What’s New in Contraception 2012

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- Sharon Schnare reports that she is a consultant for Bayer HealthCare Pharmaceuticals, Inc. and a speaker for Azur Pharma, Bayer HealthCare Pharmaceuticals, Inc, Jazz Pharmaceuticals, Merck Sharp & Dohme Corp., and Teva Women’s Health Inc. Sharon Schnare agrees to present the following information fairly and without bias.
- The planners report no relationships with businesses or industries that would pose a conflict of interest.
- No commercial support was received for this CNE activity.

Brand names may be noted for identification purposes only and off-label use will be noted as such

Contraception has reduced women’s death rates and has been the single most important factor impacting women’s health, education and freedom in the 20th century.

- It is estimated that more than a quarter of pregnancies worldwide are unintended.
- Between 1995 and 2000, approximately 700,000 women died as a result of unintended pregnancy; and morbidity from pregnancy affected even more women.
- This is why ALL options must be available to ALL women.

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CDC Prepregnancy Contraceptive Use Among Teens with Unintended Pregnancies –Pregnancy Risk Assessment Monitoring System (PRAMS)

- Approx. 400,000 teens aged 15-19 give birth every yr in U.S. Highest rate in developed world.
- Study: Hispanic, White, Black teens in 37 states & NY City (75% of all live births in U.S.)

PRAMS Data

- 50.1% teens were not using contraception at time of conception
- 22.1% of teens said: “I did not mind if I got pregnant.”
- 23.6% said partner did not want to use contraception
- 31.4% believed they could not get pregnant at time of conception

THIS IS AMBIVALENCE

Why is Teen Pregnancy a Problem?

More likely suffer negative social outcomes:
- School drop out
- Infants: increased low birth wt.
- Daughters of teen mothers: more likely to become teen mothers themselves
- Lower academic achievement

The Good News: Teen Pregnancy has Declined this year 2012

Perceptions of Risk

Remind women and men that NO method of contraception confers a higher risk of death than pregnancy

Contraception is not as Effective Without Counseling & Education

- SHOW women & men actual methods, encourage them to touch and handle methods. Carry methods in your pocket!
- Use motivational interviewing style of counsel—may be more effective.
- Realize ambivalence is normal
- Ask women what they want to know; avoid telling people what to do.
**Pill Side-Effects: The “Nocebo” Response**

“nocebo”? Negative placebo effect. Non-specific complaints caused by negative perceptions of pill which WE bring up NO evidence for most complaints! Telling women to expect side effects becomes a “self fulfilling prophecy”; increases discontinuation

**BENEFITS: FAR OUTWEIGH THE DANGERS**

Frequency of most pill side-effects are no greater than placebo pills!

Optimistic Counseling Discussion of Beneficial Effects of Pills! Grimes 2011

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**Should Contraceptive Pills be Over the Counter? YES  Cont...**

**Border Contraceptive Access Study N= >1000 Latina low-income women-9 mo study. Half received Rx (El Paso), other half went to Juarez, Mexico for OTC pills Those in US: 60% more likely to stop pills, than those getting pills in Mexico. If given fewer than 6 packs: 80% more likely to stop pills than those taking OTC pills Potter 2011**

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**Cont...Should Contraceptive Pills be Over the Counter? YES  Cont...**

ACCESS decreases unintended pregnancy. Mexican women using OTC pills in Mexico more likely to have health conditions: HTN, smoking >34 (more relative contraindications but no absolute contraindications 13% vs 9% in Rx grp.) However no medical complications occurred. PROVIDE YEAR SUPPLY WHEN POSSIBLE (40) Potter 2011

Potter 2011

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**WHO and CDC Medical Eligibility Criteria for Contraception at last...evidence-based contraceptive management!**

Is changing contraceptive practice in the U.S and Worldwide

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http://www.cdc.gov/reproductivehealth/unintendedpregnancy/USMEC.htm

CDC/MEC
Medical Eligibility Criteria for Contraceptive Use CDC, 2010

What’s new (July 8, 2011)

Safety of CHC’s during postpartum period
First 21 days postpartum:
   Changed from category 3 to category 4: unacceptable risk for all women
Days 21-42 Postpartum
   changed from category 1 to category 2 or 3 depending on other risk factors
>42 days postpartum: category 1 unless other medical conditions present

CDC 2011

Rationale for the Change

- Risk of VTE first 42 days postpartum 22-84 times greater than non-postpartum women
- Risk decreases rapidly post delivery over first 21 days
- Most women will not ovulate until 42 days postpartum so no clear benefit to CHC
- Women can be given Rx at delivery and advised to start after 42 days
- Recommendation is not based on any direct evidence on postpartum use of CHC

Jackson 2011, CDC 2011

CONTRACEPTION AND THROMBOSIS

Risk Factors for Thrombosis Related to Pregnancy

Age > or = 35 years
Previous VTE
Thrombophilia
Smoking
Immobility
BMI > or = 30

Postpartum hemorrhage
Transfusion at delivery
Caesarean delivery
Pre-eclampsia
Peripartum cardiomyopathy

CDC 2011

Drospirenone: Thrombogenic…or just bad press? Cont...

