DOSIS DE ESTRÓGENOS VS NUEVOS PROGESTÁGENOS: SU IMPACTO EN TROMBOEMBOLISMO VENOSO

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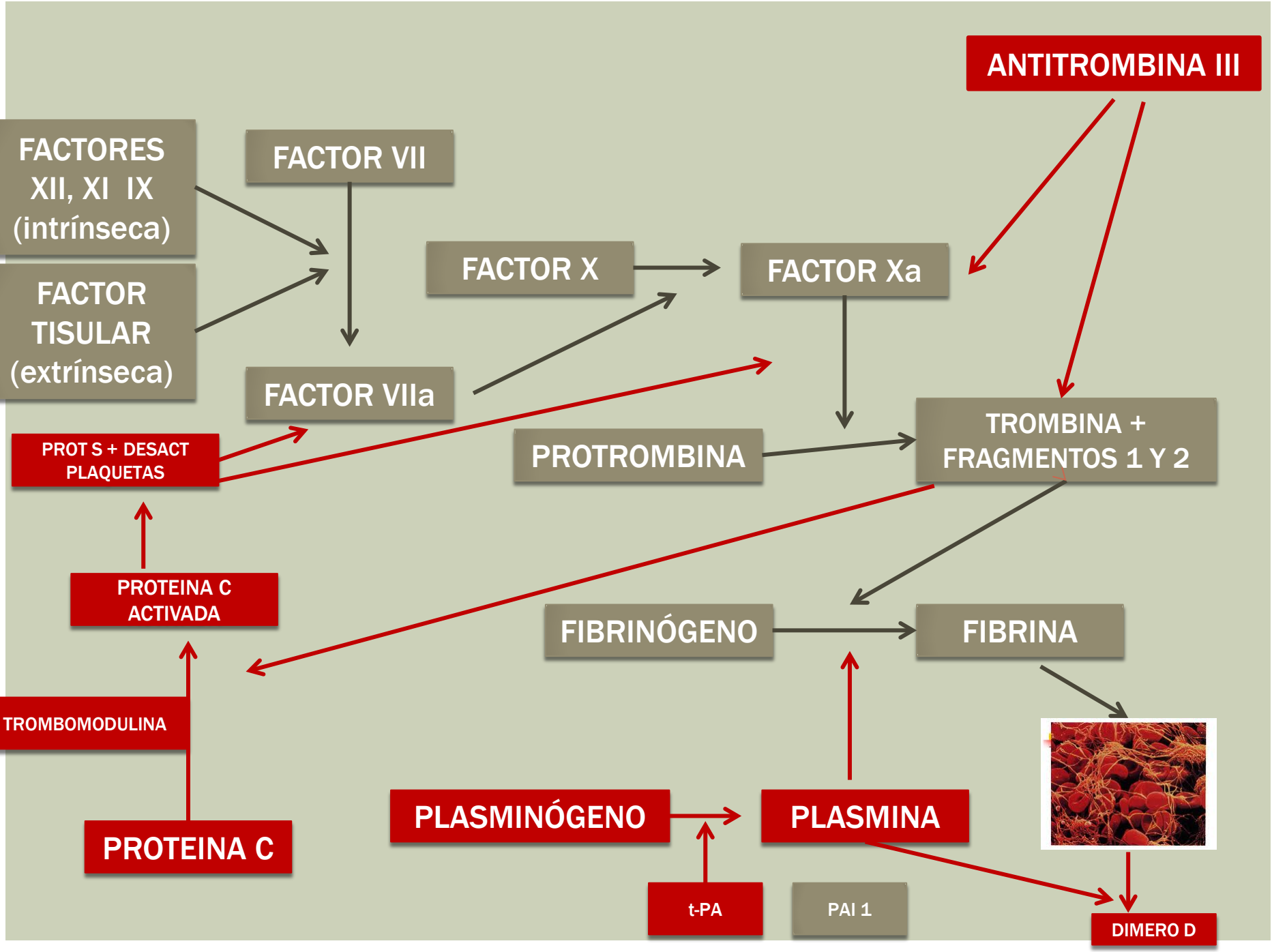
EL PROBLEMA

