

Alternatives to Hysterectomy

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600,000 Hysterectomies Performed Annually in US

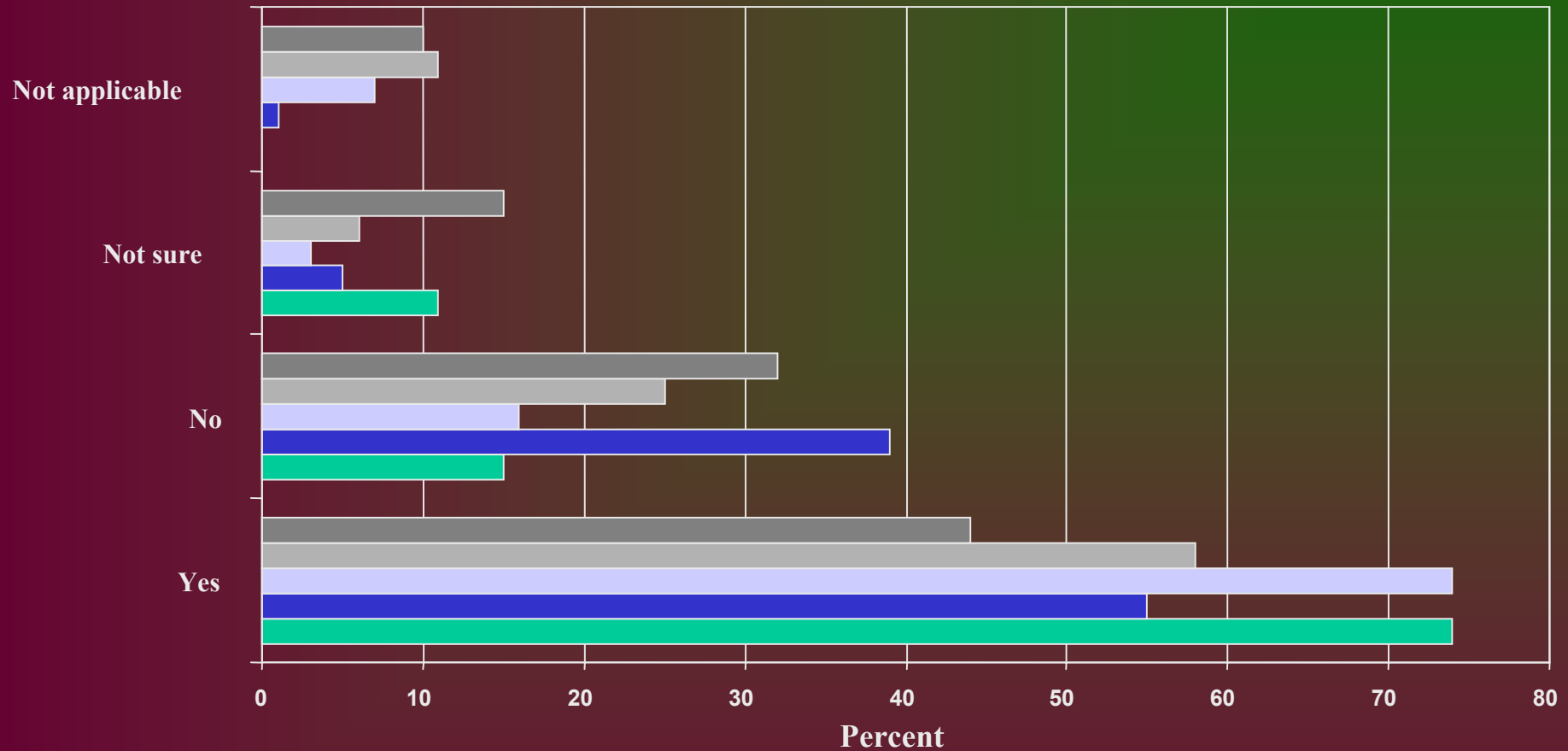
- *120,000 (20%) for bleeding*
- *240,000 (40%) for leiomyomata*
- *Estimated cost – \$2 billion*

Wilcox, et al. Obstet and Gynecol. 1994.

Homa Keshavarz, et al..MMWR, 2002



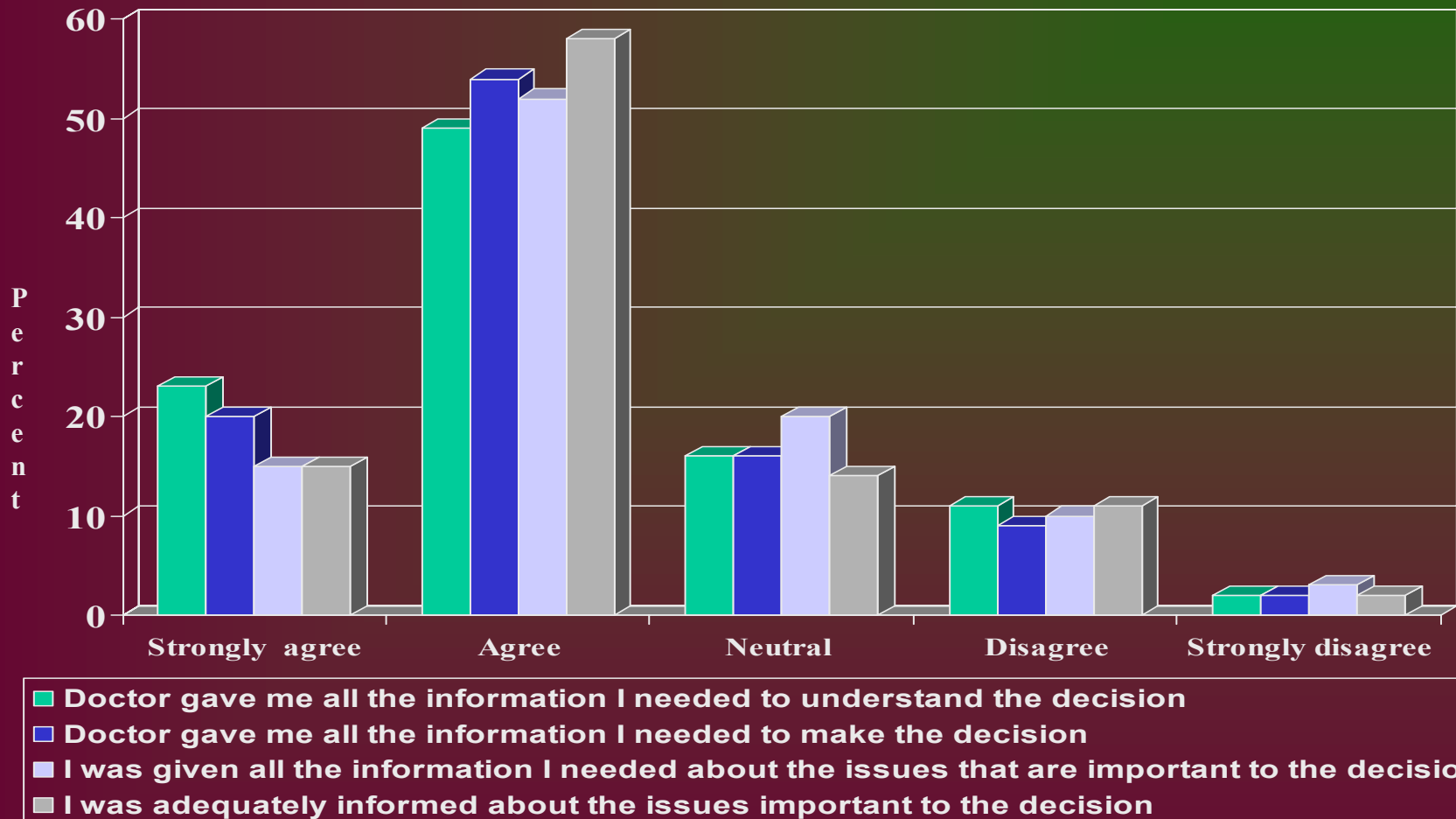
Decision-Making About Hysterectomy



- Advantages of hysterectomy
- Treatments other than hysterectomy
- Disadvantages of treatments other than hysterectomy
- Possible risks & side effects of hysterectomy
- Advantages of treatments other than hysterectomy



Decision Making Questionnaire



Current Clinical needs for Leiomyomata

- *Determine an effective prevention strategy in genetically predisposed individuals;*
 - *Slow the growth of leiomyomata;*
 - *Identify the mechanisms of infertility;*
 - *Improve early detection;*
 - *Develop better surgical techniques;*
 - *Reduce recurrences after myomectomy;*
 - *Develop nonextirpative options*
 - *Evaluate their long-term results.*



Management



Surgical Management of Leiomyomata

- *Hysterectomy*
 - *Abdominal vs. laparoscopic assisted vaginal hysterectomy*
- *Myomectomy*
 - *Abdominal*
 - *Laparoscopic*
 - *Hysteroscopic*
- *Myolysis*
 - *Cryo*
 - *Coagulation*
- *Uterine embolization*



Medical Management

- *GnRH agonist*
- *SERMS*
 - *Tomoxifen*
 - *Raloxifene*
 - *Arzoifene*
- *Mifepristone*
- *Progesterone Receptor Modulation*



Hysterectomy vs Medical Treatment: Mean Change from Baseline in QoL at 2 Years

<i>HR-QoL Outcome</i>	<i>Hysterectomy (n=28)</i>		<i>Crossed over to Hysterectomy (n=16)</i>		<i>Medicine Medicine only (n=14)</i>	
	<i>Change</i>	<i>P Value</i>	<i>Change</i>	<i>P Value</i>	<i>Change</i>	<i>P Value</i>
MOS SF-36 MCS score	7	<.001	6	.007	2	.32
MOS SF-36 PCS score	7	<.001	8	<.001	11	<.001
Symptom resolution	71	<.001	75	<.001	35	<.001
Satisfaction with symptom level	47	<.001	49	<.001	31	<.001
Body image	12	.001	15	.002	8	.11
Pelvic problems interference with sex	41	<.001	37	<.001	29	<.001
Sexual desire	20	<.001	14	.02	0.5	.94
Orgasm frequency/quality	12	.005	16	.004	9	.17
Satisfaction with sex	17	<.001	23	<.001	13	.04

Hysterectomy vs Medical Treatment: Mean Change from Baseline in QoL at 2 Years

<i>HR-QoL Outcome</i>	<i>Hysterectomy (n=28)</i>		<i>Medicine</i>			
	<i>Change</i>	<i>P Value</i>	<i>Crossed over to Hysterectomy (n=16)</i>		<i>Medicine only (n=14)</i>	
	<i>Change</i>	<i>P Value</i>	<i>Change</i>	<i>P Value</i>	<i>Change</i>	<i>P Value</i>
Mental health						
Psychological well-being	7	.009	4	.22	0.6	.86
Health distress	30	<.001	20	.001	23	.001
Sleep problems	10	.001	10	.06	4	.46
General health perceptions						
Overall health	11	<.001	13	<.001	5	.21
Satisfaction with health	27	<.001	30	<.001	20	.001

Hormonal Modulation Treatment Strategies

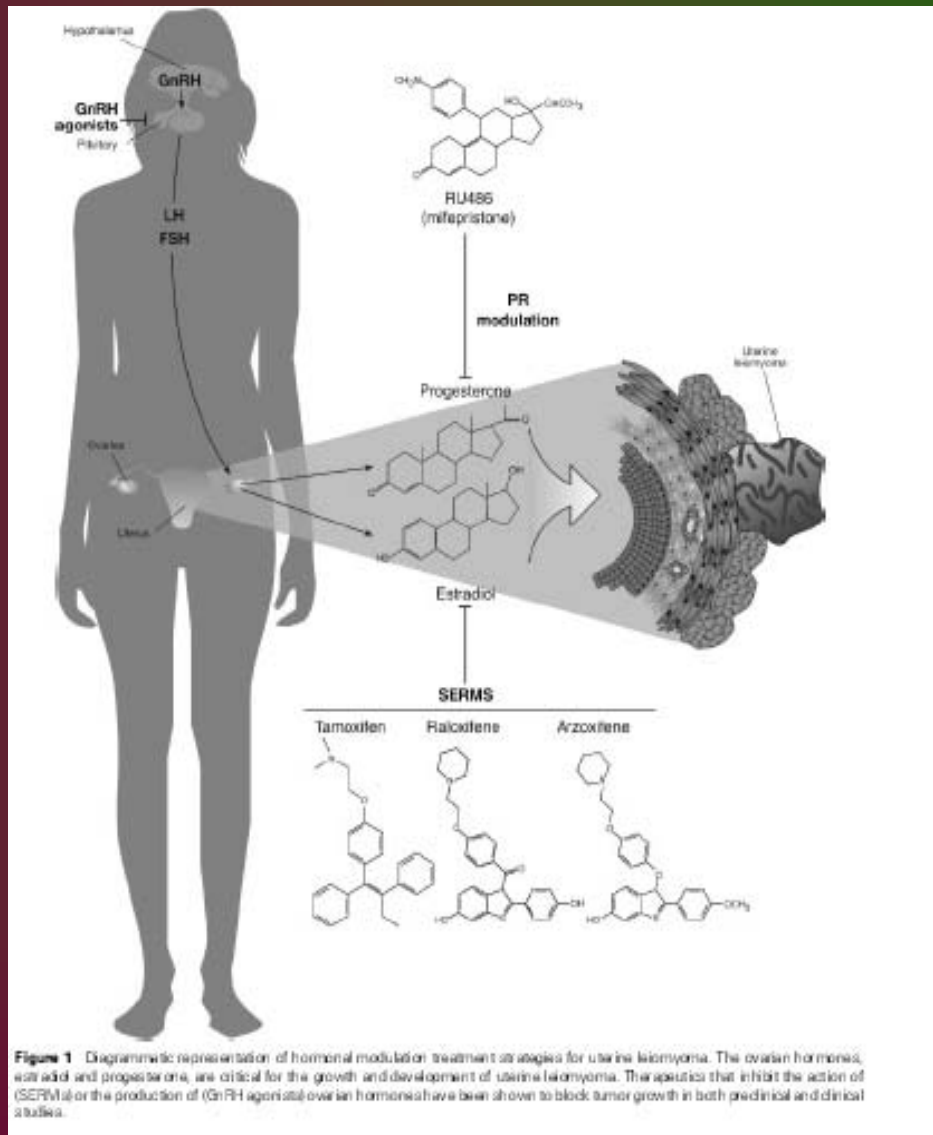


Table 1 Possible Hormonal Contribution to Known Risk Factors for Uterine Leiomyoma

