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Additional Benefits of Oral Contraceptives

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History of COC

1914-1921 Activist Margaret Sanger coins the term “birth control,” opens first birth control clinic in Brownsville
1934 Endocrinologist Gregory Pincus creates a test tube rabbit — and is vilified as a Frankenstein
1951 Sanger and Pincus meet at a dinner party in New York; she persuades him to work on a birth control pill
1951 Carl Djerassi, a chemist in Mexico City, creates a pill by synthesizing hormones from Mexican yams. On a chemical level, the pill has been invented, but Djerassi isn’t equipped to test, produce or distribute it
1952 Pincus tests progesterone in rats and finds it works
He meets gynecologist John Rock, who has already begun testing chemical contraception in women.
Frank Colton, chief chemist at the pharmaceutical company
Searle, also independently develops synthetic progesterone

1953 Sanger is the activist behind the pill and Pincus the scientist, Katherine McCormick — biologist, women’s rights activist and heiress to a great fortune — is the money. She writes Pincus a check for $40,000 to conduct research

1954 Rock and Pincus conduct the first human trials on 50 women in Massachusetts. It works.
1956 Large scale clinical trials are conducted in Puerto Rico
The pill is deemed 100 percent effective, but some serious side effects are ignored
1957 The FDA approves the pill, but only for severe menstrual disorders, not as a contraceptive
An unusually large number of women report severe menstrual disorders

1960 The pill is approved for contraceptive use

1960s

- Envoid-10 is introduced in the US by Searle
- Anvolar® (Schering) is introduced in West Germany (the 1st oral contraceptive in Europe) and Australia
- Ovosistron® (VEB Jenapharm) is the 1st hormonal contraceptive introduced in East Germany
- In Europe, the pill is only recommended for regulating menstrual disorders and in married women

1970s

- The "mini pill"—i.e., the progestin-only pill—is introduced
- Initial reports are published correlating COCs and thromboembolic events

1980s

- Biphasic pills are introduced, allowing two dose levels of progestin during a woman's menstrual cycle
- Three triphasic pills are introduced
- Use of high-dose estrogen pills is reduced to 3.4% of the oral contraceptive market
- FDA recognizes several possible health benefits of pill use, including a decreased incidence of ovarian and endometrial cancers
- FDA committee states that the benefit of the pill may outweigh the possible health risks in healthy, non-smoking women over 40 years

1990s

- Low-dose oral contraceptives are introduced
- Low-dose estrogen is added to the placebo week in some COCs

2000s

- Extended - (24/4, 84/7) and continuous-regimen COCs allow women to experience fewer or no yearly menstrual cycles
- New progestins (e.g., dienogest, drospirenone, trimegestone, Nestorone, nomegestrol acetate) are introduced and/or under investigation
- Non-oral combined hormonal contraceptives, e.g., the vaginal ring and transdermal patch, are available

2010s

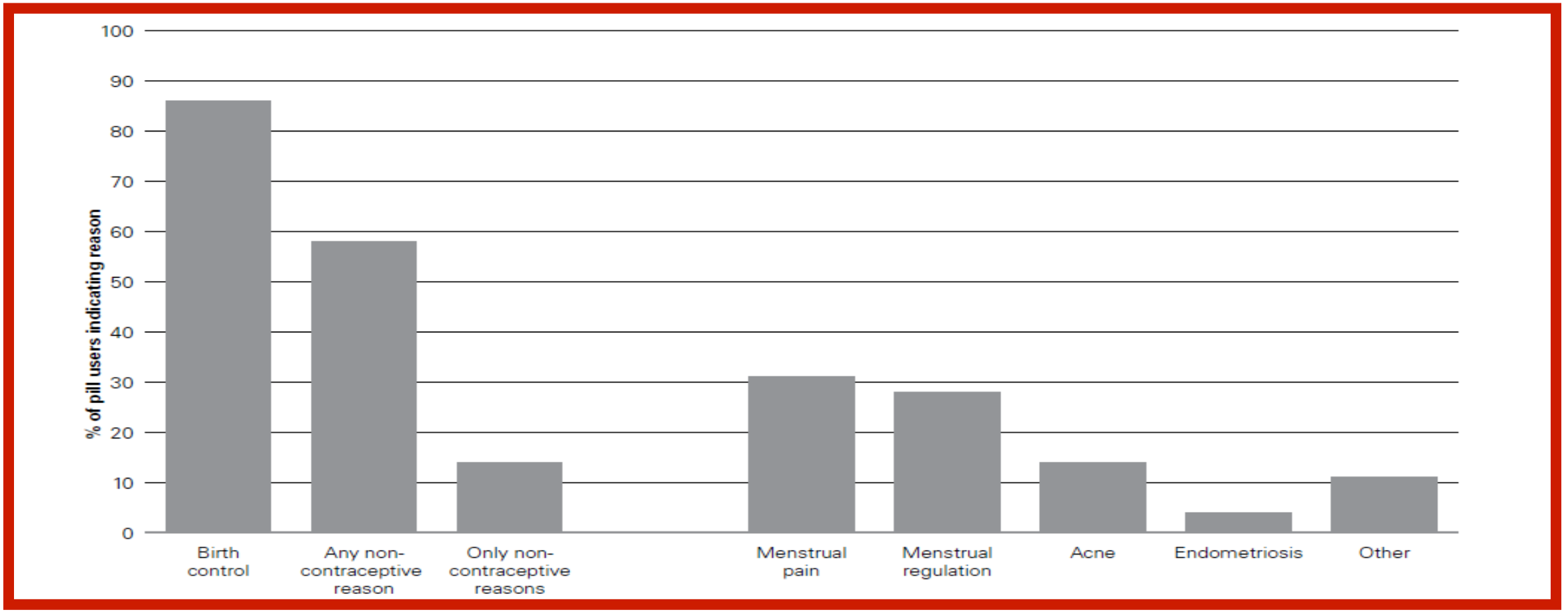
- Use of natural estrogens (17β-estradiol and estradiol valerate) may be used in COC regimens
- New progestins are investigated
- Genetic and proteomic targets are under investigation for contraception

11.2 million women use oral contraceptive pills

- 58% of these use least in part for noncontraceptive reasons
- Moreover, 14% of pill users (more than 1.5 million women), about half of whom have never had sex, use the pill exclusively for noncontraceptive reasons
- **Related to noncontraceptive benefits of COC, drug industry was focused on new compounds**

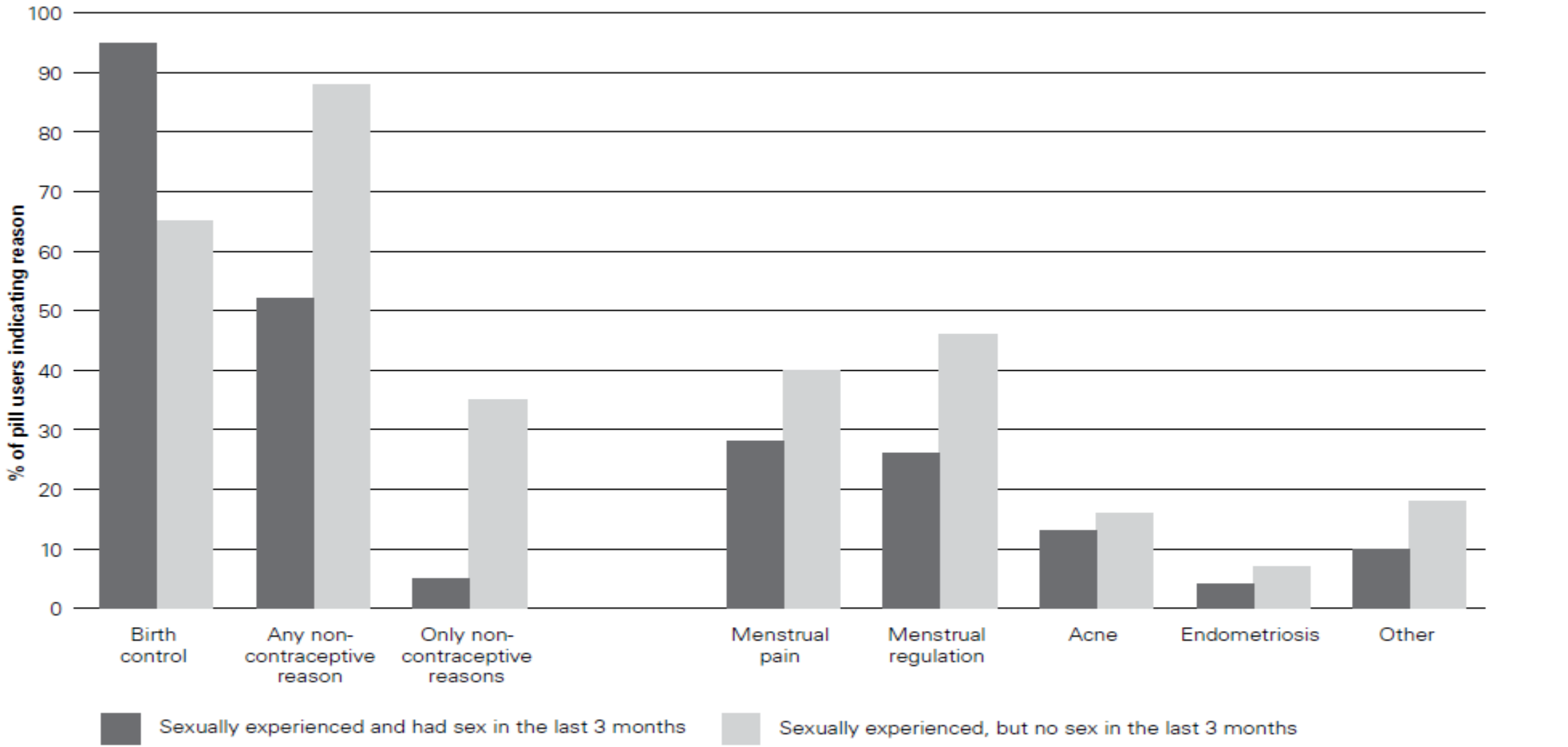
Contraception and Beyond: The Health Benefits of Services Provided at Family Planning Centers. Guttmacher Institute 2013

