What have we learned about uterine fibroids from clinical practice and clinical studies?

Elizabeth (Ebbie) Stewart, M.D.
Professor of Obstetrics and Gynecology
Mayo Clinic College of Medicine and Science

Extreme heterogeneity of size, number and location makes study and treatment difficult.

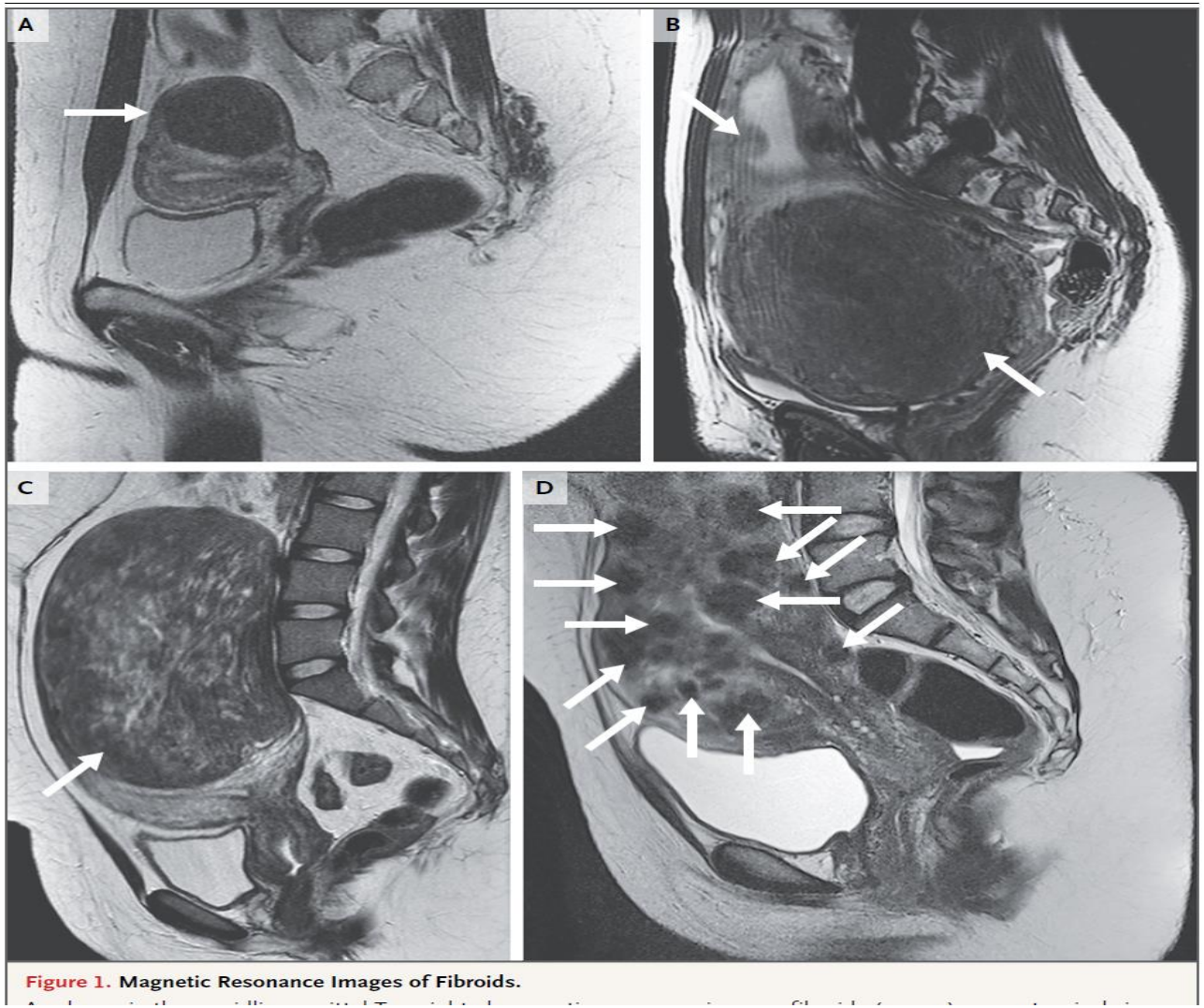

Figure 1. Magnetic Resonance Images of Fibroids.

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Stewart E.A.: NEJM 372:17 1646-55, 2015

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Many Fibroid Symptoms are Unrecognized or Attributed to Other Issues

- **“I pee every hour, but I drink a lot of water”**
- **“ All the women in my family have periods that last 10 days”**
- **“I’ve always been anemic”**
- **“I had a colonoscopy because of the anemia.”**
- **“ I’m a nurse so I have back pain from lifting patients.”**
- **“ My husband has erectile dysfunction so I think that’s why we can’t have sex.”**

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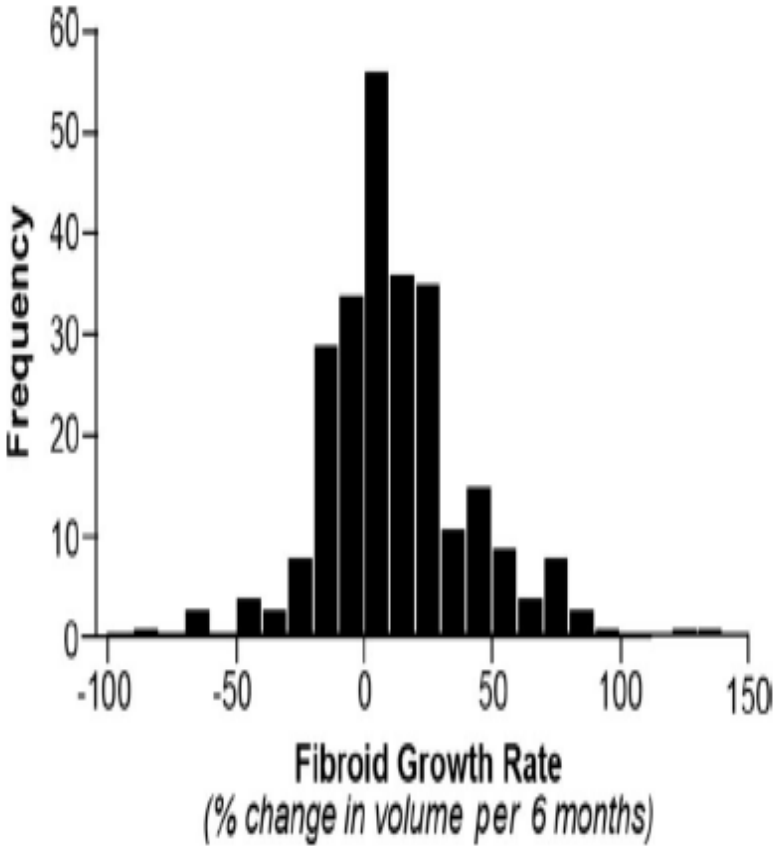
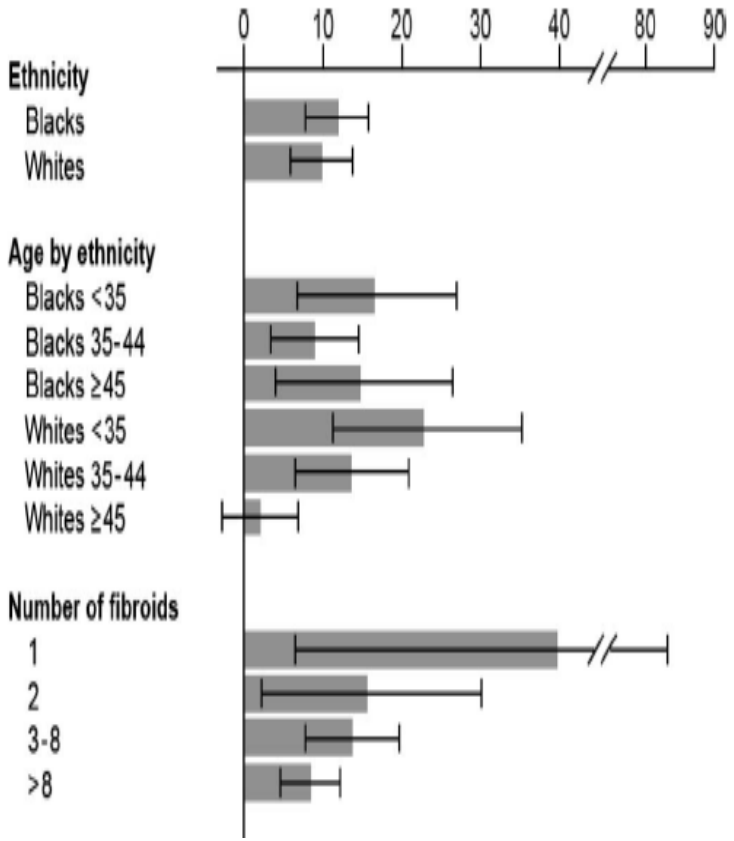
Fibroid Growth Study:

Fibroids Grow and Regress





Peddada *et al.* PNAS 105: 19887-92, 2008.

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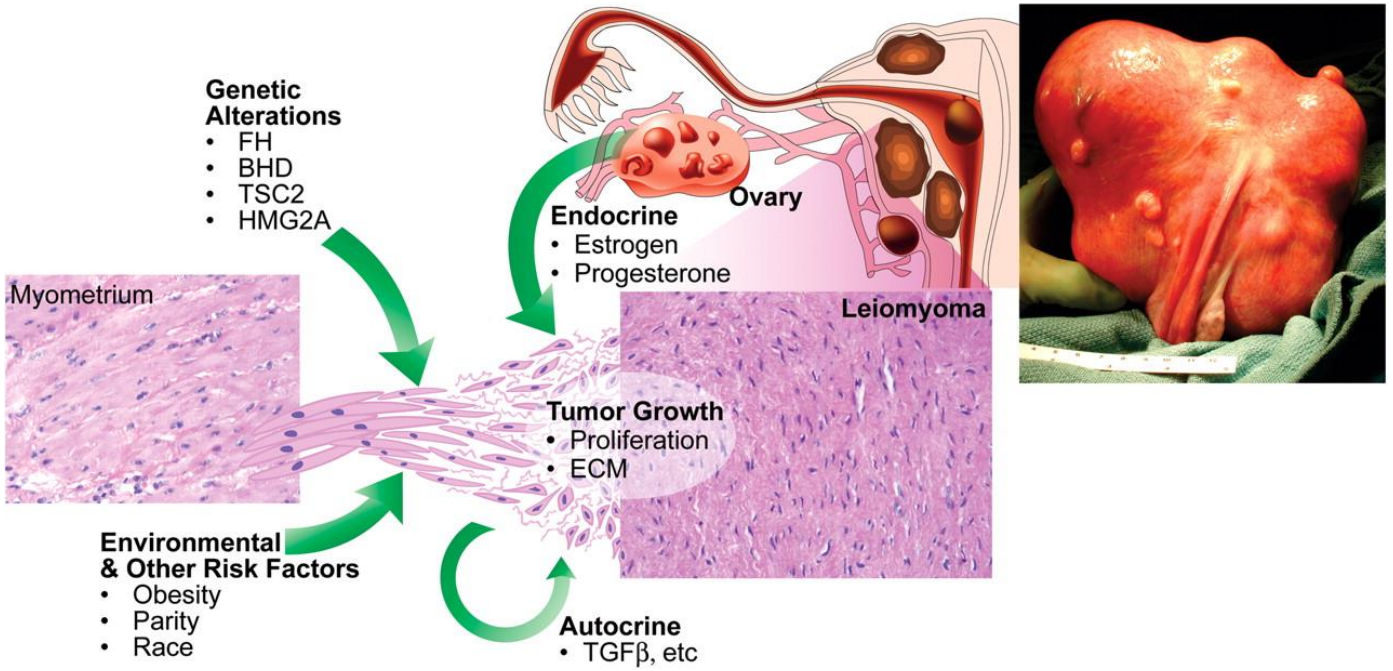
Heterogeneous etiology of uterine fibroids

