

# Modern management of Fibroids

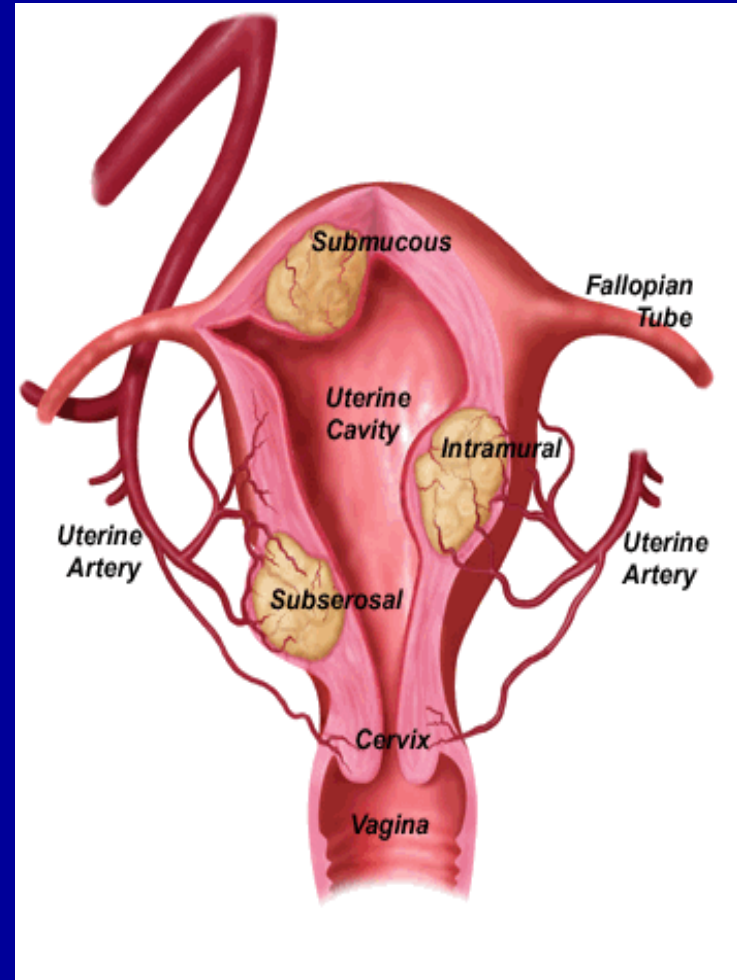
**Mary Ann Lumsden  
University of Glasgow**

**June 2010**



# Background

- Commonest benign tumour
- Incidence 25-40%
- Malignant potential < 1%
- Main aim of treatment – symptom relief and improve quality of life
- Clinical symptoms
  - heavy bleeding +/- dysmenorrhea
  - reproductive dysfunction
  - bulk-related
- Treatment options
  - surgical
  - medical
  - minimally invasive surgical & non-surgical techniques



