

Nelson: Contraception Update: Best Practices in Contraceptive Counseling

Contraceptive Update: Best Practices in Contraceptive Counseling

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Conflict of Interest Disclosure Anita L. Nelson, MD

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Learning Objectives

- At the conclusion of this presentation, the participant will be able to:
- Counsel patients on the full array of contraceptive choices, including mechanisms of action, failure rates, contraindications, potential side effects and complications, and non-contraceptive benefits
 - Suggest ways of increasing successful patient utilization of contraceptive methods
 - Describe new approaches to older contraceptive methods

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Global Perspectives

- 35 countries have birth rates of ≥ 5 children
- < 5% of lowest income young people in developing countries use contraceptives
 - ◆ In Afghanistan
 - 4% of people use any contraceptive
 - 78% have never heard of family planning

World Bank. "Fertility Regimen Behaviors and Their Costs". 2008

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UNICEF Study: Maternal Morbidity

- 15,000,000 pregnancy- and birth-related injuries, infections, and disabilities each year worldwide
 - ◆ They most often go untreated
 - ◆ 80,000 develop fistula
- 300,000,000 women live with debilitating health problems as a result of pregnancy- and birth-related complications
 - ◆ More than 1/4 of adult women in lower-income economies

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Importance of Contraception

Country	% Women Using BCM	Fertility Rate	Lifetime Risk of Death from Pregnancy/related causes
Niger	11%	7.2	1:7
Afghanistan	10%	7.1	1:8
Uganda	24%	6.5	1:25
Haiti	37%	3.6	1:44
India	56%	2.8	1:70

UNICEF Information by Country. <http://www.unicef.org/infobycountry/index.html>

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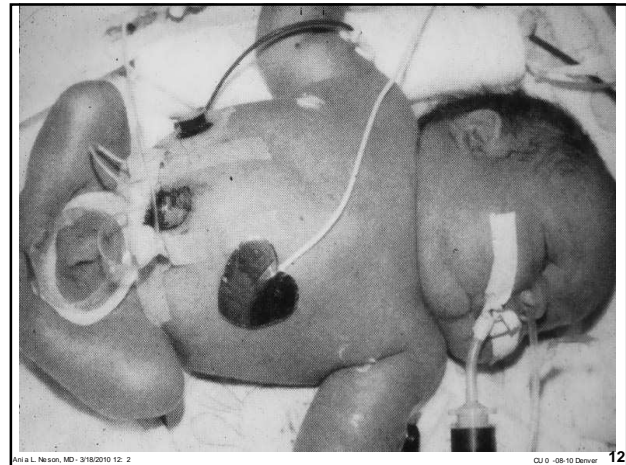
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Importance of Contraception

Country	% Women Using BCM	Fertility Rate	Lifetime Risk of Death from Pregnancy/related causes
Honduras	65%	3.3	1:93
Egypt	59%	2.9	1:230
Mexico	71%	2.2	1:670
U.S.	76%	2.1	1:4,800
China	85%	1.7	1:1,300
Canada	75%	1.5	1:11,000
Italy	60%	1.4	1:26,600
Czech Republic	69%	1.2	1:18,100

UNICEF Information by Country. <http://www.unicef.org/infobycountry/index.html>

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PRAMS Survey: Unintended Pregnancy Reasons for Unprotected Intercourse

- 33% thought they could not get pregnant at that time
- 10% thought they or partner were sterile
- 30% ambivalent
- 22% partner did not want to use contraceptives
- 16% side effects
- 10% access problems
- 18% other

Nettleman MD. *Contraception*. 2007;75(5):361-66

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Timely Refill Rates up to 12 Months

Contraceptive Methods	Number starting	30 days		90 days		360 days	
		%	%	%	%		
1 Month Methods							
Contraceptive Ring	96,598	59.4	51.1	26.0			
Contraceptive Patch	433,403	68.4	49.8	25.9			
Branded Pills							
Ortho Tri-Cyclen	182,479	69.2	43.2	16.3			
Ortho Tri-Cyclen Lo	309,535	74.5	58.6	29.5			
Ovcon	103,671	65.9	47.7	20.3			
Yasmin	321,834	75.1	61.2	34.5			
3 Month Methods							
DMPA	161,226	N/A	52.6	21.0			
Seasonale	80,647	N/A	53.4	31.0			

Nelson AL, et al. *Obstet Gynecol*. 2008;112(4):782-7

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High Typical Use Failure Rates: First Year Estimates

- Injectables: 6.7%
- Oral contraceptives: 8.7%
- Condoms: 17.4%
- Withdrawal: 18.4%
- Fertility awareness methods: 25.3%

Kost K, et al. *Contraception*. 2008;77(1):10-21

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The Need for Forgettable Contraception

- 1/3 of all US women will have had an induced abortion by age 45
- 1 million pregnancies/year are due to incorrect or inconsistent use of OCs
- 20% of women who select sterilization at age ≤ 30 years later express regret¹
- Noncontraceptive benefits

¹Curtis, et al. *Contraception*. 2006;73:205-210

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Importance of Contraceptive "Fit"

- Contraceptive "fit" – the safest, most effective birth control method that will work well for the user
- A good fit depends upon a woman's
 - ◆ Individual health profile
 - ◆ Lifestyle
 - ◆ Reproductive stage
 - ◆ Preferences

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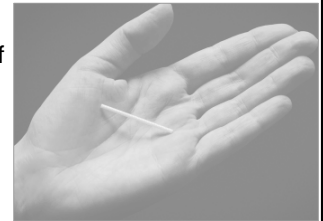
Tiers of Contraceptive Efficacy

Longer Term	Implants, IUDs, Monthly Injections
Combined Hormonal	DMPA Injections
	Vaginal Rings, Transdermal Patches
	Oral Contraceptive Pills
Barriers and Behaviors	Male Condoms
	Diaphragms, Withdrawal, FAM, NFP
	Caps, Female Condoms, Shield
	Spermicides

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Etonogestrel Contraceptive Implant

- Single implant rod (4 cm x 2 mm) made of ethylene vinyl acetate
- Contains 68 mg of etonogestrel (3-keto-desogestrel)
- Effective for 3 years
- 6 pregnancies in 20,648 cycles
- Inhibits ovulation and thickens cervical mucus
- Rapid return of fertility



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Etonogestrel Implant Efficacy and Mechanism of Action

- 0 pregnancies in clinical trials with 58,900 cycles
- Ovulation suppression over time:
 - ◆ ≤ 1 year: 0%
 - ◆ 1-2 years: 0%
 - ◆ 2-3 years: 3.1%
- Thickens cervical mucus

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Etonogestrel Implant

- Provided unsurpassed contraceptive efficacy
 - ◆ By ovulation suppression and thickened cervical mucus
- Very low levels of progestin
- Follicular phase estrogen
- Rare medical contraindications
- Rapid reversibility
- Bleeding patterns better than Norplant
- Weight changes less well tolerated

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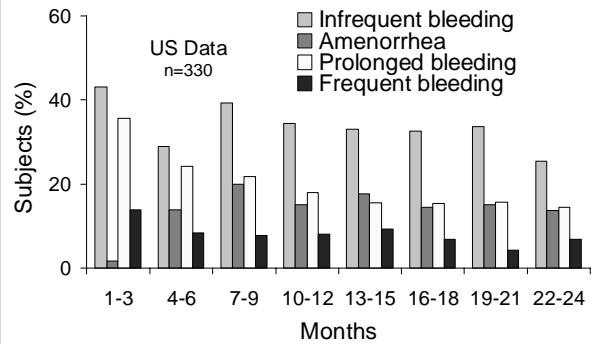
Etonogestrel Implant Rapid Reversibility

- Etonogestrel levels undetectable within 1 week¹
- > 90% of subjects ovulated within 1 month post removal²
 - ◆ 44 of 47 women who were studied with ultrasound and serum progesterone levels

1. Davies GC, et al. *Contraception*. 1993;47:251-261
 2. Croxatto HB. *Contraception*. 1998;58(6):91S-97S

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Etonogestrel Implant: Bleeding Patterns



Data on file, Organon Inc. Study Report 069001.

