Uterine Leiomyomas

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Uterine Leiomyoma-Outline

Definition
Prevalence
Epidemiology and types
Differential diagnosis
Clinical manifestations including
reproductive dysfunction in pregnancy
Diagnosis and imaging
Natural history

Uterine Leiomyoma

Definition:
- benign monoclonal tumors from the smooth muscle cells of the myometrium
- contain extracellular mature collagen proteoglycin and fibronectin
- Surrounded by thin pseudocapsular aerolar tissue and compressed muscle fibers.

Treatment plan
- Medical
  - Contraceptive steroids
  - GnRh Agonists
  - aromatase inhibitors
  - progestin modulators
- Surgical
  - Myomectomy: abdominal, laparoscopic, hysteroscopic, robotic-assisted
  - Uterine artery embolization
  - MRI/ultrasound ablation
Perioperative/operative adjuncts GnRh, vasopressin, tourniquets

Prevalence and epidemiology:
- Genesis of the monoclonar tumor unclear
- Parallels the ontogony and life cycle changes of the reproductive system
- Noted in approximately 80% of uterine pathological examinations
- Clinical significance in about 25% of reproductive women
- Relative risk and incidence is 2-3 fold greater in black than white women
- Other risk factors: parity ↓, early menarche ↑, smoking ↓, familial ↑, injectible progestins ↓, OCP ↓, EtOH ↑
- Most common solid pelvic tumor in women
Uterine Leiomyoma
Types: (defined by location)
• Intramural can become transmural (serosal-mucosal)
• Submucosal, protrudes into the endometrial cavity.
• Subserosal, originates from the serosal Surface
  – Broad
  – Pedunculated,
  – Intraligamentary
• Cervical - below the uterine vessels
• Metastatic
• Combined

Uterine Leiomyoma
Types further defined for treatment
Submucosal:
• Subdivided by European Society of Hysteroscopy classification system.
• Clinically relevant in predicting outcomes of hysteroscopic myomectomy.
• Type 0: Completely intracavitary
• Type 1: at least 50% of volume is in cavity
• Type 2: at least 50% of volume is in uterine wall.

Uterine Leiomyoma
Differential Diagnosis:
• Adenomyosis—much different pathology and treatment plan
• Leiomyosarcoma
  • very rare, about .25%
  • Not necessarily associated with rapid growth, but considered
  • postmenopausal patients with pelvic mass abnormal bleeding, and pain.
Uterine Leiomyoma

Differential Diagnosis - Continued

- Benign metastasizing leiomyomas: leiomyoma into lesion are present in uterus and distant locations
- Leiomyomas of uncertain malignant potential: mitotic index, cellular atypia, extent and pattern of necrosis
- Cellular leiomyoma: typically considered benign histological variant but may be more similar to a sarcoma
- Others: lymphangioleiomyomatosis, intraveneous leiomyomatosis, leiomyomatosis peritonealis disseminate

Clinical Manifestations

Main Three

1. Increased uterine bleeding → menorrhagia → location mainly submucosal → menorrhagia, iron deficiency anemia, interference with life function, social, and productivity.
2. Pelvic pressure and pain → Pressure → urinary frequency, difficulty emptying bladder, rarely obstructive, constipation, dyspareunia, rarely silent uterine compression
3. Reproductive dysfunction
Uterine Leiomyoma

Reproductive Dysfunction
- Difficult to quantify the impact
- Associated with sub-fertility and adverse pregnancy outcomes.
- Pregnancy
  - Increases risk of 1st trimester bleeding, abortion, breech presentation, dysfunctional labor and increased risk of cesarean section.
  - Related to the size of leiomyoma and position of the placenta
- Myomectomies - not indicated to prevent pregnancy complications except in women with a history of obstetric complications that appear to be related to the myoma
- Fertility - estimated to account for 1-2% of infertility
- Location is a key factor, mainly submucosal