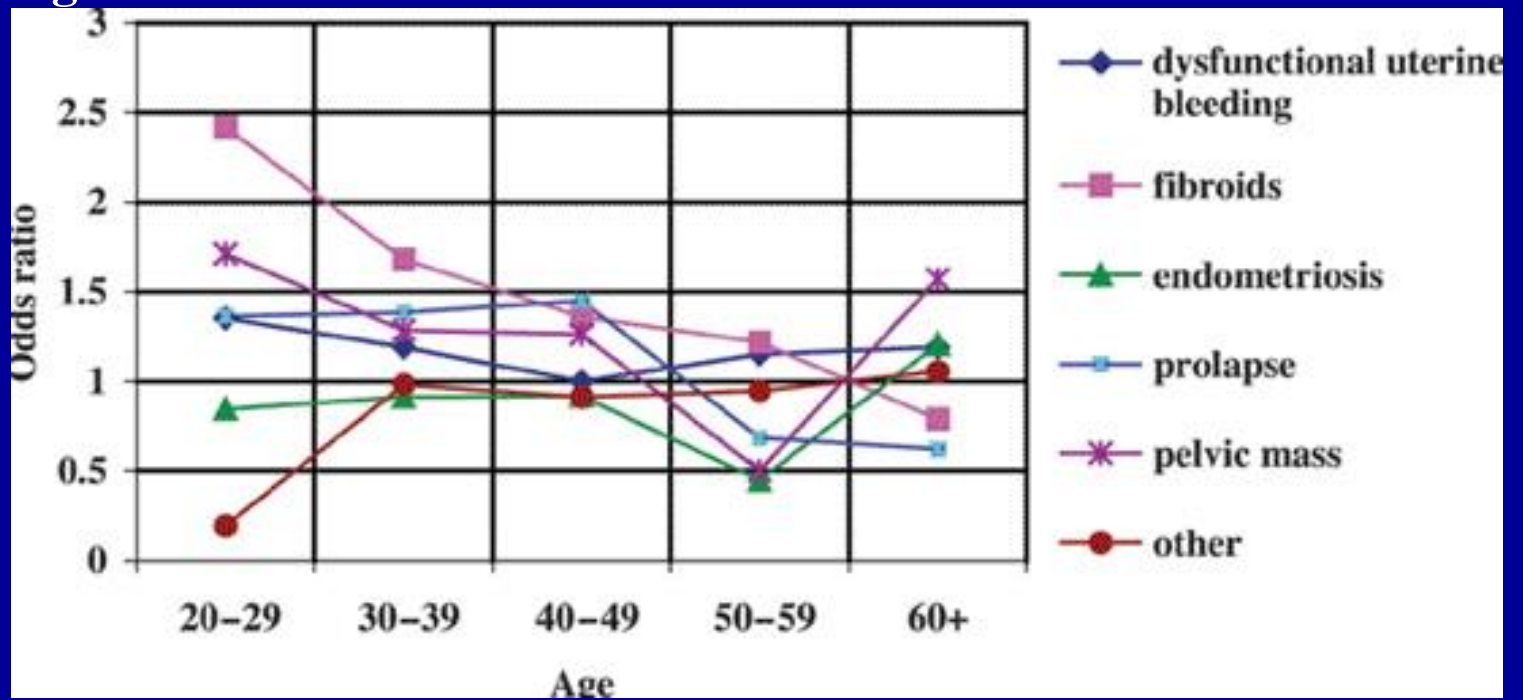
# Treatment

- Medical
- Surgical
- Minimally invasive

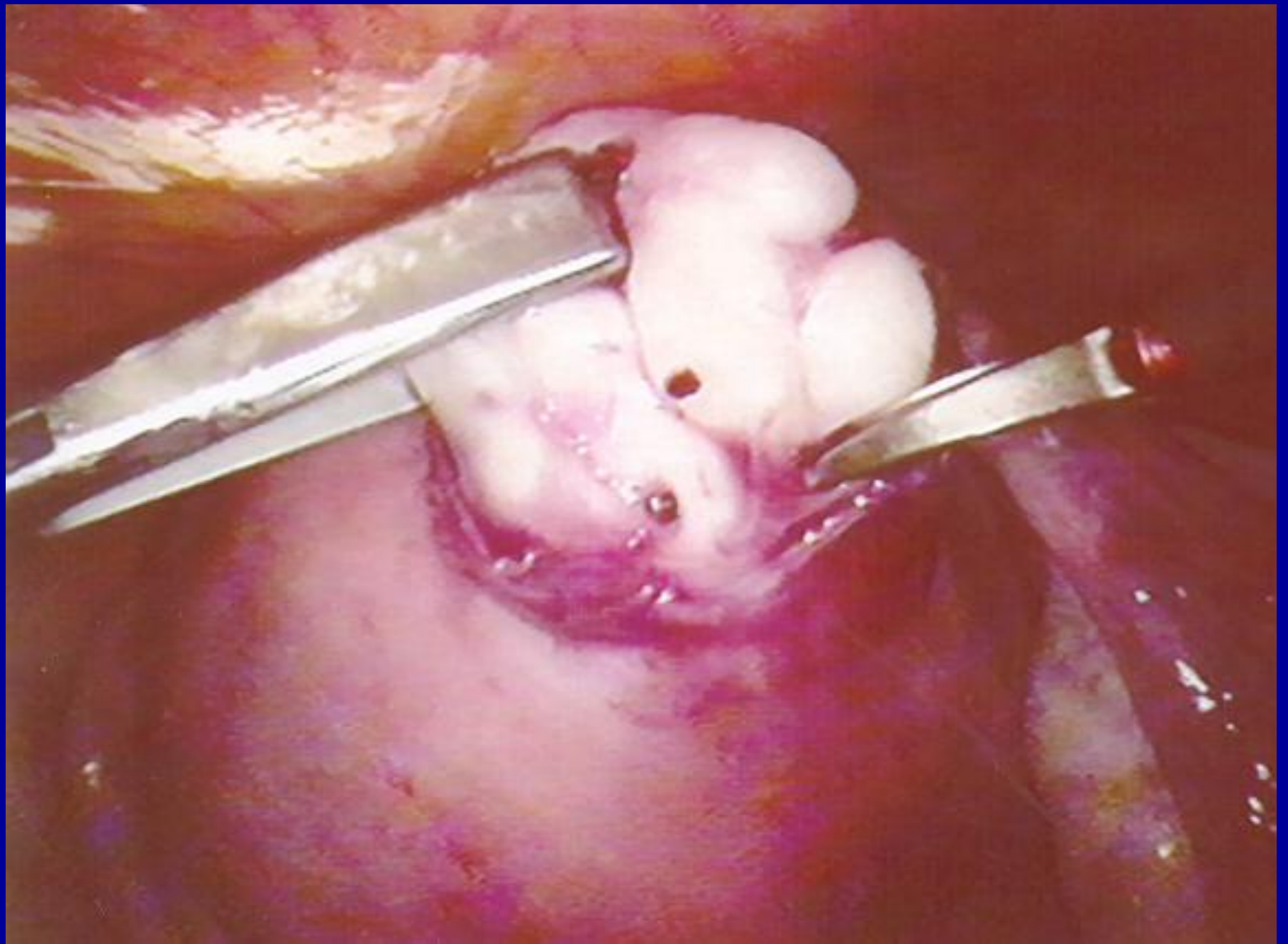
# Hysterectomy

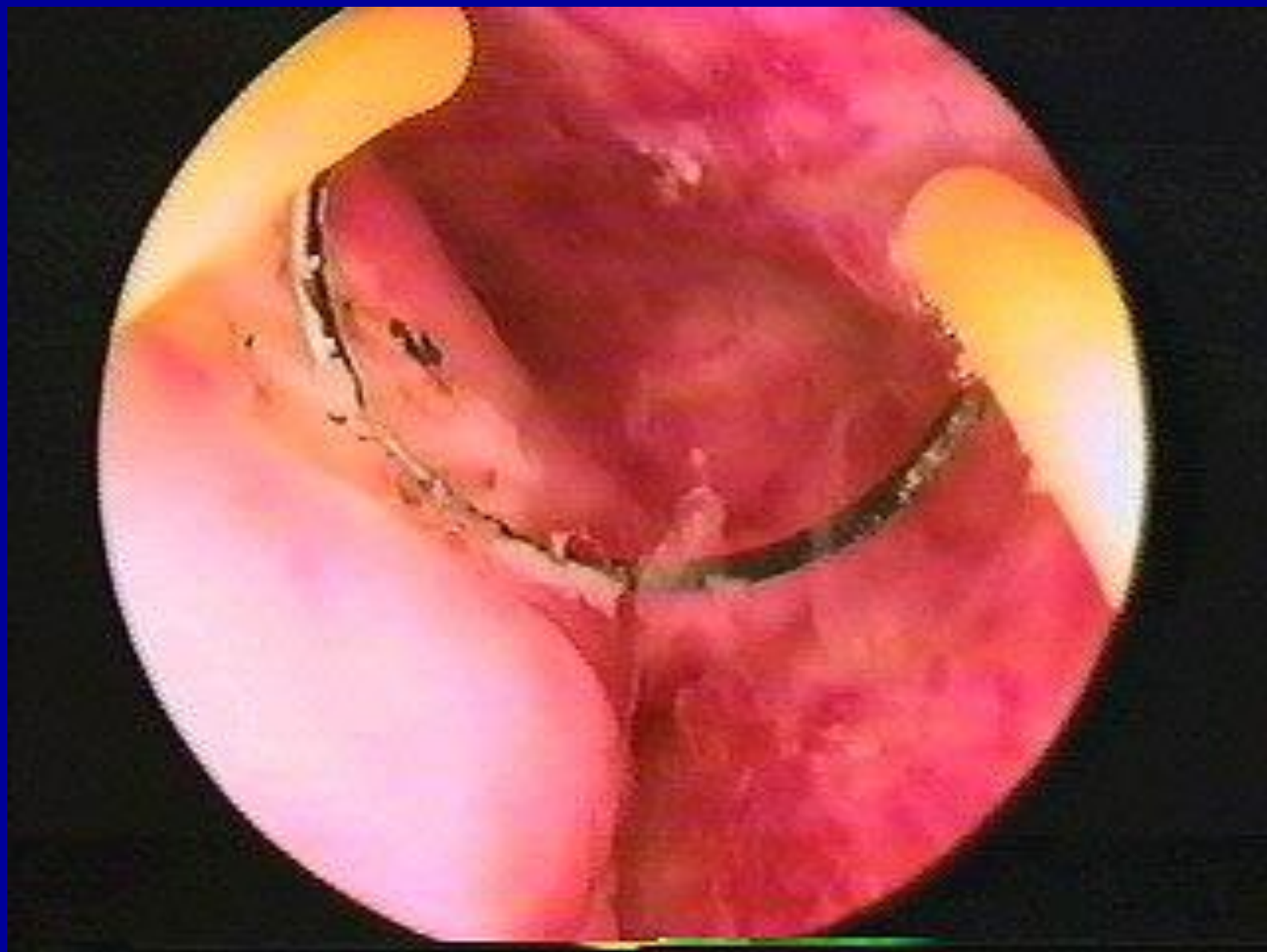
- Small mortality
- Major complications
  - Abdominal 6.2%
  - Vaginal 9.5%
  - LAVH 10% (approx)
  - Overall 9.6%
  - (usually haemorrhage or bladder/ureteric)

**Fig. 1**



# Myomectomy

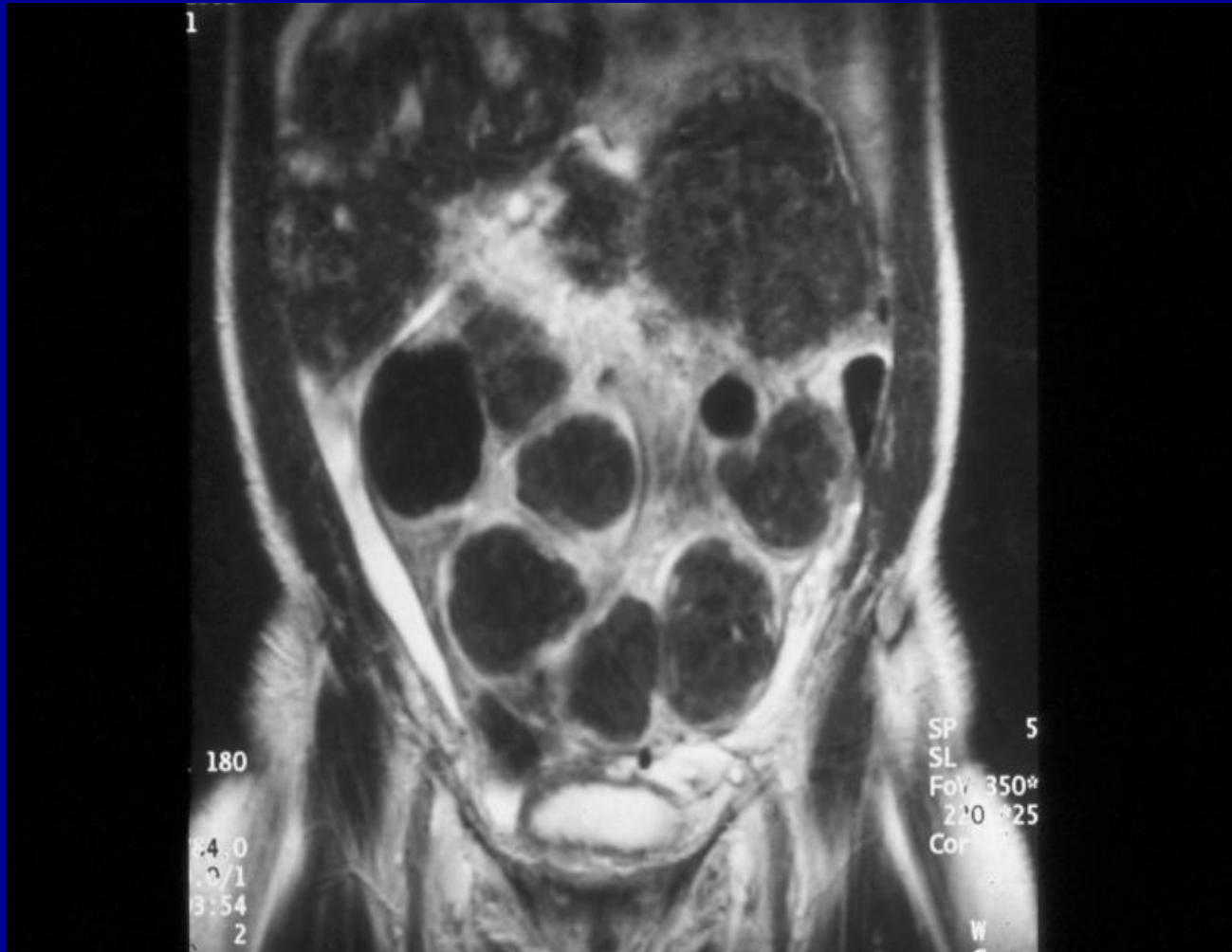




# Myomectomy

- Haemorrhage
- Conversion to hysterectomy
- Adhesion formation
- Uncertain effect on fertility
- Recurrence and incomplete removal
- Unsuitable for large numbers (?)

# Uterine Fibroids - Coronal image



# Impact of number

- Decreases the success of myomectomy
- Increases complication rate of surgery
- Impact on fertility - unknown

# Problems of surgical treatments

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- Removal of uterus
- Hospital stay – variable length
- Local adhesions
- Substantial post procedural pain
- Effect on fertility often not beneficial

# Control of Growth

- Oestrogen
  - GnRH agonists
  - antioestrogens
- Progesterone
  - Progesterone receptor antagonists
    - mifepristone
  - progesterone receptor modulators
    - asoprisnil

