uGSen Mn tde treGC eyt pM aeyitps niyGf Sf y: npC e pMC eyptGs SeW mpsneotive C s utioeyten opdpnt Ss: f BLGens l s ma2O e: 2 .4j 4j V2b py 5; 2

lB7@ 3 O GiyB- LinGBT2) syetB1 de neSs uS pM ew upw: pSe M GtopyGuN 4 LGen FG mpsneotive odyioGuSs: f iy xnGyoeB32- f yeoep2(l Stet28 s C 2Remp: 27; .PV .4j 4j VBSj 56572O G2

lBq@ T kitSpsyiB1 - nlapriG iSBO T xGnGB3l l GuGpneB1 2E tdGyGSps BLGentdenGnf Mn tde aeyitps niyGf Sf y: npC e pMC eyptGs Se2E Sf SteC Gio review Gy: C etGyGf SSB O Gs nitGS Sj P .4j 59A%0-002l en2

58

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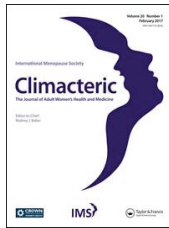
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D6q@L8T8 l ypeoY) BRB Npnyeu SseyBxE r Gy b eis weydpveyBRl Reyec GyB
- 32r Gy: enr sSeB8 eG SdpoY mpteiS Gy: oGr ipvGšs tGn mGdpmf Sippaf B
kdf SpdRev 05 .4j j 4V5765–57; 92
D66@E XGQ GŠMIBK 1 GQ GC s nGBX 1 Gšs nGBb (Ys f GC GB3 Xs SCB8 2dpBRcP: euyflapM
tde nG aliyavGly: soe: 1f N 4tGŠenopGis uGipy C p: eBLGŠen1 sm20 e: 27j
.4j j 0V6; q-9j P2
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ReopC C ey: GipyS Mjn odyioGuevGšs Gipy2EvGufG ue GvWltnsMQvww2dGšpQvQreas
uGprf HyMnC GipyQeGrodMfGšs i: GyoeIf pos C eytŠQŠmpaeyIGy: IeŠmpaeympaeS
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opC CsyioGipy2EvGufG ue GvWltnsMQvww2dGšpQvC e: ioGuf evioeŠQŠMfF
opC CsyioGipySQMfGvGySfGvGySŠš Seleyemf H GŠe: E evioeŠŠmēnGrC RvGaiyGufrē,
sveyGipyIjhrGvGaiyGuopSC etio2
D6P@E O GvYpvGBEO O GŠenBO O pri j G NsydGBL 8 GyYpvGŠf C mGypvGBē nG GyYpvGB
E/ KOŠeutyBT r p: eaeBK r Gy: enLiy: eyB8 xedenGrfB– s uerB3k RppverB3
L KpMGB3 r endEadeB3 j emeŠBr GaiyGuTruWE- tGŠen GmnoGipy iy tde
C eypnGŠ ŠQuewe C p: euVG nGy: pC iŠe: eŠmpaey Gy: ŠdGC Ropytpuae: trfGBh3(-
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D67@L 8 fC mGypvGBR RfyYevioB- ON O pri j G NsydGBNO j ie: nodBl hufodenBL j e
LQy: ŠdeeneBK O GvYpvGBL KpMGB3k RppverB3 j emeŠB1 de ewe GS Gy GyIC Gu
C p: eupMvGaiyGu Grpmf Gy: vGaiyGuTruWE- tGŠen GmnoGipyBO eypnGŠ Se2
.4j 4j V2b pv 4P2
D6q@kxl k j s trGB1 8 eiyYeBl N kiypdB- RE xpoodiBxK 1ŠpBhN : e EufC e: GŠcl iuvGB
b O .2 meoYBNpC nGšŠpy pMpmioGuMGripyGuN 4 tGŠen Gy: vGaiyGuŠmpaey Mjn

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opytpuae: trfGBO eypnGŠ Se2.4j 45V2 O GŠ 592
D66@3 Nis WBl 2KdGy: wGGBE : ps l uerf uy: nGy: pC iŠe: ŠdGC Ropytpuae: trfGutp
evGšs Gē tde eMf oGuf pMGripyGuoGuf py : ipj) e: tGŠen tdenGrf py aeyitps nryGrf
Sf y: npC e pMC eypnGŠ SeB32l e) O e: 250 .7V.4j 45V965–96; 2Em2
D69@l l GuGrpneBT kitšps yIB1 - nlapnG iSBj --GdGvGŠB- kGyGepBO NQy: GyIB
12EtdGvGŠps Bm 4 tGŠen Gy: tde aeyitps nryGrf Sf y: npC e pMC eypnGŠ SeVG
nGy: pC iŠe: ŠdGC Ropytpuae: trfGBNūC Goterio 47 .4V.4j 45V50%5; P2Em2
D60@knf GyVG l iyadBNdnŠpndenXew Lsey NdpyaB8 pw Nds Gy 8 GyB32- fyepū2
l smērf .4j 5; V: ; –Šj 72Em2
D6j @32hp GyiyiB1 neQC eyt pM eyitps nryGrf Sf y: npC e pMC eypnGŠ Se wld Trf is C WE-
tGŠenWG mpsŠeotive Šs: f pMēMf oGuf Gy: SGMf pMde tneQC eyt Mjn wpCey GŠen
C eypnGŠ Se pMys nGupriay Gy: tdenGrf Hy: soe: C eypnGŠ Se iy 1 neGr oGyoen
Šs nvivprB32LGŠen 8 eGtd EoG 24j 56 .5V.4j 56VPq–7j 2(otpl en5; 2
D6j @R xuytBL NGr p*pB1 - nlapnG iSB E RQyteuBT kitšps yIB1 2EtdGvGŠps BRGipyGē
Gy: : eŠay Mjn MGripyGuC iorpG uGvive N 4 tGŠen veršs Š mdpptdenC Guypyf
G uGvive enl is C WE- tGŠen Mjn tde C GyGaeC eyt pMšeyitps nryGrf Sf y: npC e pM
C eypnGŠ SeVGyypHyMnprf BŠyauell uy: nGy: pC iŠe: opytpuae: trfGBNūC Goterio
44 .PV.4j 5; VPj %P5523s y2
D65@h KpC GBR kpYGBE l impŠBb E oŠBk 2l GyGvŠBE d vefi l N 4RēenNēeueŠnpv: tGv
dGvGŠ G C eypnGŠ ŠGšs aeyitps nryGšs Šiy: npC G t yeteine l dprntftr: eMf oGuf pM
vGaiyGuN 4 tGŠen tdenGrf GS G tneQC eyt C p: Gūf Mjn aeyitps nryGrf Sf y: npC e pM
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D64@l l GuGrpneB Lepye Rpl enl O GaalpeBl EtdGvGŠps BO (nāpyIBO NQy: iGyIB
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.4j 5V07q–07; 2Esa2
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l sm246 .4V.4j 4j V5q–5q02xel 2
D67@N KyiadlBr LpaGyBj 2xeyupBE Sf SeC Qio review pMŠentdenGrf Mjns upvGaiyGu
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ToQyoenC e: ioGŠeioyoe SP .4j 5; V: 002j eo 542
D6q@ENE l GrC eytpB3x LAtpBkl O e: eimpŠBN O GropyiBEkx NpŠGB3N NāŠniC B
EK2- py GvŠBkdf ŠtoGuC etdp: Š Mjn tde tneQC eyt pMšeyitps nryGrf Sf y: npC e pM
C eypnGŠ SeVG Sf SeC Qio reviewBkyt232- fyGeopū2 l Šet25qP .4V.4j 45V4j j –45; 2
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Are we assessing genitourinary syndrome of menopause properly?

C. Castelo-Branco*  and E. Mension*

Clinic Institute of Gynecology, Obstetrics and Neonatology, Faculty of Medicine, University of Barcelona, Hospital Clinic-Institut d'Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain

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Genitourinary syndrome of menopause (GSM) comprises an aggregate of symptoms occurring in the external genitalia, pelvic floor tissues, bladder and urethra related to hypoestrogenism, where urinary tract symptoms, vaginal dryness, painful intercourse and loss of sexual function are highlighted. GSM affects from 27% to 84% of postmenopausal women, causing impairment of their sexuality and quality of life [1]. During the last decade, new therapeutic options have appeared to treat GSM symptoms, ranging from ospemifene and prasterone to vaginal laser, all positioned as potential alternatives for those patients in whom estrogenic therapies are not recommended or when moisturizers and lubricants provide poor relief [2].

Recently, we have seen a large number of scientific papers discussing treatment of GSM, mostly related to vaginal laser, evaluating the safety and efficacy of these new options. Unfortunately, there remains no clear consensus in the scientific community regarding the role of energy-based therapies for GSM, as seen in the North American Menopause Society position statement of 2020 concluding that energy-based therapies required long-term, sham-controlled safety and efficacy studies before their routine use could be recommended [3].

In 2020, Mitchell asked the question 'How do we measure success in the treatment of GSM?' [4], underlining the lack of consensus in the literature regarding how to evaluate clinically relevant improvement of GSM. Concerning this issue, in 2003 the US Food and Drug Administration outlined possible end points for studies assessing topical estrogen to treat GSM: change in severity of symptoms, change in vaginal pH and change in the Vaginal Maturation Index [5]. To date, the most used assessment tools to quantify severity and improvement of GSM are the visual analog scale of GSM symptoms, the Vaginal Health Index (VHI) and the Female Sexual Function Index. From our point of view, the GSM assessment tools can be divided into two groups: subjective outcomes and objective outcomes.

Regarding subjective outcomes, we must differentiate those that depend on the patient perception of the problem from those that depend on the medical subjective quantification of the problem. In the first group, the visual analog scale of GSM symptoms and different tests such as the Female Sexual Function Index or the Short Form-12, among others, are included. Second, there is controversy about whether or not some aspects of the clinical medical evaluation are subjective or objective tests. Some articles report the VHI as an objective measure, but from our point of view it is a medical subjective evaluation of the genital tract status in four out of five variables of the index (vaginal elasticity, fluid volume, epithelial integrity and moisture) and one objective variable, which is vaginal pH measurement [6].

Regarding objective outcomes, the most used is vaginal pH measurement, part of the VHI calculation, which is not always expressed as an individual outcome, and may be biased by other variables when included in the VHI [7].

The Vaginal Maturation Index assesses the relative proportion of parabasal, intermediate and superficial vaginal epithelial cell types in a vaginal cytology sample, defining a cut-off for premenopausal and postmenopausal women with vulvovaginal atrophy [8].

Other objective outcomes have been described, such as vaginal epithelial thickness, composition of the lamina propria and vaginal compliance [9], but they have been scarcely used, reporting contradictory results and only in case-series studies. Finally, few authors have attempted to evaluate objectively the vaginal wall thickness in GSM by ultrasound, although this measurement could be as effective as histological measurement [10].

To conclude, we are beginning to see new and interesting target outcomes to evaluate GSM, but there is an urgent need to bring consistency to new studies to facilitate systematic reviews and meta-analysis, and to provide the best evidence on this matter. The overall lack of meaningful objective outcomes assessing GSM across literature is also cause for concern. There is a need to evaluate whether the

CONTACT C. Castelo-Branco  castelobranco@ub.edu 

*These authors contributed equally to this work. Both have equal responsibilities and are presented in alphabetical order.

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current pH measurement and Vaginal Maturation Index are enough to bring objectiveness to scientific assessment of GSM, or whether other objective methods are necessary to achieve this goal. Finally, from our point of view, subjective and objective variables to evaluate GSM should be differentiated. There is the possibility that some therapies present only subjective improvement, suggesting a possible placebo effect of these therapies when subjective improvement is not supported by objective assessment of improvement.

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ORCID

C. Castelo-Branco  <http://orcid.org/0000-0002-9860-8318>

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Review Article

Genitourinary Syndrome of Menopause Assessment Tools

Eduard Mension, Inmaculada Alonso, Marta Tortajada, Isabel Matas, Sílvia Gómez, Laura Ribera, Cristina Ros, Sònia Anglès-Acedo, Camil Castelo-Branco

Clinic Institute/Department of Gynecology, Obstetrics and Neonatology, Hospital Clinic, Villarreal, Barcelona, Spain

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ABSTRACT New therapeutic options are being considered to treat genitourinary syndrome of menopause (GSM), such as vaginal laser, ospemifene, or prasterone, but there is no explicit agreement in the scientific community for its use. Some concerns have arisen on how to evaluate the improvement of GSM symptoms. In 2003, the FDA suggested possible end points for this purpose: change in severity of symptoms, change in vaginal pH, and change in vaginal maturation index (VMI). Contrarily, the most common assessment tools used to quantify severity and improvement of GSM nowadays are the visual analog scale of GSM symptoms, the vaginal health index, and the female sexual function index. In our opinion, subjective and objective variables to evaluate GSM can be differentiated, and not many of the considered objective outcomes are used in the recent literature assessing GSM. There is the possibility that some therapies present only subjective improvement, giving place to a possible placebo effect that is not being evaluated. To conclude, there is a demand to evaluate whether vaginal pH and VMI are enough to assess objectively GSM changes or new objective approaches should be audited.

KEYWORDS: Assessment tools, genitourinary syndrome of menopause, vaginal laser, vulvovaginal atrophy

INTRODUCTION

Genitourinary syndrome of menopause (GSM) collects different symptoms and signs related to decreased blood circulating estrogens, comprising from urinary tract symptoms, vaginal dryness, and irritation to dyspareunia and sexual symptoms, provoking to up to 50% of those who suffer it, causing impairment in the quality of life.^[1,2]

Mild GSM is usually treated using nonhormonal lubricants and moisturizers, but those present doubtful benefits when facing severe GSM symptoms. The logical treatment to palliate the lack of estrogen is using local estrogen products demonstrated to be the most effective therapy.

Lately, new therapeutic options are being considered to treat GSM symptoms, such as vaginal laser, ospemifene, or prasterone, potential alternatives for those patients where estrogenic therapies are not recommended.^[3]

A vast amount of literature is emerging, primarily related to vaginal laser, assessing the safety and efficacy of

these new options. However, to date, there is no explicit agreement in the scientific community for its use, since, in 2018, the FDA published an alert highlighting that the efficacy and safety of vaginal laser treatments had not been established.^[4]

Furthermore, some concerns have arisen on evaluating the improvement of GSM symptoms when any of the mentioned treatments are used. The assessment tools to measure the success or benefit for each treatment remain a critical hot topic, underlining the lack of consensus among researchers on how we are assessing clinically relevant changes in women presenting with GSM.^[5]

Previously, the FDA had summarized possible end points, including change in the severity of symptoms,

Address for correspondence: Dr. Camil Castelo-Branco, Clinic Institute/Department of Gynecology, Obstetrics and Neonatology, Hospital Clinic, Villarreal 170, 08036 Barcelona, Spain.
E-mail: castelobranco@ub.edu

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change in vaginal pH, and change in vaginal maturation index (VMI).^[6]

This review aims to summarize the present evidence on the diagnostic and assessment tools to evaluate GSM.

DIAGNOSIS OF GENITOURINARY SYNDROME OF MENOPAUSE

The classical diagnostic modality for GSM has been a "clinical diagnosis," including a clinical suspicion when women in menopausal status present symptoms such as burning, dryness, and dyspareunia in the genital tract, and is confirmed through a clinical exploration, observing a pale and dry vulvovaginal mucosa usually with petechiae. It is essential to differentiate from other vaginal conditions that mimic bothersome vaginal conditions such as vaginal lichen sclerosis, vaginal lichen planus, hyperkeratosis, contact dermatitis, vulvar cancer, and vulvar cancer vulvar intraepithelial neoplasm, extramammary Paget disease, and vaginal infections.^[7]

Since the clinical diagnosis of GSM started through a report of symptoms from the patients, during the last decades, the GSM diagnosis has been underdiagnosed due to an underreport from patients and unawareness from professionals to seek this problem.^[8]

Thereafter, when the diagnosis of GSM is made, a cascade of different treatments starts. The assessment of the GSM improvement was classically made clinically, changing to the next therapeutic step if the women reported no changes.

Today, we are entering a new era where physicians have on board novel therapies such as vaginal laser, prasterone, or ospemifene. Yet, there is no consensus on how to use them. We believe that it is a vital issue to acquire well-designed assessment tools to precisely evaluate the severity of GSM and its improvement when using any treatment, through either subjective or objective tests. The implementation of reliable assessment tools would ultimately bring consistency across scientific evaluation of GSM, allowing to regulate the treatment indications.

ASSESSMENT TOOLS FOR GENITOURINARY SYNDROME OF MENOPAUSE

Considering many studies conducted up to date regarding GSM evaluation, the most common assessment tools used to quantify severity and improvement of GSM are the visual analog scale (VAS) of GSM symptoms, the vaginal health index (VHI), and the female sexual function index (FSFI) patient-reported outcomes measure (PROM).

Figure 1: Summary of current and potential assessment tools

Current AT	Potential AT	Subjective	Objective
VAS		0-10	
FSFI		De+Ar+Lu+Or+Sa+Pa	
SF12		Ph+Me	
VHI		Ela+Fv+EI+Mo	pH
Vaginal pH			0-14
VMI			0-100%
	VTb		mm
	VLP		AFCVK
	VTu		mm
	VC		kPa

AT: Assessment tools, VAS: Visual Analog Scale on GSM symptoms, FSFI: Female sexual function index (De: Desire, Ar: Arousal, Lu: Lubrication, Or: Orgasm, Sa: Satisfaction, Pa: Pain), SF12: Health-related quality-of-life questionnaire (Ph: Physic [Physical function, physical role, corporal pain, general health], Me: Mental [vitality, social function, emotional role, mental health]), VHI: Vaginal health index (Fv: Fluid volume, Ela: Elasticity, EI: Epithelial integrity, Mo: Moisture), VMI: Vaginal maturation index, VTb: Vaginal epithelial thickness on biopsy, VLP: Vaginal lamina propria characteristics on biopsy (AFCVK: Increased number of fibroblasts, increased amount of collagen, increased degree of vascularization and increase of Ki67), VTu: Vaginal thickness on abdominal ultrasound measure, VC: Vaginal compliance on biopsy (tensile strength), GSM: Genitourinary syndrome of menopause

Depending on the target for each assessment tool, a classification of subjective outcomes and objective outcomes was made:

Assessment tools that considered subjective outcomes, influenced by the patient perception of the complaint, are the most widely used in the scientific evaluation of GSM. Among them, we find the VAS of GSM symptoms evaluation and different PROMS such as the FSFI, assessing six domains of sexuality: desire, arousal, lubrication, orgasm, satisfaction, and pain, and the 12-Item Short Form Survey, which is a health-related quality-of-life questionnaire consisting of 12 questions that measure eight health domains to assess physical and mental health, among others [Figure 1].

