

Contraception

What Every Internist Should Know

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Workshop Overview



- Background
- Small group exercises
- Small group presentations
- Short series of didactics
- Reconvene for conclusions and questions
- Evaluations
 - (please fill them out!)

Why are contraception updates important?



- Internists routinely prescribe potentially teratogenic medications to women of childbearing age
- Yearly U.S. unintended pregnancy rate
 - 1 in 20 for all reproductive age women
 - 1 in 10 for women ages 18–24
- 2001 unintended pregnancy rate was 49%
 - 42% in abortions
 - 14% in fetal losses

Schwartz et al. Ann Intern Med. 2007
Finer and Henshaw, Perspectives on Sexual and Reproductive Health, 2006

Luckily.....



- Women make over 125 million visits to primary care providers each year

National Ambulatory Medical Care Survey: 2002 Summary

There are several methods of contraception currently available....



We are internists...



- We see women with a variety of medical conditions and contraceptive needs
- Important to match the contraceptive option appropriately
 - Minimize and manage risk
 - Maximize contraceptive and non-contraceptive benefits

Goals for today's workshop



- Review available contraceptive methods
- Provide updates on new oral preparations
- Introduce novel hormone delivery systems
 - Transdermal
 - Transvaginal
 - Injectable
 - Intrauterine
 - Implantable
- Discuss the indications, benefits, and drawbacks of each method

Learning Objectives



- By the end of the workshop, participants will be able to:
 - Compare and contrast risks and benefits of newer oral contraceptive preparations and novel hormone delivery
 - Outline the non-contraceptive benefits of hormonal contraceptives
 - Discuss the cost-effectiveness, safety and efficacy data, and acceptability to patients
 - Counsel and educate patients on selecting appropriate contraceptive option based on patient preferences, age, lifestyle, and medical history

Vignette #1



- 27 year old woman presents to you for advice about whether or not she should begin an oral contraceptive.
 - She has terrible dysmenorrhea and bloating for the 3 days leading up to her menses which are heavy and last 6 days. She smokes a pack of cigarettes per week. Her maternal aunt was diagnosed with breast cancer at age 60.
- 1) How would you explain to her the mechanism of action of OCPs and their efficacy?
 - 2) What are the risks/benefits she might receive from OCPs?
 - 3) Would you choose an extended spectrum or conventional OCP?

Combined Oral Contraceptives (COC)

Abby Spencer, MD, MS
Assistant Professor of Medicine
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Combined Oral Contraceptives



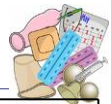
What are they?

- Combination of ethinyl estradiol (EE) and progestin (P)
- Dosage of EE varies between 20 to 35 mcg
- Dosage and type of progestin varies

How do they work?

- Block LH surge, preventing ovulation
- Thicken cervical mucus
- Alters endometrial lining

COC: Efficacy



Method	% Women Experiencing Pregnancy in First Year	
	Perfect Use	Typical Use
Oral Contraceptives	0.1-3%	3-8%
Ortho-Evra	0.3-1%	8%
NuvaRing	0.3-1%	8%
Depo-Provera	0.3%	0.3-3%
IUD	0.1-6%	0.1-8%

Westoff, C. *Contraception* 68 (2003): 75-87; Trussell J. Contraceptive efficacy. In Hatcher RA et al. *Contraceptive Technology*: 18th Revised Edition. New York NY: 2004.

What are the non-contraceptive benefits to using COC's?



Benefits

- Cycle control and regularity
- Reduces Fe-deficiency anemia
- Improves dysmenorrhea
- Elevate sex-hormone binding globulin
 - Decrease free testosterone
 - Improves acne & hirsutism

Risk reduction:

- Endometrial cancer
- Ovarian cancer
- Pelvic inflammatory disease
- Ovarian cysts
- Ectopic pregnancy
- Benign breast disease
- Dysfunctional uterine bleed

How Do I Counsel about Side Effects?



Most Common Side Effects

- Nausea, headaches, breast tenderness
- Breakthrough bleeding
- Typical use failure rate of 3-8%
- No protection against STDs

Most Serious Side Effects

- Increased risk for thromboembolism (VTE) and stroke
 - Desogestrel may further increase VTE risk
- Increased cardiovascular risk in smokers >35 years
 - Risk increase with estrogen formulations ≥ 50 mcg

COC Contraindications



Unacceptable

Cardiovascular Risk

- Smokers > 35 yrs old
- Hypertension >160
- Diabetes with end-organ damage
- Migraines with aura or focal neurologic symptoms

CI to Estrogen

- If breast-feeding
- Breast cancer history
- Unexplained bleeding
- Thromboembolic disorder or VTE history
- Liver disease

Excess Cases of MI, Stroke, & DVT Attributable to low-dose COCs



Number of excess cases of MI or Stroke (per 100,000 woman-yr)	20-24 yrs
Among nonsmokers	0.4
Among smokers	1
Among women with HTN	4
# pregnancy-related deaths (per 100,000 live births)	10



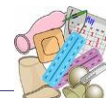
Excess Cases of MI, Stroke, & DVT Attributable to low-dose COCs



Number of excess cases of MI or Stroke (per 100,000 woman-yr)	20-24 yrs	30-34 yrs	40- 44 yrs
Among nonsmokers	0.4	0.6	2
Among smokers	1	2	20
Among women with HTN	4	7	29
# excess cases VTE (norethindrone,levonorgestrel)	6	9	12
# excess cases VTE (desogestrel)	16	23	30

Petitti, NEJM 2003

DVT Risk and Progestin



Meta-analysis comparing third vs. second generation OCPs on VTE risk

- 3rd generation progestin (desogestrel): Mircette, Orthocept
- 2nd generation progestin (levonorgestrel): Alesse, Triphasil

	Odds ratio
Overall	1.7 (1.4 -2.0)
First time users	3.1 (2.0 - 4.6)