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Copper T 380



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Copper T 380 IUD

	Net cumulative rates (%) by year					
	1	2	3	4	7	10
Pregnancy	0.7	1.0	1.6	1.8	2.3	2.7
Expulsion	5.7	8.2	9.8	11.0	11.9	14.2
Bleeding/pain	11.9	21.7	28.7	32.2	41.6	50.0
Other medical events	2.5	4.6	6.2	7.9	9.3	10.1

Prescribing Information. 2005

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Life Table Pregnancy Rate Per 1000: Years 11-15 and 16-20

	Average Annual Pregnancy Rate	Cumulative Pregnancy Rate	Woman Years	Cumulative Pregnancy Rate	Woman Years
IUD	Years 11-15		Years 16-20		
TCu380A	0.0	0.0	1050	NA	7
TCu380Ag	0.0	0.0	154	0.0	70
TCu220C	0.0	0.0	682	NA	0

Sivin I et al. *Contraception*. 1991 Nov;44(5):473-80

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Candidates for Copper IUD

- Nulliparous women
- Women with untreated vaginitis
 - ◆ Unresolved abnormal pap smear not suspicious for carcinoma
 - ◆ Increased susceptibility to infection (HN, AIDS, etc)
 - ◆ Multiple sexual partners if not at high risk for PID
 - ◆ History of ectopic pregnancy
 - ◆ History of PID

Note: Immediate IUD placement following first trimester pregnancy loss is safe and effective

Grimes DA, et al. *Contraception*. 2007 Jun;75(6 Suppl):55-9

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Copper Intrauterine Devices Mechanisms of Action

- Interference with sperm transport from cervix to fallopian tube
- Inhibition of sperm capacitation or survival
 - ◆ Viable sperm scarce in fallopian tubes of IUD users
- Inhibition of fertilization: no normally dividing fertilized ova in tubes or uterus
- Not an abortifacient

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Condition of Ova Recovered From Fallopian Tubes at Ovulation

Group	Normal Development	No Development	Uncertain Or Abnormal Development
Control	10	3	7
All IUDs	0	9	5
Lippes loop	0	3	1
TCu 200	0	2	3
Progestin IUD	0	4	1

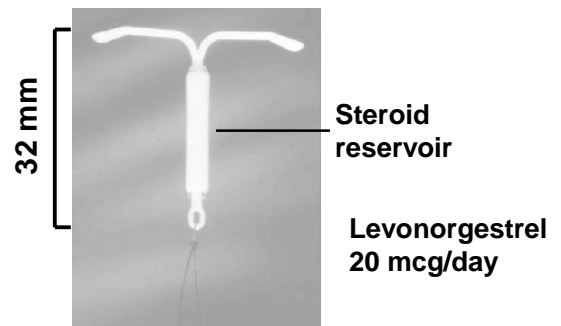
Alvarez F, et al. *Fertil Steril.* 1988;49(5):768-73 CU 0 -08-10 Denver 55

Estimates of Cost Savings for Various Methods of Birth Control for a Fertile, Sexually Active Woman Over a Five-Year Period

Birth Control Method	\$ Saved Over 5 Years
IUD	14,122
Vasectomy	13,898
Implants	13,813
Injections	13,373
Oral Contraceptives	12,879
Barriers, Spermicides, Withdrawal	8,933-12,239

Trussell J, et al. *Am J Public Health.* 1995;85:494-503 CU 0 -08-10 Denver 60

Levonorgestrel-Releasing Intrauterine System (LNG IUS)



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LNG IUS Typical Use Failure Rates (Pearl Index)

- First year 0.14%
- 5-year cumulative 0.71%
- Meta-analysis of comparative clinical trials showed no differences in efficacy compared to copper IUDs with $\geq 250 \text{ mm}^2$ copper

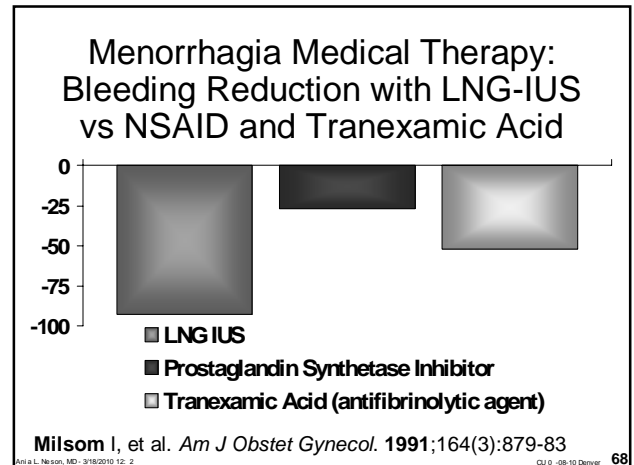
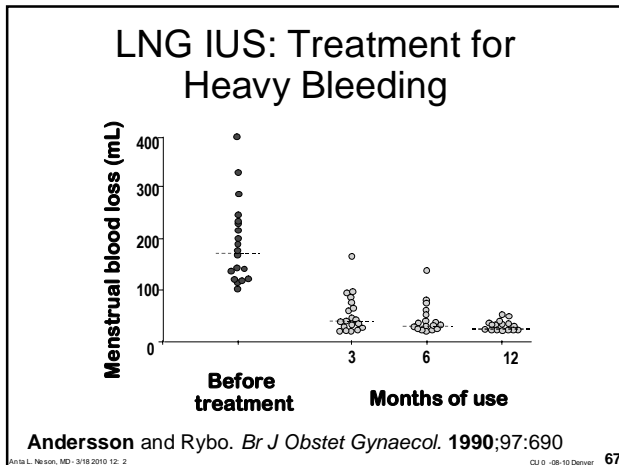
Anderson K, et al. *Contraception.* 1994;49:56
 Luukkainen T, et al. *Contraception.* 1987;36:169
 French RS, et al. *Br J Obstet Gynecol.* 2000;107:1218-25 CU 0 -08-10 Denver 62

LNG IUS: Menstrual Cycle Changes

- Months 1-4: increased days of spotting and bleeding (mean 1st month 16-17 days of spotting)
- After 6 months: average 1 day bleeding per month with some residual, unpredictable spotting
- By 12 months: mean bleeding days = 0; 80% had 1-3 days of spotting; 90% reduction in blood loss in women with menorrhagia; \uparrow hemoglobin 0.4
- Amenorrhea: 20% by 12 months; 30% by 24 months; 60% by 12 years

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Mirena® vs. Medroxyprogesterone Acetate

- Randomized, multicenter, open-label clinical trial, about 50 sites in US, Canada and Brazil
- Women (n=138), >18 years of age, with at least 2 cycles of menorrhagia of ≥80 mL each within a 3-cycle screening phase
- Exclusion: women with diagnosed organic cause of menorrhagia or contraindication to Mirena® or MPA
- Treatments: 6 cycle
 - ◆ Mirena® for 6 months
 - ◆ MPA (Provera®) tablets 10 mg/day for cycle days 16–25

Bayer HealthCare Pharmaceuticals, Data on file.

