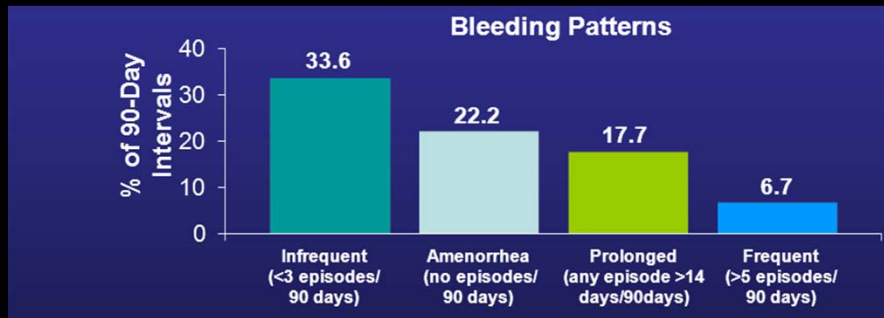


Nelson: Update on Contraceptive Implants

Counseling Her on What to Expect with Etonogestrel Implant

Bleeding Profile During the First 2 Years with ENG implant



Based on 3,315 recording periods of 90 days duration in 780 women following administration of ENG implant, excluding the first 90 days after implant placement
Bleeding/spotting episode = 1 or more consecutive days during which bleeding or spotting occurred

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Number of Days of Bleeding/Spotting by 90 Day Reference Period

RP	n	Bleeding Spotting Days		Bleeding Spotting Episodes	
		Med	Mean	Med	Mean
1	808	22.0	27.9	3.0	2.8
2	783	15.0	20.5	2.0	2.5
4	693	14.0	17.2	2.0	2.3
6	618	15.0	17.3	2.0	2.4
8	547	13.0	17.4	3.0	2.5
10	227	15.0	16.9	2.0	2.4
12	202	16.0	18.1	3.0	2.6

Mansour D, et al. *Eur J Contracept Reprod Health Care.* 2008;13(S1):13-28.

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Nelson: Update on Contraceptive Implants

Percent of Women with Bleeding Patterns by 90-Day Reference Period

	Amenorrhoea No Bleeding/Spotting (B-S)	Infrequent <3 B-S episodes	Normal 3-5 B-S episodes	Frequent >5 B-S episodes	Prolonged >14 B-S days uninterrupted
1	10	39	39	12	31
2	19	34	39	8	21
4	23	32	39	6	17
6	21	33	41	6	15
8	17	33	47	4	15
10	17	35	44	4	17
12	12	34	52	2	17

Mansour D, et al. *Eur J Contracept Reprod Health Care*. 2008;13(S1):13-28.

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Why Unscheduled Bleeding with Continuous Progestin?

- Endometrial changes:
 - ◆ Increased and disordered microvessels (structurally compromised)
 - ◆ Decreased stromal and glandular support
 - ◆ Reduced epithelial integrity
- Altered endometrial matrix metalloproteinase (MMP) activity predisposes to:
 - ◆ Irregular vessel breakdown and bleeding
 - ◆ Vascular fragility

Weisberg E, et al. *Hum Reprod*. 2006;21(1):295-302.

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NSAIDs for Irregular ENG Implant Bleeding

- 50 women randomized placebo-controlled study
- Mefenamic acid 500 mg PO TID x 5 days

	Mefenamic Acid	Placebo
% bleeding stopped in 7 days	65.2%	21.7%
No bleeding > 20 day/28 days	56.5%	21.7%
Mean number B + S days	10.5	16.8

Phaliwong P, et al. *J Med Assoc Thai.* 2004;87(3):S64-8.

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14-Day COC Treatment for Implant Bleeding

- Double blind, randomized trial of 32 women with ≥ 7 consecutive days of bothersome bleeding
- 30 mcg EE/0.15 mg LNG pill x 14 days vs. placebo
- Temporary cessation of bleeding
 - ◆ 87.5% COC
 - ◆ 37.5% placebo
- But 85.7% of those who stopped with COCs restarted bleeding in 10 days after treatment

Guiahi M, et al. *Obstet Gynecol.* 2015;126(3):508-13.

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Tamoxifen for Unscheduled Bleeding with ENG Implant

- 56 women with frequent or prolonged bleeding randomized
 - ◆ Tamoxifen 10 mg vs. placebo BID x 7 days
 - Starting at beginning of bleeding episode
 - Repeated as needed every 30 days for up to 18 days
- At baseline women in tamoxifen group had more unscheduled bleeding and spotting (23 vs. 20/30d)

Simmons K, et al. *Obstet Gynecol.* 2016;127 Suppl 1:9S.

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Tamoxifen for Unscheduled Bleeding with ENG Implant

	Events Within 30 Days Following Treatment Median Days Duration	
	Bleeding/Spotting	Amenorrhea
Tamoxifen	6 days	30 days
Placebo	12 days	8 days

- Satisfaction scores higher with tamoxifen
- Side effects similar
- Impact on efficacy? (ALN)

Simmons K, et al. *Obstet Gynecol.* 2016;127 Suppl 1:9S.

