Uterine Fibroids – Clinical Trial Design & Small Studies: A Clinical Perspective

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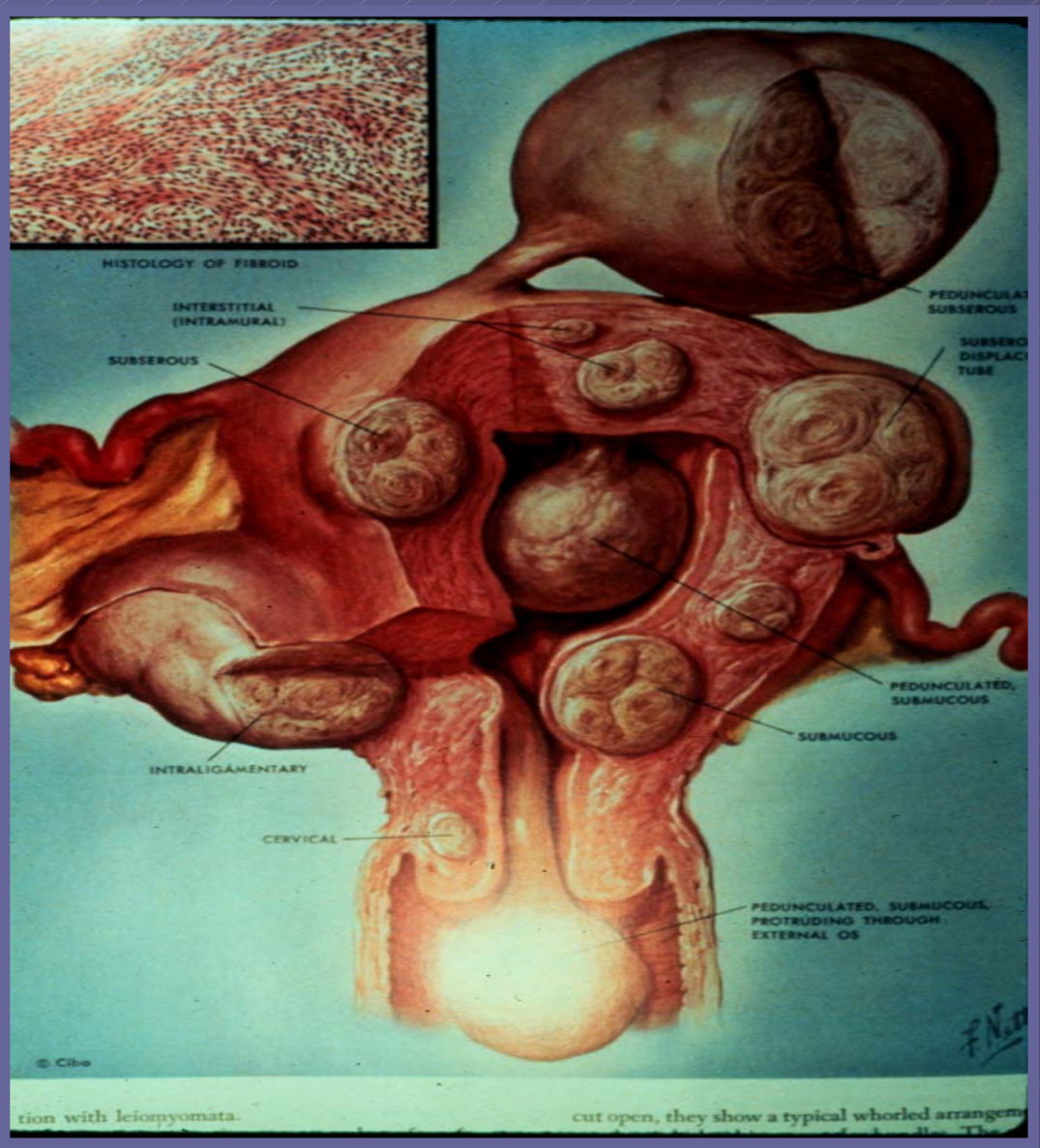
Clinical Considerations

- Uterine fibroids are benign tumors
- Uterine fibroids should only be treated for symptom relief – mostly subjective
- Uterine fibroid symptoms are related to size, number, location and degeneration, increase with age (>40 y/o)
  - 15% submucous
  - 50% intramural
  - 35% subserososal/pedunculated
- Treatment outcomes should consider
  - Recurrence rates
  - Affect on fertility
  - Unique outcomes i.e. pain, adhesions, uterine rupture