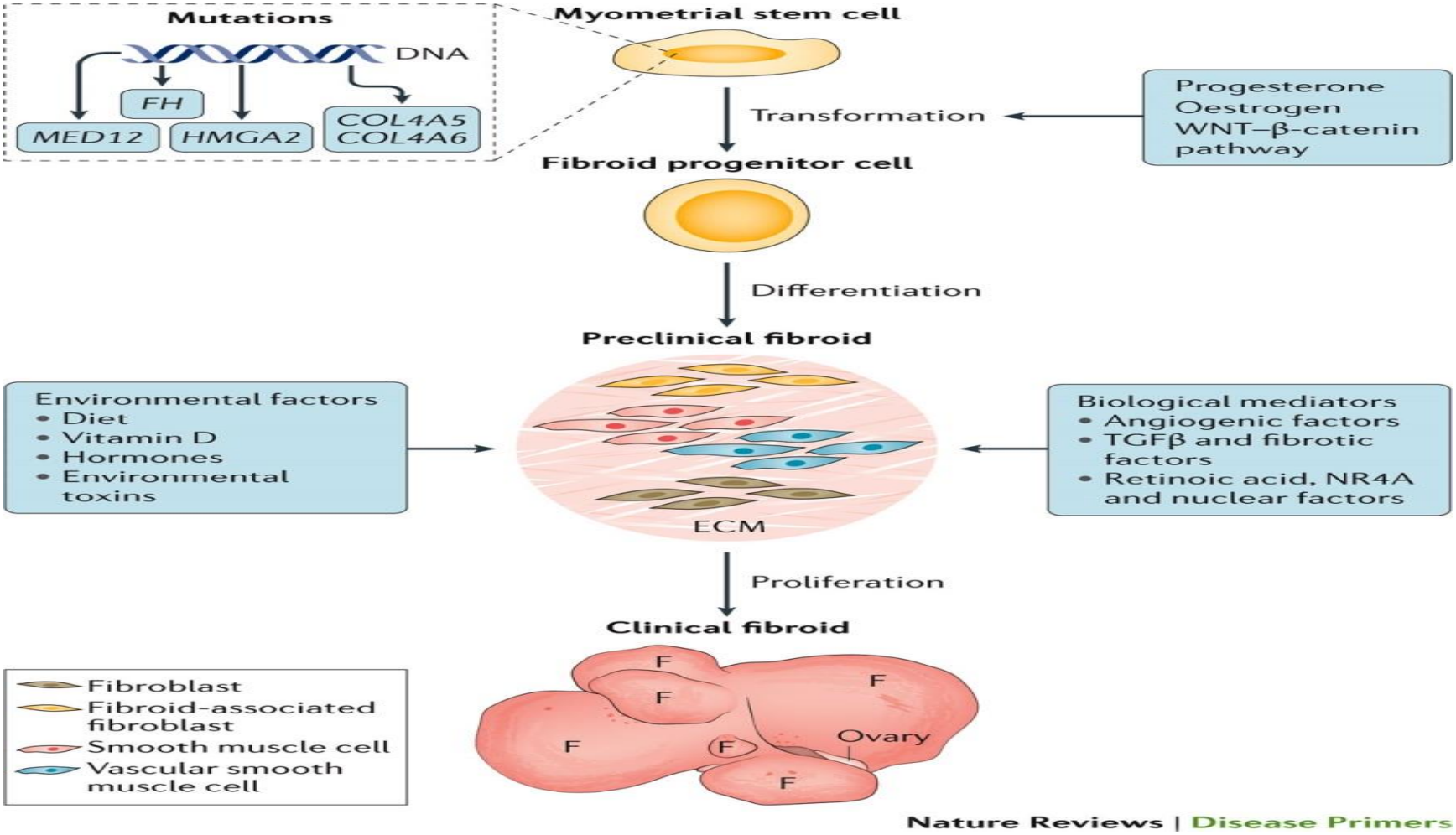


C. L. Walker and E. A. Stewart., Science 308, 1589 -1592 (2005)

Published by AAAS

Science AAAS

Can we target the stage before clinical fibroids for prevention?



Most women have an effective alternative to hysterectomy

- Birth control pills
- Medicated IUDs
- Tranexamic acid during period
- GnRH analogues
- Myomectomy
- Uterine artery embolization
- RF Ablation (Acessa)
- Focused Ultrasound

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Beyond “birth control”: More effective medical therapy is now available

Old	New
GnRH Agonist (leuprolide)	GnRH Antagonist (elagolix, relugolix, linzagolix)
Shots	Pills
“Flare” at start	Immediate shut down
Medication alone	Medication with low dose estrogen and progestin
Menopausal hormone level so symptoms like hot flashes, bone loss are common	Low normal hormone levels so symptoms uncommon

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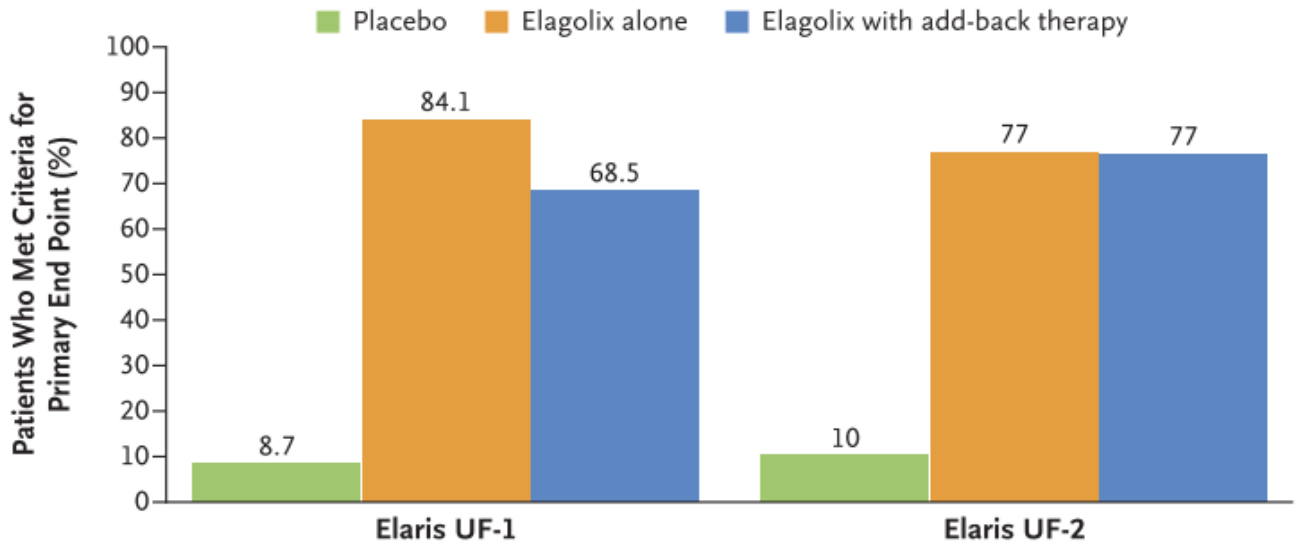
Elagolix, An Oral GnRH Antagonist, is Safe and Effective Treatment of Uterine Fibroids



Difference from placebo — % (95% CI)		75.4 (66.2–84.6)	59.8 (51.1–68.5)		66.4 (55.5–77.3)	66.0 (57.1–75.0)
Risk ratio (95% CI)		9.7 (5.0–18.9)	7.9 (4.1–15.5)		7.1 (3.8–13.4)	7.2 (3.9–13.5)
Two-sided P value			<0.001			<0.001
No. of women	102	104	206	94	95	189
No. imputed by multiple imputation	8	3	16	6	11	12

Figure 1. Reduction in Heavy Menstrual Bleeding in Women with Uterine Fibroids.

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

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Elagolix Demonstrated Improvement in other Secondary Endpoints

Adapted from Table 2	Significant in both trials
Volume of menstrual blood loss	**Yes**
Suppression of bleeding at 1, 3, 6 and final month	**Yes**
Correction of anemia if present at start	**Yes**

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

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US Approval for Elagolix/E2/NETA for Uterine Fibroids for up to 24 months.


FDA NEWS RELEASE

FDA Approves New Option to Treat Heavy Menstrual Bleeding Associated with Fibroids in Women

https://www.fda.gov/news-events/press-announcements/fda-approves-new-option-treat-heavy-menstrual-bleeding-associated-fibroids-women May 29,2020

