Intrauterina preventivmetoder

– ett alternativ för alla åldrar

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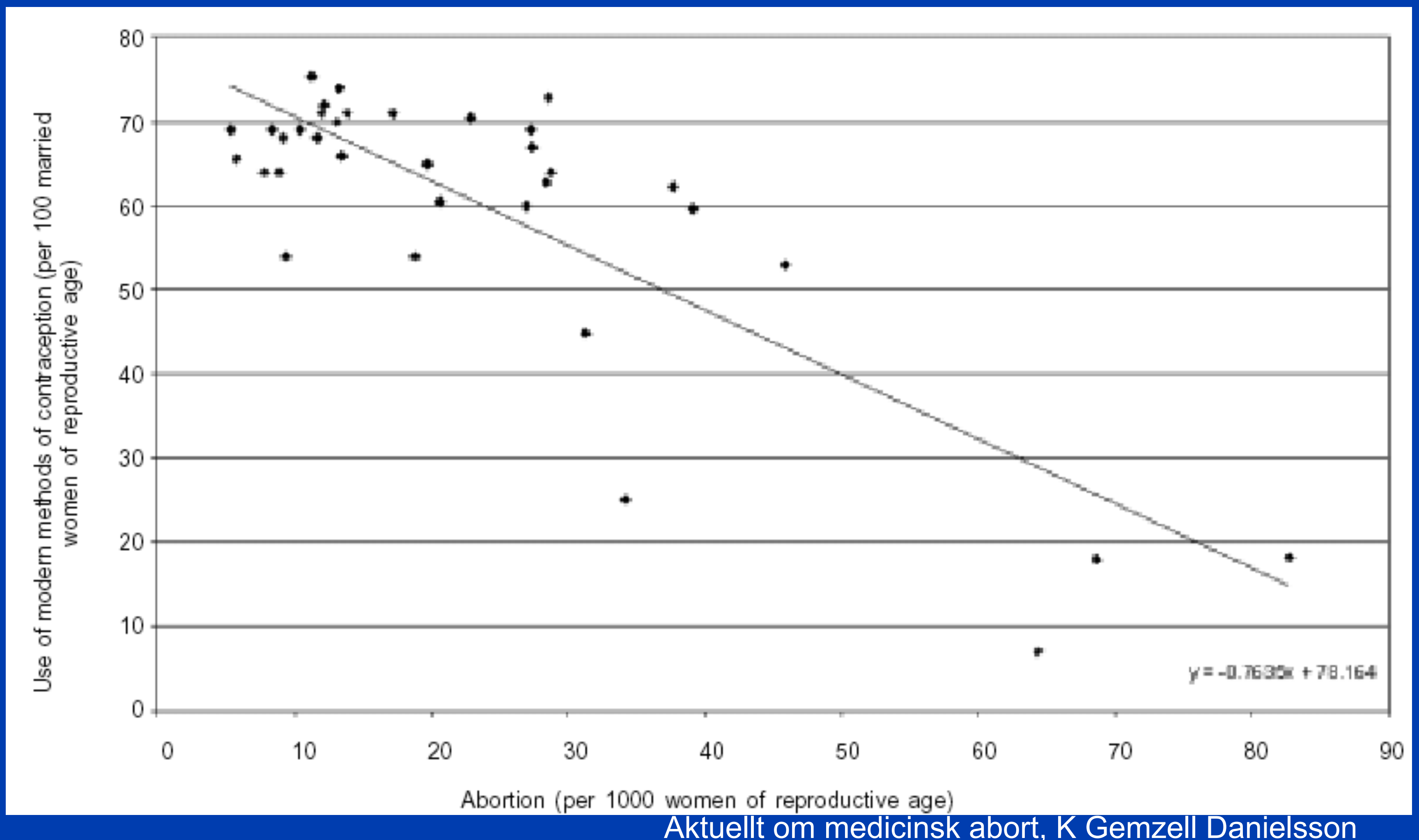
The link between contraceptive prevalence and abortion

Levels of use of modern contraception and abortion rates
countries with total fertility rate between 1.7 and 2.2.



WHO; Progress in Reproductive Health, 2003

Effectiveness of female contraceptive options

Method	% of women experiencing an unintended pregnancy within the first year of use	
	Typical use*	Perfect use†
No method[‡]	85	85
Female condom[§]	21	5
Diaphragm[‖]	12	6
Oral contraceptives: COC/POP	9	0.3
Transdermal patch	9	0.3
Vaginal ring	9	0.3
Injectable	6	0.2
Cu-IUD	0.8	0.6
Female sterilization	0.5	0.5
LNG-IUS: Mirena®	0.2	0.2
Subdermal implant	0.05	05

Increasing effectiveness in 'typical use'

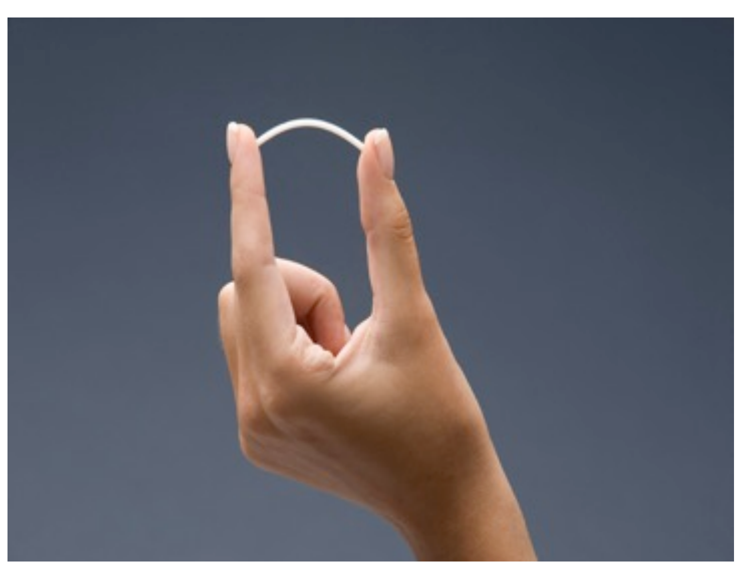
Trussell J. Contraception 2011; 83(5): 397–404
COC, combined oral contraceptive;
Cu-IUD, copper intrauterine device;
LNG-IUS, levonorgestrel intrauterine system;
POP, progestin-only pill

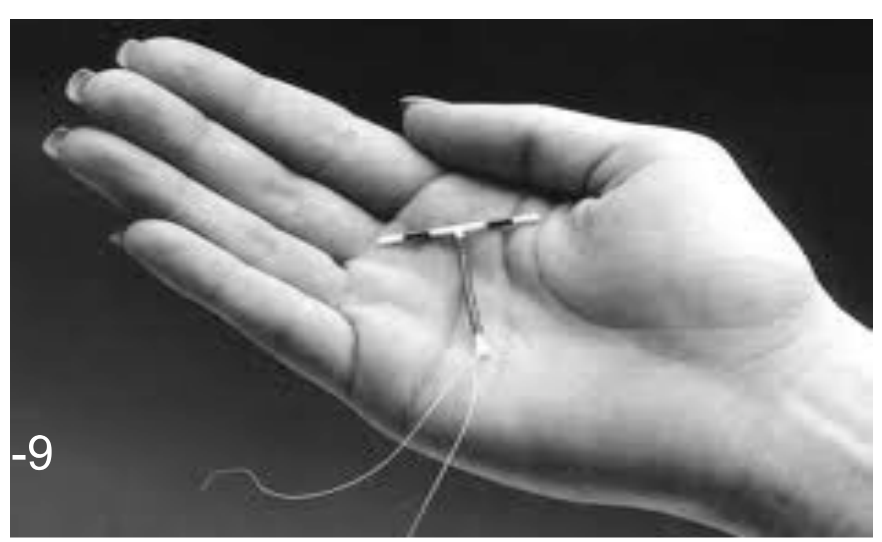
* Typical use: includes both incorrect and inconsistent use
† Perfect use: correct and consistent use
§ without spermicides
‖ with spermicidal cream or jelly

LARC

“forgettable contraception”

that can be ignored for years….





Goal 5

Improve maternal health

TARGET
Reduce by three quarters, between 1990 and 2015, the maternal mortality ratio

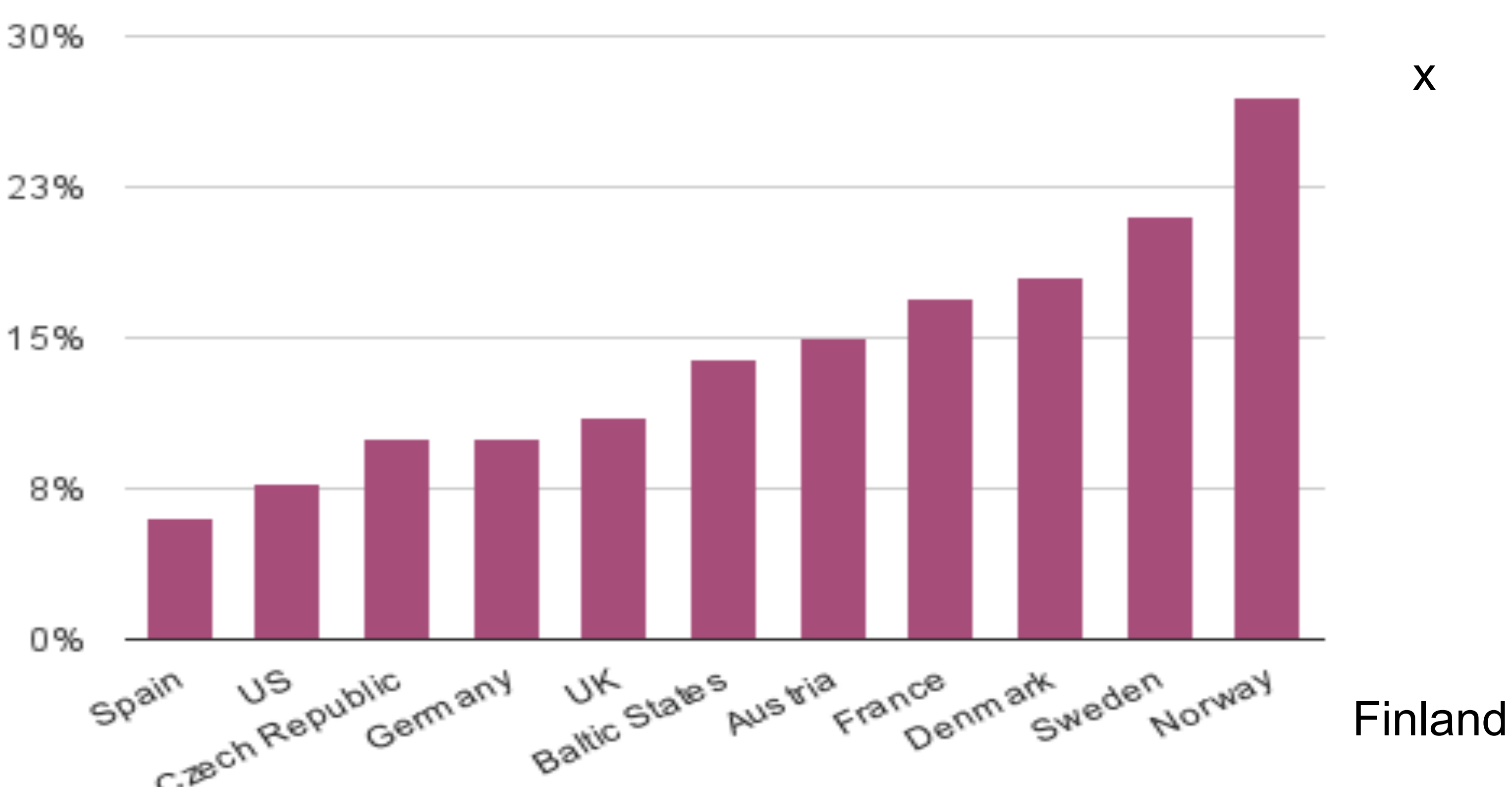
Achieving good maternal health requires quality reproductive health services and a series of well-timed interventions to ensure a women's safe passage to motherhood. Failure to provide these results in hundreds of thousands of needless deaths each year—a sad reminder of the low status accorded to women in many societies.

The Bellagio statement on LARC, 2008

common, and estimates lie within large ranges of uncertainty. Nevertheless, an acceleration in the provision of maternal and reproductive health services to women in all regions, along with positive trend data on maternal mortality and morbidity, suggest that the world is making some progress on MDG 5.

Millenium development goals, MDG 5 Target:
To reduce by three quarters, 1990 -2015, the MMR

IUD Usage Among Contraceptive Users



Data from 2006 except for the US, which is from 2009. Source: Guttmacher Institute

Contraception, Sweden

60
50
40
30
20
10
0

16-20 yrs
21-29 yrs
30-39 yrs
40+ yrs

LARC
SARC
other
no method
permanent

Pills – the most common method

Kopp-Kallner et al., PlosOne 2015

The Contraceptive CHOICE Project in the United States[1,2]

Objective To decrease unintended pregnancy by promoting the use of long-acting reversible contraception (LARC) in St. Louis, USA

Methods Recruited sexually active women who wanted to avoid pregnancy but were not currently using a contraceptive or wanted to start a new reversible method. Counseling was provided to increase awareness of LARC methods. Each participant was provided her contraceptive method of choice at no cost for 3 years.