Uterine fibroid symptoms are related to size, location and degeneration



Uterine fibroids are benign tumors

- Benign fibroids do not transform into sarcomas – de novo formation[1]
- Sarcoma – 0.13% - 0.29% of all fibroids removed[2,3]
- Sarcoma – most common in the 6th and 7th decades of life
- 90% of sarcomas present with postmenopausal bleeding, not rapid growth

1 –Levy et al. Cancer Genet Cytogent 2000:121 2 – Montague et al. Am J Obstet Gynecol, 1965;92 3 – Parker eta al Obstet Gynecol:1994; 414

Uterine fibroids should only be treated for symptom relief – mostly subjective

- Most patients are symptom free
- Menorrhagia (40% primary symptom)
  - Vascular alteration of the endometrium
  - Obstructive effect of uterine vasculature – proximal congestion
  - Ineffective myoconstriction of vasculature
  - Dysregulation of local growth factors and abnormal angiogenisis

Uterine fibroids should only be treated for symptom relief – mostly subjective

- Pressure (bulk symptoms) (45% primary sx)
  - Urinary frequency, outflow obstruction, ureter compression, constipation, tenesmus, abdominal fullness

Uterine fibroids should only be treated for symptom relief – mostly subjective

- Infertility (5% primary symptom)
  - Submucous myoma
    - Interfere with implantation and sperm transport
    - Recurrent pregnancy loss, preterm labor and delivery, infertility
  - Intramural myoma
    - Lower IVF implantation and pregnancy rates in patients with intramural myoma[1]

Stoval et al.Human Reprod 1998:13

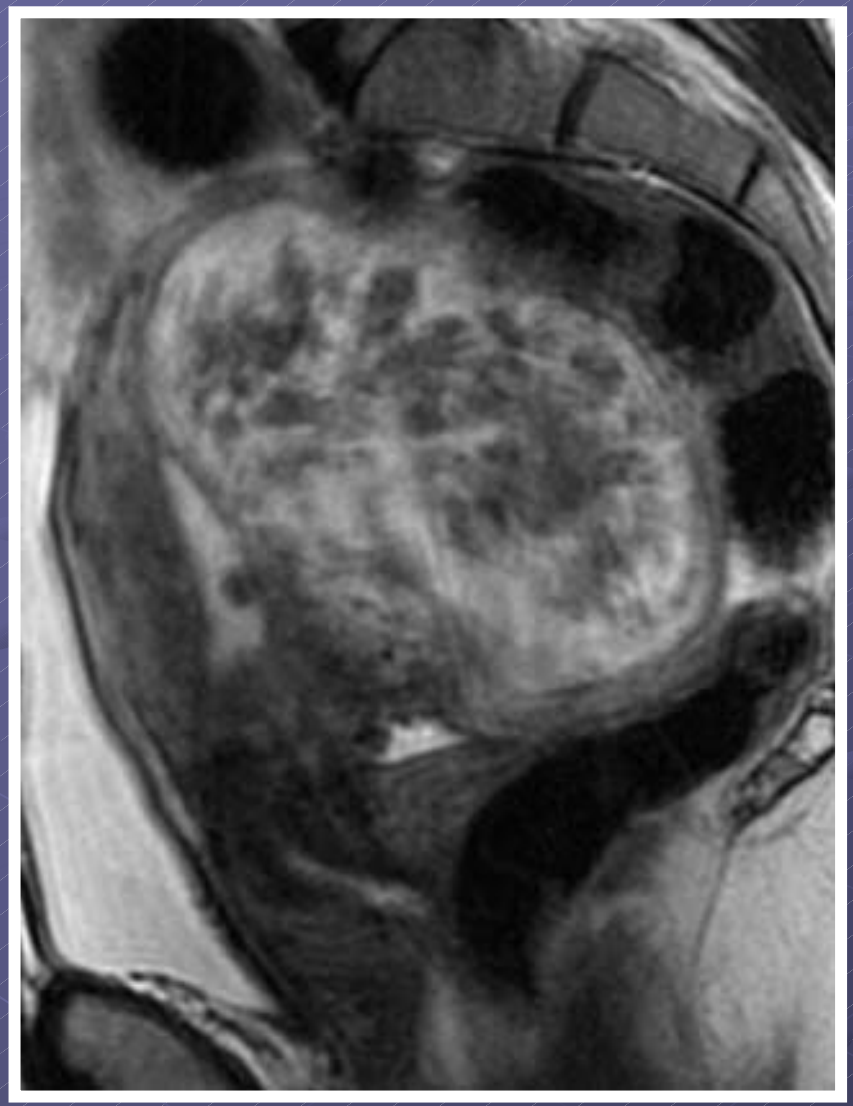
Uterine fibroids should only be treated for symptom relief – mostly subjective

