Who Needs Estrogen? An Update on Progestin-Only Contraception

Patty Cason MS, FNP-BC
Envision SRH
Envisionsrh.com
patty@envisionsrh.com

Objectives

- List 2 contraindications to progestin-only contraceptives
- Discuss use of progestin-only contraceptives during breastfeeding
- Prescribe therapies for unscheduled bleeding

Etonogestrel Contraceptive Implant

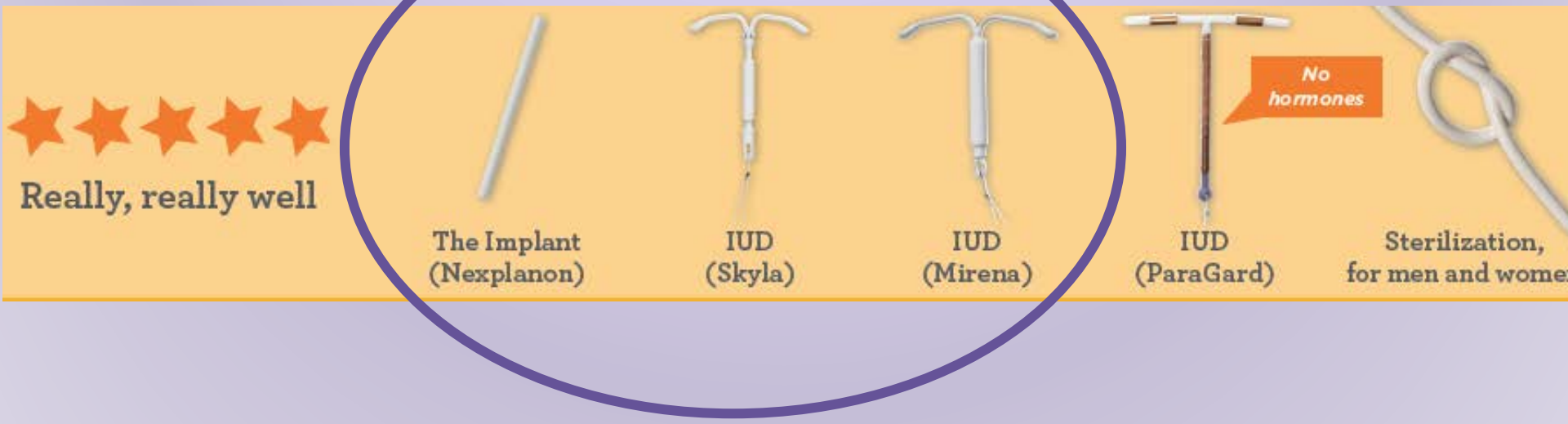
Levonorgestrel IUDs (LNG IUD)

Depot Medroxyprogesterone Acetate (DMPA)

Progestin-Only pills/ The mini pill (POP)

PRIMER ON METHODS

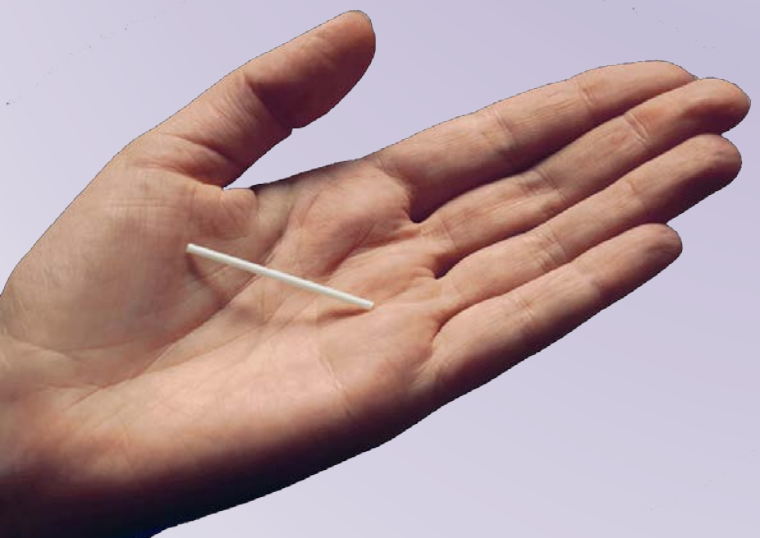
TOP TIER



<1% failure

Single-rod Etonogestrel (ENG) Contraceptive Implant Nexplanon®

- Most effective method
- Suppression of ovulation
- Thickens cervical mucus

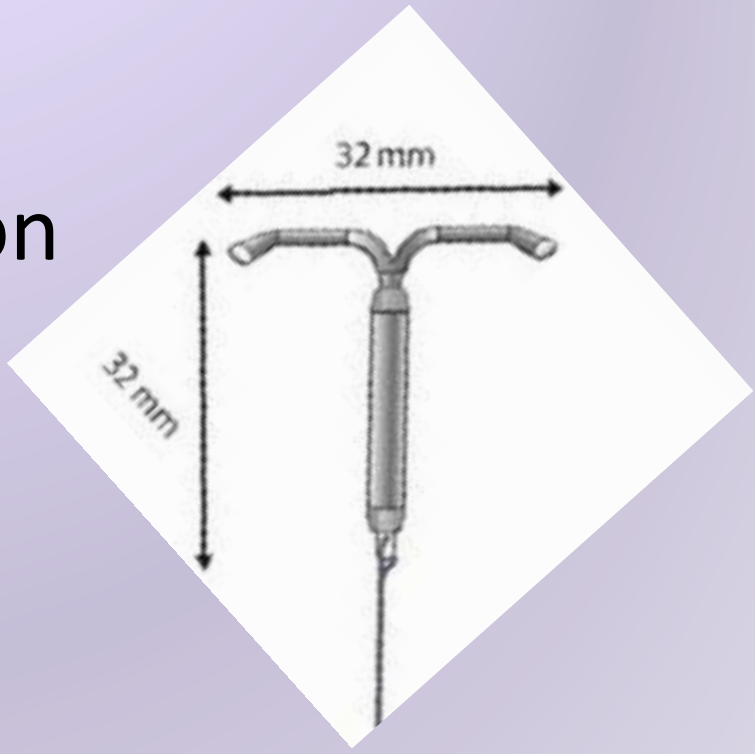


Moderate progestin dose not associated with a hypo-estrogenic state

(Darney, Patel et al. 2009)

LNG IUDs Mechanism of Action

- Cervical mucus thickened
- Sperm motility and function inhibited
- Alterations in ovulation



(Jonsson, Landgren et al. 1991; Lewis, Taylor et al. 2010; Natavio, Taylor et al. 2013; Ortiz, Croxatto 2007; Rivera, Yacobson et al. 1999; Stanford, Mikolajczyk 2002; Videla-Rivero et al. 1987)

Levonorgestrel 52 IUDs: Ovulatory Effects

- 93% of the cycles were ovulatory but just 58% of these 'ovulatory' cycles showed normal follicular growth and rupture.

