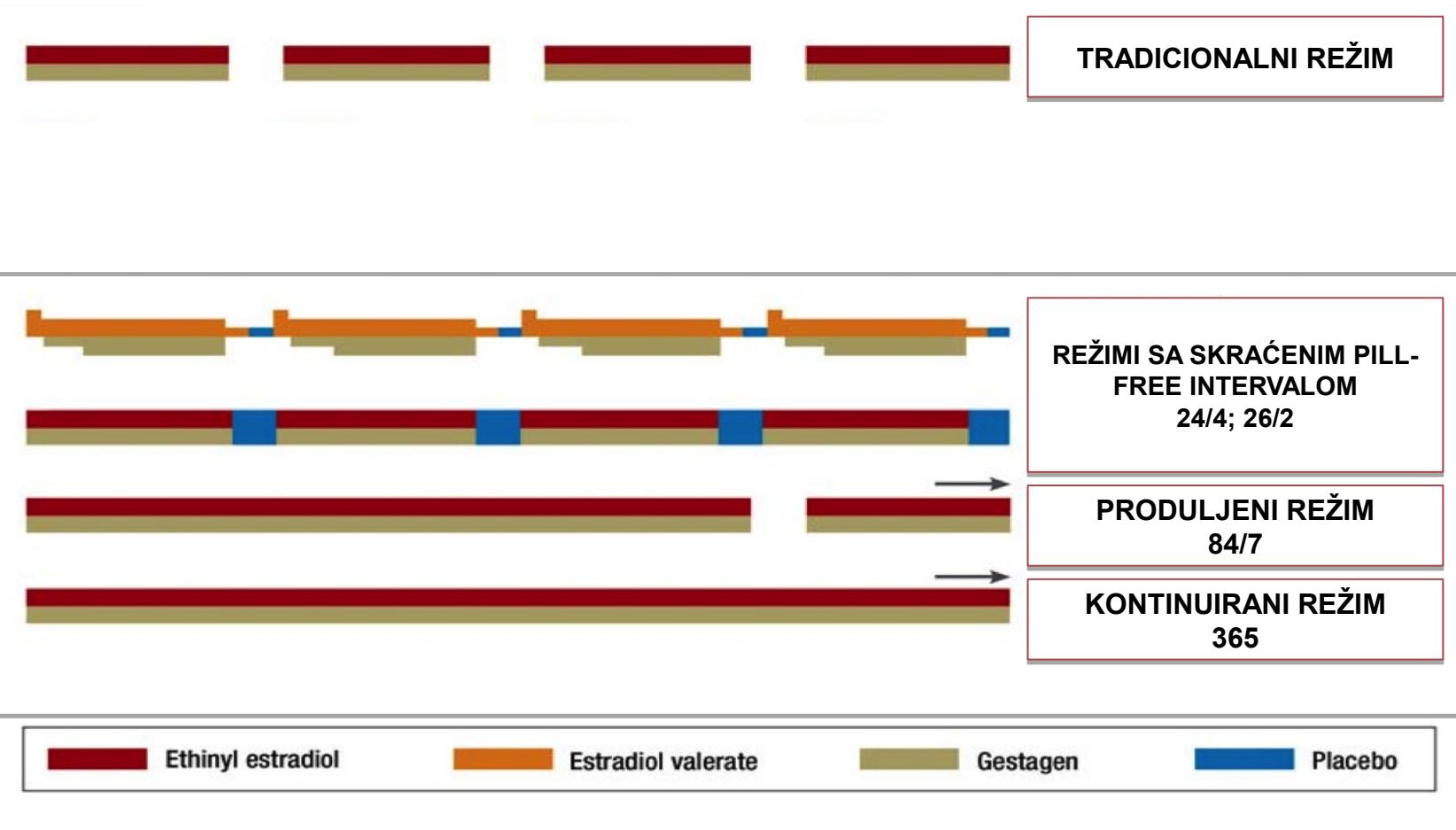




SEASONIQUE® - PRODULJENA KONTRACEPCIJA

Prof. dr. sc. Dinka Pavičić Baldani
Klinika za ženske bolesti i porode,
Medicinski fakultet Sveučilišta u Zagrebu, KBC Zagreb

REŽIMI IZDAVANJA ORALNIH HORMONSKIH KONTRACEPTIVA



Pincus, Rock 1958. uz primjenu OHK može se postići ciklus bilo
koje dužine - kontinuirani režim - stanje pseudotrudnoće

Religious pressure



"Pilula" odobrena za liječenje
medicinskih stanja povezanih s
menstruacijom, kontracepciski
učinak "indirektan"

Mora biti imitacija normalnog
menstruacijskog ciklusa



Gladwell M. John Rock's Error. The New Yorker. Vol March 10, 2000.

New York, New York: The New Yorker.

