

## Contraceptive Technology Update

Satellite Conference and Live Webcast  
Wednesday, October 25, 2006  
2:00 - 4:00 p.m. (Central Time)

Produced by the Alabama Department of Public Health  
Video Communications and Distance Learning Division

## Faculty

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## Program Objectives

- Describe current thinking on contraceptive efficacy and the status of experimental contraceptives.
- Describe the interrelationships of medical contraception methods with specific drugs, reproductive disorders and other health problems.

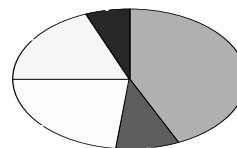
## Program Objectives

- Describe the new World Health Organization's (WHO) medical eligibility criteria; Intrauterine Device (IUD) and teens, IUD and Pelvic Inflammatory Disease (PID); spermicides; and known thrombogenic mutations and oral contraceptives.
- Discuss management of common contraceptive problems.

## Contraceptive Use in the US: 2002 Report

- Percentage of men and women who used contraception ranged from 67% (Guam) to 88% (Idaho).
- Women reported OC's as the predominant method in 49 areas followed by tubals, condoms and vasectomy.
- Men reported tubal, vasectomy, OC's, and condoms.
- Note lack of "new methods" in the top four.

## Half of All Pregnancies in the United States Each Year Are Unintended



Pregnancies  
(6.3 Million)

## The Oral Contraceptive Cycle



- Progestin prevents luteinizing hormone (LH) surge.
- Estrogen suppresses follicle-stimulating hormone (FSH) and follicular development.
- Together, the hormones in combination OCs inhibit proliferative changes in uterus, leading to endometrial atrophy.
- When placebo pills are taken, a “pill period” results.

## OC Developments

- New Progestin: Drospirenone; Yasmin.
- Berlex has obtained FDA approval for Yaz (20 mcg EE/3 mg drospirenone) for BC and PMDD (unique dosing 24 days active pills and 4 placebo pills).

## OC Developments

- New Estrogen doses: 25mcg; Cyclessa, Ortho-Tricyclen Lo.
- Extended Cycle Use: Seasonale, Seasonique.
- Widening EC use.
- “Natural” estrogen pills and nonsteroidal progesterone agonist (tanaproget).

## Depo-Provera

- November 17, 2004: the FDA issued a “black box” warning recommending that Depo-Provera be used long-term (i.e. more than two years) only if all other pharmacologic contraceptives are not appropriate or tolerated due to bone loss data in adult women.

## Depo-Provera and BMD in Teens

- NIH-funded study (J. Adoles Health 2004)
  - 370 girls (mean age, 15).
  - 53 chose Depo, 165 chose OC's (20 ug of estrogen) and 152 chose no hormonal contraception.
  - BMD values after 12 months.
    - At lumbar spine: -1.4%, +2.3% and +3.8%.
    - At the hip: -2.2%, +0.3% and +2.3%.
  - Clinical relevance ?

## Effect of Contraception on Bone Mineral Density

- Studied women ages 18-33 seeking contraception.
- Injectable Depo medroxyprogesterone acetate 150mg vs. 0.030 mg EE plus 0.15 mg desogestrel vs. 0.035 mg EE plus 1.0 mg norethindrone vs. controls (no hormonal contraception).
- Followed for 2 years.

### **Effects of Contraception on Bone Mineral Density**

- Depo users-average loss from baseline of 5.7 % (in spinal BMD).
- Desogestrel OC-average loss from baseline of 2.0 % (not statistically significant).
- Norethindrone- no significant change in BMD.
- Controls-average gain of 2.6 % in BMD.
- Clinical relevance?

### **DMPA and Bone Health**

- Three studies that indicate BMD is comparable in former and never users following discontinuation of DMPA.
  - Petitti DB et al (Obstet Gynecol 2000;95:736-744).
  - Scholes D et al (Epidemiology 2002; 13:581-587).
  - Scholes D et al (Arch Pediatr Adolesc Med 2005; 159: 139-144).

### **Effect of Pregnancy and Lactation on Bone Mineral Density**

- Bone turnover is reduced in early pregnancy, returned to normal during the third trimester and increased in postpartum lactating women (Cole et al. 1987)
- No evidence that high parity is associated with an increased incidence of osteoporotic fractures in later life (Alffram, 1964; Walker et al. 1972).

