Modern Management of Adenomyosis

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Who identified adenomyosis?

• D. Schron (1690) described the first case of what we would today call endometriosis or adenomyosis (thesis Diputatio Inauguralis Medica de Ulceribus Uteri)

• C. Rokitansky (1860) described endometrial glands in the myometrium and designated this finding as “cystosarcoma adenoids uterinum”

• N. Iwanoff (1898) reported a microscopic evaluation of the glands found in cystic myoma, they “were derived from the serosal epithelium”

Knapp VJ: How old is endometriosis? Late 17th- and 18th century European descriptions of the disease. Fertil Steril 72:10, 1999
Summary of factors of adenomyosis

• Increased risks
  - Parity
  - Spontaneous miscarriage
  - Endometriosis
  - Menorrhagia
  - Infertility
  - Surgical termination/curettage in pregnancy
  - Endometrial hyperplasia
  - Preterm birth
Pregnancy and Adenomyosis

- It should be taken into consideration the pregnancy in adenomyosis is highly risky
- Spontaneous miscarriage has been observed more frequently
- Sharp curettage increases the risk by disrupting the endometrial-myometrial interface and facilitating embedding of the endometrium within the myometrium
- Suction curettage should be recommended
- Sharp curettage of non pregnant uterus does not increase the risk of adenomyosis
Decreased risk

- Smoking
- ???
No risk

• Age of menarche
• Menopausal status
• Age at the first childbirth
• Contraception
• Indication for surgery
• Patient’s age at surgery
• Caesarean section
• D&C

Ob&Gyn 2009, 11
Classification (by Wyczik, Dueholm, Bazon and Hauth)

• Types
  - Polypoid adenomyoma
  - Cystic adenomyoma
  - JZ adenomyoma
  - Outer myometrium adenomyoma
  - Extrauterine adenomyoma

• Locations
  - Retrocervical
  - Retrovaginal
  - Fallopian tube
  - Bladder
Classification by L. Adamyan (1992, 1998)

- Stage I – pathological process is limited by submucuos of the uterus
- Stage II – myometrium is involved in this pathological process
- Stage III – pathological process is spread over the myometrium till subserous
- Stage IV – besides the uterus pelvic peritoneum and adjoining organs are involved in the pathological process
Treatment

- **Surgery**
  - Radical
  - Conservative
- **Uterine artery embolization**
- **Magnetic Resonance Guided Focused Ultrasound Surgery**
- **Hormonal treatments**
  - GnRH agonists
  - Levonorgestrel-Releasing Intrauterine System
  - Danazol-loaded Intrauterine Devices
- **Novel approaches**
  - Aromatase Inhibitors
  - Inhibitors of Angiogenesis
Surgery

- Radical surgery (LTH, VH or LATH)
- No place for Subtotal Hysterectomy
- LH can be “method of choice” due to what we call “see and treat”
- VH doesn’t influence negatively on QoL (1050 patients were questioned who were undergone to V, Ls or Open Hysterectomy due to symptomatic adenomyosis)
Conservative surgery

• Superficial adenomyosis (superficial or submucous) can be treated by Ls or Transcervical procedures.

• Cystresection by Hs is the “method of choice” in case of infertility

• Endometrial ablation could be performed in case of uterine bleeding

• This procedure could stimulate the progress of adenomyosis in pain symptoms
OLD and NEW techniques of reduction surgery

The post-operative clinical evaluation included use of the visual analogue scale (VAS) to assess the degree of hypermenorrhoea and dysmenorrhoea, initially every 3 months for the first year and thereafter 24 months post-operatively. To assess the level of menstrual bleeding, a system similar to VAS was used. The patients were asked to rate the amount of post-operative menstrual flow against that of the pre-operative level considered as 10. This permitted a more accurate semi-quantitative comparison with the pre-operative levels. The extent of dysmenorrhoea was similarly assessed using a VAS scale, also comparing the post-operative level to that of the pre-surgical level rated as 10. The reason VAS was not used in such a way as to measure bleeding and pain before the procedure was because it was thought that the patients would find it very difficult to rate the level of the pain using VAS before the operation, as it is so arbitrary what kind of pain (or blood flow) they should rate as maximum. So, the easiest and the clearest way to judge the level of pain alleviation and reduction of menstrual blood flow was to have the patient rate the pre-operative pain or blood flow level at 10 before the operation and then have them rate again after the operation. So this was a modified VAS. Student's unpaired t-test was used to compare difference between pre-surgical and post-surgical levels of dysmenorrhoea/hypermenorrhoea and a \( P < 0.01 \) were considered significant.

