

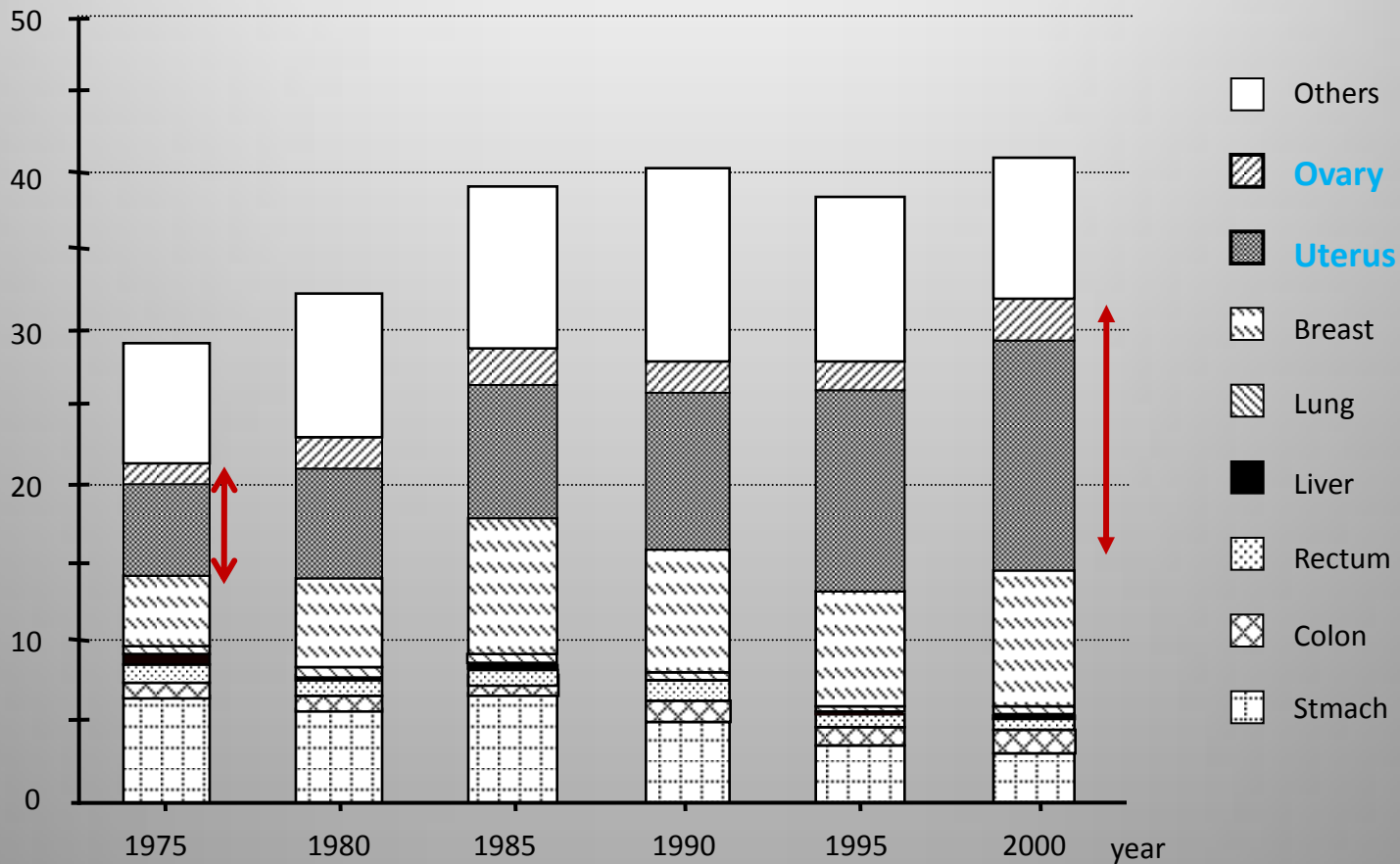
Fertility-Sparing Treatment for Endometrial Cancer and Atypical Hyperplasia in young women

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Changes in site distribution of cancer incidence rate in Japan (female) [0-39] (1975 ~ 2000)

per 100000 population



Younger patients is increasing, especially in gynecologic cancer.