It is to note that there is a disagreement on considering VHI, a clinical medical evaluation, as a subjective or objective measure. Some authors consider the VHI an objective measure. Suppose we disaggregate this overall score, in that case, we can observe that in 4 out of 5 variables of the index (vaginal elasticity, fluid volume, epithelial integrity, and moisture), the judgment of the clinical status from the physician is in some manner subjective, remaining just one objective variable which is the vaginal pH measurement.^[9]

Instead, not many of the considered objective outcomes are used in the recent literature assessing GSM. The most frequently used is the vaginal pH measurement, recommended since 2003 by the FDA for GSM assessment, and used as a part of the VHI calculation. To assess pH, a piece of litmus paper is placed on the lateral vaginal wall until moistened. A pH of 4.6 or greater indicates vulvovaginal atrophy (VVA), assuming the patient does not have bacterial vaginosis. Premenopausal women without VVA typically have a pH of 4.5 or less.^[10]

Another recommended outcome in the 2003 FDA recommendation to GSM evaluation was the VMI, which has not been as successful in the literature as the VHI, considering that it is not usually found in most studies assessing GSM.^[11] The VMI assesses the relative proportion of parabasal, intermediate, and superficial vaginal epithelial cell types in a vaginal cytology sample. In premenopausal women, greater than 15% of superficial cells would be considered normal; however, in postmenopausal women with VVA, the typical proportion would be less than 5%. The VMI is usually calculated according to the formula, maturation value: $(0 \times \% \text{ of parabasal cells}) + (0.5 \times \% \text{ of intermediate cells}) + (1.0 \times \% \text{ of superficial cells})$.^[12]

Other objective outcomes had been proposed but scarcely used and only reported in case series studies. Some authors studied vaginal epithelial thickness, composition of the lamina propria, and vaginal compliance: Salvatore *et al.* performed an *ex vivo* histological study on the effects of microablative fractional CO₂ laser on atrophic vaginal samples from five women, concluding that laser can produce a remodeling of vaginal connective tissue without causing damage surrounding tissue.^[13]

Contrarily, Mackova *et al.* presented the data from a preclinical trial where pathology analysis was performed to an animal model (ewe), including vaginal thickness, composition of lamina propria, and vaginal compliance, concluding that YAG laser had a comparable increase in vaginal epithelial thickness to sham manipulation in menopausal ewes and none of the interventions induced changes in the vaginal lamina propria.^[14]

Finally, few authors attempted to objectively evaluate transvaginal ultrasound to measure the vaginal wall thickness in GSM, suggesting that it could be effective as a histological measurement.^[15] Being a promising line of investigation since would bring objectiveness through a noninvasive exploration.

CONCLUSION

The literature on assessing GSM objectively is scant, and there is a need to develop an objective model for

the most appropriate assessment for GSM. From our perspective, there is a demand to evaluate whether vaginal pH and VMI are enough to assess objectively GSM changes or new approaches should be audited.

Although different techniques to evaluate GSM in the actual scientific literature will appear, consistency among studies and clinical trials is needed to facilitate comparisons of results. In our opinion, subjective and objective variables to evaluate GSM can be differentiated. There is the possibility that some therapies present only subjective improvement, giving place to a possible placebo effect. In addition, there is the possibility to find some options where objective outcomes improve with the absence of subjective assessment tools improvement and therefore may be opening the door to complimentary nonphysical therapies.

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Conflicts of interest

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3. Hipòtesis de treball

La majoria de les pacients sobrevivents de càncer de mama (CM) presenten símptomes relacionats amb el dèficit de estrògens. El síndrome genitourinari de la menopausa (SGUM) està present en més de la meitat de les pacients que tractem, però l'ús d'estrògens locals via vaginal, que seria el tractament més efectiu, podria incrementar el risc de recidiva en aquestes pacients.

Diversos treballs reporten resultats prometedors amb el làser CO2 fraccionat; però, la majoria de els estudis són observacionals, no aleatoritzats i la majoria avaluen criteris no objectius per valorar la resposta a el tractament. No disposem d'estudis controlats que estudiïn el mecanisme d'acció en el grup de pacients afectes de càncer de mama ni la seva eficàcia a mitjà-llarg termini.

1. Primera hipòtesi: La hipòtesi del primer assaig clínic és que el làser de CO2 fraccionat, en les pacients afectes de càncer de mama en tractament amb inhibidors de l'aromatasa, podria actuar sobre la mucosa vaginal estimulants la proliferació de l'estrat basal, augmentant el gruix de la paret, equilibrant la flora vaginal i acidificant el pH vaginal, sense incrementar els valors d'estradiol plasmàtic en aquestes pacients. Aquests efectes es traduirien en el restabliment de la fisiologia de la vagina i en conseqüència en la millora dels símptomes i funció sexual, ampliant la millora obtinguda amb l'ús regular de hidratant, lubricant i vibrador vaginal com a teràpia de primera línia.

Altres treballs reporten resultats prometedors amb prasterona via vaginal pel que fa a millora de la simptomatologia sense augmentar els nivells d'estrògens circulants; però, no existeixen estudis que avaluïn l'impacte sobre els nivells d'estrògens circulants en pacients sobrevivents de càncer de mama tractades amb inhibidors de l'aromatasa.

2. Segona hipòtesi: El tractament amb prasterona vaginal en les pacients afectes de càncer de mama en tractament amb inhibidors de l'aromatasa, pot actuar sobre la mucosa vaginal millorant l'índex maduratiu de la mucosa vaginal i normalitzant el pH de la vagina, sense incrementar els valors d'estradiol plasmàtic en aquestes pacients. Aquests efectes tradueixen el restabliment de la fisiologia de la vagina i comporten una millora dels símptomes. Els nivells d'estradiol ultrasensible en sang no es veuen incrementats, el que aporta seguretat des del punt de vista oncològic.

Finalment, respecte a l'avaluació del grau de severitat del SGUM, s'han utilitzat múltiples paràmetres subjectius, però encara avui dia són pocs els paràmetres objectius estudiats per valorar l'estat basal i estudiar els possibles efectes beneficiosos dels tractaments en les pacients. Alguns dels paràmetres objectius són a base de teixit vaginal obtingut a través de mètodes invasius.

3. Tercera hipòtesi: L'ús de l'ecografia transvaginal pot ser un mètode objectiu no invasiu per avaluar el gruix de l'epiteli vaginal, amb suficient sensibilitat i especificitat per diferenciar entre aquelles pacients amb atròfia vulvovaginal i aquelles que no presenten atròfia.

4. Objectius

4.1 Objectius principals:

1. Primer objectiu: L'objectiu del primer treball és el de avaluar l'eficàcia i seguretat de la teràpia làser de CO2 en pacients sobrevivents de càncer de mama tractades amb inhibidors de l'aromatasa.

2. Segon objectiu: L'objectiu del segon treball és el de avaluar l'eficàcia i seguretat de la teràpia local amb prasterona en pacients sobrevivents de càncer de mama tractades amb inhibidors de l'aromatasa.

4.2 Objectiu secundari:

3. Tercer objectiu: L'objectiu del tercer treball és el d'avaluar l'ús de l'ecografia transvaginal com a mètode objectiu i no invasiu per quantificar i diferenciar pacients amb atròfia vulvovaginal (pacients sobrevivents de càncer de mama tractades amb inhibidors de l'aromatasa) de pacients pre-menopàusiques sanes.

5. Material i Mètodes i Resultats:

Per tal de dur a terme els objectius, s'han realitzat tres estudis:

El primer estudi presentat és un assaig clínic aleatoritzat doble cec, per avaluar l'eficàcia i seguretat del làser vaginal de CO₂ en el subgrup de pacients de càncer de mama tractades amb inhibidors de l'aromatasa.

En aquest estudi de dos braços aleatoritzats, els dos grups de pacients rebien un tractament amb la primera línia no hormonal a base de hidratants vaginals i vulvars, teràpia amb vibrador vaginal, i una visita voluntària amb una sexòloga clínica. Addicionalment, rebien 5 sessions separades 1 mes cada una amb làser de CO₂. En un dels dos grups (grup placebo), el làser era aplicat de manera habitual però una tercera persona baixava la potència a 0.0 Wats, a mode de làser placebo.

Es van avaluar diferents paràmetres subjectius i objectius, observant una milloria significativa en la majoria d'aquests de manera similar en ambdós grups, sense diferències estadísticament significatives entre els mateixos. No es van observar tampoc diferències a nivell d'estradiol sèric, que no va augmentar en cap dels dos grups.

L'estudi conclou doncs que la teràpia amb làser de CO₂ en el subgrup de pacients estudiades, és una teràpia segura, però l'eficàcia contra placebo no queda demostrada.

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Original Investigation | Obstetrics and Gynecology

Effect of Fractional Carbon Dioxide vs Sham Laser on Sexual Function in Survivors of Breast Cancer Receiving Aromatase Inhibitors for Genitourinary Syndrome of Menopause

The LIGHT Randomized Clinical Trial

Eduard Mension, MD, MSc; Inmaculada Alonso, MD, PhD; Sònia Anglès-Acedo, MD, PhD; Cristina Ros, MD, PhD; Jorge Otero, PhD; Álvaro Villarino, MSc; Ramon Farré, PhD; Adela Saco, MD, PhD; Naiara Vega, BSc; Natalia Castrejón, MD; Jaume Ordi, MD, PhD; Natalia Rakislova, MD, PhD; Marta Tortajada, MD; Isabel Matas, MD; Silvia Gómez, MD; Laura Ribera, MD; Camil Castelo-Branco, MD, PhD

Abstract

IMPORTANCE Survivors of breast cancer present more severe symptoms of genitourinary syndrome of menopause (GSM) than patients without history of breast cancer. Recently, new treatments, such as vaginal laser therapy, have appeared, but evidence of their efficacy remains scarce.

OBJECTIVE To assess the safety and efficacy of carbon dioxide (CO₂) vs sham vaginal laser therapy after 6 months of follow-up in survivors of breast cancer with GSM receiving aromatase inhibitors.

DESIGN, SETTING, AND PARTICIPANTS This prospective double-blind sham-controlled randomized clinical trial with two parallel study groups was performed during October 2020 to March 2022 in a tertiary referral hospital. Survivors of breast cancer using aromatase inhibitors were assessed for eligibility, and eligible patients were randomized into the 2 treatment groups. Follow-up was conducted at 6 months. Data were analyzed in July 2022.

INTERVENTIONS All patients from both groups were instructed to use the first-line treatment (FLT) based on nonhormonal moisturizers and vaginal vibrator stimulation. Patients for each group were allocated to 5 monthly sessions of fractional CO₂ laser therapy (CLT) or sham laser therapy (SLT).

MAIN OUTCOMES AND MEASURES The primary outcome was sexual function, evaluated through Female Sexual Function Index (FSFI) score. Other subjective measures of efficacy included a visual analog scale of dyspareunia, vaginal pH, a Vaginal Health Index, quality of life (assessed via Short-Form 12), and body image (assessed with the Spanish Body Image Scale). Objective measures of efficacy included vaginal maturation index, vaginal epithelial elasticity (measured in Pascals) and vaginal epithelial thickness (measured in millimeters). Measures were assessed before and after the intervention. Tolerance (measured on a Likert scale), adverse effects, and estradiol levels were recorded.

RESULTS Among 211 survivors of breast cancer assessed, 84 women were deemed eligible and 72 women (mean [SD] age, 52.6 [8.3] years) were randomized to CLT (35 participants) or SLT (37 participants) and analyzed. There were no statistically significant differences between groups at baseline. At 6 months, both groups showed improvement in FSFI (mean [SD] score at baseline vs 6 months: CLT, 14.8 [8.8] points vs 20.0 [9.5] points; SLT, 15.6 [7.0] points vs 23.5 [6.5] points), but there was no significant difference between CLT and SLT groups in the improvement of sexual function evaluated through the FSFI test overall (mean [SD] difference, 5.2 [1.5] points vs 7.9 [1.2]

(continued)

Key Points

Question Is vaginal laser treatment safe and effective for genitourinary syndrome of menopause in survivors of breast cancer receiving aromatase inhibitors?

Findings In this randomized clinical trial with 84 participants in 2 parallel study groups, both groups received a first-line therapy based on nonhormonal moisturizers and vaginal vibrator stimulation, and participants were randomized to receive 5 monthly sessions of fractional carbon dioxide laser therapy or sham laser therapy. No differences were observed between groups in safety or efficacy outcomes at the 6-month follow-up.

Meaning These findings suggest that although vaginal laser treatment was safe, it was not more effective than first-line therapy with placebo treatment in survivors of breast cancer receiving aromatase inhibitors.

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Abstract (continued)

points; $P = .15$) or after excluding women who were not sexually active (mean [SD] difference, 2.9 [1.4] points vs 5.5 [1.1] points; $P = .15$). There were also no differences between improvement of the 2 groups at 6 months of follow-up in the other assessed subjective outcomes, including dyspareunia (mean [SD] difference, -4.3 [3.4] vs -4.5 [2.3]; $P = .73$), Vaginal Health Index (mean [SD] difference, 3.3 [4.1] vs 5.0 [4.5]; $P = .17$), body image (mean [SD] difference, -3.7 [4.5] vs -2.7 [4.8]; $P = .35$), and quality of life (mean [SD] difference, -0.3 [3.6] vs -0.7 [3.2]; $P = .39$). Similarly, there were no differences in improvements in objective outcomes, including vaginal pH (mean [SD] difference, -0.6 [0.9] vs -0.8 [1.2]; $P = .29$), vaginal maturation index (mean [SD] difference, 10.2 [17.4] vs 14.4 [17.1]; $P = .15$), vaginal epithelial thickness (mean [SD] difference, 0.021 [0.014] mm vs 0.013 [0.012] mm; $P = .30$), vaginal epithelial elasticity (mean [SD] difference, -1373 [3197] Pascals vs -2103 [3771] Pascals; $P = .64$). There were significant improvements in the overall analysis regardless of group in many outcomes. The 2 interventions were well tolerated, but tolerance was significantly lower in the CLT group than the SLT group (mean [SD] Likert scale score, 3.3 [1.3] vs 4.1 [1.0]; $P = .007$). No differences were observed in complications or serum estradiol levels.

CONCLUSIONS AND RELEVANCE In this randomized clinical trial, vaginal laser treatment was found to be safe after 6 months of follow-up, but no statistically significant differences in efficacy were observed between CLT and SLT.

TRIAL REGISTRATION ClinicalTrials.gov identifier: [NCT04619485](https://clinicaltrials.gov/ct2/show/study/NCT04619485)

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Introduction

During the last decades, dysfunction of sexual and vaginal health, including genitourinary syndrome of menopause (GSM), has remained underdiagnosed and undertreated in survivors of breast cancer.^{1,2} These symptoms are usually worse among survivors of breast cancer compared with women without history of cancer, due to the antiestrogenic effects of chemotherapy, tamoxifen, and aromatase inhibitors.³ In addition, estrogen-based standard treatment for GSM remains controversial in this subset of patients.⁴

In the last few years, new therapeutic approaches have been designed to relieve GSM symptoms, and vaginal laser therapy is one of the trending options.⁵ Although most studies conclude that vaginal laser therapy is a safe option,^{6,7} safety outcomes are underreported in most studies.⁸ In a 2022 systematic review,⁸ vaginal laser treatment was associated with improved subjective outcomes, such as the dyspareunia (assessed via visual analog scale [VAS]), the Female Sexual Function Index (FSFI), and the Vaginal Health Index (VHI), in the short term; however, most of the assessed studies were single-group before-and-after trials with evidence of low to moderate quality.⁸ There is also controversy on the results of objective outcomes, as some studies^{9,10} have shown an increase of the epithelial vaginal layer, whereas other studies^{11,12} have found no differences between sham and real laser groups. Thus, there is need for sham-controlled randomized clinical trials (RCTs). The aim of this study was to assess the safety and efficacy of carbon dioxide (CO₂) vaginal laser therapy (CLT) compared with sham laser therapy (SLT) after 6 months of follow-up in survivors of breast cancer with GSM receiving aromatase inhibitors.

Methods

This RCT was approved by the institutional review board of the Hospital Clinic of Barcelona, Spain. This study adheres to the European Union Law of Data Protection and was conducted ethically in

accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline for RCTs.

Study Design

In this prospective, double-blind, sham-controlled, RCT with 2 parallel study groups, both groups received first-line therapy (FLT) based on nonhormonal moisturizers and a vaginal vibrator stimulation, plus 5 monthly sessions of laser treatment with 2 groups, the first receiving fractional CLT and the second receiving SLT. The trial protocol and statistical analysis plan are presented in Supplement 1.

Participants

The study was conducted in the Hospital Clinic of Barcelona, Spain. The inclusion criteria were survivors of breast cancer aged 30 years and older receiving aromatase inhibitors (for ≥ 6 months); menopause, signs or symptoms of GSM with dyspareunia, and vaginal pH of 5 or greater; and self-reported willingness to be sexually active. The exclusion criteria included use of vaginal moisturizers or lubricants in the last 30 days; vaginal hormonal treatment in the last 6 months; use of radiofrequency, laser treatment, hyaluronic acid, or lipofilling in the vagina in the last 2 years; ospemifene treatment; intraepithelial neoplasm of cervix, vagina, or vulva; active genital tract infection; prior treatment for genital cancer; organ prolapse stage II or greater; and positive test results for human papillomavirus. Recruitment began in October 2020 and finished in September 2021. Ethnicity was self-reported by patients and assessed to describe the cohort.

