

ADENOMYOSIS AND INFERTILITY

update in diagnosis and treatment

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INTRODUCTION

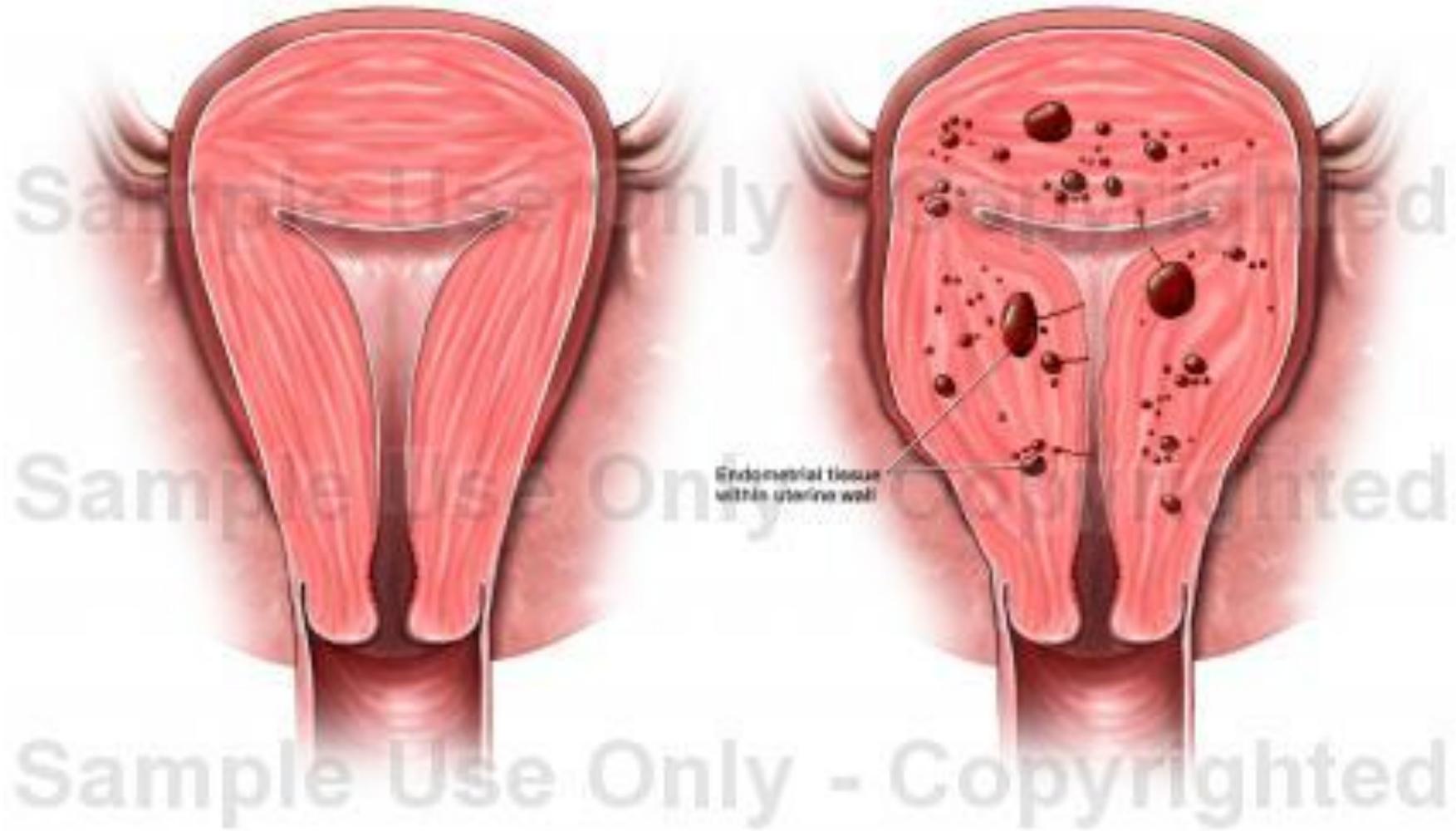
- ▶ Bird defined adenomyosis in 1972 as “the benign invasion of endometrium into the myometrium, producing a diffusely enlarged uterus which microscopically exhibits ectopic, non-neoplastic,”
- ▶ Endometrial glands and stroma surrounded by the hypertrophic and hyperplastic myometrium
- ▶ In late 19th and early 20th century, the termination “adenomyoma” was used to describe these phenomena . Origin of invasion of endometrium was in controversy for last decades
- ▶ In 1925 Frankl used the termination “adenomyosis”
- ▶ 1927: Sampson: Retrograde menstruation implants: endometriosis. These two diseases are independent

- ▶ In 1960's : with the development of endoscopic surgery, only endometriosis was taken into account. Adenomyosis was mentioned in retrospective research or diagnosed after hysterectomy
- ▶ In 1980's: Advanced imaging diagnosis allow to diagnose adenomyosis prior to operation

Comparison of Normal Uterus with Adenomyosis

Normal Uterus

Adenomyosis



JZ (Junctional zone)

- ▶ The junction between the endometrium and the inner myometrium (Hricak et al., 1983)
- ▶ Thickness changes cyclically : Thickest in day 8–16 of menstrual cycle
- ▶ 2005: Hoad showed the thickness of a normal JZ was found to be around 4 mm on average and can vary during the cycle by 0.9 mm on average
- ▶ 2007: Hauth : MRI study did not find a significant difference in JZ thickness between the two phases of the menstrual cycle in 100 healthy women

Pathological diagnosis

▶ Uterine Biopsy

- 102 pre-menopause women prepared for hysterectomy due to dysmenorrhea with or without pelvic pain: Transvaginal ultrasound assessment and uterine posterior wall biopsy with 14G needle

| | sensitivity | specificity |
|--------|-------------|-------------|
| TVUSS | 82.7 | 67.1 |
| Biopsy | 44.8 | 95.9 |

