WOMEN'S HEALTH:
Beyond the Annual Visit

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Optimizing Medical Management of Uterine Fibroids: Achieving Patient-Centered Goals and Outcomes

Anita L. Nelson, MD
Professor Emeritus, Obstetrics & Gynecology
David Geffen School of Medicine at UCLA
Clinical Professor, Obstetrics & Gynecology
University Southern California
Professor and Chair, Obstetrics & Gynecology
Western University of Health Sciences

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Conflict of Interest Disclosure
Anita L. Nelson, MD

Grants/ Research	Mylan Pharmaceuticals, Myovant Sciences, Organon/Merck & Co., Sagami Rubber Industries, Sebela Pharmaceuticals
Honoraria/ Speakers Bureau	Agile Therapeutics, Bayer HealthCare, Mayne Pharma, Myovant Sciences, Organon/Merck & Co., TherapeuticsMD
Consultant/ Advisory Board	Agile Therapeutics, Bayer HealthCare, Mayne Pharma, Pfizer, TherapeuticsMD

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Learning Objectives

At the end of this presentation, the participant will be able to

- Recognize the role of early diagnosis and culturally sensitive care in improving outcomes for patients with uterine fibroids
- Formulate strategies to engage patients in discussions about their fibroid symptoms and therapy preferences
- Evaluate the latest evidence on the MOA, safety, and efficacy of GnRH antagonists for the management of uterine fibroids

Prevalence of Leiomyoma in the US

- Most common uterine neoplasm (70%-80%)
- Estimates of prevalence vary
  - Survey of women → ultrasound studies
- Consistent patterns seen across all studies
  - Prevalence increases during reproductive years
  - Black women have higher rates than White women
  - 25%-50% of women with fibroids are symptomatic
    - Often significant delays in diagnosis
- Significant adverse impacts seen on health (annually) and QoL
  - Annual costs in US $6-34 billion
- Substantial increase in number of ED visits

Al-Hendy A, et al. *N Engl J Med*. 2021;84(7):630-642.

Fascinating Facts About Fibroids

- Each tumor is monoclonal
- May be asymptomatic or cause life-threating bleeding, excruciating pain, infertility, miscarriage
  - Location, size, and number of myoma are important
- Can grow to very large dimensions, parasitize, invade other structures
- Both genetic and environmental factors trigger tumor formation and growth
  - Potential targets for prevention?
- Growing but still limited number of treatment options

Estrogen Dependence

- Supporting evidence
  - Rare before puberty
  - Shrink after menopause
  - Grow in pregnancy
  - Estrogen and progesterone receptors in higher concentration than in normal myometrial cells
  - Smokers have lower incidence of myoma
  - GnRH agonists cause reduction in myometrial volume
- Refuting evidence
  - Many women have small fibroids that do not grow

Uterine Fibroid Risk Factors

- Risk factors (>2x): Black race, age, perimenopause, hypertension, family history, time since last birth, food additives, and soy milk consumption
- Protective factors: COC, DMPA, smoking with low BMI, parity

