

The USE of HORMONAL THERAPY AFTER SURGICAL MENOPAUSE with ENDOMETRIOSIS

Yücel Karaman M.D.

Professor

Brussels Woman Health, Endoscopy and IVF Center

Istanbul – TURKEY

Cliniques Edith Cavell- CHIREC

Brussels - BELGIUM

www.brukseltupbebek.com

Strategy for HRT after surgical menopause

- Best QOL after HT
- Less recurrence
- Less side-effects
- Easy to use for a long time
- Coast
- Less risk of malignant transformation

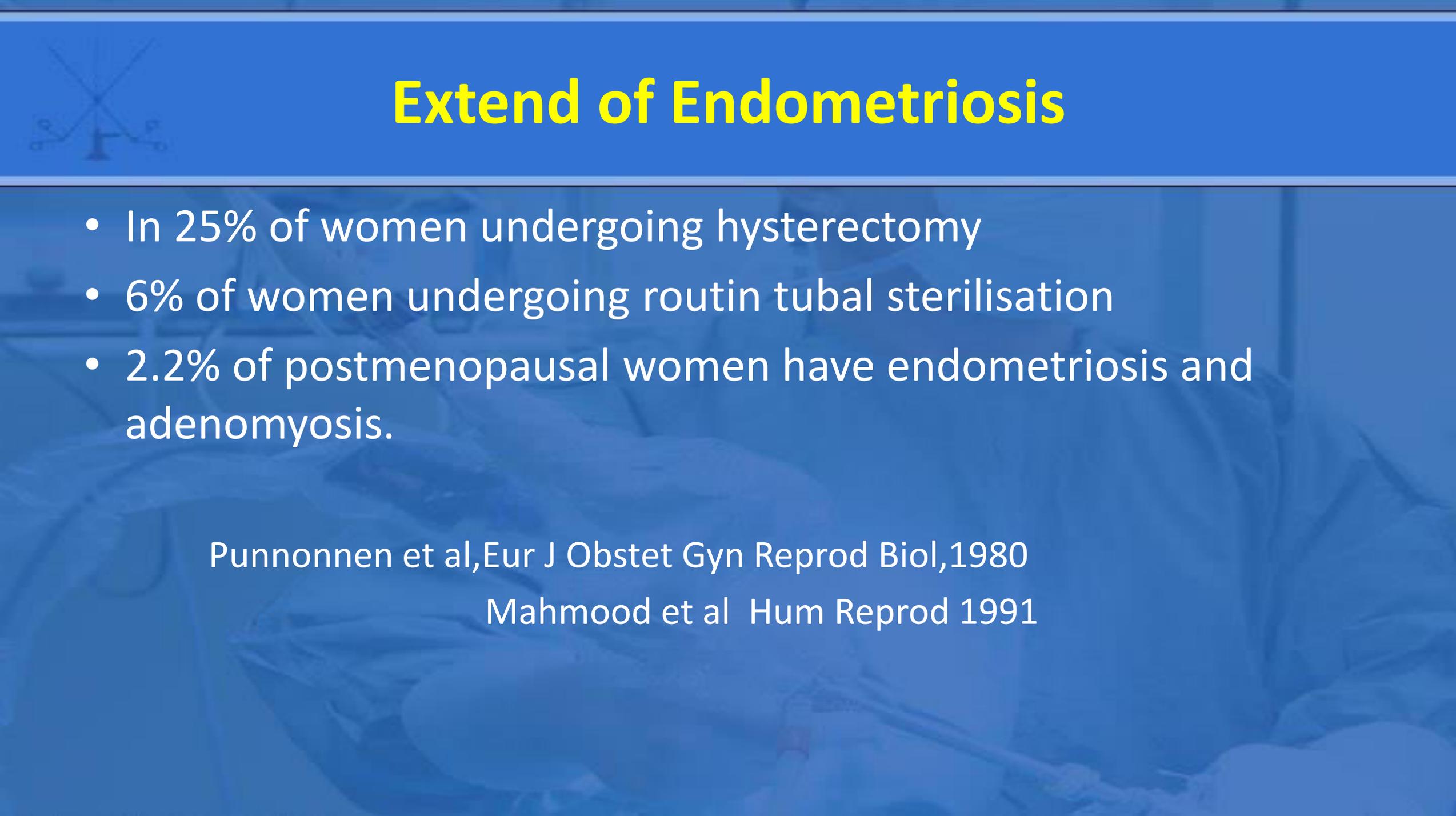


Objective

- Assess the recurrence risk of endometriosis after HRT
- Adjust the risk of malignant transformation after HRT
- Assess HRT for LASH

HRT

- HRT remains the most efficient treatment to alleviate climacteric symptoms
- Benefits might be more important than harm in 50-60 year old women
- Younger women with surgical menopause or POF may use HRT for many years, until the age of the natural menopause



Extend of Endometriosis

- In 25% of women undergoing hysterectomy
- 6% of women undergoing routine tubal sterilisation
- 2.2% of postmenopausal women have endometriosis and adenomyosis.

