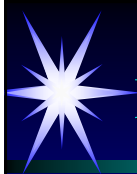


Kontrception

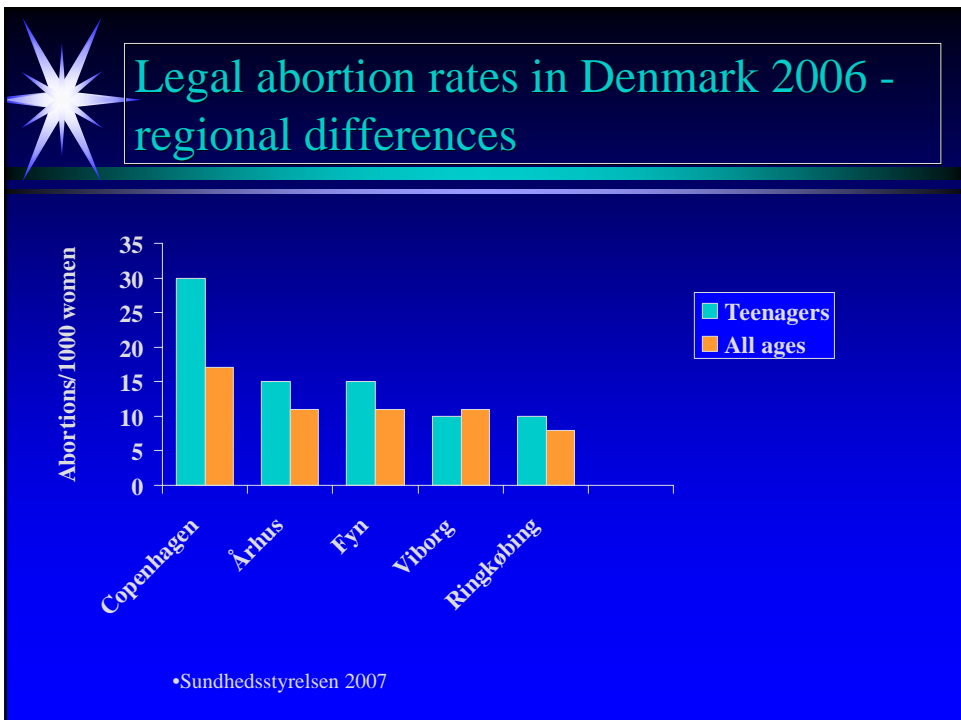
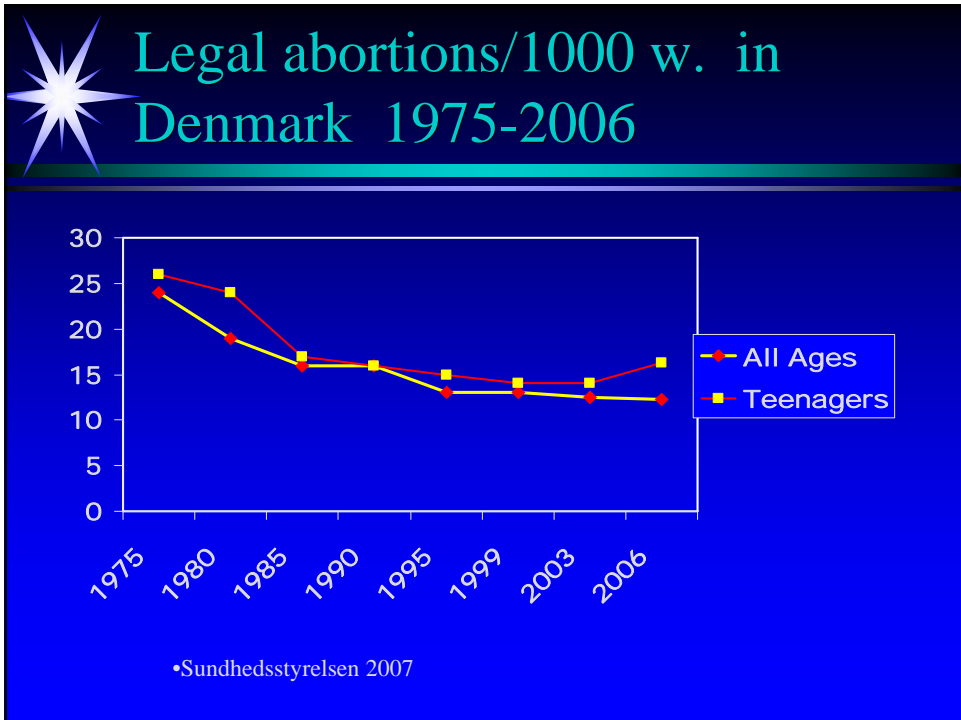
U-kursus 2010

