

Ginecologia ed Ostetricia Cagliaritana

President del Corso:
A.M. Paoletti, G.B. Melis

5,6 crediti ECM

CAGLIARI

19 Novembre 2019

T HOTEL CAGLIARI
Via dei Giudicati, 66

Cagliari • 19 Novembre 2019

Trattamento con DHEA

C. Di Carlo

Autocertificazione conflitto di interesse

Io sottoscritto COSTANTINO DI CARLO

Ai sensi all'art.76 (Conflitto di interesse ECM) comma 4 dell'Accordo tra il Governo, le Regioni e le Province autonome di Trento e Bolzano -
La formazione continua nel settore "Salute" del 2 febbraio 2017

DICHIARO

Che ho collaborato nell'ambito delle tematiche di questo Congresso ECM nell'arco degli ultimi due anni con le seguenti società:

- BAYER
- FARMITALIA
- GEDEON RICHTER
- IBSA
- LUPIN Pharmaceuticals
- MSD
- MYLAN
- SANDOZ
- SHIONOGI
- TEVA
- THERAMEX

Dichiaro inoltre che gli eventuali rapporti con soggetti portatori di interessi commerciali in campo sanitario non influenzерanno comunque l'attività formativa che svolgo in occasione di questo specifico Evento Formativo.

MENOPAUSA E TERAPIA ORMONALE SOSTITUTIVA

Raccomandazioni della Società Italiana della Menopausa

A cura del Direttivo della Società

Sindrome Genitourinaria della Menopausa

La TOS migliora i sintomi da atrofia urogenitale. La terapia estrogenica vaginale a basso dosaggio è la terapia di scelta per le donne che lamentano unicamente la sindrome genitourinaria. Tutti i preparati estrogenici locali mostrano un'efficacia paragonabile. I preparati estrogenici vaginali per la terapia dell'atrofia urogenitale non richiedono l'associazione progestinica in quanto i dosaggi utilizzati e/o il tipo di estrogeno somministrato (come il promestriene e l'estriolo) non sono in grado di determinare una proliferazione dell'endometrio.

Per il trattamento dei sintomi dell'atrofia vulvovaginale è disponibile ospemifene, un SERM indicato per il trattamento dell'atrofia vaginale, con una efficacia simile a quella delle terapie estrogeniche vaginali.

RECOMMENDATIONS

2016 IMS Recommendations on women's midlife health and menopause hormone therapy

R. J. Baber, N. Panay, A. Fenton and the IMS Writing Group

Postmenopausal vulvovaginal atrophy

All local estrogen preparations (creams, pessaries, tablets, vaginal ring) are effective in decreasing signs and symptoms of vaginal atrophy but they differ slightly in their adverse-event profiles^{5–8}. <1++> Ospemifene, a SERM derived from toremifene, has also been shown to be effective in treating vulval and vaginal atrophy^{9–13}. <1++> Vaginal moisturizers and lubricants as well as regular sexual activity may be helpful to such women. Vaginal moisturizers may have an equivalent efficacy to topical vaginal estrogen and should be offered to women wishing to avoid the use of hormonal therapy¹⁴. <1+>

Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence



*Collaborative Group on Hormonal Factors in Breast Cancer**



www.thelancet.com Published online August 29, 2019

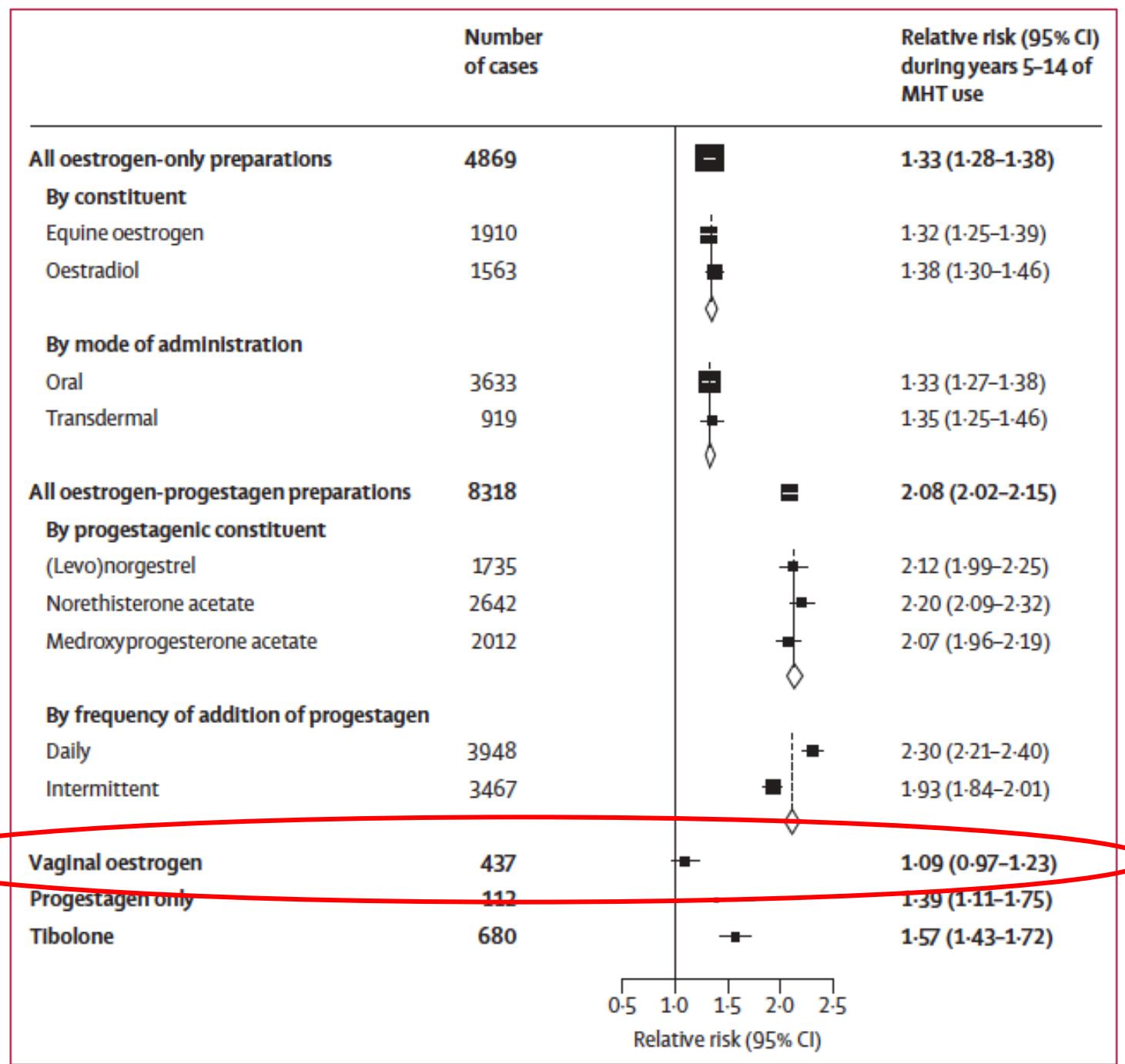


Figure 4: Main types of MHT: relative risks during years 5–14 of current use

La storia dell'introcrinologia

Inizia con la scoperta che le cellule della prostata normale e dei tumori prostatici sono in grado di sintetizzare androgeni
al loro interno

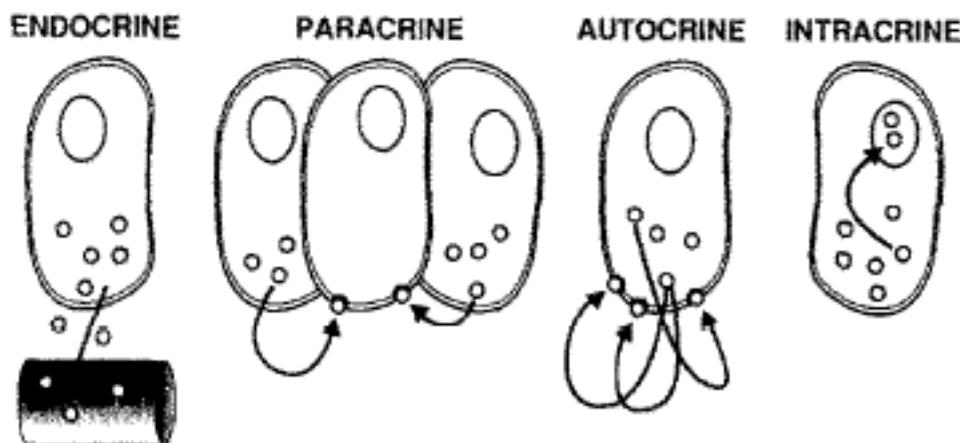
Labrie et al., Clin. Invest. Med. 5, 267-275, 1982;
Labrie et al., Important Adv Oncol, 193-217, 1985.
Labrie Mol. Cell. Endocrinol 1, C113-C118, 1991.

MOLCEL 02559

At the Cutting Edge

Introcrinology

Fernand Labrie





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Fernand Labrie

From Wikipedia, the free encyclopedia

Fernand Labrie, OC OQ MSRC (June 28, 1937 – January 16, 2019) was a Canadian medical researcher who specializes in endocrinological research and prostate cancer research.