Data Analyses Include Continuation and satisfaction rates for the different methods; pregnancy rates for LARCs vs shorter-acting agents

Secura GM et al. *Am J Obstet Gynecol.* 2010;203:115.e1–115.e7. **2.** Peipert JF et al. *Obstet Gynecol*. 2011;117(5):1105–1113.

The CHOICE-study; choice of method when all methods are free (2007-2011, St Louis, USA)

	Andel kvinnor (%)
LARC* (n=6942)	75
Depo (n=648)	7
COC, patch, ring (n=1666)	18

*Long-acting reversible contraceptives

K.Gemzell Danielsson

Peipert JF, et al. Obstet Gynecol 2011;117;1105-13

CHOICE USA: Less failures with LARCs

LARC* Depo Pill, Patch, Ring (PPR)

*p=0,001 vs PPR

Failures (%)

12
10
8
6
4
2
0

* *

1 2 3

År

Bild gjord av Winner, modifierad av Bayer

*LARC, Long acting reversible contraceptive

K.Gemzell Danielsson

Winner B, et al. NEJM 2012;366:1998-2007

Many births to teenagers/adolescents are unintended

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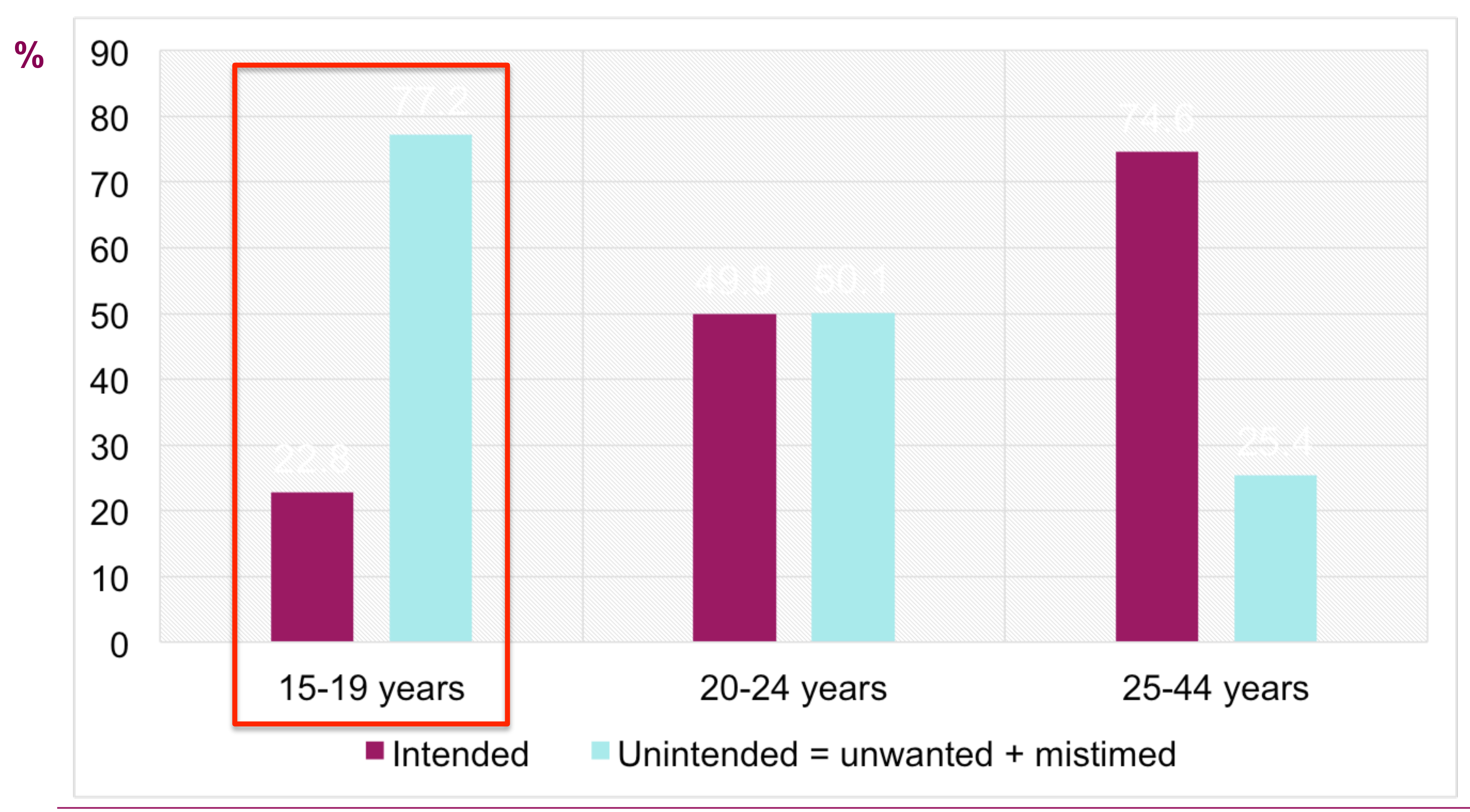
Intendedness of births by mother's age at conception, USA, 2006-2010

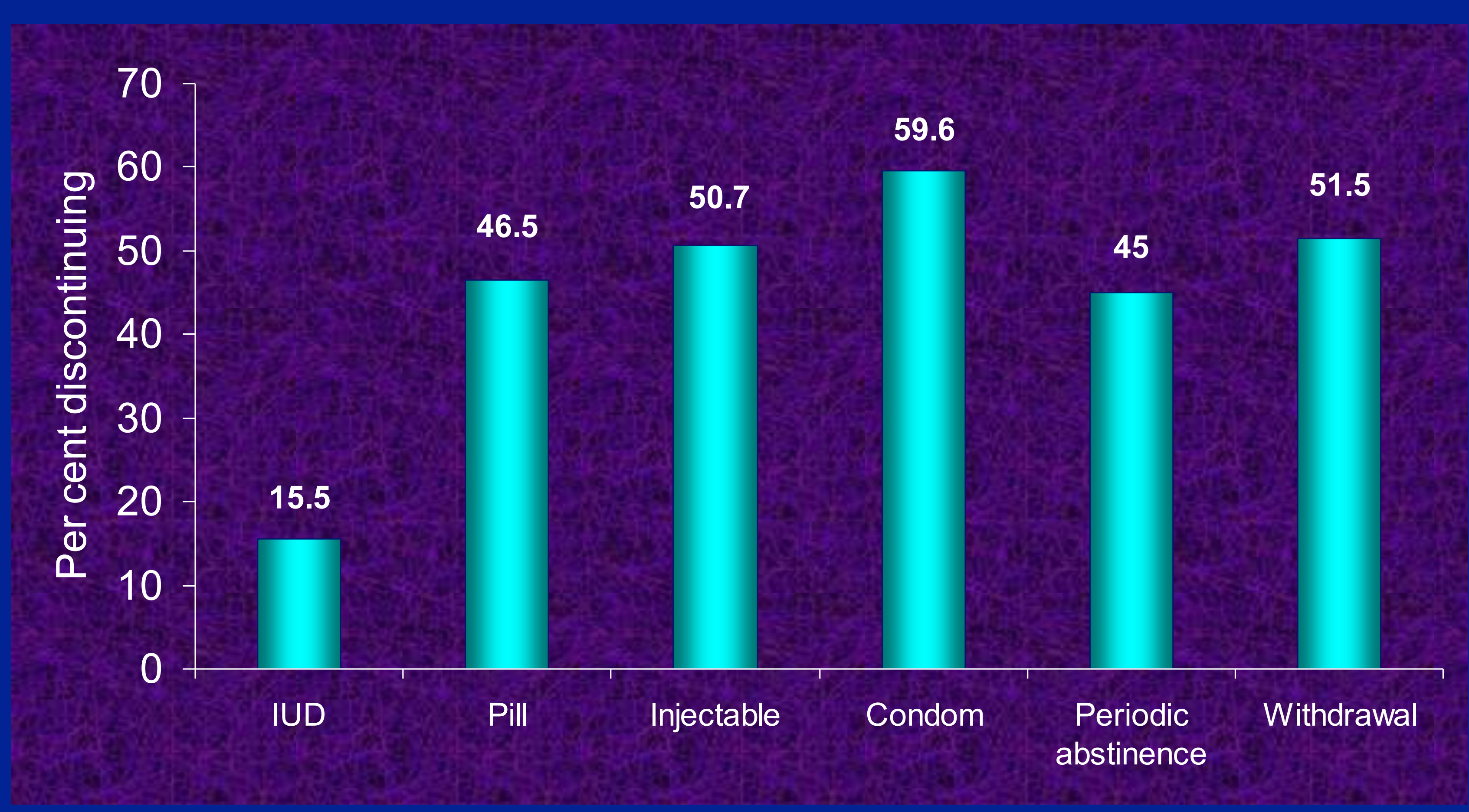


Adapted from: Mosher WD, et al. Natl Health Stat Report. 2012; 55:1-28

Effektivitet vid typisk användning

Produkt	Metod – maximal användning	PI typisk användning 1a året
Nexplanon	Stav – 3 år	0.05
Mirena	Spiral – 5 år	0.2
Kayleena **Jaydess**	Spiral – 5 år Spiral – 3 år	0.29 0.33
Kopparspiral	Spiral -5 el 10 år	0.8
Depo-Provera	Injektion – 3 mån	6

12-month cumulative probability of overall discontinuation per 100 women, 18 developing countries



(Source: UN Population Division,2004; Courtesy P Van Look)

In the CHOICE-study highest satisfaction reported with LARCs

evaluation at 12 months FU

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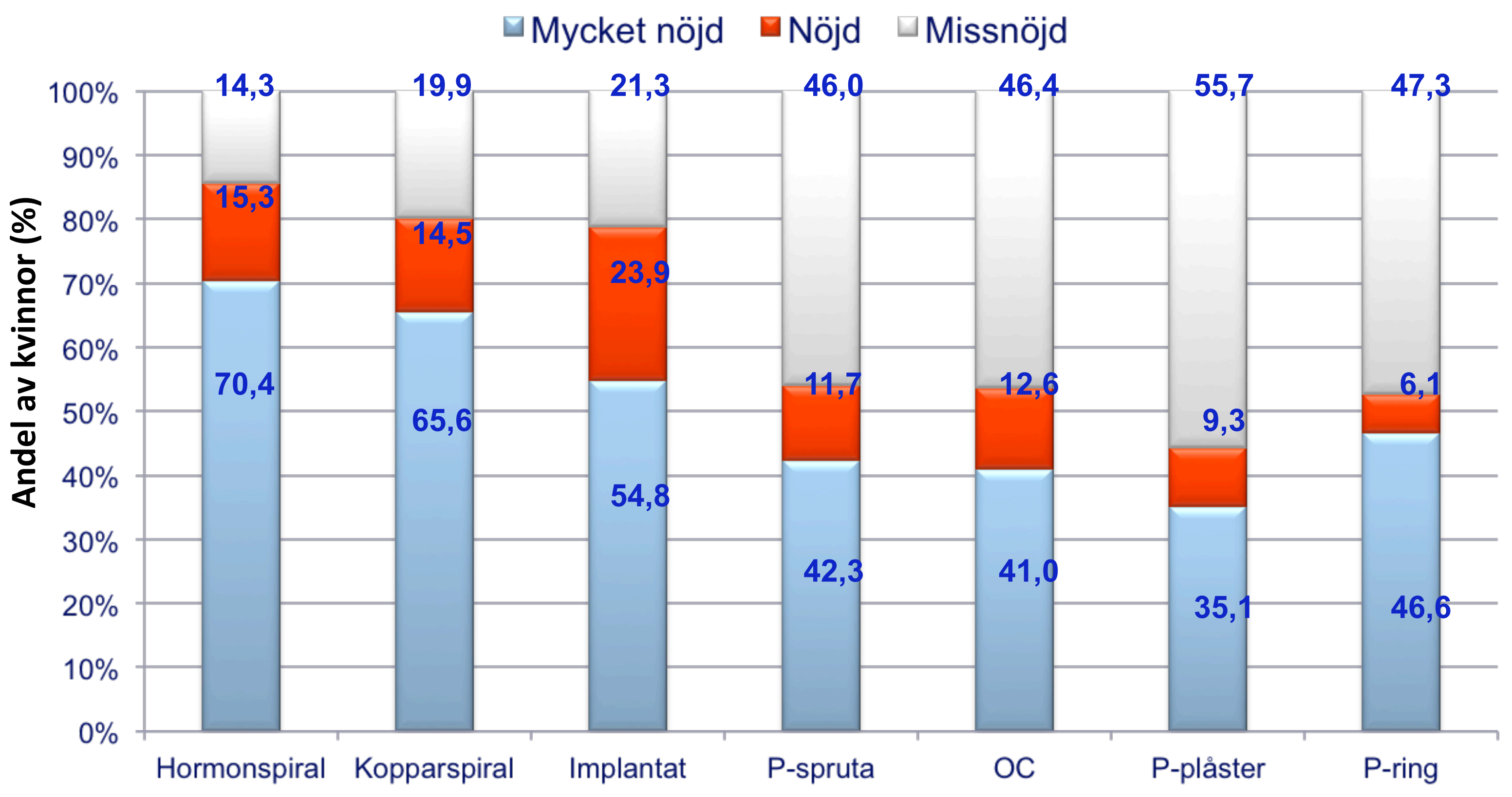

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Peipert JF, et al. Obstet Gynecol 2011;117:1105-13