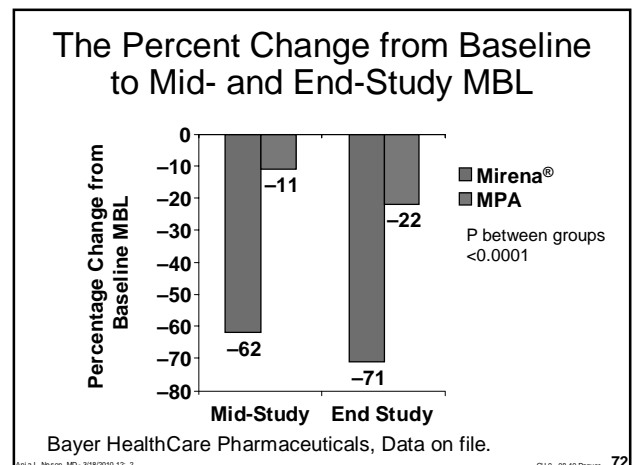
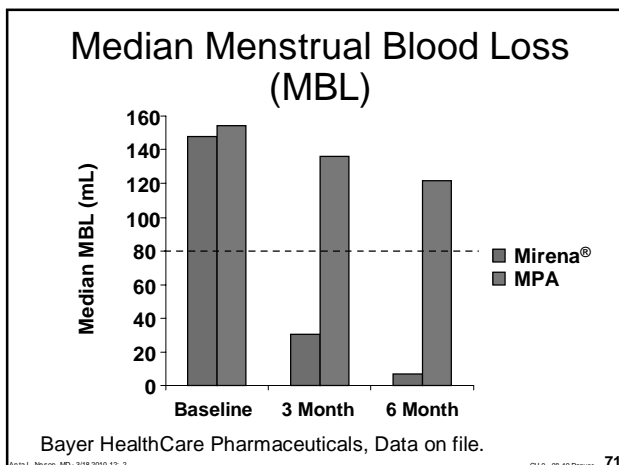
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Baseline Characteristics

	Mirena® (n=82)		MPA (n=83)	
	Mean	SD	Mean	SD
Age (year)	38.3	5.19	39.3	5.44
BMI	27.2	3.9	27.4	4.6
Cycle length (days)	27.2	3.39	27.3	2.29
Days of Flow	6.2	1.64	6.3	1.54

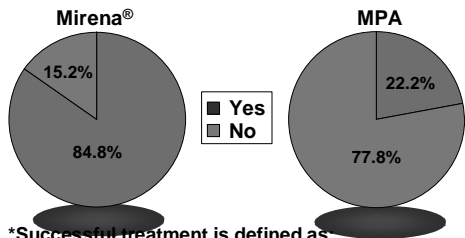
Bayer HealthCare Pharmaceuticals, Data on file. SD=standard deviation

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The Proportion of Subjects with Successful Treatment*



- *Successful treatment is defined as:
1. End-study MBL <80 mL
 2. Decreased MBL at end of study ≥50% of baseline MBL
- P between groups <0.001

Bayer HealthCare Pharmaceuticals, Data on file.

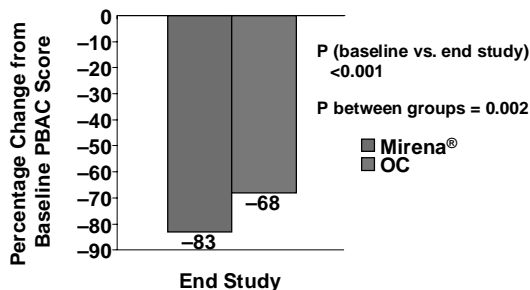
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Mirena® vs. Combined Oral Contraceptive Pill

- 12-month prospective, randomized, open-label study conducted in nine centers in Canada of women with idiopathic HMB
 - MBL estimated using pictorial blood assessment charts (PBAC). For inclusion: PBAC score ≥100 (MBL ≥80 mL)
 - Women randomized to: Mirena® (n=20), OC (n=19) (1 mg norethindrone acetate, 20 mcg ethinyl estradiol, Minestrin®) cyclic use
 - Primary endpoint: change in MBL from baseline to 12 months
- Endrikat, et al. *J Obstet Gynaecol Can.* 2009;31(4):340-347.

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The Percent Change from Baseline



Endrikat, et al. *J Obstet Gynaecol Can.* 2009;31(4):340-347.

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Menorrhagia: Conclusion from Trial Data Comparing LNG-IUS to Surgery

“Surgery reduces menstrual bleeding at one year more than medical treatments, but levonorgestrel IUS appears equally beneficial in improving quality of life and may control bleeding as effectively as conservative surgery over the long term”

Marjoribanks, et al. *Cochrane Database Syst Rev.* 2003

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Newer Meta-Analysis: Mirena® vs. Ablation for HMB

- Systematic review of randomized clinical trial using PBAC scores
 - ◆ 6 studies evaluated
 - 3 first-generation ablation vs. Mirena®
 - 3 second-generation ablation vs. Mirena®
- Mirena® and ablation associated with similar blood loss at 6, 12 and 24 months
 - ◆ No difference when Mirena® compared to separate generations

Kaunitz, et al. *AJOG.* 2009 May;113(5):1104-16b.

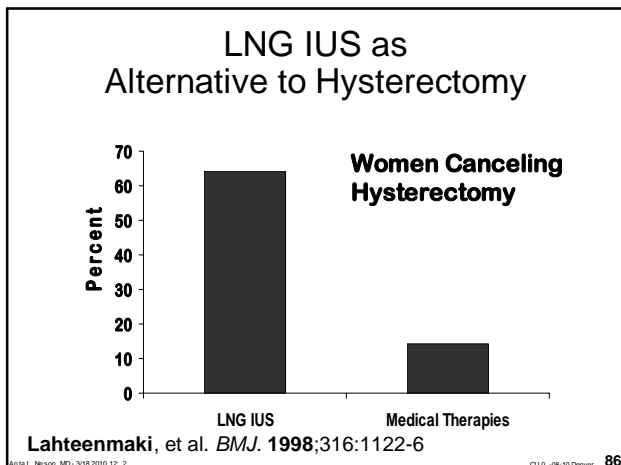
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Newer Meta-Analysis: Mirena® vs. Ablation for HMB

- No apparent difference between rates of treatment failures
 - ◆ 21.2% vs. 17.9%
 - Both methods resulted in similar improvements in quality of life
 - Less need for analgesia/anesthesia in Mirena® group
 - Ablation requires additional effective contraceptive method
 - ◆ Postablation placentation problem
- Kaunitz, et al. *AJOG.* 2009 May;113(5):1104-16b.