- ▶ 2003: Transvaginal ultrasound and biopsy in 100 patients presented with symptoms of adenomyosis: 98% sensitivity , 100% specificity

▶ Hysterctomy

- Golden standard
- Provide accurate diagnosis, affect chances of pregnancy

Verhulst et al. *Hum Reprod* 2003; 18: 2884

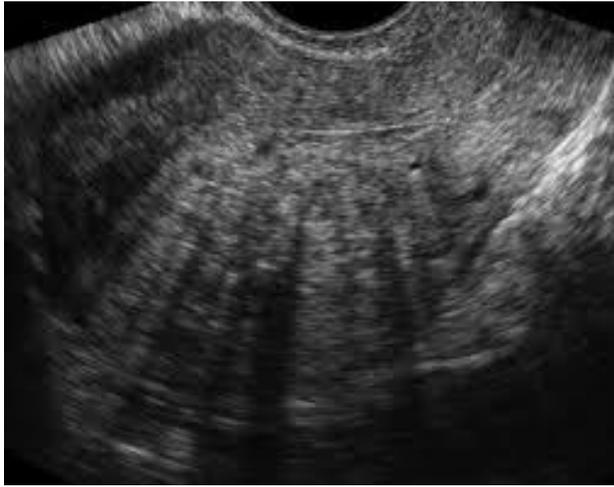
Transvaginal ultrasound(TVU)

▶ Ultrasound

- TVU :sensitivity 50% – 87%
- Better than transabdominal ultrasound
- Limited in cases of big uterus and fibroids

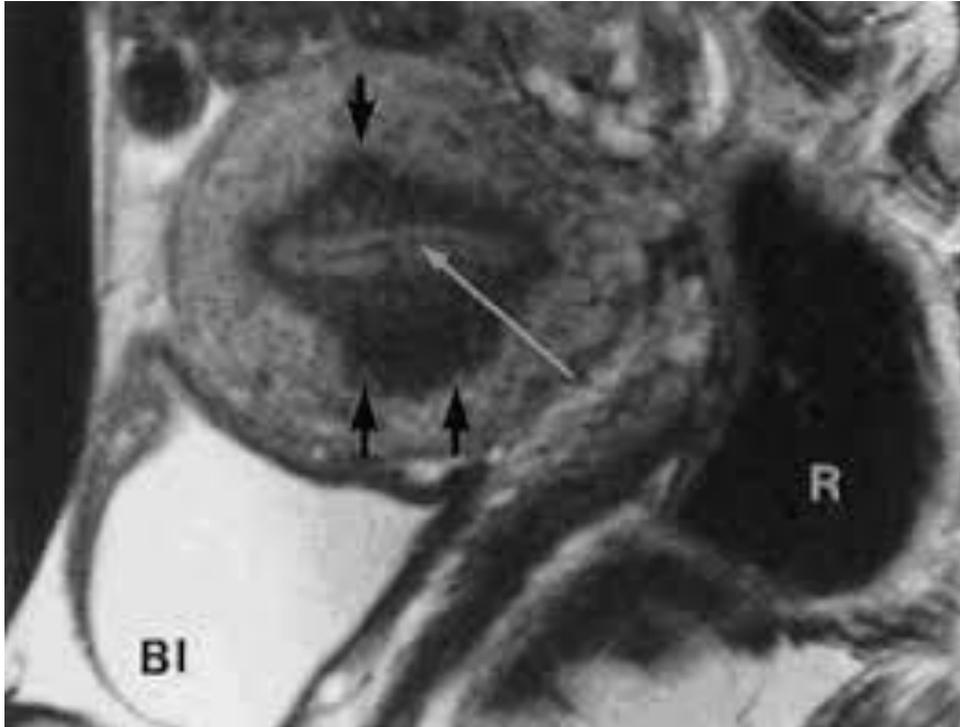
Levgur M. J Reprod Med. 2007; 52: 177

Diagnosis: more than 1 of following signs in TVU



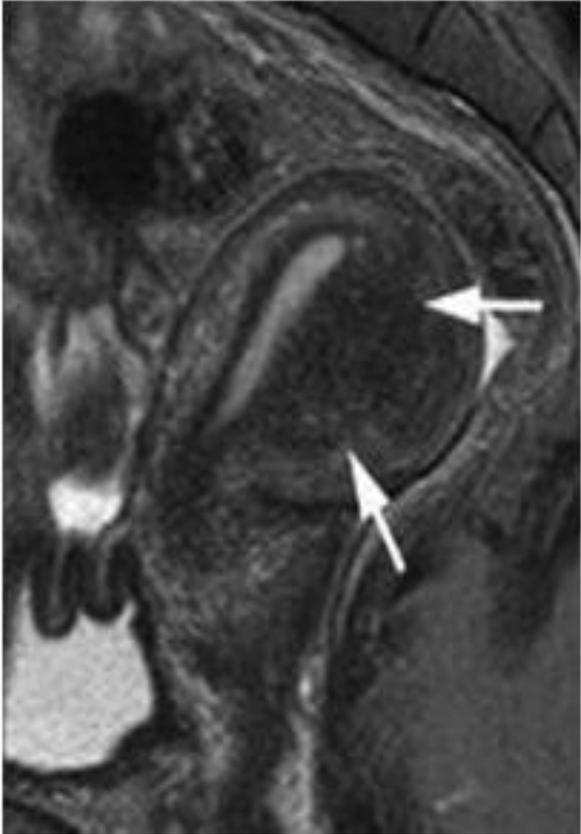
- ▶ Uterine enlargement: Spherical uterus
- ▶ Obscure endometrial/myometrial border
- ▶ Subendometrial echogenic linear striations
- ▶ Heterogeneous echo texture
- ▶ The uterine wall thickening can show anteroposterior asymmetry
- ▶ Cystic anechoic spaces or lakes in the myometrium