- Ovulation 63% of amenorreic group; 58% in regularly menstruating group

(Barbosa, Olsson et al. 1995; Nilsson, Lahteenmaki et al. 1984)

Second Tier
DMPA and Progestin Only Pills (POP)

Progestin Only Pills (POP)

POP Mechanism of Action

- Cervical mucus thickened
- Some ovulation inhibition
- Endometrium altered
- Cilia action in fallopian tube hindered

POPs

- Taken continuously--no placebo pills
- Given to lactating women postpartum because not thought to interfere with lactation
- Used for women with contraindications to use of EE

Safety

Effectiveness

Side effects and non-contraceptive benefits

SAFETY

Category 4
All Hormonal Methods

Current breast cancer

Category 3
All Hormonal Methods

History of breast cancer 5 years NED

Category 3 DMPA

- Multiple risk factors for cardiovascular disease
- Blood pressure ≥ 160/100
- Vascular disease
- Stroke
- Current or history of ischemic heart disease

Category 3 DMPA

- Severe thrombocytopenia
- Antiphospholipid Antibodies
- Diabetes with nephropathy, retinopathy or neuropathy or > 20 years
- Long-term corticosteroid therapy with a history of, or with risk factors for, non-traumatic fractures

Category 3 POP, Implant, LNG IUD

- Antiphospholipid Antibodies
- Severe decompensated cirrhosis
- Hepatocellular adenoma
- Malignant (hepatoma)
- Current and history of ischemic heart disease (continuation)

DMPA Risk of HIV Acquisition

- Concern about increased risk of HIV acquisition in populations with high prevalence of HIV
- Systematic review:
  - possible increased with RR 1.4
  - some methodologic concerns with individual studies

(Polis, Curtis et al. 2016)

DMPA and Risk of HIV Acquisition?

- Injectable progestin possible ↑ risk

9 studies:

  - 3 showed a significant ↑ risk
  - 5 showed no significant increase in risk

- Methodological issues or biological effect??

No data suggesting an ↑ risk with use of POP, implant or LNG IUD

DMPA and HIV

"Biologically plausible" effect from:

- hormonally mediated changes in vaginal epithelium
- alterations in local and systemic immune responses

(Polis, Curtis et al. 2016)

DMPA and HIV US MEC

- Category changed from 1 → 2 in 2017

- Change is meant to encourage more discussion with patients at high risk for HIV acquisition and to discuss preventive measures (condoms, PrEP, limiting sexual partners) rather than restricting access to DMPA

Progestin-only Contraception and Depression?

JAMA Psychiatry | Original Investigation

Association of Hormonal Contraception With Depression

Charlotte Wessel Skovlund, MSc; Lina Steinrud Mørch, PhD; Lars Vedel Kessing, MD, DMSc; Øjvind Lidegaard, MD, DMSc

(Skovlund, Morch et al. 2016)

What about depression?

- Danish database study of > 1 million women age 15 to 34 years followed over 6 years, 56% used hormonal contraception
- Women excluded with preexisting depression/antidepressant use, pregnancy and 6 months postpartum
- Controlled for age, smoking, PCOS and endometriosis

Small Increased RR

- RR for first use of an antidepressant based on prescription records.
  - POPs: 1.3
  - LNG-IUD: 1.4
  - DMPA: 2.7
- Risk peaked at 6 months then declined
- Strongest association among adolescents

Limitations

- Not randomized
- Small RR (weak association)
- Cannot assume causation
- Other confounding factors (sexual activity, relationships) or other bias (detection bias) not taken into account

Systematic Review: Depression and Progestin-only Contraception

Contents lists available at ScienceDirect

Contraception

journal homepage: www.elsevier.com/locate/con

Review article

The relationship between progestin hormonal contraception and depression: a systematic review

Brett L. Worly [a,b,*], Tamar L. Gur [a,b,c,d], Jonathan Schaffir [a]

[a] Department of Obstetrics & Gynecology, The Ohio State University, Columbus, OH
[b] Dept of Psychiatry & Behavioral Health, The Ohio State University, Columbus, OH
[c] Dept of Neuroscience, The Ohio State University, Columbus, OH
[d] Institute for Behavioral Medicine Research, Wexner Medical Center at The Ohio State University, Columbus, OH

(Worly, Gur et al. 2018)

Systematic Review

- A minority of progestin-only contraception users may experience depression symptoms
- The most robust studies show no association
- DMPA: rare, 3-6 mos to manifest
  - 3 prospective trials (validated surveys) show no depression effects & 1 shows a decrease in depression scores.

Systematic Review

Additional research needed to evaluate the magnitude and causality of progestin-induced depression effects before additional recommendations can be made

- Randomized controlled trials
- validated measures

All methods are USMEC Category 1

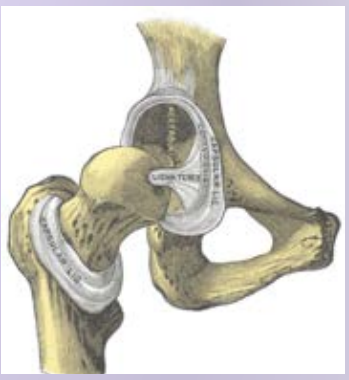
DMPA and Weight Gain

- Most DMPA users who gain excessive weight, gain ≥ 5% within 6 months.

- We can use this information to predict who is at risk of excessive gain and counsel them appropriately

(Bonny, Secic et al. 2011; dos Santos Pde, Modesto et al. 2014; Le, Rahman et al. 2009; Lopez, Ramesh et al. 2016; Pantoja, Medeiros et al. 2010; Risser, Gedter et al. 1999)

DMPA and Bone



No need for DEXA scans, limit on use, or estrogen supplementation.

	< 18 years	18-45 years
US MEC Category	2	1

DMPA and Bone

Lanza et al. retrospective cohort study:

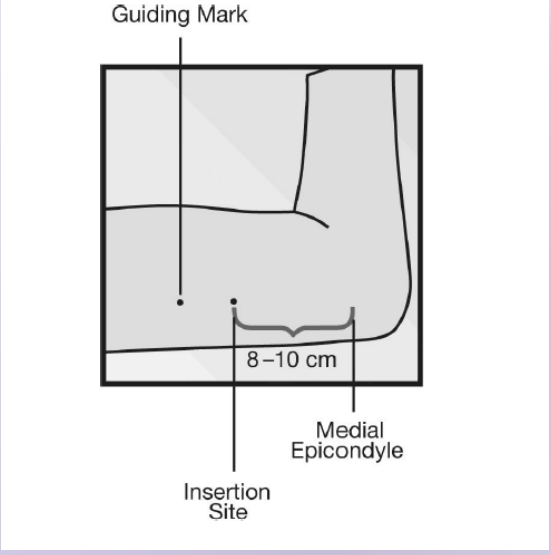
"although ever users of DMPA had OR 1.44 for fracture, elevated risk was present *prior* to using DMPA."

Population using DMPA at baseline different than population that does not.

(Lanza, McQuay et al. 2013)

Formal (Merck) training for insertion/removal required

Migration of Implant



N=38 cases of migration:

- lung/pulmonary artery (n=9)
- chest wall (n=1),
- vasculature at locations other than the lung/pulmonary artery (n=14)
- extravascular migrations (n=14) to other body sites (e.g., the axilla and clavicle/neck line/shoulder)

(Kang, Niak et al. 2017)

1.3 Migrations per Million Placements

- 7 cases reported pain, discomfort, dyspnea
- 3 cases describe pulmonary fibrosis and skin reactions from migration to the vasculature, chest wall and other distant body sites
- 16 cases reported surgical removal in an operating room setting

(Kang, Niak et al. 2017)

Clinicians are now advised
to avoid placement in the biceps groove,
no matter how superficial that placement might be.