Reasons women use oral contraceptive pills



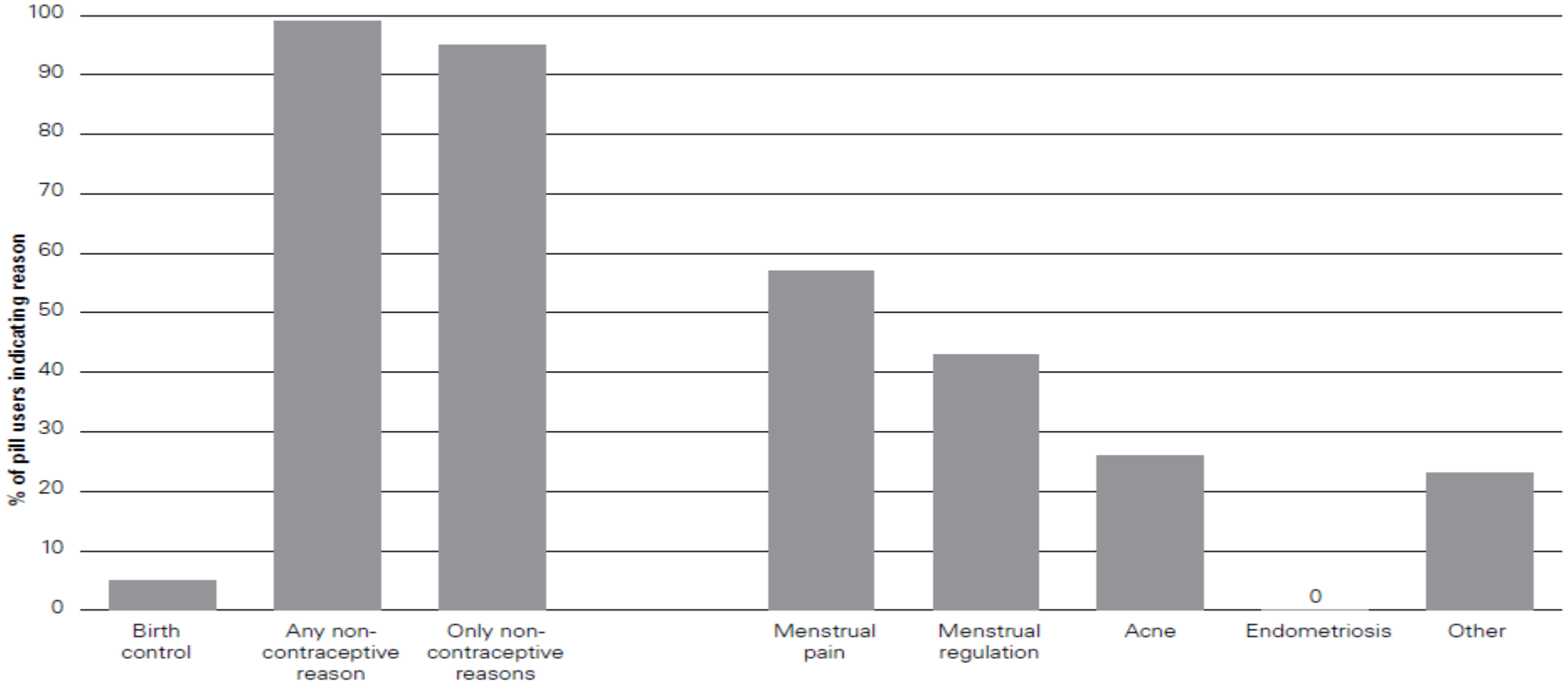
Guttmacher Institute

Reasons for pill use, by sexual activity status



Guttmacher Institute

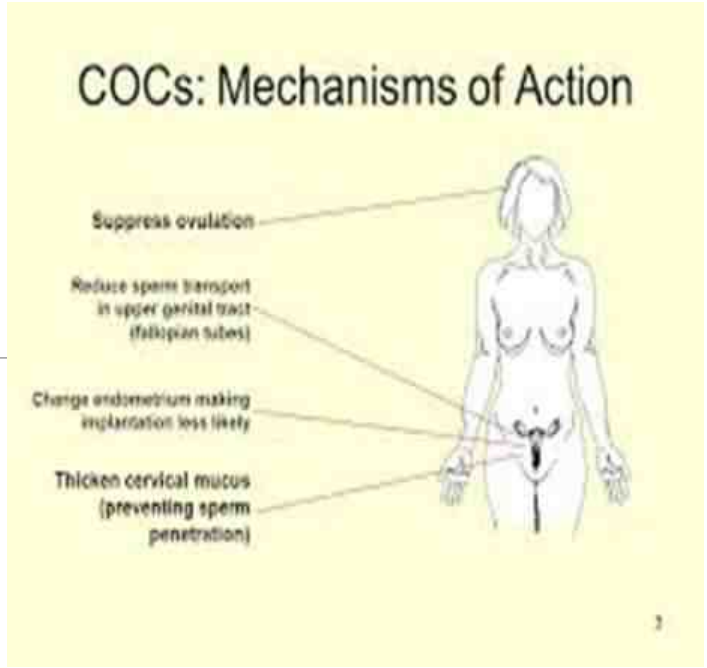
Reasons for pill use among women who have never had sex



Guttmacher Institute

Mechanisms of Oral Contraceptives

Interrupts the hypothalamic-pituitary gonadal axis by suppressing secretion of luteinizing hormone (progestogen) and follicle stimulating hormone (estrogen) to primarily prevent ovulation



Crosignani PG, et al.Contraception 1996

Progestogen;

- endometrial atrophy
- cervical mucus thickening
- decreased tubal motility
- provide the dominant contraceptive benefit

Estrogen;

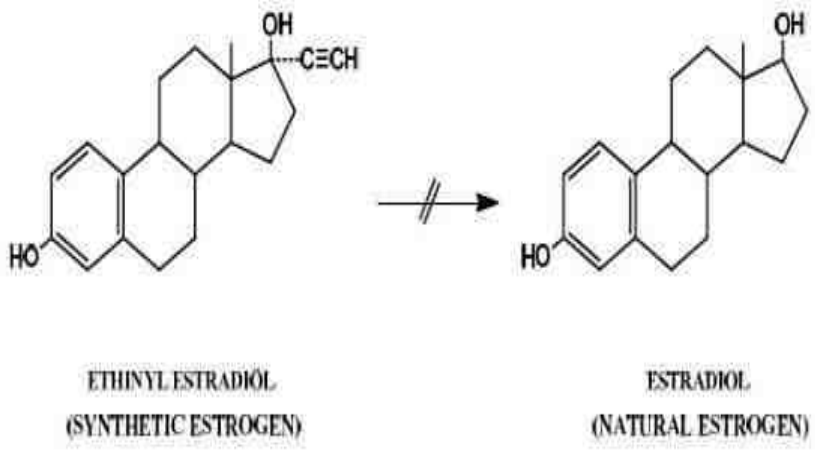
- stabilizes the endometrium to minimize breakthrough bleeding
- potentiates the action of progestogens

  Schindler AE, Campagnoli C, Druckmann R, et al. Maturitas 2008

- inhibiting the release of follicle-stimulating hormone from the pituitary

  Shulman LP, et al. Cancer Treat Res 2010

Estrogens

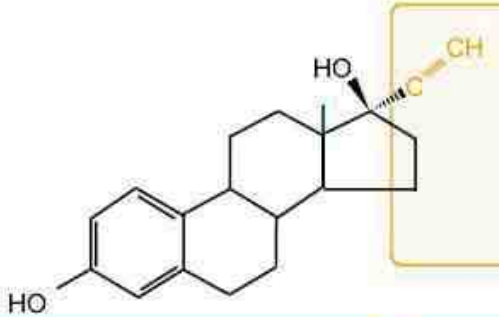


ETHINYL ESTRADIOL
(SYNTHETIC ESTROGEN)

ESTRADIOL
(NATURAL ESTROGEN)

Ethinyl group at C17 prevents metabolism to E2,
and prevents also metabolism to Estrone, E1,
which is one of the main reasons for cyclical stability
using COC with EE as component !

Chemistry
Estradiol vs. Ethinyl Estradiol



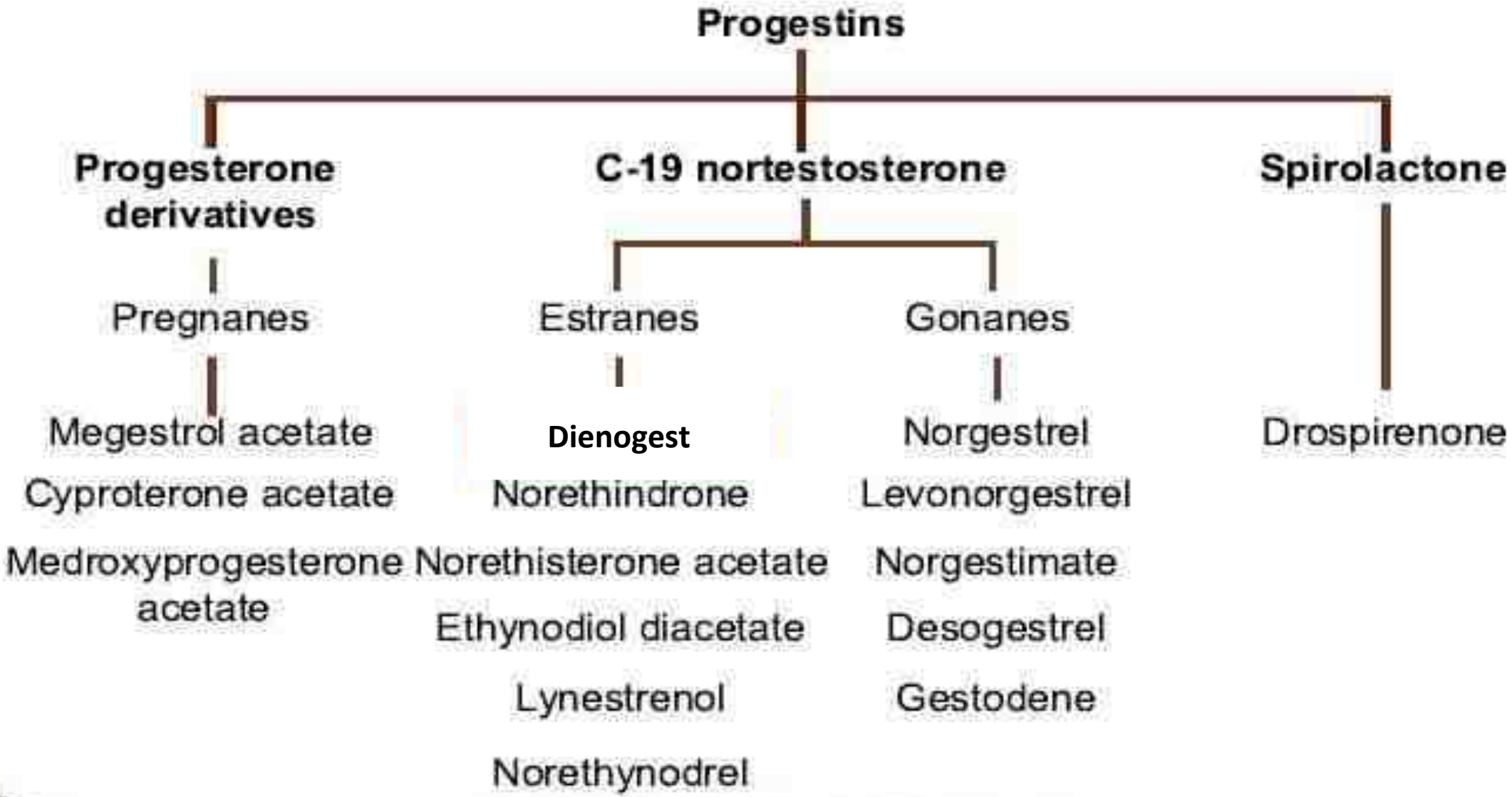
Change in:
Reactivity
Pharmacokinetics
Metabolism
Receptoraffinity
hepatic activity