Early life [edit]

Born in Laurierville, Quebec, he received a Bachelor of Arts degree in 1957 from the Séminaire de Québec. He received his Doctor of Medicine in 1962 and a Ph.D. in 1966 from Université Laval. From 1966 to 1969, he took his postdoctoral studies at the University of Cambridge and the University of Sussex.^[1]

In 1966, he joined the faculty of Université Laval as an Assistant Professor. In 1969 he was made an Associate Professor, and in 1974 he was made a Full Professor. In 1990, he was made the Head of the Department of Physiology. In 1969, he was made the Director of the Molecular Endocrinology Research Centre.^[1] Labrie died at the age of 81 in January 2019.^[2]

Honours [edit]

In 1981, he was made an Officer of the Order of Canada in recognition for being "one of the leading authorities in contemporary endocrinological research".^[3] In 1991, he was made an Officer of the National Order of Quebec. In 1990, he was awarded the Government of Quebec's Prix Michel-Sarrazin. In 1998, he was awarded the Izaak-Walton-Killam Award. In 2007, he was awarded the King Faisal International Prize.

References [edit]

1. ^ ^a ^b Elizabeth Lumley, ed. (July 1997). *Canadian Who's Who 1997: Volume 32*. University of Toronto Press. ISBN 0802049966.
2. ^ "Le Dr Fernand Labrie s'est éteint à 81 ans" (in French). radio-canada.ca. 17 January 2019. Retrieved 17 January 2019.
3. ^ "Order of Canada citation" (in).

Authority control BIBSYS: 90375399 · BNF: cb119104156 (data) · CINII: DA02569022 · ISNI: 0000 0000 8078 6541 · LCCN: n84140373 · NKC: ola2004235478 · ORCID: 0000-0003-4825-8767 · SUDOC: 026957698 · VIAF: 13135 · WorldCat Identities (via VIAF): 13135

Categories: 1937 births | 2019 deaths | Canadian medical researchers | Canadian endocrinologists | Fellows of the Royal Society of Canada | Officers of the National Order of Quebec | Officers of the Order of Canada | Université Laval faculty | Université Laval alumni | People from Centre-du-Québec

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Steroid assays using validated liquid chromatography tandem mass spectrometry



1- Labrie *et al*, J. Steroid. Biochem. Mol. Biol. 99, 182-188, 2006; 2- Ke, Gonthier *et al*, Horm. Mol. Biol. Clin. Invest. 24, 117-29, 2015; 3- Ke, Labrie *et al*, J. Ster. Biochem. Mol. Biol., 154, 186-196, 2015.

Utilizzando la cromatografia seguita dalla spettrometria di massa tandem in donne in postmenopausa si osservano livelli di estradiolo molto bassi

Serum steroid levels in intact and castrated elderly men and in postmenopausal women.

	Testo ^a	ADT-G ^a	3 α -diol-3G ^a	3 α -diol-17G ^a	ADT-G + 3 α -diol-3G + 17G	E ₁ ^b	E ₂ ^b	E ₁ S ^a
<i>Population-based Swedish cohort (69–80-year-old)</i>								
Intact men (n = 911)	4.57 ± 0.05	32.12 ± 0.89	1.46 ± 0.04	2.67 ± 0.07	36.26 ± 0.95	37.4 ± 0.5	21.5 ± 0.3	0.470 ± 0.011
Castrated men (n = 34)	0.12 ± 0.01	12.84 ± 1.99	0.52 ± 0.06	0.35 ± 0.04	14.89 ± 1.56	20.8 ± 1.4	3.0 ± 0.3	0.178 ± 0.020
Castrated Swe/intact Swe × 100	2.6%	40.0%	35.6%	13.1%	41.1%	55.6%	13.8%	37.9%
<i>Population-based Canadian cohort</i>								
Intact men (n = 391) (48–86-year old)	4.47 ± 0.08	30.37 ± 0.96	1.52 ± 0.05	3.57 ± 0.11	35.46 ± 1.04	30.2 ± 0.6	19.2 ± 0.3	0.515 ± 0.019
Castrated Swe/intact Can × 100	2.7%	42.3%	34.2%	9.8%	42.0%	68.9%	15.5%	34.6%
Intact women (n = 377) [18] (55–65-year-old)	0.14 ± 0.004	15.83 ± 0.65	0.64 ± 0.03	0.57 ± 0.02	17.04 ± 0.68	17.8 ± 0.5	4.2 ± 0.2	0.222 ± 0.011
Castrated men/intact women × 100	85.7%	81.1%	81.2%	61.4%	87.4%	117%	71.2%	80.2%

Data are presented as mean ± SEM. Percentages are in bold to highlight these data.

^a ng/ml.

^b pg/ml.

Livelli medi plasmatici di ormoni steroidi nelle donne (metodiche immunologiche)

	Età Fertile ^a (n = 15)	Menopausa Naturale (n = 18)	Ovariectomizzata (n = 8)
Estrone (pg/ml)	58	49	48
Estradiolo (pg/ml)	40	20**	18
Testosterone (ng/dl)	44	30**	12 [‡]
DHT (ng/dl)	30	10**	<5 [‡]
Androstenedione (ng/dl)	166	99**	64 [‡]
DHEA (ng/dl)	542	197**	126 +

^a Mean value during early follicular phase

⁺P<0.05 for comparison with naturally menopausal

[‡]P<0.01 for comparison with naturally menopausal

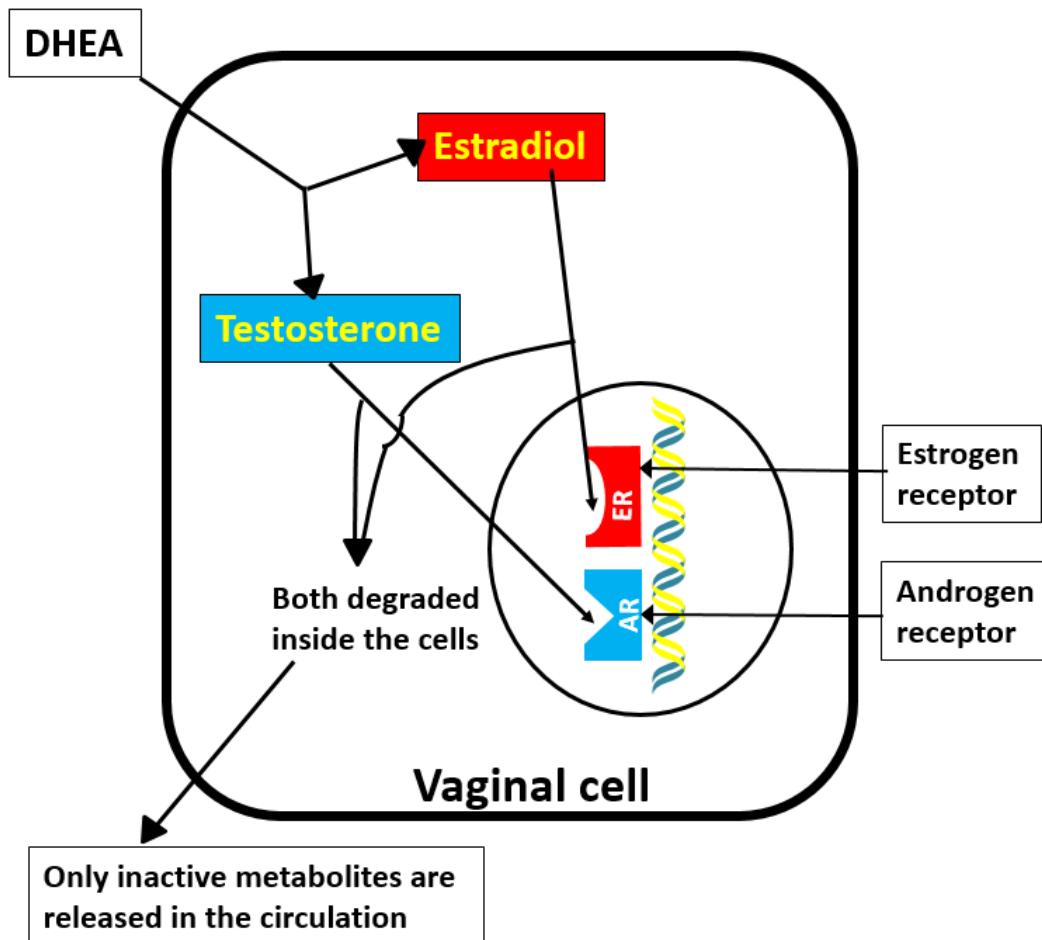
** P<0.01 for comparison with reproductive age

Since ovarian estrogen secretion stops in all women at menopause, and not all women suffer from the menopausal symptoms and signs mentioned above, there must be another factor or another variable source of sex steroids which could explain why some women are clinically free from menopausal symptoms while others (about 75%) suffer from menopausal symptoms and signs at various degrees [10-12].

Introcrinologia

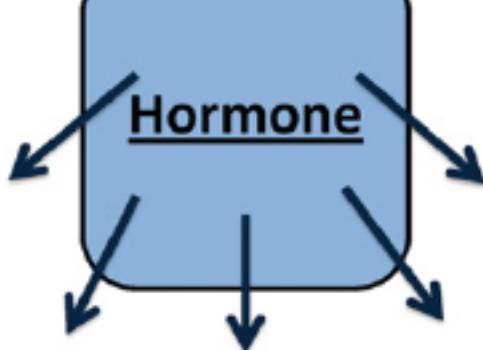
Sintesi intracellulare di estradiolo e testosterone a partire dal DHEA seguita dalla loro azione e dalla loro inattivazione a livello locale, con successiva escrezione di metaboliti inattivi.