Place over the triceps

(Rowland, Mansour et al. 2017)

Hormone Effect on Anti-epileptic Drugs (AEDs)

- Only EE affects the metabolism of AEDs.
- There is no convincing data suggesting any clinically relevant effect on the metabolism of lamotrigine or any other AED from progestins

(POP, implants, DMPA injections, hormonal IUDs, emergency contraception pill)

(Reimbers 2016)

PROGESTIN-ONLY CONTRACEPTIVES AND LACTATION

Contraceptive steroids in milk

- Theoretic concern about effect on neonatal liver, brain, and sex organs
- No data has shown any measurable effect on children
- Amount transferred to milk is low:
  - 0.1% levonorgestrel IUD
  - 2.6-3.7% etonogestrel

Implant and Lactation

- Started 4 weeks PP: no effect on duration of lactation, milk composition, or infant weight and development
- Immediate postpartum: 2 studies show no effect on onset of lactation and infant weight gain

	< 6 weeks	≥ 6 weeks
US MEC Category	2	1

DMPA and Lactation

Early initiation prior to hospital discharge has not been shown to affect breastfeeding continuation or supplementation in observational studies

	< 6 weeks	≥ 6 weeks
US MEC Category	2	1

POPs and Lactation

- No effect on initiation or duration of lactation or infant weight or development
- Studies ranged from starting prior to hospital discharge to 6 weeks postpartum

	< 6 weeks	≥ 6 weeks
US MEC Category	2	1

CDC Review on Progestin-only Contraception

US MEC
US SPR

- Systematic review of 47 studies
- No adverse effects on breastfeeding outcomes or deleterious effects on infants; restricted growth, health problems, or impaired development
- Largely consistent with previous evidence

(Phillips, Tepper et al. 2016)

Caveat per USMEC
High Risk For Breastfeeding Difficulties

- Previous breastfeeding difficulties
- Certain medical conditions, and perinatal complications
- Those who deliver preterm
- SDM; risks, benefits, and alternatives.

Safety

Effectiveness

Side effects and non-contraceptive benefits

EFFECTIVENESS

Quickstarting Hormonal Contraception After UPA

*"After using ella, if a woman wishes to use **hormonal contraception**, she should do so **no sooner than 5 days after the intake of ella**, and she should use a reliable barrier method until the next menstrual period."*

FDA change to ella label (March 2015)

TOP TIER

0-1 pregnancy per 1000 users

Implant 11 Clinical Trials

- No pregnancies reported while the implants were in place

- Six pregnancies occurred during the first 14 days after ENG implant removal

(Darney, Patel et al. 2009)

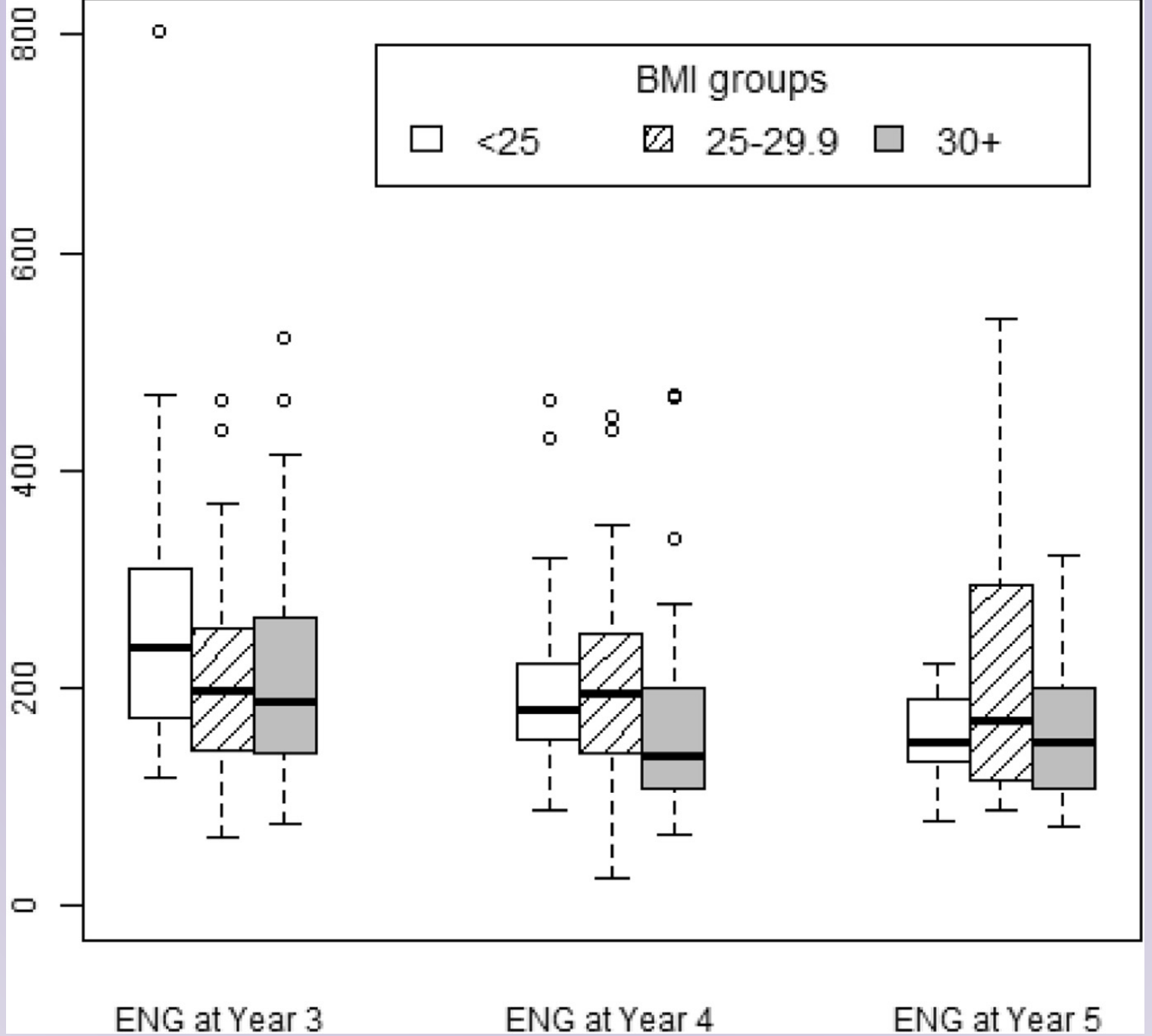
Is the Implant Effective in Obese People?

- Package insert states:

"No Studies in women >130% of their ideal body weight"

- Highly effective even among obese women

(Lopez, Bernholc et al. 2016; Mornar, Chan et al. 2012; Morrell, Cremers et al. 2016; Xu, Wade et al. 2012



(McNicholas, Swor et al. 2017)

Second Tier

Pretty well
The Pill
The Patch
The Ring
The Shot
For it to work best, use it...
Every. Single. Day.
Every week
Every month
Every 3 months

POP Vulnerable efficacy?

