



**Universidad
de Cartagena**

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ANTICONCEPCIÓN ORAL DE SOLO PROGESTINAS: PRESENTE Y FUTURO. ¡LOS ESTRÓGENOS CONTRAATACAN !



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CONFLICTOS DE INTERES

El autor de la presentación es explorador de la anticoncepción hormonal en toda su dimensión.

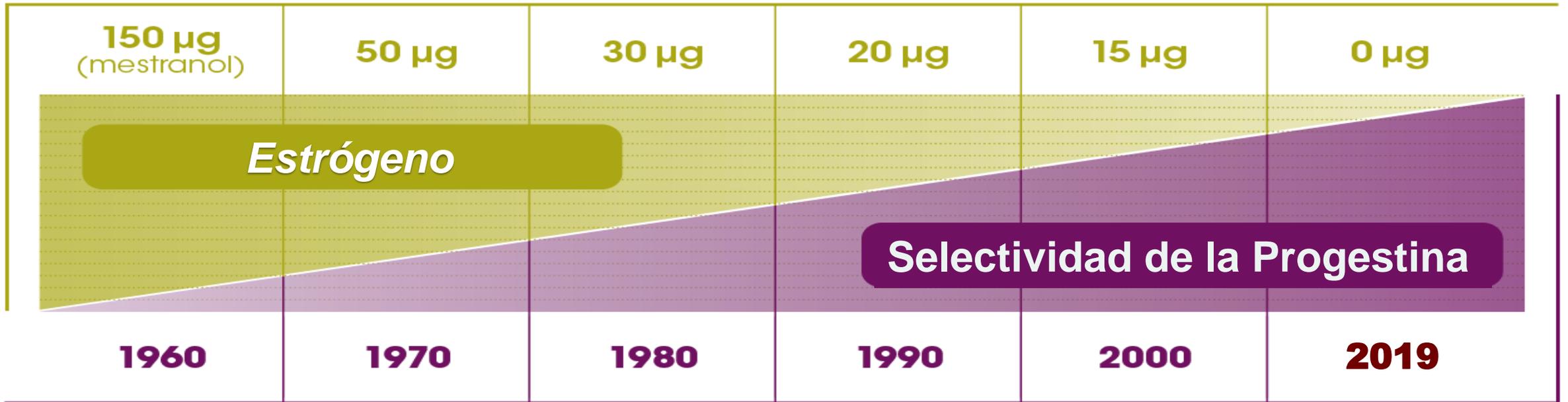
Tiene publicaciones sobre diferentes moléculas disponibles y sobre hormonoterapia en general.

No ha tenido ni tiene compromisos con la industria farmacéutica que le limiten su libre pensamiento y actuación.

Conferencia preparada para el Simposio de Anticoncepción de la Asociación Antioqueña de Ginecología y Obstetricia. 2022



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www.grupodeinvestigacionlaluddelamujer.com.co



