Fibroids: Novel non-surgical & medical therapies – is the Holy Grail in sight?

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Conflict of interest - None
FIBROIDS – DISEASE BURDEN

- Commonest tumour in women of reproductive age
- Symptomatic in 50%
- Peak incidence of symptoms – 30s & 40s
- Symptoms vary depending on the site, size etc.
- Symptoms not uncommon in age >50 years
- Major impact on women’s health and their quality of life
Why we should optimize treatments for fibroids?

• Because fibroids are the commonest tumour in women of reproductive age, negatively impact on women’s quality of life, and have a major impact on health costs.

• Because fertility in the older woman, when fibroids are more prevalent & symptomatic, is increasing.

• Because women are busy, and they want, and deserve, to be treated with what is best.

  – The old adage: babies, then fibroids, then hysterectomy no longer works for an increasing number of women!
Women are delaying pregnancy until later in life when fibroids are more prevalent & symptomatic.
Historical / current therapies

SURGICAL?

Hysterectomy

Myomectomy –
  Abdominal

  Laparoscopic

  Robotic

Hysteroscopic

Vaginal
HYSTERECTOMY

Conventional & ‘Cure’

SHORTCOMINGS
• Major operation
• Anaesthetic and operative risks
• Not suitable for women wishing to retain fertility potential
MYOMECTOMY

Fertility preservation

SHORTCOMINGS
- Associated morbidity and mortality risks.
- Adhesions may compromise fertility
- Recurrence

"If it has the word 'ectomy' after it, I've already had it!"
Choices! Choices! Choices?

SURGICAL?
Hysterectomy
Myomectomy –
  Abdominal
  Laparoscopic
  Robotic
  Hysteroscopic
  Vaginal

MEDICAL THERAPY?
GnRHα+/− add-back therapy
SERMS
Aromatase Inhibitors
Antiprogestins
Androgens
SPRMs - UP

Less invasive Interventions?
UAE
MRgFUS
Therapeutic choices:

Less invasive Interventions?
UAE
MRgFUS

MEDICAL THERAPY?
GnRHa+/- add-back therapy
SERMS
Aromatase Inhibitors
Antiprogestins
SPRMs - UP

Surgery is NOT women’s first or preferred option!
Therapeutic choices:

Less invasive RADIOLOGICAL Interventions?

UAE – uterine artery embolization

MRgFUS – magnetic resonance-guided focussed ultrasound surgery
MRgFUS for treating Uterine Fibroids

How does it work?
How does MRgFUS work?

MR guided focused ultrasound combines:

- High intensity focused ultrasound that heats and destroys targeted tissue, non-invasively.

- Magnetic Resonance Imaging system (MRI) which allows the physician to identify and target tumors, and provides *temperature monitoring* of the treated tissue in real time.

*Focused Ultrasound* generates heat by focusing ultrasound waves, ablating tissue *only* at the focal point… an effect similar to a magnifying glass used to focus the sun’s energy on a single point.
MRgFUS

- Approved by FDA in 2004
- NICE – Audit & Research setting only

Advantages
- Non-invasive uterus sparing procedure
- No hospitalization
- No general anesthesia
- Faster recovery, next day return to normal activity
- Low rate of complications
- No ionizing radiation
- Treatment can be repeated
- Decreased risk of infections
- Absence of post-treatment scarring and adhesion formation

Disadvantages:
- MRgFUS is a complex technology and initial set-up is expensive (requiring MR and Focused Ultrasound machines)
- Only small volumes of fibroid can be treated at a time: 2-4h per treatment.
- Not suitable for massive fibroids
- Minimal head-to-head comparative data with other uterus sparing procedures
Uterine Artery Embolization (UAE) for Fibroids
Pre -procedure

- Gynaecological assessment
- Counselling
- Diagnosis- US/MR
- Exclude pregnancy, infections
- Remove IUCDs
TECHNIQUE

Percutaneous femoral artery puncture with selective catheterisation of each uterine artery in turn
Uterine Fibroid Embolization Technique

Small vessels are accessed using a microcatheter. Once the catheters are in place, PVA particles are introduced until blood flow is stopped.
Pre-embolization

