

Fertility preservation in young patients with endometrial cancer !

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Epidemiology

Endometrial cancer is the most common gynecologic malignancy typically in the postmenopausal women.



- 1-Benshushan A. Endometrial adenocarcinoma in young patients: evaluation and fertility-preserving treatment. *Eur J Obstet Gynecol Reprod Biol* 2004; 117:132–137.
- 2-Crissman JD, Azoury RS, Barnes AE, et al. Endometrial carcinoma in women 40 years of age or younger. *Obstet Gynecol* 1981; 57:669–704.
- 3-Gallup DG, Stock RJ. Adenocarcinoma of the endometrium in women 40 years of age or younger. *Obstet Gynecol* 1984; 64:417–420.
- 4- Lowe MP, Bender D, Sood AK. Two successful pregnancies after conservative treatment of endometrial cancer and assisted reproduction. *Fertil Steril* 2002; 77:188–189.
- 5- Randall TC, Kurman RJ. Progesterin treatment of atypical hyperplasia and well differentiated carcinoma of the endometrium in women under age 40. *Obstet Gynecol* 1997; 90:434–440.



Common Types of Cancer	Estimated New Cases 2017	Estimated Deaths 2017
1. Breast Cancer (Female)	252,710	40,610
2. Lung and Bronchus Cancer	222,500	155,870
3. Prostate Cancer	161,360	26,730
4. Colon and Rectum Cancer	135,430	50,260
5. Melanoma of the Skin	87,110	9,730
6. Bladder Cancer	79,030	16,870
7. Non-Hodgkin Lymphoma	72,240	20,140
8. Kidney and Renal Pelvis Cancer	63,990	14,400
9. Leukemia	58,130	24,500
10. Endometrial Cancer	61,380	10,920

Endometrial cancer represents 3.6% of all new cancer cases in the U.S.

3.6%

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Endometrial cancer is most frequently diagnosed among women aged 55-64.

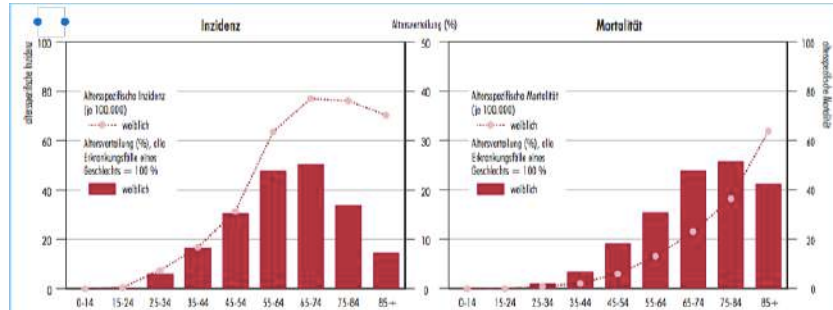
Median Age At Diagnosis

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1. Inzidenz des Endometriumkarzinoms in Österreich (Altersverteilung und altersspezifische Inzidenz bzw. Mortalität der bösartigen Neubildungen der Gebärmutter [ICD 10: C53-C55], 2009-2011). Quelle: Statistik Austria, Österreichisches Krebsregister (Stand: 17.10.2013) und Todesursachenstatistik. Nachdruck mit freundlicher Genehmigung aus: Statistik Austria (Hrsg.), Krebsinzidenz und Krebsmortalität in Österreich 2014. Wien, 2014.

2015 NATIONAL SUMMARY

Comparison of success rates across clinics may not be meaningful. Patient medical characteristics and treatment approaches vary (see page 11-20).

2015 ART and Procedural Factors ^a		Patient Demographics ^b	
Type of clinic	100% IVF, 0% ESU, 0% ESU	Taken fertility	12%
Location	100% Fertility	Partner factor	5%
Female partner	100%	Maternal factor	5%
Male partner	0%	Other factors	17%
Unknown	0%	Unknown	17%
Other	0%	Other	0%
Unknown	0%	Unknown	0%

2015 ART SUCCESS RATES^a Total number of cycles^b: 211,008 (includes 4,082 cycles using frozen eggs)

Type of Cycle	<35	35-37	38-40	41-42	43-44	≥44
Fresh Embryos from Nucleolar Eggs						
Number of cycles	84,200	13,275	10,181	6,870	6,849	1,760
Number of transfers	4.4	4.4	4.2	4.0	3.7	3.5
Average number of attempts (transfers)	1.9	1.9	1.7	1.7	1.7	1.7
Percentage of cycles resulting in live births (%)	40.3	37.0	35.1	33.3	32.3	31.1
Percentage of live births resulting in pregnancies (%)	36.7	33.6	31.7	29.8	28.8	27.7
Outcomes per Cycle						
Percentage of cycles resulting in live births (single or twinning) (%)	21.3	17.0	15.1	13.7	12.8	12.0
Percentage of cycles resulting in pregnancies (live births) (%)	25.1	22.2	20.3	18.5	17.5	16.7
Percentage of cycles resulting in live births (%)	7.9	5.0	3.9	3.2	2.9	2.7
Percentage of cycles resulting in pregnancies (%)	20.1	16.1	14.4	12.3	11.6	10.9
Percentage of cycles resulting in pregnancies (%)	38.8	35.9	33.1	30.1	27.7	26.7
Outcomes per Transfer						
Number of transfers	27,220	12,644	10,273	4,763	3,849	1,102
Percentage of transfers resulting in live births (single or twinning) (%)	36.0	32.0	29.9	27.5	26.5	25.6
Percentage of transfers resulting in pregnancies (live births) (%)	38.2	35.1	32.3	29.3	27.8	26.8
Percentage of transfers resulting in live births (%)	12.6	8.1	6.1	5.2	4.8	4.5
Percentage of transfers resulting in pregnancies (%)	46.3	42.9	39.9	36.5	34.6	33.6
Percentage of transfers resulting in pregnancies (%)	55.8	52.0	48.9	45.5	43.8	42.8
Frozen Embryos from Nucleolar Eggs						
Number of cycles	32,204	10,806	12,289	4,782	2,249	886
Number of transfers	32,204	10,806	12,289	4,782	2,249	886
Average number of attempts (transfers)	1.0	1.0	1.0	1.0	1.0	1.0
Percentage of cycles resulting in live births (single or twinning) (%)	45.1	42.6	38.2	35.2	32.4	30.2
Percentage of cycles resulting in pregnancies (live births) (%)	38.4	35.8	32.7	29.7	27.3	25.8
Percentage of cycles resulting in pregnancies (live births) (%)	31.1	28.5	25.4	22.4	20.1	18.6
Percentage of cycles resulting in live births (%)	18.3	15.5	13.2	11.1	10.1	9.4
Percentage of cycles resulting in pregnancies (%)	46.3	42.9	39.9	36.5	34.6	33.6
Percentage of cycles resulting in pregnancies (%)	55.8	52.0	48.9	45.5	43.8	42.8
Number of Egg/Embryo Donor Cycles	12,289	11,283	9,963	3,998	1,981	781
Donor Eggs						
Number of cycles	1,228	1,128	996	398	198	78
Number of transfers	1,228	1,128	996	398	198	78
Percentage of cycles resulting in live births (single or twinning) (%)	42.2	39.1	35.1	31.1	28.1	26.1
Percentage of cycles resulting in pregnancies (live births) (%)	35.1	32.1	28.1	24.1	21.1	19.1
Percentage of cycles resulting in live births (%)	15.1	12.1	10.1	8.1	7.1	6.1
Percentage of cycles resulting in pregnancies (%)	42.2	39.1	35.1	31.1	28.1	26.1
Percentage of cycles resulting in pregnancies (%)	55.8	52.0	48.9	45.5	43.8	42.8

CURRENT SERVICES & PROFILE Number of reporting clinics: 404

Service	Percentage of clinics	Clinic profile
Donor eggs	8%	IVF/ESU
Donor embryos	27%	ESU/IVF
Single women	40%	ESU/IVF
		ESU/IVF
		ESU/IVF

CDC Centers for Disease Control and Prevention
CDC 24/7: Saving Lives. Protecting People™

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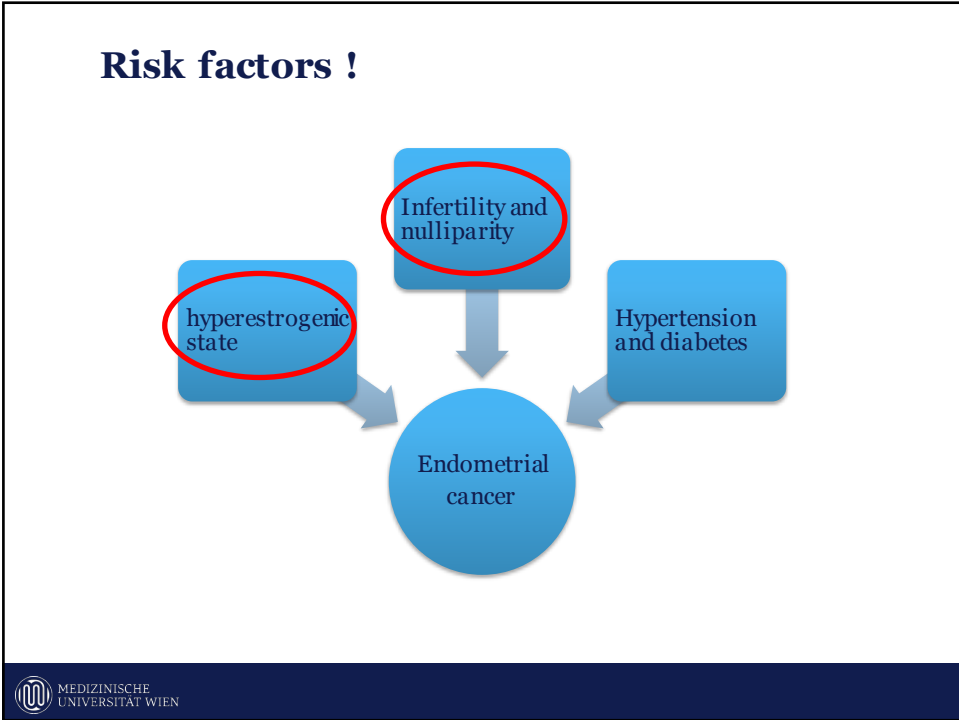
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■ < 26 Jahre
 ■ 26 bis 30 Jahre
 ■ 31 bis 35 Jahre
 ■ 36 bis 40 Jahre