Si evita così qualsiasi azione a livello di altre cellule in altri tessuti.



ENDOCRINOLOGY

Endocrine Gland



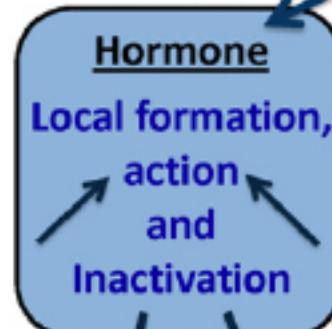
TO ALL TISSUES AS
ACTIVE HORMONE

INTRACRINOLOGY

Peripheral

Tissue

DHEA

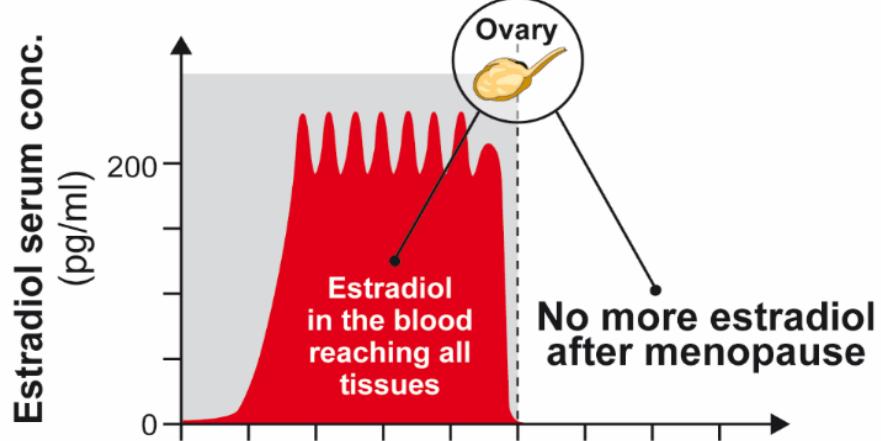


INACTIVE
METABOLITES ONLY

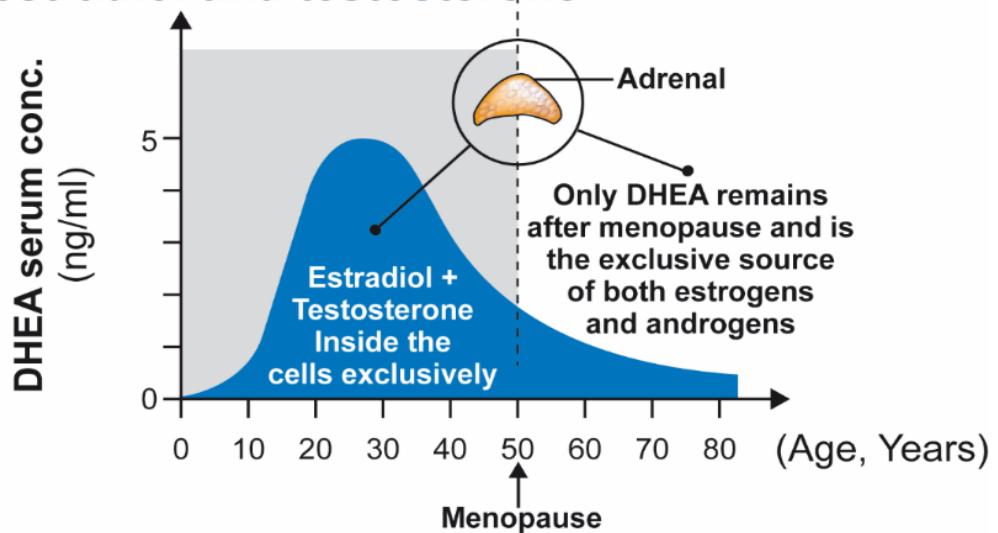
BLOOD

Prima della menopausa gli steroidi sessuali originano da due fonti

A- Estradiol (from the ovary) which is secreted in the blood to reach all tissues

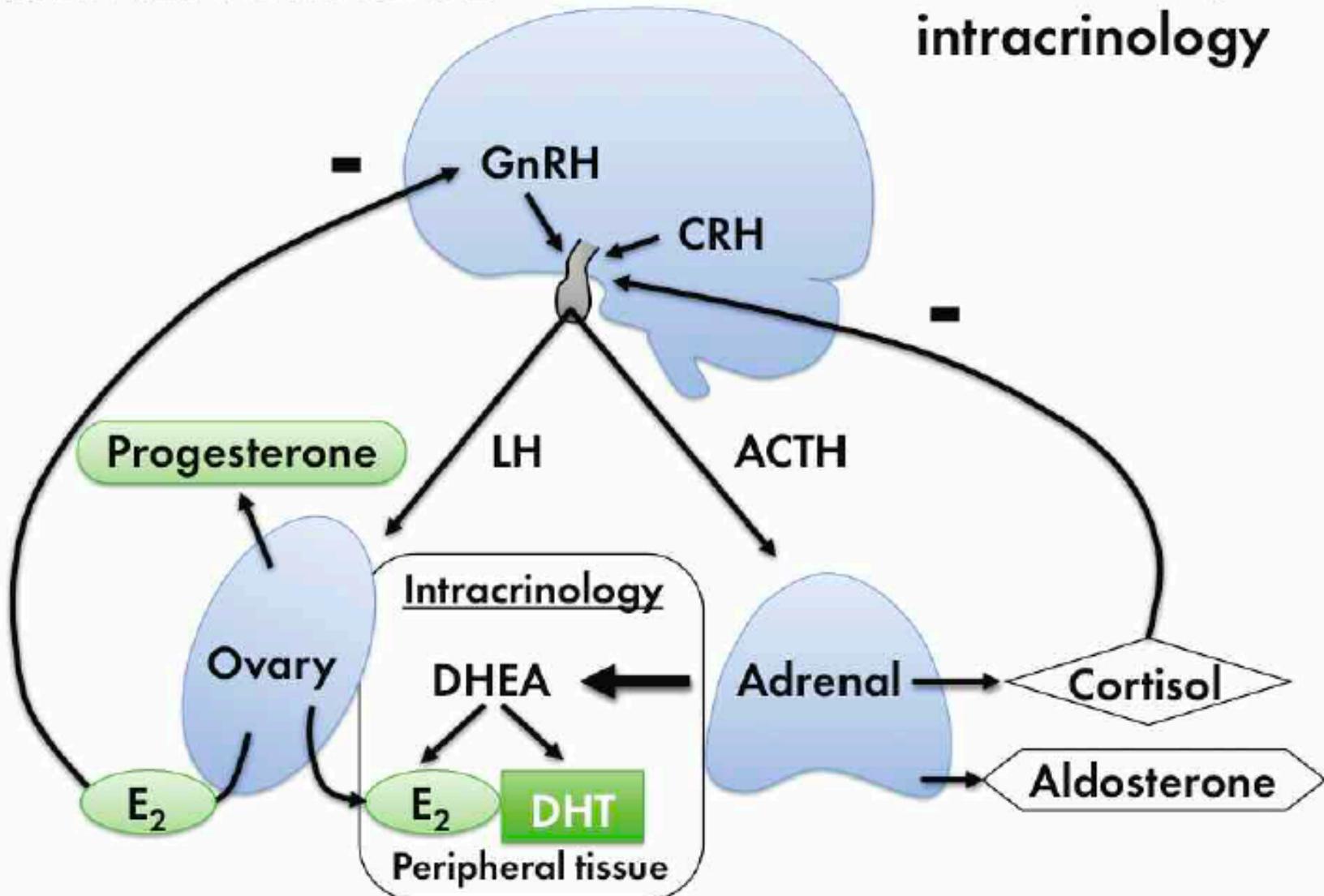


B- DHEA (mainly from the adrenals) for the tissue-specific intracellular formation of estradiol and testosterone