Post-embolization
Uterine Fibroid Embolization
Side effects after treatment

Post Embolization Syndrome
- Pain for four to five days
- Nausea and vomiting
- Fever
- Vaginal Discharge
Indications

- Women who have been advised surgical treatment but who wish to conserve their uterus
- Surgery contra-indicated eg medical conditions, Jehovah’s witnesses, previous unsuccessful fibroid surgery
- Women who may wish to become pregnant
- Adenomyosis
Contra-indications

ABSOLUTE

• Current infection
• Refusal to consent to hysterectomy
• Pregnancy
Contra-indications

**RELATIVE**
- Pedunculated subserosal fibroids
- Fibroids > 10cms
Results

• **Improvement of symptoms by 85-90%**
  – menstrual bleeding
  – pressure
  – pelvic pain

• **Shrinkage of fibroids**
  – uterine volume 50%
  – fibroid volume 60-70%

• **Improvement of Quality of Life**
Complications of UFE

- **Chronic vaginal discharge**: ~5%
- **Fibroid expulsion**: 1-2%
- **Amenorrhea**: 2-5%
  - **Permanent amenorrhea**: <2%
    - (patient of perimenopausal age)
- **Infection**: 1-2%
- **Hysterectomy**: 0-10%
- **Deaths**: <0.1%
Fibroid Extrusion

DA 33 :- Large 16cm solitary submucous fibroid protruding into cavity. Readmitted at 5 weeks with infection (coliforms and anaerobes) & impaction. Removal of fibroid under GA.
Fibroid Extrusion

JJ 49:- Multiple fibroids. Readmitted @4 weeks with urinary retention & pyrexia (coliforms, anaerobes and enterococci). Necrotic fibroid removed under GA.
Pregnancy after UFE

Successful full term pregnancies documented but caution advised as no long term studies on the effect of embolization on pregnancy and its outcome
Emergence of oral medical therapies – Selective Progesterone Receptor Modulators (SPRMs)

Ulipristal Acetate (UP) – 1st in Class SPRM

UA has completed Phase III Clinical Trials (PEARL I, II, III & IV), and now has a European License for use for 3 months prior to surgery.
PEARL I – versus placebo
PEARL II – versus GnRHa
PEARL III – expanded use of UP
PEARL IV – expanded use of UP
PEARL I: Randomised, double-blind Phase III trial of ulipristal acetate (UPA) vs placebo

Patients with symptomatic uterine fibroids and anemia

Randomisation

3 months

Once-daily oral UPA 5 mg + concomitant iron

Once-daily oral UPA 10 mg + concomitant iron

Once-daily oral placebo + concomitant iron

Surgery

Follow-up Period

6 months
PEARL II: Randomised, double-blind Phase III trial of ulipristal acetate (UPA) vs Leuproreline (GnRH agonist)

Patients with symptomatic uterine fibroids and anemia

Randomisation

3 months

Once-daily oral UPA 5 mg + concomitant iron

Once-daily oral UPA 10 mg + concomitant iron

Intramuscular leuprorelin 3.75 mg once every 4 weeks

Surgery

6 months

Follow-up Period
Key outcomes with Ulipristal acetate:

- Rapid amenorrhoea in most women
- Diminish or alleviate discomfort
- Reduce fibroid volume
- Correct anaemia
- Non-inferior to, and has advantages over GnRHa
Ulipristal Acetate in the management of symptomatic fibroids:

Could this be the Holy Grail!?

Alas .... No!
Need to exercise caution – Progesterone has wide-ranging actions!

- Current license is for 3 months treatment leading to surgery
- Long-term impact of therapy unknown eg on endometrium
- Impact on surgery yet to be defined
- Potential as a stand-alone therapy unknown

But …… V promising: watch this space!
Take home message

Effective alternatives to surgery now available for the treatment of fibroid disease:

**UAE** – recommended by NICE as an alternative to hysterectomy and myomectomy.

**MRgFUS** – limitations on current use

**Medical therapy** – ESMYA: early days yet, but very promising
Acknowledgements:
Vikram Talaulikar, Nasera Banu,
Sahana Gupta, Fusun Sirkeci
Anna-Maria Belli