- **PROGESTINA:**
Anticoncepción
- **ESTRÓGENO:**

Complementario – Control del Ciclo

Riesgos tromboembólicos venosos

Sangrado impredecible o mal Control del Ciclo



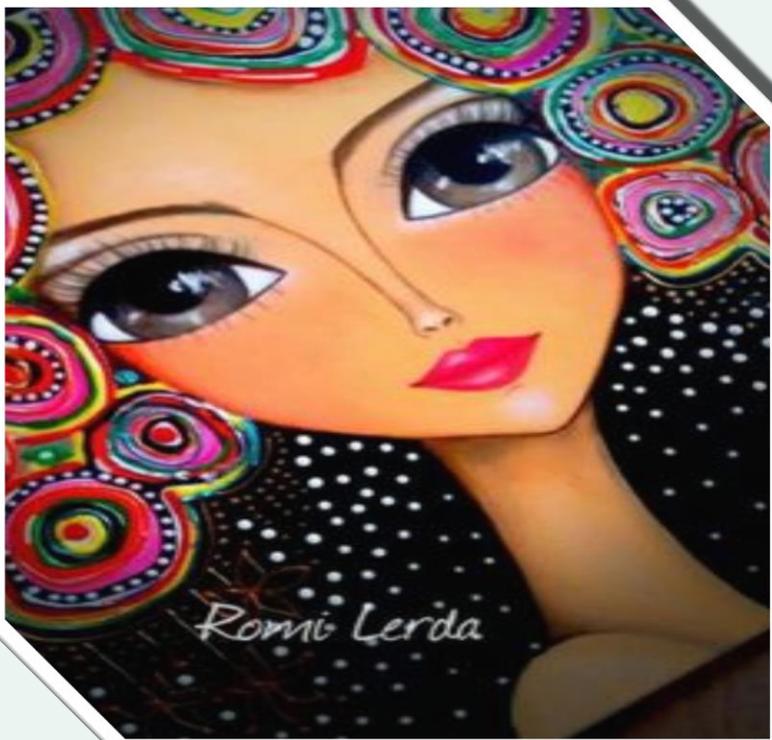
CLASIFICACIÓN DE LAS PROGESTINAS

	19 NOR TESTOSTERONA DERIVADOS	17 α PROGESTERONA DERIVADOS		HÍBRIDOS
Estranos	Gonanos	Pregnanos	Norpregnanos	
Noretindrona Noretinodrel Linestrenol Etinodiol Norgesterona Quingestanol Norgestrieno	Norgestrel Levonorgestrel Desogestrel Gestodeno Norgestimato	Ciproterona Clormadinona Megestrol Medroxipro- gesterona Superlutina	Nomegestrol Trimegestona Promogestona	Drospirenona Dienogest
			MODULADOR SELECTIVO DEL RECEPTOR PROGESTERONA	
			Acetato de Ulipristal	
19 NORPROGESTERONA DERIVADOS (NO ANDROGENICOS) Acetato de Segesterone o Nesterone				

PILDORAS DE SOLO PROGESTINAS CLASIFICACIÓN SEGÚN PROGESTINA Y FORMA DE ADMINISTRACIÓN



Grupos	Progestinas	Concentración/tableta
<i>Administración continua sin días de pausa</i>		
Mini píldoras o progestinas tradicionales	Norethisterona	0.350 mg 0.500 mg 0.600 mg
	Norethindrone	0.350 mg
	Ethinodiol diacetate	0.500 mg
	Linestrenol	0.500 mg
	Norgestrel	0.075 mg
	Levonorgestrel	0.030 mg
Solo progestina de desogestrel	Desogestrel	0.075 mg
<i>Administración continua por 24 días y cuatro días de pausa</i>		
Progestina de solo drospirenona (Drospirenone Only Pill)	Drospirenona	4.0 mg



Alteración Biofísica del Moco Cervical
Acción Tubárica
Altera el Ciclo Menstrual
Efecto Anovulatorio
Efecto Endometrial – Espermiático
Ambiente Intrauterino Inhóspito Gametos
No interrumpen embarazo
No causan defectos al nacer

Current Knowledge of Progestin-Only Pills

Alvaro Monterrosa-Castro ^{1*}, Velia Redondo-Mendoza ¹, Angelica Monterrosa-Blanco ¹

*Grupo De Investigación Salud de la Mujer. Facultad de Medicina.
Universidad de Cartagena. Colombia.*

Electron J Gen Med. 2021;18(6):em320

ARTICLE INFO

ABSTRACT

Since the 1960s, contraceptive pills have been at the service of humanity. They are one of the innovations that have contributed the most to the changing role of women in society and to women achieving the role they play today. Combined oral contraceptives (COCs) opened up opportunities to increase knowledge about the effects of estrogens and progestins in the female organism. The overall results of this evolution were progestin-only contraceptives in general and estrogen-free oral contraceptives as progestin-only pills (POPs) in particular. To identify the position currently held by POPs, a bibliographic review was carried out in the following databases: PubMed, ScienceDirect, EBSCOhost, OvidSP, Embase, and SciELO in Spanish. POPs have evolved notably from restricted use only during breastfeeding to a broader context. The absence of estrogen in the pill currently offers more advantages than disadvantages. The recent introduction of POP containing 4.0 mg of drospirenone, administered in a 24/4-day regimen, offers better cycle control than previous POPs, as it allows much more predictable bleedings and the same contraceptive efficacy as COCs. Hormonal contraception use continues to grow. The options to regulate reproduction are numerous, and users have a greater number of options to choose the one that suits their needs and comforts. Health professionals must provide high-quality contraceptive counseling, offering all available tools, including POPs.