Incidence of endometrial cancer in young women (under 40 years of age)

- 2-14% of all endometrial cancer
- Incidence in Japanese young women is increasing (from JSGO tumor committee report)

1983	4.9% (48/976)	stage I:70.8%
1994	5.1% (109/2115)	stage I:68.0%
2005	7.0% (297/4267)	stage I:70.3%

Not only the over all incidence of endometrial cancer, but also proportion of younger patient is increasing.

Characteristics of Endometrial Cancer in Women under 40 years of age

- Risk factors:
 - Obesity, PCO, nulliparity
- Histology: 90% Grade 1 tumor
 - Accompanied with Hyperplasia (Type1)
 - Less Myometrial Invasion
 - (incidence of more than $\frac{1}{2}$ invasion :
younger 24% vs older 49%)
 - low incidence of lymph node metastasis
- Prognosis : excellent (**after TAH,BSO**)

As the number of young women with endometrial cancer increased, fertility-sparing treatment came to be paid serious attention.

Since the early 1980's, there have been several reports on conservative treatment with progestins for early stage endometrial cancer in young women.

Nevertheless, most of them were small series and retrospective studies from single institutions.

Hormonal therapy as a conservative treatment for Endometrial Adenocarcinoma (EC) and Atypical Hyperplasia (AH)

Diagnosis	Response rate		Recurrence rate	
Adenocarcinoma				
Kim 1997	4/7	57%	2/4	50%
Randall 1997	9/12	75%	1/9	11%
Kaku 2001	9/12	75%	2/9	22%
Niwa 2005	12/12	100%	8/12	67%
Atypical Hyperplasia complex				
Randall 1997	16/17	94%	2/16	12.5%
Kaku 2001	15/18	83%	2/15	13%
Jobo 2003	11/12	92%	4/11	36%

- Treatment dose and treatment duration of Progestin are various in each study.
- All of these studies were from single institution and retrospective studies.

Questions of pretreatment diagnosis of EC or AH

pretreatment diagnosis of EC or AH from endometrial biopsy is not reproducible

- Discrepancy of diagnosis between pre and post operative diagnosis was found in 43/182(23.6%) by retrospective study.
Jacques et al 1998 Fertil Steril
- Concomitant of EC was found in 42.6% (123/289) of the patients who diagnosed as AH by community hospital.
Trimble et al 2006 Cancer
- Reproducibility of diagnosis of EM biopsy between five pathologists was only 64%.
Bergeron et al 1999 Am J Surg Pathol
- Discrepancy of postoperative EM pathology between institutional diagnosis and Central pathological review was found in 20/59(34%).
Kaku et al 2001 Cancer Letter

Questions of pretreatment diagnosis of EC or AH

The accuracy of imaging study by MRI or Ultrasonography in detecting myometrial invasion is limited.

- CT scan failed to identify myometrial invasion in 39% of patients.
Vinker et al 1999 Eur J Obstet Gynecol Reprod Biol,
- The accuracy of MRI T2-weighted images in the determination of myometrial invasion was 68-82%. Shachar et al 2004 Gynecol Oncol
- The probability of the absence of myometrial invasion by MRI was only 42.2%, even in the dynamic study only up to 60.0%

Nakao et al 2006 Gynecol Oncol

Unsolved Questions for Hormonal treatment for Endometrial Cancer in women under 40 years of age

- Indication of conservative treatment
- Accuracy of preoperative diagnosis
(histology, and staging)
- Appropriate dose and interval of treatment
- Toxicity of treatment
- Response or remission rate of treatment
- Pregnancy rate after treatment
- Recurrence rate after treatment

There were no definite resolution for conservative treatment in EC or AH in young women, because no prospective trials ever existed.