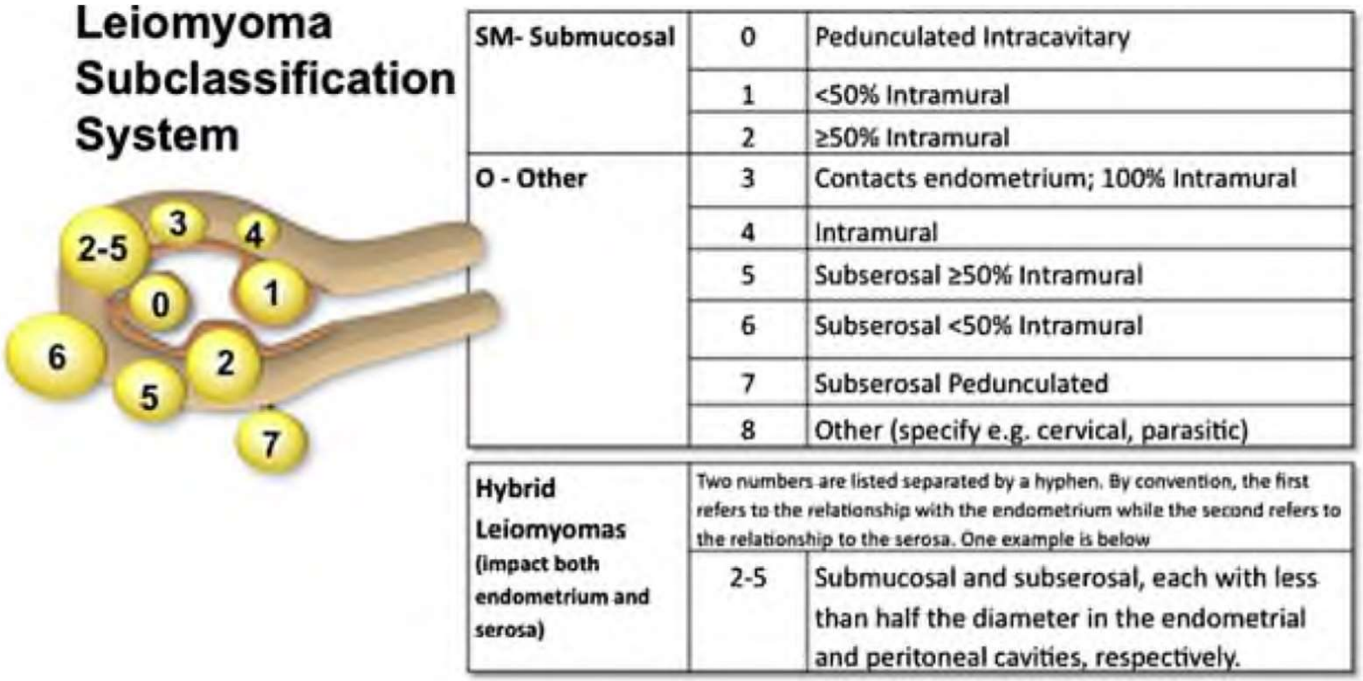
Stewart EA, et al. *BJOG*. 2017;124(10):1501-1512.

Leiomyoma: Natural History

- May grow into large (50 lb) size to fill pelvis
- Average growth is 1.2 cm in 2.5 years
  - Range is -0.9 cm to +6.8 cm in 2.5 years
- May outgrow blood supply and degenerate or necrose
- Generally shrink without estrogen
  - Postmenopausal women
  - Do not shrink reliably

DeWaay DJ, et al. *Obstet Gynecol*. 2002;100(1):3-7.

Leiomyoma Sub-Classification System



SM- Submucosal	0	Pedunculated Intracavitary
	1	<50% Intramural
	2	≥50% Intramural
O - Other	3	Contacts endometrium; 100% Intramural
	4	Intramural
	5	Subserosal ≥50% Intramural
	6	Subserosal <50% Intramural
	7	Subserosal Pedunculated
	8	Other (specify e.g. cervical, parasitic)
Hybrid Leiomyomas (impact both endometrium and serosa)	Two numbers are listed separated by a hyphen. By convention, the first refers to the relationship with the endometrium while the second refers to the relationship to the serosa. One example is below	
	2-5	Submucosal and subserosal, each with less than half the diameter in the endometrial and peritoneal cavities, respectively.

Munro MG, et al. *Fertil Steril*. 2011;95(7):2204-2208.

Leiomyoma Classification Variants

- Submucosal: grow into cavity of uterus
  - Aborting variant on long pedicle may be delivered through cervix
- Subserosal: grow into outer surface of uterus and can become:
  - Pedunculated: on long stalk in peritoneal cavity
  - Parasitic: establishes new blood supply from another organ
  - Broad ligament myoma

Common Clinical Presentations for Symptomatic Uterine Myoma

GYN	OB
Heavy menstrual bleeding	Preterm delivery
Dysmenorrhea	Abnormal presentation
Pelvic pain	Lower birth weight
Urinary problems (frequency, retention)	Short cervix
Constipation	
Infertility	
Recurrent pregnancy loss	
Dyspareunia	

Czuczwar P, et al. *Ultrasound Obstet Gynecol*. 2015;45(6):744-750.