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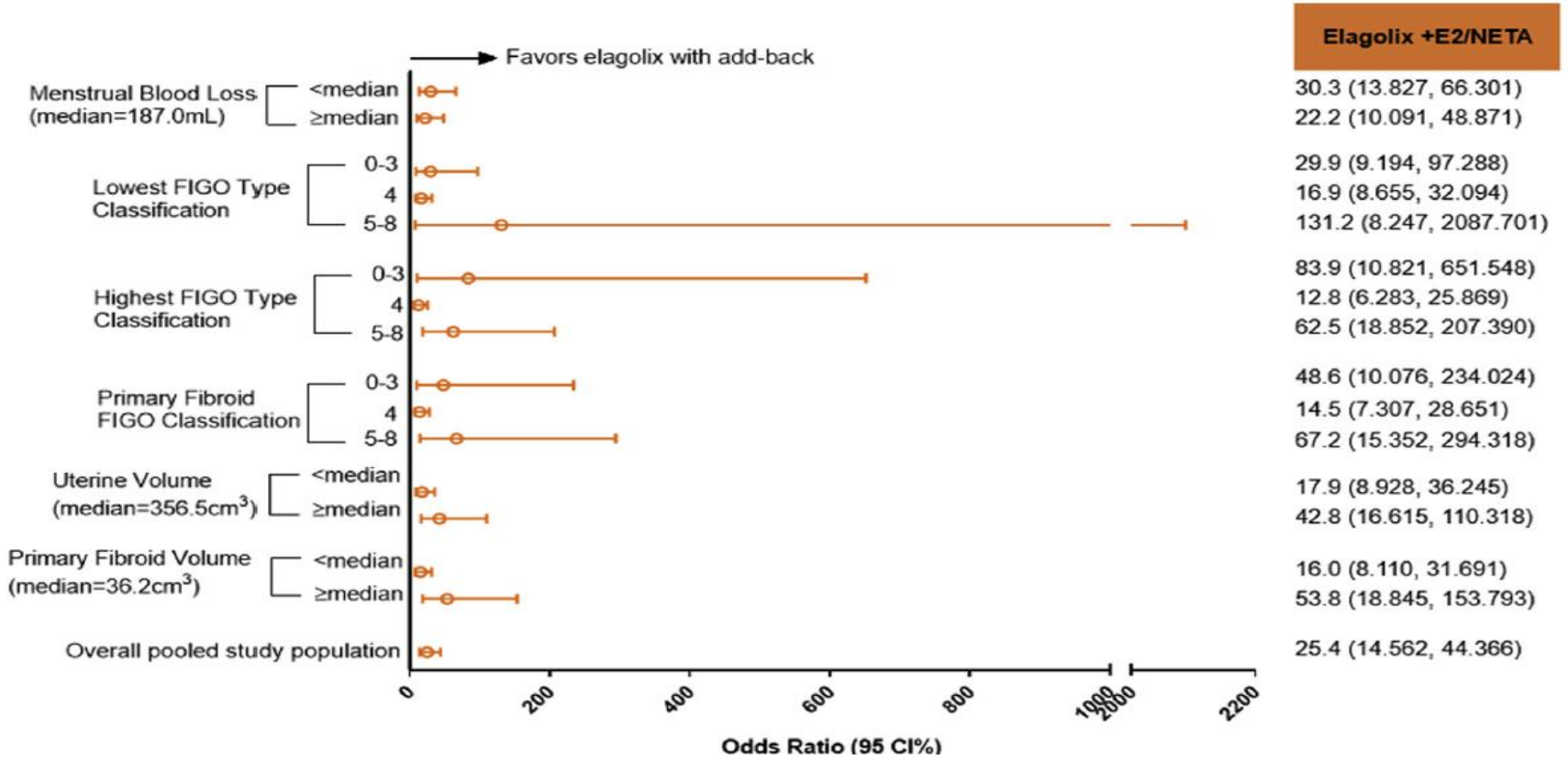
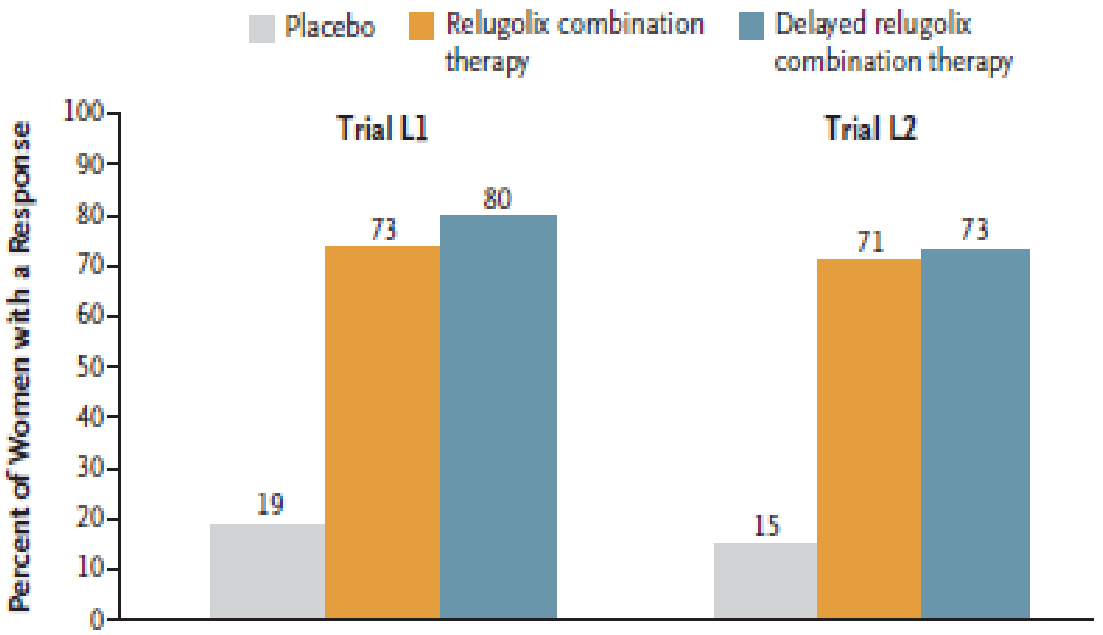
Elagolix Response Appears Consistent Across Clinical Parameters

FIGURE 1
Odds ratios for primary endpoint by factors contributing to disease severity



Al-Hendy *et al*. Am J Ob Gyn. 2021; 224:72.e1-50.

Relugolix is also Safe and Effective Treatment of Uterine Fibroids



	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	

Figure 1. Participants with Reduction in Heavy Menstrual Bleeding.

Al-Hendy *et al*. *N Engl J Med*. 2021;384:630-42.

Relugolix Demonstrated Improvement in Most other Secondary Endpoints

Adapted from Table 2	Significant in both trials
No periods in last 35 days of treatment	Yes
Percentage decrease in menstrual blood loss	Yes
Decrease in Pelvic Discomfort Score	Yes
Correction of anemia if present at start	Yes
Pain ≤ 1 over last 35 days of treatment	Yes
Decrease in volume of largest fibroid	No
Decrease in uterine volume	Yes

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Al-Hendy *et al*. *N Engl J Med*. 2021;384:630-42.

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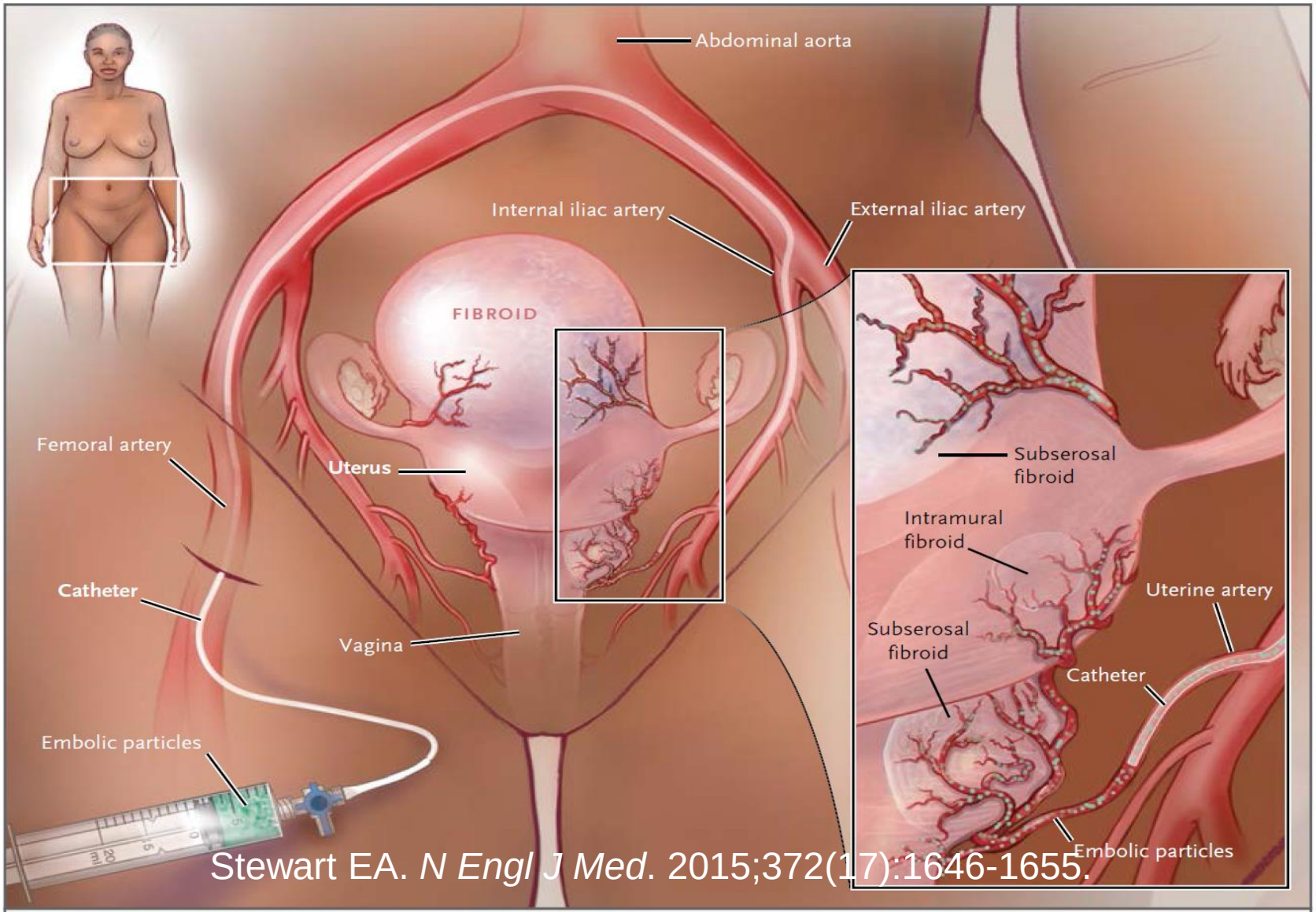
Uterine Artery Embolization