The long way of developing safe and effective IUDs

The long way of developing safe and effective IUDs

Cupper added
1969

Improved forms of IUDs >1980

Progesterone IUD 1990

Stem pessaries
≈1900

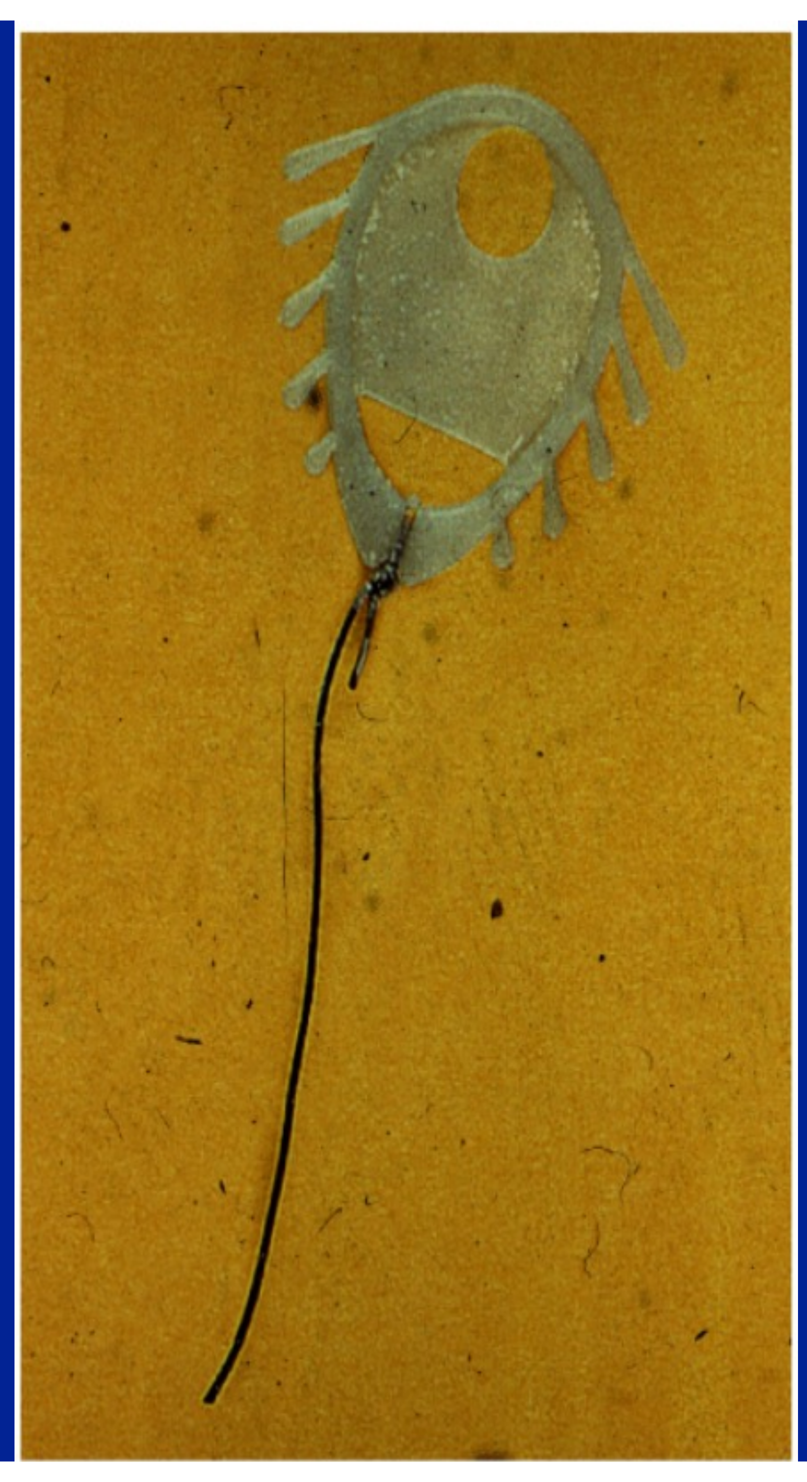
Silk rings
>1900

Stainless steel
rings 1920

Plastic devices
1960

IUD/IUS, K.Gemzell

LIPPES´ LOOP



DALKON SHIELD

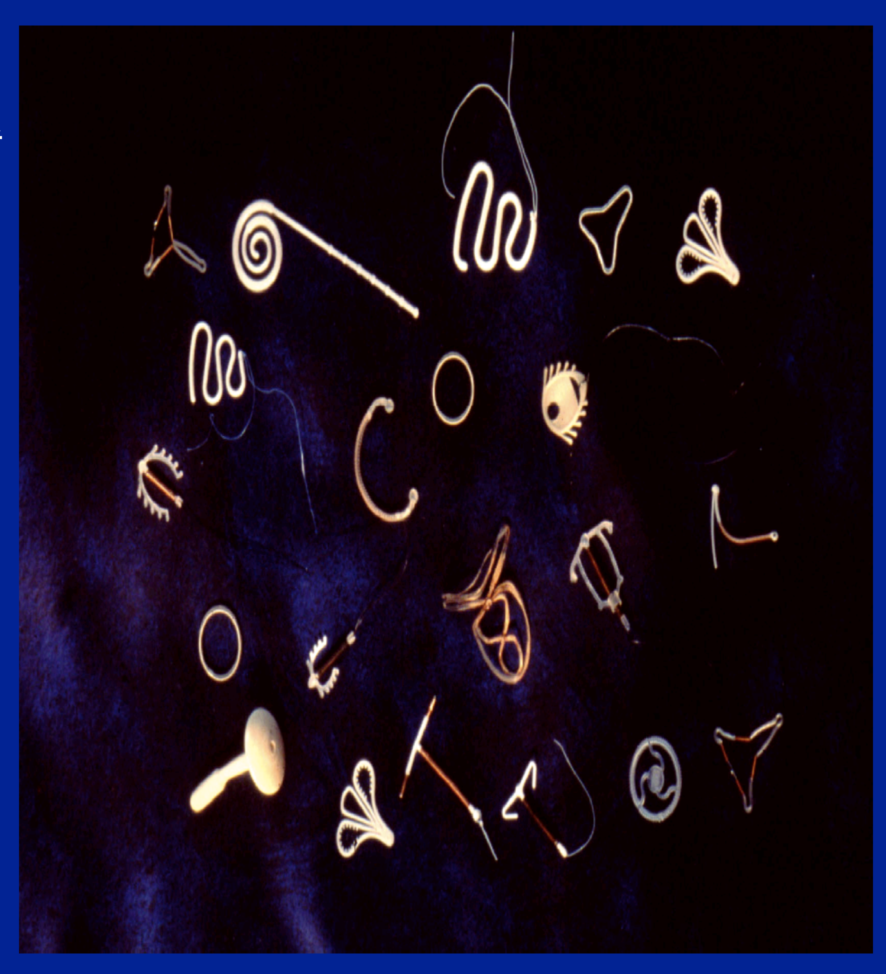
Medication with copper increased efficacy

(*Zipper et al 1968*)

Development of intrauterine contraception

EFFICACY IMPROVEMENT

	Pearl Index
Metal rings (1920)	8-10
Plastic devices (1950)	3-5
Copper added (1970)	1,5-4
Expanded Cu (1980)	1-1,5
Frameless Cu (1990)	1-1,5
Progestagen (1990)	0,5-1



IUD use

160 miljoner spiralbärare!

Efter sterilisering den mest använda preventivmetoden globalt 15% av fertila kvinnor

Vanligast i Asien

Används av 20-25% sexuellt aktiva kvinnor i Norden

USA 8%

Den mest kostnadseffektiva preventivmetoden

MECHANISM OF ACTION
Copper IUD

Spermatotoxic

Local reaction in the endometrium

PREVENTION OF FERTILISATION

Cu-IUD

A prototype of “forgettable contraception” that can be ignored for years….

Modern Cu-IUDs with >300 mm^2 and with good documentation regarding efficacy and usage (in utero) should be chosen

Approved for 5 (or 10 years)

Failure rate of 1% up to 10 years

Fördelar Cu IUD

Effektiv

Icke hormonell metod

Långverkande

Snabb återgång till fertilitet

Ej korrelerat till samlag

Hög compliance

Skydd mot endometrie-, tubar- o cervixcancer

(Cochrane)

Nackdelar

Dysmenorre

Ökad blödning (50-75%)

Utstötning

Ger ej skydd mot STI

(Ej ökad virusutsöndring vid HIV)

Ökad frekvens vaginos

Insättning kräver träning, kan vara smärtsam

Mirena

Mirena (Leiras Oy, Turku, Finland)

Invented by T Lukkainen. Developed by the Population Council in collaboration with Leiras

- •Releasing 20 mcg LNG daily
- •Length 32mm
- •Total with of horizontal arms 32mm

Medication with progestagen originally to prevent expulsion

LNG IUS: Mechanism of Action
Prevention of fertilisation

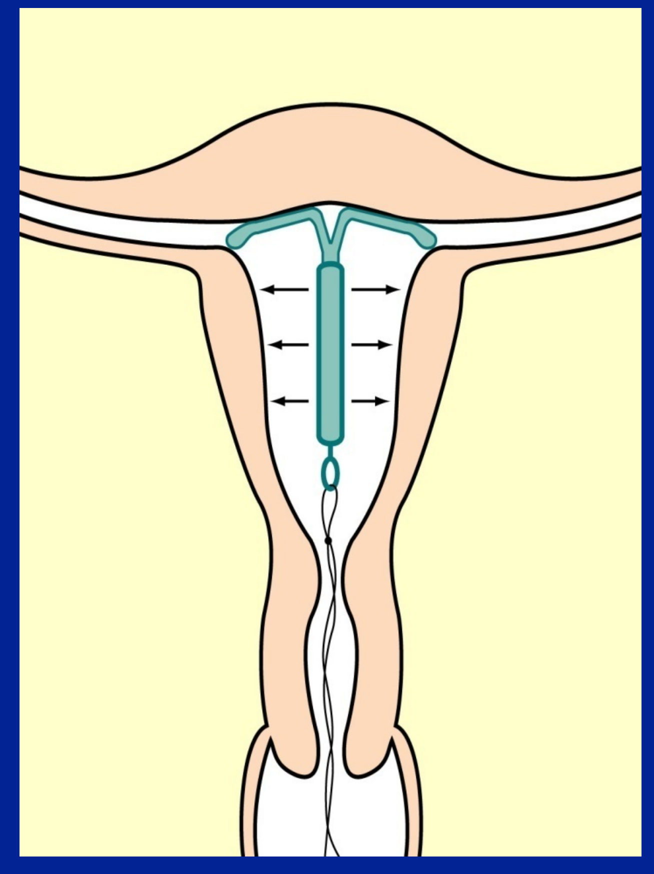
Fertilization inhibition:

- Cervical mucus thickened
- Sperm motility and function inhibited

Endometrium suppressed

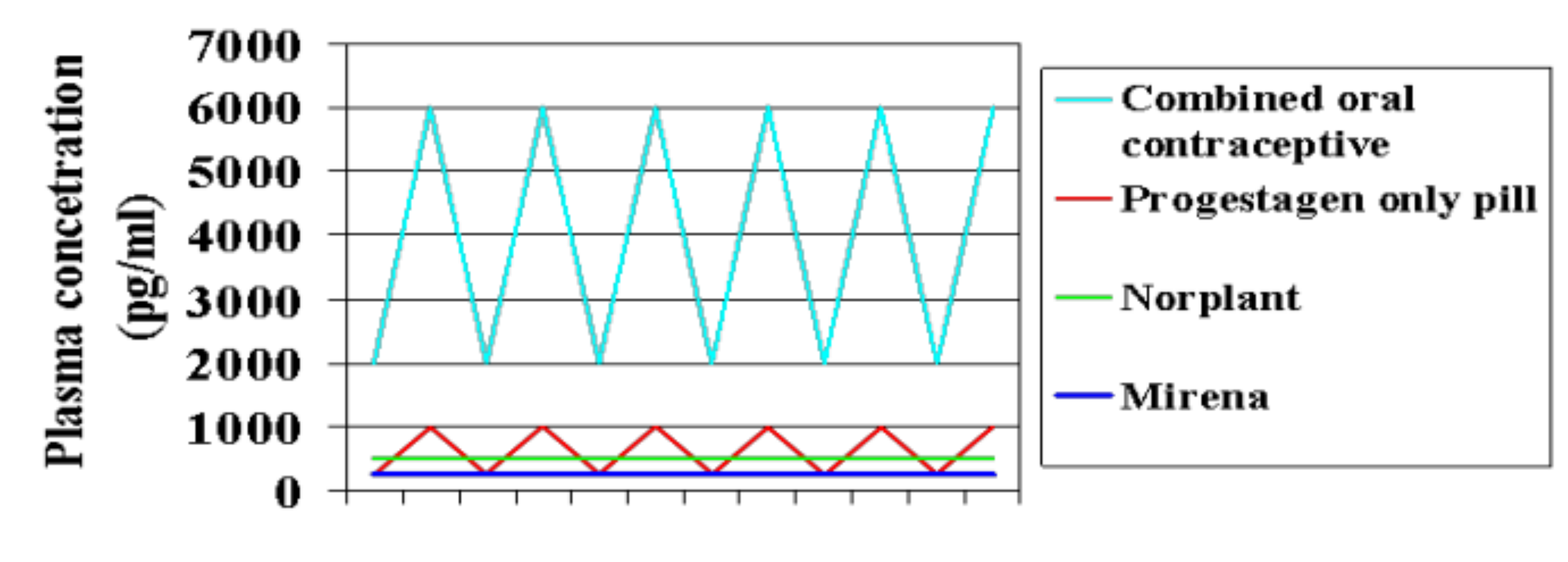
- Weak foreign body reaction induced

Minor effects on ovarian function



Jonsson et al. *Contraception* 1991;43:447
Videla-**Rivero et al.** ***Contraception*** **1987;36:217**