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Gynækologisk Obstetrisk afd.
Odense Universitetshospital



Disposition

- Alment om kontrception
- Case om alvorlige bivirkninger ved hormonal AC
- Case om alm. Bivirkninger ved hormonal AC samt spiraler



Oral contraceptives and more Recently Developed Steroidal Contraceptives



LNG IUS



Single-rod Implant



Monthly Injectable



Vaginal Ring



Patch

Contraceptive efficacy of hormonal contraception - % women pregnant during first year

<u>Method</u>	<u>Lowest expect</u>	<u>Typical</u>
None	85	85
Comb. OC	0.1	5-8
POP	0.5	5
LNG-IUD	0.1	0.1
Norplant	0.1	0.1
Depo-Provera	0.3	0.3



Use of contraceptive methods in DK

	1996	2001	2003	2005
COC	314.485	331.358	372.260	340182
POP	6.612	8.924	10,101	7657
Cu-IUD	15085	-	-	
LNG-IUD	4.737	8160	10.973	14755
Implanon	-	3358	1487	
Emerg. Con.	23.670	40.415	61.120	Ca. 80.000



Use of contraception in women seeking legal abortion

	Number	No contra- ception (%)	User failure (%)
Sørensen 1994	589	34	26
Hansen 1996	354	41	-
Andreasen 1996	831	32	33

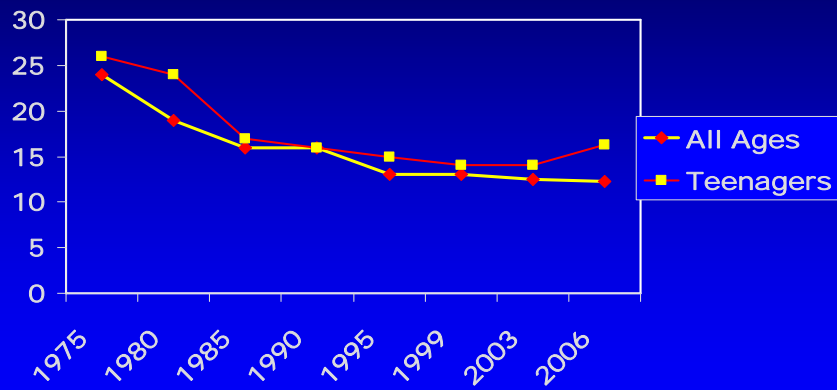
•Sørensen Ugeskr Læg 1994;156:4145

•Hansen Ugeskr Læg 1996;158:5773

•Andreasen Ugeskr Læg 1996;158:5928



Legal abortions/1000 w. in Denmark 1975-2006



• Sundhedsstyrelsen 2007



Hormonal contraception

Combined oral contraceptives

Combined parenteral contraception

Progestogen only contraception
(pills, implants, injectables)

Emergency contraception



Non contraceptive effects of OCs

Positive:

Bleeding disturbances, endometriosis, dysmenore, hirsutism, ovarian cysts, endometrial- and ovarian cancer

Negative:

Vascular disease



Combined contraceptives - mechanisms of action

Inhibition of FSH and LH secretion by a combined (?) action on hypothalamus and the pituitary.

Estrogen suppress FSH: Prevents follicular maturation

Progestogen block mid-cycle LH-peak: Anovulation

Progestogens change cervical mucus: No sperm penetration

Progestogen change endometrium: Inhibits implantation (??)



