個人化避孕新趨勢

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Introduction

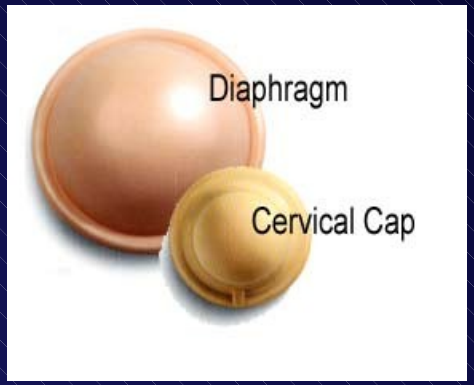
- Nearly half (49%) of the pregnancies in the United States are unintended, despite the availability of numerous highly effective forms of contraception.
- The majority of these pregnancies (53%) occur among women who reported using contraception during the month of conception.
- Adolescents (aged 15 to 19 years) and young women (aged 20 to 24 years) have the highest rates of unintended pregnancy (82% and 60%, respectively).

Contraception Today: Lots of Choices!

- Pills (combined and progesterone only)
- Injections
- Contraceptive Devices (patch, ring)
- IUD / IUS
- Barrier Methods (condoms, diaphragm)
- Spermicides
- Implants
- Sterilization

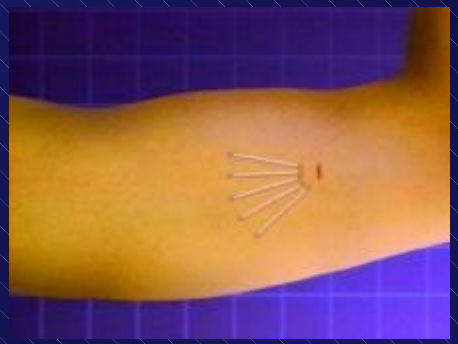
Types of Non-hormonal Contraception

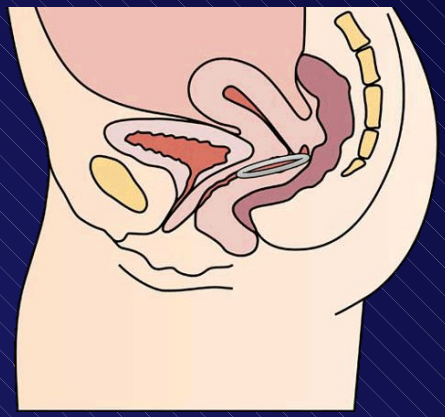
- Barrier methods (condoms, sponge, spermicidal gels)
- Calendar method
- Withdrawal method
- Prescription barrier options (diaphragm, cervical cap)
- Copper intrauterine device (IUD).



Types of Hormonal Contraception

- Oral Contraceptives
  - Monophasic
  - Multiphasic
  - Progestin only
- Transdermal Patch
- Injectable Formulations
- Hormonal Implants
- Vaginal Contraceptives





Which Methods Are the Most "Forgettable"?

Less "forgettable" — More "forgettable"

With Every Act of Coitus	Daily Use	Weekly use	Monthly Use	Quarterly Use	Multiple-Year Use
Condoms	OCs	Patch	Ring	DMPA	Single implant = 3 years
Spermicides					LNG IUS = 5 years
Withdrawal					CuT380A = 10 years
					Sterilization = forever

Courtesy of Susan Wysocki, WHNP-BC, FAANP.

Clinician Considerations for Contraception

- Contraindications or safety concerns
- Side-effect profile
- Potential for consistent/correct use
- Method bleeding profile
- Non-contraceptive benefits

Patient Considerations for Contraception

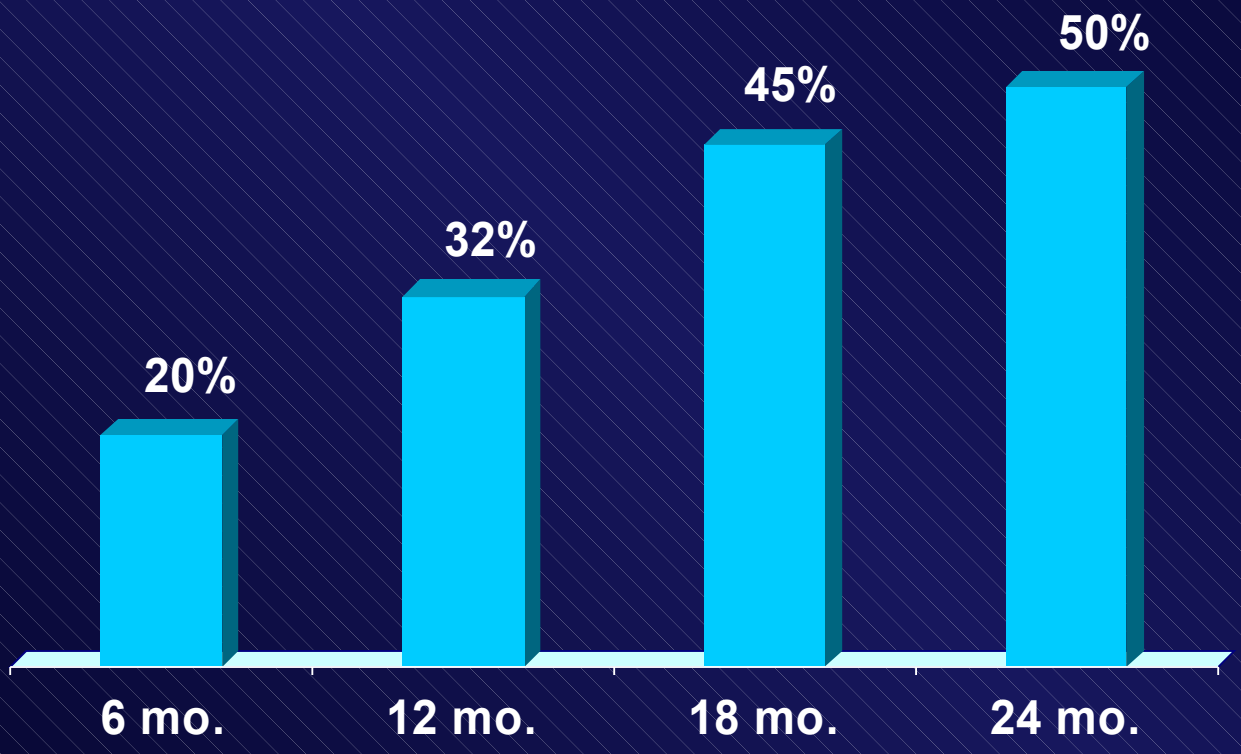
- Hormonal vs nonhormonal
- Daily or nondaily
- Side effects/safety profile
- Effectiveness
- Perceptions/misperceptions of methods
- Future childbearing plans

Oral Contraceptives

- COCs continue to be the most common method of contraception in the United States, followed by female sterilization.
- The pill is the leading method of contraception among women less than 30 years of age.
- However, more than 1 in 3 pill users (37%) decide to discontinue COCs because of side effects.

Discontinuation Rate Is High

Cumulative Rates of Contraceptive Discontinuation



Reference: Grimes DA, ed. *Contraception Rep*. 1999;10:8-11.

Side effects of Oral Contraceptives

- Oestrogenic
  - Nausea
  - Dizziness
  - Bloating
  - Breast engorgement
  - Vaginal discharge
  - Premenstrual tension
  - Migranes
- Progestogenic
  - Vaginal dryness
  - Body weight increase
  - Reduced libido
  - Acne
  - Mastalgia
  - Depression
  - Lethargy
  - Scanty menses

Achieving A Balancing Act

BTB=breakthrough bleeding

Reference: Freeman S. Available at: http//www.npwh.org/evolution/. Accessed September 27, 2005.

Types of Combined Oral Contraceptives(COCs)

- Monophasic: All 21 active pills contain same amount of Estrogen/Progestin (E/P)
- Biphasic: 21 active pills contain 2 different E/P combinations (e.g., 10/11)
- Triphasic: 21 active pills contain 3 different E/P combinations (e.g., 6/5/10)
- Biphasic and triphasic pills contain a lower total hormone dose but have not been found to perform differently than monophasic pills.

口服避孕藥的成分

動情素

- Ethinyl estradiol
- Mestranol
- 所謂的「低劑量」口服避孕藥指其動情素劑量小於 0.05 毫克 (=50 ug)， 而黃體素劑量小於 0.15 毫克 (=150ug) 。

黃體素

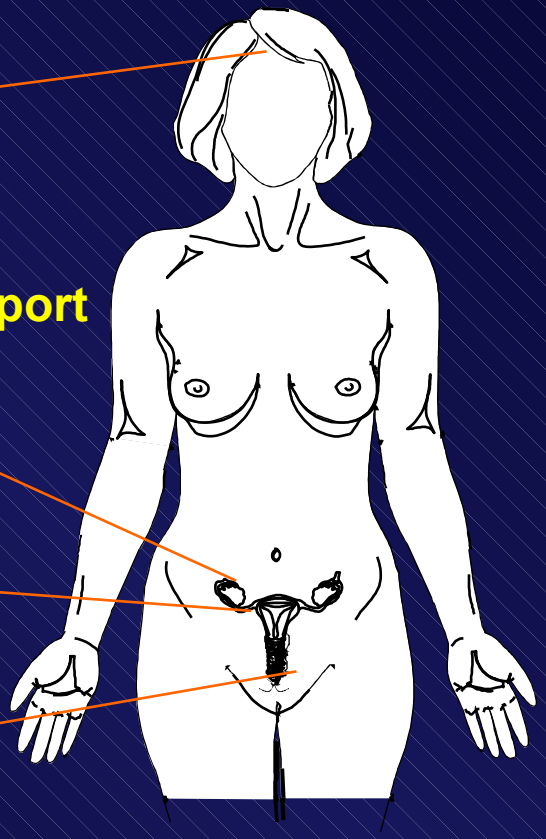
- Levonorgestrel
- Norethindrone
- 由睪脂酮改造合成。保留些微的男 性化的潛在影響。

口服避孕藥的成分

- First generation oral contraceptives
  Containing 50ug or more of ethinyl estradiol
- Second generation oral contraceptives
  Containing levonorgestrel, norgestimate and other members of northindrone family and 30 or 35ug ethinyl estradiol
- Third generation oral contraceptives
  Containing desogestrel or gestodene with 20 or 30ug ethinyl estradiol

Type of progesterone	Monophasic pills	Triphasic pills
Levonorgestrel	Microgynon 30/EE Ovranette (30 EE) Eugynon (30 EE)	Trinodial Logynon
Norethisterone	Ovysmen / Brevinor (35 EE) Norimin(35) Loestrin 20/30	Trinovum Binovum Synphase
Norgestimate	Cilest (35 EE)	
Desogestrol	Mercilon 20 EE Marvelon 30 EE	
Gestogene	Femodene (30EE) Minulet (30 EE) Femodette(20 EE)	Tri-Minulet
Drospirenone	Yasmin (30 EE)	

口服避孕藥的作用機轉



Failure rate is 0.2-0.5 per 100 woman years

COCs: Contraceptive Benefits

- Highly effective when taken daily
- Effective immediately if started by day 7 of cycle
- Do not interfere with intercourse
- Few side effects
- Convenient and easy to use
- Can stop use

[1]Hatcher et al 1998.

COCs: Noncontraceptive Benefits

- Decrease menstrual flow (lighter, shorter periods)
- Decrease menstrual cramps
- May improve anemia
- Protect against ovarian and endometrial cancer
- Decrease benign breast disease and ovarian cysts
- Prevent ectopic pregnancy
- Protect against some causes of PID

COCs: Who Should Not Use

- Is pregnant (known or suspected)
- Is breastfeeding (< 6 weeks postpartum)
- Is jaundiced (symptomatic viral hepatitis or cirrhosis)
- Has ischemic heart disease or stroke (current or history of)
- Has blood clotting disorders (deep vein)
- thrombophlebitis or pulmonary embolus)

***Source*: WHO 1996.**

COCs: Who Should Not Use

- Is a smoker and age 35 years or older
- Has diabetes (> 20 years duration)
- Has headaches (migraine)
- Has high blood pressure (> 180/110)
- Has breast cancer
- Has liver tumors
- Has to undergo major surgery with prolonged bed rest

***Source*: WHO 1996.**

Progesterone only Pill (POP)

- Becoming increasingly popular
- They can be used with no age limits,in smokers, during lactation and even for women at risk of VTE
- Efficacy

  Failure rate of 0.3-5 per 100 woman per years
- Mode of action

  Mainly thickening cervical mucus

  Atrophy of endometrium, hinders implantation

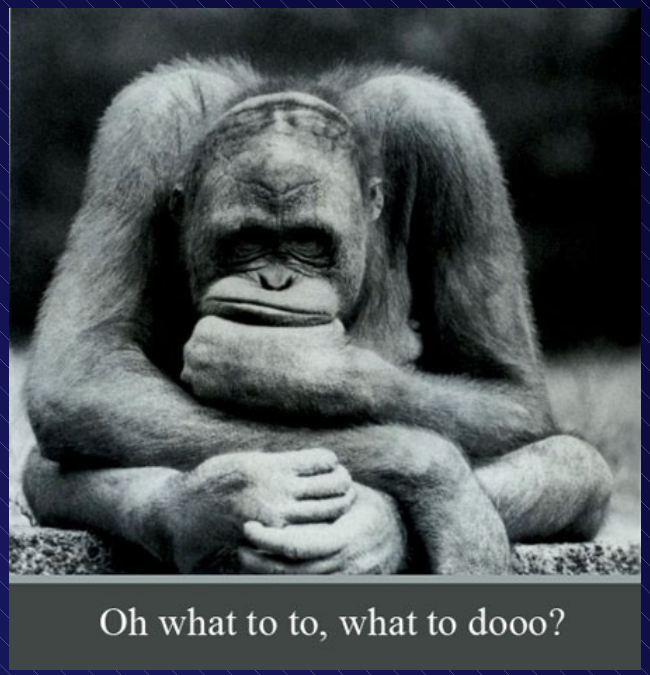
  Interfere with tubal transport of ova

Contraindications

- Uncontrolled hypertension
- Active hepatitis/ decompensated cirrhosis/ liver tumours
- Malabsorption
- Current DVT
- Undiagnosed Genital tract bleeding
- Recent trophoblastic dx with high bHCG
- Current IHD
- Current breast Ca
- Past severe side effects
- Acute porphyria

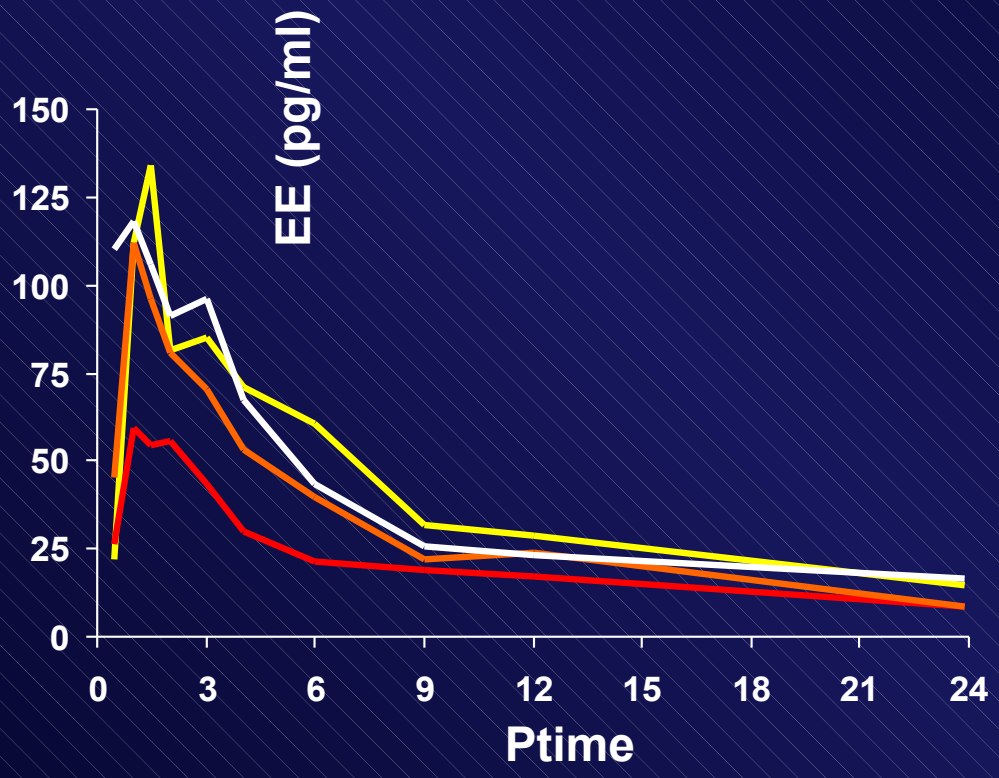
Oral administration drawbacks

- Daily intake required
- Fluctuating serum levels
- High maximum serum levels
- Influenced by many factors (food, vomiting, antibiotics)
- First-pass effect



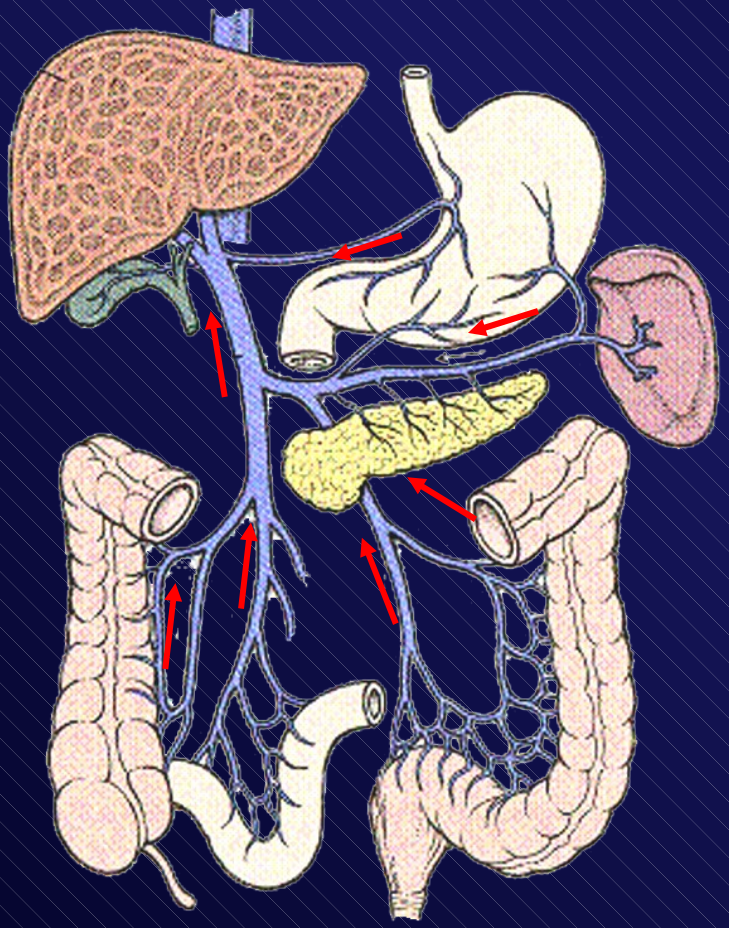
Variability

With oral hormonal pills, the inter-individual variation in the blood levels of exogenous hormones has been estimated to vary 10-fold and intra-individual differences also occur.



Reference: Guillebaud J. Practical Prescribing of the Oral Contraceptive Pill, Contraception:Science and Practice

Hepatic First-Pass Effect of Estrogen



DRUG

↔ Ingestion

STOMACH

↔ Dissolution

INTESTINE

↔ Metabolism
Absorption

PORTAL VEIN

LIVER

↔ Metabolism

SYSTEMIC CIRCULATION

CDC Guidelines for Combined Hormonal Contraceptive Use in Postpartum Women

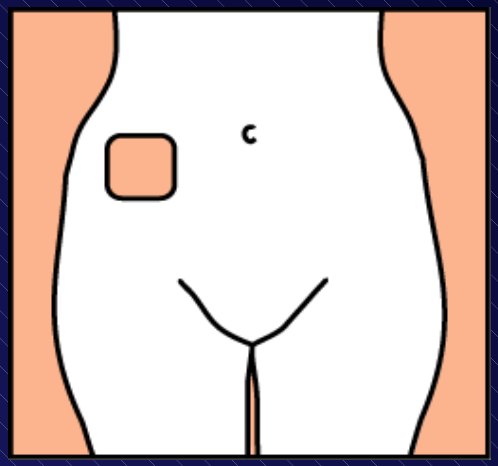
- Women who are less than 21 days postpartum should not use combined hormonal contraceptives because of the increased risk for venous thromboembolism.
- Those at 21 to 42 days postpartum who don't have other VTE risk factors can generally start combined hormonal contraceptives. Those with VTE risk factors should not.
- Women who are beyond 42 days postpartum do not have any restrictions.

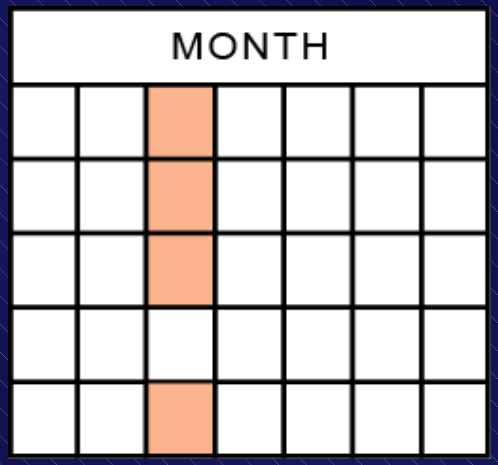
Transdermal Contraceptives

- Transdermal

Weekly administration

- Increased compliance
  New route of administration, quick adoption in some markets
- Avoidance of hepatic first-pass metabolism

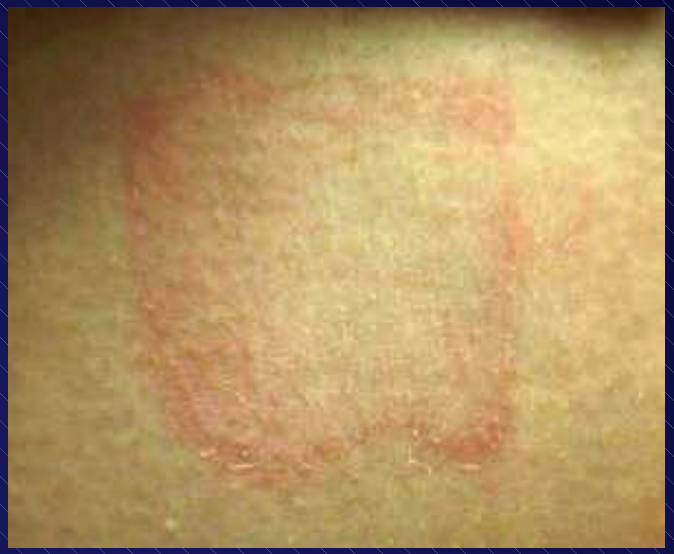




Reference: Potts R et al. *Obstet Gynecol*. 2005;105:953-961.

Skin administration drawbacks

- Fluctuating serum levels
- Local irritation
- Must avoid lotions, powders, perfumes
- Must change sites
- Transdermal contraceptive systems may be less effective in these women due to altered skin and body fat composition.
- Visible



Injections

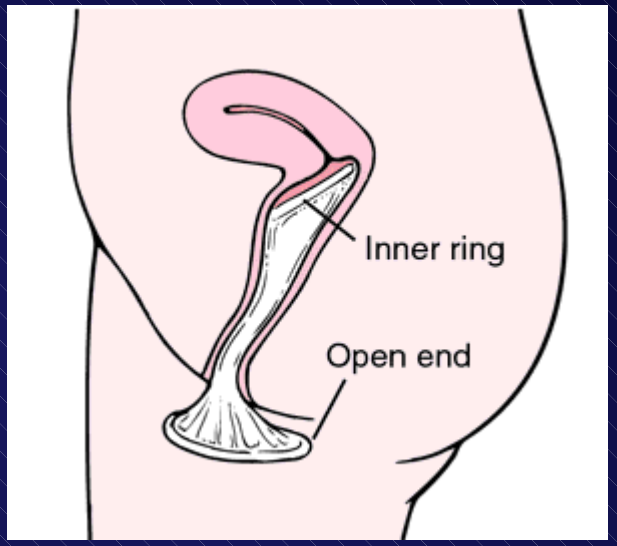
- Depo Provera IM (1992) *may* allow for self-injection at some point)
- Repeat injections every 3 months; must be given on time
- Irregular bleeding at first – mostly amenorrhea after a few months
- Concerns about bone de-mineralization with teens and long term users
- Rx only; No protection against STDs
- Failure Rate: perfect use 0.3%

Diaphragm (contraceptive)

Diaphragm (contraceptive)

- Traditionally, the diaphragm has been used with spermicide, and it is widely believed the spermicide significantly increases the effectiveness of the diaphragm
- The diaphragm be left in place for at least six or eight hours after intercourse
- Failure rate of the diaphragm with spermicide is 6% per year

Female Condom



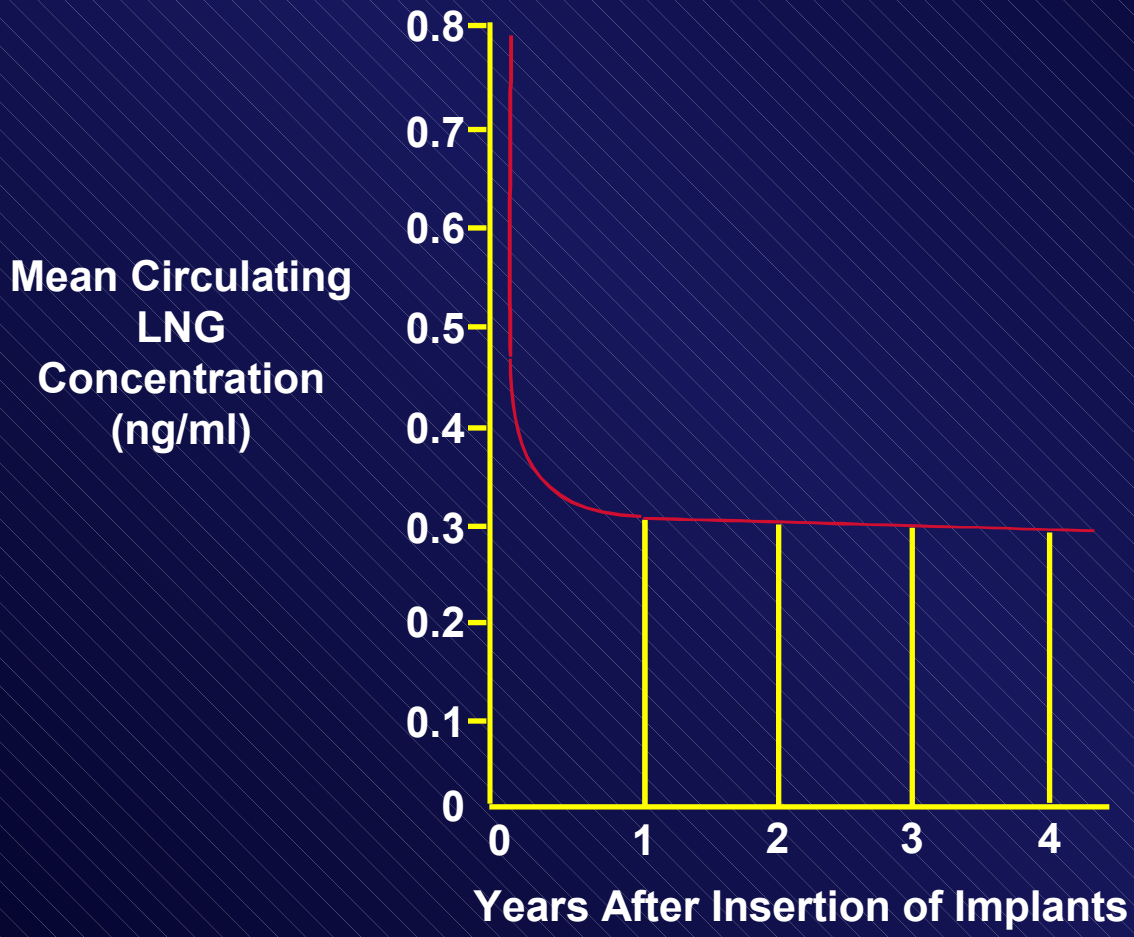
Norplant® Implants

Norplant® is the registered trademark of the Population Council for six-capsule subdermal levonorgestrel implants.