GnRH agonists

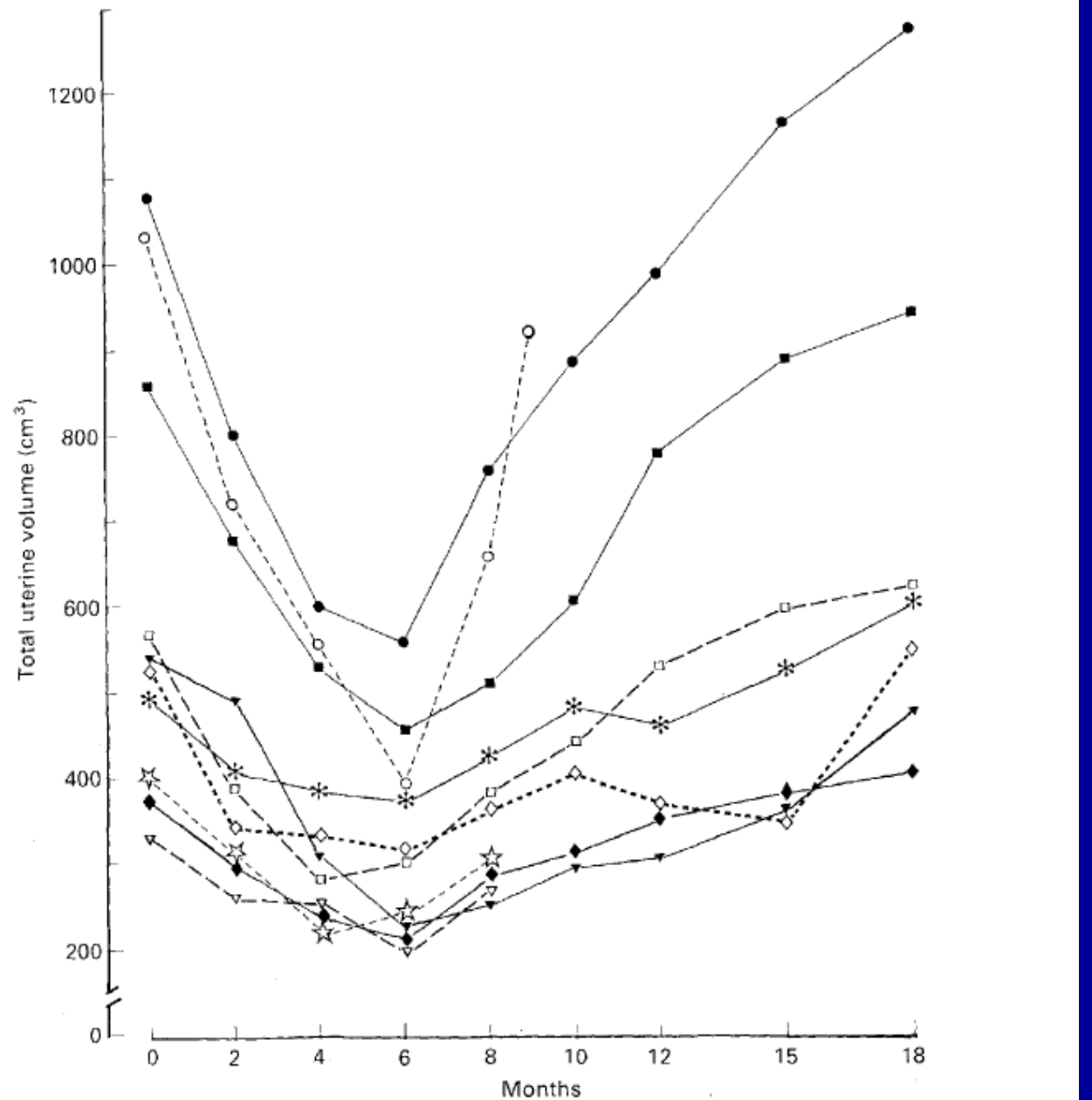


Fig. 2. Total uterine volume (cm<sup>3</sup>) changes in 10 patients with uterine fibroids, during and after treatment with intranasal buserelin.

# GnRH agonists

- Useful before surgery
  - Anaemia
  - Very large fibroids
  - Prior to MRgHIFU
- Can be combined with HRT ‘add back’
  - Unsuitable for surgery

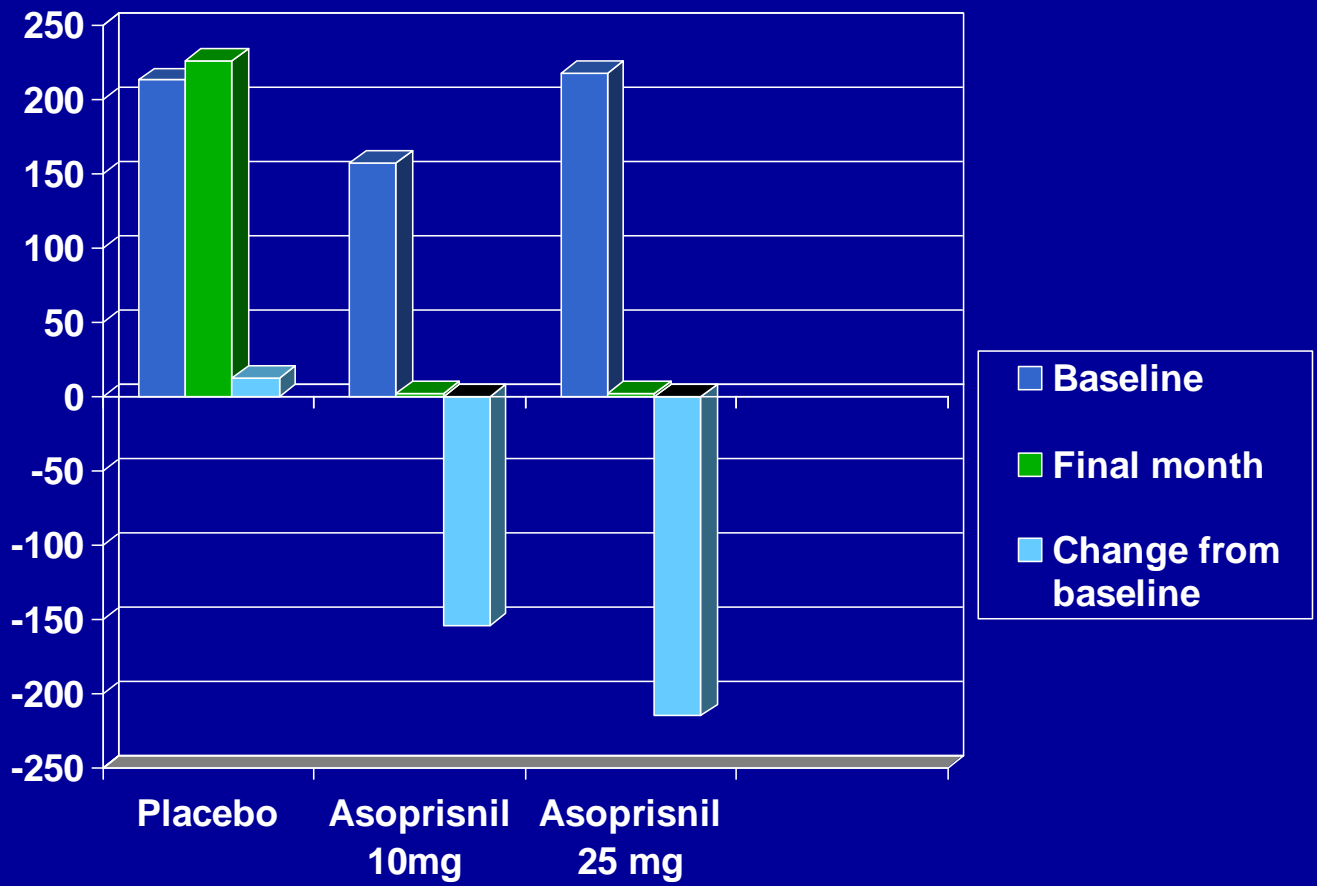
# Progesterone Receptor Modulators

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- Agonist and antagonistic effects of progesterone
- Bind principally to PR
- Little effect on ovarian function
- Act directly on endometrium (mainly on blood vessels)
- Induce amenorrhoea
- Shrink fibroids (14%)
- Well tolerated

# Asoprisnil

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Wilkins et al JCEM 93: 4664-4671

# Asoprisnil

- Conclusion
  - Significant decrease in menstrual blood loss
  - Minimal spotting and breakthrough bleeding
  - Modest decrease in uterine size
  - Well tolerated

# Minimally Invasive Techniques

- MRI-guided laser ablation
- High Intensity Focused Ultrasound (HIFU)
- Myolysis
- Laparoscopic occlusion of uterine vessels
- Uterine artery embolisation