Diagnosis:
- Physical exam: Enlarged, mobile, irregular uterus

Imaging:
- Ultrasound - highly sensitive 95-100%
- Sonohistogram enhances endometrial cavity assessment
- Hysterosalpingography (HSG) - good technique for defining the contour of the endometrial cavity otherwise limited
- MRI considered best modality for imaging the size, location of all myomas, differentiation of myomas, adenomyosis, adenomyoma, and possible leiomyosarcoma (pre-op for robotic)
- CT - very helpful as well, combination with ultrasound
Leiomyoma: cystic degeneration

Leiomyoma: Cystic Degeneration-hemorrhagic

Leiomyoma: pedunculated

Leiomyoma-Angiomyoma
Leiomyoma-Stump

Adenomyosis

Adenomyosis

- Endometrial tissue within myometrium
- Underdiagnosed
- Cause of uterine / pelvic pain / central
- Subendothelial, but not limited to that area
- Asymmetric myometrial thickening
- Avascular-(less)
- Small sonolucent areas-myometrial cysts-2-4mm
- Diffuse infiltrative process
- U/S findings may vary with cycle/hormonal rx
**Uterine Leiomyoma - Treatment**

**Hysterectomy for leiomyomas**
- Hysterectomy is the only definitive therapy
- Risk of recurrence should be balanced with potential benefits of uterine sparing procedure.
- Consideration of surgical morbidity and mortality for particular patients should be considered (obesity and other medical conditions)
- Age, fertility, and other co-factor variables should be discussed and well documented. Might include future pregnancy complications and outcomes.
- Consent for therapy and procedure should be documented including possible unanticipated events
- Can be a very complex and emotional issue to discuss.
Uterus with 28wk size mass-
Robotic assisted Hysterectomy

Pharmacological Options:
• Contraceptive steroids- first in line therapy for controlling menstruation and dysmenorrhea, less beneficial in the long run for patients with uterine leiomyomas.
• Variable results, but usually do not stimulate significant growth
• Progestin alone may decrease leiomyoma size (or control symptoms and maintain stability-DepoP)
• Combined therapy and progestin may decrease risk of developing clinically significant leiomyoma

Levonorgestrel IUD
• Excellent delivery method of levonorgestrel
• Localized beneficial effect – may equal endometrial ablation Rx.
• but may have higher rates of expulsion and spotting- submucosal / endometrial distortion

NSAIDs agents
• Effective in reducing dysmenorrhea
• No major studies documenting improvement with dysmenorrhea secondary to leiomyomas.
• Patients often self treated prior to presentation

GnRh Agonists:
• Luprolide acetate approved by FDA for preoperative therapy in women with anemia in conjunction with supplemental iron.
• Leads to amenorrhea in most women and provides 35-65% reduction in volume in 3 months of therapy
• Effects are temporary with gradual recurrent growth to previous size (~ 6-24 months)
• Limited to 6 months without add-back therapy (?) (Only low-dose preparations have been studied)
• Maximal results using sequential regimen GnRh for down regulation and steroid add-back therapy after 1-3 months of therapy.
### Uterine Leiomyoma-Treatments

#### Aromatase inhibitors
- Block ovarian and peripheral estrogen production
- Decrease E2 levels after 1 day of therapy (fewer side effects, rapid onset)
- Several small studies and case reports note reduction in leiomyoma size and symptoms
- Further research needed
- Not FDA approved

#### Progestin Modulators
- Anti-progestin agents act at level of P4 receptors.
- P4 or progestin receptors found in high concentrations of uterine leiomyoma.
- Mifepristone – most extensively studied compound
- Research studies show usefulness in controlling symptoms
- Several studies report reduction in volume (26-74%)
- Comparable to GnRh analogs with slower rate of re-growth

### Uterine Leiomyoma-Treatments

#### Progestin Modulators
- Amenorrhea up to 90%, stable bone mineral density and decreased pelvic pressure
- Potential SE including endometrial hyperplasia without atypia (14-28%)
- Transient elevation in transaminase levels
- Need to use compounding pharmacy for clinically relevant doses
- May have short-term role in perioperative management – further studies needed