EURAS European Active Surveillance study (2000-2004) requested by regulators. 58,674 enrolled followed for 142,475 person yrs. DRSP with 30 mcg EE with 2 comparators (Lng & other COCs) Each women checked q 6 mos for adverse events. Results: no increase risk of VTE, ATE (arterial thrombotic events): MI, ischemic stroke or mortality between grps. Adjusted for age, BMI, smoking, HTN, duration of use, VTE Hx. Showed NO difference between Lng, DRSP or other COCs

Dinger 2007
Drospirenone and Thrombotic Events

FDA requested U.S. based study: i3 Ingenix (2001-2004): to identify all instances of death, hospitalization, syncope, arrhythmia, hyperkalemia, electrolyte disturbances, dialysis & MI among DRSP initiators.
Reviewed insurance claims, medical records
Risk of VTE: >40 yrs, DM, HTN, Hx MI, arrhythmia;
BUT suggested no difference in incidence of VTE between users of DRSP and other COCs.
Seeger 2007, Eng 2008

Comparison Hazard Ratio (HR) 95% CI

VTE venous thromboemboli

DRSP vs LNG 1.0 0.6-1.8
DRSP vs CHC 0.8 0.5-1.3

ATE (arterial thrombotic events-stroke, MI)

DRSP vs LNG 0.3 0.1-1.2
DRSP vs CHC 0.3 0.1-1.5

Dinger 2007

MEGA Study Study listed in package insert by FDA

Compared to nonusers Relative Risk of DVT Odds Ratio

Levonorgestrel 3.6 2.9 — 4.6
Gestodene 5.6 3.7 — 8.4
Desogestrel 7.3 5.3 — 10
Cyproterone 6.8 4.7 — 10
Drospirenone 6.3 2.9 — 13.7

van Hylckama Vlieg 2009

Lidegaard Re-analysis Lidegaard 2011

Reanalysis and time extension of Danish retrospective cohort study of national database hospital discharge and prescriptions 2001-2009---8,010,290 woman-years
DVT events compared to levonorgestrel + 30-40 mcg of EE:

<table>
<thead>
<tr>
<th>Comparison groups</th>
<th>Events</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drosiprenone + 30 µg EE</td>
<td>196 v 123</td>
<td>2.12 (1.68 to 2.66)</td>
</tr>
<tr>
<td>Desogestrel + 30 µg EE</td>
<td>168 v 123</td>
<td>2.20 (1.74 to 2.77)</td>
</tr>
<tr>
<td>Gestodene + 30 µg EE</td>
<td>575 v 123</td>
<td>2.07 (1.70 to 2.52)</td>
</tr>
</tbody>
</table>

FDA Funded Study Continued

Retrospective cohort study data from 2 US HMO sites and Medicaid data from WA and TN 2001-2007 835,826 women, ages 10-55 years

drospirenone/ethinyl estradiol tablets (DRSP)
norelgestromin/ethinyl estradiol transdermal patch (NGMN)
etonogestrel/ethinyl estradiol vaginal ring (ETON)
group of 4 common COCs with progestins: LNG, NETA, NGM with EE doses ranging from 20-35 mcg (COMP)
group of COCs with LNG and EE 30 mcg (LNG2)

FDA 2011

Continued FDA study: Relative hazard of study endpoints associated with study exposure CHCs relative to the combined comparator CHCs group

<table>
<thead>
<tr>
<th></th>
<th>ATE</th>
<th>VTE</th>
<th>CVD mortality</th>
<th>Total mortality</th>
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</thead>
<tbody>
<tr>
<td>All Users</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRSP</td>
<td>0.99 (0.58, 1.69)</td>
<td>1.74 (1.42, 2.14)</td>
<td>0.37 (0.11, 1.29)</td>
<td>0.85 (0.59, 1.23)</td>
</tr>
<tr>
<td>NGMN</td>
<td>1.31 (0.63, 2.74)</td>
<td>1.55 (1.17, 2.07)</td>
<td>0.20 (0.03, 1.56)</td>
<td>0.80 (0.51, 1.28)</td>
</tr>
<tr>
<td>ETON</td>
<td>1.72 (0.61, 4.83)</td>
<td>1.56 (1.02, 2.37)</td>
<td>0.82 (0.08, 4.72)</td>
<td>1.31 (0.71, 2.40)</td>
</tr>
<tr>
<td>New Users</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRSP</td>
<td>2.01 (1.06, 3.81)</td>
<td>1.77 (1.33, 2.38)</td>
<td>0.25 (0.03, 1.59)</td>
<td>0.88 (0.52, 1.53)</td>
</tr>
<tr>
<td>NGMN</td>
<td>1.07 (0.36, 3.23)</td>
<td>1.35 (0.95, 2.02)</td>
<td>Insufficient data</td>
<td>1.07 (0.56, 2.05)</td>
</tr>
<tr>
<td>ETON</td>
<td>1.69 (0.38, 7.12)</td>
<td>1.35 (0.99, 2.02)</td>
<td>Insufficient data</td>
<td>0.96 (0.29, 3.14)</td>
</tr>
</tbody>
</table>

FDA 2011
Problems with Progestin Studies

- Technical design flaws especially with using data collected for other purposes
  - Difficulty validating diagnosis coding for billing vs chart review
  - Matching controls
  - Lumping various CHC’s as comparison
  - Including rarely prescribed drugs and drugs not relevant to US prescribers

So…?