# High Intensity Focused Ultrasound

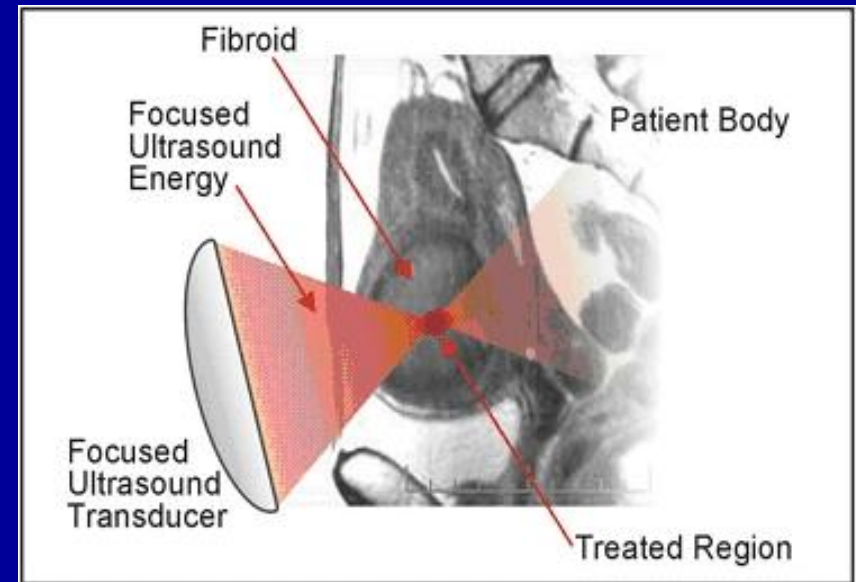
# Principles of thermoablation

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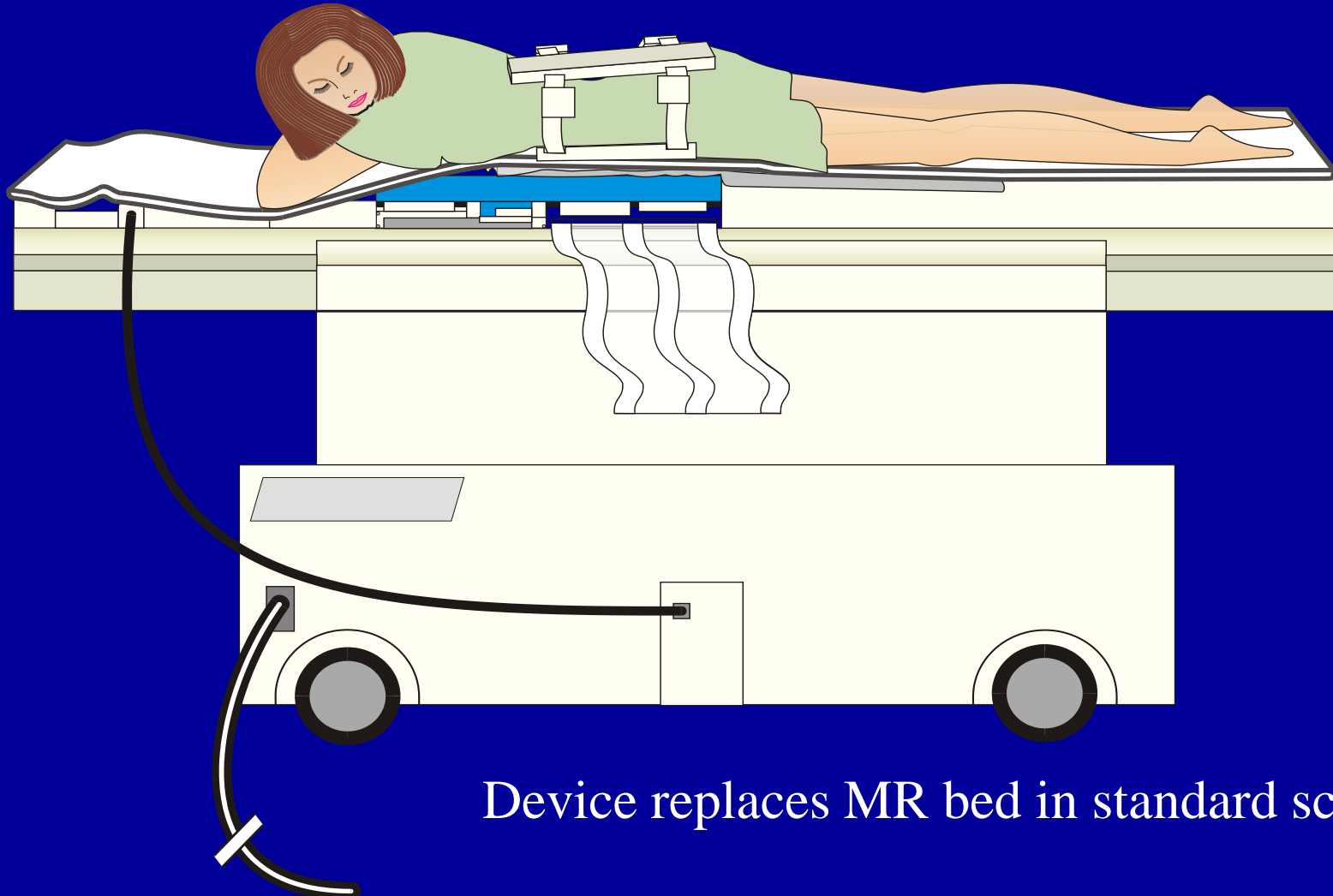
- Destroy tissue by local application of heat
- Cell proteins are coagulated leading to cell necrosis
- Coagulative necrosis not an ischaemic necrosis
- No associated infarction like syndrome
- Procedures are performed as an outpatient

# What is Focused Ultrasound?

- Non-invasive thermo-coagulation
- High frequency Ultrasound (HIFU)
- 5-10,000 times power diagnostic US
- Energy converted to heat at the focus
- Temp  $>56^{\circ}\text{C}$  causes coagulative necrosis



# Patient positioned on ExAblate FUS device

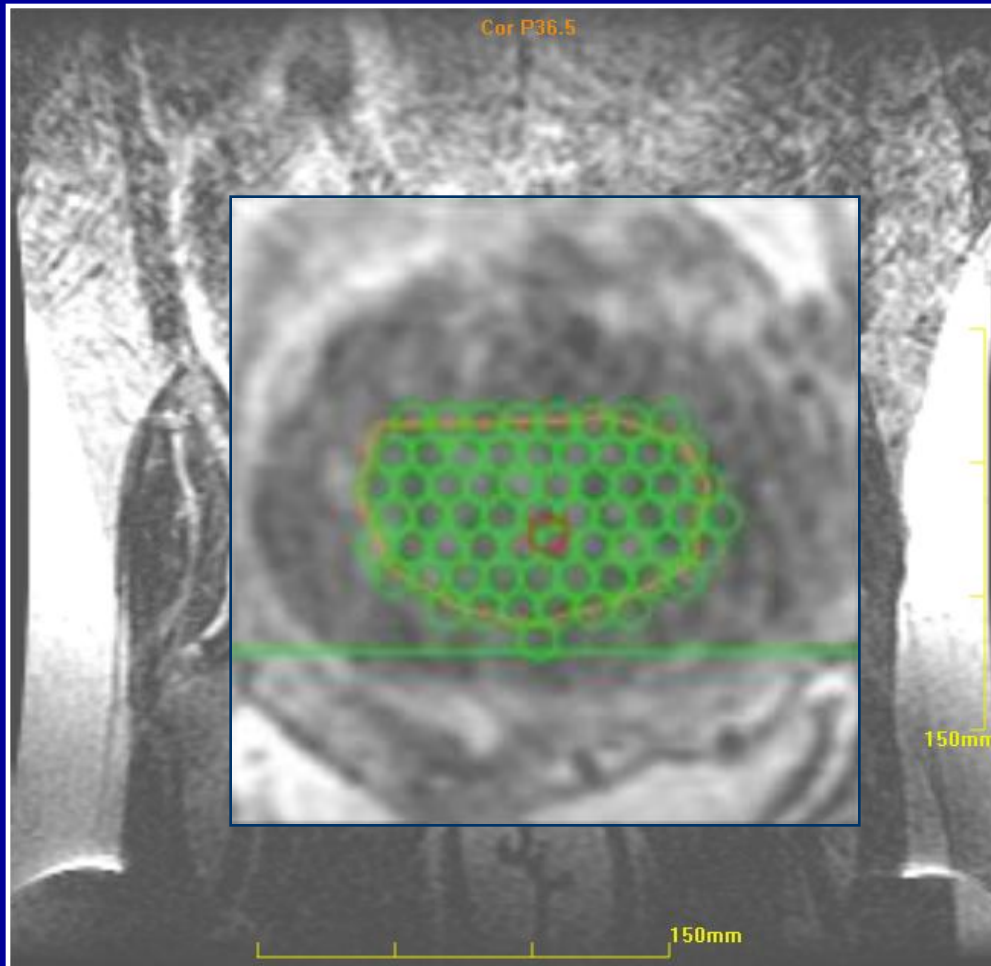


Device replaces MR bed in standard scanner.

# Patient positioned on ExAblate FUS device



# Treatment Plan



FUS planned using axial MR images.

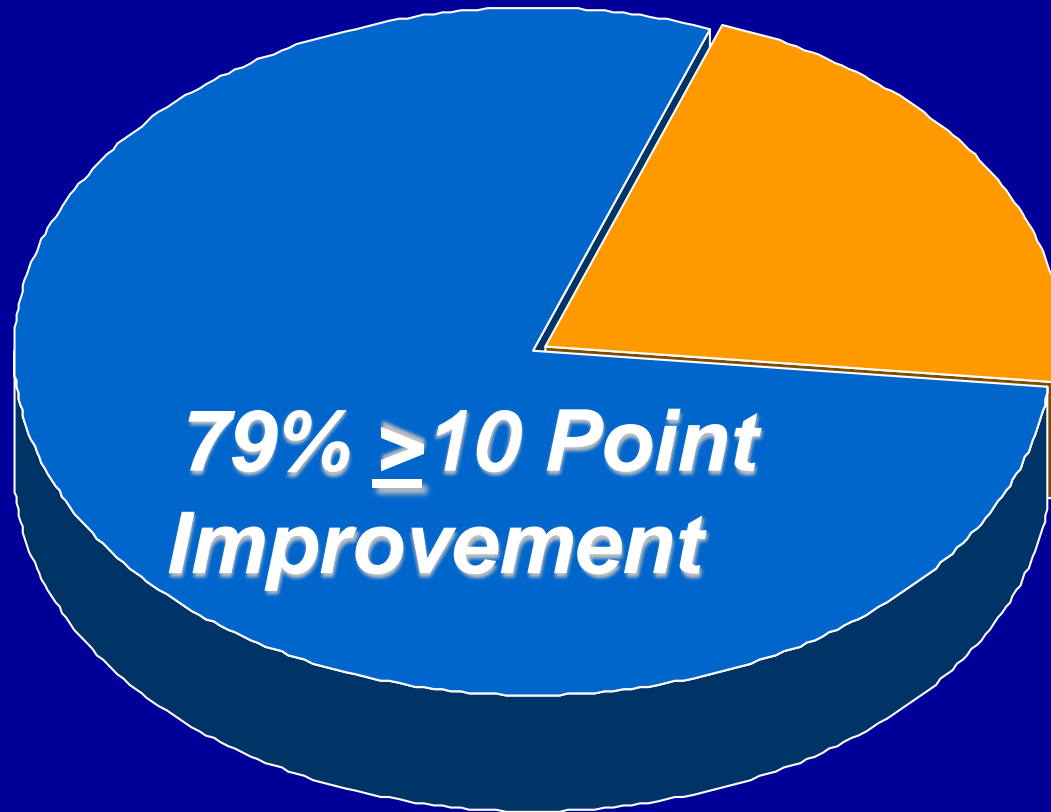
Each green circle represents an individual treatment pulse or 'sonication', to build up a confluent lesion