- Aumento de los eventos tromboembólicos en mujeres jóvenes en los últimos 10 años: 4 x 10.000 mujeres.
- Cambios en la incidencia de factores de riesgo como causa probable:
  - Aumento del IMC
  - Disruptores endocrinos ambientales
  - Uso de anticoncepción hormonal
  - Subregistro
  - Mejores métodos diagnósticos para TEV

G Plu-Bureau et al. Best Pract Res Clin Endocrinol Metabl 2013:27:25-34.
Lidegaard Ø. Acta ObstetGynecol Scand 2012;91:769


ANTITROMBINA III
FACTORES XII, XI IX (intrínseca)
FACTOR VII
FACTOR TISULAR (extrínseca)
FACTOR X
FACTOR Xa
FACTOR VIIa
PROT S + DESACT PLAQUETAS
PROTROMBINA
TROMBINA + FRAGMENTOS 1 Y 2
PROTEINA C ACTIVADA
FIBRINÓGENO
FIBRINA
TROMBOMODULINA
PLASMINÓGENO
PLASMINA
PROTEINA C
t-PA
PAI 1
DIMERO D

ESTRÓGENOS

ANTITROMBINA III

FACTORES XII, XI IX (intrínseca)

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PROT S + DESACT PLAQUETAS

PROTROMBINA

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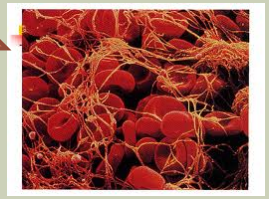
FIBRINÓGENO

FIBRINA

TROMBOMODULINA



PLASMINÓGENO

PLASMINA

PROTEINA C

t-PA

PAI 1

DIMERO D

HEMOSTASIA 50 VS 30 VS 20 MCGR

Effects of different OCs on the primary variables (prothrombin) fragment 1+2 and D-Dimer

Comparison at Cycle 6	(Prothrombin) fragment 1+2 (nmol/L)			D-Dimer (mg/L)		p-value[b]
	Estimated difference (%)[a]	97.5% confidence interval (%)[a]	p-value[b]	Estimated difference (%)[a]	97.5% confidence interval (%)[a]	
Progestogen effects						
30 EE/150 DSG vs. 30 EE/150 LNG	9.6	(1.0, 19.0)	0.012	3.6	(−8.6, 17.4)	0.526
30 EE/75 GSD vs. 30 EE/150 LNG	6.9	(−1.4, 15.9)	0.062	1.8	(−10.1, 15.2)	0.750
35 EE/250 NGM vs. 30 EE/150 LNG	12.8	(3.9, 22.3)	<0.001	3.1	(−8.9, 16.7)	0.579
Estrogen dose-effects						
50 EE/125 LNG vs. 30 EE/150 LNG	14.0	(4.4, 24.5)	<0.001	8.1	(−5.5, 23.8)	0.192
30 EE/150 DSG vs. 20 EE/150 DSG	11.9	(2.0, 22.9)	0.006	11.2	(−3.4, 28.1)	0.091
30 EE/75 GSD vs. 20 EE/75 GSD	7.9	(−1.2, 17.9)	0.054	4.4	(−9.1, 19.8)	0.485

[a] Results of analysis of covariance, estimates and confidence intervals for treatment effects were adjusted for center effects.
[b] p-values are considered statistically significant if ≤ 0.025.

707 pacientes sanas evaluadas por 6 ciclos con diferentes ACO

The Oral Contraceptive and Hemostasis Study Group. Contraception 2003;67:173.

ELSEVIER

Contraception

Contraception 65 (2002) 215–221
Original research article

An open label, comparative study of the effects of a dose-reduced oral contraceptive containing 20 μg ethinyl estradiol and 100 μg levonorgestrel on hemostatic, lipids, and carbohydrate metabolism variables

J. Endrikat[a,*], C. Klipping[b], M. Cronin[a], C. Gerlinger[a], A. Ruebig[a], W. Schmidt[c], B. Düsterberg[a]

Fueron evaluadas 48 pacientes por 13 ciclos.
Edad promedio 22 años y peso promedio 63 kg.