Uso adecuado del esquema
Quistes Lúteos: Normales (50%)
Seguras en lactancia: Madre-Neonato
Sin retardo en la Fertilidad
Mal control del Ciclo/ Sin medidas efectivas
Posible Protección EPI
Posible Protección A. Células Falciformes
Posible Reducción Cáncer Endometrial

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No Se Asocia a Cáncer de Seno

RR: 1.7 [IC95%:0.8-3.7]

RR: 1.6 [IC95%:0.9-2,6]

RR: 1.0 [IC95%: 0.9-1.29]

Más de 5 años: RR: 1.4 [IC95%:1.03-2.00]

Por cada año adicional: RR:1.03 [1.01-1.06]

Sin impacto en Utero, Hígado, Colorectal

Posible Protector Cancer Epitelial Ovario

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**Sin Efecto sobre el peso o IMC
Utilidad en Transición a la Menopausia
Utilidad en Fumadoras.
Desogestrel – Drospirenona: Ovulación
Beneficio adicional en tratamiento:
Endometriosis
Desogestrel: Abrió camino a la píldora sin
Estrógenos fuera de la lactancia**

DOP (Drospirenona Only Pill)



2002

Rosembaum: Reducción Actividad ovárica con Drospirenona sola

0.5 mg/día: 36%

1.0 mg/día: 25%

2.0 mg/día: 50%

3.0 mg/día: 91% - Sin ovulación.

2003

Elger. Perfil farmacodinámica Drospirenona

2003

Estudios con diferentes dosis para administrar con periodos de pausa

2014

2015

**Duijkers: “Progestagen Only Pills”
Desogestrel (continuo) versus
Drospirenona 4.0 mg (esquema 24/4)**

2015

Archer: Eficacia, Seguridad, Tolerabilidad y Control del Ciclo

2019

Aprobado por la FDA para anticoncepción y manejo de la dismenorrea

DOP (Drospirenona Only Pill)

Drospirenona 4mg (Esquema 24/4) Sin Estrógenos

Eficacia similar a los Anticonceptivos Combinados

Buen perfil de Sangrado – Buen Control Ciclo

Pocos días de sangrado y poca Cantidad Sangrado

Continua protección pese 24 horas de olvido

Reducción de la dismenorrea

Sin cambios en Parámetros Hemostáticos

Seguro en la Lactancia – No Eventos Adversos

No Eventos Tromboembólicos Venosos

La Obesidad no Reduce la Eficacia

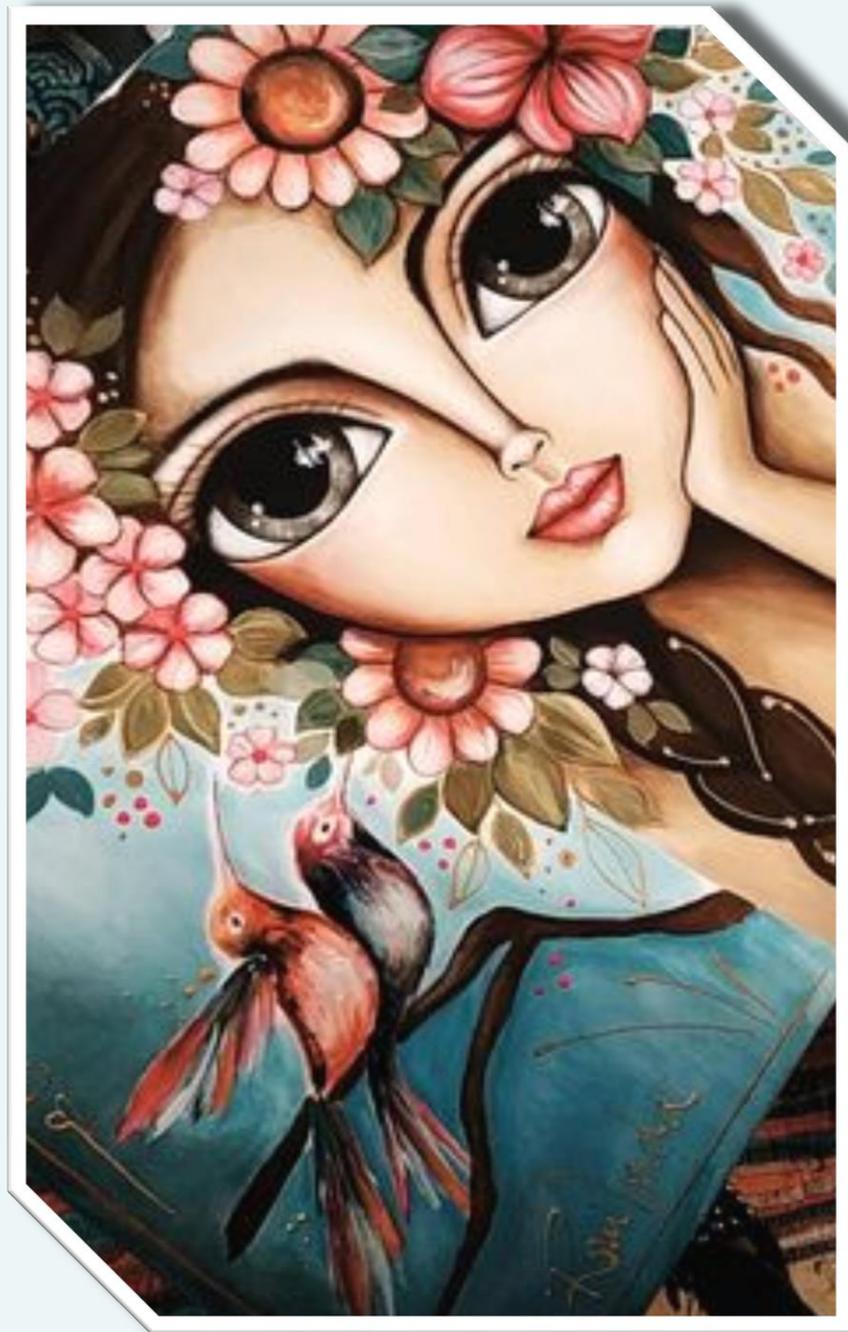
Beneficios del Perfil Anti androgénico de la DRSP