- Available only as 0.35 mg norethindrone in the U.S.
- By 24 hours after administration, serum steroid levels are near baseline
  - Based on drug levels, > 3 hours late is considered a “missed” pill
  - No clinical evidence available

St John's Wort

St. John's Wort likely increases the clearance and alters the bioavailability of norethindrone

- 15% reduction in "dose exposure"
- Increased breakthrough bleeding

(Murphy, Kern et al. 2005)

Drug-drug Interactions
Category 3 POP Category 2 implant

- Certain enzyme inducing anticonvulsants
  - phenytoin, carbamazepine, barbiturates, primidone, topiramate, oxcarbazepine
- Antimicrobials (ALL OTHERS OK)
  - rifampicin or rifabutin

(Simmons, Haddad et al. 2017; Simmons, Haddad et al. 2018)

Enzyme Inducing Anti-Epileptic Drugs (AEDs)

Generic name	Brand	P reduction
Carbamazepine	Tegretol ®	58%
Felbamate	Felbatol ®	42%
Oxcarbazine	Trileptal®	32%
Phenytoin	Dilantin ®	42%
Topiramate	Topamax ®	None
Phenobarbital	generic	None

(Thorneycroft, Klein 2006; O'Brien, Guillebaud 2006; Zupanc 2006)

NOT Inducers of Hepatic Enzymes

Generic name	Brand name
Ethosuximide	Zarontin
Levetiracetam	Keppra
Tiagabine	Gabitril
Valproic acid	Depakote
Vigabatrin	Sabril
Zonisamide	Zonegran
Clonazepam	Klonopin
Pregabalin	Lyrica

(Thorneycroft, Klein 2006; O'Brien, Guillebaud 2006; Zupanc 2006)

Antiretroviral Therapy Category 2 POP, implant

- Non-nucleoside reverse transcriptase inhibitors
  - Efavirenz (EFV)
- Ritonavir-boosted protease inhibitors (Pls)
  - Ritonavir-boosted ataznavir (ATV/r)
  - Ritonavir-boosted darunavir (DRV/r)
  - fosemprenavir (FPV/r)
  - saquinavir (SQV/r)
  - tipranavir
- Protease inhibitors without ritonavir
  - Fosamprenavir (FPV)
  - Nelfinavir (NFV)

(Patel, Morroni et al. 2017)

HIV Medications Category 2

4 pharmacokinetic studies that show 50–70% reductions in plasma progestin concentrations in women concurrently using efavirenz-based ART as compared to women not on any ART

(Patel, Morroni et al. 2017)

HIV Medications Category 2

- Observational study from Kenya
  - implants + efavirenz-based ART had 3X ↑ risk of pregnancy than implants + nevirapine-based
- The pregnancy rates when using the implant + efavirenz still lower than in those using alternative methods (injectables)

(Patel, Morroni et al. 2017)

Safety

Effectiveness

Side effects and non-contraceptive benefits

SIDE EFFECTS AND NON-CONTRACEPTIVE BENEFITS

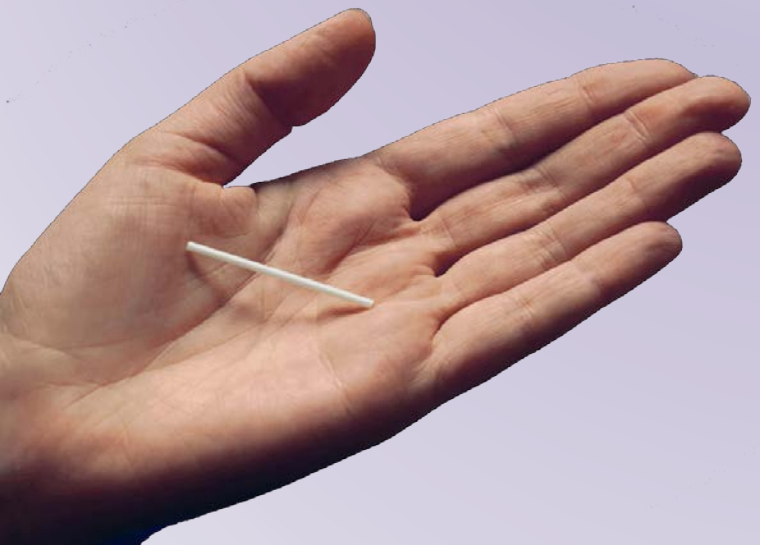
Best Question

"Do you have a sense of what is important to you in your birth control method?"

(Dehlendorf, Henderson et al. 2016)

Implant and DMPA Non-Contraceptive Benefits

- Reliable ovulation suppression
- Decreased dysmenorrhea
- Likely reduction in risk of endometrial cancer and ovarian cancer



LNG 52
Non-contraceptive Benefits

- Decreased
  - –Heavy menstrual bleeding
  - –Dysmenorrhea
  - –Iron deficiency anemia
  - –Long term risk of endometrial cancer
- Can be left in place during and after transition to menopause for use with ET

(Sitruk-Ware 2007)

LNG 52 IUD
Additional Therapeutic Uses

- Endometrial hyperplasia
- Symptomatic endometriosis, adenomyosis
- Decreased bleeding from symptomatic fibroids

(ACOG Practice Bulletin 2014; Bragheto, Caserta et al. 2007; Chan, Tam et al. 2007; Cho, Nam et al. 2008; Fraser 2013; Haimovich, Checa et al. 2008; Heikinheimo and Gemzell-Danielsson 2012; Kaunitz 2007; Kaunitz, Bissonnette et al. 2012; Matteson, Rahn et al. 2013; Soysal, Soysal 2005; Sturdee 2006; Varila, Wahlstrom et al. 2001; Varma, Sinha et al. 2006; Varma, Soneja et al. 2008; Wildemeersch 2016; Wong, Chan et al. 2013)

DMPA Non-Contraceptive Benefits

- Adjunctive therapy and palliative tx of inoperable, recurrent and metastatic endometrial or renal carcinoma
- Endometriosis

Does DMPA Decrease Seizures?

- N=14
- 10 mg MPA 2-4 X/day →120-150 mg DMPA IM q. 6-12 weeks
- Significant reduction in seizure activity
- Associated with amenorrhea

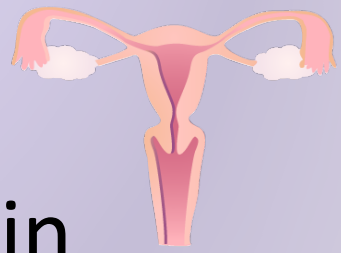
(Mattson, Cramer et al. 1984)

DMPA Return to Fertility Precaution

- May not return to ovulation, menstruation or fertility for > 1 year
- Regardless of the length of use

PROGESTIN ONLY CONTRACEPTIVES AND UNSCHEDULED BLEEDING

Unscheduled Bleeding with Progestin-Only Contraceptives



- Etiology poorly understood
- Depends on dose/route of progestin
- Initially due to rapid endometrial thinning caused by progestin
- Sustained exposure may lead to endometrial instability and atrophy leading to fragile endometrium that bleeds easily