HEMOSTASIA 30 VS 20 MCGR

		% change baseline to cycle 13		p-value
		20 EE	30 EE	
Pro-coagulatory				
Fibrinogen	g/L	16.1 (21.4)	22.7 (19.2)	n.s.
F VII Act	%	−10 (−22)	−8 (19)	n.s.
F VII Ag	%	15.5 (35)	9 (16)	n.s.
F VIIa	mU/mL	68.8 (65)	44 (66)	n.s.
F VIII	%	−6.7 (35)	3.0 (27)	n.s.
Anti-coagulatory				
AT III	%	−9.2 (−2)	−4.3 (−8)	n.s.
PCAT	%	−4.2 (22.7)	−5.8 (25.4)	n.s.
Thrombin turnover				
TAT	μg/L	20 (105)	0.0 (98)	n.s.
F 1+2	μg/L	40 (59)	17 (42)	n.s.
Pro-fibrinolytic				
Plasminogen	%	31.1 (17)	45.2 (17)	0.0002
tPA Ag	ng/mL	−31.1 (29)	−47.6 (14)	0.0009
tPA Act	nkat/L	25.9 (76)	37.5 (95)	n.s.
Anti-fibrinolytic				
PAI-Ag	ng/mL	−58.4 (48)	−75.8 (14)	0.0008
PAI-Act	nkat/L	−73.4 (45)	−83.3 (15)	0.0102
Plasmin turnover				
PAP	mg/L	52.5 (42)	71.1 (59)	0.0287
Fibrin turnover				
D-Dimer	mg/L	0.0 (50)	0.0 (91)	n.s.
FbDP	mg/L	20.8 (53)	33.8 (128)	n.s.

Efectos hemostáticos sin cambio

Endrikat J Contraception 2002;65:215

COMPARACIÓN ENTRE BAJAS DOSIS DE ETINIL ESTRADIOL

Table 1
Risk of venous thrombotic events associated with different doses of ethynil-estradiol (EE) within the type of progestogens.

Authors, year of publication	Years of recruitment	Type of study	Daily doses of EE (μg)	Use of levonorgestrel	Use of desogestrel	Use of gestodene	Use of drospirenone
Herings et al., 1999[a,20]	1986–1995	Cohort	30–40	1	4.2 (1.7–10.6)	3.9 (1.2–12.9)	
			20		4.5 (1.1–18.2)		
Farmer et al., 2000[a,21]	1992–1997	Case control	30–40	1	1.4 (0.9–2.4)	1.6 (1.0–2.6)	
			20		1.2 (0.6–2.4)		
Lewis et al., 1999[b,22]	1993–1995	Case control	30–40	2.9 (1.9–4.2)	2.5 (1.6–4.1)	2.3 (1.4–3.6)	
			20		1.6 (0.9–2.9)		
Bloemenkamp et al., 1999[b,23]	1982–1995	Case control	30–40	3.7 (1.9–7.2)	4.9 (2.5–9.4)	5.2 (1.3–20.6)	
			20		24.7 (2.8–213.5)		
Lidegaard et al., 2002[b,24]	1994–1998	Case control	30–40	3.4 (2.5–4.7)	5.4 (3.6–8.0)	3.5 (2.8–4.5)	
			20		4.8 (3.2–7.1)	2.0 (0.7–5.7)	
Van Hyckhlama et al., 2009[c,25]	1999–2004	Case control	30–40	1	1	1	
			20	1.1 (0.4–3.1)	0.7 (0.4–1.2)	0.3 (0.2–0.7)	
Lidegaard et al., 2011[b,d,4]	2001–2009	Cohort	30–40	2.9 (2.2–3.8)	6.6 (5.6–7.8)	6.2 (5.6–6.9)	6.4 (5.4–7.5)
			20		4.8 (4.2–5.6)	5.1 (4.4–5.9)	6.9 (4.2–11.5)

[a] Levonorgestrel as the reference category and OR were estimated for new users of oral contraceptives.
[b] Non-users as the reference group.
[c] Users of 30–40 μg daily dose of EE as the reference group within each category of pill.
[d] Risk for confirmed diagnosis.