MRI diagnosing



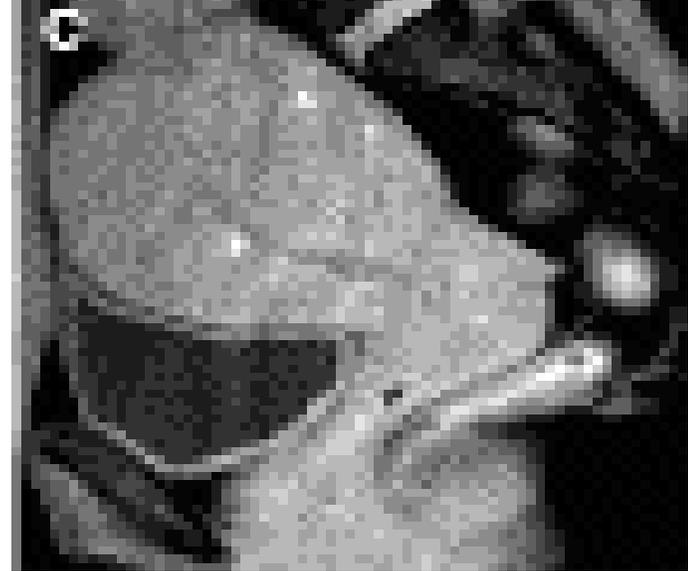
▶ MRI significance

- sensitivity 73 to 96%
 - MRI
 - Thickening of the transition zone focally or diffusely
 - A thickness of 12 mm or greater has been shown to be associated with adenomyosis.
 - Thickening of the transition zone JZ diffusely, low-signal-intensity
- Fusi . Best Pract Res Clin Obstet Gynaecol. 2006; 20: 479
- MRI : differential diagnosis between adenomyosis and fibroids



MRI Fibroids





- ▶ 42 year-old patient presented with dysmenorrhea : Diagnosis after surgical adenomyosis MRI pre-op:
 1. Coronal view: Thickening of JZ in posterior wall. White arrow shows the posterior wall is thicker due to asymmetric adenomyosis
 2. Transverse view of uterine cavity shows white spots are subendometrial cysts at the upper and right side
 3. Coronal view: 2 subendometrial cysts contained blood, increased echogenicity

TVU

MRI

| | | |
|--------------------|-----------------------------|-----------------------------|
| Sensitivity | 72 (95% CI, 65%–79%) | 77 (95% CI, 67%–85%) |
| Specificity | 81 (95% CI, 77%–85%) | 89 (95% CI, 84%–92%) |

TVU and MRI: equal accurately diagnosis

Meta analysis: comparing TVU and MRI to pathology concluded that two technique have high accuracy. MRI show standard imagine and no affection in cases of fibroids

However, TVU needs experiential imaging doctors

JZ and Infertility

- ▶ Thickening of JZ decreases the rate of pregnancy in IVF
- ▶ (Lesny and Killick, 2004). Piver(2005)
- ▶ JZ <10mm: pregnancy rate 45%
- ▶ 10–12mm: 16%
- ▶ > 12mm: 5%

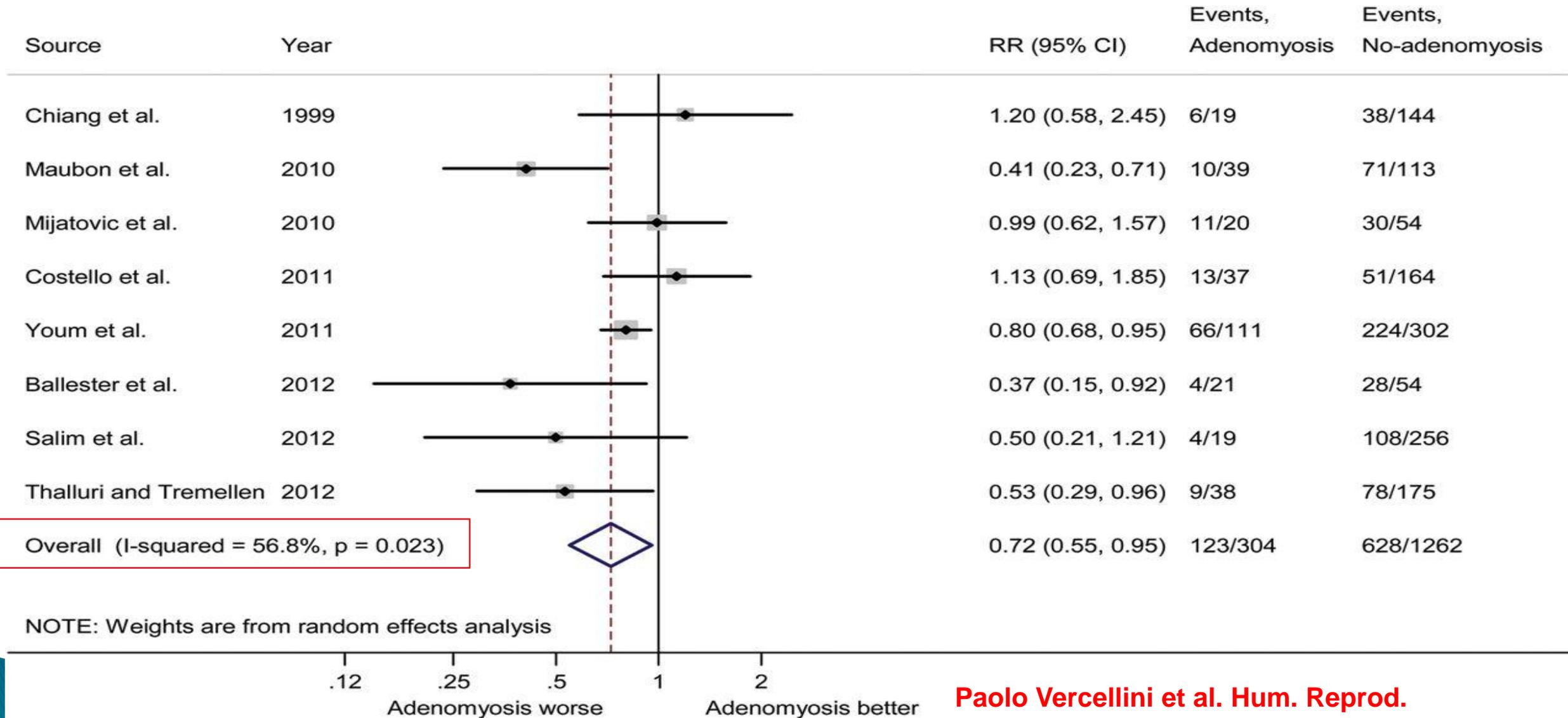
(Maubon et al., 2010)