PREMENOPAUSE

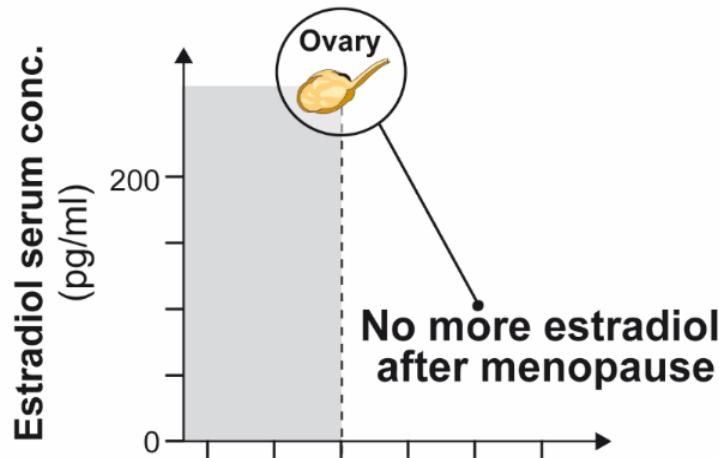
New findings:
introcrinology



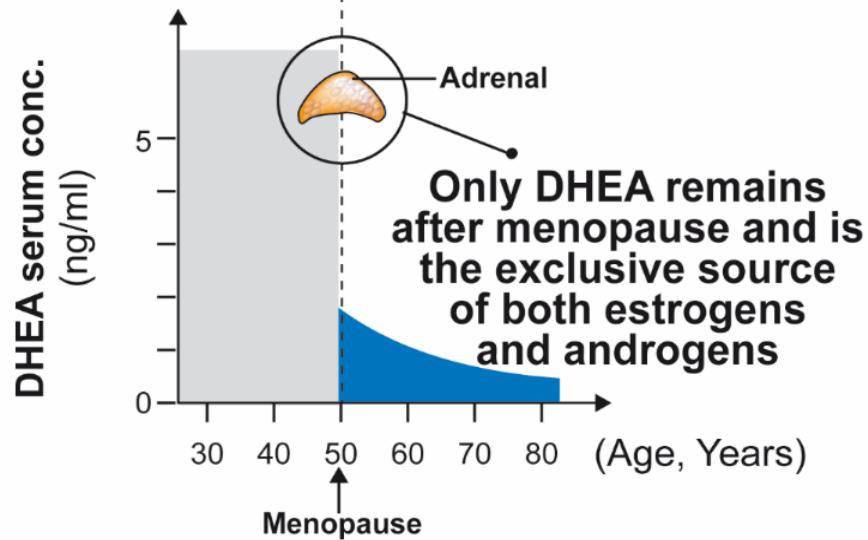
KEY: ACTH = adrenocorticotropic hormone; CRH = corticotropin releasing hormone; DHT = dihydrotestosterone; E_2 = estradiol; LH = luteinizing hormone; GnRH = gonadotropin-releasing hormone

Dopo la menopausa
il DHEA
(principalmente di
origine surrenalica è
l'unica fonte di
steroidi sessuali

A- Estradiol (from the ovary)

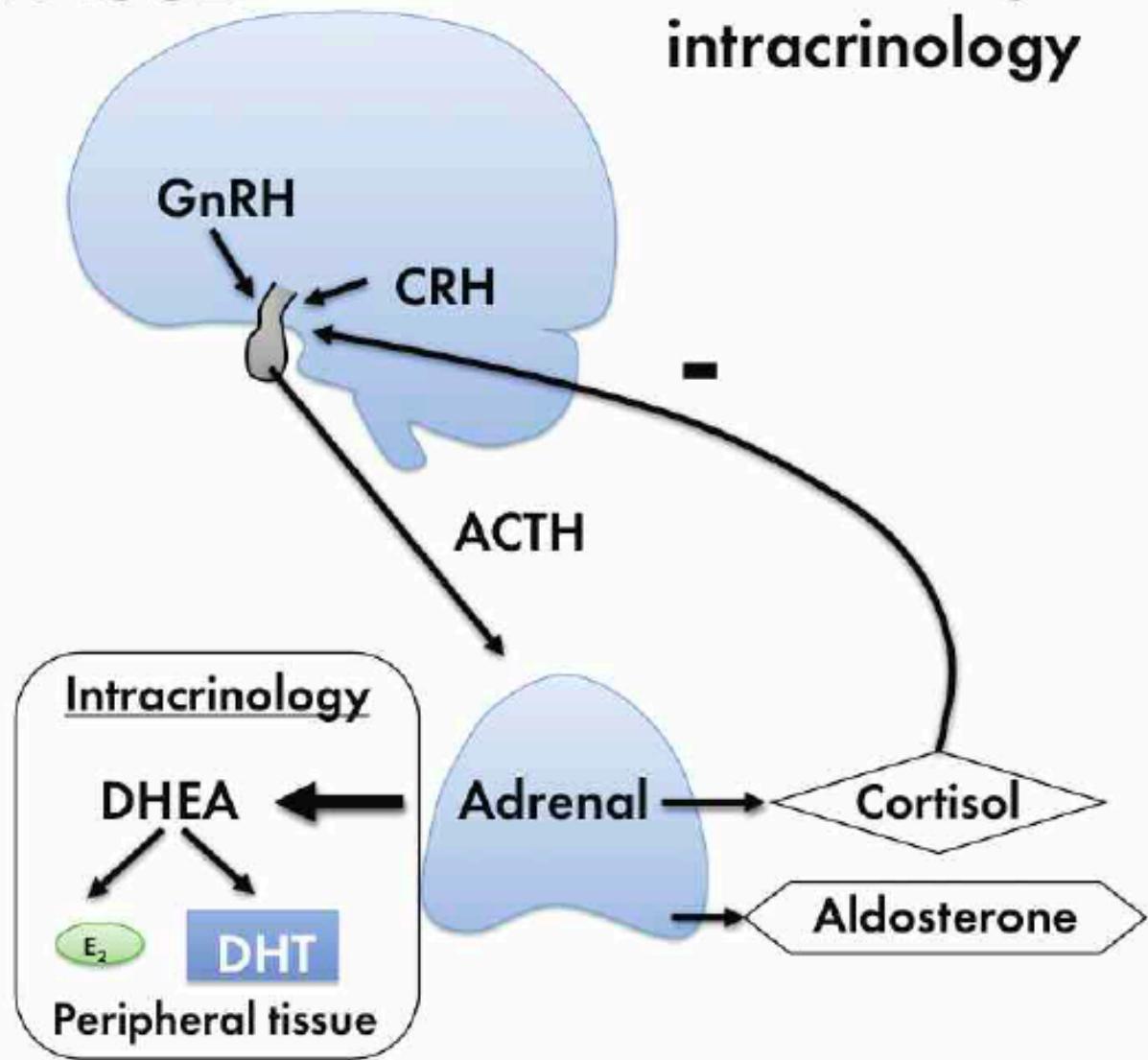


B- DHEA (mainly from the adrenals) for the tissue-specific intracellular formation of estradiol and testosterone



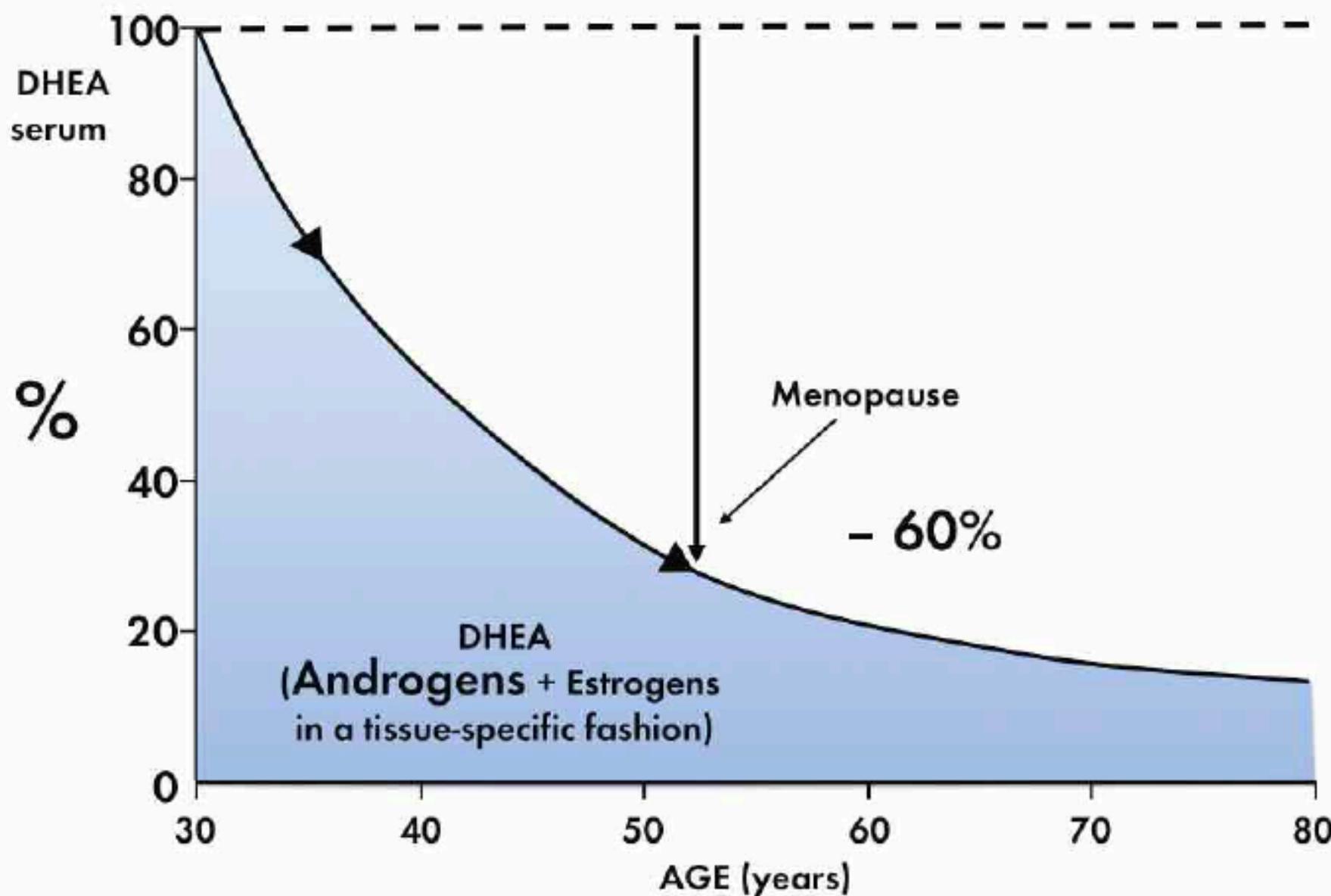
POSTMENOPAUSE

New findings:
introcrinology



KEY: ACTH = adrenocorticotropic hormone; CRH = corticotropin-releasing hormone; DHT = dihydrotestosterone; E₂ = estradiol; GnRH = gonadotropin-releasing hormone