#### Myomectomy-
- Uterine-preserving surgical procedure
- Incise, extract, and reconstruct
  - Types:
    - Abdominal → laparotomy or mini-lap
    - Laparoscopic → traditional or robotic-assisted
    - Hysteroscopic Resection
Uterine Leiomyoma- Treatment

Myomectomy- abdominal:
• Safe and effective option for treatment of symptomatic myomas
• Long time “Gold” Standard procedure
• Morbidity overall similar to hysterectomy
• Significantly improved menorrhagia symptoms (40 - 93%)
• Significantly improved pelvic pressure

• Note well-know your preop Dx, anatomy and have a preop map and surgical plan and complete informed consent

Open Myomectomy

Uterine Leiomyoma - Treatment

Myomectomy - Abdominal:
Risk of recurrence of leiomyomas
• Subsequent childbirth → risk of recurrence
• Recurrence rate dependent on number of leiomyoma present
  Single -27%, 11% hysterectomy
  multiple -59%, 36% recurrent myomectomy or hysterectomy or both
• Risk of hysterectomy is low, less than 1% even with substantial uterine size (caution – Adenomyosis)
• Blood loss and risk of transfusion increases with larger uterine leiomyoma but location is the main key
Open Myomectomy

Leiomyomas-intraop decisions

Open Myomectomy

Leiomyomas-intraop decisions
**Leiomyomas-intraop decisions**

**Uterine Leiomyomas-Treatment**

**Laparoscopic Myomectomy:**
- Complication rates between 8-11%
- Subsequent pregnancy rate 57-69%

Randomized control trial - 284 patients to laparoscopy or mini-laparotomy Alessandri (2006)
- less estimated blood loss
- reduced length of post op ileus
- shorter hospital time
- reduced analgesic
- more rapid recovery (Mini-laparotomy - shorter operating time)

A second trial (Palomba 2007) - patients with unexplained infertility noted improved reproductive outcomes

**Uterine Leiomyoma-Treatments**

Laparoscopic Myomectomy
- Minimizes size of Abdominal incisions
- Quicker postoperative recovery time
- Traditional Straight sticks - now evolving
- Considerable Surgical expertise is required for procedure
  - dissection, control of blood loss, reconstruction and suturing or repair
- *Procedure should mimic open or standard technique*

**Uterine Leiomyomas-Treatment**

Laparoscopic Myomectomy
- Previous recommendations for laparotomy included:
  - Myomas greater than 5-8cm
  - Multiple
  - Deep
  - Intramural

- Study - Wang (2006) noted >80g myomas have longer OR time, increased blood loss, but length of stay and overall complication rate the same.
Uterine Leiomyomas-Treatment

Laparoscopic / Robotic Myomectomy

- Successful outcomes primarily reported by surgeons with expertise in advanced laparoscopy in this area.
- May not be able to generalize to all gynecological surgeons.
- Robotic assistance improves:
  - Optics-high resolution
  - 3-D visualization
  - Enhanced dexterity
  - Decreased haptic sensation-preop MRI
  - Increased OR time-decreases
  - Increased cost—maybe not over time and volume

Robotic-Assisted, Laparoscopic, and Abdominal Myomectomy: A Comparison of Surgical Outcomes

- RESULTS: From a total of 575 myomectomies, 393 (68.3%) were abdominal, 93 (16.2%) were laparoscopic, and 89 (15.5%) were robot-assisted. The three groups were comparable regarding the size, number, and location. Significantly heavier myomas were removed in the robot-assisted group (223 [85–25, 391–50] g) compared with the laparoscopic group (96.65 [49, 50, 227, 50] g, P < .001) and were lower than in the abdominal group (263 [90.50, 449.00] g, P < .002). Higher blood loss was reported in the abdominal group compared with the other two groups, with a median (interquartile range) of blood loss in milliliters of 100 (50, 212.50), 200 (100, 437.50), and 150 (100, 200) in the laparoscopic, abdominal, and robot-assisted groups, respectively. The actual surgical time in minutes was 126 (95, 177) in the abdominal group, 155 (98, 200) in the laparoscopic group, and 181 (151, 265) in robot-assisted group (P < .001). Patients in the abdominal group had a higher median length of hospital stay of 3 (2, 3) days, compared with 1 (0, 1) day in the laparoscopic group and 1 (1, 1) days in the robot-assisted group (P < .001).