<i>Risk Factor</i>	<i>Impact on Uterine Leiomyoma Risk</i>	<i>Possible Hormonal Contribution</i>
<i>Pregnancy</i>	<i>Decrease</i>	<i>Hormonal changes during pregnancy and for postpartum uterine involution</i>
<i>Cigarette smoking</i>	<i>Decrease</i>	<i>Altered estrogen metabolism</i>
<i>Age postmenopausal</i>	<i>Decrease</i>	<i>Low hormone production</i>
<i>Oral contraceptive (containing progesterone)</i>	<i>Decrease</i>	<i>Exposure to estrogen appeased by progesterone</i>
<i>Early age of menses</i>	<i>Increase</i>	<i>Increased overall lifetime exposure ovarian hormones</i>
<i>Obesity</i>	<i>Increase</i>	<i>Increased estrogen levels through reorganizations of fat stores</i>
<i>Race</i>	<i>Increase</i>	<i>Genetic difference in hormone production and for metabolism</i>

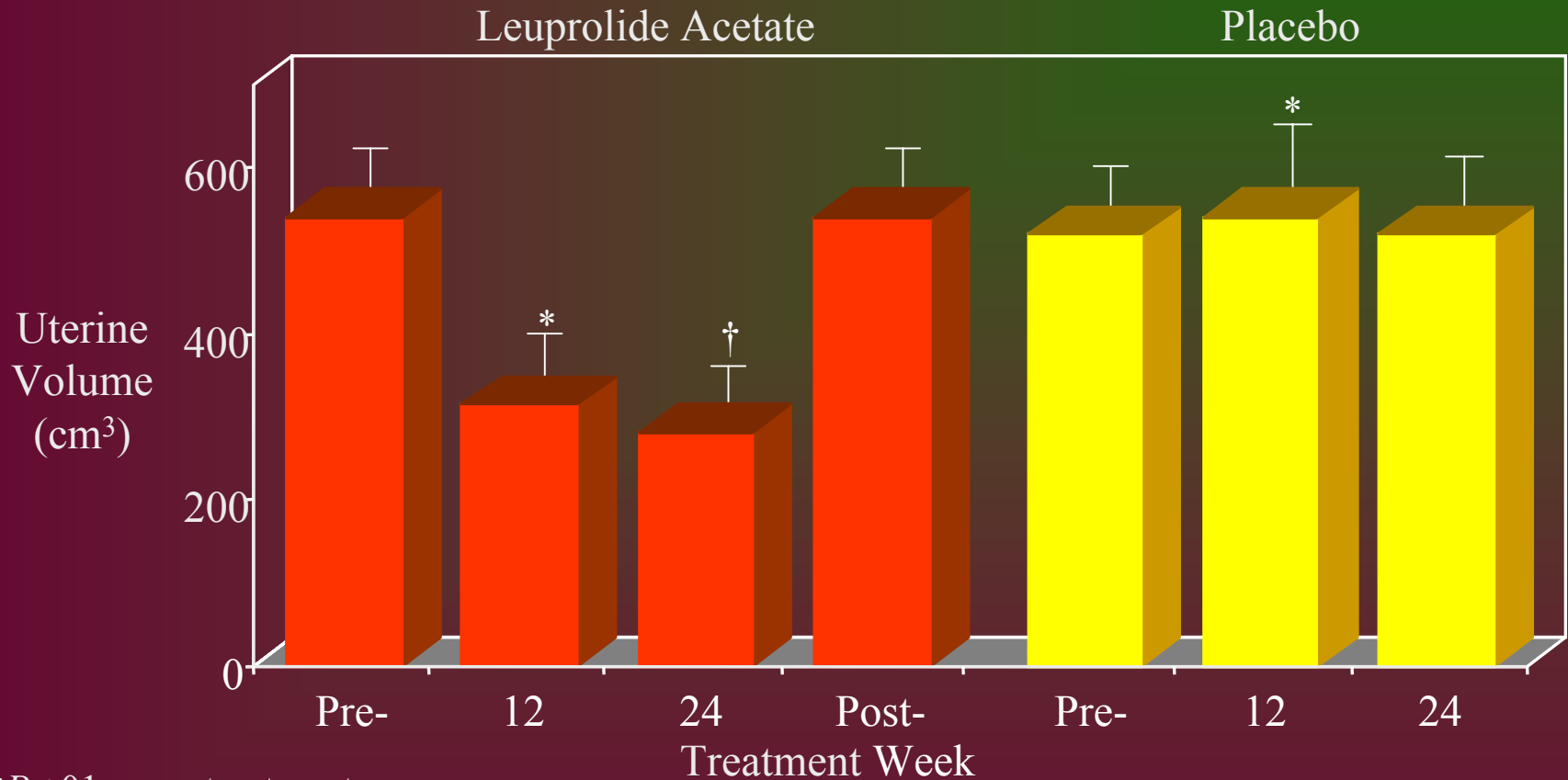


Role of GnRH Agonists

- *Shrinks fibroid 50% in volume after 3 months*
- *Reduces myoma arteriolar diameter*
 - *Less blood loss*
- *Total uterine volume reduced*
- *Amenorrhea corrects anemia*



Changes in Mean Uterine Volume in Women with Leiomyomata Treated with Leuprolide Acetate or Placebo



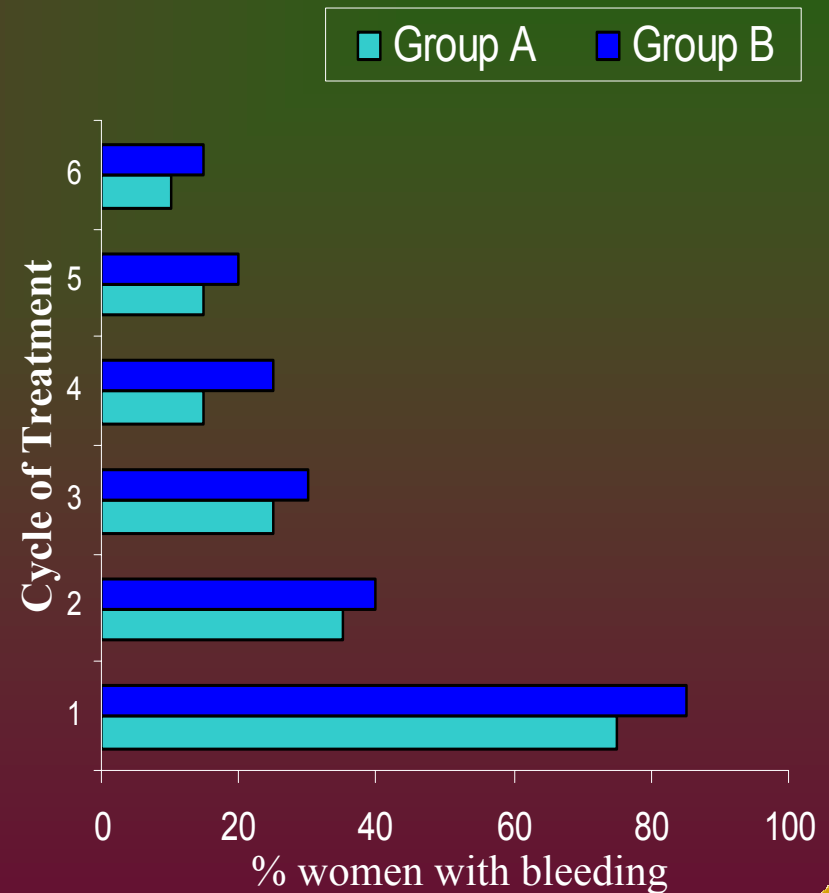
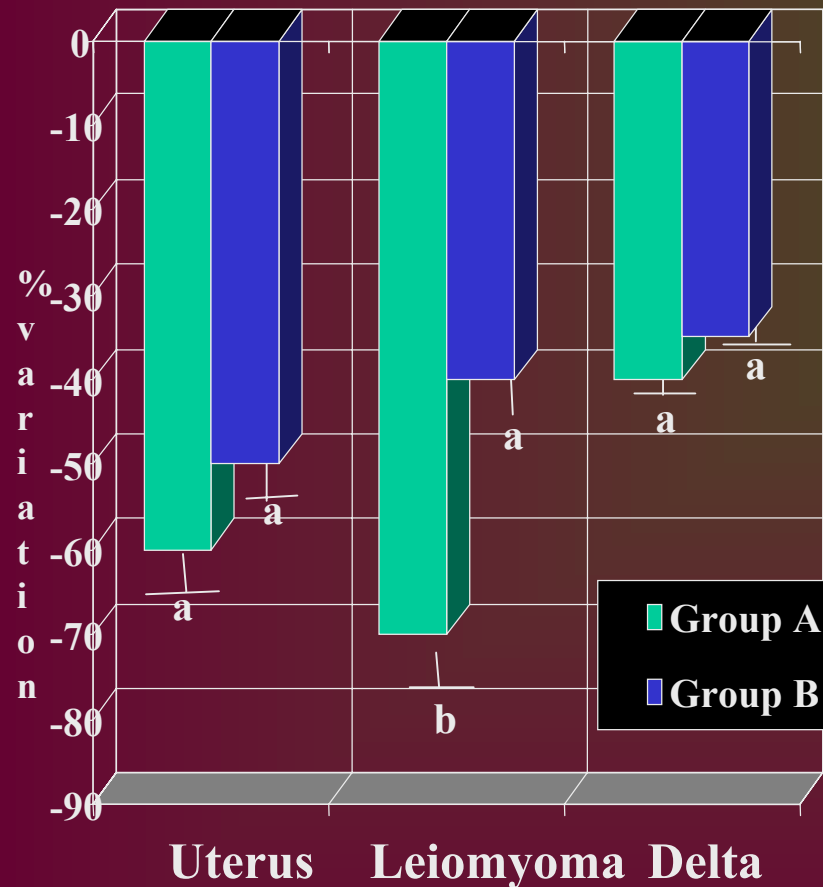
* $P < .01$ vs pretreatment

† $P < .001$ vs pretreatment

Friedman, et al. *Obstet Gynecol.* 1991;77:720-725.



GnRH plus Raloxifene in Tx of Leiomyomata



GnRH plus Raloxifene in Tx of Leiomyomata

Raloxifene (Group A) or Placebo (Group B)

Group A		
<i>Symptom</i>	<i>Baseline (n,%)</i>	<i>6th Cycle (n, %)</i>
<i>Menorrhagia</i>	7.6 ± 1.7 (45,100)	- (0, 0) ^a
<i>Pelvic pressure</i>	6.8 ± 1.5 (39,68.7)	3.5 ± 0.8 (3, 6.7) ^a
<i>Pelvic pain</i>	7.0 ± 1.7 (18,40.0)	3.4 ± 1.0 (2, 4.4) ^a
<i>Urinary frequency</i>	5.9 ± 1.6 (22, 48.9)	2.0 ± 0.9 (3, 6.7) ^a
<i>Constipation</i>	5.2 ± 1.7 (8, 17.8)	- (0, 0) ^a

Group B	
<i>Baseline (n,%)</i>	<i>6th Cycle (n, %)</i>
7.8 ± 1.9	- (0, 0) ^a
7.8 ± 1.7 (37, 80.4)	3.6 ± 0.9 (3, 6.5) ^a
7.1 ± 1.8 (16, 34.8)	3.5 ± 1.1 (3, 6.5) ^a
5.7 ± 1.5 (22, 47.8)	1.9 ± 0.8 (2, 4.3) ^a
4.9 ± 1.3 (6, 13.0)	- (0, 0) ^a

Values are reported as mean \pm SD. The number and the percentage of symptomatic women are shown in parentheses. Symptoms were graded according to severity on a 10-point scales

^ap < 0.05 versus baseline

Vercellini, Fert&Ster 2003



Low Dose Mifepristone for Uterine Leiomyomata

- *Advantages for women with fibroids*
 - *Alternative to GnRH analogues for preoperative application*
 - *Perimenopausal women may be able to take it until menopause*
 - *Younger women who wish to retain their fertility*
- *Disadvantages*
 - *Incidence of hot flushes*
 - *Simple hyperplasia in 28% of subjects*



Asoprosnil

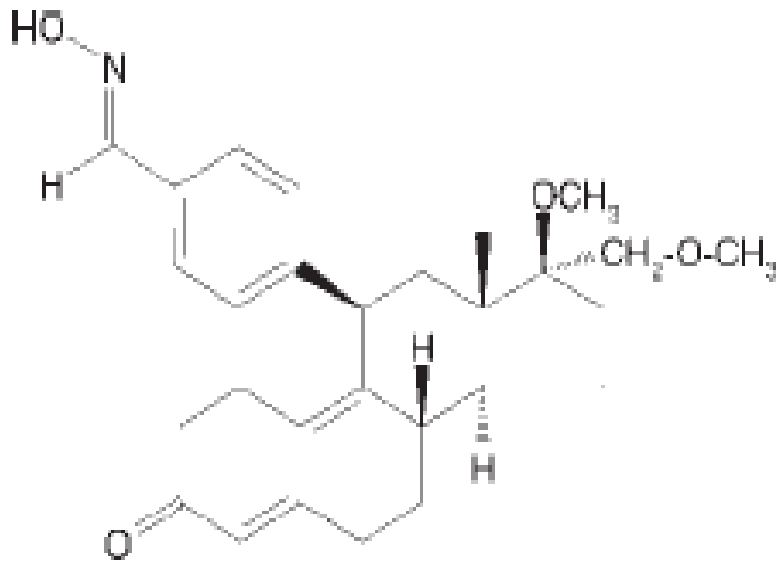


Figure 1 The chemical structure of asoprosnil.