Rationale for DHEA



Menopause: The Journal of The North American Menopause Society
Vol. 16, No. 5, pp. 858-859
DOI: 10.1097/gme.0b013e3181ae1fca
© 2009 by The North American Menopause Society

EDITORIAL

Transvaginal dehydroepiandrosterone: an unconventional proposal to deliver a mysterious androgen that has no receptor or target tissue using a strategy with a new name: Hormone Precursor Replacement Therapy (HPRT)

L'efficacia e la sicurezza del DHEA per via vaginale sono stati valutati in una serie di studi clinici. Studi fondamentali

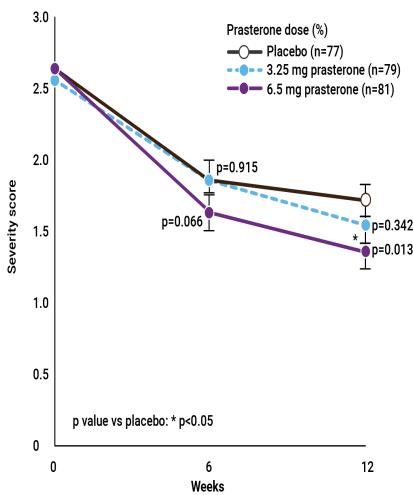
Study ID	Type of study/design	Dose(s) evaluated	Objective	Duration	Study population	Primary endpoint	Mean age (age range), gender, ethnicity, mean BMI or weight
ERC-231 (PIVOTAL)	Phase III study Randomized, double-blind, placebo- controlled Multi centre	Placebo Prasterone: • 3.25mg (0.25%) – off licence • 6.5mg (0.50%) Once daily	To confirm the efficacy of intravaginal prasterone on the symptoms and signs of vaginal atrophy	12 weeks	255 subjects enrolled Postmenopausal women with vaginal atrophy; dyspareunia as MBS	4 co-primary endpoints (vaginal maturation index*, vaginal pH, improvement in MBS)	59 years (40–75 years)/ 100% Female/ 92% White/ BMI = 26.1
ERC-238 (PIVOTAL)	Phase III study Randomized, double-blind, placebo- controlled Multi centre	Placebo Prasterone: 6.5mg (0.50%) Once daily	To confirm the efficacy of intravaginal prasterone on moderate to severe pain at sexual activity (dyspareunia) as MBS of vulvovaginal atrophy	12 weeks	558 subjects enrolled Postmenopausal women with vaginal atrophy; dyspareunia as MBS	4 co-primary endpoints (vaginal maturation index*, vaginal pH, improvement in MBS)	59 years (40–80 years)/ 100% Female/ 91% White/ BMI = 26.4
ERC-230 LONG TERM (PIVOTAL)	Phase III Open-label Multi centre	Prasterone: 6.5mg (0.50%) Once daily	To assess the long-term safety of intravaginal prasterone	52 weeks	530 subjects enrolled Post-menopausal women having self-identified at least one mild to severe vaginal atrophy symptom	Endometrial biopsies and serum DHEA and DHEA metabolite levels	58 years (43–75 years)/ 100% Female/ 92% White/ BMI = 26.3

L'efficacia e la sicurezza del DHEA per via vaginale sono stati valutati in una serie di studi clinici. Studi secondari.

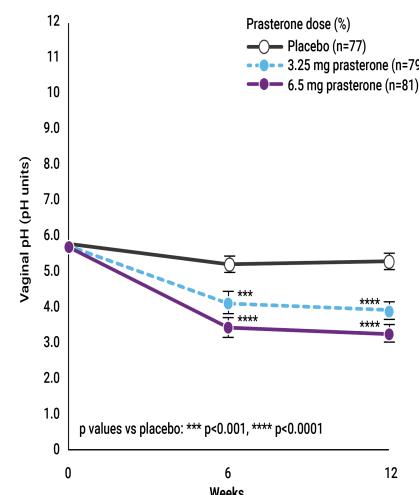
Study ID	Type of study/design	Dose(s) evaluated	Objective	Duration	Study population	Primary endpoint	Mean age (age range), gender, ethnicity, mean BMI or weight
ERC-213	Phase I/II PK study Randomized, double-blind, placebo-controlled Single centre	Placebo <ul style="list-style-type: none"> Prasterone: • 6.5mg (0.50%) • 13.0mg (1.0%) – off licence • 13.4mg (1.8%) – off licence Once daily	Systemic bioavailability of DHEA and its metabolites and the PK of vaginal suppositories at four different DHEA concentrations	7 days	40 subjects enrolled Postmenopausal women with vaginal atrophy	PK parameters	62 years (44–72 years)/ 100% Female/ 99% White/ Weight = 64 kg
ERC-210	Phase III study Randomized, double-blind, placebo-controlled Multi centre	Placebo <ul style="list-style-type: none"> Prasterone: • 3.25mg (0.25%) – off licence • 6.5mg (0.50%) • 13.0mg (1.0%) – off licence Once daily	To determine the dose-response of vaginal mucosa parameters to the local action of DHEA	12 weeks	218 subjects enrolled Postmenopausal women with vaginal atrophy	4 co-primary endpoints (vaginal maturation index*, vaginal pH, improvement in MBS)	58 years (42–74 years)/ 100% Female/ 100% White/ BMI = 26
ERC-234	Phase III study Randomized, double-blind, placebo-controlled Multi centre	Placebo <ul style="list-style-type: none"> Prasterone: • 3.25mg (0.25%) – off licence • 6.5mg (0.50%) Once daily for 2 weeks followed by twice weekly for 10 weeks – off license	To analyze the efficacy of intravaginal prasterone on vaginal dryness	12 weeks	450 subjects enrolled Postmenopausal women with vaginal atrophy; dryness as MBS	4 co-primary endpoints (vaginal maturation index*, vaginal pH, improvement in MBS)	58 years (41–75 years)/ 100% Female/ 90% White/ BMI = 26.9

ERC-231: donne in post menopausa con AVV e con dispareunia come sintomo più fastidioso