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LNG IUS Versus Hysterectomy: Outcomes and Costs

- 236 women age 35-49 with menorrhagia
 - ◆ Randomized to hysterectomy versus LNG-IUS
- 5-year follow-up
 - ◆ No difference in Health-related Quality Of Life
 - ◆ 42% of LNG-IUS users underwent hysterectomy

Discounted Indirect and Direct Costs		
LNG-IUS	\$2817	95% CI (\$2222-3530)
Hysterectomy	\$4660	95% CI (\$4014-5180)

Hurskainen R, et al. *JAMA*. 2004;291:1456-63

Depo Medroxyprogesterone Acetate (DMPA)

- Dose: 150 mg every 11-13 weeks
- Highly effective with consistent and correct use
 - ◆ First year : 0.25-0.3%
 - ◆ Five-year cumulative : 0.9%
- Typical use first-year failure rate: 7.4%
- Very convenient and private
- Special clinical applications

DMPA: Clinical Applications

- Sickle cell anemia
- Mental retardation
- Breast feeding
- Seizure disorders

DMPA and Weight Change: Recent Observational Studies

Study	Year	N	Weight Change
Mainwaring	1995	22	None
Moore	1995	50	None
Taneepanichskul	1999	100	None
Danli	2000	1994	None
Pe kman	2001	20	None
Polaneczky	1996	125	+3.3±8.6 lb
Risser	1999	130	+3.0±4.5 lb
Espey	2000	306	+5 lb
Templeman	2000	133	+9.8±10.5 lb

Mainwaring R et al. *Contraception*. 1995;51:149-3
 Moore L. *Contraception*. 1996;52:215-9
 Taneepanichskul S et al. *Contraception*. 1999;59:301-3
 Danli S et al. *Contraception*. 2000;62:15-8
 Pe kman CL et al. *Ann J Clin Nutr*. 2001;73:19-26
 Polaneczky M et al. *Fam Plan Perspect*. 1996;38:174-8
 Risser VL et al. *J Adolesc Health*. 1999;24:433-6
 Espey E et al. *Contraception*. 2000;62:55-8
 Templeman C et al. *J Pediatr Adolesc Gynecol*. 2000;13:45-6

DMPA and Bone Density ACOG Committee Study

- “Concerns regarding the effect of DMPA and BMD [bone mineral density] should neither prevent practitioners from prescribing DMPA nor limit its use to 2 consecutive years”

ACOG Committee Opinion No. 415, Sept 2008

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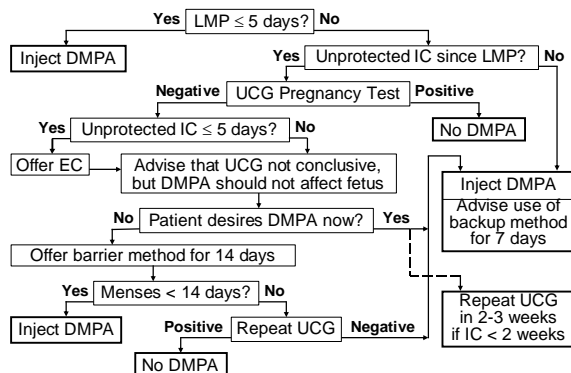
DMPA Practice Recommendation to Increase Access and Success

- No pelvic exam or pap smear needed prior to initiation
- Quick Start for initiation and late re-injection¹
- No pregnancy test needed prior to any injection unless the patient has had unprotected intercourse or has symptoms of pregnancy
- Always provide EC because patients can return late for reinjection
- Reinjection without need of pregnancy testing or back up method may be routinely scheduled to 2-4 weeks.²

1 Nelson AL, et al. *Contraception*. 2007 (75(2):84-7
 2 Steiner MJ, et al. *Contraception*. 2008;77(6):410-4

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DMPA Administration Flow Sheet



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Oral Contraceptive Pills

- Safe and well-tested -- the gold standard:
 - ◆ 49 years of clinical experience in US
 - ◆ Best studied medication in history
- Failure rate with consistent and correct use < 1%
- Typical first year failure rate is 8.7%
- Rapidly reversible:
 - ◆ Only 2 week average delay in fertility
- Extensive non-contraceptive benefits

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“Birth control pills are not dangerous, but there are dangerous women out there. Find them and keep them away from the pill, and the pill will do its work well.”

Paul Brenner, M.D.
 Professor, OB-GYN
 USC

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OC Failure by Body Weight >70.5 kg and OC Estrogen Dose

Dose EE	Pregnancy RR	95% CI
≥ 50 µg	1.2	0.4 – 3.5
< 50 µg	2.6	1.2 – 5.9
< 35 µg	4.5	1.4 – 14.4

1. Holt VL, et al. *Obstet Gynecol*. 2005;105(1):46-52
 2. Holt VL, et al. *Obstet Gynecol*. 2002;99(5 Pt 1):820-7

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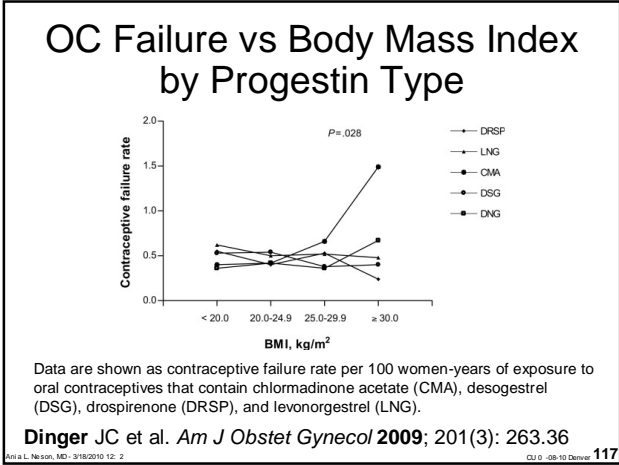
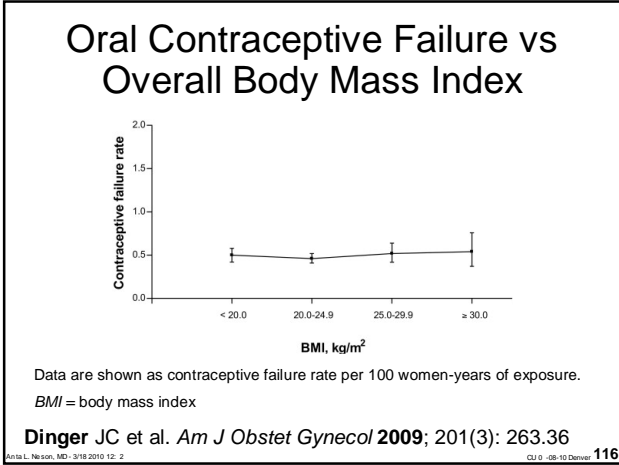
Weight Issues and Combination Hormonal Contraception

- Holt found higher failure rates in women > 154 lbs
 - ◆ No consistent dose relationship
- Not clear if failure related to obesity or behaviors
- ACOG advises that women over the age of 35 with a BMI ≥ should be prescribed estrogen containing hormonal methods with caution
- British authorities prohibit use of COCs in woman with BMI > 40

1. Holt VL, et al. *Obstet Gynecol*. 2005;105(1):46-52
 2. Holt VL, et al. *Obstet Gynecol*. 2002;99(5 Pt 1):820-7
 3. *Obstet Gynecol*. 2006;107(6):1453-72.