Punnonen et al, Eur J Obstet Gyn Reprod Biol, 1980

Mahmood et al Hum Reprod 1991

Concomitant Cancer, Infection and Endocrine Disease Among Endometriosis Patients

	Women with endometriosis, n (%)	Prevalence among women with endometriosis (per 1000)	Estimated prevalence in the general U.S. female population (per 1000)	Prevalence odds ratio	95% CI	P	Sensitivity analysis threshold ^d
Cancers (25):							
Melanoma	29 (0.67)	6.70	1.76	3.81	2.60, 5.56	<0.0001	>25 / >75
Breast	16 (0.37)	3.69	6.82	0.54	0.32, 0.90	0.016	>90 / >90
Ovary	10 (0.23)	2.31	0.67	3.43	1.74, 6.54	<0.0001	25 / 50
Non-Hodgkin's lymphoma	2 (0.05)	0.46	0.55	0.84	0.14, 3.37	NS	<i>b</i>
Infectious diseases:							
Recurrent upper respiratory infections (26)	1523 (35.17)	351.65	70.14	7.19	6.73, 7.68	<0.0001	>50 / >50
Candidiasis (27)	1372 (37.65)	376.51	374.88	1.01	0.87, 1.16	NS	<i>b</i>
Recurrent vaginal infections (28)	1267 (29.25)	292.54	100.00	3.72	3.48, 3.98	<0.0001	50 / 50
History of mononucleosis (29)	596 (13.76)	137.61	900.00	0.02	—	<0.0001	>90 / >90
Endocrine diseases:							
Addison's disease (30) ^f	10 (0.23)	2.31	0.09	—	—	<0.0001	<i>b</i>
Cushing's syndrome (28) ^f	4 (0.09)	0.92	0.00	—	—	<0.0001	<i>b</i>
Other diseases:							
Mitral valve prolapse (31)	632 (14.59)	184.36	76.19	2.74	2.32, 3.24	<0.0001	25 / 50
Congenital birth defects (26)	118 (2.72)	27.25	30.00	0.91	0.75, 1.09	NS	<i>b</i>

	Crude		Stratified only		Stratified and adjusted	
	OR (95% CI)	p value	OR (95% CI)*	p value	OR (95% CI)†	p value
Invasive	1.49 (1.34-1.65)	<0.0001	1.53 (1.37-1.70)	<0.0001	1.46 (1.31-1.63)	<0.0001
Clear-cell	3.73 (3.04-4.58)	<0.0001	3.44 (2.78-4.27)	<0.0001	3.05 (2.43-3.84)	<0.0001
Endometrioid	2.32 (1.94-2.78)	<0.0001	2.20 (1.82-2.66)	<0.0001	2.04 (1.67-2.48)	<0.0001
Mucinous	1.09 (0.76-1.58)	0.63	1.04 (0.71-1.51)	0.86	1.02 (0.69-1.50)	0.93
High-grade serous	1.11 (0.96-1.29)	0.16	1.16 (1.00-1.35)	0.056	1.13 (0.97-1.32)	0.13
Low-grade serous	2.02 (1.38-2.97)	<0.0001	2.22 (1.48-3.31)	<0.0001	2.11 (1.39-3.20)	<0.0001
Borderline	1.26 (1.05-1.50)	0.012	1.19 (0.99-1.43)	0.062	1.12 (0.93-1.35)	0.24
Mucinous	1.27 (0.97-1.67)	0.078	1.19 (0.90-1.57)	0.23	1.12 (0.84-1.48)	0.45
Serous	1.31 (1.05-1.63)	0.015	1.28 (1.02-1.61)	0.034	1.20 (0.95-1.52)	0.12

OR=odds ratio. *Stratified by age (5 year categories), ethnic origin (non-Hispanic white, Hispanic white, black, Asian, and other). †Stratified by age (5 year categories), ethnic origin (non-Hispanic white, Hispanic white, black, Asian, and other), and adjusted for duration of oral contraceptive use (never, <2 years, 2-4.99 years, 5-9.99 years, ≥10 years), and parity (0, 1, 2, 3, ≥4 children).

Table 3: Association between history of endometriosis and the histological subtypes of ovarian cancer



Menopause in Endometriosis

- May be part of the treatment
 - Medically induced by GnRH
 - Surgically induced after BSO
- May be a complication of ovarian surgery
- May occur naturally

TLH vs. TLH+BSO

Endometriosis Associated Pain

	Hysterectomy (n=29)	TH-BSO (n=109)
Recurrent Pain	62 %	10 %
Re-operation	31 %	4 %
Relative Risk for Pain Recurrence	6.1 (95% CI 2.5-14.6)	1
Relative Risk for Re-operation	8.1 (95% CI 2.1 31.3)	1