ESTRADIOL:
Hormone Replacement Therapy

Strong effects on endometrium, breast and CNS
mild effects in liver proteins

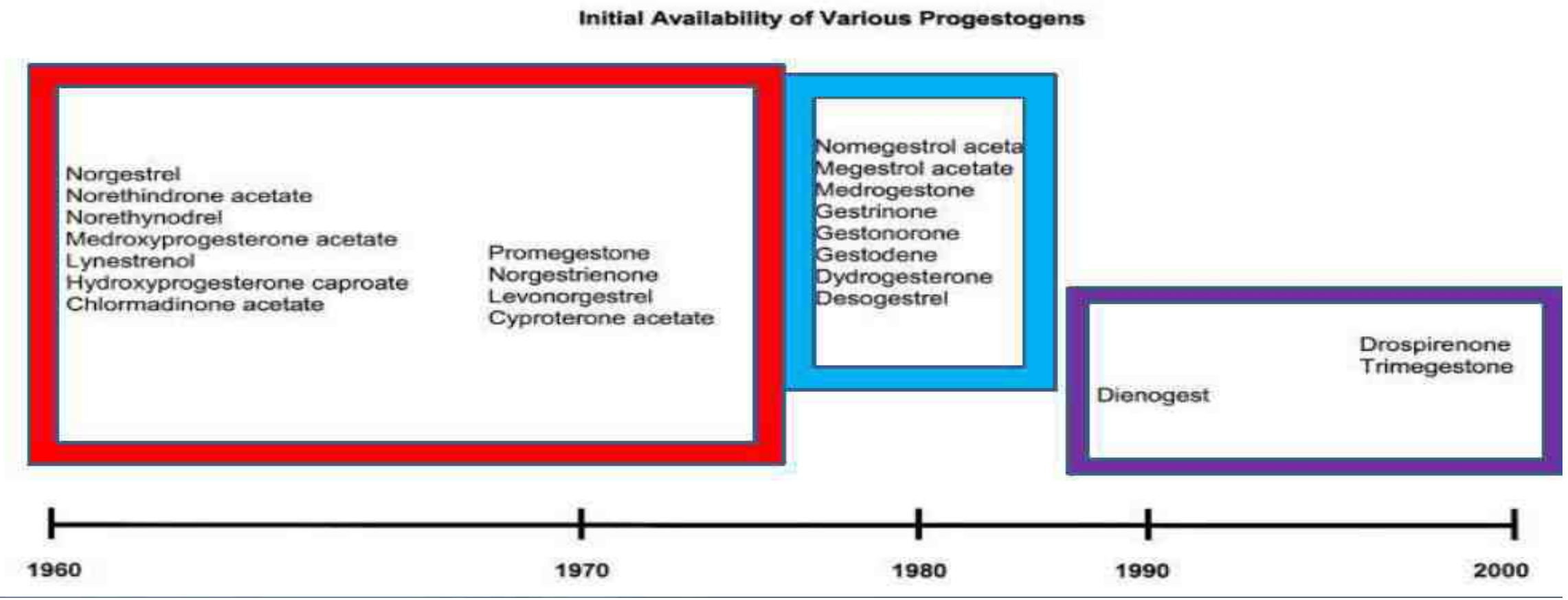
ETHINYL ESTRADIOL:
Contraception

Main reason for use:
to ensure cyclic stability in combination with a progestin



Schindler *et al*. Maturitas 2008;61:171–80; Sitruk-Ware R. Maturitas 2004;47:277–83

History of Progestins



Biological activities of natural progesterone and synthetic progestins

Progestin	Progesto-genic	Anti-gonado-tropic	Anti-estrogenic	Estro-genic	Andro-genic	Anti-andro-genic	Gluco-corticoid	Anti-mineralo-corticoid
Progesterone	+	+	+	−	−	±	+	+
Dydrogesterone	+	−	+	−	−	±	−	±
Medrogestone	+	+	+	−	−	±	−	−
17α-Hydroxy-derivatives								
Chlormadinone acetate	+	+	+	−	−	+	+	−
Cyproterone acetate	+	+	+	−	−	++	+	−
Megestrol acetate	+	+	+	−	±	+	+	−
Medroxy-progesterone-acetate	+	+	+	−	±	−	+	−
19-Nor-progesterone-derivatives								
Nomegestrol acetate	+	+	+	−	−	±	−	−
Promegestone	+	+	+	−	−	−	−	−
Trimegestone	+	+	+	−	−	±	−	±
Spirolactone-derivatives								
Drospirenone	+	+	+	−	−	+	−	+
19-Nortestosterone derivatives								
Norethisterone	+	+	+	+	+	−	−	−
Lynestrenol	+	+	+	+	+	−	−	−
Norethinodrel	±	+	±	+	±	−	−	−
Levonorgestrel	+	+	+	−	+	−	−	−
Norgestimate	+	+	+	−	+	−	−	−
3-Keto-desogestrel	+	+	+	−	+	−	−	−
Gestoden	+	+	+	−	+	−	+	+
Dienogest	+	+	±	±	−	+	−	−

Taken from reference [5,7,8,10–15]. (+) effective; (±) weakly effective; (−) not effective.

Health Benefits of COCs

Gynecological	Reproductive	Oncologic	Other
Menstruel Bleeding Disorders	Endometriosis / Adenomyosis	Benign Breast Disease	Rheumatoid Arthritis
Dysmenorrhea	Androgenisation	Ovarian Cancer	Voice
PMS		Endometrial Hyperplasia / Cancer	Multiple Sclerosis
Ovarian Cysts		Colorectal Cancer	Bone Structure
Leiomyoma			Asthma
PID			Menstrual Migraine
Ectopic pregnancy			Social

Menstruel Bleeding Disorders

Significant blood loss decrease → %40 – 50 (Fraser IS. Aust N Z J Obstet Gynaecol. 1991)

- Cyclic Fashion → Decreaement of the hormone free interval → Better result (Sulak PJ.Obstet Gynecol.2000)
- Extended Cycle → Significant Endometrial safety (Anderson. Am J Obstet Gynecol.2006)
- Currently marketed OCs → Not approved by FDA except «Dienogest / Estradiol Valerate» (2012)

especially newer and lower-dosed COCs, all reduce the volume of blood loss with conventional use

Luis Bahamondes et al. Human Reproduction Update, 2015

Dysmenorrhea

- Progestin dominant effect → Endometrial atrophy → Relatively lower cytokines
- Combined OC vs Placebo → Pain improvement OR 2.01 **(Wong CL. Cochrane Data Sys Rev. 2011)**
- **COCs** → Uterine prostoglandins

Symptomatic relief upto %70-80 **(Hendrix SL. Contraception 2002)**

- Low or medium dose estradiol is effective
- Third generation progestins → More effective than the previous ones

Oral contraceptives for pain relief from dysmenorrhea: a review

Author	Date	Study size (no. of women)	Treatment length	Control measure	Drug 1	Drug 2	Drug 3	Dysmenorrhea outcome	Significance (yes/no)
Hormonal contraception									
Randomized controlled trials									
Davis et al. [80]	2005	76	3 months	Placebo	EE (0.02 mg)/ LNG (0.1 mg)	n/a	n/a	OC superior to placebo for reduction of pain severity	Yes
Winkler et al. [81]	2004	998	6 months	Comparison	EE (0.02 mg)/ DSG (0.15 mg)	EE (0.02 mg)/ LNG (0.1 mg)	n/a	Equal decrease in both groups	No statistics
Nonrandomized controlled trials									
Ahrendt et al. [82]	2007	406	3–4 months	None	DSG (0.075 mg)	n/a	n/a	Improvement in 93%	No statistics
Harel et al. [83]	2005	28	Up to 1 year	None	EE (0.075 mg)/ norelgestromin (6 mg)	n/a	n/a	39% decrease, 11% increase, 50% no change	No statistics
Kido et al. [84]	2007	41	3 months–4 year	No-OC control group	EE (0.03–0.05 mg)/ LNG (0.03 and 0.04 mg), NES (0.035 mg) or NGS (0.05 mg)	n/a	n/a	Degree of experienced pain lower in the OC group, no severe menstrual pain in the OC group	Yes
Matsumoto et al. [85]	2007	110; 39 in the dysmenorrhea subgroup	3 months	None	Unspecified OCs	n/a	n/a	QoL scores significantly improved over all domains	Yes
Sabatini et al. [86]	2007	156	6 months	Comparison	EE (0.03 mg)/ CMA (2 mg)	EE (0.03 mg)/ DRSP (3 mg)	n/a	Progressive and significant reduction in mild and moderate dysmenorrhea in the EE/CMA group	Yes
Schramm and Heckes [87]	2007	16,781; 6169 in the dysmenorrhea subgroup	4 months	Comparison	EE (0.03 mg)/ CMA (2 mg)	Former contraception	n/a	61.1% complete resolution; 5.4% unchanged	No statistics

Hans-Peter Zahradnik, 2010

ACOG

Noncontraceptive Uses of Hormonal Contraceptives (Jan 2010)

- Limited data suggest that **COCs can reduce the severity of dysmenorrhea** in women with endometriosis
- **Continuous COCs may offer** additional benefit by **elimination of menstruation and associated dysmenorrhea**

PMS

- Maybe first line therapy

  (Lopez LM. Cochrane Database Syst Rev. 2009)