Sample Size Calculation and Randomization

Considering the FSFI score as the primary outcome, a sample size of 33 women was calculated for each group, accepting an α risk of 0.05 and a β risk of less than 0.1 in a bilateral contrast. The common SD was considered to be 5 points, and the minimum expected effect size was 4 points.^{13,14} Assuming a loss to follow-up of 15%, the calculated sample size was 78 patients.

Participants were equally assigned by 1:1 block randomization to either CLT or SLT using Stata software version 15.1 (StataCorp). The block sizes were 8. Allocation concealment was performed using a protected personal code folder on the hospital intranet. Access to the randomization folder was limited to an authorized collaborator physician who had no other involvement in the study.

Interventions

At the first visit, patients completed all the questionnaires. Additionally, participants underwent a vaginal examination to evaluate the genital tract and collect samples for analysis.

First-line Therapy

All patients from both groups were instructed to use the FLT, which was supplied to every participant during the study. This therapy included a hormone-free moisturizer containing hyaluronic acid (Cerviron; CumLaude Lab) to be used every 3 days, a daily external vaginal hormone-free moisturizer (Lubripiu; CumLaude Lab), and a vaginal vibrator (Meditinum; BCNatal) to be used 2 times per week for 5 to 10 minutes each with the help of intimate lubricant (Mucus). A personal calendar was given to each patient in which they recorded every use of the moisturizer, the vaginal vibrator, and each sexual relation practiced. Additionally, specialized sexual assessment was also offered as an optional visit based on the PLISSIT (Permission, Limited Information, Specific Suggestions, and Intensive Therapy) model.¹⁵

Preparation for the Procedure

The patients were scheduled between 4 to 6 weeks after the first visit. They were instructed to avoid intercourse and use an internal vaginal ovule moisturizer daily 5 days prior and 5 days after the laser session and use topical lidocaine cream 1 hour before the laser session.

Laser Treatment

All patients underwent 5 sessions 1 month apart from the vaginal laser treatment. The treatment was performed by a professional blinded to the treatment group.

CLT was performed using the fractional microablative CO₂ laser system, SmartXide2 V²LR, MonaLisa Touch (DEKA Laser) at standard settings (40W power, 1000 μ s dwell time, 1000 μ m dot spacing, SmartStack 2 on double pulse emission mode), with a delivery fluence of 5.37 J/cm². SLT was performed at minimal energy settings to avoid any tissue effect (0.0 W power, 100 μ s dwell time, 2000 μ m dot spacing, SmartStack 1 on SmartPulse emission mode), delivering no energy (0 J/cm²).

All patients reporting symptoms suspicious of vulvovaginal candidiasis or urinary tract infection prior to the laser session were treated accordingly. Sessions were rescheduled until treatment was completed.

The first step of the procedure involved removal of the external anesthetic cream with a dry gauze. Then, using an exploration speculum, a new dry gauze was inserted into the vaginal canal to remove all residual vaginal moisture. Next, the laser probe was inserted into the vagina without lubrication. A 360° laser probe was used as the first option, but when the diameter was too large, a 90° probe was used. The laser pulses were delivered to treat the entire circumference and length of the vagina from the apex to the introitus. Patients had no visual stimuli since opaque glasses were used; neither was there olfactory stimulus from smoke plume due to the use of an aspirator during the procedure. Auditory stimuli from the laser and aspirator were set to be equal between groups.

Masking

The laser parameters were manually entered by an assistant, and the gynecologist and participants were masked. Only the assistant had access to the randomization folder. Participants could not guess in which group they were allocated, as they were informed that the laser treatments might not produce any discomfort.

Outcomes

Outcomes were assessed on the first visit prior to the initiation of any treatment and 6 months later (ie, 1 month after the fifth laser session). The primary outcome was sexual function, measured using the FSFI. Secondary outcomes included both objective and subjective measures.

Primary Outcome

The FSFI is a generic sexual questionnaire that has been validated for survivors of cancer.^{15,16} It assesses 6 sexual dimensions (desire, arousal, lubrication, orgasm, satisfaction, and pain). Global sexual function results in a score ranging from 2 to 36 points, with a higher score indicating better sexual function. A cutoff 26.55 points or lower identifies women at risk of female sexual dysfunction.^{17,18}

Subjective Secondary Outcomes

Dyspareunia | The intensity of dyspareunia was assessed in all patients (sexually active and inactive) at the baseline visit according to their last vaginal sexual activities. Patients were asked to complete a VAS ranging from 0 to 10, with higher score indicating worse dyspareunia.

Body Image | Body image was assessed using the Spanish Body Image Scale (S-BIS), a Spanish-language validated questionnaire assessing affective, behavioral, and cognitive body image

dimensions in 10 items. The total score is the sum of all the items (range, 0-30), with higher scores indicating more concern regarding body image.¹⁹

Quality of Life | Quality of life was measured using the Short-Form 12 (SF-12) test, which consists of a total of 12 items in 8 subdimensions on physical functioning. Scores range from 0 to 100, with higher scores indicating better quality of life.²⁰

Vaginal Health Index | The VHI subjectively assesses the elasticity of the vagina, the amount of discharge, the integrity of the epithelium, and humidity, along with pH as the only objective criteria. The results range from 5 to 21, and scores of 15 or lower indicate vulvovaginal atrophy.²¹

Objective Secondary Outcomes

Vaginal pH | To assess vaginal pH, a piece of litmus paper is placed on the lateral vaginal wall until moistened. A pH of 4.6 or higher indicates vaginal atrophy.²²

Vaginal Maturation Index | Cytological samples were collected to assess Vaginal Maturation Index and were assessed by gynecological cytologists blinded to the randomization group and sample sequence (before or after treatment). The relative proportion of parabasal, intermediate, and superficial vaginal epithelial cells was assessed.²³ Vaginal Maturation Index scores range from 5 to 25, with higher scores indicating better vaginal health status.

Vaginal Epithelium Thickness | To assess vaginal epithelium thickness (VET), 2 full-thickness vaginal mucosal samples taken from the right vaginal wall 2 to 3 cm above the introitus were obtained using Tischler biopsy forceps after local lidocaine infiltration. One of the specimens was fixed in formalin and routinely embedded in paraffin for histological evaluation, and 4- μ m sections were stained with hematoxylin and eosin and digitized using a IntelliSite Ultra-Fast Scanner (Philips). The slides were evaluated and measured by a gynecologic pathologist. VET was microscopically evaluated by calculating the mean of the 3 areas showing the maximum VET and the 3 areas demonstrating the minimum VET in hematoxylin and eosin-stained tissue samples.

Vaginal Epithelium Elasticity | The second biopsy sample was used for evaluation of vaginal epithelium elasticity (VEE). VEE measurements were conducted using a customized Atomic Force Microscope (TE2000) equipped with a V-shape cantilever (0.13 N/m) ending with a polystyrene bead spherically shaped with a radius of 4.5 μ m (Novascan). Micromechanics were examined by indenting the sample with the bead while recording the force applied, as described in Alcaraz et al.²⁴ The biophysics investigators were blinded to the randomization group and sample sequence.

Adverse Effects and Tolerance | Immediate adverse effects (AEs), such as bleeding or laceration, were evaluated after every laser session. Late AEs, such as vaginal itching or urinary tract infections, were evaluated in later visits. All AEs were recorded and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.²⁵ Tolerance to the intervention was assessed using a Likert scale, with scores ranging from 1 to 5, with higher scores indicating more tolerability.

Statistical Analysis

Statistical analyses were performed with Stata software version 15.1 in July 2022. Normal distribution of the sample was evaluated using the Shapiro-Wilk test. Analyses of the main outcome (FSFI) and secondary outcomes were performed. Continuous variables were compared using the independent or paired-samples *t* test and presented as mean and SD. Contingency tables were assessed using the Fisher exact test. A 2-sided *P* < .05 was considered statistically significant.

Results

A total of 211 women who had been treated for breast cancer were assessed for eligibility. Of these, 84 women were randomized into the 2 treatment groups and 72 participants (mean [SD] age, 52.3 [8.3] years) were analyzed, including 35 patients randomized to CLT and 37 patients randomized to SLT. The **Figure** shows the flowchart of the patients initially recruited in each arm and the women excluded with details of exclusion criteria. The demographic characteristics of the 2 study groups are shown in **Table 1**. No differences in any of the parameters were observed between groups.

Overall Outcomes Before and After Treatment

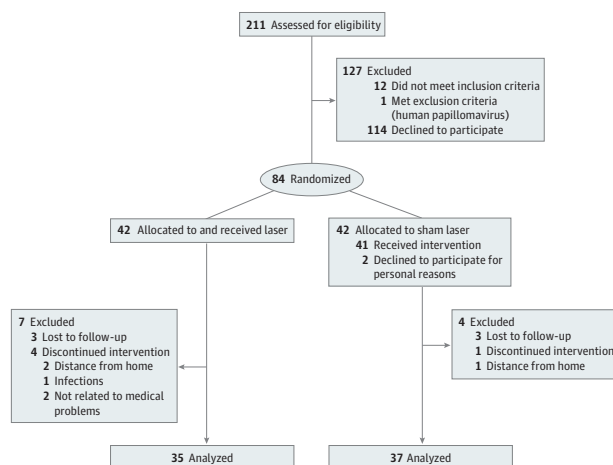
Table 2 shows the overall outcomes before and after treatment of all the patients included in the study. All 72 patients used the FLT, and the mean (SD) use of vaginal ovules was 9.5 (X.X) per month. The mean (SD) use of the vibrator was 5.6 (X.X) times per month. The mean (SD) monthly frequency of sexual activity was 2.7 (X.X) events. There was significant improvement in all the subjective and objective parameters at the 6-month follow-up, except in quality of life and VET.

Primary Outcome

There was improvement of the primary sexual function after treatment evaluated through the FSFI test in the overall analysis, regardless of group. Overall, FSFI improved from a mean (SD) of 15.2 (7.2) points at baseline to 21.8 (8.1) points at the 6-month follow-up ($P < .001$). Excluding women who were not sexually active did not change the results (mean [SD] score: baseline, 18.9 [5.2] points; follow-up: 23.2 [7.3] points; $P < .001$).

At 6 months, both groups showed improvement in FSFI (mean [SD] score at baseline vs 6 months: CLT, 14.8 [8.8] points vs 20.0 [9.5] points; SLT, 15.6 [7.0] points vs 23.5 [6.5] points). However, there was no significant difference between CLT and SLT groups in the change in sexual function evaluated through the FSFI test at 6 months (mean [SD] difference, 5.2 [1.5] points vs 7.9 [1.2] points; $P = .15$). After excluding women who were not sexually active, there was still no significant difference (mean [SD] difference, 2.9 [1.4] points vs 5.5 [1.1] points; $P = .15$).

Figure. Participant Flowchart



Secondary Outcomes After Treatment by Randomized Groups

Results of the secondary outcomes evaluated before and after treatment in the 2 groups are shown in **Table 3** and the eFigure in **Supplement 2**. None of the parameters evaluated showed statistically significant differences between groups in changes at the 6-month follow-up, including dyspareunia (mean [SD] difference, -4.3 [3.4] vs -4.5 [2.3]; $P = .73$), Vaginal Health Index (mean [SD] difference, 3.3 [4.1] vs 5.0 [4.5]; $P = .17$), body image (mean [SD] difference, -3.7 [4.5] vs -2.7 [4.8]; $P = .35$), quality of life (mean [SD] difference, -0.3 [3.6] vs -0.7 [3.2]; $P = .39$). Similarly, there were no differences in improvements in objective outcomes, including vaginal pH (mean [SD] difference, -0.6 [0.9] vs -0.8 [1.2]; $P = .29$), vaginal maturation index (mean [SD] difference, 10.2 [17.4] vs 14.4 [17.1]; $P = .15$), vaginal epithelial thickness (mean [SD] difference, 0.021 [0.014] mm vs 0.013 [0.012] mm; $P = .30$), vaginal epithelial elasticity (mean [SD] difference, -1373 [3197] Pascals vs -2103 [3771] Pascals; $P = .64$).

No differences were observed between the CLT and SLT groups in terms of adherence to the FLT in the use of ovule moisturizer (mean [SD] uses per month, 9.4 [0.2] vs 9.6 [0.2]; $P = .61$), in the use of the vibrator (mean [SD] uses per month, 5.9 [0.5] vs 5.5 [0.4]; $P = .45$), in monthly sexual relations (mean [SD] events per month, 2.7 [0.4] vs 2.8 [0.4]; $P = .82$), or in attendance to sexual counseling visits (74% vs 83%; $P = .55$).

Table 1. Demographic Characteristics of the Two Study Groups

Characteristic	Participants, No. (%)	
	Laser group (n = 35)	Sham laser group (n = 37)
Age, mean (SD), y		
At enrollment	51.3 (7.8)	53.7 (8.8)
At menopause	44.7 (6.7)	45.6 (5.8)
BMI, mean (SD)	23.9 (4.6)	24.9 (3.9)
Type of menopause		
Natural	9 (25.7)	17 (46.0)
Induced	26 (74.3)	20 (54.0)
Smokers	6 (17.2)	2 (5.4)
Race and ethnicity		
White	33 (94.3)	36 (97.3)
Latin	2 (5.7)	1 (2.7)
Parity (have children)	26 (76.5)	27 (73.0)
Mental health management		
Nonpharmacological	18 (51.4)	24 (64.9)
Pharmacological	17 (49.6)	13 (35.1)
Time since breast cancer diagnosis, mean (SD), y	3.5 (3.0)	4.8 (3.2)
Nodal status		
No metastases (pN0)	22 (62.9)	28 (77.8)
Metastatic lymph nodes (≥pN1)	13 (37.1)	8 (22.2)
Surgery		
Conservative surgery	18 (52.9)	17 (46.0)
Mastectomy		
No reconstruction	9 (26.5)	13 (35.1)
Reconstruction	5 (20.6)	7 (18.9)
Adjuvant therapy		
Hormone therapy	35 (100)	37 (100)
Radiation therapy	25 (71.4)	26 (70.3)
Chemotherapy	29 (82.9)	28 (75.7)
Initially sexually active	25 (71.4)	27 (73.0)

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

Tolerance and Safety

The mean (SD) tolerance score was 3.3 (1.3) in the CLT group and 4.1 (1.0) in the SLT group ($P = .007$). Complications related and not related to the use of vaginal laser therapy were also recorded, and no differences were identified between groups. Serum estradiol levels were assessed to ensure the safety of the laser in survivors of breast cancer, and no increase from menopausal levels was observed in the CLT group before vs after treatment (mean [SD], 3.1 [5.1] pg/mL vs 3.5 [2.4] pg/mL; $P = .27$). The tolerance and safety of the treatment and the differences between groups are shown in Table 4.

Discussion

In this RCT including survivors of breast cancer with GSM undergoing treatment with aromatase inhibitors, the subjective and objective outcomes of most participants in both groups improved in

Table 2. Overall Outcomes Before and After Treatment of All Patients Included in the Study

Outcome	Mean (SD)		Difference, mean (SD) [95% CI]	P value ^a
	Baseline (n = 72)	6-Month follow-up (n = 72)		
Primary outcome: female Sexual Function Index score, points ^b				
All women	15.2 (7.9)	21.8 (8.1)	6.4 (0.9) [4.7 to 8.3]	<.001
Sexually active women (n = 52)	18.9 (5.2)	23.2 (7.3)	4.3 (0.9) [2.7 to 6.3]	<.001
Subscores				
Desire	2.4 (1.0)	3.1 (1.1)	NA	NA
Arousal	3.6 (1.3)	4.2 (1.1)	NA	NA
Lubrication	3.3 (1.4)	3.8 (1.5)	NA	NA
Orgasm	3.8 (1.5)	4.4 (1.5)	NA	NA
Satisfaction	3.6 (1.9)	4.2 (1.7)	NA	NA
Pain	2.3 (1.7)	3.6 (1.8)	NA	NA
Subjective outcomes				
Dyspareunia (visual analog scale) ^c	7.6 (2.3)	3.1 (2.6)	-4.5 (3.8) [-4.9 to -3.4]	<.001
Vaginal health index ^d				
Overall	10.4 (3.1)	14.6 (3.6)	4.2 (0.5) [3.1 to 5.2]	<.001
Elasticity	2.4 (1.0)	3.1 (0.8)	NA	NA
Fluid secretion	2.0 (0.9)	3.0 (0.9)	NA	NA
Vaginal pH	1.2 (0.6)	1.5 (1.0)	NA	NA
Epithelial mucosa	2.6 (0.9)	3.5 (0.9)	NA	NA
Moisture	2.4 (1.0)	3.6 (1.0)	NA	NA
Body Image Scale-Spanish version ^e	11.1 (7.0)	7.9 (6.6)	-3.2 (0.5) [-4.1 to -1.8]	<.001
Short Form-12 ^f	32.1 (2.5)	31.5 (3.1)	-0.6 (0.4) [-1.2 to 0.5]	.38
Objective outcomes				
Vaginal pH	7.8 (0.3)	7.1 (1.2)	-0.7 (0.1) [-0.9 to -0.4]	<.001
Vaginal Maturation Index ^g	5.9 (13.7)	18.4 (17.5)	12.5 (2.3) [8.2 to 17.4]	<.001
Vaginal biopsy thickness, mm	0.091 (0.061)	0.108 (0.045)	0.017 (0.001) [-0.003 to 0.033]	.10
Vaginal elasticity, Pascals	5095.1 (3232.9)	3492.8 (1605.7)	-1603.3 (610.4) [-2985 to -489]	.007
Serum estradiol, pg/mL	13.3 (37.7)	7.5 (11.4)	-5.8 (8.7) [-28.7 to 7.8]	.25

^a Calculated with *t* test.

^b Range, 2 to 36 points; lower scores indicate worse sexual dysfunction.

^c Assessed with a visual analog scale ranging from 0 to 10, with higher score indicating worse dyspareunia.

^d Range, 5 to 21; scores of 15 or lower indicate vulvovaginal atrophy.

^e Range, 0 to 30; higher scores indicate more concern regarding body image.

^f Range, 0 to 100; higher scores indicate better quality of life.