### **DMPA and Bone Health**

- Data presented at the May 2005 ACOG meeting (co-author Andrew Kaunitz, MD).
- Loss of BMD of approximately 1%-2% annually, with slower loss after that and substantial recovery following discontinuation (followed patients for 2 years after DMPA was discontinued).

### **DMPA and Bone Health**

- Complete recovery of BMD was not found at all skeletal sites assessed (but would it have if followed for > 2 years post DMPA?).

### **World Health Organization DMPA Statement**

- July 2005: There should be no restriction on the use of DMPA, including no restriction on duration of use, among women ages 18-45 who are otherwise eligible to use the method.

### **World Health Organization DMPA Statement**

- Among adolescents (menarche to less than 18) and women over 45, the advantages of using DMPA generally outweigh the theoretical safety concerns regarding fracture risk.

### **World Health Organization DMPA Statement**

- Since the data are insufficient to determine if this is the case with long term use among this age group, the overall risks and benefits for continuing use of the method should be reconsidered over time with the individual user.

### **Lower Dose, Subcutaneous Depo-Provera**

- Study compared LDSQ Depo (104mg/0.65ml) with IM Depo (150 mg/ml).
- Confirmed study participants were ovulatory.
- Received single injection and followed up until they ovulated (up to 12 months).
- 19 women who received IM and 39 received SQ were evaluated.

### **Lower Dose, Subcutaneous Depo-Provera**

- Ovulation was suppressed in all participants for at least 3 months.
- Median time to return to ovulation was similar in the two groups (183 days in the IM group and 212 days in the SQ group).
- Dose and maximum serum concentration are substantially lower with the SQ formulation...so ? Less side effects?

### **NuvaRing**

- Non-biodegradable, flexible, transparent vaginal ring.
- Contains two active components: ethinyl estradiol and etonogestrel (an estrogen and a progestin).
- Releases 0.015 mg/day of ethinylestradiol and 0.120 mg/ day of etonogestrel over a three week period.

### **NuvaRing®: Metabolic and Safety Conclusions**

- Minimal effect on lipid parameters.
- No clinically relevant effect on carbohydrate metabolism.
- Minimal effect on hemostatic variables, comparable with 30 EE/150 LNG COC.

### **NuvaRing®: Metabolic and Safety Conclusions**

- Low androgenic effects.
- No adverse effect on blood pressure.
- No unfavorable effects on the cervix and vagina.

### **Nuva Ring Update**

- Effectiveness not lower in very heavy women (Westhoff-ACOG 2005).
- Continuous use can be based on a “calendar approach” since the Nuva Ring is active for 35 days, not 21 (Timmer et al Clin Pharmokin 2000;39:233).
- Clinicians can obtain free fitting rings by going to [www.nuvaring.com](http://www.nuvaring.com)

### **Emergency Contraception: The Nations Best-Kept Secret**

### **California Women’s Health Survey**

- 6198 women (age 18-44) were asked “If a woman has unprotected sex, is there anything she can do in the 3 days after intercourse that will prevent pregnancy?”
  - Slightly more than \_ said yes, 1/3rd said no and around 10% said they didn’t know.

### **California Women’s Health Survey**

- 19% of those who answered yes listed incorrect responses to “what can she do?” (included RU 486 and douche) and 7% gave ambiguous answers (“seek medical help”).

### **Why Everyone Should Know About EC**

- 43% of the decrease in abortions in the US in the last 5 years has been attributed to the use of EC.
- Up to 51,000 pregnancies are prevented annually by the use of EC.
  - (Finer et al. Perspec on Sexual and Reprod health 2003)
- Works like LAM.

### **Emergency Contraception Mechanism of Action**

- Inhibition of ovulation.
- Decreases the probability of fertilization after ovulation.
- Changes in the endometrium (decreasing the likelihood of implantation).
- Does NOT interfere with an established, post implantation pregnancy.

### **EC's Effects on Ovulation**

- Studied 58 women with regular menstrual cycles (either had tubals or IUD).
- Treatment regimens: two 0.75 mg doses of levonorgestrel (12 hours apart), single 0.75 mg dose of levonorgestrel plus placebo or double dose of placebo.
- Randomized to take meds when leading follicle reached a diameter of 12-14 mm (Group I), 15-17 mm (Group II) and > 18 mm (Group III).

