HOW CAN WE MANAGE WOMAN WITH MENOPAUSAL ENDOMETRIOSIS ?

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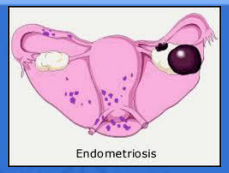
ENDOMETRIOSIS and MENOPAUSE

- Natural Menopause
- Surgically Induced Menopause

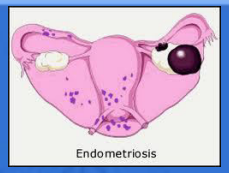
Endometriosis

- Endometriosis is a hormone-dependant inflammatory disease
- Usually caracterized by infertility and pain symptoms
- Mainly occurs during reproductive years,
- Rarely diagnosed after menopause (2.5%)
- Treatment options and the risk of malignant transformation.



How common is endometriosis after Menopause?

- True prevalance in general population is unknown !



How common is endometriosis after Menopause?

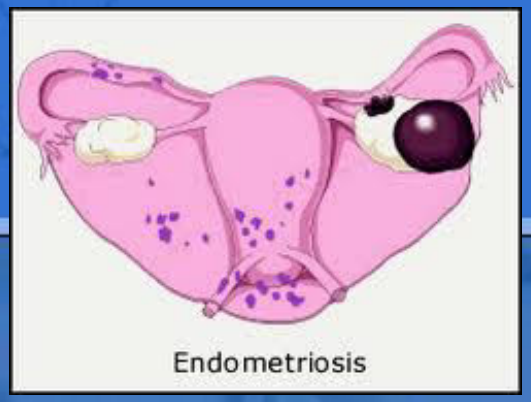
- 2.5 % of women with endometriosis are postmenopausal

Nikkanen V, Acta Obstet Gynecol Scand 1984

How common is endometriosis after Menopause?

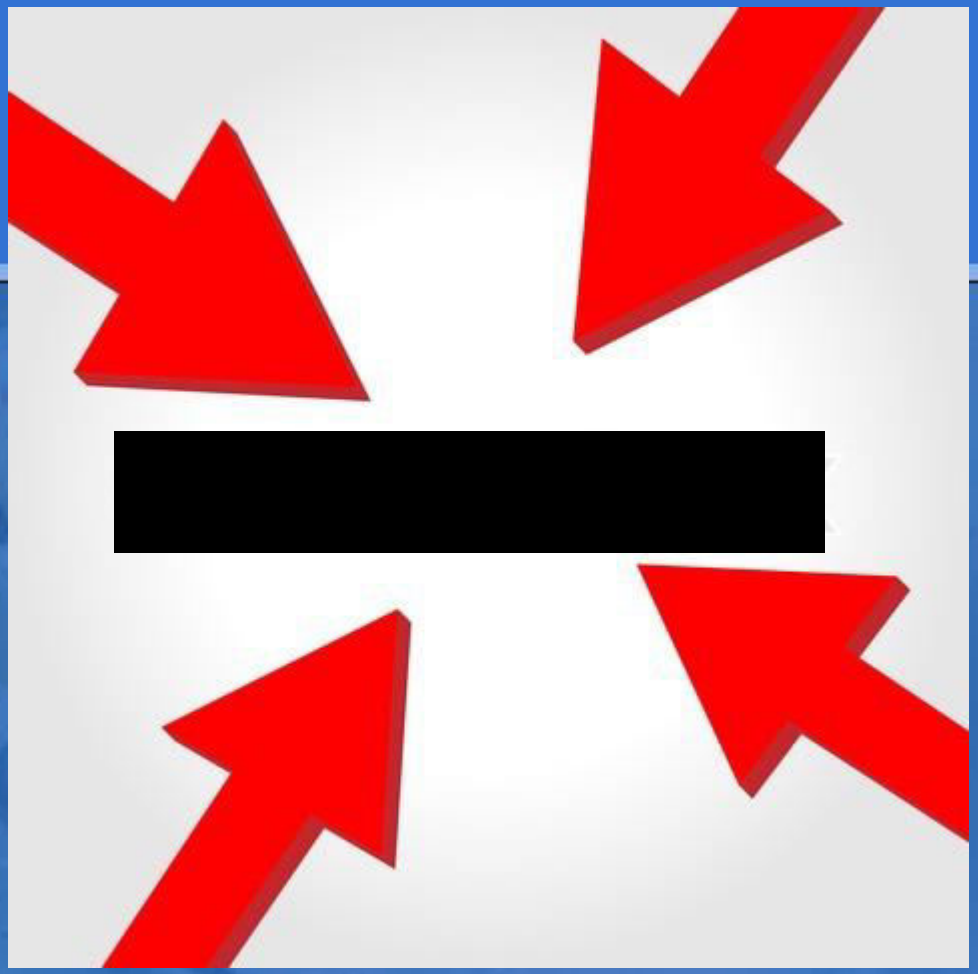
- 2005-2006 German Federal Statistical Office data
- 42,079 women with histologically confirmed endometriosis
- 1074 (2.55 %) patients were postmenopausal