- CONCLUSION: Robotic-assisted myomectomy is associated with decreased blood loss and length of hospital stay compared with traditional laparoscopy and open myomectomy. Robotic technology could improve the utilization of the laparoscopic approach for the surgical management of symptomatic myomas.

- LEVEL OF EVIDENCE: II
Uterine Leiomyoma-Treatment

**Hysteroscopic Myomectomy**
- Method of management of AUB caused by submucosal leiomyomas
- Submucosal myoma classification system predictive of success of surgical resection
- Complete resection → most predictive of success
- Uterine size and number also variables for success
- Success rate 85-95%, decreases over time
- Complication rates 1-12%
  - Fluid overload with secondary hyponatremia, pulmonary edema, cerebral edema, intraoperative and postoperative bleeding, uterine perforation, gas embolization, and infection

**Surgical Myomectomy**
- Risk of rupture of uterus with pregnancy, including labor
- Trial of labor is not recommended in patients at high risk of uterine rupture including extensive transfundal surgery
- Garnett 1964 study → no uterine rupture in 212 patients (level 3)
- Pooled data → 1 out of 730 cases of laparoscopic myomectomy with rupture
- Risk of rupture is low, but because of the serious complications, a high index of suspicion must be maintained

Submucosal Myoma-Hsg, MRI

Risk factors for uterine rupture after laparoscopic myomectomy.
Parker WH, Einarssson J, Istre O, Dubuisson JB.

- Case reports for uterine rupture subsequent to laparoscopic myomectomy were reviewed to determine whether common causal factors could be identified. Published cases were identified via electronic searches of PubMed, Google Scholar, and hand searches of references, and unpublished cases were obtained via E-mail queries to the AAGL membership and AAGL Listserve participants.
- Nineteen cases of uterine rupture after laparoscopic myomectomy were identified. The removed myomas ranged in size from 1 through 11 cm (mean, 4.3 cm). Only 3 cases involved multilayered closure of uterine defects. Electrosurgery was used for hemostasis in all but 2 cases. No plausible contributing factor could be found in one case [corrected].
- It seems reasonable for surgeons to adhere to techniques developed for abdominal myomectomy including limited use of electrosurgery and multilayered closure of the myometrium. Nevertheless, individual wound healing characteristics may predispose to uterine rupture.
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Uterine Leiomyoma- Treatment

Uterine Artery Embolization
Treatment by I.R.- embolizing uterine vasculature with polyvinyl alcohol particles of trisacylgelatin microspheres, may also supplement with metal coils. Collaboration with I.R. and gynecologist important to ensure appropriateness plan of therapy.

Short Term Outcome
Pron (2003)- greater than 500 patients
  Favorable 3 month outcome
  42% reduction in dominant myoma volume, decreased symptoms

EMMY (2006)- UAE vs TAH
  Uterine Artery Embolization
  - less pain over 24 hours
  - return to work sooner
  - more minor complications
  - higher readmission rate 11% vs 0 %

Uterine Leiomyoma- Treatment

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UAE- Conclusion
  - Safe and effective method if patient desires to retain her uterus.
  - Important for Ob/Gyn-I.R. collaboration

Long Term Outcomes-
Broder (2002) 81 patients
  - Reoperation rate-UAE 29%, Myomectomy 3%
  - Subjective variables-UAE 39% failure, Myomectomy 30% failure
Spies (2005) 5 year follow-up of 200 patients
  - Re-operation rate UAE 20%
  - Subjective symptoms 25% failure
Mara (2006)
  - Re-operation rate UAE 33%
  - Myomectomy 6%
Uterine leimyoma-Cervical?