G Plu-Bureau et al. Best Pract Res Clin Endocrinol Metabl 2013:27:25-34.

ESTUDIO DANÉS

Variables	Progestogen				
	Norethisterone	Levonorgestrel	Norgestimate	Desogestrel	Gestodene
Woman years	157 962	411 099	329 463	676 105	1 332 157
Thrombotic event	71	238	151	442	928
Crude rate	4.5	5.8	4.6	6.5	7.0
Rate ratio*					
Oestrogen dose and duration of use					
Oestrogen 50 µg:					
<1 year	2.89 (1.37 to 6.07)	3.06 (1.53 to 6.14)	—	—	—
1-4 years	2.35 (1.30 to 4.26)	2.00 (1.11 to 3.63)	—	—	—
>4 years	4.05 (2.18 to 7.54)	2.78 (1.75 to 4.43)	—	—	—
Oestrogen 30-40 µg:					
<1 year	2.81 (1.66 to 4.77)	1.91 (1.31 to 2.79)	3.37 (2.38 to 4.76)	5.58 (4.13 to 7.55)	4.38 (3.65 to 5.24)
1-4 years	1.76 (1.12 to 2.77)	2.23 (1.78 to 2.78)	2.27 (1.74 to 2.96)	3.48 (2.74 to 4.42)	3.85 (3.39 to 4.36)
>4 years	1.55 (0.83 to 2.89)	1.91 (1.55 to 2.36)	2.20 (1.70 to 2.85)	3.19 (2.53 to 4.02)	3.34 (2.95 to 3.78)
Oestrogen 20 µg:					
<1 year	—	—	—	4.89 (3.83 to 6.23)	4.43 (3.25 to 6.04)
1-4 years	—	—	—	2.83 (2.29 to 3.49)	3.27 (2.61 to 4.10)
>4 years	—	—	—	2.69 (2.17 to 3.35)	2.79 (2.15 to 3.63)

*All estimates adjusted for age, calendar year, and education and with non-users of oral contraceptives as reference group.

Se evaluaron 10,4 millones de mujeres/año

Registro Nacional de pacientes 1995-2005

Disminución de 18% del riesgo de TEV con dosis de 20 mcgr con desogestrel y gestodeno.

Lidegaard O et al. BMJ 2009;339:b2890

ESTUDIO DANÉS

Table 2| **Exposure time, number of events of venous thromboembolism, crude incidence per 10 000 user years, and adjusted relative risk of venous thromboembolism in current users of different oral contraceptives and hormone releasing intrauterine device with non-users as reference group**

Group	Women years	No of events*	Crude incidence per 10 000 user years*	Adjusted relative risk† (95% CI)
Non-use	4 960 730	1812	3.7	1 (reference)
Progestogen with 50 µg ethinylestradiol:				
Norethisterone	6848	11	16.1	5.66 (3.12 to 10.3)
Levonorgestrel	23 691	31	13.1	3.54 (2.48 to 5.05)
Progestogen with 30-40 µg ethinylestradiol:				
Norethisterone	27 355	10	3.7	1.57 (0.84 to 2.92)
Phasic levonorgestrel	105 970	89	8.4	2.28 (1.85 to 2.83)
Levonorgestrel combined	104 251	78	7.5	2.19 (1.74 to 2.75)
Norgestimate	267 664	165	6.2	2.56 (2.18 to 3.01)
Desogestrel	170 249	201	11.8	4.21 (3.63 to 4.87)
Gestodene	668 355	738	11.0	4.23 (3.87 to 4.63)
Drospirenone	286 859	266	9.3	4.47 (3.91 to 5.11)
Cyproterone	120 934	109	9.0	4.10 (3.37 to 4.99)
Progestogen with 20 µg ethinylestradiol:				
Desogestrel	470 982	322	6.8	3.26 (2.88 to 3.69)
Gestodene	472 118	321	6.8	3.50 (3.09 to 3.97)
Drospirenone	23 055	23	10.0	4.84 (3.19 to 7.33)
Progestogen only:				
Norethisterone	44 168	9	2.0	0.56 (0.29 to 1.07)
Desogestrel	29 187	6	2.1	0.64 (0.29 to 1.42)
Levonorgestrel releasing intrauterine device	155 149	55	3.5	0.83 (0.63 to 1.08)

*Events are venous thromboembolisms.
†Adjusted for age, year, and level of education.