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Oral Contraceptives and the Risk of Breast Cancer for Women of Age 35-64

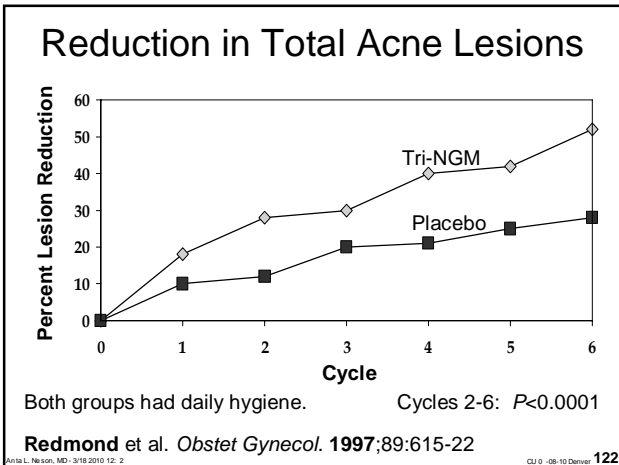
- Population based, case control study
- 4,575 women with breast cancer
- 4,685 control women
- Current users: RR = 1.0 (0.8-1.3)
- Former users: RR = 0.9 (0.8-1.0)
- No consistent increases with increasing estrogen dose or duration of use
- No association with family history of breast cancer or young initiation

Marchbanks PA, et al. *N Engl J Med.* 2002;346:2025-32

Non-Contraceptive Health Benefits of Oral Contraceptives

Proven Reduction in Risk:	Possible Reduction in Risk:
<ul style="list-style-type: none"> ● Ovarian Cancer ● Endometrial Cancer ● Pelvic Inflammatory Disease ● Ectopic Pregnancy ● Benign Breast Disease ● Menorrhagia ● Dysmenorrhea ● Iron Deficiency Anemia ● Low Bone Density 	<ul style="list-style-type: none"> ● Cardiovascular Disease ● Uterine Fibroids ● Endometriosis ● Rheumatoid Arthritis

Adapted from: **Ory HW.**
Fam Plann Perspect. 1982;14:182-4



Incidence of Events Commonly Attributable to OC Use

Data displayed as:	Triphasic Norgestimate/EE (N=228)	Placebo (N=234)	p-value
Headache	42 (18.4)	48 (20.5)	0.639
Nausea	29 (12.7)	21 (9.0)	0.231
Dysmenorrhea	23 (10.1)	21 (9.0)	0.752
Breast pain	21 (9.2)	11 (4.7)	0.067
Abdominal pain	13 (5.7)	9 (3.9)	0.270
Back pain	13 (5.7)	8 (3.4)	0.597
Vomiting	8 (3.5)	6 (2.6)	0.597
Breast enlargement	6 (2.6)	3 (1.3)	0.333
Emotional lability	6 (2.6)	1 (0.4)	0.065
Weight gain	5 (2.2)	5 (2.1)	1.000

Redmond et al. *Contraception.* 1999;60:81-5

Nelson: Contraception Update: Best Practices in Contraceptive Counseling

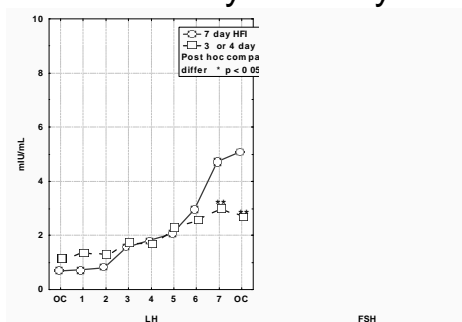
Hormone-Withdrawal Symptoms in OC Users

Symptoms	Hormone Treatment % (21 days)	Hormone-Free % (7 days)	p-value
Pelvic pain	21	70	<0.001
Headaches	53	70	<0.001
Breast tenderness	19	58	<0.001
Bloating/swelling	16	38	<0.001
Use of pain medications	43	69	<0.001

Sulak P, et al. *Obstet Gynecol.* 2000;95:261-6

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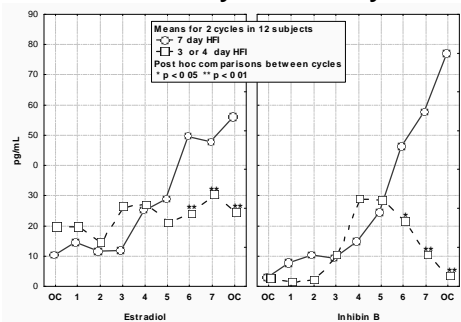
LH/FSH: Comparing 7-day Versus 3-day or 4-day HFI



Willis SA, et al. *Contraception* 2006;74(2):100-3

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Ovarian Response for 7-day Versus 3-day or 4-day HFI



Willis SA, et al. *Contraception* 2006;74(2):100-3

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Treatment of PMDD with 24/4 drospirenone with 20 mcg EE

Symptoms	Baseline		Treatment		p-value
	OC	Placebo	OC	Placebo	
Depression	9.7	9.7	4.0	4.6	.005
Mood swings	8.3	8.5	3.3	4.5	<.001
Anger	8.2	8.4	3.7	4.7	<.001
Overwhelmed	6.8	7.3	2.8	3.3	<.001
Physical	13.4	13.3	7.4	8.6	<.001

Yonkers KA, et al. *Obstet Gynecol.* 2005;106(3):492-501

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Ingenix Study: Design

- Ingenix study
 - ◆ US phase IV, claims-based, prospective, cohort study
 - ◆ 22,429 women using Yasmin®; 44,858 using other OCs
 - ◆ Primary variables:
 - Hyperkalemia and related clinical outcomes, e.g., death, hospitalization, syncope, arrhythmia, other electrolyte disturbances, dialysis, myocardial infarction
 - VTE/ATE
 - ◆ Data from study submitted to the FDA on regular basis

Seeger JD et al. *Obstet Gynecol* 2007; 110: 587-593.

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EURAS Study: Design

- European Active Surveillance (EURAS) study
- Comparative, prospective, non-interventional cohort study
- 16,534 women using Yasmin®; 42,140 using other OCs
- Variables:
 - ◆ Primary: VTE hazard ratio between users of Yasmin® and users of LNG-containing OCs
 - ◆ Other variables: risk of ATE, risk of arrhythmia, and sudden death
- Data from study submitted to the FDA on regular basis

Dinger JC et al. *Contraception* 2007; 75: 344-354.

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Incidence of VTE

(events per 100,000 woman-years)

- Estimates of VTE incidence in OC users
- EURAS data¹
 - ◆ OCs containing levonorgestrel: 80/100,000
 - ◆ OCs containing drospirenone: 91/100,000
 - ◆ OCs containing other progestins: 99/100,000
- INGENIX data²
 - ◆ OCs containing drospirenone: 130/100,000
 - ◆ OCs containing other progestins: 140/100,000

1. Seeger JD et al. *Obstet Gynecol.* 2007;110:587-593

2. Dinger JC et al. *Contraception* 2007; 75: 344-354.

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Extended OC Applications: Control of Menstrual Cycle Timing For Convenience

- Honeymoons
- Business meetings
- Travel
- Sporting events
- Military campaigns
- Examinations
- Life

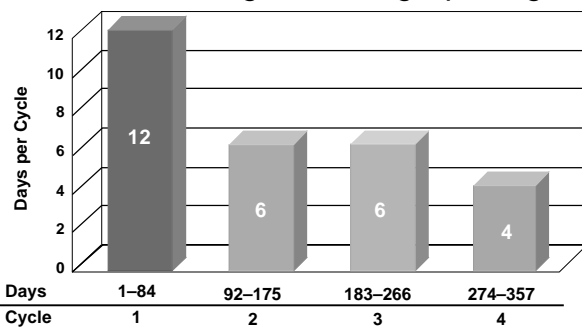
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Counseling Points for Women Considering Extended Cycle