### **EC's Effects on Ovulation**

- Within 5 days of treatment, there was no ultrasound evidence of follicular rupture (i.e., no ovulation) in 44%, 50% and 36% of cycles with 2 levo. doses, 1 dose and placebo.
- Ovulatory dysfunction (disordered surges in LH and FSH) in 35%, 36% and 5%.

### **EC's Effects on Ovulation**

- Percentage of cycle either ovulatory dysfunction or no follicular rupture was similar in with 3 regimens in Group 1, significantly higher with levo than placebo in Group II and significantly higher with one dose levo than placebo in Group III.

### **EC's Effects on Ovulation**

- Caution in interpreting results: used hormonal parameters and ultrasound and did not test EC's efficacy.
- 13% of women with dominant follicle (i.e. > 18 mm) did not ovulate when treated with placebo.
- Single dose used in this study was not the "single dose" used in treatment studies.  
– (Contraception 2004 Dec.)

### **Emergency Contraception**

- Most effective if taken within 72 hours of unprotected intercourse (the sooner the better).
- New data suggests equal effectiveness if both doses are taken together and may be used up to 120 hours after unprotected intercourse.
- EC treatment is indicated regardless of the cycle day on which unprotected intercourse occurred.

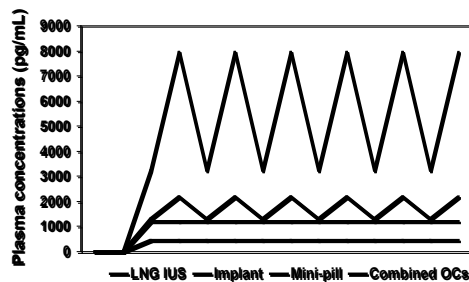
## Emergency Contraception

- No absolute contraindications.
- Initiate long term contraception immediately following EC (emergency contraception does NOT continue to prevent pregnancy during the rest of the cycle).
- Resumption of next menstrual cycle.
- Over the counter status.

## Mirena – A Levonorgestrel Releasing System

- T-shaped frame, 32 mm in length, that holds a cylinder that contains levonorgestrel.
- Releases levonorgestrel into the uterine cavity at a rate of 20 mcg a day.
- Approved for five years of use.

## Plasma Concentrations of Levonorgestrel



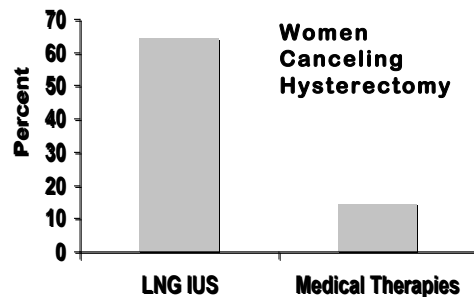
## Mirena – A Levonorgestrel-Releasing System

- Safety:
  - Ectopic pregnancy
    - One of 5 contraceptive failures associated with the Mirena is an ectopic pregnancy, resulting in an annual ectopic pregnancy rate of 0.02%.

## Mirena – A Levonorgestrel-Releasing System

- Changes in bleeding pattern:
  - Initially there is an increase in bleeding days (menstrual days and intermenstrual spotting days combined).
  - Irregular spotting during the first 3-6 months.
  - Bleeding may remain irregular in some women.
  - ~20% will become amenorrheic within the first year of use.

## LNG IUS as Alternative to Hysterectomy



### **Paraguard**

- Lasts 10 years.
- Highly effective.
- Has no systemic effects (e.g. headaches, acne).
- Most women have regular menses.
- Women may experience increased duration of menses and increased amount of bleeding.

### **Perhaps the Copper IUD is Permanent, Reversible Contraception?**

- In 1984, the FDA approved the copper IUD for 4 years of use.
- Eventually the FDA said it was “good for up to 10 years.”

### **Perhaps the Copper IUD is Permanent, Reversible Contraception?**

- WHO reported the copper IUD was effective for 12 years (contraception 1997;56:341).
- Brazilian study followed women up to 16 years of use..this study needs corroboration. Expulsion (? caused by fibroids?) may be a concern (contraception 2005 Nov; 72:337-41).

### **Paraguard Package Insert**

- The new insert does not recommend that this IUD be avoided by women who are:
  - Nulliparous.
  - Have a history of PID.

### **Ortho Evra Contraceptive Patch**

- Once-a-week combination hormonal patch.
- Changed on the same day of the week, three times a month, with the fourth week patch-free.
- Carrier for ethinyl estradiol and norelgestromin.
  - EE – 20 µg released daily.
  - Norelgestromin - 150 µg released daily.