Versuche je Paar	Altersklasse der Frauen				Summe Paare		Summe Versuche
	< 26 Jahre	26 bis 30 Jahre	31 bis 35 Jahre	36 bis 40 Jahre	absolut	Prozent	
1	213	948	1.572	1.306	4.039	60,9	4.039
2	95	419	757	603	1.874	28,3	3.748
3	33	107	221	222	583	8,8	1.749
4	13	28	41	45	127	1,9	508
> 4	-	3	5	2	10	0,2	50
Summe	354	1.505	2.596	2.178	6.633	100,0	10.097
in Prozent	5 %	23 %	39 %	33 %	100 %		

Quelle: CÖG/ÖBIG 2017, IVF-Register 2016



Hyperestrogenic state

1. Obesity
2. PCO
3. Anovulation
4. Irregular menses
5. Functional ovarian tumors



Presence of two or more polyps in patients with polycystic ovary syndrome increases the probability of pre-malignant and malignant changes !

1-Montz FJ, Bristow RE, Bovicelli A, et al. Intrauterine progesterone treatment of early endometrial cancer. Am J Obstet Gynecol 2002; 186:651-657.
 2- Kilecdağ EB, Haydardeoglu B, Cok T, Parlakgumus AH, Simsık E, Bolat FA. Polycystic ovary syndrome and increased polyp numbers as risk factors for malignant transformation of endometrial polyps in premenopausal women. Int J Gynaecol Obstet 2011; 112: 200-203.

Key Symptoms ?

1. Abnormal bleeding !
2. Prolonged anovulation



EXAMPLE OF COMPLETED CHART

Towel		1	2	3	4	5	6	7	8
1									
5									
20									
TAMPON		1	2	3	4	5	6	7	8
1									
5									
10									
DAILY SCORE		2	13	10	21	3	2		
TOTAL SCORE = 260									

**Subset of young women with
endometrial cancer are slim
with regular menses !**

Gynecologic Oncology 83, 388–393 (2001)
doi:10.1006/gyno.2001.6434, available online at <http://www.idealibrary.com on> **IDEAL**[®]



Endometrial Cancer in Women 40 Years Old or Younger

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Yuchiao Chang, Ph.D.,[§] and Arlan F. Fuller, M.D.^{*§}

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Brigham and Women's Hospital, Boston, Massachusetts 02115

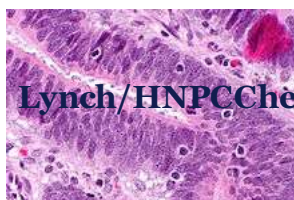
**In the current study the normal-weight
woman does seem to be at higher risk to
develop higher stage disease and is
more likely to have high-risk histology !**

Other malignancy !

Ovarian malignancy

Young women with endometrial cancer are at
significant risk for concomitant adnexal disease:

- 1- Synchronous primary ovarian tumors (10-29,4 %)
- 2- Endometrial metastases to the ovary (5%)



Gilisch G, Hanzal E, Jensen D, et al. Endometrial cancer in premenopausal women 45 years and younger. *Obstet Gynecol* 1995; 85:504–508.
Walsh C, Holschneider C, Hong Y. Coexisting ovarian malignancy in young women with endometrial cancer. *Obstet Gynecol* 2005; 106:693–699.
Morice P, Fourchotte V, Sideris L. A need for laparoscopic evaluation of patients with endometrial carcinoma selected for conservative treatment. *Gynecol Oncol* 2005; 96:245–248

Human Reproduction vol.12 no.5 pp.959-962, 1997

CASE REPORT

Endometrial carcinoma in a young patient with polycystic ovarian syndrome: first suspected at time of embryo transfer

O.Salha^{1,3}, P.Martin-Hirsch², G.Lane² and V.Sharma¹

¹State Conception Unit, ²Department of Obstetrics and Gynaecology, St James' University Hospital, Leeds, UK

³To whom correspondence should be addressed

At the time of embryo transfer, a small but steady trickle of blood was noted as soon as the embryo transfer catheter was introduced into the uterine cavity. There had been no trauma in the insertion of the catheter which could have explained this loss. Hence this unprovoked bleeding was thought to be suspicious and needed further investigations. The embryo transfer was abandoned and all the embryos were frozen.

O.Salha et al.

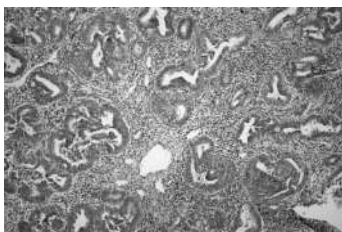
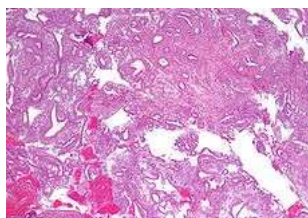


Figure 1. Endometrial curettings showing severe atypical hyperplasia and intra-endometrial adenocarcinoma (original magnification $\times 200$).

Endometrial Hyperplasia Precursor of EM-Ca !

- Simple hyperplasia without atypia - 1 %
- Complex hyperplasia without atypia - 3 %
- Simple atypical hyperplasia - 8 %
- Complex atypical hyperplasia - 29 %



Staging FIGO 2010

Carcinoma of the Endometrium

- IA Tumor confined to the uterus, no or < 1/2 myometrial invasion
- IB Tumor confined to the uterus, > 1/2 myometrial invasion
- II Cervical stromal invasion, but not beyond uterus
- IIIA Tumor invades serosa or adnexa
- IIIB Vaginal and/or parametrial involvement
- IIIC1 Pelvic node involvement
- IIIC2 Para-aortic involvement
- IVA Tumor invasion bladder and/or bowel mucosa
- IVB Distant metastases including abdominal metastases and/or inguinal lymph nodes

ER+/PR+ (by either ligand binding or immunohisto- chemistry)

Grade

Grade 1 tumors have 95% or more of the cancerous tissue forming glands.

Grade 2 tumors have between 50% and 94% of the cancerous tissue forming glands.

Grade 3 tumors have less than half of the cancerous tissue forming glands.

Early endometrial carcinoma is defined as low-grade cancer limited to the uterus !

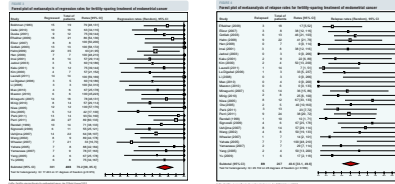
Good prognosis

The available data suggest relative safety and efficacy of progestin treatment for a short window to allow the woman to achieve her reproductive goals!



5-year disease-specific survival rate of 93% in younger patients, in contrast to older patients (86%)

Fertility Preservation !



complete resolution rates ranging from 65.8% to 74% for CAH and 48.2% to 72% for EM Cancer patients

Duska LR, Garrett A, Rueda BR, Haas J, Chang Y, Fuller AF. Endometrial cancer in women 40 years old or younger. *Gynecol Oncol* 2001;83:388-93
 Lee NK, Cheung MK, Shin JY, et al. Prognostic factors for uterine cancer in reproductive-aged women. *Obstet Gynecol* 2007;109(3):655-62



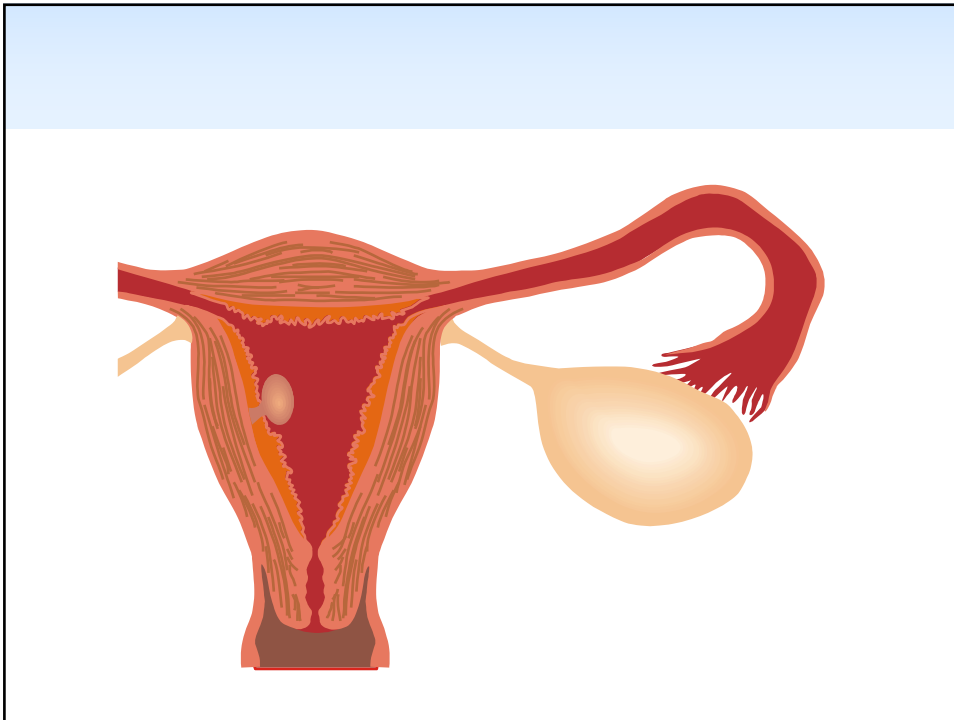
Staging of endometrial carcinoma

1. Pelvic exam
2. Pap smear
3. D&C / Endometrial Biopsy
4. Hysteroscopy
5. Transvaginal ultrasound
6. CT/MRI
7. CA125
8. LSK



Larson DM, Johnson KK, Broste SK, et al. Comparison of D&C and office endometrial biopsy in predicting final histopathologic grade in endometrial cancer. *Obstet Gynecol* 1995; 86:38-42.