Haas D et al, Arch Gynecol Obstet 2012

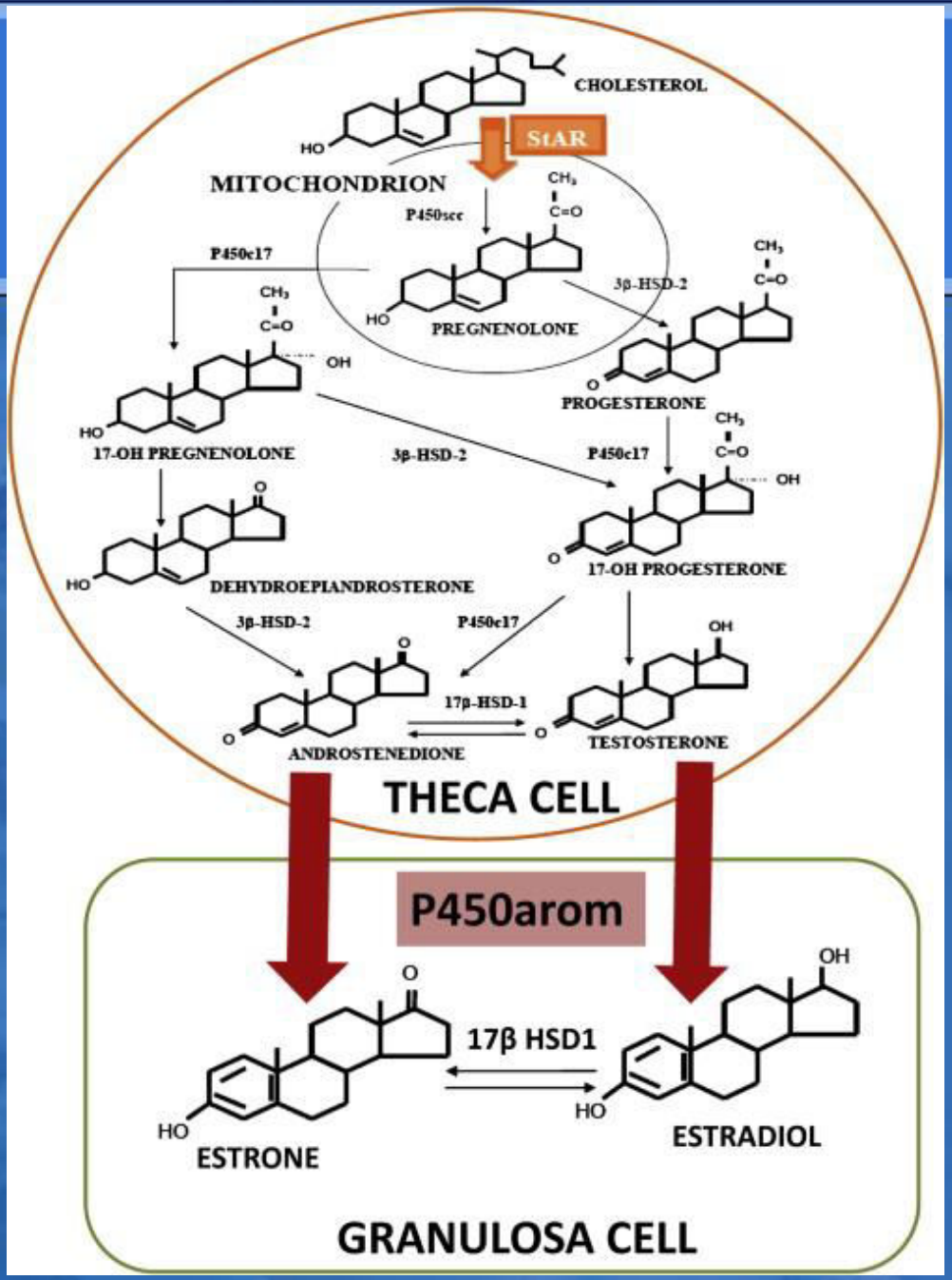


Endometriosis

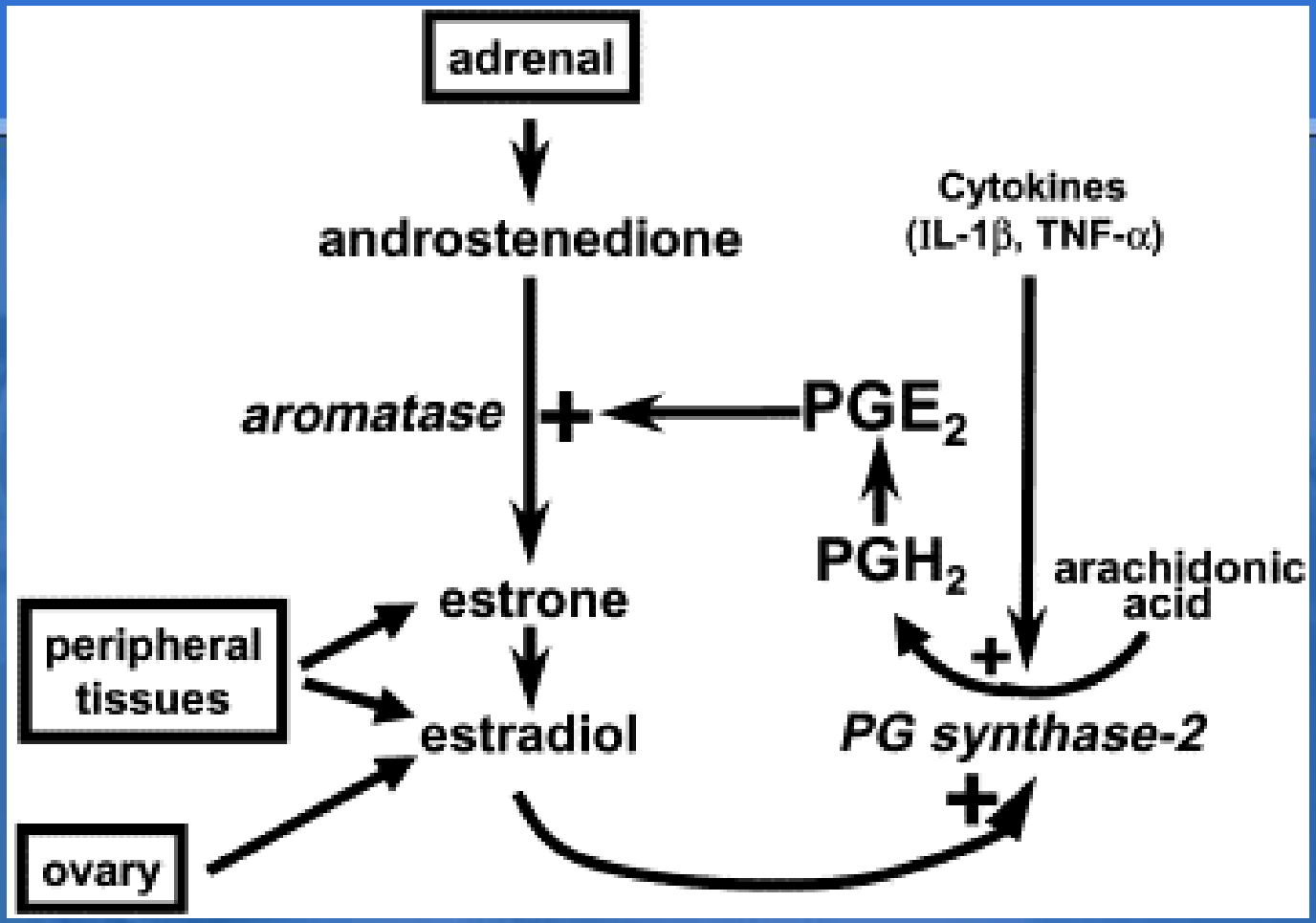
- Occurence or progression of postmenopausal endometriosis