Combined oral contraceptives - effects on the cervix

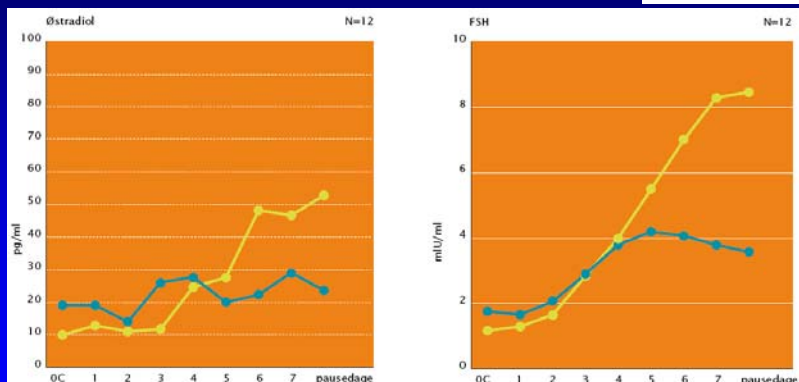
Stomal edema and pseudodecidualization
Endocervical hyperplasia

Decreased water and salt content of cervical mucus
Changed arrangement of proteins
Increased viscosity
Decreased penetration of sperm
Inhibition of capitation



20 mcg EE og 3 mcg Drospirinon 24 aktive p-piller 4 dages pause

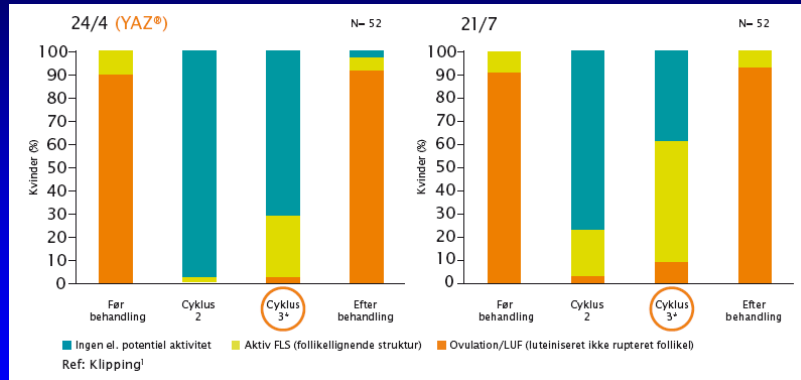
7-dage pause
3- eller 4-dage pause



Ref: Willis



Hvad sker der, hvis man glemmer 3 p-piller i starten af cyklus?



➤ Ved 24/4: 2% ovulation – ved 21/7: 8% ovulation



Efficacy of COCs - Estrogen or progesteron ?

- EE in doses of 30 mcg inhibits follicular development but ensures anovulation in approx. 90 %
- Daily dose of progesterons used in OCs is approx. twice the one required for anovulation
- Progesterons responsible for contraceptive effect
- Estrogens required for cycle control



Estrogen used in OCs

Ethinyl estradiol

Superior to estradiol because of less conversion to estrone inside the endometrium = better cycle control



Estrogen used in OCs

17-beta estradiol has been used in OC in DK in dose of 4 mg combined with NETA.

The freq. of bleeding disturbances was unacceptable



Estrogen used in Ocs New development – genuine estrogen

Estradiol valerate

Has proven to have acceptable cycle control when combined with Dienogest in a multicyclic manner



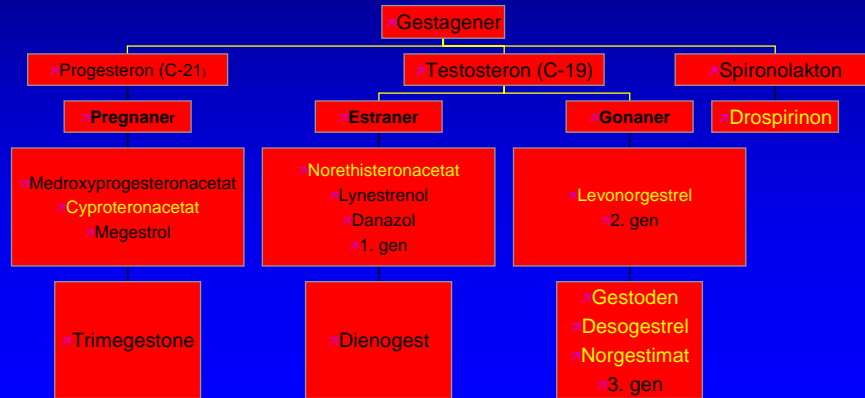
Comparative biological effects of E2V and EE