(Zigler, McNicholas 2017)

It Just Gets Better and Better…

Decreased bleeding with placement of subsequent LNG IUD

(Heikinheimo, Inki et al. 2014)

POP Menstrual Effects

Bleeding pattern not “scheduled” can have:

- Amenorrhea, short cycles, irregular periods, intermenstrual bleeding, spotting
- May allow for physiologic cycling since ovulation suppression is not main mechanism of action

Addressing Unscheduled Bleeding

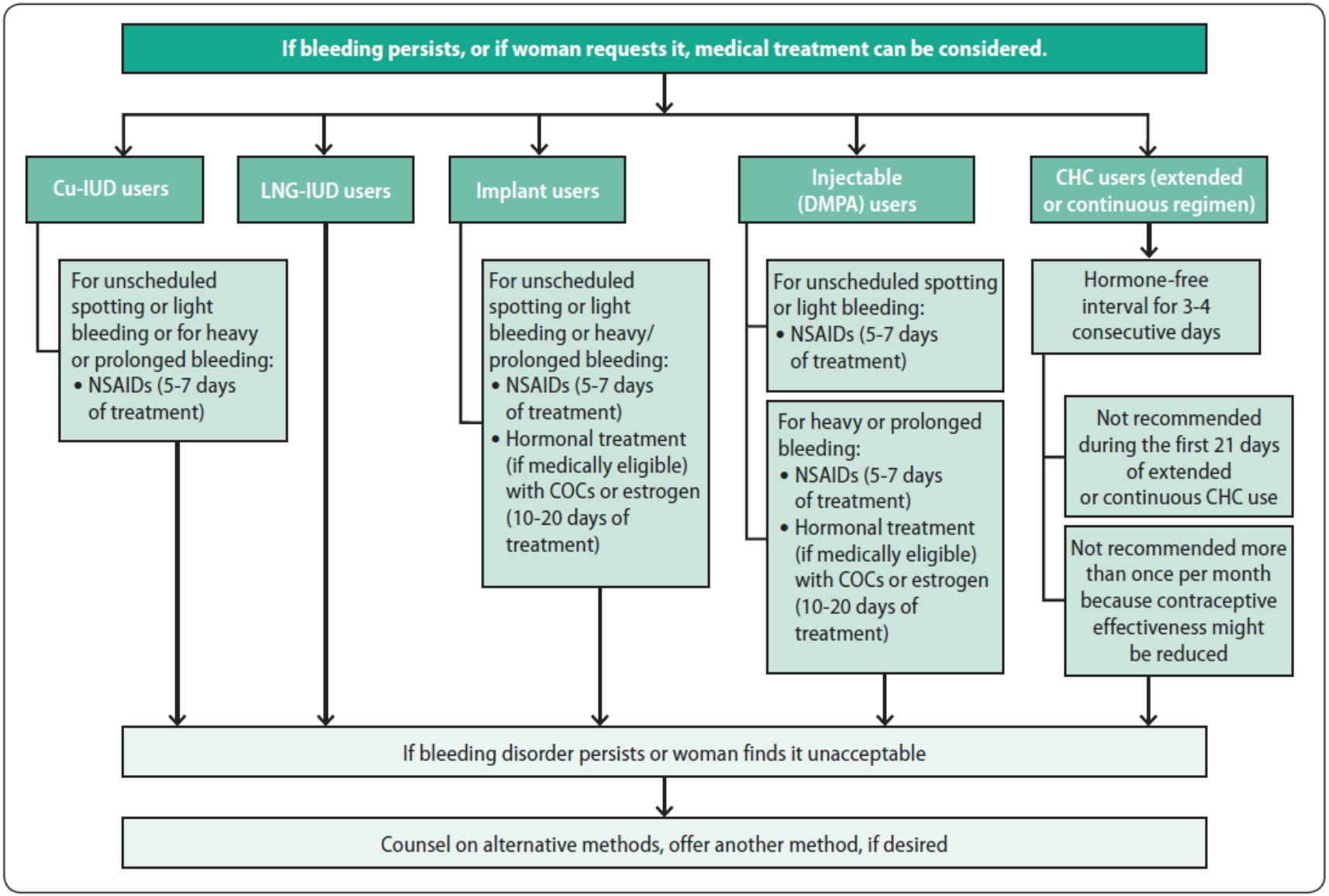
- Anticipatory guidance
- Ask **what concerns her**
- Normal side effect, not dangerous, doesn't indicate reduced effectiveness
- Ensure using the method correctly (DMPA/POPs)
- Any concomitant medications that may reduce effectiveness of progestin

Work up of unscheduled bleeding

Work up in context of other symptoms (pain, vaginal discharge, postcoital bleeding.
Consider:

- Pregnancy test
- Speculum and bimanual exam
- Cervical cancer screening
- GC/CT
- Pelvic ultrasound
- EMB

Management of Women with Bleeding Irregularities While Using Contraception*



* If clinically warranted, evaluate for underlying condition. Treat the condition or refer for care. Heavy or prolonged bleeding, either unscheduled or menstrual, is uncommon among LNG-IUD users and implant users.

Abbreviations: CHC = combined hormonal contraceptive; COC = combined oral contraceptive; Cu-IUD = copper-containing intrauterine device; DMPA = depot medroxyprogesterone acetate; LNG-IUD = levonorgestrel-releasing intrauterine device; NSAIDs = nonsteroidal anti-inflammatory drugs.

Source: For full recommendations and updates, see the U.S. Selected Practice Recommendations for Contraceptive Use webpage at http://www.cdc.gov/reproductivehealth/unintendedpregnancy/usspr.htm.

Centers for Disease Control and Prevention
National Center for Chronic Disease Prevention and Health Promotion

Estrogen for Unscheduled Bleeding

- Estrogen to build/support/ repair endometrium
- Options
  - Monophasic combined OCP
  - Vaginal Ring
  - Estradiol 2 mg PO
  - Conjugated Equine Estrogen 1.25 mg PO

(Zigler, McNicholas 2017)

NSAIDs for Unscheduled Bleeding

- Inhibit prostaglandin synthesis which is increased in the endometrium of women with abnormal bleeding
  - Best if bleeding is “heavier”
- Options
  - Naproxen sodium 220 mg PO BID
  - Ibuprofen 800mg PO TID
  - Mefanamic acid 500 mg PO TID

(Zigler, McNicholas 2017)

Tranexamic acid For Unscheduled Bleeding

- Tranexamic acid
  - Anti-fibrinolytic to treat heavy menstrual bleeding, decreases clot breakdown
  - 650-1300 mg PO TID
- Contraindicated in women with ↑risk of VTE

(Zigler, McNicholas 2017)

Management of unscheduled bleeding

Other therapies not useful, practical or still experimental:

- Doxycycline
- Mifepristone
- Tamoxifen

(Zigler, McNicholas 2017)

Treatment for Bleeding with LNG IUD in the First 90 days

- Naproxen sodium may work-- particularly if bleeding is heavy

- Transdermal E2 and tranexamic acid likely not to work

(Madden, Proehl et al. 2012; Sordal, Inki et al. 2013; Varma, Sinha et al. 2016)

NHeLP

If your state Medicaid program does not cover a particular LARC method or a removal, or if your state places inappropriate limits or restrictions on these services:

nhelp@healthlaw.org with “reproductive health” in the subject line.