- ▶ 152 patients with implantation failure
- ▶ Junctional zone thickness increase was significantly correlated with implantation failure at IVF
- ▶ implantation failure rate was 95.8% for patients with an average junctional zone superior to 7 mm and a maximal junctional zone superior to 10 mm, versus 37.5% in other patient groups ($P < 0.0001$), independently from the cause of infertility or patients' age

Paolo Vercellini et al. Hum. Reprod. 2014

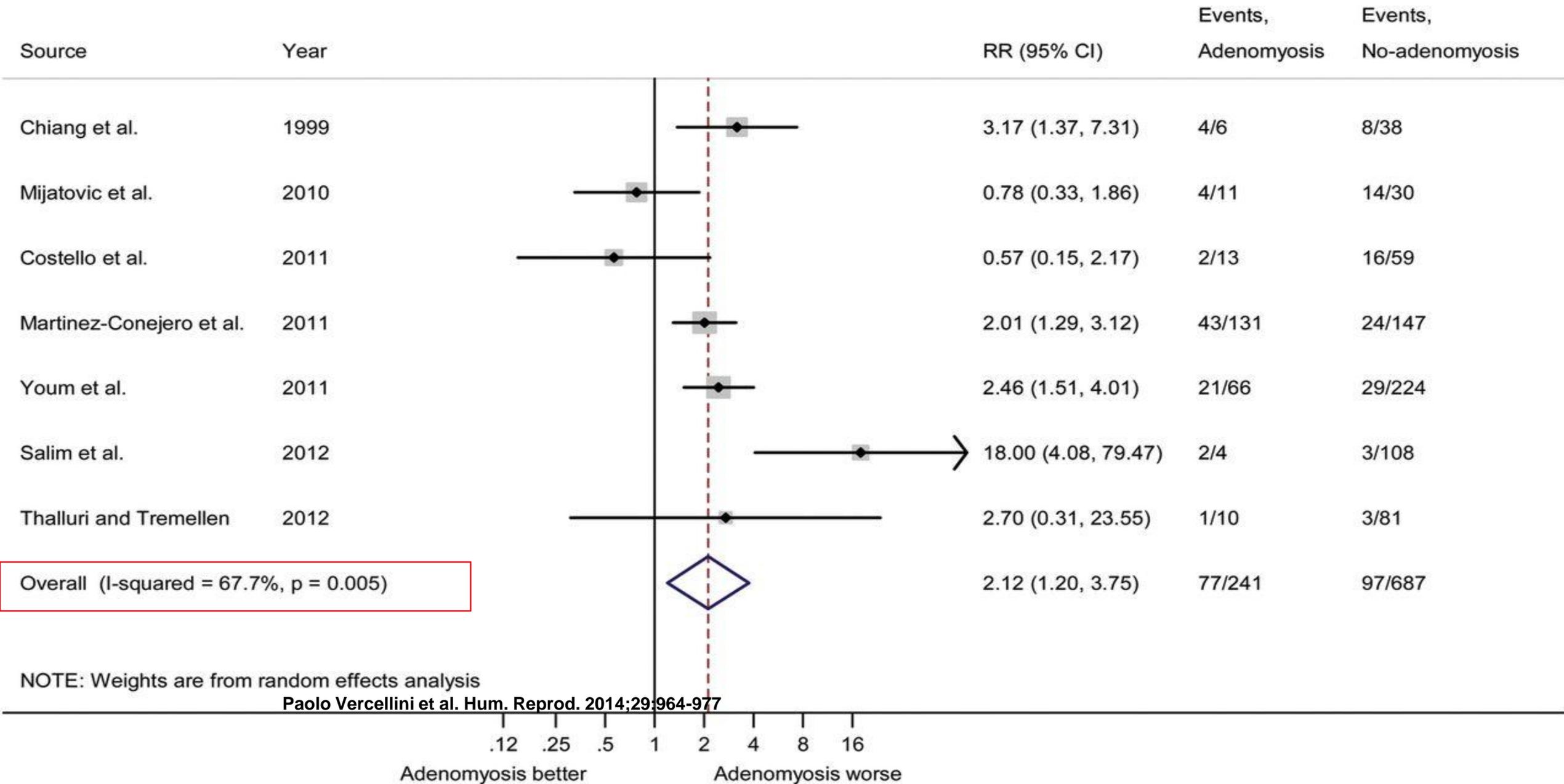
- ▶ Meta analysis: 9 selected studies, 1865 patients
- ▶ The clinical pregnancy rate achieved after IVF/ICSI was 123/304 (40.5%) women with adenomyosis versus 628/1262 (49.8%) in those without adenomyosis ($p = 0.023$)
- ▶ The rate of miscarriages is higher in women with adenomyosis

The clinical pregnancy rate achieved after IVF/ICSI in women with or without adenomyosis



Paolo Vercellini et al. Hum. Reprod. 2014;29:964-977

Miscarriages rate after IVF/ICSI in women with or without adenomyosis.