Japanese Gynecologic Cancer Study Group
(supported by Grant-in Aid for Research of Cancer Treatment from the Ministry of Health, Labor and Welfare of Japan)
conducted **multicenter prospective phase II trial** to assess the efficacy of fertility-sparing treatment using medroxyprogesterone acetate (MPA) for EC and AH in young women.

26 institutions of Japan included in this prospective phase II study

Entry Criteria

Patients aged **20 to 39** with **histologically confirmed AH or stage Ia EC G1** who desire preserving fertility.

Endometrial samples were obtained from D&C and diagnosis of EC or AH were confirmed by **central pathological review (CPR)**.

Exclusion of myometrial invasion was assessed by transvaginal ultrasonography and magnetic resonance imaging (MRI)

Eastern Cooperative Group (ECOG) performance status (PS) of 0-1

No prior treatment about endometrial lesion

Body mass index (BMI) < 35

Adequate bone marrow function, no abnormal renal or liver function

No abnormal coagulation function or no prior history of thrombosis

The protocol was reviewed and approved by the institutional review board of each participating center, and all patients gave written informed consent before participation.

Therapy

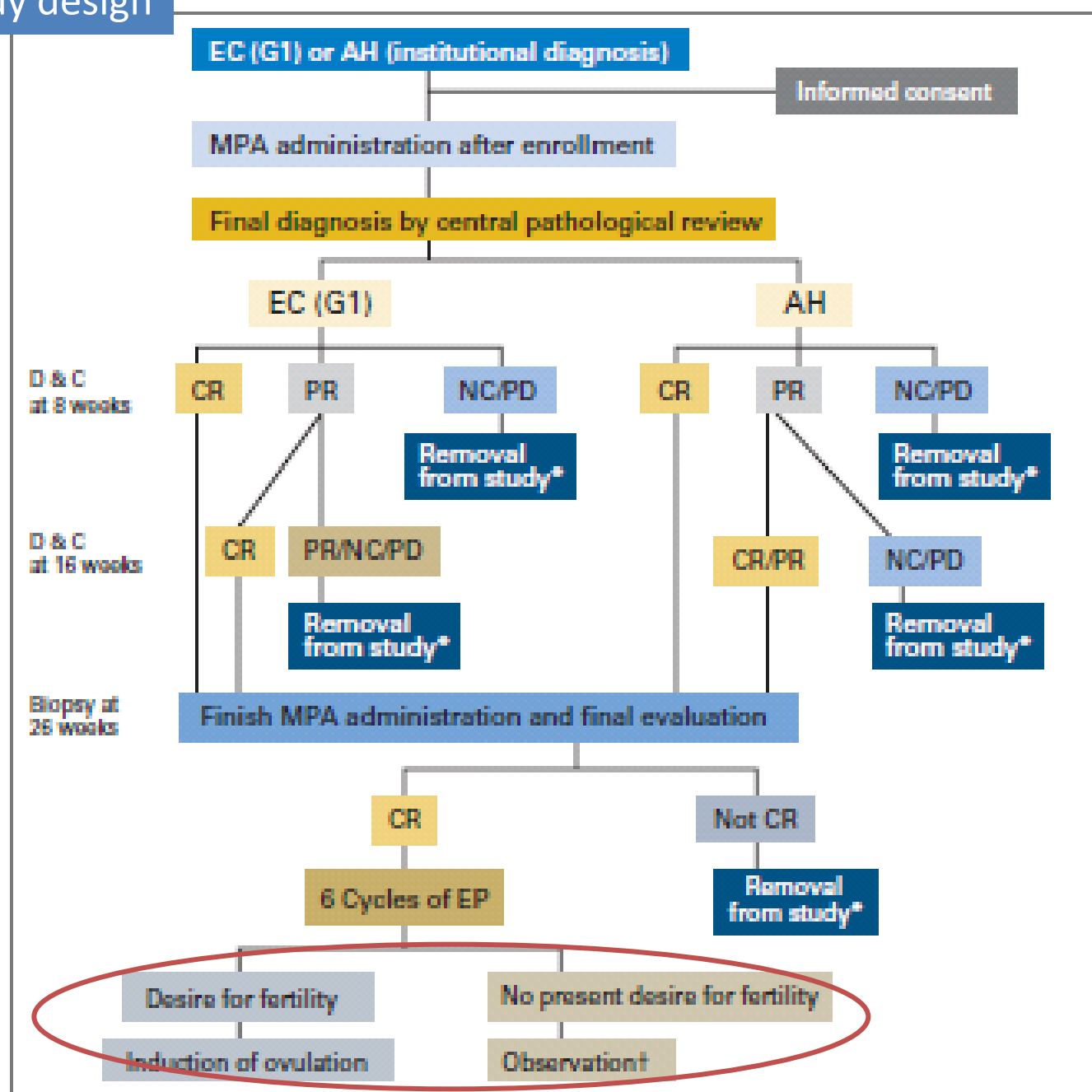
Medroxyprogesterone Acetate (MPA):