- Drospirenone → Strongest evidence for PMS / PMDD

  (strong anti-mineralocorticoid effect)

  Yonkers KA. Obstet Gynecol. 2005 , Lopez LM. Cochrane Database Syst Rev. 2012

  Sillem M. Et al. Womens Health (Lond Engl). 2006

- 4 days of interval better than 7 days

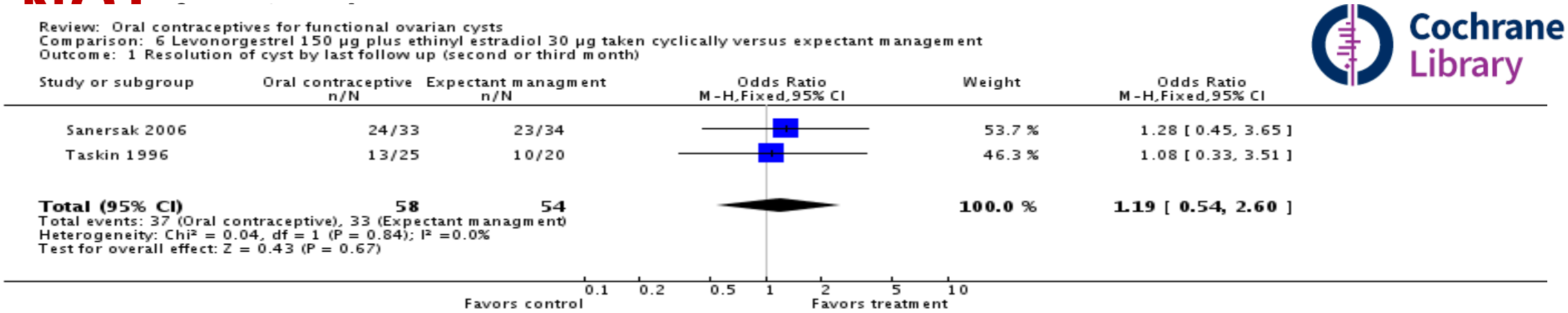
Ovarian Cysts

Cyclic suppression → FSH suppression → Reduce follicular and luteal cysts

No clinical significance

- **Combined OCs → Do not hasten the resolution of existing cysts** (Bayar U. Int J Gynaecol Obstet. 2005)
- **Cystic masses that did not resolve within several months were probably**

NOT



Cochrane Library

Leiomyomas

Endometrial atrophy

- Risk of myoma reduced among post-treatment and constant users of COC
- The risk decreases with longer use

Ross Rk et al. Br Med J (Clin Res Ed). 1986

- **70% reduction of myoma size, who used the pills for <u>seven and more years, demonstrated a 50% reduction of myoma size</u>**

Chiaffarino F, et al. Br J Obstet Gynaecol. 1999

BUT THEY ARE OLD STUDIES AND THERE IS NOT ANY HIGH LEVEL NEW EVIDENCE

Pelvic Inflammatory Disease (PID)

- Progestin → Cervical mucus thickening → Inhıbiting the ascending pathway
- Diminished menstruation → Decresased retrograde menstruation
- Reduction in hospitalization days, amount of medication and operative procedures and also the risk of ectopic pregnancy and infertility problems

(Kaunitz AM. Contraception. 1999)

- Do not have a role in reduction of upper genital tract infection

(Ness R. AJOG. 2001)

- **Reduce the risk of PID by 50% to 60%**

(Burkman RT. Et al. Clin Obstet Gynecol. 2001)

Ectopic pregnancy

- The primary mechanism providing effective pregnancy prevention
- **COCs** use reduce the risk of PID and related to this reduces the risk of ectopic pregnancy

Burkman R, et al. Am J Obstet Gynecol 2004

- There is evidence that women who become pregnant while on progestin-only oral contraceptives may have a higher likelihood of that pregnancy being extrauterine

Furlong LA. Et al. J Reprod Med 2002

Androgenisation

- Decreasing serum-free testosterone concentrations
- Inhibiting luteinising hormone stimulation of ovarian androgens
- Increasing SHBG
- Inhibiting 5-alpha reductase

Thorneycroft IH, et al. Contraception 1999

Arowojolu AO, et al. Cochrane Database Syst Rev 2009;(7):CD004425.29

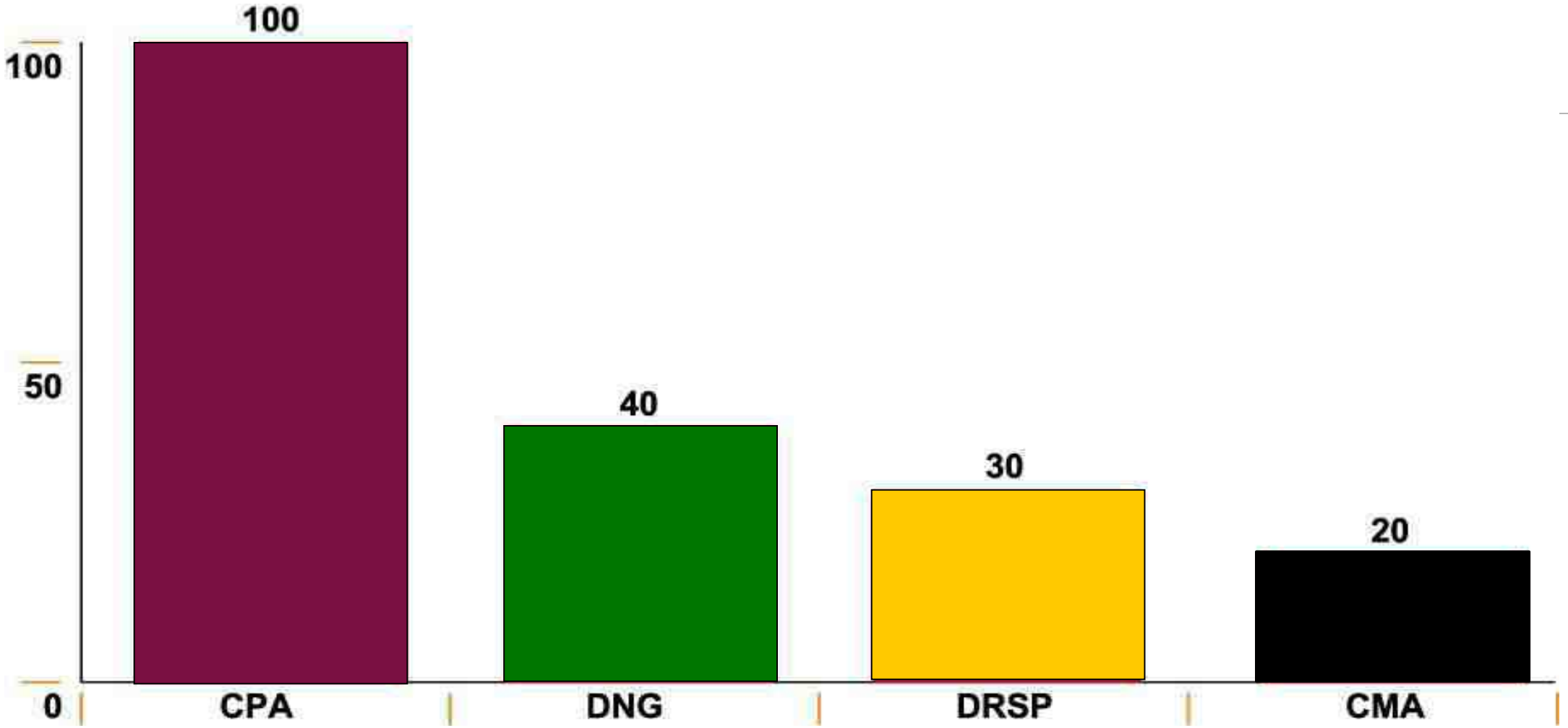
Acne: OCs vs placebo for 6 cycles OR: 3.41 (Koltun W. Eur J Obstet Gynecol Reprod Bio. 2011)

Total lesion count reduction: %55 vs %39 (Palombo-Kinne E. Contraception. 2009)

Androgenic Effects of Progestins

Progestogens	Biological activities				
	Progestogenic	Androgenic	Anti-androgenic	Anti-aldosterone	Glucocorticoid
Progesterone	+	-	±	+	-
Drospirenone	+	-	+	+	-
Cyproterone acetate	+	-	+	-	±
Dienogest	+	-	+	-	-
Levonorgestrel	+	±	-	-	-
Medroxyprogesterone acetate	+	±	-	-	±
Norethisterone	+	±	-	-	-
Trimegestone	+	-	±	±	-
Norgestimate	+	±	-	-	-

Anti-androjenic effect



Androgenisation (hirsutism–acne)

- The **highest anti-androgenic** progestogen **is cyproterone acetate**

  Schindler AE. Eur J Obstet Gynecol Reprod Biol. 2004

- **Normalization of the ovaries in structure and size** in women with PCOS
- COCs are likely to be effective in the treatment of acne
- COCs **reduced acne severity** and **lesion counts**

  Carey and Allen. 2012 Royal College of Obstetricians and Gynaecologists

- The effect **lasted after the pill cessation**
- **Drospirenone and dienogest** containing COCs are effective in hirsutism

  Breitkopf DM, et al. Contraception 2003; Batukan C, et al . Fertil Steril 2006;

- **COCs with lower androgenic progestins should be used**

Endometriosis

Progestogenic effect and ovulatory inhibiton → Endometrial atrophy in ectopic tissue

- Risk of endometriosis is reduced in pill users — ***Vercellini P, et al. Hum Reprod Update. 2011***
- COC reduce the severity of dysmenorrhea in women with endometriosis. Significant reduction in pain
  Harada T. Fertil Steril. 2008, Schindler AE. Et al. Minerva Ginecol. 2004
- Symptoms presumed due to endometriosis with combined hormonal contraceptives
  ESHRE guideline: management of women with endometriosis Human Reproduction, 2014
- Significant postoperative prevention — ***Serrachioli R. Hum Repord.2009***
- Continiuous OC vs GnRH agonist: Similar effect — ***Guzick DS. Fertil Steril. 2011***
- Continuous use of a combined oral contraceptive pill is more effective **Vercellini P, et al.Fertil Steril 2003**
- After cystectomy for endometrioma, hormonal contraceptives (COCs…) → secondary prevention
  Vercellini et al., Reprod Biomed Online 2010

Adenomyosis

- Adenomyosis related symptoms is reduced by oral hormonal contraceptives

Maia H, et al. Gynecol Endocrinol. 2006.