Aceptabilidad en el 99% de las Usuaris

0.4% Abandono por sangrado no tolerado



¿Una píldora de solo progestina puede Amenazar la existencia de los Anticonceptivos Combinados?



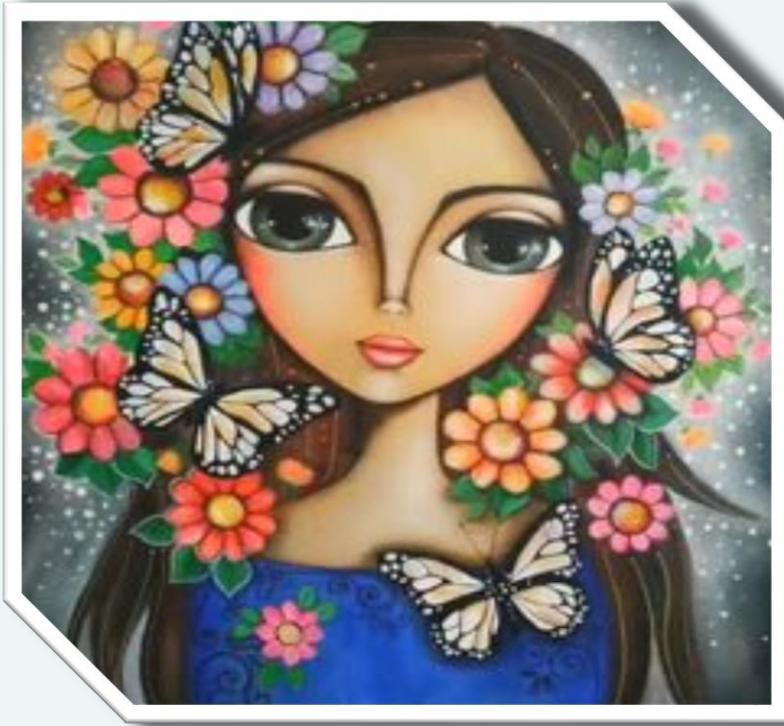
LA PILDORA DE SOLO PROGESTINA AL 2022

**Minipíldora de Levonorgestrel
Administración continua
Solo en la lactancia**

**Solo Progestina de Desogestrel
Administración continua
Dentro y fuera de la lactancia**

**“Drospirenona Only Pills”
Drospirenona
Administración en Esquema 24/4
(24 activas y 4 de pausa)
Dentro y fuera de la lactancia**

Anticoncepción de solo progestina al 2022



- Libre de Estrógeno
- Para Fumadoras
- Con Riesgo Cardiovascular
- Con Temor al Estrógeno
- Pueden Causar Sangrados
- Pueden Causar Amenorreas
- Beneficios no contraceptivos

Vía Oral: Levonorgestrel – Desogestrel – “Drospirenona Only Pills (24/4)

Vía Oral: Levonorgestrel - Ulipristal (A. Emergencia)

Vía IM - SC: Acetato Medroxiprogesterona (Trimestral)

SIU- Implantes SC: LARCs (Long-acting reversible contraceptives)

¿La anticoncepción de solo progestina amenaza la existencia de los Anticonceptivos Combinados?