Se evaluaron 8 millones de mujeres/año
Registro Nacional de pacientes 2001-2009
Disminución de 23% y 17% del riesgo de TEV con dosis de 20 mcgr con desogestrel y gestodeno.

Lidegaard O et al. BMJ 2011;343:d6423

AH NO ORALES Y TROMBOSIS (ESTUDIO DANÉS)

Table 2| **Crude incidence rate and adjusted relative risk of venous thrombosis in current users of non-oral hormonal contraception and combined oral contraceptives (COC) with non-users as reference**

Outcome, contraception type	Woman years	No with venous thrombosis	Incidence per 10 000 exposure years	Adjusted relative risk* (95% CI)	P value
All venous thromboses:					
Non-use	5 892 182	2262	3.84	1.00 (reference)	—
COC with levonorgestrel and 30-40 µg oestrogen	231 675	201	8.68	2.37 (2.05 to 2.74)	<0.001
COC with norgestimate	298 566	198	6.63	2.63 (2.27 to 3.05)	<0.001
Patch	6178	7	11.33	4.40 (2.09 to 9.24)	<0.001
Vaginal ring	50 334	55	10.93	4.29 (3.27 to 5.62)	<0.001
Implant	29 497	15	5.09	2.08 (1.25 to 3.46)	0.005
Levonorgestrel IUS	239 841	88	3.67	0.80 (0.65 to 0.99)	0.040
Confirmed events:					
Non-use	5 892 182	1209	2.05	1.00 (reference)	—
COC with levonorgestrel and 30-40 µg oestrogen	231 675	144	6.22	3.21 (2.70 to 3.81)	<0.001
COC with norgestimate	298 566	135	4.52	3.57 (2.98 to 4.27)	<0.001
Patch	6178	6	9.71	7.90 (3.54 to 17.65)	<0.001
Vaginal ring	50 334	39	7.75	6.48 (4.69 to 8.94)	<0.001
Implant	29 497	5	1.70	1.40 (0.58 to 3.38)	0.450
Levonorgestrel IUS	239 841	33	1.38	0.57 (0.41 to 0.81)	0.002

Patch=transdermal contraceptive patch (EVRA; Johnson & Johnson, NJ, USA); implant=subcutaneous implant (Implanon; MSD; NJ, USA); vaginal ring=combined hormonal vaginal ring (NuvaRing; MSD, NJ, USA); levonorgestrel IUS=levonorgestrel intrauterine system (Mirena: Bayer Pharma, Berlin, Germany).
*Adjusted for age, calendar year, and education.

Lidegaard O. BMJ 2012;344:e2990

AH NO ORALES Y TROMBOSIS (ESTUDIO DANÉS)

- Las mujeres que utilizan AH combinados en parches o anillos vaginales tienen un riesgo 7,5 y 6,5 mayor que las no usuarias.
- Hay un incremento modesto en las usuarias de implantes con progestágenos de 1,4.
- NO hay incremento en las usuarias de endoceptivo con levonorgestrel.
- En este estudio no se ajustó por predisposición familiar ni IMC.

Lidegaard O. BMJ 2012;344:e2990

PARCHE VS ACO

ACO: 35 microgr EE + 250 microgr de Norgestimato.

Table 1
Mean (SD) serum SHBG, TBG, CBG and CRP levels in women treated with transdermal EE/NGMN and oral EE/NGM

Variable	Transdermal ($n=10$)		OC ($n=9$)	
	Baseline	Cycle 3	Baseline	Cycle 3
SHBG (nmol/L)	55.7 (17.0)	304 (116)*,†	57.7 (22.5)	201 (67.2)*
TBG (μg/mL)	20.6 (2.3)	34.4 (6.0)*,†	19.3 (1.5)	29.3 (3.2)*
CBG (μg/mL)	60.8 (17.0)	130.8 (36.5)*	62.9 (12.5)	144.4 (14.6)*
CRP (mg/L)	1.6 (0.17)	7.3 (0.62)*	1.9 (0.21)	5.0 (0.43)**

* $p<.05$, baseline versus end of therapy.
** $p=.056$, baseline versus end of therapy.
† $p<.05$, change from baseline, transdermal versus OC.