- Validate patient's beliefs in need for monthly menses without hormonal contraception
 - ◆ Absence could be sign of pregnancy, hormonal imbalances, endocrinopathy or risk for cancer.
- Menses represents reproductive failure. A clean up operation to prepare for better luck next cycle.
- Dispel her concerns proactively
 - ◆ Blood not building up
 - ◆ Ovaries not swelling
 - ◆ Fertility will return (not menopausal)
 - ◆ Cancer risk not increased

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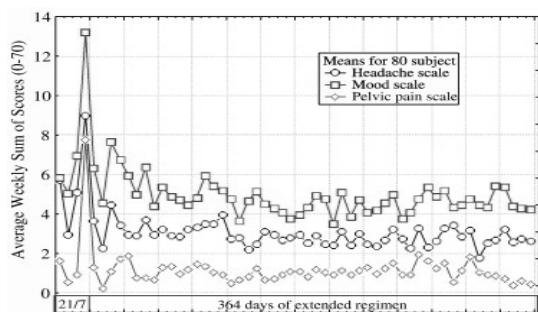
Extended Cycle OC Trial: Median Days of Breakthrough Bleeding/Spotting



Data on file, Barr Research

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Pain Scores 24/7 Cycle US Extended Cycle 30 mg EE/3 mg Drospirenone



Coffee AL, et al. *Contraception.* 2007;75:444-449

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Hopefully to be Approved Soon Estradiol Not Ethinyl Estradiol

- Estradiol Valerate + Dienogest
 - ◆ Sequential formulation a.k.a. "dynamic dosing"
 - ◆ Estradiol valerate circulates as estradiol
 - ◆ Dienogest:
 - Progestin with potent effects on endometrium and its blood supply
 - ◆ Seeking approval for both
 - Contraception
 - Treatment of heavy menstrual bleeding

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Not Here Yet . . . Estradiol Not Ethinyl Estradiol

- Estradiol + nomegestrol acetate (NOMAC)
- NOMAC – nonandrogenic 19-norprogesterone derivative
 - ◆ Binds more selectively to progesterin receptor
 - ◆ Monophasic formulation
- Seeking approval as contraceptive in 'EU now'

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Oral Contraceptives: Quick Start

- With conventional start of OCs, up to 25% of women do not start their pills due to:
 - ◆ Pregnancy
 - ◆ Change in method
 - ◆ Confusion about pill instructions
 - ◆ Fear of possible side effects
- Quick start with OCs protocol
 - ◆ Start with first pill in pack
 - ◆ Provide backup method for 7 days
 - ◆ Provide EC if indicated

Westhoff CW, et al. *Fertil Steril.* 2003;79:322-9

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Quick Start Pills Clinical Trial With Young Women

- 1716 women ≤ 25 years
- Quick Start users continued into next cycle more often than did conventional start users
 - ◆ OR = 1.5 [95% CI 1.0-2.1]
- Quick Start did not improve continuation rates at 3 and 6 months
 - ◆ 60% of all users discontinued OC use
 - ◆ 8% became pregnant
- 81% of women rated Quick Start as acceptable or preferable

Westhoff C, et al. *Obstet Gynecol.* 2007;109(6):1270-6

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Documented 3-cycle Continuation Rates for 668 Women Given Combined Hormonal Contraceptives

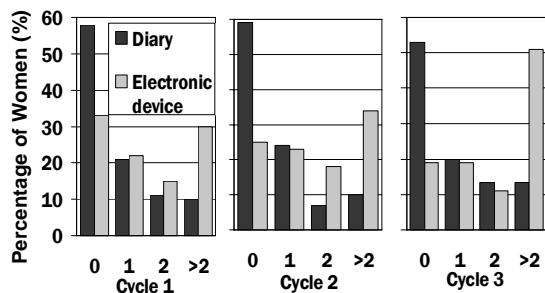
Subgroups of Women	Continuation Rates (%)		
	All Methods	OC Users	Patch Users
Dispensed < 3 cycles at initial visit	31.9	29.7	33.8
Dispensed ≥ 3 cycles at initial visit	47.8	49.0	43.5
P value	p<.0001	p=.005	p=.16

Nelson AL, et al. *Am J Obstet Gynecol.* 2007;196(6):599.e1-5

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Oral Contraceptive Compliance: Number of Active Pills Missed



Potter L, et al. *Fam Plann Perspect.* 1996;28:154-8

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Application of Contraceptive Patch on Abdomen



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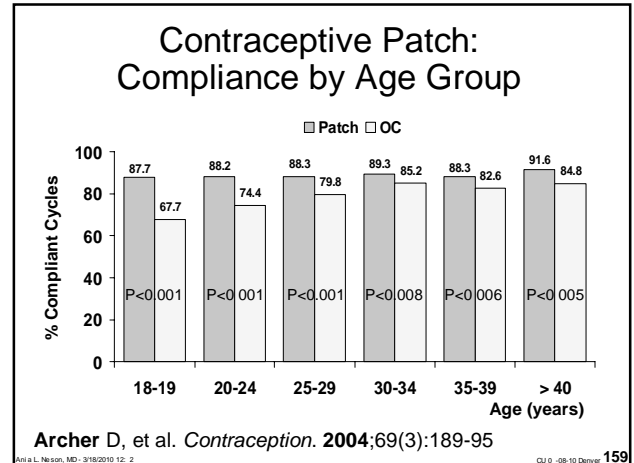
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Contraceptive Patch: Distribution of Pregnancies by Baseline Body Weight Deciles (n=3319 subjects)

Body Weight Decile	Weight Range (kg)	Total Pregnancies
1	<52	1
2	52 - <55	2
3	55 - <58	0
4	58 - <60	0
5	60 - <63	2
6	63 - <66	0
7	66 - <69	1
8	69 - <74	0
9	74 - <80	2
10	≥80	7
	80 - 85	1
	85 - 90	1
	≥90	5

Zieman M, et al. *Fertil Steril.* 2002;77(2 Suppl 2):S13-8

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VTE Risk of Patch vs OCs

Study	Comparator OC	OR (95% CI)
i3 Ingenix	NGM/35 mcg EE	2.4 (1.1-5.5) ¹
BCDSP NGM	NGM/35 mcg EE	0.9 (0.5-1.6) ² 1.1 (0.6-2.1) ³
BCDSP LNG	LNG/35 mcg EE	2.0 (0.9-4.1) ⁴

VTE = venous thromboembolism; OR = odds ratio
 NGM = norgestimate; EE = ethinyl estradiol; LNG = levonorgestrel
 BCDSP = Boston Collaborative Drug Surveillance Program

- Cole JA, et al. *Obstet Gynecol.* 2007;109(2):339-46
- Jick SS, et al. *Contraception.* 2006;73(3):223-8
- Jick S, et al. *Contraception.* 2007;76(1):4-7
- BCDSP. http://download.veritasmedicine.com/PDF/CR014383_REF1.pdf

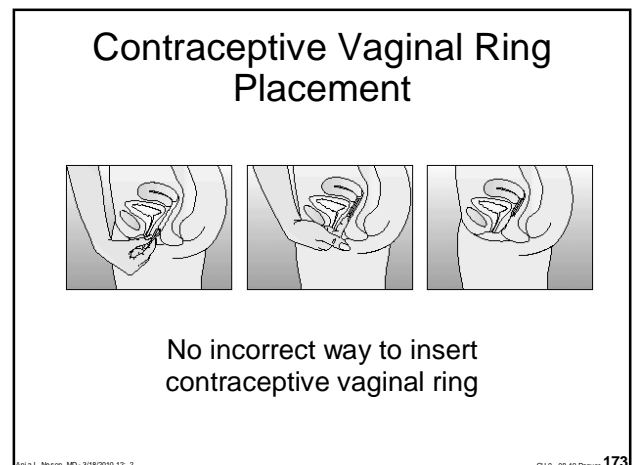
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Contraceptive Vaginal Ring