- Has a greater thrombotic risk in CHC with some progestins been firmly established? NO
  - Multiple studies with various methods, strengths and weaknesses and varying results
- Will we ever get level I evidence to answer this question? NO
  - Events too rare to do a prospective randomized trial
- Will we ever get consensus on this question? Maybe.
  - More and better comparable studies needed

Result of FDA inquiry: Label Change DRSP containing COC’s

- New Yasmin label approved February 2012 by the FDA
- Added reference to new data from FDA funded study
- No specific indication that FDA considers drospirenone more of a risk than other COC’s

Result of FDA inquiry: Label Change DRSP containing COC’s

- Safety Announcement 4/10/2012
  - “FDA has concluded that drospirenone containing birth control pills may be associated with a higher risk for blood clots than other progestin-containing birth control pills.”
- New labeling approved April 2012 by the FDA for all drospirenone containing OC’s
Lable added reference to new data from FDA funded study

No Increase in VTE Risk with:

Levonorgestrel
Norethisterone
Hormone releasing and copper IUD’s

Thrombotic Risk with Combination Patch: Update

Risk of VTE with patch appears to be equivalent to risk of COCs with norgestimate, some studies show equal risk (3)(5)(6)(8); while other data suggest a higher risk (4)(9) Stroke and MI were so rare that risks could not be estimated. However, the risk of VTE with the transdermal combination patch is still less than the risk associated with pregnancy.

Putting VTE Risk in Perspective: the Data

200,000 new cases diagnosed in U.S./each year
2/3 VTE’s are DVTs; DVTs have 6% mortality rate
1/3 are pulmonary emboli (12% mortality rate)
40% of VTEs are idiopathic

VTE and COC’s

VTE risk pregnancy: 98.5 per 100,000 women yrs, BUT rises to 511.2 per 100,000 women-yrs in postpartum period!
Risk of PE during pregnancy: 10.6 per 100,000 women-yrs
During Postpartum the risk rises to 159.7 per 100,000 women-yrs.
VTE risk is reversible within 30 days after discontinuation

When is the Greatest Risk of VTE?

In the 1st 3 to 12 mos of COC use, then declines thereafter
Obese users have 3 fold increased risk
ACOG recommends women over 35 with BMI>30 should use estrogen containing contraception with caution; however US MEC rates obesity as Cat 2
Smokers 18-39 yrs who DID NOT use COC’s had 2X VTE risk; smokers who did: 8.8 X higher risk

Nelson 2011
Nelson 2011
Nelson 2011
Nelson 2011
Risk Factors for VTE

Contraceptive Technology 2011

- Obesity: >1/3 adult women have BMI>30
- Age, smoking, hypertension

*Thrombophilias: factor V Leiden accounts for 30% of ALL DVT’s
  - Other clotting defects: prothrombin factors
  - Deficiencies in antithrombin, protein C, Protein S

With these defects the VTE risk may be 120-150 /100,000 a year  Nelson 2011

Antimicrobial, Antifungals and Antiparasitics Medications: Impact on Contraceptive Efficacy CDC MEC 2010

- Broad spectrum antibiotics: All Cat 1
- Antifungals: All Cat 1
- Antiparasitics: All Cat 1
- Rifampicine or Rifabutin
  - Cat 3 for CHC’s and POP
  - Cat 1 for MPA injection
  - Cat 2 for Implant
  - Cat 1 for IUDs

Contraception for Women with UNcomplicated Organ Transplant CDC MEC

- Lng IUD 2
- Cu IUD 2
- Uncomplicated All methods: 2

CONTRACEPTION: Medical Illnesses and Postpartum

Morbidly Obese Women Following Roux-en-Y Gastric Bypass Procedure

- Pregnancy should be avoided for 12-18 mos post surgery
- Etonogestrel (ENG) implant (Implanon®) subcutaneous delivery unaffected by malabsorptive surgery (N=3)
- ENG serum levels decreased with wt loss, but remained above level necessary for effective contraception for at least 6 mos

DMPA Injection: Postpartum

- Breastfeeding < 1 mo PP
- Breastfeeding 1 mo or more PP
- Postpartum < 21 days
- Postpartum 21-42 days with other risk factors for VTE
- More than 42 days PP

U.S. Med Eligibility Criteria for Contraceptive Use June 2012
Magnetic Resonance Imaging and IUDs and Implants

YES is safe for women with IUDs, implants, microimplants (inserted during hysteroscopy)


NEWER CONTRACEPTIVES

2010-New Quadriphasic COC

Estradiol valerate /dienogest (aka Natazia® (US) Qlaira ® (EU)
19-nortestosterone-derived DNG (dienogest) an antiandrogenic progestin with estradiol valerate (E2V)
No clinically relevant effects on most hemostatic parameters.

Nelson 2010, Borgelt 2012

Cont... Cycle Control with new COC Dienogest (DNG) (19-nortestosterone-derived with estradiol valerate (E2V)
† Ist 2 days: 3 mg estradiol valerate (E2V) alone (primes endometrium)
† Then 5 days of 2 mg E2V with DNG 2 mg
† Dose of DNG is raised the next 17 days to 3 mg while E2V dose stays at 2 mg
† Then 2 active pills contain only E2V 1 mg
† 2 placebo pills end the 28 day cycle

Cont... New Oral Contraceptive Pill Dienogest + Estradiol valerate
Showed superior bleeding profile to EE 20 mcg with Lng 100 mcg pills
67% reduction in bleeding compared with typical OC reduction of 35% to 43%
Low discontinuation rate
New Drug application (NDA) requested indication for “prolonged menstrual bleeding ...” BUT approved by FDA 5/6/2010 only for contraception.