Pharmacokinetics of levonorgestrel with Mirena®



Continuous drug delivery ➞ Mirena® does not cause ‘peaks’ and ‘troughs’, as with oral progesterone

Nilsson et al., 1982

LNG concentrations

Endometrium	470- 1500 ng/g
Myometrium	1.8-2.4 ng/g
Plasma	0.1-0.2 ng/ml

Nilsson et al. Tissue concentration of LNG in women using LNG-releasing IUD. Contraception 1982

Return of fertility after removal of Mirena®

- Cyclic ovarian function is immediately restored
- The endometrium recovers quickly and

  normal menstruation is established within 30 days
- Overall fertility is unaffected
- Cumulative conception rate after removal:

  79 - 96 % after 24 months
- Pregnancies progress as normal

Rybo et al., Ann Med 1993
Andersson K. et al, Contraception 1992; 45: 575-584
Sivin I. et al, Am J Obstet Gynecol. 1992; 166: 1208-13
Belhajd H. et al, Contraception 1986; 34: 261-7

Tolerability and safety of Mirena®

- Side effects are rare and reversible
- Transient hormone-related side effects can occur in first months of use:
  - e.g. headache, breast tenderness, acne, and mood lability
- Enlarged ovarian follicles may occur (as with other progesterone-only methods) (<8%)

- No clinically significant changes in serum lipid profile, haemostasis or carbohydrate metabolism
- No effects on blood pressure and body weight

- Mirena® improves serum haemoglobin and serum ferritin levels through reduced menstruation

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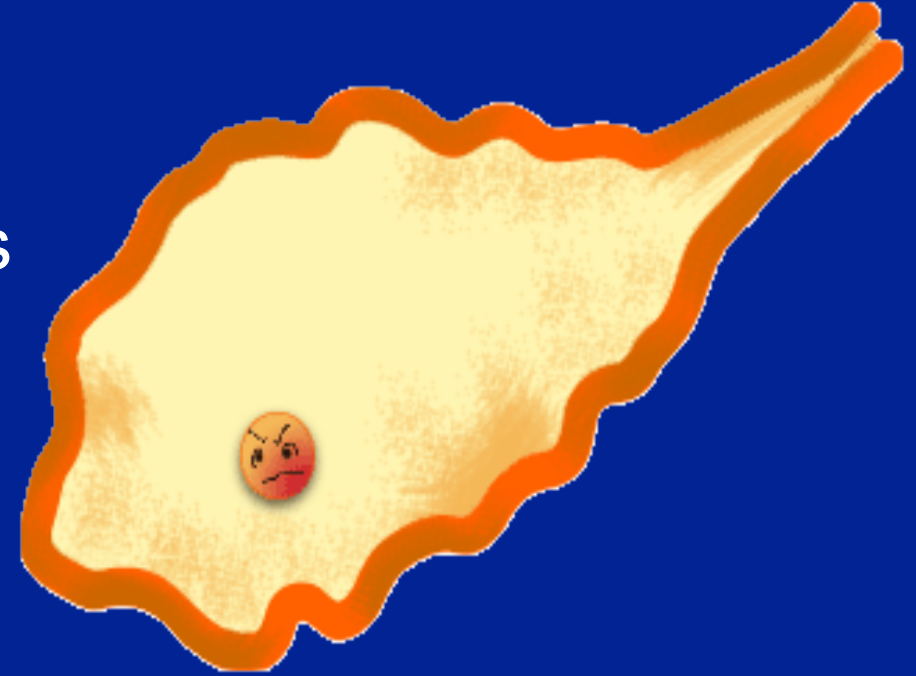
For further information pls. see the product prescribing information.

LNG IUS: Persistent Follicles

As with other progestin-only methods, persistent follicles can occur (in less than 8 % of women).

They do not require treatment!!



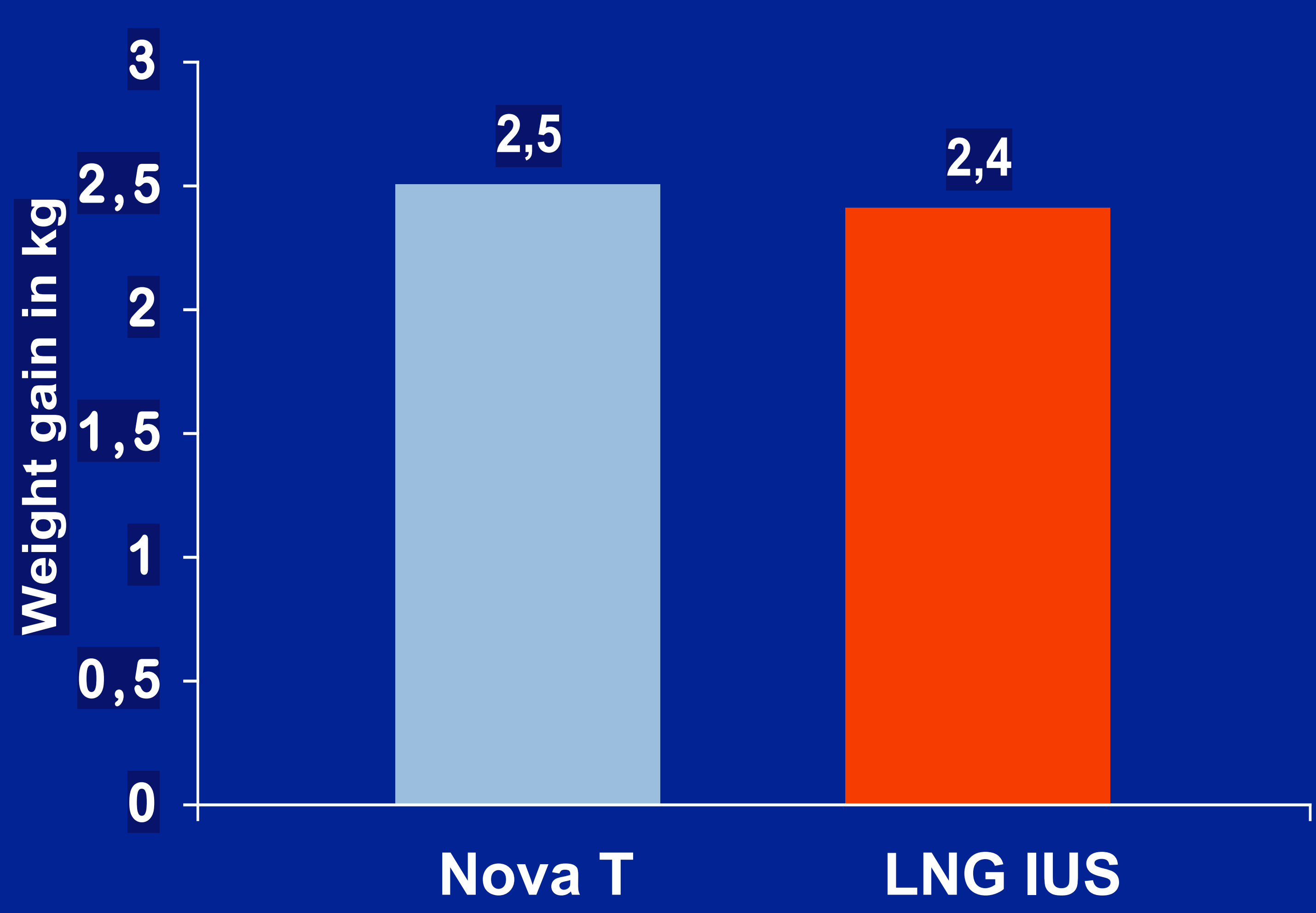
Pakarinen et al. *Fertil Steril* 1997;68:59

Side effects of Mirena

	3 months(%)	5 år(%)
Lower abdominal pain	10.5	3.1
Acne, skin problems	3.5	1.2
Back pain	3.1	1.0
Mastalgia	3.1	1.0
Headache	3.8	1.6
Vaginal discharge	2.7	<1
Mood changes	2.5	<1
Nausea	2.4	<1
Edema	1.1	<1

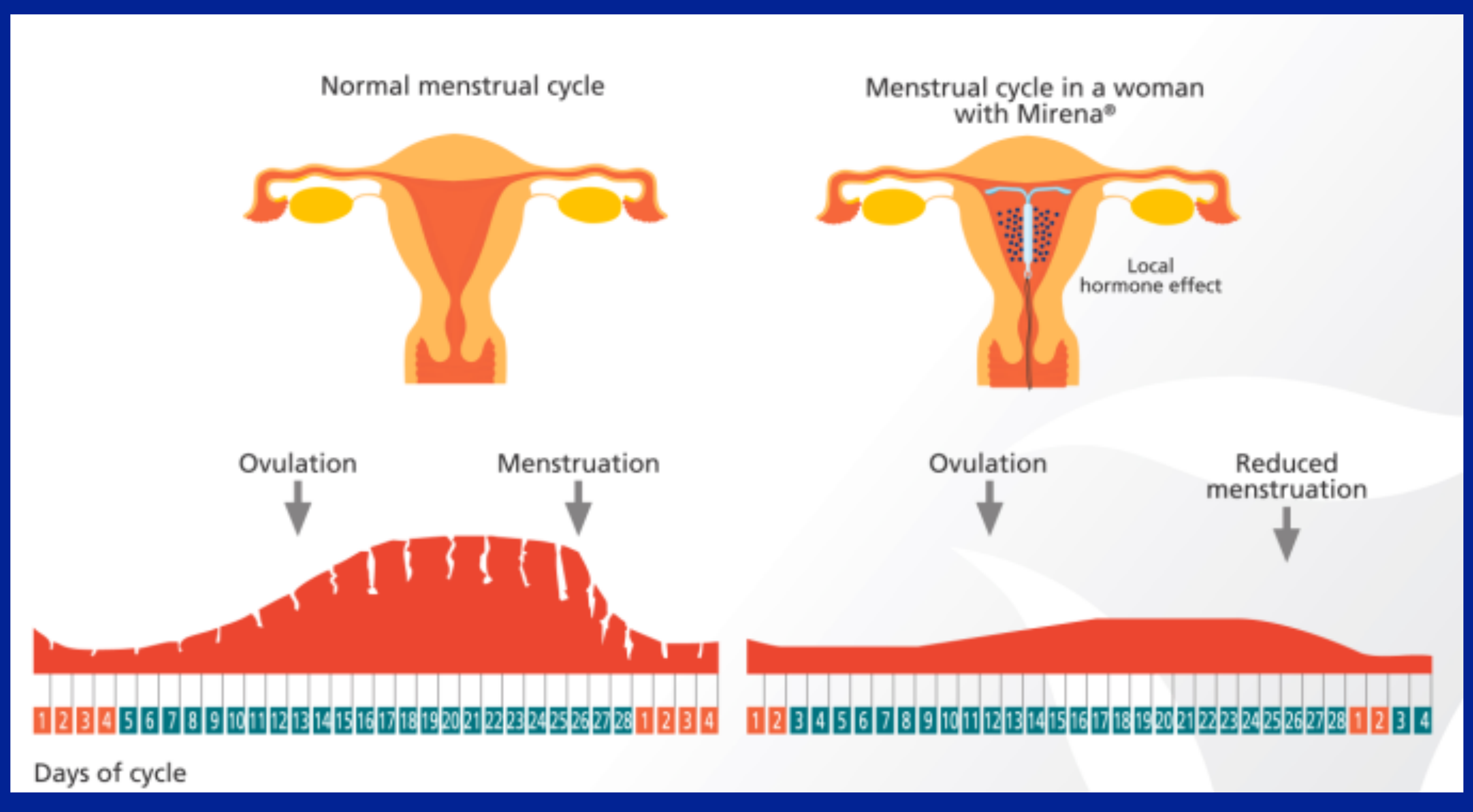
(Andersson et al 1994)