Stewart EA. *N Engl J Med*. 2015;372(17):1646-1655.

UAE is an Effective Fibroid Treatment:
7 RCTs of nearly 8000 women

Endpoint	Quality of Evidence	Key Findings
Volume Reduction	**High**	**Consistent reduction is size which continued for 5 years**
Bleeding Reduction	**High**	**Improvements in days of bleeding, hemoglobin, patient-rated bleeding**
Quality of Life	**Moderate**	**Improvements in a variety of measures**

https://effectivehealthcare.ahrq.gov/topics/uterine-fibroids/research-2017

©2012 MFMER

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UAE vs. Myomectomy: *Level A Evidence*

- **Risk of transfusion reduced (OR 0.07, 95 % CI 0.01-0.52)**
- **More rapid recovery**
- **Fewer major but increased minor complications**

Hartmann *et al.* AHRQ Comparative Effectiveness Report, 2017; Gupta JK et al. *Cochrane Database Syst Rev*. 2012;(5):CD005073; NICE guidelines 2010

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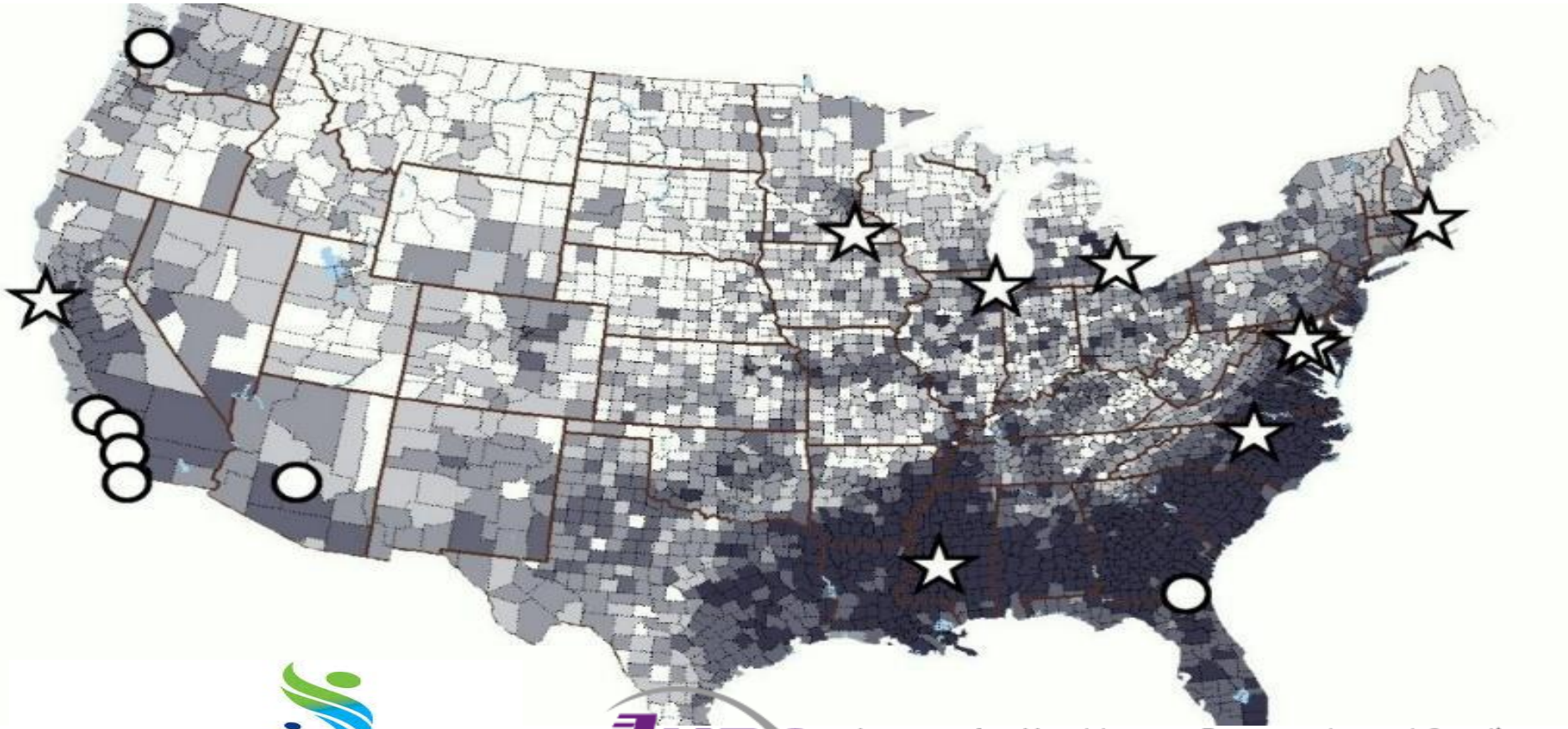
FEMME: RCT of UAE vs. Myomectomy Reproductive Outcomes

	UAE	Myomectomy
Pregnancies	**9 (8%)**	**5 (4%)**
Livebirths	**6**	**4**

New Eng J Med 383, July 30,2020

COMPARE-UF



pcori
PATIENT-CENTERED OUTCOMES RESEARCH INSTITUTE

AHRQ
Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

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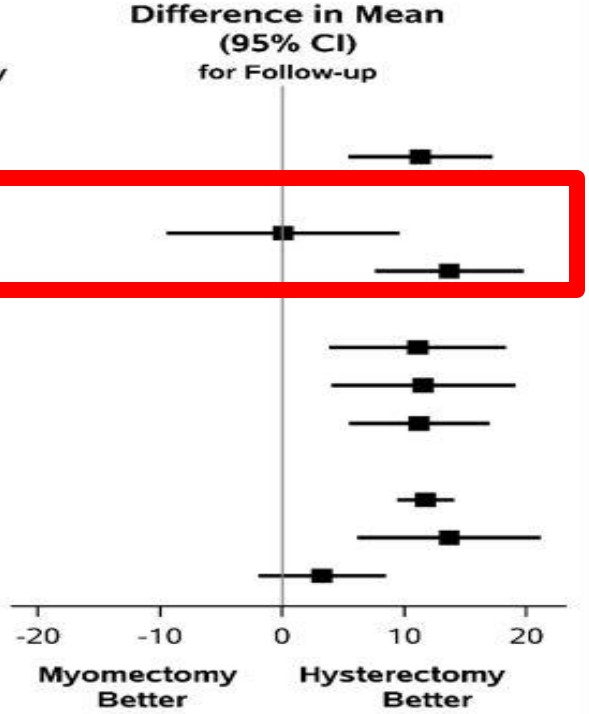
A national registry to recruit women undergoing treatments