HMB Due to Uterine Leiomyoma

- US survey: 73% of women with self-reported fibroids had heavy menstrual bleeding (HMB)[1]
  - 39% had passage of clots and needed more than 1 form of protection
  - 68.3% had anemia/fatigue
- International survey: 60% of women with self-reported fibroids had heavy bleeding, 37% prolonged bleeding[2]

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1. Marsh EE, et al. *J Womens Health (Larchmt).* 2018;27(11):1359-1367.
2. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. *Lancet*. 2017;390(10100):1211-1259.

HMB Due to Uterine Leiomyoma

- Anemia is #1 cause of years lived with disability in women[1]
- For 47% of women hospitalized with hemoglobin <5 from HMB, the cause was found to be fibroids[2]
- Strongly diminished QOL and productivity[3]

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1. Fernández-Jiménez MC, et al. *Womens Health Rep (New Rochelle)*. 2020;1(1):26-35
2. Nelson AL, et al. *Am J Obstet Gynecol*. 2015;213(1):97.e1-97.e6.
3. Zimmerman A, et al. *BMC Womens Health*. 2012;12:6.

Impacts of Fibroids

- Uterine fibroids associated with disability similar to other chronic diseases
  - Lower vitality and social function than women with breast cancer
- Fibroid-related hysterectomies account for 45% of all US hysterectomies (~200,000)[1]
- Lifetime hysterectomy risk in US is 45%[2]

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1. Go VAA, et al. *Am J Obstet Gynecol*. 2020;223(5):674-708.e8.
2. Parker WH. *OBG Management*. 2017;29(2):42-48.

Uterine Fibroids and Emotional Well-Being

- Among women with symptomatic uterine fibroids:

58%	Report feeling sad or hopeless
69%	Feel uneasy about physical presence of fibroids
65%	Worry about bleeding and soiling clothes or bedding

Borah BJ, et al. *Am J Obstet Gynecol*. 2013;209(4):319.e1-319.e20.
Pron G, et al. *Fertil Steril.* 2003;79(1):112-119.

Clinical Presentation

- History
  - Abnormal uterine bleeding: heavy, prolonged, painful
  - Anemia (iron deficiency)
  - Pressure symptoms: urinary frequency, urinary retention, lower back pain
  - History of subfertility
  - Acute pelvic pain from necrosis
- Physical exam
  - Usually enlarged, irregularly contoured uterus

Diagnostic Imaging

- Transvaginal ultrasound is a rapid and cost-effective way to evaluate uterine fibroids, but limitations include:
  - Size and number of fibroids
  - Acoustic shadowing
- Positive predictive value of diagnosing endometrial cavity distortion is as low as 47%[1]
- Saline infusion sonography hysteroscopy improves the ability to see the distortions
- 3D ultrasound
- MRI most useful for mapping location, size, and anatomic relationship of fibroids