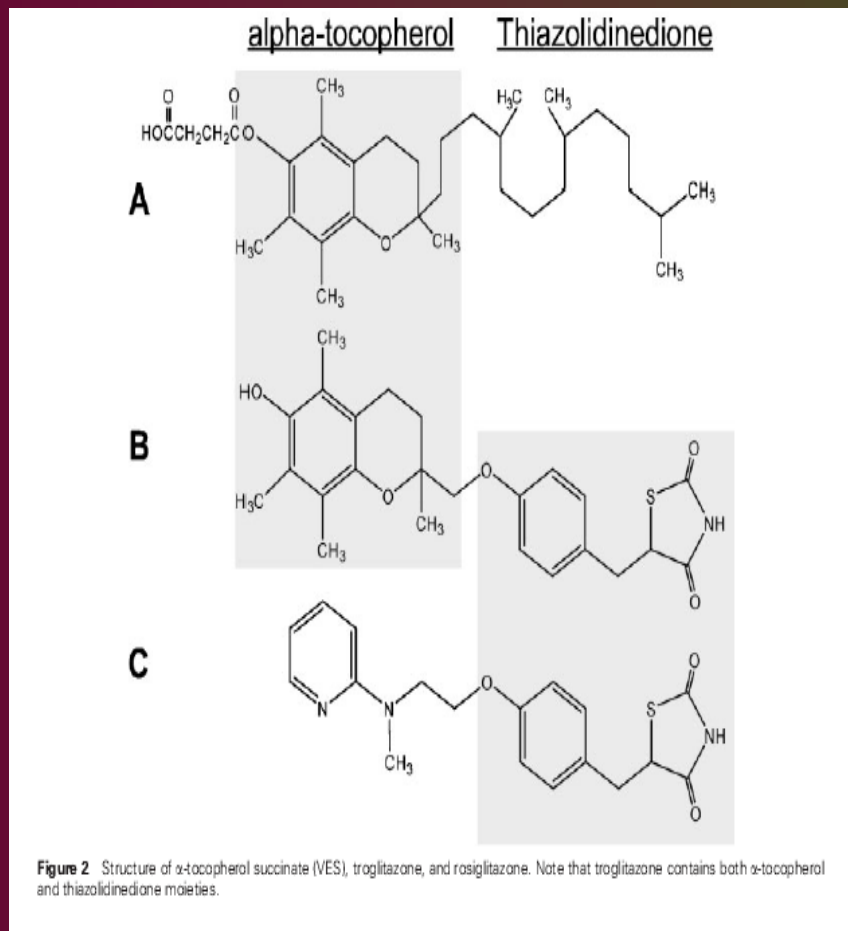
- Selective progesterone receptor modulator
- Shows tissue-selective and PR –specific effects in humans and animals
 - Suppresses uterine bleeding by targeting the endometrial vessels
 - Inhibits leiomyomata growth at doses of 10-25mg/day

Four Classes of Growth Factors

- *Transforming TGF-Beta*
- *Heparin-Binding Factor*
- *Angiogenic Growth Factor*
- *Insulin Like Growth Factors*



Nonhormonal Therapeutics for Medical Treatment of Leiomyomas



Compound	Adm	Mode of Action	Clinical Tx
Pirfenidone	Oral	Inhibition of TGF-B	Pulmonary fibrosis
IFN-a		Prevent TGF-B synthesis; inhibit proliferation	Hepatitis C, melanoma, condyloma
Heparin	IV, SC	Inhibitor of growth factors	Anticoagulant
Rosiglitazone	Oral	Bind to nuclear receptor, PPAR	Type 2 diabetes
Vitamin E	Oral	Restrict growth and induce cell death	supplement

Surgical Management of Leiomyomata

- *Hysterectomy*
 - *Abdominal vs. laparoscopic assisted vaginal hysterectomy*
- *Myomectomy*
 - *Abdominal*
 - *Laparoscopic*
 - *Hysteroscopic*
- *Myolysis*
 - *Cryo*
 - *Coagulation*
- *Focused Ultrasound Thermoablation*
- *Uterine embolization*

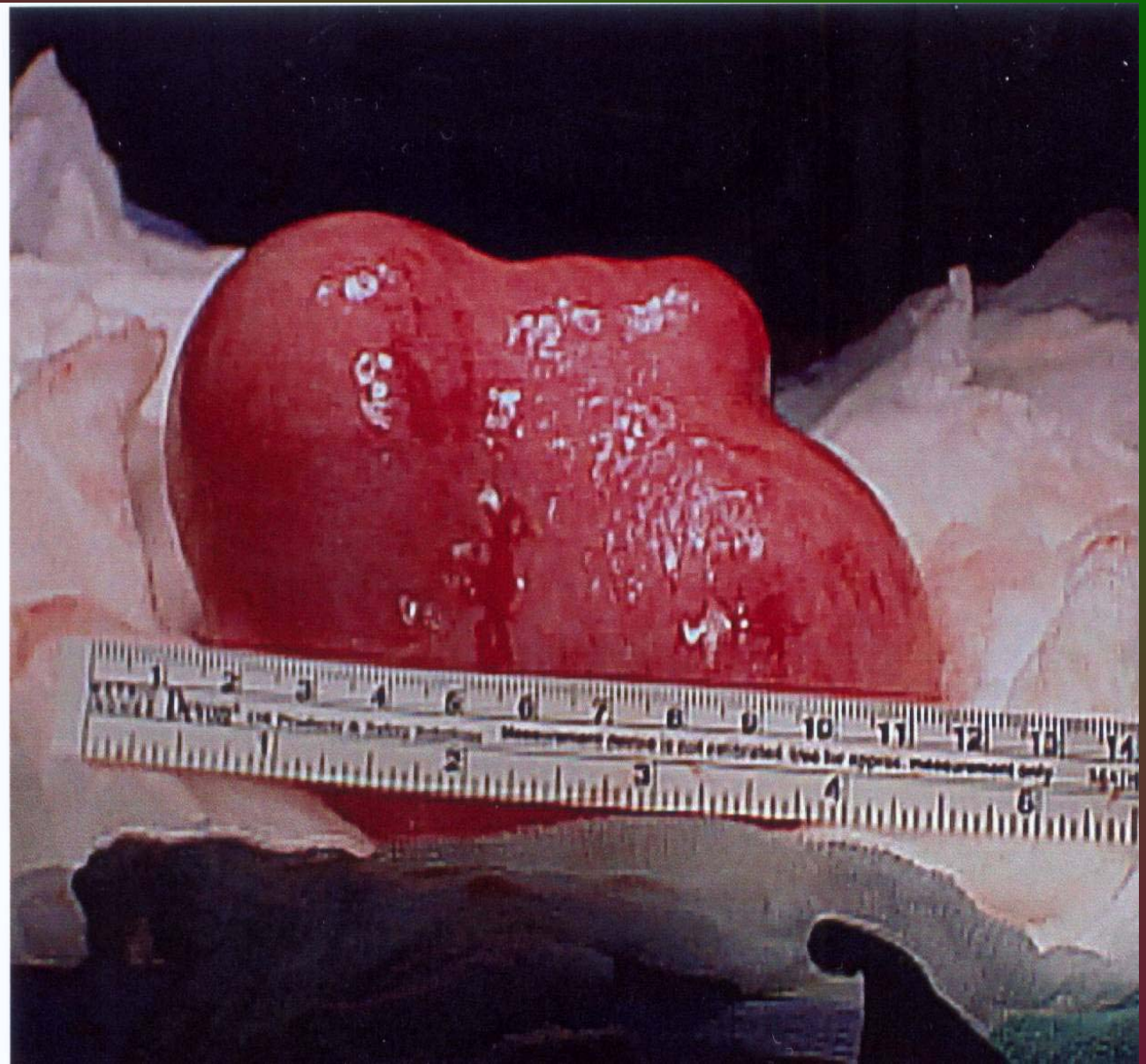


Choice of Surgical Therapy

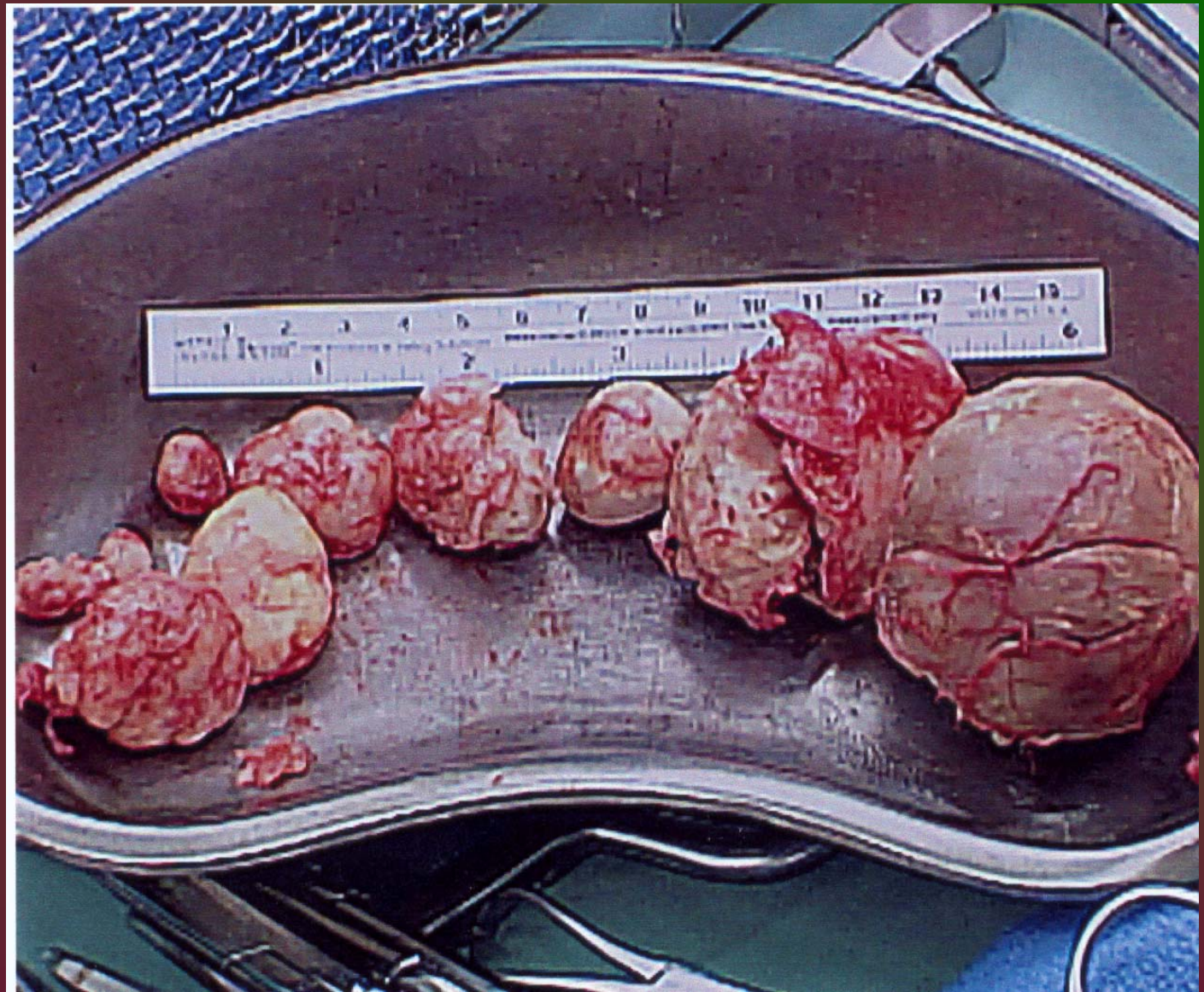
- *Size and number of myoma(s)*
- *Age of the patient*
- *Preservation of fertility*
- *Preservation of the uterus*



CASE 1



CASE 1



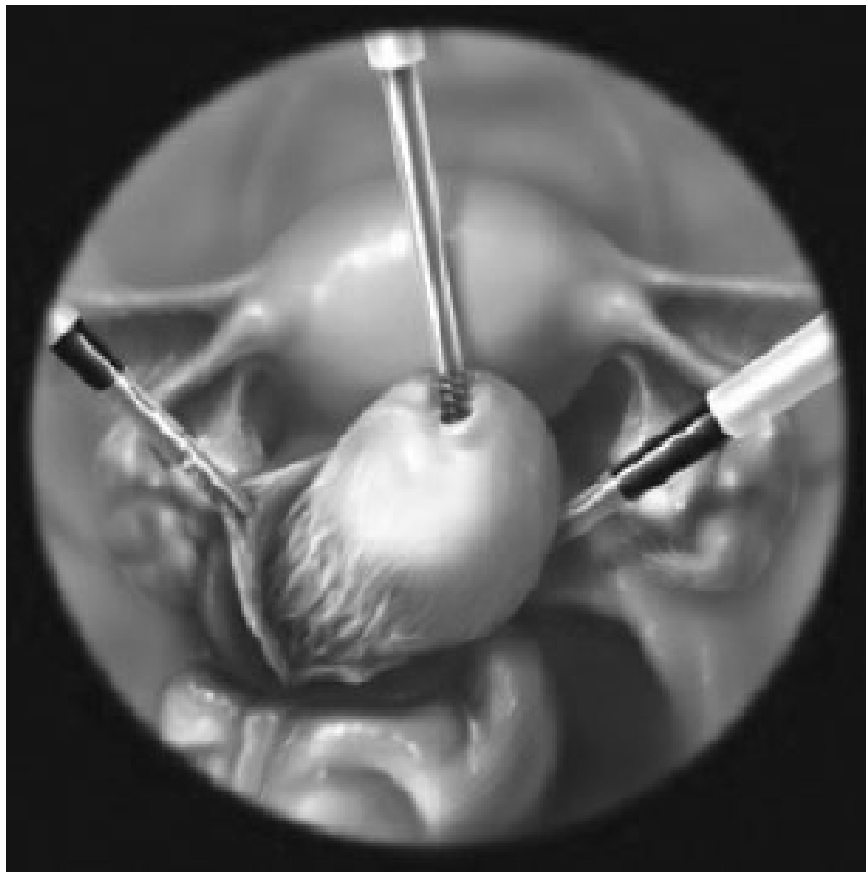


Figure 1 Laparoscopic removal of posterior uterine fibroid.