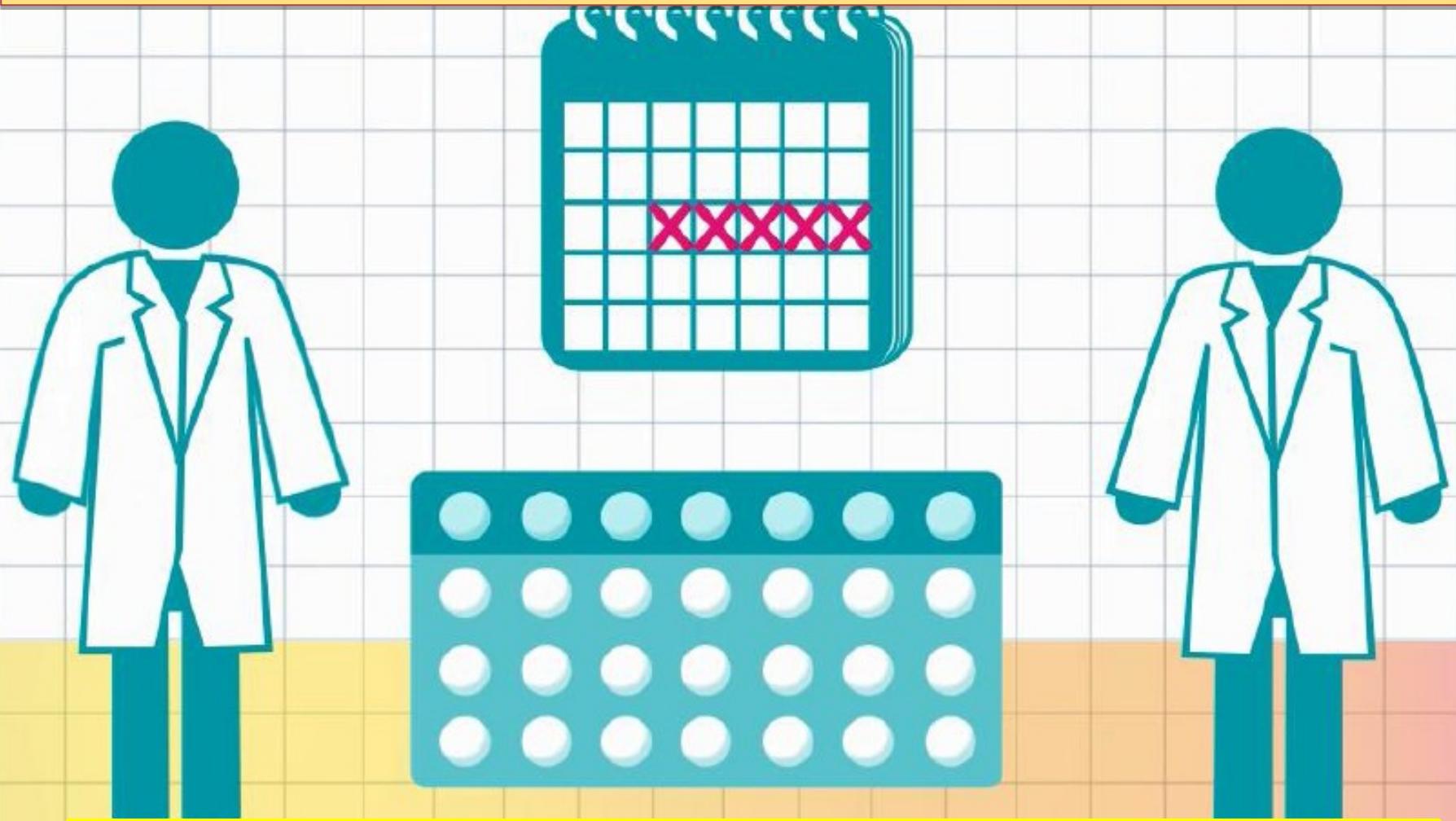
Social pressure



- Nerazumijevanje javnosti
mehанизma djelovanja "pilule"
na osovinu H-H-O
- Menstruacija shvaćena kao
dokaz zadržavanja fertilitosti
- Visoka doza hormona u prvima
pilulama - simptomi trudnoće
- Testovi na trudnoću - rezultati
tek za 6 tjedana

ARBITRALNO UVEDENA STANKA OD 7 DANA

(potrebno 4-5 dana da prestane djelovanje hormona na endometrij i omoguće se mjesecna krvarenja)



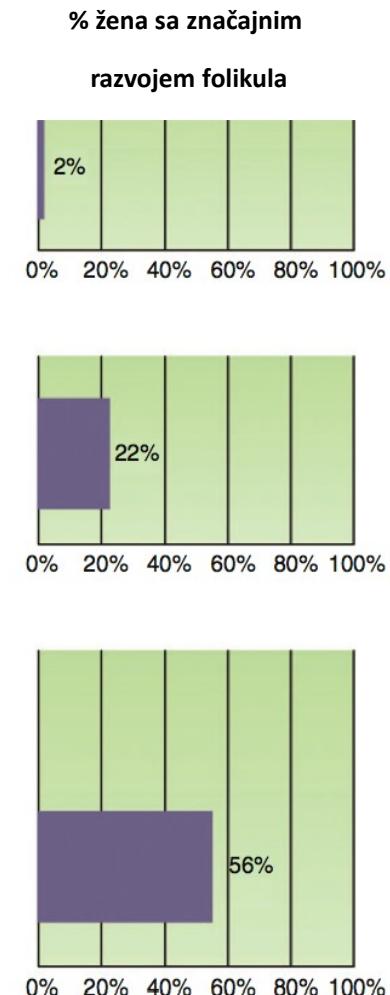
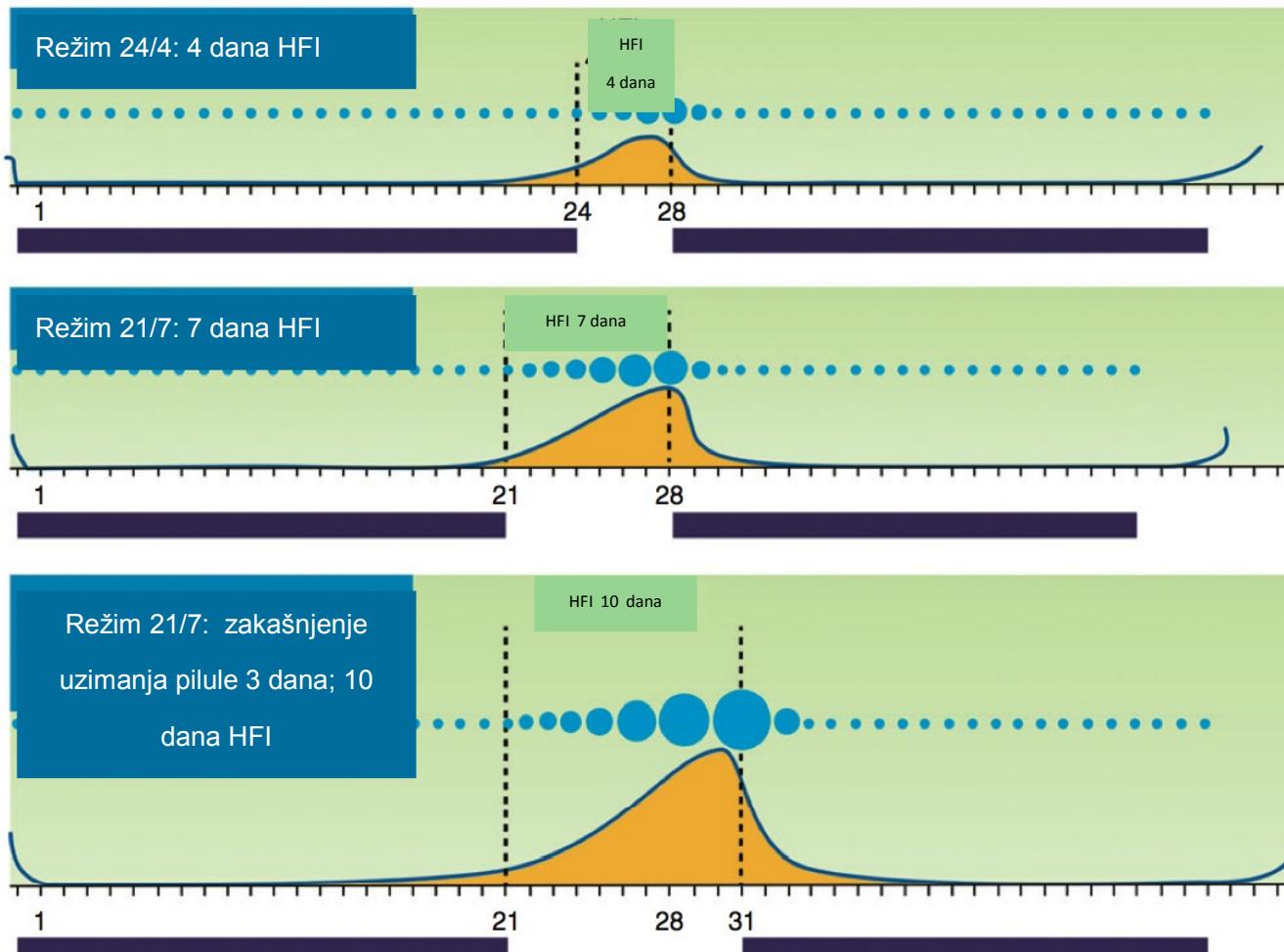
**NEMA MEDICINSKOG RAZLOGA KOJI BIO OGRANIČIO
PRIMJENU AKTIVNIH TABLETA**