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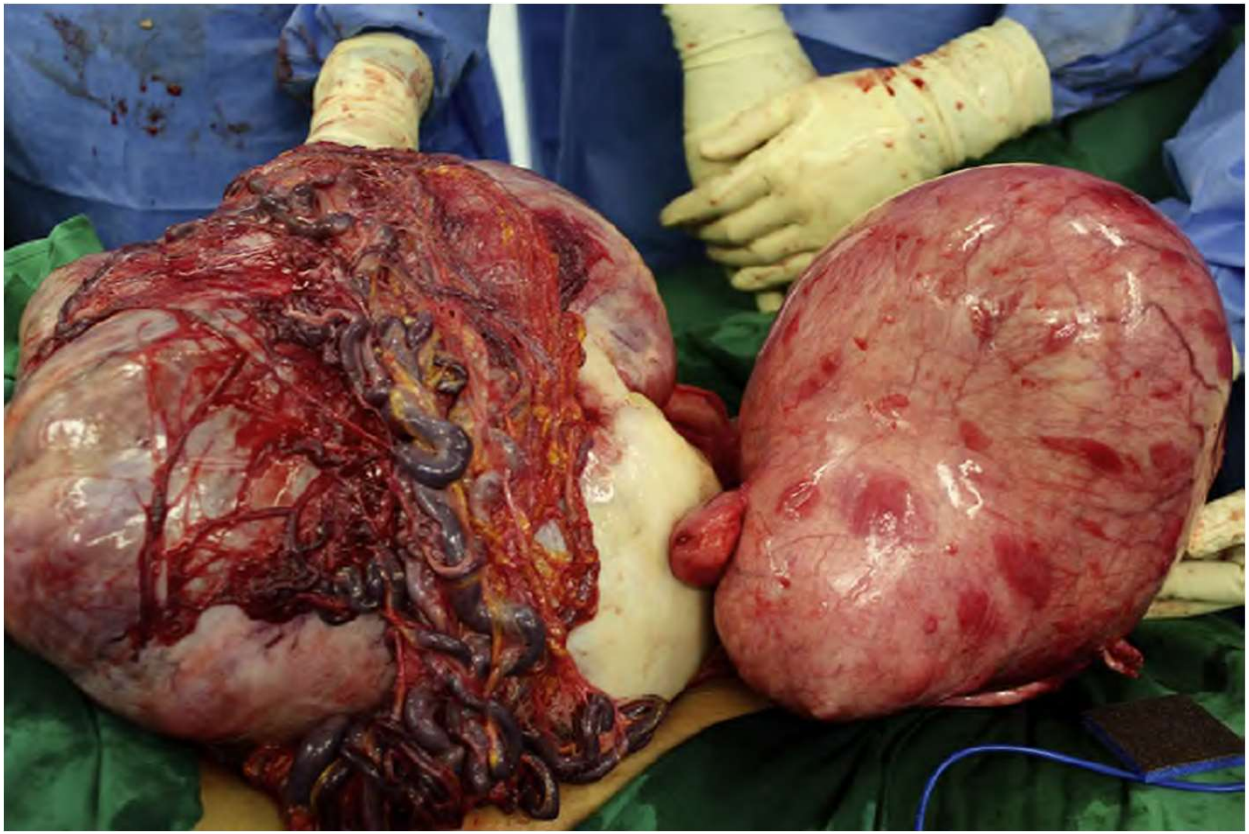
1. Morin SJ, et al. *Contemporary OB/GYN*. 2017;21-26.
https://www.contemporaryobgyn.net/view/optimal-approaches-fibroid-management

Intraoperative Findings



Dashraath P, et al. *Am J Obstet Gynecol*. 2016;215(5):665.e1-665.e2.

Surgical Options

- Endometrial ablation
- Myomectomy
  - Cold knife
  - Electrosurgery
  - Harmonic scalpel
- Myoma destruction
  - Uterine artery embolization (UAE)
  - Transvaginal uterine artery occlusion
  - MRI-guided focused ultrasound
  - Percutaneous laser ablation
  - Cryoablation
- Hysterectomy

Kuo HH, et al. *Taiwan J Obstet Gynecol*. 2017;56(1):73-76.
Czuczwar P, et al. *Menopause Rev*. 2016;15(4):205-209.

Factors to Consider When Reviewing Treatment Options for HMB With Uterine Fibroids

- Fertility desires
- Desire for uterine preservation
- Size and sites of fibroid(s)
- Symptoms caused by fibroids
- Intensity of impacts on health and QOL
- Patient preference
- Cost-effectiveness of different therapies

ACOG's Committee on Practice Bulletins–Gynecology. *Obstet Gynecol*. 2021;137(6):e100-e115.

Shared Decision-Making in Uterine Fibroids

- General
  - Listen to your patient attentively
  - Develop relationship of trust and teamwork
  - Use decision aids when appropriate
- Treatment risk and benefits
  - Assess patient expectations and goals
  - Explain goals of therapy
  - Personalize treatment selection
  - Management plans should consider
    - Symptom severity
    - Desire for fertility
  - Describe risks that are common, including feared risks
  - Monitor for tolerance, compliance, persistence, and effectiveness

Patient Considerations with Medical Therapies

- Does this seem safe?
- Long-term effects
- Healthcare provider explanation
- Peer support/feedback
- Impact on short-/long-term health/fertility goals
- Ease of administering

Case 1

30-year-old nulliparous woman from the African diaspora presents with HMB for 6 years; mother had early hysterectomy