Kemmeren BMJ 2001

Starting COCs



- Monophasic-fixed dose EE + P in each pill
- Multiphasic-vary dose of EE and/or P
- Traditional 21+7 day cycle vs extended cycle
- Hormonal contraception can be safely provided based on medical history and BP alone*
 - Pelvic and breast examination not necessary
- Educate early about common and serious SE's, missed pills, common drug interactions & taking pills at the same time every day

*Stewart et al. JAMA. 2001

Newer Oral Contraceptives



- Yasmin
- Extended-Cycle Regimens
 - Yaz
 - Loestrin
 - Seasonale
 - Seasonique
 - Lybrel



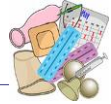
Newer Oral Contraceptives: Yasmin



- Contains 30 mcg EE + 3mg drospirenone
- Synthetic progestin chemically related to spironolactone
 - Anti-androgen and anti-mineralocorticoid activity
- Cause less weight gain & water retention; greater reduction in acne, hirsutism, PCOS
- Shown to reduce blood pressure
- SE: K retention; CI in patients with renal, hepatic or adrenal insufficiency

Clin Endocrinol Metab. 1995
Circulation. 2005

Extended-Cycle Regimens



What are they?

- Combination of EE + P
- Dosage of EE varies between 20 to 35 mcg
- Dosage and type of progestin varies
- Traditional 7-day hormone-free interval (HFI) is shortened or eliminated

How do they work?

- Lack of ovarian suppression during standard 7-day HFI leads to endogenous estradiol production
- Fluctuating hormone levels allow endometrial build up, exacerbate premenstrual symptoms, and allow spotting
- Shorter HFI reduce this

Extended-Cycle Regimens: What are they?



- Studies show that women utilizing standard 21+7 COCs experience worsening premenstrual symptoms during the last week of active pills
- Symptoms extend into and peak in intensity during the 7-day hormone-free interval (HFI)
- Contraceptive regimens with shorter HFIs suppress ovarian hormone production more effectively than those with the traditional 7-day HFI
- Minimizes hormone withdrawal symptoms, excess bleeding, and risk of ovulation

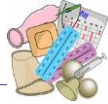
Extended-Cycle Regimens: How do they work?



- Theory: shorter hormone-free intervals reduce
 - Hormone withdrawal symptoms
 - PMS and PMDD
 - Irregular bleeding
 - Headaches and pain scores
 - Risk of ovulation → lower risk of unintended pregnancy

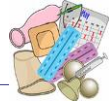
AL Coffee et al. Contraception 2007
AL Coffee et al. AJOG 2006
SA Willis et al. Contraception 2006
P Vercellini et al. Fertil Steril 2003
AB Edelman et al. Cochrane Database Syst Rev 2005

Extended-Cycle Regimens: Yaz



- Contains synthetic progestin drospirenone
- Anti-androgen and anti-mineralocorticoid activity
- Differs from Yasmin in dose and cycle length
 - Contains **20 mcg EE** (vs 30) + 3mg drospirenone
 - Contains **24 active pills** (vs 21) with 4 placebo pills
- Causes less weight gain & water retention; greater reduction in acne*, PMDD*, hirsutism, PCOS, BP
- SE: higher risk ovulation with only 20 mcg EE; may increase K levels

Extended-Cycle Regimens: Loestrin 24



- Contains 24 hormonally active pills, 4 placebo
 - In contrast to Loestrin: 21 active pills, 7 placebo
- Contains 20 mcg EE + 1mg norethindrone
- Associated with fewer and lighter bleeds
- Lower failure rate than typical COC

Nakajima et al. Contraception 2006

Extended-Cycle Regimens: Seasonale

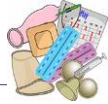


Extended-Cycle Regimens: Seasonale



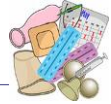
- Extended 3-month cycle with 4 withdrawal bleeds per year
- 84 consecutive days of EE + P, followed by 7 days placebo
- 30mcg EE + 0.15 mg levonorgestrel
- Equal efficacy to traditional COC
- Offers similar non-contraceptive benefits as COCs
- Profound reduction in dysmenorrhea & endometriosis
- Initial unscheduled bleeding followed by amenorrhea
- Unknown whether extra 7 weeks of hormone exposure increase risk of thromboembolism

Extended-Cycle Regimens: Seasonique



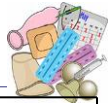
- ❑ Extended 3-month cycle
- ❑ 84 consecutive days of EE + P
- ❑ **Followed by 7 days 10 mcg EE rather than placebo**
- ❑ Equal efficacy to traditional COC
- ❑ Offers similar non-contraceptive benefits as COCs
- ❑ Profound reduction in dysmenorrhea & endometriosis
- ❑ Initial unscheduled bleeding followed by amenorrhea
- ❑ No head to head trials with Seasonale, but less bleeding
- ❑ Unknown whether extra weeks of hormone exposure increase risk of thromboembolism

Extended-Cycle Regimens: Lybrel



- ❑ First FDA-approved low-dose COC taken 365 days/yr
- ❑ No placebo or pill-free interval
- ❑ Pills contain 20mcg EE + .09mg levonorgestrel
- ❑ Failure rate= 1.55%
- ❑ Rapid resolution of fertility
- ❑ Similar non-contraceptive benefits to COCs
- ❑ SE: spotting; risks assumed to be similar to COCs- unknown if additional days hormone exposure increase risk of VTE

Extended-Cycle Contraceptives Summary



Product	Formulation
YAZ	24 tabs: 3mg drospirenone + 20 mcg EE 4 placebo pills
Loestrin 24	24 tabs: 1mg norethindrone + 20 mcg EE 4 placebo pills
Seasonale	84 tabs: 0.15 mg levonorgestrel + 30 mcg EE 7 placebo pills
Seasonique	84 tabs: 0.15 mg levonorgestrel + 30 mcg EE 7 tabs: 10mcg EE
Lybrel	28 tabs: 0.09 mg levonorgestrel + 20 mcg EE 0 placebo pills

Modified from medical letter 7/07

Vignette 2

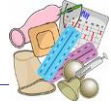


- ❑ 17 year old woman comes to see you for her annual exam.
- ❑ She has never been sexually active. She does have a boyfriend but is not planning on becoming sexually active in the near future.
- ❑ She nonetheless would like to be prepared should she make the decision to become sexually active.
- ❑ She has never used contraceptives in the past and would like your recommendation.
- ❑ How would you counsel her?