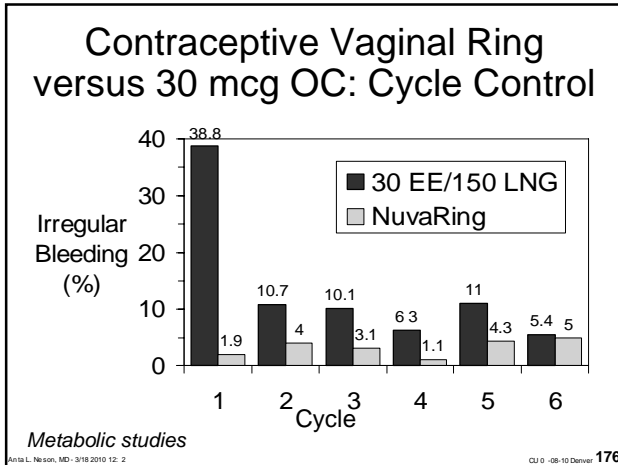
- Very low dose
 - ◆ 120 mcg/day etonogestrel
 - ◆ 15 mcg/day ethinyl estradiol
- Flexible
- Transparent
- Outer diameter: 54 mm
- Thickness: 4 mm
- One ring per cycle: 3 weeks ring-in
1 week ring-free

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- Contraceptive Vaginal Ring Advantages**
- A monthly method
 - Easily placed by the woman
 - Discreet
 - Lowest EE dose (15 µg/day)
 - Constant serum concentrations
 - Avoids GI interference with absorption
 - Avoids hepatic first-pass metabolism
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- ### Contraceptive Vaginal Ring Local Effects
- Interaction with vaginal medications
 - ◆ Spermicides/water-based formulation: **No**
 - ◆ Anti-mycotics/oil-based formulation: **Yes, but:**
 - Interaction most likely caused by formulation
 - No effects on efficacy and safety
 - Impact on infection
 - ◆ Decrease in recurrence of BV
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Quick Start Ring vs Pill: Bleeding Patterns

84-day Reference Period	Ring (n = 78)	Pill (n = 78)	Diff.	95% CI
Bleeding-spotting days	14.5	19.2	4.7	2.1,7.3
Bleeding-only days	9.1	11.9	2.8	1.1,4.5
Spotting-only days	5.4	7.3	1.9	0.18,3.7
Bleeding-spotting episodes	2.4	3.0	0.58	0.24,0.92
Bleeding-spotting episode days	6.0	6.5	0.50	-0.28,1.2
Bleeding-spotting-free interval days	21.2	19.0	-2.2	-4.3,-0.03

Westhoff C, et al. *Obstet Gynecol.* 2005;106(1):89-96

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Contraceptive Vaginal Ring: Extended Use (Off Label)

	Median Days			
	28 d	48 d	91 d	364 d
Total bleeding days				
First 90 days	7	4	4	0
Last 90 days	8	6	2	3.5
Total bleeding/spotting days				
First 90 days	15	9	17	12
Last 90 days	17	11	7	14
Completers	77%	72%	62%	59%

Miller L, et al. *Obstet Gynecol.* 2005;106:473-82

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“Ten months ago, I would have called this (the condom) an invention of the devil, but now I find that its inventor must have been a man of good will ...”

Jacques Casanova, 1758

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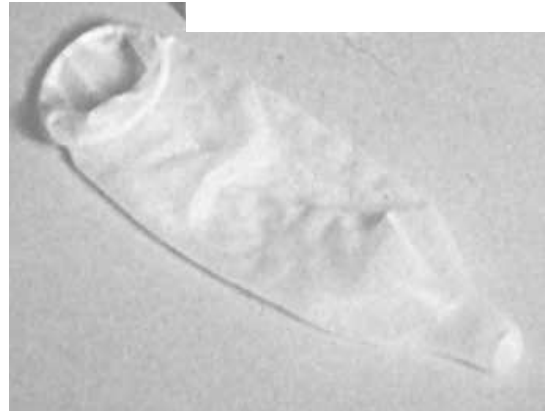
- ### Male Condom
- Typical first year failure rate: 17.4%; range 2-20%
 - Advantages:
 - ◆ Male participation
 - ◆ Inexpensive
 - ◆ Readily available
 - ◆ Protects well against STDs
 - ◆ Cervical dysplasia reduced
 - Special applications:
 - ◆ Premature ejaculation
 - ◆ Antisperm antibody
 - ◆ Female allergy to sperm
- Kost K, et al. *Contraception.* 2008;77(1):10-21**
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Polyurethane Condom

	Polyurethane	Latex
Breakage & slippage, 1997	8.5%	1.6%
Breakage & slippage, 1990	10.5%	1.7%
Breakage	66/1804	7/1882
Slippage	6/1804	1/1882
Uncorrected pregnancy rate	4.6 (2.6)	6.1 (1.0)
Corrected pregnancy rate	5.3 (3.1)	6.5 (1.2)

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Consistent Condom Use Reported by Women Who Had Sexual Intercourse in the Prior 14 Days by Coital Activity

Acts of coitus	# women who had coitus	% used condoms consistently
1	48	67%
2	34	65%
3	35	66%
4	28	61%
5 *	29	38%
More than 5 *	43	40%
All	217	56%

* Cochran-Armitage test for trend over number of acts of coitus: $p=0.001$

Nelson AL. Am J Obstet Gynecol. 2008;194(6):1710-6

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Reasons Given for Not Using a Condom

Reason	Percent of responses
Not perceived to be at risk	44%
He withdrew / pulled out / "took care"	33%
Used "rhythm" / Not at risk	12%
Ran out/did not have any condoms	39%
Dislike/Did not want to use condoms	33%
Dislike condoms	15%
Did not want to use condoms	19%

Nelson AL. Am J Obstet Gynecol. 2008;194(6):1710-6

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Other Worrisome Reasons Offered for Non-Use of Condoms

- "Too drunk"
- "He wanted me to use EC"
- "I do not know how to use it"
- "I did not think about it"
- "I see the same person"
- "In a rush"
- "I never check"
- "He told me to get on the pill"

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The Top 5 Reasons For Not Using A Condom

1. "I didn't know him well enough to ask him to use one."
2. "After two months, I knew we were in love, so we stopped using them."
3. "He would get mad at me if I asked him to."
4. "He's from Kansas, so I know he's disease-free."
5. "We don't like them."

Real excuses collected by the PPLA clinic in Santa Monica, 1993

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The Top 12 Reasons For Not Using A Condom

6. "I know I should, but..."
7. "I'm on the pill."
8. "Well, I did once!"
9. "He's too big for the condom to fit."
10. "I'm in a monogamous relationship."
11. "We didn't have any."
12. "S/He looked clean."

Real excuses collected by the PPLA clinic in Santa Monica, 1993
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The Top 18 Reasons For Not Using A Condom

13. "She's a virgin."
14. "You can't get AIDS from a woman."
15. "He worked for TRW. He must be clean."
16. "Well, I already have herpes and warts."
17. "I'm not in a high-risk group."
18. "I can't feel anything when we use them."