Norplant® Implants

- Six thin, flexible capsules filled with levonorgestrel (LNG) that are inserted just under the skin of a woman's upper arm

Levonorgestrel Serum Levels in Norplant Users



Source: Nash 1990.

Norplant Implants: Limitations

- Cause changes in menstrual bleeding pattern (irregular bleeding/spotting initially) in most women
- Require trained provider for insertion and removal
- Woman must return to healthcare provider or clinic for insertion of another set of capsules or removal

Norplant Implants: Limitations

- Woman cannot stop whenever she wants (provider dependent)
- Effectiveness may be lowered when certain drugs for epilepsy (phenytoin and barbiturates) or tuberculosis (rifampin) are taken
- Cost-effectiveness dependent on length of use
- Do not protect against STDs (e.g., HBV, HIV/AIDS)

Norplant Implants: Insertion Site Problems

Problem	Percentage of Women
Infections	< 1.0
Expulsions	< 0.5
Cellulitis	< 0.5

***Source*: Population Council 1990.**

Emergency Contraceptives

- Mechanism of action
  - Inhibiting or delaying ovulation
  - Interfering with fertilization or tubal transport
  - Preventing implantation by altering endometrial receptivity
  - Causing regression of the corpus luteum.

Potential indications for using emergency contraception

When no contraceptive was used during sexual intercourse within the previous 120 hours
When there is a contraceptive failure or incorrect use of a contraceptive within the previous 120 hours, including:
Condom breakage, slippage, or incorrect use
Three or more 30 to 35 mcg ethinyl estradiol pills have been missed (or two or more 20 to 25 mcg pills)*
Progestin-only pill (minipill) taken more than three hours late
More than two weeks late for injection of depot-medroxyprogesterone acetate
Dislodgment, breakage, tearing, or early removal of a diaphragm or cervical cap
Dislodgment, delay in placing, or early removal of a contraceptive hormonal skin patch or vaginal ring
Failed coitus interruptus (eg, ejaculation in vagina or on external genitalia)
Failure of a spermicide tablet or film to melt before sexual intercourse
Miscalculation of the periodic abstinence method or failure to abstain on fertile day of cycle
Expulsion of intrauterine contraception

Efficacy

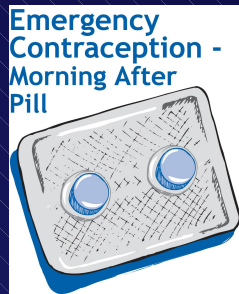
- Generally reported pregnancy rates:

  Oral emergency contraception: 0.2 - 3 %

  Copper intrauterine contraception 0.0-0.2%

- Systematic reviews:

  Easier access to emergency contraception led to higher utilization, but did not result in a significant drop in the pregnancy rate of the population



Emergency Contraception

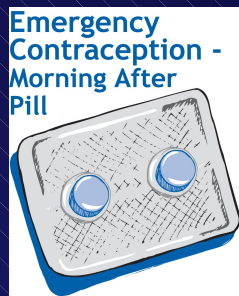
Postcoital contraceptive methods

Method	Dose	Reported efficacy
Levonorgestrel	0.75 mg given twice, 12 hours apart, or 1.5 mg single dose (not FDA approved)	89 percent of pregnancies prevented
Estrogen plus progesterone (Yuzpe regimen)	100 microgram ethinyl estradiol plus 0.5 mg levonorgestrel, each given twice, 12 hours apart	75 to 80 percent of pregnancies prevented
Mifepristone	Single 600 mg dose	100 percent
Copper intrauterine device	Inserted within 120 hours after intercourse	Over 90 percent

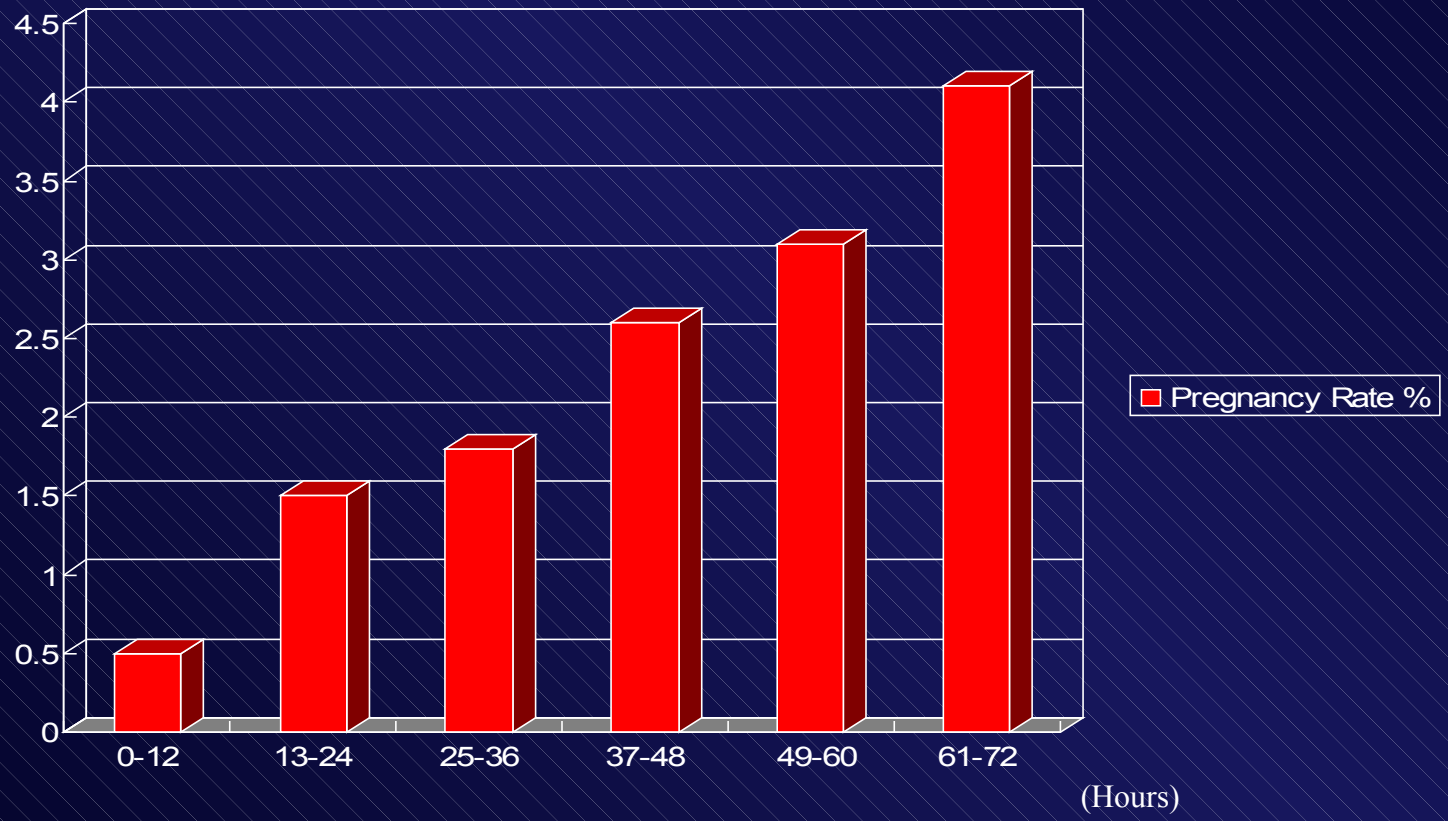
FDA: Food and Drug Administration (United States). *Adapted from Glasier, A, N Engl J Med 1997; 337:1058.*

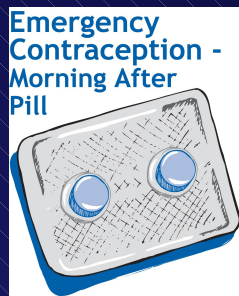
Administration

- Neither physical examination nor any laboratory tests are needed before providing oral emergency contraception
- Contraindications: based on their medical history (WHO criteria)
- For emergency contraception, these drugs (Levogesterel, Yuzpe) appear to have efficacy up to 120 hours after intercourse, but patients should be informed that efficacy may be reduced compared to earlier administration (0 to 72 hours)



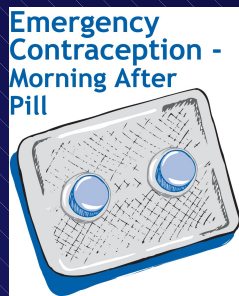
Efficacy of emergency contraception declines with increase since unprotected intercourse





Administration

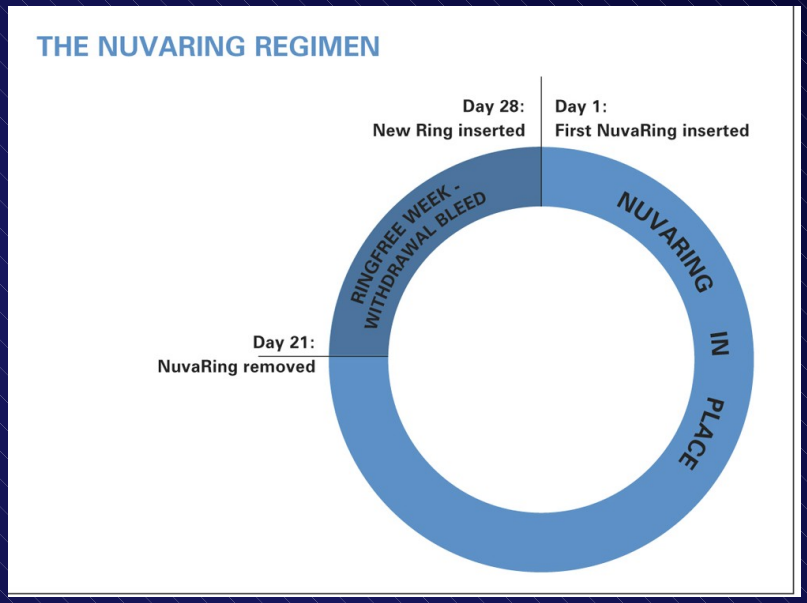
- If a split dose regimen is planned, the interval between the two doses of levonorgestrel can be lengthened to **24 hours** apart without significantly changing efficacy
- Side effects — Nausea and vomiting are the most common side effects of the oral hormonal drugs, and are more common with estrogen-progestin regimens than the levonorgestrel-only regimen




A Very Low Dose Novel Contracptive Method, One Monthly
NuvaRing

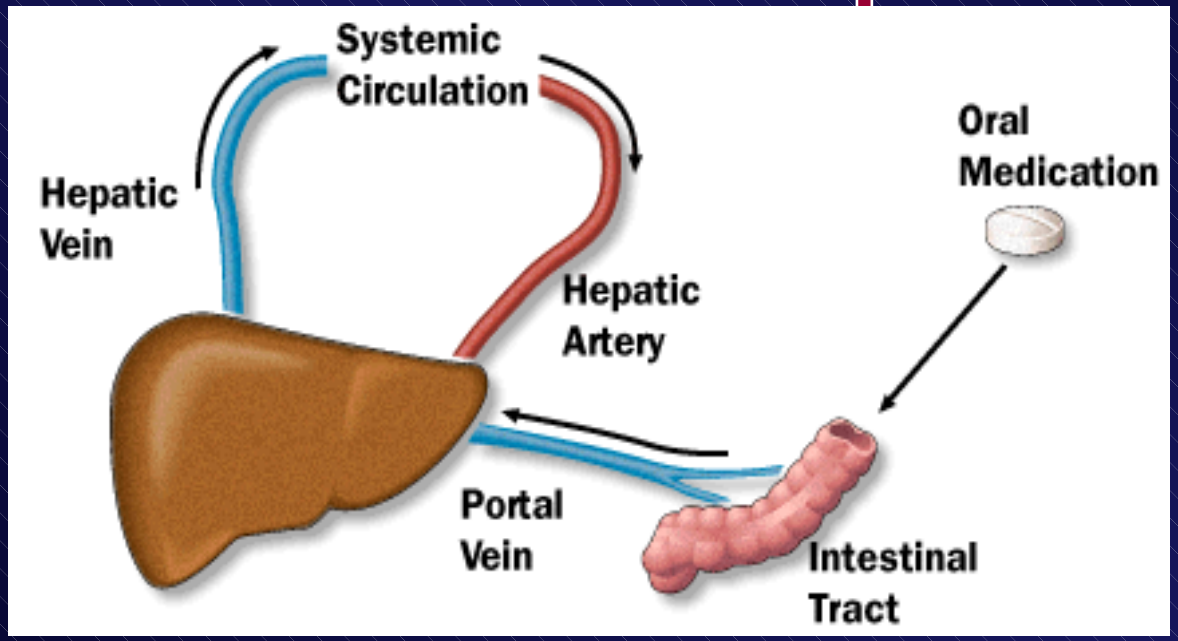
NuvaRing

- 1 ring per cycle
- Regimen:
  - 3 weeks of ring use
  - 1 ring-free week
- Daily release:
  - 15 µg ethinylestradiol
  - 120 µg etonogestrel



First-pass effect

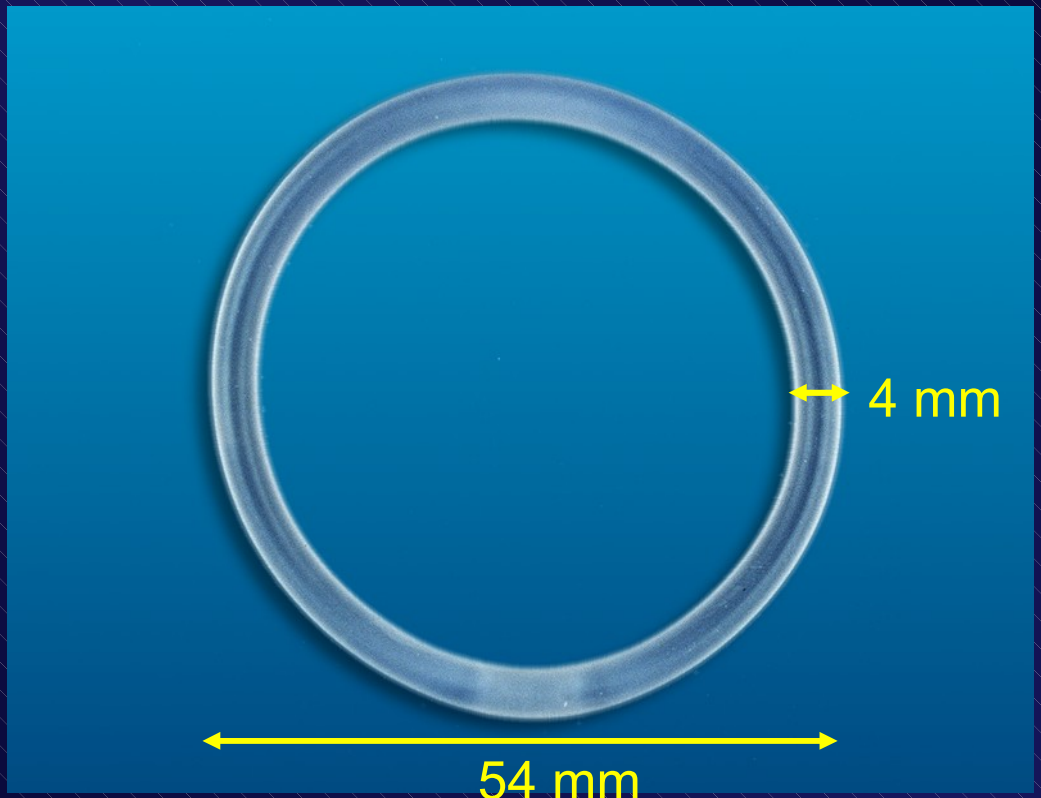
- Oral drugs must pass through the liver, where they undergo metabolism, a reduced amount of active drug available drugs may have to be given in higher doses.Drugs administered via the vagina are not subject to first- pass effect .



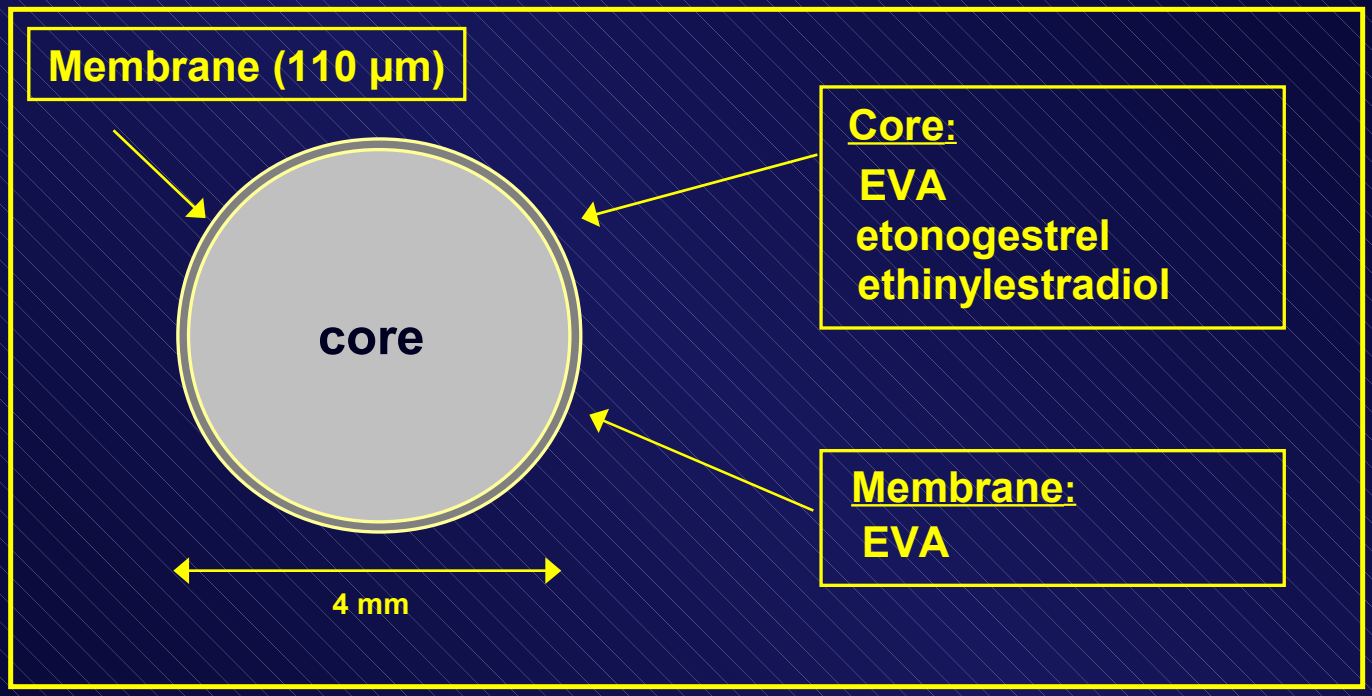
Vaginal Ring Developing History

- First prototype developed in the mid-1980s
- First clinical exposure in 1985
- Pharmaceutical redesign started in 1993
- Final clinical development started in 1997
- Global dossier submitted in 1999

NuvaRing

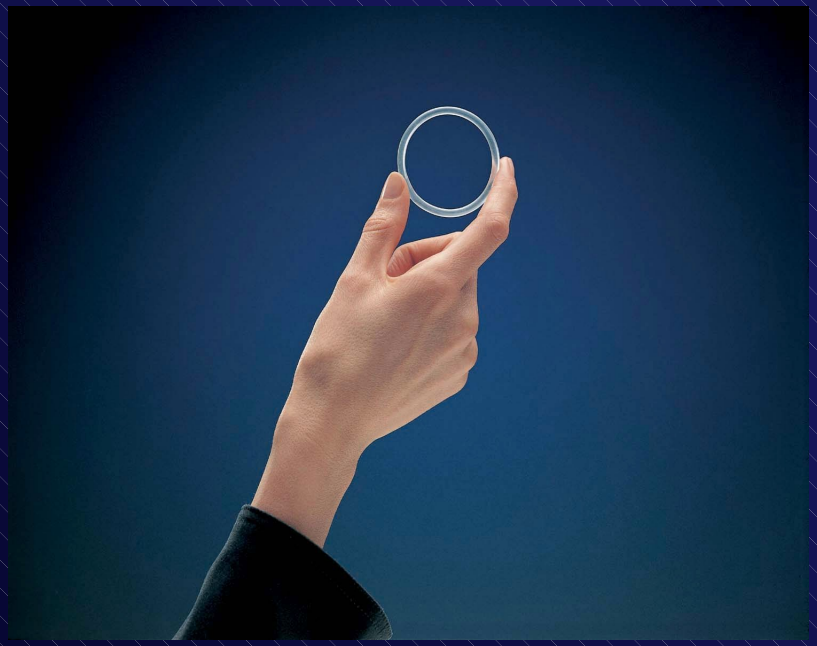


NuvaRing design



Polymers

NuvaRing is a nonabsorbent smooth plastic ring - bacteria cannot grow on it.



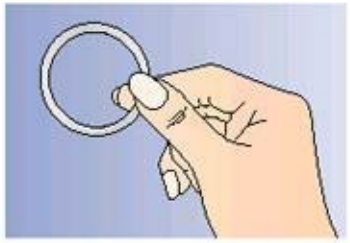


Figure 1 :
Otez NuvaRing® du sachet.

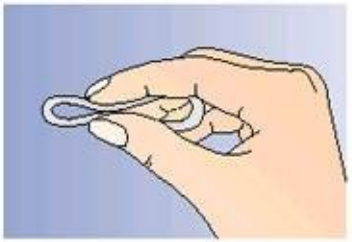


Figure 2 :
Pincez l'anneau.

Figure 3 :
Choisissez une position confortable pour insérer l'anneau.

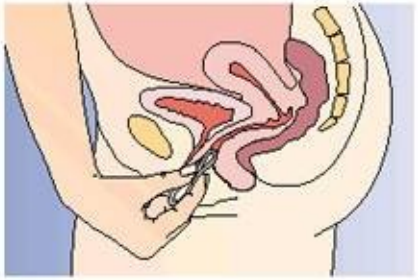


Figure 4A

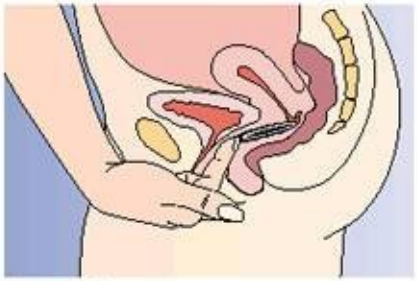


Figure 4B

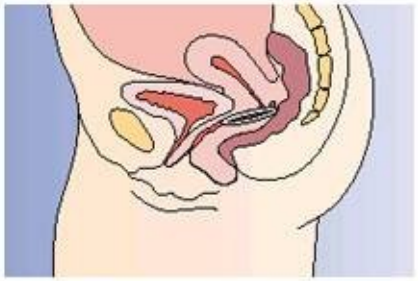
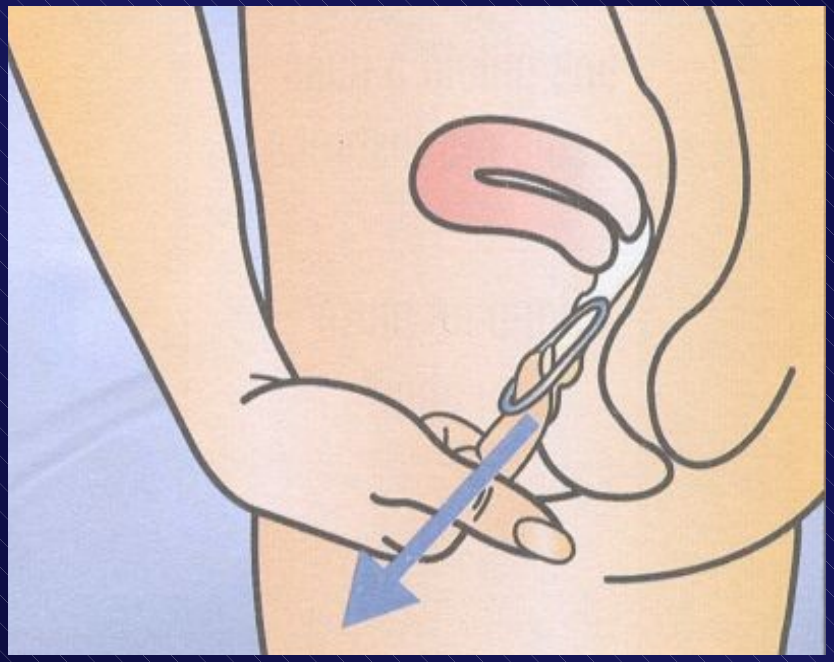


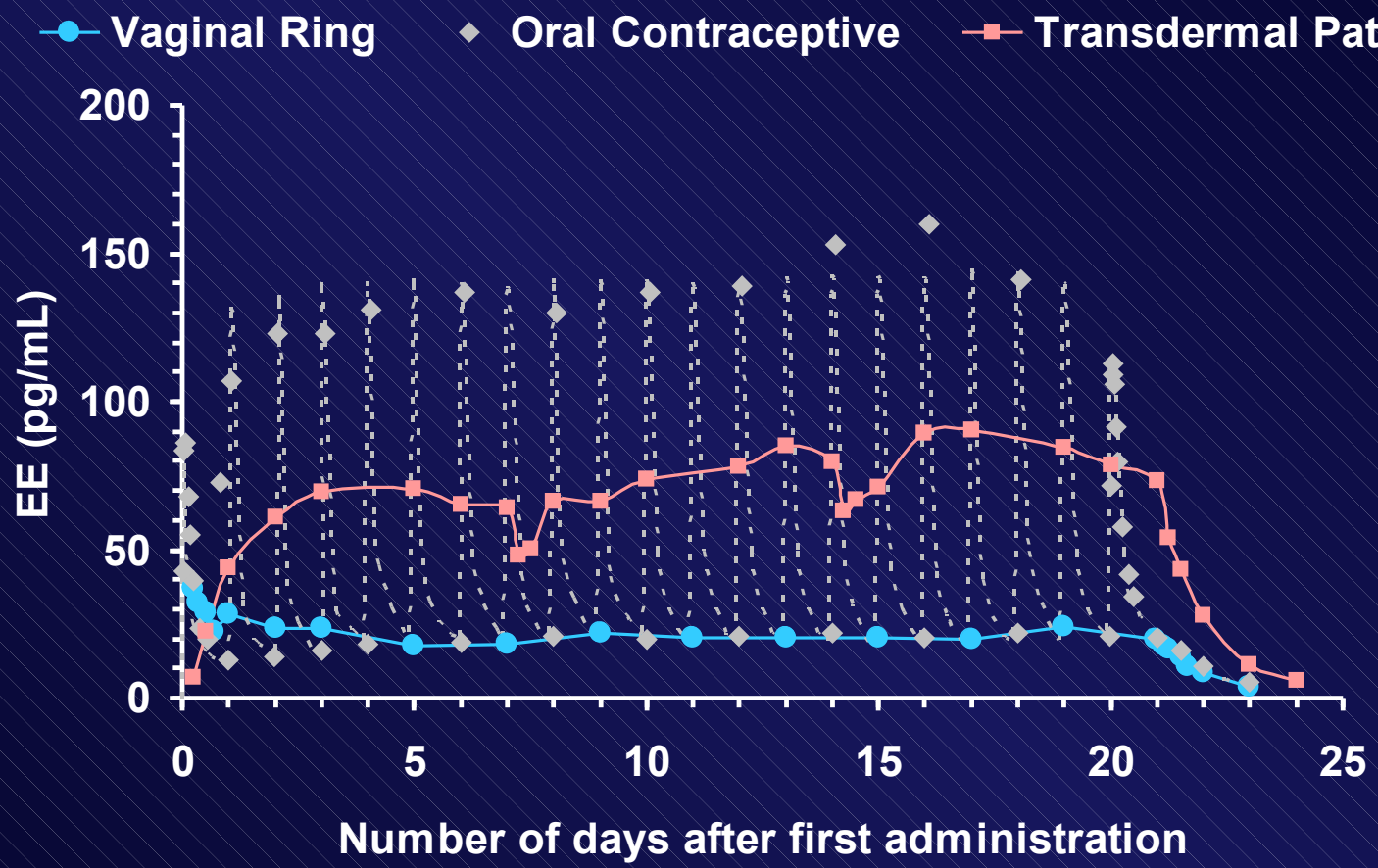
Figure 4C

Insérez l'anneau dans le vagin avec une main (Figure 4A), en écartant les lèvres à l'aide de l'autre main si nécessaire. Poussez l'anneau dans le vagin jusqu'à ce qu'aucune gêne ne soit perçue (Figure 4B). **Laissez l'anneau en place pendant 3 semaines** (Figure 4C).