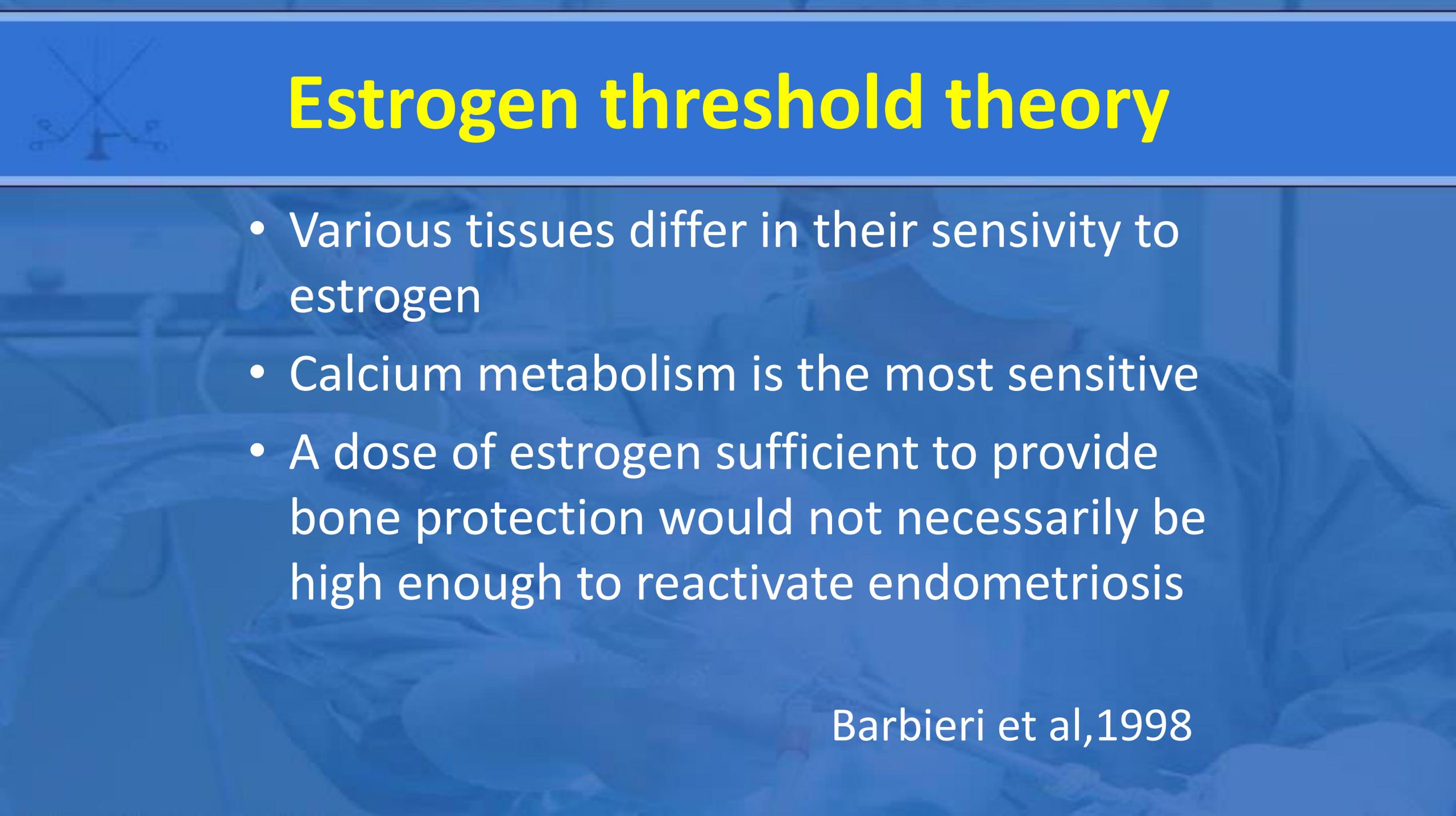
Surgical Menopause

- Patients are relatively young
 - Start HRT after Surgery to prevent
 - Urogenital atrophy
 - Loss of libido
 - Bone loss
 - Prevention of cardiovascular disease
- in early menopause



Recurrence during HRT

- The risk of endometriosis recurrence during HRT is not completely definitive.
- Theoretically, estrogen therapy can reactivate the disease, even where there has been apparent surgical removal of all the endometriotic tissue, but the risk appears to be small.



Estrogen threshold theory

- Various tissues differ in their sensitivity to estrogen
- Calcium metabolism is the most sensitive
- A dose of estrogen sufficient to provide bone protection would not necessarily be high enough to reactivate endometriosis

Barbieri et al, 1998

E or E+P

- **E+P** HRT:oral combined,Estrogen TTS+cyclic MPA
 - 0-2.4 % recurrence of endometriosis
 - 0-4 % recurrence of pain
- **Estrogen only**:oral or Estrogen TTS
 - 2% recurrence of endometriosis
 - 6% recurrence of symptoms