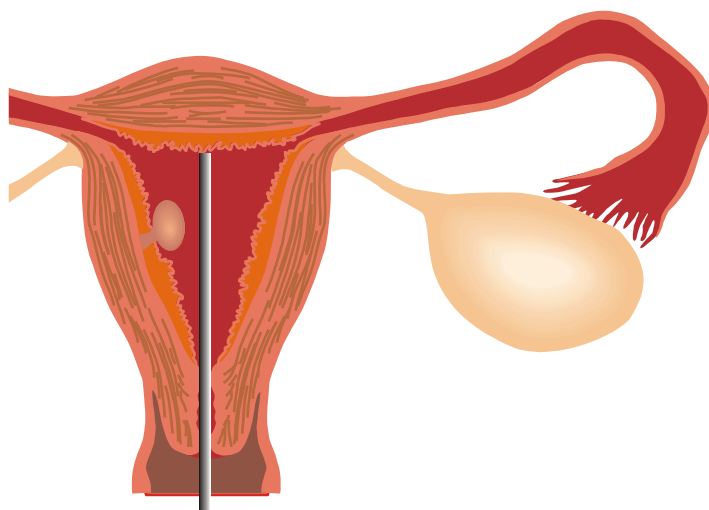
simple endometrial biopsy ?

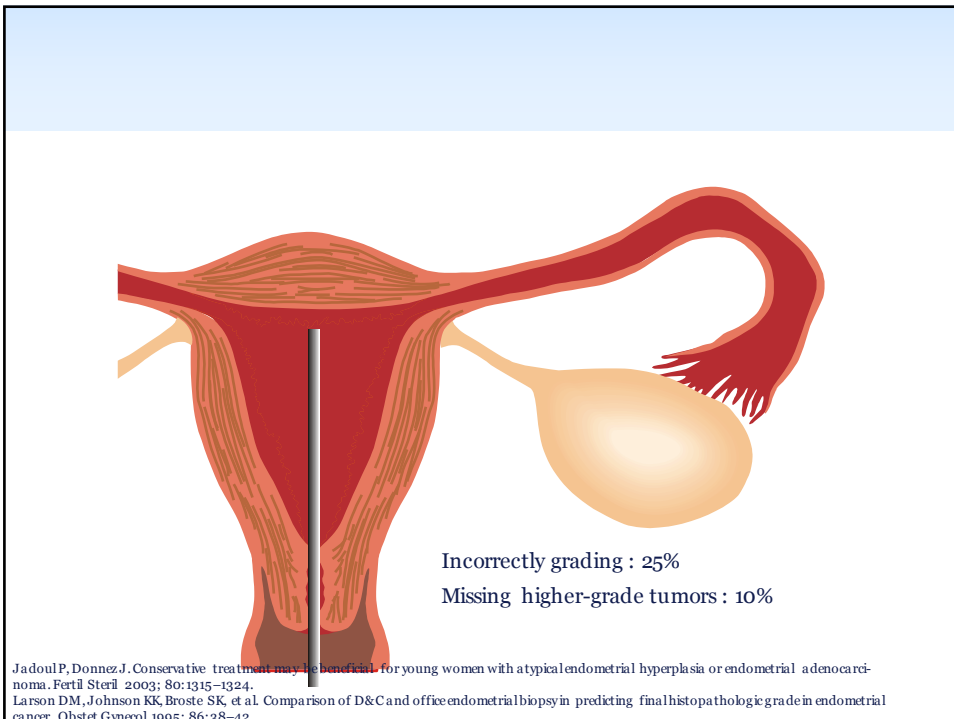
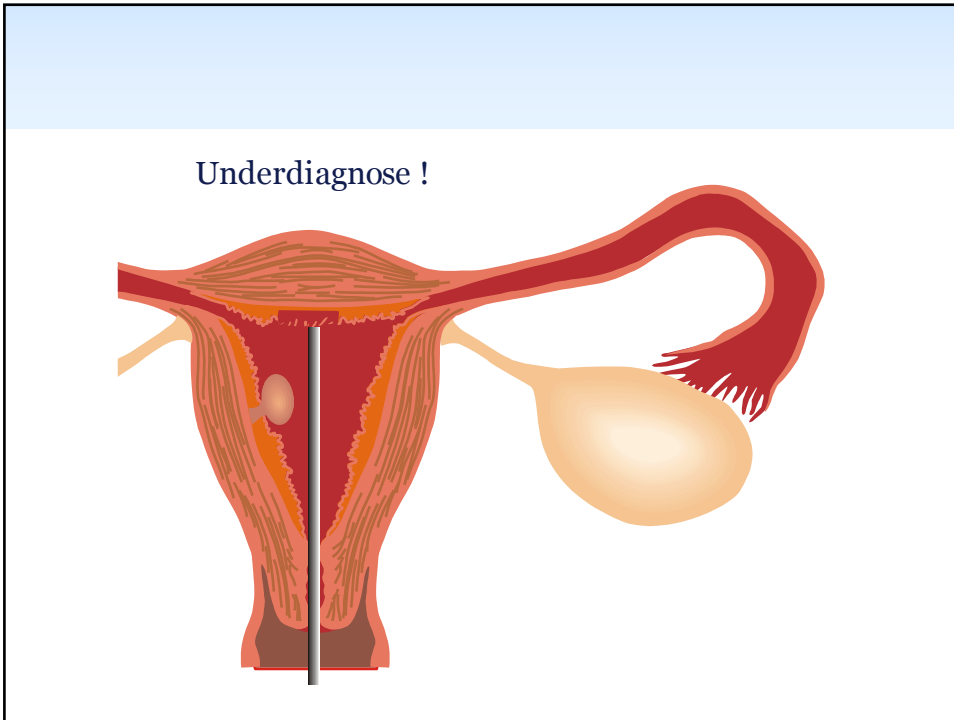


Only D & C?

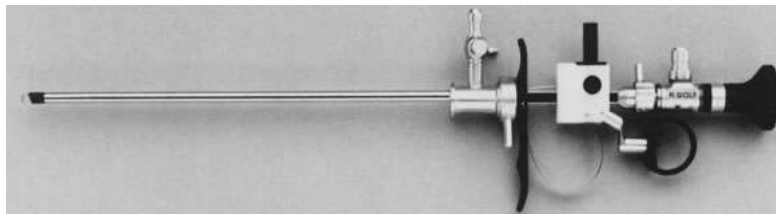


Jadoul P, Donnez J. Conservative treatment may be beneficial for young women with a typical endometrial hyperplasia or endometrial adenocarcinoma. *Fertil Steril* 2003; 80:1315-1324.
Larson DM, Johnson KK, Broste SK, et al. Comparison of D&C and office endometrial biopsy in predicting final histopathologic grade in endometrial cancer. *Obstet Gynecol* 1995; 86:38-42.





Hysteroscopy with D&C



- 1-Hysteroscopy with directed biopsies and D&C
- 2-Following the lesion during the course of therapy
- 3-Sensitivity and specificity of hysteroscopy
in diagnosis of endometrial carcinoma: 86.4% and 99.2%

Huang SY, Jung SM, Ng KK, et al. Ovarian metastasis in a nulliparous woman with endometrial adenocarcinoma failing conservative hormonal treatment. *Gynecol Oncol* 2005; 97:652-655

Conservative surgical management of stage IA endometrial carcinoma for fertility preservation

Ivan Mazzon, M.D.,^a Giacomo Corrado, M.D., Ph.D.,^b Valeria Masciullo, M.D., Ph.D.,^c
Daniela Morriconi, M.D.,^a Gabriella Ferrandina, M.D.,^b and Giovanni Scambia, M.D.^c

^a Endoscopic Gynecologic Unit, Nuova Villa Claudia, Rome; ^b Department of Oncology, Catholic University of the Sacred Heart, Campobasso; and ^c Division of Gynecologic Oncology, Catholic University of the Sacred Heart, Rome, Italy

Objective: To describe an innovative method to preserve fertility in young women with stage IA endometrial cancer with use of hysteroscopic resection followed by administration of 160 mg of megestrol acetate.