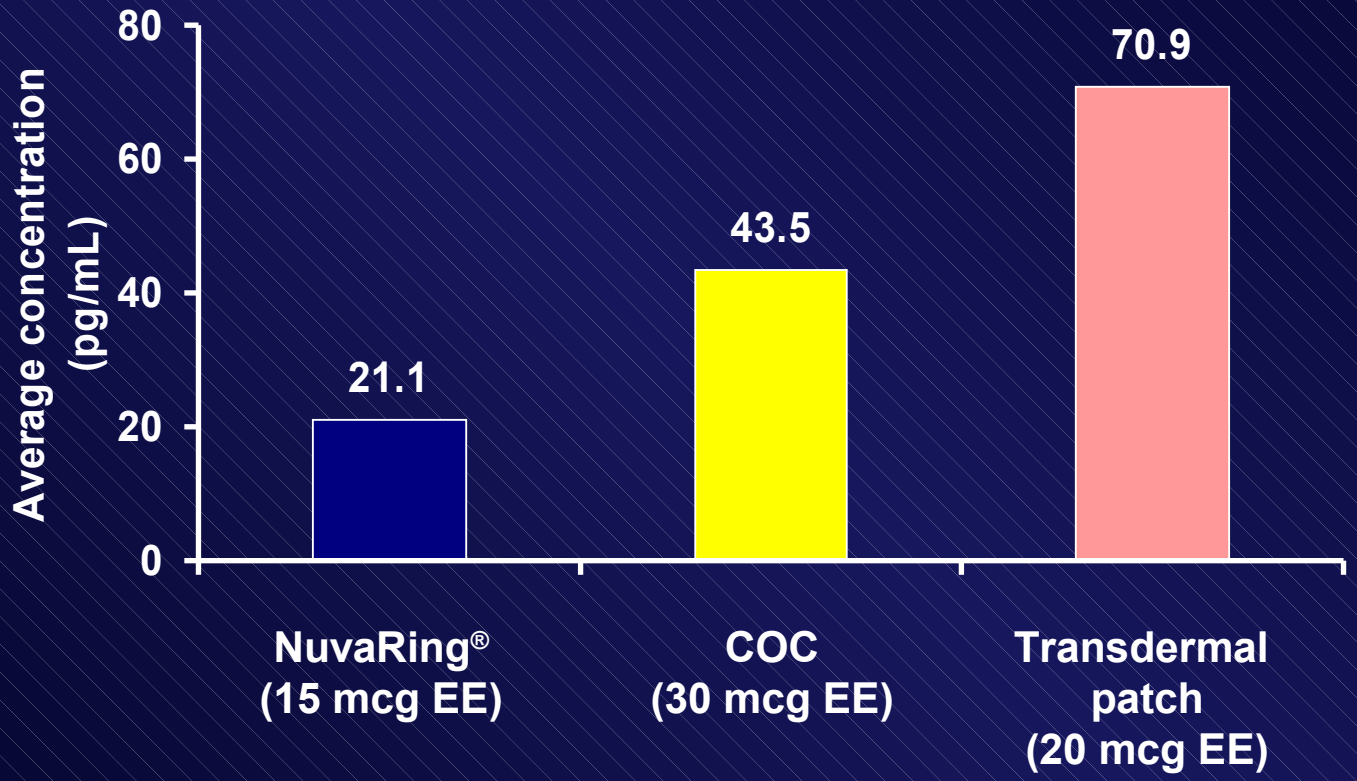

Pharmacokinetics and Drug Interactions
Kunsthistorisches Museum Wien,
Gemäldegalerie, Vienna

Comparison Chart of EE Serum Levels



Reference: van den Heuvel MW et al. *Contraception*. 2005;72:168-174.

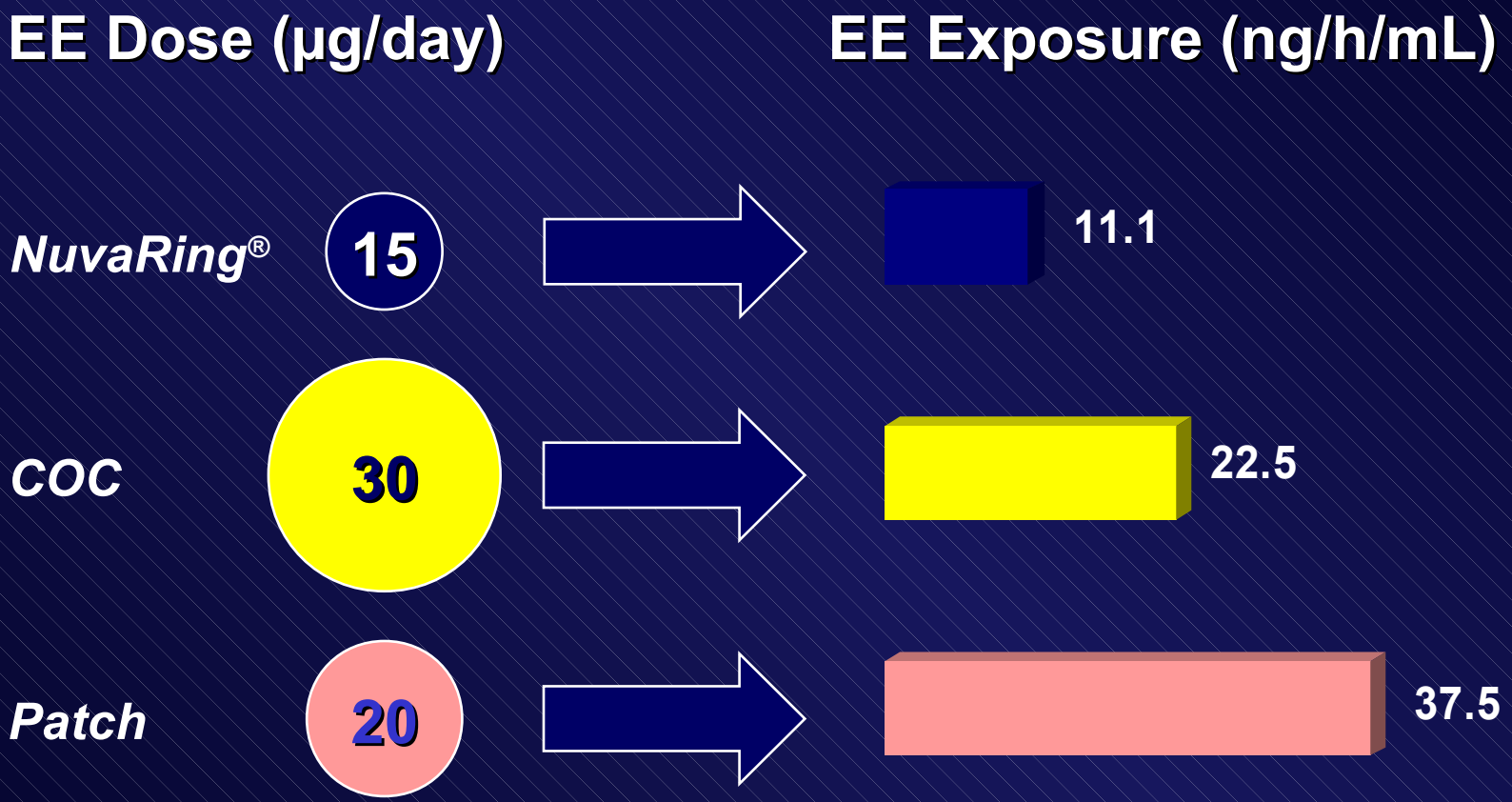
Average Serum EE Concentrations



All differences statistically significant.

Reference: van den Heuvel MW et al. *Contraception*. 2005;72:168-174.

Correlation of EE Dose and Exposure



Reference: van den Heuvel MW et al. *Contraception*. 2005;72:168-174.

NuvaRing

Summary of pharmacokinetics and drug interactions

- No daily fluctuations in serum hormone concentrations
- EE exposure is half of that with a 30 µg COC
- ENG exposure is comparable with the COC 30 EE/150 DSG
- Spermicide or antimycotic coadministration have not been shown to impair hormone release and/or absorption


Ovulation inhibition
Kunsthistorisches Museum Wien,
Gemäldegalerie, Vienna

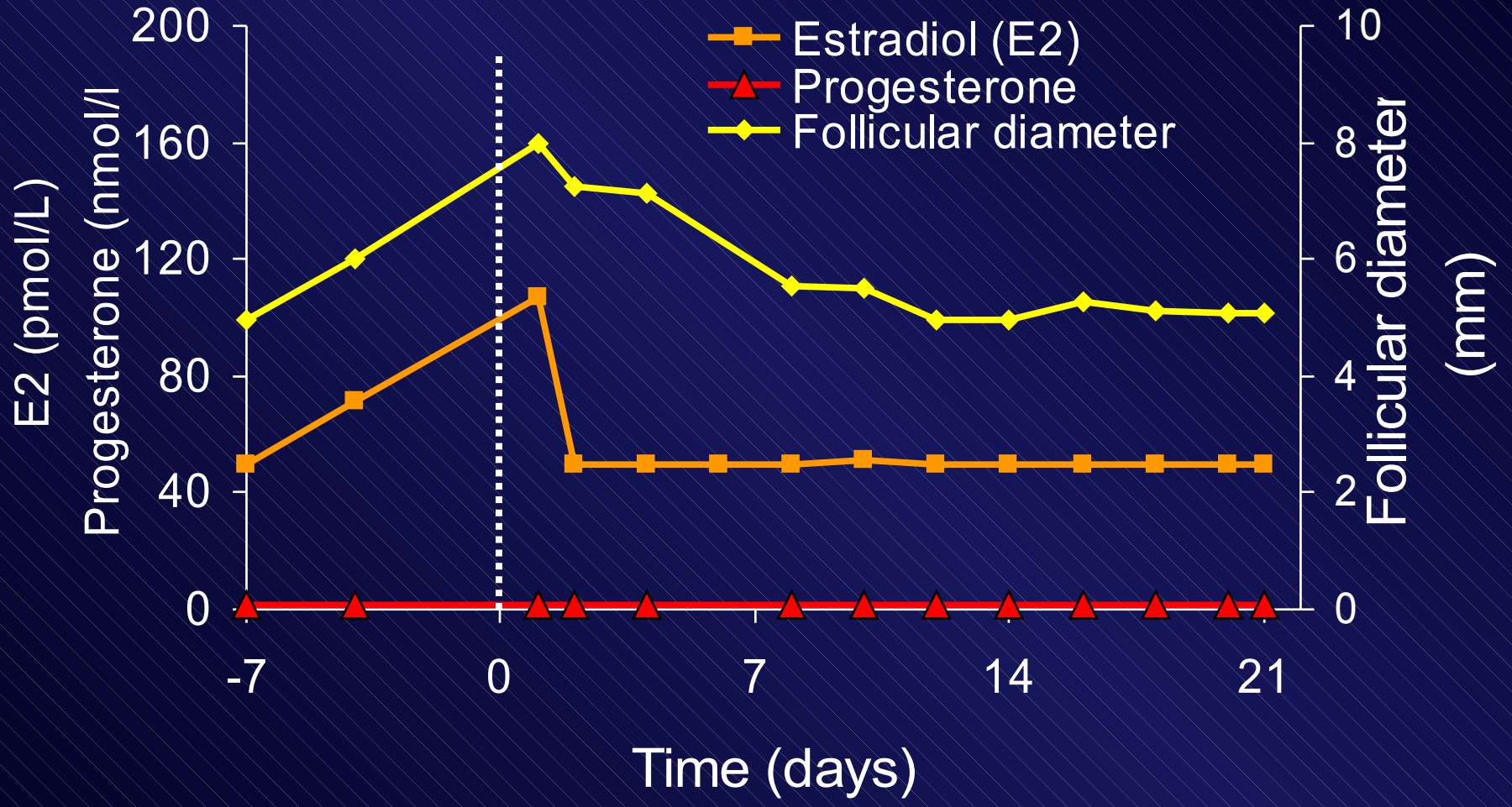
Ovulation inhibition with NuvaRing
Study design

- Ovarian function assessed by:
  - Vaginal ultrasound
  - Serum hormone concentrations
- 16 women enrolled
- Women used NuvaRing continuously for 3 weeks

Mulders & Dieben, Fertil Steril, 2001;75:865–70

Ovulation inhibition with NuvaRing

Median follicular diameter, E2 and P concentrations



Mulders & Dieben, Fertil Steril, 2001;75:865–70

Ovulation inhibition with NuvaRing
Summary

- During the 3 weeks of continuous NuvaRing use:
  - Largest follicles and estradiol levels occurred in first week
  - FSH concentrations were low
  - LH surge did not occur
  - Progesterone levels were low (<2.9 nmol/L)
- Ovulation was completely inhibited during NuvaRing use

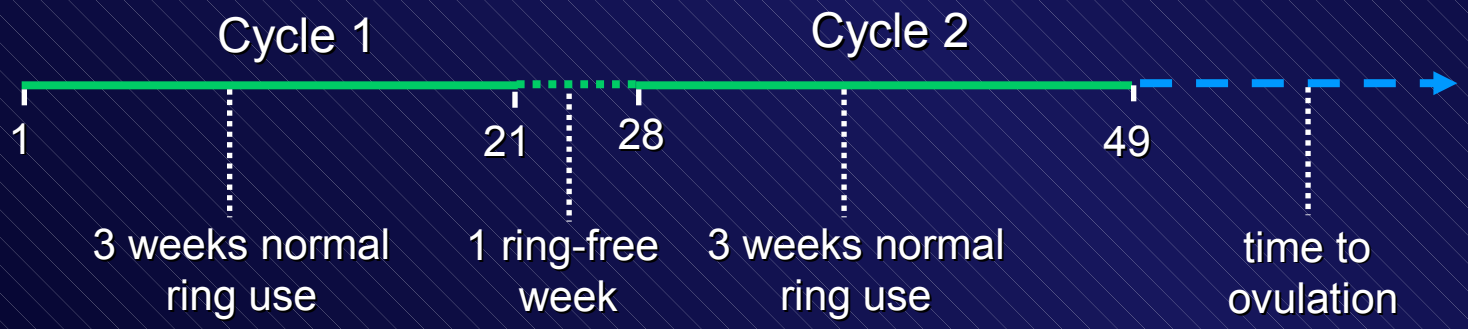
Mulders & Dieben, Fertil Steril, 2001;75:865–70

Return to ovulation after ring removal

Study design

- Time needed for return of ovulation after completing 2 normal cycles of NuvaRing use

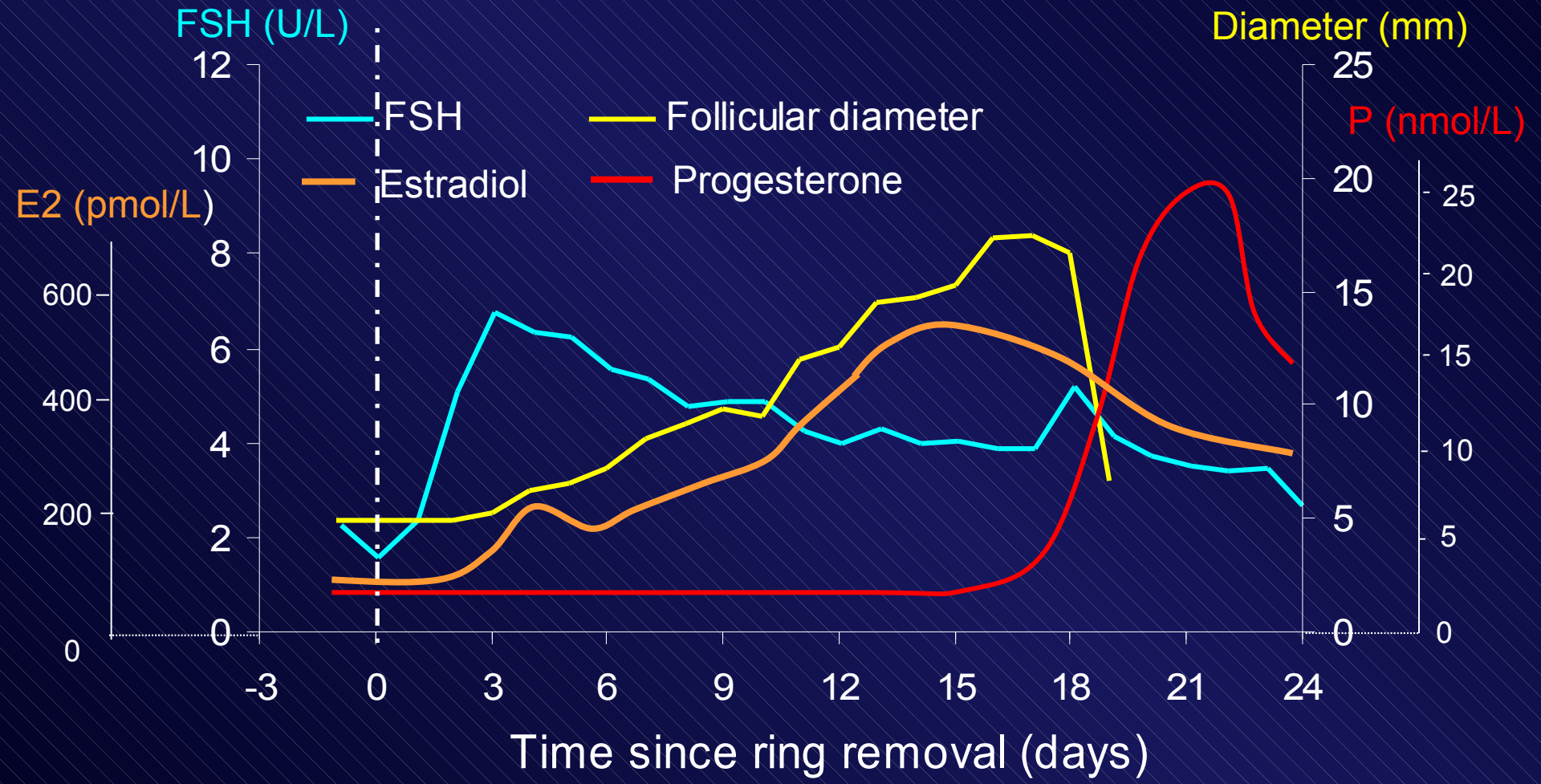
- Study design:



Mulders et al, Hum Reprod, 2002;17:2594–9

Return to ovulation after ring removal

Median follicular diameter, FSH, E2 and P concentrations



Mulders et al, Hum Reprod, 2002;17:2594–9

Return to ovulation after ring removal

- After ring removal:
  - FSH peak after 3 days
  - LH surge after 17 days
  - Maximum follicular diameter approx 18 mm
- The median time to ovulation was 19 days (range 13 to >28 days)
- There is a rapid return to ovulation following ring removal

Mulders et al, Hum Reprod, 2002;17:2594–9

Ovarian activity after deviations from the recommended regimen

Investigated deviations from regimen:

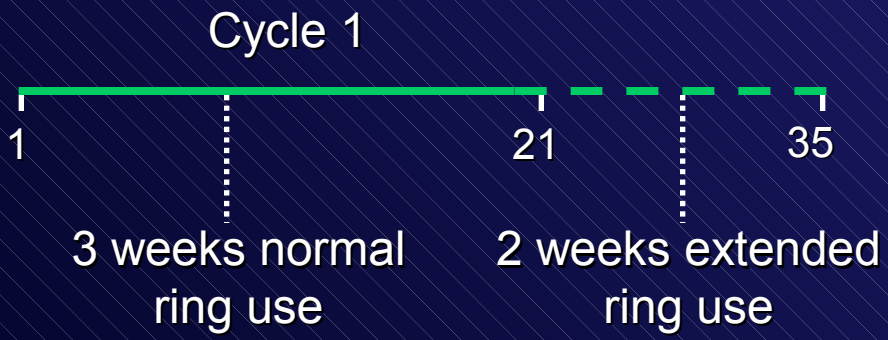
1. Forgotten ring removal[1]
2. Early ring removal[2]
3. Delayed ring insertion[2]

[1]*Mulders & Dieben, Fertil Steril, 2001;75:865–70*
[2]*Mulders et al, Hum Reprod, 2002;17:2594–9*

Forgotten ring removal
Study design

- Ovarian activity was assessed during the 3 weeks of recommended ring use and during a 2-week extended ring-use period (n=16)

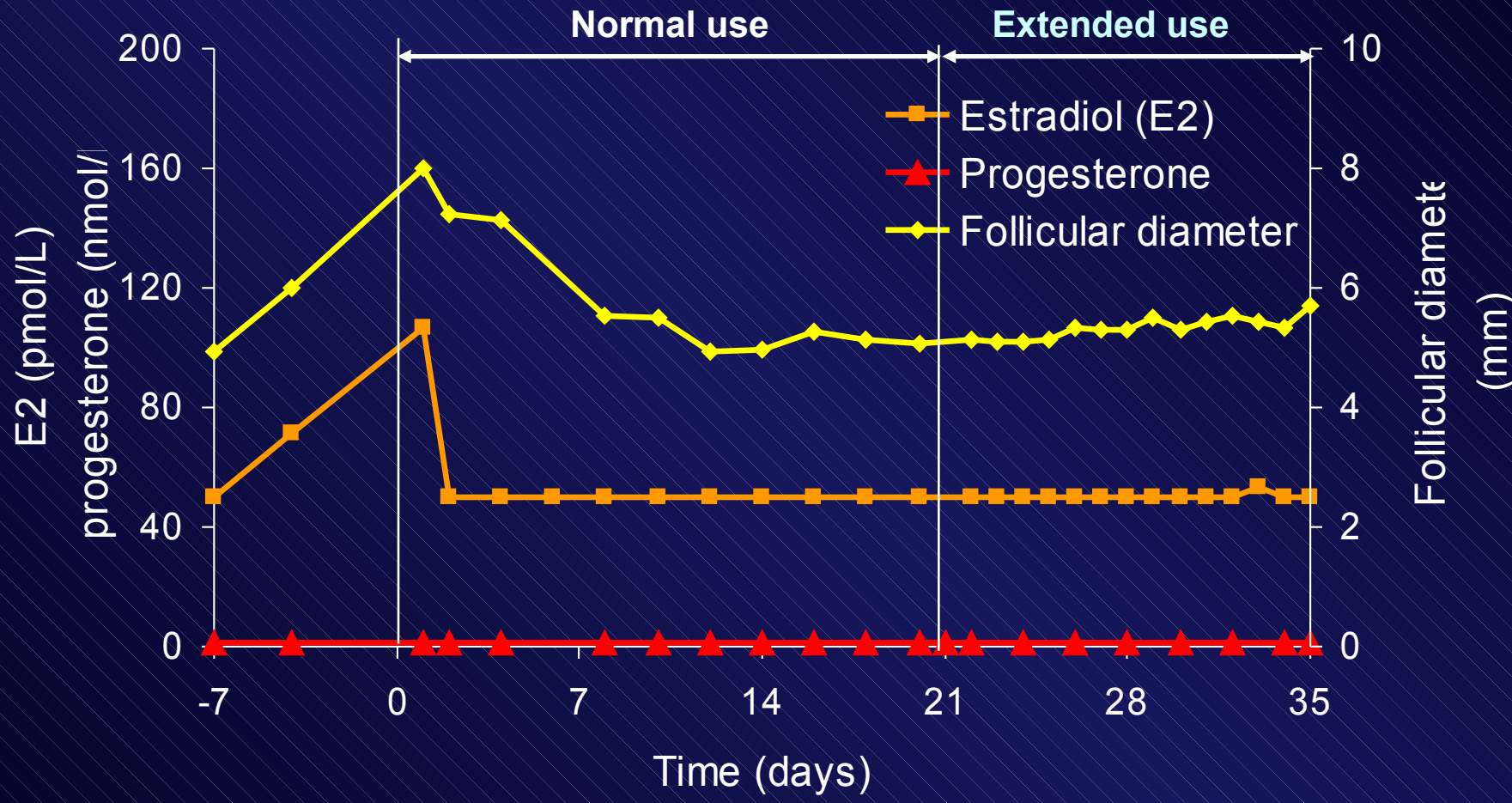
- Study design:



Mulders & Dieben, Fertil Steril, 2001;75:865–70

Forgotten ring removal

Median follicular diameter, E2 and P concentrations



Mulders & Dieben, Fertil Steril, 2001;75:865–70

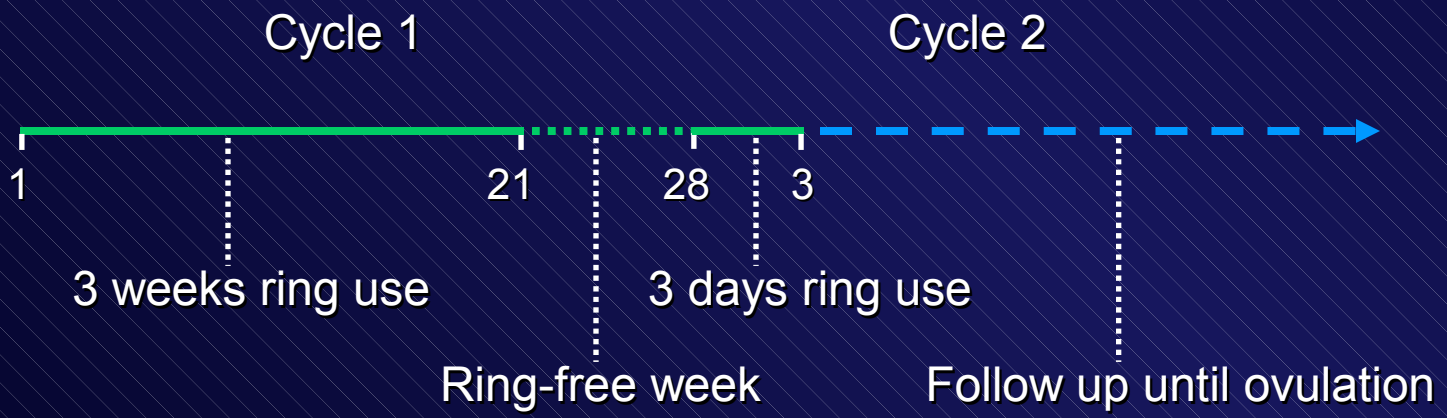
Forgotten ring removal
Summary

- Ovulation remains completely inhibited when the recommended 3-week ring-use period is extended by two weeks
- However, for general population, only 1 week of extended ring-use is advised to maintain adequate contraceptive efficacy