Contrast enhanced MR images showing that individual fibroids have been damaged (not enhanced) leaving the myometrium intact



# MRgFUS fibroids - Primary Endpoint

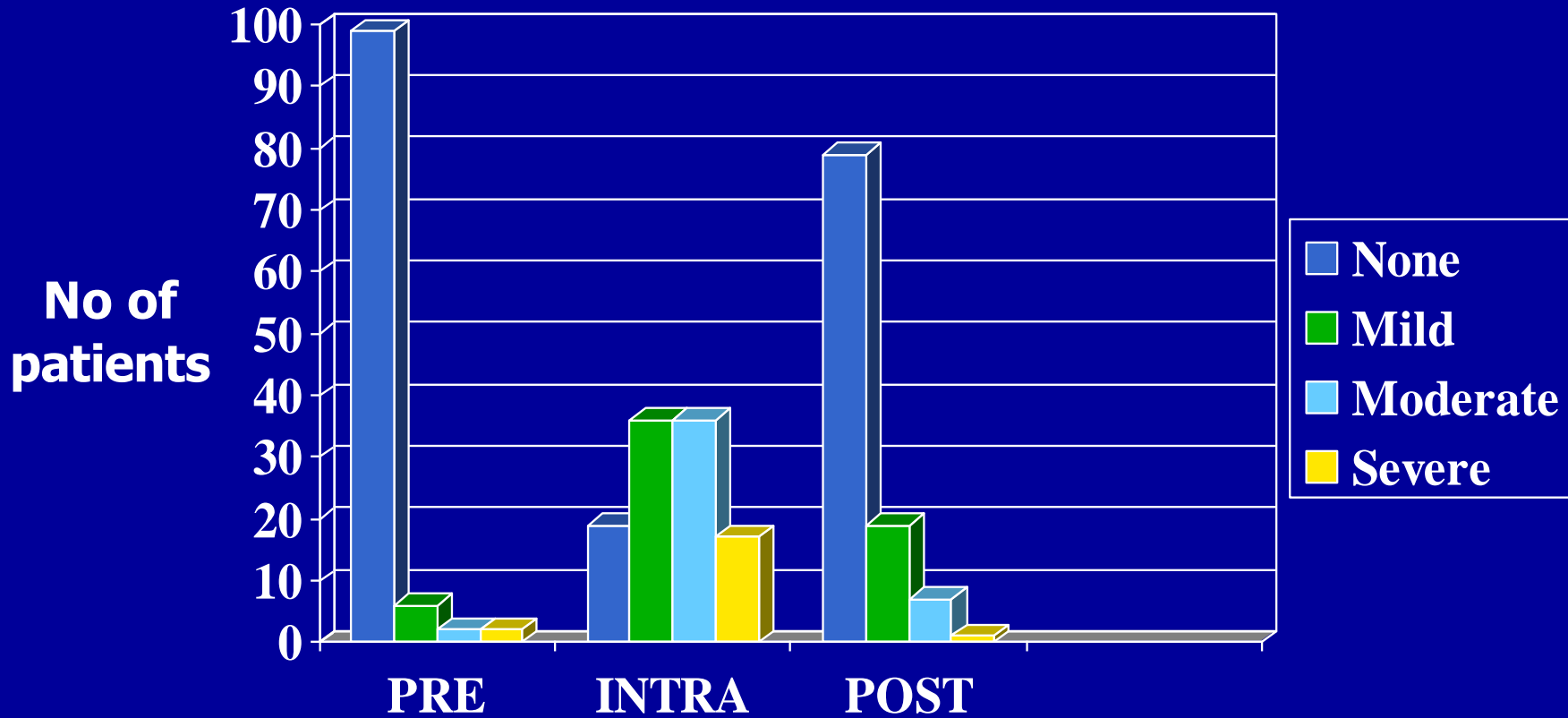
## Quality of Life Symptom Severity Score



$P < 0.0001$

Pivotal Trial; Hindley et al AJRadiology 2004;  
Stewart et al Fertility & Sterility 2006

# MRgFUS - Pain Experienced



# MRgHIFU

- Not suitable for large fibroids
- Not suitable for large numbers of fibroids
- Impact on recurrence rate unclear
- Modest effect on size
- Impact on menstrual blood less than UAE

# MRgFUS - adverse events – 5000 patients

## Minor

- Oral temperature  $>38^{\circ}\text{C}$
- Pain in the area of treatment (both acute and chronic)
- Swelling or firmness in treated area
- Minor ( $1^{\circ}$  or  $2^{\circ}$ ) skin burns less than 2 cm in diameter

## Significant

- 1 case of temporary nerve damage, resolved naturally (after protocol revised – no such events occurred)
- 5 cases skin burns with ulceration of the skin

## MRg FUS patients experienced:

- No patient deaths
- No urgent unintended procedures
- No bowel injuries
- No hospitalizations for pain control
- No post-embolization syndrome

# Of 178 patients at St Mary's hospital

- **3 Hysterectomies:** 1 within 1 year of MRgFUS,  
2 within 2 years
- **6 Myomectomies:** 1 within 6 months of MRgFUS,  
4 within 1 year  
1 within 2 years
- **8 Uterine Artery Embolisations:**  
1 within 6 months of MRgFUS,  
3 within 1 year  
4 within 2 years

TOTAL 17 (10%)

# Pregnancy after HIFU

- 54 pregnancies in 51 women
- Conceived 8 months after treatment
- Live Births in 41%
- Spontaneous Abortion in 28%
- Vaginal delivery in 64%

Rabinovici et al Fertil Steril 2008

May 1<sup>st</sup> 2010

## Post MR guided FUS Pregnancy data

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|                       |      |               |
|-----------------------|------|---------------|
| Total no. pregnancies | 72   | (68 patients) |
| Mean age (range)      | 36.6 | (28-44)years  |
| Months to conception  | 8.4  |               |

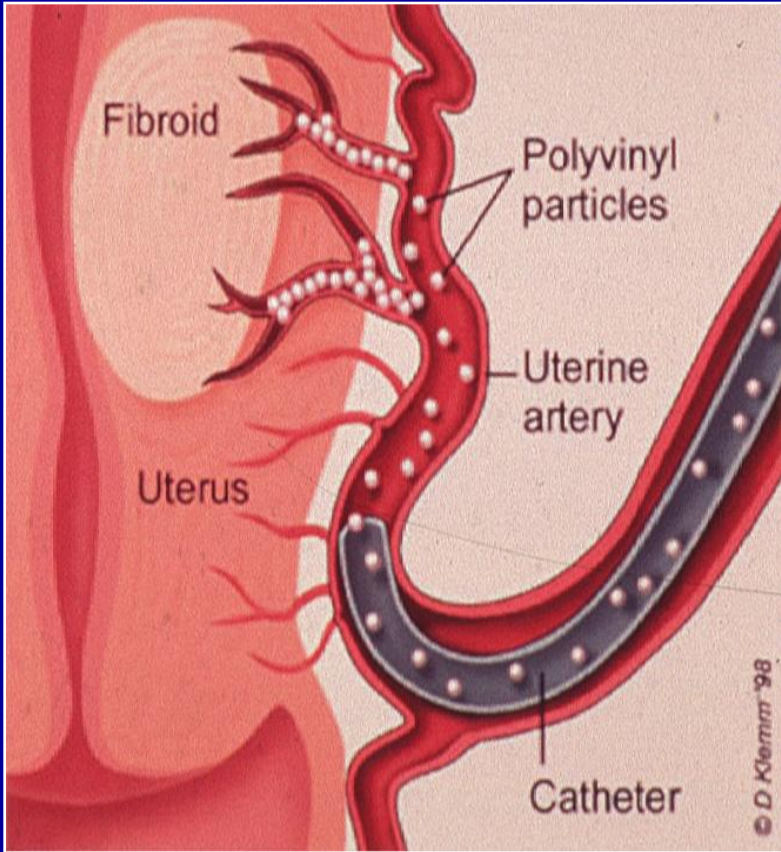
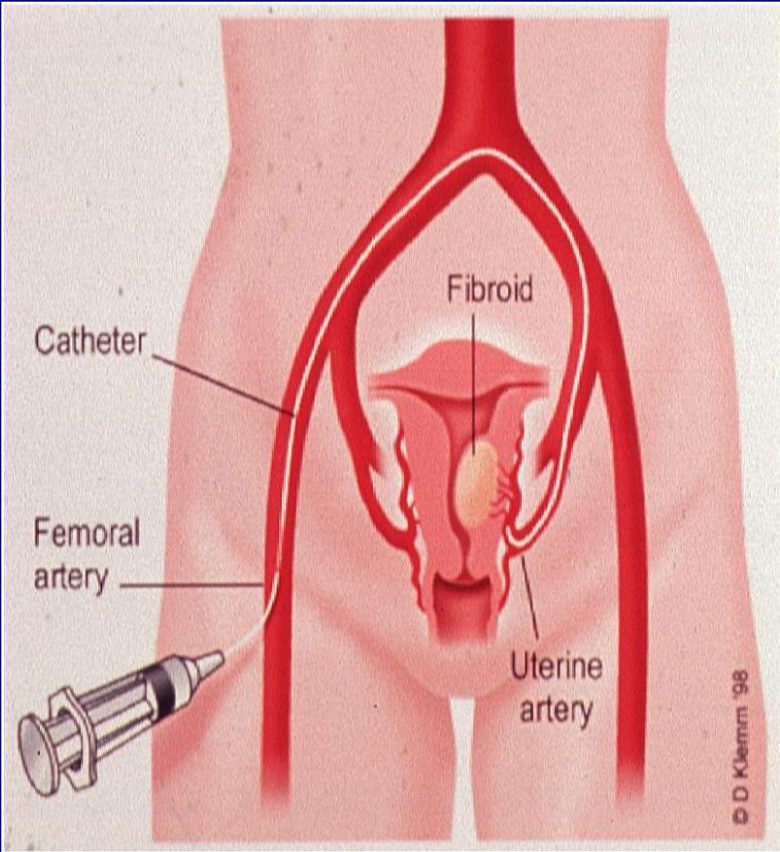
**TOTAL deliveries 35**

|                      |       |       |
|----------------------|-------|-------|
| Term vaginal         | 24    |       |
| Term C-Section       | 11    |       |
| Elective TOP         | 8     |       |
| Miscarriages         | 18    | (25%) |
| Ongoing pregnancies  | 3     |       |
| Mean delivery weight | 3.1kg |       |

