How to treat the complex patients: endometriosis, adenomyosis & uterine fibroids

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Conflicts of interest

Paid lectures for:
Astra Zeneca, Bayer, Jansen, Roche, Storz, MSD

Advisory board for:
Astra Zeneca, Bayer, Roche, MSD
How to treat the complex patients: endometriosis, adenomyosis & uterine fibroids

Hysterectomy
Prevalence 15 - 50 yrs

Endometriosis
[10 – 15 %]

Adenomyosis
[10 – 30%]

Myoma
[20 – 25%]

co-prevalence rate
22 - 48%

co-prevalence rate
15 - 25%

co-prevalence rate
20 - 50%

co-prevalence rate
40 - 80%
Common symptoms:

- dysmenorrhea
- chronic lower abdominal pain
- dyspareunia
- chronic lower back pain
- abnormal uterine bleeding

→ negative impact on Quality of Life
Infertility

➢ Endometriosis ➔ in ~50% of infertile women
   Adenomyosis ➔ in 25% of infertile women
   Myoma ➔ in 5–10% of infertile women (but cause of infertility only in 2-3%)

➢ Mild endometriosis ➔ monthly conception rate 2% - 4.5%
   Moderate & severe endometriosis ➔ < 2% (normal couples 15% - 20%)

➢ Focal AD ➔ mean pregnancy rate 52.7%
   Diffuse AD ➔ mean pregnancy rate 34.1%
Treat the pain without influencing fertility or even with increasing fertility?
Age at diagnosis

➢ Endometriosis: 2/3 of patients have symptoms < 30 yrs
➢ Adenomyosis: affects ~ 30% of young women diagnosed in 22% of infertile women < 40 yrs undergoing ART
➢ Myoma: 20-25% represent the range

Effective management plan for more than 20 years!
Treatment of women with endometriosis, adenomyosis and uterine leiomyomas must be individualized based on:

➔ symptomatology
➔ size & location of lesions
➔ age
➔ need & desire to preserve fertility or the uterus
➔ availability of therapy
Persistence of dysmenorrhea and nonmenstrual pain after optimal endometriosis surgery may indicate adenomyosis

(A) Dysmenorrhea severity before and 3 months after surgery for women with endometriosis. Junctional zone thickness <8 mm: \(P<.0001\), VAS decreased 4.3 ± 0.6; JZ thickness ≥8 and <11 mm: \(P<.02\), VAS decreased 4.8 ± 1.3. (B) Nonmenstrual pain severity before and 3 months after surgery for women with endometriosis. Junctional zone thickness <8 mm: \(P<.0001\), VAS decreased 4.0 ± 0.7.

1) Diffuse adenomyosis
   - Thickening of the Junctional Zone (JZ = yellow mark)
     (JZmax ≥ 12 mm; JZmax-JZmin; or JZmax/myometrial thickness > 40%)
   - Numerous foci of endometrial glands and stroma dispersed diffusely within
     the myometrium (white arrow)

2) Focal adenomyosis
   Circumscribed nodular aggregates
   3 subtypes according to foci location: outer, middle & inner myometrium

3) Cystic adenomyosis (resp. adenomyoma)
   Rare variation of focal adenomyosis with additional compensatory hypertrophy of
   the surrounding myometrium
Relationship between MRI appearance of adenomyosis & endometriosis phenotypes

292 pts scheduled for benign surgery, preoperative MRI: 237 with endometriosis compared to 55 symptomatic women without endometriosis

Diffuse adenomyosis:
→ observed in 1/3 of the pts whether endometriosis pts or not
→ failed to reach significant correlation with endometriosis phenotypes

Focal Adenomyosis of the Outer Myometrium (FAOM):
→ more frequent in women with endometriosis
→ significantly associated with DIE

Define preoperatively the goal of the operation with the patient according to her wishes!
Endometriosis, Adenomyosis and Myoma
Microarray Analysis on Eutopic Endometrial Samples in Adenomyosis Patients

[B. McKinnon, K. Nirgianakis, …, Montgomery G, Mueller MD: work in progress]
## Disease comparison