QUESTIONS?

References

- ACOG Practice Bulletin No. 110: noncontraceptive uses of hormonal contraceptives. (2010). *Obstet Gynecol, 115*(1), 206-218.
- Ali, M., Akin, A., Bahamondes, L., Brache, V., Habib, N., Landoulsi, S., & Hubacher, D. (2016). Extended use up to 5 years of the etonogestrel-releasing subdermal contraceptive implant: comparison to levonorgestrel-releasing subdermal implant. *Hum Reprod, 31*(11), 2491-2498.
- Bachmann, G., & Korner, P. (2009). Bleeding patterns associated with non-oral hormonal contraceptives: a review of the literature. *Contraception, 79*(4), 247-258.
- Backman, T., Huhtala, S., Luoto, R., Tuominen, J., Rauramo, I., & Koskenvuo, M. (2002). Advance information improves user satisfaction with the levonorgestrel intrauterine system. *Obstet Gynecol, 99*(4), 608-613.
- Bahamondes, L., Fernandes, A., Bahamondes, M. V., Juliato, C. T., Ali, M., & Monteiro, I. (2017). Pregnancy outcomes associated with extended use of the 52-mg 20 mug/day levonorgestrel-releasing intrauterine system beyond 60 months: A chart review of 776 women in Brazil. *Contraception.*
- Barbosa, I., Olsson, S. E., Odlind, V., Goncalves, T., & Coutinho, E. (1995). Ovarian function after seven years' use of a levonorgestrel IUD. *Adv Contracept, 11*(2), 85-95.
- Bhardwaj, N. R., & Espey, E. (2015). Lactation and contraception. *Curr Opin Obstet Gynecol, 27*(6), 496-503.
- Bonny, A. E., Secic, M., & Cromer, B. (2011). Early weight gain related to later weight gain in adolescents on depot medroxyprogesterone acetate. *Obstet Gynecol, 117*(4), 793-797.
- Bragheto, A. M., Caserta, N., Bahamondes, L., & Petta, C. A. (2007). Effectiveness of the levonorgestrel-releasing intrauterine system in the treatment of adenomyosis diagnosed and monitored by magnetic resonance imaging. *Contraception, 76*(3), 195-199.
- Chan, S. S., Tam, W. H., Yeo, W., Yu, M. M., Ng, D. P., Wong, A. W., . . . Yuen, P. M. (2007). A randomised controlled trial of prophylactic levonorgestrel intrauterine system in tamoxifen-treated women. *Bjog, 114*(12), 1510-1515.

References

- Cho, S., Nam, A., Kim, H., Chay, D., Park, K., Cho, D. J., . . . Lee, B. (2008). Clinical effects of the levonorgestrel-releasing intrauterine device in patients with adenomyosis. *Am J Obstet Gynecol, 198*(4), 373.e371-377.
- Creinin, M. D., Jansen, R., Starr, R. M., Gobburu, J., Gopalakrishnan, M., & Olariu, A. (2016). Levonorgestrel release rates over 5 years with the Liletta® 52-mg intrauterine system. *Contraception, 94*(4), 353-356.
- Darney, P., Patel, A., Rosen, K., Shapiro, L. S., & Kaunitz, A. M. (2009). Safety and efficacy of a single-rod etonogestrel implant (Implanon): results from 11 international clinical trials. *Fertil Steril, 91*(5), 1646-1653.
- Dehlendorf, C., Henderon, J. T., Vittinghoff, E., Grumbach, K., Levy, K., Schmittdiel, J., . . . Steinauer, J. (2016). Association of the quality of interpersonal care during family planning counseling with contraceptive use. *AM J Obstet Gynecol, 215*(1), 78.e71-79.
- dos Santos Pde, N., Modesto, W. O., Dal'Ava, N., Bahamondes, M. V., Pavin, E. J., & Fernandes, A. (2014). Body composition and weight gain in new users of the three-monthly injectable contraceptive, depot-medroxyprogesterone acetate, after 12 months of follow-up. *Eur J Contracept Reprod Health Care, 19*(6), 432-438.
- Espey, E., Ogburn, T., Leeman, L., Singh, R., Ostrom, K., & Schrader, R. (2012). Effect of progestin compared with combined oral contraceptive pills on lactation: a randomized controlled trial. *Obstet Gynecol, 119*(1), 5-13.
- FFPRHC; FFPRHC Guidance: Drug Interactions with hormonal contraception. *J Fam Plann Reprod Health Care 2005*: 31:139.
- Fraser, I. S. (2013). Added health benefits of the levonorgestrel contraceptive intrauterine system and other hormonal contraceptive delivery systems. *Contraception, 87*(3), 273-279.
- Gallon, A., Fontarensky, M., Chauffour, C., Boyer, L., & Chabrot, P. (2017). Looking for a lost subdermal contraceptive implant? Think about the pulmonary artery. *Contraception, 95*(2), 215-217.

References

- Gemzell-Danielsson, K., Schellschmidt, I., & Apter, D. (2012). A randomized, phase II study describing the efficacy, bleeding profile, and safety of two low-dose levonorgestrel-releasing intrauterine contraceptive systems and Mirena. *Fertil Steril, 97*(3), 616-622.e611-613.
- Haimovich, S., Checa, M. A., Mancebo, G., Fuste, P., & Carreras, R. (2008). Treatment of endometrial hyperplasia without atypia in peri- and postmenopausal women with a levonorgestrel intrauterine device. *Menopause, 15*(5), 1002-1004.
- Heikinheimo, O., & Gemzell-Danielsson, K. (2012). Emerging indications for the levonorgestrel-releasing intrauterine system (LNG-IUS*). Acta Obstet Gynecol Scand, 91*(1), 3-9.
- Heikinheimo, O., Inki, P., Schmelter, T., & Gemzell-Danielsson, K. (2014). Bleeding pattern and user satisfaction in second consecutive levonorgestrel-releasing intrauterine system users: results of a prospective 5-year study. *Hum Reprod, 29*(6), 1182-1188.
- Helms, S. E., Bredle, D. L., Zajic, J., Jarjoura, D., BrodellR. T., Krishnarao, I. (1997). Oral contraceptive failure rates and oral antibiotics. *J Am Acad Dermatol, 36*(5 Pt 1), 705-710.
- Herzog, A. G. (2015). Differential impact of antiepileptic drugs on the effects of contraceptive methods on seizures: Interim findings of the epilepsy birth control registry. *Seizure, 28*, 71-75.
- Hidalgo, M., Bahamondes, L., Perrotti, M., Diaz, J., Dantas-Monteiro, C., & Petta, C. (2002). Bleeding patterns and clinical performance of the levonorgestrel-releasing intrauterine system (Mirena) up to two years. *Contraception, 65*(2), 129-132.
- Ilse, J. R., Greenberg, H. L., & Bennett, D. D. (2008). Levonorgestrel-releasing intrauterine system and new-onset acne. *Cutis, 82(*2), 158.
- Jonsson, B., Landgren, B. M., & Eneroth, P. (1991). Effects of various IUDs on the composition of cervical mucus. *Contraception, 43*(5), 447-458.