Ortho Evra Patch NuvaRing

Alda Maria Gonzaga, MD, MS
Assistant Professor of Medicine
University of Pittsburgh

How does one pick a method?



- Has she used a method before?
 - What was that experience like?
- How often does she want to think about it?
- Does she mind wearing a patch?
- Does she mind inserting a vaginal device?
- Personal health history
- Family health history

Other historical points to consider



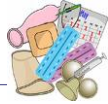
- Within 6 weeks postpartum and lactating
 - Progestin only
- After 6 weeks postpartum and lactating
 - May consider all hormonal options

Other historical points to consider



- What if she can't remember to take a daily pill, but still desires the contraceptive and non-contraceptive benefits of combined EE + P hormonal contraception?

Ortho Evra Patch



Ortho Evra Patch



What is it?

- Thin, matrix-type transdermal patch
- EE 0.75mg + norelgestromin 6mg
 - Active metabolite of norgestimate
- Applied to abdomen, buttock, upper arm, or outer torso

How does it work?

- Applied once weekly for 3 weeks
- "Placebo" is one patch-free week – withdrawal bleeding usually occurs
- Blocks LH surge, preventing ovulation
- Thickens cervical mucus
- Alters endometrial lining

Ortho Evra Efficacy



- Highly effective
- Studies show higher perfect use rates with patch versus oral contraceptive pill
 - Better adherence in younger users
 - Better adherence has not translated into better efficacy than COCs
- Some evidence that patch is less effective in women who weigh >90 kg
- May be used continuously if desired

Ortho Evra Efficacy



Method	% Women Experiencing Pregnancy in First Year	
	Perfect Use	Typical Use
Oral Contraceptives	0.1-3%	3-8%
Ortho Evra	0.3-1%	8%
NuvaRing	0.3-1%	8%
Depo-Provera	0.3%	0.3-3%
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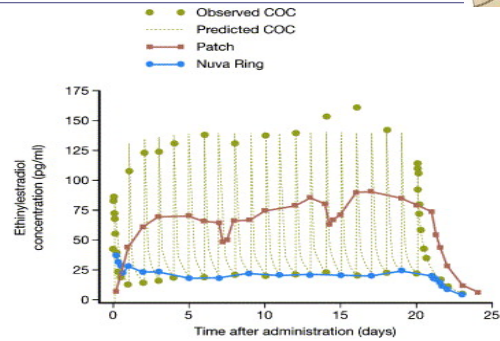
Westoff, C. *Contraception* 68 (2003): 75-87; Trussell J. Contraceptive efficacy. In Hatcher RA et al. *Contraceptive Technology: 18th Revised Edition*. New York NY: 2004.

Ortho Evra Hormonal Concentrations



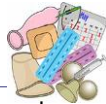
- Compared to OCPs containing 35mcg EE + 250mcg norgestimate:
 - Systemic exposures are higher
 - 60% more estrogen is absorbed over a 21 day cycle
 - Peak concentrations lower

Concentration of EE in COCs, Ortho Evra Patch, and NuvaRing



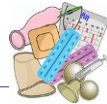
MW van den Heuvel, et al. Contraception 2005; 72:168

Ortho Evra Common Side Effects



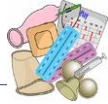
- Similar side effects, cardiovascular risks, and contraindications as other combined hormonal contraceptives
 - Breakthrough bleeding in first 2 cycles
 - Nausea, breast tenderness, headaches
- Patch Specific
 - Application site reactions (20% of users in one study)
 - Approximately 1-2 patches per year per user will fall off
 - Increased risk of VTE compared to COCs (probably)

Ortho Evra and Non-Fatal VTE Risk



- Three epidemiologic, case-control studies evaluating risk of VTE in women aged 15-44
 - Ortho Evra users compared to users of COCs containing 30-35mcg EE and norgestimate or levonorgestrel
- Approximate doubling in rate of VTE in Ortho Evra users in 2 of these studies
 - Basis of FDA updating of Ortho Evra label in 1/08
- Does not exceed risk of VTE associated with pregnancy!

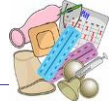
Ortho Evra and Non-Fatal VTE Risk



Epidemiologic Study	Comparator Product	Odds Ratio	95% CI
i3 Ingenix 2007*	Norgestimate/ 35 mcg EE	2.4	1.1-5.5
BCDSP Norgestimate 2006§ 2007¶	Norgestimate/ 35 mcg EE	0.9	0.5-1.6
		1.1	0.6-2.1
BCDSP Levonorgestrel 2007€	Levonorgestrel/ 30mcg EE	2.0	0.9-4.1

*Cole et al. Obstetrics & Gynecology 2007; 109:339; §Jick et al. Contraception 2006; 73:223; ¶Jick et al. Contraception 2007; 76:4; €BCDSP accessed at <http://www.clinicaltrials.gov/ct2/show/NCT00511784>

Ortho Evra Patch – VTE Risk



- FDA recommends that women with concerns or risk factors for VTE talk with their PCP regarding Ortho Evra versus other contraceptive options
- These data do not preclude the recommendation of Ortho Evra for certain women
- Carefully assess for VTE risk and history of potential inherited hypercoaguable state
- Educate about the signs and symptoms of VTE

NuvaRing



NuvaRing



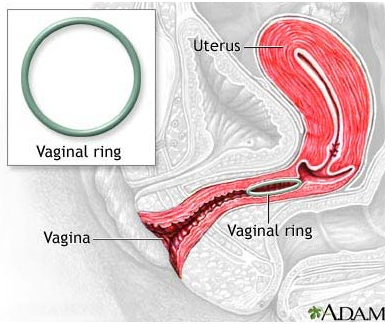
What is it?