600 mg p.o.

with **81 mg of aspirin** p.o.

daily during **26 weeks** .

Scheme of study design



Patients Characteristics (n=45)

Endometrioid Adenocarcinoma (EC G1) 28

Atypical Endometrial Hyperplasia (AH) 17

Age (mean) 31.7±2.8 yrs.(22-39)

BMI (mean) 22.8±3.9 (16-32.7)

Irregularity of period 27/45 (60%)

Polycystic Ovary Syndrome 7/45 (15.6%)

All patients has no history of pregnancy

Over all Treatment Response of MPA

Response	EC (n=22)*	AH (n=17)
CR	12/22 (55%)	14/17 (82%)
PR	7/22 (32%)	4/17 (24%)
NC	3/22 (14%)	0

over all CR rate : 67% (26/39)

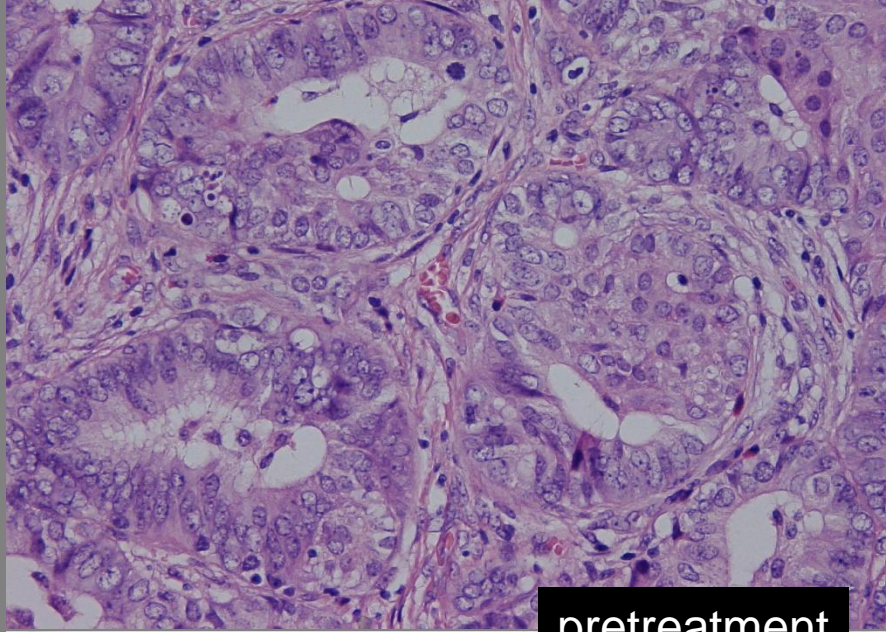
*Six patients dropped out from the study by patient's will

