Management of Abnormal Uterine Bleeding in Adolescents

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Learning Objectives

1. Review terminology and causes of abnormal uterine bleeding
2. Outline the clinical evaluation of the patient with abnormal uterine bleeding
3. Discuss treatment options with emphasis on extended oral contraceptives

Abnormal Uterine Bleeding (AUB)

- It is one of the most common medical problems in adolescents (12-37%)
- It includes several different types of bleeding patterns.
- The terminologies are not agreed upon.

Wilkinson, Kadir: Management of Abnormal Uterine Bleeding in Adolescents. J Pediatr Adolesc Gynecol (2010) 23:S22-S30

Menorrhagia

- Prolonged (more than 7 days) or excessive (greater than 80 ml) uterine bleeding occurring at regular intervals

Heavy Menstrual Bleeding (HMB)

- Heavy menstrual blood loss, regardless of the pattern of the cycles
- Synonymous with hypermenorrhea

Wilkinson, Kadir: Management of Abnormal Uterine Bleeding in Adolescents. J Pediatr Adolesc Gynecol (2010) 23:S22-S30

***Polymenorrhea*: Frequent irregular bleeding at less than 18-day intervals.**

***Oligomenorrhea*: Infrequent irregular bleeding at intervals of more than 45 days.**

***Metrorrhagia:* Intermenstrual bleeding between regular periods.**

Dysfunctional Uterine Bleeding

Excessive, prolonged or unpatterned bleeding from the uterine endometrium that is unrelated to anatomic lesions of the uterus.

Dysfunctional Uterine Bleeding

- **The most common cause of DUB is** anovulation **secondary to a disturbance of the normal hypothalamic-pituitary-ovarian axis.**
- **ACOG considers DUB synonymous with anovulatory uterine bleeding.**

Anovulation

- The adolescent female often has anovulatory cycles for the first 2-4 years.
- Anovulation is the most common cause of AUB in adolescents.

Wilkinson, Kadir: Management of Abnormal Uterine Bleeding in Adolescents. J Pediatr Adolesc Gynecol (2010) 23:S22-S30

Anovulation

- No cyclic production of progesterone
- A state of unopposed estrogen occurs
- The endometrial lining becomes abnormally thickened
- Spontaneous superficial breakage of lining results in asynchronous bleeding

Differential Diagnosis of Abnormal Uterine Bleeding (AUB)

- Bleeding (coagulation) disorders
- Medications
- Uterine polyps or myomas
- Trauma / sexual assault
- Foreign body

Differential Diagnosis of AUB

- Pregnancy: abortion, ectopic, GTD
- Genital tract infection
- Neoplasms of the genital tract
- Endocrine disorders

Endocrine Disorders

- Anovulation
- Polycystic ovarian syndrome
- Hyperprolactinemia
- Thyroid disorder

Bleeding (Coagulation) Disorders

- Prevalence rates range from 7 to 48% of adolescents with heavy menstrual bleeding
- Low threshold for screening

Wilkinson, Kadir: Management of Abnormal Uterine Bleeding in Adolescents. J Pediatr Adolesc Gynecol (2010) 23:S22-S30

Bleeding (Coagulation) Disorders:

- Von Willebrand disease
- Immune thrombocytopenic purpura or platelet function defects

History

- Age of menarche; Last menstrual period
- Menstrual interval; Duration of flow
- How heavy? (How often does patient change pad or tampon during a school day? Is she passing clots?)

- Heavy: changing a pad every 1-2 hours;
  >6 pads/day; passing clots; anemia

Wilkinson, Kadir: Management of Abnormal Uterine Bleeding in Adolescents. J Pediatr Adolesc Gynecol (2010) 23:S22-S30

History

- Medications
  - Contraceptive agents; seizure or psychotropic medications
- Sexual history
- Bleeding after surgery, wounds or tooth extraction

Review of Systems

- Hirsutism
- Acne
- Galactorrhea
- Weight changes
- Abnormal bruising or bleeding
- Stress

Physical Examination

- Tanner staging
- Weight / BMI
- Acne
- Hirsutism
- Source of bleeding
- Foreign body
- Pregnancy
- Neoplasm

Laboratory Evaluation

- CBC, TSH
- Pregnancy test, if indicated
- PCR (if sexually active)
- If patient has hirsutism:
  - Total testosterone
  - DHEAS
  - 17OH Progesterone

Laboratory Evaluation

- PT, PTT
- Von Willibrand screen if history of excessively heavy bleeding or anemia

* Do Von Willibrand testing before starting hormone therapy

Management

- Tranexamic acid
- Combined contraceptive hormones
- Progestins: pills, injections, implants or LNG-IUS

Combined Contraceptive Hormones

- Combined oral contraceptives (COC)
- Transdermal patches
- Vaginal rings

Benefits of Combined Contraceptive Hormones

- Regular, predictable menses
- Shorter, lighter menses
- Less menstrual pain and premenstrual symptoms
- Can extend pills/ring and space out menses

Concerns of COC

- Must remember to take a pill daily
- Possible side effects:
  breakthrough bleeding, weight gain, nausea, headaches, venous thromboembolism

Reasons To Modify The Standard
21/7 COC Regimen

- Decreases estrogen withdrawal symptoms during the hormone free interval: headaches, bloating, pelvic pain, & breast tenderness
- Helps prevent: endometriosis anemia, ovarian cysts, seizures, etc
- Convenience

Sulak et al., Obstet Gynecol 2000, 95:261-6.

Changing the Standard COC Regimen: Current/Future Ideas

1. Shorten the hormone free interval from 7 days to 3 to 5 days to provide greater ovarian suppression and decrease the incidence/severity of hormone withdrawal symptoms
2. Extend the # of days of active OCs to greater than 21 days
3. Add estrogen during the hormone free interval

Types of COC Use

- Cyclic: 21/7 24/4
- Extended: 6 weeks on/4 days off or 84/7
- Continuous

*Vaginal ring can also be used in a continuous fashion

Extended COC Regimen: Helpful Hints

- When initiating COCs, begin with the standard regimen for 3- 4 months because of high incidence of BTB.
- Have patient return during the third or fourth cycle to assess compliance & side effects

Extended COC Regimen: Helpful Hints

- If patient having withdrawal symptoms during the hormone free interval or wants to delay menses, discuss extending the active pills.
- Instruct to extend active pills to 6-9 weeks or until BTB occurs; take a 3- 4 day hormone free interval and restart (relabel pack to correct day of week).