<https://www.fda.gov/news-events/press-announcements/fda-approves-new-vaginal-ring-one-year-birth-control>

Nueva Progestina

Acetato de Segesterone o Nestorene

- Pertenece al grupo: 19-Nor-progesterona
- Se une específicamente en el receptor de progesterona
- No se une al receptor de andrógenos ni de estrógenos
- Sin efectos glucocorticoides, escasa unión a ese receptor
- No es activo por vía oral - Adecuado para otras rutas
- 100 veces más potente que la progesterona
- Sin eventos Tromboembólicos venosos 20.000 ciclos
- Population Council desarrolla equipo farmacológico

“Contraceptive Vaginal System (CVS)”

Liberación: Etinil Estradiol 13 μ /día +

Acetato de Segesterone 150 μ /día

- 10- Agosto -2018: Aprobado por la FDA

Contraceptive Vaginal System (CVS)



Anticoncepción Hormonal Combinada – Ruta Vaginal

- Anillo Anticonceptivo Vaginal Anual

Nueva estructura polimérica: mejor y regular liberación

LARCS: paciente controlado, sin intervención profesional

Se recoge en la farmacia una vez al año

Se aplica por 21 días - Se retira por 7 días - Se lava y guarda

No Necesita Refrigeración y se vuelve a aplicar

Duración del sistema: 13 ciclos

Eficacia, Seguridad, Tolerabilidad y Control del Ciclo

Sin afectar la flora vaginal normal

Archer D.
Efficacy of the 1-year
(13-cycle) Segesterone
Acetate and
Ethinylestradiol
contraceptive vaginal
system: results of two
multicentre, open-
label, single-arm,
phase 3 trials
The Lancet. Global
Health. 2019; 7(8):
E1054-E1064



Gemzell-Danielsson. K.
 Segesterone acetate/ethinyl estradiol 12-
 month contraceptive vaginal system safety
 evaluation. *Contraception*. 2019;99(6):323-328



Etinilestradiol / Etonorgestrel	Etinilestradiol / Segesterone
Liberación diaria: Etonorgestrel 120 µ/día Etinilestradiol 15 µ/día	Liberación diaria: Segesterone 150 µ/día Etinilestradiol 13 µ/día
Diámetro 54 mm	Diámetro 54 mm
Grosor 4 mm	Grosor 8.4 mm
Vida útil: un ciclo	Vida útil: 13 ciclos
Amerita refrigeración	No amerita refrigeración

Review

Long-Lasting, Patient-Controlled, Procedure-Free Contraception: A Review of Annovera with a Pharmacist Perspective

Jennifer J. Virro ^{1,*}, Kathleen Besinque ², Christiane E. Carney ¹, Danielle Gross ¹, Brian Bernick ¹ and Sebastian Mirkin ^{1,*}

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² School of Pharmacy, Chapman University, Orange, CA 92866, USA; besinque@chapman.edu

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Received: 22 July 2020; Accepted: 25 August 2020; Published: 28 August 2020



Abstract: Annovera (segesterone acetate and ethinyl estradiol vaginal system) is a US Food and Drug Administration FDA-approved long-lasting, reversible contraceptive that is fully administered by the user and does not require a procedure for insertion or removal. The vaginal system is in the shape of a ring and contains low doses of a novel progestin, egesteron acetate, and ethinyl estradiol. It is made of silicone and is fully pliable and flexible. The vaginal system is reusable for 13 cycles, using a 21 days in/7 days out regimen, providing women with the ability to control their fertility. Particularly now during the COVID-19 pandemic when access to contraception has been further reduced, patients may benefit from a method that is both long-lasting and patient-controlled.