<table>
<thead>
<tr>
<th></th>
<th>No. of significantly different pathways</th>
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</thead>
<tbody>
<tr>
<td>1. Adenomyosis v No pathology</td>
<td>180</td>
</tr>
<tr>
<td>2. Adenomyosis v Other pathologies</td>
<td>65</td>
</tr>
<tr>
<td>3. Adenomyosis mixed v No pathology</td>
<td>243</td>
</tr>
<tr>
<td>4. Adenomyosis mixed v Other pathology</td>
<td>102</td>
</tr>
</tbody>
</table>

[B. McKinnon, K. Nirgianakis, ..., Montgomery G, Mueller MD: work in progress]
Androgen receptor signaling pathway

[B. McKinnon, K. Nirgianakis, ...., Montgomery G, Mueller MD: work in progress]
Endometriosis develops in a unique microenvironment

Angiogenesis

[Mc Kinnon B, Mueller MD, Hum Reprod Update (2016)]
Pathogenesis of adenomyosis

Figure 1 – Pathogenetic mechanisms of adenomyosis.

Figure 2 – Pathogenic mediators in adenomyosis.

Symptomatic patient with endometriosis, adenomyosis and myoma

Conservative treatment

- Enhance fertility
- Retain fertility

Radical surgery

- Retain Uterus
Medical Therapy

➢ To the contrary of endometriosis or myoma, no drug is currently labelled for adenomyosis ➔ no specific guidelines

➢ As endometriosis, adenomyosis and uterine fibroids often coexists all three conditions have to be considered in the management plan

➢ All 3 entities are sex steroid hormone-dependent disorders, characterized by increased inflammation, impaired apoptosis, and neuroangiogenesis

➢ The principles of medical therapy are inhibition of ovulation, abolition of menstruation and establishment of a stable steroid milieu

➢ First or second line treatment choice should be according to the side effects and not finances as proposed by some authors

➢ New drugs might play an increasing role
Medical Therapy

Non-specific therapies

Non-steroidal anti-inflammatory drugs; combined oral contraceptives

Combined Oral Contraceptives (COC)

➢ No COCs with an approved indication for endometriosis or adenomyosis

➢ Reduces dyspareunia, dysmenorrhoea & non-menstrual pain [Vercellini et al., 1993]

➢ No evidence that low-dose OC cause fibroids to grow ➔ not contraindicated in pts with uterine fibroids

➢ Effective in reducing AUB in adenomyosis and myomas

➢ Continuous use more effective [Vercellini et al., 2017]

➢ May use a vaginal contraceptive ring or a transdermal (oestrogen / progestin) patch to reduce endometriosis-associated dysmenorrhoea, dyspareunia and chronic pelvic pain (Vercellini et al., 2010)
Past use of OC for treating severe primary dysmenorrhea is associated with DIE

Cross-sectional study: **566 patients without & 410 patients with endometriosis**

History of OC use for severe primary dysmenorrhea is associated with surgical diagnosis of endometriosis, especially **DIE, later in life** (adjusted OR = 16.2, 95% CI 7.8-35.3)

Progestin-only pills may be a better first-line treatment for endometriosis than combined estrogen-progestin contraceptive pills

➢ The dose of EE in a low-dose OCP is equivalent to 4 to 6 times the physiologic dose of estrogen

➢ Presence of supraphysiologic concentrations of estrogen with OCP, during menstrual phase, may rescue endometrial cell clusters deposited in the pelvis during retrograde menses

[Vercellini P. et al; Hum Reprod Update 2011]

Medical Therapy

Non-specific therapies

- Non-steroidal anti-inflammatory drugs
- Combined oral contraceptives

Specific therapies

- e.g. progestins (NETA, dienogest)
- danazol (IUS; vaginal ring)
- LNG-IUS
- GnRH agonists

References:

1. Nothnick WB. Reprod Biol Endocrinol (2011); 9: 87
2. Bedaiwy MA et al., Fertil Steril (2017); 107(3): 555-565
Rationale for the Use of Progestins in the Treatment of Endometriosis +/- Adenomyosis +/- Myoma

Progestins

- Reduction of serum estrogen levels
- Immunomodulatory effect
- Anti-inflammatory effect
- Decidualisation + atrophy of endometrial tissue
- Inhibition of matrix metalloproteinases
- Anti-angiogenic effect