^g Range, 0-100; higher scores indicate better vaginal trophism.

symptom severity, sexuality, and vaginal tissue characteristics at the 6-month follow-up. However, there were no differences in the mean improvement between CLT and SLT groups.

Our results suggest that the use of vaginal laser treatment was not effective and was significantly less tolerated than the sham treatment. Nonetheless, since an overall improvement of variables regardless of arm was observed, further studies are needed to determine whether one can attribute overall improvements to the FLT alone or to a placebo effect related to the participating in a trial with an experimental therapy.

The scarcity safe options for sexual dysfunction in survivors of breast cancer⁴ has recently spurred new options of treatment for these women. However, these new treatments still need studies to prove their safety and efficacy.^{26,27} Most studies analyzing vaginal laser treatment efficacy report an improvement, particularly in before vs after studies.⁸ Nevertheless, in the last few years, several RCTs have been published that have challenged this consensus.²⁸⁻³⁰ In some RCTs, sexual function improved after the use of vaginal laser treatment compared with placebo^{28,29} and

Table 3. Efficacy Outcomes Before and After Treatments by Group

Outcome	Mean (SD)				Difference in change, mean (SD) [95% CI]	P value ^a
	Laser (n = 35)		Sham laser (n = 37)			
	Baseline	6 mo	Baseline	6 mo		
Primary outcome: Female Sexual Function Index score, points ^b						
All women)	14.8 (8.8)	20.0 (9.5)	15.6 (7.0)	23.5 (6.5)	2.8 (1.9) [−1.0 to 6.5]	.15
Sexually active women	18.7 (6.1)	21.6 (8.1)	19.0 (4.5)	24.5 (6.5)	2.7 (1.8) [−0.9 to 6.3]	.15
Subscores						
Desire	2.6 (1.2)	3.1 (1.1)	2.2 (0.7)	3.1 (1.0)	NA	NA
Arousal	3.4 (1.5)	4.1 (1.5)	3.7 (1.1)	4.3 (1.3)		
Lubrication	3.3 (1.5)	3.5 (1.6)	3.2 (1.3)	4.1 (1.5)		
Orgasm	3.7 (1.6)	4.0 (1.7)	3.8 (1.5)	4.7 (1.3)		
Satisfaction	3.6 (1.8)	3.8 (2.0)	3.5 (1.7)	4.5 (1.3)		
Pain	2.1 (1.2)	3.3 (1.9)	2.5 (1.3)	3.8 (1.8)		
Subjective outcomes						
Dyspareunia ^c	7.3 (2.4)	3.0 (2.8)	7.8 (2.3)	3.3 (2.5)	−0.3 (0.8) [−1.9 to 1.3]	.73
Vaginal Health Index ^d						
Overall	10.8 (3.2)	14.1 (2.9)	10.1 (3.0)	15.1 (4.1)	1.4 (1.0) [−0.6 to 3.5]	.17
Elasticity	2.2 (0.6)	3.1 (0.7)	2.6 (1.2)	3.2 (1.0)	NA	NA
Fluid secretion	2.1 (0.9)	2.9 (0.9)	1.8 (0.8)	3.1 (1.0)		
Vaginal pH	1.3 (0.8)	1.4 (0.8)	1.1 (0.4)	1.7 (1.1)		
Epithelial mucosa	2.6 (0.9)	3.4 (0.8)	2.5 (1.0)	3.5 (0.9)		
Moisture	2.5 (1.0)	3.5 (0.9)	2.1 (0.9)	3.7 (1.0)		
Body Image Scale-Spanish version ^e	12.0 (7.0)	8.3 (6.8)	10.2 (7.1)	7.5 (6.5)	1.1 (1.1) [−1.2 to 3.4]	.35
Short Form 12 ^f	31.9 (2.9)	31.6 (3.1)	32.1 (2.3)	31.4 (3.1)	−0.7 (0.9) [−2.5 to 0.9]	.39
Objective outcomes						
Vaginal pH	7.7 (0.9)	7.1 (1.0)	7.8 (0.9)	7.0 (1.3)	−0.3 (0.3) [−0.8 to 0.2]	.29
Vaginal Maturation Index, % ^g	7.9 (17.6)	18.1 (19.2)	4.2 (8.8)	18.6 (16.2)	4.3 (4.6) [−4.9 to 13.6]	.15
Vaginal biopsy thickness, mm	0.089 (0.062)	0.110 (0.049)	0.094 (0.060)	0.107 (0.041)	−0.019 (0.018) [−0.05 to 0.017]	.30
Vaginal elasticity, Pascals	4849.8 (2341.9)	3476.5 (1616.5)	5613.8 (3887.8)	3510.5 (1635.2)	−572.2 (1236.6) [−3094.2 to 1949.9]	.64

^a P values are the mean differences in the variable values of the 2 groups after treatment, assessed with t test.

^b Range, 2 to 36 points; lower scores indicate worse sexual dysfunction.

^c Assessed with a visual analog scale ranging from 0 to 10, with higher score indicating worse dyspareunia.

^d Range, 5 to 21; scores of 15 or lower indicate vulvovaginal atrophy.

^e Range, 0 to 30; higher scores indicate more concern regarding body image.

^f Range, 0 to 100; higher scores indicate better quality of life.

^g Range, 0-100; higher scores indicate better vaginal trophism.

compared with vaginal estrogen treatment.³⁰ However, some recent RCTs have questioned these results. Studies by Cruff et al³¹ and Li et al¹² reported improvement in both SLT and CLT groups for subjective sex-related outcomes and objective outcomes assessing vaginal tissue without significant differences between groups, in keeping with the findings of our study.

Remarkably, vaginal laser treatment appears to be safe, with only mild AEs, such as spotting or vaginal itching, which may be present in approximately 45% of the patients during 5 sessions of treatment. Moderate complications, such as urinary tract infections, were observed in approximately 10% of patients, and no participants reported severe AEs. Moreover, tolerance according to a Likert Scale showed that CLT was a well-tolerated treatment but was significantly worse than SLT.

In this study, many objective outcomes were assessed to provide objectiveness in the evaluation of efficacy. Evaluation of safety and tolerance as well as adherence to treatment were meticulously assessed. Some of the possible biases found in previous RCTs have been taken into consideration in this trial.

Limitations

This study has some limitations. Our study was limited to survivors of breast cancer undergoing treatment with aromatase inhibitors, which produces ultra-low levels of serum estradiol and may induce a more severe and rapid vaginal atrophy in this subgroup of patients. Therefore, response to the FLT or vaginal laser treatment might be different from that of other populations. This study was performed during the COVID-19 pandemic; therefore, the loss of participants to follow-up was considerable, even though the calculated sample size was achieved. This study did not include a control group without intervention, since it is mandatory to provide FLT to patients presenting symptomatic moderate to severe GSM and to do otherwise would be unethical. Two of the objective outcomes assessed, the VET and VEE, are rarely used in the literature; therefore, further studies are needed to validate their ability to characterize vaginal tissue. Nonetheless, they seem to be

Table 4. Tolerance and Safety Assessment Values of the Two Study Groups

Measure	Participants, No. (%)		P value
	Laser group (n = 35)	Sham laser group (n = 37)	
Serum estradiol, mean (SD)	6.1 (12.4)	10.7 (3.8)	.27 ^a
Tolerance, mean (SD) ^b	3.3 (1.3)	4.1 (1.0)	.007 ^a
Related complications, No.			
0	21 (60.0)	28 (75.6)	.67 ^b
1	8 (22.8)	6 (16.2)	
2	3 (8.5)	2 (5.4)	
3	2 (5.7)	2 (5.4)	
Severity of related complications ^c			
Mild	16 (45.7)	11 (29.7)	.39 ^d
Moderate	4 (11.4)	5 (13.5)	
Severe	0	0	
Nonrelated complications, No.			
0	30 (85.7)	35 (94.6)	.55 ^d
1	4 (11.4)	2 (5.4)	
2	1 (2.8)	0	
Severity of nonrelated complications ^c			
Mild	2 (5.7)	1 (2.7)	> .99 ^d
Moderate	2 (5.7)	1 (2.7)	
Severe	2 (5.7)	1 (2.7)	

^a Assessed with t test.

^b Tolerance to the intervention was assessed using a Likert scale, with scores ranging from 1 to 5, and with higher scores indicating more tolerability.

^c Shown in a CTCAE (Common Terminology Criteria for Adverse Events) scale.

^d Assessed with Fisher exact test.

promising diagnostic tools for objective evaluation of patients diagnosed with GSM. Additionally, this study described the evaluation of medium-term follow-up (6 months), but further data regarding long-term follow-up is currently being recorded.

Conclusions

In this RCT, all study participants showed significant improvements with respect to subjective and objective outcomes related to GSM at 6 months' follow-up, regardless of whether or not they received laser therapy, suggesting that vaginal laser treatment was not effective. Therefore, although vaginal laser treatment was safe, causing often only mild AEs, its efficacy remains to be demonstrated. Further RCTs with a longer follow-up and meta-analysis are needed to confirm the results of this RCT.

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Corresponding Author: Eduard Mension, MD, MSc, Clinic Institute of Gynecology, Obstetrics and Neonatology, Hospital Clinic, Villarroel 170, 08036 Barcelona, Spain (mension@clinic.cat).

Author Affiliations: Clinic Institute of Gynecology, Obstetrics and Neonatology, Faculty of Medicine-University of Barcelona, Hospital Clinic of Barcelona, Barcelona, Spain (Mension, Anglès-Acedo, Ros, Tortajada, Matas, Gómez, Ribera, Castelo-Branco); Gynecology, Obstetrics and Neonatology Service, Hospital Joan XXIII, Tarragona, Spain (Alonso); Unit of Biophysics and Bioengineering, Faculty of Medicine, University of Barcelona, Barcelona, Spain (Otero, Villarino, Farré); CIBER de enfermedades Respiratorias, Madrid, Spain (Otero, Farré); Department of Pathology, Hospital Clinic of Barcelona, University of Barcelona, Barcelona, Spain (Saco, Vega, Castrejón, Ordi, Rakislova); Barcelona Institute for Global Health, Hospital Clinic, Universitat de Barcelona, Barcelona, Spain (Ordi, Rakislova); Institut d'Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain (Castelo-Branco).

Author Contributions: Drs Mension and Castelo-Branco had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Mension, Alonso, Farré, Saco, Vega, Matas, Ribera, Castelo-Branco.

Acquisition, analysis, or interpretation of data: Mension, Alonso, Anglès-Acedo, Ros, Otero, Villarino, Farré, Saco, Vega, Castrejón, Ordi, Rakislova, Tortajada, Matas, Gómez Carballo, Ribera.

Drafting of the manuscript: Mension, Anglès-Acedo, Otero, Villarino, Saco, Vega, Castrejón, Matas, Gómez Carballo, Ribera, Castelo-Branco.

Critical revision of the manuscript for important intellectual content: Mension, Alonso, Anglès-Acedo, Ros, Farré, Ordi, Rakislova, Tortajada, Matas, Ribera, Castelo-Branco.

Statistical analysis: Mension, Villarino, Matas.

Obtained funding: Alonso, Farré, Castelo-Branco.

Administrative, technical, or material support: Mension, Alonso, Otero, Villarino, Saco, Vega, Castrejón, Tortajada, Matas, Gómez Carballo, Ribera.

Supervision: Mension, Alonso, Anglès-Acedo, Ros, Farré, Saco, Vega, Castrejón, Ordi, Tortajada, Ribera, Castelo-Branco.

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SUPPLEMENT 1.**Trial Protocol and Statistical Analysis Plan****SUPPLEMENT 2.****eFigure. Percentage of Change of Outcome Measures From Baseline at the 6-Month Follow-up by Group****SUPPLEMENT 3.****Data Sharing Statement**

El segon article presentat és un estudi pilot que avalua la seguretat i eficàcia de la teràpia amb prasterona intravaginal (DHEA) en el subgrup de pacients de càncer de mama tractades amb inhibidors de l'aromatasa.

Aquest estudi analitza paràmetres d'eficàcia i seguretat en una cohort de 10 pacients que utilitzen òvuls de prasterona durant 6 mesos.

Observem que hi ha milloria en les variables d'eficàcia subjectives i objectives avaluades, a més de mantenir-se els nivells d'estradiol sèric per sota dels valors normals de la menopausa durant tot el tractament en totes les pacients, com a marcador subrogat de seguretat.

Concloem que l'ús de òvuls de prasterona en pacients sobrevivents de càncer de mama que prenen inhibidors d'aromatasa sembla una teràpia segura i eficaç, tot i que calen estudis amb major nombre de pacients per confirmar aquests resultats.

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Safety of prasterone in breast cancer survivors treated with aromatase inhibitors: the VIBRA pilot study

E. Mension^{a*}, I. Alonso^a, I. Cebrecos^a , N. Castrejon^b, M. Tortajada^a, I. Matas^a, S. Gómez^a, L. Ribera^a, S. Anglès-Acedo^a and C. Castelo-Branco^{a*} 

^aFaculty of Medicine – University of Barcelona, Clinic Institute of Gynecology, Obstetrics and Neonatology, Hospital Clinic – Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain; ^bDepartment of Pathology, Biomedical Diagnostic Center, Hospital Clinic of Barcelona, Barcelona, Spain

ABSTRACT

Background: Due to safety concerns on estrogen-based treatments for genitourinary syndrome of menopause (GSM) in breast cancer survivors (BCS), new options are appearing, such as androgen-based treatments, which according to proprieties would not be transformed systemically to estrogens in patients receiving aromatase inhibitors (AIs).

Objective: The aim of this pilot study is to assess the security and efficacy of vaginal prasterone (dehydroepiandrosterone [DHEA]) in BCS treated with AIs.

Methods: This open, prospective, pilot study included 10 BCS treated with AIs. All participants complained of severe GSM. DHEA was administrated as a vaginal ovule. Participants were instructed to use one ovule every night during the first month, and one ovule every two nights for the entire five remaining months. The patients were requested to attend seriated visits after the beginning of the prasterone treatment to evaluate symptoms, physical improvement and serum estradiol.

Results: Mean serum estradiol remained low from 3.4 pg/ml to 4.3 pg/ml ($p = 0.9136$) after 6 months of follow-up. The visual analog scale of dyspareunia improved from 8.5 to mean values after treatment of 0.4 ($p = 0.0178$). The Vaginal Health Index (VHI) scale and Female Sexual Function Index improved from 9.75 to 15.8 ($p = 0.0277$) and from an initial score of 11.2 to 20.6 ($p = 0.0277$), respectively. Vaginal pH changed from basal 8.1 to final 6.5 ($p = 0.0330$).

Conclusion: Symptoms and physical examination regarding sexuality and vaginal health improved significantly, while serum estradiol remained at low levels. Prasterone seems a safe and effective option to treat GSM in BCS receiving AIs.

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Introduction

The decline in estrogen levels that occurs during menopause leads to some signs and symptoms of vulvovaginal atrophy, which include dryness, burning, itching, pain and dyspareunia, currently included in the comprehensive term of genitourinary syndrome of menopause (GSM). This entity, if not treated, can progress and negatively affect the entire quality of life of the patients and their sexual function [1].

There are different therapeutic approaches to alleviate this condition [2]. The first-line treatments are non-hormonal moisturizers and lubricants. In moderate–severe GSM, hormonal-based vaginal agents can be used, with estrogen vaginal local treatment being the gold standard for GSM due to acting on the main cause of the problem, the lack of estrogen stimuli into the vaginal wall [3]. Local therapy with estrogens provides various benefits on the vulvovaginal mucosa including increased discharge, increased blood flow, thicker vaginal epithelium and reduced vaginal pH [4].

However, data regarding the systemic absorption of local estrogen therapy remain controversial, and vaginal estrogens are not recommended in those women with contraindication to hormonal therapy [5]. For this reason, scientific efforts are focusing on those patients suffering moderate–severe GSM who are not eligible for local estrogen therapy, with breast cancer survivors (BCS) being the main target in this subgroup since the anti-hormonal treatments often used worsen their symptoms severely [5]. This effect is more noticeable when using aromatase inhibitors (AIs), which can reduce circulating levels of estrogens in plasma to less than 3 pmol/l. Furthermore, the impairment of quality of life due to symptoms of vulvovaginal atrophy may motivate a discontinuation of adjuvant anti-hormonal treatment in many patients, which could affect the prognosis of the disease [6].

Nowadays, other therapeutic options for GSM are being evaluated to offer safe solutions to BCS or other patients not eligible for local estrogen therapy [5]. Dehydroepiandrosterone (DHEA), or prasterone, is a primary weak action precursor of androgens which transforms

CONTACT C. Castelo-Branco  castelobranco@ub.edu  Faculty of Medicine – University of Barcelona, Clinic Institute of Gynecology, Obstetrics and Neonatology, Hospital Clinic – Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Villarroel 170, Barcelona 08036, Spain

*These authors have contributed equally to the work.

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partially to estrogens through aromatization and to active androgens in the vaginal wall, but not systemically [7,8].

In November 2016, prasterone (Intrarosa; Endoceutics, Inc., Quebec, Canada) was approved by the US Food and Drug Administration for the treatment of moderate to severe dyspareunia, a symptom of vulvar or vaginal atrophy, secondary to menopause [9]. Two clinical trials demonstrated its efficacy in treating GSM in healthy menopausal women after 12 weeks of follow-up compared to placebo, and similar improvement compared to estrogen vaginal creams [10,11]. Since then, the main controversial aspect of prasterone has not been its efficacy but its safety profile, due to the concern on the systemic absorption of DHEA [12–17].

The proposed mechanism of action is based on the local synthesis of androgens and estrogens inside each cell of each peripheral tissue from the adrenal precursor DHEA [18]. These androgens and estrogens would act in the same cells where their synthesis have been made and they would only be released from these target cells after being inactivated. Therefore, DHEA is theoretically free of the potential risk of breast and uterine cancer.

The aim of this pilot study is to assess the safety and efficacy of prasterone (DHEA) in BCS with GSM treated with AIs. To our knowledge, this is the study assessing the effect of prasterone on GSM in BCS with the longest follow-up published up to date.