- Ethylvinyl acetate ring (soft plastic)
- 5.5 cm diameter
- EE 0.015 mg/day + etonogestrel 0.12 mg/day
 - Active metabolite of desogestrel
- Inserted intravaginally for 3 weeks

How does it work?

- Rings may be removed for intercourse (up to 3 hours) without affecting efficacy
- “Placebo” is ring-free week
- Blocks LH surge, preventing ovulation
- Thickens cervical mucus
- Alters endometrial lining

NuvaRing In Position



NuvaRing Efficacy

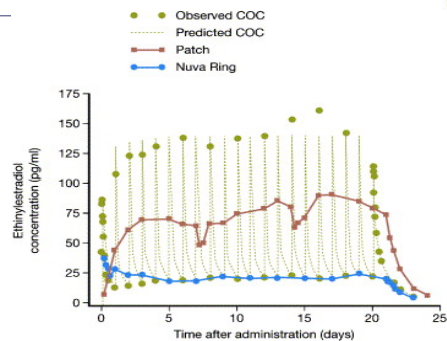
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Westoff, C. *Contraception* 68 (2003); 75-87; Trussell J. Contraceptive efficacy. In Hatcher RA et al. *Contraceptive Technology: 18th Revised Edition*. New York NY: 2004.

NuvaRing Benefits

- Enough hormone to be effective for 4-5 weeks
 - Some women may chose to use ring for 4 weeks continuously; having 10 rather than 13 periods/year
 - Some women may chose to use ring continuously without the need to buy extra contraceptives
- Each ring releases about ½ the level of hormones as the average oral contraceptive pill
- Weight does not affect efficacy of NuvaRing

Concentration of EE in COCs, Ortho Evra Patch, and NuvaRing



MW van den Heuvel, et al. *Contraception* 2005; 72:168

NuvaRing Acceptability



- Novak et al. studied 1950 women using NuvaRing
- At baseline 66% preferred OCPs, but after 3rd cycle 81% preferred ring
- Most women felt
 - Instructions for use clear (97%)
 - Never/rarely felt ring during intercourse (85% women, 71% of partners)
 - Partners never/rarely minded use of ring (94%)
- 97% would recommend the ring

Novak et al. Contraception 2001; 67:187

NuvaRing Side Effects



- Similar side effects, cardiovascular risks, and contraindications as other combined hormonal contraceptives
 - Breakthrough bleeding in first 2 cycles
 - Nausea, breast tenderness, headaches
- Ring Specific
 - Approximately 2.5% of women will experience one event where ring falls out per year
 - Leukorrhea/vaginitis

Vignette 3



- 31 y.o. female G1P1 on Depo-Provera since 2001
- No longer having menses, sexually active with 1 partner
- Likes using Depo-Provera very much, and doesn't want to switch
- No medical problems, non-smoker, not interested in getting pregnant soon
- Just read this on the Internet: "*Women are suing the makers of Depo-Provera birth control, saying it has caused them severe bone loss leading to osteoporosis.*"
- "Doc: Is it ok for me to stay on this medication?"

Depo-Provera

Megan Cunnane, MD, MSc
Assistant Professor of Medicine
University of Pittsburgh Medical Center



Depo-Provera



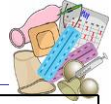
What is it?

- Depot-medroxyprogesterone acetate (DMPA)
- Progestin-only injectable contraceptive
- Two formulations: 150 mg IM or 104 mg SC given every 12 weeks

How does it work?

- Alters endometrial lining
- Thickens cervical mucus
- Blocks LH surge, thereby preventing ovulation

Depo-Provera Efficacy



Method	% Women Experiencing Pregnancy in First Year	
	Perfect Use	Typical Use
Oral Contraceptives	0.1-3%	3-8%
Ortho Evra	0.3-1%	8%
NuvaRing	0.3-1%	8%
Depo-Provera	0.3%	0.3-3%
IUD	0.1-6%	0.1-8%

Westoff, C. *Contraception* 68 (2003); 75-87; Trussell J. Contraceptive efficacy. In Hatcher RA et al. *Contraceptive Technology: 18th Revised Edition*. New York NY: 2004.

When Should I Consider Using Depo-Provera?



- Patient has a history of:
 - CVA/CAD/CHF
 - Complicated migraines
 - Diabetes
 - Lipid disorders
 - Liver disorders
 - SLE
 - Peripheral vascular disease
 - Thromboembolism

- Patient is using:
 - Anti-convulsants
 - Tobacco

- Patient is scheduled for:
 - An upcoming surgical procedure with a high risk of thromboembolism

Westoff, C. *Contraception* 68 (2003) 75-87.

What Are Some Non-Contraceptive Benefits of Depo-Provera?



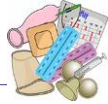
DECREASED RISK OF:

Endometrial cancer
Pelvic inflammatory disease
Ectopic pregnancy
Uterine leiomyomas

IMPROVEMENT OF:

Seizures
Hemoglobinopathies
Premenstrual symptoms
Endometrial hyperplasia

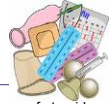
Ok, Sounds Great, But is it Safe?



Considerations

- ✓ Risk for cardiovascular disease
- ✓ Risk for breast cancer
- ✓ Effects on bone mineral density

Does Depo-Provera Increase the Risk of Vascular Disease?



Multicenter international case-control study assessing risk of CVD among users of steroid hormonal contraception: 3697 cases, 9997 controls

Outcome	Cases	Controls	OR*	CI
All stroke				
DMPA users	25	81	0.89	0.53-1.48
Non-users	1774	5183		
VTE				
DMPA users	11	34	2.19	0.66-7.26
Non-users	635	2388		
AMI				
DMPA users	1	7	0.66	0.07-6.00
Non-users	259	795		

Does Depo-Provera Increase the Risk of Breast Cancer?