Real excuses collected by the PPLA clinic in Santa Monica, 1993
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Male Condoms: Sizes

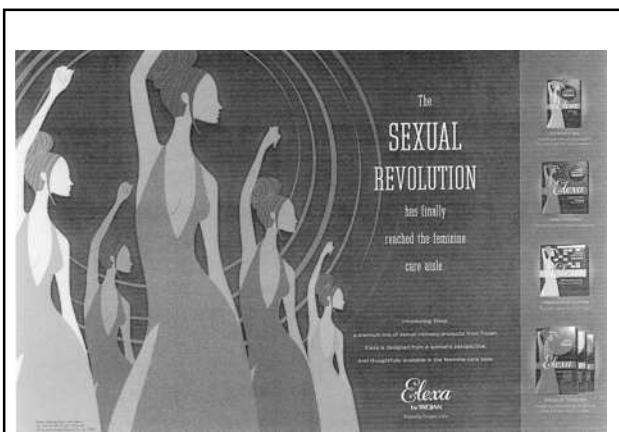
- Snug fitting
 - ◆ Beyond7, Studded Beyond 7, Exotica Snugger Fit, LifeStyles Snugger Fit, Trojan Ultra Fit
- Larger size—more headroom
 - ◆ Trojan Ultra Pleasure, Trojan Very Sensitive, Bareback, Trojan Her Pleasure, Midnight Desire, Pleasure Plus, LifeStyles Xtra Pleasure, Inspiral, Durex Enhanced Pleasure, LifeStyles Natural Feeling
- Larger size—roomy from top to bottom
 - ◆ Maxx, Trojan Large, Magnum XL, Magnum, Durex Maximum, LifeStyles Large, Avanti, Crown, Trojan Supra

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Male Condoms: Other Characteristics

- Sensitivity, texture, extra strength, desensitizing, pleasure producing, flavor/scent, color, lubrication
- Desensitizing condoms with "climax control lubricant featuring benzocaine that helps prolong sexual pleasure and aids in prevention of premature ejaculation" (Durex Performax, Trojan Extended Pleasure)
- Spermicidally lubricated condoms

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Withdrawal

- Typical failure rate 18.4% - on par with female barrier method failure rates
- Counseling critically important
 - ◆ sexual practices
 - ◆ pinch techniques
 - ◆ what to do about the woman after ...

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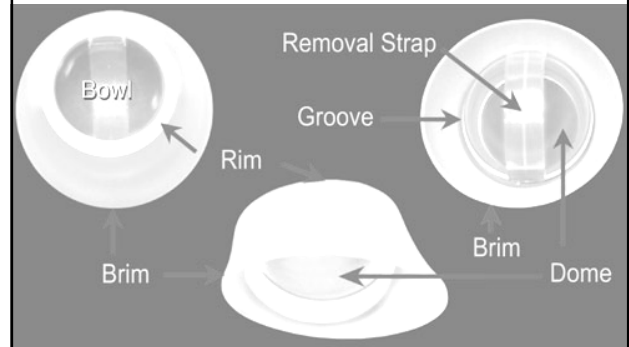
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Female Barrier Methods Failure Rates

Users	Perfect Use			Typical Use
	Nulliparous	Parous	All	
Diaphragm	no difference		5.2-6.9	16-18
Cervical Cap	8.8	26.4	11.4	16-20
Spermicide	no difference		6	18-21
Female Condom	unknown		3	21-25

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FemCap



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Contraceptive Sponge

- Approved by FDA in 1983, withdrawn in 1994, and reapproved in 2005
- Disposable polyurethane foam disk containing 1 gram N-9
- Single use device moistened and placed high in vault to cover cervix
- Mechanisms of action: spermicide (24 hours) plus device absorbs semen and blocks cervix



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Female Condom – Take 2 FC2

- Made of nitrile (synthetic latex) FDA approved
 - ◆ Reduced cost compared to FC1
 - ◆ Still more expensive than male condom
 - ◆ Comparable to FC1 in breakage, invagination, slippage and misdirection, efficacy, ease of insertion, comfort and overall experience
- ◆ Internationally, other female condoms:
 - The Reddy Condom
 - National Sensation Party Condom

Schwartz J. *The Female Patient*. 2009 June;34:26-9

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Cycle Beads

- Color coded string of beads helps women identify days of cycle pregnancy is likely and unlikely



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2-Day Method

- Simplified Billings technique
- Woman checks introital secretions daily and asks herself 2 questions:
 - ◆ Was I dry yesterday?
 - ◆ Am I dry today?
- Only if the answers to both questions are yes is intercourse allowed
- Failure rates comparable to other FAMs

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Natural Family Planning "TwoDay Algorithm": A New Idea

- Intended for illiterate couples
- Woman asks herself 2 simple questions:
 - ◆ Did I note secretions today?
 - ◆ Did I note secretions yesterday?
- Intercourse OK only if answers to both questions are "No"

Sinai, Jennings, Arévalo. *Contraception*. 1999;60:65-70.

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LNG-only EC Single-dose Versus 2-dose Regimens

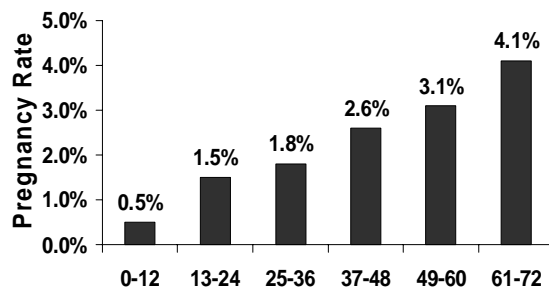
	2 doses 0.75 mg	1 dose 1.5 mg
Pregnancies	7/560	4/600
Effectiveness	86.8%	92.9%
Headaches	14.5%	21.3%
Breast tenderness	8.8%	12.9%

- No differences seen in nausea, vomiting, dizziness, lower abdominal pain, or heavy menses.

Arowojolu AO, et al. *Contraception*. 2002;66:269-73

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How Long After the Morning After? WHO Pooled Data (Yuzpe and LNG), 1998



Piaggio G, et al. *Lancet*. 1999;353:721

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LNG EC Mechanisms of Action

- 99 women
- Ovulation (day 0) calculated from LH, E₂ and P₄ levels obtained just prior to EC ingestion
- Cycle day of IC derived from patient history
- No pregnancies occurred when IC occurred day -5 to day -2 and EC taken before or on day 0
 - ◆ 4-5 pregnancies expected, 0 occurred
- All pregnancies occurred when IC was day -1 to day 0 and EC was day +2
 - ◆ 3-4 pregnancies expected, 3 occurred

Novikova N, et al. *Contraception* 2007;75:112-8

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Cycle Phase: Endocrinological vs Patient Estimate

	Women in Cycle Phase		
	Follicular	Periovulatory	Luteal
Number	41	30	20
Percent believing they are in phase			
Follicular	39%	13%	7%
Periovulatory	17%	23%	18%
Luteal	39%	53%	68%
Unknown	5%	11%	17%

Novikova N, et al. *Contraception* 2007;75:112-8

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Summary of Recommendations

- Find out what she will use
- Make it attractive to her
- Start it now
- Give EC now, and for future use
- Give lots of cycles of contraception
- Give backup method
 - ◆ Her back up method becomes primary method if she discontinues her first choice method
- Encourage her to plan and prepare for future pregnancy

NOW and LOTS and MORE

Antia L. Nelson, MD - 3/18/2010 12: 2 CU 0 - 08-10 Denver 230