At 1-Year Post Procedure, HR-QoL is Strongly Influenced by Route of Surgery

HRQoL improved overall, by route of procedure, age and race

(a) Propensity Adjusted Mean at Baseline and One Year Follow-up HRQOL Summary Score

	Baseline		One Year Follow-up	
	Myomectomy	Hysterectomy	Myomectomy	Hysterectomy
Total				
Overall	45.9	45.7	82.0	93.3
Route				
Abdominal	45.7	45.1	88.4	88.4
Minimally Invasive	46.7	45.9	80.7	94.4
Age				
31-40	42.1	41.3	79.9	91.0
40-45	43.8	45.3	82.7	94.2
45+	49.8	48.5	82.7	93.9
Race				
Caucasian	48.1	49.5	85.6	97.3
African American	42.2	41.3	74.6	88.3
Other	44.2	44.4	89.7	92.9



HRQOL Summary Score: high=good

Nicholson WK et al. *Obstet Gynecol*. 2019;134(2):261-269.

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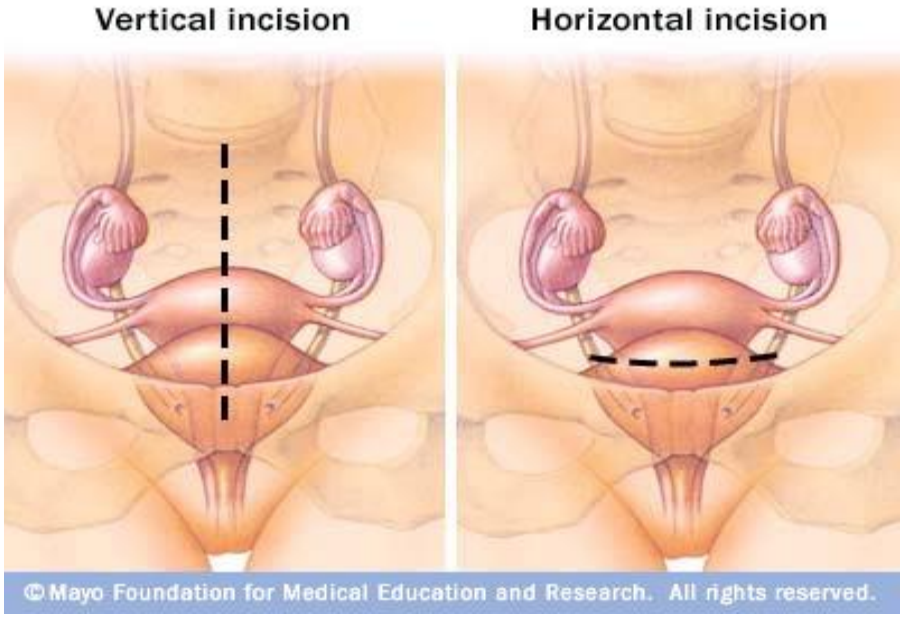
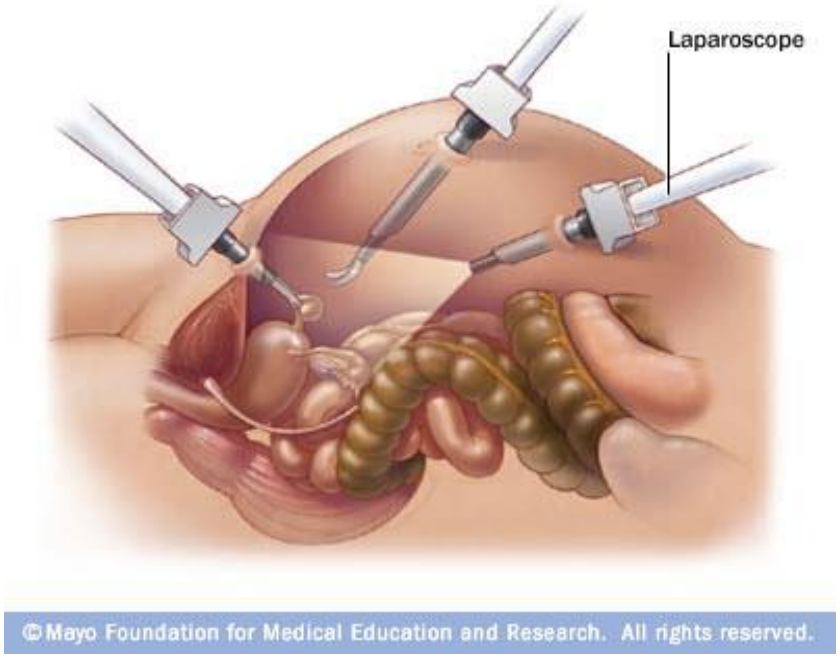
Myomectomy: Removing Fibroids; Repairing the Uterus