Design: Prospective study.

Setting: Division of Gynecologic Oncology, Catholic University of the Sacred Heart, and the Endoscopic Gynecologic Unit, Nuova Villa Claudia, Rome, Italy.

Patient(s): Six young patients with stage IA endometrial cancer.

Intervention(s): Conservative resectoscopic treatment using a three-step technique in which each step is characterized by a pathologic analysis: the removal of the tumor (step 1), the removal of the endometrium adjacent to the tumor (step 2), and the removal of the myometrium underlying the tumor (step 3).

Main Outcome Measure(s): Therapy of stage IA endometrial cancer and pregnancy.

Result(s): The conservative surgery was effective because results of transvaginal ultrasound examination and diagnostic hysteroscopy with target biopsies at 3, 6, 9, and 12 months after surgery were negative for atypia or malignancy. Moreover, four out of six patients (66%) achieved childbearing.

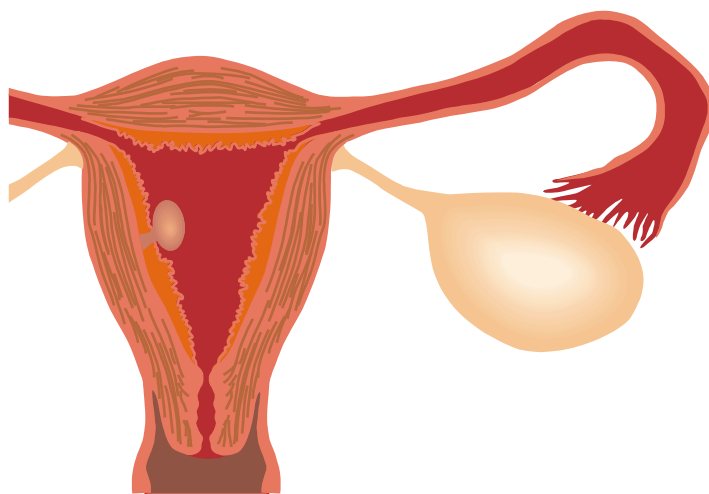
Conclusion(s): This method, under a close postsurgical follow-up, might represent a novel therapeutic option for those women with stage IA endometrial cancer who wish to preserve fertility. (*Fertil Steril*® 2010;93:1286-9. ©2010 by American Society for Reproductive Medicine.)

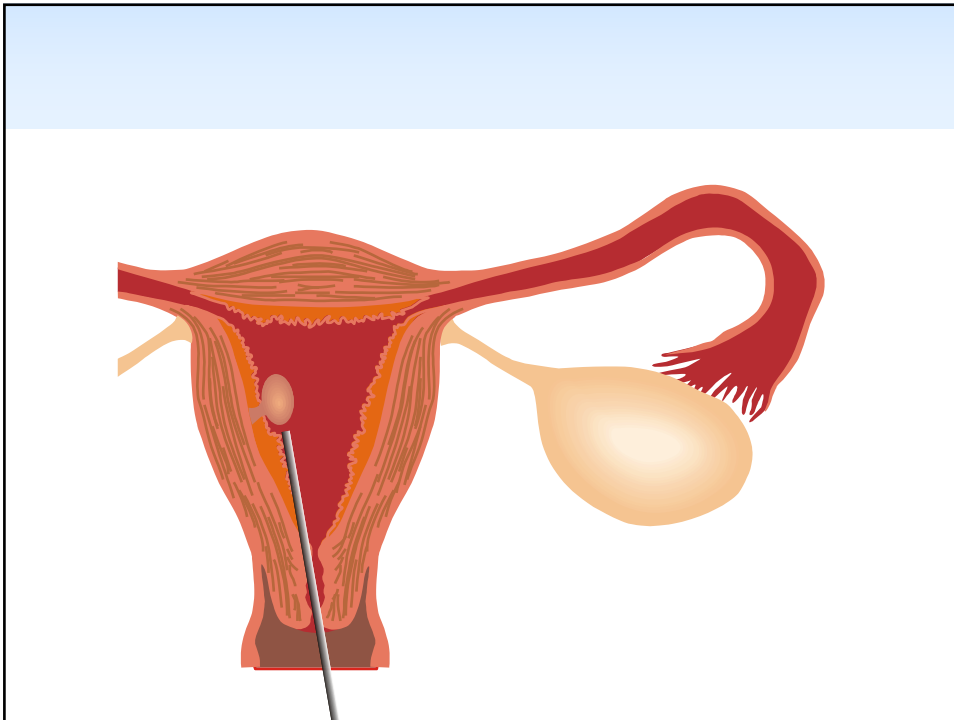
Key Words: Endometrial cancer, fertility preservation, hysteroscopy, hormone therapy

TABLE 1						
Clinical characteristics of our 6 patients.						
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age (y)	31	31	26	38	36	30
BMI	22	23	18	22	23	25
Parity	0	0	0	0	0	0
Infertility	I	I	I	I	I	I
Menarche (y)	12	11	15	12	11	12
Symptomatology	Haematic endless	–	Bleeding	Haematic endless	Haematic endless	Bleeding
Ultrasound scan	Increased endometrial thickness	Increased endometrial thickness	Increased endometrial thickness	Increased endometrial thickness	Increased endometrial thickness	Increased endometrial thickness
HYS + biopsy	EEA G1	EEA G1	EEA G1	EEA G1	EEA G1	EEA G1
ER/PR	+/+	+/+	+/+	+/+	+/+	+/+
Stage of disease assessed by MRI	IA	IA	IA	IA	IA	IA

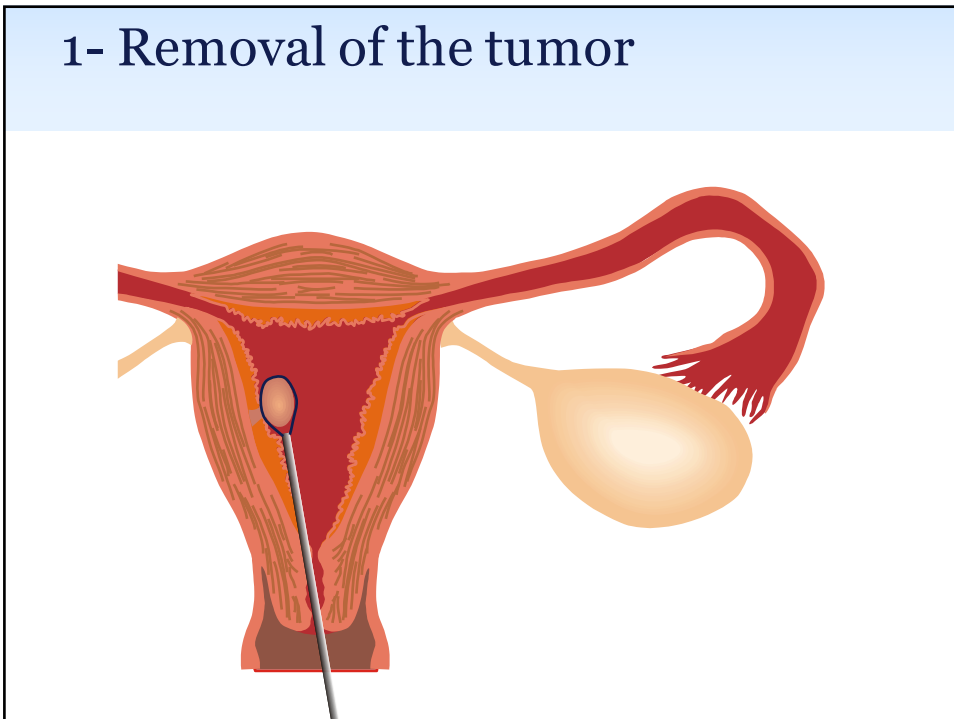
Note: HYS = hysteroscopy; MRI = magnetic resonance imaging; EEA = endometrioid endometrial adenocarcinoma; G1 = grading 1.

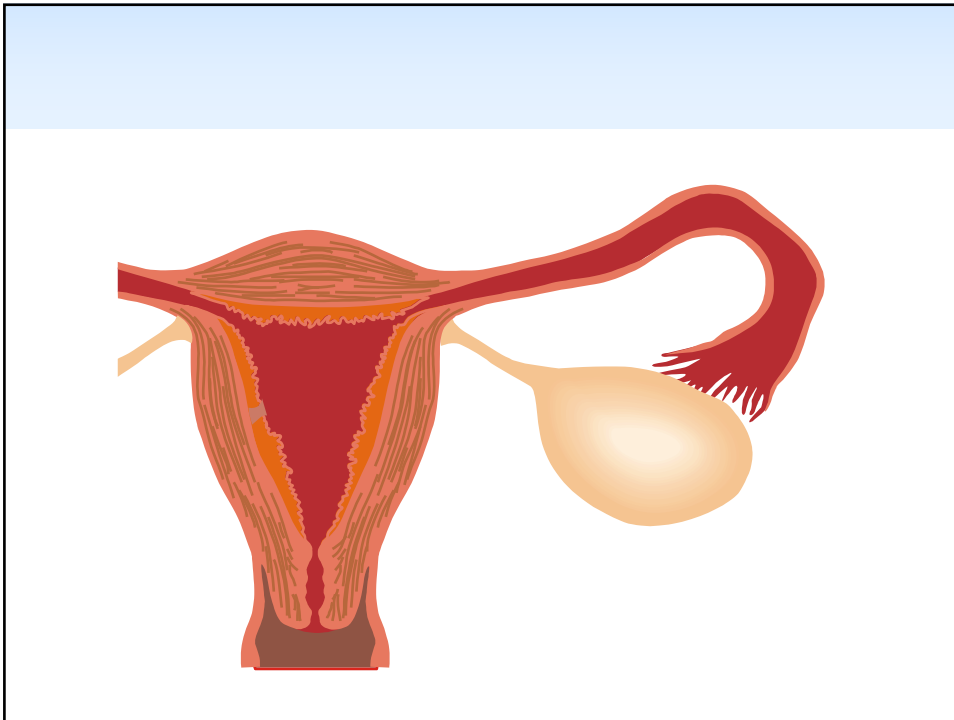
Mazzon. Fertility preservation in endometrial cancer. Fertil Steril 2010.