Extended COC Regimen: Helpful Hints

- Or do continuous pill regimen (see instructions- “Rule of 3’s”)
- Make sure your patient understands and is comfortable with this extended or continuous regimen; if not, use standard regimen or 84/7 COC

Extended COC Regimen: Negatives

- Increases counseling time in the office; your patient must understand how to extend
- Side effects?? - no extensive data; studies underway

Extended COC Regimen: Negatives

- Possibly increased cost because more active weeks per year (prescribe 3 months at a time/4 packs)
- Some insurances/pharmacy will only give patient one pack at a time
- Confusing for some patients

Extended COC Regimen: Negatives

- Increased lifetime steroid use, but no theoretical reason to anticipate increased complications (i.e. DVT, MI, stroke, etc.); no extensive data
- No reported increase in complications; extended regimens used for decades in patients with endometriosis

Which pill do I pick?

If heavy, prolonged or painful bleeding:

COC with a strong progestin-

Levonorgestrel or Norgestrel

If acne, hirsuitism, weight concerns, PMDD:

COC with a less androgenic progestin-

Desogestrel or Drosperinone

COC-strong progestins

Original Brand Name	Branded Generic Names	Ethinyl Estradiol	Progestin (mg)	Regimen
Nordette Levlen	Levora Portia	30	Levonorgestrel 0.15	21/7
Alesse	Levlite Aviane Lessina Lutera Sronyx	20	Levonorgestrel 0.1	21/7
Seasonale	Quasense Jolessa	30	Levonorgestrel 0.15	84/7
Seasonique	Intera	30		84/7 EE
Lo/Ovral	Low-Ogestrel Cryselle	30	Norgestrel 0.3	21/7

COC-medium strength progestins

Ortho-Novum	Necon 1/35 Nortel 1/35 Norinyl 1+35	35	Norethindrone 1	21/7
Modicon	Brevicon Necon 0.5/35 Nortel 0.5/35 Ortho Novum 777	35	Norethindrone 0.5	21/7
Ovcon-35	Balziva	35	Norethindrone 0.4	21/7
Femcon FE (chewable)		35		21/7 (with iron)
Loestrin Fe 1/20	Junel Fe 1/20 Microgestin Fe 1/20	20	Norethindrone acetate 1	21/7 (with iron)
Loestrin 24 Fe		20		24/4 (with iron)
Loestrin Fe 1.5/30	Junel Fe 1.5/30 Microgestin Fe 1.5/30	30	Norethindrone acetate 1.5	21/7 (with iron)
Demulen 1/35	Kelnor 1/35 Zovia 1/35	35	Ethynodiol diacetate 1	21/7
Ortho-Cyclen	Sprintec Mononessa	35	Norgestimate 0.25	21/7

COC-less androgenic progestins

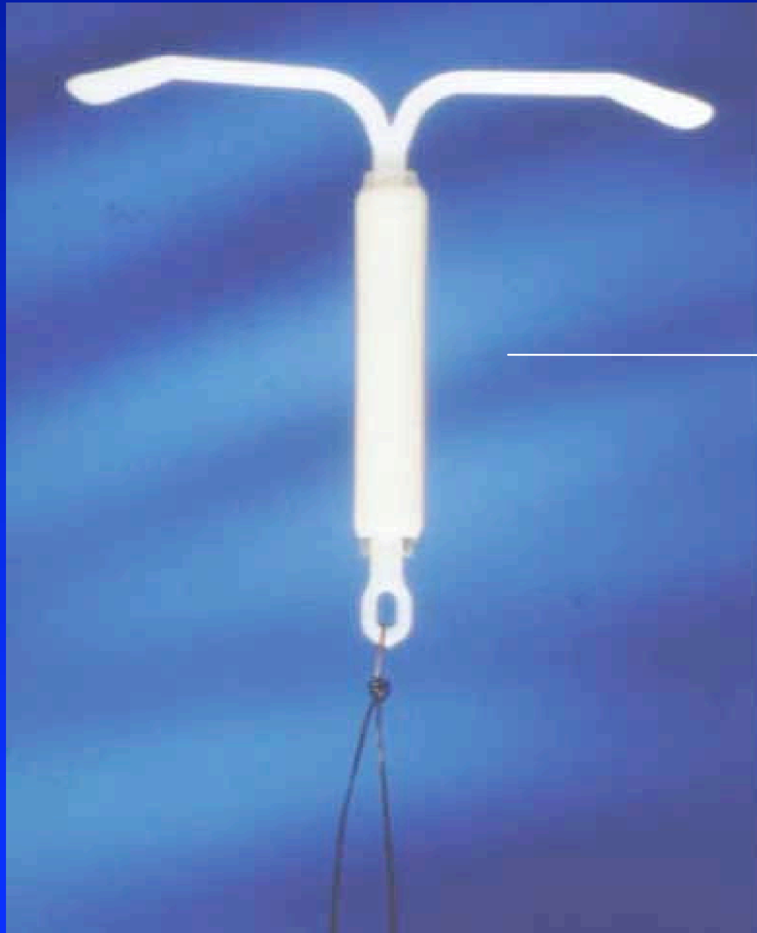
Original Brand Name	Branded Generic Names	Ethinyl Estradiol	Progestin (mg)	Regimen
Desogen Ortho-Cept	Apri Reclipsen Solia	30	Desogestrel 0.15	21/7
Mircette	Kariva Azurette	20		21/2/5 EE 10 mcg
Yasmin	Ocella	30	Drosperinone 0.3	21/7
Yaz	Gianvi	20		24/4

Other Progestins that alter menstrual bleeding

- LNG-IUS
- Depot medroxyprogesterone acetate (DMPA)
- Levonorgestrel implants
- Progesterone only oral contraceptives

Levonorgestrel Intrauterine System (LNG IUS)