Myomectomy: Indications

- *Desire to maintain fecundity*
- *Desire to retain uterus*
- *Solitary pedunculated subserous myoma*
- *Causal relationship between leiomyomata and infertility suspected*
- *Large or multiple symptomatic leiomyomata*
- *Failure to shrink on GnRH agonist therapy*



Myomectomy: Complications

- *Mortality rate* 0.12%
- *Transfusion rate* 18%
- *Adhesion formation* 40% - 65%
- *Recurrence rate* 5% - 30%
- *Subsequent surgical therapy* 10%
- *Subsequent hysterectomy rate* 5%
- *Emergency hysterectomy rate* 1%
- *Blood loss >1,000cc* 20%



Reproductive performance before and after myomectomy

	Before Myomectomy, n (%)	After Myomectomy, n (%)
Subjects in the study (n)	72	72
Subjects who became pregnant (n)	20	51
Total number of pregnancies	26	68
First trimester	14 (54)	15 (22)
Second trimester	3 (11)	—
Pregnancy loss		
Third trimester	1 (4)	—
Ectopic	—	2 (3)
Total^a	18 (69)	17 (25)
Live birth^a	8 (31)	51 (75)

^aResults before and after myomectomy are significantly different (P <.001).

n=72



Impact of age, number, size and location of Fibroids and surgical findings on reproductive outcome after myomectomy

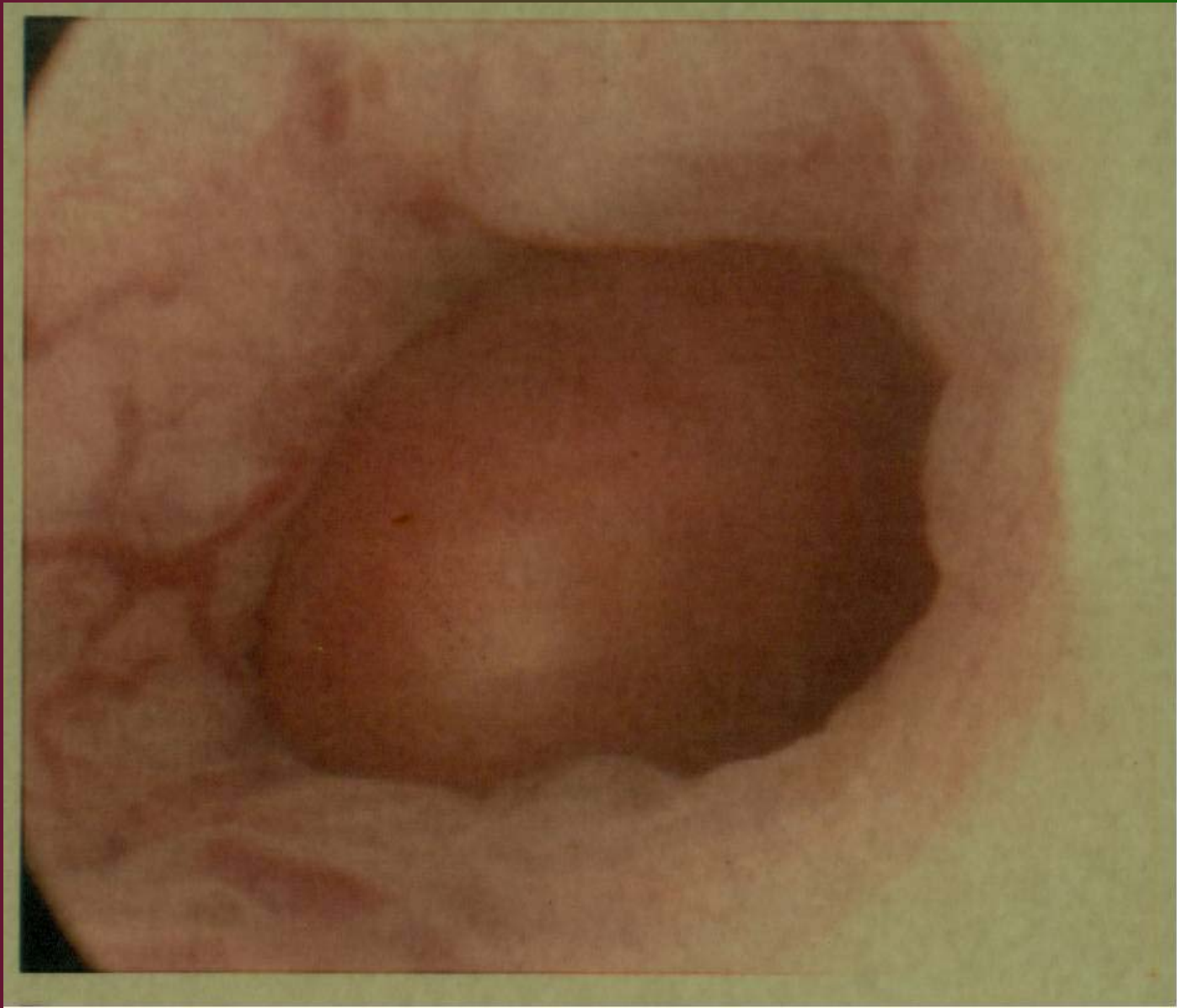
	Live Birth	Miscarriage	Total pregnant	Not pregnant	P value ^a
Age (y)					
≤30	19	2	21	2	.01
>30	25	5	30	19	
Number of Fibroids					
1	24	4	28	5	.02
>1	20	3	23	16	
Endometriosis					
No	43	7	50	18	.07
Yes	1	—	1	3	
Location of fibroids					
Intramural	27	3	30	13	.7
Subserous	13	3	16		
Size of fibroids (cm)					
≤5	21	1	22	6	.4
>5	22	6	28	14	
Opening of endometrial cavity					
No	41	5	46	19	1
Yes	3	2	5	2	

^aResults were analysed by 2 X 2 contingency table analysis, pregnant versus non-pregnant.

Note: Data are expressed as n







Techniques for Hysteroscopic Myomectomy

Versapoint

- Coaxial 5 mm bipolar electrode system*
- Normal saline as distention media*
- Reduction in energy spread during resection*

Hysteroscopic Myomectomy Using Wire Loop

- Tedious*
- Numerous “chips” produced*
- Bleeding common*
- Danger of intravasation*

Hysteroscopic Myomectomy

Reproductive Outcome Following HSC Myoma Resection

Author	# Cases	Preg Rate*	Del Rate*
Donnez et al	24	16(67)	16(67)
Valle	16	10(62)	8(50)
Corson et al	13	10(77)	8(61)
Goldenberg et al	15	7(47)	6(40)
Total	68	43(63)	38(56)

Goldenberg et al

*values in parentheses are percentages



Thermoablative Treatment: Using Heat or Cold to Destroy Tissue

- *Cryotherapy* for cervical dysplasia
- *Myolysis and cryomyolysis* for *fibroids*

Goldfarb: JAAGL; 2:175-9

Goldfarb: ObGyn Clinics N.A 1995; 22:807-19

Zreik et al: JAAGL 5:33-8, 1998

Myolysis

• Coagulation	Fibroid Shrinkage*
– Nd:YAG Laser	50%
– Bipolar needles	60%
– Cryomyolysis	50%
• Electromyolysis	NR

All studies report 10-50% incidence of dense adhesions

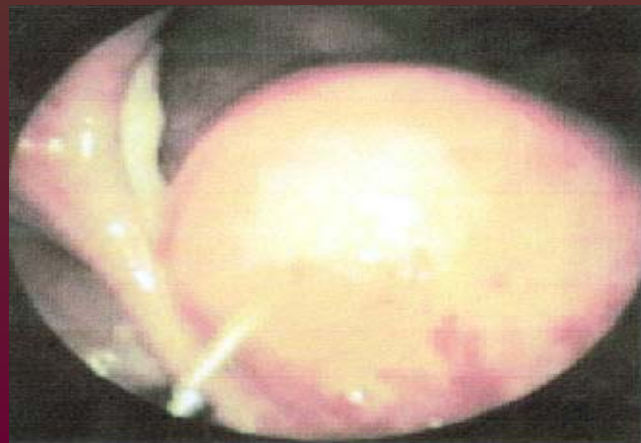
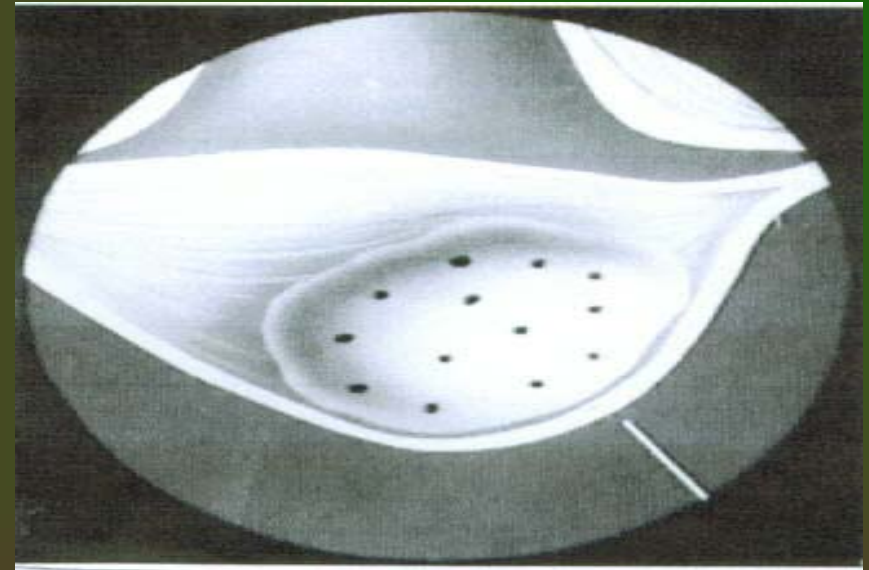
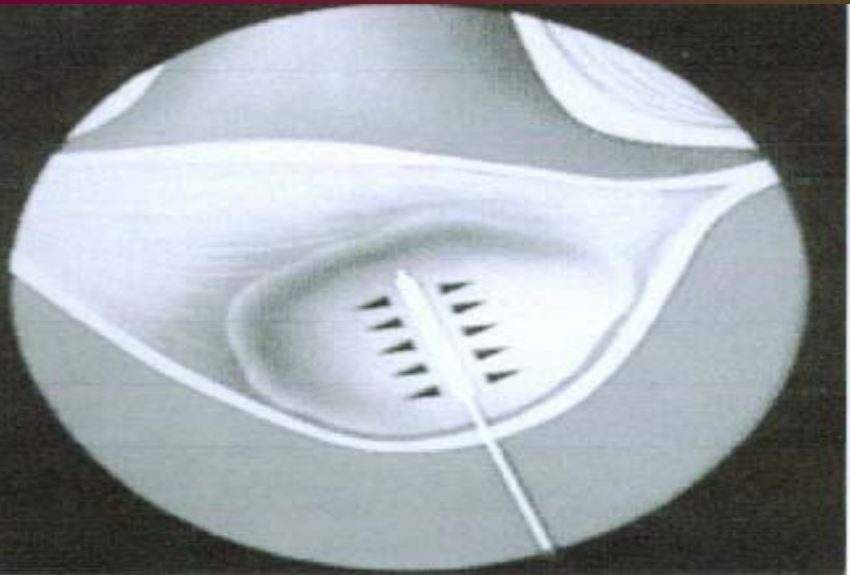
*6 months