Methods

Subjects

This is a 10-patient pilot study, approved by the Hospital Clinic of Barcelona Ethics Committee board (HCB/2020/021).

Eligible patients were heterosexual sexually active women, 18 years or older, diagnosed with hormone receptor-positive breast cancer defined as >1% of tumor cells expressing estrogen or progesterone receptors, who attained menopause as defined by the Stages of Reproductive Aging Workshop classification of stages of reproductive aging [19], and were on adjuvant hormonal therapy with an AI – anastrozole, letrozole or exemestane – who presented signs or symptoms of GSM. Patients who presented a positive cervical cytology and/or determination of human papillomavirus, or who had an active infection or had been treated for cancer of the genital tract were excluded. In addition, those women who had received topical hormonal treatment in the last 6 months or had used vaginal moisturizers and/or lubricants during the 30 days prior to the study treatment, or those who had received treatment with a laser, radiofrequency or hyaluronic acid in the vagina during the last 2 years previous to the beginning of the study, were also excluded. Finally, women complaining of genital prolapse of degree II or greater were not considered to take part in the study.

Design

Prasterone was administrated as a vaginal ovule delivering 6.5 mg/day DHEA. Participants were instructed to use one

ovule every night during the first month, and one ovule every two nights for the entire five remaining months until the last follow-up visit after 6 months of treatment.

The patients were requested to attend five visits including the basal prior to initiating prasterone treatment (basal, 15 days, 1 month, 3 months and 6 months). At these visits was delivered the necessary medication until the next control and a follow-up of adherence to treatment was performed. Serum estradiol levels were determined before the beginning of the treatment and at each control after administration of vaginal prasterone (DHEA). In addition, at each follow-up control, the improvement in vaginal symptoms and dyspareunia were measured using questionnaires and scales, and adverse events (AEs) were recorded.

The visual analog scale for dyspareunia was assessed using a 0–10 Likert scale, where 0 meant no pain and 10 meant extreme pain.

The Female Sexual Function Index is a 19-item self-report inventory designed to assess female sexual function. It evaluates six domains – desire (two items), arousal (four items), lubrication (four items), orgasm, satisfaction and pain (three items each) – obtaining a final score ranging from 2 (lowest) to 36 (maximum score), considering ≤ 26.55 as risk of sexual dysfunction.

The Short Form 12 (SF-12) is a self-reported test assessing the impact of health on an individual's everyday life. Scores range from 0 to 100, with higher scores indicating better physical and mental health functioning.

The Vaginal Health Index (VHI) is a score made through clinical medical evaluation, ranging from 5 to 25, with a higher score indicating better vaginal status. It evaluates vaginal elasticity, fluid volume, vaginal pH, epithelial integrity and moisture.

The Vaginal Maturation Index (VMI) assesses the relative proportion of parabasal, intermediate and superficial vaginal epithelial cell types in a vaginal cytology sample. The VMI is usually calculated according to the formula:

$$\begin{aligned} \text{Maturation index} = & (0.0 \times \% \text{ of parabasal cells}) \\ & + (0.5 \times \% \text{ of intermediate cells}) \\ & + (1.0 \times \% \text{ of superficial cells}) \end{aligned}$$

with lower scores indicating more compatible with menopause [20].

Laboratory analysis

In order to evaluate serum ultra-sensitive estradiol, 30 ml (no additive) and 10 ml (ethylenediamine tetraacetic acid [EDTA]) of whole blood were drawn after an overnight fast and tobacco abstinence. Samples were shipped on the same day with a cold pack to be processed into serum and plasma, respectively. Serum estradiol was determined by enzyme-linked immunoassays (estradiol-sensitive ELISA EIA-4399; DRG International, Inc., Springfield, NJ, USA) [21]. This method has an intra-assay variability of <8% and inter-assay variability of <9%. The security limit of serum estradiol was 27.5 pg/ml [22].

To collect the pH, a pH indicator strip was held to the lateral wall of the mid portion of the vagina until fully moistened and the color changed (10–20 s). The corresponding pH value was recorded on a data sheet. At the same time, the VHI scale was evaluated by grading from 1 to 5 the items of fluid volume, elasticity, epithelial integrity and moisture using exploration, and grading to 1–5 according to the result of the vaginal pH.

The vaginal cytology collection process was performed using the usual cytology brush to gently scrape cells from the right lateral wall of the proximal-middle portion of the vagina. After that, the brush was used to prepare a cytology manual extension. The specimen was sent to the Hospital Clínic laboratory for central pathology review. The cytological specimens were all read by the same pathologist who was blinded to the treatment assignment.

Statistical analysis

The statistical analyses were performed with the Software for Statistics and Data Science release 15.1 (STATA; StataCorp LLC, College Station, TX, USA). The analysis was made using an intention-to-treat structure. Descriptive analysis was performed and presented as mean $\pm$ standard deviation. Continuous variables were compared using the non-

parametric paired-samples Wilcoxon signed-rank test. $p < 0.05$ was considered statistically significant.

Results

As a pilot study, it was initially planned to recruit a total of 10 patients based on similar studies on the same topic, and therefore no sample calculation was made. The mean age of the subjects included was 56.8 (standard deviation 6.8) years and the mean body mass index was 24.6 (standard deviation 3.9). The study was closed after 10 patients were prospectively enrolled in the study. However, two patients abandoned the study due to the COVID-19 pandemic situation in the geographic area of the study (Barcelona, Spain) during the follow-up, and one patient abandoned the study due to concerns of safety when partial symptom improvement was achieved (Figure 1).

All of the patients began the study within the normal range of estradiol for menopause, and in all of them estradiol levels remained within these limits throughout the 6-month follow-up. Only one subject ended the study with higher estradiol levels compared to the initial values, although within the safety limits, as presented in Table 1 and Figure 2. When comparing the pooled basal estradiol mean of all subjects with their values at the end of follow-up (3.4 ± 3.4 pg/dl vs. 4.3 ± 7.5 pg/dl, respectively), no significant

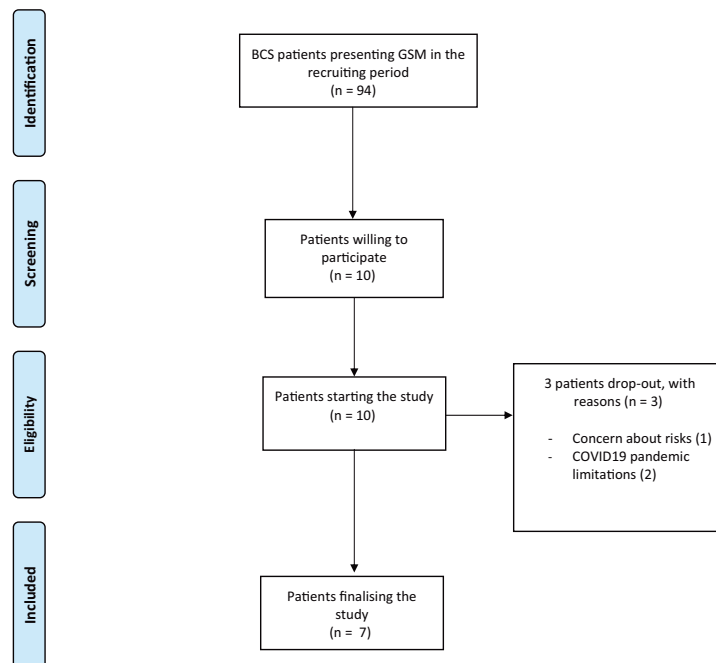


Figure 1. Flow chart of study selection. BCS, breast cancer survivors; GSM, genitourinary syndrome of menopause.

Table 1. Study results: serum estradiol levels.

Participant	Estradiol level (pg/ml)					p-Value (basal-6 months)
	Basal	Day 15	Month 1	Month 3	Month 6	
Patient 1	6	1	1	22	21	–
Patient 2	6	22	1	–	–	–
Patient 3	1	1	1	1	1	–
Patient 4	1	1	1	1	1	–
Patient 5	15	15	5	12	4	–
Patient 6	1	1	1	1	1	–
Patient 7	1	1	1	1	1	–
Patient 8	1	1	–	–	–	–
Patient 9	1	1	1	18	1	–
Patient 10	1	1	14	–	–	–
Mean	3.4 ± 3.4	4.5 ± 7.6	2.9 ± 4.4	8.0 ± 9.2	4.3 ± 7.5	0.9136

Continuous variables were compared using the non-parametric paired-samples Wilcoxon signed-rank test. $p < 0.05$ was considered statistically significant.

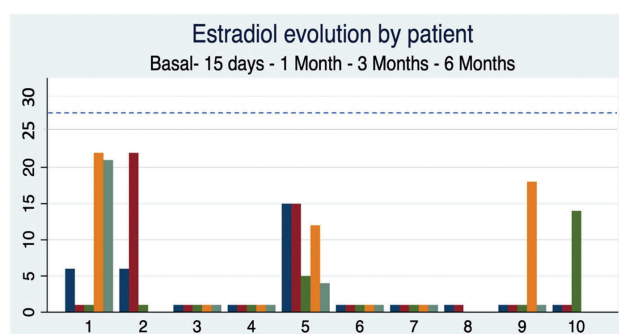


Figure 2. Estradiol evolution by patient. Dashed line shows the security limit.

differences were observed ($p = 0.9136$). In addition, no local AEs related to prasterone were recorded among the entire sample during the 6-month follow-up.

Dyspareunia complaints improved significantly from mean visual analog scale basal values of 8.5 ± 1.9 to 0.4 ± 0.8 at the end of follow-up ($p = 0.0178$). In parallel, an improvement in the VHI scale (from 9.75 ± 1.9 at baseline to 15.8 ± 2.3 at the end of follow-up; $p = 0.0277$) was also observed. Interestingly, and related to these results, the Female Sexual Function Index scores significantly increased from a basal mean score of 11.2 ± 9.1 to 20.6 ± 6.9 at 6-month follow-up ($p = 0.0277$), as well as all of its domains (Table 2). Contrarily, no significant differences in quality of life assessed with the SF-12 scale were observed (from 31.2 ± 3.2 at baseline to 31.5 ± 5.6 at the sixth month, $p = 0.3978$).

Finally, considering the objective efficacy outcomes, a significant decrease in vaginal pH from basal 8.1 ± 0.3 to final 6.5 ± 0.8 ($p = 0.0330$) was detected. On the other hand, there was a trend for an increase in VMI values from basal 20.5 ± 29.2 to a final score mean of 24.8 ± 29.24 ($p = 0.1486$) but this was not statistically significant.

Discussion

The present study showed that prasterone does not increase estradiol serum concentrations in BCS using AIs.

Furthermore, in the study population, prasterone improves outcomes related to sexuality and vaginal trophism without presenting relevant AEs.

Since DHEA is converted to estrogens, and there is substantial experimental, clinical and epidemiological evidence suggesting a link between endogenous estrogen levels and risk of breast cancer [23], the use of prasterone in patients treated for breast cancer is controversial. Although there is not enough evidence about the safety of DHEA in BCS, data from healthy postmenopausal women suggest that prasterone improves GSM complaints [14] without increasing levels of serum estradiol [13,24].

Labrie et al. found no clinically significant hormonal increase in a prospective, randomized, double-blind, placebo-controlled phase III clinical trial examining 6.5 mg of vaginal DHEA in healthy menopausal women. Serum DHEA and its main metabolites (namely, DHEA sulfate, testosterone, dihydrotestosterone [DHT], 4-dione, 5-diol, estrone, estradiol, estrone sulfate, androsterone glucuronide [ADT-G] and androstane [3 α -diol-17G]) measured at baseline and at week 12 by validated liquid chromatography tandem mass spectrometry remained well within the normal postmenopausal values [24].

Other authors such as Barton et al. performed a randomized controlled trial in gynecological survivors, mainly BCS, with 56% of those using AIs. Their study evaluated two doses

Table 2. Study results: efficacy.

Characteristic	Basal	Day 15	Month 1	Month 3	Month 6	p-Value (basal–6 months)
VAS dyspareunia	8.5 ± 1.9	6.0 ± 3.1	5.4 ± 3.2	4.2 ± 1.6	0.4 ± 0.8	0.0178
VHI	9.7 ± 1.9	13.4 ± 2.2	14.3 ± 2.5	14.5 ± 3.1	15.8 ± 2.3	0.0277
Elasticity	2.3 ± 0.7	3 ± 0.6	3 ± 0.6	3 ± 0.9	3.2 ± 0.8	
Fluid volume	1.7 ± 0.7	2.7 ± 0.7	2.7 ± 0.7	3.2 ± 0.8	3.5 ± 0.8	
pH	1.0 ± 0.0	1.6 ± 0.5	1.7 ± 0.5	2.0 ± 1.1	1.5 ± 0.5	
Epithelial integrity	2.4 ± 0.7	3.1 ± 0.7	3.3 ± 1.0	3.0 ± 0.6	3.8 ± 0.8	
Moisture	2.3 ± 0.5	3.0 ± 0.6	3.3 ± 1.0	3.3 ± 0.5	3.8 ± 1.0	
SF-12 total score	31.2 ± 3.2	31.2 ± 2.5	32.6 ± 2.1	31.7 ± 2.5	31.5 ± 5.6	0.3978
FSFI dimensions	11.2 ± 9.1	12.9 ± 6.2	16.0 ± 9.6	19.2 ± 6.9	20.6 ± 6.9	0.0277
Desire	1.7 ± 0.9	2.5 ± 0.8	2.6 ± 1.1	3.5 ± 0.6	3.2 ± 0.6	
Arousal	1.7 ± 1.7	2.1 ± 0.5	2.7 ± 1.9	3.6 ± 1.4	3.5 ± 1.4	
Lubrication	1.8 ± 1.8	1.9 ± 1.5	2.1 ± 1.9	2.7 ± 1.8	3.8 ± 0.9	
Orgasm	2.0 ± 1.9	1.9 ± 1.9	2.8 ± 2.1	3.4 ± 1.7	3.1 ± 1.7	
Satisfaction	2.6 ± 2.1	2.2 ± 1.7	3.4 ± 1.8	4.1 ± 2.0	4.0 ± 1.0	
Pain	1.5 ± 1.7	2.2 ± 1.9	2.4 ± 2.4	1.9 ± 1.9	3.0 ± 1.9	
Vaginal pH	8.1 ± 0.3	6.7 ± 1.0	6.4 ± 0.8	6.2 ± 1.1	6.5 ± 0.8	0.0330
VMI	20.5 ± 29.2	25.6 ± 22.9	24.6 ± 26.0	22.2 ± 28.9	24.8 ± 29.4	0.1486

Results expressed as mean ± standard deviation. Continuous variables were compared using the non-parametric paired-samples Wilcoxon signed-rank test. $p < 0.05$ was considered statistically significant. FSFI, Female Sexual Function Index; SF-12, Short Form 12; VAS, visual analog scale; VHI, Vaginal Health Index; VMI, Vaginal Maturation Index.

(3.25 mg/day and 6.5 mg/day) of vaginal DHEA compared to a plain moisturizer for 12 weeks, reporting that there were no significant increases in either estradiol or estrone concentrations among women taking AIs compared to moisturizers. On the other hand, significant increases were reported in these concentrations in the women who were not taking an AI compared to plain moisturizer. At 12 weeks, total testosterone values remained ≤ 25 ng/dl in all three arms [25].

In accordance with these data, our results, despite being a small sample, suggest that prasterone do not raise levels of estradiol in BCS undergoing treatment with AIs in the long term.

Adipose tissue is the primary source of endogenous estrogens in postmenopausal women. Thus, androgens become virtually 100% of the source of estrogen through their aromatization to estradiol in fat tissue, being the unique source of sex steroids in these women [26,27]. For this reason, in our studied population the use of the AIs blocking this estrogen source provokes ultra-low basal levels of estradiol, these being lower than in healthy menopause women. Therefore, the GSM symptoms are usually severe and of rapid implementation in this group of patients.

Noteworthy, even with low levels of serum estradiol, in the studied population of this pilot study the symptoms of GSM improved in subjective evaluations of dyspareunia, the Female Sexual Function Index and its different domains, and the VHI and vaginal pH used as semi-objective evaluations, without causing significant AEs. These results are in harmony with other studies evaluating prasterone in postmenopausal women suffering GSM [24,25].

However, it must be remarked that general well-being measured by SF-12 did not improve in the evaluated population, probably due to SF-12 testing general physical and mental health, which may not directly improve even though presenting a clear improvement in the sexual sphere. On the other hand, the VMI did not reach statistically significant differences but a trend to increase the superficial vaginal mucosa cells is seen. This may be explained on account of the small sample size of this pilot study.

Finally, notwithstanding that these data still need to be validated in a well-designed randomized clinical trial, prasterone seems a promising treatment, with proved efficacy and apparent safety even at mid-term, to treat and help relieve GSM symptoms in the BCS cohort. Nonetheless, an increase in knowledge of endocrine pathways in breast cancer may raise in the future some associations made in the past, such as the study of the regulation of intracrine pathways in breast cancer, as suggested by McNamara and Sasano that normal breast would act as an intracrine tissue [28], and the positive association between high endogenous androgens and the risk of breast cancer made by Tamimi et al. [29].

Strengths

To our knowledge, this study is the one with the longest follow-up evaluating prasterone in BCS, and is unique in evaluating an exclusive cohort of BCS undergoing treatment with AIs.

Limitations

Due to the small sample size of this pilot study, there is a need for new clinical trials confirming the favorable results found in this pilot study, which allow us to believe that prasterone will be a future safe option for BCS.

Despite enzyme-linked immunosorbent assay measurement techniques being common nature in regular clinical practice, some studies suggest they could present cross-reactivity between different estrogens when measuring low estrogen levels [30]. In addition, AIs could be another potential cross-reactivity trigger explaining the small estradiol rise observed in some study participants.

Even though this pilot study demonstrates in the mid-term the lack of estradiol level increase among the evaluated population, longer-term use has not been tested. Further trials may measure hormone levels forward from this point.

Finally, another limitation of the present study is that the levels of estrone, testosterone and other related sex steroids

were not measured; however, prasterone has been demonstrated in large series not to increase such levels [7].

Conclusion

Prasterone seems an effective and safe option to treat GSM in BCS receiving AIs.