- Has required transfusion in the past
- Tried hormonal contraceptives with little effect
- Told she needed a hysterectomy
- Does not understand why something that is not cancer needs such drastic surgery

Fibroids in Black and White

- 25% of Black women will suffer from fibroids by the age of 25; 80% will have them by age 50
- Black women suffer from fibroids 2 to 3 times more than White women
- Clinically relevant fibroids are detectable in 35% of White and 50% of Black perimenopausal women
- Black women experience more severe disease (increased volume and duration of bleeding, greater likelihood of surgery, larger masses) compared with White women
  - May result in delay in care

ACOG's Committee on Practice Bulletins–Gynecology. *Obstet Gynecol*. 2021;137(6):e100-e115.

Counseling Points

- Listen to her frustrations
- What are her fears?
- What workup has she had? Try not to duplicate.
- What are her goals – short and long term?
- Why does she think earlier methods did not work?
    - Often misunderstanding of treatments vs cure

Prevalence of Symptoms Remaining in Women Currently Being Treated for Uterine Fibroids

Constipation/bloating/diarrhea	56.2%
Heavy menstrual bleeding	56.1%
Pelvic pressure	52.7%
Passage of clots	45.4%
Intermenstrual bleeding	35.6%

- We all know women with fibroids for whom current options do not match their preferences
- New options needed

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Fuldeore MJ, et al. *Int J Womens Health*. 2017;9:403-411.

Case 2

45-year-old White women with HMB with bulky uterine fibroids who wants uterine preservation. Does not want to “become a statistic.” New things are being developed all the time. Can’t she just stick it out until menopause?

- Concerns here: baseline HMB may be worsened by impending anovulatory cycling of perimenopause.

Uterine Fibroids and Anxiety

- Concerns expressed by women with uterine fibroids

69%	Fear health complications
75%	Fear future fibroid growth
55%	Fear need for hysterectomy
54%	Fear risk of cancer

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Borah BJ, et al. *Am J Obstet Gynecol*. 2013;209(4):319.e1-319.e20.

Medical Management Options for Heavy Menstrual Bleeding

- Nonsteroidal anti-inflammatory drugs
- Antifibrinolytics
- Combined hormonal contraceptives
- Progestin-only contraceptives
- GnRH (agonist/antagonist)
- SPRMs and aromatase inhibitors

ACOG's Committee on Practice Bulletins–Gynecology. *Obstet Gynecol*. 2021;137(6):e100-e115.

Initial Medical Therapies for HMB in Women with Uterine Fibroids

- Retrospective analysis of large commercially insured US population
- 41,561 women with HMB from fibroids 2000-2013

79.4%	SARC	(COC, patch, ring)
9.5%	LARC	(implant, injection, LNG-IUS)
8.5%	GnRH analogues	
2.7%	Tranexamic acid	

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Yao X, et al. *BJOG*. 2017;124(12):322-330.

Systemic Review of Combined Oral Contraceptives for Treatment of HMB with Myoma

- Only 2 studies met criteria – one randomized, the other "pseudorandomized"
- COCs performed less well than LNG-IUS at:
  - Controlling HMB
  - Improving QOL
  - Improving hemoglobin
- "Evidence regarding use of COCs as treatment for women with symptomatic fibroids is very scarce and of low quality, and we are very uncertain about the real efficacy of such treatment."

Moroni RM, et al. *Gynecol Obstet Invest*. 2015;79(3):145-152.

DMPA for Treatment of Heavy Menstrual Bleeding with Fibroids

- 20 premenopausal women
- DMPA 150 mg/month for 6 months
- At 6 months
  - 30% Amenorrheic
  - 70% Improved bleeding
  - 15% Increased hemoglobin
  - 48% Decrease in mean uterine volume

Venkatachalam S, et al. *J Obstet Gynaecol*. 2004;24(7):798-800.

