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

- Asses the reccurence 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 menapouse or POF may use HRT for many years,until the age of the naturel menopause

Extend of Endometriosis

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

Punnonnen 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[a]
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	*b*
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	*b*
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)[c]	10 (0.23)	2.31	0.09	—	—	<0.0001	*b*
Cushing's syndrome (28)[c]	4 (0.09)	0.92	0.00	—	—	<0.0001	*b*
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	*b*

Gemmill JA et al Fertil Steril 2010

	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**

From the Ovarian Cancer Association Consortium Lancet Oncology 2012

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

Namnoum et al. Fertil Steril 1995

Surgical Menopause

- Patients are relatively young
- Start HRT after Surgery to prevent

--Urogenital atropy

--Loss of libido

--Bone loss

--Prevantion of cardiovascular disease in early menopause

Palep-Singh et al,Menopause Int 2009

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 sensivity 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
Mattoras 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®

2009

- There were only two radomized 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 syptomatic patients from this treatment.

Higher Recurrence Risk after HRT

- Presence of DIE
- Residual disease on intestine,bladder
- Peritoneal involvement >3 cm
- Incomplet surgery for endometriosi (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 (with in 6 weeks of surgery)

- 20% in late HRT group (after 6 weeks of surgery)

We could recommend starting HRT shortly after surgery

Hickman et al Obst Gynecol 1998

Risk of malignant transformation

- Estrogen only therapy has been associted with an incresed 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 esrogen increases the risk of cervical adeno Ca (OR:2.7)
- Estrogen metabolit 16 alfa hydroxyestrone acts as a co-factor together with oncogenic HPV

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

Comprison 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 involvment ,6 patient in RV septum,6 DIE) after bilateral oophorectomy +/- hysterectomy
- 1.group : HRT with trasdermal E2, 50mg twice weeekly + 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

Fedele et al. Maturitas 1999

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%)

Matorras et al.Fertil Steril 2002

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):Continous 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.

Rattanachaiyanont et al.J Med Assoc Thai 2003

Why Surgery?

- For diagnosis
- And traetment

Conclusion

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