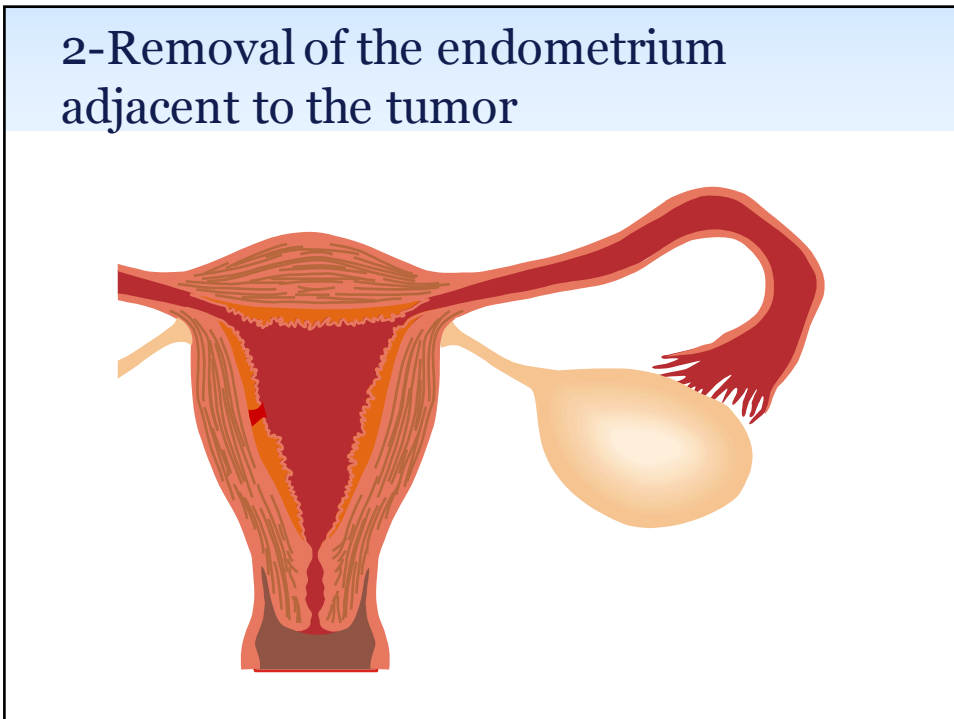


1- Removal of the tumor

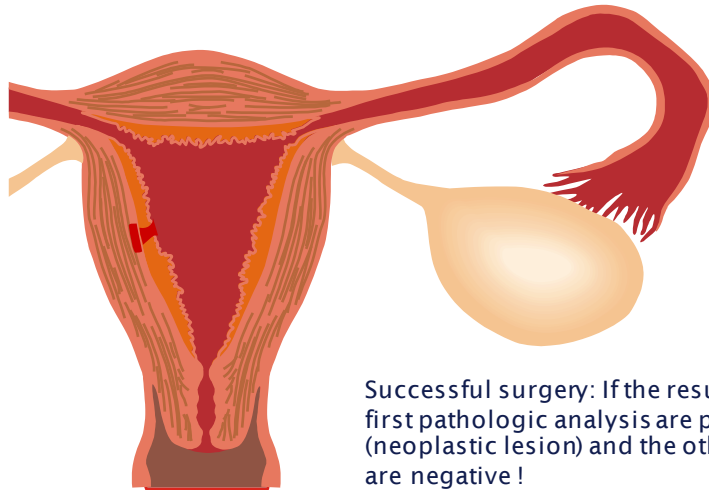




2-Removal of the endometrium adjacent to the tumor



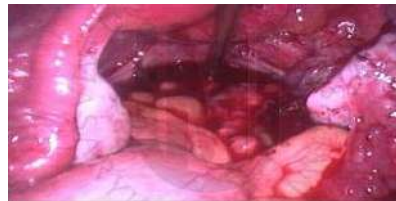
3-Removal of the myometrium underlying the tumor.



Successful surgery: If the results of the first pathologic analysis are positive (neoplastic lesion) and the other two are negative !

Hysteroscopy with D&C

Fluid based hysteroscopy could cause retrograde seeding of the peritoneal cavity with malignant cells, the prognostic significance of positive peritoneal cytology in clinical stage I endometrial adenocarcinoma remains controversial !

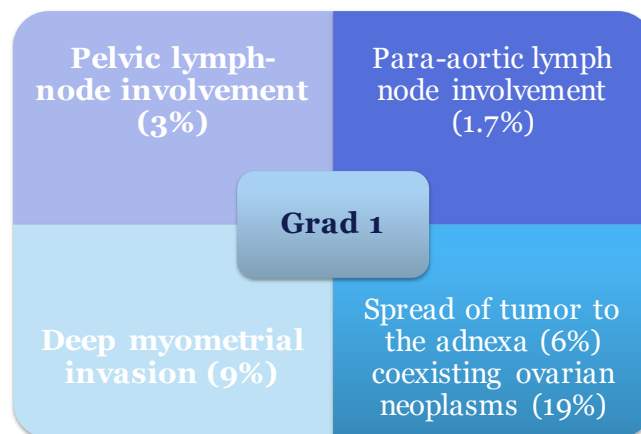


Bradley WH, Boente MP, Brooker D. Hysteroscopy and cytology in endometrial cancer. *Obstet Gynecol* 2004; 104:1090-1093.
Egarter C, Krestan C, Kurz C. Abdominal dissemination of malignant cells with hysteroscopy. *Gynecol Oncol* 1996; 63:143-144.
Revel A, Tsafir A, Anteby SO, Shushan A. Does hysteroscopy produce intra-peritoneal spread of endometrial cancer cells? *Obstet Gynecol Surv* 2004; 59:280-284.

Imaging ?



Grade 1 Endometrial carcinoma



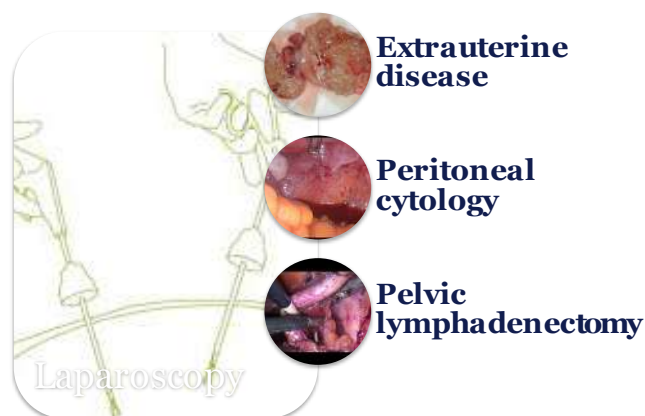
MRI?

1-For the detection of myometrial invasion, contrast-enhanced MRI, is superior to ultrasonography and computed tomography scan

(Sensitivity and specificity of 74%)

2-MRI can also be used to evaluate lymph nodes. Lymph nodes over 1 cm and with central necrosis are suspicious.

The Role of Laparoscopy



Benshushan A. Endometrial adenocarcinoma in young patients: evaluation and fertility-preserving treatment. *Eur J Obstet Gynecol Reprod Biol* 2004;117:132-137.

Morice P, Fourchotte V, Sideris L. A need for laparoscopic evaluation of patients with endometrial carcinoma selected for conservative treatment. *Gynecol Oncol* 2005; 96:245-248.

Coexisting Ovarian Malignancy in Young Women With Endometrial Cancer

Christine Walsh, MD, Christine Holschneider, MD, Yen Hoang, MD, Khai Tieu, MD, Beth Karlan, MD, and Ilana Cass, MD

OBJECTIVE: In premenopausal women with endometrial cancer, ovarian preservation may be a consideration. Our objective was to examine the occurrence of coexisting ovarian malignancy and to identify predictors of adnexal involvement.

METHODS: With institutional review board approval, a retrospective chart review was conducted of young women with endometrial cancer identified at 4 affiliated institutions from 1996 to 2004.

RESULTS: Among 102 young women (aged 24–45 years) who underwent hysterectomy for endometrial cancer, 26 (25%) were found to have coexisting epithelial ovarian tumors: 23 were classified as synchronous primaries, and 3 as metastases. Ovarian cancer histology was endometrioid in 92% of cases. Among the 26 cases of coexisting ovarian involvement, 12 (46%) had grade 1 endometrial cancer on preoperative biopsy, 4 (15%) had normal preoperative imaging of the adnexa, and 4 (15%) had benign-appearing ovaries at the time of intraoperative assessment. On final pathology, 18 of 26 cases (69%) occurred in patients with grade 1 endometrial cancers, and 15 (58%) occurred with inner myometrial invasion. Our study further highlights the risk of conservative management with 1 case of ovarian cancer diagnosed 9 months after hysterectomy with ovarian conservation for a stage IA, grade 1 endometrial cancer and a case of advanced endometrial cancer metastatic to the ovaries developing 3 years after successful resolution of a grade

1 endometrial cancer treated with megestrol acetate (Megace).