Systematic Review of LNG-IUS in Women with Uterine Fibroids

- 11 of 202 studies[1] and 11 of 645 studies[2] in searches met criteria
- Menstrual blood loss decreased among LNG-IUS users who continued to use LNG-IUS until end of study[1,2]
  - Hemoglobin, hematocrit, and ferritin level rose
- Irregular bleeding reported
- 2 studies found higher expulsion rates in women with fibroids (11%) than in women without fibroids (0.3%)[1]
- Range of expulsion in noncomparative studies 0%-20%[1]
- Expulsion related to fibroid size (>3 cm) but not location[2]

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1. Zapata LB, et al. *Contraception*. 2010;82(1):41-55.
2. Jiang W, et al. *Steroids*. 2014;86:69-78.

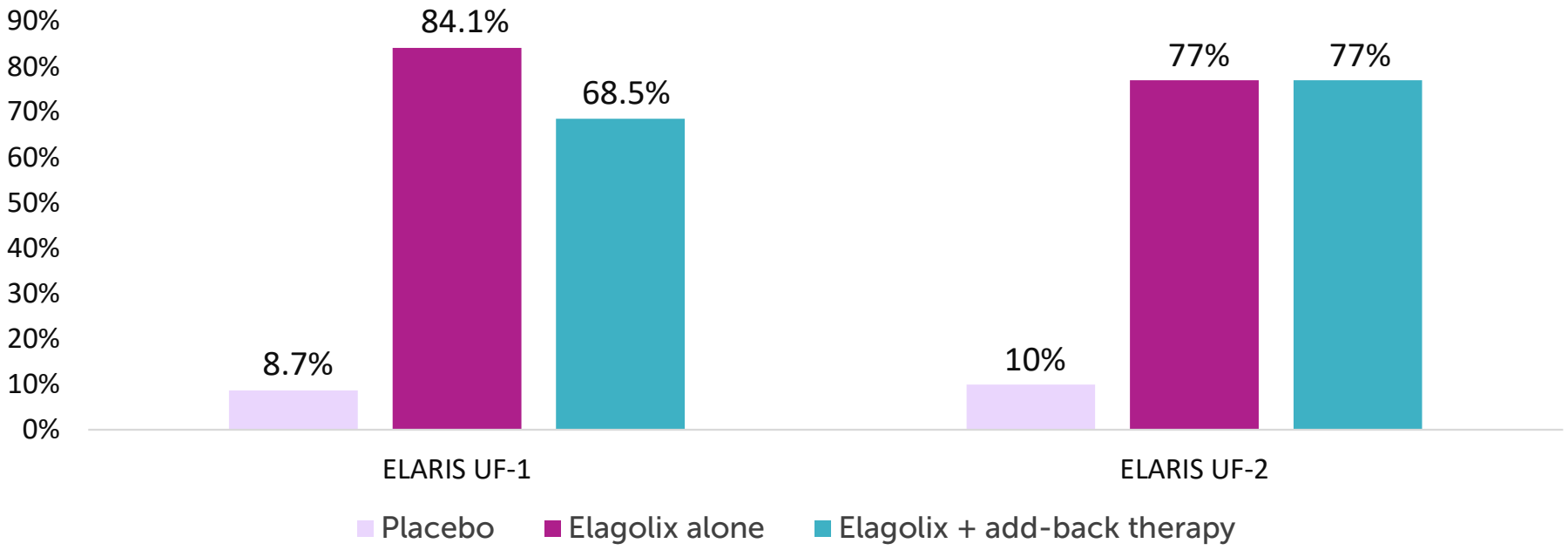
Other Options

- GnRH agonists generally used preoperatively to shrink uterine size; delayed onset of action
- SERMs not used in US due to questions of hepatic toxicity
- GnRH antagonists – new class of drugs with rapid onset
  - Two FDA-approved agents: elagolix, relugolix
  - In clinical trials: linzagolix

Elagolix Overview

- Oral, nonpeptide GnRH antagonist
- Results in rapid, reversible suppression of gonadotropins and ovarian sex hormones
  - Effects occur within 24 hours after initiation of treatment
  - Reversed on discontinuation of drug
- FDA-approved for the treatment of fibroid-related heavy menstrual bleeding
- Formulated with low-dose steroidal add-back to limit hypoestrogenic side effects

ELARIS UF-1 & ELARIS UF-2 RESULTS



*Primary endpoint: menstrual blood loss (MBL) volume of <80 mL in the final month and a ≥50% reduction in MBL volume from baseline to final month. Final month defined as last 28 days before and including the last treatment period visit date.