### **“Seventeen Deaths in Users of Ortho Evra Patches”**

- In October 2004, AP found 17 deaths among users of the Ortho Evra patch.
- We know NOTHING about the denominator data and very little about the numerator number.
- Two epidemiological studies may reveal more about this rare but serious complication.
- Biologic plausibility.



### FDA “Bolded” Message

“You will be exposed to 60% more estrogen if you use Ortho Evra than if you use a typical birth control pill containing 35 mcg of estrogen. In general, increased estrogen exposure may increase the risk of side effects. However, it is not known if there are differences in the risk of serious side effects based on the differences between Ortho Evra and a birth control pill containing 35 mcg of estrogen.”

### Distribution of Pregnancies by Baseline Body Weight Deciles (n=3319 subjects)

Decile Pregnancies (N)	Weight Range (kg)	Total
1 (334)	<52	1
2 (285)	52 - <55	2
3 (354)	55 - <58	0
4 (256)	58 - <60	0
5 (433)	60 - <63	2
6 (346)	63 - <66	0
7 (276)	66 - <69	1
8 (379)	69 - <74	0
9 (304)	74 - <80	2
10 (352)	≥80	7
	(80- <85)	1
	(85- <90)	1
	≥90 (N=83)	5

### Weight and Risk of OC Failure

- NICHD-sponsored study.
- 618 OC users (2822 women-years OC use).
  - 106 confirmed pregnancies.
- Women in highest body weight quartile (>70.5 kg or 155 lbs) had 1.6 x significantly increased OC failure compared to women who weighed <155 lbs.

### Weight and Risk of OC Failure

- Risk ↑ in women with the highest body weight and taking low- (<50 mcg EE = 2.6x) and very low-dose (<35 mcg EE = 4.5x) OCs.
- Findings suggest that high body weight may compromise oral contraceptive effectiveness.

### Overweight Women Are at Increased Risk for OC Failure

- Study in Seattle: 248 women became pregnant while using OC's and 533 age-matched controls did not.
- Odds of becoming pregnant while on OC's were 58% higher for women with BMI's > 27.3 and were highest for women with BMI's > 32.2.

–(Obstet Gynecol 2005 Jan.)

### Contraceptive Patch Precautions

- Body weight ≥198 lbs. (90 kg)
  - Results of clinical trials suggest that the contraceptive patch may be less effective in women with body weight >198 lbs (90 kg) than in women with lower body weights.
- No other changes.
- Consider body weight in OC users also.

### **Single-Rod Implant Contraceptive: Description**

- Single 40-mm x 2-mm rod.
- Rod is made of ethylene vinyl acetate copolymer.
- Contains 68 mg of etonogestrel (3-keto-desogestrel), the active metabolite of desogestrel, and comes in disposable sterile inserter.
- Inhibits ovulation during the entire treatment period.
- Effective for 3 years.

### **Single-Rod Implant Contraceptive Efficacy**

- No pregnancies during 1200 woman-years of exposure (Pearl Index, 0; 95% CI 0.0-0.2).
- Effective contraception that lasts for 3 years.

### **FDA Approved July 2006**

- Implanon
  - Return to fertility – 94% of women ovulated within 3 weeks of removal.
  - Side effects.
    - Changes in vaginal bleeding (30% discontinuation).
    - Amenorrhea.
    - Weight changes (1.5% discontinuation).
    - Acne (1.0% discontinuation).

### **ESSURE**

- New procedure for non-incisional permanent birth control.
- Micro-inserts are placed in the fallopian tubes to prevent pregnancy.
- The system is introduced with a standard hysteroscopic approach with tubal cannulation.
- Can be performed without general anesthesia.

### **Contraceptive Case Studies**

#### **Young Teenager with Severe Dysmennorrhea**

- 13 year old female, never sexually active.
- Menses began at age 11 and painless for 6 months.
- Now periods are extremely painful, causing her to miss 1-2 days of school/month.

### **Young Teenager with Severe Dysmenorrhea**

- Tried heat, NSAIDs, aspirin, exercise...nothing works.
- PE- normal B/P.

### **Would You...**

- A. Prescribe a stronger prescription NSAID because OCP's are not appropriate in this age group.
- B. Start her on Depo Provera to decrease her menstrual bleeding.
- C. Do a pap smear and give her whatever method she wants.
- D. Defer the Pap and start her on OCP's.