Treatment Response (at 8, 16, 26 weeks)

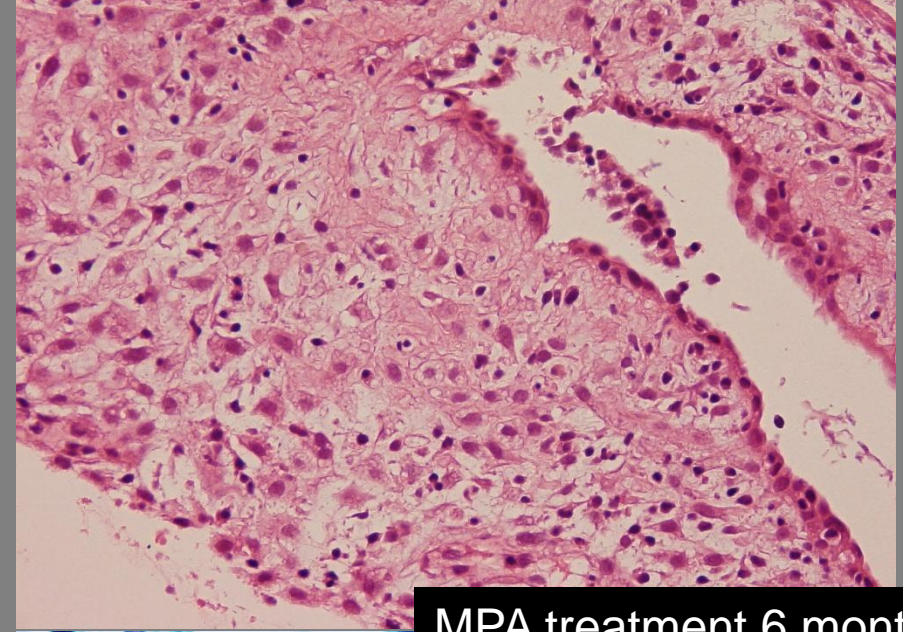
Histology	No.of CR patients			
	Treatment period	at 8w	at 16w	at 26w
EC (CR=12)		6/12(50%)	11/12(92%)	12
AH (CR=13)		9/13(69%)	12/13(92%)	13

Most responders could be identified at 8 weeks of treatment.