CONCLUSION: Careful preoperative and intraoperative assessment of the adnexa is mandatory in young women with endometrial cancer. Those who desire ovarian preservation should be counseled regarding the high rate of coexisting ovarian malignancy.

(*Obstet Gynecol* 2005;106:693–9)

LEVEL OF EVIDENCE: II-3

Coexisting ovarian malignancy

Retrospective analysis of 102 subjects
ages 24 to 45 years

Ovarian malignancies were identified in 26 subjects (25%)
23 S. synchronous primaries, 3 S. metastases

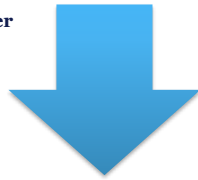
18 (69%) had grade 1 endometrial
cancer on final pathology

4 (15%) had normal
preoperative imaging

4 (15%) had benign-
appearing ovaries
during surgery

Coexisting Ovarian Malignancy

Stage I ovarian cancer
Excellent prognosis



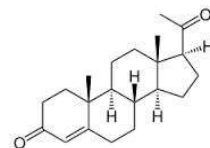
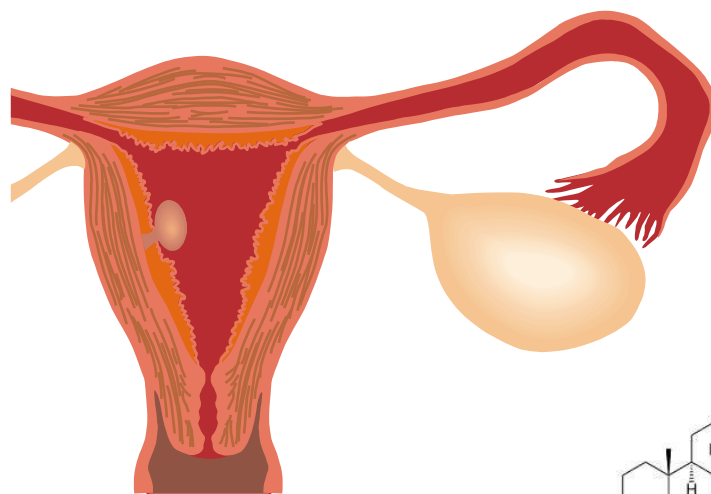
2-4,6%
In Women
>45

10-29% in
Women
<45



Higher stage tumors
and poorer
prognosis

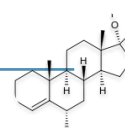
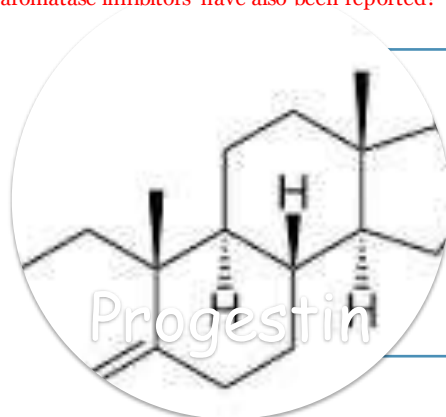
Wahs C, Holschneider C, Hoang Y. Coexisting ovarian malignancy in young women with endometrial cancer. Obstet Gynecol 2005; 106:693-699.



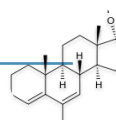
Conservative management :

- 1-With what ?
- 2-How lang ?

Uses of gonadotrophin-releasing hormone agonists, anti-estrogens and aromatase inhibitors have also been reported!



**Medroxypro-
gesterone
acetate
(MPA) 500-
1000 mg/d**



**Megestrol-
acetate
80-160
mg/d**



IUD

Benshushan A. Endometrial adenocarcinoma in young patients: evaluation and fertility-preserving treatment. Eur J Obstet Gynecol Reprod Biol 2004; 117:132-137.

Montz EJ, Bristow RE, Bovicelli A, et al. Intrauterine progesterone treatment of early endometrial cancer. Am J Obstet Gynecol 2002; 186:651-657.

Risks of conservative management !

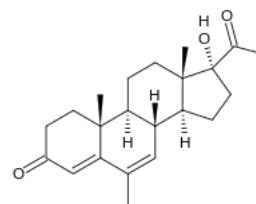
- 1-The risk of disease progression during conservative management of grade 1 endometrial carcinoma: 6%
- 2-Clinical understaging of a more advanced cancer
- 3- Presence or development of a simultaneous primary ovarian malignancy
- 4- Fertility options ?

**Deferral of definitive surgery to achieve childbearing,
but no replacement !!**

Pinto AB, Gopal M, Herzog TJ, et al. Successful in vitro fertilization pregnancy after conservative management of endometrial cancer. Fertil Steril 2001; 76:826-829.
Vinker S, Shani A, Open M, et al. Conservative treatment of adenocarcinoma of the endometrium in young patients. Is it appropriate? Eur J Obstet Gynecol Reprod Biol 1999; 83:63-65.

Complications of Progestin therapy ?

- 1-thrombophlebitis
- 2-weight gain,
- 3-mood or libido changes
- 4-headaches,
- 5-breast tenderness
- 6-sleep disorders
- 7-leg cramps
- 8-Liver dysfunction
- 9- Thrombus formation



600 mg MPA

**A-thromboembolism history,
B-breast cancer**

C- hepatic dysfunction

Kaku T, Yoshikawa H, Tsuda H. Conservative therapy for adenocarcinoma and atypical endometrial hyperplasia of the endometrium in young women: central pathologic review and treatment outcome. Cancer Lett 2001; 167: 39-48.
Ushijima K, Yahata H, Yoshikawa H, Konishi I, Yasugi T, Saito T, et al. Multicenter phase II study of fertility-sparing treatment with medroxyprogesterone acetate for endometrial carcinoma and atypical hyperplasia in young women. J Clin Oncol 2007; 25:2798-803.

IUD ?

- 1- high-risk surgical patients with grade I endometrial cancer and no evidence of extrauterine disease.
- 2- It releases 20 mcg of levonorgestrel per day , generating a localized effect within the endometrium !
- 3- higher concentrations of progestin to the uterine mucosa compared to oral MA,
- 4- Superior results in endometrial hyperplasia compared with oral MA



How long ?

10 weeks to 12 Months !



Surveillance ?



Sampling or D & C or HSC every 3 to 6 months



Regression : Conception (3 Months reevaluation)

RESEARCH

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GENERAL GYNECOLOGY

Regression, relapse, and live birth rates with fertility-sparing therapy for endometrial cancer and atypical complex endometrial hyperplasia: a systematic review and metaanalysis

Ioannis D. Gallos, MD; Jason Yap, MBChB; Madhurima Rajkhowa, MD; David M. Luceley, MD; Arri Coomarasamy, MD; Janesh K. Gupta, MD

OBJECTIVE: The objective of the study was to evaluate the regression, relapse, and live birth rates of early-stage endometrial cancer (EC) and atypical complex hyperplasia (ACH) with fertility-sparing treatment.

STUDY DESIGN: This was a metaanalysis of the proportions from observational studies with a random-effects model and a meta-regression to explore for heterogeneity.

RESULTS: Thirty-four observational studies, evaluating the regression, relapse, and live birth rates of early-stage EC (408 women) and ACH (151 women) with fertility-sparing treatment. Fertility-sparing treatment for EC achieved a pooled regression rate of 76.2%, a relapse rate

of 40.6%, and a live birth rate of 28%. For ACH the pooled regression rate was 85.6%, a relapse rate of 26%, and a live birth rate of 26.3%. Twenty women were diagnosed with ovarian cancer (concurrent or metastatic) during follow-up (3.6%) and 10 progressed to higher than stage I EC (1.9%) from which 2 women died.

CONCLUSION: Fertility-sparing treatment of EC and ACH is feasible and selected women can satisfy their reproductive wishes.

Key words: atypical complex hyperplasia, endometrial cancer, fertility-sparing treatment, live births, progestogens

Cite this article as: Gallos ID, Yap J, Rajkhowa M, et al. Regression, relapse, and live birth rates with fertility-sparing therapy for endometrial cancer and atypical complex endometrial hyperplasia: a systematic review and metaanalysis. Am J Obstet Gynecol 2012;207:286.e1-12.

Assisted reproduction versus spontaneous pregnancy

From the 451 women that had fertility-sparing treatment for EC or ACH, 142 had assisted reproduction treatment to achieve pregnancy and 56 of them achieved at least 1 live birth. This amounts to a 39.4% live birth rate. The remaining 309 women are presumed to have tried to spontaneously conceive and 46 women achieved at least 1 live birth, with a rate of 14.9%. This difference between assisted reproduction and spontaneous conception in achieving a live birth was statistically significant ($P = .001$) in meta-regression analysis.



Other options?