	2 mg E2V	20 mcg EE
FSH suppression and inhib. of ovulation	++	++
Endometrial stimulation	++	++
Vag. surface cell maturation	+++	++
Hepatic protein synthesis (SHBG, angiotensin, haemostasis var.)	++	+++



Division of progestagens

➤Classes of progestogens



Recently Developed Steroidal Contraceptives



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Single-rod Implant



Monthly Injectable



Vaginal Ring



Patch



Hormonal contraception

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Emergency contraception

Progestogen IUDs



Parenteral combined methods

- Patches
- Vaginal Rings

- **Potential advantages:**
- Efficacy comparable to Ocs
- Non-daily administration
- Lower hormonal dose
- Stable serum levels of hormones
- No hepatic first pass effect



Ring and patches

➤ Same contraindications as OCs

➤ Patches:

- 20 mcg EE + 150 NGT
- 3 x1 w.patch 1 w without
- Pearls index < 1.5
- Continuous use

➤ Rings

- 15 mcg EE + 120 ETO
- 3 w.ring 1 w without
- Pearls index < 1
- Can be removed for 3 h



NuvaRing





Common questions. Can the ring be felt ??

- 87 % of the women never/seldomly felt the ring during intercourse
- 74% of the partners never/seldomly felt the ring during intercourse
- 5% considered it a problem

Dieben et al. Obstet Gynecol 2002;100:585-93

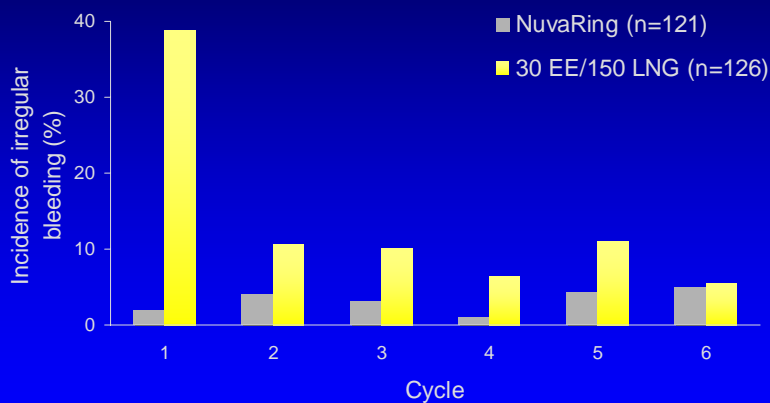


Comparison of self-reported adverse effects (%) with NuvaRing and a COC

	NuvaRing (n=123)	OC (n=126)
Headache	3.3	2.4
Breast tenderness	4.1	4.0
Nausea	5.0	3.2
Vaginitis + leuc.	6.6	1.6
Mood changes	5	6.4
Decreased libido	8.3	0

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

Irregular bleeding with NuvaRing Comparison with a COC



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

Pharmacokinetics of EE in different contraceptive formulations:

Daily homonal dose:	AUC 0-21 value for EE (ng x h/ml)
Ring: 15 mcg EE/120 mcg ENG	10.6
OC: 30 mcg EE/150 mcg LNG	21.9
Patch: 20 mcgEE/150 mcg NGT	35.8

➤Van den Heuvel MW et al. Contraception 2005;72:168-74



Hormonal contraception

Combined oral contraceptives
Combined parenteral contraception
Progestogen only contraception
(pills, implants, injectables)
Emergency contraception



Oral progestogen-only contraceptives.