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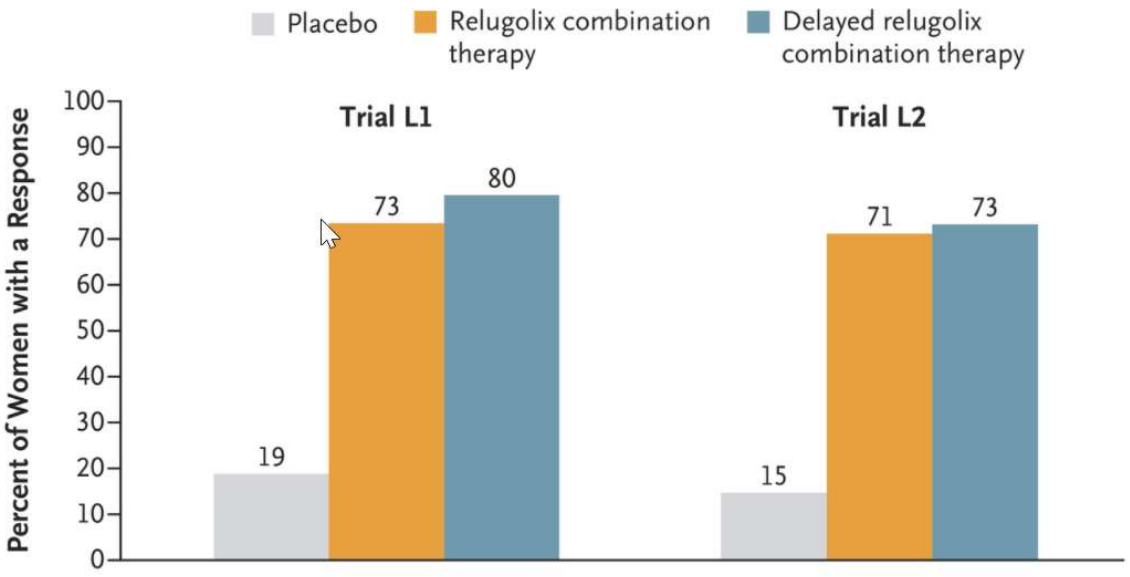
Schlaff WD, et al. *N Engl J Med*. 2020;382(4):328-340.

Relugolix Combination Therapy Overview

- Relugolix is an orally active, nonpeptide GnRH-receptor antagonist that is suitable for daily use
  - It competitively binds to pituitary GnRH receptors, blocking the binding and signaling of endogenous GnRH23, thus leading to reversible, dose-dependent decreases in gonadotropin concentrations and subsequent suppression of ovarian estradiol and progesterone production
- Combination therapy administered once daily: relugolix + estradiol + norethindrone acetate
- May have efficacy in woman with uterine fibroids and heavy bleeding while avoiding hypoestrogenic effects

LIBERTY 1 & LIBERTY 2 RESULTS

Shown are the percentages of women who had a response, which was defined as a volume of menstrual blood loss of less than 80 mL and a reduction of at least 50% from the baseline volume of menstrual blood loss, as measured by the alkaline hematin method, over the last 35 days of the treatment period. The primary endpoint analysis in each trial was the comparison of relugolix combination therapy with placebo.



	Trial L1			Trial L2		
No. of Patients	127	128	132	129	125	127
Difference vs. Placebo — percentage points (95% CI)		55 (44–65)	61 (51–70)		56 (46–66)	58 (49–68)
P Value vs. Placebo		<0.001			<0.001	