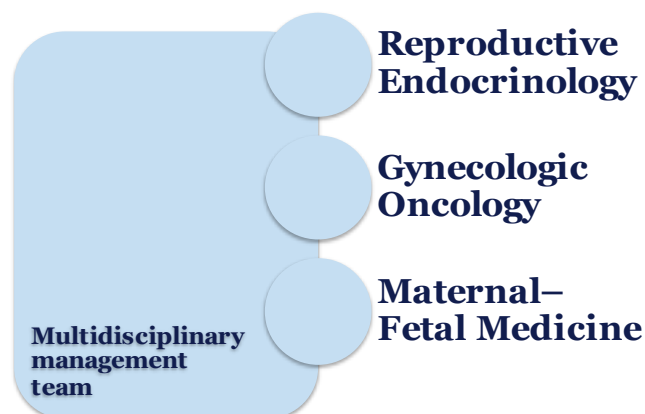
Gestational carrier!

- 1- egg/embryo freezing prior to hysterectomy,
- 2- Hysterectomy with lymph node dissection and preservation of ovaries with the future use

Disadvantages:

- 1- Diminish ovarian reserve or reduce accessibility to the ovaries for oocyte retrieval.
- 2- Risk of microscopic metastatic or concurrent disease to the ovaries or development of metachronous ovarian cancer

[Am J Obstet Gynecol](#). 2014 Mar;210(3):255.e1-4. doi: 10.1016/j.ajog.2013.11.001.
 Reproductive and oncologic outcomes after pregestin therapy for endometrial complex atypical hyperplasia or carcinoma.
 Kulesia R, Singer T, Caruso EA, Holcomb KM, Klibanoff R, Rosenwaks Z, Gupta D.



Conclusiones

1- Detailed informed consent

2-Both physician and patient should be aware of the potential risks of deviation from standard therapy .

Current recommendations are based on a small number of case series and case reports, but no prospective data !

3-Careful oncologic, psychotherapeutic, genetic and reproductive counseling is essential before starting conservative management



**Thank you for
your attention !**

Complete remission?

A thinning of the endometrium as seen on transvaginal ultrasound is associated with an increased chance of responding to progestin therapy.

Total absence of tumor cells during the follow-up diagnostic hysteroscopy with biopsy after hormone therapy!
If the patient does not respond on the first assessment, recommendation to switch to traditional surgery should be performed.

Fertility outcomes of patients with early stage endometrial carcinoma

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Bulent Haydardedeoglu¹, Tayfun Cok¹, Pinar Caglar Aytac¹, Tayfun Bagis² and
Serkan Erkanli²

¹Department of Obstetrics and Gynecology, Baskent University Faculty of Medicine, Ankara, and ²Department of Obstetrics and Gynecology, Acibadem University Faculty of Medicine, Istanbul, Turkey

Table 1 Patients who preferred surgery

Age at diagnosis	Parity	Risk factors for endometrial carcinoma	Risk factors for infertility	Accompanying gynecologic disease	First suspicion at	Polyp	Histology	Grade	Treatment	Medical treatment	Endometrial biopsy negative at	Stage	IVF trial after medical treatment	Pregnancy course
40	G: 4 P: 0	Oligomenorrhea	Uterine septum	Uterine septum	Pap smear	Yes	Endometrioid type adenocarcinoma	2	Surgical	—	—	1B	—	—
37	G: 0 P: 0	Oligomenorrhea	Anovulation	None	Referred with biopsy result	Yes	Endometrioid type adenocarcinoma	1	Surgical	—	—	1A	—	—
37	G: 1 P: 0	Oligomenorrhea	Anovulation + tubal factor	Ovarian cyst	SIS	Yes	Endometrioid type adenocarcinoma	1	Surgical	—	—	1A	—	—
37	G: 0 P: 0	Diabetes	None	Myoma uteri	SIS	Yes	Endometrioid type adenocarcinoma	2	Surgical	—	—	1A	—	—

IVF, *in vitro* fertilization; SIS, saline infusion sonography.

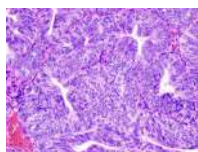
Table 2 Patients who had medical treatment

Age at diagnosis	Parity	Risk factors for endometrial carcinoma	Risk factors for infertility	Accompanying gynecologic disease	First suspicion at	Polyp	Histology	Grade	Treatment	Medical treatment	Endometrial biopsy negative at	Stage	IVF trial after medical treatment	Pregnancy course
37	G: 2 P: 0		Premature ovarian ageing	Myoma Uteri	SIS	Yes	Endometrioid type adenocarcinoma	1	First medical, later surgical	160 mg/day megestrol acetate	3 months	1A	4 times	None
36	G: 0 P: 0		Male Factor	Ovarian cyst	HSG	Yes	Endometrioid type adenocarcinoma	2	First medical, later surgical	80 mg/day megestrol acetate	3 months	Stage 2B clear cell ovarian carcinoma	None	None
28	G: 0 P: 0	Oligomenorrhea	Anovulation + Uterine septum	Uterine septum	SIS	Yes	Endometrioid type adenocarcinoma	1	Medical	160 mg/day megestrol acetate	3 months		7 times	Term delivery of a healthy male baby
38	G: 3 P: 0		Premature ovarian ageing	None	SIS	Yes	Endometrioid type adenocarcinoma	1	Medical	160 mg/day megestrol acetate	6 months		1	None
36	G: 2 P: 0	Oligomenorrhea	Anovulation	None	SIS	Yes	Endometrioid type adenocarcinoma	2	First medical, later surgical	Dydrogesterone 10 mg/day	6 months	1A	1	Pregnant from a thawing cycle, missed abortus *Recurrence at the D&C material, final surgery afterwards

35 ± 4† 0 20% 100% 60% 100% 4.2 ± 1.6† 3.25[§]†7

†Mean ± standard deviation, D&C, dilation and curettage; HSG, hysterosalpingography; IVF, *in vitro* fertilization; SIS, saline infusion sonography.

Reevaluating the safety?



4 Patients with endometrium. ca



persistent to progestin

Concomitant Ovarian disease at Laparoscopy!

Yang YC, Wu CC, Chen CP, et al. Reevaluating the safety of fertility-sparing hormonal therapy for early endometrial cancer. *Gynecol Oncol* 2005; 99: 287–293.
Morice P, Fourchotte V, Sileri L. A need for laparoscopic evaluation of patients with endometrial carcinoma selected for conservative treatment. *Gynecol Oncol* 2005; 96: 245–248.

Human Reproduction vol.12 no.5 pp.959-962, 1997

CASE REPORT

Endometrial carcinoma in a young patient with polycystic ovarian syndrome: first suspected at time of embryo transfer

At the time of embryo transfer, a small but steady trickle of blood was noted as soon as the embryo transfer catheter was introduced into the uterine cavity. There had been no trauma in the insertion of the catheter which could have explained this loss. Hence this unprovoked bleeding was thought to be suspicious and merited further investigations. The embryo transfer was abandoned and all the embryos were frozen.

- 1- Medoxyprogesterone acetate 30 mg twice daily for 6 months
- 2- Hysteroscopy and D&C was
- 3- Well-differentiated adenocarcinoma with no myometrial invasion.
- 4- HE Cum Adenxe + LN

The patient has since requested that her sister-in-law acts as a 'host' to her frozen embryos from the IVF cycle

O.Salha^{1,2}, P.Martin-Hirsch², G.Lane² and V.Sharma¹

¹Assisted Conception Unit, ²Department of Obstetrics and Gynaecology, St James's University Hospital, Leeds, UK
³To whom correspondence should be addressed

O.Salha et al.

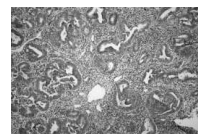


Figure 1. Endometrial curettings showing areas atypical hyperplasia and early endometrial adenocarcinoma (original magnification $\times 200$).

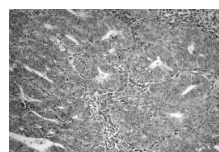


Figure 2. Hysterectomy specimen showing endometrial adenocarcinoma (original magnification $\times 200$).



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Medically complicated cases!



2 Questions !



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No evidence of disease by post-partum serial endometrial samplings or hysterectomy.

Worst case senario

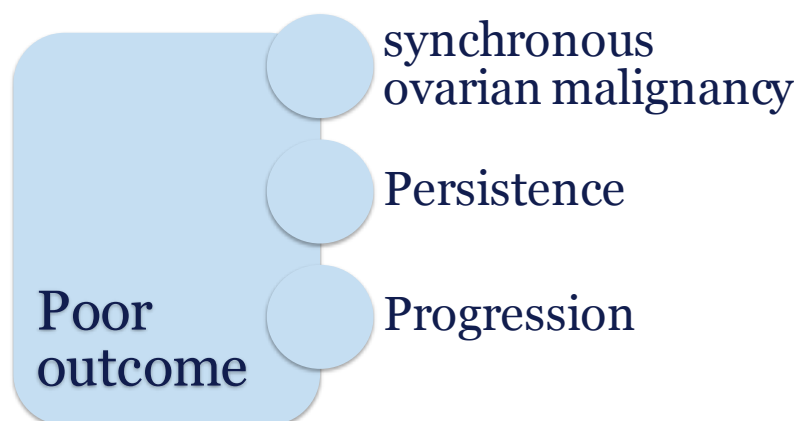


Table 1 Outcomes with conservative treatment of well differentiated endometrial adenocarcinoma from retrospective case series

Study and year [reference]	n	Treatment protocol	Duration of treatment	Tumor regression (n)	Tumor recurrence (n)	Tumor progression (n)	Pregnancy (n)
Ota <i>et al.</i> 2005 [28]	12	MPA 600 mg/day	9–12 months	5	3	5	4
Niwa <i>et al.</i> 2005 [25]	12	MPA	6–10 months	12	8	1	5
Yang <i>et al.</i> 2005 [33]	6	Megestrol acetate	2–5 months	4	2	4	2
Jadoul and Donnez 2003 [21]	5	Endometrial resection + GnRHa	3–6 months	5	0	0	4
Gotlieb <i>et al.</i> 2003 [20]	13	Megestrol acetate or MPA	2–8 months	13	6	0	3 (several pending)
Wang <i>et al.</i> 2002 [17]	9	Megestrol acetate ± tamoxifen ± GnRHa	At least 8 weeks	8	4	0	4
Kaku <i>et al.</i> 2001 [22]	12	MPA	1–12 months	9	2	1	2
Kim <i>et al.</i> 1997 [23]	7	Megestrol acetate	3 months	4	2	0	0
Randall and Kurman 1996 [5]	12	Megestrol acetate or MPA	3–18 months	9	1	0	4

MPA, medroxyprogesterone acetate.