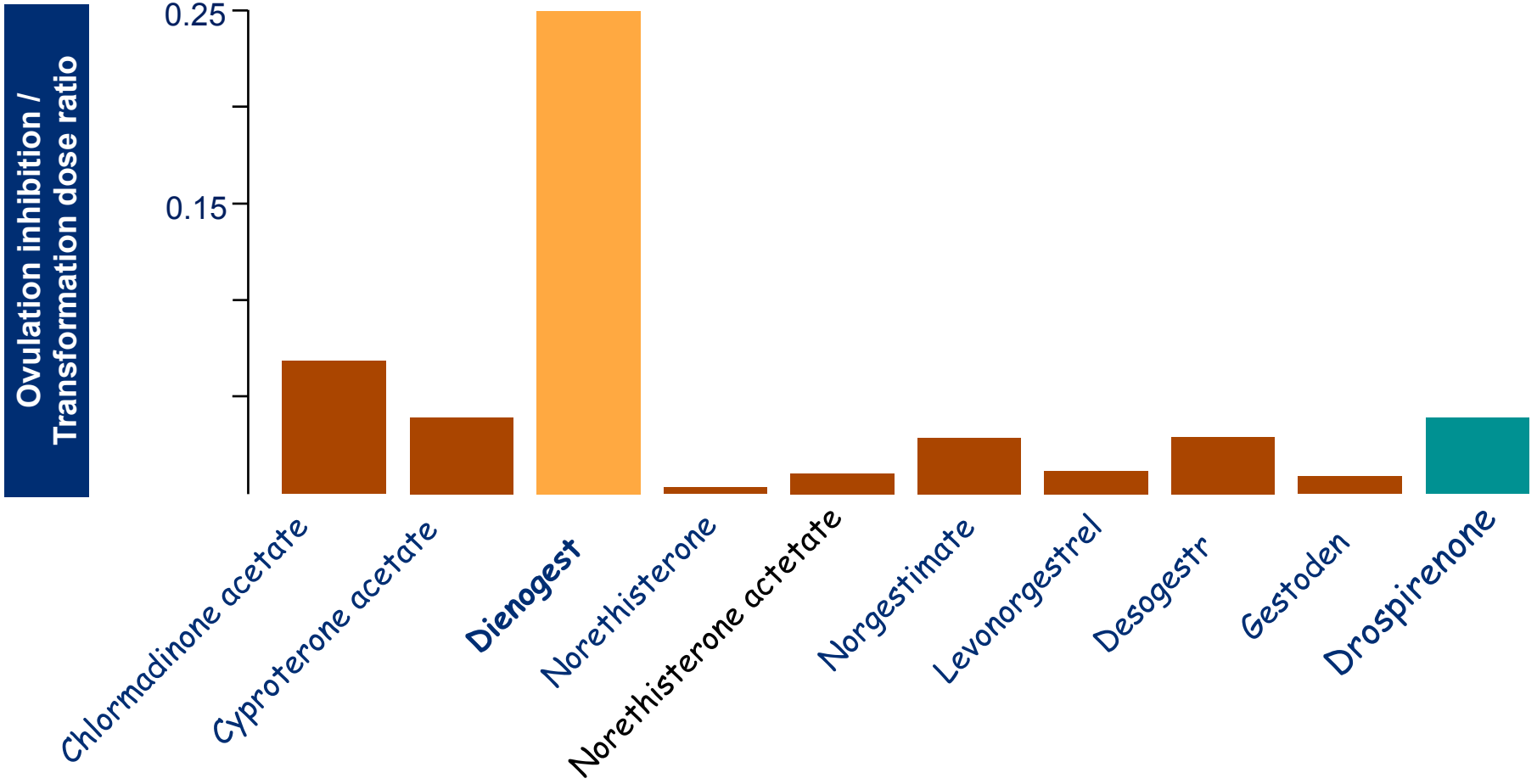
- **<u>Best choice for adenomyosis-related pain is continuous use</u>**

  Monophasic, low-dose COC

  - safety
  - good efficacy
  - appreciable tolerability
  - low cost,

Vercellini P, Vigano P, Somigliana E, Fedele L. Endometriosis: pathogenesis and treatment. Nat Rev Endocrinol 2013;

Progestogenic effect of progestagens



Oettel M et al. Gynecol Endocrinol 2001

Benign Breast Disease

- Older studies with 50 mcg estradiol → Protective effect

L.A. Brinton. Am J. Epid 1981

- < 50 mcg estradiol → Similar effectivite
- **All types of COCs reduce the incidence of benign breast disease**
  - Fibrocystic breast disease
  - Fibroadenoma
  - Undefined breast lumps
- Controversy COC use in BRCA1/2 mutation carriers increases their risk of developing breast cancer
- **COCs** use consistently →increased risk is small →but statistically significant

Ovarian cancer - I

- **Possible mechanisms;**
- reduction/elimination of ovulation
- significant increase in apoptosis of the ovarian epithelium with progestins, either alone or in combination with an estrogen

  in animal studies
- a high potency progestin may be more effective ??

  Rodriguez GC,et al. J Soc Gynecol Investig 1998, Rodriguez GC, et al. Cancer Prev Res (Phila) 2013, Schildkraut JM, et al. J NatlCancer Inst 2002
- high-grade serous EOCs arise the distal fallopian tube COCs may be relevant to a similar effect on the fallopian tube
- low-dose COCs (<35 micrograms estrogen) as protective effect as high ones

Ovarian cancer - II

- a significant reduction in ovarian cancer in ever-users compared with never-users
- duration–response relationship, with a reduction in incidence of 50% among women using COCs for 10 or more years

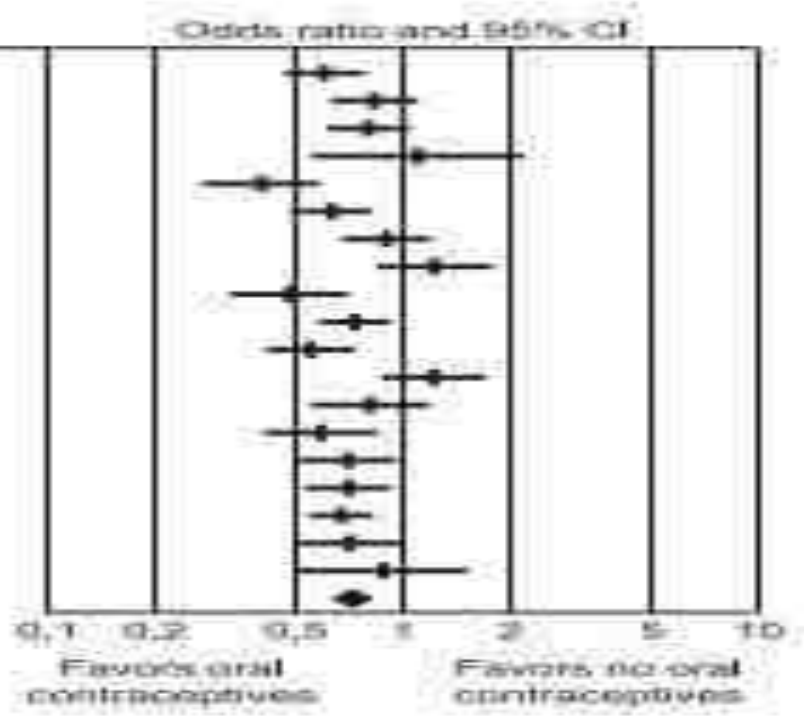
Havrilesky LJ, et al.Obstet Gynecol 2013

- risk decreases by 20% for each 5 years of use the protective effect presents 30 years after stopping.

Beral V, et al. Lancet 2008

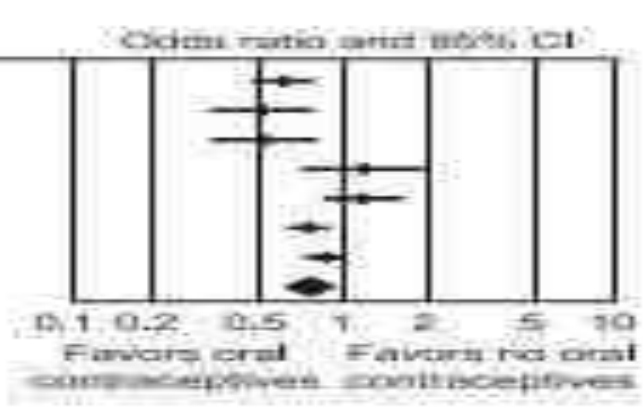
Ovarian cancer - III

Author	Odds ratio	Lower limit	Upper limit
Ness, 2000	0,500	0,472	0,763
Parazzini, 2000	0,830	0,636	1,083
Sanderson, 2000	0,800	0,621	1,031
Beard, 2002	1,100	0,581	2,155
Gnaggi, 2000	0,400	0,280	0,571
Purdie, 2001	0,630	0,490	0,810
Chiaffarino, 2001	0,900	0,688	1,177
Riman, 2001	1,230	0,860	1,760
Royar, 2001	0,480	0,334	0,689
Riman, 2002	0,730	0,591	0,902
McGuire, 2004	0,550	0,420	0,720
Quirk, 2004	1,220	0,883	1,686
Husoom, 2006	0,810	0,563	1,166
Lurie, 2006	0,590	0,417	0,834
Soegaard, 2007	0,700	0,521	0,941
Moorman, 2008	0,703	0,543	0,910
Ness, 2011	0,670	0,562	0,813
Wilailak, 2012	0,710	0,512	0,984
Urban, 2012	0,860	0,518	1,486
Meta-analysis result	0,721	0,645	0,806



A

Author	Odds ratio	Lower limit	Upper limit
Kurtz, 2004	0,600	0,472	0,763
Vessey, 2006	0,500	0,329	0,759
Hannaford, 2007	0,510	0,332	0,784
Dorjgochoo, 2009	1,190	0,711	1,992
Rosenblatt, 2009	1,170	0,858	1,596
Yang, 2012	0,740	0,630	0,870
Tsilidis, 2011	0,680	0,735	1,007
Meta-analysis result	0,763	0,615	0,923