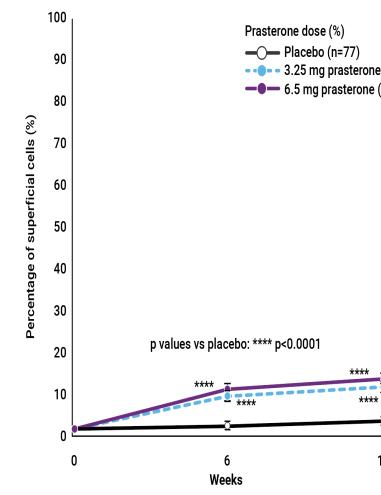
Gravità della dispareunia



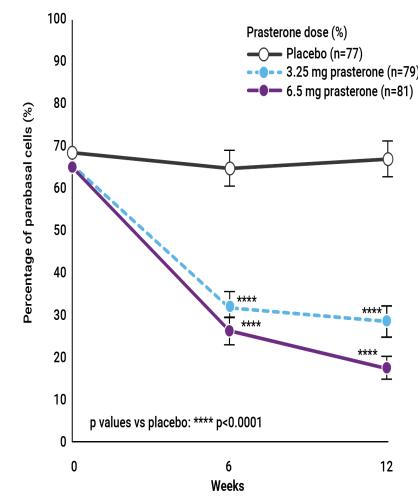
pH vaginale



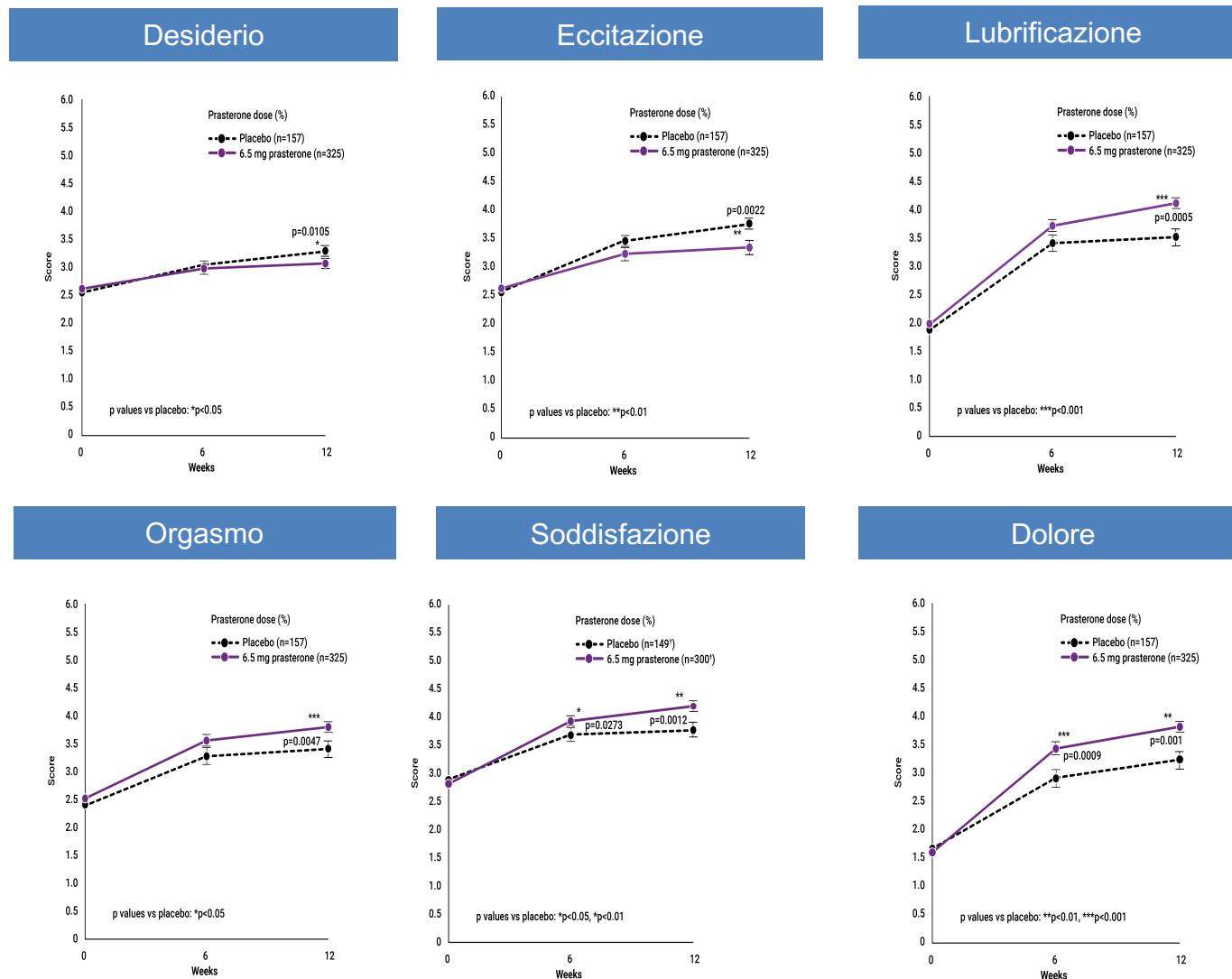
% cellule superficiali



% cellule parabasali



ERC-238: donne in post menopausa con AVV e con dispareunia come sintomo più fastidioso. Effetti sulla funzione sessuale (FSFI)



ERC-230: Studio di sicurezza. 389 donne in post menopausa con AVV lieve, moderata o severa trattate con 6.5 mg di prasterone per 52 settimane

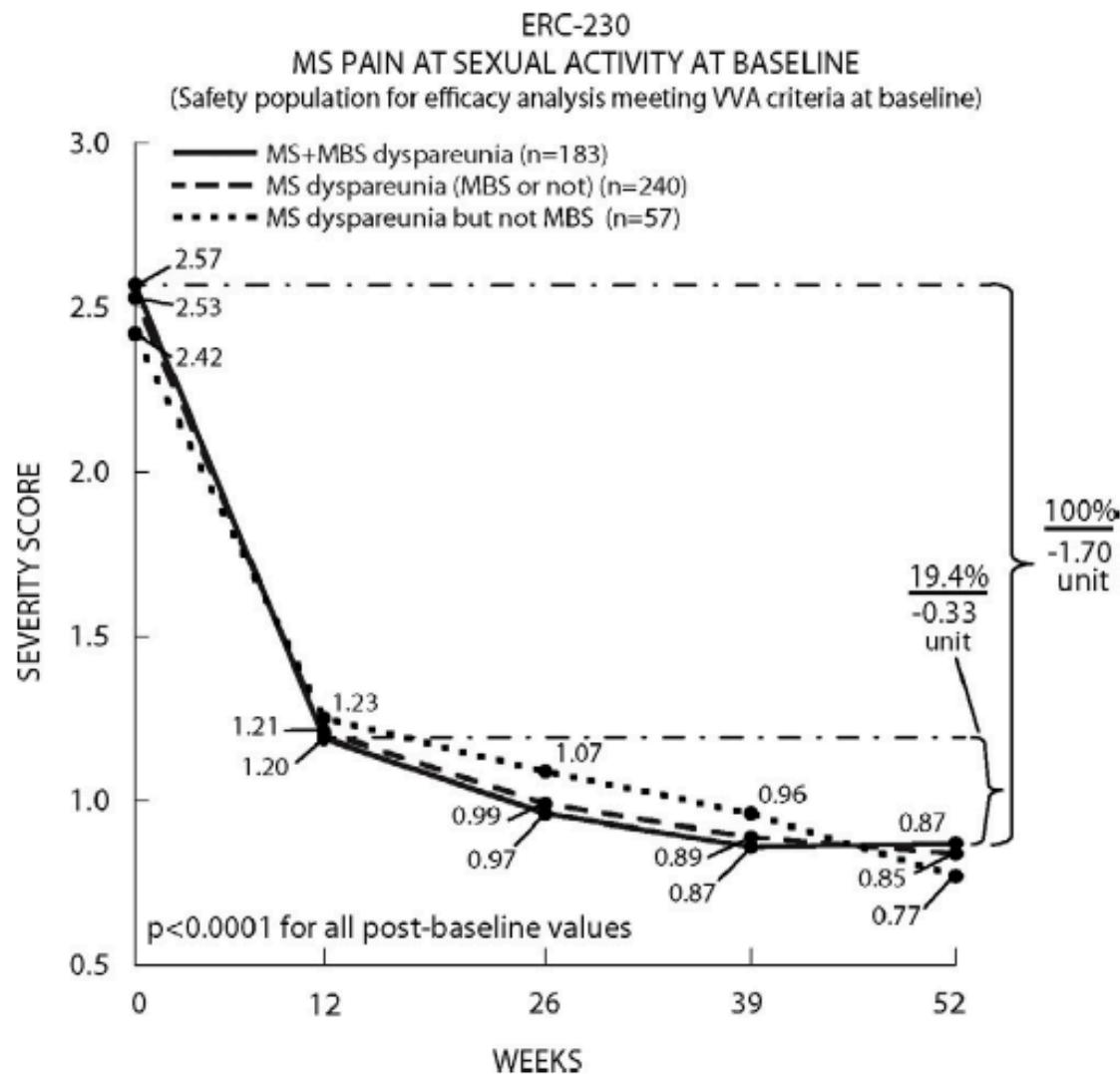
Istologia endometriale

- **385 (99%) endometrio atrofico**
- **4 (1%) endometrio inattivo**

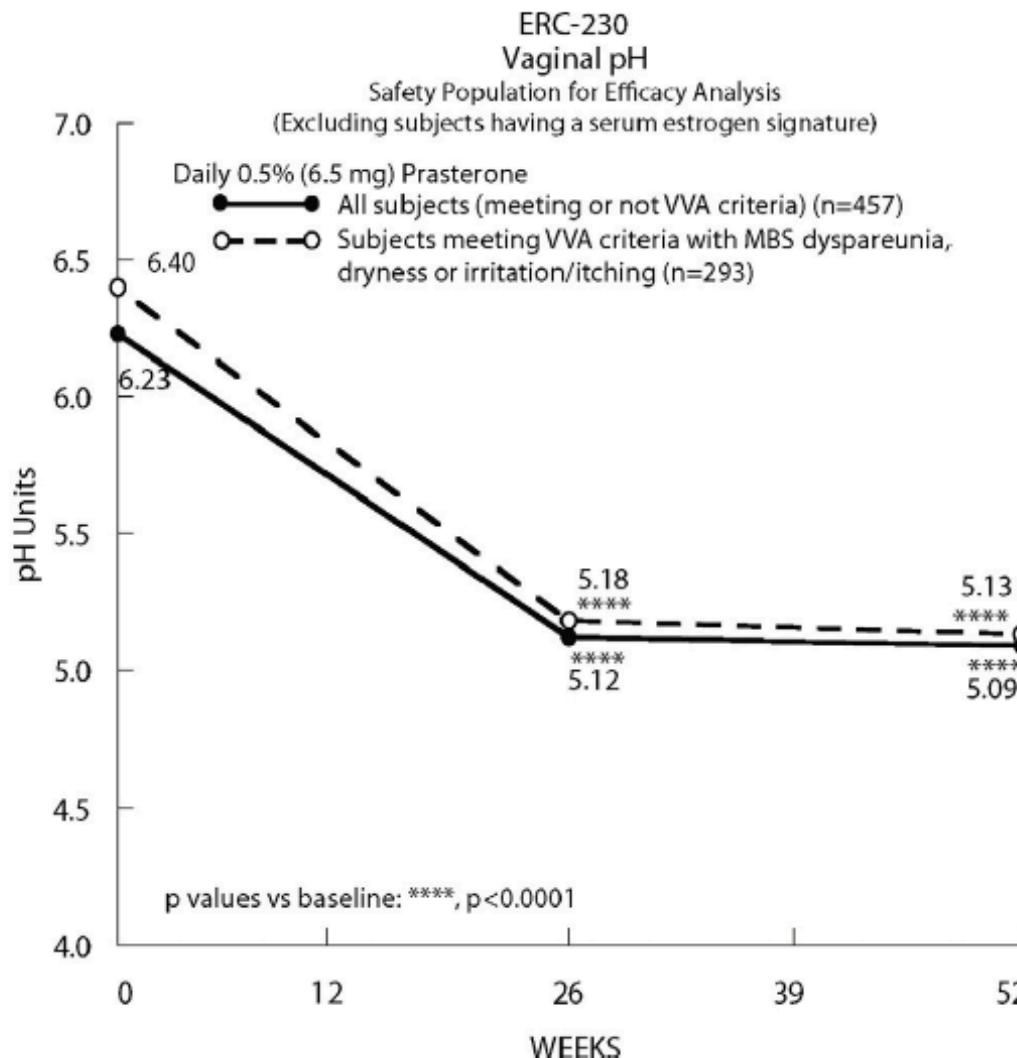
Valutazione ecografica dell'endometrio

- **Nessuna modifica dello spessore endometriale**

ERC-230: Studio di sicurezza. 389 donne in post menopausa con AVV lieve, moderata o severa trattate con 6.5 mg di prasterone per 52 settimane