Goldfarb, 1992,1995

Phillips, 1995,1997

Chapman, 1993

Zreik, 1998



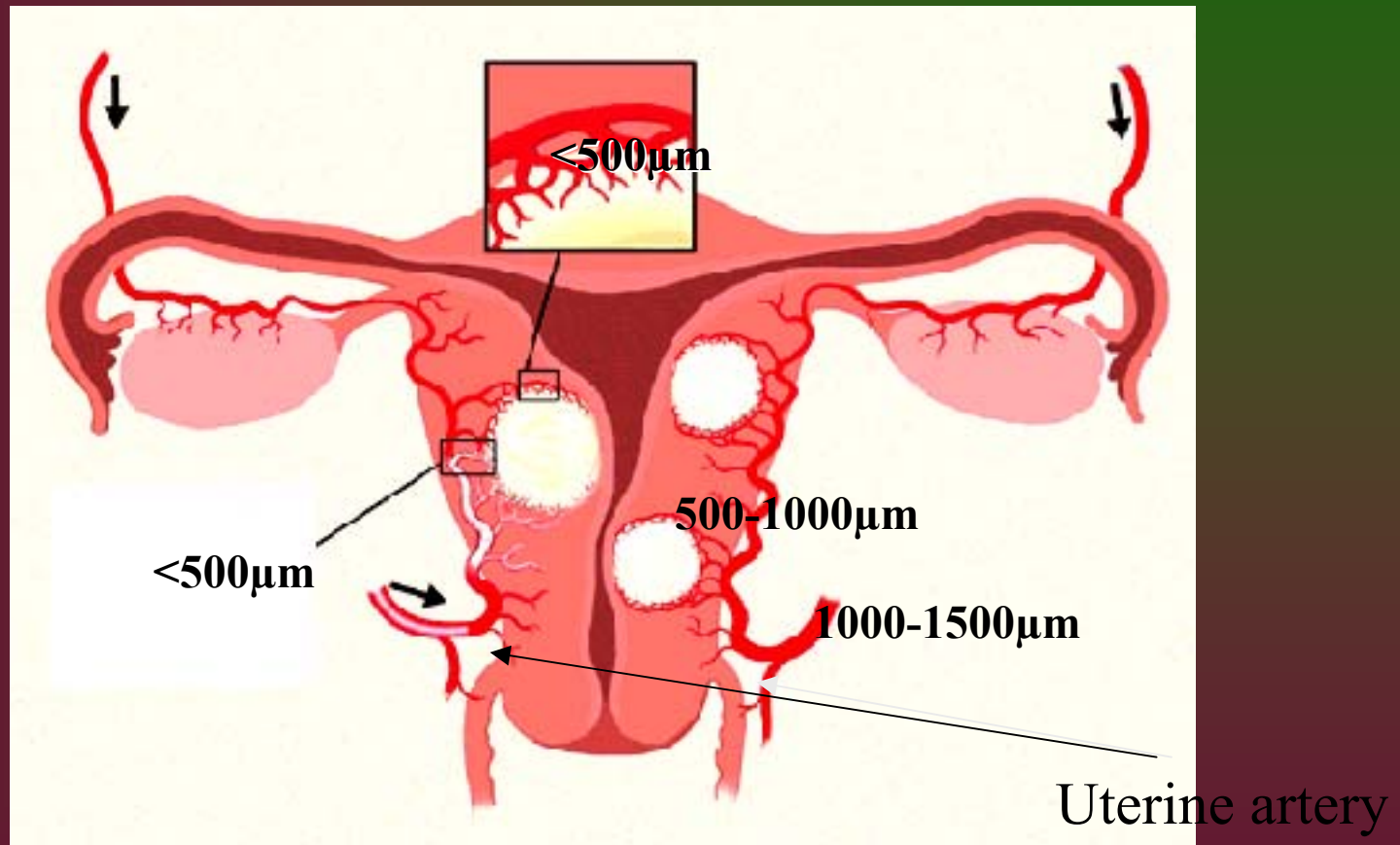
Uterine Artery Embolization (UAE)

- *Embolization of the uterine arteries is a promising new minimally invasive approach to the management of symptomatic uterine fibroids*
- *Favorable anatomy makes catheterization easy and inadvertent embolization on non-target tissues unlikely*
- *Embolization has been used successfully as both an adjunct and alternative to myomectomy in selected cases*