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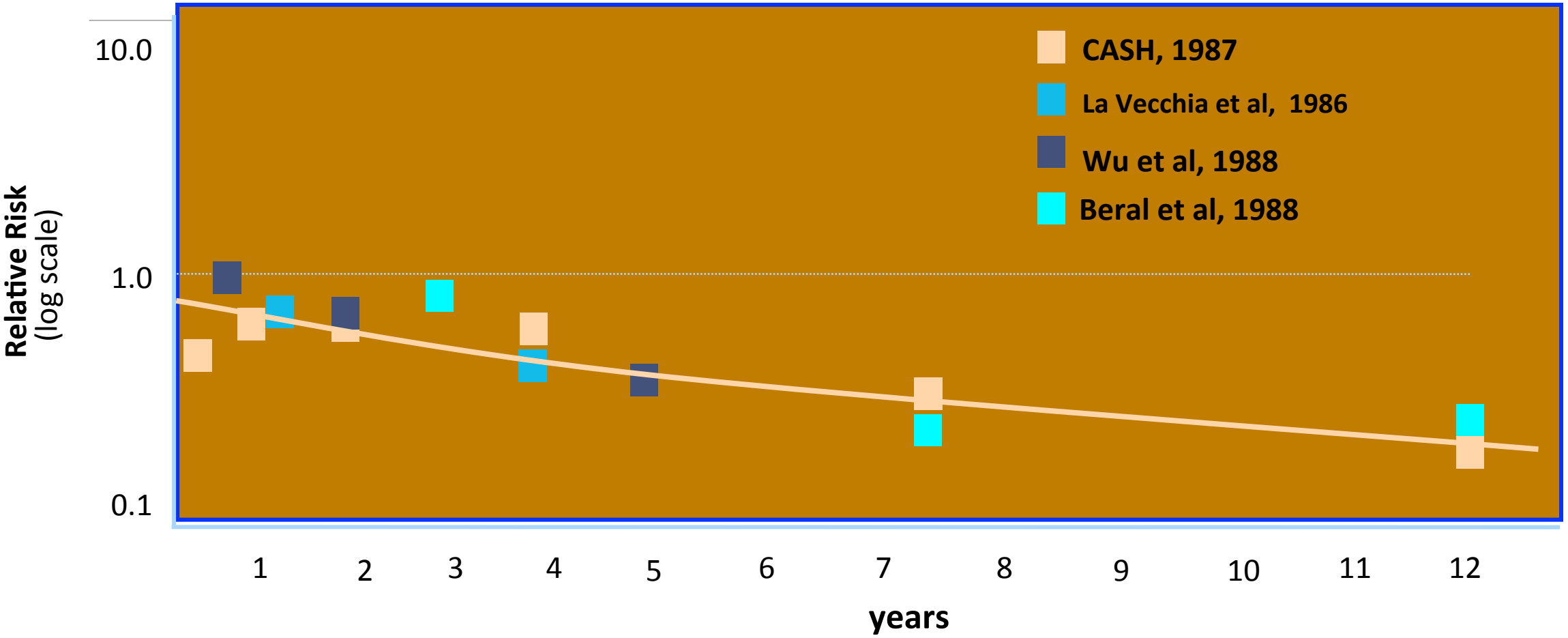
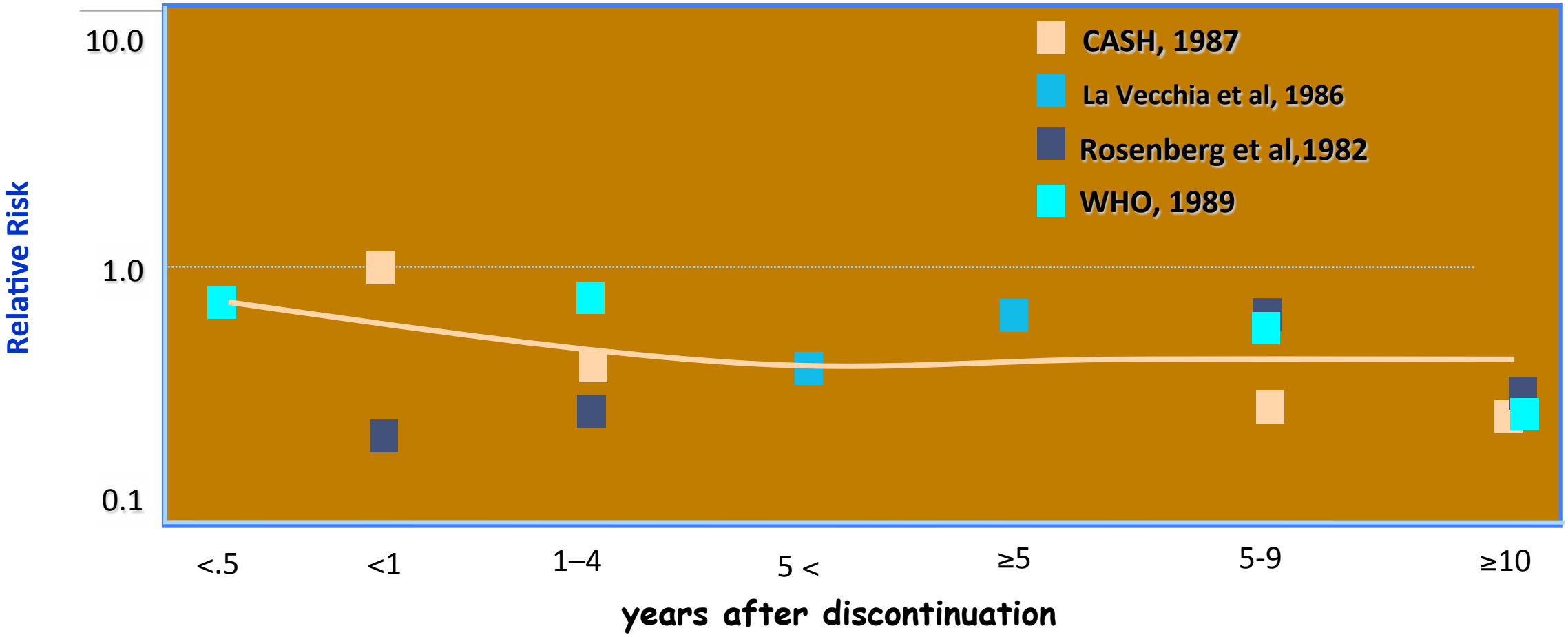
Risk Reduction by Years of Use



Adapted from Grimes DA et al, eds. Modern Contraception: Updates from The Contraception Report. Emron, 1997.

COCs Protect Against Ovarian Cancer after Discontinuation



Stanford JL. *Contraception.* 1991;43:543-556.

Use of COCs on high risk women

BRCA1 and BRCA2 mutations increase the risk of ovarian cancer

- BRCA 1 → 45% risk
- BRCA 2 → 25% risk

COCs reduce the ovarian cancer risk for women BRCA1 and BRCA2 mutation

- COCs use → ≤3 years → 20% ↓
- COCs use → ≥6 years → 60% ↓

Narod SA et al. N Engl J Med. 1998, Shulman LP, Dungan JS. Et al. Cancer Treat Res 2010, Gadducci A, et al. Ann Oncol 2013

Endometrial cancer - I

- **The mechanism:**

➢ overall suppressive effect of COCs on endometrial proliferation

Endometrial cancer - II

- compared with never-users of COC, ever-users a significant reduction in the risk of endometrial cancer

Hannaford PC, et al. BMJ 2010

- 50% reduction in the risk of endometrial cancer→used at least for one year.
- the risk-reducing effect persists after discontinuation

Luis Bahamondes et al. Human Reproduction Update, 2015

- protective effect increases with the duration of use and persists more than 20 or more years after discontinuation