Fraser 1991, Jensen 2011, Nelson 2010

Two New Drospirenone Combined COC’s with Folate
† FDA approved two new drospirenone (DRSP) containing pills with folate
† Beyaz 24/28 pills with 20 mcg EE & 3 mg DRSP
† Safyral 21/28 pills with 30 mcg EE & 3 mg DRSP
Levomefolate calcium 0.451 mg per tablet in all 28 pills in both brands
The “Chewable” Pill
Norethindrone 0.8 mg
Ethinyl estradiol 25 mcg
Ferrous fumarate 75 mg (no therapeutic value: Prenatal dose is 325 mg/d)
24 active pills and 4 “inactive pills” which contain iron
iPhone app available as pill reminder (Generess Fe)

WHAT’S NEW ON THE HORIZON

New Injectable Contraceptive: On the Horizon
Levonorgestrel butanoate suppresses ovulation for up 5-6 months after single injection of 50 mg; 12.5 mg dose... inhibited ovulation for another 2-3 months
CCNT: Contraceptive Clinical Trial Network investigation potential
Garza 1991, Jensen 2011

Progestin-Only Patch In Development
Progestin-only (levonorgestrel)
Benefits women with contraindications to estrogen:
Migraine with aura
Thrombophilias
Postpartum or nursing mothers
http://clinicaltrials.gov/ct2/show/NCT01166412

New Transdermal Combination Patch on the Horizon PHASE 3 TRIALS COMPLETED
Using 50 mcg gestodene, a synthetic progestin from the 19-nortestosterone family and ethinyl estradiol 20 mcg
Patch is applied once/week: 21 days on and 1 week off
Inhibits ovulation
Heger-Mahn 2004, Jensen 2011,

Progestin-Nestorone Vaginal Ring
Potent 19-norprogesterone derivative, neutral metabolic effects (not active orally); can be used in gel, ring or spray formulas
2 Phase 3 trials completed
Vaginal ring releasing 150 mcg/d nestorone with 15 mcg/d of EE
21 days on, 7 days off regimen
The same ring reinserted every month for 1 year
Developed by Population Council
Sitruk-Ware 2007
**Natural Progesterone as a Contraceptive Ring?**

- Designed for lactating women
- 10 mg/d progesterone release vaginal ring
- Effective for 3-4 months
- No effects on breast-feeding or infant development

Nath 2010, Massai 2005

**New Oral Contraceptive pill...On the Horizon: Nomegestrol Acetate**

- Estradiol with nomegestrol acetate (NOMAC)
- 19-norprogesterone derivative lacks affinity for steroid receptors other than progesterone receptors: antiestrogenic and antigonadotropic effects on endometrium without androgen or glucocorticoid effects
- Treatments: dysmenorrhea, heavy menstrual bleeding, premenstrual syndrome
- Combined with estrogen for OC, inhibits ovulation & follicle development

2011 Jensen, Lello 2011

**Oral Contraceptives: Treatment for Hirsutism?**

- Prospective RCT comparing 2 drospirenone OC’s:
  1. 21/7 grp: 3 mg DRSP+0.03 mg EE
  2. 0.02 mg EE + 3 mg DRSP
- N=50 (24 and 23 pts in each grp) 6 mo study
- Both grps comparable effects; well tolerated (T & free T decreased significantly; SHBG increased; no change in DHEAS levels)

Oner 2011

**Contraceptive Vaccines**

- GnRH: Gonadotropin-releasing hormone
  - Male & Female Felines
  - Causes impotency
  - Equity®, Improvac® Repro-BLOC®
- FSH: follicle stimulating hormone
  - Male & Female Primates
  - Oligospermia
  - No
- Luteinizing hormone
  - Male and Female lab animals, primates
  - Causes impotency
  - No
- HCG: Human chorionic gonadotropin
  - Women and female primates
  - Successful in women. Difficult to get high antibody titre
  - No
- Zona pellucida (ZP)
  - Female animals, dogs, primates,
  - Causes irreversible oophoritis
  - Wildlife/dogs P2P vaccine/Spayvac®

**Can Nurse Clinicians Perform Manual Vacuum Aspiration (MVA)?**

- YES
- Study from India determined that nurses performing MVA’s are as safe as physician colleagues.
- Nurse provided MVA’s increases access to safe abortions

Shireen J et al Contraception 84(2011) 615-21

Jejeebhoy 2011

**Vaginal Contraceptive Ring**
Extended use Vaginal Ring Contraceptive

- No hormone-free interval
- Potential for breakthrough bleeding
- Probably continuous 30 day cycle

Teaching Women How to Use the Ring: It's easy!

- Hand a ring sample to her- "soft, small"
- Quick demonstration of insertion and removal technique(s) and positions ("Ring Macarena")
- Assure her that vast majority of women find it very easy to use and she will too.

LARC: Long-acting Reversible Contraceptive Methods

Methods that are as effective as surgical sterilization, yet reversible.
IUD’s (copper and levonorgestrel)
Implant
Cost effective, reduce need for clinic visits, safe
Implant and IUCs effective for 3, 5 or 10+ years.

EMERGENCY CONTRACEPTION: WHAT'S NEW?

Gestrinone and Mifepristone for Emergency Contraception

- Double-blind controlled trial N=998 with 499 in each arm; unprotected intercourse within 72 hrs.
- Pregnancy rate for 10 mg gestrinone (anti-progestin not available in U.S.): 2.5%
- Pregnancy rate for 10 mg mifepristone: 1.8%

Wu 2010 Obst Gynecol
Cheng 2012 Cochrane Database Syst Rev
Emergency Contraception (EC): What's on the Horizon?