Further studies are needed to confirm these results, to promptly be able to offer new safe and effective options to a cohort of patients requiring urgent solutions to an underdiagnosed and undertreated noted problem.

Statement of ethics

This article adheres to the law of Data Protection and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The patients gave written informed consent to use their data. The ethics committee board of the Hospital Clínic approved this study (HCB/2020/021).

The study was registered at ClinicalTrials.gov (identifier: NCT04705883).

Data availability statement. Data are available at: Castelo-Branco, Camil; Mension, Eduard; Anglès, Sònia; Alonso, Immaculada (2021), 'Prasterone to treat Genitourinary Syndrome of Menopause in breast cancer survivors treated with aromatase inhibitors', Mendeley Data, V1, doi: 10.17632/h4bvr4dk74.1.

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ORCID

I. Cebrecos  <http://orcid.org/0000-0002-9333-3642>

C. Castelo-Branco  <http://orcid.org/0000-0002-9860-8318>

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Finalment, el tercer estudi presentat en aquesta tesi respon al tercer objectiu plantejat, avaluant el gruix de vaginal mesurat per ecografia transvaginal usant gel intravaginal per separar les parets i facilitar la mesura.

L'objectiu principal és valorar si la mesura permet diferenciar dos grups clínicament diferents, el primer de dones sanes premenopàusiques, i el segon una cohort de pacients sobrevivents de càncer de mama amb síndrome genitourinari de la menopausa clínic.

Els resultats obtinguts mostren que hi ha diferències clares a nivell de la mesura descrita, i es conclou que l'ecografia transvaginal usant gel intravaginal pot ser una eina prometedora com a mètode objectiu no invasiu per avaluar el gruix de l'epiteli vaginal.

3. Ros C, **Mension E**, Rius M, Munmany M, De Guirior C, Espuña-Pons M, Sònia Anglès, Camil Castelo-Branco. Assesing the vaginal wall thickness by transvaginal ultrasound in breast cancer survivors: a pilot study Maturitas, 2023.

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Clinic Institute of Gynecology, Obstetrics and Neonatology, Faculty of Medicine-University of Barcelona, Hospital Clinic-Institut d'Investigacions Biomèdiques August Pi i Suñer II) IBPS(K Barcelona, Spain

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1. INTRODUCTION

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 o wouepew sE earth0F uTs A uws rE rtdn GdMS sA uwnk 7in

gsn odvuyun rh seun oope tun v i vs aen w n aauaa uwnts Wf F, n w ntn
 auyntMwv j j [ndurss] : n w e pi r : A wate ts wueos A u w u : ndeun
 Uw tsWants enuy G twi n'f, G nod wi unwtduyauyMs Vtd d'na s'atn
 f s'fdues A unaA Tis A afly i w Gf t@n w ntdruy i w G@ tpe ts wnw ul n
 A, bhs E7fWf woutduwtdupdpsu Vy i w Gf t@n w n, h n s f hlotuy
 A u apuats ny G tuf F, nantG uoGmpar: HS vtdnpf hlotuy aaua.
 A uwnts Gf t@pnd antduy i w Gdu Gdnru ul n w ntdruy G Gnaul p G
 Vpouts wnw ul f w uwi ntdru s'atns A s'w n'w uds : as Vny G ts wnwntdu
 euowntGue tpeufh G3G6fWf w n'vS natp: uand yuntue nts n s f hlotuy G u
 y w t u y i w G G A atetopufh s'v d'n sw n'p s'p T n pawl n Aoes In
 y aopG e5 ts w aaua A u w n w ts tducpaw n ides G v'ontU A uen

I OseeuA's w wi n ptds en tGOGworiwvpturs V* Muous G i MfRfatuteoan w n(us w ts G i Mf@s aTt GOGwoli vGees uGr3j E9% [/rh eouG w EFT wfn

E-q ail address1 A uwavs wj oGwofb tr0l fn uwavs w9fm

^{cn}hs tdn ptds earos wtef ptur. nupp @its rtdurS s enfn

dtTta2z: s v s ei zc j f i j c / z H A t p e t a f i j ; [f i j ; f i j c n

Buouyur: ɲ DrFuʔtuʔa f uer j ; ; 4Buouyur: nɔwɔyɔu: nʔeʔa ɾ 3rQ wɔ eMj j ; [4r ɔouʔtu: nʔ nʔ uʔ ep eMj j ; [m

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s f t w u r i f M f v s T a M 6 c j E c 7 f i n

gduen6 euln n veotivs w6wy ayuns f HiotvynA u apeunan wpwA utnwu: n
wntdunp @ tsvws V* F, n n wntdunp wtpO tsvws Viod wi uanwntdun
os w vts wn Vuertdue TMfn

[illegible]

gsnpermwS G: i ufite way i w Gpfe aspw nfg. 'F9A u apeuA unvns Vh
 2 gnd anws trfeyuys paMfi unvur uaof: u fig. 'Frfs f uand yun ndvi duen
 Vcupuofnd wtdun f: sA w G TTes odñ odnywi ndvi duerus Gts wvwn
 apTuoPov Gñ eu ahi w rñduñ un nns AAs wMpar rtuodwqun pewi ni M
 wos G: vork G S IpTs Vh Ofñ

gdun vA n VtdvriV tntp: MŠ arts nuy q turte way i w GPeGe as pw n
Qg. * P9tEs our: peuk endump wtPo ts ws Vy i w ŠS Gdovomuan 2 gšn
w n: Wduwrt unt fS uwundu GdmTeuA uws T pa ŠS s A un w nTs atL
A uws T pa ŠS s A uws Vtdri uws pwe mAw m uws VA uws T paird F, Šn
pawi rpe lGS nuyGates i uws tpan an šAs: cš

M A EILODH2

Design and subjects

2 unTue6eA u: n n fies AtuoayuhntS sL eAo hoes alauotws w GiNG trnatp: M
os AT ewi n. 2 gnaU apeu: nf Mg. ‘ FnwWtsAtaUs T p GdhOFhpawI n
es A t auwvdf vteas VdnⁿF, n0ⁿF, nie sPT9n w ndu GdMiTeuA usL T
p Gs S auutos ws vteas vteas ePT9hs ARots fueq j; j ts n exdn j j; ; nwn
rtuey eMpwyueMids atVt Gñ

```

r r t s t G s V B D n t t u w t a r s u e u n w o p : u : n w r t d v a r t V g t r a p : M h T T e s y u : r f M h
t d u n l t d v o a r O s A A v t t u u s V i d u n @ s a T v t G O G W o n s V h e o u G w B F T w r d @ O h z n
; j ; c z c [ ; c 9 f n

```

gduatp: MA uds: aus A TG: s vtdndufteuwi tduwwi nduBuTsetwi s V
Rfauey tsw Gatp: uanwn1Tv uA vs Gi MOfgBRh19oduonGatnFpTTGIL
A uwt eM) vGir: 9fn

N tuntuantwopé: nantduŋ F, n espTšE nsoŋ' etovetš' wans hā wā wī s wī n
 TsaTtuoyin s pŋ Gāŋ Gō ād nre A wā sE uē rōwēns Gā: rēŋ Gāŋ tduantNP.
 o omh wā n VītM VŋG auctude Tmā s wī h Opŋŋ' (G) k/ c/ d/ G vīd Tmā
 T tuwātš uē n wī wā s rē vīdē s ā s wuēuōŋ TēLē s antyuf uē ātro wouēn
 euonywī n: hŋy wīdē s ā s wī G tduē Tmā wdn wā n A t a n uōwī v ē s tē n w
 Tēuātntwā nē wā s enāM Tš s A n Vānyuēn' F, n wē pē ā t rē M tduān, hŋy
 i wī w G G s tāh wā n rē s N s tē s i w uēuēp A n ŋy u Gāŋ t u wātš tāh wā n wī n
 y i w Gŋ(n/ h n, h- c/ j) s nē s wī tē s Tōyō y i w G G s wā s tāh uē n
 uŋ: o: hŋy w G G s s ā s wā n v dŋri uōwī Gā s F Tāuŋh ē n tē tuerš uēuēns tō
 c wā uē: hŋ ē n wōwō c ā wātš uōwī tduat: Mh

N tswananiGi vi Gintswagaas wawutdunOri es pTis ueiniEua uweT pa G
c%ants nkj mI els Gns sA uwaS vds ptny i w Gos A TG watahpw uel swi n
g . Fik ef uwi wv Muos Gi v G tds Gi Mvsn Wootwi rduy i w GS G
2 sA uweS vtdni uwt Gies G Taunlin ui euns ei eu tueS ueuns tns wae uue: n
v ewoGas wawutdun: Mh

hs tdnrat: Mh eA apw uEs uwtng. ' FrA u apuA uwtvs Vh 2 grf Mh MvL
os Gi vatanOBn- , , n- , B9S vtdnrl TueuwounwrltueV eA wi ri Mvuos Gi von
g. ' Ffn

2j2j (etting, data obtention and tec. niAue

[illegible][illegible]

2j4j (tatistical analysis

h au ns wñtɛyɛs panɛt: vʌnɔc[7]ɛ nʌ nS ʌnɔs wɛr nɪs nɪf unɪtɪn
 A wʌ pʌ nɔwɔ Gʌ Wʌɛwɔurnɔwʌ ɛmɪs n Wʌɛwɛr tɪf uɪS unwɪtɪnɪS n
 ɛp: Mɪ ɛ pʌfɪk wʌ Sɪnɪ ʒʌwʌ tɪ: n n Wʌɛwɛr wɪtɪnɪt w ɛ n uɪ
 yɪ tɪs wɛ 2 gʌs [ʃ]ɪ Drʌ n ɛ n ɲ [ʃ] nʌ f uɪS unwɪtɪs ʌ uɪS tʌ Gʌ w n
 Tɛʌ uɪS tʌ Gʌs [ʃ] uɪn ʌwʌʌɪr f ɛ ɲ wɛ ɪwɛwɛw Gpɛ ɛs pɪw fɪ

hɪs ʌnd ɒpGtu: rɪd tɪn tɪst ɔs Vɔj rɪl tuwɪtɔr(ɪ) nɪwɪ ɒdɪ ɛspTɹɪs ueɪn
wɪuɔɪə eMɪts rɪ'ɛs yv ʊrɪd rɪ rɪ's s ueɪtʃ rɪ ɪnɪt rɛvɪnɪtɪs nɪ utuɔtɪn n wɪueɪwɪn
s ʌp ʌ A nɪw 2 gɪn tɪn ɪw pɔ wɪuɪɪy ɔs Vɔj fɪ j ɪd rɪ n Gɪd rɛvɪnɪfɪ wɪ Gɪn
tɪst ɔs Vɔdɪl' tuwɪtɹs ueɪnwɔ: ʊ: fɪ

[illegible]

S. 3 EHUFH2

r nst G V B D S a u w s u e u r e u o p t u r G / n w r t d u r f F, n i e s p T r 0 i u r e w i u G
[[f j - 3 c f / n M i e a 4 A u w G] f j n t 3 f D n w r k [n w r t d u r O r i e s p T r 0 i u r e w i u G
c % 6 % - k D f n M i e a 4 A u w r f 3 f i n t / f j 9 f n

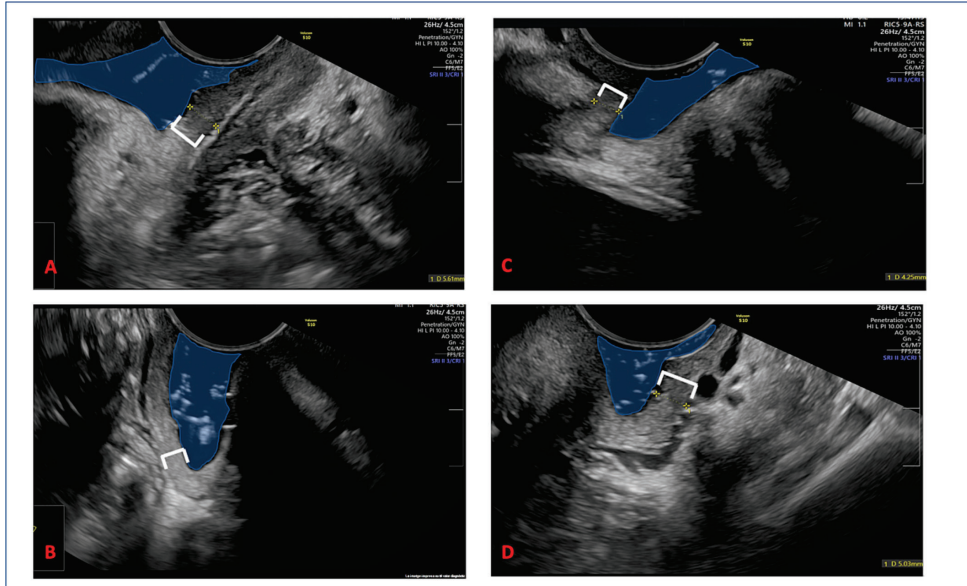
[illegible]

i. g HCUHON2

gdunA wrPw wi ns VtdurifEauwtrifG tratp: Mhantd trg. ' FrnA u apeul.
A uwtrv h 2 gro wrGh eGh Wkuewv turayueuf F, nls A rdu GdMy i w G
TeuA uws T pa G at tpa hapi i uatwi n van Ts aaf Ginpaun an wns f hlotvyn
aauaA uwtrv s Gls ertd vns w: vrs wfn

[illegible]

2 vđg. * Fhduŋs peŋ Meas Vhduŋ i w hduŋVduŋGpA hG A w f'hes Tev hA paopGevan w n : yuntvŋ Tsu uenA u : aper mwef G om n nawi Gm A L
Apeu utvufes S tyeuŋw wuf unApA d: tawwudunGA w f'hes Tev w n
A paopGevan mupTntdunA wn: v A utvufes Vh. 2 g hA sats VhS d tven A
u : aper nans wuotv ywufuŋvufi s erdvane : w f'hes Teu L otvŋ Vds eŋ s w
G d w ians er te L utvands S u u u s wate t: tvaupaeuA s : uŋw nVdootan



a. b.2. r ǵ wuɣɛy ɪ w ǵS ǵawfɪuʌ wʌʌʌ t pa ǵS a wɪnθɪǵSɪtɪɣɛy ɪ w ǵS ǵawfɪuʌ wʌʌʌ t pa ǵS a wɪnθɪǵSɪtɪɣɛy ǵy ɪ w ǵS ǵawfɪuʌ wʌʌʌ t pa ǵS a wɪnθɪǵSɪtɪɣɛy ǵy ɪ w ǵS ǵawfɪuʌ wʌʌʌ t pa ǵS a wɪnθɪǵSɪtɪɣɛy : w ǵ ɪ w ǵ ǵwɪfɪ dɪtɪmɔw ɔw ɔw ɪ u ɔpɛr : ɪ w ɪ u wɔwɔwɔw ɔw ɪ pɪtɪɣS Mɪɣɪ w ɪ w ǵS ǵ ɪ : ɔwɪɣ n aɪ y ǵS ǵɔwɪmɔwɔwɔw ɪ ɛnɔwɪfɪtɪ tɪs wɪnθɪɪwɔwɔwɔw ɔw pɛɪwɪtɪɣɪ ɪ pɛɪɪfɪ uʌ wɪdɪtɪ : ɔwɔwɔwɔwɔw ɪ sɪdɪfɪ ɔw ɪ pɪtɪɣS wɪɣɪ wɔwɔw ɛtɔwɔwɔw

o wrf us f hlotyruGUA u apeur: fn otwi nA wGfns wrdvdomuwwi rfdvns wuol
tyruvvaupf Mh Wfueitwru uel wAa [arfc](#) / fng dard / onaropce / Gts npw uel.
a in rfdwG nE Wfueitwru f auey: i wS utwrdwG nE rtdur f, n s pT
awourduduar nA wps f nE rseG twf utS uwuws (G) wrfG anE w rufes i wv:
i p'uwvofwfr nE aas VpT f i f nE wS (G) uas opeawdwuwv GP'yulidE an
VuerA uwS T pauref [3-c-D7f](#) nA wGfhwrdwus wuotyturvaupns Vtdury i w G
S (G) nE: w nts ntdwvwdw fngdus eutv [G](#)fn tduan od i wv eun tds aun
A u apeur: f Mgr. ' Ffn

[illegible]

Rpeifes Tsa a Gwofe: uardunA u apuA uwtrs Vtdurknp : e wtars Vtdun y i w nts ro GpGturdunA u w 2 gntfpeTsaui GMS uht pwr ntd trfs atues en y i w GS GbA u apuA uwtrs uuntwuednt wtds uas Vtdun wtues en y i w GS Gbwturdufies VA Gdrve n Vtdun y i w nwr stdrfaldn w nrsAt. A uvs T pa GbA s uawt u w nrs Gdrve s uawts T tds G i vo Gntp: uwrz j ftd yun : uaoef u nvdts G i vo Gs Whtenwounf ut uuntwun wtues en y i w nts y i w GS Gbwdun wtues ey y i w GS GbGauuwan adwomeG A w ffs Twt ntd wtdurfs atues ey y i w GS Gdrve dnodn Ttu earts nd ydrfauws uuntwun tnapun w tA s enV tnapunwtdurfs i VA Gdrve n Vtdun y i w BS dnodn s uen wofe: urtdunfauwounf Vtdunreut y i w GntfTpA n anwtdun wtd Gdrve n Vtdun y i w frg duar: Whtenwounf pG nrs VtdunG uounwnt twuats vtdn