could be releated to extraovarian production of estrogen by endometriosis lesions and adipose tissue



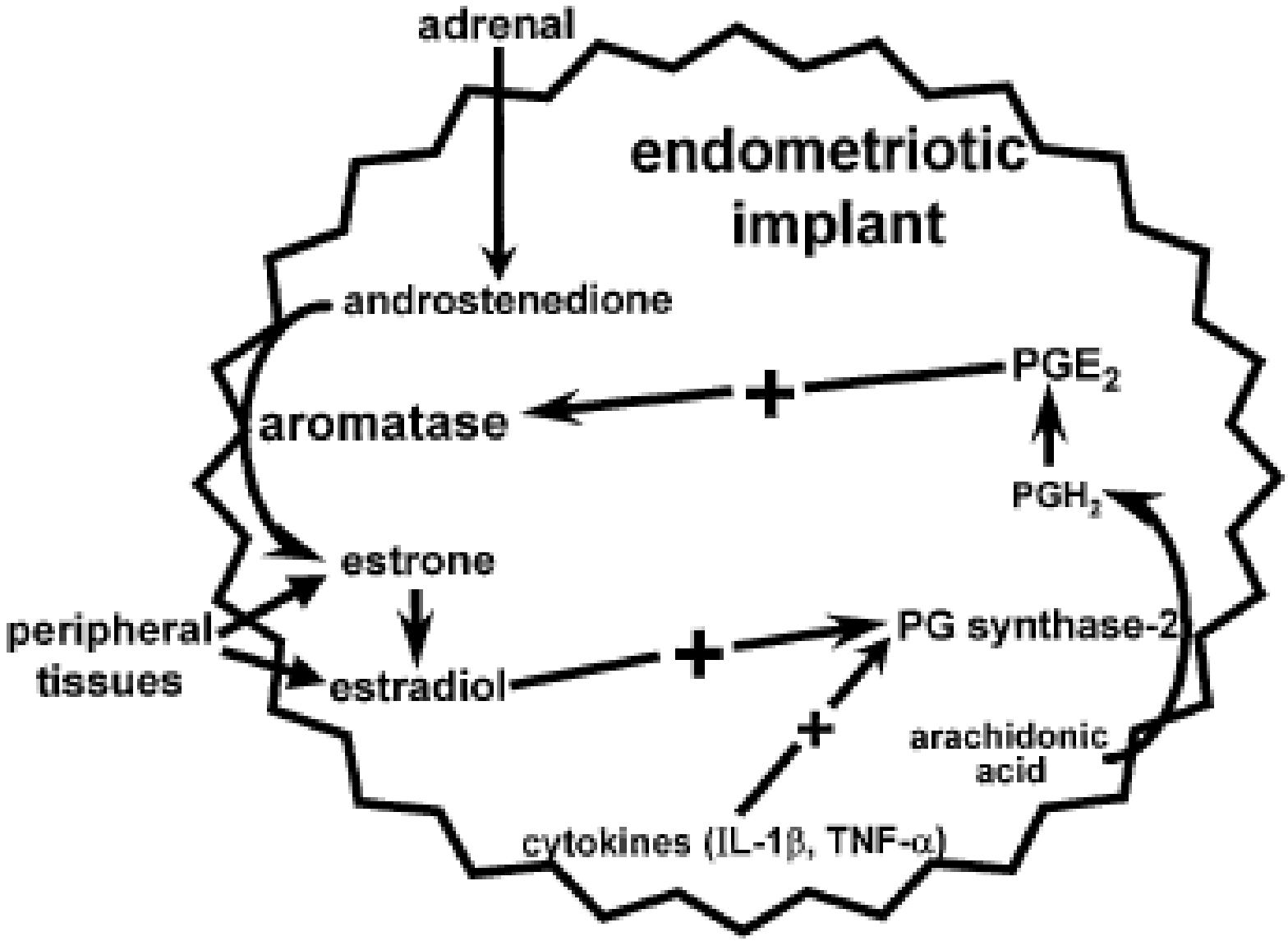
Estrogens play a central role in endometriosis