Mifepristone 25-50 mg superior to Lng IUD and Yuzpe (combined COC regimens)
Ulipristal acetate may be more effective than Lng IUD
Lng IUD more effective than Yuzpe
COPPER IUD MOST EFFECTIVE EC and
ONLY METHOD TO PROVIDE ONGOING CONTRACEPTION WHEN LEFT IN SITU

Cheng Cochrane Database Syst Rev. 2012
Richardson Clin Ther. 2012

Cu IUD for Emergency Contraception

Emergency placement of Cu-IUD: significantly more effective (99%) than EC pills.
May also prevent pregnancy after fertilization
Can be placed within 120 hrs of UPIC (only 0.23 preg/100 women)

Cheng 2008

IUD UPDATE and NEWER USES

Frameless (FibroPlant) LNG-IUD reduces menstrual blood loss in women with/without heavy menstrual bleeding
Releases 14 mcg LNG/day for contraception
Amenorrhea occurred in 80% of women
Andrade 2009
Smaller devices may be beneficial for nulliparous women.
Jensen 2011

Lng IUD: What’s New?

Look for smaller version of the Lng IUD
Greater use of post-placental placement of IUDs

Immediate Post-placental Placement of IUDs

Safe, effective
Expulsion rates appear higher than interval placements
Early F/U to identify expulsions
Grimes Cochrane Database Syst Rev. 2010
No increase in excessive bleeding or endometritis Welkovic Contraception. 2001
Broader Use of Cu IUD

- Immediate post abortion (copper) IUD insertion is safe. Can decrease repeat unintended pregnancy and decrease repeat abortion by two-thirds!
- Higher expulsion rates: typical rate 1-3%, post abortion rate: 5-6%

Grimes 2004, Goodman 2008

Broader Use of Lng IUD

- Nulliparous women & adolescents (smaller IUCs will be available)
- With previous history of PID
Levonorgestrel (Lng) IUD: Treatment of:
  - idiopathic menorrhagia (19)(20)(29) and pelvic pain due to endometriosis (15)(17)(18) or adenomyosis (14) or dysmenorrhea (14)(20) chronic pelvic pain (16) protection against ectopic pregnancy Naz 2011 and for HRT


Offer LARC Contraceptives Immediately Post Abortion

Data: Having a previous abortion does not deter future abortions.
Women are more likely to choose IUD or implant if offered immediately post abortion compared with women without Hx of recent AB. Offer LARC methods IMMEDIATELY post AB…don’t wait for another visit!

In clinic: Candidates for IUDs should have them placed on same day visit

Broader Use of Lng IUD

- Prevent iron deficiency anemia
- Endometrial polyp & fibroid protection for women using tamoxifen. In lieu of endometrial ablation for uterine bleeding and an alternative to hysterectomy
- Menopausal women- inhibit hyperplasia with estrogen therapy (a smaller version of the Lng IUD is in progress)
- Immediate postpartum & post abortion- regardless of lactation status


Lng IUC as Therapy for Endometriosis?

- Prospective, non-randomized 12 month VERY SMALL STUDY
N=11 symptomatic women with endometriosis: recto-vaginal septum
Pelvic pain, deep dyspareunia, dysmenorrhea greatly improved. Size of endometriomas significantly reduced per TVUS

Fedele 2001

Lng IUD: Endometrial Protection with Tamoxifen & ERT

- 122 postmen-1 yr tamoxifen use- randomized to endometrial surveillance or Lng IUD with surveillance x 12 months
- Baseline-all women showed only benign changes
- Lng IUD-protective against tamoxifen, initial bleeding resolved, no new polyps, 13% fewer fibroids
- Lng IUD may be used with ERT to inhibit hyperplasia

Gardner 2009, Wan 2011
Cu and Lng IUDs Lower Risk of Endometrial Cancer
OFF LABEL
Mechanism of action of Cu IUD unknown; may be related to alteration in endometrium & preferred for recent breast cancer; Lng IUD is used with tamoxifen tx
Lng IUD prevents endometrial hyperplasia in peri & post menop women on estrogen and used in tx of non-atypical hyperplasia
May be effective for atypical hyperplasia, and 1I endometrial cancer as well.
Contraceptive Tech 2011

IUDs may lower cervical cancer risk
May reduce risk of cervical cancer by 45%
Protective affect occurred in 1st year and continued up to 10 yrs (>15,000 women)
Squamous cell ca reduced by 44%
Adenosquamous risk reduced by 54%

Lng IUD: Treatment for Menorrhagia and HRT
Systematic review: Lng IUD use for menorrhagia- 9 studies showed statistically significant reduction in blood loss (74% to 97%)
- 1 study- 64% women with menorrhagia (given Lng IUD) cancelled surgery vs 14% of controls
- Acceptance and continuation of Lng IUD for HRT has been high
Stewart 2001, Luukkainen 2000

Risk of PID Reduced with IUDs
- RCT: PID rates in Lng IUD vs. Nova-T (Cu)
  Salpingitis significantly lower in Lng IUD vs. Nova-T users at 3 and 5 yrs.
  7 yr randomized study, PID rates did not differ between devices and mild to marked increases in hemoglobin levels occurred in users of BOTH IUDs AND...Continuation rates were similar: 29.4% for the CuT380A IUD and 24.9% for the Lng IUD

IUD’s, Implant: Duration of Efficacy
Lng IUD, approved duration-5 yrs, some studies show efficacy to 7 yrs
Implant approved for 3 yrs; but stable concentrations of etonogestrel up to 36 months
OFF LABEL

PAIN MANAGEMENT FOR IUD PLACEMENT
Pain Management for IUC Placements

Paracervical block (PCB) generally not indicated; may not reduce overall pain
May be useful for difficult placements or cervical dilation. PCB is used for ALL IUC placements in Finland.