Levonorgestrel-releasing Intrauterine System


➢ Less side effects when compared to oral treatment (relatively low serum levels but locally high concentrations of LNG in the endometrium & adjacent tissues)

➢ Cost effective, simple and reversible method for the long-term treatment of chronic pelvic pain associated with endometriosis, adenomyosis and myoma

➢ Long-term maintenance therapy is not effective for preventing endometrioma recurrence (RCT) [Qiu H et al., AFOG (2017); 6: 708 – 709]
GnRH Analogues

- systemic and local hypoestrogenic effect through central downregulation and suppression of gonadotropin secretion
- direct antiproliferative effect within the myometrium through the action on GnRH receptors
- Goserelin, leuprolide and nafarelin are commonly used in clinical practice causing uterine size reduction and improvement in pelvic pain and bleeding in all three conditions
- Hypoestrogenic side effects: vasomotor syndrome, reduced bone mineral density, genital atrophy, and mood instability
- Add-back therapy (no specific indication on when and which type) should be used to minimize side effects
- Long-term treatment should be restricted to women unresponsive to other medications or in surgically high-risk patients
- Upfront therapy with 2 doses of GnRHa might be helpful when instoring a long-term treatment with progestins

[Römer Th (2018), unpublished data]
Medical Therapy

Non-specific therapies

- Non-steroidal anti-inflammatory drugs; combined oral contraceptives

Specific therapies

e.g. progestins (NETA, dienoestrogens), danazol (IUS; vaginal ring); LNG-IUS; GnRH agonists

Experimental therapies under investigation, including

- Aromatase inhibitors
- GnRH antagonists
- Selective estrogen receptor modulators (SERMs)
- Selective progesterone receptor modulators (SPERMs)
- Preimplantation Factor
- Thiazolidinediones

References:

1. Nothnick WB. Reprod Biol Endocrinol (2011); 9: 87
2. Bedaiwy MA et al., Fertil Steril (2017); 107(3): 555-565
4. Sbracia M et al., PLoS One (2017); 12(9): e0184399
Infertility in the complex patient

- The influence of myomas and adenomyosis on fertility is still under debate
- The use of GnRHa for adenomyosis and it’s positive effect on fertility is mostly based on case reports
- Adenomyosis has a detrimental effect on IVF clinical outcomes
- Pretreatment with the use of long-term GnRHa or long protocol could be beneficial.

Live birth rate per IVF-cycle in women without and with adenomyosis

[Younes G, Tulandi T; Fertil Steril (2017); 108: 483 – 90]
Patients with endometriosis undergoing ART have additional risk of placenta previa [(OR 2.96 (95% CI 1.25–7.03); p = 0.01)]

Despite the inability to determine if endometriosis alone or endometriosis plus ART increase the risk, physicians should be aware of the potential additional risk that endometriosis patients undergoing ART harbor
Symptomatic patient with endometriosis, adenomyosis and myoma

Conservative treatment

- Enhance fertility
- Retain fertility

Radical surgery

- Retain Uterus
Uterine Artery Embolization

➢ Effective for treating symptoms in myoma & Adenomyosis (reduction in bleeding, dysmenorrhea fibroid and uterine size)

➢ Risk of reoperation:
   - 15–20% after successful UAE
   - up to 50% in cases of incomplete infarction

➢ Desire for future pregnancy ➔ relative contraindication
   Surgical myomectomy: more favorable outcome than UAE (RCT)

➢ No effect on endometriosis

[Goodwin & Spies (2009); Kaump (2013); Gupta (2014); Vilos (2015), Spies (2016); de Bruijn AM (2017); Liang E (2018); Alvi FA (2018)]
High-frequency magnetic resonance-guided focused ultrasound

➢ Ultrasonic energy is directed to a point inside the fibroid and coagulation tissue necrosis is induced in the myoma

➢ Limitations:  
  - only a fraction of patients with fibroids meet the inclusion criteria  
  - future fertility may be compromised  
  - financial burden may be too heavy

➢ Only very few studies in adenomyosis

➢ 30% of women undergo further surgery or procedures 2 years after MRgFUS

➢ Desire of future pregnancy ➔ relative contraindication

➢ No effect on endometriosis

[Clark (2014); Park (2014); Fischer (2015); Jacoby (2015); Kim (2015); Zuppi (2015); Chen J (2017)]
Hysteroscopy

Use of utero-spirotome under ultrasound guidance: (A) ultrasound guided insertion of spirotome; (B) spirotome with 1 cm corkscrew; and (C) representative biopsy obtained after use of the spirotome.