Mulders & Dieben, Fertil Steril, 2001;75:865–70

Early ring removal
Study design

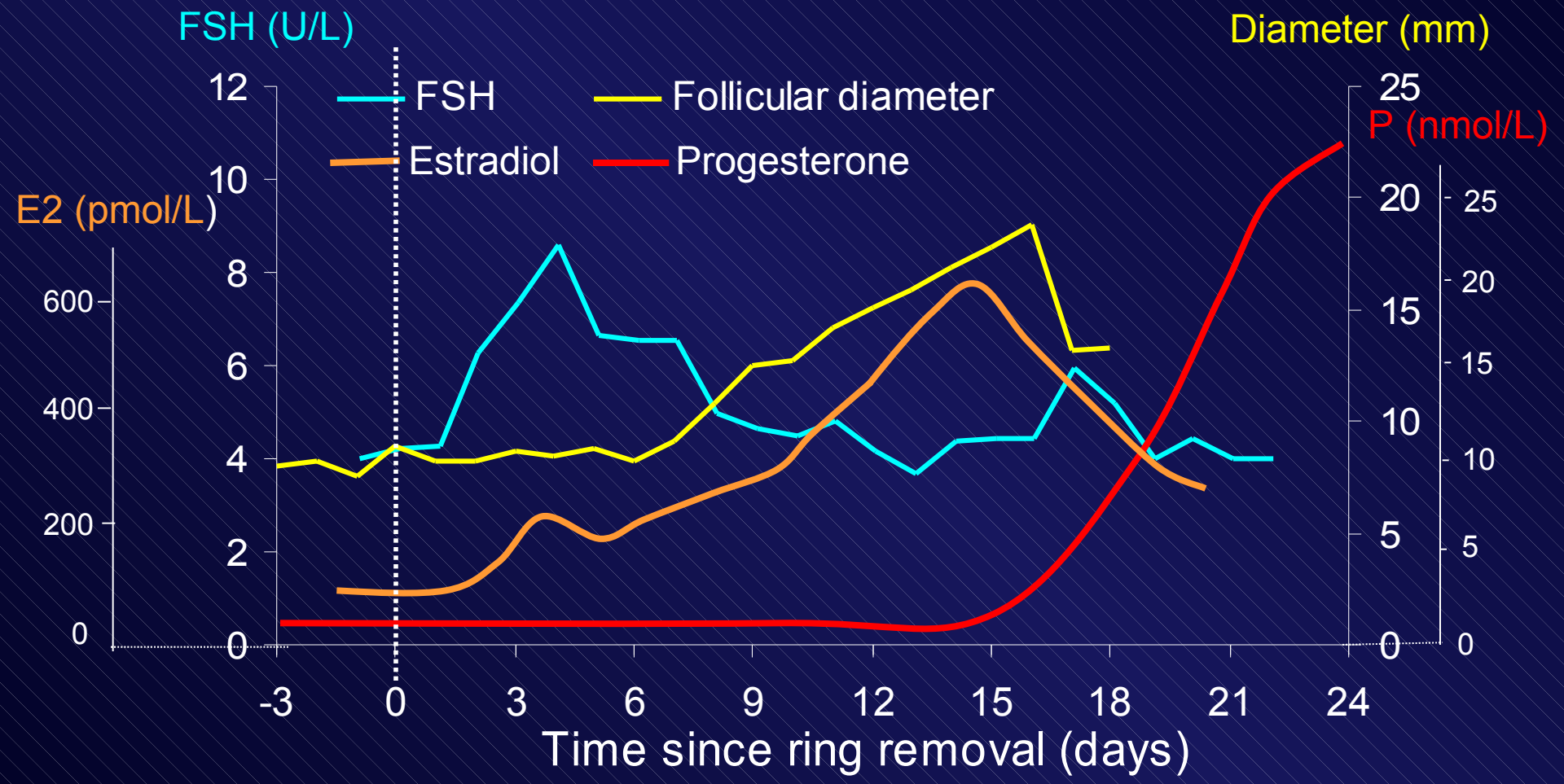
- Ovarian function was assessed in 15 women who removed the ring after only 3 days of use
- Study design:



Mulders et al, Hum Reprod, 2002;17:2594–9

Early ring removal

Median follicular diameter, FSH, E2 and P concentrations



Mulders et al, Hum Reprod, 2002;17:2594–9

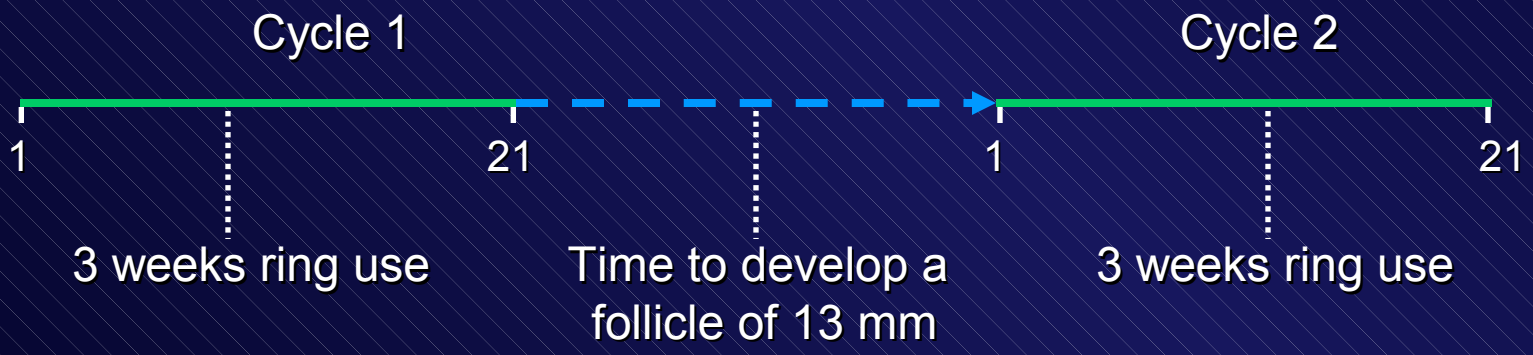
Ovarian activity after early ring removal

- Ovarian activity after early ring removal was comparable with that after recommended use
- Median time to ovulation was 17 days (range 12 to >28 days)
- In the event of early ring removal, a new cohort of follicles has to be recruited
- Three days of NuvaRing use is sufficient to suppress the HPO axis

Mulders et al, Hum Reprod, 2002;17:2594–9

Delayed ring insertion
Study design

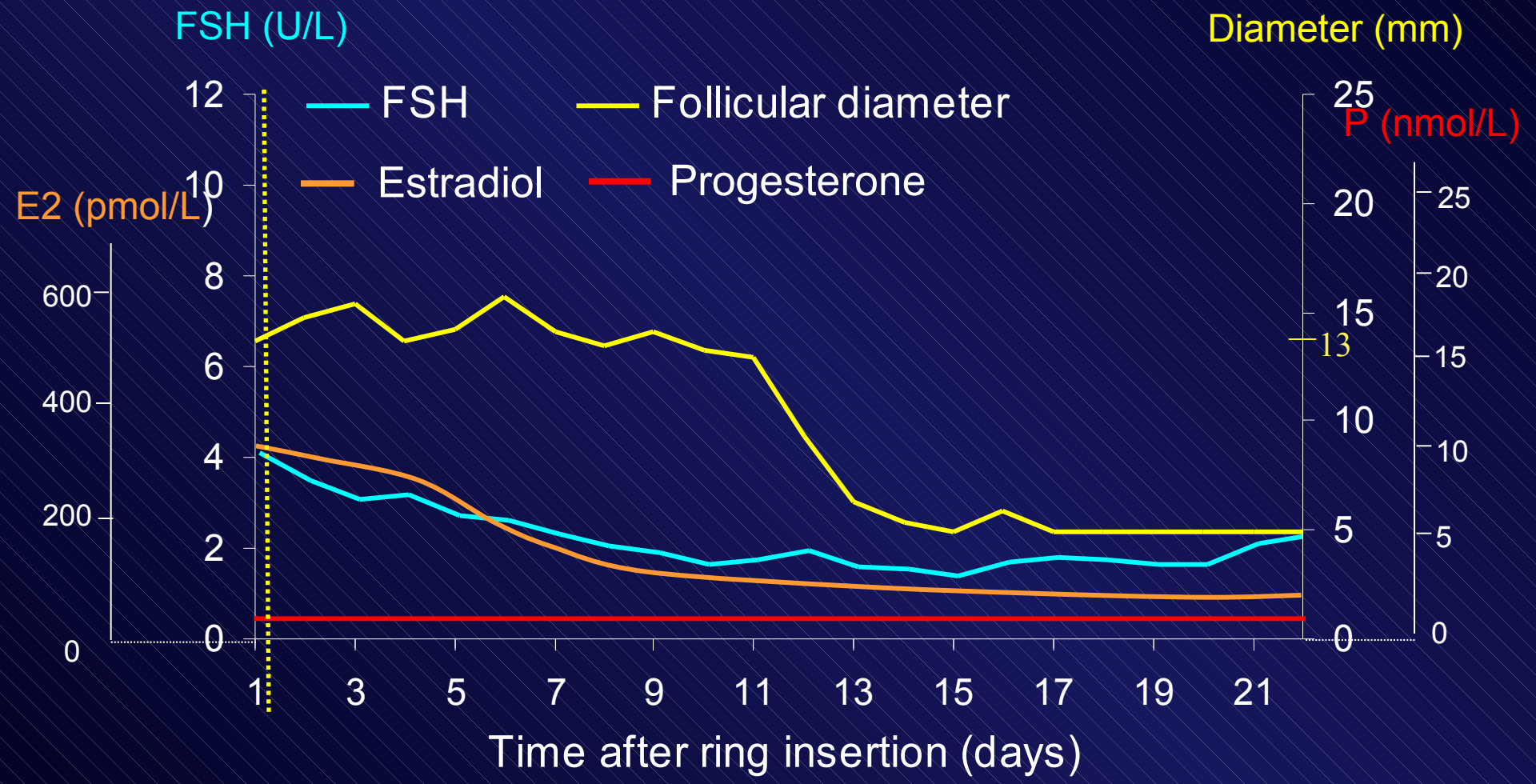
- Ovarian function was assessed in 15 women who delayed insertion of the second ring until a 13 mm follicle was detected
- Study design:



Mulders et al, Hum Reprod, 2002;17:2594–9

Delayed ring insertion

Median follicular diameter, FSH, E2 and P concentrations

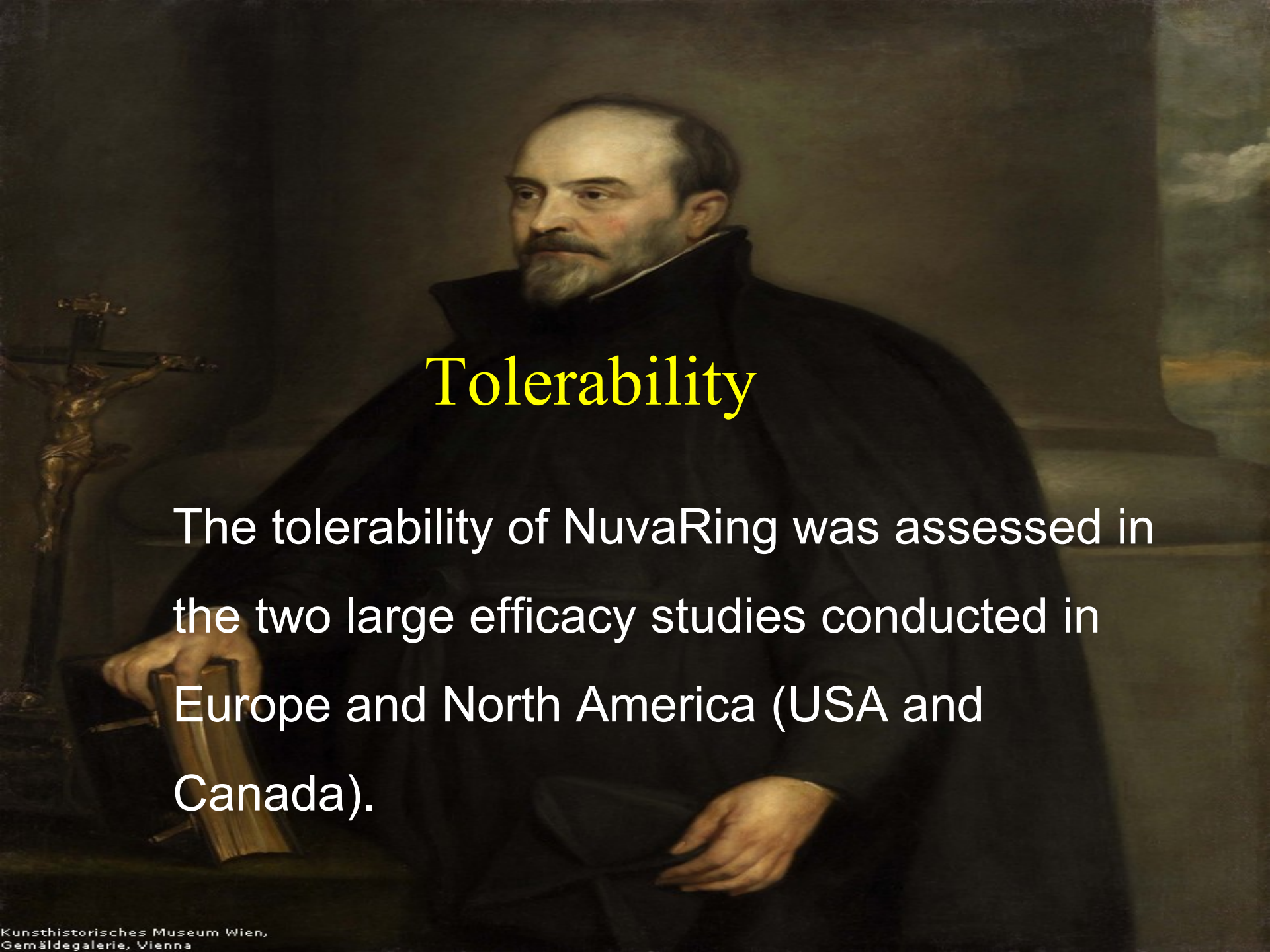


Mulders et al, Hum Reprod, 2002;17:2594–9

Ovarian activity after delayed ring insertion

- Median time to develop a 13 mm follicle was 11 days (range 8–21 days)
- After insertion of the second ring, no women ovulated
- Using NuvaRing can block the development of follicles up to 13 mm in diameter

Mulders et al, Hum Reprod, 2002;17:2594–9



Tolerability

The tolerability of NuvaRing was assessed in the two large efficacy studies conducted in Europe and North America (USA and Canada).

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Gemäldegalerie, Vienna

Tolerability of NuvaRing

Data from the European efficacy study:

- 52 centers in 12 different countries.
- 1182 women enrolled; 1145 women treated
- 1 year duration (up to 13 cycles of ring use)
- Incidence of adverse events and effect on body weight were assessed

Roumen et al, Hum Reprod, 2001;16:469–75

Incidence of adverse events
(n=1145)

Adverse event	Treatment-related	Total
Headache	6.6%	11.8%
Nausea	2.8%	4.5%
Breast tenderness	1.9%	2.8%
Acne	1.1%	1.6%

Roumen et al, Hum Reprod, 2001;16:469–75

Incidence of local adverse events
(n=1145)

Adverse event	Treatment-related	Total
Leukorrhea	5.3%	5.9%
Vaginitis	5.0%	13.7%
Device-related events	3.8%	4.1%
Vaginal discomfort	2.2%	2.4%

Roumen et al, Hum Reprod, 2001;16:469–75

Adverse events resulting in study discontinuation

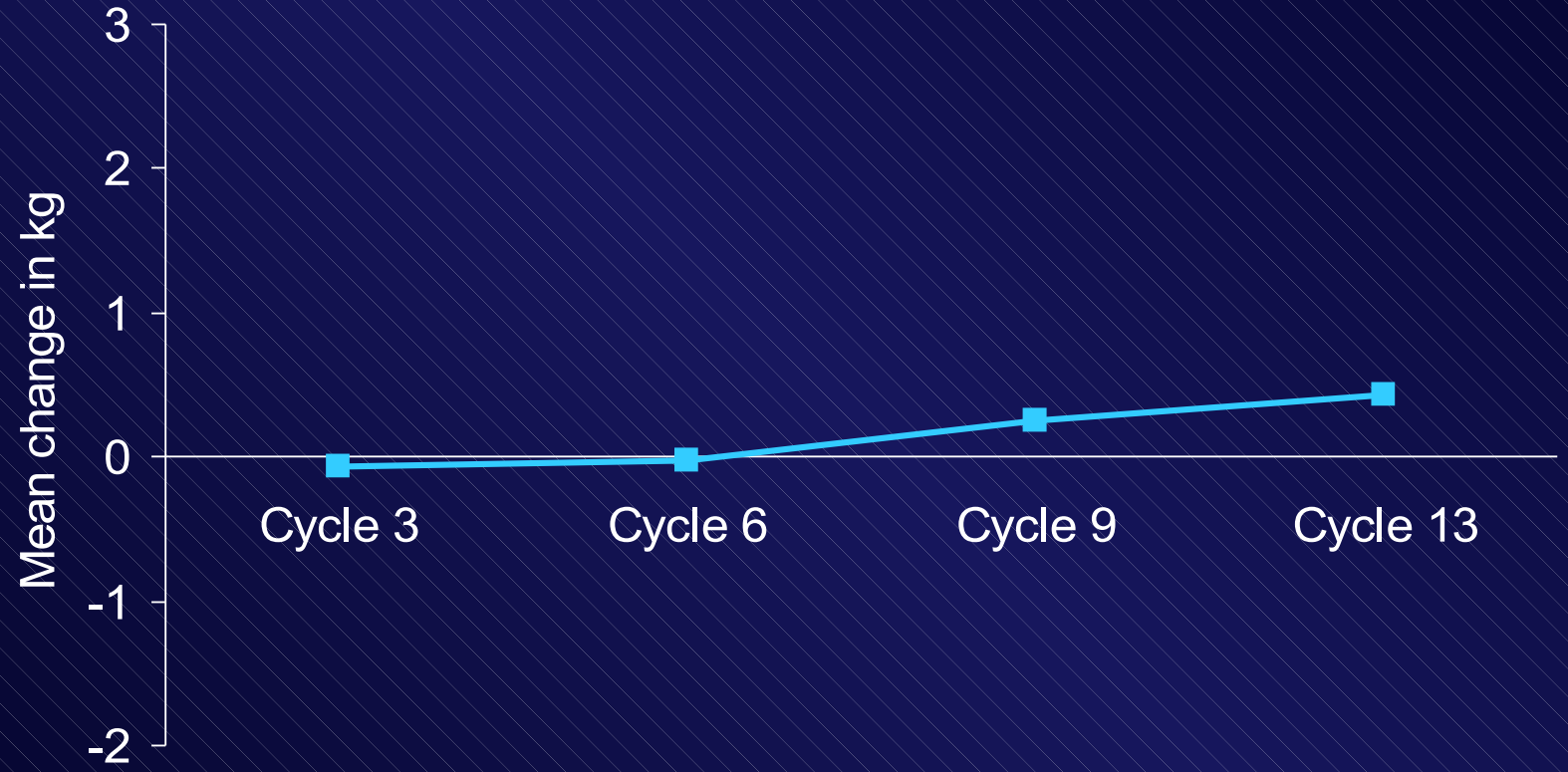
(discontinuation rate 15.1%; n=173)

Adverse event	Percentage of women (%) n=1145
Device-related events	2.6%
Headache	2.1%
Vaginal discomfort	1.0%
Nausea	1.0%
Bleeding irregularities	0.1%
Vaginitis	0.6%

Roumen et al, Hum Reprod, 2001;16:469–75

Effect of NuvaRing on body weight

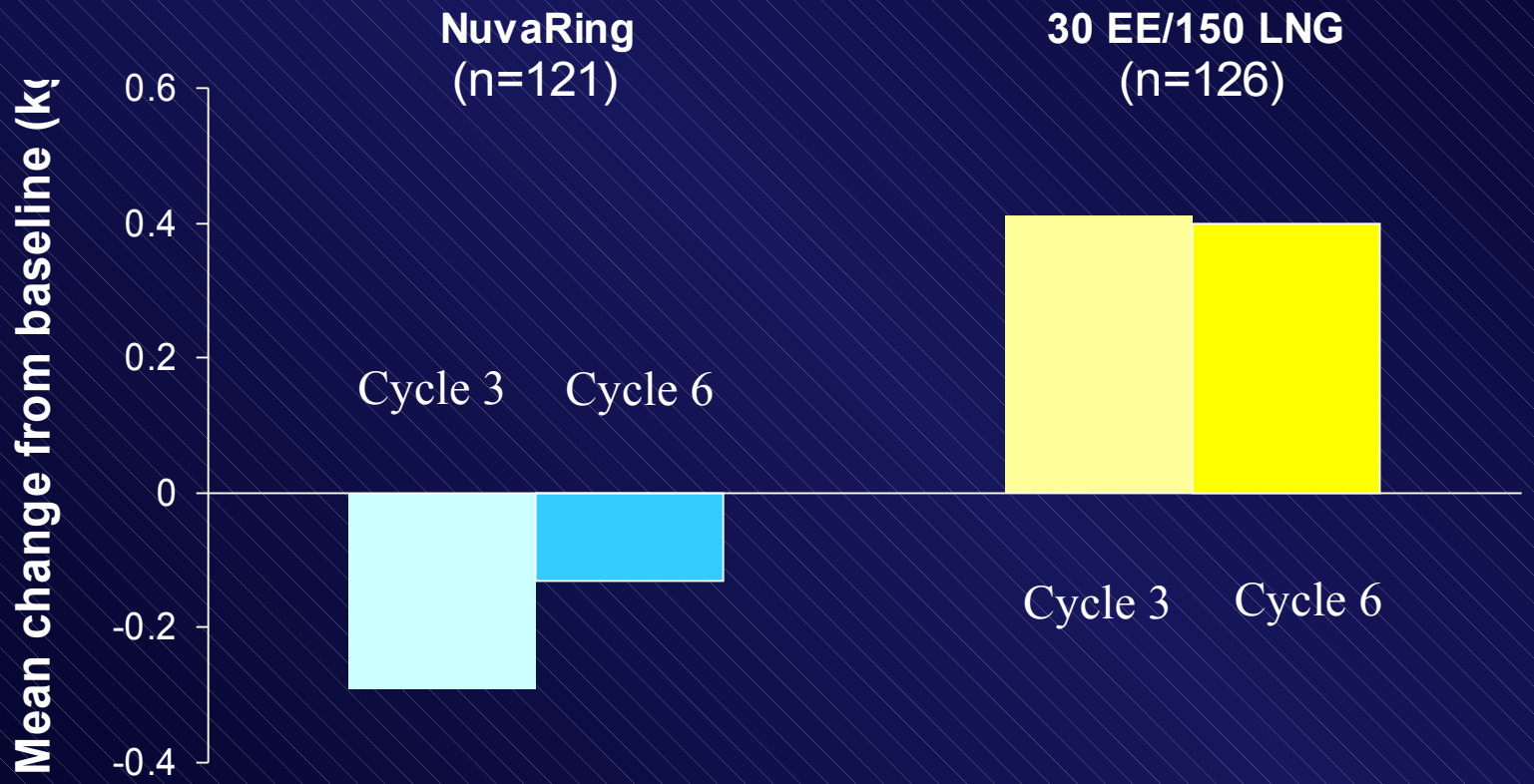
Mean change from baseline (n=1145)



Roumen et al, Hum Reprod, 2001;16:469–75

Effect of NuvaRing on body weight

Comparison with COC after cycles 3 and 6



Bjarnadóttir et al, Am J Obstet Gynecol, 2002;186:389–95

Tolerability of NuvaRing
Summary

- NuvaRing is well tolerated.
- NuvaRing has a low incidence of adverse events such as headache, nausea, breast tenderness.
- NuvaRing has a neutral effect on body weight.

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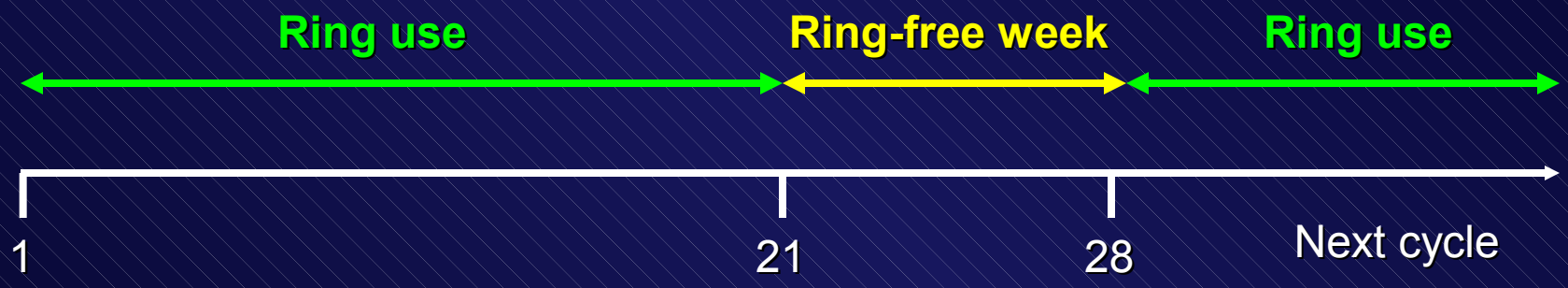
Gemäldegalerie, Vienna

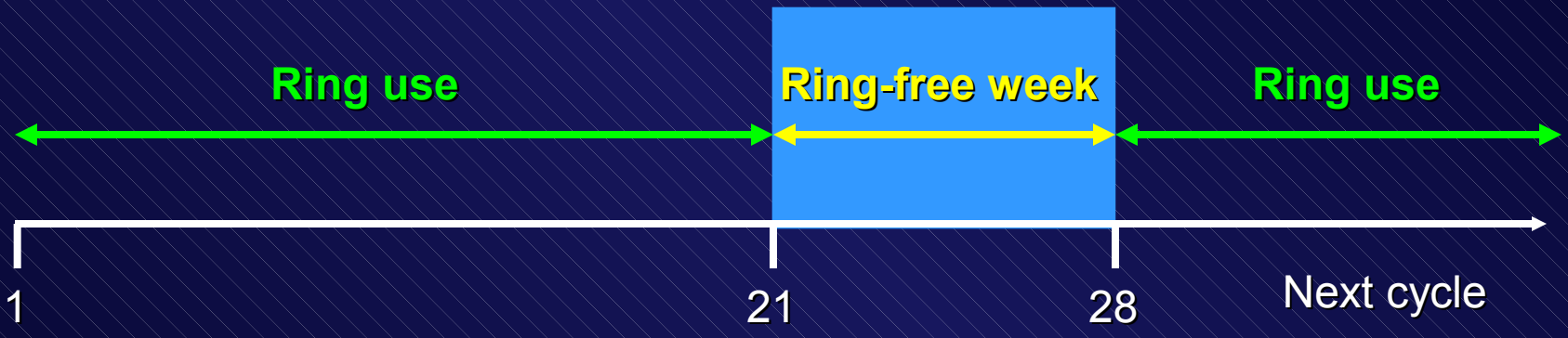
Cycle control

Each NuvaRing is intended for one cycle of use.