Insightec central register

UAE

# Procedure



# Uterine artery embolisation



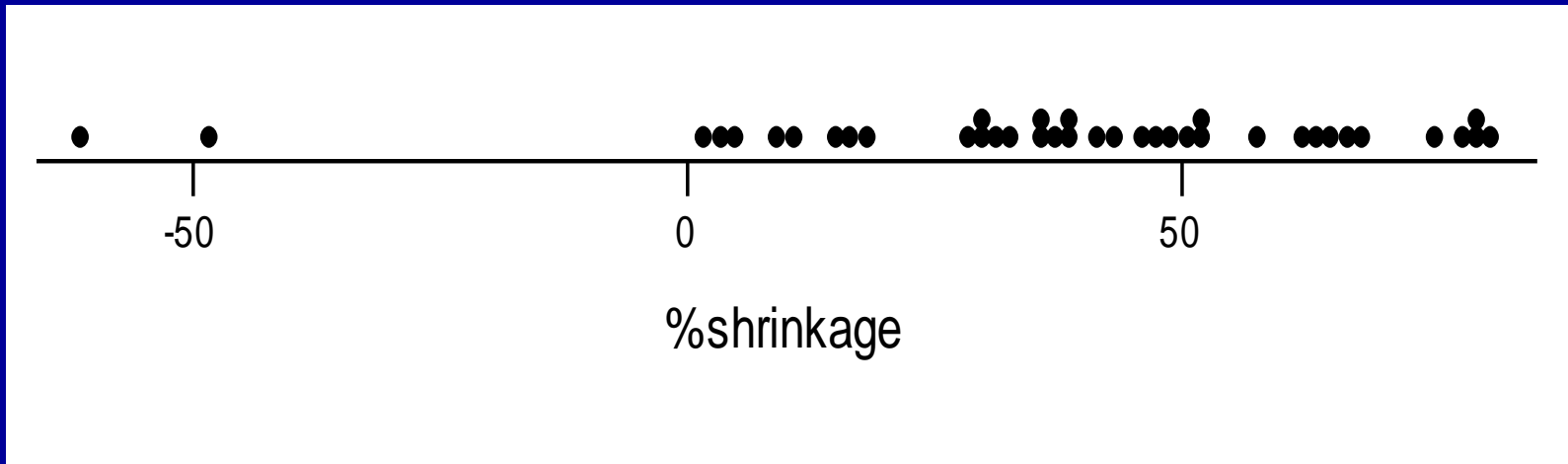
Pre



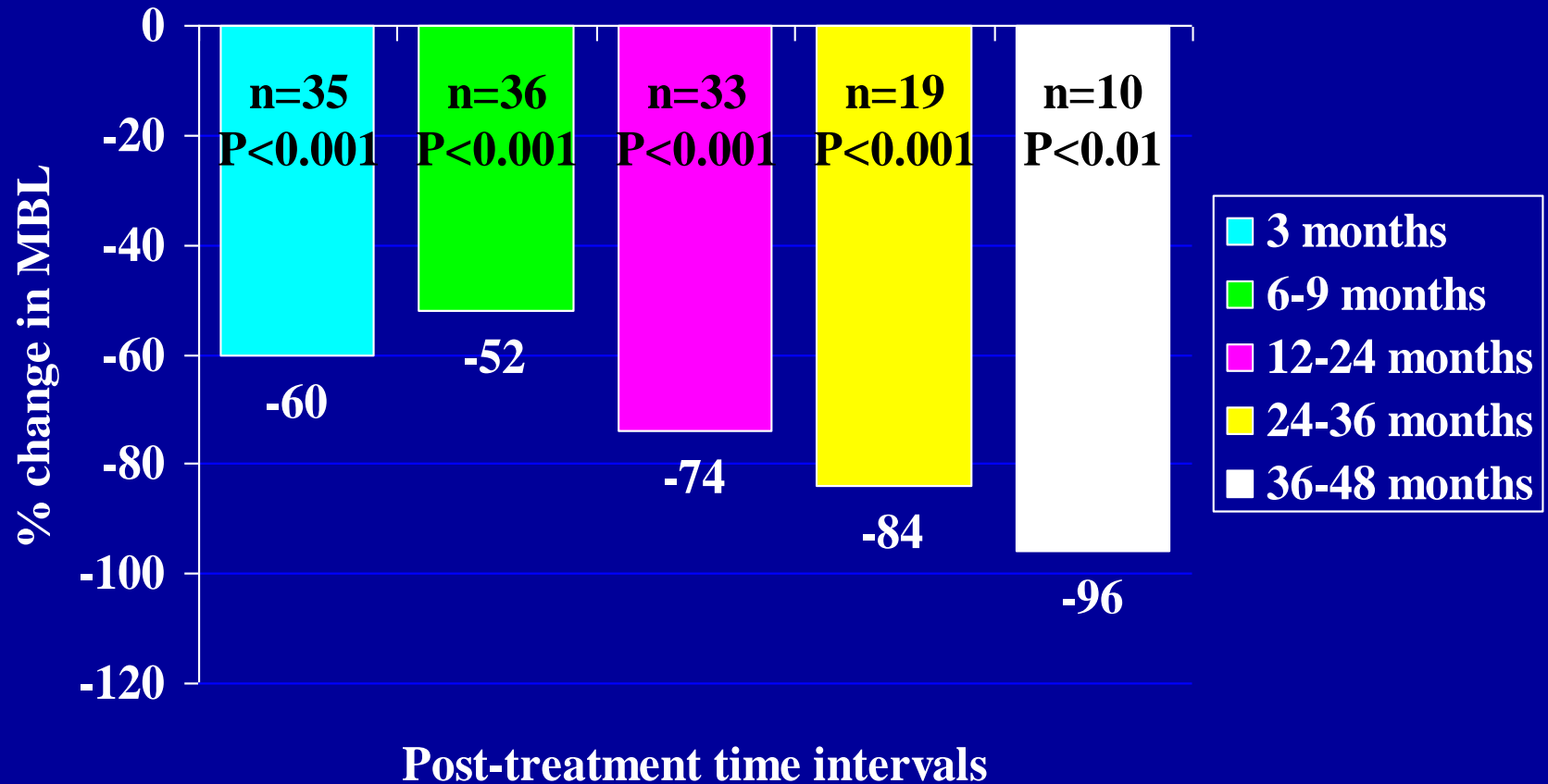
Post

*Image courtesy of Dr J Moss, Dept Of Radiology, GGH.*

# Impact of UAE on size



# Median % reduction in MBL



# HOPEFUL STUDY

- Audit of UAE versus hysterectomy for fibroids
- UAE patients from large units
- Hysterectomy patients from VALUE audit
- Concluded that UAE at least as safe as hysterectomy with 3% serious complication rate
- Cost effective alternative

# REST

Symptomatic fibroid requiring surgical treatment



Randomisation

157

**UFE**  
**106**

**Surgical treatment**  
**51**

# REST – end points

- **Primary endpoint**
  - Quality of life at 1 year
- **Secondary endpoints**
  - Patient satisfaction
  - Length of hospital stay
  - Morbidity
  - Economic Evaluation
  - Pain Score
  - Requirement for further treatment
  - Resumption of normal activities

# SHORT FORM 36 (SF 36)

- previously validated questionnaire
- used to assess health status
- **36 questions** assessing 8 dimensions of health
  - **PHYSICAL**
  - **EMOTIONAL**
  - **SOCIAL**