POTICAJ ZA RAZVOJ PRODULJENE HORMONSKЕ KONTRACEPCIJE

1. SNIŽENJE DOZE HORMONA – VEĆI RIZIK RAZVOJA FOLIKULA

FHTA Women's Health





POTICAJ ZA RAZVOJ PRODULJENE HORMONSKE KONTRACEPCIJE

2. JAVLJANJE SIMPTOMA U PILL-FREE INTERVALU

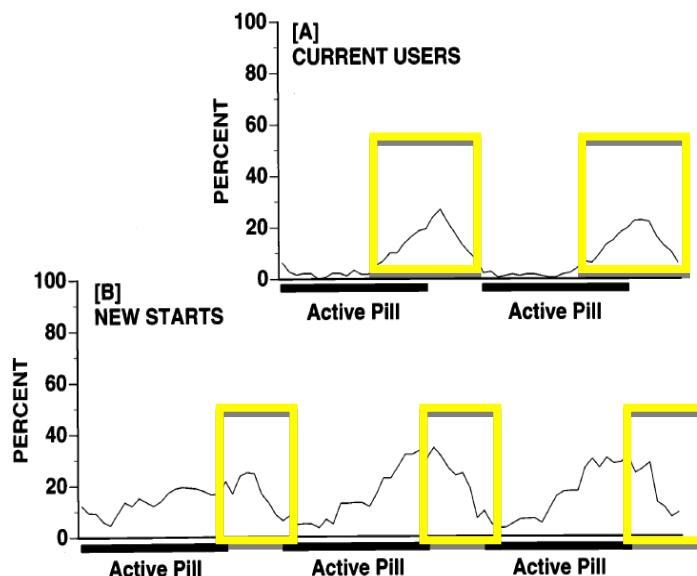


Figure 4. Percentage of subjects with breast tenderness by cycle day for current users (A) and new starts (B).

Hormone Withdrawal Symptoms in Oral Contraceptive Users

PATRICIA J. SULAK, MD, ROGER D. SCOW, MD, CHERYL PREECE, MS,
MARK W. RIGGS, PhD, AND THOMAS J. KUEHL, PhD

Objective: To measure the timing, frequency, and severity of hormone-related symptoms in oral contraceptive (OC) users, specifically to compare active-pill with hormone-free intervals.

Methods: Using daily diaries, women recorded pelvic pain, bleeding, headaches, analgesic use, nausea or vomiting, bloating or swelling, and breast tenderness during active-pill intervals and hormone-free intervals. Participants either had no prior OC use, had taken OCs and were restarting, or had been taking OCs continuously for 12 months or longer.

Oral contraceptives (OCs), the most common method of reversible birth control, are used by approximately 80% of women in the United States at some time during their reproductive years.¹ Despite the continuous reduction in hormone content since OC introduction almost 40 years ago, side effects continue to affect compliance.²⁻⁴ The most commonly reported side effects are nausea and vomiting, breakthrough bleeding and spotting, headaches, bloating or swelling, and breast tenderness.⁵⁻⁷

Svi se simptomi značajno pogoršavaju tijekom 7-dnevног HFI intervala u odnosu na vrijeme aktivnog uzimanja pilula (21 dan)

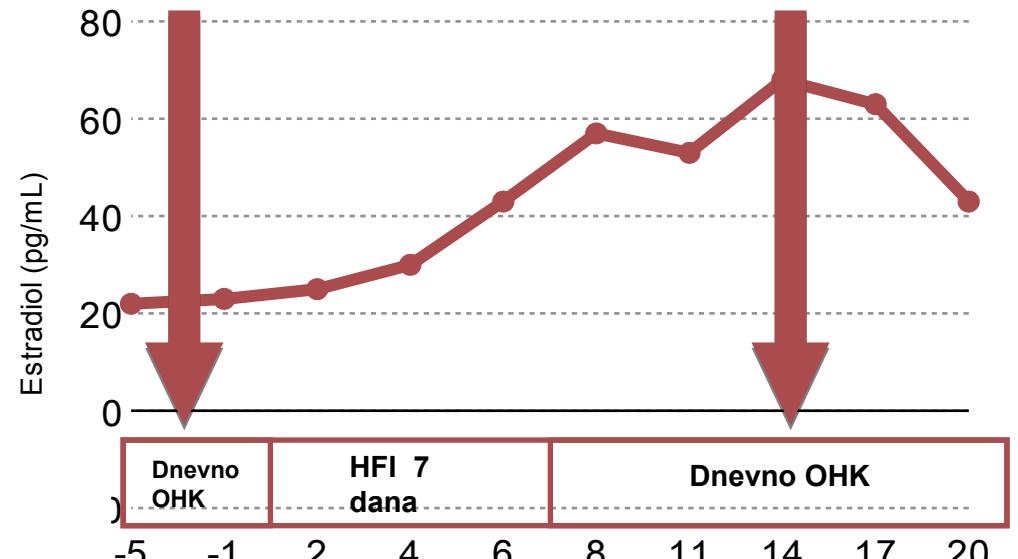
Patricia J. Sulak, Medical Biochemistry and Genetics, Scott and White Clinic and Memorial Hospital, Texas A&M University Health Science Center College of Medicine, Temple, Texas.
Supported by a grant from Scott, Sherwood, and Brindley Foundation, Temple, Texas.

starts because they were never users or were not taking OCs for a minimum of 3 months before enrollment. All patients used a combination low-dose OC of 21 active pills containing 35 µg or less of ethinyl estradiol (E2).



KOJI JE MEHANIZAM?

Kada se aktivne tablete počnu uzimati, endogeno stvaranje estradiola postepeno pada idućih 2 tjedna uzimanja aktivnih tableta. U cirkulaciju ostaju samo estrogeni iz pilula.



U pill free intervalu endogeni estrogeni su niski, a povlače se i egzogeni hormoni - što dovodi do pojave simptoma povlačenja estrogenai