ERC-230: Studio di sicurezza .389 donne in post menopausa con AVV lieve, moderata o severa trattate con 6.5 mg di prasterone per 52 settimane



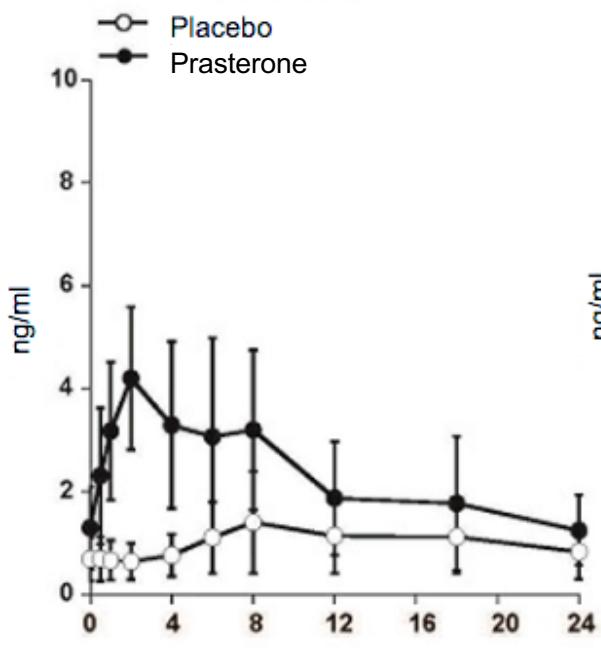
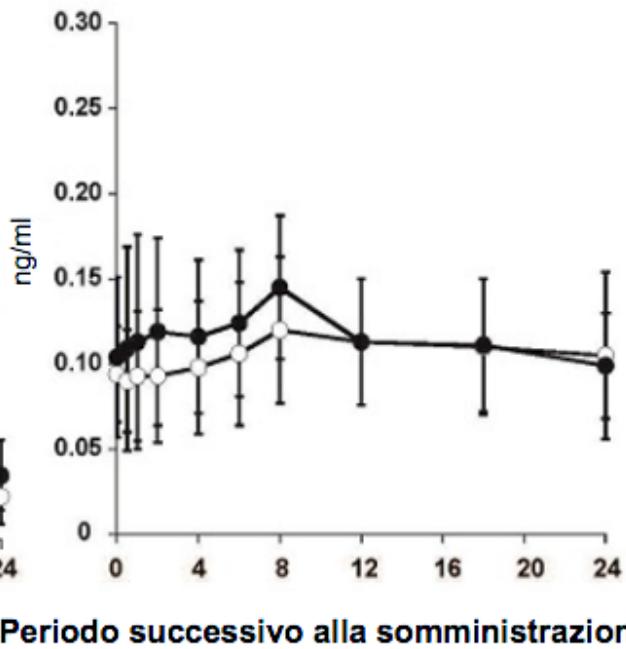
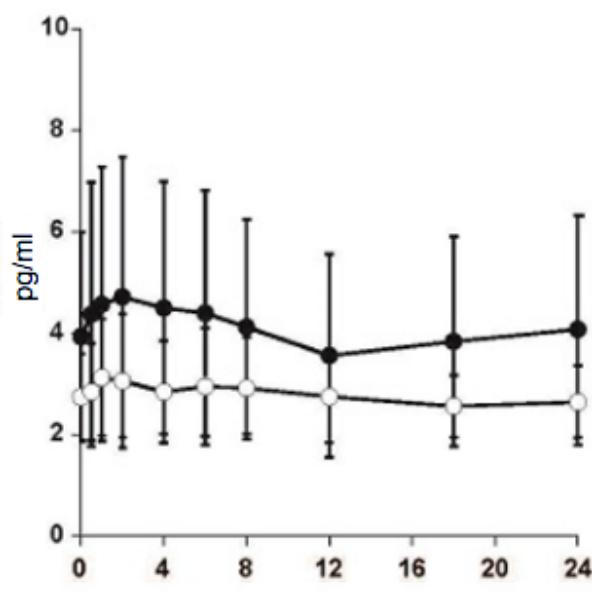
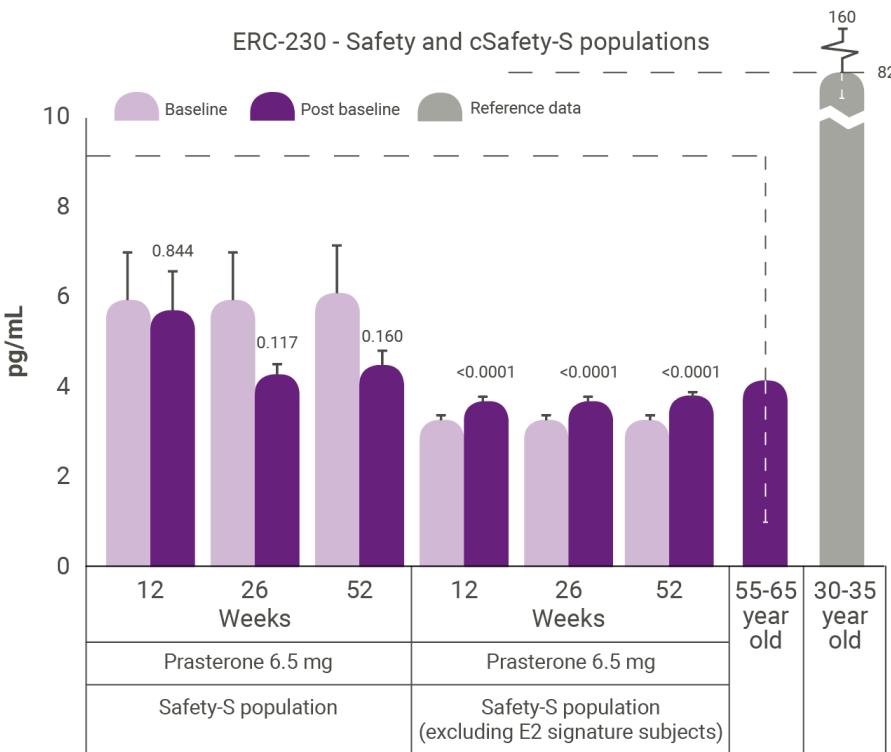
A- Prasterone**B- Testosterone****C- Estradiolo (E_2)**

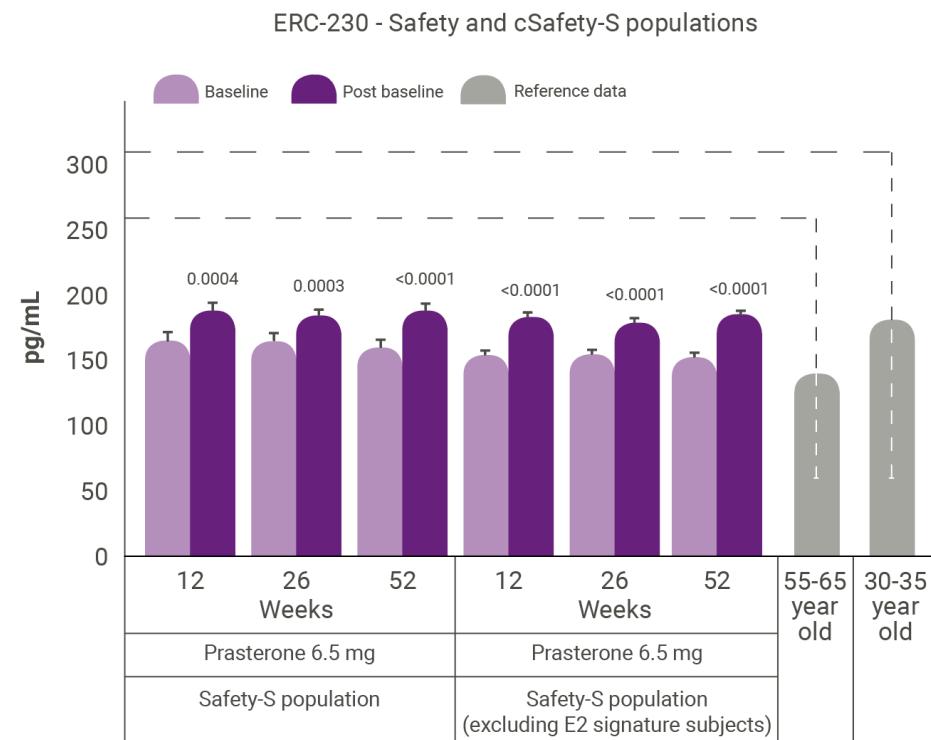
Figura 1. Concentrazioni sieriche di prasterone (A), testosterone (B) ed estradiolo (C) misurate in un periodo di 24 ore al 7° giorno successivo alla somministrazione quotidiana di placebo o di prasterone (media \pm S.D.)