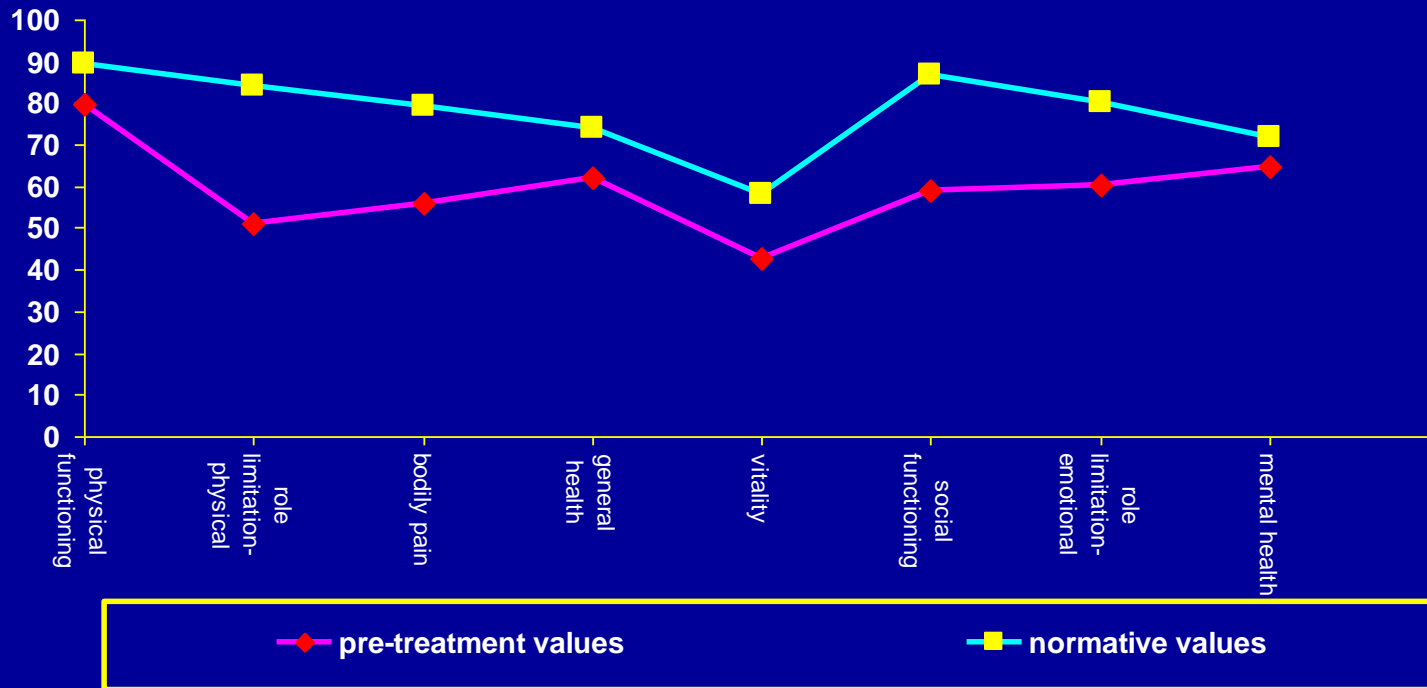
## Variables of the SF 36

- **PF-** Physical functioning
- **RP-** Role limitation as a result of physical problems
- **BP-** Bodily pain
- **GH-** General health
- **VI-** Vitality
- **SF-** Social functioning
- **RE-** Role limitation resulting from emotional problems
- **MH-** Mental health

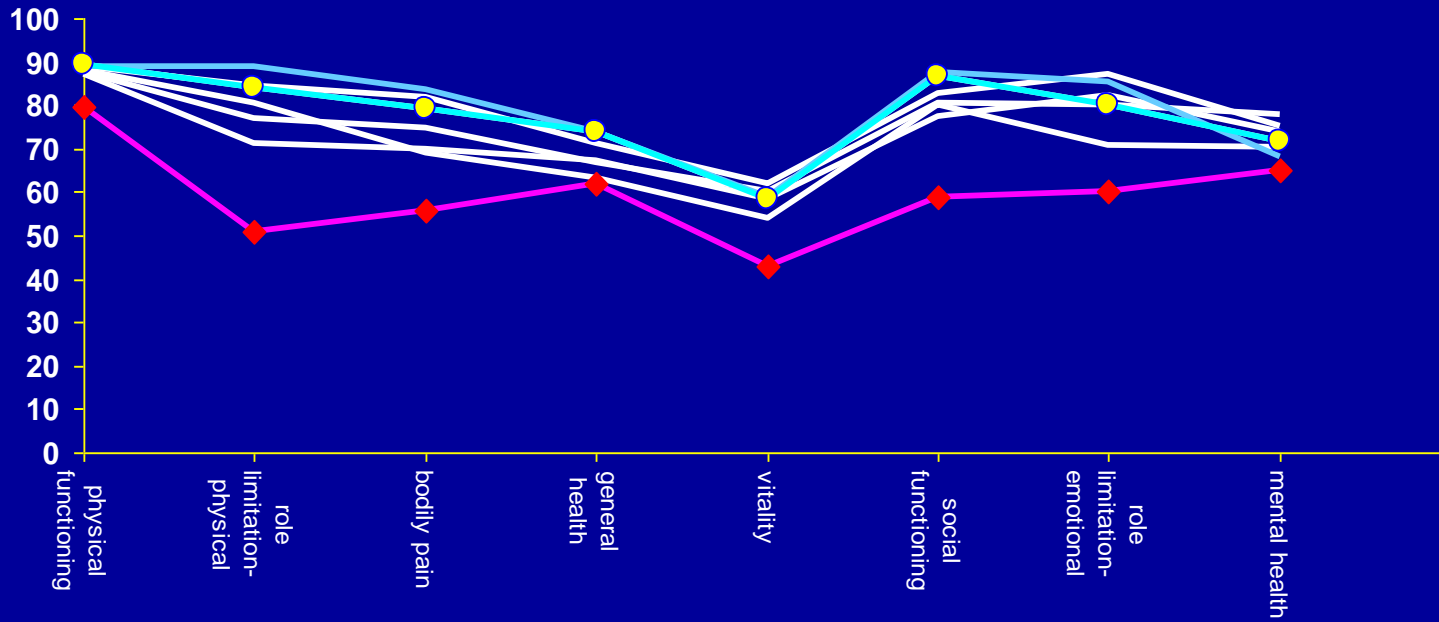
# RESULTS

Mean SF36 scores for women with symptomatic fibroids (pre-treatment) and age-matched women in the normal population

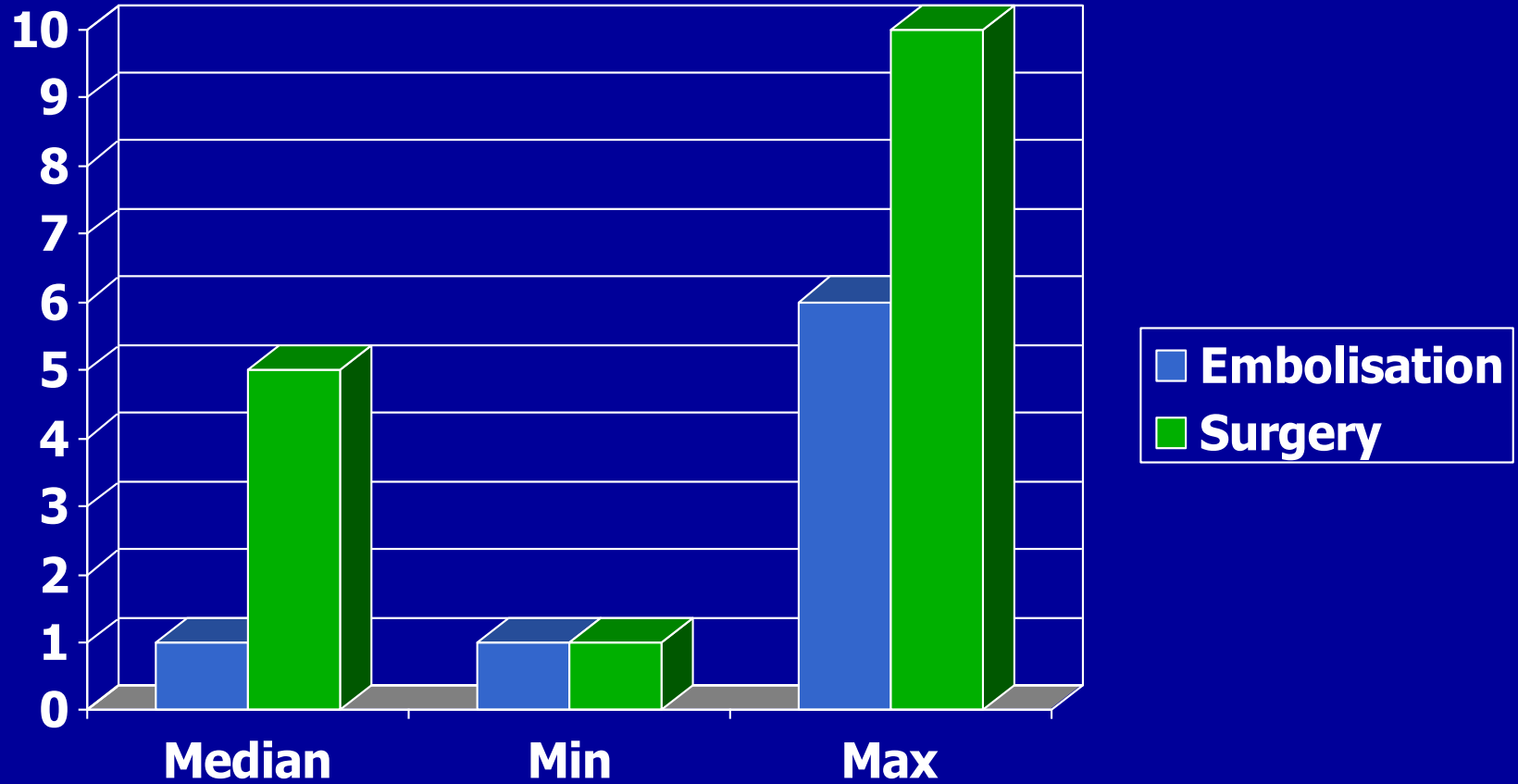
[N = 47]



# Mean SF 36 scores at ALL time intervals



# Hospital Stay



# Complications

- Puncture site. Contrast allergy
- Radiation exposure
- Non-target embolisation
- Post embolisation syndrome
- Fibroid expulsion
- Persistent vaginal discharge
- Amenorrhoea & premature menopause
- Infection
- Emergency hysterectomy - < 1%
- Death

# REST Trial Complications

- Major Adverse Events

|              | Surgery   | UAE   |
|--------------|---|---|
| Up to 1 year | Wound Problems<br>Anaesthetic Problems<br>Per-operative<br><br>10             | Pain<br>Chronic discharge<br>Temporary<br>amenorrhoea<br><br>13 |
| 1-5 years    | Death (unrelated)<br>Anal sphincter repair<br>Urinary tract problems<br><br>3 | Death (unrelated)<br>Severe pain<br>Sepsis<br><br>7             |

