

NORTHWEST AIDS EDUCATION AND TRAINING CENTER



Contraceptive – Antiretroviral Drug Interactions: Issues to consider when prescribing contraceptives to HIV + patients

Emily M. Godfrey MD MPH FAAFP

Associate Professor, Departments of Family Medicine and Obstetrics and Gynecology, University of Washington

Guest Researcher, Centers for Disease Control and Prevention

Outline

- Epidemiology of HIV in the United States
- Available contraceptive methods in the United States
- Pharmacokinetics of hormonal contraception and antiretrovirals
- **Evidence-based national contraceptive guidelines**

BACKGROUND

Epidemiology of HIV – United States

HIV among Women in the United States

- One in four people living with a diagnosis of HIV infection are women
- Women accounted for 20% of estimated 47,500 new HIV infections
 - Most new infections were from heterosexual contact with a person known to have or be at high risk of infection
 - Women aged 25-44 accounted for majority of new HIV infections

Role of Contraception Among HIV infected Women

- Prevention of unplanned or mistimed pregnancies
 - Optimize HIV-infected health of woman prior to pregnancy
 - Decrease maternal-to-child transmission

BACKGROUND

Prescription contraceptive methods – United States

Long-acting Reversible Contraceptive Methods

- Progesterone-only contraceptive implant
 - Inhibition of hypothalamic-pituitary-ovarian axis
 - Cervical mucus thickening
 - Uterine atrophy
 - FDA approved for 3 years
 - Unpredictable bleeding
- Progesterone-only IUDs
 - Partial inhibition of hypothalamic-pituitary-ovarian axis
 - Cervical mucus thickening
 - Uterine atrophy
 - FDA approved for 5 years, although shown to be effective for 7 years
 - Smaller IUD, FDA approved for 3 years
 - Reduced menstrual flow
- Copper IUD
 - Sterile inflammatory response
 - Enhanced prostaglandin production/Inhibition of various endometrial enzymes
 - FDA approved for 10 years, although shown to be effective for 12 years
 - Some increased cramping and bleeding with periods
- NO STI protection



Injectable Contraceptive Methods

- Depot medroxyprogesterone acetate (DMPA)
- Progesterone-only
 - Inhibition of hypothalamic-pituitary-ovarian axis
 - Cervical mucus thickening
 - Uterine atrophy
- Injection given every 3 months
 - Unpredictable bleeding
 - Weight gain
- No STI protection



Combined Hormonal Contraceptive Methods

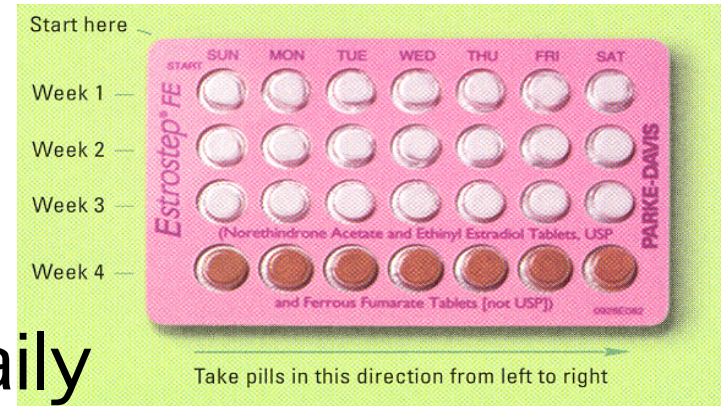
- **Estrogen and Progestin combination**

- Inhibition of hypothalamic-pituitary-ovarian axis
 - Progestin-suppress LH
 - Estrogen-suppress FSH
 - Cervical mucus thickening

- Side effects:

- breast tenderness, nausea, mood changes
- Patch-discoloration
- Ring- vaginal discharge