32 mm



Steroid reservoir

levonorgestrel 20 mcg/day

LNG IUS: Percentage Reduction of Menstrual Blood Loss

Milsom et al. Am J Obstet Gynecol 1991;164:879

LNG IUS Counseling: Changes in Bleeding

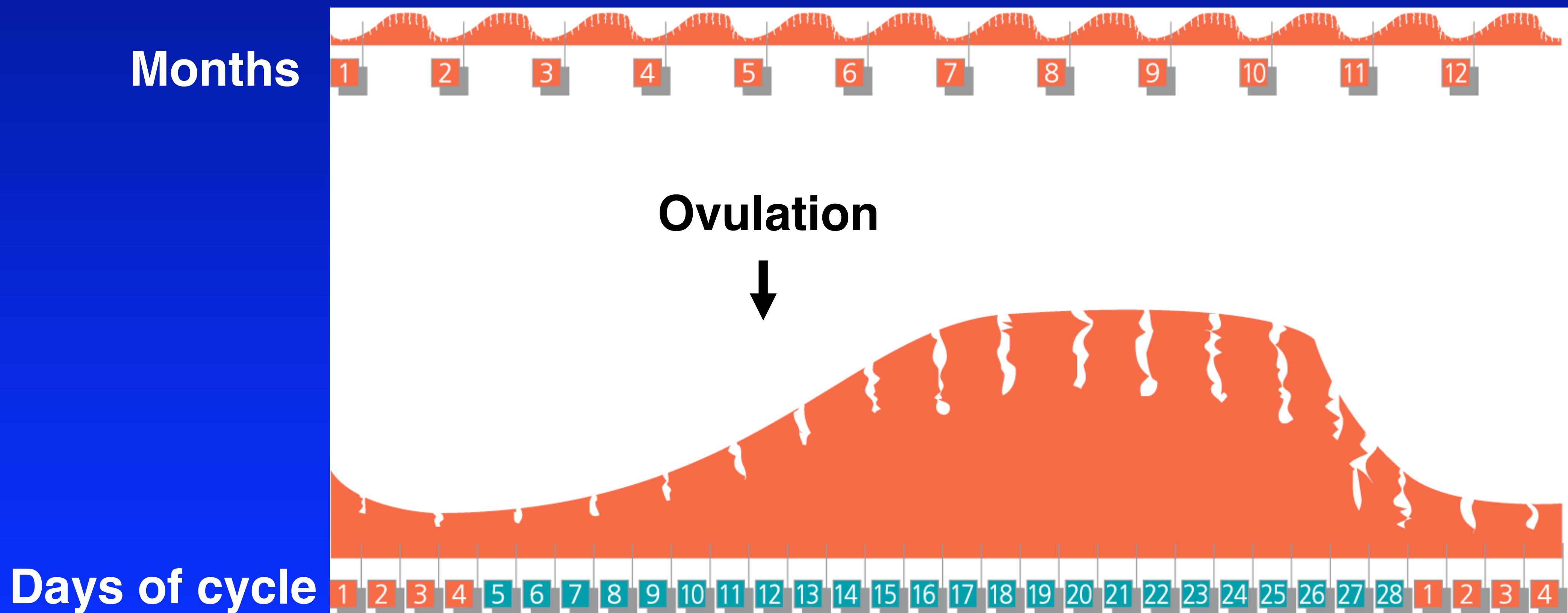
- Bleeding characteristics:
  - 1 – 4 mo frequent spotting
  - 1 – 6 mo reduced duration and amount of bleeding
  - Reduction in menstrual blood loss
  - After 12 mo, about 20 % have no bleeding

Pakarinen et al. Fertil Steril 1997;68:59

LNG IUS Counseling: Absence of Bleeding

- Local effect
  - No proliferation of endometrium
- This is expected. It is not a sign of:
  - Pregnancy
  - Ovarian or pituitary dysfunction
  - Menopause
- Rapid return to menstruation after removal