Vascular Network of Uterine Fibroids

Uterus



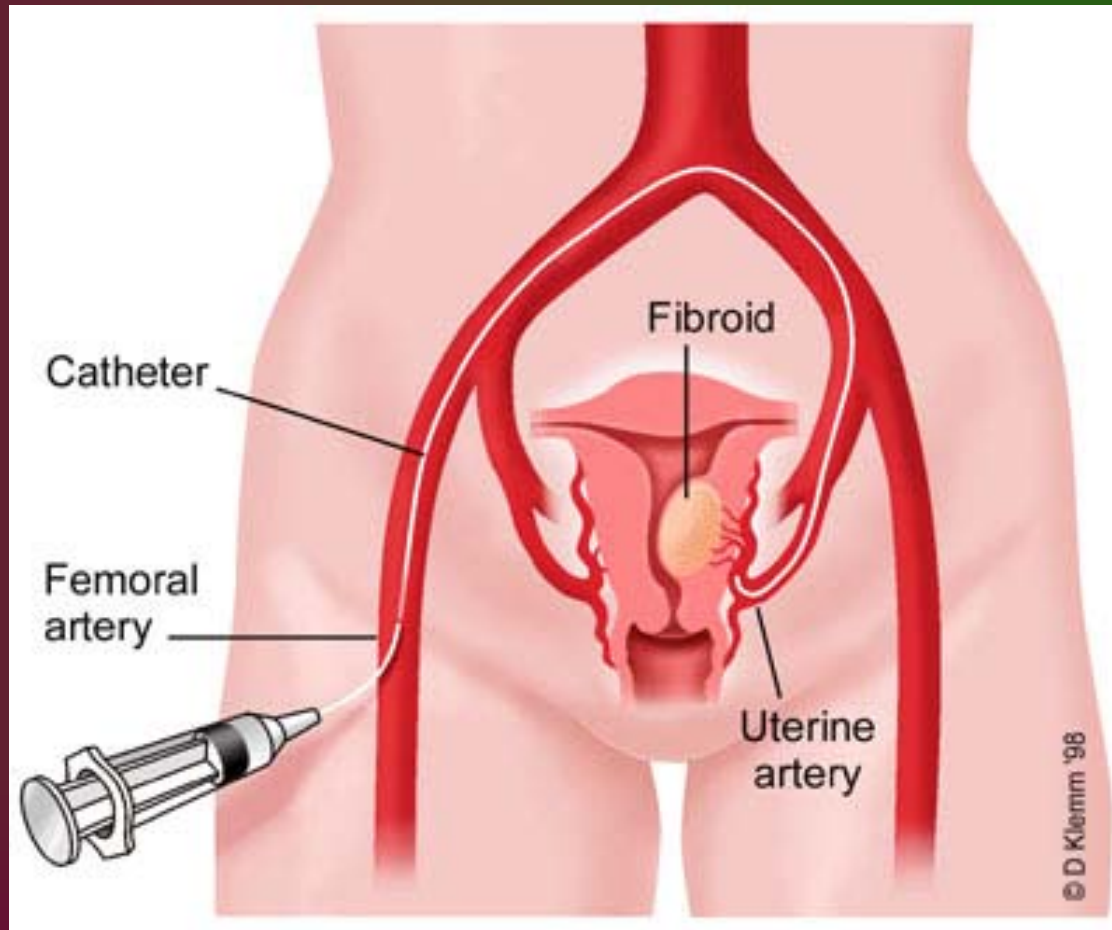
Arterial network
measured in microns

>500 μ m



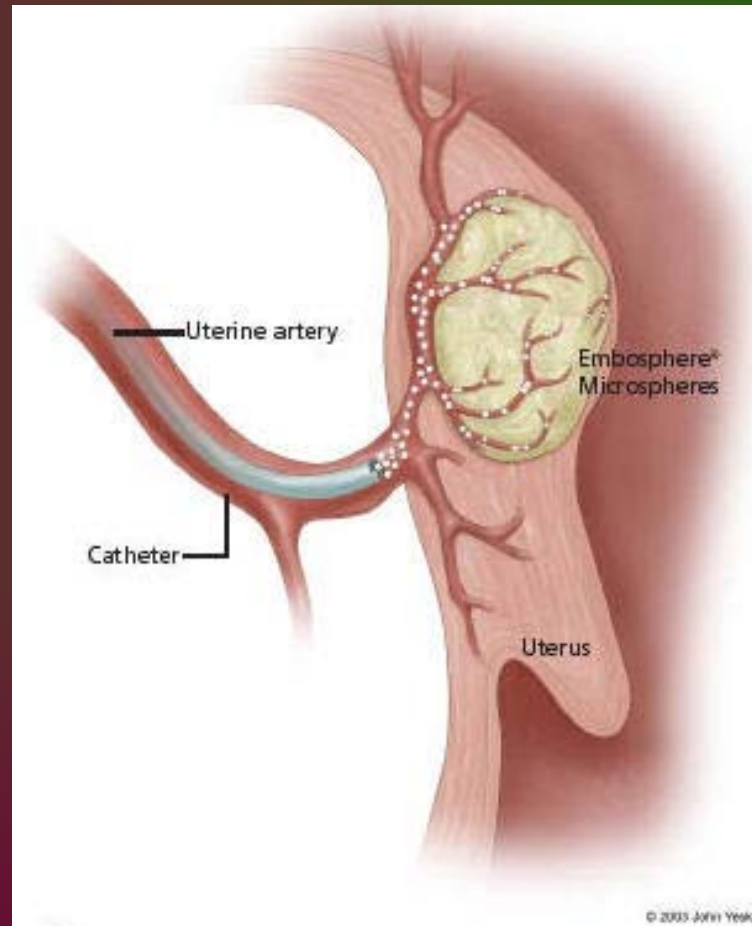
Targeted Uterine Fibroid Embolization

Accessing the Uterine Artery



Targeted Uterine Fibroid Embolization

Arterial Inflow to Fibroids



FDA Approved Embolic

Calibrated Embosphere® Microspheres



Pre-filled sterile syringe

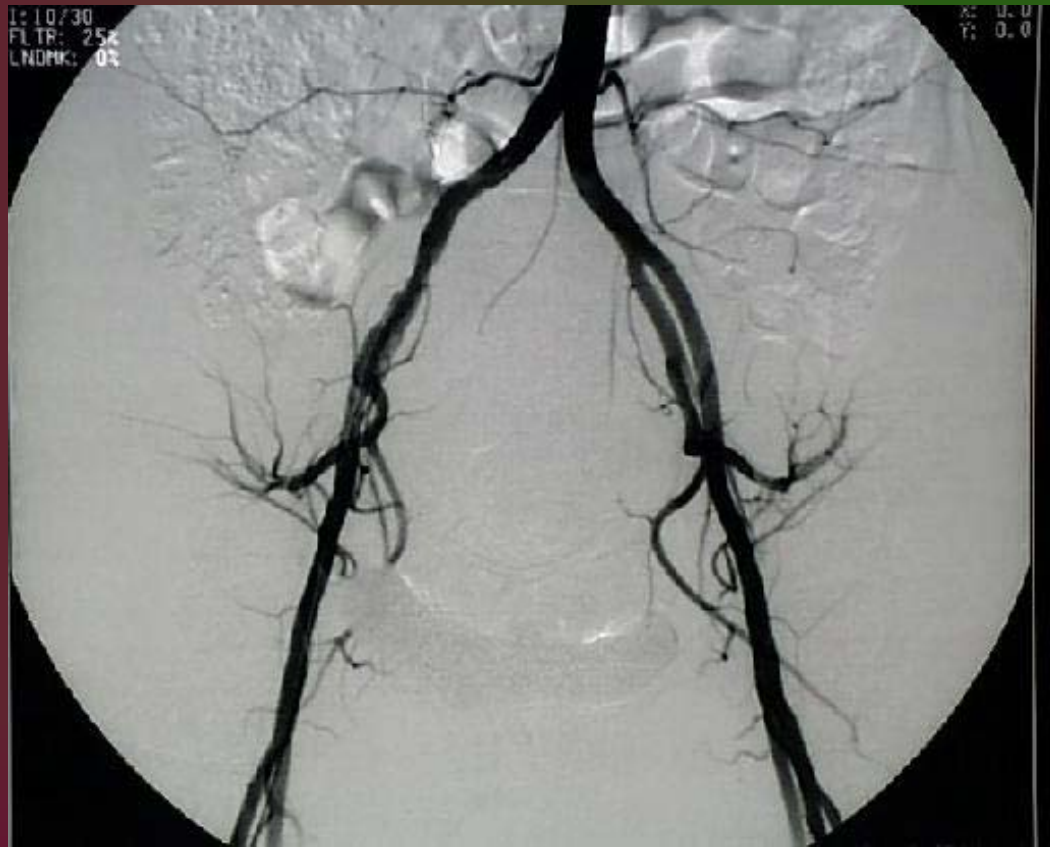


Sterile vial



Targeted Uterine Fibroid Embolization

Angiographic (x-ray) image of pelvis



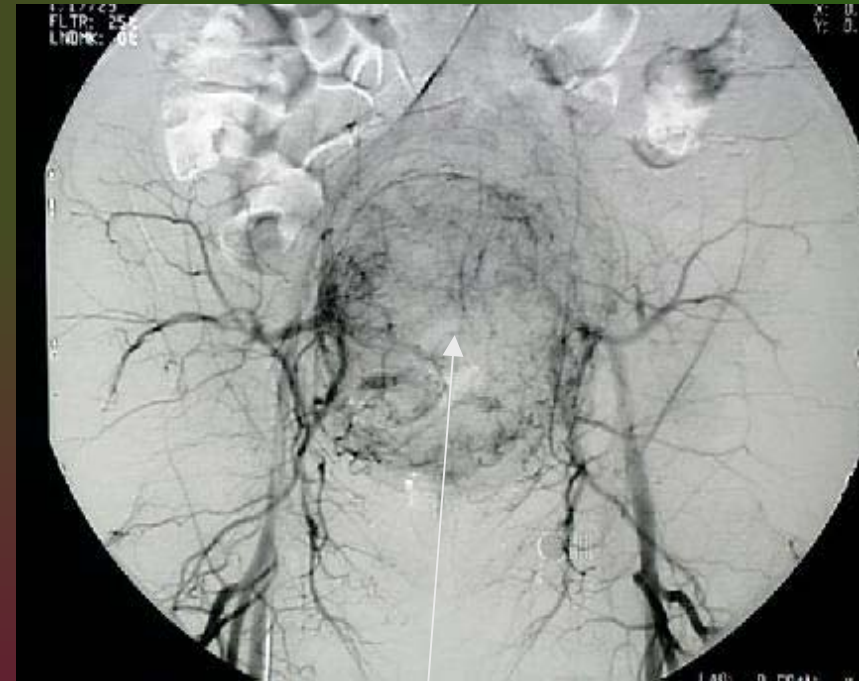
Targeted Uterine Fibroid Embolization

Pelvic angio



Uterus

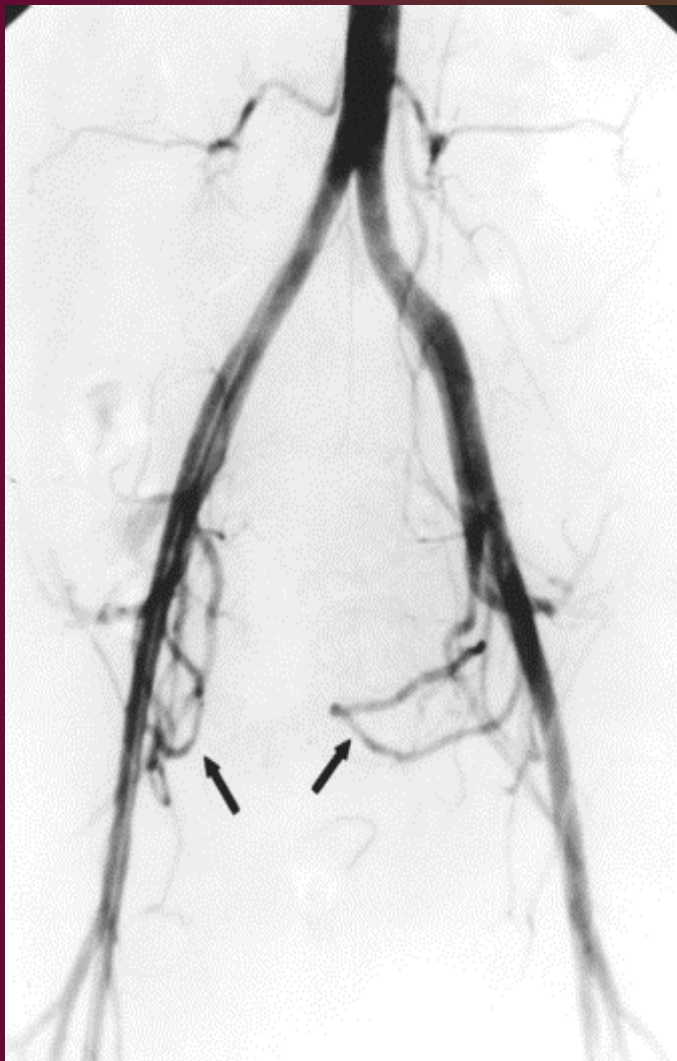
Fibroid blood supply



Fibroid

38-year-old woman with uterine fibroids. Before embolization, pelvic angiogram reveals enlarged uterine arteries (arrows) bilaterally.

Before



After

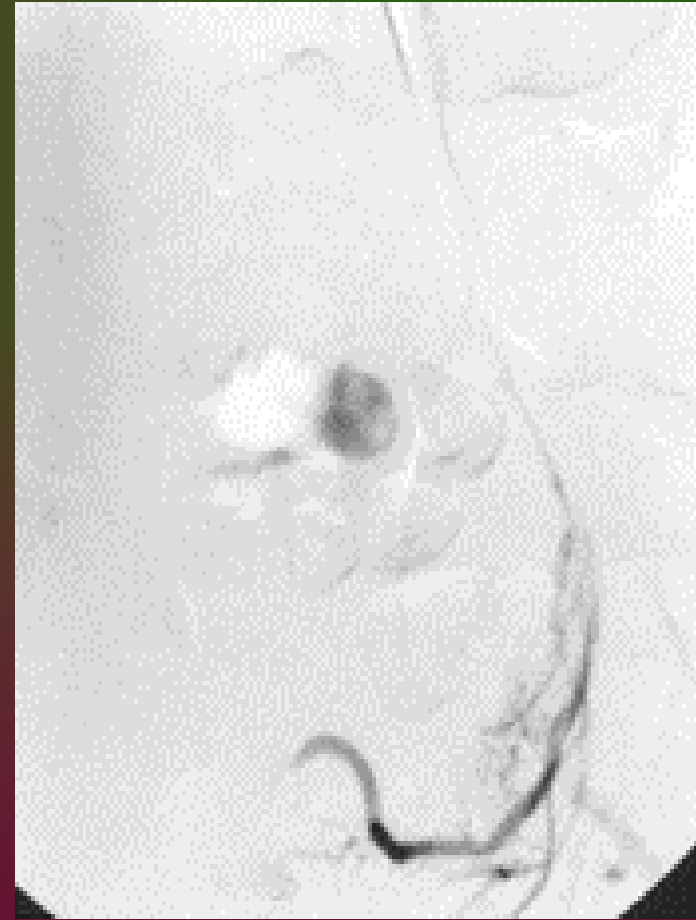


38-year-old woman with uterine fibroids. Selective right (C) and left (D) uterine angiograms show hypervascular tumor.

Before

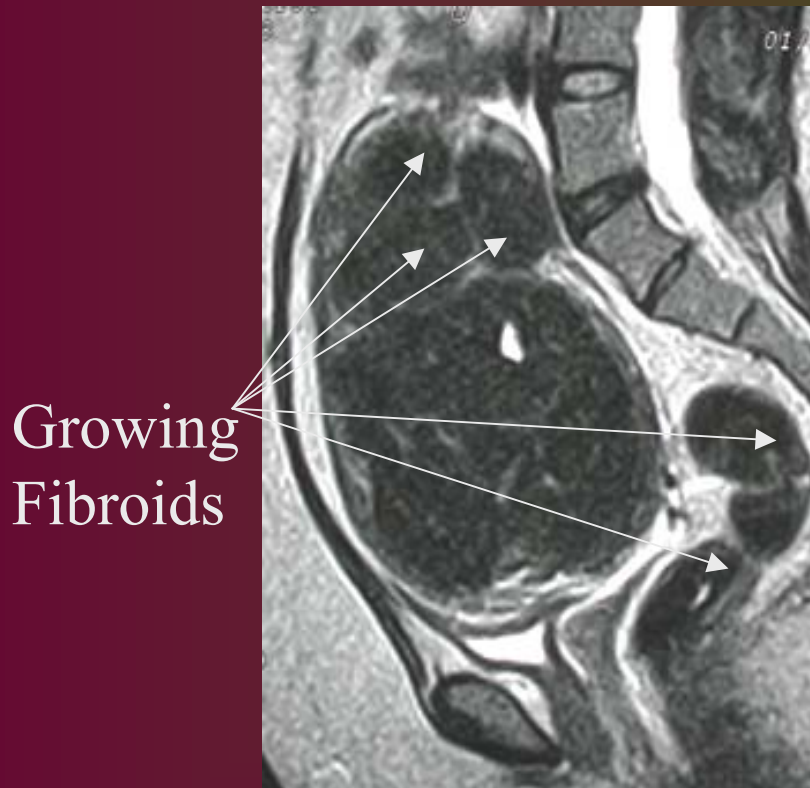


After

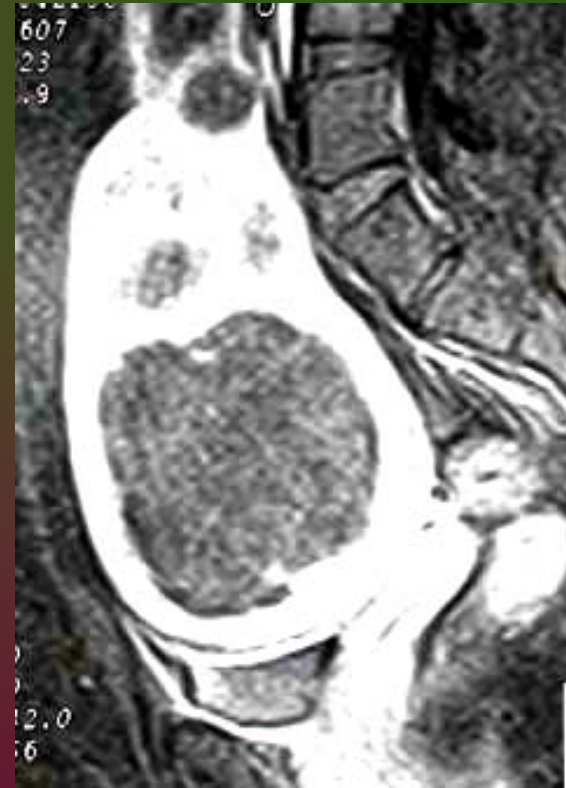


Pre- and Post-embolization with Embosphere® Microspheres

MRI images



Before UFE



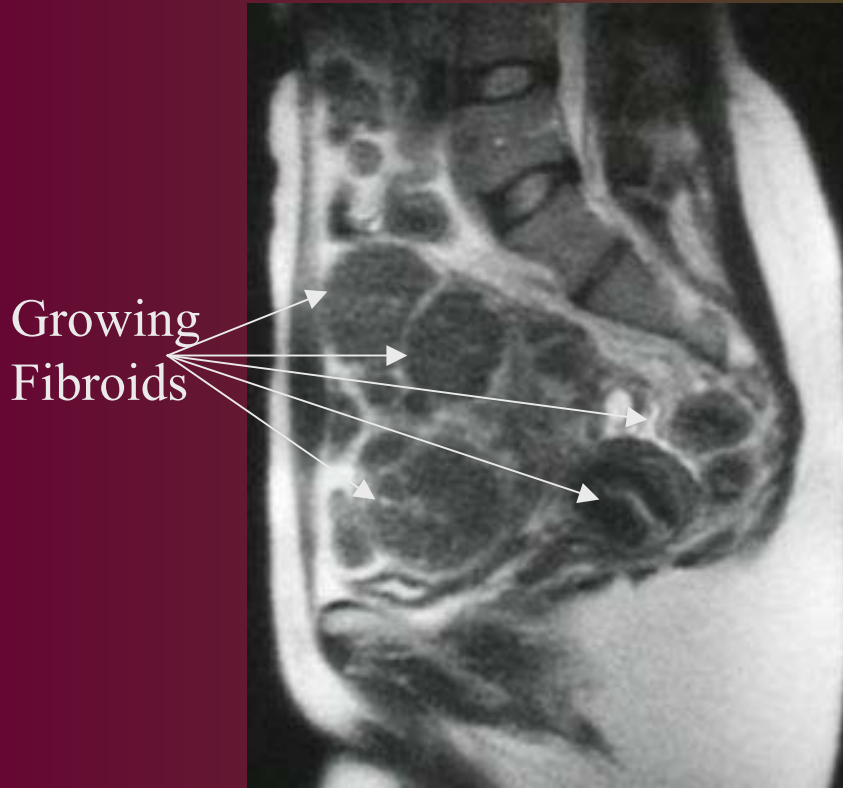
Shrinking Fibroids

Courtesy of James B. Spies, M.D., Georgetown University Medical Center

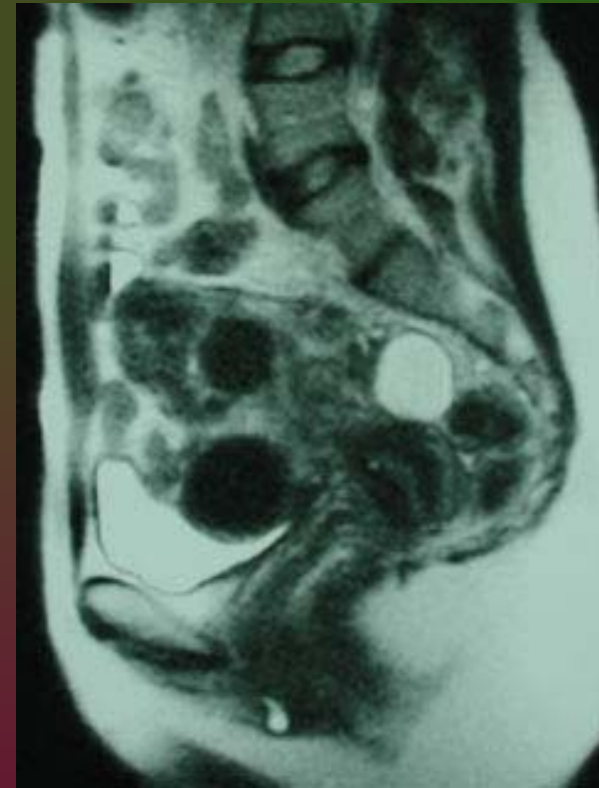


Pre- and Post-embolization with Embosphere® Microspheres

MRI images



Before UFE



3 months Post UFE

Courtesy of James B. Spies, M.D., Georgetown University Medical Center



Clinical Results of UFE

	<u>Patients</u>	<u>Bleeding</u>	<u>Pain/Bulk</u>	<u>Cx(%)</u>	<u>F/U</u>	<u>Comment</u>
<i>Pron, 03</i>	538	83%	82%	2	8 m	
<i>Spies, 02</i>	400	N/A	N/A	9	30 d	1 sarc
<i>Walker, 02</i>	400	84%	79%	13	17 m	
<i>Spies, 01</i>	200	90%	91%	0.5	21 m	
<i>McLucas, 01</i>	167	92%	70%	11	12 m	4 unilat
<i>Pelage, 02</i>	80	90%	N/A	5	24 m	4 unilat
<i>Brunereau, 00</i>	58	97%	N/A	2	24 m	
<i>Spies, 99</i>	61	89%	96%	5	9 m	
<i>Goodwin, 99</i>	60	91%	91%	4	16 m	2 endomet
<i>Worthington</i>	53	88 %	94%	0	3 m	
<i>Goodwin, 97</i>	11	85%	88%	1	6 m	1 endomet
<i>Ravina, 95</i>	16	68%	N/A	0	20 m	



UFE Efficacy-Summary

- *Menorrhagia* 87-95%
 - *Pelvic pain/dysmenorrhea* 85-97%
 - *Bulk-related Symptoms* 80-94%
 - *Reduction in Fibroid Volume* 40-65%
- »(3 months)



UFE Complications-Summary

- *Fibroid expulsion* 3-7%
- *Vaginal discharge* 0-5%
- *Endometritis/Infection* 0-3%
- *Ovarian failure* 1-2%
- *Contrast, medication allergies* 1%
- *Groin site complications* 1%



Comparison of Uterine Embolization and Hysterectomy for Leiomyomas

<i>Parameter</i>	<i>Embolization</i> (n=102)	<i>Hysterectomy</i> (n=50)	<i>P value</i>
Procedure time (mean min)	57.9	93.6	<.001
Hospital stay (mean days)	0.83	2.3	<.001
Return to work (mean days)	10.7	32.5	<.001
Improvement in:			
Pelvic pain	83%	88%	0.478
Pelvic discomfort	80%	80%	1.0
Urinary dysfunction	75%	73%	0.841
Pelvic pain at 12 mo	84%	98%	0.012
Pelvic pressure at 12 mo	83%	95%	0.055
Urinary symptoms at 12 mo	80%	79%	0.819



Reproductive Outcomes Following UAE vs LM

Complications	General Population (%)	UAE (n/N)	LM (n/N)	Odd Ratio	95% CI	P value
Spontaneous abortion	10-15	12/51 (24%)	20/133 (15%)	1.7	0.8-3.9	.175
Postpartum hemorrhage*	4-6	2/35 (6%)	1/104 (1%)	6.3	0.6-71.8	.093
Preterm delivery*	5-10	5/32 [†] (16%)	3/104 (3%)	6.2	1.4-27.7	.008
Cesarean delivery*	22	22/35 (63%)	61/104 (59%)	1.2	0.5-2.6	.662
Small for gestational age *	10	1/22 [§] (5%)	8/95 (8%)	0.5	0.1-4.4	.541
Malpresentation*	5	4/35 (11%)	3/104 (3%)	4.3	1.0-20.5	.046

*Calculations were based on the number of singleton pregnancies that continued past 20 weeks of gestation.