Bulun S et al, Fertil Steril 2012



Bulun SE et al, Journal of Steroid Biochemistry & Molecular Biology 2001



Bulun S et al, Endocr Relat Cancer 1999

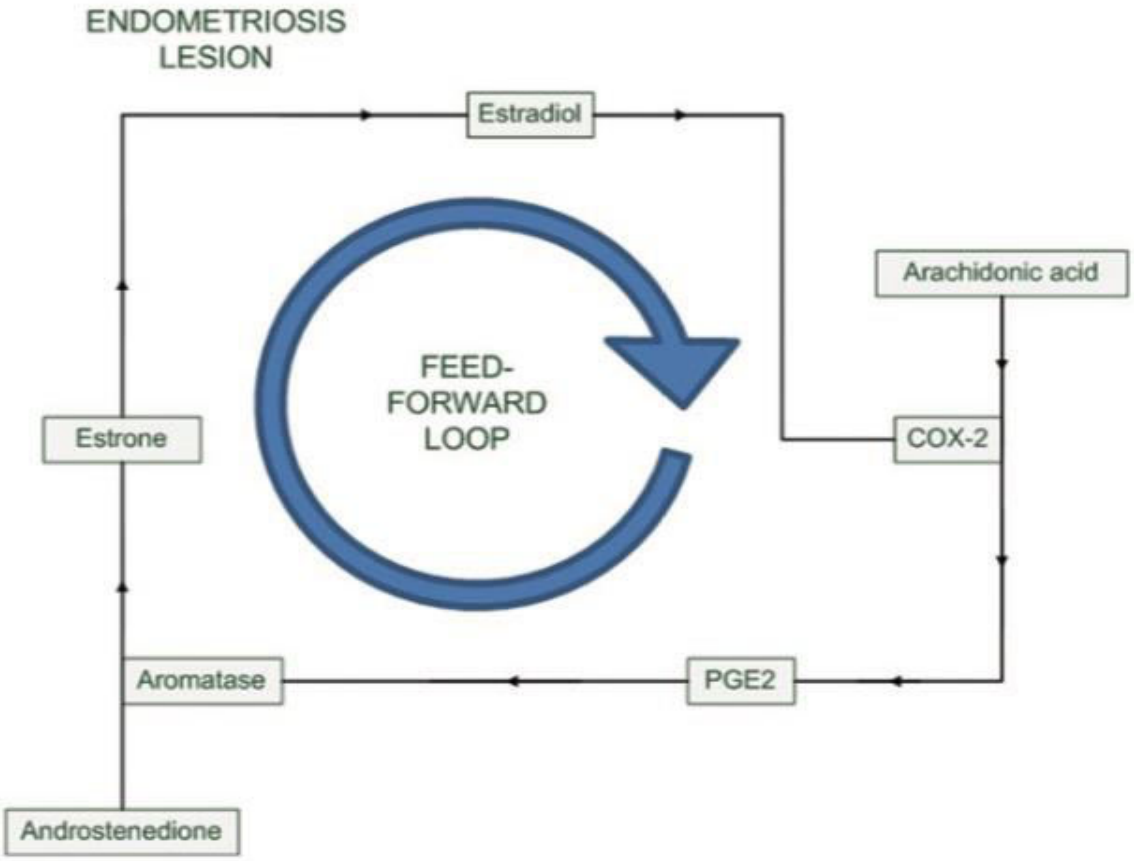


Figure 1. Feed-forward stimulation loop in endometriosis lesions. Adapted from Attar and colleagues[37]. Estrogen stimulates cyclo-oxygenase-2 (COX-2), which elevates prostaglandin E2 (PGE2) concentrations. PGE2, in turn, stimulates aromatase, allowing the androgen to convert to estrogen. This loop supports the growth of the lesion and local inflammation.

Biologic activity of the endometriosis in postmenopause

- Toki et al. reviewed 21 ectopic and eutopic endometriotic tissues in women with postmenopausal endometriosis
- Endometriotic lesions in postmenopausal patients remained biologically active,with proliferative activity and preserved hormonal responsivenes,even in the lower estrogenic environment

Toki et al.Int J Gynecol Pathol.1996

Clinical presentation of postmenopausal endometriosis?