MEHNIZAM NASTANKA SIMPTOMA U PILL FREE INTERVALU

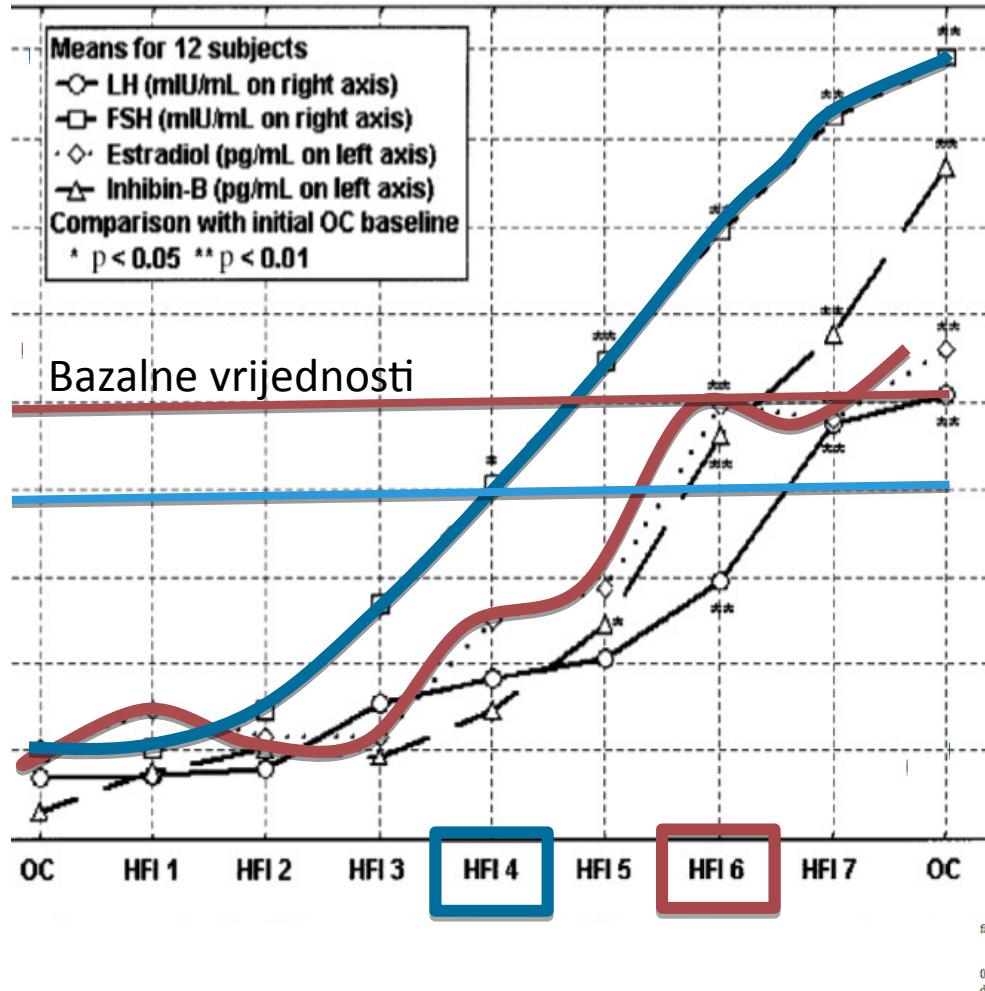
TEVIT

Women's Health



Contraception 74 (2006) 100–103

Contraception



Original research article
Greater inhibition of the pituitary–ovarian axis in oral contraceptive regimens with a shortened hormone-free interval

Sherilyn A. Willis, Thomas J. Kuehl, A. Michael Spiekerman, Patricia J. Sulak*

Departments of Obstetrics and Gynecology, Pathology, and Medical Biochemistry and Genetics, Scott and White Memorial Hospital and Clinic, Temple, TX 76508, USA

Health Science Center, College of Medicine, Texas A&M University System, Temple, TX 76508, USA

Received 1 December 2005; revised 6 February 2006; accepted 16 February 2006

U pill-free intervalu estradiol počinje rast iznad bazalnih vrijednosti tek oko 6 dana pill-free intervala kada simptomi povlačenja estrogena prestaju

method of reversible contraception, with the majority of women using them sometime during their reproductive life. Modifications have primarily involved lowering hormone content and utilizing new progestin components. The same

Laboratories, Poma, NY, USA). The 21/7-day regimen was arbitrarily created to mimic the average spontaneous menstrual cycle of 28 days.

Although OCs are very effective in preventing pregnancy, studies have confirmed an incomplete suppression of ovarian function with follicular growth and resultant endogenous hormone production and potential for follicular cysts [1–3]. Additionally, Sulak et al. [4] confirmed that an HFI of 7 days induces monthly withdrawal symptoms of bleeding, pain, breast tenderness, bloating/swelling and increased use of pain medications. This study evaluates the serum levels of four reproductive hormones during the HFI

Portions of this work were presented orally at the Annual Meeting of the American Society for Reproductive Medicine in October 2004.

* Corresponding author. Department of Obstetrics and Gynecology, Scott and White Clinic, Temple, TX 76508, USA. Tel.: +1 254 724 4034; fax: +1 254 724 1046.

E-mail address: psulak@swmail.sw.org (P.J. Sulak).

0010-7824/\$ – see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.contraception.2006.02.006



RJEŠENJE- SKRAĆENJE HFI ?

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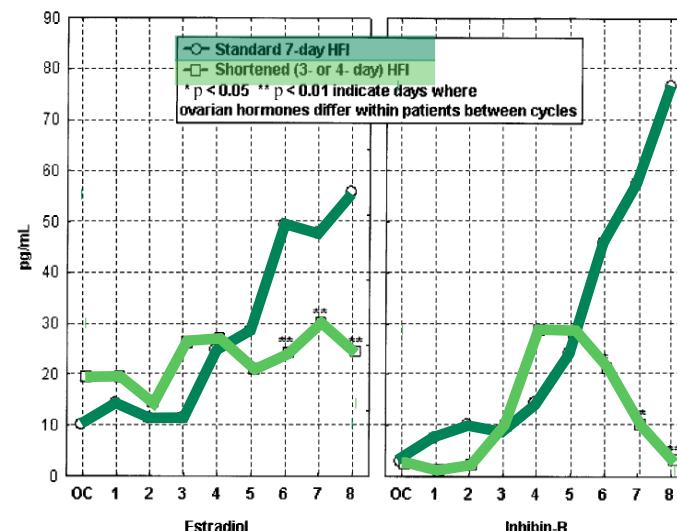
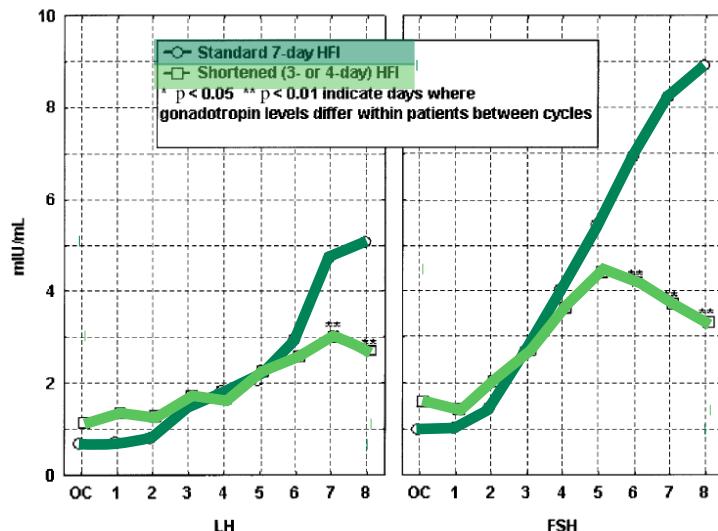
Contraception 74 (2006) 100–103

Original research article

Greater inhibition of the pituitary–ovarian axis in oral contraceptive regimens with a shortened hormone-free interval

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E-mail address: psulak@swmail.sw.org (P.J. Sulak).