### **Contraception and Pap Smears**

- Never sexually active women are at VERY low risk of HPV infection.
- Cervical cancer and HPV are linked.
- Comfort of young teens with their bodies.
- New pap screening guidelines.

### **What Factors Increase the Risk of Acquiring HPV?**

- Number of sexual partners.
- Recent new partner (5-8 months).
- Rate of new partners per month.
- History of herpes.

### **What Factors Decrease the Risk of Acquiring HPV?**

- Limited sexual exposure.
  - But HPV can be acquired without vaginal penetration.
  - 8% of virgins tested positive in 24-month study.
  - Condoms are not protective.

### **What Factors Decrease the Risk of Acquiring HPV?**

- Various studies show different results for use of oral contraceptives.
  - Winer: current oral contraceptives adjusted HR 1.41.
  - Xi: 1.6 (short duration use) to 5.4 (5-8 mon use)<sup>2</sup>.
  - Moscicki: current oral contraceptives 0.543.

### **What Is the Risk for Developing Cervical Cancer?**

- Approximately 10,000 cases in the United States per year.
- Cervical cancer risk is higher in developing countries.
- Incidence of cervical cancer in adolescents is essentially zero.

### **Will HPV Resolve?**

- Median time to resolution:
  - Ho (1998) 8 months
  - Woodman (2001) 13.7 months
  - Richardson (2003) 13.2 months
  - Xi (2002) HPV16 17.2 months

### **What Screening Is Indicated?**

- Current recommendations:
  - Initiate Pap testing at age 21 or 3 years after initiation of sexual activity, whichever comes first.
- Recommendations after vaccination:
  - Yet to be determined.

### **“Oh my gosh, I didn’t have a period, am I pregnant?!”**

- 18 year old G1P1 on OCP’s for 2 years with no problems.
- C/O no period this month.
- No symptoms of pregnancy.
- Can I start my new pack of pills Sunday?

### **Would you....**

- A. Tell her to call back on Monday and speak to an APRN and come in for a pregnancy test.
- B. Tell her “sure, start your pills”...”whatever”.
- C. Inquire about missed pills during the past month.
- D. Tell her to stop her pills and start thinking of baby names.

### **What About Family History?**

- 19 year old desires contraception, but doesn’t think she can remember to take a pill every day.
- Family history - father had MI at age 48, 29 year old sister has hypertension.
- Patient is a college student, non-smoker, gets lots of exercise, normal blood pressure.

### **Would You Tell Her**

- A. You are healthy, you can start whatever method you like.
- B. The NuvaRing has the lowest dose of estrogen, you should consider it with your family history.
- C. With that family history, your only choice is non-hormonal contraception: a P-IUD or condoms.
- D. The patch might be the best choice for you, if you can't remember to take pills.

### **Post Partum Contraception**

- 21 year old, 6 weeks post partum, "fully breastfeeding".
- Married.
- Afraid of IUD's.
- Normal B/P and pelvic exam.

### **Post Partum Contraception**

- A. Any method is OK to use while breastfeeding.
- B. No need to worry about contraception for at least 6 months while you're breastfeeding.
- C. Progestin-only methods (pills, M-IUD or Depo) are the best for you while breastfeeding.
- D. You could use condoms and EC while breastfeeding.

### **Nausea and Contraception**

- 22 year old G1P1 (child is 9 months old).
- No longer breastfeeding.
- Wants another baby when this one is 3 years old.
- Had hyperemesis gravidarum.
- Normal exam and B/P.

### **Well....**

- A. The Nuva Ring, M-IUD and Implanon all have low doses of hormones and may work for you.
- B. You should stick with progestin only pills since they're working for you.
- C. You don't really want another baby in 3 years...Do you??!!
- D. The pills definitely won't make you nauseated after all that nausea of pregnancy.

### **Acne and Weight Loss**

- 18 year old G0P0 wants "that new pill that's good for acne and causes you to lose weight".
- History of heavy periods.
- Plays softball and takes Motrin "a lot" for pain.

### Yasmin

- 30ug EE/3 mg drospirenone
- Drospirenone
  - Spironolactone analog with antimineralocorticoid and antiandrogenic activity..which means it's also a diurectic.
  - Limited data in use in women >30.
  - Good for acne and hirsutism...may benefit patients who experience “fluid retention and bloating” during their cycles.