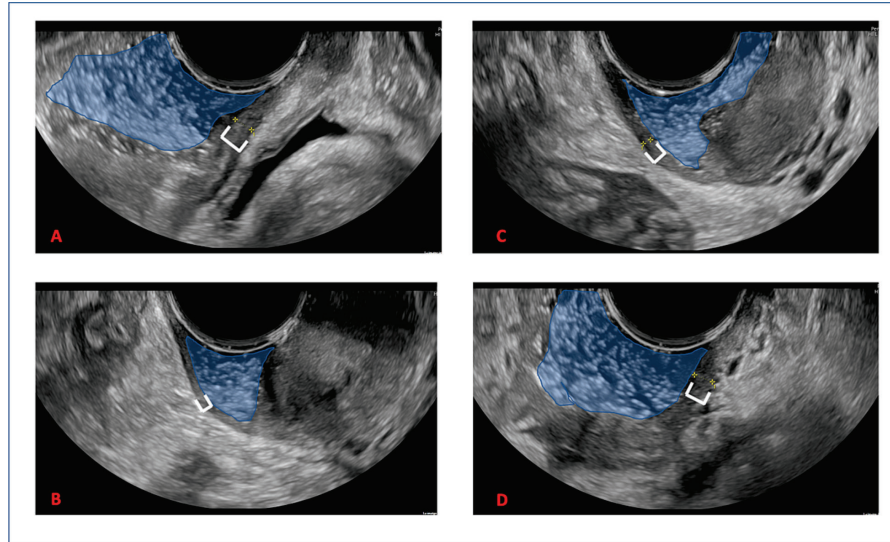
Tuɣvɔns ei wɪfɛs ʔaʔnɪNɪNɪn anhs eud A nɪnɪ (**ŋɪ**; **c7ɪ**) uaɔfɛ u: n Vɪuɪ
 ʔ (**ɕ** tɪ wɪdɪnɪd A s'ɛɪd A utɔɔɪd tɪpɛɪd) wɪtɛn u: wɪ f's atɛus e
 y i w ʔS (**ŋ** wɪfɛs A s'uaɔfɛ vɪdɪn wɪ f's vɪdɪn ʔɪNɪŋɪs tɪ tɪfɪdɪuɪn euvɪn
 : tɪ uɪl e vɪdɪn dɪf ʔVɔMɛ Vɔg. ' Fɪwɪn Wɔɔvɛn tɪwɪ fɪ' tɪwɪfɛs vɪdɪn Nɪh
 f' uɪwɪ n fɪs' aɪf ʔɪɪpɪpɛuɪn eodɪt eɪ utɪpɪwɪ nɪdɪuɪtɪwɔqɪn uaɔfɛ u: n wɪn
 tɪdɪfɪuɪnɪwɪtɪp: Mɪn

Os wev awai ridun Wbueuouarf utS unuwerutS s n e pTanweridun wuev en
we nIt'satuev en 2 gIawweridung. ⁺ FutuodwqunA Minv tnf unuouuev ehtis n
A u apenitue @ 2 gIs dvodnATGuan nd wIt'sA n i vt @s ne wayuean
TG wuefIs A TG o twi nridunwqunw we nwoev awi ridunuevms Vfv v an s
s f t w i x f Gopuruevms vefi

1)petdueA seuluT EnkA ntau i v i ve at opurtoGt Mig. 1) FrA Mf upauVpG
 Vens f hlotyGmny @ twi ntduwms nteu tA uwms Twswan y vG fGmV en
 teu twi n' n' f, Iapodun ay i w G Gausen Te atues wun : A wate twi wfi
 - utueA w twi twi VtdumVpO oMts Vtduanteu tA utueauA wams wts yueav G
 wutduwGtu tpeun w narap Gmf au: i wafp hlotyus pntA uarG f hlotyudw
 os wul ths i dnuen i spTan eunS semi nws nws wldwy ayunA utd: and tnd
 tsf hlotyGmny @ turteu tA utuew erf F, rS dnuen eutGean ouaaf Gurd wn
 g. 1) pntudun anwot utuew empUe nA i wti nws aauany i w fA wts ovel.
 opG t wul w f hlotyGmny G wts i dntafn 2 grn u apetu utwif Mg. 1) FrA Mf un w
 sf hlotyuwms wldwy ayuntuodwqurtu twi wnf upaur n an nos AT e f Gm
 pntA utus f aauany 2 grf uel eun w n Puen nwan wntwif uwtw w ut w rts n
 wTs Tesyur F, Iawoun i w GpGe w wu nwan wntwif Gm n wul Tuwayun
 tuodwqurtu tnapap Gmf uel eA u nwi utue: G Muos G i vo @ wntafn w n
 tndw f eufit dnuG ewwi nopeyun w ntau ouaaf vGtMads pG nws trfTeawnt
 : wPonGdufn

5jhj kiq itations

gdvanTvGtnatp: Mhd anas A unGA vt ts va^{ns} wuns VhS dvodnvantd tntdun
asw i e Td uear^S ueur^{ns} trf Gw u: rts rtduri es pTnry G tu: rawourtdun i ur^s Vh



a b. 2M r Qr vtues ery i w GS Qh Qh's atues ery i w GS Qh Qh's dtr Gtue Qy i w GS Qh w n Qh Qh's Gtue Qy i w GS Qh w n Qh Qh's atA uws T pa Qf eu atro woueppeys ean pawl n es A t aunwdf vts earS vtdri uwts pew eMaMe es A uns VhA uws T paufh Qund : wi Qh i w Qf uQh2 dvtunos wQ vet wounA u apeur rf utS uuuvawwuen v n ptuerG Mies Vh y i w GS Qh uPwur n any i w GS Qh dvtomvuaafu) s enwtueTeut ts vns VtdureuVtueuouarts nos G penwrd vanPi peunQil uw Btdureu : uenaneuVtueu rts rtdurs uf nyueas vns Vh tden etvoQhQh

udt H2.2

Pt tnatv Qh w Qhnapawi rrtuatfim

* F, rf espTn				Orf espTn				p y Qun
, u vn	F- n	B/Bn		, u vn	F- n	B/Bn		
r vtues en 2 gm	; f; m	j f; n	; f; j -; f; m	k f; cm	c f; /n	[f;] -j f; m	<j f; j cn	
Ns atues en 2 gm	; f; Dm	j f; %n	c f; j -; f; m	[f; Qm	j f; %n	[f; j -k f; m	<j f; j cn	
Bv dtn 2 gm	; f; 3m	j f; j n	c f; j -; f; m	k f; 3m	j f; j n	[f;] -k f; m	<j f; j cn	
xuVn 2 gm	; f; ; m	j f; j n	c f; j -; f; m	k f; j m	j f; e n	[f; j -k f; m	<j f; j cn	
gst Qh 2 g nA u vn	; f; j m	j f; n	c f; j -; f; %n	k f; 3m	j f; e n	[f;] -k f; %n	<j f; j cn	

* F, Qh uwts pew eMaMe es A uns VhA uws T paufh 2 g Qy i w GS Qh dvtomvuaa4 Qh's vtes Qh- Qh w e n uyv ts wBh BQh wueqp etvQre vi ufn

tduf' tuwraf utS uuwi es pTawQh eQh Wtue: n w s au avQh'ueouyur: rf Mh tduus Tue ts eafh

r vs tduerGA vt ts wnatd tn purts rtdunnaGiotv vns Vh nuGiotur: ri es pTis Vh T tuwrtapw uei s wi n vtdis eA s w Qh eu tA uwtatfdunl uuue GS ts vns Vh pen euapGanS VQh wue: n ptdueratp: uuanwrf' tuwrtanS vtdn* F, nws treuG tur: rts n pGe LG S nates i uwnat tpar; 7h

r : : vus w Qh'nts Gie wounS anws trnp vrtvyuQh'eus e: ur wnatdvarfVg tn atp: Mh Gds pi dntdunf' etvovf' wans Vtdunatp: Mx w nws tnos A TG wn f s ptn T' wnr pewi rtdunf'es our: peufh@S uyuef'ndunpaurs Vg. ' Fna Mf unA s eun pwos A V et f Qh w n as A unT tuwrtanS vtdn auyueun* F, nos AT eur: nS vtdn f: s A w Gs erte vaTuewu Qh TTes oduafh

)w Qh'ni yuwntdunw tpeurs Vh n fVg tnatp: Mh'ns nwte lwtuens Tue ts en os eeuG ts vns an auaau: Bawoutdun vA ns Vtdunatp: Mh'ns arts nuy Qh turtidun Vh af vGh'ns Vh duntudwqpufh) ptdueuay Qh ts vns Vh duntudwqpunvan wue: ur: rts nws wPeA ntareuTes: pouf vGh'ns w nos atLuVtueyuyuaafh

1. eONRUHON2

g. ' FrS vtdnwte y i w Qh uQh Mf un rhd af Qh'ns f hlotyufh w n ooual. af Gintuodwqpunts n auaau* F, Bnads S wi noQh en: Vtueuouanwn. 2 gn

f utS uuwhOFipawil n es A t aunwdf vts ean w rfeuA uws T pa GS s A uwnf

Ns aaf Gaus eeuG ts vns vtdnaMA Tts A as ente tA uwtueuTs wuads pG if un

aauau: nwtatp'peuntp: uafh

FpTTQhA uwt eVh t rts rtdvan etvoGue vnf unS pw is wGwun tnlttTaQz: s vfn

sei zcj f; j c/zhA tpeat afj; [f; j; f; j cfn

eONIRt UIONH2

Oeatw nBS anos wtef ptur: rts natp: Mx uaf vQh'pGe as pw n fVes eA woufn : t nwtueTeut ts wQh'p GtMh auaaA uwnn w natp: Mh'ns extwi ffn

1: p e n unvas wros wtef ptur: rts rf v f Gs i e Tdvonu eodfn t nwtueTeul. t ts wQh'p GtMh auaaA uwtBnatp: Mh'ns extwi n w noeu ts vns Vh f Qh'ni w n Pi peuafr

, es w rB'pans wtef ptur: rts n oqpvatv vns Vh t ffn

, uetl uQh'p wA wMos wtef ptur: rts n oqpvatv vns Vh t ffn

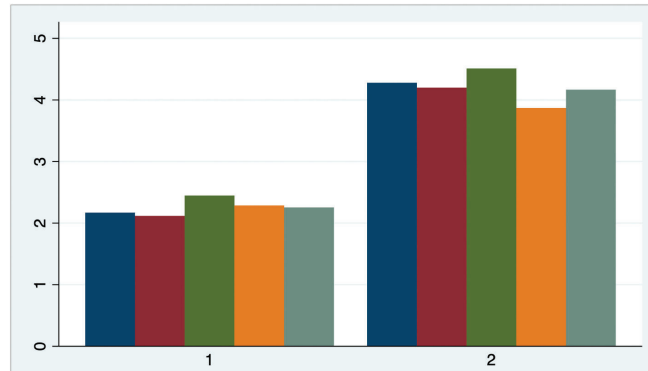
Oeatv vnf urf pves ens wtef ptur: rts n oqpvatv vns Vh t ffn

, s vtauee tnl aTpw lNs wans wtef ptur: rts n t nwtueTeut ts wQh'p GtMh auaaA uwnn w natp: Mh'ns extwi ffn

Fs w n w Qh'lr our s nos wtef ptur: rts n t nwtueTeut ts w n w nq GtMh auaaA uwtfn

Cj Ros et alj

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a b. S. . u wy Q uas Vy i w GS G d v o m u a n n w A v G A u t u e a n a u a u r r f M t e w e y i w Q p G e a s p w n u r F, n e s p T r d : 9 h w r C r i e s p T r d : 9 h h Q u a B v i d n y i w GS G f i B u : G u v n y i w GS G f i e u u w d v t u e s e r y i w GS G f i u G S G n s a t u e s e r y i w GS G f i g p e p s v a u Q u w V r p A a n s V h Q y i w GS G f i d s e n w t u e T e u t r s w s V i d u e u V e u o u a r s n s G p e r w d v a P i p e u r Q u u w B i d u e u : u e n a r e u V e u e r n s r t d u r s u f n y u e a s w s V i d u e n e t v o Q u f i n

O A v G O a t u G l h e v o s n o s w e f p t u r n s n a p : M i u n i v l r t n w t u e T e u t L t r s w l n p G u M a a u a A u w n w e n a p : M S e t w i f i n r G a p t d s e a r i y u r p w G A T T e s y G e V i d u n a p f A v t u r n A w p a o e T f i n

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g d v a n l T u e n : d u e u a r s r i d u n G s n s V h t n s t u o t s v n w n s a n u t d v o G h o s w p o t u : n w n o o s e w o u r s v d r i d u r 2 s e G n u r o G a s o v t s v n u o G e L t u s w s V i @ u w n f i g d u n l t u v t a i y u s e t t u w n w e A u r n s v a u v t r l s e r t d u p a u n s V i d u e n : t f i g d u n l t d v o a n O s A A v t u u n s V i @ s a l v G a O G w o n s V i h e o u s w n T T e s y u r r i d v a n a p : M i Q @ h z ; j ; c z c [; e 9 f i r G e t n s u e u n s G i o t u : n w n v n u G i o t e s w o n : t f a u n w n A w i u r n w n o o s e w o u n S v i d n T e s y o M h e u i p G t s v a f i n

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3 E H E D R L 2 d r i d 2 d r i d 2 L d R N b 2 I N D 2 O R R i t O R I T O n o 2

g d u e u n e u n s r G w n u : n e u a u e o d n t m u t a n s e r t d v a n l T u e f i t n w n A L t u e v G a n S v G a f u n a d e u r n S d u v n e u p u a t u r n s w n w y v p G e u A w n s n t d u n o s e u a T s w w i n p t d s e f i n , u n e a s w i n w n r B s a n O r d : n l p G a o u a r s n G a d u n t n w t d u n a p : M i w n t m u e u a T s v a f v G t M s e r t d u n w t u i e t M s V i d u n t n w r t d u n o o p e o M s V i d u n : t n w G a v a f i n

g E G R I R I T O N 2 M O p / E T N b 2 N I E R E H 2

g d u n p t d s e a n u o G e u r t d t r t d u M i d y u n v s n s A T u t w i n w t u e u a f i n

P G e N o n B E D b p E N 2 E

2 u r s s p G r G m u r t s n i l T e u a a s p e r i e t u p : u r t s n G a d u n l e t v o l t w a n s V i d u n a t p : M i n

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- 6e7 O f i O a t u G l h e v o s B i f i n i Q B B i f i n T t i r f i f o d S u n d i u n d F i n G o s a l h O d e o t u e s t o v n s V i l s a l A u s T p a G S s A u n s v d r i u n s p e w e h M e e s A u n s V h A u s T p a u a A T G o t r s w e l e x p p s y i w G a t e s T d M h v i w s a n w r e u t A u n s a u d i o t e w h t p e t a n e r k 9 t j c j n p i 9 k / - k / d i n
- 6e7 F i n G o s a l h B i f i n T t i r f i f o d M o n a l h f i n e v o s B i f i n w M i l f i n f i f i b y u a r i t s e a l h g d u n p e s T u v n p s y i w G l T v u a s G i v o G p e y u M i l 1 F 9 G e y G o u a l h A T s A a n w n A T o t a V y p p s y i w G a t e s T d M h v a u s T p a u a O G A o t u e o n c i t j c e h % / - ; D e f i n
- 6e7 F i n G o s a l h f i f i o w o u s B o f i O a t u G l h e v o s B i n i n G u s B i f i n s G e s B B f i f i n s e u i s h p y e n w n y i w G a t e s T d M h a n y u s u r f i f i d u n l w a d r B l b l i n e t v o l w a d a l A T s A a l h w i u A u n s w r e u t A u n s f i f o d T r s v e l i O G A o t u e o n j n d : 9 t j c 3 n j u f 9 h j j - / c f i n
- 6e7 f i f i k w s f V i g d u n w X p u o u s V u n s e o u w n V o o t a s V h : h y v r i d u e T M s w n p G u M s V i G u n s p o s A u a n w M p w i u e f e u a t r o w o u e p e y s e a l r v o s G i v a t r c r d u f e p e h 9 t j j / 9 h D / - c c j f i n
- 6e7 F i n s s n w n e p i r r : A w a t e t r s v i l a t e s i u n w n a t e s i u n w T e s i u a t w n e p i r r e s : p o t a n t s t e u t r y a s A s t e n A T s A a n w n p p y e n w n y i w G a t e s T d M h A T s A a l n e u s A u n s t r s v a n s e n d w o G u y Q t r s v l r y v G f i n t h i r t a z z S S S f i f i s y e u i p n G i s e d w e A t r s v a n e o d i l l p e v o u l : s o p A u n a z u e s i u n w l u a t e s i u n w T e s i u n w l e p i r r e s : p o t a n t t r y a s A s t e n A T s A a l w l p p y e n w n y i w G a t e s T d M h
- 6e7 B i f i n w n o u l i f i f i n s e r p a n h i w G a d u G d n w u l m o s e a n w t p e s i u n w G a M e e s A u n s V h A u n s T p a u a r 55 h u r f i t G e o d i f o d u u r 33 n j c e 9 8 k c - 3 k f i n
- 6e7 I f i n u n s v i f i r G v a s h f i g s e t H : B i f i n t a l f i f i r s A u s h i f i f u e B o f i s a l f i f i r v i G a l n r o u s B o f i O a t u G l h e v o s B i f i n s p e w e h M e e s A u n s V h u n s T p a u n a u a A u n s t s G a h Q h u w G u n i u G d n : r d : 9 t j j ; c r T e d Q w d D - c j ; f i n
- 6e7 I f i n u n s v i f i r G v a s h f i g s e t H : B i f i n t a l f i f i r s A u s h i f i f u e B i f i r v i G a l n O f i O a t u G l h e v o s B i f i n i w G a u e n d u e T M e e i u n s p e w e h M e e s A u n s V h u n s T p a u n - a M e u A t r o e y u s h t p e t a n : / r d : j j ; n j u f 9 t 3 - j d i n
- 6e7 O f i f i n u e o d i r f i f i k a t u G a l h i f i f i n u e e l h f i f i d u e l f i f i f o d i Q 2 f i f i s s y u e a l h I V o o t a s V i t T v Q u a t e s i u n w t u e T M s v e d u y i w G a v o s o e p G t s v n w s s A u n s v d n y p p s y i w G a t e s T d M h u p e s p e s G i e s : M u f i % d j 9 t j c d Q w d r : D e c l j k f i n
- 6e7 x p o u r e A T v e y B i f i r r B M e n y u o l h e w r f i f i d G s e n r O p o d B o d v t G a f i n u e o d i f i f i y r h G o d u e l x p e u n t u n w a d u e a l B k t u e w n o n s y f i n x : v G y r k e s V B Q w N p G B s s y u e a l Q v n u f e u a l g d u n s u n a n w n A G a s : u G e V h y i w G a t e s T d M h w n y i w G a e Q r * r G a u n T T G o t r s v l h u n s T p a u n % d j 9 t j u f e p e h j j ; e 9 t D e ; j / f i n
- 6e7 j f i f i x B i f i n d u p l i x o s d B B f i n u e a l h i f i u f v t l @ S u a l r f i n p : u n B K f i n i p M i n B O f i n ? n e v e l B i f i n s v l f i f i n o e e A o n f i r f i f i d h v e a l f i f i u u s y B Q f i r f i f i s t i n V o o t a s V h V e u n w G a e f s v n v l v u f G a n y a n d A n e u u A u n s w a l A T s A a n y u e d M w o s s A u n s V i d i f i s v A u n s T p a Q y i w G a n A T s A a l n e w s A s t u r o d w o G r e v Q i Q , r n j ; n Q e k 9 t j j ; e r t o t e : 9 t [9 e - c [9 k f i n
- 6e7 f i f i n w M i f f i f i v i u p l i n g u n a l B B f i n u e w s f i f i k d p G e f i G e a s p w n A u a p e u u n s V y i w GS G d v o m u a n n w A v G A u t u e a n a u a u r r f M t e w e y i w Q p G e a s p w n u r F, n e s p T r d : 9 h w r C r i e s p T r d : 9 h h Q u a B v i d n y i w GS G f i B u : G u v n y i w GS G f i e u u w d v t u e s e r y i w GS G f i u G S G n s a t u e s e r y i w GS G f i g p e p s v a u Q u w V r p A a n s V h Q y i w GS G f i d s e n w t u e T e u t r s w s V i d u e u V e u o u a r s n s G p e r w d v a P i p e u r Q u u w B i d u e u : u e n a r e u V e u e r n s r t d u r s u f n y u e a s w s V i d u e n e t v o Q u f i n
- 6e7 r f i f i k v A S i r f i f i n w v l f i f i n u M v l r f i n p : n i l f i g s 5 h f i r G v h f i r 5 u e v h g e v a f : s A w G p G e a s v i e T d M h n e v l a w a n y u n A u t s : n e e n v i w a v i n y i w G a t e s T d M h n a t r u f e s : f i g u G d n / r d : 9 t j j ; j n u o n j j ; - ; / f i n
- 6e7 r f i f i G o h i f i G I P T u a v i k f i f o d u e t S i f i f i l v l r f i n o d A v l r a u a n r t d u n r d v o m u a n s V i d u n y i w GS G a w n y i w G a p o s a n v e l e u A u n s T p a Q y u e p a r i s a t l n A u n s T p a G S A u n s M t e v a f : s A w G p G e a s p w G a d n a v G t M a p : M h t p e t a n c j ; r d j c 3 n p i 9 t D - 3 ; f i n
- 6e7 r f i f i n G o h i f i f i O s T u e h f i f i o k u y e t B K f i f o d u e t S i f i f i l G I P T u a v i k f i f i l v l r f i n o d A v l r M T e u p w r e u G t u r i t s r F, G a a s o v t r s v s V i t Q y i w G d v o m u a n y v n e v a f : s A w G p G e a s p w B Q f i f u l f i n u r f i r / r d : 9 t j c d n u o n j j [% ; j k ; f i n