Cu vs LNG IUC:
Mean Weight Change After 5 Years



Andersson et al. Contraception 1994;49:56

Endometrial effects with Mirena®



Bleeding with Mirena®

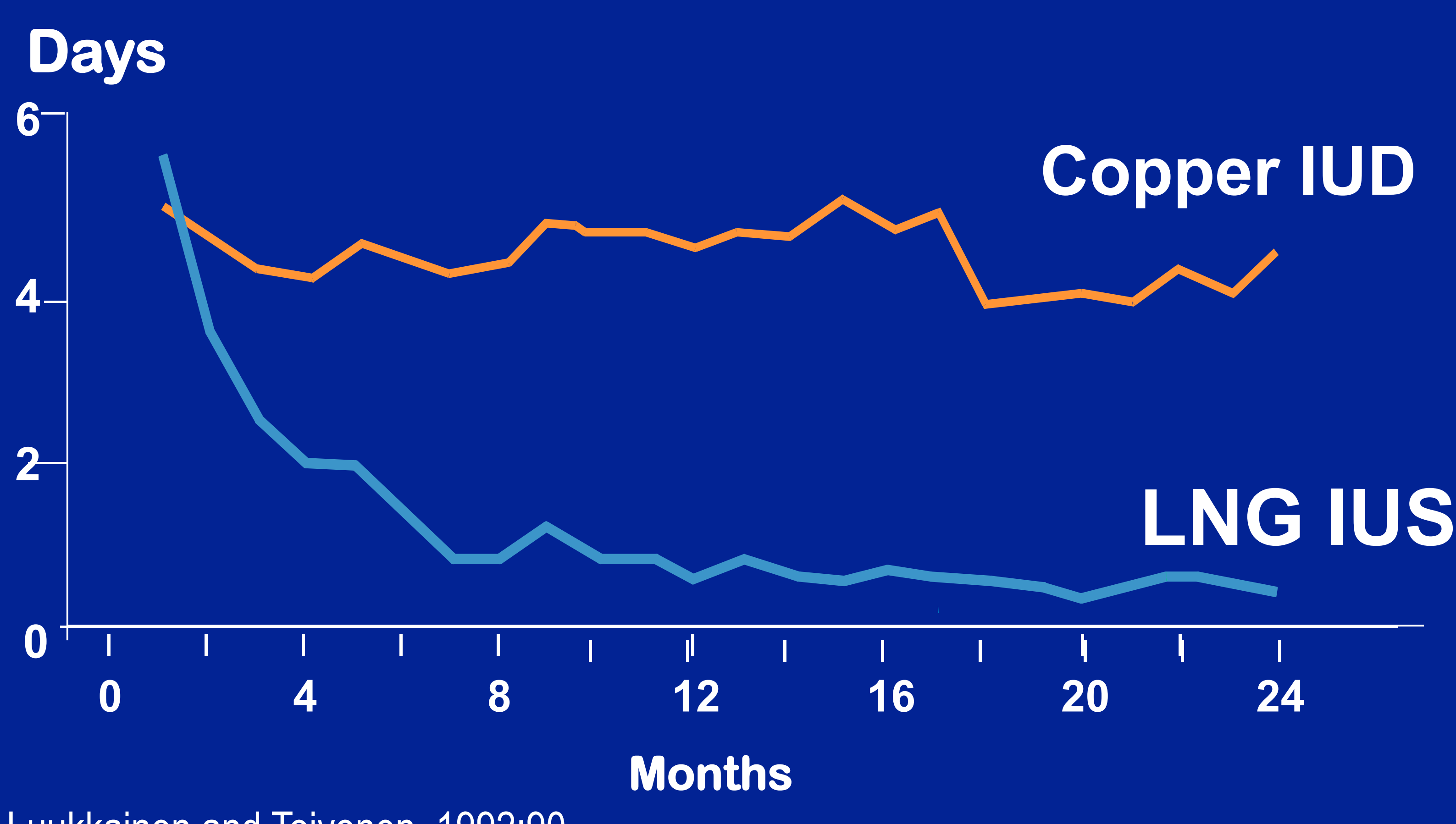
Endometrial growth is reduced or blocked

Oligo- or amenorrhea in most patients

Inform patients about positive impact of reduced menstruation or amenorrhoea

Remember: irregular bleeding or spotting occurs during the first months!

Number of Bleeding Days: Cu vs LNG



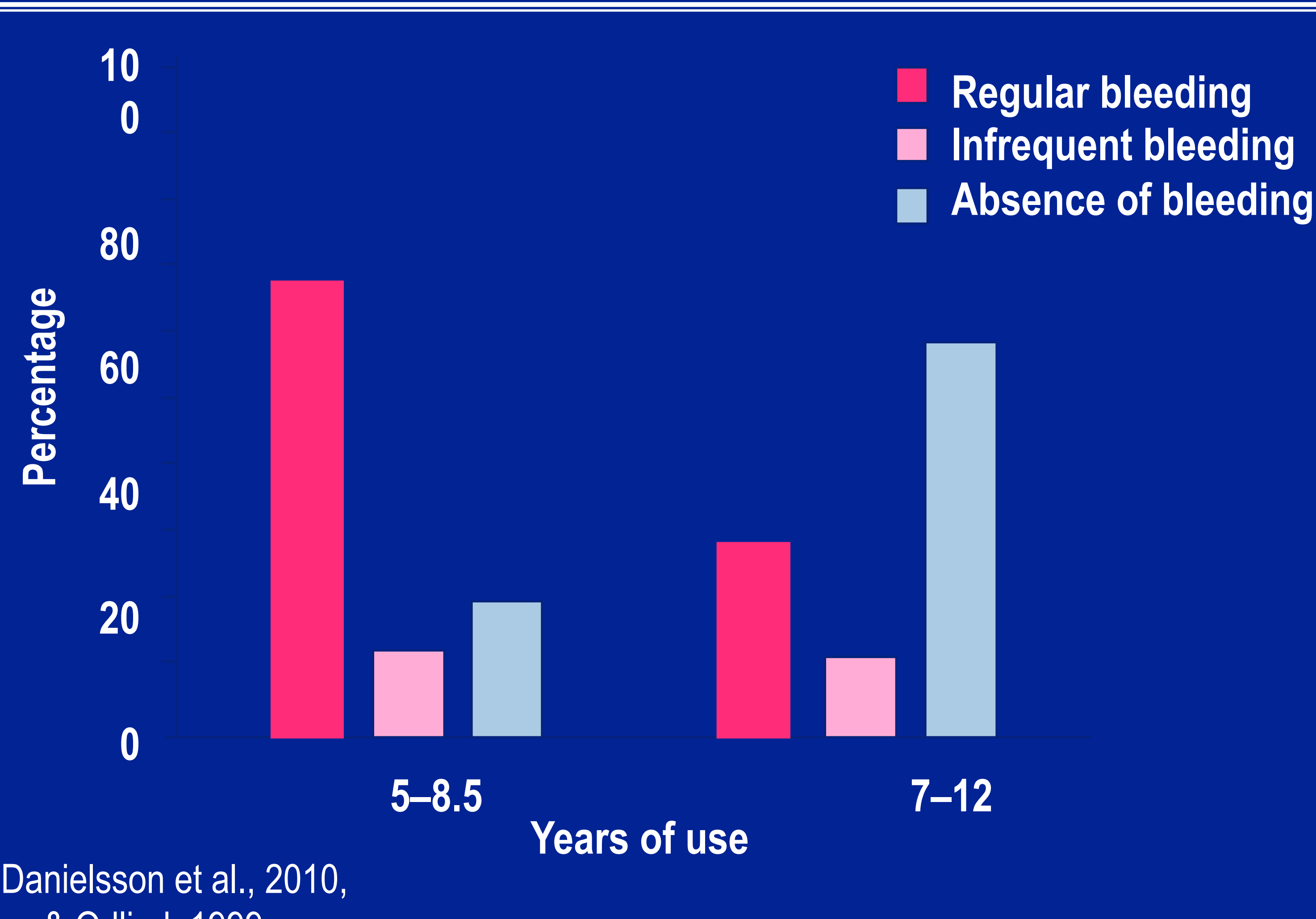
Luukkainen and Toivonen. 1992;90

Menstrual blood loss

A limitation with Cu-IUD in young nulliparous women is increased menstrual flow (Milsom et al.,1989)

Older large inert IUDs	+100%
Modern copper-IUDs	+50-75%
LNG-IUS	-60-90%

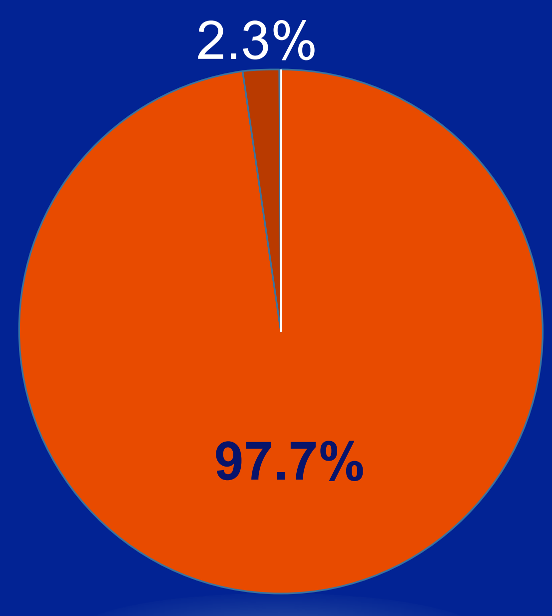
Byte direkt från en Mirena till nästa efter 5 års användning ger minskad blödning!



Gemzell Danielsson et al., 2010,
Rönnerdag & Odlind, 1999

Satisfaction with Amenorrhea

All women who did not experience bleeding while using Mirena® were satisfied with it



IUS/IUD and young nulliparous women

Myth: Nulliparas cannot use

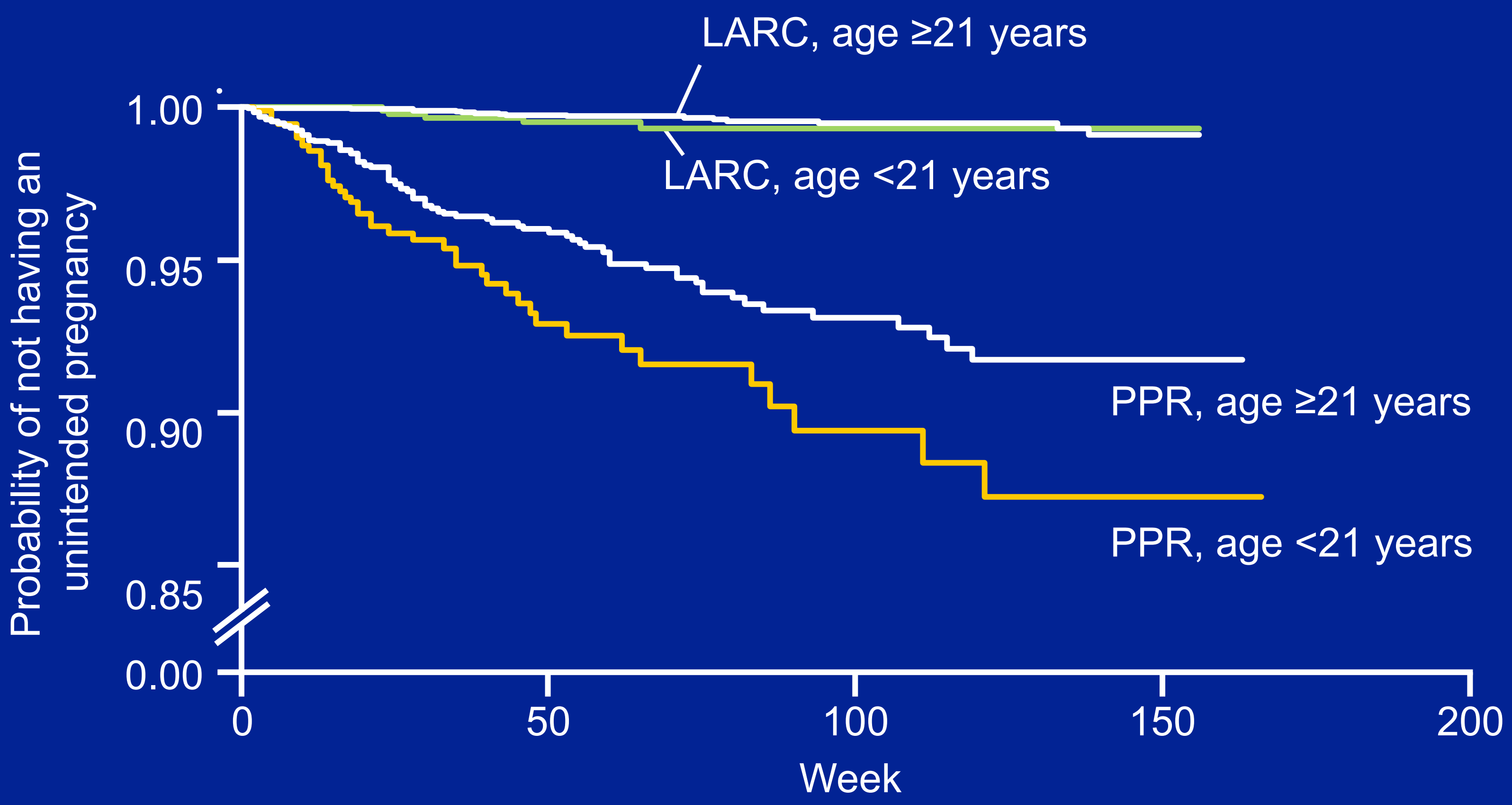
Benefits	Concerns/ Barriers
Highly effective	IUD and risk for PID
Reduce mentrual blood loss	Ectopics
Reduce menstrual pain	Infertility
Long term contraceptive	Less accepted than COC ?
Immediate return of fertility after removal	

IUD highly effective contraceptive method also in young or nulliparous women

WHO 1987

Adolescents and nulliparous

Women <21 years of age using pills, patch, or ring had almost twice the risk of unintended pregnancy as older women (hazard ratio 1.9; 95% CI 1.2–2.8; p=0.02)



LARC, long-acting reversible contraceptive; PPR, pill patch or ring; 95% CI, 95% confidence interval

1. Winner B, et al. N Engl J Med 2012;366:1998–2007

CHOICE: LARCs associated with improved continuation rates & reduced teenage pregnancies/ abortions