- No STI protection



Daily

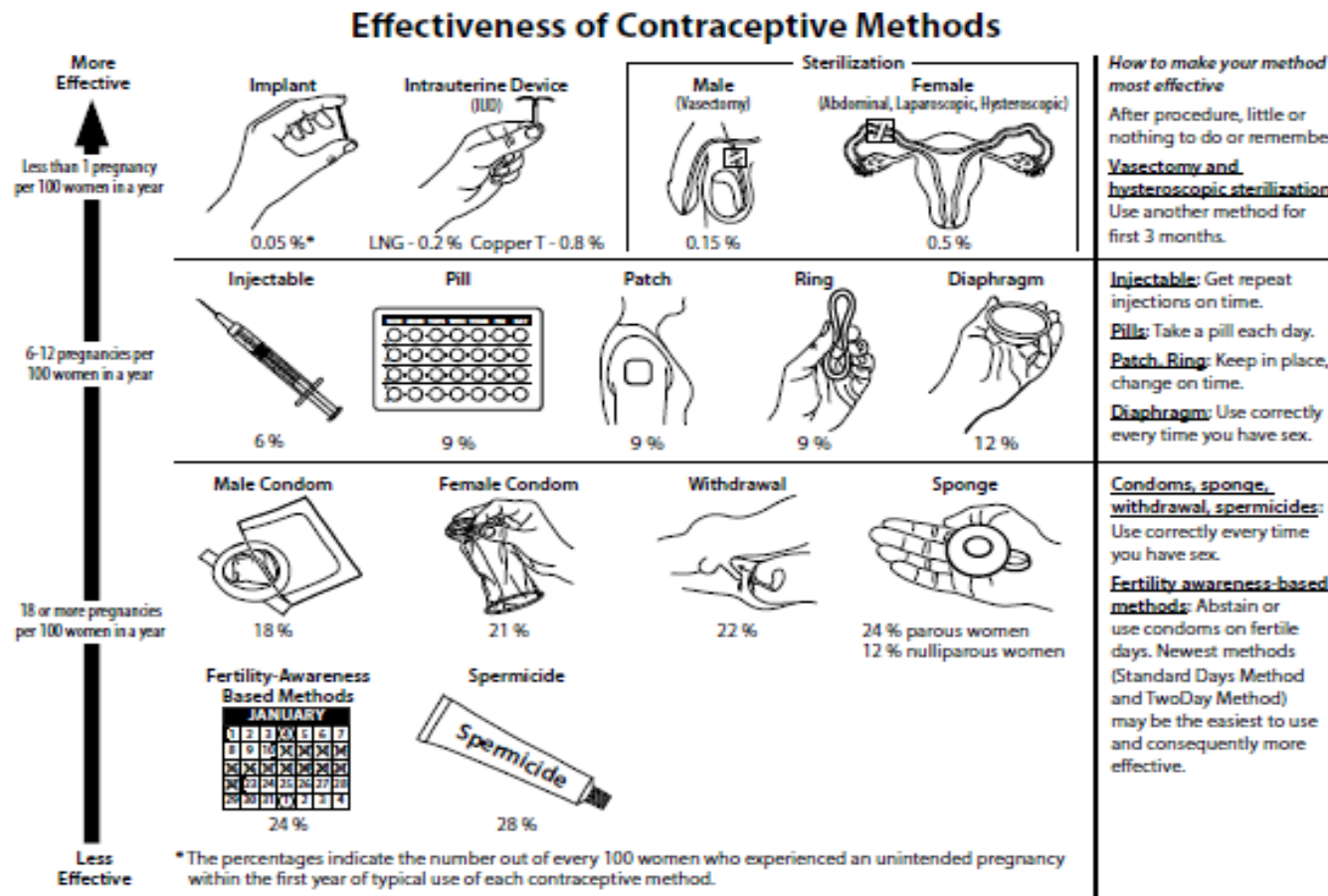


Weekly

Monthly



Typical effectiveness of Contraception



Tier 1

Tier 2

Tier 3



U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

CONDOMS SHOULD ALWAYS BE USED TO REDUCE THE RISK OF SEXUALLY TRANSMITTED INFECTIONS.

Other Methods of Contraception

Lactational Amenorrhea Method: LAM is a highly effective, temporary method of contraception.

Emergency Contraception: Emergency contraceptive pills or a copper IUD after unprotected intercourse substantially reduces risk of pregnancy.

Adapted from WHO's Family Planning: A Global Handbook for Providers (2001) and Trussell et al (2011).