UAE: pre and post

Multiple Myoma –corpus and cervical
**Uterine Leiomyoma-Treatment**

**MRI-guided Focused Ultrasound Surgery**
- FDA approval in 2004
- Non-invasive high intensity ultrasound waves directed into focal volume of leiomyoma
- Energy penetrates soft tissue producing protein denaturation, irreversible cell damage and coagulative necrosis

**Uterine Leiomyoma-Treatment**

**Preoperative Adjuvants**
- GnRh agonists
  - Widely used for preoperative therapy for myomectomy and hysterectomy
  - Beneficial when significant volume reduction would modify surgical approach
  - Improves hematological parameters, shorter stay, decreased blood loss, OR time, and postoperative pain
  - Expensive (iron supplements are helpful)
  - Caution-May be disadvantageous for myomectomy as softens up the myoma and loss of surgical planes.

**Preoperative Adjuvants**
- GnRh Antagonists
  - Study reported by Flierman (2005)
  - Avoids initial steroidal flare
  - Rapid effectiveness with less side effects- decreased volume 25-40% in 19 days
  - Not FDA approved for pre-op therapy

**Intraoperative Adjuvants**
- Vasopressin- decreases blood loss with infiltration- myometrium, cervix
- Tourniquets- penrose drains, vascular clamps

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### Uterine Leiomyoma

#### Leiomyomas and Fertility
- Complicated and confusing clinical issue
- High prevalence of uterine leiomyomas
- Incidence of leiomyomas increases with age, as does infertility
- Many women with myomas conceive and have uncomplicated pregnancies
- Leiomyomas noted in 5-10% of infertile women
- Sole factor in infertile women 1-2%
  - Intramural and submucosal myomas can distort cavity or obstruct tubal ostia.
  - Subsequent pregnancy rates after abdominal myomectomy 40-60% after 1-2 years
  - Several studies have shown increased pregnancy rates with myomectomy if cavity was distorted by intramural or submucosal myomas.

#### Leiomyomas- asymptomatic women
- In past, hysterectomy for large uterine myomas
  - Complicated assessment of ovaries and early surveillance for ovarian cancer
  - Larger uterus “had” increased rate of morbidity during surgery
- Compression of ureters and secondary compromise of renal function- rare
- Ureteral dilatation in uterus greater than 12 weeks is seen but is rare to cause secondary renal compromise
- Concern of sarcoma with rapid growth
  - Parker (1994) 1332 hysterectomy specimens with pre op diagnosis leiomyoma, sarcoma 2-3 per 1000, no more common in sub group with rapid growth
  - Reiter (1992) prevalence of incidental sarcoma 1 in 2000, mortality rate for hysterectomy with benign disease 1 to 1.6 in 1000

**Conclusion:** in general insufficient evidence to support hysterectomy for asymptomatic leiomyomas for above.

### Uterine Leiomyomas- Summary:

**Level A**
1. Abdominal myomectomy- safe and effective alternative to hysterectomy based on long and short term outcomes
2. GNRH agonists- shown to improve hematological parameters, shorter hospital stay, decreased blood loss, operative time and post operative pain when given 2-3 months preoperatively. Benefits should be weighed in against cost and side effects.
3. Vasopressin infiltration- decreases blood loss at the time of myomectomy.
Uterine Leiomyomas- Summary:

Level B
4. Clinical diagnosis in a rapidly growing leiomyoma should not be used as an indicator for myomeotomy or hysterectomy.

5. Hysteroscopic myomectomy is an acceptable method for treatment of abnormal uterine bleeding with an etiology of a submucosal myoma.

Level C
6. There is insufficient evidence to support hysterectomy for asymptomatic uterine leiomyoma.
7. Leiomyomas should not be considered the cause of infertility or significantly impact infertility without complete infertility assessment.
8. Hormonal therapy may cause some moderate increase in leiomyoma size but does not appear to have an impact on clinical systems.

References


References - Continued