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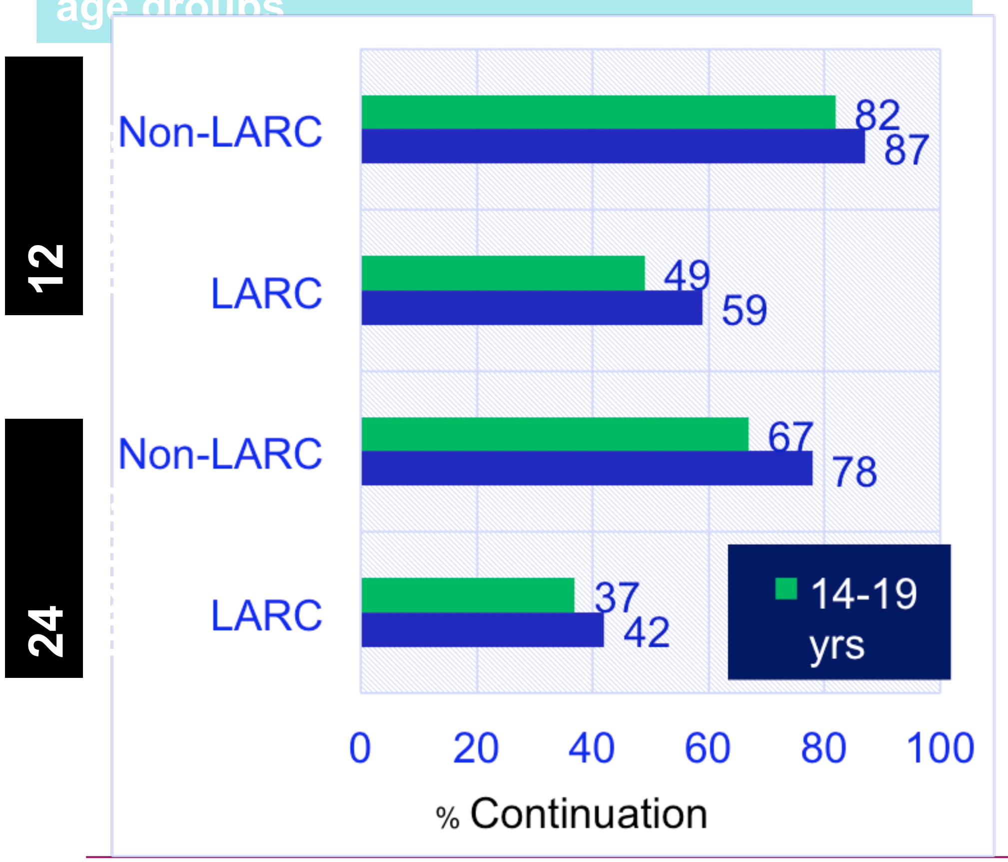
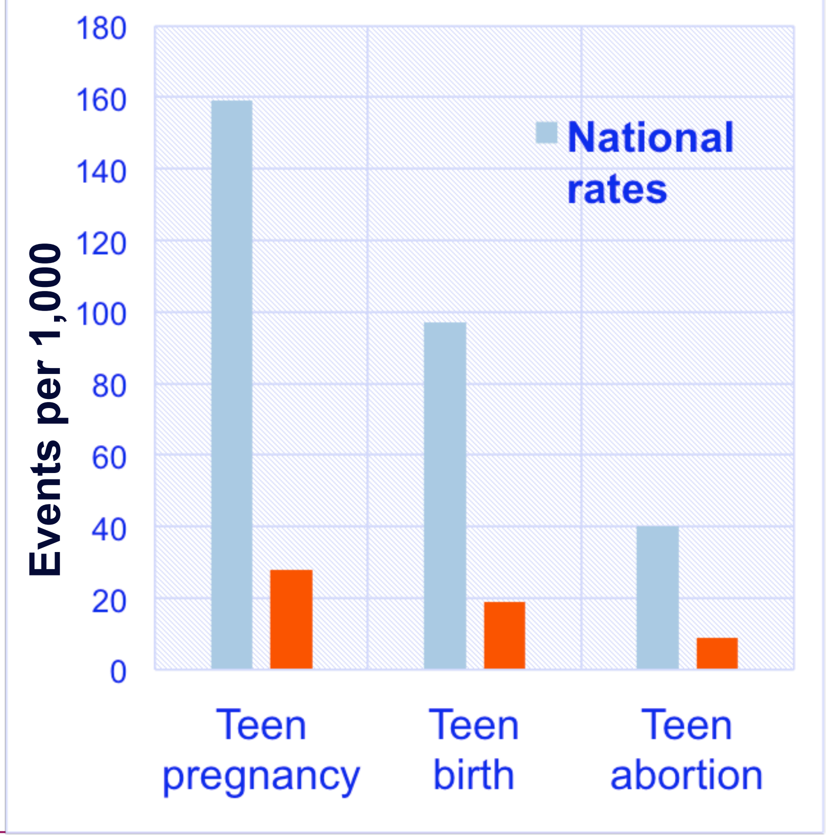
Continuation rates with LARC greater than with non-LARC method at 12 and 24 months, in both 14-19 year and 20-45 year age groups

75% reduction in teen pregnancy, birth and abortion for each during CHOICE *vs.* national rates





K.Gemzell Danielsson

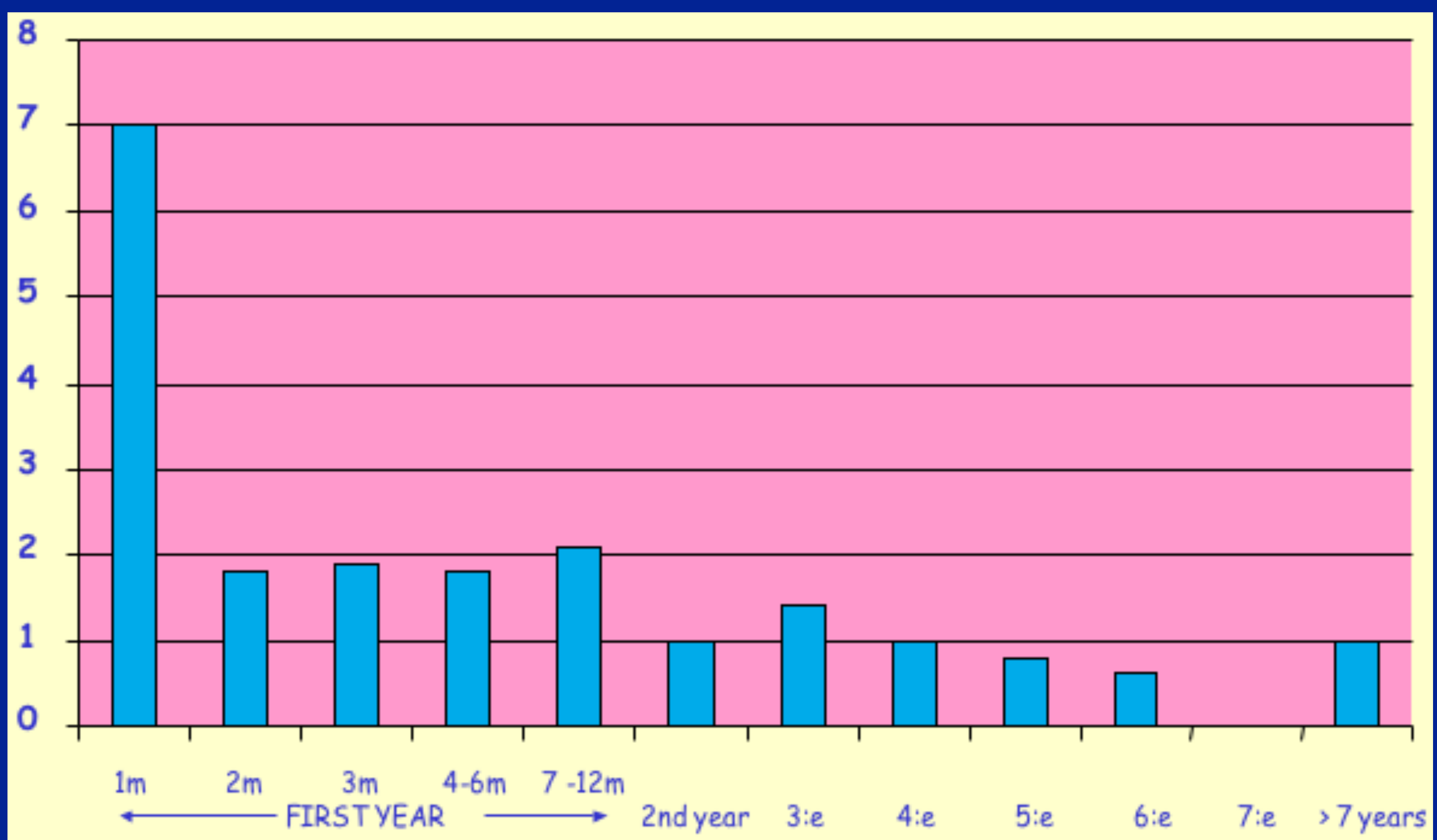
Adapted from: McNicholas C, et al. Clin Obstet Gynecol. 2014;57:635-43

Does an IUD cause PID?

PID is caused by bacteria

- which are transmitted sexually
- or introduced from the cervix at IUD insertion

Does an IUD cause PID?



Number of PID cases per 1000 woman years after insertion of Cu-IUD

Modified after Farley et al, Lancet 1992;i:785-788

Pelvic inflammatory disease
5-year cumulative gross termination rates

Age	Nova T	Mirena
≤ 25	5.6	0.3*
26–30	3.0	1.4
31–35	1.4	0.7
≥ 36	0	0.3
Total	2.2	0.8*

*$p < 0.01$

Mirena® reduces the rate of PID

Andersson, Odlind, Rybo Contraception1994

IUD use in nulliparous women and tubal infertility

Odds ratio of tubal infertility in nulliparous women after previous use of a copper IUD:

OR 1,0 (0,6, 1,7)

Hubacher et al N Engl J Med 345:561-567, 2001

IUD and ectopic pregnancy

Type of device	Woman years	Pregnancies per 1000	Ectopics per 1000
Non-medicated	4,600	19.0	0.87
T Cu<200 mm^2	21,200	20.8	0.75
T Cu>200 mm^2	39,200	7.3	0.23
LNG-IUS	5,600	0.9	0.20

Mirena protects against ectopic pregnancies

Sivin, Obstet Gynecol 1991

When to insert after post-partum

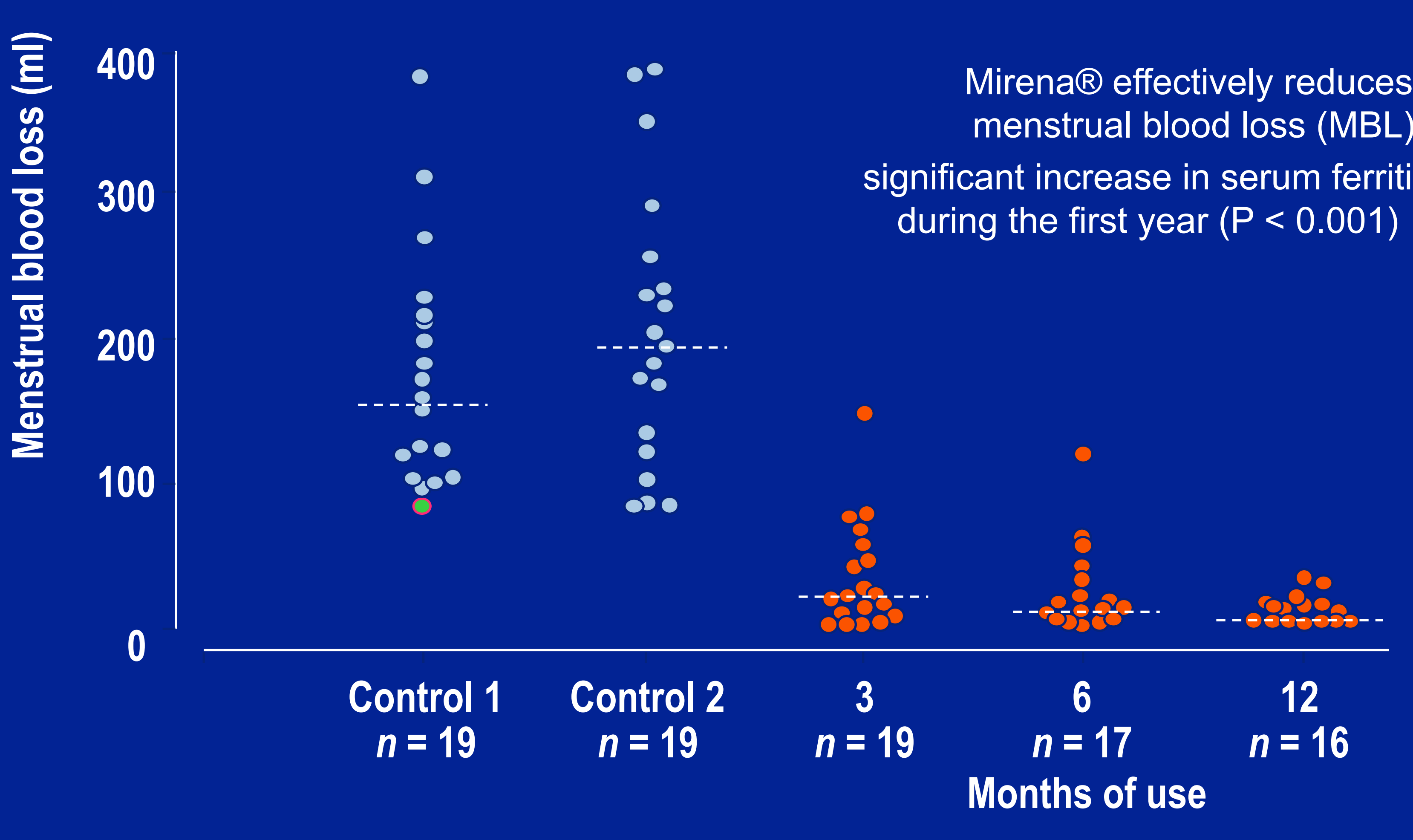
- Mirena® can be inserted immediately after placenta expulsion or after the uterus is fully involuted
- WHO medical eligibility criteria supports fitting of IUDs after 6 weeks post-partum
  - uterus fully involuted
  - reduced risk of infection
  - Higher risk for perforation (reduced pain)