# REST Trial

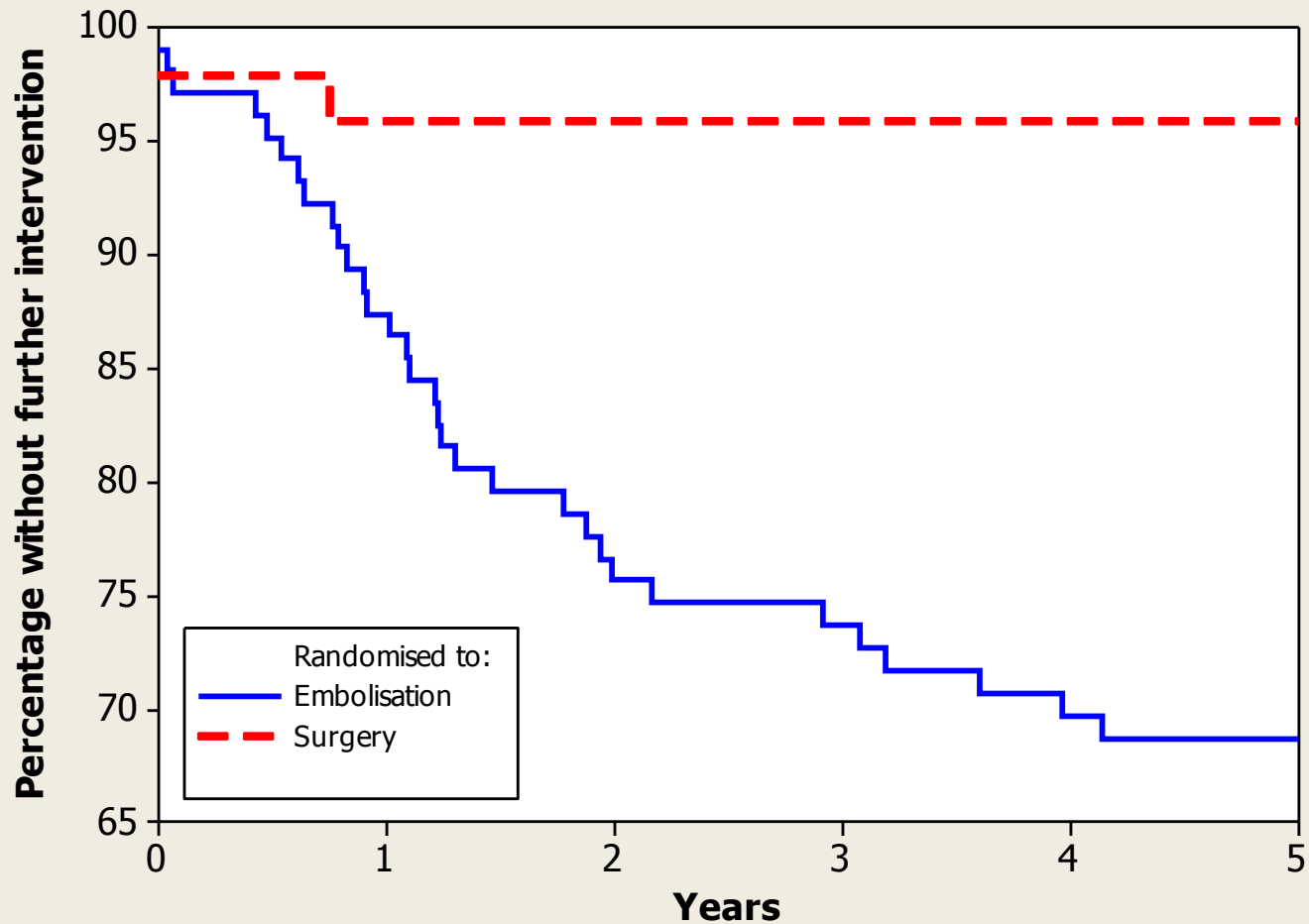
- Minor Complications
    - Total of 82 over 5 years (20 surgery, 62 UAE)
    - 20 % of women in UAE group
    - 34 % women in surgical group
- (vaginal discharge, urinary symptoms, pain etc)

# REST Trial Further Interventions

|              | UAE                          | Surgery |
|--------------|------------------------------|---------|
| 1-12 months  | 11 (10%)                     | 1 (2%)  |
| 13-60 months | 17 (16%)<br>(UAE 4, Hyst 13) | 0       |

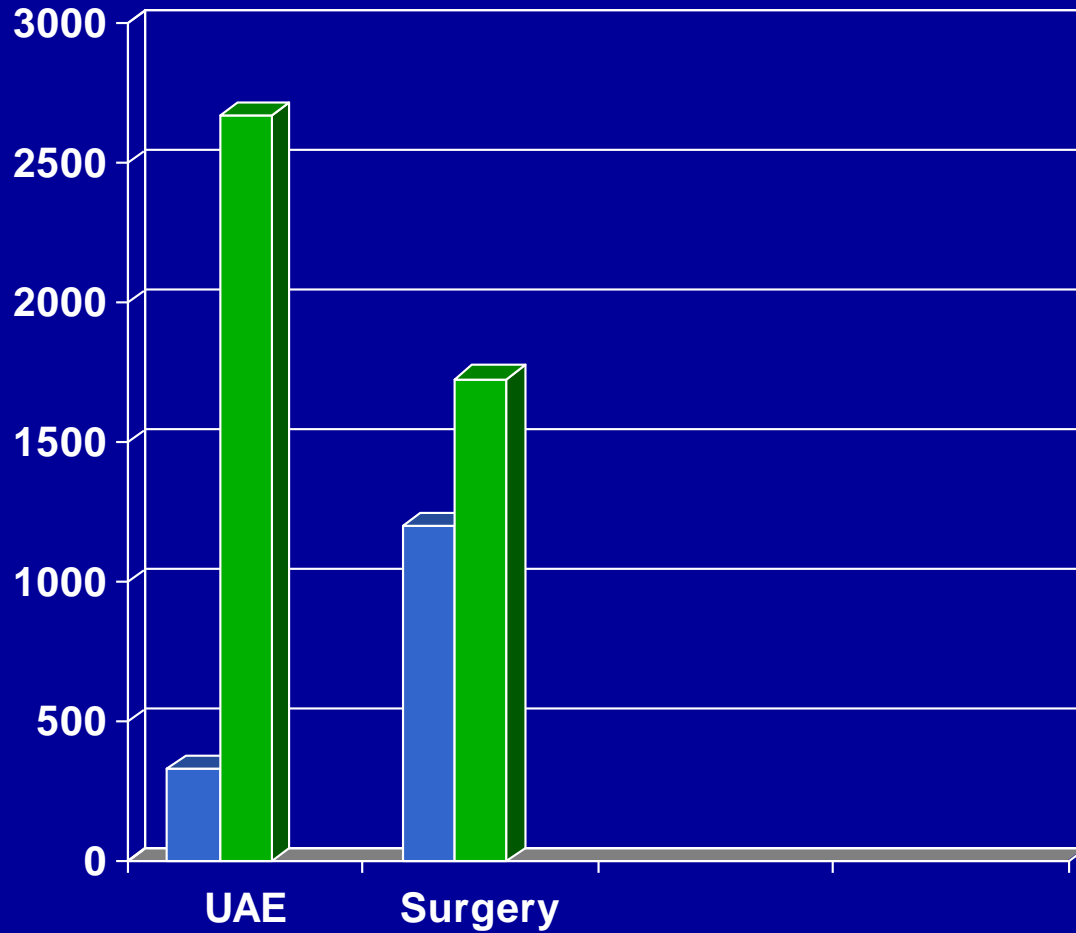
# REST Trial 5 year Follow Up

Freedom from further intervention for treatment failure or complication



# REST Trial

## Economic Evaluation



# REST

## Pregnancies

- 24 women wished to retain uterus
- 16 UAEs and 8 myomectomies
- Myomectomy Group
  - 1 patient and 2 elective LSCS at term
- UAE Group
  - 40% miscarried (4/10)
  - 10% ectopic (1/10)
  - 75% LSCS (3/10)
  - 4 live births
    - 34,35,38 and 41 weeks
  - Morbidly adherent placenta 20% (2/10)

# Pregnancy Complications

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## Normal Population

## UAE

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IUGR

5%

3%

Preterm Delivery

5%- 10%

18%, 13%

PPH

5%

18%, 15%, 20%

LSCS

22%

67%, 72%, 80%

Walker et al 2006,  
Dutton et al 2007

# Ovarian function

# REST Trial

## Ovarian Failure

|            | UAE                   | Surgical |
|------------|-----------------------|----------|
| <40 years  | 0                     | 0        |
| > 40 years | 16<br>(14 > 45 years) | 3        |

# Impact of number

- Decreases the success of myomectomy
- Increases complication rate of surgery
- Impact on fertility - unknown

- There was no statistically significant difference in the mean cycle interval pre- and post-treatment

|                                   | Pre-       | 6 months   | 12 months                                       |
|-----------------------------------|------------|--|---|
| Duration of menstrual flow (days) | 7.0 ± 3.3  | 5.7 ± 2.6;<br>95% CI (-2.19, -0.56);<br>P= 0.001 | 5.6 ± 2.8;<br>95% CI (-2.55, -0.75)<br>P= 0.000 |
| Length of menstrual cycle (days)  | 27.4 ± 2.8 | 27.2 ± 3.3<br>95% CI (-1.12, 0.62);<br>P= 0.563  | 28.0 ± 4.3<br>95% CI (-0.49, 1.84)<br>P= 0.249  |

# Conclusions

- UAE is successful in treating fibroid related symptoms such as heavy menstrual bleeding
- Complications appear no more likely than after surgery.
- UAE causes a change in ovarian function although ovarian failure is very rare in younger women
- Any change in gonadotrophins were not reflected by a change in menstrual cycle length.
- The effect on fertility and pregnancy is still unclear, RCT needed
- Should be considered in parous women with heavy menstrual bleeding particularly if they have completed their families.
- Possibly most appropriate treatment where there are multiple fibroids

# Acknowledgements

- Dr Mona Khaund
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- Prof Ian Cameron
- Prof Lesley Regan