- Pain – typically acute (<5% primary sx)
  - Torsed pedicle
  - Fibroid degeneration - pregnancy
  - Rule out adenomyosis

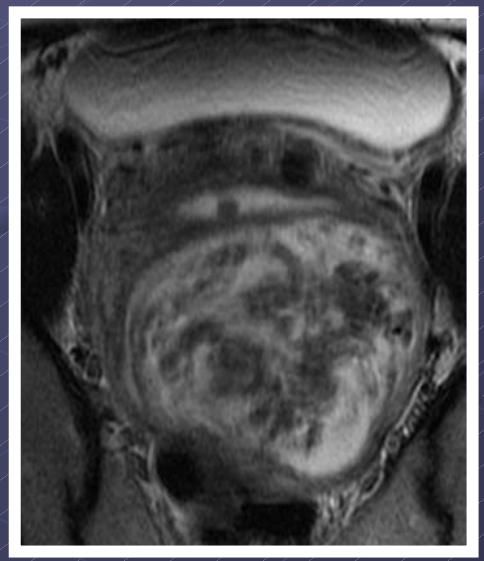
Torsed Pedunculated Fibroid

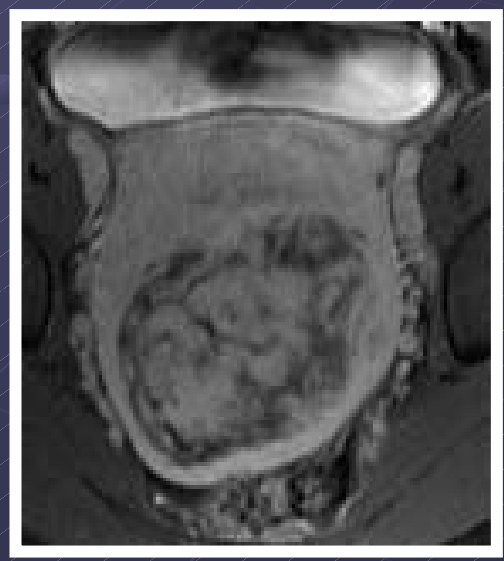
- Thirteen case reports since 1966
- 33 y/o - menorrhagia, acute pain treated with narcotics in ER. Referred for laparoscopy 7 d later.

Degenerating Fibroid



47 yo with pelvic pain and DFUB





Gold Standard therapy (based on quality of outcome data)

- Hysterectomy
  - Abdominal, vaginal, laparoscopic
- Myomectomy
  - Abdominal, laparoscopic, hysteroscopic

Limited Outcome Data

- UFE
- Myolysis
  - Bipolar, cryotherapy, HIFU
- Medical therapies
  - GnRHa
  - Estrogen/progesterone antagonists, SERMs, Aromatase inhibitors

Clinical implications- What can we accomplish with small trials?

- Patients with fibroids can have one or more symptoms that require therapy
- Therapy for uterine fibroids should clearly state the targeted symptom. The symptom should be clearly related to the fibroid. (bulk symptoms vs. infertility)
- Should small studies should include a cohort of patients undergoing a gold standard therapy? Ideally randomized and prospective but historical cohorts or no cohort.
  - Difficult recruitment

Example - Cohorts

- Treatment of menorrhagia due to submucous myomata
  - Cohort – historic hysteroscopic myomectomy data
  - Device – Reduction in PBLAC scores, recurrence rates, complication rates
  - No need for QOL, fertility data etc.
- Treatment of bulk symptoms
  - Cohort – abdominal or laparoscopic myomectomy
  - UAE – QOL, Visual pain assessment. Can be successful without reducing menstrual flow

TABLE 1. Results of Submucous Fibroid Resection*

Study	Total Cases (n)	Controlled Menorrhagia (n [%])	Failed (n [%])
Neuwirth (1983)[54]	26	17 (65)	9 (35)
DeCherney (1983)[55]	8	8 (100)	0
Hallez (1987)[57]	61	57 (93)	4 (7)
Baggish (1989)[50]	23	22 (96)	1 (4)
Brooks (1989)[58]	50	46 (92)	4 (8)
Loffer (1990)[49]	43	40 (93)	3 (7)
Corson (1991)[48]	80	65 (81)	15 (19)
Derman (1991)[56]	94	71 (76)	23 (24)
Serden (1991)[52]	84	77 (92)	7 (8)
Indman (1993)[53]	11	11 (100)	0
Wamsteker (1993) [44]	51	48 (94)	3 (6)
Total	531	462 (87)	69 (13)

* Patient follow-up 3 months to 16 years.