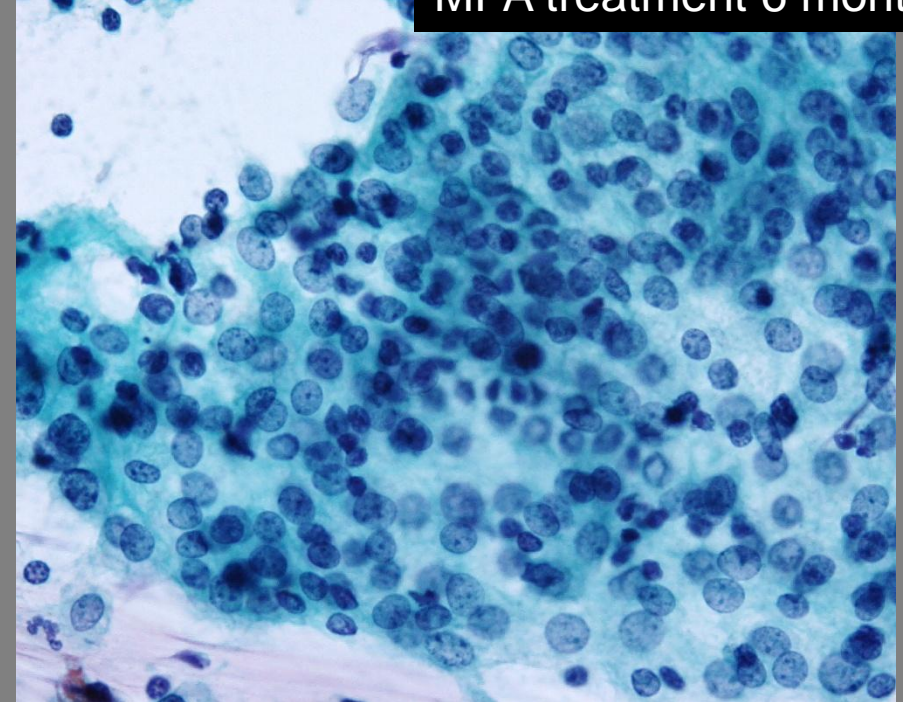
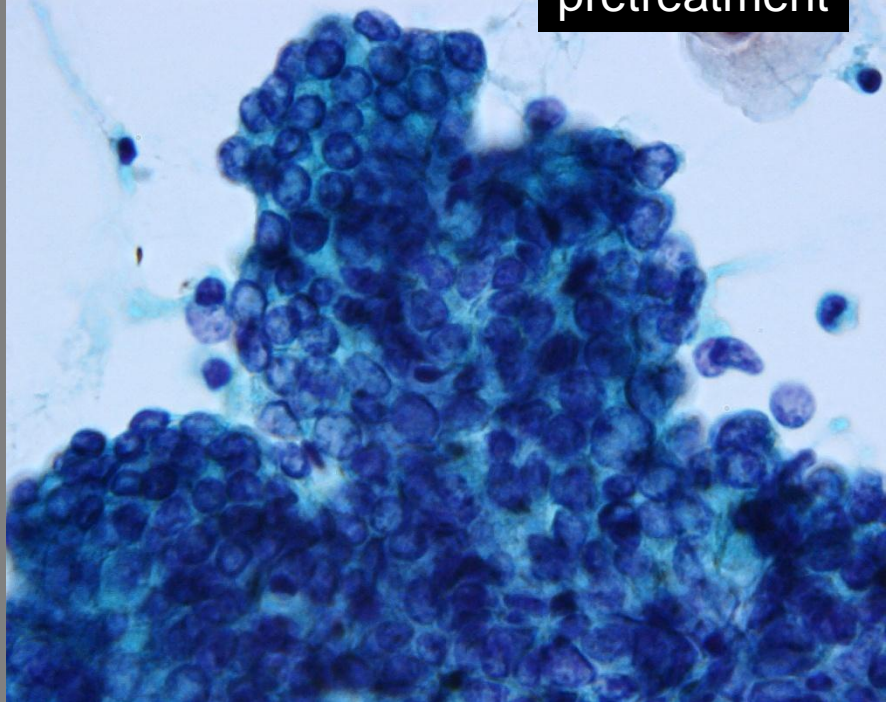
Morphological change of endometrium by MPA treatment



pretreatment



MPA treatment 6 month



Adverse effects of MPA

Toxicity (grading)*	No. of patients
Body weight gain (G3)	2
(G2)	2
Liver dysfunction (G3)	1
(G2)	3
(G1)	2
AT III level abnormality (G1)	1
Fibrinogen level elevation (G1)	1

None of TLD or thromboembolisms were noted

Pregnancy after treatment (for 5 years follow up)

15 pregnancies (12 patients) were noted among 20 CR patients desiring fertility

Normal delivery 9

(including 2 twin pregnancy)

Spontaneous abortion 6

most pregnancies (11/15) were brought by **ART** (7 of 11 were IVF-ET)

Pregnancy rate and abortion rate after MPA treatment

- Relatively low pregnancy rate even in ART (11pt /18pt: 61%)
- High abortion rate (6 /15 cases :40%)

TABLE 3			
Endometrial thickness on the day of hCG administration in IVF cycles of women given conservative treatment for endometrial adenocarcinoma and controls.			
Endometrial thickness on hCG administration	IVF cycles of women with endometrial adenocarcinoma (n = 12 cycles)	IVF cycles of controls (n = 3,239 cycles)	P value
4–7.9 mm	5 (41.6%)	370 (11.4%)	.007
8–10 mm	7 (58.3%)	1,449 (44.7%)	NS
>10 mm	0	1,420 (43.8%)	.001
Mean (mm) (SD)	7.9 (1.7)	10.3 (2.3)	.001
Median (mm)	8	10	
Range (mm)	4.3–10	4–20	

Elizur. IVF in women with endometrial carcinoma. Fertil Steril 2007.