Parche tiene efectos estrogénicos importantes.

White T et al. Contraception 2006;74<.293.

ESTUDIO MEGA

Table 4 | The risk of venous thrombosis associated with different doses of ethinylestradiol in monophasic oral contraceptives. Data are odds ratios adjusted for age (95% CI) unless stated otherwise

Ethinylestradiol dose (µg)	Percentage use among controls*	Levonorgestrel	Gestodene	Desogestrel
20	11.2	1.1 (0.4 to 3.1)	0.3 (0.2 to 0.7)	0.7 (0.4 to 1.2)
30†	84.4	1	1	1
50	4.4	2.2 (1.3 to 3.7)	—	—

*In total, 51 women used a monophasic preparation with 20 µg ethinylestradiol, 385 women used one with 30 µg, and 20 used one with 50 µg (total 456).
†Reference category is the most commonly used dose of oestrogen among controls.

Evaluación de 1.524 pacientes con trombosis vs 1.760 controles.
Comparación de dosis de EE en 456 pacientes: 51 con 20 mcgr, 385 con 30 mcgr y 20 con 50 mcgr.
Riesgo de trombosis asociado a dosis de estrógeno pero dependiente de tipo de progestágeno.

Van Hylckama Vlieg A et al. BMJ 2009;339:b2921

REVISIÓN AH TROMBOSIS VENOSA

- Búsqueda en PubMed con las palabras “anticoncepción hormonal”, “anticoncepción oral”, “tromboembolismo venoso” y “trombosis venosa profunda”.
- De 200 artículos se seleccionaron 19 artículos en inglés que incluían nuevas formulaciones.
- Riesgo de TEV entre usuarias de LNG vs progestágenos de 2da y 3era generación

Lidegaard Ø. Acta ObstetGynecol Scand 2012;91:769

Table 5

Relative risk of venous thromboembolism in current users of different types of hormonal contraception. Reference group: Non-pregnant non-users.

	Norethisterone	*Levonorgestrel*	*Norgestimate*	*Desogestrel or Etonogestrel*	*Gestodene*	*Drospirenone*	*Cyproterone*
High dose EE			5-6*	5-6**			
30-40 ug EE	3	3	3.4	6	6	6	6
20 ug EE				5	5	6	
POP	0.6			0.6			
Estradiol/dienogest	na						
Levonorgestrel IUS		0.7					
Depot progestogen	0.5			na			

* transdermal patch; ** vaginal ring. Abbreviations: EE, ethinylestradiol; POP, progestogen-only pill; IUS, Levonorgestrel releasing intrauterine system; na, not available.