### Yasmin

- Restricted labeling for drospirenone.
  - Contraindicated in women with renal insufficiency, hepatic insufficiency and adrenal insufficiency (patients at risk for hyperkalemia).
  - Warning for patients on chronic meds.
    - NSAID's (long term use).
    - Potassium supplements.
    - K+ sparing diurectics, ACE's, ARB's, heparin (check K+ level in 1<sup>st</sup> month for pts on these meds).

### Drospirenone and Weight Loss

- Same side effect profile.
- Same effectiveness.
- 1 open label trial.
  - Small amount of temporary weight loss in first 6 months, at 1 year, weight returned to baseline or slightly above.
    - (Contraception 2000, Eur. J Contra Reprod Health Care 2000)

### Hypertension and Contraception

- 40 year old G3P3 on OCP's for 5 years.
- Annual exam..B/P is 150/98.
- B/P last year 120/80.

### Low Dose OCP's and CV Risk

Number of Excess Cases of MI and Stroke Attributable to OC

	20-24 years	30-31 years	40-44 years
Non-Smokers	0.4	0.6	2
Smokers	1	2	20
Hypertension	4	7	29
Number of Pregnancy Related Deaths (per 100,000 live births)	10	12	45

### Contraception and “Migraine” Headaches

- 19 year old nulliparous patient.
- c/o “migraine headaches”.
- B/P normal.
- Exam and FH unremarkable.

### **OCP's and Migraine Headaches**

- Increased risk of stroke in women > 45 years with migraines.
- Migraine with aura is associated with greater risk than migraine without aura.
- WHO states prescribing OCP's to women < 35 years with migraine without aura is safe.
- "Menstrual migraines" may improve on OCP's.

### **Smoking and Contraception**

- 34 year old G2P2 on OCP's for 8 years.
- Smokes \_-1 pack of cigarettes/day.
- Likes that her periods are regular on the pill.
- Doesn't want a tubal.
- Turns 35 years old next month.

### **Age and Contraception**

- 42 year old G3P3 on OCP's for 12 years.
- Non-smoker.
- B/P normal (120/70).
- Doesn't want an IUD or tubal.
- Partner doesn't like condoms.

### **Contraception and CAM**

- 38 year old G2P2 with history of hypothyroidism and irregular menses and "perimenopausal" symptoms.
- On Progesterone cream and "natural thyroid replacement".
- Worried that "condoms aren't enough".
- Doesn't want "more hormones" now that she's "getting better with natural meds".

### **Complicated Patient**

- 30 year old G3P3 (living children 1).
- Had 2<sup>nd</sup> trimester fetal demise, 3<sup>rd</sup> child born with congenital cardiac defect.
- History of DVT between 2<sup>nd</sup> and 3<sup>rd</sup> pregnancy.
- Diagnosed with Anticardiolupin Antibody, Factor 5 Leiden.

### **OCP's and Inherited Hypercoagulable States**

- In OCP user:
  - Risk of VTE increases 35-99 fold in carriers of Factor V Leiden.
  - Risk of VTE in carriers of Protein C and antithrombin deficiency increased 2 fold and 9 fold respectively.
  - Safety of progestin only contraceptives in hypercoagulable states is unknown.

### **Complicated Patient**

- 41 year old G7P0.
- Non-smoker.
- Regular menses.
- Married/monogamous relationship.
- History of OCD.

### **Non-Contraceptive Benefits**

- 39 year old G2P2.
- S/P BTL after last child (age 6).
- Non-smoker.
- Heavy, irregular menses.

### **What Now?**

- 24 year old G3P2.
- Non-smoker.
- Conceived first child while on OCP's, conceived second child while using the patch, got pregnant with third child with P-IUD in place.
- Doesn't want sterilization.

### **Any Suggestions?**

- 18 year old G3P2 (currently 24 weeks pregnant).
- 2 prior C-sections, Wants a tubal this time.
- Can't remember to take pills, weighs 240 pounds, doesn't want an IUD, tried the ring and didn't like it, doesn't like Depo, partner won't use condoms.

### **Upcoming Programs**

**Ensuring Quality in the Collaborative Practice Agreement**  
Thursday, October 26, 2006  
10:00 a.m. - 12:00 Noon (Central Time)

**Infection Control Update**  
Wednesday, November 1, 2006  
2:00 - 4:00 p.m. (Central Time)

For complete list of upcoming programs visit: [www.adph.org/alphtn](http://www.adph.org/alphtn)