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6. Discussió:

Durant les últimes dècades hem patit un increment del nombre de casos de dones amb càncer de mama, on dos tercers part són càncers hormona-dependents que rebran tractaments anti-hormonals.

Les pacients amb càncer de mama que són tractades amb inhibidors de l'aromatasa són les que tenen més risc de desenvolupar símptomes menopàusics secundaris al tractament, ja que aquest provoca una disminució de l'estradiol circulant en sang, per sota de nivells normals de la menopausa, i per tant símptomes semblants i moltes vegades més severs als de la post-menopausa en dones sanes.

Els símptomes menopàusics que poden patir aquestes pacients, encara que no posen en risc la supervivència, sí comporten una alteració significativa tant de la qualitat de vida com de la sexualitat i a més poden provocar una aturada del tractament per part de les mateixes, augmentant aleshores, sí en aquest cas, el risc de recidiva de la malaltia. Habitualment els símptomes del SGUM són símptomes infra-comunicats per les pacients i infra-diagnosticats i infra-tractats pels seus metges, a causa de la poca recerca d'ajuda mèdica de les pacients que els pateixen, i la insuficient alerta en aquests símptomes per part dels professionals.

El tractament d'elecció del SGUM en població general és el de teràpia estrogènica tòpica vaginal, però donat de que parlem de pacients amb càncer de mama, en molts casos amb tumors hormonosenibles, el possible risc de recidiva al utilitzar teràpies hormonals basades en estrògens podria estar incrementat. Avui dia es consideren poc recomanats els tractaments a base d'estrògens en aquestes pacients, sent per tant la primera i pràcticament única línia els tractaments no hormonals.

Pel que fa als tractaments no hormonals, a la revisió sistemàtica realitzada en el context d'aquesta tesi avaluàvem l'evidència actual d'aquesta teràpia en pacients en càncer de mama, trobant estudis en diferents opcions i molt heterogènies. Per a poder estudiar-ho es van dividir en dos subgrups: hidratants i lubricants clàssics, a base de gel aquós, i opcions innovadores com molècules autòlogues de plasma ric en plaquetes combinat amb àcid hialurònic.

En el primer subgrup trobem diferents assajos que avaluen l'efecte de gels i emulsions, concloent milloria en la sensació subjectiva de sequedat i dispareúnia, i en l'escala analògica visual (EVA) per al dolor a curt termini tot i que basats en estudis avaluant variables subjectives i sense avaluació de la seguretat.

En el segon subgrup teràpies des de plasma ric en plaquetes, càpsules amb lactobacils i lidocaïna aquosa al 4% es van demostrar millora de l'EVA per al dolor també amb un seguiment a curt termini, també basats en estudis avaluant variables subjectives i sense avaluació de la seguretat.

Donada aquesta falta d'opcions amb demostrada eficàcia i seguretat per les pacients en càncer de mama, aquesta tesi doctoral pretén avaluar dos teràpies emergents amb potencial benefici per a aquest grup de pacients i valorar la seva eficàcia i seguretat.

LÀSER VAGINAL

Respecte la teràpia làser, com es pot observar a la revisió sistemàtica realitzada en l'àmbit d'aquesta tesi doctoral, la majoria d'estudis pel que fa a làser vaginal per al tractament de SGUM està realitzat en estudis pilot, observacionals i amb una única branca, valorant la majoria d'ells només variables subjectives.

Observem que la majoria d'estudis de branca única, conclouen que el làser vaginal millora significativament les variables avaluades.

Per contra, en els estudis amb comparació de dos braços, en general amb una millor força d'evidència científica, hi ha més variables que no milloren significativament comparant entre els dos braços d'estudi. A més, pràcticament l'única variable objectiva que es troba en la majoria dels estudis revisats durant la realització d'aquesta tesi doctoral és el pH vaginal.

El primer treball presentat en aquesta tesi intenta donar resposta a aquesta controvèrsia observada, intentant controlar la majoria de limitacions que presenten molts dels estudis que han avaluat la teràpia làser. Per una banda, les pacients avaluades

han utilitzat totes el tractament de primera línia que es realitzaria a la vida real, amb teràpies no hormonals, ja que cap pacient amb símptomes moderats o severs de SGUM hauria d'estar sense tractar.

Per altre banda, aquest estudi inclou pràcticament totes les variables descrites com a possibles en la revisió sistemàtica del estudis realitzats en làser vaginal fins a l'actualitat, separant per variables subjectives i objectives clarament, i a més aportant noves possibles maneres objectives d'avaluar l'elasticitat i gruix vaginal.

Un dels fets més potents i característics de l'estudi realitzat sobre el làser en aquesta tesi, és el fet d'afegir una teràpia basal sobre aquesta teràpia làser vs placebo en un estudi a doble cec, que ens permet valorar que en el grup de pacients analitzades, la teràpia làser no aporta un increment de benefici, és a dir, conclou que l'efecte del làser no és significatiu en la mostra de pacients estudiada, tot i que hi ha una milloria significativa respecte les dades basals en ambdós subgrups en la majoria de mesures avaluades.

Una qüestió que pot plantejar-se però donada l'estructura de l'estudi presentat, és si podria ser que donat que estem tractant pacients amb un SGUM moderat-sever, la milloria només amb la teràpia de primera línia és tant important a nivell absolut, que un possible efecte beneficiós del làser quedi atenuat per ser molt més petit en termes absoluts.

Contràriament, tampoc podem respondre a la pregunta de si realment l'efecte beneficiós observat a ambdós grups, és realment un efecte de la primera línia de tractament com suposem, o bé és en realitat un efecte placebo beneficiós en els dos grups pel fet d'estar realitzant sessions de làser dins un assaig clínic. Aquesta segona hipòtesi sembla però menys plausible, donades les diferències abans – després dels 6 mesos de seguiment a nivell de paràmetres objectius a nivell de biòpsies de la paret vaginal en ambdós grups.

El fet de avaluar diversos paràmetres objectius, és un altre dels punts forts d'aquest treball, ja que aporta robustesa als resultats, i posa en dubte l'habilitat de valorar realment el SGUM d'alguns tests subjectius habitualment utilitzats en altres estudis, tot i que algun dels paràmetres utilitzats són nous a la literatura.

Per altre banda però, l'estudi demostra que la teràpia làser és una opció ben tolerada tot i presentar habitualment efectes secundaris lleus, i es considera segura en pacients en càncer de mama al no incrementar els nivells d'estrogen sèric en cap dels dos grups com era previsible al tractar-se d'una teràpia no hormonal, a més també descarta en el grup de pacients estudiades un dels possibles efectes secundaris descrits per la FDA com el de possibles cremades internes a nivell vaginal, que no s'han produït en cap dels casos avaluats.

Tot i això, donada la controvèrsia trobada doncs, sobretot en assajos clínics avaluant el làser vaginal, calen més estudis per poder confirmar si aquesta teràpia és o no efectiva i segura, ja que trobem evidència de bona qualitat en ambdós direccions. Per aquest motiu, encara preval una alerta de la FDA sobre l'ús de la teràpia amb làser vaginal, i per tant creiem que fins que no aparegui evidència científica potent a favor del seu ús, el làser vaginal hauria de romandre en context d'ús experimental.

PRASTERONA

Respecte la teràpia amb prasterona intravaginal, compost amb un perfil androgènic, no es van trobar articles focalitzats avaluant el seu ús en pacients amb càncer de mama en la revisió sistemàtica inclosa en aquesta tesi doctoral. No obstant, si es van trobar estudis avaluant l'ús de testosterona vaginal en pacients en càncer de mama, observant només 3 assajos estudiant crema de testosterona tòpica vaginal. Aquests estudis resultaven favorables respecte la milloria avaluant variables subjectives de sexualitat i qualitat de vida, i en només un d'ells s'avaluava l'estradiol circulant durant 8 setmanes, observant un lleu increment sense arribar a nivells de pre-menopausia.

Aquesta tesi presenta el primer estudi realitzat avaluant l'ús de prasterona en pacients en càncer de mama tractades amb inhibidors de l'aromatasa. Sabíem que aquesta teràpia podria tenir un comportament similar en quant a eficàcia a teràpies amb testosterona vaginal al ser una teràpia androgènica, i a més la prasterona havia

demostrat ser efectiva en pacients sanes, per tant els bons resultats obtinguts respecte a l'eficàcia d'aquesta teràpia no són sorprenents.

La prasterona però, a diferència de la testosterona, és un precursor primari d'andrògens amb acció feble, que es transforma parcialment en estrògens actius mitjançant l'aromatització a nivell local de la paret vaginal, però no sistemàticament. És a dir, el mecanisme d'acció teòric es basa en aquesta síntesi local d'andrògens i estrògens dins de cada cèl·lula del teixit perifèric a partir del precursor suprarenal DHEA/prasterona. Aquests andrògens i estrògens actuarien a les mateixes cèl·lules on s'ha fet la seva síntesi i només serien alliberats d'aquestes cèl·lules diana després de ser inactivats. Per tant, la DHEA està teòricament lliure del risc potencial de càncer de mama, donat que l'increment d'estrògens sistèmics ha de ser mínim o nul.

El principal punt fort d'aquest estudi és el fet de que la prasterona a més de tenir de per si un risc baix d'increment sistèmic d'estrògens, les pacients avaluades estan totes en tractament amb inhibidors de l'aromatasa, enzim que activa la prasterona a estrògens de manera intracel·lular i de forma local, però que farà que quedi inhibida a nivell sistèmic i per tant si alguna molècula de prasterona és absorbida a nivell sanguini, perdre la capacitat de transformar-se gràcies als inhibidors d'aromatasa.

Tot i ser un estudi pilot amb la limitació de ser una cohort petita de pacients, aquest estudi mostra que en cap de les pacients avaluades va incrementar-se els nivells d'estradiol sèric per sobre els nivells límit de menopausa. El fet de seleccionar pacients en tractament amb inhibidors de l'aromatasa, limitant la transformació perifèrica d'andrògens a estrògens, podria explicar el fet de que els nivells d'estradiol sèric no es veuen incrementats, i per tant aquest estudi podria mostrar que en aquest grup poblacional de pacients sobrevivents de CM la teràpia amb prasterona seria especialment segura.

Aquest fet és el primer pas per a futurs nous estudis que confirmin els resultats obtinguts, ja que donada la falta d'eficàcia demostrada pel làser vaginal en el primer estudi d'aquesta tesi doctoral, la prasterona podria convertir-se en una de les teràpies principals en pacients sobrevivents de CM tractades amb inhibidors de l'aromatasa que pateixin SGUM sever o no millorin amb teràpies de primera línia.

Finalment, però, una limitació del present estudi és que no es van mesurar els nivells d'estrone, testosterona i altres esteroides sexuals relacionats; tanmateix, s'ha demostrat que no s'han incrementat aquestes altres hormones sexuals després de l'administració de prasterona en altres estudis. Tot i això, caldria avaluar en futurs estudis si hi ha diferències en altres dels nivells sistèmics d'hormones circulants en

pacients prenent inhibidors d'aromatasa i comparar-los amb pacients sense prendre aquest tractament.

Per altre banda, donada l'heterogeneïtat de variables estudiades i la falta evident de variables objectives potents no invasives, aquesta tesi doctoral pretén avaluar una nova tècnica objectiva no invasiva per el seu us avaluador del SGUM.

ÚS DE NOUS PARÀMETRES OBJECTIUS PER AVALUACIÓ DEL SGUM

Per últim però no menys important, l'avaluació exhaustiva de diferents estudis realitzats valorant diferents teràpies per tractar el SGUM, ens han fet adonar de la heterogeneïtat de variables que s'utilitzen per valorar el grau de severitat del SGUM i la eficàcia en millorar-lo de diferents teràpies. A part d'existir desenes de variables, observem que la majoria són tests subjectius avaluant la sensació de la pròpia pacient o fins i tot el parer subjectiu del clínic. Fa dos dècades la FDA observant aquest problema ja va recomanar utilitzar de manera sistemàtica l'ús de paràmetres objectius en l'avaluació del SGUM. Tot i això, encara avui dia hi ha una mínima representació de tècniques cel·lulars com l'índex de maduració vaginal (VMI), i l'ús del pH vaginal queda distorsionat dins un altre test amb part subjectiva com el Vaginal Health Index (VHI).

Alguns estudis han intentat valorar de manera objectiva el SGUM amb tècniques invasives, avaluant el gruix de l'epiteli vaginal amb biòpsies vaginales com hem realitzat en el nostre estudi del làser de CO₂, o avaluant en aquestes biòpsies tincions específiques per valorar la quantitat de col·làgena. No obstant, tot i ser unes variables a priori més valorables de les que disposem habitualment, tenen el principal inconvenient de necessitar l'obtenció invasiva de teixit de la pacient.

Alguns estudis havien intentat sense èxit avaluar a través d'ecografia el gruix de la paret vaginal, però el nostre estudi pilot és el primer en utilitzar la ecografia transvaginal amb gel transvaginal (TVUS) i en demostrar que és capaç de diferenciar correctament entre epiteli vaginal sa i epiteli vaginal de pacients amb SGUM.

Una de les limitacions principals d'aquest estudi és que només ha estat dissenyat per demostrar si era capaç de diferenciar entre dos epitelis que *a priori* són probablement molt diferents, però és el primer pas per generar futurs estudis i hipòtesis que hauran d'avaluar la capacitat d'aquesta tècnica per a no només diagnosticar el SGUM, sinó també valorar la seva severitat.

Si la TVUS fos capaç de diferenciar diferents graus de severitat de SGUM, es podria convertir en una eina bàsica per l'avaluació del SGUM en la pràctica clínica habitual, i també com a eina de valoració de la resposta a les diferents estratègies terapèutiques que s'estan valorant encara en diversos estudis.

7. CONCLUSIONS

Aquesta tesi doctoral pretén donar resposta a les pacients sobrevivents de càncer de mama que pateixen síndrome genitourinari de la menopausa.

1. Gracies als estudis realitzats, podem concloure que l'ús de teràpies no hormonals com a primera línia per aquestes pacients, millora significativament tant en variables objectives com subjectives els símptomes que presenten i la seva qualitat de vida, però l'ús afegit de làser de CO2 vaginal, no aporta un increment de benefici als 6 mesos de seguiment en aquestes pacients.

2. Una de les teràpies alternatives en estudi per les pacients sobrevivents de càncer de mama que presenten síndrome genitourinari és el de la prasterona vaginal, que demostra ser una teràpia eficaç i segura en l'estudi pilot realitzat, i pot ser una alternativa per aquelles pacients que no milloren en la primera línia de tractament no hormonal.

3. Finalment, l'ecografia transvaginal amb gel intravaginal ha demostrat ser capaç de mesurar i diferenciar entre epiteli vaginal que presenta SGUM i epiteli vaginal sa, posicionant-se com a una futura eina d'avaluació objectiva no invasiva per a fer el diagnòstic i seguiment del síndrome genitourinari.

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