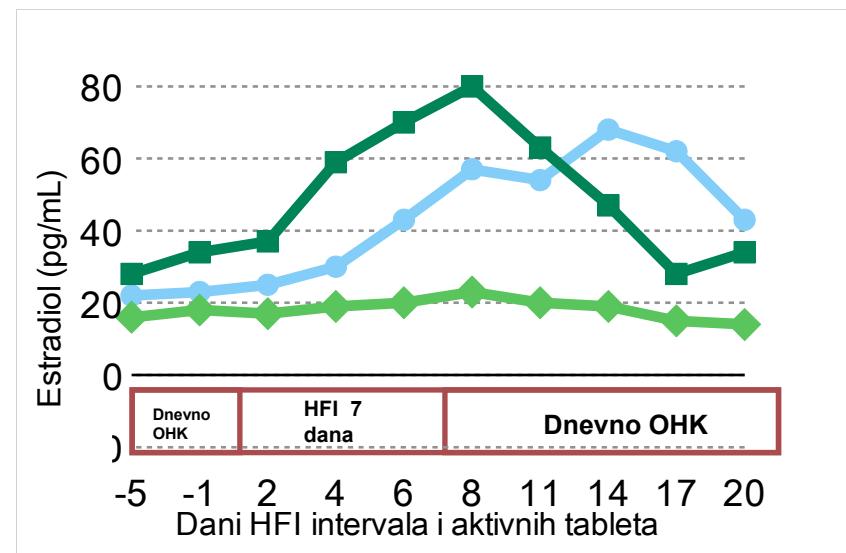
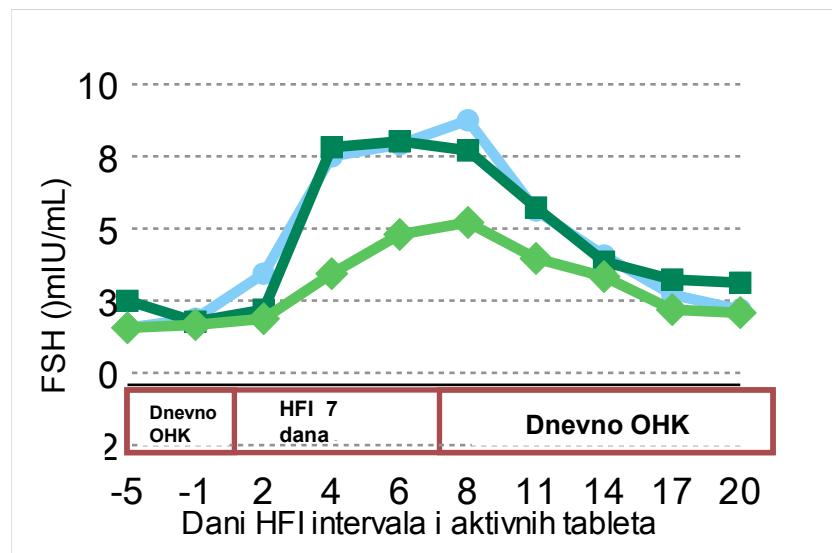
HFI of 7 days induces monthly withdrawal symptoms of bleeding, pain, breast tenderness, bloating/swelling and increased use of pain medications. This study evaluates the serum levels of four reproductive hormones during the HFI.

- Skraćenje pill-free intervala omogućava izraženiju supresiju hipofize i ovarija
- Smjenujuje se rizik ovulacije, formacije cista i simptomi povlačenja hormona



RJEŠENJE: PRODULJEN REŽIM?

● 21/7 ■ 84/7 ♦ 84/7EE



Dodatak male doze estradiola (10 mcg EE) nakon 84 aktivne tablete omogućava

spajajući supresiju hipofizno-ovarijske osovine:

- Slična situacija
- Manji fizički razvoj folikula
- fluktuacije hormona u cirkulaciji
- Nema fluktuacije hormona u cirkulaciji



SEASONIQUE®- oralni kontraceptiv s produljenim režimom uzimanja i EE u pill free intervalu

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- Sastoji se od 84 tablete (kombinacija 30µg etinilestradiola i 0.15 mg levonorgestrela (ružičaste tablete) te 7 tableta od 10µg etinilestradiola (bijele tablete))
- Tablete se uzimaju kontinuirano tijekom razdoblja od 91 dan.
- Nova kutija započinje se dan nakon uzimanja zadnje tablete iz prethodnog pakiranja
- Predviđeno prijelomno krvarenje treba se javiti tijekom 7 dana primjene bijelih tableta.

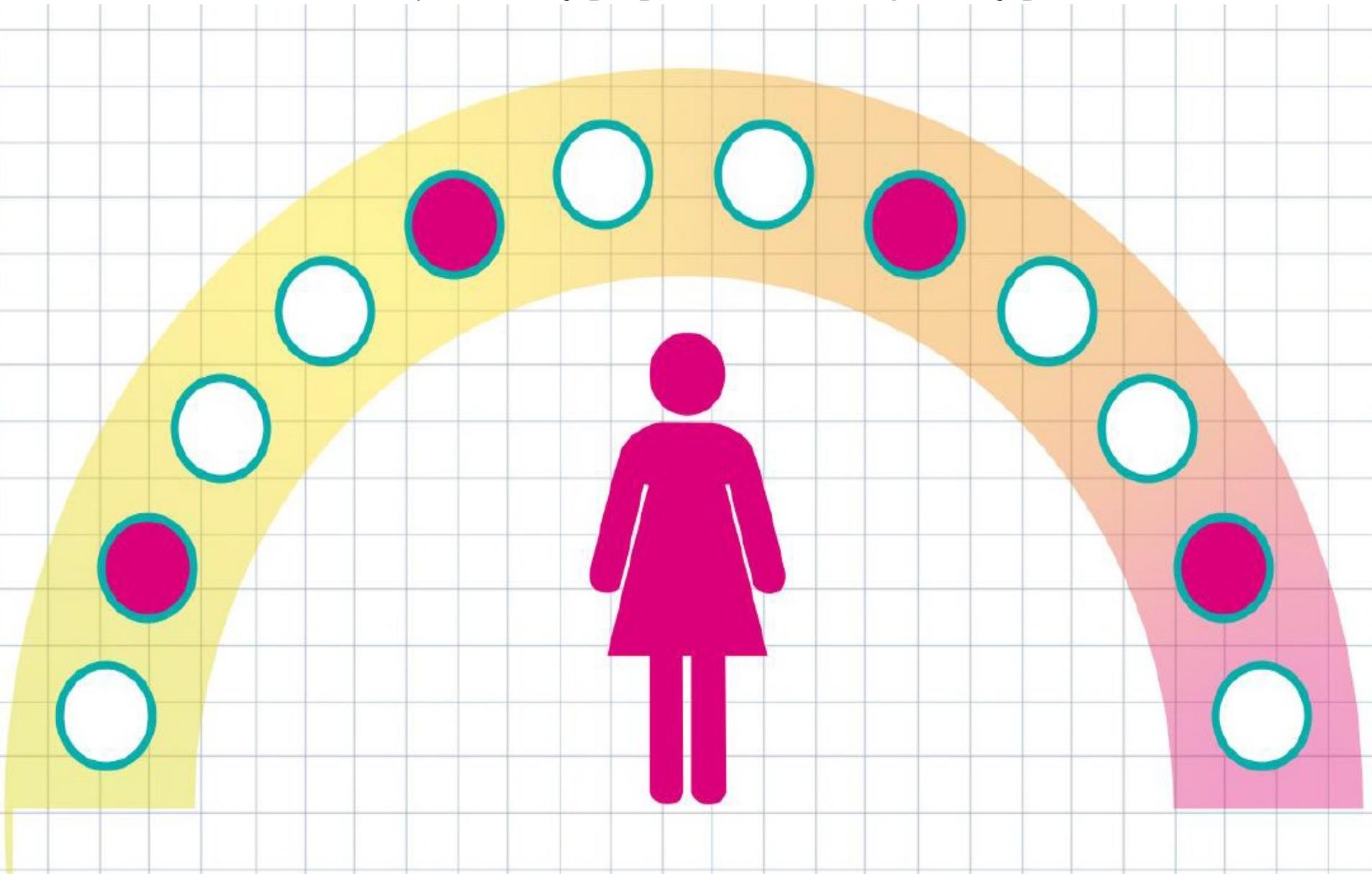
Kandidati za produljenu kontracepciju

Žene bez simptoma koje žele imati rjeđa krvarenja





KRVARENJA UZ PRODULJENI REŽIM 84/7 - SVAKA 3 MJESECA - 4X GODIŠNJE



Kandidati za produljenu kontracepciju

Žene s patologijom ili simptomima koji se pogoršavaju tijekom menstruacije





Table 1 Medical conditions that may benefit from menstrual suppression

Gynecologic conditions

- Chronic pelvic pain³²
- Dysmenorrhea³³
- Endometriosis^{34,35}
- Heavy menstrual bleeding^{30,32}
- Uterine leiomyomata
- Anemia due to heavy menstrual bleeding
- Irregular bleeding/anovulation
- Polycystic ovary syndrome (PCOS)³⁶
- Perimenopausal symptoms³²
- Premenstrual syndrome (PMS)/premenstrual dysphoric disorder (PMDD)^{37–39}