Arch Gynecol Obstet
DOI 10.1007/s00404-012-2473-5

REPRODUCTIVE MEDICINE

Endometriosis in menopause: a single institution experience

Matteo Morotti · Valentino Remorgida · Pier Luigi Venturini · Simone Ferrero

- 72 women with postmenopausal endometriosis
- 14 (16.7%) had previous history of endometriosis

Marotti et al, Arch Obstet 2012

Arch Gynecol Obstet
DOI 10.1007/s00404-012-2473-5

REPRODUCTIVE MEDICINE

Endometriosis in menopause: a single institution experience

Matteo Morotti · Valentino Remorgida · Pier Luigi Venturini · Simone Ferrero

- ✓ 40.3% (29/72)…. Asymptomatic endometrial cyst
- ✓ 26.4% (19/72)…. Abnormal uterine bleeding
- ✓ 26.4% (19/72)…. Abdominal pain
- ✓ 2.8% (2/72)…. Rectal bleeding
- ✓ 2.8% (2/72)…. Urinary dysfunction

Marotti et al, Arch Obstet 2012

Endometriosis in postmenopause

- Median BMI 25.0 kg/m^2 (18-34.3)
- 15% (11/72) BMI>30 kg/m^2

- HRT use
  - Current…. 4.2% (3/72)
  - Past……. 5.6% (4/72)
- TMX use…..2.7%(2/72)

Marotti et al, Arch Obstet 2012

- In 1942 Edgar Haydon reported the first case of postmenopausal endometriosis:

78-year-old woman with endometriosis

- After 1950’s:
- Case reports, case series and some retrospective analysis of postmenopausal women with endometriosis

Case reports

- 74 year old women with intestinal obstructive endometriosis without any HRT: Rectosigmoidectomy (Popoutchi 2008)
- 56 year old (5 years postmenopause)with a huge ovarian endometrioma (Matsushima 2016)
- 62-78-54 years old with endometriomas and DIE (Rosa Silva 2008)
- 69 year old with unusual postmenopausal diffuse endometriosis mimicking metastatic ovarian malignancy (Agarwal 2016)

Case reports

- 65 year old (TAH+BSO for endometriosis at age 43) with acute vaginal bleeding,hematuria and pelvic mass and she had a pelvic exenteration (pathologic exams showed invasive endometriosis without malignancy)

Klenov Obstet Gynecol.2015

How about the pathophysiology of endometriosis after the menopause?

- Continuing premenopausal disease ?
- De novo lesion?

- It is difficult to say if postmenopausal endometriosis is a continuation of the previous disease or it occurs de novo

Continuing premenopausal disease?

- Some cases have a history of previous surgery due to endometriosis
- There are also cases without any clue of previous disease

Continuing premenopausal disease?

- 65 years old woman who presented hematuria and pelvic pain
- Vesical endometriosis
- Had hysterectomy due to myomas (34 yrs ago!)
- No endometriosis at that time!

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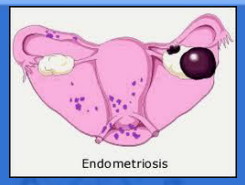
Maeda T et al, Int Urogynecol J Pelvic Floor Dysfunct 2009



What are the locations of postmenopausal endometriosis?

- Ovaries
- Peritoneum
- Ureter
- Bladder
- Abdominal wall
- Liver
- Vaginal vault
- Skin

Location of endometriosis in postmenopause

- Primarily located in the ovaries
- Also in the ureter,bladder and intestines
- More rarely in the vagina
- Very rare location are skin and liver

Vorstman et al	Urology 1983
Habuchi yet al	J.Urology 1991
Venter et al	S Afr Med J 1979
Jolevsek et al	Am J Obstet Gynec 2004

Treatment Options

- Surgery is the first choice of treatment in women with postmenopausal endometriosis mainly due to risk of malignancy,anatomic distortion,DIE or big mass
- There is little experience with medical treatment
- For recurrent endometriosis or in patients that are not suitable for surgery, Aromotase Inhibitors can be used.

Absolut indication for the surgery

- Anatomic (intestinal,ureteric) distortion
- DIE
- Big masses
- Suspicion of malignancy
- High risk for malignancy (Obesity,Diabete…)

How Radical Surgery?

- Remove all endometriotic lesions with all peritoneal and retroperitoneal lesions
- Avoid the ovarian remnant syndrome

Recurrence after the surgery

- Hormonal treatment (E/P)
- AIs treatment
- If malignancy risk or malignancy mimicking lesions >> re-surgery