Progestogen type:

Lynestrenol, norethisterone, levonorgestrel, desogestrel

Mode of action:

Effects on cervical mucus

- starts after 2-4 h
- is effective after approx. 48 h. during cont. intake.
- last 22 h. after last pill.

Back-up method for 48 h. if pill intake is more than 3 h . late !

Inhibition of ovulation or interference with luteal function
(50%)



Oral progestogen-only contraceptives Mini-pills.

Clinical side effects:

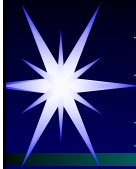
Menstrual disturbances due to interference with ovarian function and endometrial effects:

- 40 % normal
- 40 % short, irregular cycles
- 20 % non-cyclic bleeding

Headache, mood changes, weight gain ect.

Should be taken within a time window of 3 h

Contraindicated in women with abnormal liver function



Progestogen injectables and implants.

Progestogen type:

Medroxyprogesterone acetate (Depo-Provera)

Etonorgestrel (desogestrel, Implanon)

Mode of action:

Inhibition of ovulation (blocks LH-peak)

Minor effects on FSH (E2 level at early follicular level)

Effects on cervical mucus and endometrium

Side effects.

Unpredictable, anovulatory bleeding pattern

Amenore (after 2 y. with Implanon: 20%. Depo-Provera: 60%)



Etonorgestrel implant Contraceptive effect - 3 y

- At registration
 - 73429 cykles
 - No pregnancies
- Latest post marketing report*:
 - 218 pregnancies in 205.000 insertions
 - 13 directly method related

➤ Harrison. Contraception 2005;71:306



Etonogestrel Implant Bleeding pattern - 2 years

- 21%: amenorrhoe
- 26%: infrequent bleeding
- 6%: frequent bleeding
- 12 %: prolonged bleeding

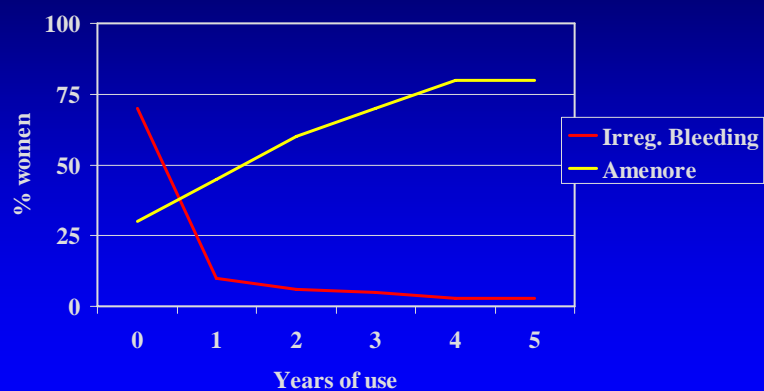


Depo Provera

- 150 mg MPA given i.m. every 3 months
- Pearls index far below 1
- Well suited for women with questionable compliance



Bleeding pattern during long term use of Depo-Provera



Speroff 1999



Hypoøstrogenicitet og Depo-Provera – effekt på knoglerne ??

- 2004: FDA Black Box warning: Kvinder på DP kan miste bone mineral density
- Kvinder skal kun anvende DP i mere end to år, hvis andre midler ikke er tilrådelige (advisable).
- **Facts:**
- Reduktion på mindre end 1 % of BMD pr. år. – sandsynligvis reversibelt.
- ACOG, WHO, Society of Adolescent Medicine:
- Ingen restriktioner hos voksne.
- Blandt unge piger vejer risikoen for uplanlagt svangerskab betydeligt højere end den teoretiske risiko for frakturer senere i livet.



What about Cupper IUDs ????