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How Does Anti-Progestin Help?

- Dose-dependent effect:
 - ◆ Mifepristone 50 mg shortens duration without pregnancy¹
 - ◆ In Mouse model mifepristone highly effective²
 - Extremely rapid endometrial repair in presence of ENG implant-like device
 - ◆ Estrogen added to maximize the efficacy of estrogen in stimulating endometrial epithelial repair by up regulating estrogen receptors¹

1. Weisberg E, et al. *Hum Reprod.* 2006;21(1):295-302.

2. Morison NB, et al. *Reproduction.* 2008;136(2):267-74.

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ENG Implant Frequent/Prolonged Bleeding Pilot Study

3 Treatments vs. placebo ≥ 3 Months Bleeding	
Drugs	Mean Days to Bleeding Cessation
Mifepristone 25 mg BID x 1	5.9
Mifepristone 25 mg BID x 1 + 20 mcg EE x 4d	4.3
*Doxycycline 100 mg BID x 5d	4.8
Placebo	7.5

* Not effective in follow-up study

Weisberg E, et al. *Hum Reprod.* 2006;21(1):295-302.

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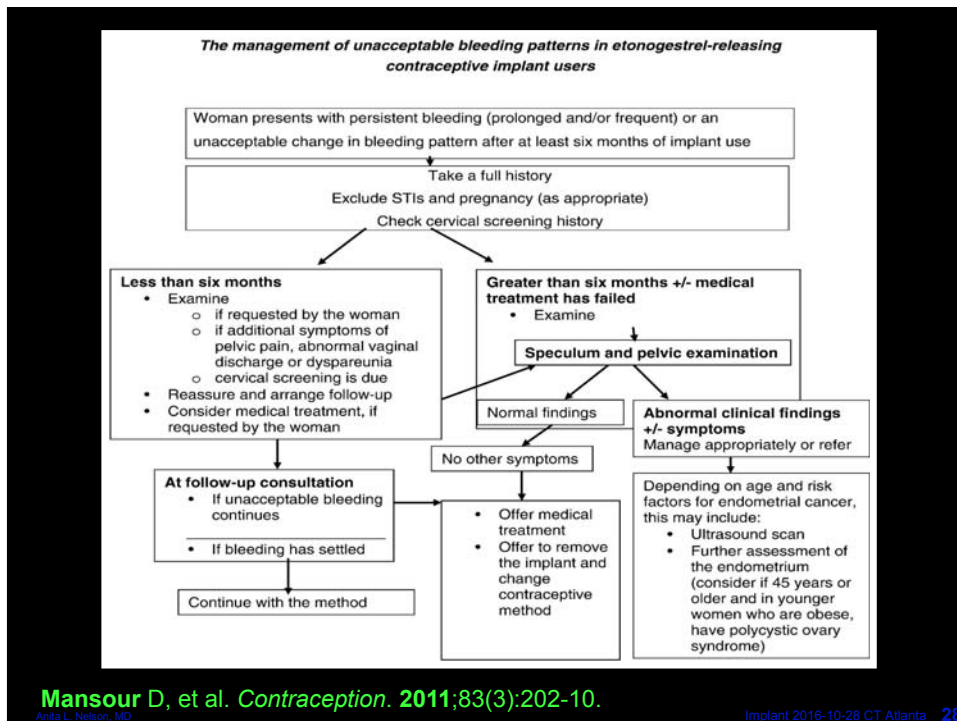
Recommendations for Stopping Unscheduled Bleeding with ENG Implant

- COC taken cyclically for up to 3 months
- MPA 10mg BID or NETA 5mg BID X 21 days
- POP (desogestrel) for 3 months
- NSAIDs, esp. Cox-2 inhibitors for 5-10 days
- Tranexamic acid 500mg BTD for 5 days

Mansour D, et al. *Contraception*. 2010;(3):202-10.

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Mansour D, et al. *Contraception*. 2011;83(3):202-10.

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Prophylaxis to Prevent Early Bleeding with ENG Implant

- 129 women, 12 week therapies
 - ◆ Started on day of placement
- Treatment arms
 - ◆ Naproxen 500 mg BID x 5 day Q 4 weeks x 3 months
 - ◆ Estradiol patch 0.1 mg weekly x 3 months
 - ◆ Placebo
- Bleeding diaries
- Median # days B + S

	Naproxen	E ₂	Placebo
Mean # days B + S	27.5	44	32

Madden T, et al. *Am J Obstet Gynecol.* 2012;206(2):129e1-8.

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Etonogestrel Implant: Most Common Adverse Side Effects

Side Effect	% of Women Complaining
Acne	14
Headache	13
Weight gain	10
Mastalgia	9.4
Emotional lability	5

Urbancsek J. *Contraception.* 1998;58(6 Suppl):109S-115S.

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