Pre-procedure

- Obstructing utero-vaginal anomalies pre-operative endometrial thinning prior to surgery

Menstrual molimina⁴²

- Breast pain
- Headaches
- Nausea/cyclic vomiting

Hematologic conditions

Anticoagulation⁴³

- Malignancy requiring chemotherapy/BMT⁴⁴

Inherited anemia/bleeding disorders^{45,46}

- Sickle cell disease⁴⁷

Thalassemias

- Fanconi anemia

Von Willebrand disease⁴⁸

Hemophilia, clotting factor deficiencies

Other hematologic conditions

- ITP/thrombocytopenia⁴⁹

Mental retardation/developmental disorders

Behavioral issues/PMS symptoms

Contraception

Hygiene/inability to manage menstrual problems

Neurologic disease

Migraine headaches^{52,53}

- Menstrual migraines

Menstrual-associated migraines

Seizure disorders^{54–56}

Catamenial seizures

Other conditions associated with menstruation

Anaphylactoid reactions⁵⁹

Asthma^{60,61}

Catamenial pneumothorax⁶²

Diabetes mellitus⁶³

Irritable bowel syndrome^{64,65}

Pancreatitis⁶⁶

Rheumatoid arthritis

Skin conditions

Acne⁶⁰

Other

Deployed military personnel⁶⁷

Female athletes³²

Physical difficulty with managing menstrual bleeding

Cerebral palsy

Rheumatoid arthritis

Abbreviations: BMT, bone marrow transplant; PMS, premenstrual syndrome.

Menstrual suppression: current perspectives

This article was published in the following Dove Press journal:

International Journal of Women's Health

23 June 2014

Number of times this article has been viewed

Abstract: Menstrual suppression to provide relief of menstrual-related symptoms or to manage medical conditions associated with menstrual morbidity or menstrual exacerbation has been used clinically since the development of steroid hormonal therapies. Options range from the extended or continuous use of combined hormonal oral contraceptives, to the use of combined hormonal patches and rings, progestins given in a variety of formulations from intramuscular injection to oral therapies to intrauterine devices, and other agents such as gonadotropin-releasing hormone (GnRH) antagonists. The agents used for menstrual suppression have variable rates of success in inducing amenorrhea, but typically have increasing rates of amenorrhea over time. Therapy may be limited by side effects, most commonly irregular, unscheduled bleeding. These therapies can benefit women's quality of life, and by stabilizing the hormonal milieu, potentially improve the course of underlying medical conditions such as diabetes or a seizure disorder. This review addresses situations in which menstrual suppression may be of benefit, and lists options which have been successful in inducing medical amenorrhea.

Keywords: menstrual molimena, amenorrhea, inducing amenorrhea, quality of life

Background

Suppression of menstrual periods to provide relief of menstrual-related symptoms has been used in a variety of medical conditions since the availability of steroid hormone therapy. This option has gained legitimacy through its use in treating symptoms, but is now being used more frequently by women for personal preference. A recent Cochrane review of trials comparing 28-day and extended cycles found comparable contraceptive efficacy and safety.¹ The review found overall discontinuation rates and discontinuation for bleeding problems to be similar. Extended cycling resulted in improved headaches, genital irritation, tiredness, bloating, and menstrual pain.¹

The term "therapeutic amenorrhea" was first used in the mid-1960s to describe the suppression of menstrual bleeding in women with hematologic disorders and coagulation defects leading to heavy menstrual bleeding.^{2,3} A small randomized trial in 1971 in the US compared a high-dose combination oral contraceptive pill, given continuously, with depot medroxyprogesterone acetate (DMPA) or DMPA plus daily conjugated estrogens.³ The differences among these regimens were not significant.

When oral contraceptives containing a synthetic estrogen and a progestin were initially developed, an arbitrary regimen comprising 21 days of hormonally active pills followed by 7 days of placebo or a hormone-free interval were devised to mimic the natural menstrual cycle ("the Pill"). It was even the belief of one of the original developers of oral contraceptives, John Rock, MD, that this cycling would provide a

GINEKOLOŠKI PROBLEMI: obilna menstruacijska krvarenja

- Dismenoreja
- Endometrioza
- PMS/PMDD
- Menstruacijska molimina
- Napetost dojki
- Menstrualne glavobolje
- Cikličko povraćanje...

HEMATOLOŠKI POREMEĆAJI:

- Nasljedne anemije
- Von Willebrandova bolest
- Talasemija
- Hemofilije...

NEUROLOŠKI POREMEĆAJI

- Menstrualne migrene
- Katamenijska epilepsija

DRUGI POREMEĆAJI POVEZANI S MENSTRUACIJSKIM CIKLUSOM:

- Egacerbacija asthme
- Katamenijski penumotorax
- Reumatoидни artritis
- Akne...

KVALITETA ŽIVOTA

- Sport
- Vojna služba ...

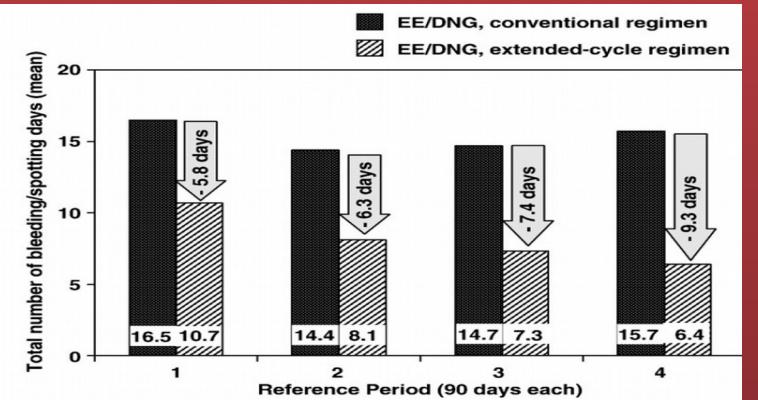


DOBROBITI PRODULJENOG REŽIMA KORIŠTENJA HORMONSKE KONTRACEPCIJE

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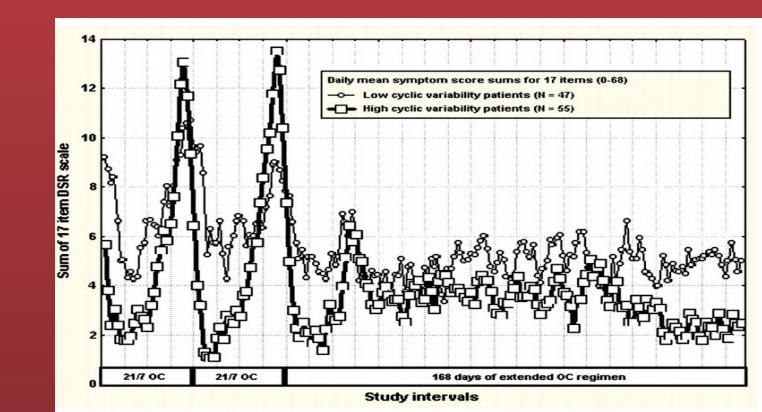
Women's Health