Pathophysiology

puberty

reproductive age

Menopause

Dysmenorrea

Infertility
miscarriage

pelvic pain
Abdominal
pain

Internal Treatment

- ▶ Assisted reproductive: GnRH agonist

- Pituitary gland inhibition
- GnRH agonists changes inflammation response of endometrial

Khan. Hum Reprod 2010;25:642

- GnRh agonists decreases thickness of JZ

Imaoka. J Magn Reson Imaging 2002;15:2850

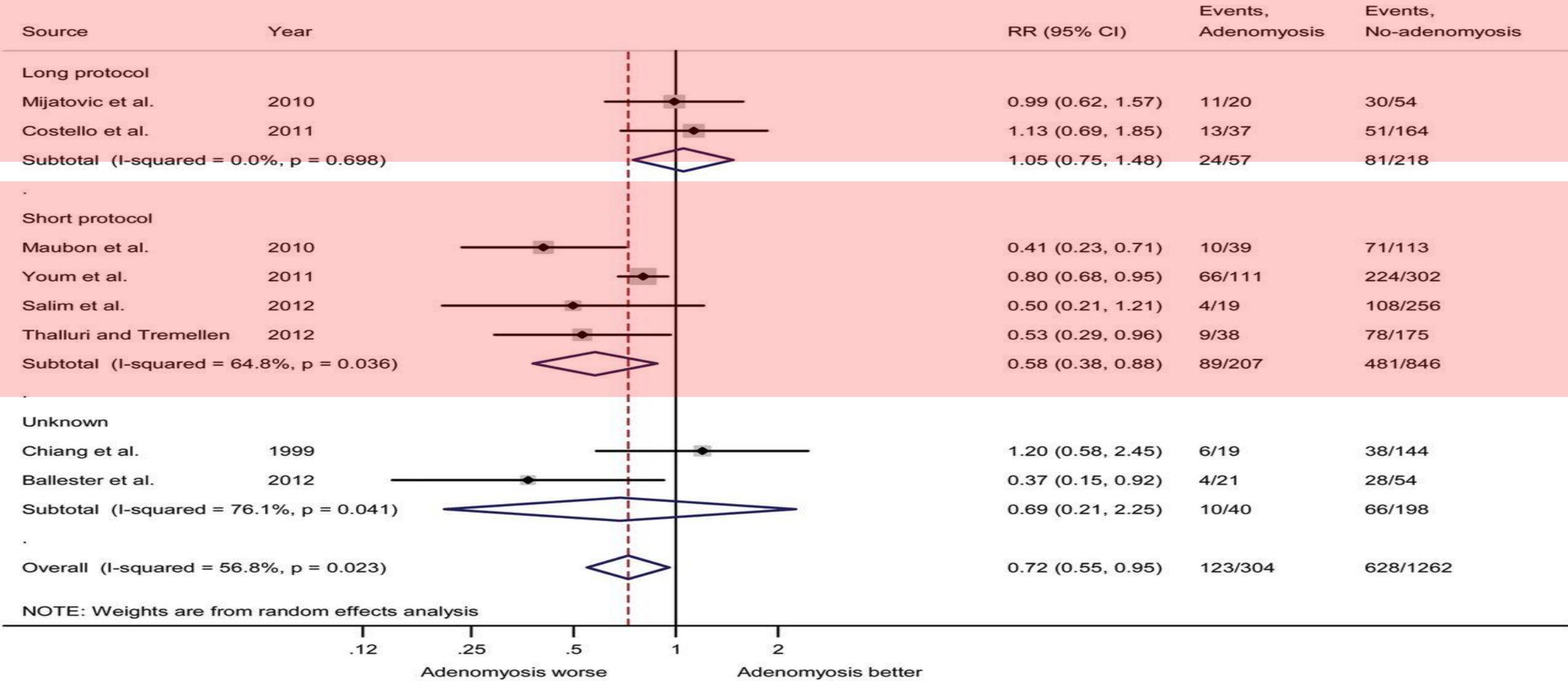
Internal Treatment Điều trị nội khoa

- ▶ ART: GnRH agonist
 - Clinical cases show GnRH agonist improved pregnancy rate in patients with adenomyosis

Tremellen. Aust N Z J Obstet Gynaecol 2011;51: 280

Vercilini. Human Reproduction 2014, 29: 964

Clinical pregnancy rate in patients with adenomyosis undergoing IVF/ICSI after a short or long protocol down regulation



Internal treatment

- ▶ ART: GnRH agonist
 - Improved pregnancy rate after freezed embryo transfer

Niu Z1. Gynecol Endocrinol. 2013, 29:1026

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Updates on GnRHa in infertility treatment in patients with adenomyosis and endometriosis

- ▶ GnRHa diminishes the expression of Aromatase cytochrome p450 (over expression in endometriosis and adenomyosis converting androgens to estrogens) (Ishihara 2003)
- ▶ GnRH analogues did not significantly influence the extent of decidualization of endometrial stromal cells. In addition, no adverse effect of GnRH analogues was seen on human blastocyst invasion.(Klemmt 2000)
- ▶ GnRHa inhibits NO synthase, suppresses production of peroxynitrit – a tissue injury substance (kamada 2000)
- ▶ GnRHa : treating endometriosis before IVF may improve pregnancy rate (Tavmergen 2007)