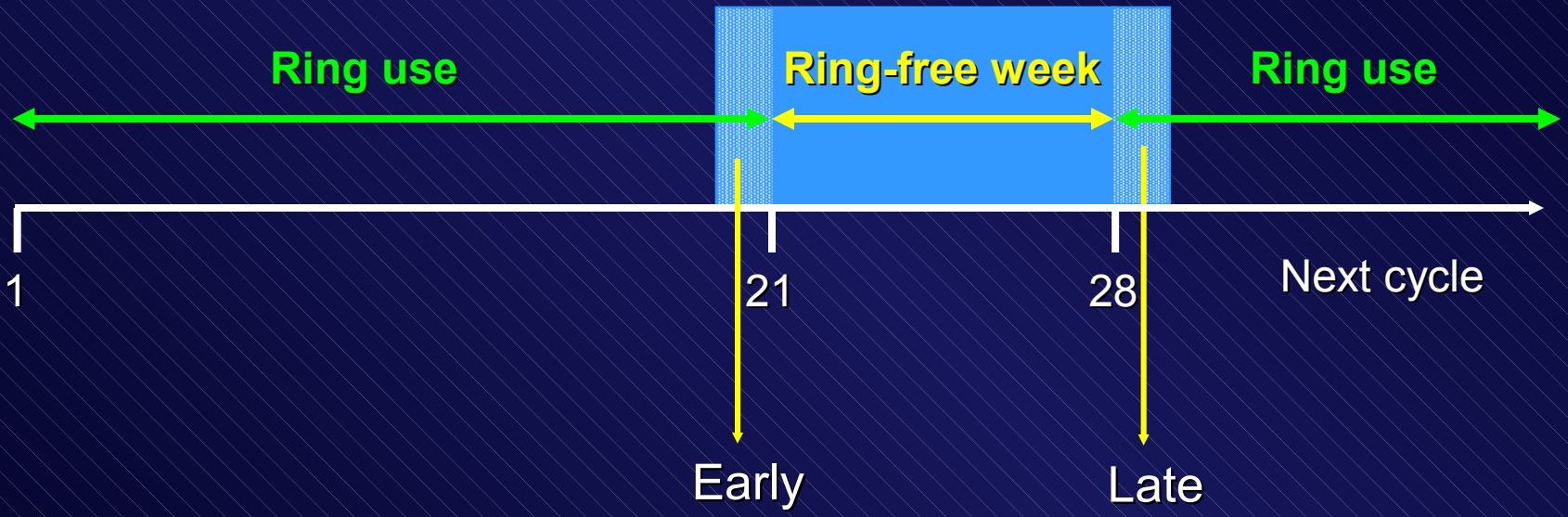
Cycle control

Definition: Withdrawal bleeding



Cycle control

Definitions: Early and late withdrawal bleeding

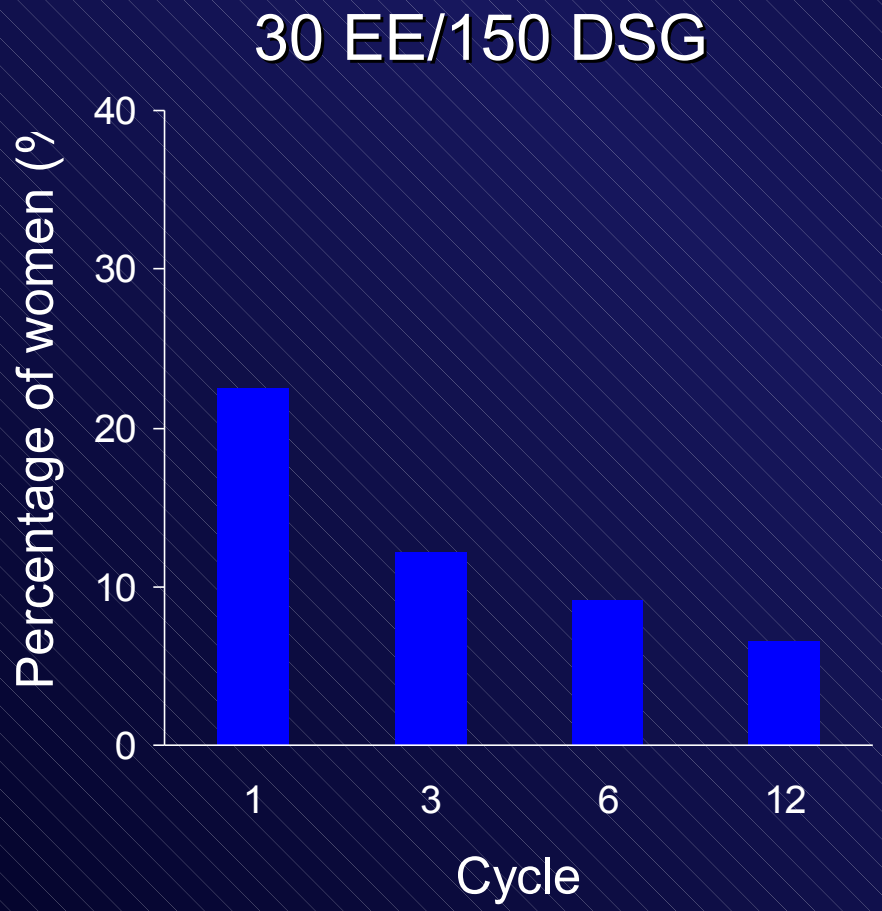


Cycle control

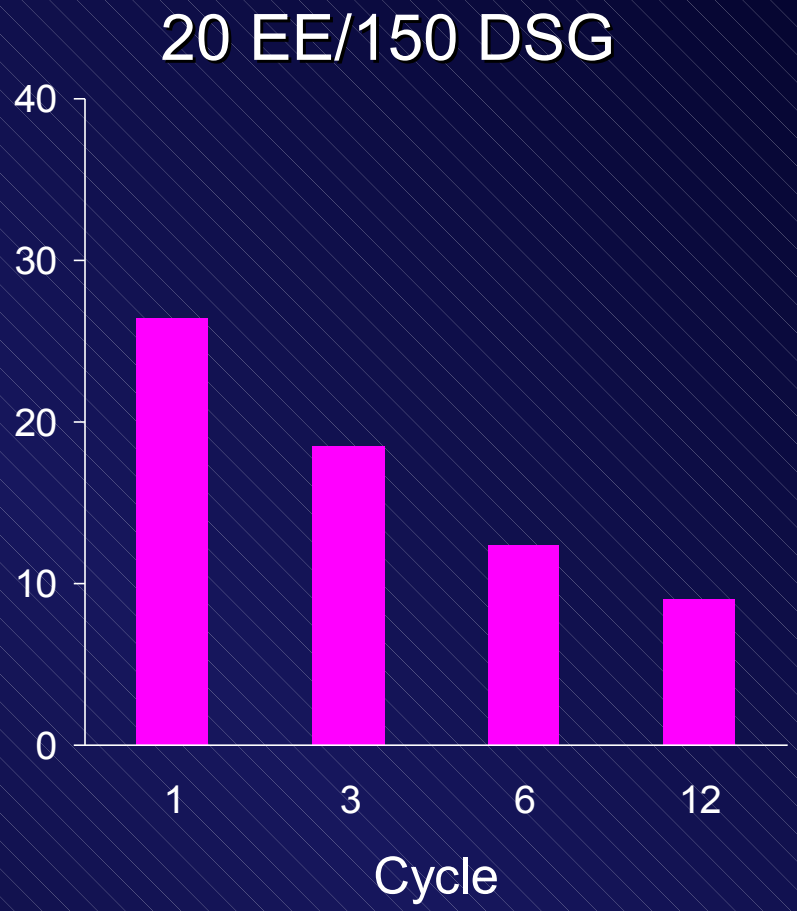
Definition: Irregular bleeding(breakthrough bleeding ; spotting)

Cycle control with desogestrel COCs

Incidence of irregular bleeding



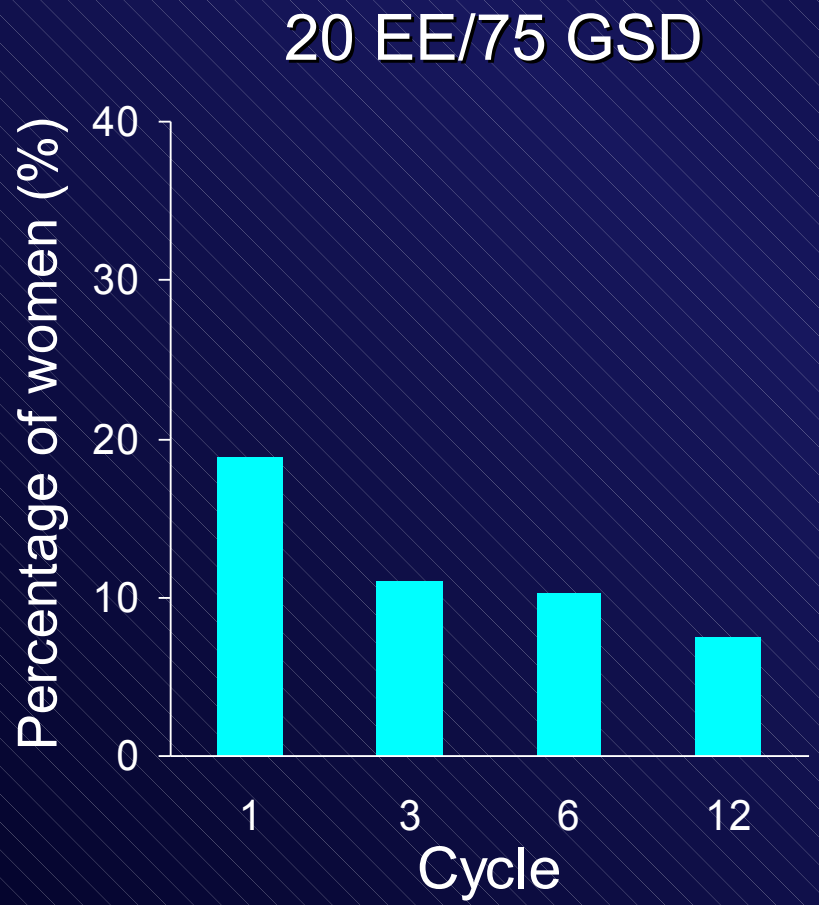
Rekers, Acta Obstet Gynecol Scand, 1988;67:171–4

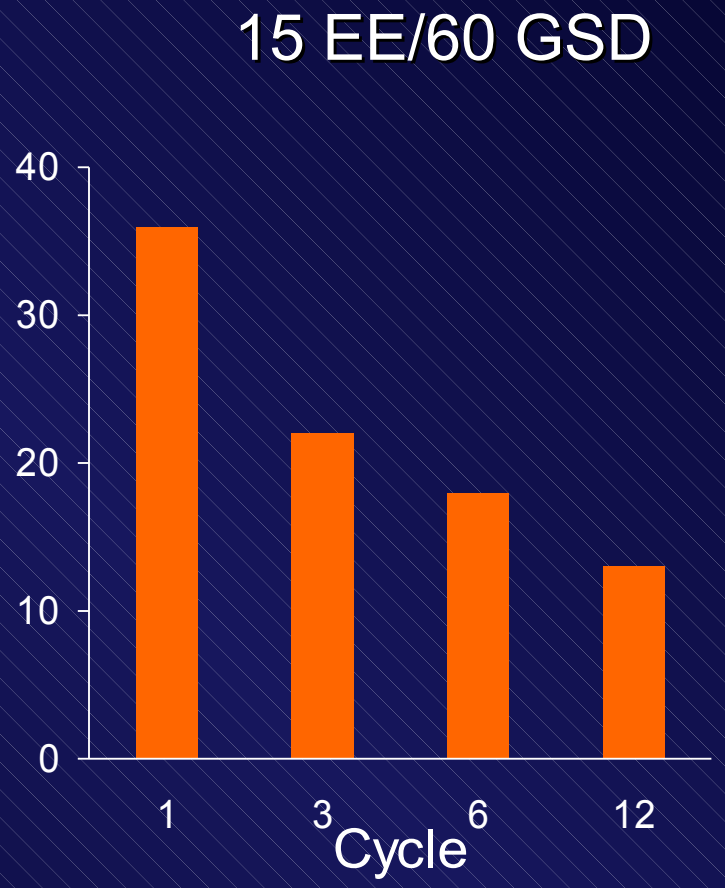


Lammers & Op ten Berg, Acta Obstet Gynecol Scand, 1991;70:497–500

Cycle control with gestodene COCs

Incidence of irregular bleeding

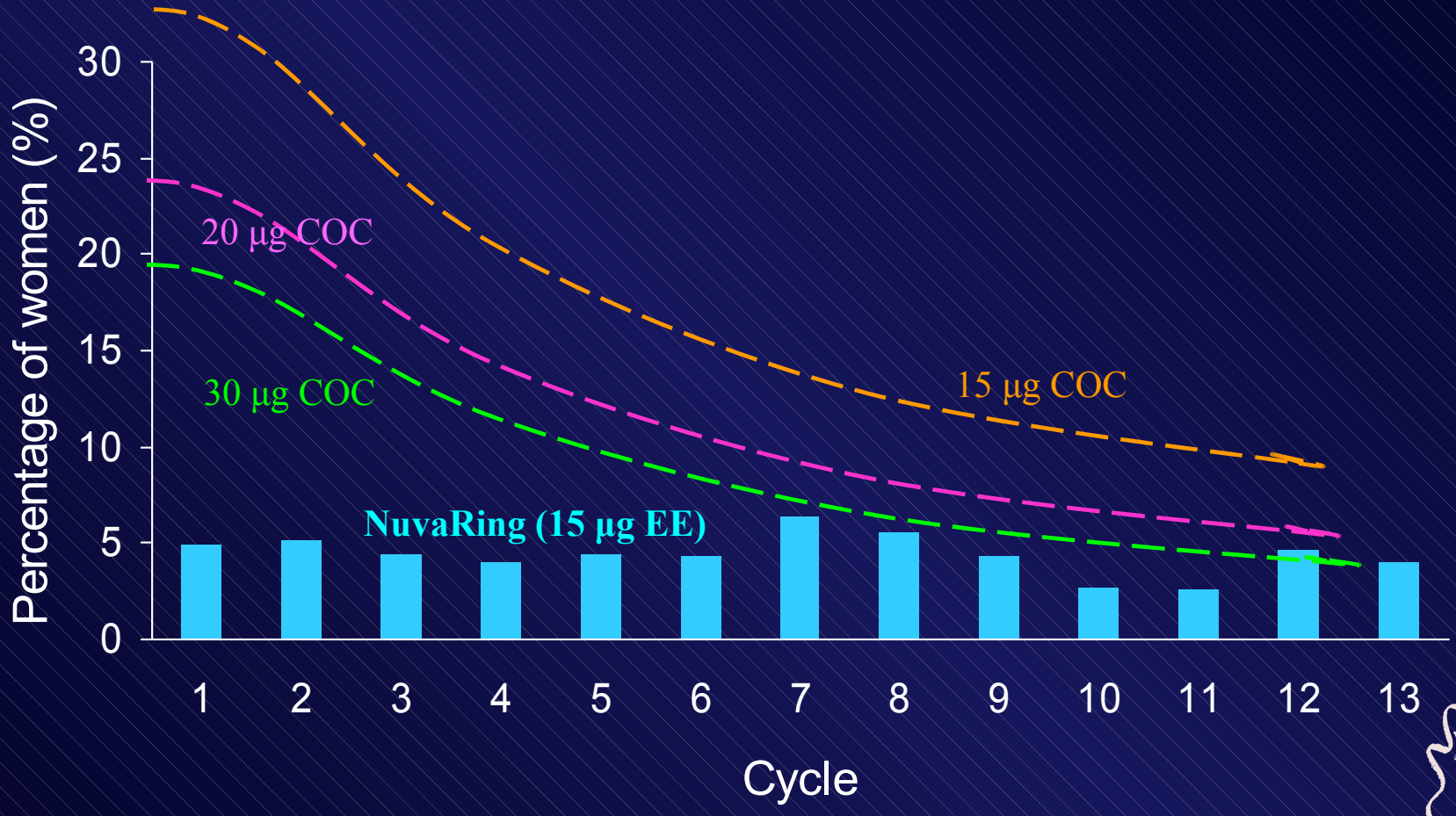




Düsterberg et al, Gynecol Endocrinol, 1996;10:33–9

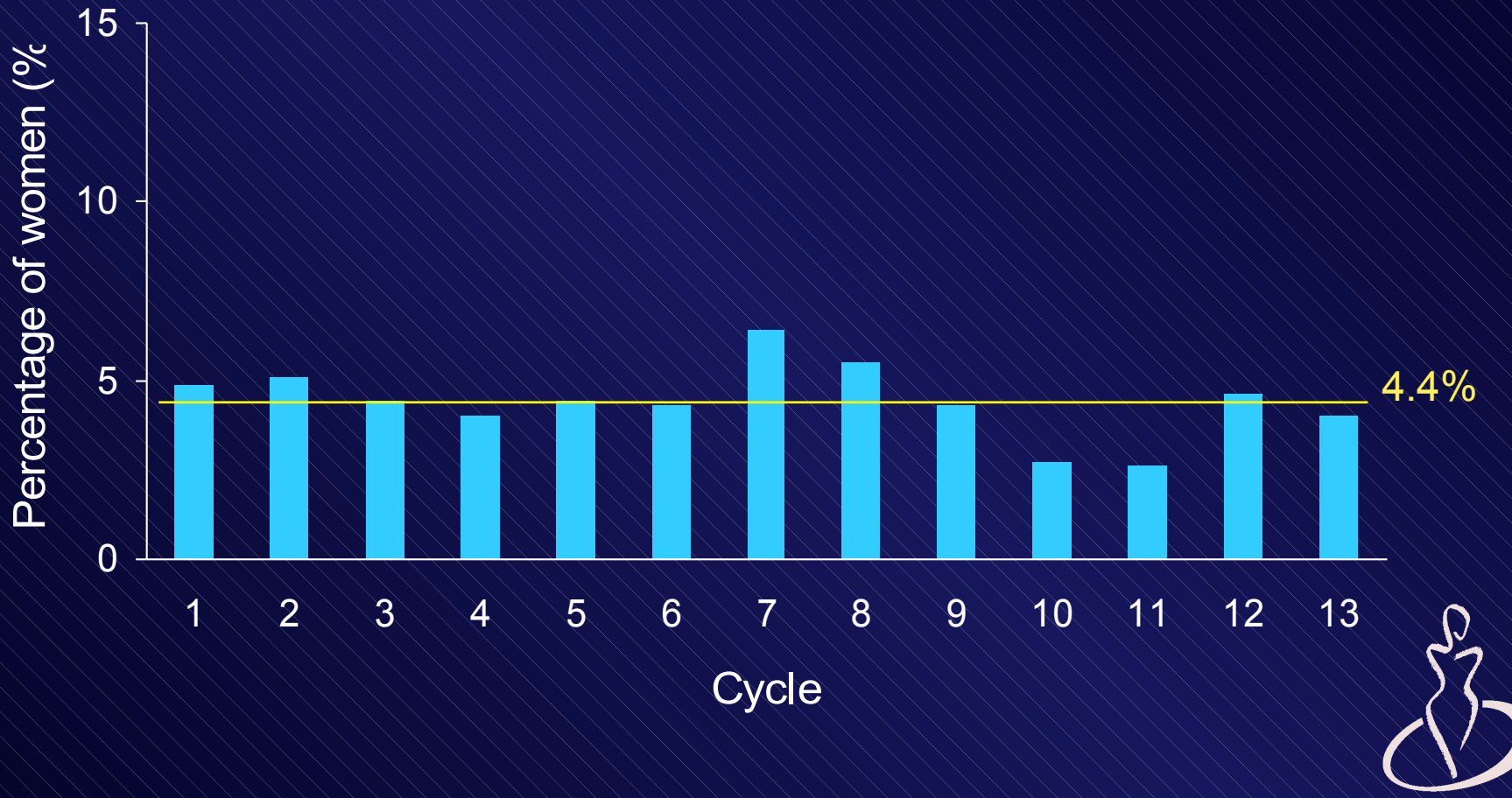
Gestodene study group, Eur J Contracept Reprod Health Care, 1999;4(suppl 2):9–15

Irregular bleeding with NuvaRing
(n=1182)



Roumen et al, Hum Reprod, 2001;16:469–75

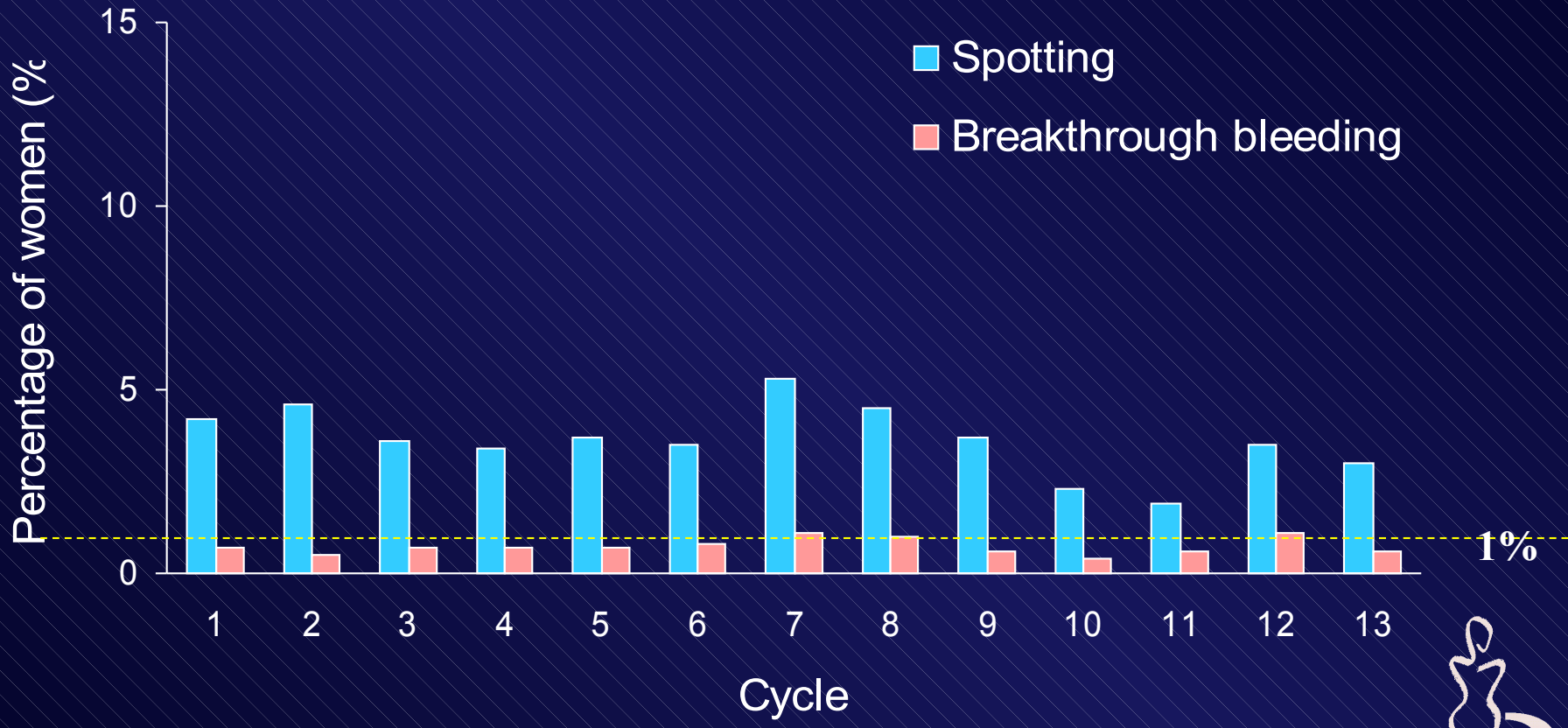
Irregular bleeding with NuvaRing
(n=1182)



Roumen et al, Hum Reprod, 2001;16:469–75

Irregular bleeding with NuvaRing

Breakthrough bleeding and spotting (n=1182)

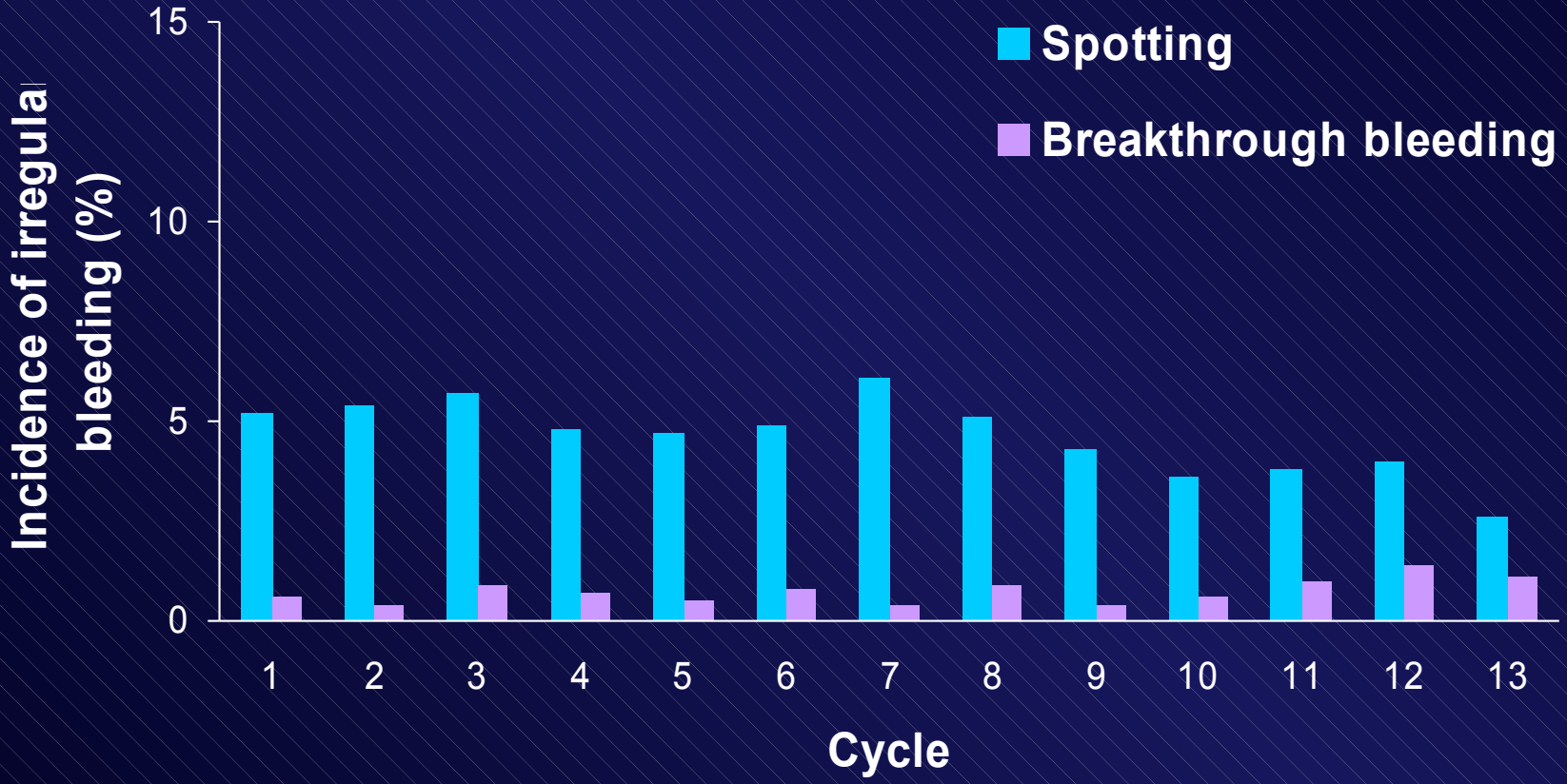


Roumen et al, Hum Reprod, 2001;16:469–75

Irregular bleeding with NuvaRing

Combined European and North American studies (n=2322)

Breakthrough bleeding and spotting



Dieben et al, Obstet Gynecol, 2002;100:585–93

Cycle control with NuvaRing
Summary

- Excellent cycle control with a daily dose of 15 µg EE
- Cycle control superior to that with a 30 EE/150 LNG COC
- Excellent cycle control is probably due to the continuous stable release of hormones from the ring


Safety aspects
Kunsthistorisches Museum Wien,
Gemäldegalerie, Vienna

NuvaRing: safety aspects

- Effect on metabolic parameters
  - Lipid metabolism
  - Carbohydrate metabolism
  - Hemostatic variables
- Effect on blood pressure
- Local cervical and vaginal effects
- Effect on SHBG and CBG concentrations