Results

All patients observed immediate relief of symptoms of hypermenorrhoea and dysmenorrhoea and their post-operative course was generally unremarkable.

The procedure was performed on 104 patients during the period from June 1998 to August 2008. The mean age of the patients in the series was 37.6 years. All candidates for surgery suffered from severe dysmenorrhoea and hypermenorrhoea and 94 women (90.4%) were found to be anaemic. The time required to perform these procedures was (mean ± SD) 182.7 ± 62.2 min, the volume of blood loss during surgery was 372.0 ± 314.4 ml, and the weight of the excised tissues was 292.6 ± 254.1 g.

The results of the post-operative examination using contrast-enhanced MRI or an endovaginal ultrasonography with colour Doppler imaging showed that the blood flow in the operated area had returned to normal within 6 months in almost all cases (99/104, 95.2%). However, in a few cases (5/104, 4.8%) the blood flow took nearly a year to return to normal. Post-operative complications were observed in six cases (5.8%); they were all small haematomas, under 1 cm in diameter, formed at the operated area and were all spontaneously absorbed within 2 months. There were no suture diastases (failures), infections or uterine cavity adhesions observed.

The VAS findings (mean ± SD) for dysmenorrhoea, based on a score of 10 pre-surgically, were 1.61 ± 1.43 at 3 months, 1.54 ± 1.62 at 6 months, 1.44 ± 1.65 at 1 year and 1.67 ± 1.79 at 2 years post surgery. The VAS findings for hypermenorrhoea were 3.27 ± 2.17 at 3 months, 2.89 ± 1.77 at 6 months, 2.63 ± 1.3 at 1 year and 2.87 ± 1.77 at 2 years post surgery (Figure 4). Differences between the VAS scores for pre-surgical and post-surgical dysmenorrhoea and hypermenorrhoea were statistically significant (\( P < 0.01 \) determined by Student's unpaired t-test). There was a recurrence (defined by return of pre-op symptoms and recurrent adenomyomatous growth) in only four cases (3.8%) over the 10-year time of the study.

The outcome of the surgical treatment is shown in Table 1. Twenty-six women (25.0%) wished to conceive following the surgical removal of the adenomyosis. Their age (mean ± SD) was 36.9 ± 4.7 years. Sixteen of them (61.5%, 16/26) subsequently conceived. Of these, four women conceived spontaneously and 12 women conceived by IVF/ET. Two women who had IVF/ET experienced a spontaneous abortion (at 5 weeks and 16 weeks); 14 went to term and all were delivered by elective Caesarean section. There were no cases of uterine complications to the pregnancies.
Conservative surgery

- 11 studies were published till 2012
  - Two studies reported live birth rates (Tadjerouni et al, 1995, Takeuchi et al, 2006)
  - One reported pregnancy (Strizhakov et al, 1995)

An overall PR of 36.2% (21 of 58) was achieved following the conservative surgery

A. Maheshwari et al, 2012
Conservative surgery
Expert Opinion by C. Chapron et al.

• Non-radical surgical intervention with resection of adenomyoma (adenomyectomy) and/or the adenomyotic tissue with uterine repair are particularly difficult intervention performed at very few centers

• Medical treatment plays a major role in the management of adenomyosis

• It is particularly important in women with an association of adenomyosis and endometriosis compared to women suffering from endometriosis alone, in which surgery can improve both fertility and pain symptoms

I. Streuli et al., 2014
Uterine artery embolization

• The first procedure was performed by Ls (C. Wang et al., 2002)
• UAE is an effective therapy for adenomyosis, improves dismenorrhea and menorrhagia with a decrease in uterine size in most of patients.
• Prospective studies are needed to establish its safety and efficacy in women with adenomyosis-associated infertility
Magnetic Resonance-Guided Focused Ultrasound Surgery

• HIFU has been used to treat patients with symptomatic adenomyosis. It induces thermal ablation and coagulative necrosis. The margin between the treated and untreated regions is well defined.