[†] Excludes 3 patients with unknown gestational age at delivery.

[§] Excludes 13 UAE patients and 9 LM patients with no birth weight data available.



MRI-guided cryomyolysis

- 9 women treated at laparoscopy
- Direct probe insertion
- Average volume reduction of 66%
- 3 Significant complications
 - Bleeding requiring myomectomy
 - Peroneal nerve dysfunction
 - Severe nausea

Cowan et al: Am J Ob Gyn 186:1183-7,2002

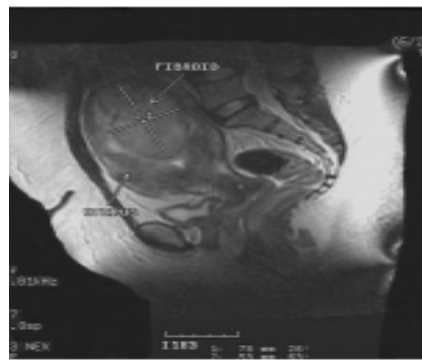


Myomectomy and MRI-Directed Cryotherapy

Bryan D. Cowan, M.D.¹



Figure 1 The patient is placed supine, and diked between the two magnets of the dual magnet MRI.



This is a longitudinal section of a uterine fibroid that 78 x 53 mm. The uterus is easily seen with the MRI.



Figure 3 A 3-mm cryoprobe that has been inserted into water and activated for 30 seconds. This image shows the profile of the image.

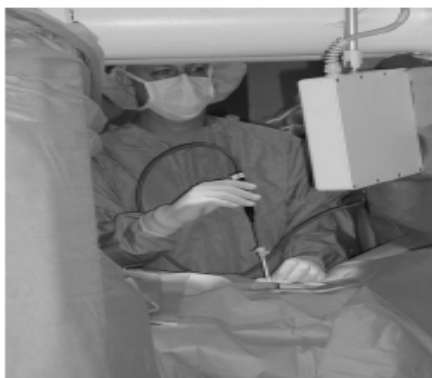


Figure 4 The shield and cryoprobe have been inserted, and under best MRI guidance the probe is advanced to its optimum position.



Figure 5 Three probes have been placed.

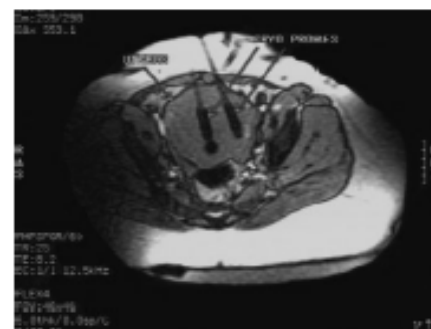


Figure 6 A transverse section of the uterine fibroid that shows two of the five cryoprobes. They have each been activated for ~3 minutes.

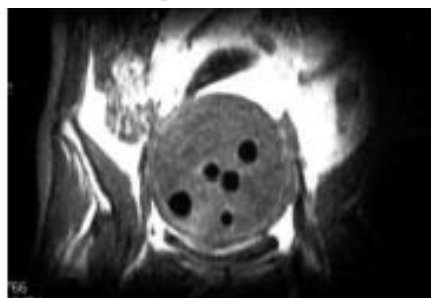


Figure 7 This is an AP projection of the uterine fibroid with five cryoprobes that have been activated for ~2 minutes. Each MRI probe is easily seen.

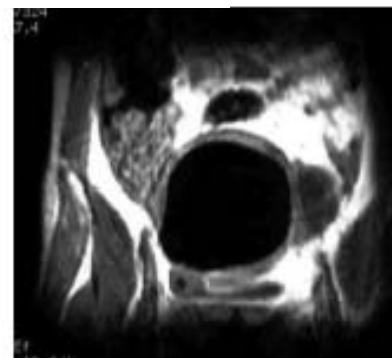


Figure 8 Entire consumption of the uterine fibroid after ~40 minutes of treatment.

Myomectomy and MRI-Directed Cryotherapy

Bryan D. Cowan, M.D.¹

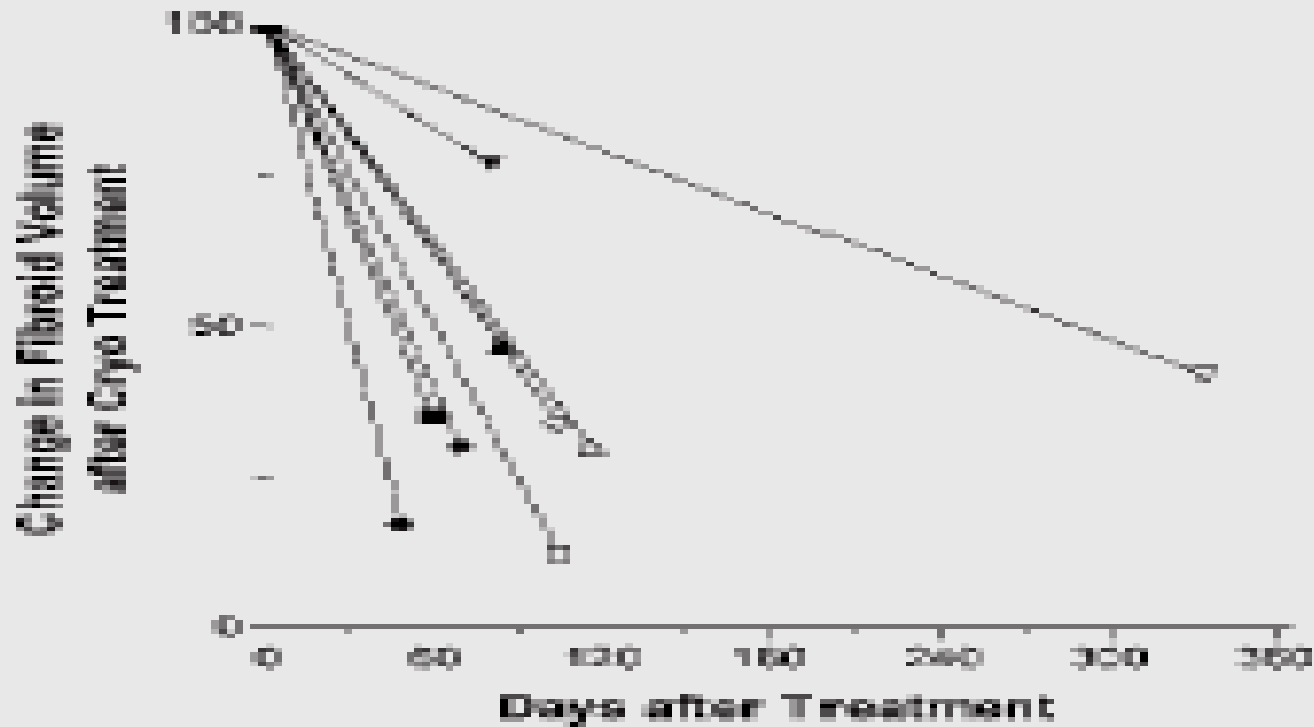


Figure 9 Change in fibroid volume after cryotreatment. The average reduction in fibroid tumors was 65.0% ± 7.0%.

Postoperative Size and Complications in 10 Women

Patient	Operation Time (h/min)	Preoperative Size of Myoma (cm ³)	Postoperative Size of Myoma (cm ³)	Days (no.)	Overall Reduction (%)	Immediate Complications
01	5/10	289	102	59	65	None
02	4/15	258	121	84	53	None
03	4/45	170	131	80	33	None
04	4/50	151*	56	69	70	Peripheral nerve injury, resolved
05	4/15	99	41	334	59	None
06	—	42	7	48	83	Transient abdominal pain
07	5/15	998	NA	NA	NA	Emergent myomectomy
08	3/25	259 [†]	44	105	88	Transient abdominal pain
09	4/25	561	170	116	70	Transient abdominal pain
10	3/15	360	122	104	66	None

•Approximate size of three treated myomas

†Approximate size of two treated myomas.