Example – no comparison groups

- Fibroid therapy for menorrhagia
  - Primary endpoint – pblac scores
  - Does it matter if it is better or worse than myomectomy?
- Fibroid therapy for pain or bulk symptoms
  - Visual pain assessment scores (or QOL) pre and post therapy.
  - Does it matter if there is a placebo effect?
    - Reduced with time from therapy
  - Is size (reduction) important?

Post Market follow-up Symptom dependent

- Bulk symptoms – 1 to 2 years
- Menorrhagia – 1 to 2 years
- Pain – 1 to 2 years
- Recurrence of fibroids symptoms and/or uterine growth – 2-5 years
- Fertility – 2-5 years
  - Adhesions
  - Uterine integrity during pregnancy

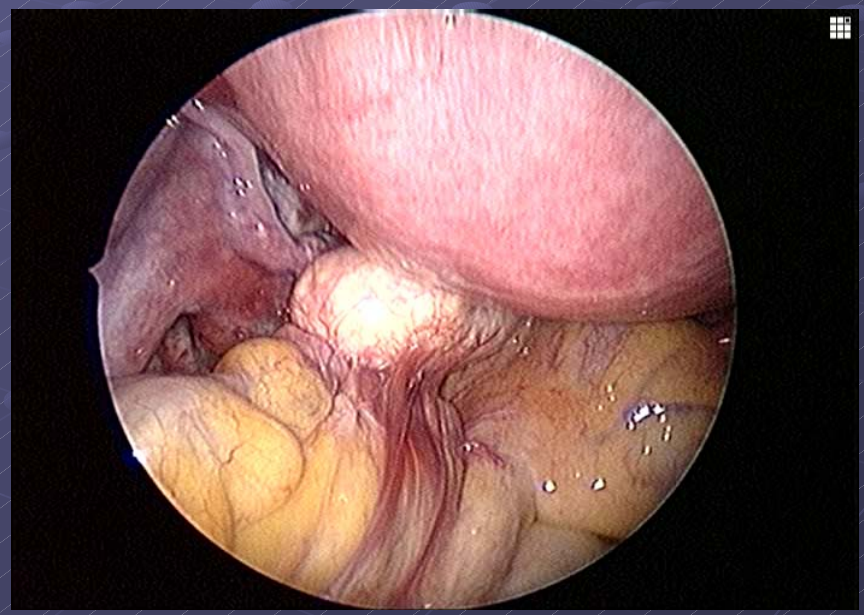
Uterine rupture

Published cases after laparoscopic myomectomy

Reference	Type	Size (mm)	Location	Sutured	Uterine Cavity opened	Gest. Age (weeks)	Labor	Infant outcome
Pelosi and Pelosi (1997)	Subserous	50	Fundal	No	No	33	No	Perinatal death
Friedmann et al. (1996)	Intramural	50	Fundal	NR	Yes	28	No	good
Mecke et al. (1995)	Intramural	NR	NR	NR	Yes	30	No	Good
Dubuisson et al. (1995)	Intramural	30	Posterior	Yes	No	32	No	Good
Harris (1992)	NR	30	Posterior	Yes (superficial)	NR	34	No	Good

Post Therapy Adhesions

- 35 y/o, pain, infertility
- Enlarging fibroid
- Bulk symptoms 1 yr
- U/S 3 cm intramural and 6 cm subserosal myoma



Recurrence

- Higher risk of recurrence in laparoscopic myomectomy versus abdominal?[1,2,3]
- Rosetti et al - 1991-1998. 81 patients randomized to abdominal or laparoscopy
  - Followed with q6mo TVUS for 40 months
  - 23% recurrence in abdominal group, 27% in laparoscopic group[4]

[1]Nezhat et al., 1998
[2]Butram and Reiter, 1981
[3]Candiani et al., 1991
[4]Rossetti A et al., *Human Reproduction* 2001;16(4):770-4

Conclusion

- Consider FDA approval for treatment of a symptom related to the fibroid. Not for global treatment of uterine fibroids.
  - UAE – approved to treat bulk symptoms, menorrhagia but not fertility
  - HIFU – approved for bulk symptoms but not for menorrhagia
  - Endometrial ablation – Treats menorrhagia due to fibroids but not bulk symptoms.