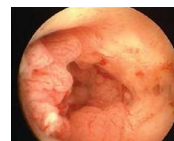
Epidemiology

Endometrial cancer is the most common gynecologic malignancy in the United States, with over 40,000 cases diagnosed each year, typically in the postmenopausal women. In 2013, the National Cancer Institute estimates 49,560 new cases in the United States and 8190 deaths.

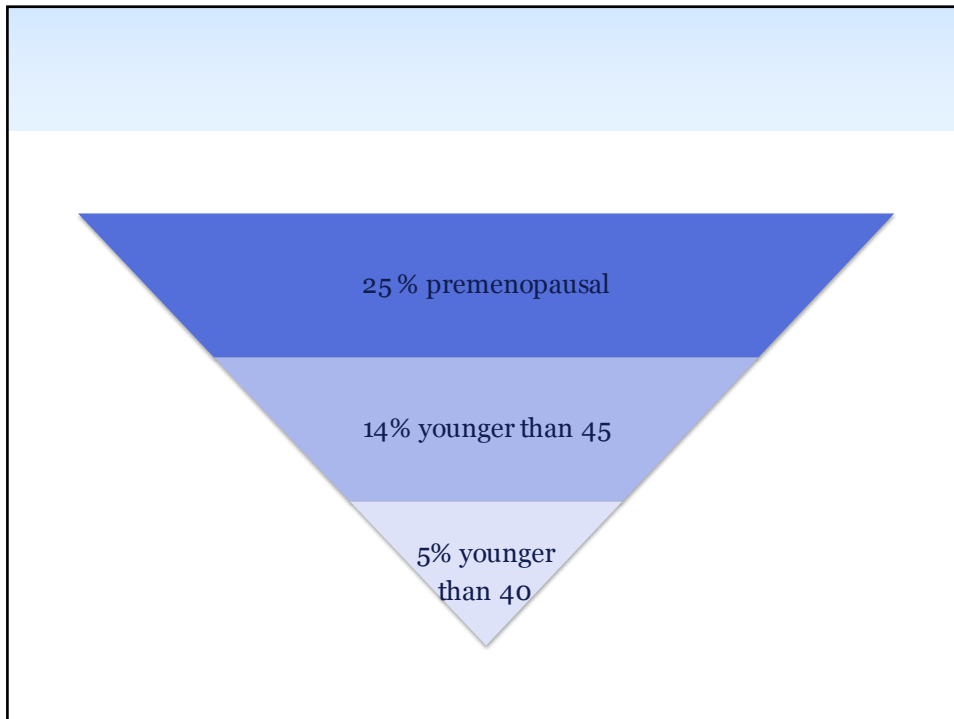
25% of cases affect premenopausal women.

14% of endometrial cancers are diagnosed in women younger than 45 years old

5% of these tumors are diagnosed in women younger than 40 years old



- 1-Benshushan A. Endometrial adenocarcinoma in young patients: evaluation and fertility-preserving treatment. *Eur J Obstet Gynecol Reprod Biol* 2004; 117:132–137.
 2-Crissman JD, Azoury RS, Barnes AE, et al. Endometrial carcinoma in women 40 years of age or younger. *Obstet Gynecol* 1981; 57:699–704.
 3-Gallup DG, Stock RJ. Adenocarcinoma of the endometrium in women 40 years of age or younger. *Obstet Gynecol* 1984; 64:417–420.
 4- Lowe MP, Bender D, Sood AK. Two successful pregnancies after conservative treatment of endometrial cancer and assisted reproduction. *Fertil Steril* 2002; 77:188–189.
 5- Randall TC, Kurman RJ. Progestin treatment of atypical hyperplasia and well differentiated carcinoma of the endometrium in women under age 40. *Obstet Gynecol* 1997; 90:434–440.



Disease free window!

The available data suggest relative safety and efficacy of progestin treatment for a short window to allow the woman to achieve her reproductive goals!



Gynecologic Oncology 83, 388–393 (2001)
doi:10.1006/gyno.2001.6434, available online at http://www.idealibrary.com on IDEAL[®]

Endometrial Cancer in Women 40 Years Old or Younger

Linda R. Duska, M.D.,*¹ Audrey Garrett, M.D.,[†] Bo R. Rueda, Ph.D.,* Jacqueline Haas, M.D.,[‡] Yuchiao Chang, Ph.D.,[§] and Arlan F. Fuller, M.D.*[‡]

**Vincent Gynecology Service, Division of Gynecologic Oncology, [‡]Department of Pathology, and [§]Medical Practices Evaluation Center, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts 02114; and [†]Division of Gynecologic Oncology, Brigham and Women's Hospital, Boston, Massachusetts 02115*

Received June 7, 2001

Majority of women had stage I and grade I disease, However 19 of 95 patients (20%) had disease beyond the uterus, including 10 with advanced disease. Four women died as a result of their disease!

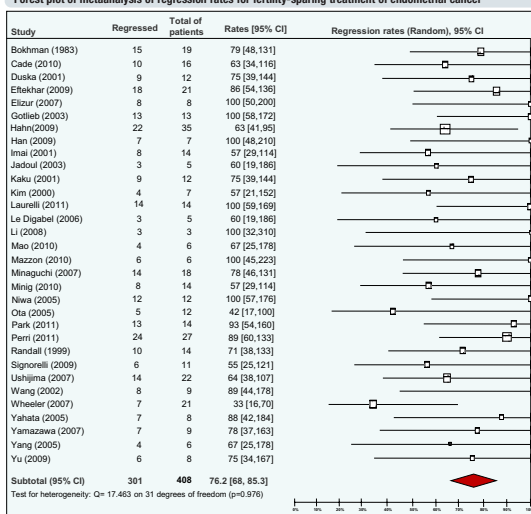


Regression rate !

Metaanalysis of the 32 studies (408 women) of women with EC managed with fertility-sparing treatment found that 301 women regressed with a pooled regression rate of 76.2% (95% CI, 68– 85.3)

Regression, relapse, and live birth rates with fertility-sparing therapy for endometrial cancer and atypical complex endometrial hyperplasia: a systematic review and metaanalysis
Ioannis D. Gallos, MD, Jason Yap, MBChB, Madhurima Rajkhowa, MD; David M. Luesley, MD; Arri Coomarasamy, MD; Janesh K. Gupta, MD AJOG

FIGURE 3
Forest plot of metaanalysis of regression rates for fertility-sparing treatment of endometrial cancer



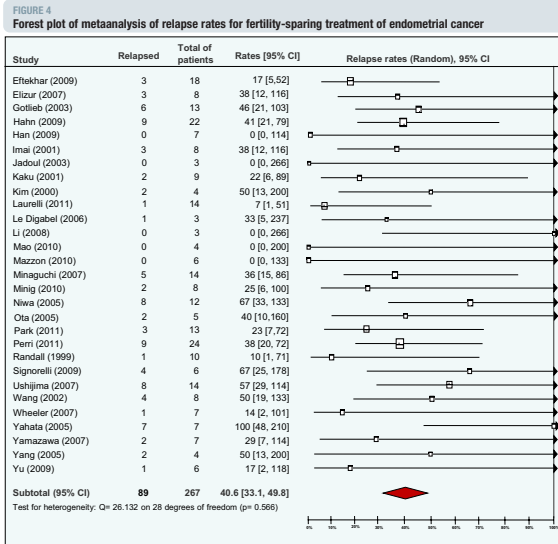
Gallos. Fertility-sparing therapy for endometrial cancer. Am J Obstet Gynecol 2012.



Relapse rate!

In 29 studies (267 women), women were followed up over time with the median ranging from 11 to 76.5 months, 89 women after an initial regression of the EC relapsed during follow-up, which amounts to a pooled relapse rate of 40.6% (95% CI, 33.1– 49.8)

Regression, relapse, and live birth rates with fertility-sparing therapy for endometrial cancer and atypical complex endometrial hyperplasia: a systematic review and meta-analysis
Ioannis D. Gallos, MD; Jason Yap, MBChB; Madhurima Rajkhowa, MD; David M. Luesley, MD; Arri Coomarasamy, MD; Janesh K. Gupta, MD AJOG



Gallos. Fertility-sparing therapy for endometrial cancer. Am J Obstet Gynecol 2012.



Hysteroscopy and direct resection



Mazzon I, Corrado G, Morricone D, Scambia G. Reproductive preservation for treatment of stage IA endometrial cancer in a young woman: hysteroscopic resection. Int J Gynecol Cancer 2005; 15:974–978.