CIS 231556



Pharmacokinetics of Hormonal Contraception and Antiretrovirals (ARV)

Pharmacokinetics of ethinylestradiol (EE) and progestins

Absorption:

Oral EE and progestins are absorbed from the small intestine



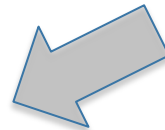
Metabolism [First Pass]: Conjugated with glucuronic acid and sulfate



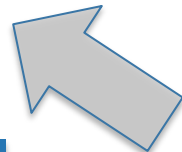
Excretion through gallbladder:

Conjugated EE unconjugated by bacteria in large intestine, reabsorbed by colon

EE activates CYP3A4, increasing rate at which drugs are cleared by liver from the blood-stream. Less is known about progestins



Enzyme-inducing drugs decrease circulating EE and progestins, potentially reducing effect of oral contraceptive



Antiretroviral Drug Profiles

Drug	Effect on CYP450 System
Non-nucleoside reverse transcriptase inhibitor	CYP3A4 inducer
Protease inhibitor	CYP3A4 inhibitor
Nucleos(t)ide reverse transcriptase inhibitor	None
Integrase strand transfer inhibitor	None

Interaction of Hormonal Contraceptives & Ritonavir-boosted protease inhibitors

Interaction of Hormonal Contraceptives and Ritonavir-Boosted Protease Inhibitors		
Medication	Effect on Drug Concentrations	Dosing Recommendation
Atazanavir/r	ethinyl estradiol AUC ↓ 19%, C _{min} ↓ 37% norgestimate ↑ 85%	Oral contraceptive should contain at least 35 mcg of ethinyl estradiol. Oral contraceptives containing progestins other than norethindrone or norgestimate have not been studied.
Darunavir/r	ethinyl estradiol AUC ↓ 44% norethindrone AUC ↓ 14%	Use alternative or additional contraceptive method.
Fosamprenavir/r	ethinyl estradiol AUC ↓ 37% norethindrone AUC ↓ 34%	Use alternative or additional contraceptive method.
Lopinavir/r	ethinyl estradiol AUC ↓ 42% norethindrone AUC ↓ 17%	Use alternative or additional contraceptive method.
Saquinavir/r	↓ ethinyl estradiol	Use alternative or additional contraceptive method.
Tipranavir/r	ethinyl estradiol AUC ↓ 48% norethindrone: no significant change	Use alternative or additional contraceptive method.

Interaction of Hormonal Contraceptives & Non-nucleoside reverse transcriptase inhibitors

NNRTI	Effect on Drug Concentration	Dosing Recommendation
Efavirenz	ethinyl estradiol ↔ levonorgestrel AUC ↓ 83% norelgestromin AUC ↓ 64% ↓etonogestrel (implant) possible	Use alternative or additional contraceptive methods. Norelgestromin and levonorgestrel are active metabolites of norgestimate.
Etravirine	ethinyl estradiol AUC ↑ 22% norethindrone: no significant effect	No dosage adjustment necessary.
Nevirapine	ethinyl estradiol AUC ↓ 20% norethindrone AUC ↓ 19%	Use alternative or additional contraceptive methods.
	depomedroxyprogesterone acetate: no significant change	No dosage adjustment necessary.
Rilpivirine	ethinyl estradiol AUC ↑ 14% norethindrone: no significant effect	No dosage adjustment necessary.

Evidence-based National Contraceptive Clinical Guidelines

Contraceptive guidelines for women with certain characteristics or co-morbidities



MMWR™

Morbidity and Mortality Weekly Report

www.cdc.gov/mmwr

Recommendations and Reports

June 18, 2010 / Vol. 59 / No. RR-4

U.S. Medical Eligibility Criteria for Contraceptive Use, 2010

**Adapted from the World Health Organization
Medical Eligibility Criteria for Contraceptive Use, 4th edition**

CDC MEC covers more than 60 characteristics or medical conditions

US Medical Eligibility Criteria: Categories

1	No restriction for the use of the contraceptive method for a woman with that medical condition
2	Advantages of using the method generally outweigh the theoretical or proven risks
3	Theoretical or proven risks of the method usually outweigh the advantages – or that there are no other methods that are available or acceptable to the women with that medical condition
4	Unacceptable health risk if the contraceptive method is used by a woman with that medical condition

BOX 2. Conditions associated with increased risk for adverse health events as a result of unintended pregnancy