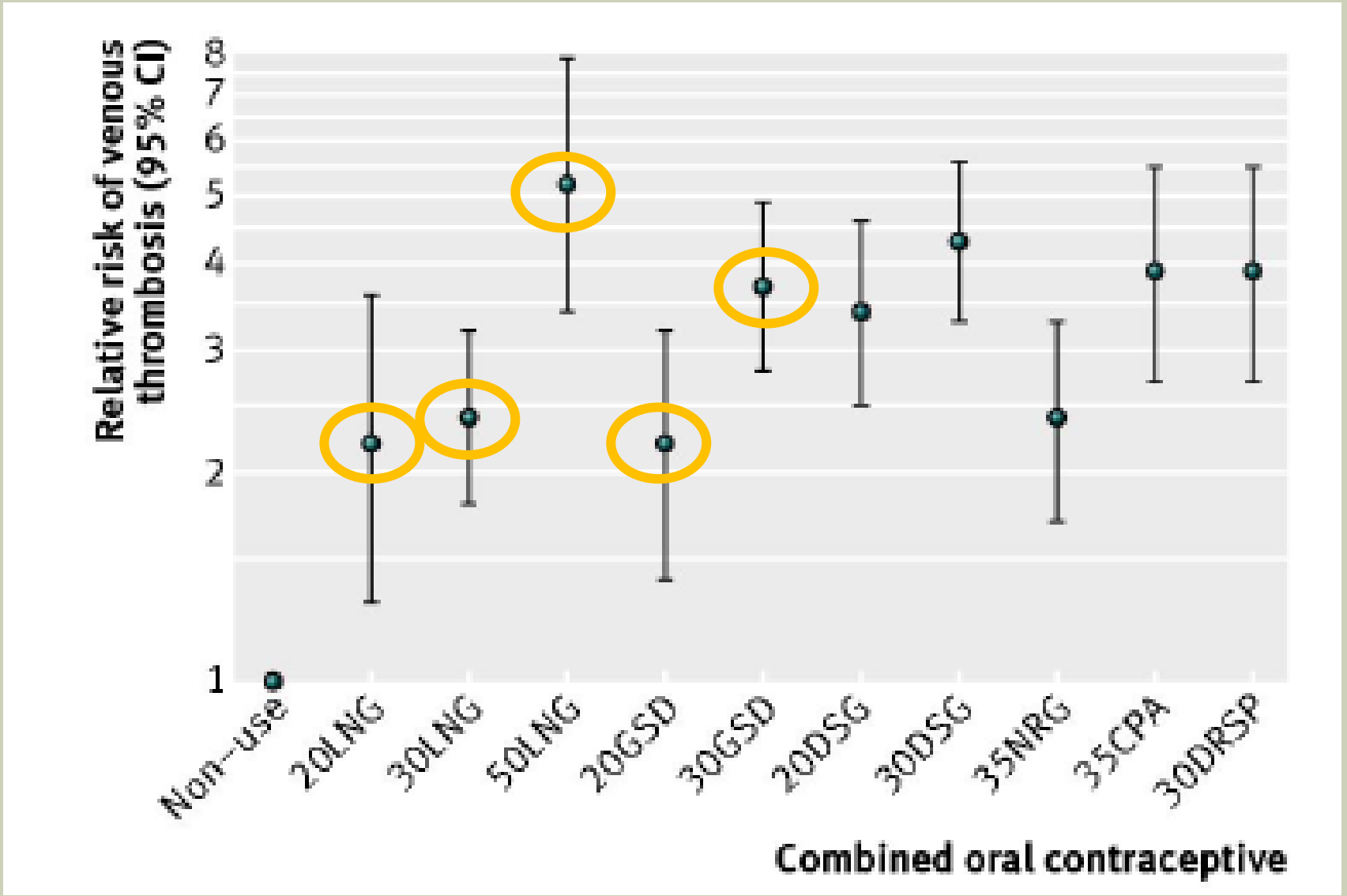
Pareciera tener más importancia la estrogenicidad total del producto que la dosis de estrógeno.

Lidegaard Ø. Acta ObstetGynecol Scand 2012;91:769

REVISIÓN Y METAANÁLISIS DE REDES (COCHRANE)

- Se evaluaron 25 estudios observacionales
- Se utilizaron varias bases de datos
- Diagnóstico objetivo de evento trombótico en pocos estudios
- La dosis de EE se correlacionó con riesgo de trombosis en LNG, GSD y DSG.
- No se incluyó Drospirenona ni clormadinona con 20 mcgr de EE

Stegeman BH et al. BMJ 2013;347:f5298



Stegeman BH et al. BMJ 2013;347:f5298

CONCLUSIONES

- Los eventos trombóticos son multifactoriales
- Los AHC aumentan el riesgo de TEV
- La disminución de la dosis de EE en los AHC disminuye el riesgo de trombosis
- El riesgo de trombosis venosa no desaparece ni se atenúa por vías diferentes a la oral en AHC.
- El riesgo de trombosis inducido por AHC no depende solamente de la dosis de EE, sino también del tipo de progestágeno utilizado
- Estudios a futuro que evalúen riesgo en combinaciones con EE 20 mcgr y estradiol

Las mujeres tenemos derecho a planificar nuestra familia…
pero no todas somos iguales.

GRACIAS POR SU ATENCIÓN