Mode of action:

Foreign body reaction in endometrium

Cu ions are toxic to spermatozoos

Reduced fertilisation

Main concerns:

Increased menstrual flow and pain

Decreased fertility due to PID



➤No. of publications comparing 12-months event rates
➤for nullips and parous women

IUD	No of studies	Expulsions		Bleeding and pain	
		Nullips	Parous	Nullips	Parous
Cu7	4	++++		+++	+
T-200	4	++	+	++++	
T-200	1	+			+
T-380	1	+			
Nova-T	4	+	++	++++	
ML-250	2	+		++	
ML-375	3	++	+	++	
GyneFix	1	+			+
Total	20	13	4	15	3

➤Hubacher. Contraception 2007;75:S8-S11

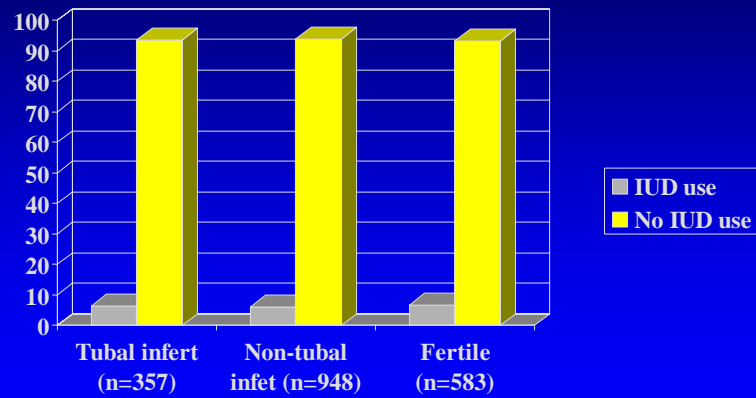


IUDs in nulliparous women

	Wiener 1978 (n=226, 6 months)	Skouby 1981 (n=120, 12 month)	Petersen 1991 (n=236, 12 month)
Termination (%)			
Expulsion	12	7	10
Bleeding/pain	5	14	13
Pregnancy	2	2	0
PID	2	6	9
Personal	0	6	3
Continuation	79	66	65



Proportion of women with tubal infertility, non-tubal infertility and fertile women who had used IUDs



Hubacher. N Engl J Med 2004;345:561-67



1 year clinical performance of OCs and LNG-IUDs in nullips – a randomized study

	OC (n=99)	LNG-IUD (n=94)
Pain	0	6,7*
Hormonal	9,8	4,9
Bleeding/spotting	1,3	2,5
Expulsion	NA	1,2
Other medical	1,1	2,1
Pl. pregnancy	2,6	0
Personal	15,4	4,6*
Cont. rate	72,7	79,8

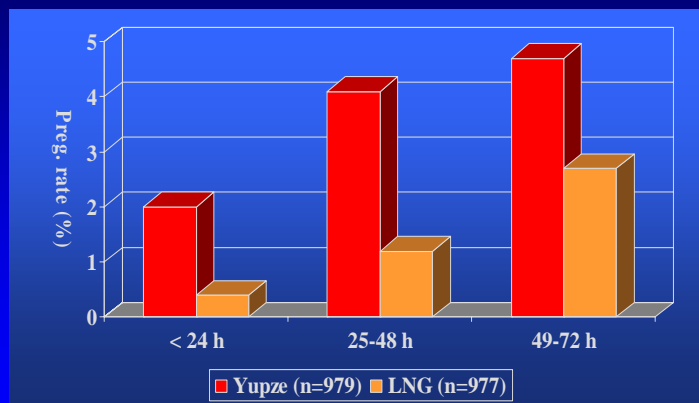


Emergency contraception

Method	Time limit	Efficacy (% of exp. preg.)
LNG 1,5 mg	72 (120 ?) h	85
Cu-IUD	5 d. after ovul.	100 ?
Mifepriston 10-600 mg	4 d. after IC	>85
100 mcg EE + 500 mcg LNG x2 (12 h. interv.)	72 h	75-80



Emergency contraception with Yupze or LNG - efficacy



Yupze: 31 obs.,
72 exp. : 57%
LNG: 11 obs.,
75 exp.: 85%

➤ Lancet 1998;352:428



Emergency contraception Mode of action

- LNG (+EE): Inhibition of ovulation.
Inhibition of implantation ?

- IUD: Inhibition of implantation ?



Hormonal emergency contraception

No medical contraindications

Secure effective contraception

Pregnancy test after 3 w.