Surgical Treatment: Hysteroscopy
Adenomyosis Surgical Treatment

➢ Remains a matter of debate, not only in terms of indications, but also the technical aspects of surgery

Focal adenomyosis
Triple-flap Method

- complete extraction of the adenomyosis
- Reconstruction of a uterine cavity (preparation of an endometrial uterine muscle flap by metroplasty through opening the uterine cavity and removing the uterine adenomyosis under palpation)
- reconstruction of a uterine wall

Adenomyosis Surgical Treatment

➢ Remains a matter of debate, not only in terms of indications, but also the technical aspects of surgery

➢ Overall patients with focal AD $\rightarrow$ higher pregnancy rates after conservative surgery compared to diffuse AD

➢ higher incidence of uterine rupture after surgery for diffuse AD

➢ Prospective controlled trials are required to further elucidate the benefits of fertility preserving surgery over medical or expectant management for AD-related infertility

➢ In view of the debatable benefits of conservative surgery and the possible increase in adverse pregnancy outcomes particularly in cases of diffuse adenomyosis, clinicians should be very careful in considering surgery for AD in complex cases where Endometriosis and Myoma might interfere with the results
35 yrs old women

- 6 x IVF (one pregnancy with spontaneous abortion)
- Oligozoospermie
- Symptoms: lower abdominal pain, dysmenorrhea, no dyschezia, no dyspareunia
Frequency of uterine rupture:
- In non-scarred uteri: 0.005%
- After cesarean sections: 0.27%–0.7%
- After myomectomy: 0.26%
- After removal of a uterine adenomyosis: >1.0%

Delivery after surgery for DIE
- Matched controlled study after complete excision of posterior DIE
- 62 patients with history of surgery for DIE vs 186 pregnancies matched for maternal age, parity, history of cesarean and mode of conception
- Higher risk for placenta previa, gestational hypertonia and IUGR in the DIE group
- Previous surgery for DIE does not predispose to failed vaginal delivery or higher delivery risks

Take home message

➢ The complexer the patient the more individualised the therapy has to be
➢ Conservative medical treatment as long as possible and needed
➢ Try to avoid unnecessary recurrences ➔ only one surgery (the right one @ the right moment)
➢ Thorough preoperative evaluation before surgery (sonography, MRI)
➢ Define the extent of the surgery according to the goal of the patient
➢ Complex patients are at higher risk to develop complications during pregnancy
➢ Better no surgery than bad surgery!!
Thank you!
«Hot topics in gynecology»
Bern 7. – 8.3.2019
Non-steroidal anti-inflammatory drugs (NSAIDs)

➢ Symptomatic treatment for dysmenorrhea and heavy bleeding (but less effective than hormonal treatment or tranexamic acid)

➢ There is no evidence that one NSAID is more effective than another

➢ Women taking NSAIDs must be aware that these drugs may cause unintended effects (nausea, vomiting, headache and drowsiness)

➢ NSAIDs are linked to reversible female infertility: inhibition of COX-2 might cause luteinised unruptured follicle (LUF) syndrome (= anovulatory condition characterised by clinical signs of ovulation but in the absence of follicular rupture and ovum release)
Progestins

Danazol

- Androgenic & hypoestrogenic milieu
- Effective in the short term treatment of symptomatic leiomyomas (but less effective than GnRH agonists)
- Side effects are very common (weight gain, muscle cramps, edema, hot flushes, hirsutism, headaches, depression, skin rash, acne, etc.) → its systemic use is generally discouraged
- Also used in an IUD → reduction of the size of the uterus & of pain symptoms, pregnancy in 66.6% cases, ovulation not inhibited and no side effects reported
- Long-term vaginal administration of 200 mg danazol tablet every day is effective in reducing heavy menstrual bleeding and pain
- significant improvement of dysmenorrhea & bleeding (5 mg/d dose)
- “3 weeks on, 1 week off” regime to minimize breakthrough bleeding
- effective, well tolerated and inexpensive medical treatment for adenomyosis
- No studies comparing NETA to other progestins or other drug
- No evidences on long term effects on symptoms and sonographic or MRI appearance of adenomyosis after discontinuation of NETA treatment
**Dienogest**