Moen et al Maturitas 2010

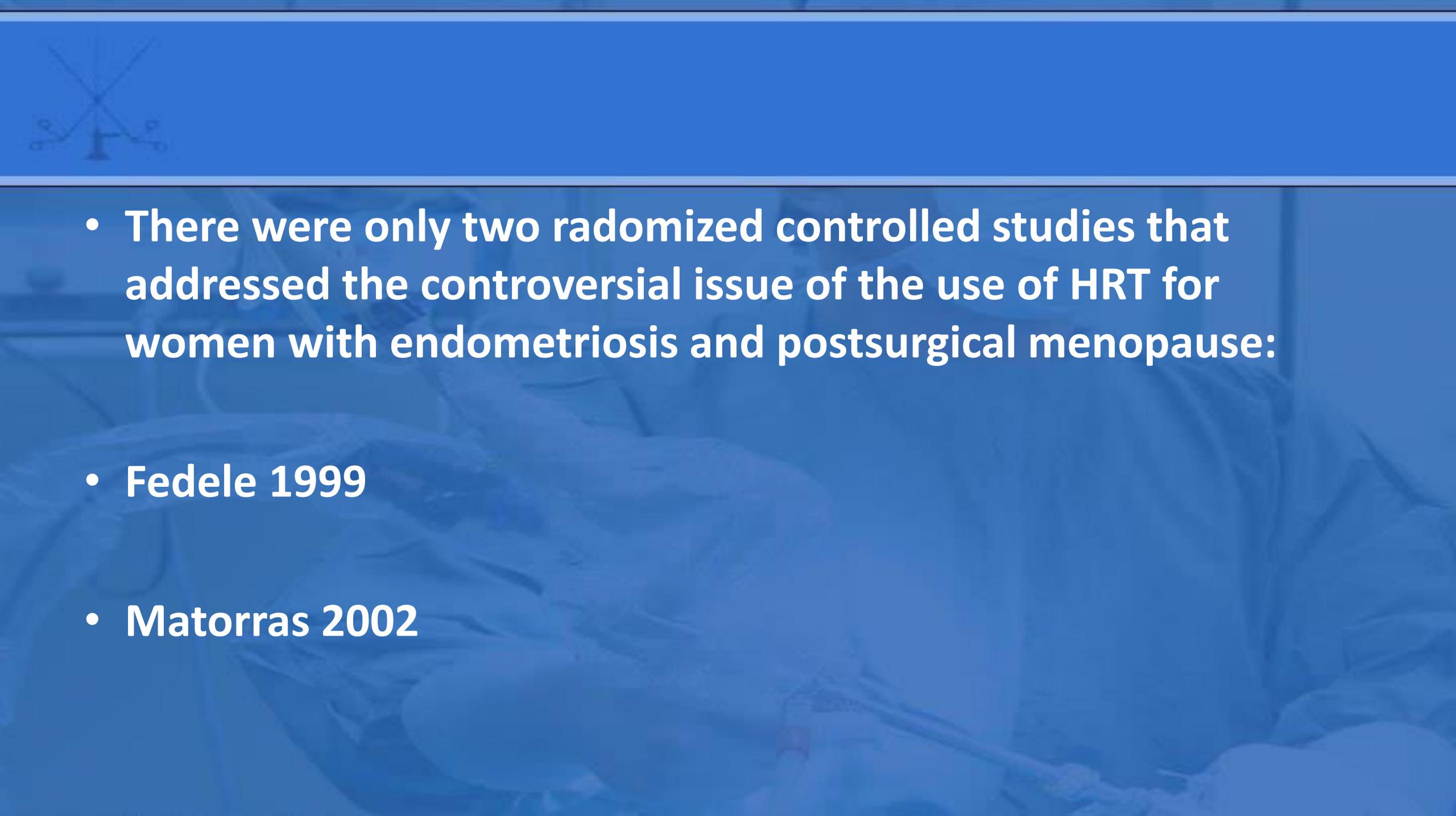
Mattaras et al Fertil Steril 2002 , Fedele et al Maturitas 1999

Hormone therapy for endometriosis and surgical menopause (Review)