ERC-230: Studio di sicurezza .389 donne in post menopausa con AVV lieve, moderata o severa trattate con 6.5 mg di prasterone per 52 settimane

Serum concentrations of oestradiol in Safety-S and cSafety-S populations



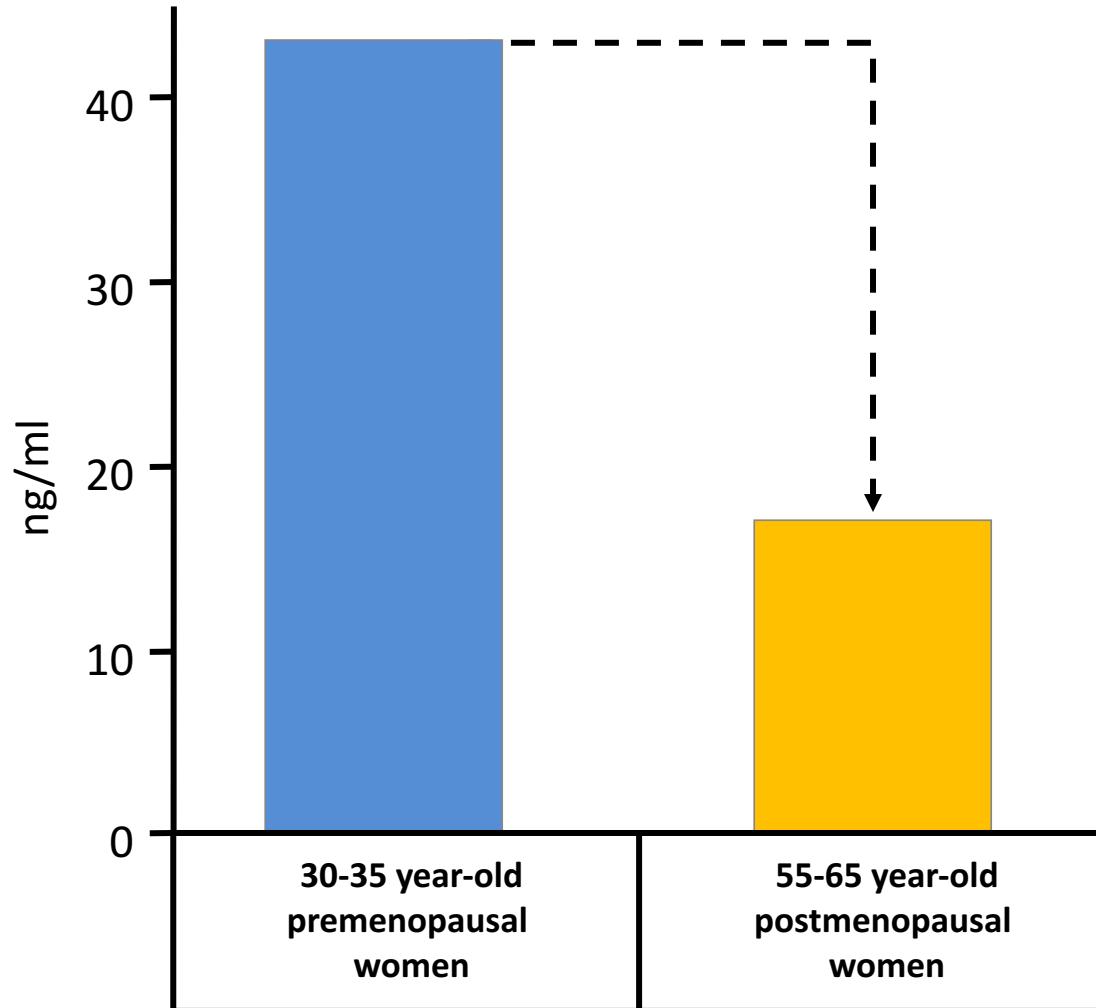
Serum concentrations of testosterone in Safety-S and cSafety-S populations

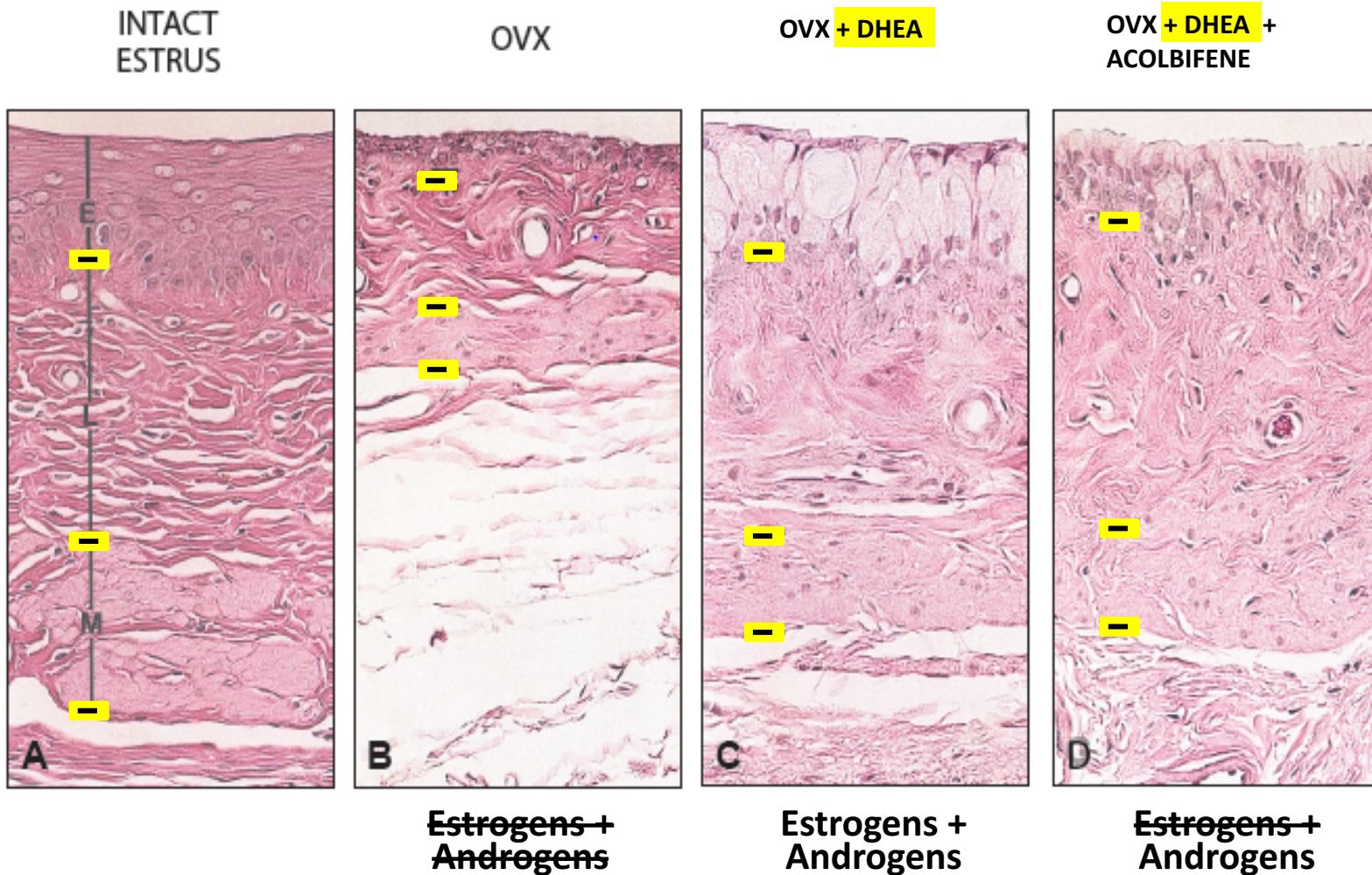


Non ci sono dati su donne con:

- Iperplasia endometriale
- Endometriosi
- Cancro mammario attivo o pregresso
- Cancro ovarico attivo o pregresso
- PAP test anomalo
- TVP attiva o pregressa
- Ipertensione non controllata
- Trombosi arteriosa attiva o pregressa
- In TOS estrogenica, estroprogestinica o androgenica

In postmenopausa gli androgeni totali diminuiscono del 60%





Both androgens and estrogens are responsible for vaginal health

“Consequently, treatment with estrogens is only a partial treatment.

DHEA makes estrogens and androgens in the three layers of the vagina with an exclusive androgenic action in the nerve endings possibly responsible for the benefits of intravaginal DHEA on sexual dysfunction.”

Tutte le slides sono disponibili su

www.costantinodicarlo.it