Paracervical Anesthetic Block

Anatomy: Cervical nerve innervations from Lee-Frankenhäuser plexus, located lateral to the junction of the cervix and uterus. Sensation is carried to the spinal cord at the T10-T12 and L1 segmental nerves.

Paracervical Block (PCB) for IUC Placement or Difficult Removal

- Have adequate visibility of cervix. Lift cervix with tenaculum and apply anesthetic gel to injection sites
- Use a needle extender to reach the cervix

Continued...
**Paracervical Anesthetic Block Cont...**

- At each site the needle depth should only be 2-3 mm; just cover the bevel of the needle in the tissue
- Avoid uterine arteries at 3:00 and 9:00
- Use sites 4:00 OR 5:00 and 7:00 OR 9:00
- Prior to instillation, ASPIRATE to assure the needle is not in a vessel.

**Paracervical Anesthetic Block Cont...**

- As you slowly instill 1% lidocaine **NO** epinephrine, the area around the needle tip will blanch; a good sign. There is resistance with the injection and often two thumbs are needed for instillation.

**Cont... Paracervical Anesthetic Block**

- Watch the lower vagina to assure the lidocaine is not pooling...this means the needle bevel is not covered & lidocaine is leaking. If this occurs, advance the needle slightly, ASPIRATE TO ASSURE NOT IN VESSEAL, THEN CONTINUE WITH THE INSTILLSTION.
- Wait 10 min for full anesthetic effect

**PCB Complications are Very Rare**

- Hypersensitivity to lidocaine (ask about allergies)
- Bleeding from injection sites (usually very minor)
- Infection (very rare)

**Etonogestrel Progestin Implant (Nexplanon replaces Implanon)**

- Flexible, white ethylene vinyl acetate rod with 68 mg etonogestrel, subdermal implant 4 cm x 2 mm
- Action: Inhibits ovulation
- Effective for 3 years. Releases 60-70 mcg/day in 1st-2 yrs, then 25-30 mcg in 3rd yr. of use
- Inserted subdermally between the biceps and triceps muscles
- Now radio-opaque (visible on X-ray or CT scan) and new inserter
- Must be inserted and removed only by clinicians completing a training program
**Does Etonogestrel (ETG) Implant Effect Carbohydrate Metabolism?**

ETG Implant does not affect carbohydrate metabolism after 12 months in healthy women. Use of low dose combined OC’s may cause slight insulin resistance & rise in fasting insulin levels, however glucose levels are unchanged or reduced. Non-randomized, open label, prospective controlled trial. N=40

Oderich 2012

**Cervical Neoplasia and Contraception**

Condoms marginally effective at preventing abnormal cytology by preventing HR-HPV or persistence of HPV. Hormonal contraceptives may increase HPV acquisition, but risk not as great as that of women with high parity.

Curry 2012, Nelson 2011

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**Do COCs Impact HIV Acquisition?**

**NO**

HIV uninfected women using either COCs or injectable progestins were not at any significantly increased risk for acquiring HIV compared with women who used other non-barrier methods. Contraceptive Technology 2011

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**Update to USMEC 6/22/12**

<table>
<thead>
<tr>
<th>Condition</th>
<th>COC/P/R</th>
<th>POP</th>
<th>DMPA</th>
<th>Implants</th>
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<tbody>
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<td>HIV infection</td>
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</tr>
<tr>
<td>AIDS</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

CDC 2012

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**Depo-medroxyprogesterone acetate (DepoProvera®)**

- Questionable link with epithelial ovarian cancer in premenopausal women according to WHI? WHO Collaborative Study Neoplasia Steroid Contraceptive Lancet 1991
  
  Probably not.

- May actually have a protective effect against according to Women’s CARE Study (CDC)

- Breast cancer is rare among premenopausal women. Strom Contraception 2004

---

**What’s Else is New in Women’s Contraception?**
**Newest Progestin: In Clinical Trials: Nestorone**
- Nestorone similar to progesterone
- Population Council: in clinical trials as an intra-vaginal ring (2 1/4 inches)
- Also evaluated as transdermal metered dose spray and gel
- May be efficacious for men when used with testosterone

(36) 2010 (37) 2007

**MANAGING SPOTTING AND BLEEDING WITH CONTRACEPTIVE METHODS**

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**Managing Challenging Idiopathic Spotting-Bleeding with Implant**

RCT: effect of mifepristone with EE on ovulatory function in women with Implanon®
Mifepristone 25 mg bid with EE 20 mcg q d x 2-5 days
Would this regimen work as well with IUD idiopathic bleeding? No data

Weisberg 2011

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**Managing Challenging Idiopathic Spotting-Bleeding with Hormonal Contraceptives**

Cont...
Continuous use, no pill free interval
Spotting or light bleeding (short-term treatment): Nonsteroidal anti-inflammatory drugs (NSAIDS) Ibuprofen 600-800 mg qd x 5 days
- Mefenamic acid (Ponstel®)
- Doxycycline 100 mg bid x 1-2 wks
- Heavy-prolonged bleeding
  - NSAIDS
  - Hormonal: Ethinyl estradiol or add CHC

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**Cont...Managing Challenging Idiopathic Spotting-Bleeding with Hormonal Contraceptives**
- Tranexamic acid (Lysteda®) synthetic derivative of lysine. Antifibrinolytic-inhibits activation plasminogen to plasmin: prevents degradation of fibrin; inhibits endometrial plasminogen activator; prevents break down of clots
- Dose: 1,300 mg (two 650 mg tabs) tid for max. 5 days during menses.
Consider as second line treatment to Lng IUD for treatment of heavy menstrual bleeding Naz 2011

---

**Effects of hormonal contraception on vaginal flora**

Compared to COC’s, contraceptive vaginal ring showed an increase in the number of lactobacilli in vaginal flora...this could be protective.