Al Kadri H, Hassan S, Al-Fozan HM, Hajeer A



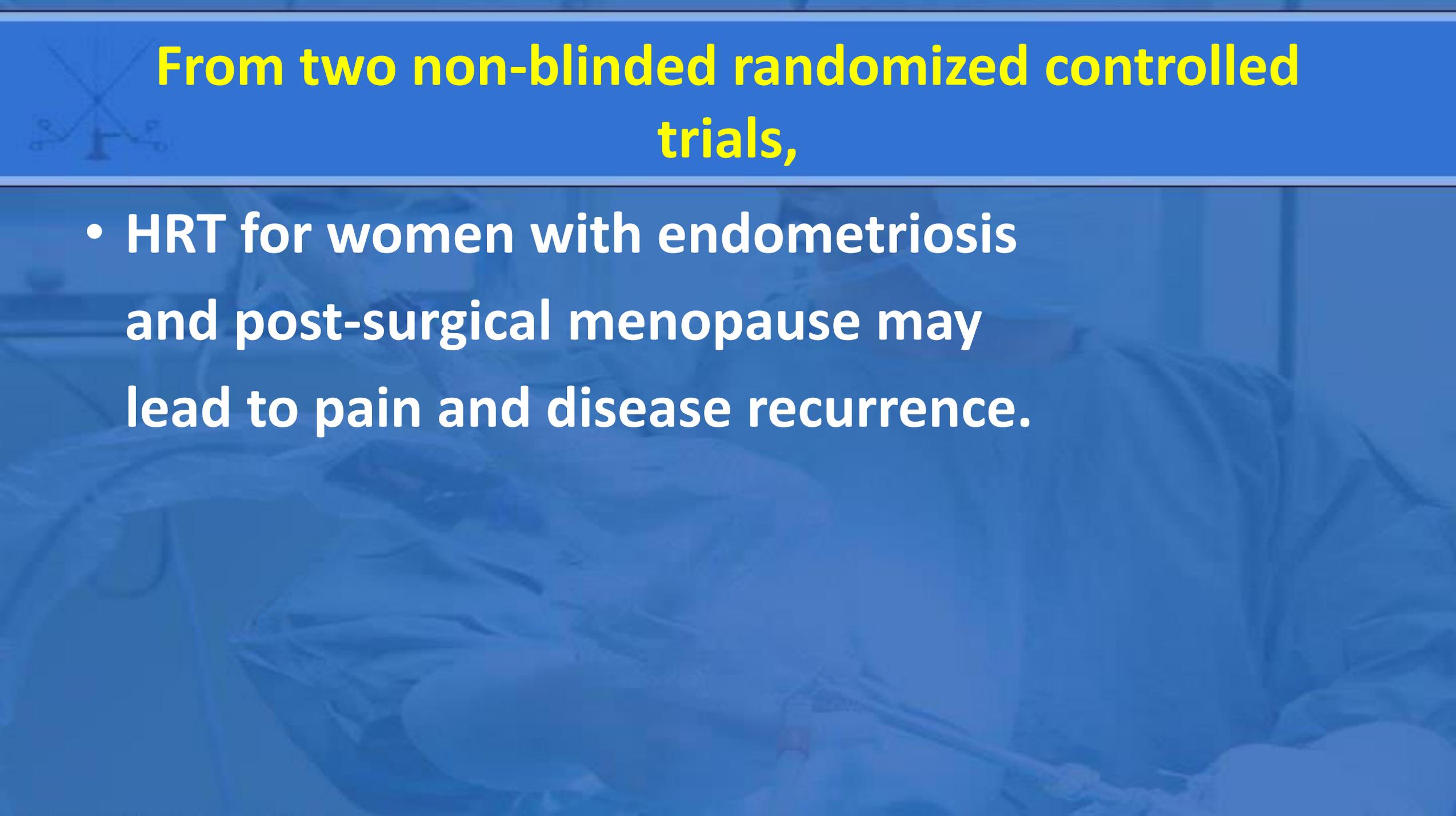
**THE COCHRANE
COLLABORATION®**



- There were only two randomized controlled studies that addressed the controversial issue of the use of HRT for women with endometriosis and postsurgical menopause:

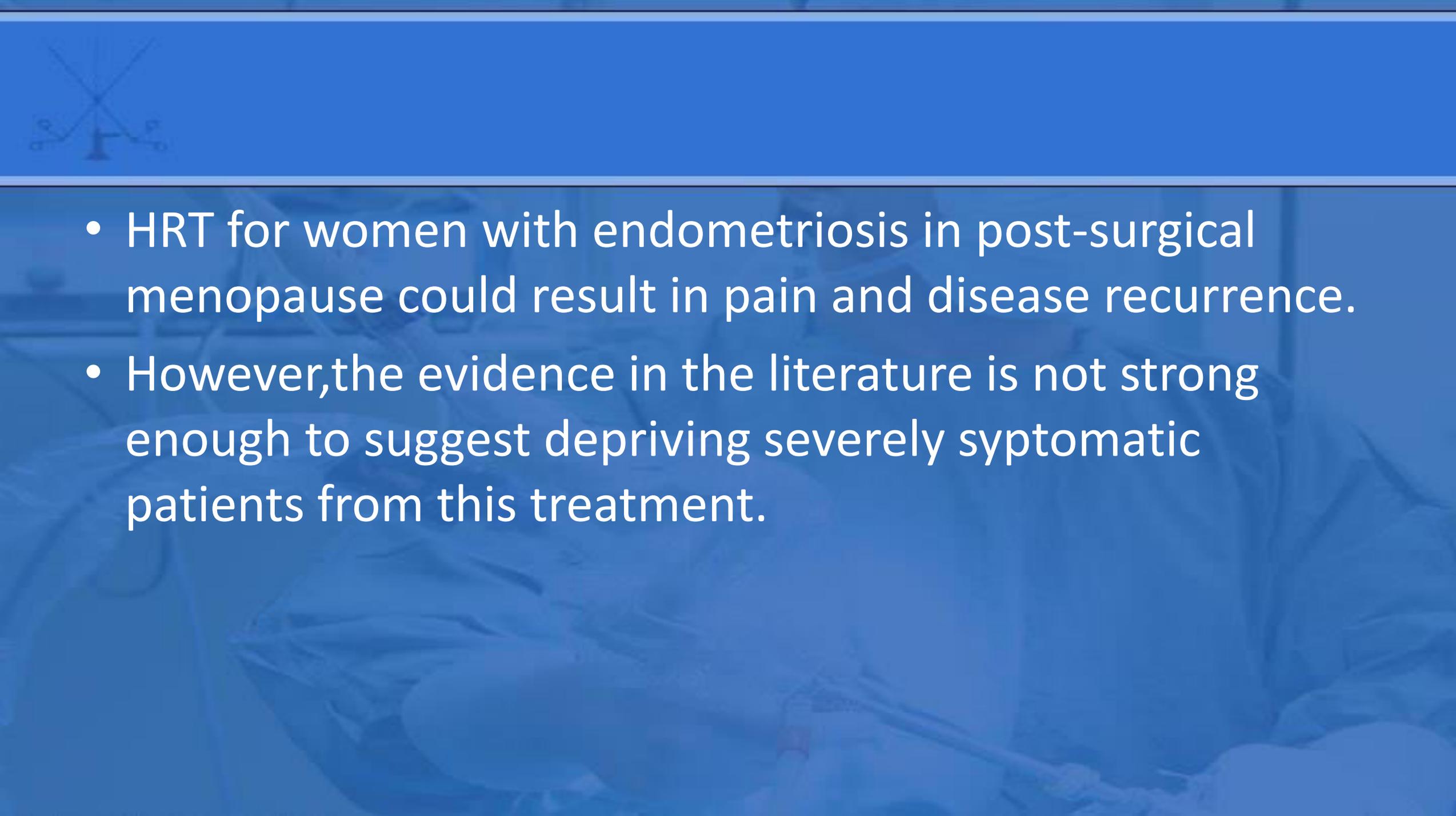
- Fedele 1999

- Matorras 2002



From two non-blinded randomized controlled trials,

- **HRT for women with endometriosis and post-surgical menopause may lead to pain and disease recurrence.**