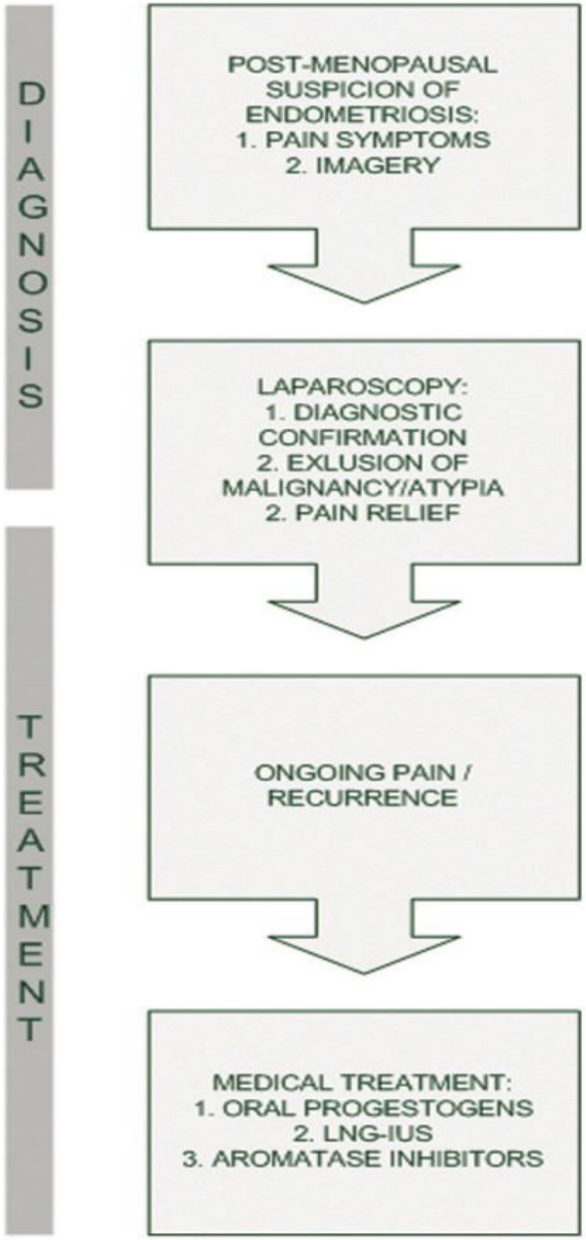


Figure 2. Algorithm of endometriosis management in postmenopausal women.

Malignant Transformation

- Age is an important risk factor for malignancies
- Thus it may be questioned whether the postmenopausal endometriosis puts at risk for malignancy

The risk factors for endometriosis and ovarian malignancy are similar:

- Low rate of parity
- Infertility
- Late childbearing age
- Short duration of OC use

Ness et al.Am J Obstet Gynecol 2003

Risk of Malignancy

- Sampson was the first to descripe the risk (1%)
- Increased risk of ovarian endometrioid and clear cell carcinomas (1.3-1.9%)

Brinton 1997,Borgfelt 2004

Malignant Transformation and/or malignity?

- De Priest reviewed 42 patients with endometrioid ovarian carcinoma and found that ovarian endometriosis was present in 11 cases (26%)
- In 4 patients carcinoma and endometriosis transition was observed
- Thus they suggested that ovarian endometriosis has a potential of malignant transformation in postmenopause

De Priest et al.Gynecol Oncol.1992

Risk of Malignancy

- 31 patient who developed ovarian and extra-ovarian cancer from endometriosis
- Half of the cancer were in the ovaries
- Risk of unopposed estrogen (9) and obesity (9) showed that either endogenously or exogenously estrogens are the risk factors for development of cancer in endometritic lesions

Zanetta et al.Gynecol Oncol.2000

Malignant transformation and/or malignity ?

- Arising from endometriosis…
  - 25 cases with ovarian carcinoma
  - 21 cases of extraovarian carcinoma

- In premenopausal women…..predominatly ovarian cancer
- In postmenopausal women….. predominatly extraovarian cancer

Modesitt SC et al, Obstet Gynecol. 2002

Table 2. Demographic Characteristics of Patients With Endometriosis-Associated Intraperitoneal Cancers

Demographic characteristic	Total (n = 115)	Ovarian cancer arising in endometriosis (n = 25)	Extraovarian cancer arising in endometriosis (n = 21)	Ovarian cancer with adjacent endometriosis (n = 33)	Ovarian cancer with incidental endometriosis (n = 36)	P*
Age (y)						.318
<40	25	4	3	6	12	
40–59	75	16	14	23	22	
>60	12	4	4	2	2	
Unknown	3	1	0	2	0	
Race						.534
White	88	17	19	24	28	
Hispanic	16	4	1	4	7	
Other	8	3	1	3	1	
Unknown	3	1	0	2	0	
Gravidity						.952
0 or 1	56	12	9	16	19	
≥2	55	13	10	16	16	
Unknown	4	0	2	1	1	
Menopausal status						.001
Premenopausal	75	17	6	22	30	
Postmenopausal	39	8	15	10	6	
Unknown	1	0	0	1	0	
Oral contraceptive use						.893
Yes	32	9	6	8	9	
No	43	9	9	13	12	
Unknown	40	7	6	12	15	
Hormone replacement use						.001
Yes	22	2	13	5	2	
No	90	21	7	28	34	
Unknown	3	2	1	0	0	

* Represents differences among the groups as a whole for the entire category.

Modesitt SC et al, Obstet Gynecol 2002

Risk of Malignancy

- Review by Somigliana et. al concluded that endometriosis should not be considered a clinically relevant risk of any specific cancer.
- The malignancy must always be kept in mind in a clinical situation.

Somigliana et al. Gynecol Oncol.2006

Endometriosis and Ovarian Cancer Risk

- Histologically, endometrioid and clear cell carcinoma are the most common types

Endometriosis and Breast Cancer Risk

- Total 14,327 women
- 1978 women with endometriosis, 236 were diagnose having breast cancer

- **Women in whom endometriosis was diagnosed at older ages (> or =40 yrs) tended to have an increased risk for breast cancer**

Bertelsen L et al, Int J Cancer. 2007

Endometriosis in Postmenopause

- Estrogen stimulate endometriosis,HRT (mostly estrogen only or combined EP)is believed to stimulate the the growth of endometriosis
- There is a risk of recurrence or de novo occurrence of endometriosis
- Also endometriosis in women not receiving exogenous hormones
- The risk of malignanat transformation is 1% (lower with combined HT compared to ET)

Risk factors for recurrence of endometriosis in women on HT

- Having BSO without hysterectomy or
- Having peritoneal implants > than 3 cm

Mattoras et al Fertil.Steril.2002

Reccurence of endometriosis in women after BSO +/-Hysterectomy

- Prospective randomised trial : Reccurence
- 1.group:Combined HT (115 women) 3.5%