Surgical treatment

TOTAL HYSTERECTOMY WITH OR WITHOUT SALPINGO-OOPHORECTOMY IS THE THOROUGH METHOD

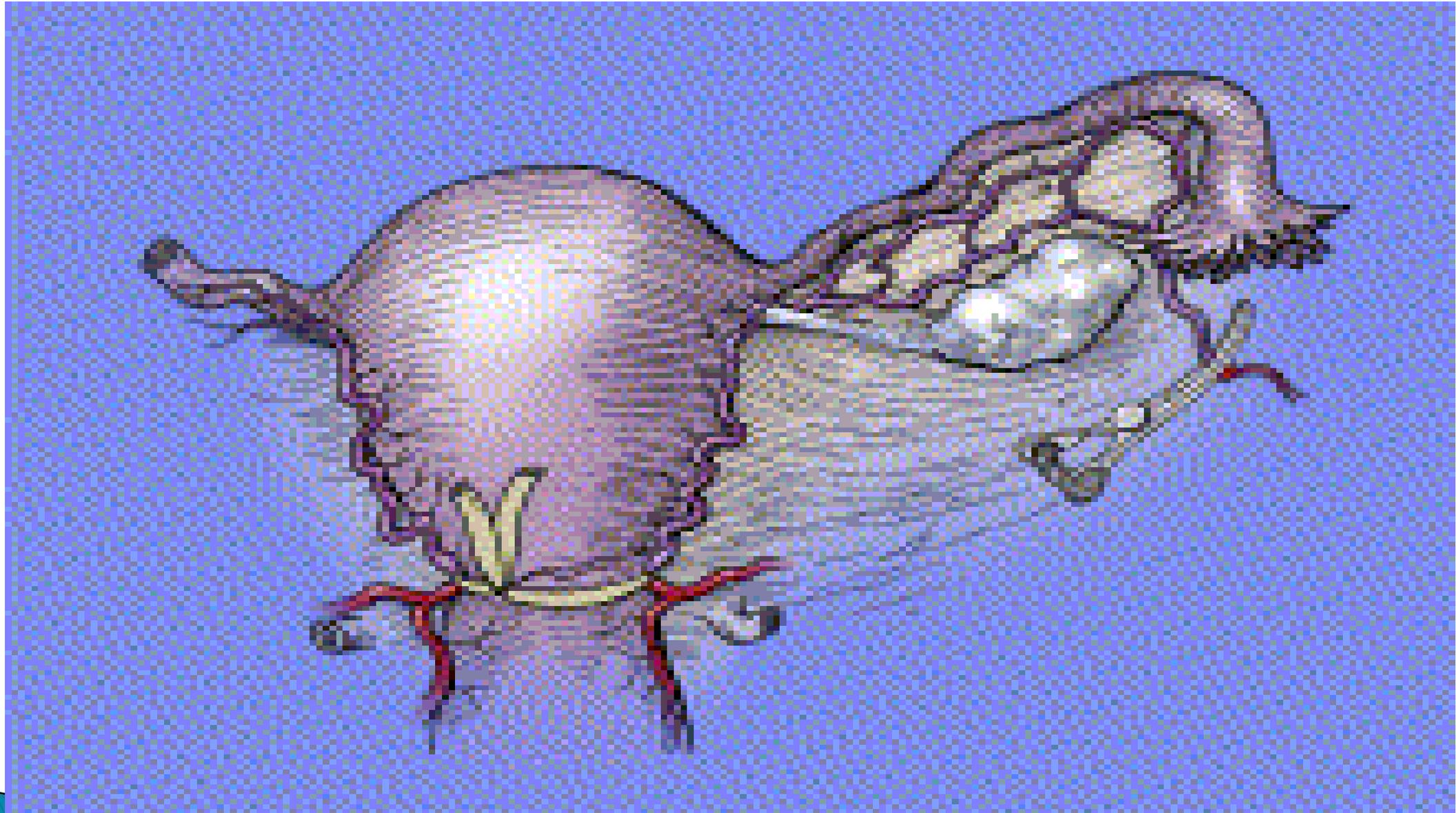
PRESERVED SURGERY

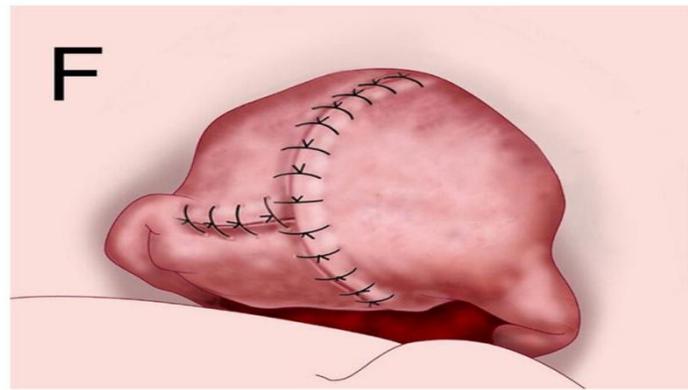
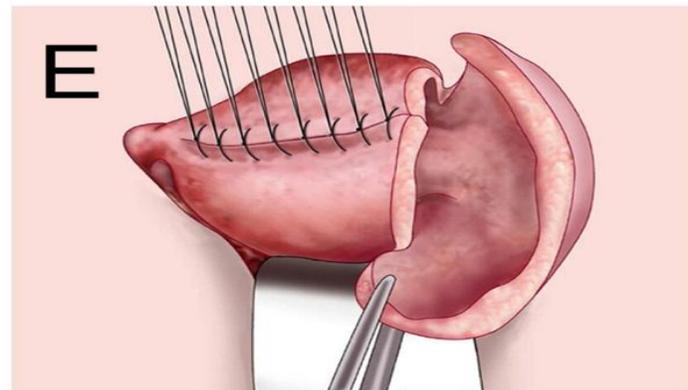
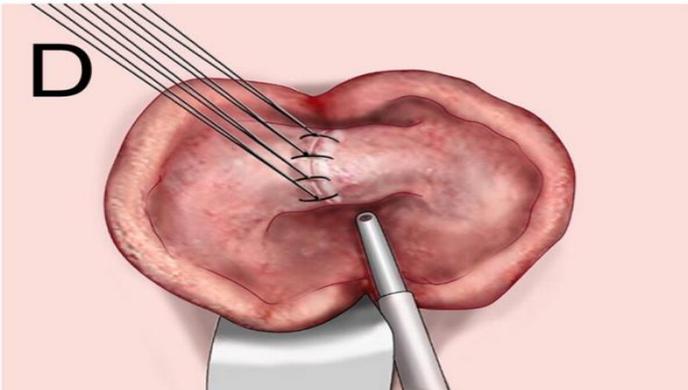
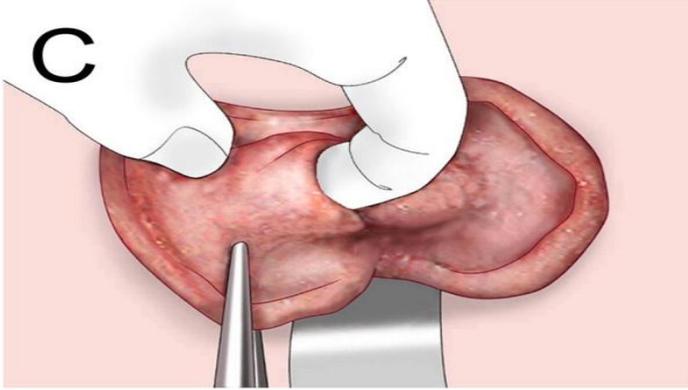
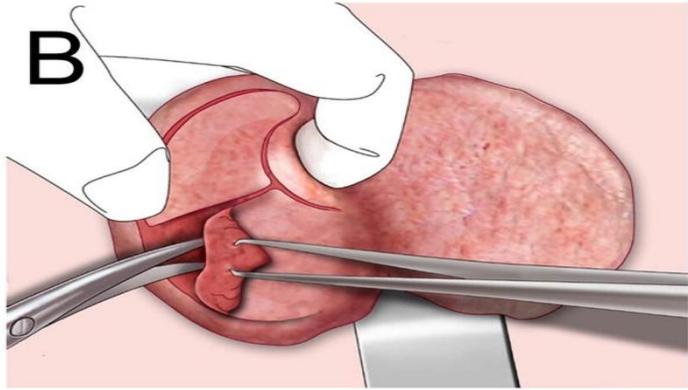
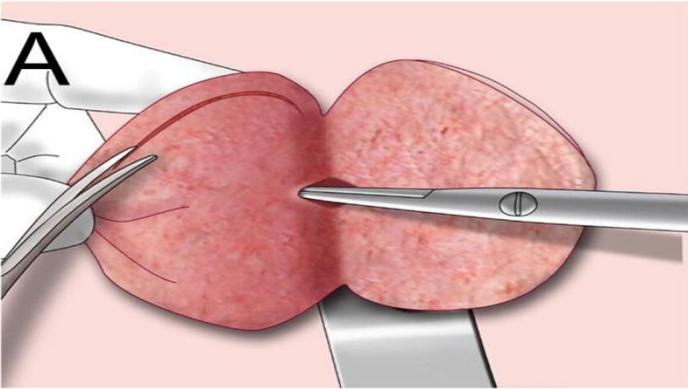
- ▶ A preserved uterus technique undergo in patient with adenomyosis wish to conceive: OSADA 2011.
- ▶ 38 cases of adenomyosis in anterior wall , (36,5%)
- ▶ 44 cases in posterior wall(42,3%)
- ▶ 22 ca in both anterior and posterior wall(2,2%)
- ▶ Technique of adenomyomectomy
- ▶ Adenomyotic tissues are radically excised and the uterine wall is reconstructed by a triple-flap method, without overlapping suture lines. This should effectively prevent uterine rupture in subsequent pregnancies
- ▶ Of 26 women who wished to conceive, 16 became pregnant and 14 (53.8%) carried their pregnancy to term, delivering a healthy infant
- ▶ No cases of uterine rupture
- ▶ Need more research before widely accepted