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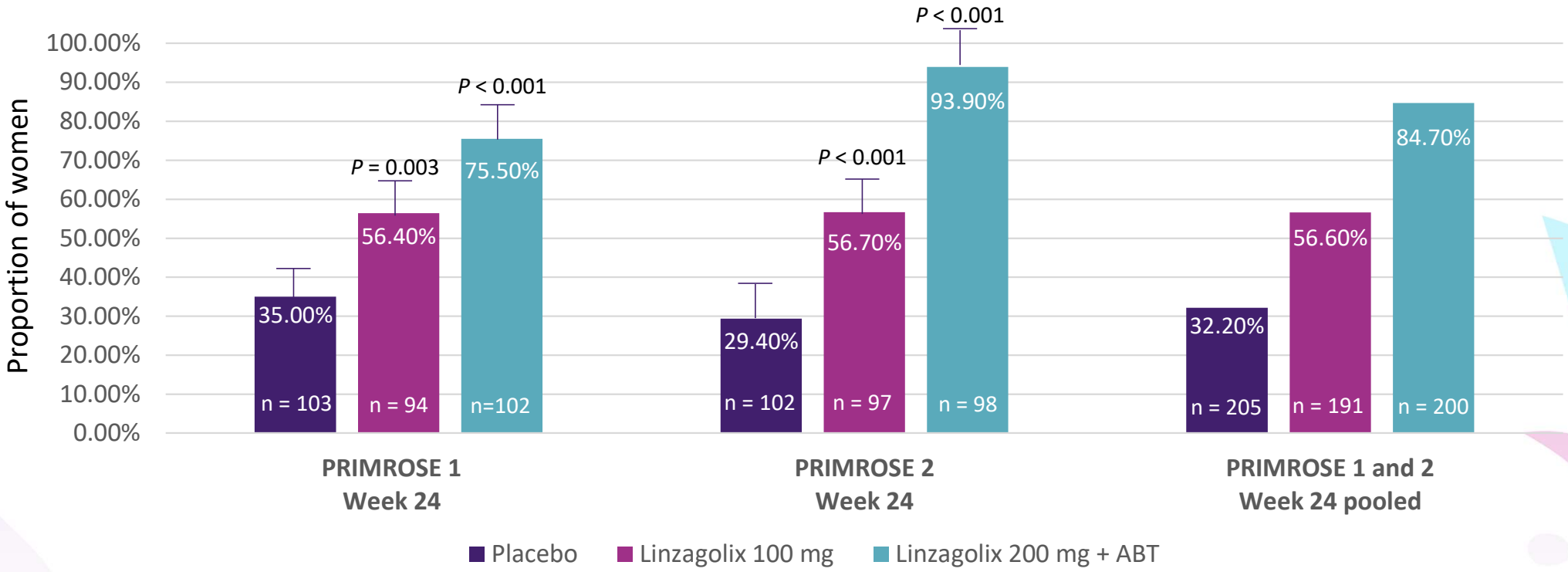
Al-Hendy A, et al. N Engl J Med. 2021;384(7):328:630-642.

Linzagolix

- Oral GnRH receptor antagonist
- Currently in late-stage clinical development for the treatment of heavy menstrual bleeding associated with uterine fibroids
- New Drug Application (NDA) to the US Food and Drug Administration (FDA) for linzagolix for the treatment of uterine fibroids
- In addition to a high dose (200 mg) with add-back therapy (1 mg E2/0.5 mg NETA), a low dose (100 mg) without add-back therapy is being assessed as a potential long-term treatment option for women with add-back therapy contraindications.

PRIMROSE 1 & PRIMROSE 2 Results



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Linzagolix effective in women with uterine fibroids. Healio. https://www.healio.com/news/primary-care/20210503/linzagolix-effective-in-women-with-uterine-fibroids. Published May 3, 2021.

Philosophical Goals of Therapy

- Allow patient to improve symptoms and decide if continued therapy is acceptable
- Permits time to consider other alternatives
- Use therapy to bridge from one treatment modality to others
  - Correction of anemia
  - Bridge from perimenopause to menopause
  - Improve comorbidities

Conclusions: Where Are We Today?

- Fibroids are a common cause of heavy, prolonged menstrual bleeding that can have serious health impacts and significantly reduce QOL
- Traditional medical therapies that offer some relief are NSAIDs, antifibrinolytics, combined hormonal contraceptives, progestin-only contraceptives (esp. LNG-IUS), androgens, and GnRH-agonists
- Newer approaches, especially oral GnRH antagonists, offer distinct benefits of rapid onset, efficacy, good tolerability, and acceptability


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