- Breast cancer
- Complicated valvular heart disease
- Diabetes: insulin-dependent; with nephropathy/retinopathy/neuropathy or other vascular disease; or of >20 years' duration
- Endometrial or ovarian cancer
- Epilepsy
- Hypertension (systolic > 160 mm Hg or diastolic > 100 mm Hg)
- History of bariatric surgery within the past 2 years
- HIV/AIDS
- Ischemic heart disease
- Malignant gestational trophoblastic disease
- Malignant liver tumors (hepatoma) and hepatocellular carcinoma of the liver
- Peripartum cardiomyopathy
- Schistosomiasis with fibrosis of the bladder
- Sickle cell disease
- Sickle cell disease
- Solid organ transplantation within the past 2 years
- Stroke
- Systemic lupus erythematosus
- Thrombogenic mutations
- Tuberculosis

Should consider long-acting, highly-effective contraception for these patients [Tier 1]

Medical Eligibility Criteria: Drug Interactions

HIV therapy								
	Combined Pill, P/R	Progestin-only pill	Injection (DMPA)	Implant	LNG-IUD		Copper-IUD	
					I	C	I	C
Nucleoside reverse transcriptase inhibitors	1*	1	1	1	2/3*	2*	2/3*	2*
Non-nucleoside reverse transcriptase inhibitors	2*	2*	1	2*	2/3*	2*	2/3*	2*
Ritonavir-boosted protease inhibitors	3*	3*	1	2*	2/3*	2*	2/3*	2*