Pooled Analysis of Data from the WHO Multinational Case-Control Study and a Case-Control Study from New Zealand

Type of Cancer	Cases	Controls	RR	CI
Breast	1768	13,905	1.1	0.97-1.4
Endometrial	122	939	0.21	0.06-0.79
Ovarian	224	1781	1.07	0.6-1.08
Cervical	2009	9583	1.11	0.96-1.29

The Controversy: Depo-Provera and Effects on Bone Mineral Density



- Depo-Provera reduces ovarian production of estradiol
- Low estrogen levels may adversely affect bone health
- Cross-sectional studies showed BMD loss during Depo-Provera use

FDA Black Box Warning 2004:

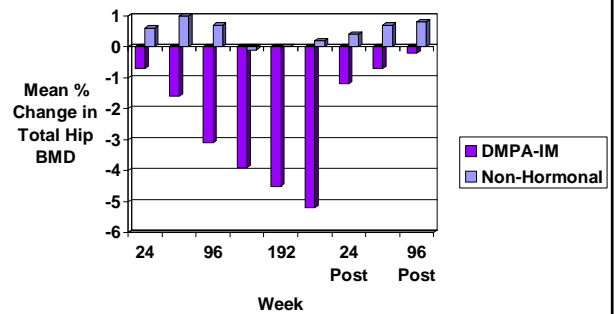
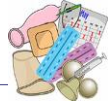
Women who use Depo-Provera Contraceptive Injection may lose significant bone mineral density. Bone loss is greater with increasing duration of use and may not be completely reversible. Depo-Provera contraceptive injection should be used as a long-term birth control method (e.g. longer than 2 years) only if other birth control methods are inadequate.

What Are the Effects of Depo-Provera on Bone Mineral Density?



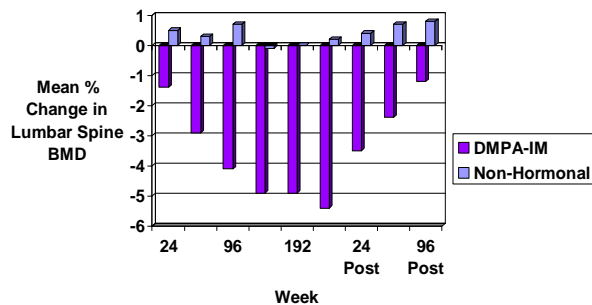
- **Study design:** Manufacturer-sponsored 7-year longitudinal matched-cohort study evaluating the effects of Depo-Provera on BMD in women ages 25-35
- **Primary endpoint:** % change in BMD from baseline to 240 weeks in the Depo-Provera and Non-Hormonal groups
- **Secondary endpoints:** % change in BMD from baseline throughout treatment and up to 96 weeks post-treatment in the Depo-Provera and Non-Hormonal groups

Longitudinal Cohort Study: Effect of Depo-Provera on BMD Among Women Aged 25-35



Kaunitz et al. Contraception 74 (2006) 90-99.

Longitudinal Cohort Study: Effect of Depo-Provera on BMD Among Women Aged 25-35



Kaunitz et al. Contraception 74 (2006) 90-99.

What Are the Effects of Depo-Provera on Fracture Risk?



- **Study Design:** Systematic review assessing the association between progestin-only contraceptive use and fracture risk or BMD
- **Results:**
 - 38 studies examined BMD as outcome, only one study assessed fracture risk
 - DMPA use at baseline was associated with higher risk of stress fracture among non-Hispanic white women (RR 1.71, CI 1.01-2.90)
 - Non-significant when adjusted for ultrasound measurement at baseline

Curtis KM, Martins, SL. Contraception 73 (2006) 470-487

What Are the Effects of Depo-Provera on BMD after Discontinuation?



- **Study Design:** Systematic review evaluating changes in BMD after discontinuation of DMPA
- **Results:**
 - 5 observational studies measuring changes in BMD among pre-menopausal women (1 cross-sectional, 4 prospective cohort)
 - BMD changes are reversible after discontinuation of DMPA and return to near baseline levels after about 2 years
 - Spine BMD increases more rapidly than hip BMD

Curtis KM, Martins, SL. *Contraception* 73 (2006) 470-487

Take-Home Points: Depo-Provera, BMD, and Fracture Risk



- **Evidence:**
 - No association between use of Depo-Provera and increased fracture risk
 - BMD decrease associated with use is transient and reverses with discontinuation
 - Scant data on association between BMD changes and fracture risk in young women
- **Practice points:**
 - No indication for routine BMD testing in Depo-Provera users at beginning, during, or end of treatment
 - No indication for treatment with anti-resorptive agents
 - Emphasize importance of adequate calcium, vitamin D, and weight-bearing exercises

WHO Position Statement: Depo-Provera and Bone Health



- There should be no restrictions on the duration of use of Depo-Provera, and the benefits of this contraceptive method generally outweigh the harms
- The overall risks and benefits of Depo-Provera should be considered over time with the individual user

Depo-Provera: Summary



- Safe, effective, and convenient method of contraception
- Ideal for use in patients with hypercoagulable states, seizure disorders, or cardiovascular disease
- Counsel patients about decrease in BMD associated with use, but reassure about reversibility
- Encourage patients using DMPA to take in adequate amounts of calcium and vitamin D and to engage in weight-bearing exercises

Vignette #4



- 35y woman G2P2 presents for follow-up visit
 - H/o of DM, HTN, chol, on Metformin, ACE-I and statin
 - Sexually active with male partner x1y
 - Does not want more kids
 - But only using condoms “sometimes”
 - When you counsel her about contraception, she mentions thinking about having her tubes tied
 - How would you counsel her about other long-term contraceptive options?