Health Benefits of Contraception

All methods of contraception are safer than pregnancy!

Health Benefits of Combined Oral Contraceptives

Protects against ovarian, endometrial cancer and possibly colorectal carcinoma
Decreases dysmenorrhea, menorrhagia, anemia, cyclic mood problems (PMS), protects against ectopic pregnancy and symptomatic PID
AND…reduces acne…and as an aside…it reduces death.

Maguire 2011

Health Benefits of Progestin-Only Pill and Lng IUD

POP: Lactation not disturbed (Cat 2 MEC)
Lng IUD: decreases menstrual blood loss, menorrhagia, PID, endometriomas, adenomyosis, endometrial hyperplasia, polyps, chronic pelvic pain, fibroids, provides progestin for HRT and reduces endometrial polyps in women using tamoxifen

Fraser 2010

Health Benefits of Medroxyprogesterone acetate

Fewer seizures
Fewer sickle cell crises
Decreased pain from endometriosis
Reduced risk ectopic
Decreased risk pelvic inflammatory disease (PID)
No estrogen
Benefits women with myomas

AND

Emergency Contraception: What’s New: Ulipristal acetate “ELLA”

Progestosterone receptor modulator
More effective than Lng EC on days 4-5 postcoital Dose: 30 mg
Advise to abstain or use a barrier method to end of current menstrual cycle.
HA (18%)
Abdominal pain (12%)
Nausea (12%)
R/O ectopic

Contraceptive technology Update 5/2010, CDC 2010
**Contraception for Women with Cancers**

- Copper T380A IUD first line for women with history of hormonally mediated cancer
- Lng IUD preferable in women using tamoxifen, or have non-hormonally mediated cancers.
- Women with IUD’s can undergo CT and MI imaging

**Cancers and Contraception**

- Breast: benign disease and family history of cancer-all methods acceptable
- Current Breast Cancer: all category 4, except Cu IUD is 1
- Past breast cancer and no evidence of current disease for 5 yrs: all category 3, except Cu IUD is 1

**Cervical Cancer and Contraception**

- Cervical cancer awaiting treatment:
  - CHC, P/R: 2; POP: 1
  - DMPA; ETG Implant: 2
  - Cu and Lng IUDs: Initiation-4, Continuation-2
- CIN: same as above, except Cu IUD is 1 and Lng IUD is 2

**“Quick Start” and Combined Hormonal Contraceptives**

- Conventional OC initiation may delay start for several weeks.
  - Applicable to Pills, Patch, Ring, DMPA, IUD insertion, Implant
  - Advise backup method first 7 days

**DMPA Initiation or Late Injections**

- Use a backup method for first 7 days post injection to allow time for cervical mucus to thicken to inhibit sperm motility.

**CONTRACEPTION FOR MEN:**

WHAT’S NEW OVER THE RAINBOW?

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Men’s Use of Contraception

In 2002 male methods accounted for 32% of contraceptive use in the U.S.
Vasectomy 9%
Condom use: 18%
Withdrawal: 4%
Periodic abstinence: 1%
Darroch 2008

Transdermal Gel for Male Contraception?

- Population Council and National Institute of Health are working on Nestorone gel combined with a testosterone gel for male contraception

Contraceptive Transdermal Gel for MEN

Testosterone transdermal gel with nestorone 8mg significantly reduced sperm concentration to 1 million/mL or less after a 20 wk tx
Testosterone levels were maintained within adult range in the men. Adverse events: minimal

Contraception for Men

- Let men know that hormonal contraceptives are over the horizon!
- Discuss effective methods their partner can use & help with cost
- Cu IUD EC with men
- Discuss state paternity laws with men for their protection

Male Contraception: Where are we at?

Progestins (cyproterone, etonogestrel) also suppress gonadotropins and work synergistically with testosterone.
- Studies on-going.
Amory 2008

Male Contraception: The Challenges

- Goal: Reducing sperm count to low enough levels to ensure infertility. Recent studies have reduced counts to 1 million sperm per mL in ~80-90% of subjects. Testosterone therapies involve injections or implants along with progestins.
- Side effects: weight gain, mood changes, acne, sweating, libido change.
Mommers 2008
Male Contraception: New Possibilities?

No new male contraceptives have emerged in the past century...but that's changing!

- RISUG (Vasalgel™): reversible inhibition of sperm under guidance (not yet approved)
  1. Polymer gel coats vas deferens lumen-kills sperm & blocks lumen.
  2. Flushing vas with dimethyl sulfoxide (DMSO) or sodium bicarbonate solution to reverse

Tulsiani 2010, Male Contraception Information Project

Male Contraception: Is Ultrasound (US) Promising?

US treatments to inhibit spermatogenesis. Post US sperm counts in dogs showed no sperm. US intensity is that used by physical therapists to treat injuries. 15 min treatment has 4-6 mos contraceptive effect. The transducer is placed directly on testes; painless.

Gates Foundation is funding FHI

Male Contraception Information Project

Vasectomies

Can nurse practitioners perform vasectomies? YES!