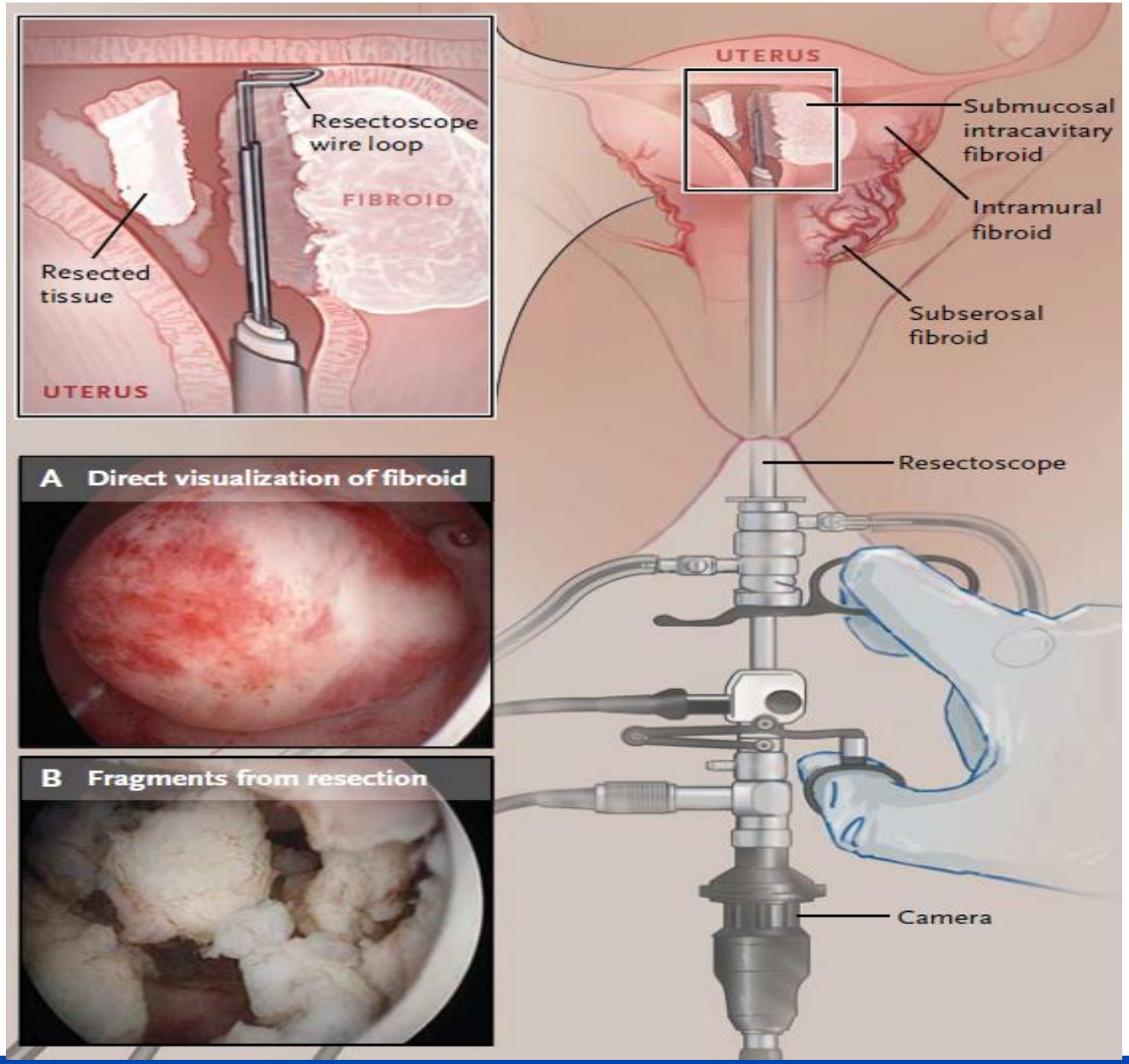




Abdominal: Any size

Laparoscopic or Robotic:

Hysteroscopic Myomectomy



Stewart EA. *N Engl J Med*. 2015;372(17):1646-1655.

Before all Types of Myomectomy, Women Have Severe Symptoms and Impaired Quality of Life

	Hysteroscopic	Laparoscopic/ Robotic	Abdominal
UFS-QoL			
Symptom Severity Score (SSS)*	**53.2**	**49.2**	**52.4**
Bleeding (%)	**92.3%**	**78.3%**	**81.3%**
Bulk (%)	**63.6%**	**80.6%**	**83.5%**
Total HRQL#	**49.1**	**52.6**	**48.7**

* Maximal symptoms= 100

Optimal quality of life= 100

Laughlin-Tommaso SK et al. *Am J Obstet Gynecol*. 2020;222(4):345.e1-345.e22.

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Even with Hysteroscopic Myomectomy There is Improvement in Bulk Symptoms

	Hysteroscopic (N=338)		Laparoscopic/ Robotic (N=519)		Abdominal (N=349)	
	Pre	Post	Pre	Post	Pre	Post
UFS-QOL SSS	53.2	22.3	49.2	20.0	52.4	19.5
HMB Symptoms (%)	92.3	50.6	78.3	45.5	81.3	40.9
Bulk Symptoms (%)	63.6	31.5	80.6	32.4	83.5	35.7
Pain (VAS)	72.7	79.4	74.5	82.7	72.5	83.3

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Laughlin-Tommaso SK et al. *Am J Obstet Gynecol*. 2020;222(4):345.e1-345.e22.

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COMPARE-UF Comparing Options for Management: Patient-centered Results for Uterine Fibroids

- 2018 https://pubmed.ncbi.nlm.nih.gov/29750955/
- 2019 https://pubmed.ncbi.nlm.nih.gov/31678093/, https://pubmed.ncbi.nlm.nih.gov/31306318/
- 2020 https://pubmed.ncbi.nlm.nih.gov/31678093/ https://pubmed.ncbi.nlm.nih.gov/32192594/
- 2021 https://pubmed.ncbi.nlm.nih.gov/33524308/

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While hysterectomy eliminates new fibroid formation, it is not a risk-free option:

This is a topic many women are not hearing about

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Reassessing Hysterectomy

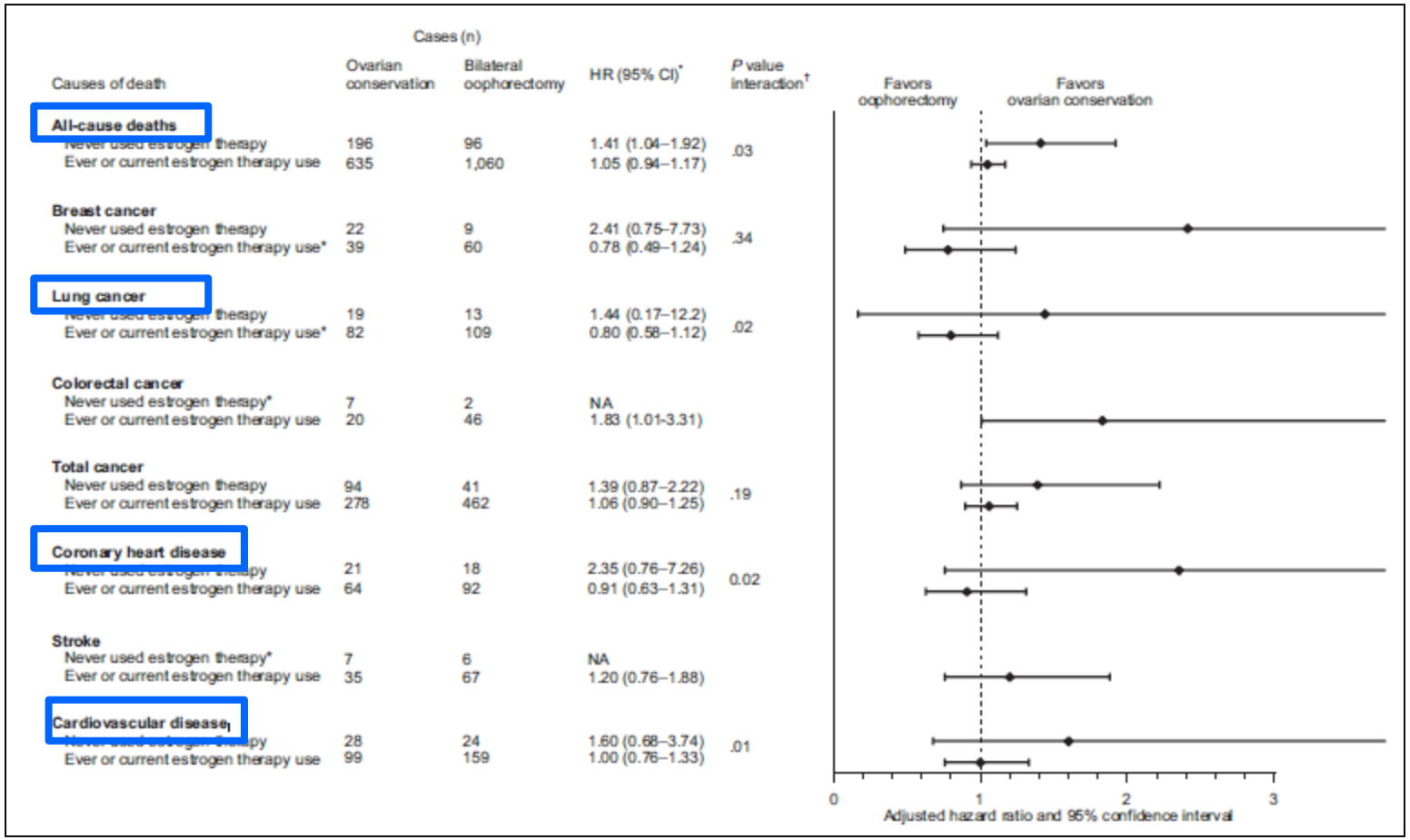
Lifetime risk in US: 45 %

Only 8% are for cancers

- **Uterine (Endometrial & sarcomas)**
- **Cervix**
- **Ovary and fallopian tube**
- **Breast**

Stewart EA, Shuster LT, Rocca WA. *Minn Med*. 2012;95(3):36-39.