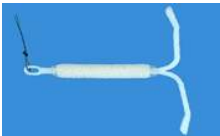
Intrauterine Devices (IUDs)

Mindy Sobota, MD MPhil
Research Fellow/GIM
Montefiore Medical Center

IUDs: What are they?



- Copper T 380A (Paragard)
 - Copper ions
 - FDA approved in 1988
 - Duration for >10 years



- LNG IUS (Mirena)
 - Levonorgestrel (progestin only)
 - FDA approved in 2000
 - Duration for 5 years

ARHP, Update in Intrauterine Contraception (www.arhp.org)

Copper T IUD



How does it work?

- Primary mechanism is prevention of fertilization
 - Inhibit sperm motility and function
 - Inhibit ovum development
- Inhibition of implantation is a secondary mechanism



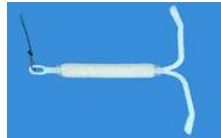
ARHP, Update in Intrauterine Contraception (www.arhp.org); Alvarez F, et al. *Fertil Steril*. 1988; Segal SJ, et al. *Fertil Steril*. 1985; ACOG. *Statement on Contraceptive Methods*. 1998.

LNG IUS



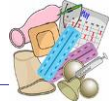
How does it work?

- Primary mechanism is fertilization inhibition
 - Anovulation (5-15% cycles)
 - Thickens cervical mucus
 - Inhibits sperm and ovum motility and function
- Inhibition of implantation is a secondary mechanism



ARHP, Update in Intrauterine Contraception (www.arhp.org); Jonsson B, et al. *Contraception*. 1991; Silverberg SG, et al. *Int J Gynecol Pathol*. 1986.

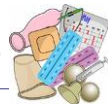
Do IUDs Cause Abortions?



- Works at similar stage to other methods
- Evidence supporting pre-fertilization mechanism:
 - Decreased risk for ectopic pregnancy
 - Highly sensitive serum pregnancy assays
 - Tubal flushing studies
 - 56 IUD users: no eggs with normal development
 - 115 controls: 50% eggs with normal development

ACOG, 1998. Segal SJ et al, *Fertil Steril*. 1985;44:214; Alvarez F et al. *Fertil Steril*. 1988;49:768

IUDs: How Do They Differ?



Bleeding Patterns

Copper T:

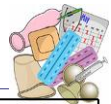
- Increases flow 50%
- Regular periods
- 7-12% remove for bleeding and/or pain within 1 year

LNG IUS:

- Decreases flow 90%
- Irregular with spotting
- 20% amenorrheic (1y)
- 7% remove for bleeding within 1 year

Andersson K, et al. *Contraception*. 1994.

IUD: Efficacy



Method	% Women Experiencing Pregnancy in First Year	
	Perfect Use	Typical Use
Oral Contraceptives	0.1-3%	3-8%
Ortho Evra	0.3-1%	8%
NuvaRing	0.3-1%	8%
Depo-Provera	0.3%	0.3-3%
IUD	0.1-6%	0.1-8%

Westoff, C. *Contraception* 68 (2003): 75-87; Trussell J. Contraceptive efficacy. In Hatcher RA et al. *Contraceptive Technology*, 2004.

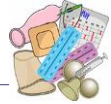
IUD: Contraceptive Benefits



- Highly effective
- Long-term
- Reversible
- Private
- Non-hormonal or hormonal
- Most cost-effective method (\$7-13/m over 5y)
- 99% of patients “very” or “somewhat” satisfied
- Highest continuation rate (80% at 1 year)

Forrest JD et al, *Obstet Gynecol Surv.* 1996;51(12 Suppl):S30-4.; Trussell J, et al, *Am J Public Health* 1995;85:494-503.; Hatcher et al, *Contraceptive Technology*, 2004

IUD: Non-Contraceptive Benefits



- Benefits (LNG only):
 - Menorrhagia/anemia
 - Bleeding fibroids
 - Counterpart to estrogen (Tamoxifen/HRT)
- Decreased Risk:
 - Ectopic pregnancy
 - PID (LNG IUS only)
 - Endometrial cancer?
 - Cervical cancer?
 - Endometriosis?

Hubacher et al, *Obstet Gynecol Surv.* 2002(57):120-8

Do IUDs Increase PID Risk?



- Only at insertion!
- Bias in prior associations between IUDs and PID
 - Inappropriate controls (women using COCs/condoms)
 - Detection bias (overdiagnosis among IUD users)
 - Confounding by sexual behavior
- No benefit of antibiotic prophylaxis at insertion
- PID Risk
 - ≤20 days: 1/100-1/1000
 - >20 days: 1/1000 (baseline)

Farley TM et al, *Lancet* 1992;339:785-788; Walsh T et al, *Lancet* 1998;351:1005-1008; Grimes DA, *Lancet* 2000;356:1013-1019

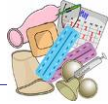
IUDs: Risks/Disadvantages



- PID risk 1/100-1/1000
- Perforation risk 1/1000
- Cramping and pain at insertion
- Expulsion risk within 1 year: 1/10-1/50
- Menstrual changes

Farley TM et al, *Lancet* 1992; Grimes DA, *Lancet* 2000; Mohllajee AP et al, *Contraception*, 2006

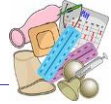
IUD: Contraindications



- Insertion-related
 - "High risk for GC/CT"
 - Current purulent cervicitis (NOT vaginitis) or PID
 - Known or suspected pregnancy
 - Uterine anatomy interfering with placement

WHO, *Medical Eligibility Criteria*, 2004

IUD: Contraindications



- Comorbidity-related
 - AIDS, not doing well on ARVs
 - Current DVT, active liver disease (LNG IUD only)
 - Allergy to copper/Wilson's disease (Copper T only)
 - Gynecologic or breast malignancies
 - Unexplained vaginal bleeding

WHO, *Medical Eligibility Criteria*, 2004

Who Is Eligible for an IUD?