  0.9% (per year)
- 2.group:Without HT (57 women) 0%

Mattoras et al Fertil.Steril. 2002

Risk of reccurence after TAH+BSO

- In 109 women no risk of reccurrence with hormone implants (combination of E2 and testosteron) after 3.4-5.3 years of follow-up

Henderson et al. Advances in Reprod Endoc.1990

EMAS (European Menopause and Andropause Society) Statement

- Today we accept that HT may reactivate residual lesions and risk of malignant transformation of endometriosis had to be considered in postmenopausal women

Moen et al. Maturitas 2010

Treatment of postmenopausal endometriosis

- Secondary treatment or if the patient is not suitable for a surgical procedure:
  Aromatase inhibitors (AIs)

Endocrine-Related Cancer (1999) **6** 293-301

Estrogen production in endometriosis and use of aromatase inhibitors to treat endometriosis

S E Bulun[1], *K Zeitoun, K Takayama, L Noble, D Michael, E Simpson, A Johns, M Putman and H Sasano*[2]

- 21 ectopic and eutopic endometriotic tissues in women with postmenopausal endometriosis

- ER were both positive in both

Toki T et al, Int J Gynecol Pathol 1996

A detailed morphologic and immunohistochemical comparison of pre- and postmenopausal endometriosis

J Cumiskey, P Whyte, P Kelehan, D Gibbons

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ABSTRACT

Background: Endometriosis depends on oestrogenic stimulation for its continued growth, accounting for its prevalence during reproductive years. There is doubt among clinicians regarding its existence in postmenopausal women in the absence of exogenous or endogenous sex hormones. We postulated that endometriosis occurring in postmenopausal women would show a different morphologic and immunohistochemical profile to the disease occurring in premenopausal women.

Methods: We reviewed the most recent 100 cases of endometriosis in our department plus all cases occurring

textbooks where cases of endometriosis in postmenopausal women are felt to be due to a reactivation of disease secondary to hormone replacement therapy (HRT) or inappropriate endogenous sex hormones produced by the ovarian stroma.[2] Indeed, it would seem to make sense that, unless there are elevated levels of circulating oestrogen (either endogenous or exogenous), following the menopause there should be at least atrophy of endometriosis, if not complete regression of the disease.

With the expected decrease in hormone levels in

- 100 cases with endometriosis (retrospectively)
- Analysis by age groups –arbitrarily- as;
  - Likely premenopausal (n=91)
  - Likely postmenopausal (n=9)

A detailed morphologic and immunohistochemical comparison of pre- and postmenopausal endometriosis

J Cumiskey, P Whyte, P Kelehan, D Gibbons

- Endometriotic tissue in likely postmenopausal vs likely premenopausal women

  - ✓ Both have the similar distributions of estrogen and progesterone receptors

  - ✓ Postmenopausal endometriotic tissue is less hemorrhagic and less extensive

TMX use and postmenopausal endometriosis : any relationship?

CASE:

- 50-year-old women
- Had a 2-year adjuvant TMX treatment due to breast carcinoma
- Had extensive pelvic endometriosis necessitated surgery

Hajjar LR et al, Obstet Gynecol. 1993

- First case of ovarian endometrioid carcinoma and endometriosis in women taking TMX due to breast cancer

Cohen I et al , Gynecol Oncol 1994

TMX use and postmenopausal endometriosis: any relationship

- According to the case reports :

There is an association between TMX use and postmenopausal endometriosis and even endometrioid carcinoma of the ovary

Tamoxifen and postmenopausal endometriosis

- TMX has antiestrogenic effect on breast tissue and exert estrogenic effect on the endometrial tissue
- Like HT,it is not clear whether TMX induces or promotes the endometriosis
- İt may be concluded that TMX use in postmenopausal women might increase the risk of endometriosis