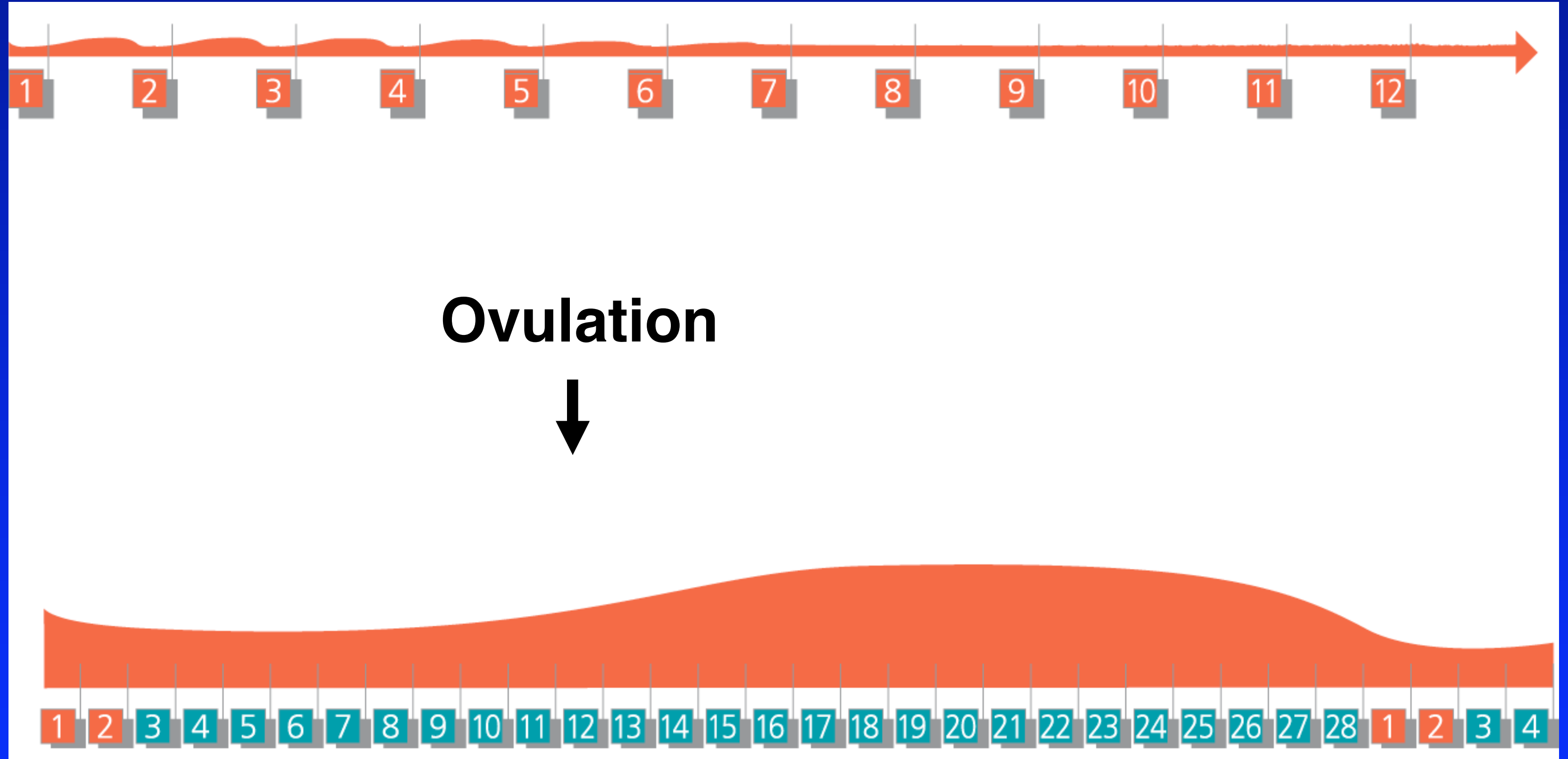
LNG IUS: Endometrial Effect



Changes in the endometrium during normal menstrual cycle

LNG IUS: Endometrial Effect

Months



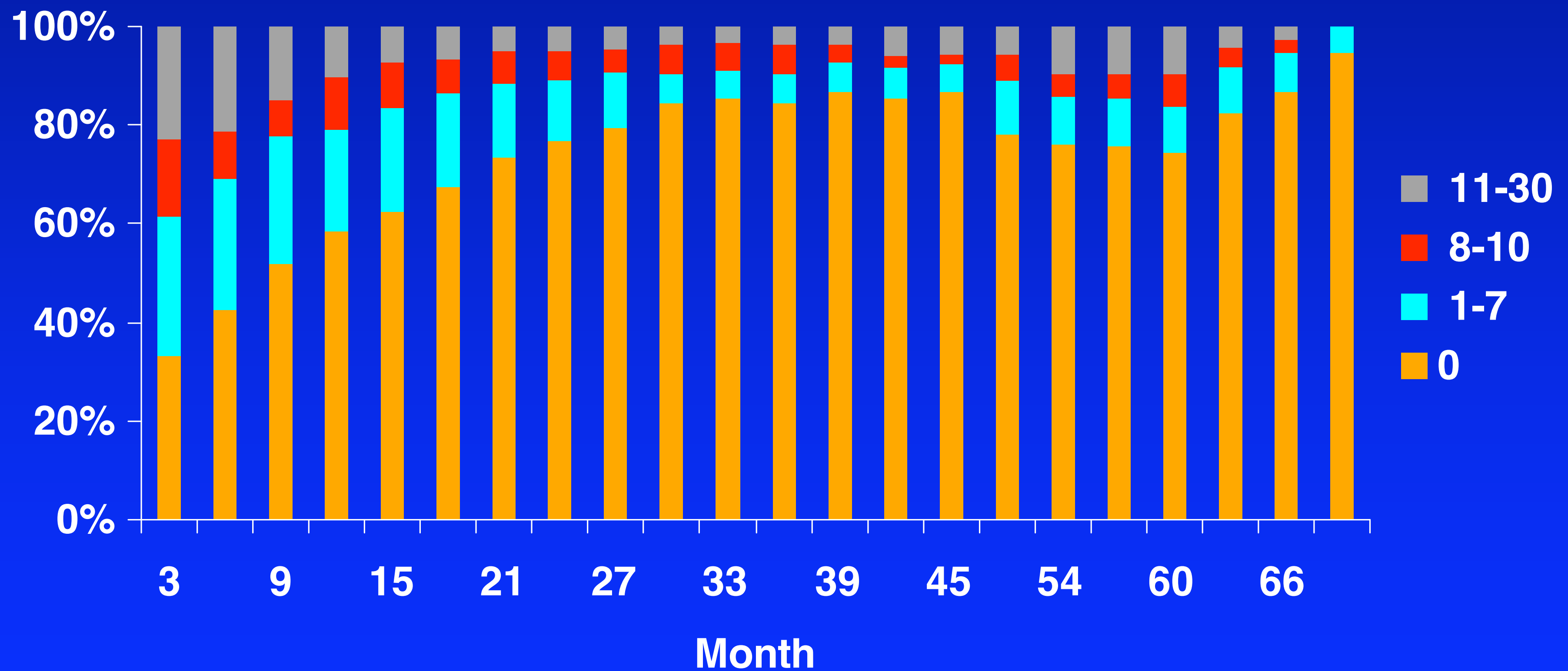
Days of cycle

Endometrium in "resting state" with LNG IUS

DMPA Intramuscular Injections

- Menstrual changes occur in almost all users
- Most experience unpredictable bleeding patterns in first few months of use
- With continued use, frequency and length of bleeding episodes decreases with most becoming amenorrheic over time

Bleeding Patterns In DMPA Users

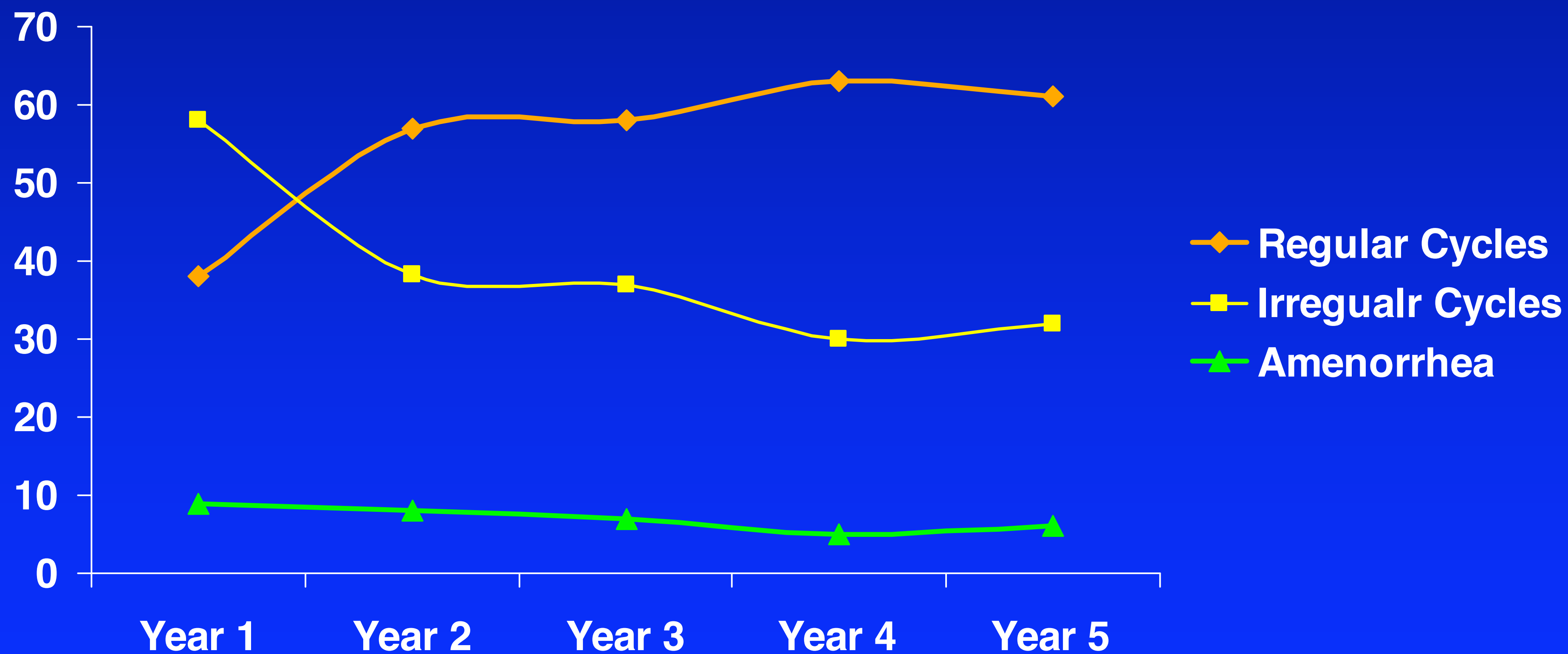


Fertil Steril 1973; 24:331

Levonorgestrel Implants

- Menstrual changes occur in almost all women
- During the first year, the majority (2/3's) experience irregular bleeding with the remainder having regular menses (1/4) or amenorrhea (about 10%)
- Over 5 years of use, the majority eventually resume a regular bleeding pattern

Bleeding Patterns in Norplant Users



Obstet Gynecol 1991; 77: 256

Progestin Only Oral Contraceptive

Original Brand Name	Branded Generic Names	Progestin	Regimen continuous
Norethindrone	Camila	0.35	
	Errin	0.35	
	Micronor	0.35	
	Nor-Q-D	0.35	
	Jolivette		
Norgestrel	Ovrette	0.075	

Conclusion

1. AUB in adolescents is a common problem.
2. The initial evaluation of the patient can be started by the pediatrician.
3. Treatment can be initiated with a combined oral contraceptive in a cyclic manner.
4. Extended or continuous COC is the most common treatment, but LNG-IUS is also being used in certain situations.