- → inhibition of ovarian function with slight hypoestrogenic effects & antiproliferative action on the endometrium

- DNG is effective against pain symptoms in adenomyosis patients
  [Hirata T et al., Gynecol Endocrinol (2014); Osuga Y et al. Fertil Steril (2017); Osuga Y et al., J Obstet Gynecol Research (2017)]

- Comparison between DNG and GnRH analogues:
  - No difference in terms of pelvic pain reduction
  - 4 mts of treatment with GnRHa → a greater reduction of AUB symptoms and uterine volume evaluated by ultrasound

- Lit investigating the effect of DNG on Myoma is sparse, but it seems that it also have a beneficial effect on uterine myoma volume [Ichigo S et al. (2011)]

![Graph showing change in pain score and pain-severity score over treatment period](image-url)

- Dotted line ➔ Placebo
- Solid line ➔ DNG

[Osuga Y et al., Fertil Steril 2017]
Novel drugs under investigation

Aromatase Inhibitors

➢ Aromatase cytochrome P450 (CYP19A1) typically found in the endometrium of women with endometriosis, adenomyosis and leiomyomas
➢ This enzyme is involved in the conversion of androstenedione and testosterone to estrone and estradiol, respectively
➢ Randomized controlled-trial comparing treatment for 3 months with an aromatase inhibitor (letrozole 2.5 mg/d) and goserelin 3.6 mg monthly showed that AIs have the same efficacy as GnRH analogues in reducing adenomyoma volume and improving symptoms. In fact in both treatments a significant difference in uterine volume after 3 months was observed, without a relevant change in adenomyotic area (41% vs. 49%) at study completion
➢ AIs seems to have a promising future for adenomyosis in cases of resistance to other treatments even though additional studies are needed

Selective Progesterone Receptor Modulators (SPRMs)

➢ SPRMs = valuable treatment option for hormone dependent conditions like uterine fibroids
➢ SPRMs exhibit progesterone agonist and antagonist activities in the endometrium, reducing pain, bleeding, cell proliferation and inhibiting inflammation ➔ may be a promising treatment for endometriosis and adenomyosis as well
➢ Previous evidences on mifepristone showed that it influences the caspase 3 expression in adenomyosis tissue, inducing cell apoptosis, inhibiting the onset and development of adenomyosis
➢ However, only a few small clinical studies on endometriosis showed the potential application of SPRMs in adenomyosis
➢ The administration of mifepristone 50-mg daily improved pain and caused regression of endometriotic lesions
➢ Similarly, asoprisnil and telapristone acetate have also been reported to relieve endometriosis-associated pain
➢ However, SPRMs require investigations and well designed, randomized controlled trials to assess their long-term effects and their clinical use in patients with adenomyosis
➢ A phase II, randomized, doubleblind, controlled trial with ulipristal acetate 10 mg/day for 3 months in patients with adenomyosis wishing to keep fertility has just been registered. The primary outcome is to evaluate the efficiency of ulipristal acetate on bleeding control and pain in adenomyosis.
Adenomyosis Therapy: Novel drugs under investigation

GnRH Antagonists
➢ Peptide compounds with a structure similar to natural GnRH that inhibit the reproductive system through an immediate antagonist action on GnRH receptors in the pituitary, blocking the secretion of gonadotropins.
➢ They are usually used in antagonist stimulation protocols in ART.
➢ Recently, two double-blind, randomized, phase 3 trials on women with endometriosis treated with different doses of elagolix, an oral nonpeptide GnRH-ant, were published.
➢ Both schedules of elagolix were effective in improving dysmenorrhea and nonmenstrual pelvic pain during a 6-month period in women with moderate to severe endometriosis-associated pain.
➢ The mechanism of action of GnRH-ant is different from that of GnRH analogues which after an initial stimulatory phase desensitize GnRH receptors in the pituitary and subsequently cause depletion of pituitary gonadotropins and full suppression of estradiol. GnRH-ant do not induce neither downregulation nor desensitization of the receptors, as they act competitively preventing endogenous GnRH from binding and activating its pituitary receptor. Thus, depending on the dose of antagonist administered, the estradiol suppression can be modulated. The treatment may partially suppress estradiol without having to administer addback therapy, or fully suppress estradiol when combined with add-back therapy. Considering the promising results of GnRH-ant in endometriosis, a future use for treating adenomyosis-related symptoms may be hypothesized.