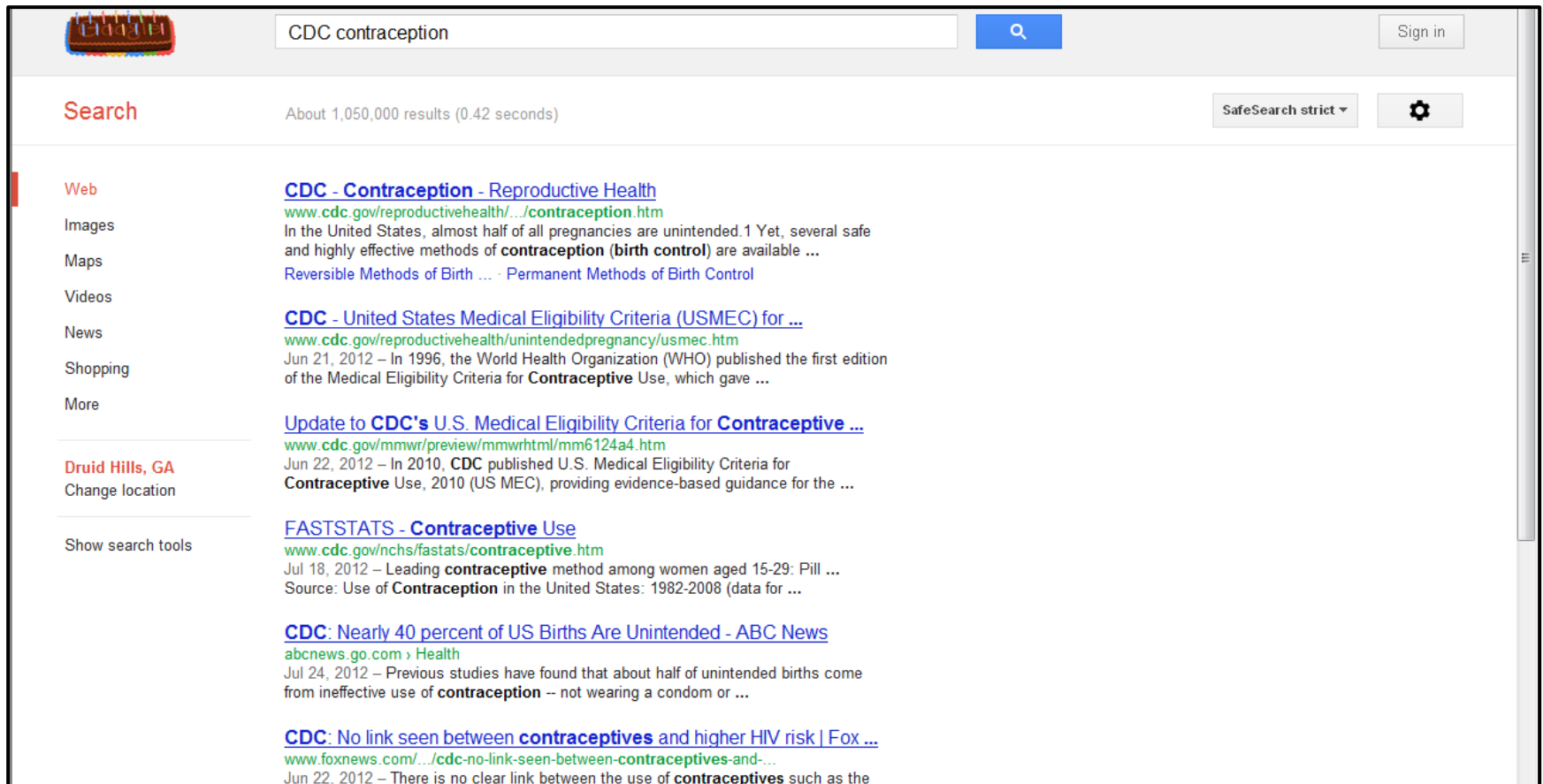
I= initiation C=continuation

Medical Eligibility Criteria: HIV

Antiretroviral therapy								
	Combined Pill, P/R	Progestin-only pill	Injection (DMPA)	Implant	LNG-IUD		Copper-IUD	
					I	C	I	C
High risk	1	1	1*	1	2	2	2	2
HIV infected (see also Drug Interactions)	1*	1*	1*	1*	2	2	2	2
AIDS (see also Drug Interactions)	1*	1*	1*	1*	3	2*	3	2*
Clinically well on therapy	If on treatment, see Drug Interactions				2	2	2	2

I= initiation C=continuation


How to find CDC's contraception guidance




The screenshot shows a Google search interface with the query "CDC contraception". The search results are categorized under "Web" and include several links to CDC resources. The left sidebar shows search filters like "Web", "Images", "Maps", "Videos", "News", "Shopping", and "More". The main results area lists the following items:

- CDC - Contraception - Reproductive Health**
www.cdc.gov/reproductivehealth/.../contraception.htm
In the United States, almost half of all pregnancies are unintended.1 Yet, several safe and highly effective methods of **contraception (birth control)** are available ...
[Reversible Methods of Birth ...](#) - [Permanent Methods of Birth Control](#)
- CDC - United States Medical Eligibility Criteria (USMEC) for ...**
www.cdc.gov/reproductivehealth/unintendedpregnancy/usmec.htm
Jun 21, 2012 – In 1996, the World Health Organization (WHO) published the first edition of the Medical Eligibility Criteria for **Contraceptive** Use, which gave ...
- Update to CDC's U.S. Medical Eligibility Criteria for Contraceptive ...**
www.cdc.gov/mmwr/preview/mmwrhtml/mm6124a4.htm
Jun 22, 2012 – In 2010, CDC published U.S. Medical Eligibility Criteria for **Contraceptive** Use, 2010 (US MEC), providing evidence-based guidance for the ...
- FASTSTATS - Contraceptive Use**
www.cdc.gov/nchs/fastats/contraceptive.htm
Jul 18, 2012 – Leading **contraceptive** method among women aged 15-29: Pill ...
Source: Use of **Contraception** in the United States: 1982-2008 (data for ...
- CDC: Nearly 40 percent of US Births Are Unintended - ABC News**
abcnews.go.com/Health
Jul 24, 2012 – Previous studies have found that about half of unintended births come from ineffective use of **contraception** -- not wearing a condom or ...
- CDC: No link seen between contraceptives and higher HIV risk | Fox ...**
www.foxnews.com/.../cdc-no-link-seen-between-contraceptives-and-...
Jun 22, 2012 – There is no clear link between the use of **contraceptives** such as the

CDC Contraceptive Guidance Health Care Provider Tools



Summary Chart of U.S. Medical Eligibility Criteria for Contraceptive Use, 2010

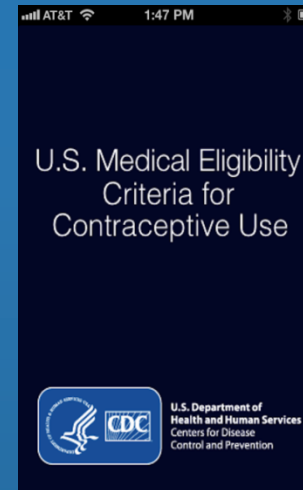


Key:
 1 No restriction (method can be used)
 2 Advantages generally outweigh theoretical or proven risks
 3 Theoretical or proven risks usually outweigh the advantages
 4 Unacceptable health risk (method not to be used)