FERTILITY AND STERILITY®
VOL. 69, NO. 4, APRIL 1998

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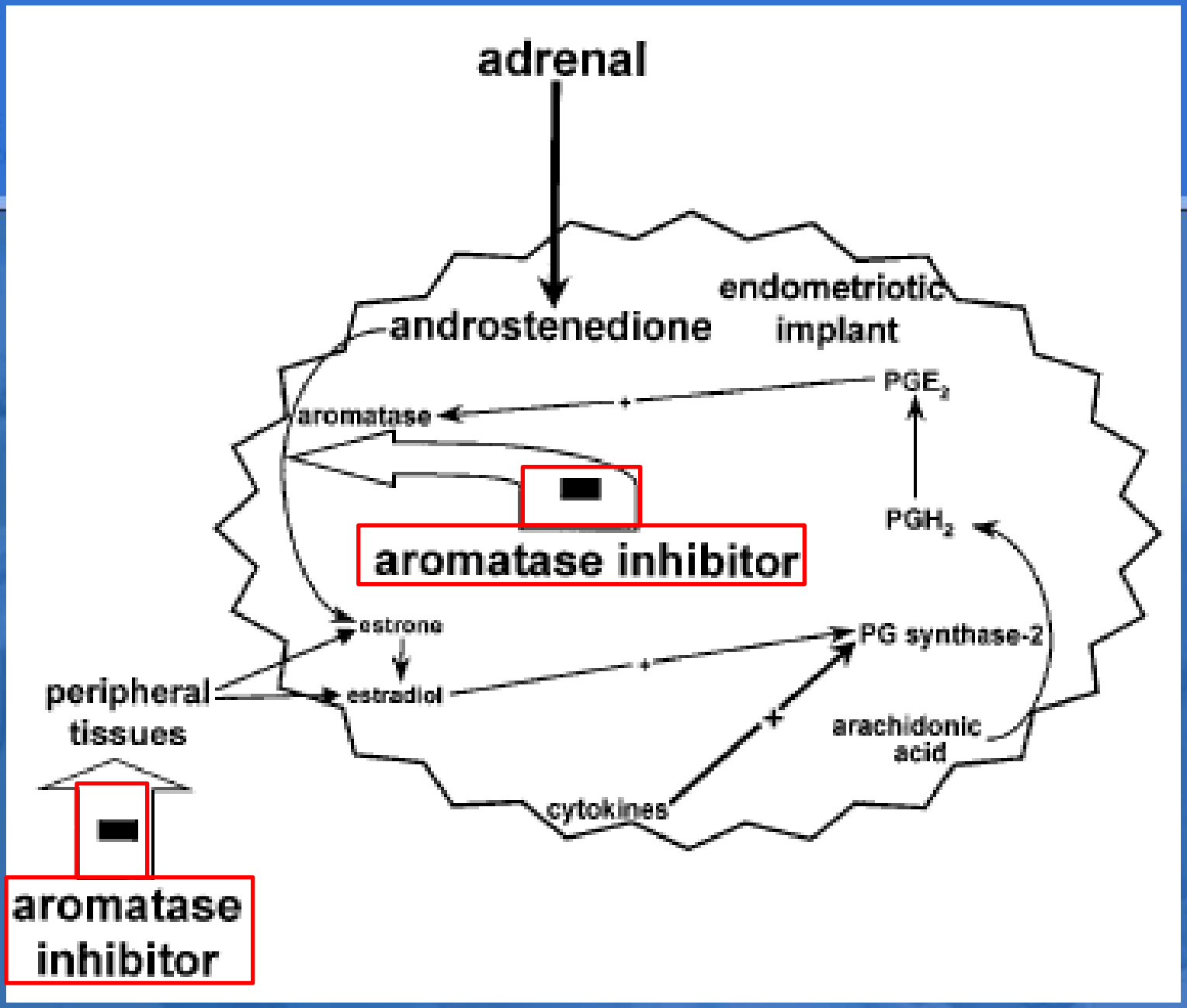
Treatment of severe postmenopausal endometriosis with an aromatase inhibitor

Kazuto Takayama, Khaled Zeitoun,* Robert T. Gunby,† Hironobu Sasano,‡ Bruce R. Carr,* and Serdar E. Bulun**

- A 57-year-old woman
- Recurrent endometriosis as a painful vaginal polypoid mass (30x30x20 mm)
- Treated with anastrazole 1mg/daily, P.O. for 9 months

Takayama et al Fertil Steril, 1998



Takayama et al Fertil Steril, 1998

Third-generation AIs

- Exemestan,letrozole,anastrozole
- In women with recurrent symptomatic endometriosis lesions
- AIs reduce the size of the bladder, gastrointestinal and ureteral lesions and alleviating pain,including urinary and digestive symptoms.
- Low-dose estrogen add-back therapy can be used.

Polyzos et al Reprod Biol Endoc 2011

Takayama et al. (1998)	Case report	1	Postmenopausal endometriosis, refractory to surgical or medical management	Anastrozole	9 mo	Pain relief, reduction in lesion size
Fatemi et al. (2005)	Case report	1	Postmenopausal endometrioma causing sciatic-like pain	Letrozole	18 mo	Regression of endometrioma, pain relief
Razzi et al. (2004)	Case report	1	Postmenopausal endometriosis, refractory to surgical or medical management	Letrozole	9 mo	Pain relief, reduction in lesion size
Mousa et al. (2007)	Case report	1	Recurrent endometriotic nodule in bladder wall in postmenopausal woman	Letrozole	8 mo	Pain relief, improvement in urinary symptoms
Bohrer et al. (2008)	Case report	1	Recurrent ureteral and bowel endometriosis in a postmenopausal woman	Anastrazole	15 mo	Pain relief, resolution of bowel symptoms
Sasson and Taylor (2009)	Case report	1	Recurrent abdominal wall endometrioma in a postmenopausal woman	Letrozole + MPA + serial cyst aspirations	34 d	Decrease in size of cystic mass

- The most important risk associated with AIs is osteoporosis and increased fracture risk !
  - Annual BMD screening
  - Bisphosphonates

Aromatase Inhibitors side effects

- Hot flushes
- Vaginal dryness
- Arthralgias
- Osteoporosis and releated fractures

HRT in Postmenopausal Patients with endometriosis

- It may be safer to give either combined HT or tibolone to reduce the risk of recurrence and malignant transformation of residual endometriosis

In Conclusion;

- Endometriosis can be found in women after the menopause
- Most affected sites are the ovaries
- Peripheral aromatisation and local production of estrogens play the key role in the pathophysiology
- TMX use increases the risk
- Surgery is the treatment of choice
- If not suitable for surgery… aromatase inhibitors
- Ovarian and breast carcinoma are more prevalant in women with postmenopausal endometriosis

Conclusion

- Treatment is still primarily surgical
- But medical treatment may be a future option
- Unoppesed ERT might potentially increase the risk of persistence or recurrence of endometriosis
- Furthermore,HT might potentially increase the risk of neoplastic transformation of residual tissue.
- Combined HT is associated with a lower risk than unopposed ET