Post-hysterectomy mortality is increased following BSO compared to ovarian conservation



Parker WH *et al. Obstet Gynecol*. 2013;121(4):709-716.

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After about 20 years of followup, women undergoing hysterectomy with conservation of both ovaries have:

- 13% increased risk of hypertension
- 14% increased risk of hyperlipidemia
- 17% increased risk of cardiac arrhythmias
- 18% increased risk of obesity
- 33% increased risk of coronary artery disease

Laughlin-Tommaso SK et al. *Menopause*. 2016;23(2):121-128.

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BMJ Open

Adverse childhood or adult experiences and risk of bilateral oophorectomy: a population-based case–control study

Liliana Gazzuola Rocca,[1] Carin Y Smith,[2] Brandon R Grossardt,[2] Stephanie S Faubion,[3,4] Lynne T Shuster,[4] Elizabeth A Stewart,[3,5,6] Walter A Rocca[1,7]

Strengths and limitations of this study

- To our knowledge, this is the first study to show an association between adverse childhood and adult experiences and bilateral oophorectomy.
- The records-linkage system of the Rochester Epidemiology Project provided a unique research infrastructure to test these life course associations using data collected historically over approximately 40 years.
- The participation of women in the study was high because of the passive nature of the records-linkage system.
- The study may have underestimated the frequency of adverse childhood or adult experiences, and the statistical power was limited for some stratified analyses.
- In analyses using the Adverse Childhood Experiences score, all adverse events were assumed to have the same weight. In addition, we did not consider the overall family environment or the presence of surrogate caring figures.

Contents lists available at ScienceDirect

Maturitas

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

Guest editorial

Adverse childhood experiences and adult abuse are predictors of hysterectomy and oophorectomy

ARTICLE INFO

Keywords:
Adverse childhood experiences
Emotional abuse
Physical abuse
Sexual abuse
Psychological trauma
Bilateral oophorectomy

Every year more than 400,000 women undergo hysterectomy with or without concurrent bilateral oophorectomy in the United States. Over 90% of these surgeries are done for a benign disease although numerous alternatives to hysterectomy exist. Some of these women bypass all alternatives even though they have no pathologic evidence of a lesion in the uterus or the ovaries to explain their pain or abnormal bleeding. Both hysterectomy and bilateral oophorectomy have now been linked to a number of mental and somatic adverse outcomes that should prompt a more restricted use of these surgeries. However, it is difficult to understand how in the 21st century the practice of removing the reproductive organs of relatively young women remains so well accepted.

Gazzuola Rocca L et al. *BMJ Open*. 2017;7(5):e016045.

Risk and Benefits of Hysterectomy with Ovarian Conservation: Educating Patients and Providers

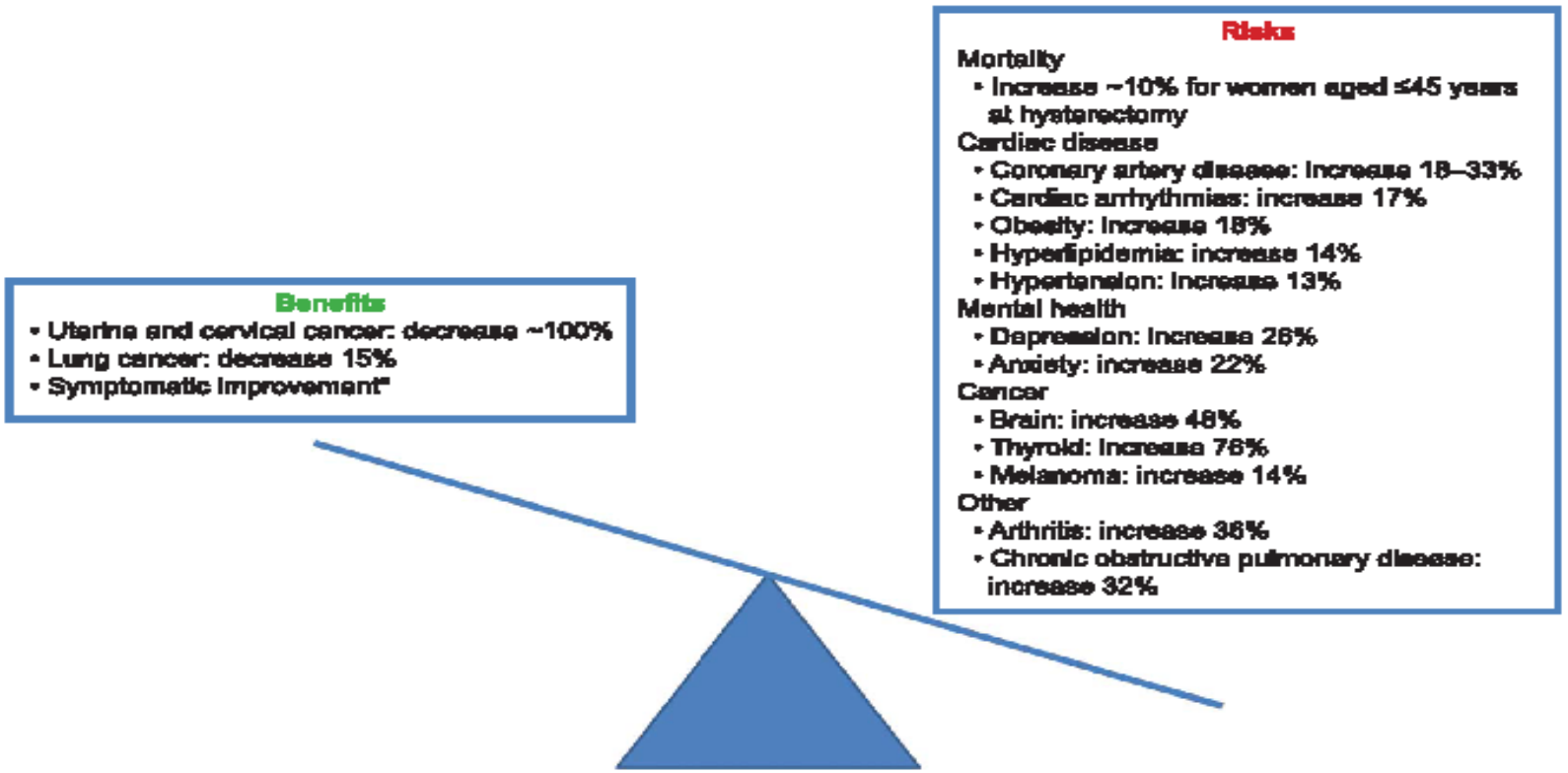

Fig. 1. Risks and benefits associated with hysterectomy with bilateral ovarian conservation at any age.[9–11,56–58]
*Although symptoms may be alleviated with other less invasive treatment options.

Laughlin-Tommaso & Stewart. Ob Gyn 132: 961-71, 2018

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