SMANJENJE OBILNOG MENSTRUACIJSKOG KRVARENJA



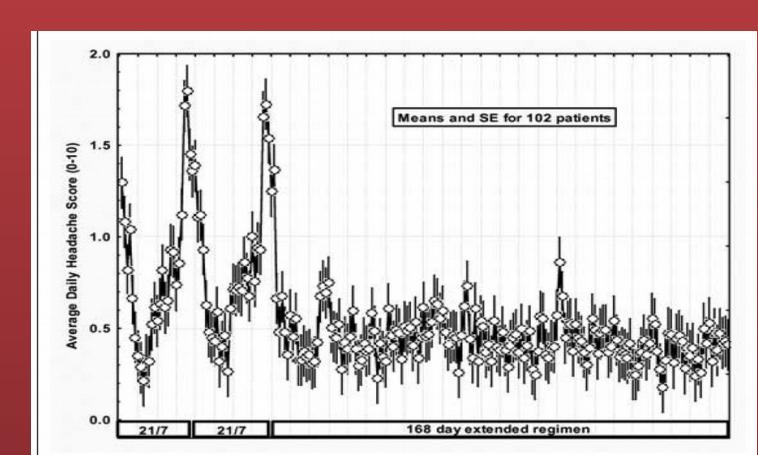
Wiegartz I. *Contraception* 2011;84:153-163

POBOLJŠANJE 17 FIZIČKIH I EMOTIVNIH PARAMETARA POVEZANIH S MENSTRUACIJSKIM CIKLUSOM (DSR 17)



Coffee AL, et al. *Am J Obstet Gynecol.* 2006;195:1311-1319.

SMANJENJE MENSTRUACIJSKIH GLAVOBOLJA



Sulak P et al. *Headache* 2007;47:27-37

POBOLJŠANJE KVALITETE ŽIVOTA

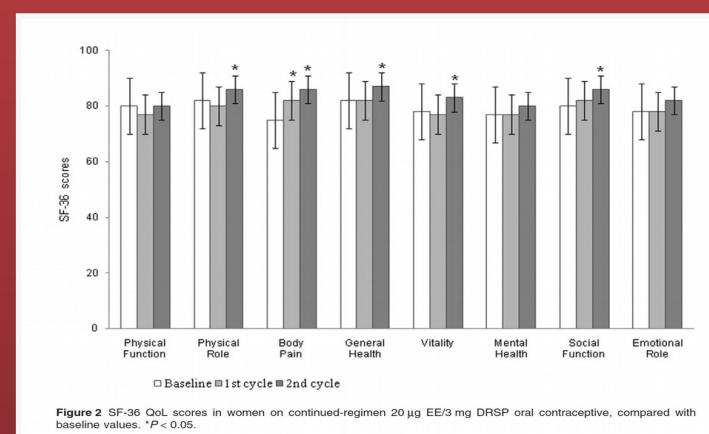


Figure 2 SF-36 QoL scores in women on continued-regimen 20 µg EE/3 mg DRSP oral contraceptive, compared with baseline values. * $P < 0.05$.

Caruso S. *J Sex Medicine* 2013;10:460-466



Human Reproduction, Vol.26, No.1 pp. 3–13, 2011
Advanced Access publication on November 11, 2010 doi:10.1093/humrep/deq302

human
reproduction

DEBATE

'Waiting for Godot'[†]: a commonsense approach to the medical treatment of endometriosis

Paolo Vercellini^{1,*}, PierGiorgio Crosignani¹, Edgardo Somigliana², Paola Viganò³, Maria Pina Frattarulo¹, and Luigi Fedele¹

¹Department of Obstetrics and Gynaecology, Istituto 'Luigi Mangiagalli', University of Milan, Milan, Italy ²Infertility Unit, Fondazione Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy ³Centre for Research in Obstetrics and Gynaecology (C.R.O.G.), Milan, Italy

*Correspondence address. E-mail: paolo.vercellini@unimi.it

ABSTRACT: Conservative surgical treatment for symptomatic endometriosis is frequently considered an important alternative or complement to surgery. The use of implants is the only available medication with a favourable evidence base for endometriosis, which is often recurrent. However, robust evidence on the long-term benefit of endometriosis metabolism is still lacking. Moreover, oral contraceptives with deeply infiltrating lesions, which are alternatives. Moreover, oral contraceptives are here proposed as the reference comparator in all future randomized controlled trials on medical treatment for endometriosis.

OHK dramatično smanjuju stopu rediciva endometrioma i moraju se smatrati nužnim dijelom dugotrajne terapijske strategije sa svrhom smanjenja rizika daljnog smanjenja fertilne sposobnosti.

Progestini i kontinuirani monofazični HK smatraju se referentnim komparatorom u svim budućim randomiziranim studijama o medikamentoznom liječenju endometrioze.

ABSTRACT

or its re...
ound is...
Because t...
be chosen. In...
mechanisms, have...
moment, the principal modality...
demonstration of a major effect on pain even in patients with more...
of more scientifically fashionable and up-to-the-minute...
post-operative endometrioma recurrence and should now be considered an essential tool to limit further damage to future fertility. Finally, women who have used OC for risk of endometriosis-associated ovarian cancer. To avoid the several subtle differences for discussing the evidence base for OCs, the favour of specific compounds, progestins and monophasic OC used continuously are here proposed as the reference comparator in all future randomized controlled trials on medical treatment for endometriosis.

Key words: endometriosis / pelvic pain / medical treatment / oral contraceptives / progestins



DOBROBITI PRODULJENE HORMONSKE KONTRACEPCIJE s dodatkom EE u pill-free intervalu - SEASONIQUE®



RJEĐA
PRIJELOMNA
KRVARENJA
4 krvarenja
godišnje

MANJA
UČESTALOST
NUS POJAVA
IZBJEGAVANJEM
PILL FREE
INTERVALA

IZRAŽENA
OVARIJSKA
SUPRESIJA
BOLJA
KONTRACEPCIJSKA
UČINKOVITOST



LONG-TERM EXTENSION STUDY



- Nakon 1 godine studije faze III, 320 žena uzimalo je SEASONIQUE dodatne 3 godine:
 - 244 (76.3%) žena uzimalo je kontraceptiv 84/EE dodatnu 1 godinu
 - 173 (54.1%) žena uzimalo je kontraceptiv 84/EE dodatnu ≥ 2 godine
 - 85 (26.2%) žena uzimalo je kontraceptiv 84/EE dodatnu 3 godine
- DUGOTRAJNI RIZICI – JEDNAKI KAO I KOD 21/7 REŽIMA
- NEMA POVIŠENOOG RIZIKA TROMBOZE
- NEMA NAZNAKA NEGATIVNOG UTJECAJA NA ENDOMETRIJ



Rezultati biopsija endometrija žena koje su SEASONIQUE uzimale do 1 godinu

Nisu nađeni hiperplazija ni karcinom endometrija
Najčešći nalaz – atrofičan endometrij

Brzi povrat u normalan ciklički endometrij nakon prestanka korištenja

Distribution of endometrial biopsy results (glandular) among 63 study subjects at baseline and end of treatment

	Baseline (N ^a =181)		End of treatment (N ^a =181)	
	n	(%)	n	(%)
No endometrium	18	9.9	24	13.3
Insufficient tissue	7	3.9	8	4.4
Inactive	38	21.0	76	42.0
Atrophic	3	1.7	14	7.7
Menstrual	3	1.7	14	7.7
Proliferative	56	30.9	29	16.0
Secretory	56	30.9	16	8.8
Hyperplasia	0	0	0	0

^a N refers to the number of biopsy reviews, not subjects.