- Women who desire long-term contraception
 - Cost effective ≥ 2 years
- WHO eligibility criteria *include* women:
 - History of an STI, PID or ectopic pregnancy
 - No prior childbirth (nulliparous)
 - HIV+ or AIDs doing well on ARVs
 - Considering sterilization
 - Menorrhagia/anemia/fibroids (LNG)
 - Do not want hormones (Copper T)

WHO *Medical Eligibility Criteria*, 2004

Vignette #5



- 31yo G0 with a history of severe endometriosis presents to establish care. She has required laparoscopy x 2 to treat her endometriosis. She is currently using extended cycling with OCPs, but still has severe symptoms q3 month with menses. Previous methods include:
 - Norplant—best controlled symptoms, no longer available
 - Depo-provera—not tolerated due to weight gain
 - OCPs with monthly cycles—severe dysmenorrhea
- She is currently sexually active and in a monogamous relationship. Annual pap smears have all been normal.
- How would you educate her on other available options?

Implanon™

Rachel Bonnema, MD
Fellow, GIM / Women's Health
University of Pittsburgh

Implanon™

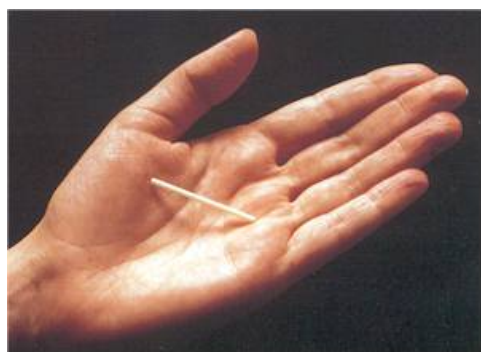


What is it?

- Etonogestrel (ENG)
- Progestin-only implanted contraceptive rod (4cm x 2mm)
- Implanted subdermally in upper arm
- Lasts 3 years

How does it work?

- Blocks LH surge, thereby preventing ovulation
- Thickens cervical mucus
- Alters endometrial lining
- No decrease in estradiol levels



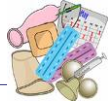
How Effective is Implanon™ at Preventing Pregnancy?



Method	% Women Experiencing Pregnancy in First Year	
	Perfect Use	Typical Use
Oral Contraceptives	0.1-3%	3-8%
Ortho-Evra	0.3-1%	8%
NuvaRing	0.3-1%	8%
Depo-Provera	0.3%	0.3-3%
Implanon™	0.1%	0.1%
Mirena IUD		

Trussell J. Contraceptive efficacy. In Hatcher RA et al. Contraceptive Technology. 18th Revised Edition. New York NY: 2004. Hobmann and Creinin. Clin Ob and Gyn 2007. 50:907-917.

Insertion/Removal



□ Insertion

- Under local anesthetic
- Applicator supplied with rod
- Position arm out to side
- Insert ~3 fingerbreadths above medial epicondyle of humerus
- Palpate to verify placement



Insertion/Removal



□ Insertion

- Under local anesthetic
- Applicator supplied with rod
- Position arm out to side
- Insert ~3 fingerbreadths above medial epicondyle of humerus
- Palpate to verify placement

□ Removal

- Apply pressure to proximal rod
- 2-3mm incision made vertically over the implant
- Grasped with forceps and pulled out
- Difficulty experienced in 2-3% patients
 - Usually placed too deep

Croxatto HB, et al. Hum Reprod. 1999;14:976-981.

Now I know what it is...how do I counsel about side effects?



□ Major effects:

- Irregular bleeding
- Dysmenorrhea

□ Reported minor effects:

- Headache
- Breast/abdominal pain
- Mood swings
- Depression
- Decreased libido

□ Other effects:

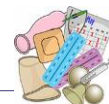
- Breast-feeding
- Weight
- Acne
- BMD

Now I know what it is...how do I counsel about side effects?



- Major effects:
 - Irregular bleeding
 - Dysmenorrhea
- Reported minor effects:
 - Headache
 - Breast/abdominal pain
 - Mood swings
 - Depression
 - Decreased libido
- Other effects:
 - Breast-feeding
 - Weight
 - Acne
 - BMD

Side Effect: Irregular Bleeding



- Review of 1716 users
 - Amenorrhea
 - ~30-40% at 3 months
 - Infrequent bleeding
 - ~50% at 3 months → ~30% at 6 months
 - Prolonged bleeding
 - ~10-20% at 3 months
- No consistent bleeding pattern can be demonstrated for any individual woman

Hickey M, et al. Contraception. 2002;75-84.

Side Effect: Irregular Bleeding



- US study of 330 women, Swiss study of 1183 women
- Number of women discontinuing Implanon™ was the highest during first 8-9 months of use
- Most frequently reported adverse event was prolonged/frequent bleeding

Funk S, et al. Contraception, 2005. 71:319-326.

*Hohmann and Creinin. Clin Ob and Gyn, 2007. 50:907-917.

Other Side Effects



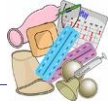
- Dysmenorrhea
 - 81% with dysmenorrhea at baseline reported decreased symptoms
- Weight Changes
 - Increase noted in ~12%
 - Increase in BMI was 0.7 kg/m²*
- Acne—mixed data
 - Majority of women experience no change in acne*
- BMD—no long term data
 - One study: no clinically significant difference in BMD over 2 years†

Funk S, et al. Contraception, 2005. 71:319-326.

*Hohmann and Creinin. Clin Ob and Gyn, 2007. 50:907-917.

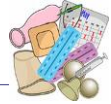
†Beerhuizen R, et al. Hum Reprod. 2000;15:118-122.