COCs and Endometrial Cancer

Risk reduction of endometrial cancer

4 years of use ⇒ %56

8 years of use ⇒ %67

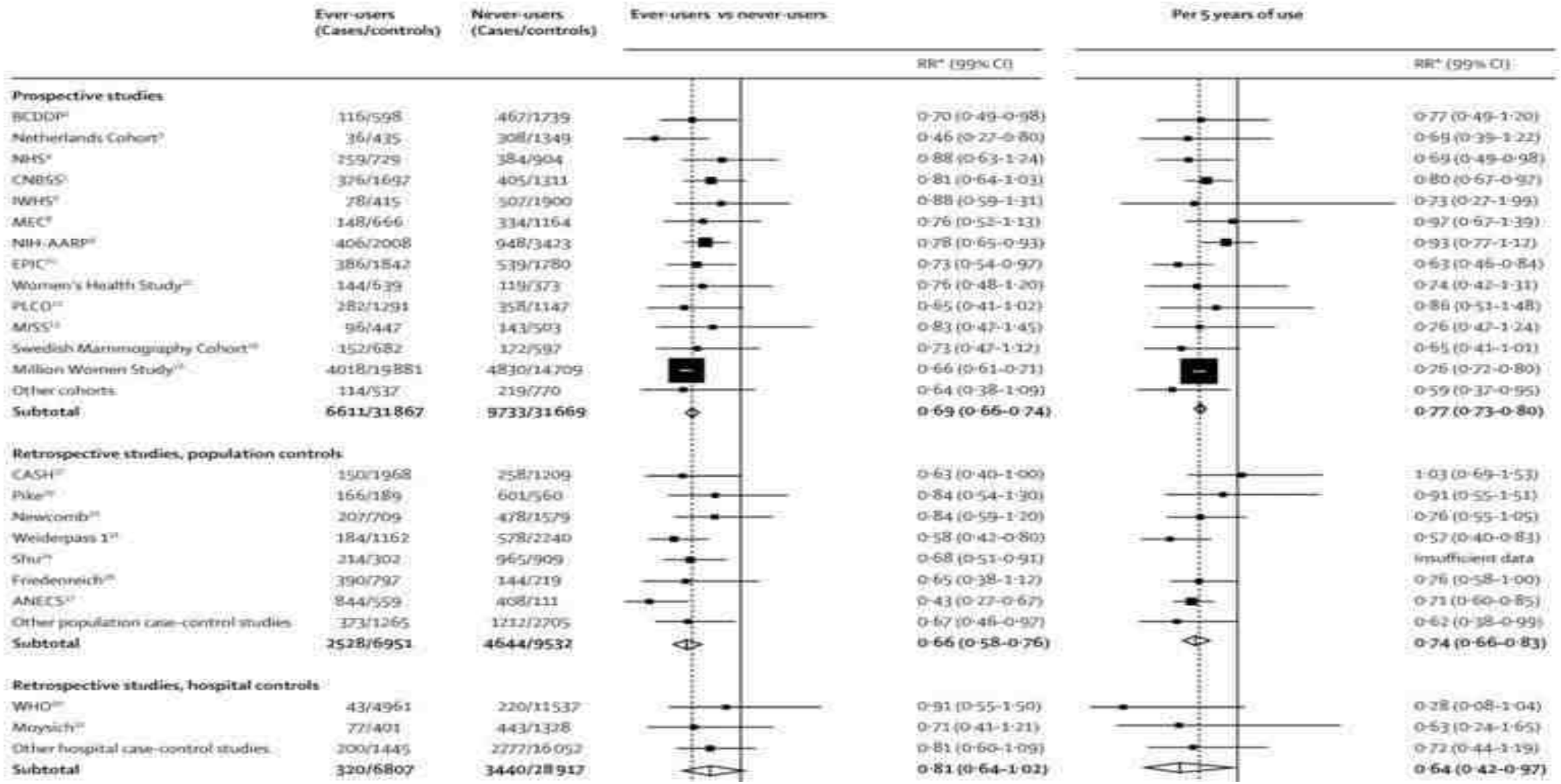
12 years of use ⇒ %72

Schlesselman, 1998

Type of end.Ca

- Adeno Ca
- Adenoskuamöz Ca
- Adenoakantoma

Endometrial Hyperplasia & Cancer



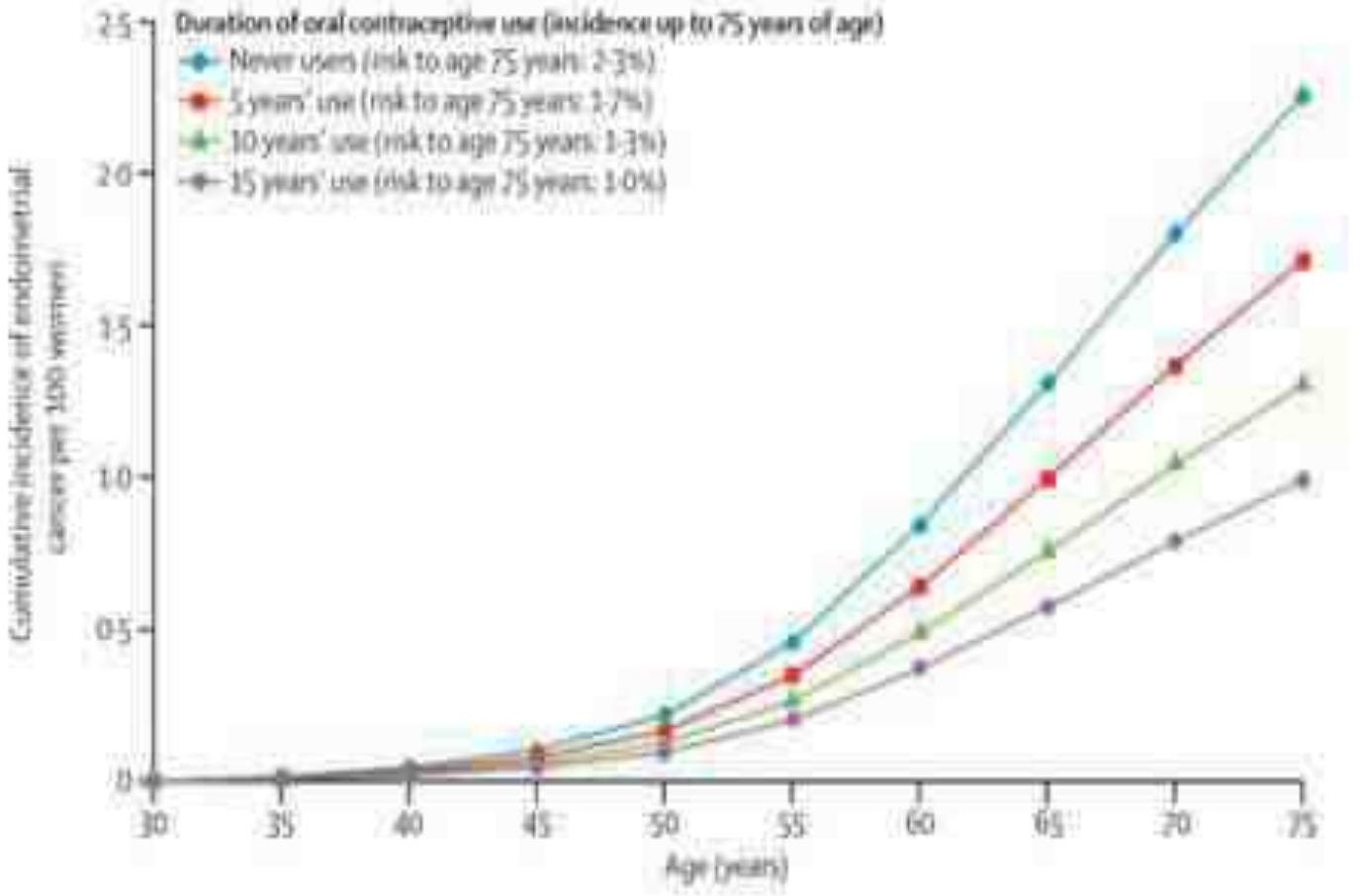
(Collaborative Group on Epidemiological Studies on Endometrial Cancer. Lancet Onco. 2016)

Endometrial Hyperplasia & Cancer

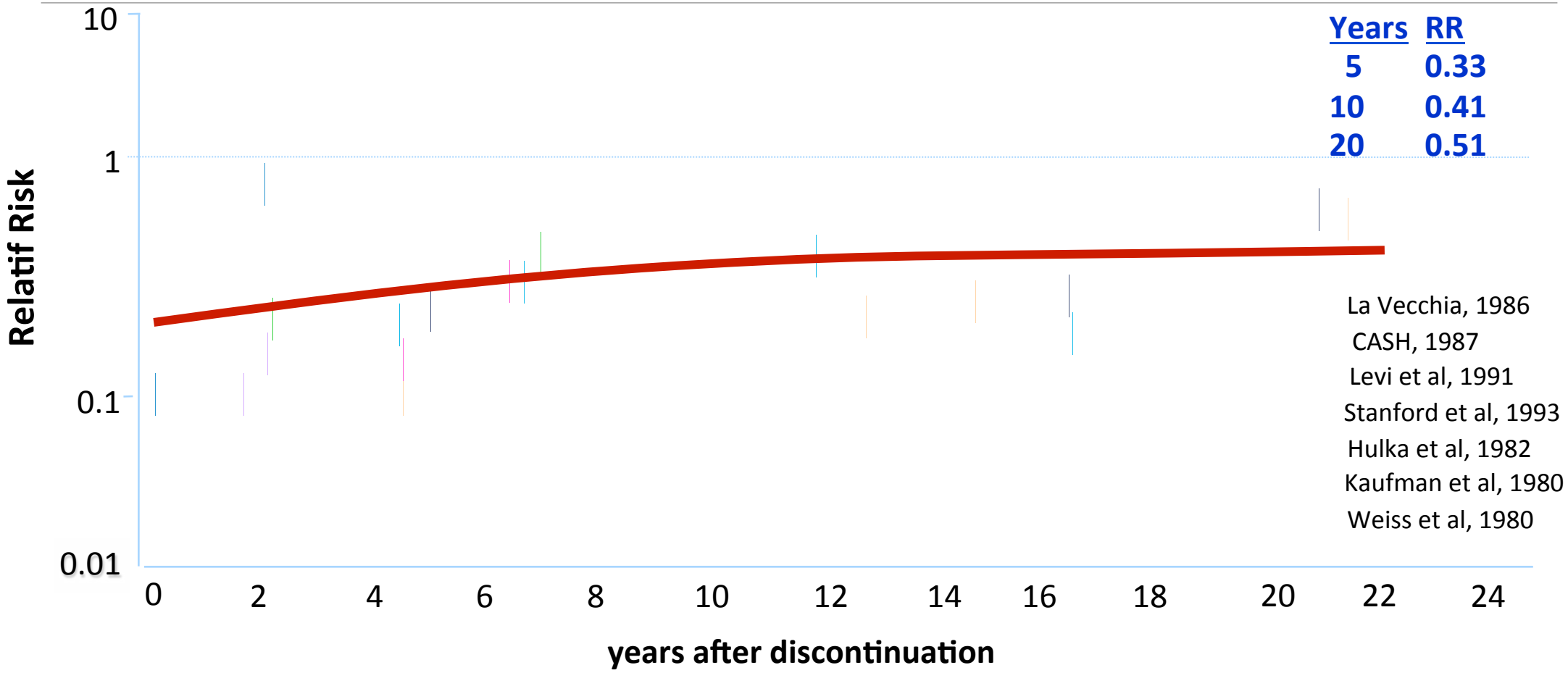
- Medium to long term use

Significant prevention

- Similar prevention rate as ovarian cancer
- Effect resumes after 30 years from cessation



COCs Protect Against Endometrial Cancer After Discontinuation



Adapted from Schlesselman JJ. *Hum Reprod*. 1997

Colorectal Cancer -I

- COCs for 96 months or longer had a 40% lower risk of developing colorectal cancer

  Martinez ME, et al. Cancer Epidemiol Biomarkers Prev 1997

- 18% reduction in colorectal cancer among COC users compared with never-users

- **RR for ever COCs use**
  - ➢ Colon Cancer: 0.80
  - ➢ Rectal Cancer: 0.85

Bosetti C. Hum Reprod Update. 2009

Table IV Case–control studies on effect of OC use and colorectal cancer risk.

Reference	Country, study acronym	Site	No. of cases	No. of controls	Relative risk* (95% CI)
Weiss et al. (1981)	Washington State, USA	Colorectum	143	707	1.58 (0.80–3.10)
Potter and McMichael (1983)	Adelaide, Australia	Colorectum	155	311	0.61 (0.52–0.72)
		Colon	99		0.50 (0.25–1.00)
		Rectum	56		0.70 (0.29–1.71)
Furner et al. (1989)	Chicago, USA	Colorectum	90	208	0.62 (0.28–1.36)
Kune et al. (1990)	Melbourne, Australia	Colorectum	190	200	1.36 (0.21–1.53)
		Colon	108		1.17 (0.59–2.31)
		Rectum	82		2.04 (1.00–4.15)
Peters et al. (1990)	Los Angeles, USA	Colon	327	327	1.03 (0.64–1.66)
Wu-Williams et al. (1991)	North America	Colorectum	189	494	0.84 (0.75–0.94)
		Colon	114		1.20 (0.52–2.78)
		Rectum	75		0.40 (0.17–0.96)
Wu-Williams et al. (1991)	China	Colorectum	206	618	0.70 (0.61–0.82)
		Colon	78		0.55 (0.19–1.59)
		Rectum	128		0.70 (0.34–1.46)
Kampman et al. (1997)	USA, KPMC	Colon	894	1120	0.86 (0.67–1.10)
Fernandez et al. (1996)	Italy	Colorectum	1232	2793	0.64 (0.49–0.85)
Talamini et al. (1998)		Colon	803		0.63 (0.45–0.88)
Fernandez et al. (1998)[b]		Rectum	429		0.66 (0.43–1.01)
Levi et al. (2003)	Switzerland	Colorectum	131	373	0.83 (0.40–1.71)
Nichols et al. (2005)	WI, USA	Colorectum	1488	4297	0.89 (0.75–1.06)
		Colon	1112		0.87 (0.72–1.06)
		Rectum	366		0.87 (0.65–1.17)

Colorectal Cancer -II

- Still unclear whether the dose of COCs plays a role in colorectal cancer prevention.