Valproic Acid
➢ Increasing evidence is showing that adenomyosis is an epigenetic disease.
➢ Class I histone deacetylases seem to be involved in the pathogenesis, as their expression has been found to be increased in eutopic and ectopic endometrium in adenomyosis, correlating with severity of dysmenorrhea.
➢ Valproic acid (VPA), a specific and potent histone deacetylase inhibitor, used for decades for treating epilepsy, has been shown to be effective in treating a small series of women with adenomyosis, decreasing dysmenorrhea and uterine bleeding, and reducing the uterus size.
➢ Studies on murine models of adenomyosis showed the mechanism of action of VPA, that suppressed myometrial infiltration, improved generalized hyperalgesia, and reduced the amplitude and irregularity of uterine contractions.
➢ Despite these promising results in favor of the use of histone deacetylase inhibitors, so far no clinical trials have been conducted to evaluate the efficacy of VPA in adenomyosis.

Anti-platelet Therapy
➢ Emerging evidence supports an important role of platelets in adenomyosis pathogenesis, according to the theory that adenomyotic lesions are wounds undergoing repeated tissue injury and repair.
➢ Platelets induce epithelialmesenchymal transition, fibroblast-to-myofibroblast transdifferentiation, leading ultimately to fibrosis.
➢ A recent study in a mouse model of adenomyosis demonstrated that anti-platelet treatment (thromboxane A2 synthesis inhibitor) is efficacious in suppressing myometrial infiltration, improving generalized hyperalgesia, reducing both uterine hyperactivity and systemic corticosterone levels.
➢ In addition a decreased expression of some proteins involved in adenomyosis fibrogenesis was demonstrated, supporting the promising role of anti-platelets therapy in adenomyosis.
➢ However, so far there are currently no studies published or registered on the use of agents targeting platelets.
Is Shifting to a Progestin Worthwhile When Estrogen-Progestins Are Inefficacious for Endometriosis-Associated Pain?

➢ Prospective study on 153 endometriosis pts to assess patients satisfaction with their treatment after a change from a low-dose oral contraceptive (OC) to norethisterone acetate (NETA 2.5 mg/d) because of inefficacy of OC on pain symptoms

➢ At 12-month assessment 70% of participants were very satisfied or satisfied with NETA treatment (intention-to-treat analysis)

Vercellini P et al., Reprod Sci (2018); 25(5): 674 - 682
**FIGURE 1**
Summary: timeline of selective progesterone receptor modulators (SPRM) development

![Timeline Diagram](image)

**MIFEPRISTONE**
- **1980s**
  - Serendipitous discovery during search for glucocorticoid ligands
  - Initially developed and marketed for pregnancy termination
- **1990s-2010s**
  - Identified as a candidate for UF management
  - Cochrane Review (Tristan et al., 2012) showed reduced bleeding and improved QoL

**Potential limitations**
- Not currently indicated for UF management
- Almost pure antagonist properties (versus other SPRMs that have mixed agonist/antagonist action)

**ASOPRISNIL**
- **2000s**
  - Dose-dependent decrease in bleeding demonstrated
  - Clinical development halted in 2007

**TELAPRISTONE**
- **2000s-2010s**
  - Dose-dependent decrease in bleeding demonstrated
  - Clinical development suspended in 2009 due to liver toxicity concerns
  - Development restarted in 2011 at lower dose

**ULIPRISTAL ACETATE**
- **2010s**
  - Decreases in bleeding and fibroid volume demonstrated
  - Approved in Europe and Canada:
    - 2013: Pre-surgical (single course)
    - 2016: Repeated intermittent treatment

**VILAPRISAN**
- **2010s**
  - In clinical development as of 2017

[Singh S et al.; Am J Obstet Gynecol (2017)]