NA, not appropriate



MRI Guidance of Focused Ultrasound for Uterine Fibroids

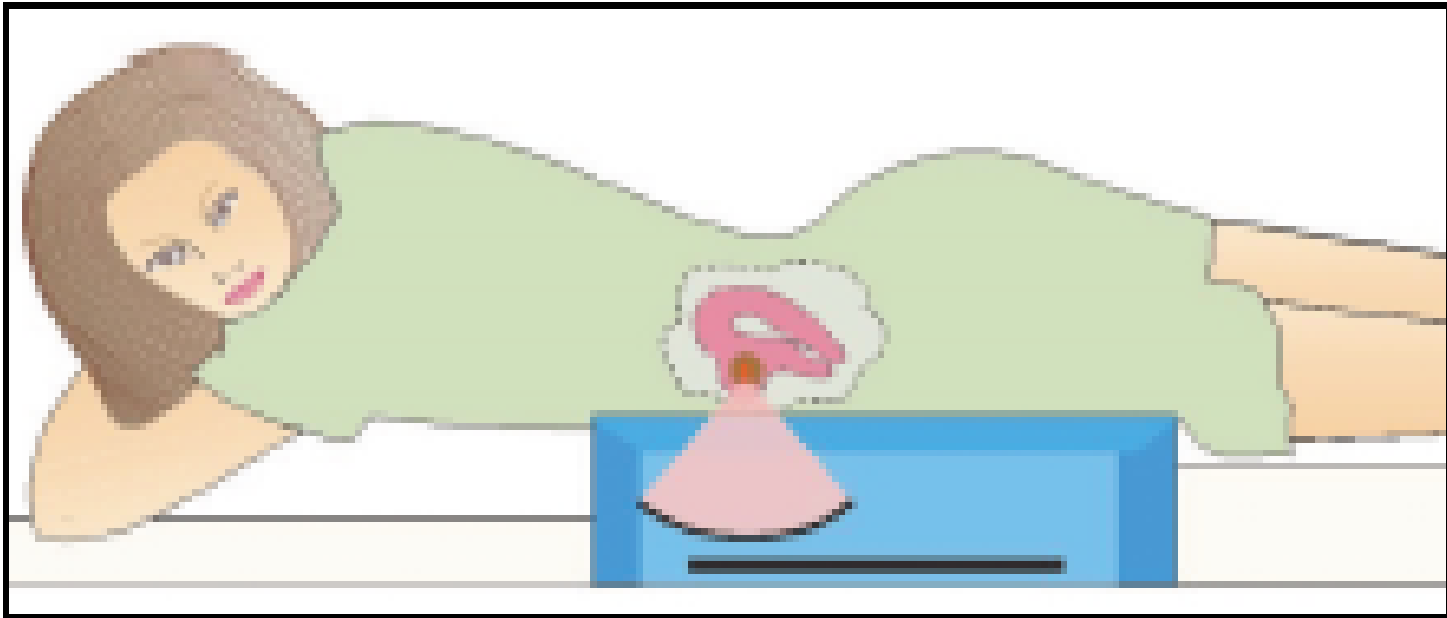
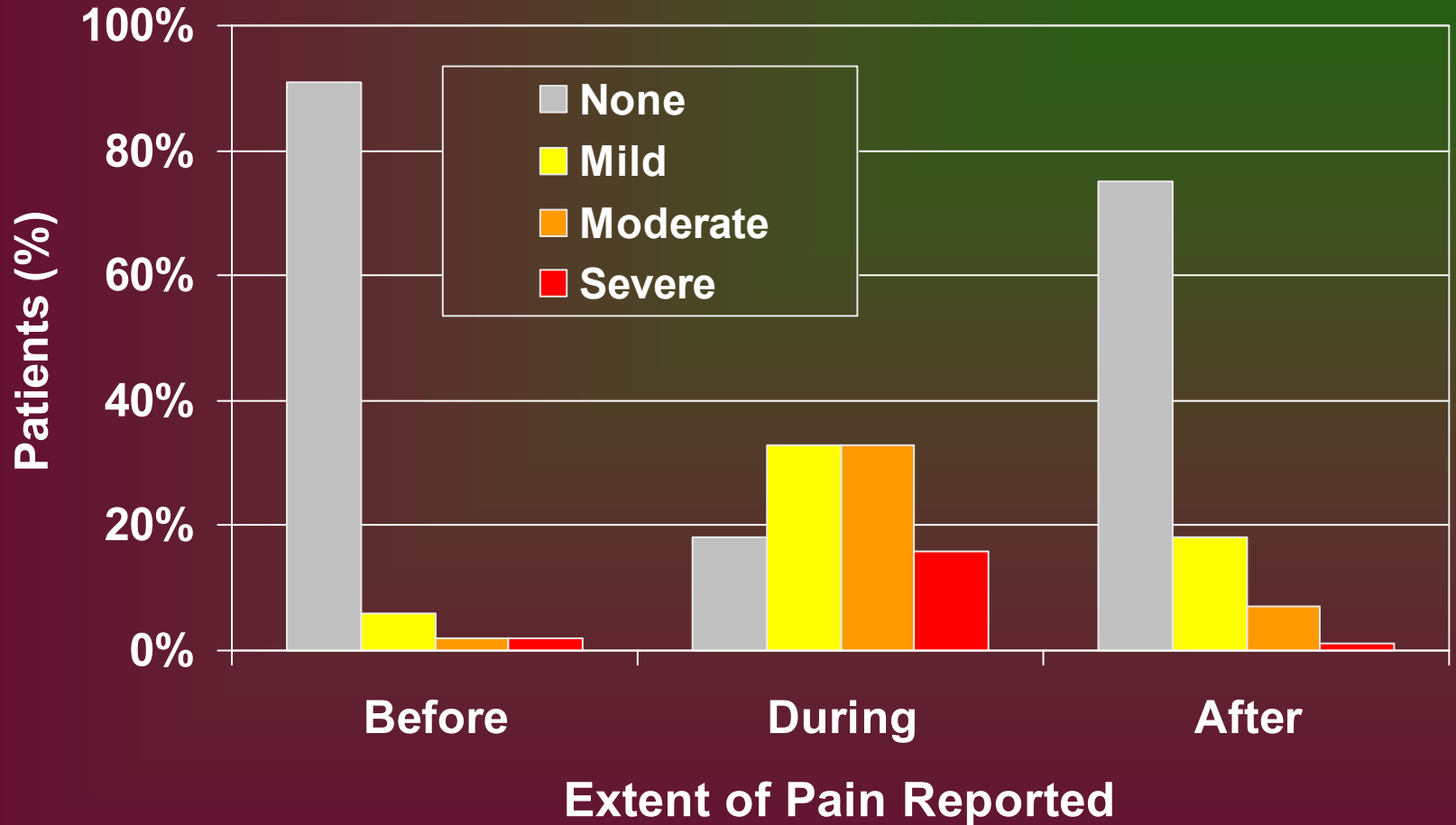
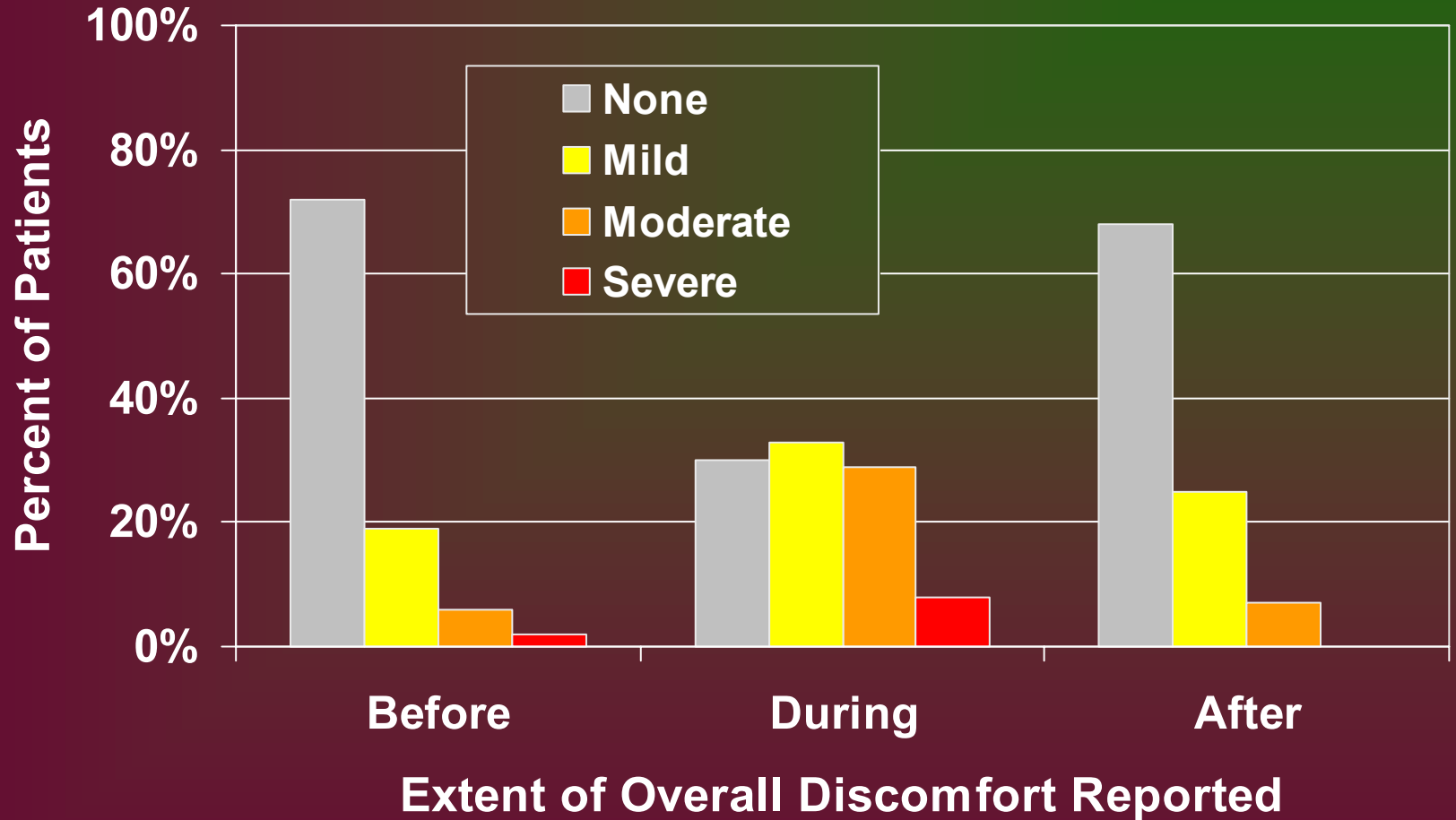


Fig. 1— Schematic representation of patient lying on E-Motion 2000 (InSightec) focused ultrasound system ready to be placed into MRI unit. Ultrasound transducer found in new bed angle both within MRI table.

Pain Before, During, and After Focused Ultrasound for Uterine Fibroids

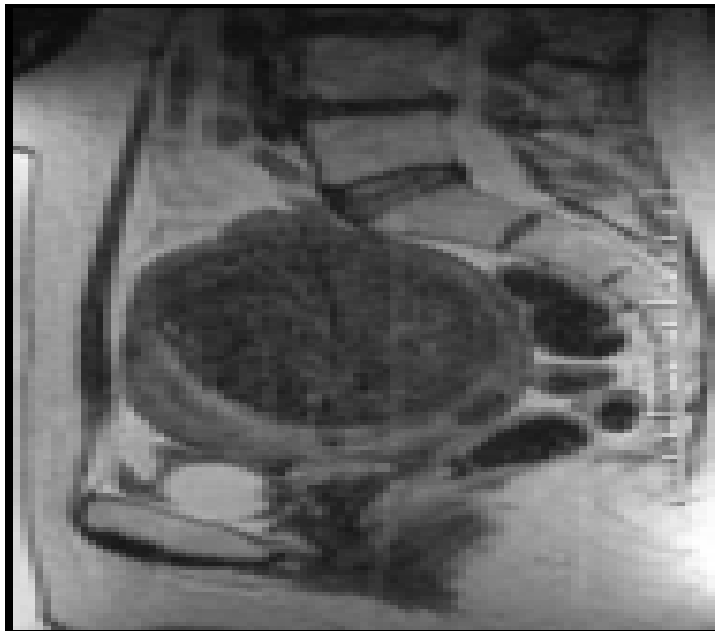


Overall Discomfort Before, During, and After Focused Ultrasound for Uterine Fibroids

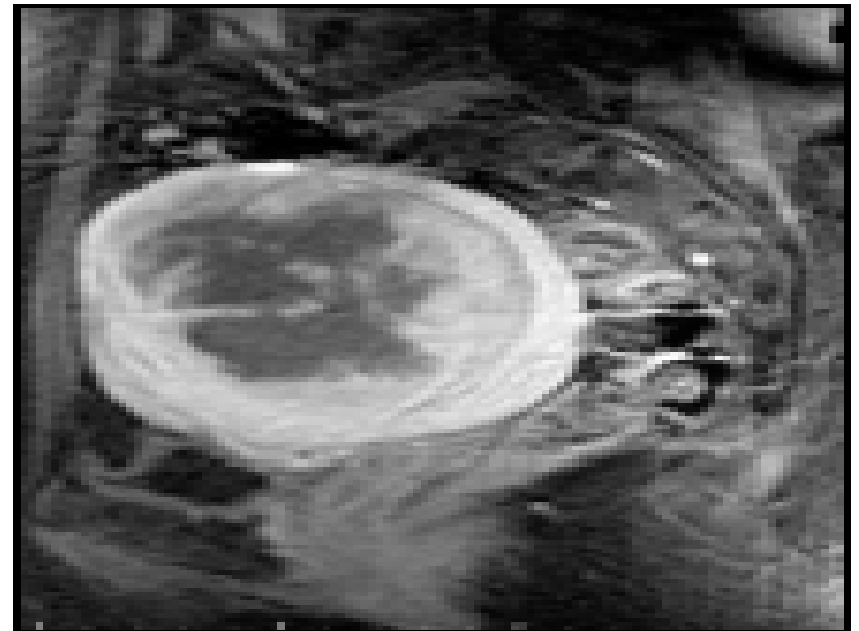


Sagittal Images of fibroid before and after MRI-guided focused US

Before

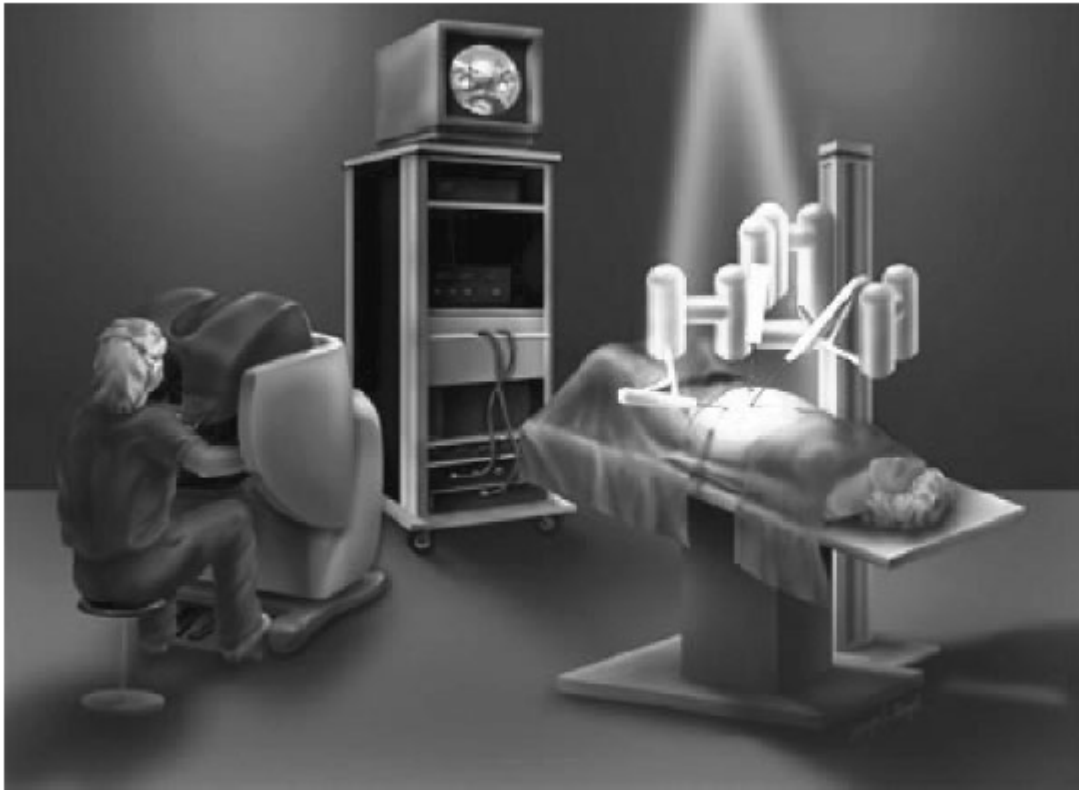


After



MRI Guidance of Focused Ultrasound for Uterine Fibroids: Results at 6 Months

- N=109, mean age 44.8
 - Mean fibroid volume: reduced 13.5%
 - Mean nonperfused volume: 51.2 cm³
- Patients achieving a greater than 10-point reduction in Uterine Fibroid Symptoms and Quality of Life Questionnaire score:
79.3% (n=82; p<0.0001)
- Mean reduction in symptom severity score: 27.3
 - Mass effect: improved by 32.8 points
 - Bleeding: improved by 32.8 points



Schematic rendering of daVinci robotic surgical system.

Future Research Needs

- *Develop a better understanding of the genetics and molecular biology of leiomyomas*
 - *Medical and gene therapy approaches to treatment and prevention*
- *Improve the training of minimally invasive procedures*
- *Obtain long term safety data on the new minimally invasive procedures*