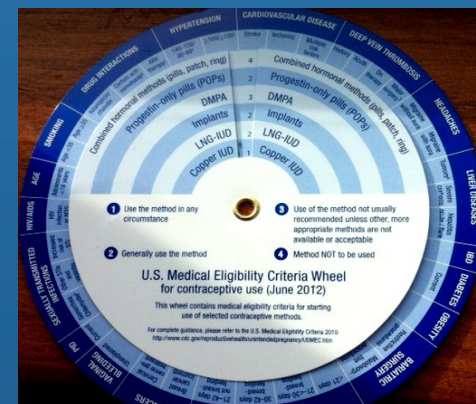
This summary sheet only contains a subset of the recommendations from the US MEC. For complete guidance, see: www.cdc.gov/reproductivehealth/unsafe
 Most contraceptive methods do not protect against sexually transmitted infections (STIs). Consistent and correct use of the male latex condom reduces the risk of STIs and HIV.

Condition	Sub-condition	Combined pill, patch, ring		Progestin-only pill		Injection		Implant		LNG-IUD		Copper IUD	
		1	2	1	2	1	2	1	2	1	2	1	2
Age		1	2	1	2	1	2	1	2	1	2	1	2
Anatomic abnormalities	a) Obstructed airway b) Other abnormalities	1	2	1	2	1	2	1	2	1	2	1	2
Asthma	a) Moderate-severe b) Severe c) On oral corticosteroids	1	2	1	2	1	2	1	2	1	2	1	2
Benign ovarian tumors (including cysts)		1	2	1	2	1	2	1	2	1	2	1	2
Breast disease	a) Undiagnosed mass b) Benign breast disease c) Family history of cancer d) Breast cancer i) current ii) past and no recurrence of current disease for 5 years e) 1 month postpartum f) 3 months or longer postpartum	2*	2*	2*	2*	2*	2*	2*	2*	2*	2*	2*	2*
Cervical cancer	a) Having treatment	2	2	1	2	2	2	2	2	2	2	2	2
Cervical ectropion		1	1	1	1	1	1	1	1	1	1	1	1
Cervical intraepithelial neoplasia (CIN)		2	2	1	2	2	2	2	2	2	2	2	2
Chlamydia	a) Mild (current/resolved) b) Severe (disseminated)	1	1	1	1	1	1	1	1	1	1	1	1
Deep vein thromboses (DVT) / Pulmonary embolism (PE)	a) History of DVT/PE, not on anticoagulant therapy b) Higher risk for recurrent DVT/PE c) Lower risk for recurrent DVT/PE d) At least DVT/PE e) DVT/PE and stabilized on anticoagulant therapy for at least 3 months f) Higher risk for recurrent DVT/PE g) Lower risk for recurrent DVT/PE h) Family history (first-degree relatives)	4	2	2	2	2	2	2	2	2	2	2	2
Diabetes	a) Mild (current/resolved) b) Severe (disseminated) c) Microvascular complications d) Minor surgery without insulin therapy	1	1	1	1	1	1	1	1	1	1	1	1
Diabetes (DM)	a) History of gestational DM only	1	1	1	1	1	1	1	1	1	1	1	1

Summary charts in English and Spanish



Smart phone app



Pocket-size wheel

Selected Practice Recommendations for Contraceptive Use (SPR)

Centers for Disease Control and Prevention
MMWR Morbidity and Mortality Weekly Report
Recommendations and Reports / Vol. 62 / No. 5 June 21, 2013

U.S. Selected Practice Recommendations for Contraceptive Use, 2013
Adapted from the World Health Organization Selected Practice Recommendations for Contraceptive Use, 2nd Edition



Continuing Education Examination available at <http://www.cdc.gov/mmwr/cme/conted.html>.



U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Purpose:
How to use
contraceptive methods

THANK YOU!

- Emily Godfrey MD MPH FAAFP
- godfreye@uw.edu
- Family Planning Clinic – Roosevelt Women's Health Clinic