Women with endometrial adenocarcinoma might have **impaired endometrial response to infertility treatments.**

(due to **progesterone treatment, repeated endometrial sampling**)

Recurrence after Remission (for 5-years follow up)

**15 recurrence occurred within 30*
remissions (50%)**

median follow-up period 74 months (25-103 months)

■ **EC 9rec /14 rem (64.2%)**

■ **AH 6rec / 16 rem (37.5%)**

Recurrence occurred at 18.9 months on an average (EC 7-58, AH 6-19) after finishing MPA administration.

*including 4 (2EC,2AH) patients reached to remission who continued MPA therapy after removal from study

Risk factors for Recurrence after MPA treatment

- | | rate of recurrence |
|--|--------------------|
| ■ Having any treatment free period after CR (2~52months) | 13/18 (72%) |
| ■ Still infertile after ART | 6/7 (86%) |
| □ Received continuous treatment of EP or ovulation induction | 2/12(17%) |

Continuous EP treatment or ovulation induction is recommended after remission

Treatment after recurrence (n=15)

treatment strategy	number	(EC	AH)
surgery (TAH+ α)	7	(5	2)
re-treatment MPA*	9	(5	4)
systemic chemo	1	(1	0)

9 patients* preferred re-challenging MPA

(Including 2 patients who received surgery after re-MPA)

8 of them achieved remission, but 7 of them recurred again

Results of MPA study

- 26 weeks of MPA 600 mg treatment for EC and AH showed 67% of overall CR rate (55% for EC and 82% for AH).
- Incidence of Grade 3 toxicities were rare.
- No treatment related death or death by progression of disease were recorded
- 15 pregnancy and 12 offspring were acquired in 20 patients.
- 50% of patients recurred after remission.
- High recurrence rate was found in the patients who had any treatment free period or unsuccessful ART. Some of recurrences were found by reproductive endocrinologist.

Synchronous ovarian neoplasma in young women with endometrial cancer in our trial

- Early stage ovarian cancer (EC and LPM) were found coincidentally in two patients during 12 months follow up period.
- One synchronous ovarian cancer (stage IIc, EMCA stage Ib, both endometrioid histology) was found as the first time recurrence at 58 months after remission.
- One patient died by peritonitis carcinomatosis at 44 months after remission. She had repeated MPA treatment three times.
- Totally, we have 4 ovarian or peritoneal cancer in 39 patients. **4 / 39 (10.2 %)**

Synchronous ovarian cancer in young women with endometrial cancer

- Over all coexisting rate of ovarian cancer in stage I endometrial cancer : 5 %
- **Higher incidence (7~30%) was reported in age of 45 years or younger.**
- **Simultaneous carcinoma (both primary) occurred in 2~7 times fold more frequently** than metastasis in coexisting adenocarcinoma of endometrium and ovary in young women.
- Most of them were endometrioid adenocarcinomas.
- Prognoses were relatively favorable, if they received TAH, BSO.