- 
- HRT for women with endometriosis in post-surgical menopause could result in pain and disease recurrence.
 - However, the evidence in the literature is not strong enough to suggest depriving severely symptomatic patients from this treatment.

Higher Recurrence Risk after HRT

- Presence of DIE
- Residual disease on intestine,bladder
- Peritoneal involvement >3 cm
- Incomplet surgery for endometriosis (6%)

Residual disease despite TAH+BSO

Moen et al. Maturitas 2010

Palep- Singh et al. Menopause Int 2009



Timing of HRT after surgery

- Pain recurrence
 - 7% in early HRT group (within 6 weeks of surgery)
 - 20% in late HRT group (after 6 weeks of surgery)

We could recommend starting HRT shortly after surgery

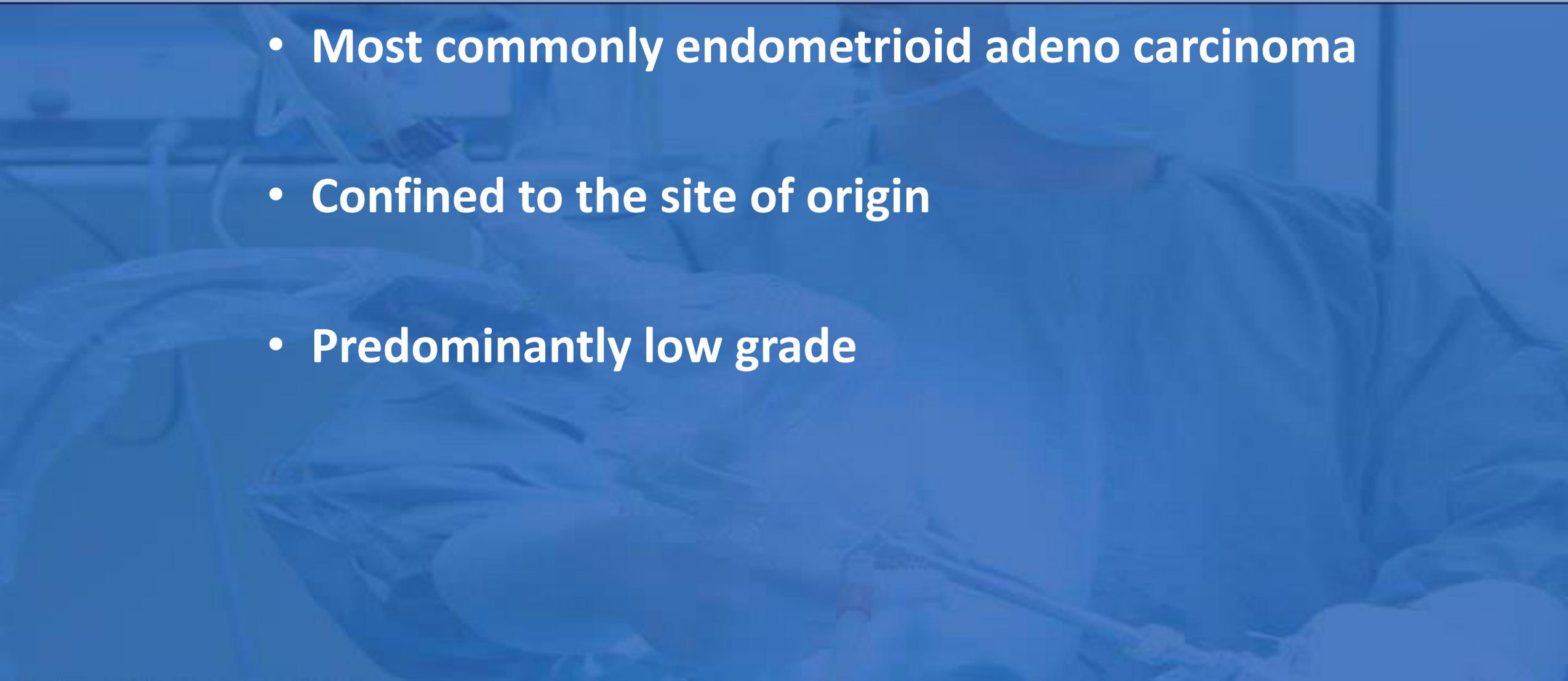


Risk of malignant transformation

- Estrogen only therapy has been associated with an increased risk of malignant transformation of ectopic foci (Oxholm 2007)
- Extragonadal adenocarcinoma may developed after BSO even at sites far from pelvis (Brunson 1988)