Sivin I
Contraceptive vaginal rings releasing Nestorone and ethinyl estradiol: a 1-year dose-finding trial.
Contraception. 2005;71:122-129

Vieira CS
Bleeding profile associated with 1-year use of the Segesterone acetate/ethinylestradiol contraceptive vaginal system: pooled analysis from Phase 3 trials
Contraception. 2019;100:438-444



Combinados

ANTICONCEPCIÓN HORMONAL SIGUE CRECIENDO oral y otras vías

Solo Progestina

Levonorgestrel (Continuo - lactancia)

Desogestrel (Continuo dentro y fuera lactancia)

Drospirenona (Esquema 24/4 – dentro y fuera lactancia)

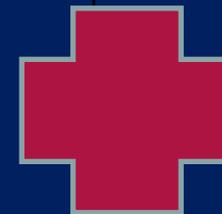
Un Estrógeno:

Etinilestradiol

17- β -Estradiol

Valerato estradiol

Estetrol

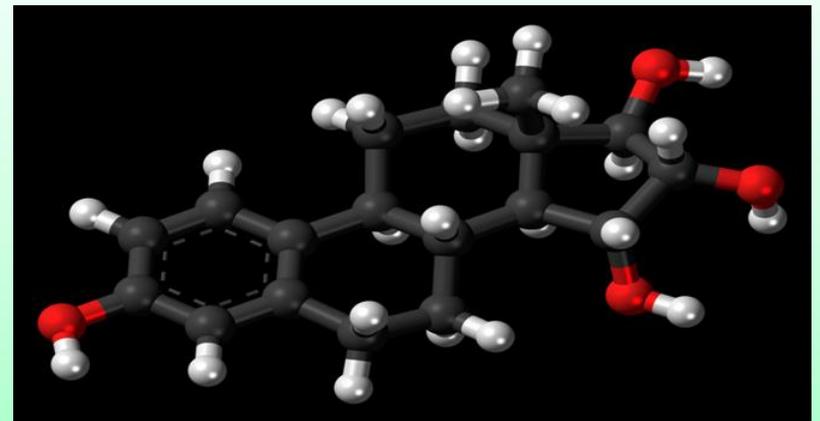


Una Progestina

**(E-1) Estrona - (E-2) Estradiol
(E-3) Estriol - (E-4) Estetrol**

Estetrol o oestetrol

- **Es una hormona esteroide de estrógeno débil que se encuentra en niveles detectables solo durante el embarazo.**
- **Se produce exclusivamente por el hígado fetal y está estrechamente relacionado con el estriol, que también es un estrógeno débil que se encuentra en grandes cantidades solo durante el embarazo**



Duijker I. Inhibition of ovulation by administration of estetrol in combination with drospirenone or levonorgestrel: Results of a phase II dose-finding pilot study. *The Eur J of Contracepy and Reprod Health Care.* 2015;20:476-489

Estetrol (E4)



Coelingh Bennink HJ.
Estetrol review: profile and
potential clinical
applications.
Climacteric. 2008;11 Suppl
1:47-58

1965	Descubierto Instituto Karolinska (Suecia)
2001	Desarrollada molécula fines terapéuticos
2008	Publican estudios preclínicos
2009 2013	Realización y publicación Estudios Fase II (Estetrol + Drospirenona y con LNG)
2015	Mirtha Pharmaceutical adquiere derechos sobre el desarrollo del Estetrol
2016	Inicios estudios fase III contracepción y fase II-B en menopausia
2018	Gedeon Richter Adquiere derechos comercializar Estetrol 4mg+Drospirenona 3mg
2020	Completados estudios fase III contracepción Estrógeno Nativo
2019	Inician estudios fase III menopausia



Kluft C.
Reduced hemostatic effects with
drospirenone-based oral
contraceptives containing estetrol
vs. ethinylestradiol.
Contraception. 2017;95(2):140-147

- Estetrol es un estrógeno selectivo
- No es un SERM
- Significativa Acción Antigonadotrópica
- No Inhibe Enzimas Hepáticas
- No interactúa con la Familia CYP450
- Impacto limitado sobre Síntesis SHBG
- Estudiado combinado con diversas progestinas
- Mejor combinación:
 - Estetrol 4mg + Drospirenona 3mg
 - Comparado con EE 20 mg + DRSP 3 mg
- Potencial Reducción Riesgo TEV
- Potencial Reducción Riesgo Cardiovascular
- Potencial Reducción Marcadores Coagulación
- Mejor Efecto Hemostático
- Alta Eficacia – Bajos Efectos Adversos