STOP HERE

Trends in HRT

Traditional HRT regimens	More recent HRT regimens
• Days 1-25 estrogen	• Continuous estrogen with cyclic progestin
• Days 16-25 progestin	• Continuous combined
• Days 26-31 no meds	

Trends in Oral Contraceptives

Traditional OC regimens	More recent OC regimens
• Days 1-21 EE+P	• Less hormone free days
• Days 22-28 Placebo	• Extended regimen
• Shift to lower doses of estrogen	• New progestins
• Shift to less androgenic progestins	

Contraceptive Effects on Menstruation: SUMMARY

- Most women prefer lighter, less frequent menses
- Current and future contraceptive methods will favorably affect menstruation
- Counseling regarding alterations in menstruation will be critical to initiation and continuation of these contraceptive methods

Contraceptive Effects on Menstruation: Elimination of Monthly Menses

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Scott and White Clinic/Hospital, Temple, Texas

Which BCP?

Necon 1/35 (generic)	Estrogen 35 mcg; Norethindrone 1 mg	medium strength
Desogen	Estrogen 30 mcg; desogestrel 0.15 mg	low progestin
Mircette	Estrogen 20 mcg; desogestrel 0.15 mg (and 5 days of estrogen only 10 mcg)	low estrogen
Nordette (generic)	Estrogen 30 mcg; levonorgestrel 0.15 mcg	strong progestin
Yasmin	Estrogen 30 mcg; drosperinone 3 mg	low progestin

Is Monthly Menstruation Natural???

VS

- Late menarche
- Early childbearing
- High parity
- Prolonged breastfeeding
- Early menopause

- Early menarche
- Late childbearing
- Low parity
- Shortened breastfeeding
- Late menopause

Why Alter Menstruation: Frequency, Duration, Amount

- Menstrual Disorders Affect Millions of Reproductive Age Women:
  – menorrhagia
  – dysmenorrhea
  – premenstrual symptomatology
  – “menstrual” migraines

Problems of Incessant Ovulation/Bleeding

- Anemia
- Endometriosis
- Ovarian cysts
- Ovarian cancer

Is Monthly Menstruation Natural???

vs

- Late menarche
- Early childbearing
- High parity
- Prolonged breastfeeding
- Early menopause

- Early menarche
- Late childbearing
- Low parity
- Shortened breastfeeding
- Late menopause

$$ Costs $$ of Monthly Menstruation

- Sanitary protection
- Medical expenses:
  - pain meds
  - office visits
  - procedures
- Lost wages/productivity

Is Monthly Menstruation Natural???

VS

- Late menarche
- Early childbearing
- High parity
- Prolonged breastfeeding
- Early menopause

- Early menarche
- Late childbearing
- Low parity
- Shortened breastfeeding
- Late menopause

Oral Contraceptive Effects on Menstruation

- Bleeding duration/quantity decreased
- Dysmenorrhea decreased
- Regulation of cycle length: predictability

Combination Oral Contraceptives

- Standard Regimen:
  - 21 days of estrogen + progestin
  - 7 hormone free days
- Rationale: mimic an average cycle length of 28 days
- Drawback: monthly hormone withdrawal symptoms

Hormone Withdrawal Symptoms In Oral Contraceptive Users

Objective

- Measure the frequency and severity of symptoms during the pill free interval compared to the active pill interval

Sulak et al., Obstet Gynecol 2000, 95:261-6.

Hormone Withdrawal Symptoms In Oral Contraceptive Users

Study Design

- **Prospective study of OC users**
- **69 New Starts: No OC use in last 3 months**
- **193 Current Users: OC use $\geq$ 12 months**

Sulak et al., Obstet Gynecol 2000, 95:261-6.

Hormone Withdrawal Symptoms In Oral Contraceptive Users

Data Collection

- Demographics
- Daily calendars to subjectively record headaches, pelvic pain, bleeding, analgesic use, and other symptomatology

Sulak et al., Obstet Gynecol 2000, 95:261-6.

Hormone Withdrawal Symptoms in Oral Contraceptive Users

	21 active	7 hormone free	p value
Pelvic pain	21%	70%	<.001
Headaches	53%	70%	<.001
Breast tenderness	19%	58%	<.001
Bloating/swelling	16%	38%	<.001
Use of pain meds	43%	69%	<.001