Tumors arising in endometriosis

- Most commonly endometrioid adeno carcinoma
 - Confined to the site of origin
 - Predominantly low grade
- 

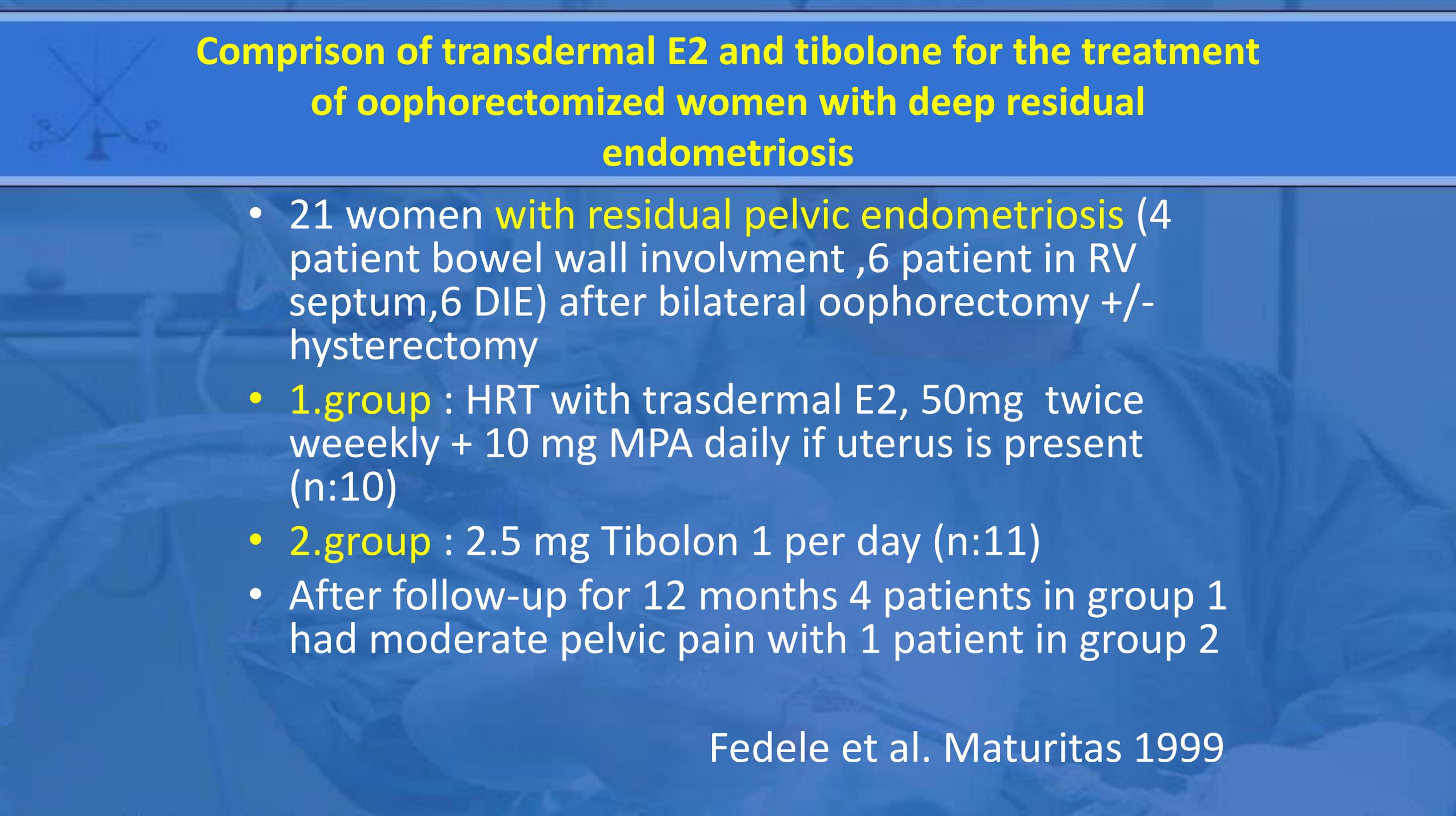
Alternative Symptomatic Menopause Treatments

- Clonidine
- Seratonine re-uptake inhibitors (SSRI)
- Seratonin and nor-adrenalin reuptake inhibitors (SNRI)
- Gabapentin
- Lubricants
- Moisturizers

HRT and Cervical Cancer

- Squamous cell Ca is not estrogen dependent
- HRT have no effect on HPV carriage or replication
- Prolonged use of OC increases the risk of adeno Ca of the cervix
- Unopposed estrogen increases the risk of cervical adeno Ca (OR:2.7)
- Estrogen metabolite 16 alpha hydroxyestrone acts as a co-factor together with oncogenic HPV

Sing P, Maturitas 2010, Smith et al. Lancet 2003



Comparison of transdermal E2 and tibolone for the treatment of oophorectomized women with deep residual endometriosis

- 21 women with residual pelvic endometriosis (4 patient bowel wall involvement, 6 patient in RV septum, 6 DIE) after bilateral oophorectomy +/- hysterectomy
- **1.group** : HRT with transdermal E2, 50mg twice weekly + 10 mg MPA daily if uterus is present (n:10)
- **2.group** : 2.5 mg Tibolon 1 per day (n:11)
- After follow-up for 12 months 4 patients in group 1 had moderate pelvic pain with 1 patient in group 2