The metabolic studies
Design

- 3 separate comparative studies; 90 women each
- NuvaRing vs. a COC containing 30 EE/150 LNG
- OCs not used for at least one month prior to study start
- Treatment duration: 6 cycles
- Assessments at baseline, cycles 3 and 6

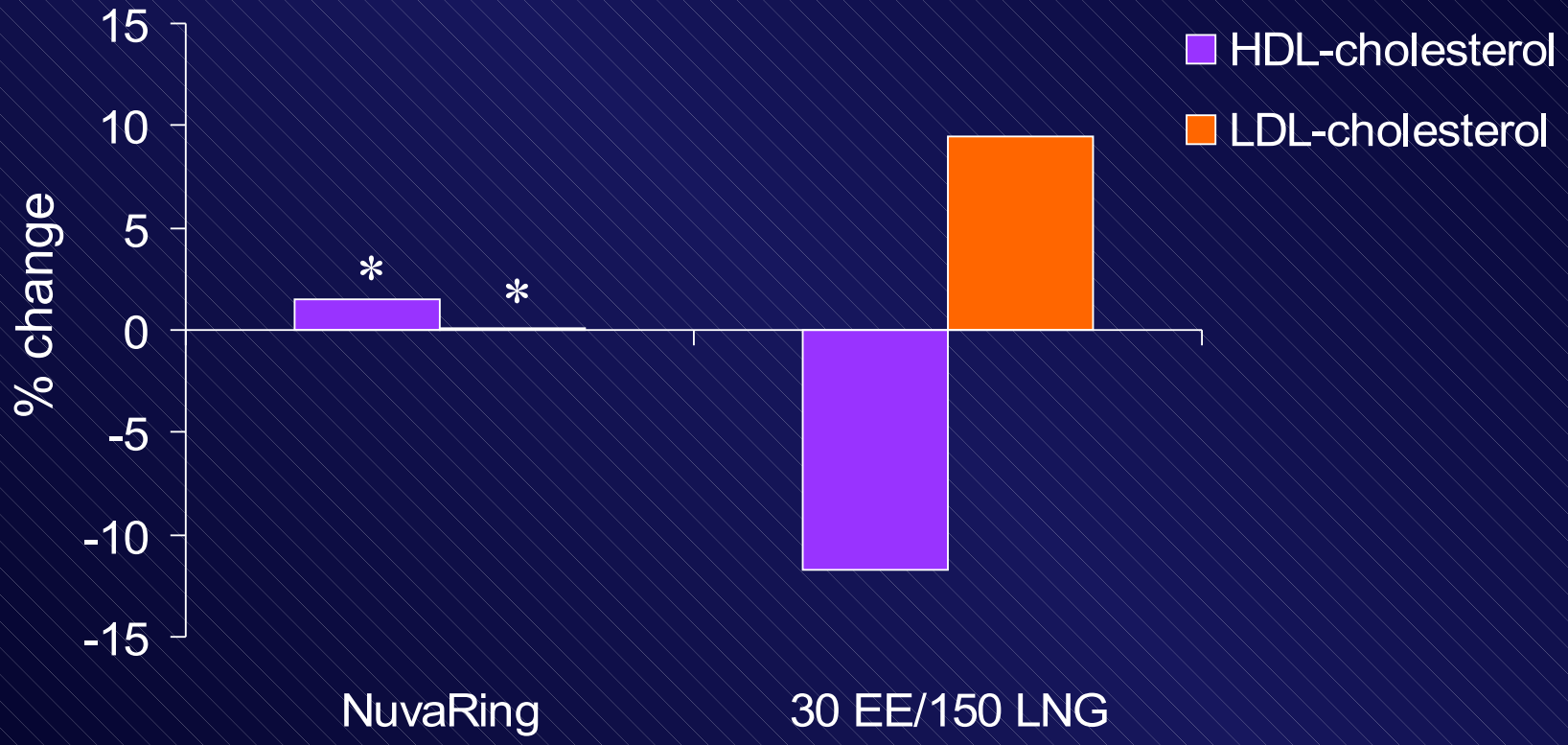
NuvaRing and lipid metabolism

Parameter	Median % change from baseline to cycle 6		
	NuvaRing	30 EE/150 LNG	P value
Total cholesterol	1.8	3.1	NS
HDL-cholesterol	1.5	-11.7	<0.0001
LDL-cholesterol	0.0	9.5	0.007
Lipoprotein(a)	-12.4	-21.2	NS
Triglycerides	23.8	8.6	NS

Tuppurainen et al, in preparation, 2003

NuvaRing and lipid metabolism

Median % change from baseline to cycle 6



Tuppurainen et al, in preparation, 2003

* P< 0.05 between groups

NuvaRing and carbohydrate metabolism

- After glucose loading:
  - No effect on glucose AUC
  - Increase in insulin AUC smaller with NuvaRing than with 30 EE /150 LNG COC
- No effect on long-term glucose metabolism
  - Glycosylated hemoglobin level unaltered
- NuvaRing has no clinically relevant effect on carbohydrate metabolism

Duijkers et al, in preparation, 2003

NuvaRing and hemostatic variables

- D-dimer
- Fibrinogen degradation products
- Prothrombin fragment 1+2
- Thrombin-antithrombin complex
- Fibrinogen
- Plasmin-antiplasmin complex
- Plasminogen activator inhibitor I (ag)

No difference between NuvaRing and 30 EE /150 LNG

Magnùsdóttir et al , 2003

Summary
Metabolic studies

- NuvaRing had a minimal effect on various lipid and hemostatic variables
- NuvaRing use had no clinically relevant effect on carbohydrate metabolism

Effect of NuvaRing on blood pressure

Combined European and North American studies (n=2322)

	Mean change from baseline			
	cycle 3	cycle 6	cycle 9	cycle 13
Diastolic (mmHg)	-0.1	-0.3	0.0	0.5
Systolic (mmHg)	-0.2	-0.1	-0.2	0.6

Dieben et al, Obstet Gynecol, 2002;100:585–93

Cervical cytology during NuvaRing use

NuvaRing has no unfavorable effects on cervical cytology.

Cervical cytology		% of women
Screening	Last assessment	(n=1941)
Normal	Normal	97.2%
Normal	PAP IIIa (low-grade SIL)	1.7%
Normal	PAP IIIb/ IV (high-grade SIL, carcinoma in situ)	0.4%
PAP IIIa (low-grade SIL)	Normal	0.4%

Dieben et al, Obstet Gynecol, 2002;100:585–93

Local effects during NuvaRing use

Other studies

No adverse changes in microbiology, cytology and colposcopy of the cervix and the vagina

- Archer D et al, Fertil Steril 2002;78(suppl 1):S25
- Roumen et al, Human Reprod 1996;11:2443–8
- Dieben et al, Obstet Gynecol 2002;100:585–93

Conclusions

NuvaRing use has:

- Minimal effects on lipid parameters
- No clinically relevant effects on carbohydrate metabolism
- Minimal effects on hemostatic variables, comparable with a 30 EE/150 LNG COC
- No adverse effect on blood pressure
- No unfavorable effects on the cervix or the vagina


Contraceptive efficacy
The European efficacy study
Kunsthistorisches Museum Wien,
Gemäldegalerie, Vienna

NuvaRing study design

- 52 centers in Europe
- 1182 women
- 1 year of treatment (13 cycles)
- One NuvaRing cycle comprises:
  - 3 weeks of ring use
  - 1 ring-free week

Roumen et al, Hum Reprod, 2001;16:469–75

Contraceptive efficacy

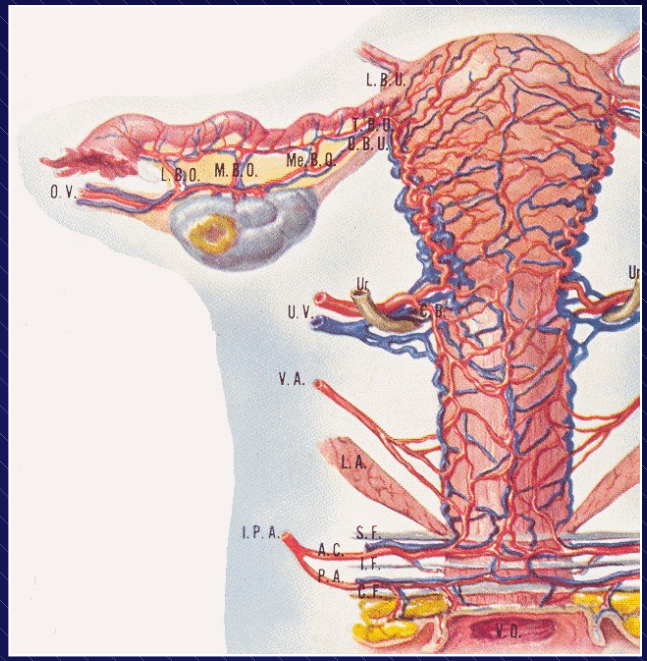
European study

Pregnancies	Cycles	Pearl Index	95% CI
6	12 109	0.65	0.24–1.41

Roumen et al, Hum Reprod, 2001;16:469–

Arteries and veins of the vagina

- The extensive vasculature surrounding the vagina is a major contributing factor in its ability to rapidly absorb medications.
- Venous blood does not immediately pass through the liver

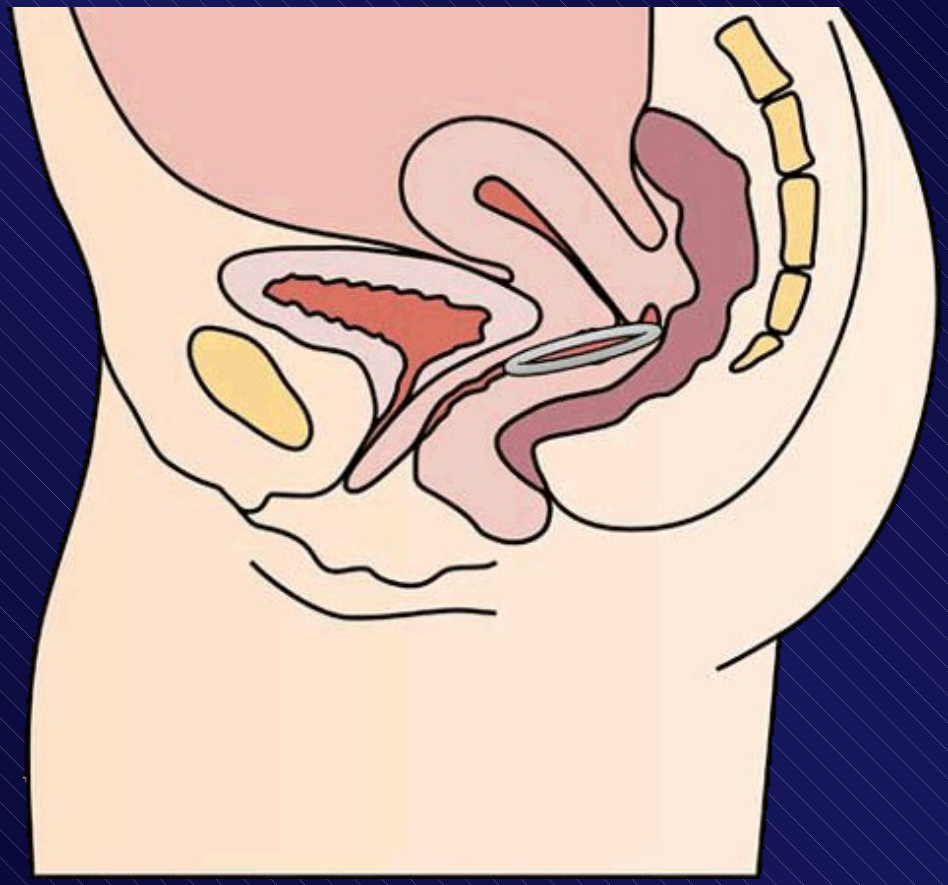


Conclusions

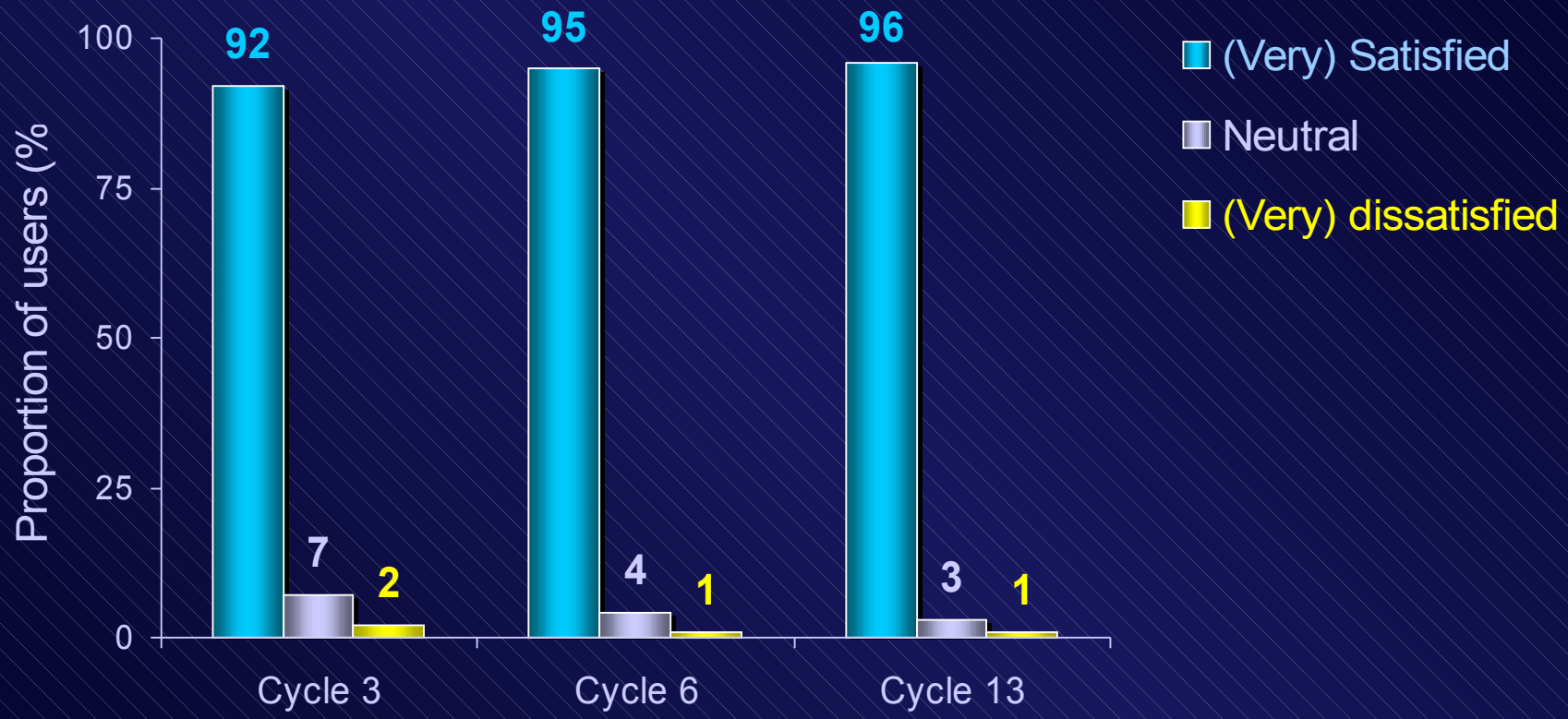
- Compliance with NuvaRing is high
- NuvaRing has good contraceptive efficacy


Question
Kunsthistorisches Museum Wien,
Gemäldegalerie, Vienna

Ring in vagina



NuvaRing® User Satisfaction

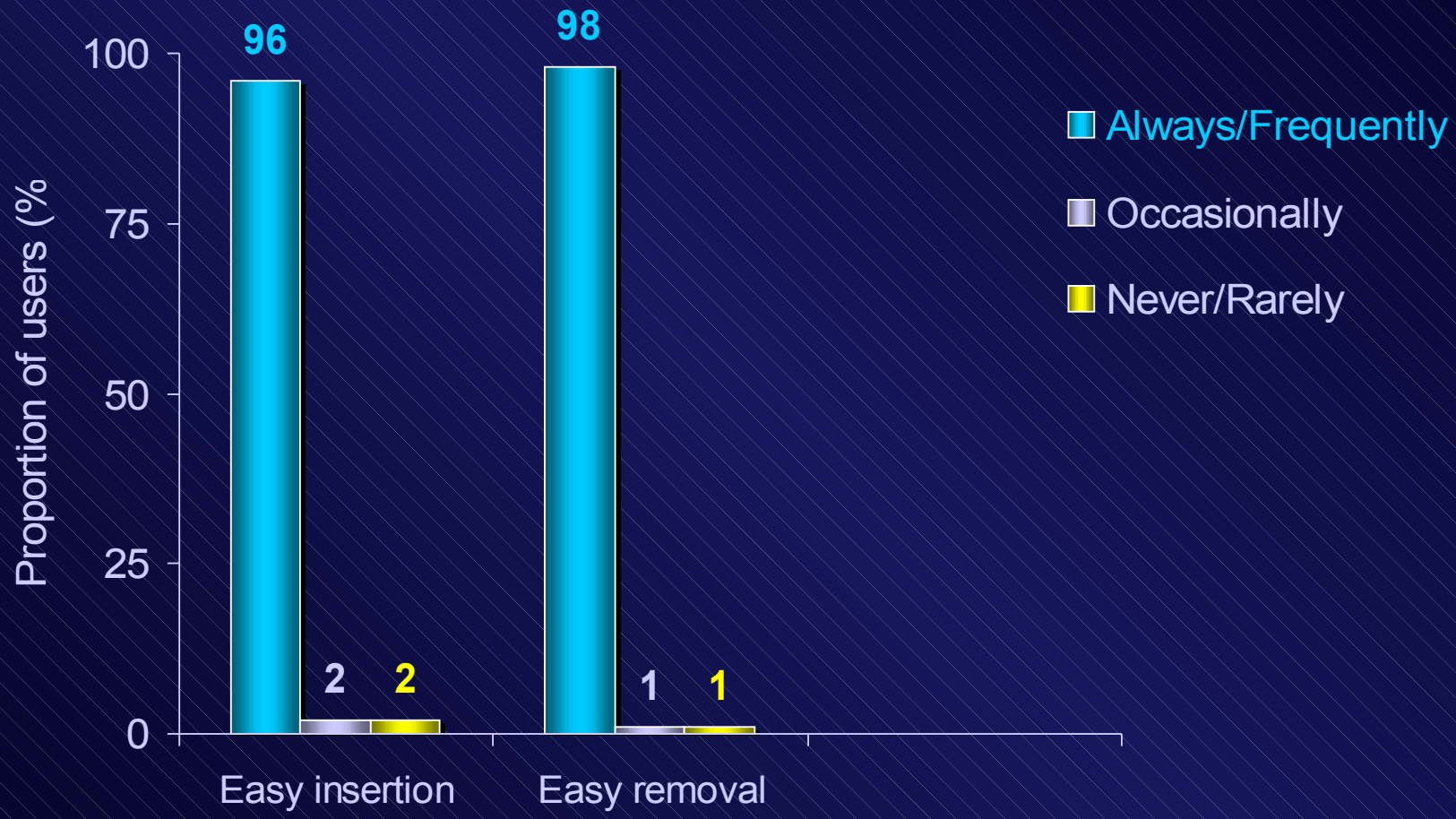


Dieben et al, Obstet and Gynecol, 2002;100:585-593

n=1500

NuvaRing® User Acceptability

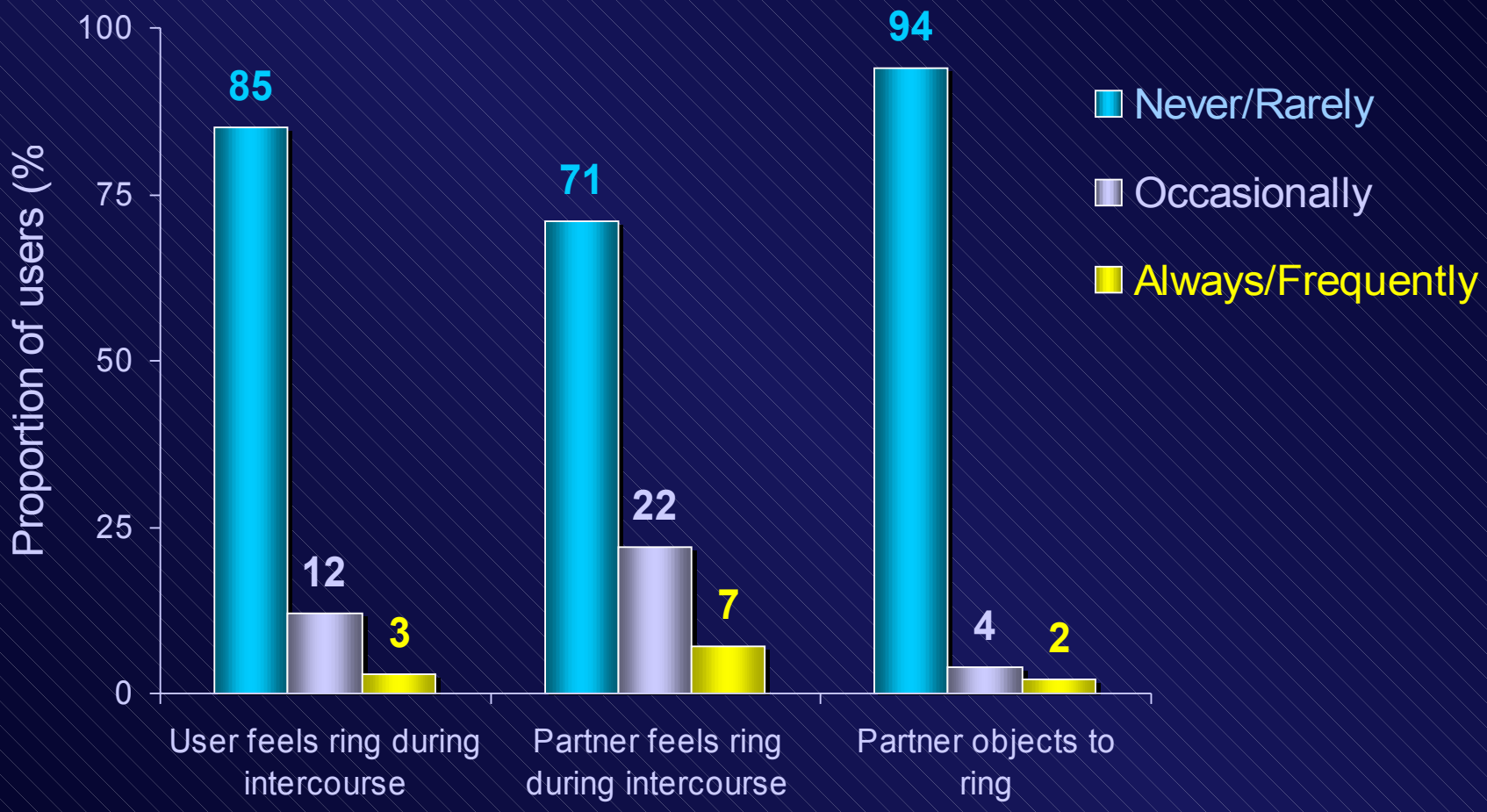
Ease of Insertion and Removal



Dieben et al, Obstet and Gynecol, 2002;100:585-593

n=2142

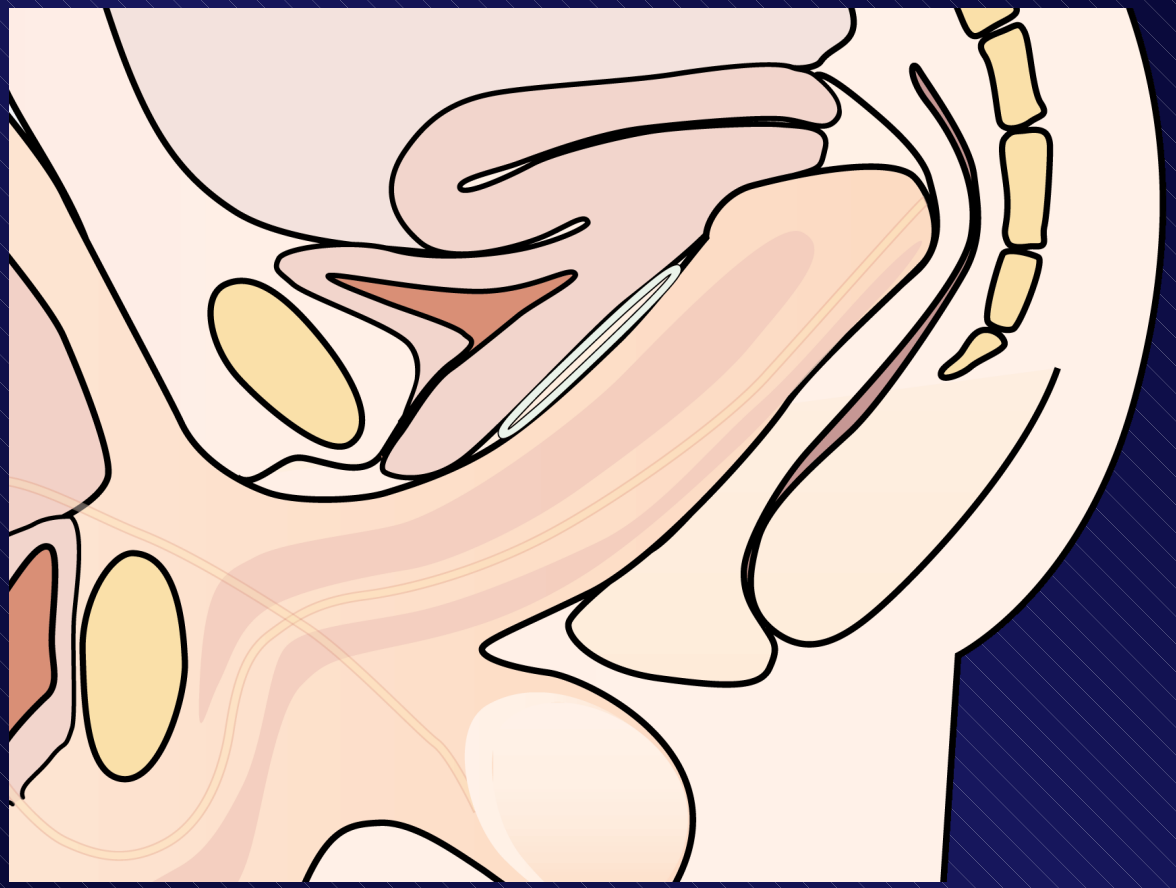
NuvaRing® User Acceptability Interference With Intercourse



Dieben et al, Obstet and Gynecol, 2002;100:585-593

n=1498

Ring in vagina during intercourse

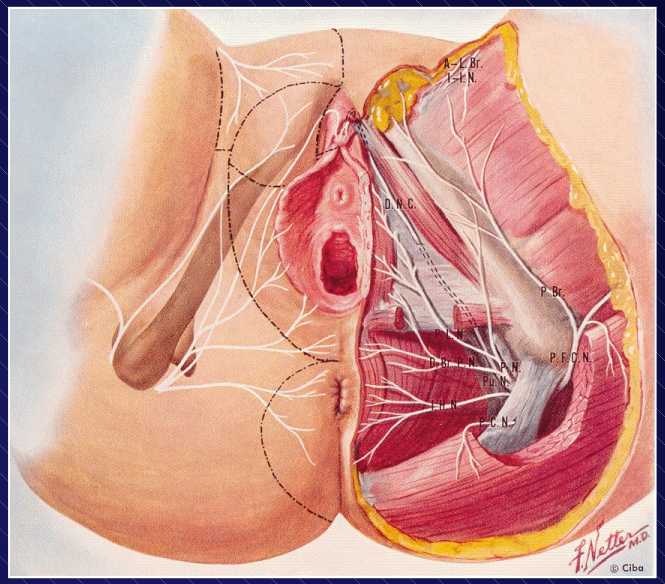


NuvaRing in situ

- The exact positioning of NuvaRing within the vagina is not important for its contraceptive effect
- Women cannot feel NuvaRing because it sits in the upper part of the vagina
- The muscles in the lower part of the vagina ensure NuvaRing stays in place