References

- Kang, S., Niak, A., Gada, N., Brinker, A., & Jones, S. C. (2017). Etonogestrel implant migration to the vasculature, chest wall, and distant body sites: cases from a pharmacovigilance database. *Contraception, 96*(6), 439-445.
- Kaunitz, A. M. (2007). Progestin-releasing intrauterine systems and leiomyoma. *Contraception, 75*(6 Suppl), S130-133.
- Kaunitz, A. M., Bissonnette, F., Monteiro, I., Lukkari-Lax, E., DeSanctis, Y., & Jensen, J. (2012). Levonorgestrel-releasing intrauterine system for heavy menstrual bleeding improves hemoglobin and ferritin levels. *Contraception, 86(*5), 452-457.
- Kew, E. P., Senanayake, E., Djearaman, M., & Bishay, E. (2017). Migration of contraceptive implant into the left pulmonary arterial system. *Asian Cardiovasc Thorac Ann, 25*(7-8), 537-539. Park, J. U., Bae, H. S., Lee, S. M., Bae, J., & Park, J. W. (2017). Removal of a subdermal contraceptive implant (Implanon NXT) that migrated to the axilla by C-arm guidance: A case report and review of the literature. *Medicine (Baltimore), 96*(48), e8627.
- Lanza, L. L., McQuay, L. J., Rothman, K. J., Bone, H. G., Kaunitz, A. M., Harel, Z., . . . Wolter, K. D. (2013). Use of depot medroxyprogesterone acetate contraception and incidence of bone fracture. *Obstet Gynecol, 121*(3), 593-600.
- Le, Y. C., Rahman, M., & Berenson, A. B. (2009). Early weight gain predicting later weight gain among depot medroxyprogesterone acetate users. *Obstet Gynecol, 114*(2 Pt 1), 279-284.
- Lewis, R. A., Taylor, D., Natavio, M. F., Melamed, A., Felix, J., & Mishell, D., Jr. (2010). Effects of the levonorgestrel-releasing intrauterine system on cervical mucus quality and sperm penetrability. *Contraception, 82*(6), 491-496.

References

- Lopez, L. M., Bernholc, A., Chen, M., Grey, T. W., Otterness, C., Westhoff, C., . . . Helmerhorst, F. M. (2016). Hormonal contraceptives for contraception in overweight or obese women. *Cochrane Database Syst Rev(8),* Cd008452.
- Lopez, L. M., Ramesh, S., Chen, M., Edelman, A., Otterness, C., Trussell, J., & Helmerhorst, F. M. (2016). Progestin-only contraceptives: effects on weight. *Cochrane Database Syst Rev*(8),
- Madden, T., Proehl, S., Allsworth, J. E., Secura, G. M., & Peipert, J. F. (2012). Naproxen or estradiol for bleeding and spotting with the levonorgestrel intrauterine system: a randomized controlled trial. *Am J Obstet Gynecol, 206*(2), 129.e121-128.
- Mansour, D. (2012). The benefits and risks of using a levonorgestrel-releasing intrauterine system for contraception. *Contraception, 85*(3), 224-234.
- Mattson, R. H., Cramer, J. A., Caldwell, B. V., & Siconolfi, B. C. (1984). Treatment of seizures with medroxyprogesterone acetate: preliminary report. *Neurology, 34*(9), 1255-1258.
- Matteson, K. A., Rahn, D. D., Wheeler, T. L., 2nd, Casiano, E., Siddiqui, N. Y., Harvie, H. S., . . . Sung, V. W. (2013). Nonsurgical management of heavy menstrual bleeding: a systematic review. *Obstet Gynecol, 121*(3), 632-643.
- McNicholas, C., Maddipati, R., Zhao, Q., Swor, E., & Peipert, J. F. (2015). Use of the etonogestrel implant and levonorgestrel intrauterine device beyond the U.S. Food and Drug Administration-approved duration. *Obstet Gynecol, 125*(3), 599-604.
- McNicholas, C., Swor, E., Wan, L., & Peipert, J. F. (2017). Prolonged use of the etonogestrel implant and levonorgestrel intrauterine device: 2 years beyond Food and Drug Administration-approved duration. *Am J Obstet Gynecol, 216*(6), 586.e581-586.e586.
- Modesto, W., de Nazare Silva dos Santos, P., Correia, V. M., Borges, L., & Bahamondes, L. (2015). Weight variation in users of depot-medroxyprogesterone acetate, the levonorgestrel-releasing intrauterine system and a copper intrauterine device for up to ten years of use. *Eur J Contracept Reprod Health Care, 20*(1), 57-63.

References

- Morch, L. S., Skovlund, C. W., Hannaford, P. C., Iversen, L., Fielding, S., & Lidegaard, O. (2017). Contemporary Hormonal Contraception and the Risk of Breast Cancer/ *N Engl J Med, 377*(23), 2228-2239.
- Mornar, S., Chan, L. N., Mistretta, S., Neustadt, A., Martins, S., & Gilliam, M. (2012). Pharmacokinetics of the etonogestrel contraceptive implant in obese women. *Am J Obstet Gynecol, 207*(2), 110.e111-116.
- Morrell, K. M., Cremers, S., Westhoff, C. L., & Davis, A. R. (2016). Relationship between etonogestrel level and BMI in women using the contraceptive implant for more than 1 year. *Contraception, 93*(3), 263-265.
- Murphy, P. A., Kern, S. E., Stanczyk, F. Z., & Westhoff, C. L. (2005). Interaction of St. John's Wort with oral contraceptives: effects on the pharmacokinetics of norethindrone and ethinyl estradiol, ovarian activity and breakthrough bleeding. *Contraception, 71*(6), 402-408.
- Natavio, M. F., Taylor, D., Lewis, R. A., Blumenthal, P., Felix, J. C., Melamed, A., . . . Mishell, D. R., Jr. (2013). Temporal changes in cervical mucus after insertion of the levonorgestrel-releasing intrauterine system. *Contraception, 87(*4), 426-431.
- Nelson, A., Apter, D., Hauck, B., Schmelter, T., Rybowski, S., Rosen, K., & Gemzell-Danielsson, K. (2013). Two low-dose levonorgestrel intrauterine contraceptive systems: a randomized controlled trial. *Obstet Gynecol, 122*(6), 1205-1213.
- Nilsson, C. G., Lahteenmaki, P. L., & Luukkainen, T. (1984). Ovarian function in amenorrheic and menstruating users of a levonorgestrel-releasing intrauterine device. *Fertil Steril, 41(*1), 52-55.
- O'Brien, M. D., & Guillebaud, J. (2006). Contraception for women with epilepsy. *Epilepsia, 47*(9), 1419-1422.
- Ortiz, M. E., & Croxatto, H. B. (2007). Copper-T intrauterine device and levonorgestrel intrauterine system: biological bases of their mechanism of action. *Contraception, 75*(6 Suppl), S16-30.
- Pantoja, M., Medeiros, T., Baccarin, M. C., Morais, S. S., Bahamondes, L., & Fernandes, A. M. (2010). Variations in body mass index of users of depot-medroxyprogesterone acetate as a contraceptive. *Contraception, 81*(2), 107-111.