COMPARACIÓN ESTETROL FRENTE EE y E2

El estetrol (E4) tendría:

1. Menor interferencia con la función hepática, especialmente en los parámetros hemostáticos y posiblemente menor impacto Tromboembólicos
2. Elevada biodisponibilidad oral y larga vida media lo que habilita una toma diaria
3. Menor incidencia de enfermedad hepatobiliar
4. No inhibición del citocromo P450 a nivel hepático con menores interacciones medicamentosas con las drogas que se metabolizan por esta vía
5. Efecto anti-tumoral sobre la mama en presencia de estradiol
6. Estetrol no tiene metabolitos activos en contraste con estradiol cuyo metabolismo conduce a la producción de catecol-estrógenos considerados carcinogénicos
7. Perfil de buena tolerancia y eficacia anticonceptiva





Estetrol (E4) 4mg + Drospirenona 3 mg Esquema 24/4 – Baja Dosis



**Bienestar, Seguridad
y Comodidad
Para la Mujer,
Nuevo Enfoque de los
Anticonceptivos
Orales
Combinados**

The results show that E4 in combination with DRSP adequately suppresses ovarian activity and inhibits ovulation.

E4 appears to be a **promising alternative** estrogen for use in contraception.

La joyería farmacéutica puede proporcionar un método novedoso de administración de fármacos, especialmente para las hormonas anticonceptivas

Journal of Controlled Release 301 (2019) 140–145

Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel



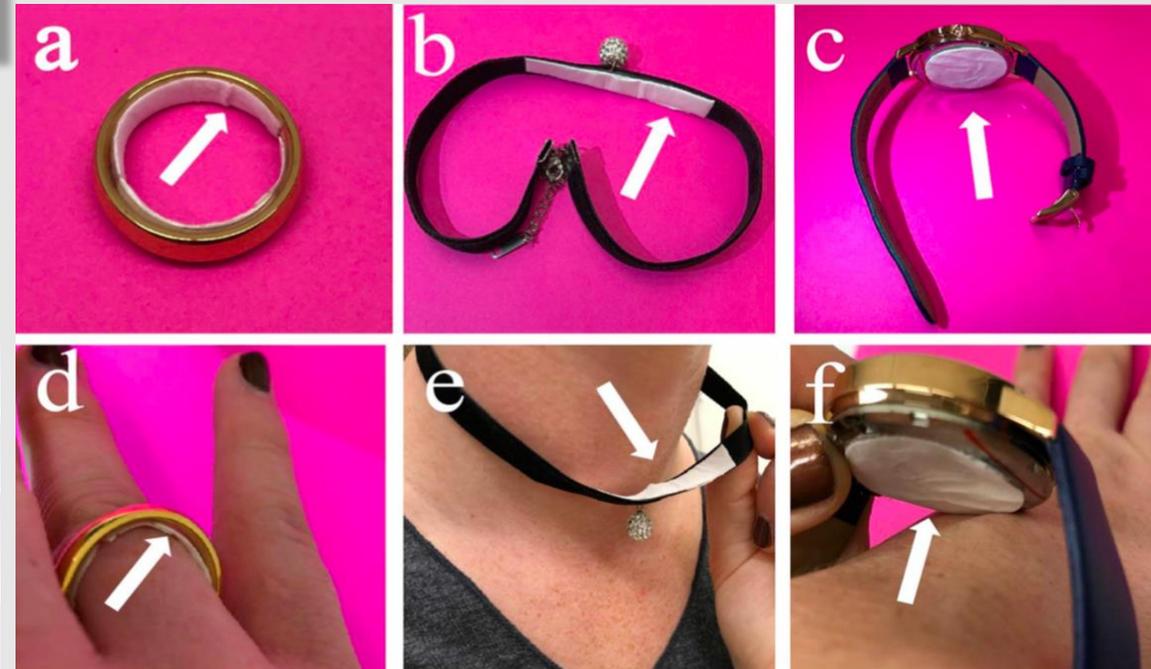
Pharmaceutical jewelry: Earring patch for transdermal delivery of contraceptive hormone