HRT and recurrence of endometriosis after BSO+/- Hysterectomy

- Prospective randomised trial (115 women receiving HRT and 57 not)
- BSO with total hysterectomy (91.8)
- No recurrence in the non treated group
- **3.5% recurrence** (0.9% per year) in the HRT group
- Risk factors for recurrence:
 - peritoneal involvement >3cm** (2.4%recurrence per year)
 - Incomplet surgery** (22.2% per patient vs 1.9%)

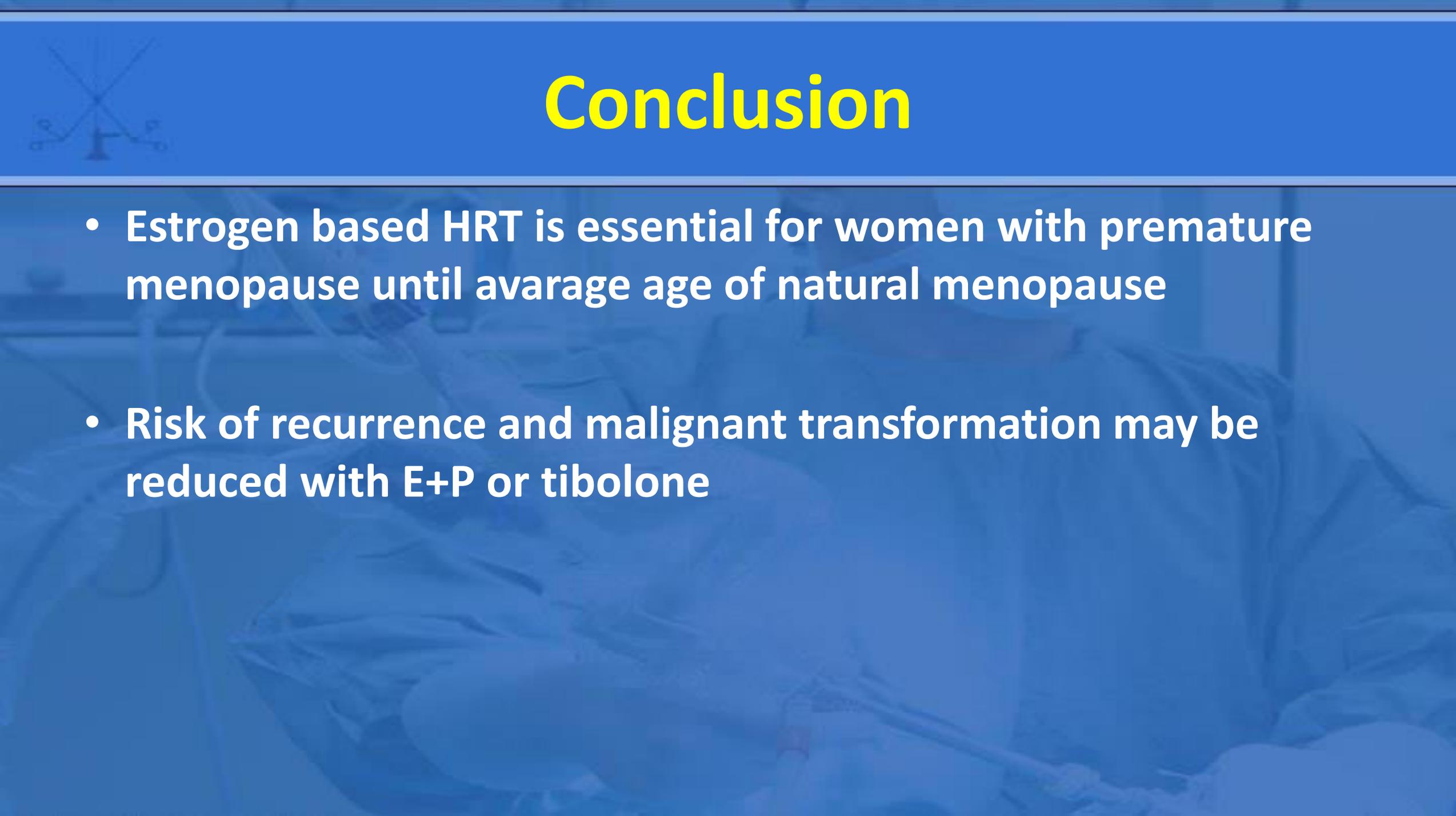
HRT in surgical menopause with underlying endometriosis

- 123 women who had TAH+BSO for endometriosis (Mean age at surgery:38.9 years old with main duration of HRT 41.2 months))
- 1.Group(17 patients): no HRT
- 2.Group(50 patients):Estrogen only (ERT)
- 3 Group(16 patients):Cyclic E/P
- 4.Group(24 patients):Continuous combined E/P
- (16 patients who received more than one regimen)
- There was 1 (2%) of recurrent endometriosis and 3(6%) of recurrent symptoms in the ERT only group.
- Malignant transformation was not found.



Why Surgery?

- For diagnosis
 - And treatment
- 



Conclusion

- Estrogen based HRT is essential for women with premature menopause until average age of natural menopause
- Risk of recurrence and malignant transformation may be reduced with E+P or tibolone