Vaginal nerves

- NuvaRing is usually not felt by patients
- Lower 1/4 of vagina has a peripheral nerve supply which is sensitive to touch / pressure/ temperature
- The nerve supply to the upper vagina is autonomic and is less sensitive



NuvaRing®

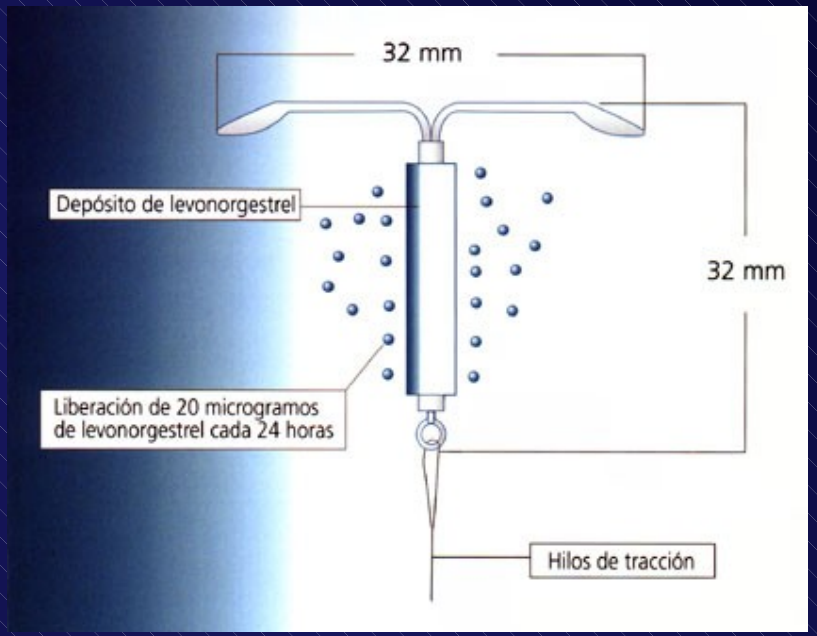
- Once-a-month convenience
- A safe method & reliable as the Pill
- Easy to use
- Few adverse events
- Good for compliance
- Low dose
- Neutral effect on body weight

MIRENA®, LNG IUS

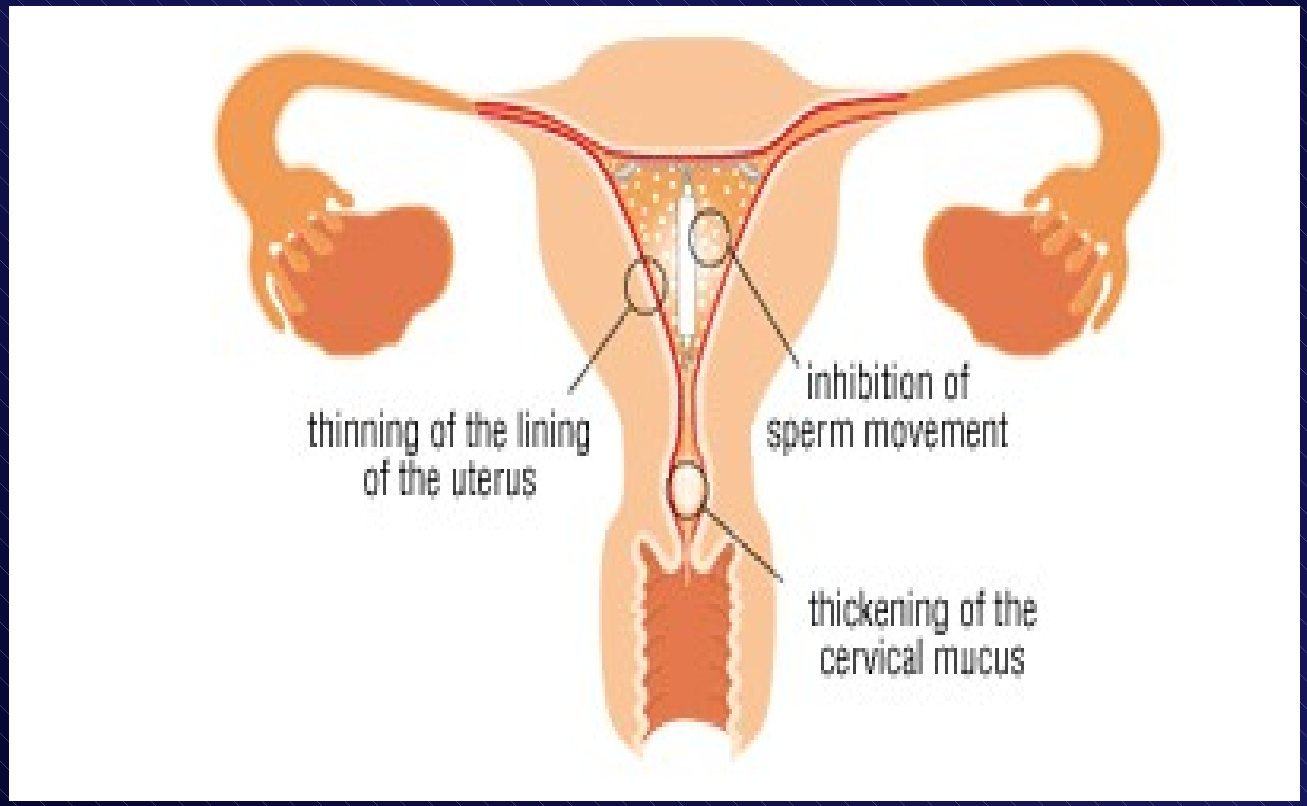
Intrauterine Levonorgestrel Releasing System
Release rate 20µg / day, LNG Loud 52mg
Life time 5 years + Safety period

MIRENA®, LNG IUS

- The LNG IUS consists of a small T-shaped frame with steroid reservoir that contains LNG.

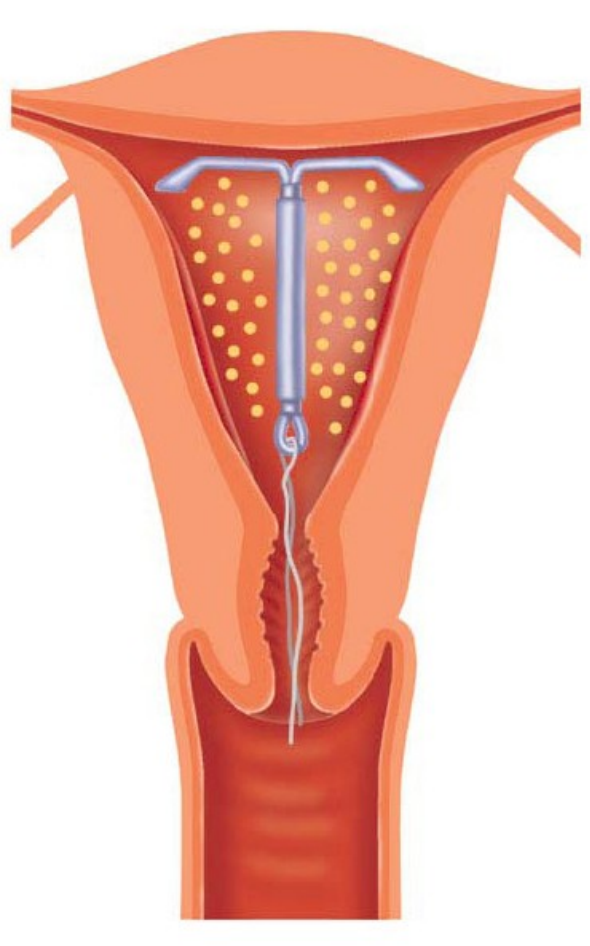


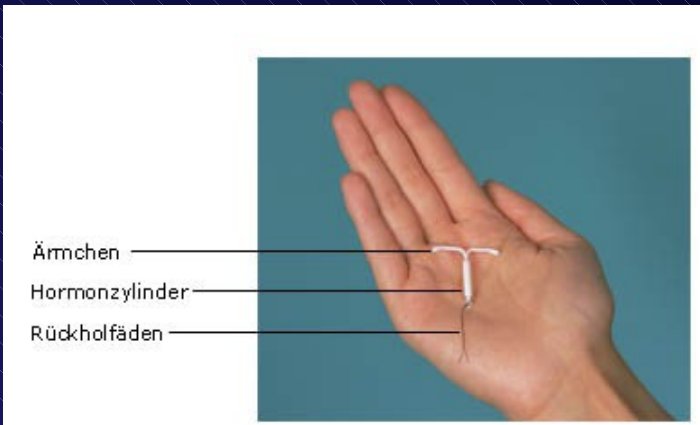
蜜蕊娜 (Mirena) 每天在子宮內釋放微量荷爾蒙 Levonorgestrel(LNG) ，藉由荷爾蒙局部作用而產生避孕效果。

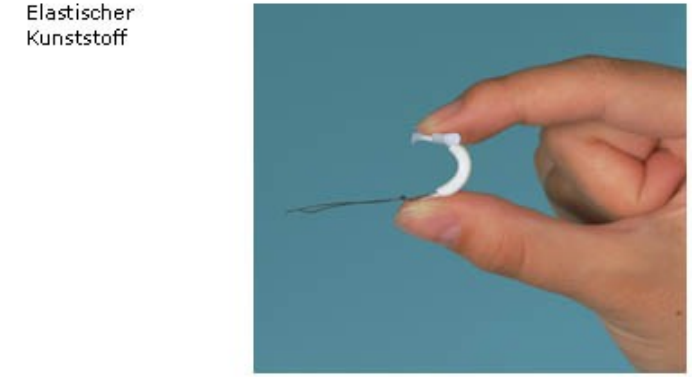


MIRENA

levonorgestrel intrauterine system(LNG IUS)

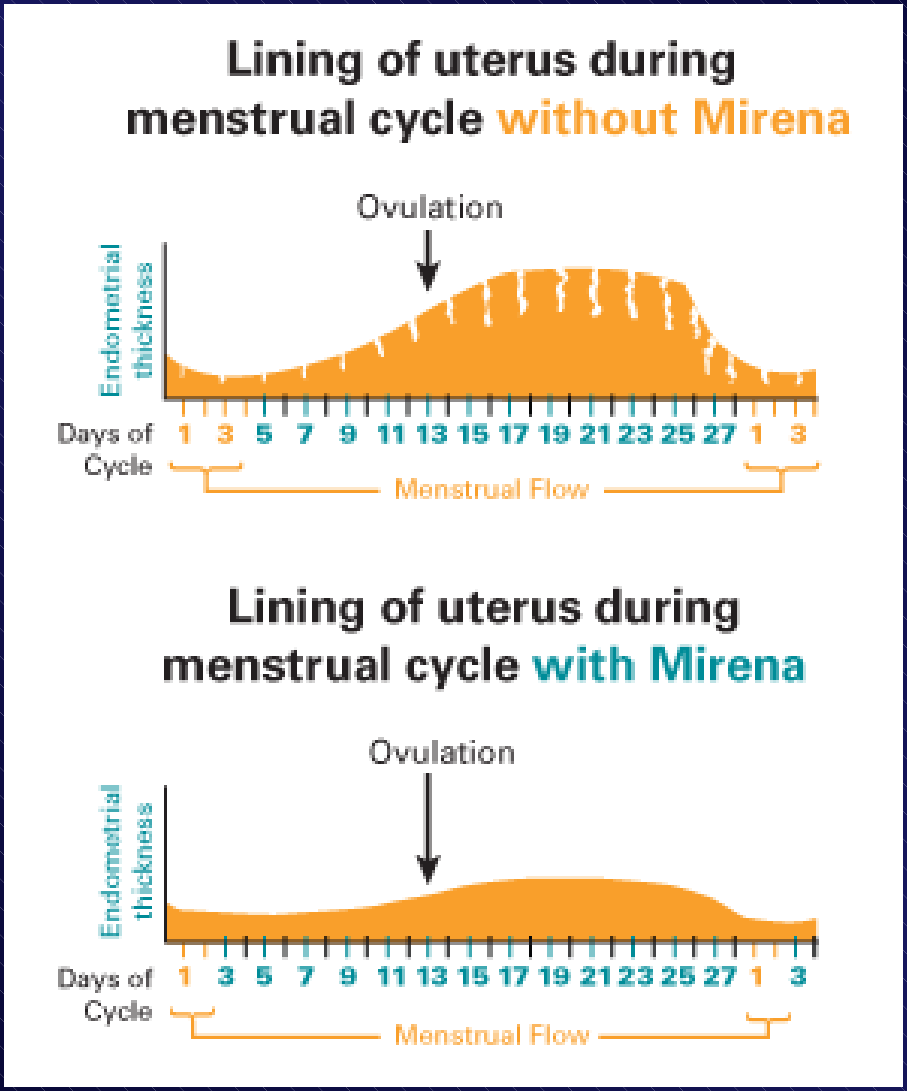






MIRENA

Endometrium Thickness

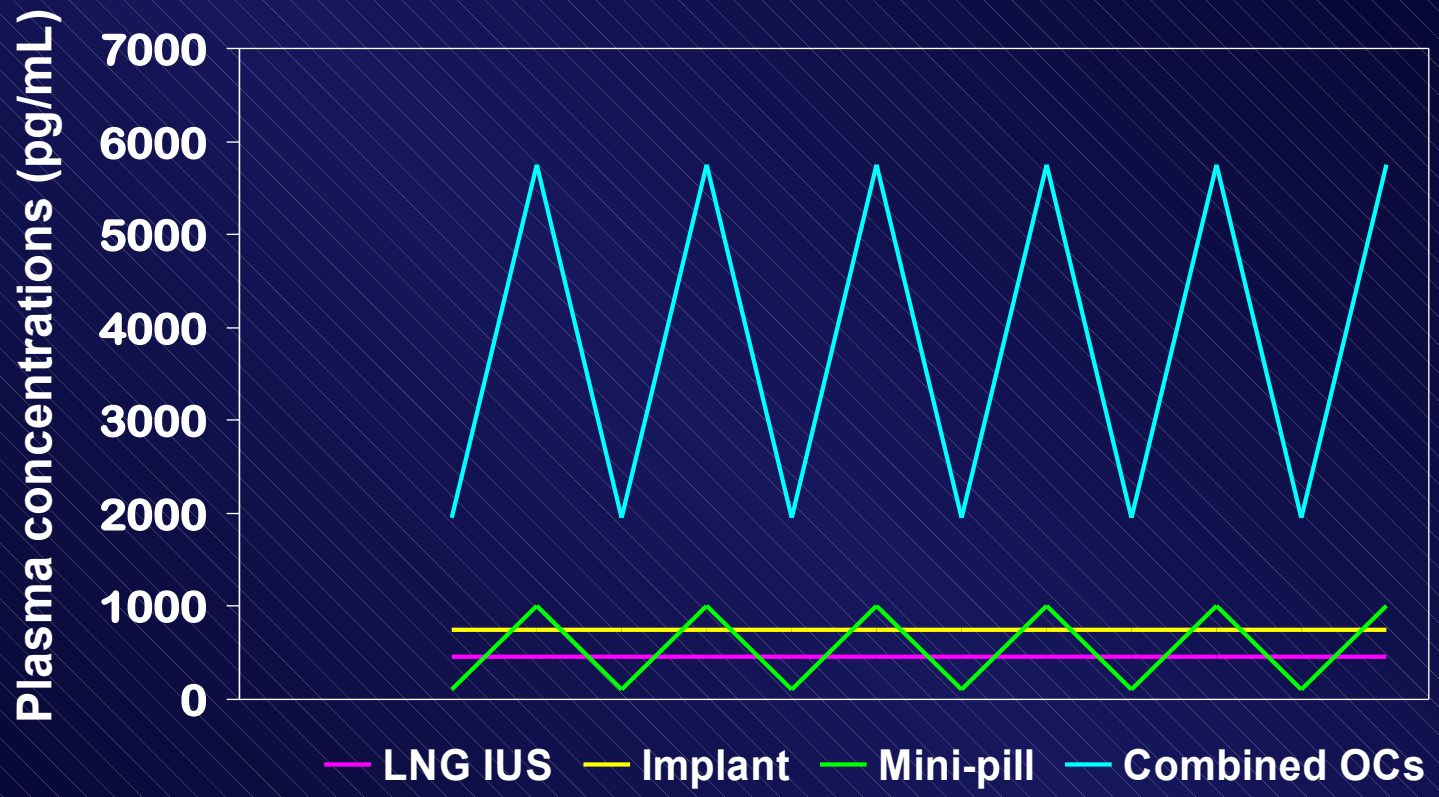


MIRENA

Local concentration of levonorgestrel

	LNG-IUS 20 µg/24 h	Oral 2 mg E_2/ 250 µg LNG
Endometrium (pg/mg dry tissue)	808 ± 511	3.5
Myometrium (pg/mg dry tissue)	2.43 ± 1.86	1.42 ± 0.46
Fallopian tube (pg/mg dry tissue)	1.8	1.7

Plasma Concentrations of LNG



- 血中濃度僅 150-200pg/ml
- 局部作用在子宮
- Hormone 引起之全身性副作用少

MIRENA

Mirena（蜜蕊娜）之適應症

- Officially approved indication
  - 避孕
  - 經血過多
  - 預防雌激素補充治療引起的子宮內膜增生
- Potential usages
  - Uterine fibroids
  - Adenomyosis
  - Dysmenorrhia
  - Adjuvant therapy for tamoxifen users

Contraceptive reliability

Method	% of women experiencing an accidental pregnancy within the first year of use*
Mirena®	**0–0.2**
Combined OCs	0.2–3.0
Progestin-only pill	1.0–4.0
Copper IUD	0.3–2.0
Sterilisation male	0–0.2
female	0–1.0
Implant	0–1.0
Injectables	0–1.0

1) Guillebaud J. 1997, Contraception Today, Third Edition. *Range in the literature

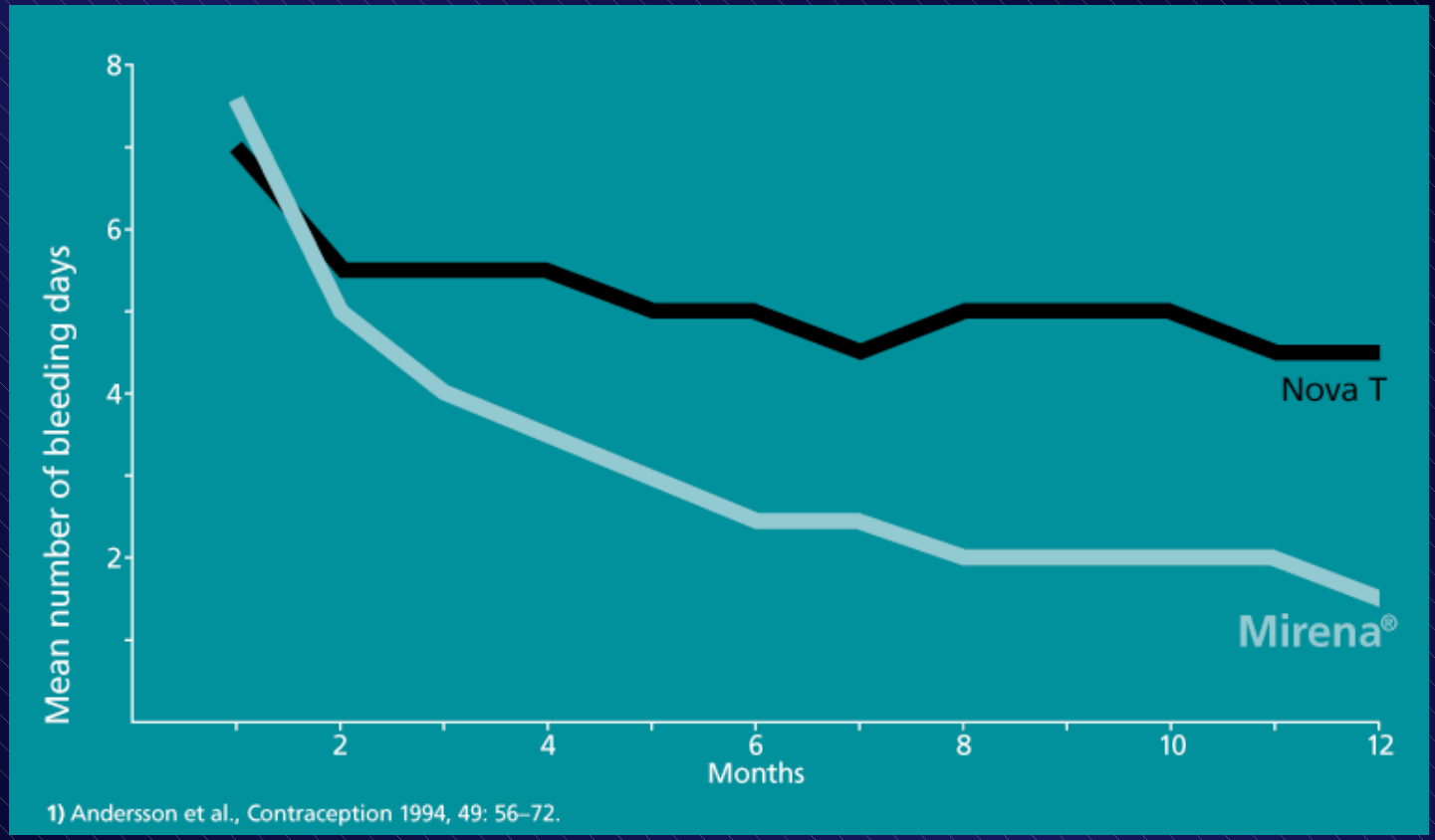
MIRENA

Discontinuation due to pelvic infection

Infection	Copper IUD	Mirena®	p value
	Gross cumulative discontinuation rates at 5 years		
PID	2.2	0.8	<0.01
Endometritis	4.0	1.5	<0.007
Cervicitis	1.1	0.6	<0.3
Colpitis	1.8	0.7	<0.1

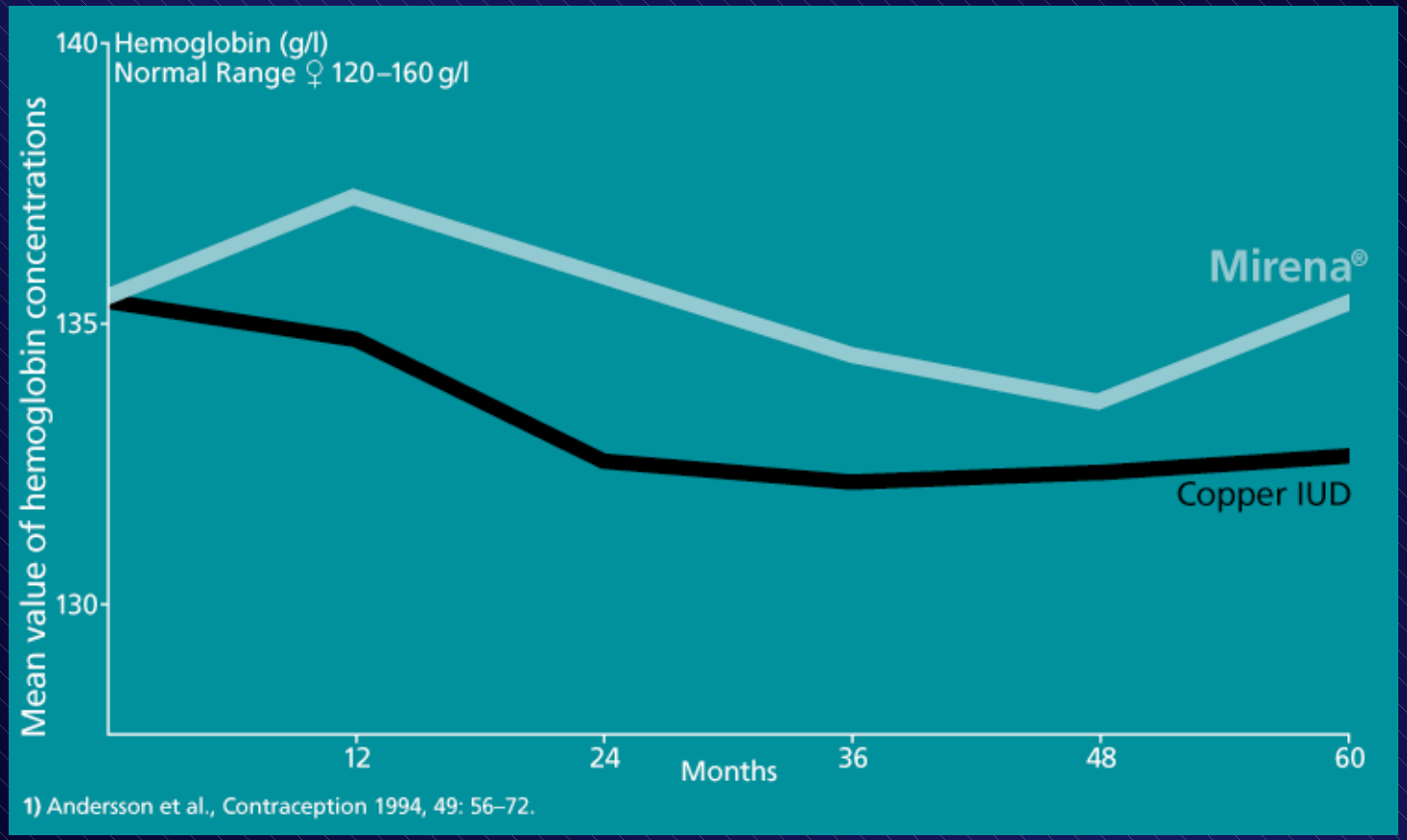
1) Leiras study report 1208, 1991

Days of Bleeding: Mirena vs Nova T



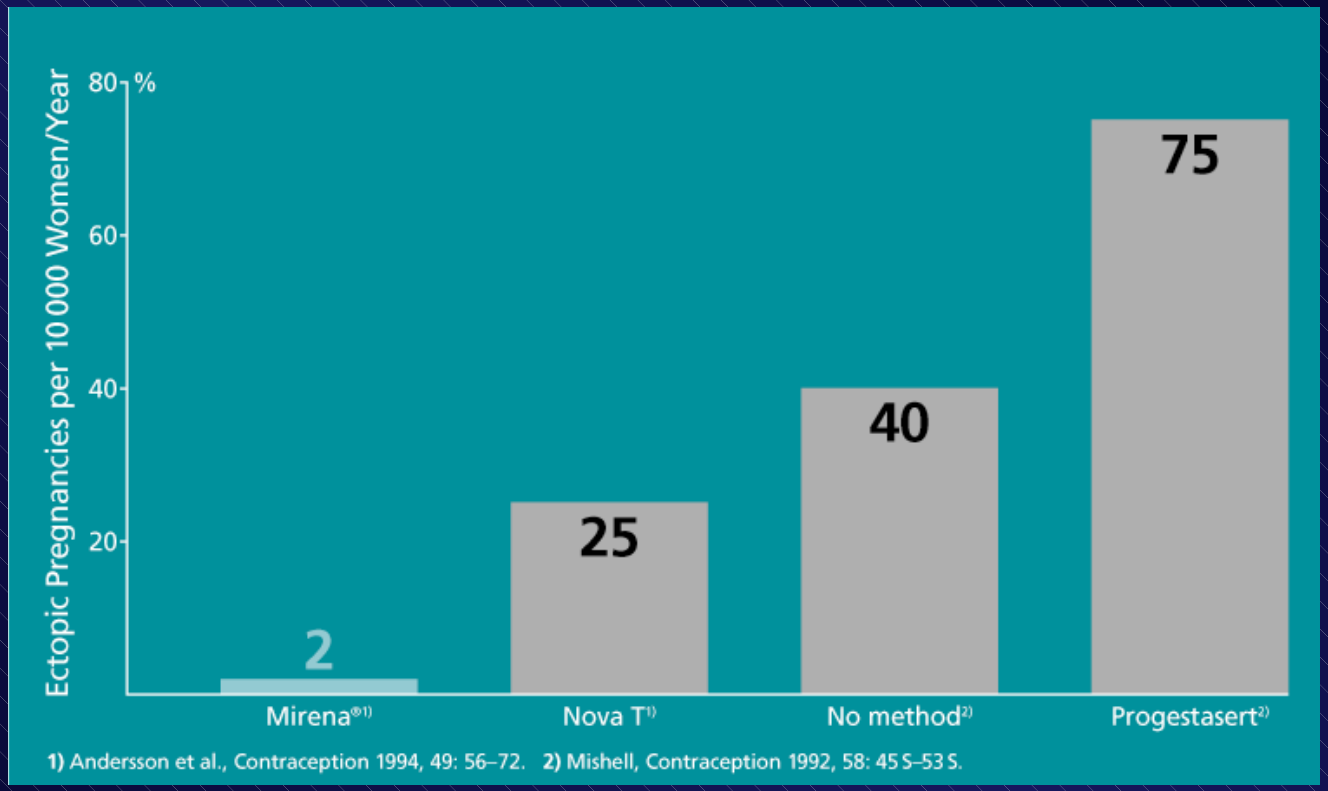
裝置一年後，經期縮短為 2 天

Hemoglobin concentration:Mirena vs Copper IUD



1) Andersson et al., Contraception 1994, 49: 56–72.