Seasonique očekivana krvarenja – u očekivano vrijeme (7-dnevni EE interval)

- Očekivano krvarenja/spotting u vrijeme 7 dnevnog EE intervala traju 2-3 dana¹
(slično kao i kod 21/7, 24/4 režima^{2,3})
- Broj dana očekivanog samo krvarenja (bez spottinga) smanjuje se nakon prvog ciklusa¹

Contraception
Original research article
Safety and efficacy of an extended-regimen oral contraceptive utilizing continuous low-dose ethynodiol dienoate
Freedolph D. Anderson^{a,*}, William Gibbons^a, David Portman^b
^aThe Jones Institute for Reproductive Medicine, Eastern Virginia Medical School, Norfolk, VA 23507-1627, USA
^bColumbus Center for Women's Health Research, Columbus, OH 43213-1562, USA
Received 3 May 2005; revised 1 September 2005; accepted 6 September 2005

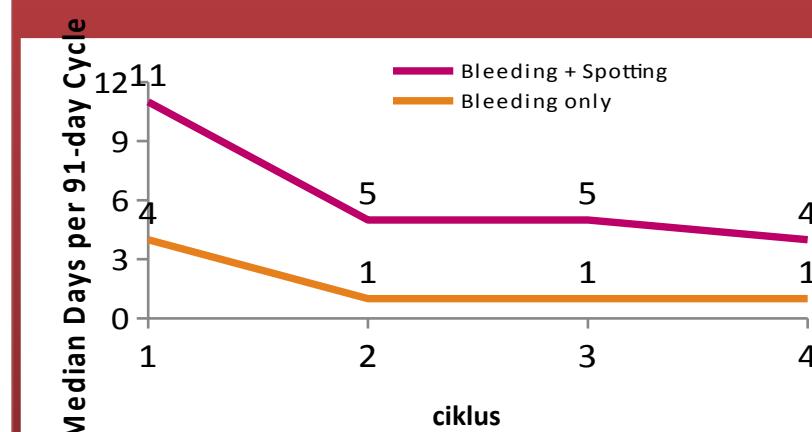
¹Anderson FD, et al. Contraception. 2006;73:229-234, ² Nakajima ST, et al. Contraception. 2007;75:16-22. ³ Bachmann G, et al. Contraception. 2004;70:191-198.

91-dnevni ciklus	Planirana krvarenja/spotting (prosječno dana)	Planirana krvarenja bez spottinga (prosječno dana)
1	3	3
2	3	2
3	3	2
4	3	2

¹Anderson FD, et al. Contraception. 2006;73:229-234, ² Nakajima ST, et al. Contraception. 2007;75:16-22. ³ Bachmann G, et al. Contraception. 2004;70:191-198.



Seasonique neplanirana krvarenja



Prosječno trajanje nepredviđenih krvarenja/spottinga

- U prvom ciklusu kao i kod drugih produljenih režima
- Pojava krvarenja se smanjuje sa svakim idućim ciklusom



SAVJETOVANJE ŽENA PRIJE KORIŠTENJA PRODULJENOG REŽIMA

TEVA

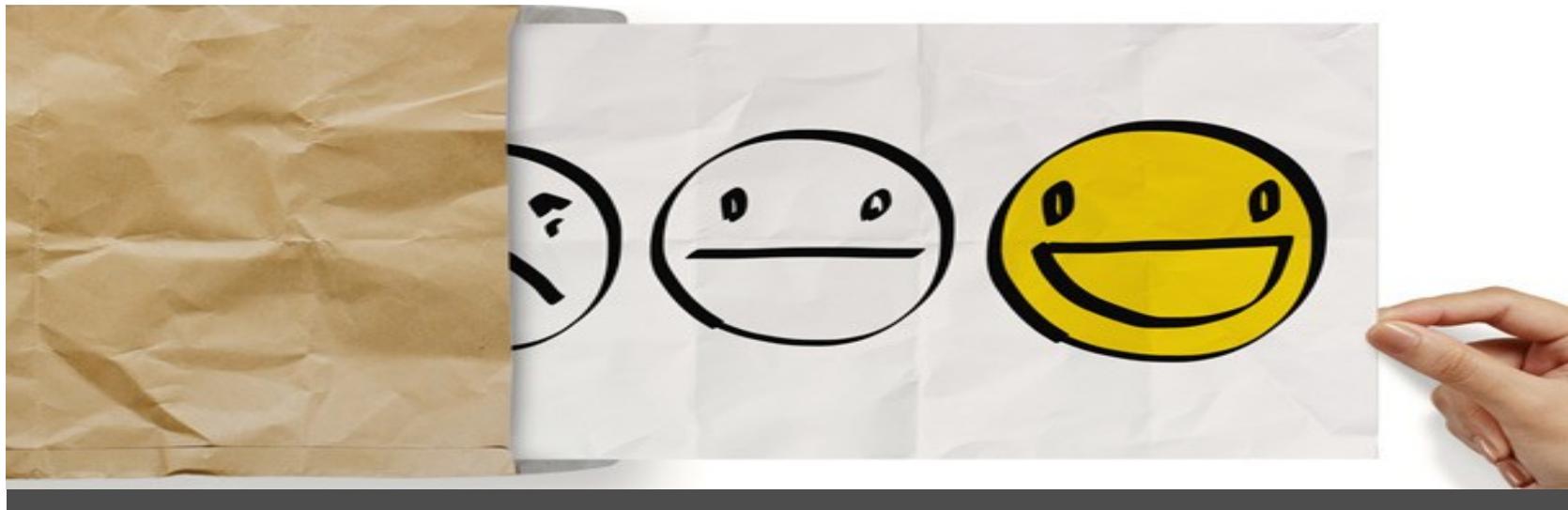
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1. Mjesečna krvarenja nisu nužna ukoliko žena uzima OHK
2. Produljenom kontracepcijom smanjuje se ukupna količina krvarenja i broj krvarenja sa 13 na 4 godišnje
3. U prvim mjesecima uzimanja može biti više nepravilnih krvarenja u odnosu na primjenu tradicionalne hormonske kontracepcije
4. Ta nepravilna krvarenja nisu medicinski zabrinjavajuća i se smanjuju se tijekom vremena
5. Rizici produljene kontracepcije su isti kao i kod tradicionalne
6. Povrat fertilne sposobnosti je brz nakon prestanka korištenja



PRODULJENA KONTRACEPCIJA – NOVA MOGUĆNOST INDIVIDUALNOG ODABIRA HORMONSKE KONTRACEPCIJE





TEVA

Wom

MENSTRUACIJA – BLAGODAT ILI PROKLETSTVO?