Sulak et al. *Obstet Gynecol* 2000; 95: 261-266

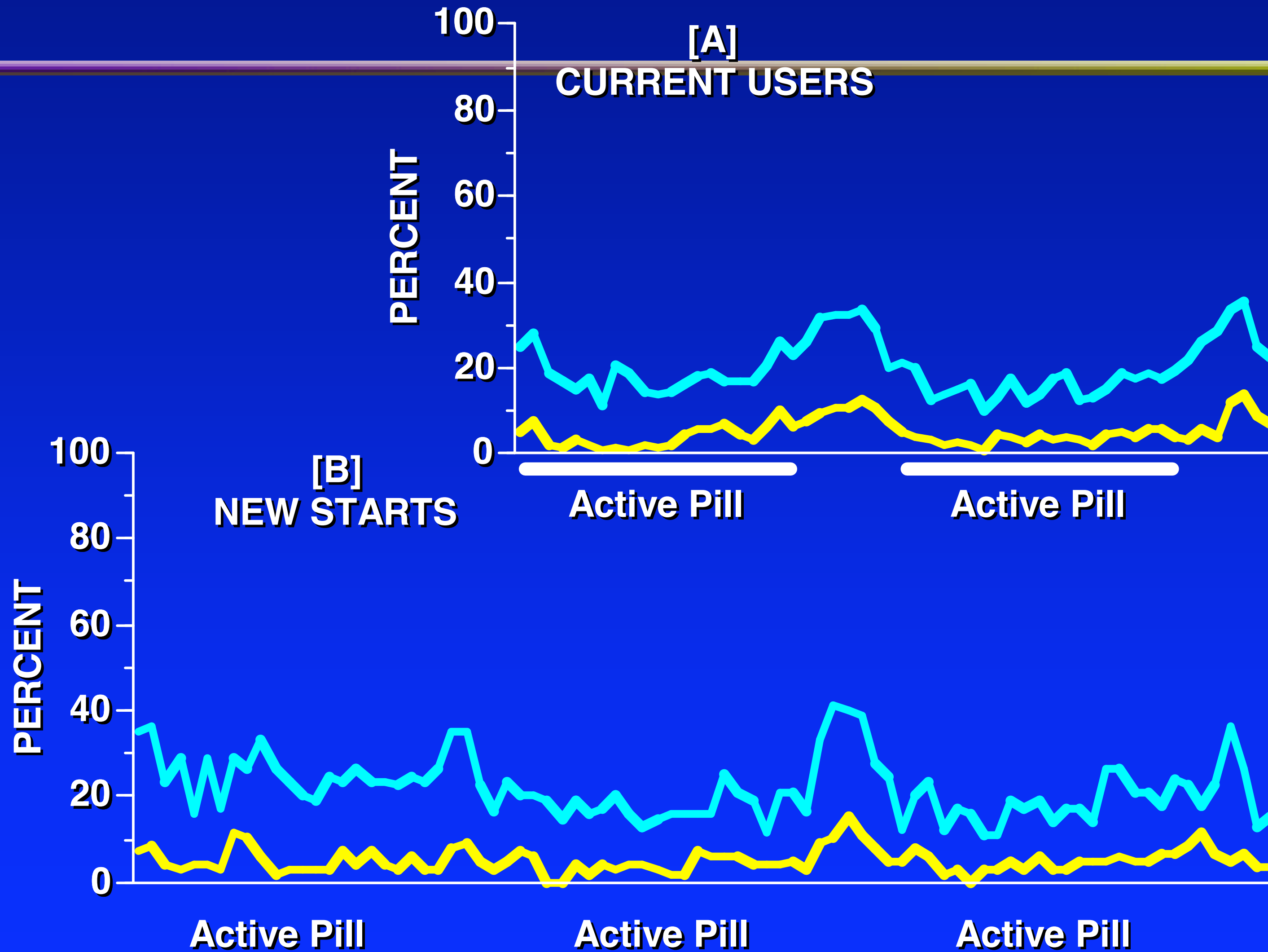
Hormone Withdrawal Symptoms In Oral Contraceptive Users

Headaches

- Headaches were more frequent and more severe during the hormone free interval

Sulak et al., Obstet Gynecol 2000, 95:261-6.

Frequency of Headaches



(Sulak et al.; Obstet Gynecol 2000; 95:261-6)

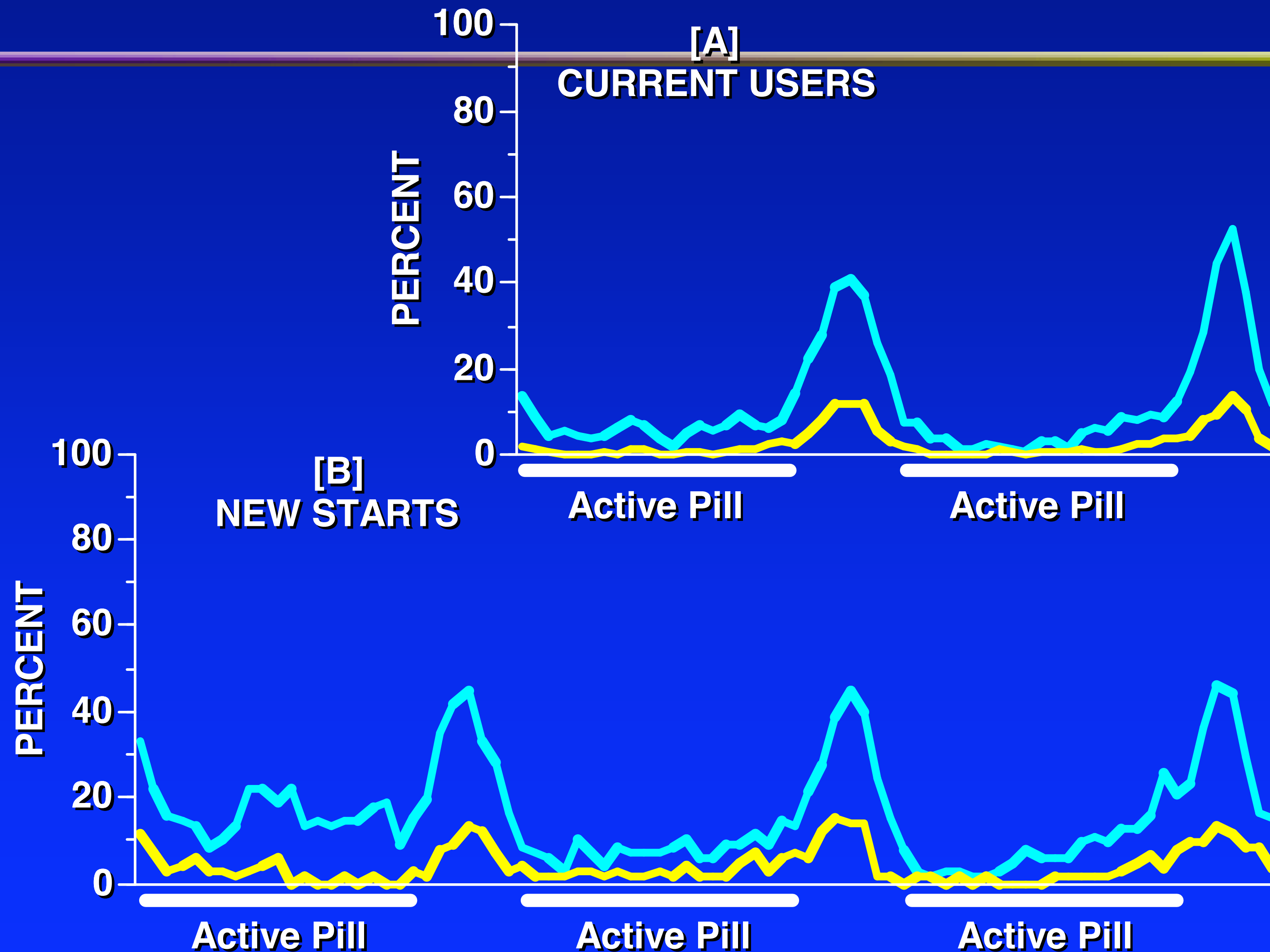
Hormone Withdrawal Symptoms In Oral Contraceptive Users

Pelvic Pain/Cramps

- **Pelvic pain/cramps were more frequent and more severe during the hormone free interval**

Sulak et al., Obstet Gynecol 2000, 95:261-6.