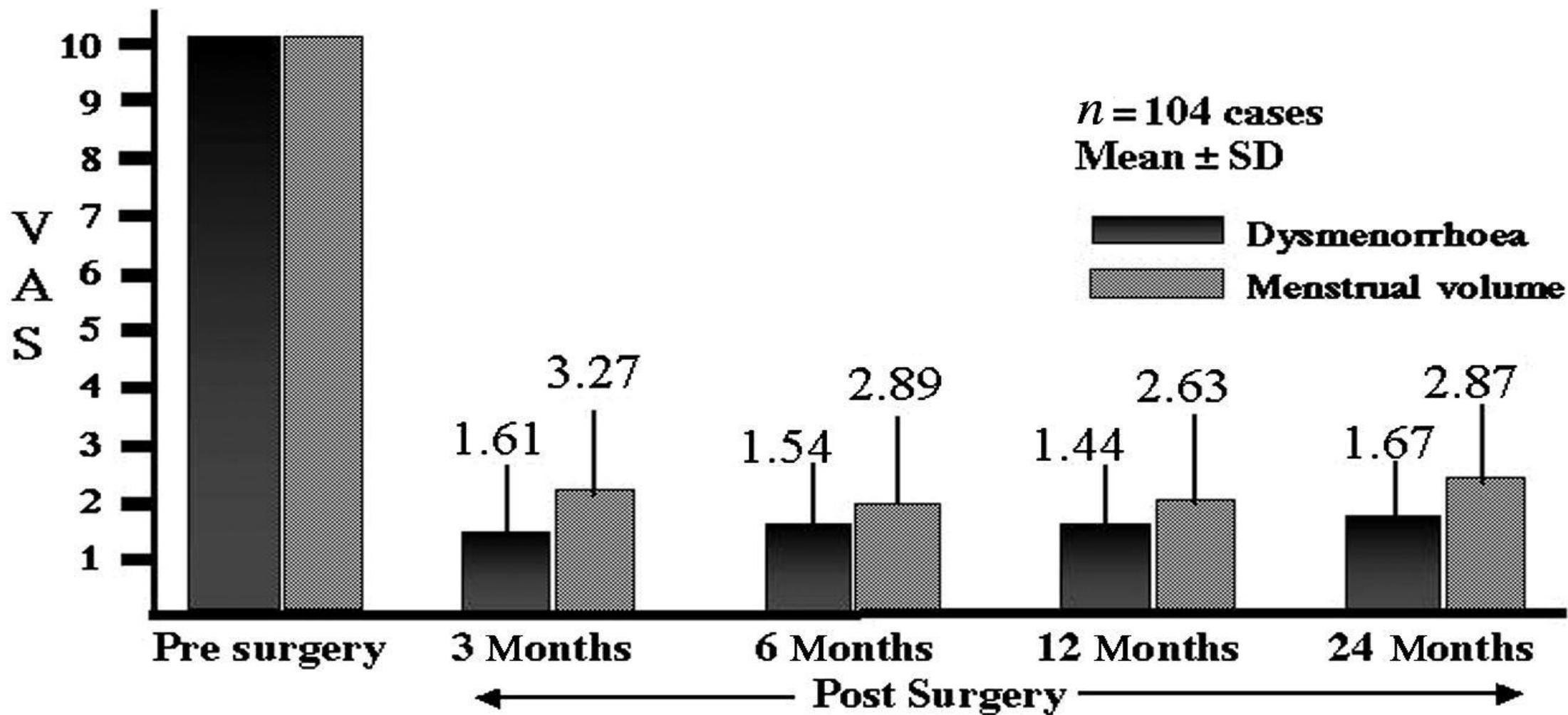
Table 1 Outcome of adenomyomectomy by the triple-flap method as an infertility treatment (June 1998–August 2008).

| <i>Parameter</i> | <i>Study data</i> |
|------------------------------|--------------------|
| Patients | 104 |
| Age (years) | 37.6 ± 6.9 |
| Patients wishing to conceive | 26/104 (25.5) |
| Pregnancies | 16/26 (61.5) |
| Spontaneous | 4 |
| IVF | 12 |
| Outcomes | |
| Elective Caesarean section | 14 |
| Abortion | 2 (16 and 5 weeks) |









Internal and surgical treatment

- ▶ In 1993 the group of Moghissi ([Hirata et al., 1993](#)) was the first to obtain a pregnancy after a 6-month course of nafarelin acetate; following discontinuation of treatment, the patient conceived quickly, but later experienced a spontaneous abortion
- ▶ Silva 1994: published the first term pregnancy in a patient with a 10-year history of secondary infertility, after 5 months of therapy with GnRH
- ▶ Ozaki 1999: 1 patient conceived after GnRHa therapy followed by preserved surgery : 5 years of second-infertility , GnRHa therapy treating dysmenorrhea. After 24 weeks, the uterus return to normal size, MRI revealed a localized low-signal-intensity myometrial mass with well-defined borders, which was easily resected.
- ▶ 2000: Wang : treated a series of patients with microsurgical resection of the visible adenomyotic areas followed by treatment of GnRHa and reported pregnancies in three patients.

| | Surgery | GnRH |
|-------------------------|----------------|-------------|
| Clinical pregnancy rate | 46.4% | 10.8% |
| Live birth | 32.1% | 8.1% |

J ObstetGynaecol Res. 2009 35: 495

- ▶ Conservative surgery or combination therapy provides more effective and longer durable symptom control in the management of symptomatic women with extensive uterine adenomyosis, compared with GnRH agonist alone
- ▶ Reproductive performance was also better in patients treated with conservative surgery with/without GnRH agonist.

Levonorgestrel –releasing intrauterine system (MIRENA)

- ▶ Pain relieve (fedele 1997)
- ▶ No prove of affect in infertile women

Uterine artery embolisation

- ▶ NICE guideline 2013: uterine artery embolisation affects in relieving pain in patient with adenomyosis wish to preserve their uterus
- ▶ *The National Institute for Health and Care Excellence (NICE) issued full guidance to the NHS in England, Wales, Scotland and Northern Ireland on Uterine Artery Embolisation for treating adenomyosis, in December, 2013.*

High intensity focused ultrasound –HIFU

- ▶ HIFU utilizes an external ultrasound energy source to induce thermal ablation at a given depth through the intact skin
- ▶ Ablation through HIFU is a new technique utilized in the treatment of patients with a variety of malignancies and its application to adenomyosis has recently been reviewed , mostly investigated in China, offers advantages over current conservative treatments, at least in patients with localized adenomyosis (2010)
- ▶ the main histological changes are coagulative necrosis of the targeted localized adenomyosis, associated to vascular damage, no haemorrhage in treated lesions.
- ▶ Only one case of successful treatment of adenomyosis–associated infertility with HIFU has been published

Surrogation

- ▶ A solution in cases of continuous implantation failure

Conclusions

- ▶ Developments in diagnosing adenomyosis: TVU and MRI
- ▶ MRI is a non-invasive technique that allows to measure thickness of JZ
- ▶ Treatment of adenomyosis depends on patient's age and her wish to conceive
- ▶ GnRHa therapy improves pregnancy rate in IVF
- ▶ Surgery + GnRHa: a solution needs more research in OSADA technique to preserve the uterus