Kennedy et al. Contraception 1997
Clinical Effectiveness Unit, J Fam Plann Reprod Health Care, 2004

Mirena® and the treatment of HMB

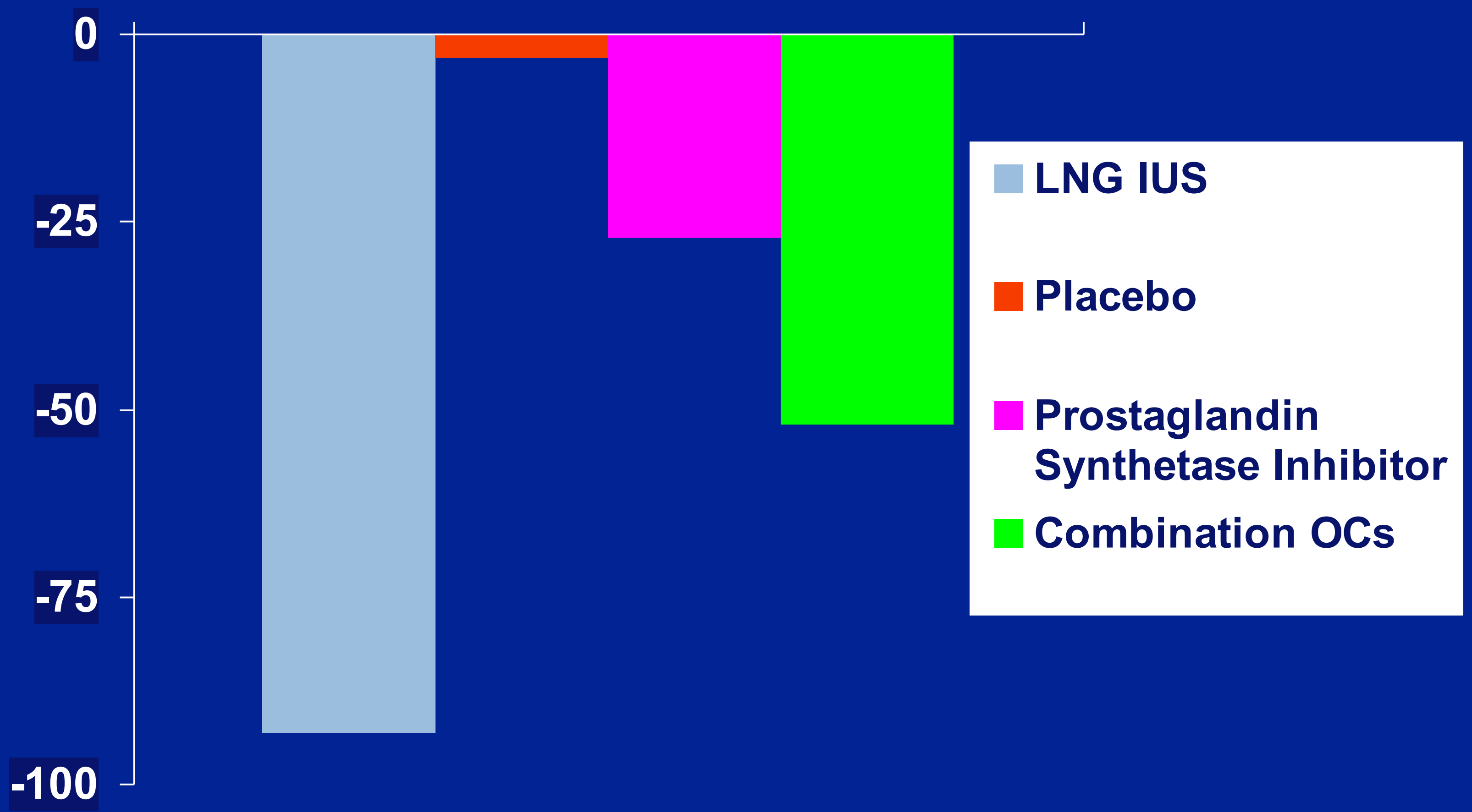
- Background
  - HMB is a common complaint: one third of fertile women complain about heavy menstrual bleeding at some point of their life
  - HMB has a significant impact on the quality of life of women with a decrease comparable to the chronically ill
  - HMB requires resources and money

Menstrual blood loss in menorrhagic women before and after Mirena® insertion



Andersson & Rybo, 1990

LNG IUS: Percentage Reduction of Menstrual Blood Loss

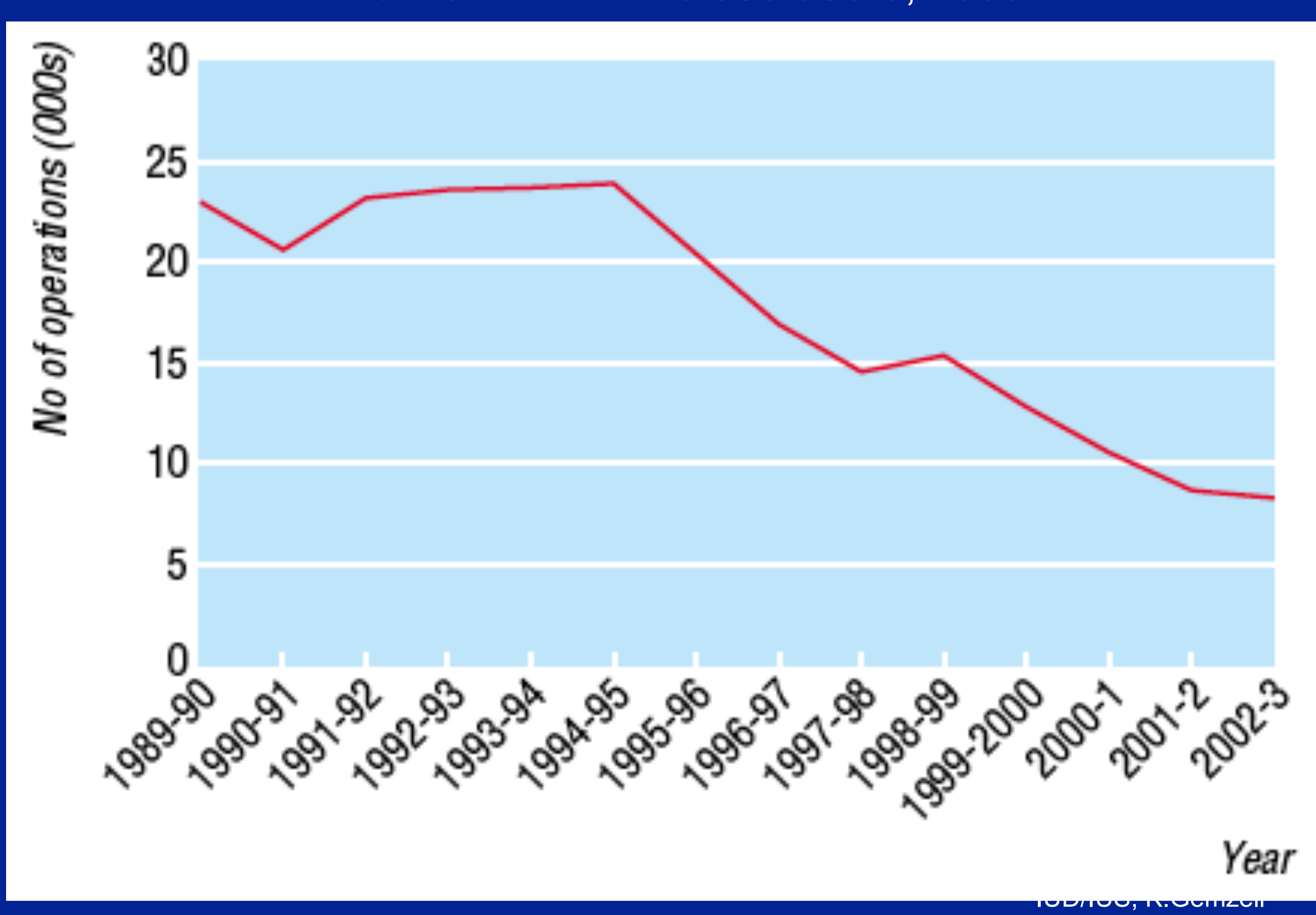


Mirena® is significantly more effective than flurbiprofen or tranexamic acid in reducing MBL

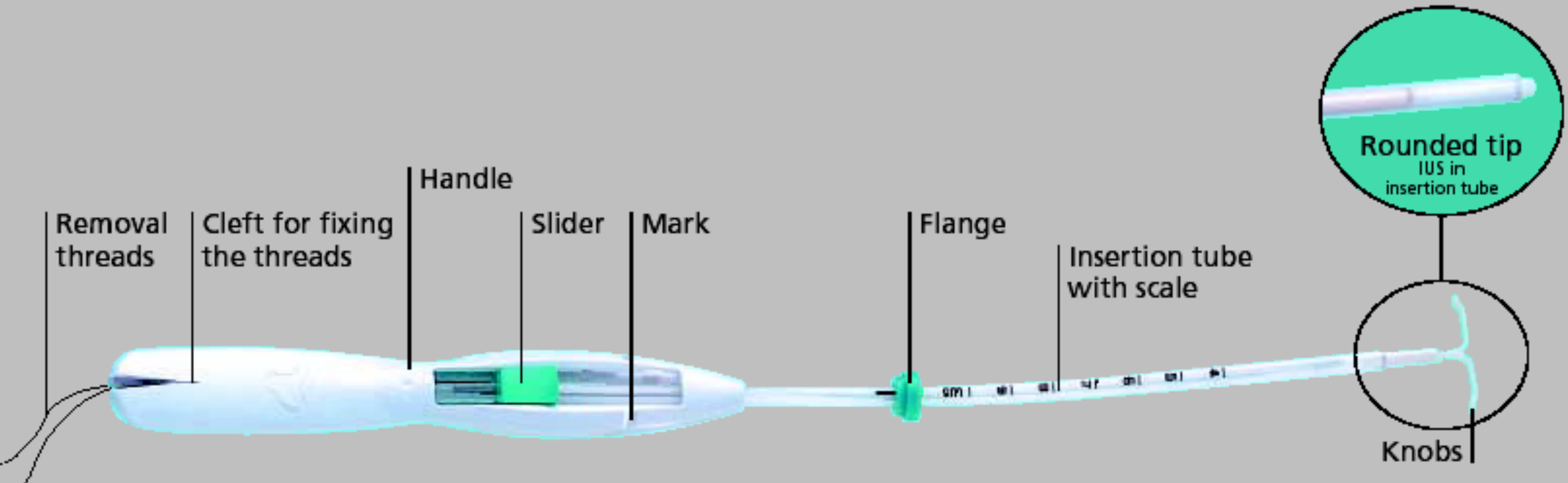
Milsom et al. Am J Obstet Gynecol 1991;164:879

Number of hysterectomies for menorrhagia from 1989/90-2002/3 in NHS in England

Reid & Mukri BMJ 330 938-9, 2005



Insertion/Removal



Technical features	Benefits
• Anatomical design of the insertion tube pre-bent and better supported inside	• Avoids need for user to bend it • Reduced risk of kinking
• Functional design of the handle	• Easy to insert with one hand
• Rounded tip can not slip into insertion tube	• Easier handling
• Scale printed on the insertion tube	Only one direction movement with the thumb
• Threads do not tangle	

Timing of insertion of IUD/ IUS

General consideration:

- Not pregnant
- Cervix open (Reduced pain and risk of perforation)
- Reduced insertion induced bleeding

↓

Menstruation is the ideal moment

But insertion can be done at any time during the cycle

Insertion/Removal

- Failed insertion, complications and side effects more common among women with no previous vaginal delivery (Wildemeersch et al., 2003)
- Fear of painful insertion may make women hesitate to use an IUD
- Cervical priming using misoprostol PGE1 analogue:
  - Widely used for cervical priming
  - Effect dependent on dose, route and duration
  - Effective also in non-pregnant women (Ngai et al., 1997, Thomas et al., 2002)
  - May make insertion easier (Sääv et al., 2007)

Myth: It takes time to explain

The importance of counselling

KISS

- Reduced bleeding/amenorrhoea: Take time to explain the advantages and to correct wrong fantasies
- Explain about the spotting which will decrease with time (Sex and tampons possible)
- Inform about the size of the IUD and explain the size of the inserter

Insertion/Removal

- **motivation!**
- Fear of painful insertion may make women hesitate to use an IUD
- Verbal anesthesia
- Hot water bottle
- PCB
- Cervical priming using misoprostol :
  - 2 table sublingualt 1h innan alt vaginalt/oralt 3h innan
- Teknik, klotång, sond
- NSAID

Spiral och graviditet

Extraktion om möjligt snarast

Ökad risk för missfall, prematur förlossning

Ingen ökad risk för fosterskada

WHO recommendations for IUD use

MENSTRUAL ABNORMALITIES, light bleeding/spotting

Spotting during first 3-6 months is common – No action

NSAID may be given during days of light bleeding

If bleeding persists – pathology must be ruled out

If bleeding persists and no pathology can be identified – switch to other method

Selected practice recommendations for contraceptive use.
Geneva, World Health Organisation, 2002