Frequency of Pelvic Pain and Cramps



(Sulak et al.; Obstet Gynecol 2000; 95:261-6)

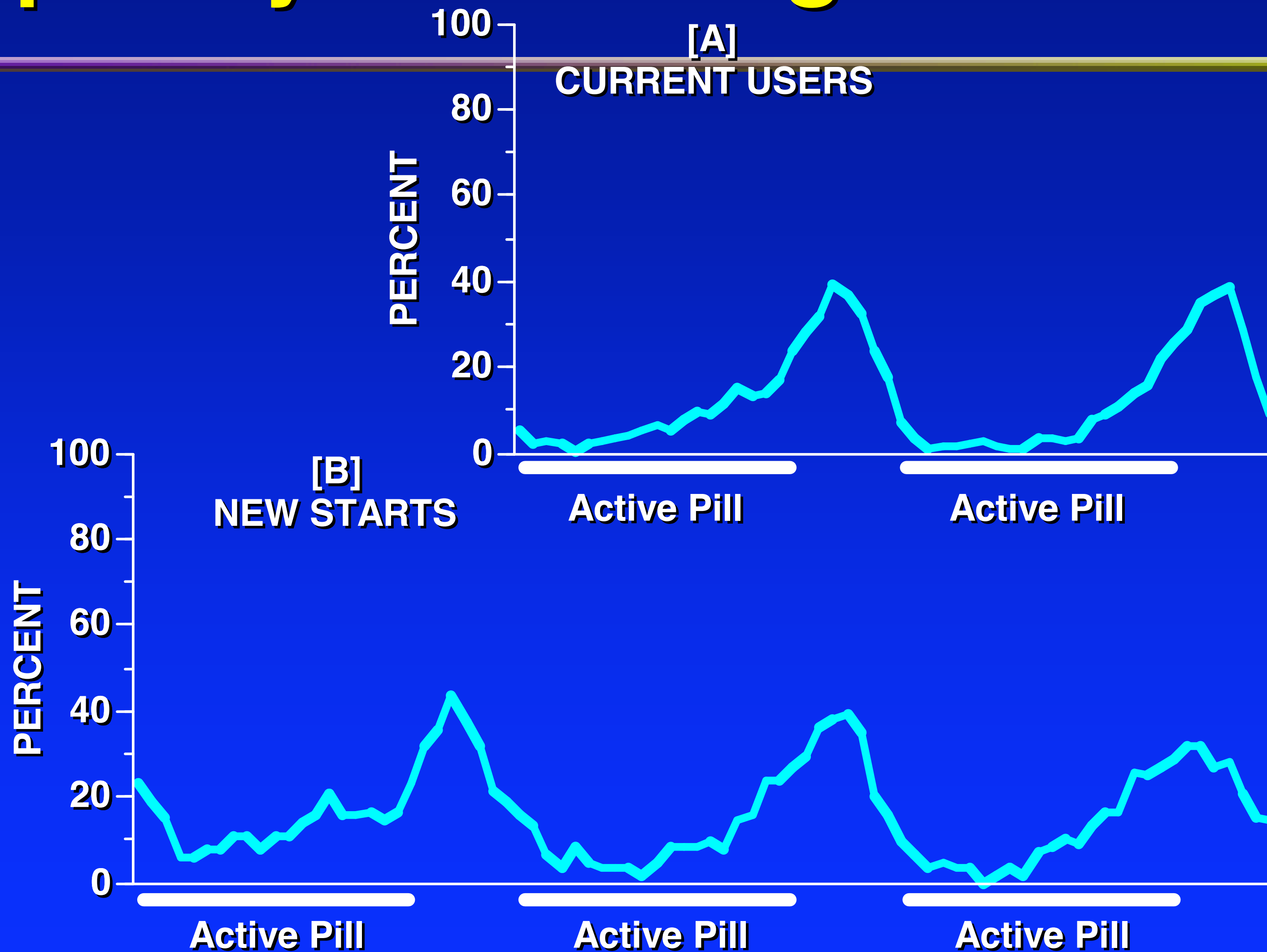
Hormone Withdrawal Symptoms In Oral Contraceptive Users

Bloating/Swelling

- **Bloating and swelling were more common during the hormone free interval**
- **Symptoms began in the preceding week prior to the hormone free interval**

Sulak et al., Obstet Gynecol 2000, 95:261-6.

Frequency of Bloating and Swelling



(Sulak et al.; Obstet Gynecol 2000; 95:261-6)

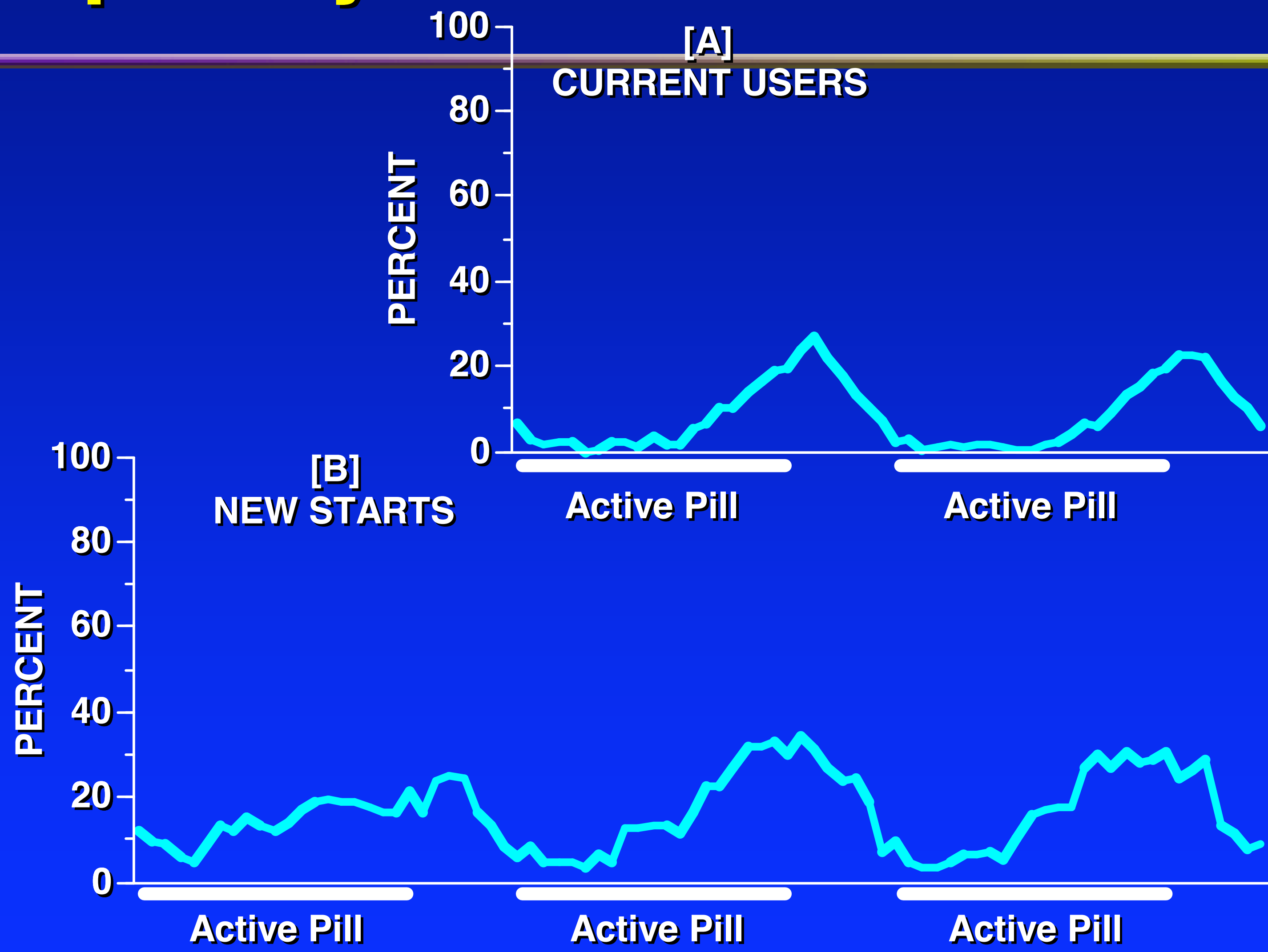
Hormone Withdrawal Symptoms In Oral Contraceptive Users