Carey and Allen. 2012 Royal College of Obstetricians and Gynaecologists

- High benefits of COCs especially among reproductive-aged women with Lynch syndrome

Lu KH, Daniels M. Cancer 2013

- No risk reduction was found for distal large bowel cancer through use of COCs

Long MD, et al. Am J Gastroenterol. 2010

Other Non-Gynecologic Benefits

- BMD: Conflicting data
  - Especially in hypoestrogenic women — **Williams JK. Int J Fertil Womens Med. 2000**
- Asthma: Reduced risk of physician diagnosed asthma OR: 0,68
  - > 3 asthma attacks: OR: 0,45 — **Nwaru BI. J R Soc Med. 2015**
- Rheumatoid Arthritis: Conflicting data
  - Symptomatic relief at inflammatory arthritis
  - Risk of RA RR=0.88, 95% CI=0.75-1.03 — **Albreth K.Arthritis Care Res. 2016, Qi S.Ther Clin Risk Manag. 2014**
- Multiple Sclerosis: Use of OC may increase incidence OR: 1.52

  Hellwig K.PLoS One.2016
  - OC + Inf β → Decreasing active brain lesions and may be used as a treatment

    Pozzilli C. Neurol Neuroimmun. 2015
- Voice : Androgen excess in climacterium can lead to voice improvement

  La FM et al. J Voice 2007
- Menstrual Migraine: without aura is just minimal changes in hormonal concentrations

  Kuhl H et al, Ther Umsch. 2009; Sulak P et al, Headache. 2007

Social and Health Benefits
Birth Control Has Expanded Opportunity for Women

Birth Control Advances **Women's Economic Empowerment**

Birth Control Advances **Women's Educational Opportunities**

Access to Contraception Has Also Led to **More College-Educated** Women Pursuing Advanced Professional Degrees

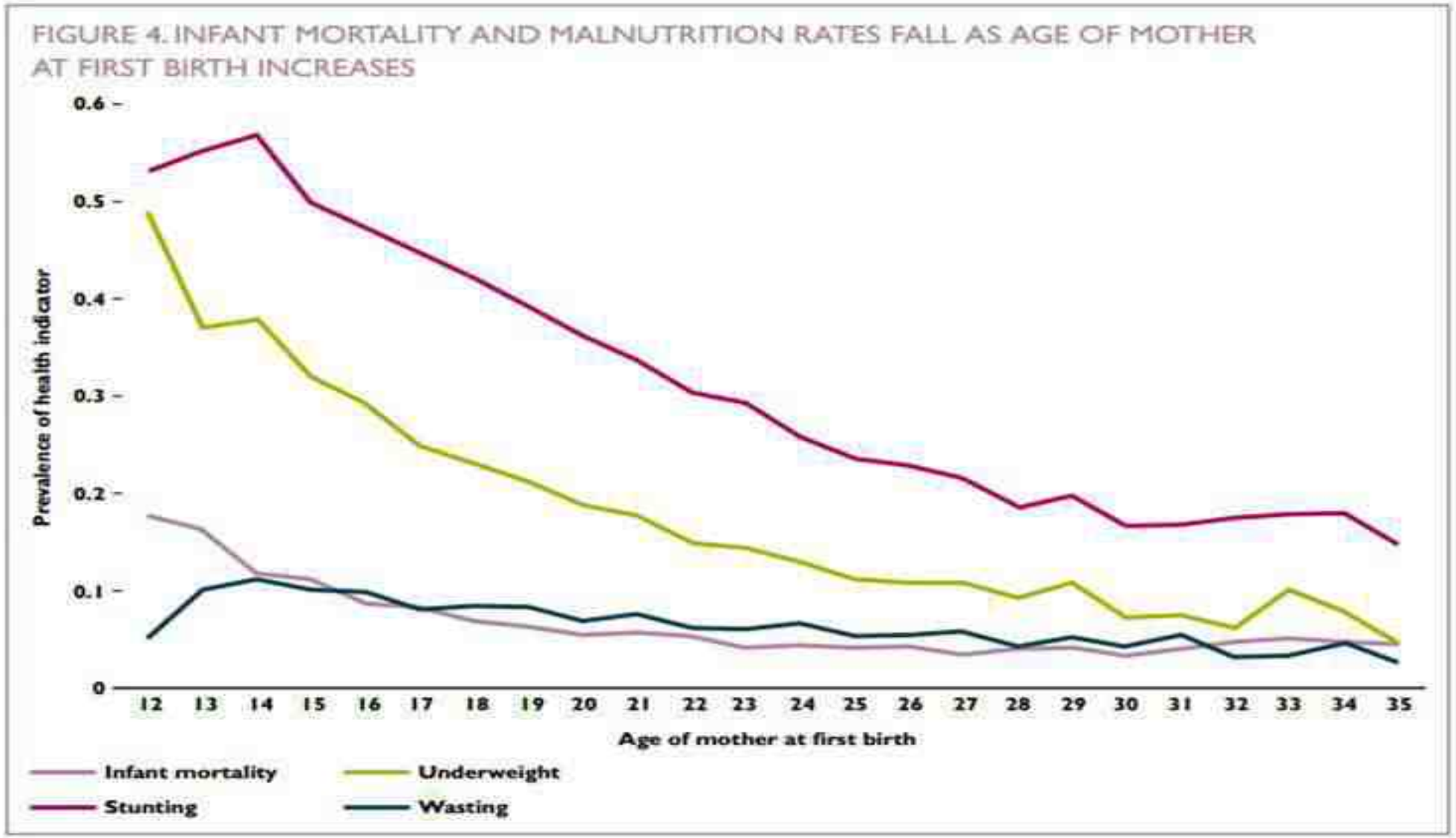
Birth Control Enhances **Children's Well-Being** in the Long Run

Birth Control **Reduces Teen Pregnancy**

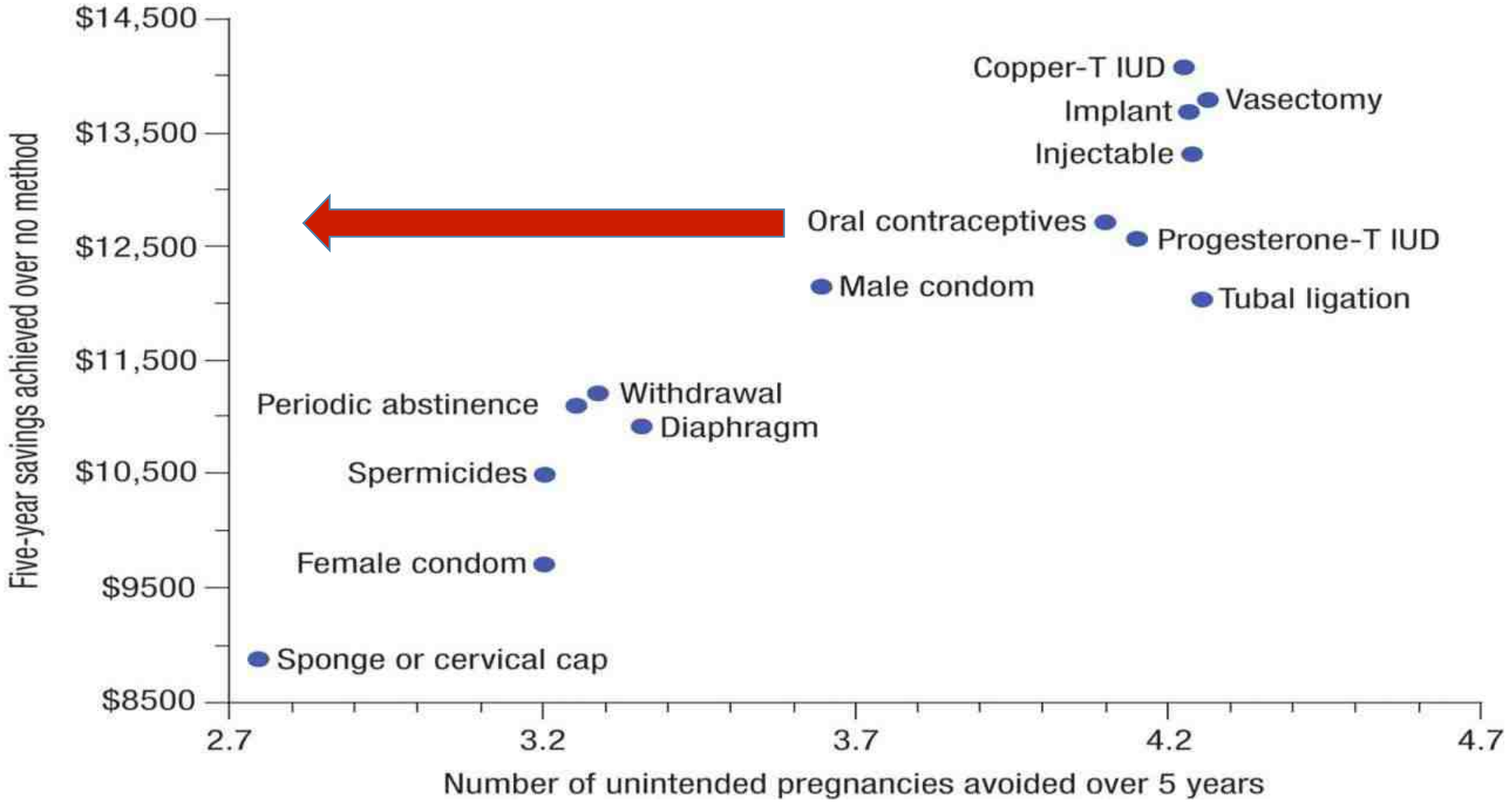
Birth Control **Reduces Unintended Pregnancy**

Mother age vs.infant mortality

EVERY WOMAN'S RIGHT



Unintended pregnancy & saving money



Thank you for your attention