WHO recommendations for IUD use

PELVIC INFLAMMATORY DISEASE:

Treat with antibiotics

There is no need to remove IUD if woman wishes to continue

Remove IUD after treatment has started, if women wishes to remove IUD

If IUD is removed, ECP can be considered

If infection does not clear – always remove IUD

Selected practice recommendations for contraceptive use. Geneva, World Health Organisation, 2002

Koppar- och hormonspiral - LV

Kopparspiral med kopparyta >300 mm^2 samt med **god** dokumentation avseende effektivitet och användningstid bör väljas

godkänd för 5 eller 10 år

Inför insättning bör infektion uteslutas och vid misstanke om infektion skall IUD inte sättas in

Profylaktisk antibiotikabehandling rekommenderas inte inför insättning

Spiral kan rekommenderas oavsett om kvinnan varit gravid eller ej

LNG-Intrauterine systems (IUS)

	Jaydess®(Skyla®)	Kyleena®	Mirena®
Total LNG content, mg	13.5[1]	19.5[2]	52[3]
Average release rate over the first year, µg/24 hours	8[4]	12[4]	20[4]
T-frame dimensions, mm	28 × 30[1]	28 × 30[2]	32 × 32[3]
Insertion tube diameter, mm	3.80[2]	3.80[2]	4.40[*3]
Maximum duration of use, years	3[1]	5[2]	5[3]
Silver ring	Yes[1]	Yes[4]	No[1]

K.Gemzell Danielsson

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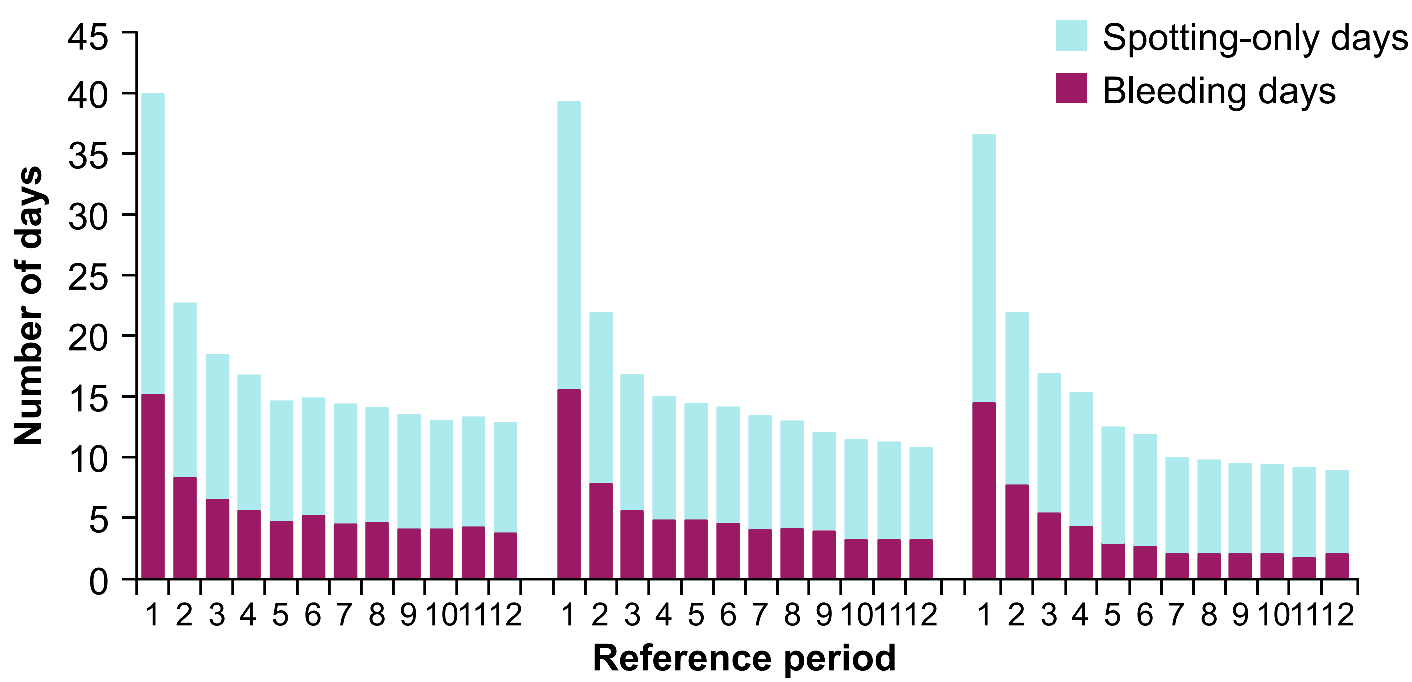
Mean number of bleeding/spotting days by 90-day reference periods



- Mean number of bleeding/spotting days decreased similarly over time in each of the treatment groups; greatest reduction between first and second 90-day period
- After the second 90-day reference period (month 6), ≥50% of subjects in each subsequent reference period had four or fewer bleeding days

With LNG-IUS12 nulliparous women are at no higher risk of expulsion vs parous women

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At least partial expulsion (crude rate),† %	LNG-IUS12(n=1,445)*
Overall	**3.7**
Age	
18–25 years (n=562)	3.7
26–35 years (n=883)	3.7
Parity	
Nulliparous (n=570)	1.8
Parous (n=875)	5.0

*Only women with a successful insertion were considered; †IUS displaced in the cervical canal and/or partially visible in the vagina

Amenorrhoea and dysmenorrhoea

Amenorrhoea

The proportions of subjects reporting amenorrhoea increase over time and is related to the LNG dose

Dysmenorrhoea

Similar improvements in dysmenorrhoea observed for all IUSs

Incidense of ectopic pregnancy

	Incidense/100 WY
Jaydess [1]	0,11
Mirena [2]	0,10
Cu-IUD[3]	0.75-0,23
Non-hormonal contraception[4]	1.2-2.6

1. Jaydess SPC 2013-09-10. 2. Mirena SPC 2013-11-07. 3. Sivin I et al. Contraception 1990;42:361-378
4. Franks AL, et al Am J Obstet Gynecol 1990;163:1120-3

LNG-IUS12 is associated with a low absolute rate of ectopic pregnancy [1]

Women with a previous history of ectopic pregnancy, tubal surgery or pelvic infection carry an increased risk of ectopic pregnancy[2]

The possibility of ectopic pregnancy should be considered in the case of lower abdominal pain*

Women who become pregnant while using LNG-IUS should be evaluated for ectopic pregnancy

The absolute risk of ectopic pregnancy in LNG-IUS 12 users is low. However, when a woman becomes pregnant with LNG-IUS12 *in situ* the relative likelihood of this pregnancy being ectopic is increased[3-6]

The overall incidence of ectopic pregnancy with LNG-IUS12 is ~0.2/100 WY[7]

This rate is lower than in women not using any contraception (0.3–0.5/100 WY)[6]

*Especially in connection with missed periods or if an amenorrheic woman starts bleeding
WY, women-years (1 WY = 365 days)

1. Kyleena™ CCDS. 2016; 2. Tuomivaara and Kauppila.1988; 3. Backman *et al*. 2004; 4. Furlong. 2002; 5. Kunz. 2007; 6. Sivan. 1991; 7. Bayer (data on file). 2015

Ease of placement
(physician's evaluation in phase II trial)

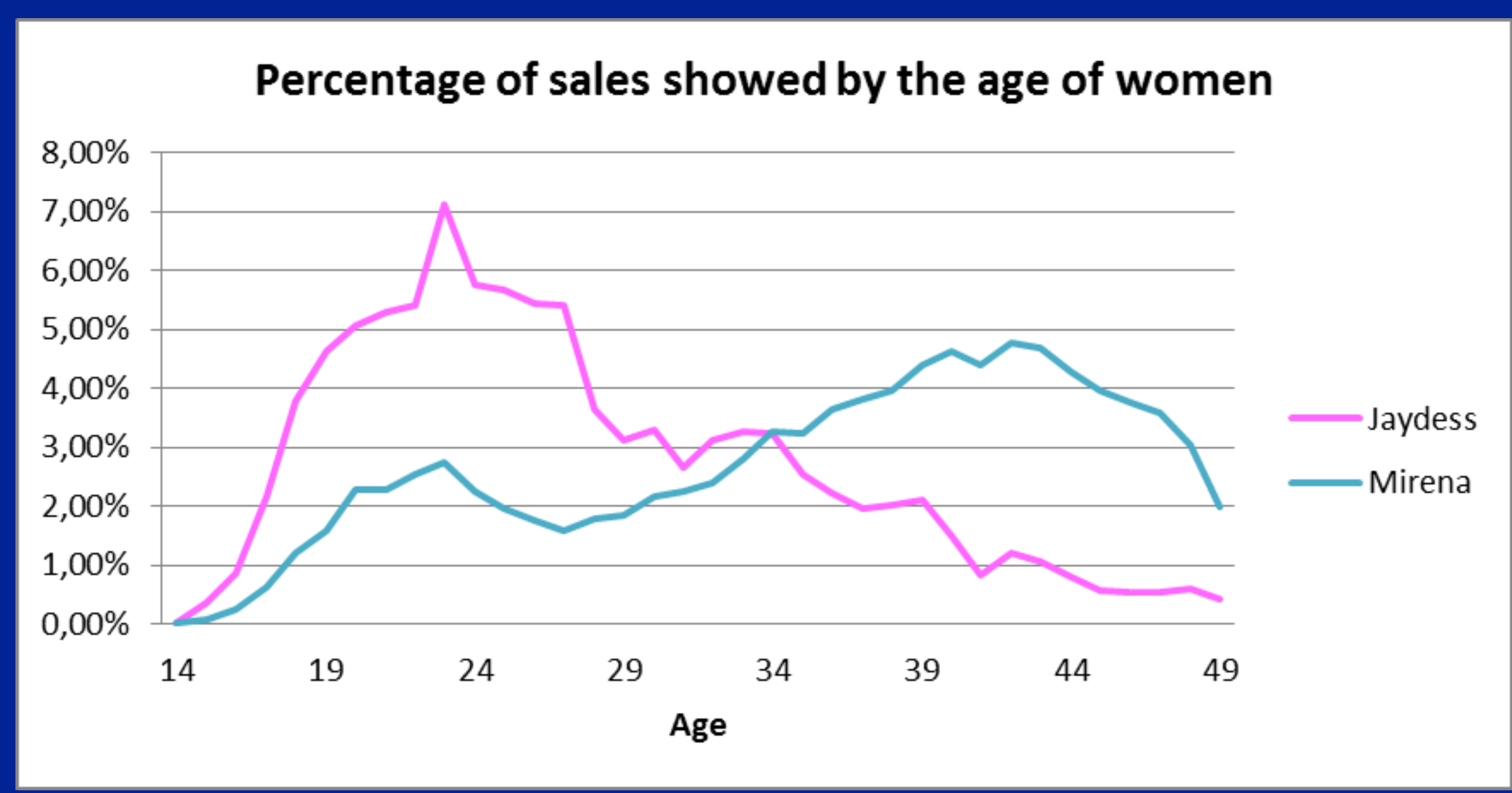
	LNG-IUS12 (n=239)	LNG-IUS16 (n=245)	Mirena (n=254)
Easy	226 (94.6%)	229 (93.5%)	219 (86.2%)
Slightly difficult	11 (4.6%)	14 (5.7%)	31 (12.2%)
Very difficult	2 (0.8%)	2 (0.8%)	4 (1.6%)
Overall difference vs Mirena	p<0.01	P=0.02	

- Diameter of LCS inserter approx 1mm smaller vs. Mirena
- Placement of LNG-IUS12/16 more frequently rated as 'easy' vs. Mirena (*P*<0.001)
- 98.5% of successful placements were achieved at the first attempt
- Cervical dilatation was used more frequently for Mirena vs LNG-US12/16 (9.4% vs 3.9%, *P*=0.004)

Less pain of placement
(subject's evaluation, phase II trial)

	LNG-IUS12 (n=239)	LNG-IUS16 (n=245)	Mirena (n=254)
None	72 (30.1%)	65 (26.5%)	44 (17.3%)
Mild	101 (42.3%)	112 (45.7%)	103 (40.6%)
Moderate	53 (22.2%)	59 (24.1%)	90 (35.4%)
Severe	12 (5.0%)	9 (3.7%)	17 (6.7%)
Not placed	1 (0.4%)	0 (0.0%)	0 (0.0%)
P-value for overall difference vs Mirena	<0.001	<0.001	

- Subjects rated the placement of LNG-IUS12 and LNG-IUS16 as less painful compared with Mirena (*P*<0.001)



Proportion of prescriptions at each age, i.e. the relative amount of users of all the prescriptions of Jaydess or Mirena, in Sweden 6 months after Jaydess launch

Jaydess is most used among 20-29 year olds, while Mirena is most widely used among 40-45 year olds.

Läkemedelsregistret, Socialstyrelsen

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UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP)

Department of Reproductive Health and Research, World Health Organization, Geneva, Switzerland

Launched by the World Health Organization in 1972, the UNDP/

The intrauterine device (IUD)—worth singing about

"When you think of it, the IUD is really an unsung, under-promoted success story."

Overheard during a conversation between two reproductive health experts attending a recent WHO meeting, this statement carries much truth. How a small piece of plastic wrapped in con-serted, can perforate the wall of the uterus. On the whole, though, the IUD is one of the safest, best tolerated methods of contraception available.

This issue of *Progress* is devoted to the IUD. It opens with a historical outline of the development of the latest, most effective versions of the IUD (page 2).