• This method is well tolerated by patents.

• The mean uterine volume decreased by 12.7%, symptom severity score improved significantly and no serious complications were observed.
GnRH agonists

• The first drugs used in the treatment of adenomyosis (D. Grow, 1991)
• Reduction in uterine volume and amenorrhoea, relief of dysmenorrhoea
• Discontinuation of therapy prompts re-growth of the uterus and recurrence of symptoms
• There are disadvantages: side effects, risk of preterm menopause, high cost etc.
• GnHRa are commonly used as a second-line treatment of adenomyosis
• GnHRa could be used at lower doses and long-term (draw-back therapy), inducing a less severe hypoestrogenism (S.Arika et al., 2009)
Progestogens

• Dienogest
There are only two small non-randomized studies on Dienogest (H.Sasa et al., 2014; C.Nagata et al., 2012)

• Levonorgestrel intrauterine system
Different mechanisms:
- Direct progestogenic effect of ectopic adenomyosis foci
- Decidualization and atrophy of the eutopic endometrium
- Modulation of endometrial factors altered in adenomyosis
LNG-IUS is the most effective treatment of adenomyosis-related symptoms
Danazol

- Danazol-loaded intrauterine device containing 300-400 mg Danazol
- Non systematic side-effects associated with oral Danazol
- Disadvantages: uterine spotting and spontaneous expulsion

M. Igarashi et al., 2000
O. Shawki, 2002
Aromatase Inhibitors

• The Aromatase phenomenon is believed to be restricted to women with proliferative reproductive tract disorders
• Ectopic endometrium produces estrogens
• Use of agents of suppressing both ovarian (GnRHas) and local (AI) estrogen biosynthesis

L. Amsterdam et al., 2005
Inhibitors of angiogenesis

- Angiogenesis is altered in heterotopic uterine mucosa in case of adenomyosis.
- Anti-angiogenic treatments should improve bleeding and pain symptoms related to adenomyosis and reduce the extent of the disease without interfering with physiological processes.

Y.-F. Zhou et al., 2003
E. Novella-Maestre et al., 2009
N. Vlahos et al., 2010
Potential new treatment targets (by I. Streuli et al., 2014)

- GnHRas (oral no-peptide antagonist Elagolix) is developed for long-term treatment of endometriosis and leiomyoma, but there are no studies on the treatment of adenomyosis.
- SPRMs are prescribed for medical termination of pregnancy, for emergency contraception, for preoperative treatment of leiomyoma. It could inhibit eutopic and ectopic endometrial cells.
- UPA could potentially be of use in AUB by two mechanisms:
  - Amenorrhea
  - Direct effect on adenomyosis foci
Potential new treatment targets (by I. Streuli et al., 2014)

- Atosiban (vasopressin V1a and OTR antagonists) showed that it can reduce myometrial activity and decrease pain symptoms. Dysperistaltism could also be implicated in the pathogenesis and symptoms associated with adenomyosis.

- Epigenetic alterations – Valproic Acid (potent deacetylase inhibitor HDACi) reduced hyperalgesia, myometrial infiltration by ectopic endometrium and uterine contractility.
Conclusions

• If the doctor diagnoses adenomyos the patient should be recommended to get pregnant as early as possible

• Middle and severe stages of adenomyosis have negative impact on reproduction. Early miscarriage rate for this group of patients might be 50-100% (23,2% in all infertile patients)
Conclusions

• Today we know well how to do surgery in cases of superficial endometriosis, OMA and DIE. We can do “masterly” surgery: bowel resection, ureter re-implantation etc.

• We did not achieve the same success in adenomyosis-associated conservative surgery as well.

• Although PR after conservative surgery and medication treatment is high, the live birth rate is much lower in cases of severe adenomyosis.
Conclusions

• If IVF or reduction surgery are not effective surrogate mother is the only decision. Quality of embryo in adenomyosis-associated infertility does not suffer