Breast Tenderness

- Breast tenderness was more common during the hormone free interval
- Symptoms began in the preceding week prior to the hormone free interval

Sulak et al., Obstet Gynecol 2000, 95:261-6.

Frequency of Breast Tenderness



(Sulak et al.; Obstet Gynecol 2000; 95:261-6)

Extending the Duration of Active Oral Contraceptive Pills to Manage Hormone Withdrawal Symptoms

Objective

- **Test the hypothesis that extending the number of consecutive active OCs will decrease the frequency of menstrual related problems**

Sulak et al., Obstet. Gynecol. 1997; 89: 179-83

Extending the Duration of Active Oral Contraceptive Pills to Manage Hormone Withdrawal Symptoms

Method

Prospective analysis of 50 patients on OCs who experienced hormone withdrawal symptoms during the pill free interval and were allowed to extend the number of consecutive active OCs

Sulak et al., Obstet. Gynecol. 1997; 89: 179-83

Symptoms During the Pill Free Interval*

Symptoms	Ranking of Symptoms* #1	#2	#3	#4	Total
Migraines	48%	14%	6%	8%	76%
Dysmenorrhea	22%	40%	16%		78%
Menorrhagia	18%	12%	6%		36%
PMS	12%	10%	10%		32%
Other**		6%			
Total	100%	82%	38%	8%	

*Most patients reported more than one symptom
+ most severe symptoms
** Acne, endometriosis, recurrent vuvular cysts

Sulak et al., Obstet. Gynecol. 1997; 89: 179-83

Method of Extending Number of Active Weeks

- Instructed to take 6 consecutive weeks of active OCs followed by a hormone free week
- The interval of active pills was increased by 3 weeks each consecutive cycle (6 wks, 9 wks, 12 wks), followed by a hormone free week
- If a patient experienced intolerable side effects, she remained on the regimen that worked best for her

Sulak et al., Obstet. Gynecol. 1997; 89: 179-83

Study Results of the 50 Patients*

- 37 patients (74%) stabilized on an extended regimen →
  - 6 week → 8
  - 9 week → 13
  - 12 week 16
- 13 patients (26%) not stabilized on an extended regimen
  - Most common reasons
    - Breakthrough bleeding
    - Breakthrough spotting
    - Headaches

*All patients were on a low dose monophasic pill

Sulak et al., Obstet. Gynecol. 1997; 89: 179-83

Menstrual Reduction With Extended Use of Combination OCPs: Randomized Controlled Trial

- 90 patients randomized to 21/7 day versus 42/7 day regimen of a 30 mcg monophasic OC
- 59% completed the 48 week study
- The 42/7 day regimen resulted in fewer bleeding days and no increase in mean spotting days or bleeding episodes

Miller L, Notter K: Obstet Gynecol 2001; 98: 771 - 778

Acceptance of Altering the Standard 21 day/7 day Oral Contraceptive Regimen to Delay Menses and Reduce Hormone Withdrawal Symptoms

Patricia J. Sulak, M.D., Thomas J. Kuehl, Ph.D., Miriam Ortiz, R.N., and Bobby L. Shull, M.D.

Am J Obstet Gynecol 2002; 186: 1142-9

Study Design

- Retrospective review of patients on 30-35 mcg OCs with hormone withdrawal symptoms during the hormone free interval, offered alterations to their 21/7 day regimen
- Electronic medical record search of the phrase "extending the number of active pills" by Patricia J. Sulak, M.D.
- Initial counseling was between December 93 and October 2000
- Counseled on increasing the number of active pills +/- decreasing the number of hormone free days

Results

- **318 counseled on “extending the number of active pills”**
- **292 had follow up**
- **26 lost to follow up**
- **hormone withdrawal symptoms: headache, dysmenorrhea, menorrhagia, premenstrual symptomatology**

Reasons For Extending Active Pills

(292 Patients)

	Primary Reason*	% with Sx**
Headache	35%	46%
Dysmenorrhea	21%	41%
Hypermenorrhea	19%	30%
Premenstrual Sxs	13%	22%
Other * **	12%	
	100%	

* most severe symptom, ** most had more than one Sx

*** convenience, endometriosis, acne

Characteristics of the 292 Patients

- Average age 35.4 with 101 age 40 or greater
- Patients citing dysmenorrhea were younger
- Patients citing menorrhagia had a greater BMI

Results of 292 Patients

		#	%
I:	Did not extend	25	9
II:	Extended then D/Ced OCs	57	19
III:	Extended then returned to 21/7	38	13
IV:	Continuing to extend	172	59
		292	100

Group I: Chose Note To Extend

[25 patients (9%)]

Reasons: Preference for monthly menses
Symptoms not severe enough
Fears/concerns
BTB on current 21/7 regimen
Increased cost of pills

Group II: Extended, then discontinued OCs

[57 patients (19%)]

Reasons: Desire for pregnancy
- Sterilization
- Became menopausal
- Pelvic surgery including hysterectomy
- No longer sexually active
- Worsening of numerous symptoms
- Cost of pills

Group III: Extended, then returned to 21/7

[38 patients (13%)]

Reasons: Bleeding issues: BTB, BTS
Side Effects
Fear/concerns
Increased costs

Group IV: Continuing to extend

[172 patients (59%)]

- typical pattern was 12 ± 12 (mean ± SD) weeks of active pills with a median of 9 weeks and a range up to 104 weeks
- typical pill-free interval was 6 ± 2 days with a median of 5 days and a range of 0 to 7; 46% reported <7 day hormone free interval with 4 or 5 days most common
- range of follow up 3 months to 90 months with an average of 25 months
- using survival analysis methods, at 5 years 46% ± 5% (mean ± SE) continued an extended regimen