References

- Patel, R. C., Morroni, C., Scarsi, K. K., Sripipatana, T., Kiarie, J., & Cohen, C. R. (2017). Concomitant contraceptive implant and efavirenz use in women living with HIV: perspectives on current evidence and policy implications for family planning and HIV treatment guidelines. *J Int AIDS Soc, 20(*1), 21396.
- Phillips, S. J., Tepper, N. K., Kapp, N., Nanda, K., Temmerman, M., & Curtis, K. M. (2016). Progestogen-only contraceptive use among breastfeeding women: a systematic review. *Contraception, 94*(3), 226-252.
- Polis, C. B., Curtis, K. M., Hannaford, P. C., Phillips, S. J., Chipato, T., Kiarie, J. N., . . . Steyn, P. S. (2016). An updated systematic review of epidemiological evidence on hormonal contraceptive methods and HIV acquisition in women. *Aids, 30*(17), 2665-2683.
- Reimers, A. (2016). Contraception for women with epilepsy: counseling, choices, and concerns. *Open Access J Contracept, 7*, 69-76.
- Risser, W. L., Gefter, L. R., Barratt, M. S., & Risser, J. M. (1999). Weight change in adolescents who used hormonal contraception. *J Adolesc Health, 24*(6), 433-436.
- Rivera, R., Yacobson, I., & Grimes, D. (1999). The mechanism of action of hormonal contraceptives and intrauterine contraceptive devices. *Am J Obstet Gynecol, 181*(5 Pt 1), 1263-1269.
- Rowe, P., Farley, T., Peregoudov, A., Piaggio, G., Boccard, S., Landoulsi, S., & Meirik, O. (2016). Safety and efficacy in parous women of a 52-mg levonorgestrel-medicated intrauterine device: a 7-year randomized comparative study with the TCu380A. *Contraception, 93*(6), 498-506.
- Rowlands, S., Mansour, D., & Walling, M. (2017). Intravascular migration of contraceptive implants: two more cases. *Contraception, 95*(2), 211-214.
- Simmons, K. B., Haddad, L. B., Nanda, K., & Curtis, K. M. (2017). Drug interactions between rifamycin antibiotics and hormonal contraception: a systematic review. *Bjog*.
- Simmons, K. B., Haddad, L. B., Nanda, K., & Curtis, K. M. (2018). Drug interactions between non-rifamycin antibiotics and hormonal contraception: a systematic review. *Am J Obstet Gynecol, 218*(1), 88-97.e14.

References

- Sitruk-Ware, R. (2007). The levonorgestrel intrauterine system for use in peri- and postmenopausal women. *Contraception, 75*(6 Suppl), S155-160.
- Skovlund, C. W., Morch, L. S., Kessing, L. V., & Lidegaard, O. (2016). Association of Hormonal Contraception With Depression. *JAMA Psychiatry, 73*(11), 1154-1162.
- Sordal, T., Inki, P., Draeby, J., O'Flynn, M., & Schmelter, T. (2013). Management of initial bleeding or spotting after levonorgestrel-releasing intrauterine system placement: a randomized controlled trial. *Obstet Gynecol, 121*(5), 934-941.
- Soysal, S., & Soysal, M. E. (2005). The efficacy of levonorgestrel-releasing intrauterine device in selected cases of myoma-related menorrhagia: a prospective controlled trial. *Gynecol Obstet Invest, 59*(1), 29-35.
- Stanford, J. B., & Mikolajczyk, R. T. (2002). Mechanisms of action of intrauterine devices: update and estimation of postfertilization effects. *Am J Obstet Gynecol, 187*(6), 1699-1708.
- Sturdee, D. (2006). Levonorgestrel intrauterine system for endometrial protection. *J Br Menopause Soc*, 12 Suppl 1, 1-3.
- Thomas, P. A., Di Stefano, D., Couteau, C., & D'Journo, X. B. (2017). Contraceptive Implant Embolism Into the Pulmonary Artery: Thoracoscopic Retrieval. *Ann Thorac Surg, 103*(3), e271-e272.
- Thorneycroft, I., Klein, P., & Simon, J. (2006). The impact of antiepileptic drug therapy on steroidal contraceptive efficacy. *Epilepsy Behav, 9*(1), 31-39.
- Varila, E., Wahlstrom, T., & Rauramo, I. (2001). A 5-year follow-up study on the use of a levonorgestrel intrauterine system in women receiving hormone replacement therapy. *Fertil Steril, 76*(5), 969-973.
- Varma, R., Sinha, D., & Gupta, J. K. (2006). Non-contraceptive uses of levonorgestrel-releasing hormone system (LNG-IUS)--a systematic enquiry and overview. *Eur J Obstet Gynecol Reprod Biol, 125*(1), 9-28.
- Varma, R., Soneja, H., Bhatia, K., Ganesan, R., Rollason, T., Clark, T. J., & Gupta, J. K. (2008). The effectiveness of a levonorgestrel-releasing intrauterine system (LNG-IUS) in the treatment of endometrial hyperplasia--a long-term follow-up study. *Eur J Obstet Gynecol Reprod Biol, 139*(2), 169-175.

References

- Vickery, Z., Madden, T., Zhao, Q., Secura, G. M., Allsworth, J. E., & Peipert, J. F. (2013). Weight change at 12 months in users of three progestin-only contraceptive methods. *Contraception, 88*(4), 503-508.
- Videla-Rivero, L., Etchepareborda, J. J., & Kesseru, E. (1987). Early chorionic activity in women bearing inert IUD, copper IUD and levonorgestrel-releasing IUD. *Contraception, 36*(2), 217-226.
- Weaver, K., & Glasier, A. (1999). Interaction between broad-spectrum antibiotics and the combined oral contraceptive pill. A literature review. *Contraception, 59*(2), 71-78.
- Wildemeersch, D. (2016). Safety and comfort of long-term continuous combined transdermal estrogen and intrauterine levonorgestrel administration for postmenopausal hormone substitution - a review. *Gynecol Endocrinol*, 1-4.
- Wong, A. W., Chan, S. S., Yeo, W., Yu, M. Y., & Tam, W. H. (2013). Prophylactic use of levonorgestrel-releasing intrauterine system in women with breast cancer treated with tamoxifen: a randomized controlled trial. *Obstet Gynecol, 121*(5), 943-950.
- Worly, B. L., Gur, T. L., & Schaffir, J. The relationship between progestin hormonal contraception and depression: a systematic review. *Contraception.*
- Wu, J. P., & Pickle, S. (2014). Extended use of the intrauterine device: a literature review and recommendations for clinical practice. *Contraception, 89*(6), 495-503.
- Xu, H., Wade, J. A., Peipert, J. F., Zhao, Q., Madden, T., & Secura, G. M. (2012). Contraceptive failure rates of etonogestrel subdermal implants in overweight and obese women. *Obstet Gynecol*, 120(1), 21-26.
- Zigler, R. E., & McNicholas, C. (2017). Unscheduled vaginal bleeding with progestin-only contraceptive use. *AM J Obstet Gynecol, 216*(5), 443-450.
- Zupanc, M. L. (2006) Antiepileptic drugs and hormonal contraceptives in adolescent women with epilepsy. *Neurology, 66*(6 Suppl 3), S37-45.