Contraindications



- Known/suspected pregnancy
- Active VTE disease
- Active liver disease
- Undiagnosed genital tract bleeding
- Known/suspected breast cancer
- Progesterone dependant tumors
- Allergy to any components
- Use of CYP3A inducing medications

Contraindications



- Active VTE disease
 - No data on VTE and Implanon™
 - 1 study on effect of Implanon™ on hemostatic elements
 - No change in PT, PTT, fibrinogen, or other coagulation variables
 - No development of resistance to APC
- Active liver disease
 - Mixed results in studies, but may be mild changes in LFTs during use
- Use of CYP3A inducing medications
 - Carbamazepine, phenytoin, rifampin, St. John's Wort

Vieria CS, et al. Hum Reprod. 2007. 22: 2196-2201.
Hohmann and Crenin. Clin Ob and Gyn, 2007. 50:907-917.

Counseling on Use



- Alternative for women who cannot use estrogen-based contraceptives
- Long-term, reversible method
- Safe to use during breast-feeding
- Quick return to normal cycles
- Discuss irregularly irregular bleeding patterns
- Cost~ \$500-750
 - Average ~ \$20/month

Summary



Other Considerations



- Emergency contraception—Plan B®
 - Effective up to 120 hours after intercourse
 - Most effective when taken sooner (within 72 hours)
 - FDA approved Plan B® for over-the-counter sales to US women and men age 18 and older in 2006
 - Government-issued ID required for proof of age
 - Women age 17 and younger still need prescription except in states with pharmacy access

Rodrigues I, et al. Am J Obstet Gynecol 2001;184:531-37.
 US Food and Drug Administration. 2006.
 Pharmacy Access Partnership. 2007.

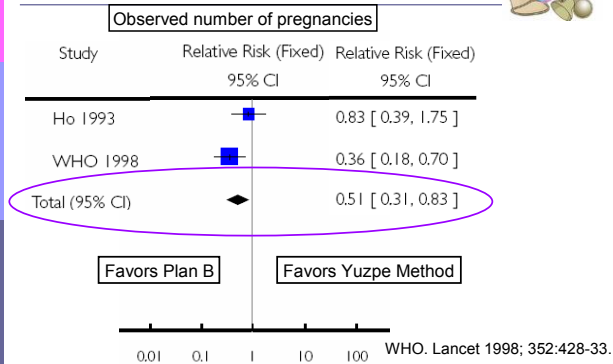
States with Pharmacy Access



- Alaska
- California
- Hawaii
- Maine
- Massachusetts
- Montana
- New Hampshire
- New Mexico
- Vermont
- Washington

www.ec.princeton.edu Accessed March 11, 2008.

Efficacy of Plan B® vs. Yuzpe Method



Most Common Adverse Events (n=977)



Nausea	23.1%
Abdominal pain	17.6
Fatigue	16.9
Headache	16.8
Dizziness	11.2
Breast tenderness	10.8
Vomiting	5.6
Other complaints (diarrhea, irregular bleeding or spotting)	13.5

WHO. Lancet 1998; 352:428-33.

Combination Estrogen-Progestin Contraception



	COCs	Ortho Evra	NuvaRing
Duration	Daily pill	Weekly application	Monthly insertion
Reversibility	Immediate	Immediate	Immediate
Cost	\$20-60/month	\$~50/mo	\$~50/mo
Major Side Effects	Spotting, nausea, VTE, stroke, MI	Dysmenorrhea, site rxn, fall off VTE	Vaginal d/c, discomfort VTE
Consider in:	No CI to estrogen PCOS, cycle control, dysmenorrhea	No CI to estrogen Unable to take daily pill	No CI to estrogen Unable to take daily pill

The Medical Letter. 2007. 5(64):101-108.

Progestin Only Contraception



	Depo-Provera	Implanon	Mirena
Duration / Reversibility	14 weeks May be delayed	Up to 3 years Immediate	Up to 5 years Immediate
Cost	\$50-90/injection ~\$16-22/mo	\$500-750 ~\$15/month	\$400-750 ~\$7-13/month
Major Side Effects	Irregular bleeding	Irregular bleeding	Irregular bleeding
Consider in:	Seizure disorder Hypercoagulable states	Dysmenorrhea Long-term contraception	Dysmenorrhea Long-term contraception

The Medical Letter. 2007. 5(64):101-108.

Specific uses/indications:



COCs

- Cycle regularity
- Dysmenorrhea
- PCOS
- Acne
- Women ≥35:
 - No CV risk factors
 - Cycle regularity
 - Ovarian/endometrial CA reduction

Progestin-only methods

- Migraine with aura
- Contraindication to estrogen (DVT, Breast Ca)
- Women ≥35 *with*:
 - Obesity
 - Smoking
 - Hypertension
 - Diabetes
 - Migraines

Adapted from Kaunitz AM. NEJM 2008;358:1262-70.

Summary



- Hormonal contraceptives using a variety of delivery methods are highly effective
 - COCs offer several non-contraceptive benefits
 - Newer formulations and extended cycling regimens are attractive options to women
 - Progestin-only methods can be used if estrogen contraindicated
 - IUDs offer the most cost-effective and lowest failure rates of all contraceptives, compliance is non-issue
- Emergency contraception is effective and easily available

Conclusions



- Internists routinely prescribe potentially teratogenic medications to women of childbearing age
 - Unintended pregnancy is very common
- Necessary for internists to be facile in helping patients choose the best contraceptive methods

Let's Go Pens!!!



Thank you!



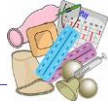
Questions??



- Extra Slides



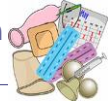
IUD: Risks



Complication	Frequency
PID <= 20 days	1/100
PID > 20 days	1/1000 (baseline risk)
Perforation	1/1000

Farley TM et al, *Lancet* 1992; Grimes DA, *Lancet* 2000; Mohllajee AP et al, *Contraception*, 2006

IUD Net Termination & Continuation Rates per 100 at 1 Year



Event	Copper T 1 year	LNG IUD 1 year
Pregnancy	0.9	0.1
Expulsion	3.4	3.4
Bleeding	5.7	5.8
Pain	1.6	1.6
Hormonal	0.1	2.3
PID	0.4	0.3
Other	4.9	6.7
Continuation	83.0	79.9

Andersson K, et al. *Contraception*. 1994.