Both scalpel and Non-scalpel vasectomies:
Less bleeding
Less infection

Male Contraception Information Project

Hormonal Contraception.... Progestins, Progestins, Progestins

1st Generation Progestins

- Estranes
  - Norethindrone
  - Norethindrone acetate
  - Ethynodiol diacetate
  - Lynestrenol (not in US)
  - Norethynodrel (not in US)

2nd Generation Progestins

Gonanes

- Norgestrel
- Levonorgestrel

More potent, longer half-lives, more androgenic activity: avoid in those with hirsutism, acne, dyslipidemia
### 3rd Generation Progestins

- Desogestrel
- Norgestimate
- Gestodene (not in US)

Less androgenic activity, allows greater expression of estrogens. Significant increase in SHBG

Labeling: For cystic acne

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### 4th Generation Progestin

- Drospirenone…parent drug is spironolactone, a potassium sparing diuretic
- Low androgenicity

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### Abbreviations

- BCM: birth control method
- OC: oral contraceptive
- OCP: oral contraceptive pills
- DMPA: depot medroxyprogesterone acetate
- BTL: bilateral tubal ligation
- VTE: venous thromboembolism
- IUD: intrauterine device
- IUC: intrauterine contraceptive
- Lng IUD: levonorgestrel intrauterine device
- Cu IUD: copper IUD
- BMD: bone mineral density

### Abbreviations

- SHBG: sex hormone binding globulin
- CHC: combined hormonal contraceptives
- STI: sexually transmitted infection
- ETG: etonogestrel
- NET-EN: norethindrone enanthate
- DVT: deep vein thrombosis
- PE: pulmonary emboli
- CDC MEC: Centers for Disease Control Contraceptive Medical Eligibility Criteria

### References

Heit JA, Kobbervig CE, James AH, Petterson TM, Bailey KR, 

Fraser IS et al. Non-contraceptive benefits of intrauterine hormonal systems. 2010 Contraception (82) 396-403.


Grigoryan OR et al. Use of the NuvaRing hormone-releasing system in late reproductive-age women with type 1 diabetes mellitus. Gynecol Endocrinol 2008 Feb;24(2):99-104.


Gronich N, Lavi I, Rennert G. Higher risk of venous thrombosis associated with drospirenone-containing oral contraceptives: Final results from the European Active Surveillance Study (EURAS) on oral contraceptives based on 142,475 women-years of observation. Contraception 2007;75:334-54.


Grigoryan OR et al. Use of the NuvaRing hormone-releasing system in late reproductive-age women with type 1 diabetes mellitus. Gynecol Endocrinol 2008 Feb;24(2):99-104.


References


References

MEGA data analysis
Multiple Environmental and Genetic Assessment of Risk Factors for Venous Thrombosis Study

Case control study
Analysis of data collected for thrombosis risk men and women
Patients at anticoagulation clinics in Netherlands 1999-2004
Analysis included women only 18-50 years
1524 patients 1760 controls (40.5% were “partners” of patients others random phone contacts)
van Hylckama Vlieg 2009

Lidegaard Re-analysis
Lidegaard 2011
Reanalysis and time extension of Danish retrospective cohort study of national database hospital discharge and prescriptions 2001-2009—8,010,290 woman-years
DVT events compared to levonorgestrel + 30-40 mcg of EE:

<table>
<thead>
<tr>
<th>Comparison groups</th>
<th>events</th>
<th>RR</th>
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</thead>
<tbody>
<tr>
<td>Drospirenone + 30 μg EE</td>
<td>196 v 123</td>
<td>2.12 (1.68 to 2.66)</td>
</tr>
<tr>
<td>Desogestrel + 30 μg EE</td>
<td>168 v 123</td>
<td>2.20 (1.74 to 2.77)</td>
</tr>
<tr>
<td>Gestodene + 30 μg EE</td>
<td>575 v 123</td>
<td>2.07 (1.70 to 2.52)</td>
</tr>
</tbody>
</table>

Estimates that 2000 women would need to switch to OC with levonorgestrel to prevent 1 venous thrombosis a year

Jick Pharmetrics US Drug Database

VTE data from prescription and insurance code database women 15-44 yo 2002-2008
Nested case-control and cohort study
Comparison of COC’s with drospirenone vs levonorgestrel
OR 2.3 (1.6-3.2)
Incidence rate 3.1/10,000 yr vs 1.3/10,000 yr
Age adjusted RR 2.8 (2.1-3.8)
Jick 2011

Parkin UK General Practice Database

Nested case control study 61 cases
Database from general practice records 2001-2009 --women 12-44 starting a new course of COC
COC’s containing 30 mcg estrogen and drospirenone vs levonorgestrel
OR 3.3 (1.4-7.6) adjusted for BMI
Incidence 3.1 vs 0.9 cases per 10,000 woman years
IRR 2.7 (1.5-4.7) age adjusted
Parkin 2011

Israeli Health Provider Study

Retrospective cohort study
Databases of a health care provider in Israel 819,749 woman-years
COC’s with Drospirenone vs second generation (norgestrel, levonorgestrel) progestins
DVT/PE RR 1.43 (1.15-1.78)
COC’s with Drospirenone vs third generation (desogestrel, gestodene, norgestimate) progestin
DVT/PE RR 1.65 (1.02-1.78)
No increase RR for arterial thrombosis
Gronich 2011
Progestins ALONE have NO impact on clotting system

BUT when some progestins are combined with estrogen they can modulate the strength of estrogens production of extrinsic clotting factors (antithrombin, fibrinolytics)

Pills with 3rd generation progestins (desogestrel & gestodene) assoc with 2-fold risk VTE compared with 2nd generation progestins (Lng & norgestrel)

Nelson 2011