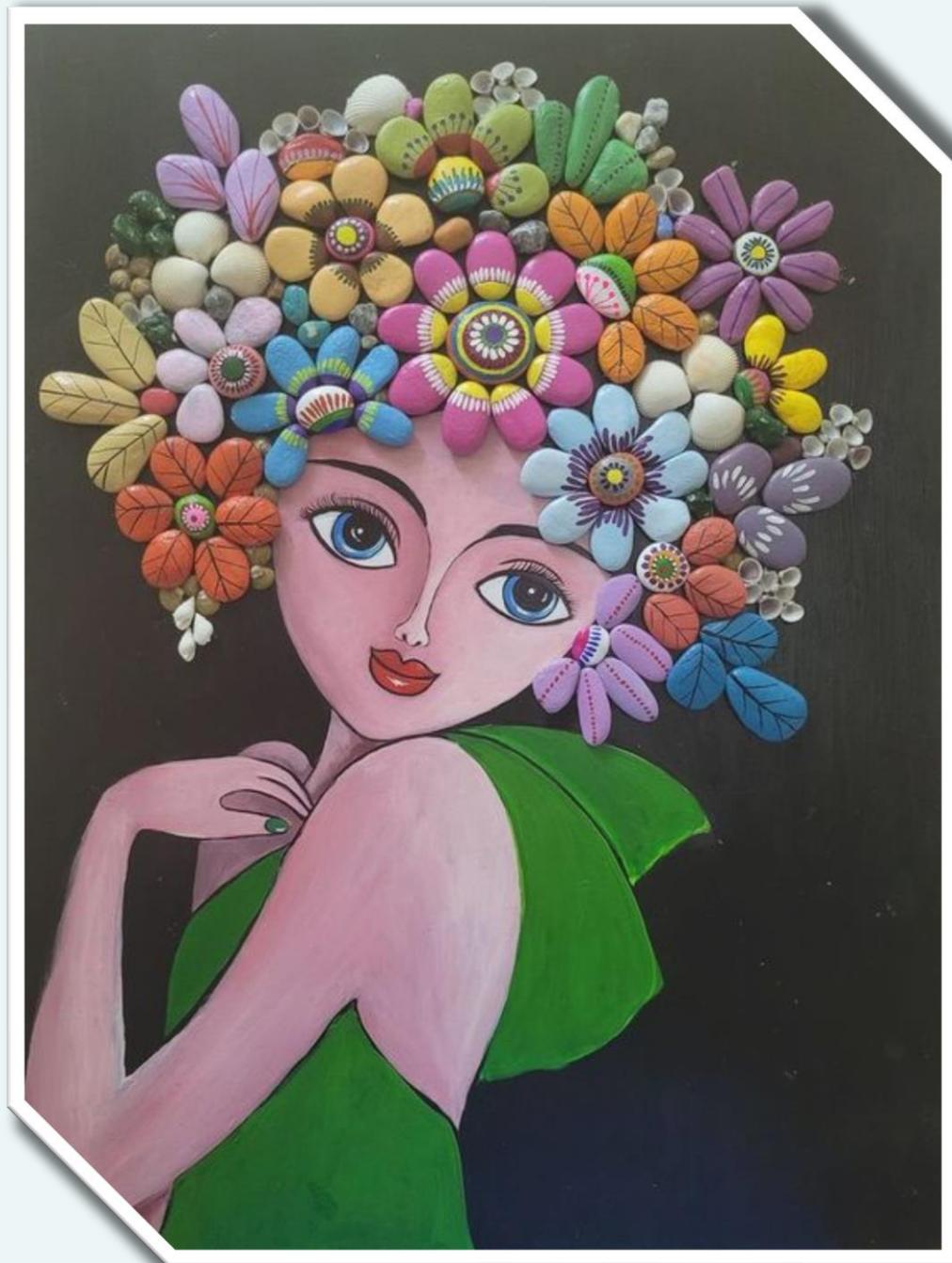
Mohammad Mofidfar^a, Laura O'Farrell^b, Mark R. Prausnitz^{a,*}

^a School of Chemical and Biomolecular Engineering, Georgia Institute of Technology, Atlanta, GA 30332, USA

^b Physiological Research Laboratory, Georgia Institute of Technology, Atlanta, GA 30332, USA

Para aumentar la aceptabilidad y adherencia a los medicamentos. Se incorpora un parche transdérmico en las joyas que se usan en contacto directo con la piel





- **La anticoncepción hormonal continua creciendo, impulsada por la necesidad de una mayor seguridad dentro de la misma eficacia contraceptiva que ha ofrecido desde los inicios**
- **La anticoncepción hormonal tiene importante y privilegiado sitio dentro de la medicina preventiva**

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