Gitsch et al 1995 Obstet Gynecol

Walse et al 2005 Obstet Gynecol

Soliman et al. 2005 Gynecol Oncol

Nishimura, et al 2005 J.Obstet.Gynaecol .Res

Coincidence of ovarian malignancy in endometrial cancer

Endometrial cancer without peritoneal or distant
metastatic lesion (2000-2007 Kurume University)

- More than 40yrs of age (mean 60.2yrs.) 14/212 (6.6 %)
- Less than 40 yrs of age (mean 33yrs.) 3/20 (15.0 %)

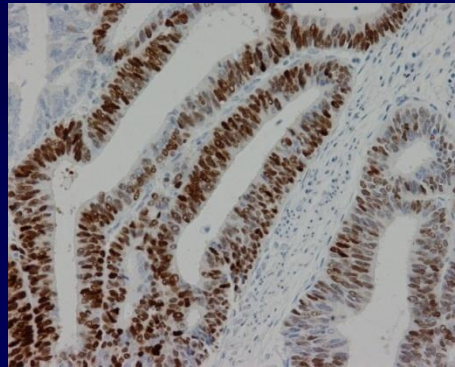
Higher incidence of coincidence of ovarian malignancy in young
endometrial cancer patients

Clonality analysis in synchronous tumors endometrium and ovary

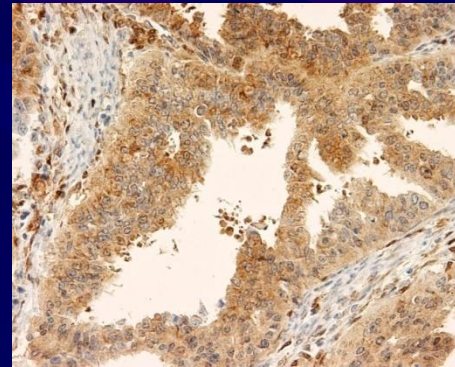
- Immunohistochemistry in ER, PR, PTEN, β -catenin in endometrium and ovary in EMCA with ovarian tumor, metastatic or independent



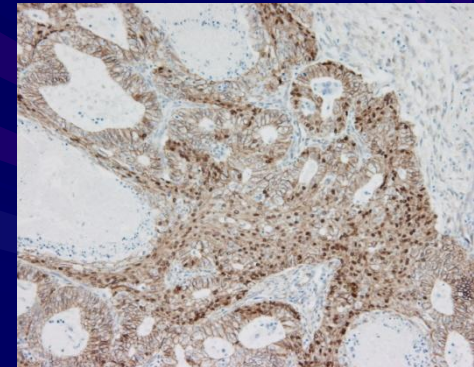
ER in EM



PR in EM



PTEN in EM



β -catenin in OV

Metastatic: both tumor shows similar expression

Individual : each tumor has different expression

Identity of onco-related genes expression in both endometrium and ovary in EMCA

	less than 40y*	over 40y**
No.of patients EMCA with OVCA	5	7
Complete Identical expression (ER, PR, PTEN, β -catenin expression were same in both EM and OV)	0/5	4/7
Complete identical expression in same histology (Endometrioid adenocarcinoma)	0/4	4/6

Both primary tumor in EM and Ovary (synchronous cancer) occurred in younger patients

* :31 cases less than 40yrs of age EMCA with ovarian malignancy (1990-2008)

** :41cases more than 40yrs of age EMCA with ovarian malignancy (2004-2007)

Synchronous ovarian cancer in young women with endometrial cancer

- endometrial cancer patients in young women also have a risk of synchronous ovarian or peritoneal cancer.
- In case of longer or repeated conservative therapy, extra uterine lesion should be paid attention.
- In surgical treatment for endometrial cancer in young women, **ovarian preservation** should be decided with taking into consideration the **high rate of coexisting ovarian malignancy**.

Conclusions

- Fertility-sparing treatment by high-dose MPA is coming to a standard care for the patients with G1 EC without myometrial invasion.
- Even in the responders, close follow up with continuous hormonal treatment or immediate infertility treatment is required because of their substantial recurrence rate. Also it should be cared about their risk for ovarian cancer.
- Close communication and collaboration between gynecologic oncologist and reproductive endocrinologist is indispensable to realize patients' wish in safe.

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Thank you for your attention !