Ectopic Pregnancy



子宮外孕發生率為 2/10,000 甚至低於未避孕者

Bleeding Problem

5-year cumulative gross termination rates

	Nova T	Levonorgestrel intrauterine system
Frequent irregular bleeding	3.9	5.3
Heavy menstrual flow	9.7	1.3 *
Prolong menstrual flow	6.5	2.3*
Spotting	2.2	1.6

*$p < 0.001$

Andersson *et al.*, 1994

Hormonal reasons

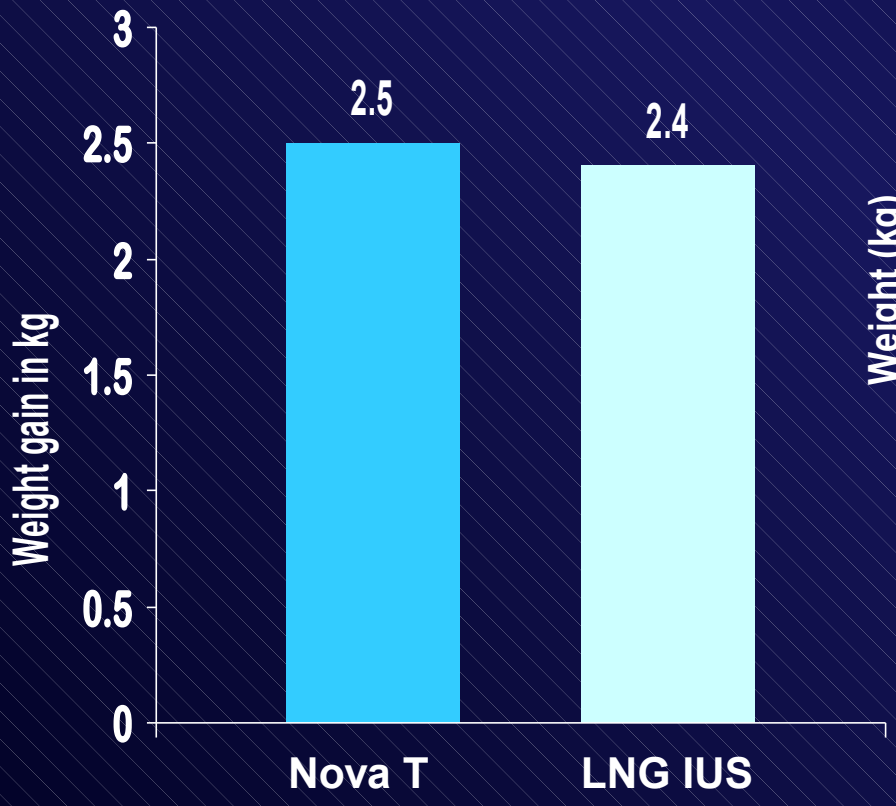
5-year cumulative gross termination rates

	Nova T	Levonorgestrel intrauterine system
Depression	0	2.9 ***
Acne	0.4	2.3 *
Headache	0.2	1.9 **
Weight change	0	1.5 **
Breast tenderness	0	0.8 *

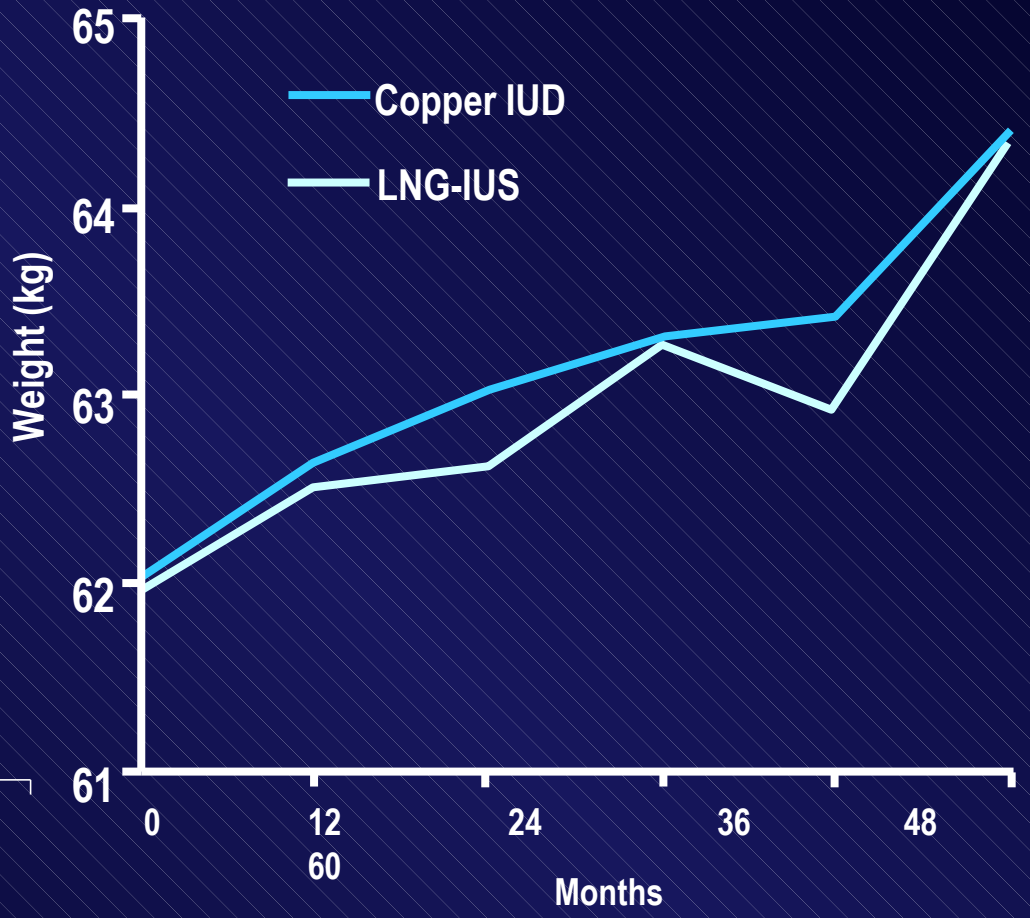
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$

Andersson *et al.*, 1994

Mean Weight Change After 5 Years



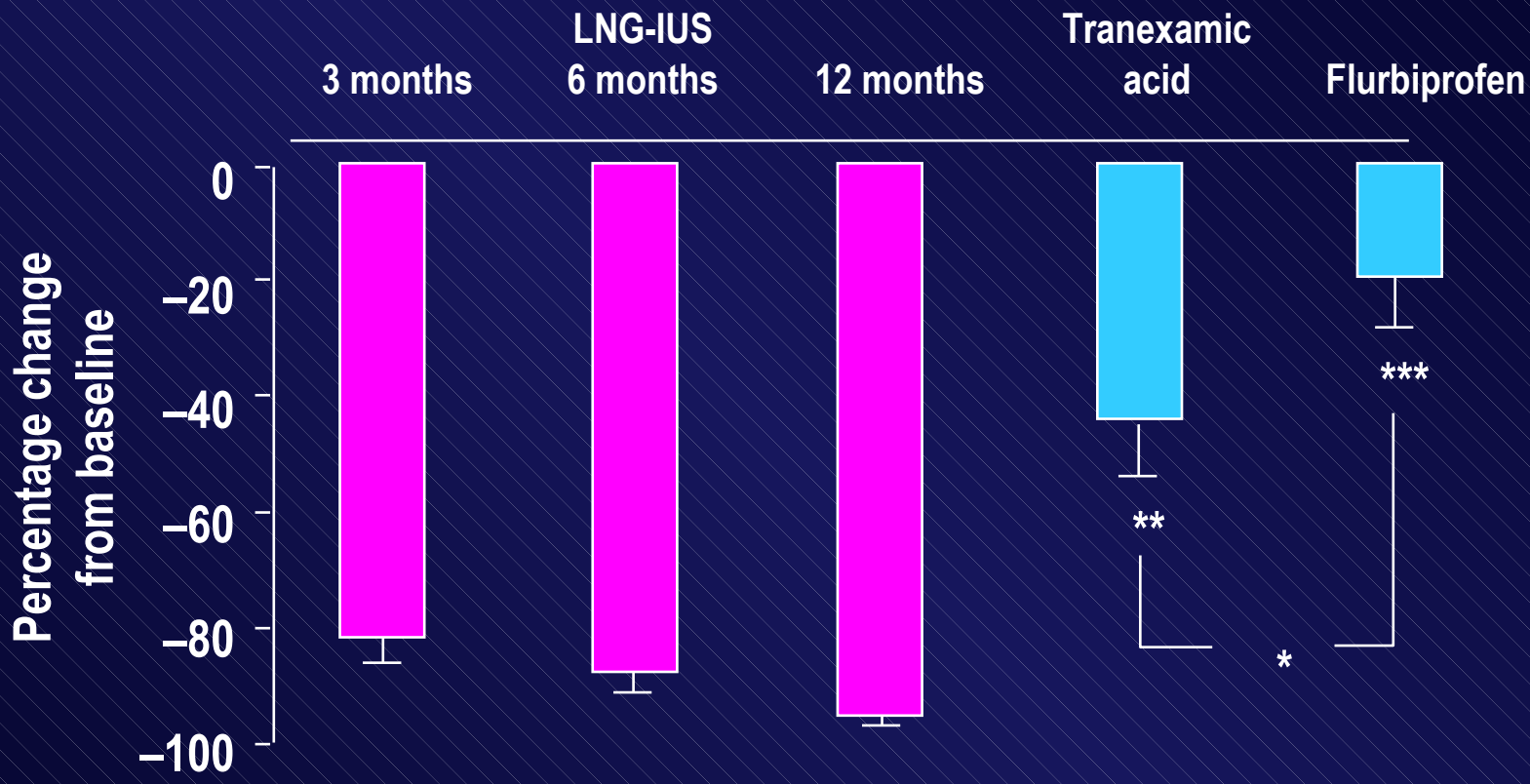
Body weight over 5 years of use



Andersson et al. *Contraception* 1994;49:56

MIRENA

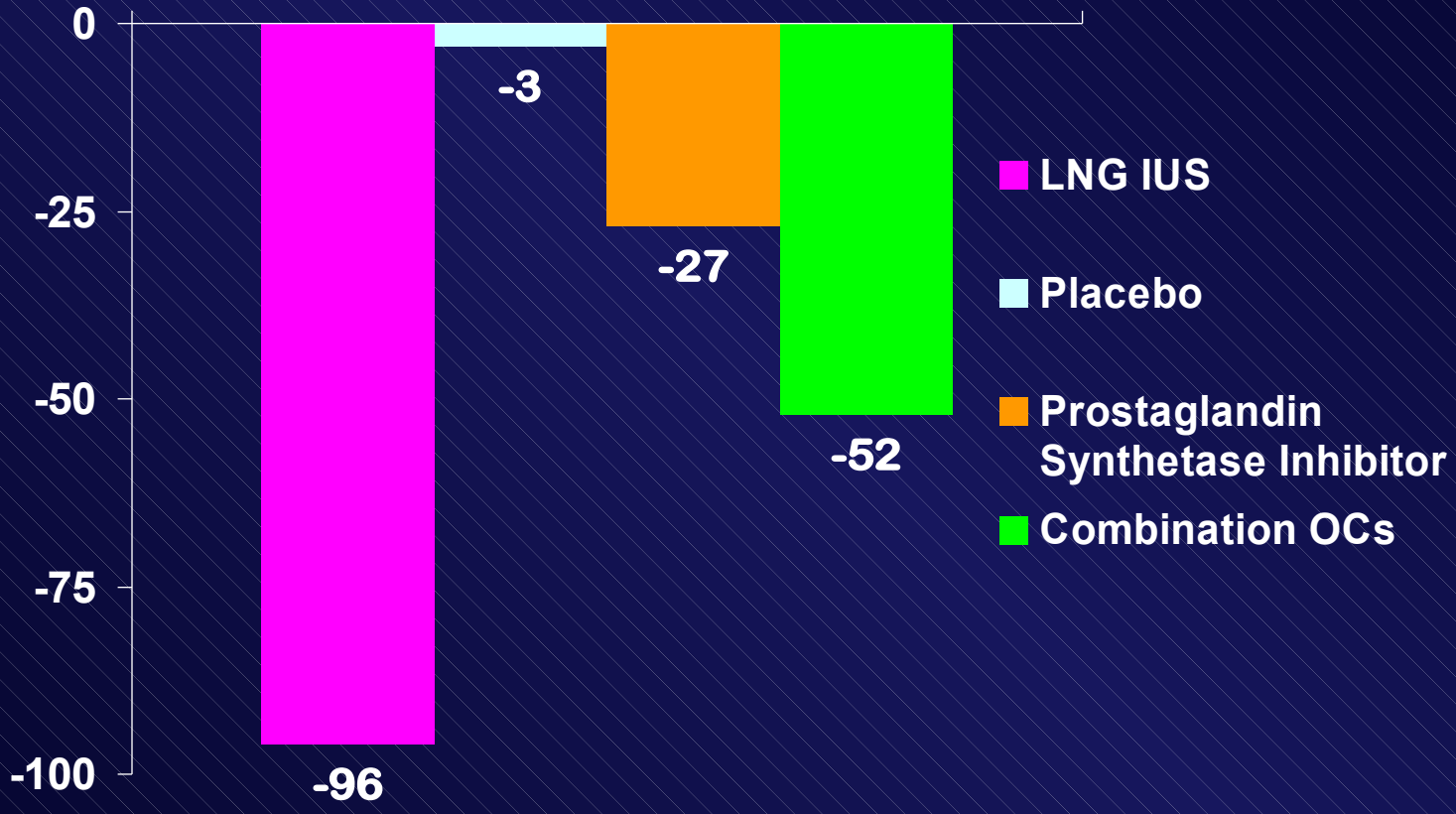
Reduction in menstrual blood loss



*p < 0.05; **p < 0.01; ***p < 0.001

Milsom et al. *Am J Obstet Gynecol* 1991;164:879

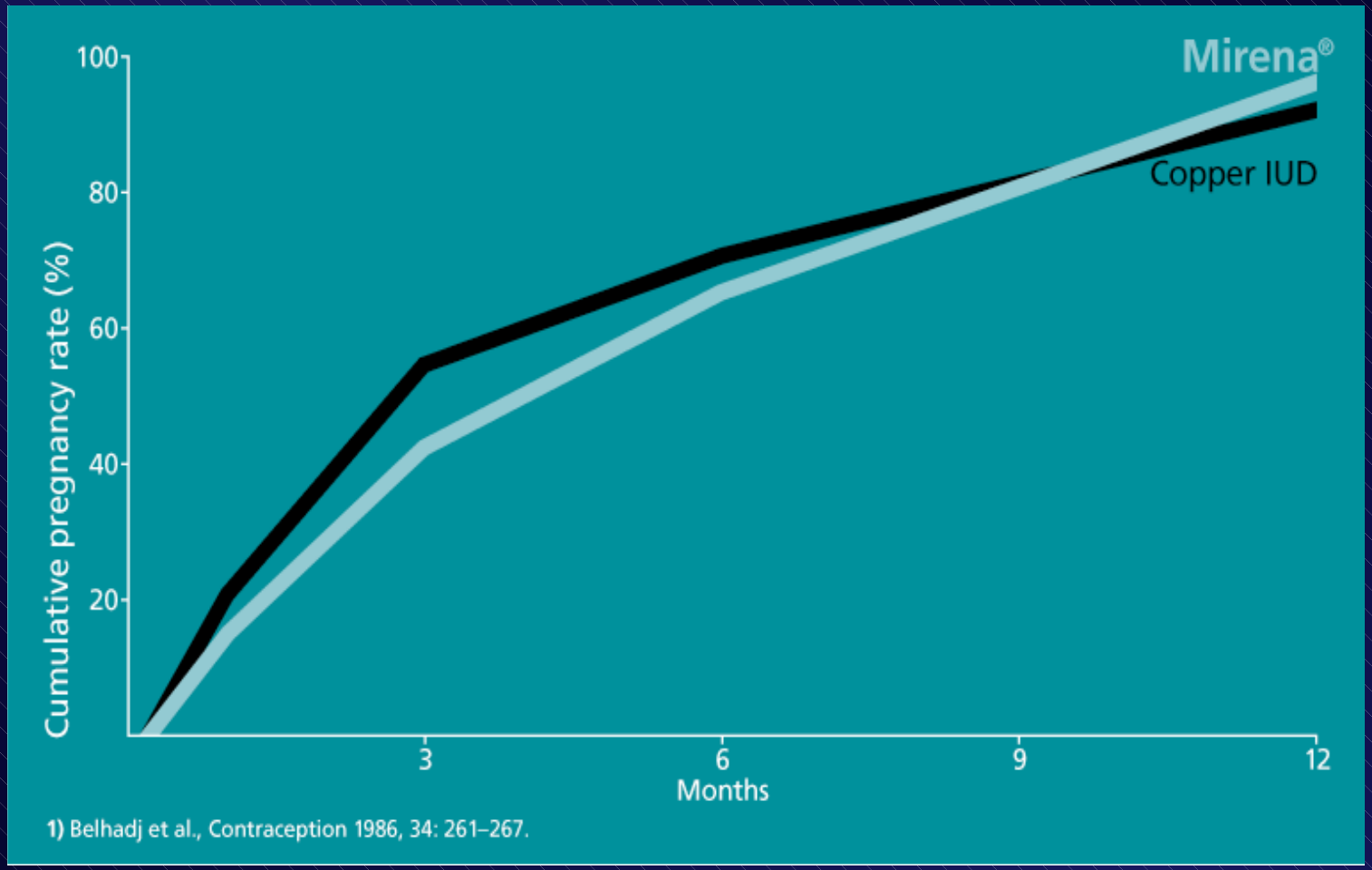
LNG IUS: menstrual blood loss



Milsom et al. *Am J Obstet Gynecol* 1991;164:879

Return to Fertility After removal

取出後生育力即可恢復，一年生育力恢復率幾達 100%



Use of a levonorgestrel-releasing intrauterine system to treat bleeding related to uterine leiomyomas

- Study design :

  67 women, age between 20-45, with at least one leiomyoma > 2.5 cm or multiple leiomyomas with at least one >1.5 cm

  Follow up : 3, 6, 12 months

Fertility and sterility, vol. 79, NO. 5, May 2003 p. 1194-1198

Fig 1. MBL before and after LNG-IUS insertion

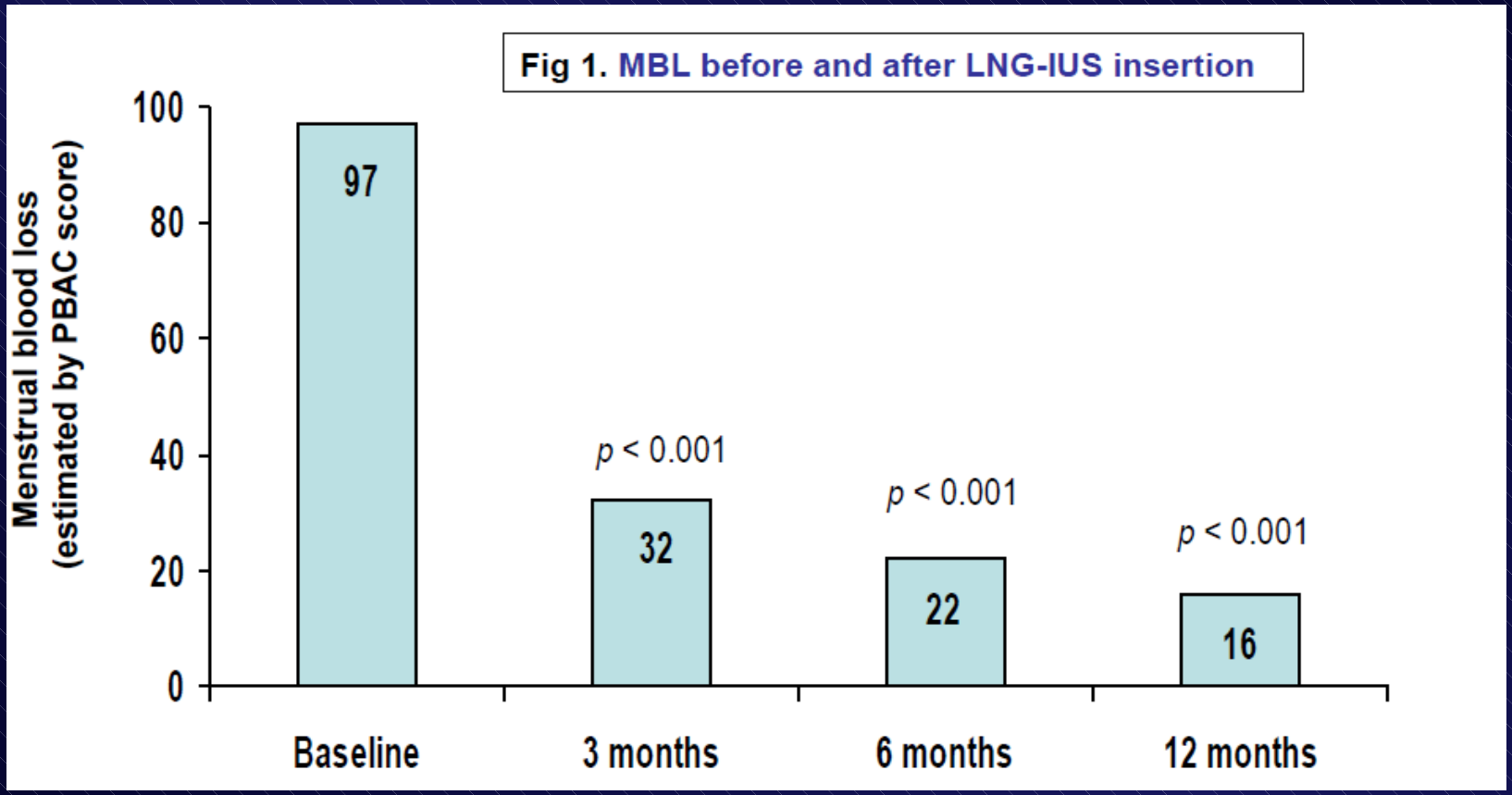


Table 2 : Changes in uterine and fibroid volume :

	Baseline (n = 67)	3 months (n = 56)	6 months (n = 56)	12 months (n = 61)
Uterine volume (mL)	138 ± 72	131 ± 68 $p < 0.01$	125 ± 58 $p < 0.01$	122 ± 73 $p < 0.01$
Total leiomyoma volume (mL)	30 ± 29	27 ± 34 $p = 0.10$	19 ± 21 $p < 0.001$	19 ± 21 $p < 0.001$

Insertion of Mirena after endometrial resection in patients with adenomyosis

- Study design :

  95 women, with diagnosis of Menorrhagia due to Adenomyosis

  Treatment scheme :

  Control: 42 women : endometrial resection

  Mirena : 54 women : endometrial resection + Mirena

  Follow up : 3, 6, 12 months

Insertion of Mirena after endometrial resection in patients with adenomyosis

	Control (n = 42)	Mirena (n = 54)
Disappearance of dysmenorrhea	20%	90%
Required a second surgical procedure	19%	0%
Amenorrhea rate after 12 month of treatment	9%	100%

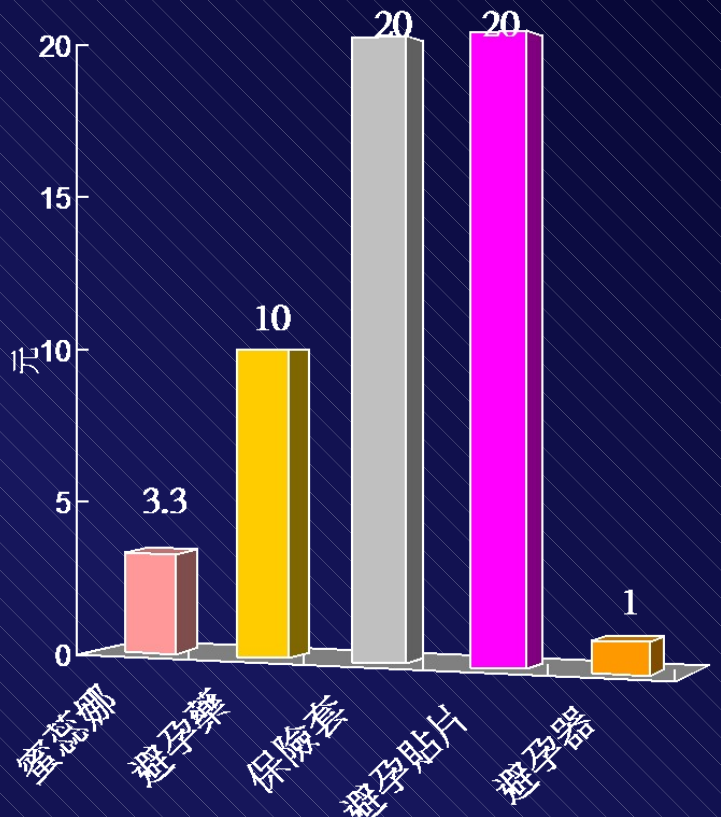
Maia *et al. J. Am. Asso.of Gyn Lapa, 2003,V. 10 N.4, p.512-516*

Mirena（蜜蕊娜）置入 (Insertion) 時間

- 一般婦女 ： 於月經週期開始後 7 天內置入
- 服用口服避孕藥者 ： 在服用最後一顆藥丸後或於出血間置入
- 產婦 ： 生產後 4-6 週置入
- 流產 ： 子宮完全清除後即可立即置入
- 使用 IUD 者 ： 移出後，立即置入 Mirena

Mirena（蜜蕊娜）適合什麼人使用？

- 使用 IUD 不適，經常生殖道感染
- 需要治療經血過多、痛經、經期過長的人。
- 哺乳的媽媽
- 子宮肌瘤及肌腺瘤患者



Mirena（蜜蕊娜）之使用禁忌

- 懷孕或可能懷孕
- 現有或復發骨盆腔發炎疾病
- 下生殖道感染
- 產後子宮內膜炎
- 過去3個月中有感染性流產
- 子宮頸炎
- 子宮頸發育異常
- 子宮或子宮頸惡性腫瘤
- 未經診斷的不正常子宮出血
- 先天或後天的子宮異常
- 增加感染機會的相關狀況
- 急性肝病或肝腫瘤
- 對本製劑成份過敏者


Thanks for your attention!