Fertility preservation in early endometrial cancer: oncological and obstetrical outcomes

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Introduction

- Most common gynecological cancer
- Typically: post menopausal women
- 20-25% before menopause,
- 7% between 20 and 44 years (obesity, diabetes, sedentarity)
- 5-10% of premenopausal women have EAH

- Young women: good prognosis
  - Early stage (limited myometrial invasion)
  - High differentiation at diagnosis

- Recommended treatment: total abdominal hysterectomy with staging depending on risk factors

Cancer of the endometrium-cancer stat facts. 2017
Adenocarcinoma of the uterus. In: Di Saia PJ,, 2002. p. 289–350.
Crissman JD et al.. Endometrial carcinoma in women 40 years of age or younger. Obstet Gynecol 1981;57:699–704.
Geisler HE, et al.. Carcinoma of the endometrium in premenopausal women. Am J Obstet Gynecol 1969;104:657–63.

Conservative Treatment: Therapeutic Challenge.

- **Risk of disease progression as high as 5-6%**
- Role of gynecologic oncologist in both treating malignant disease
- &
- offering fertility –sparing alternatives when allowed so → **Oncofertility**

Martinez et al. Best Practice & Research Clinical Obstetrics and Gynaecology 26 (2012)
Adapted from Fotopoulou et al. **Fertility-Sparing Surgery in Early Epithelial Ovarian Cancer:A Viable Option?** Obstetrics and Gynecology International Volume 2012

Candidates for conservative treatment

EAH

EEC

- Stage IA (without myometrial invasion)
- Grade1
- Endometrioid cancer

J Natl Compr Canc Netw. 2014 (NCCN)
Int J Gynecol Cancer. 2015 (ESGO)

Rationale for conservative treatment

Rationale behind conservative treatment in Grade 1 Stage 1 patients

- Recurrence rate
- Five-year survival rate
- Nodal disease
- Myometrial invasion

Relationship between Depth of Myometrial Invasion and Recurrence in Patients with Stage I Endometrial Carcinoma

Endometrial only	7/92	8%
Superficial myometrium	10/80	13%
Medium myometrium	2/17	12%
Deep myometrium	5/11	45%

Modified from DiSaia PJ et al: Am J Obstet Gynecol 151:1009, 1985

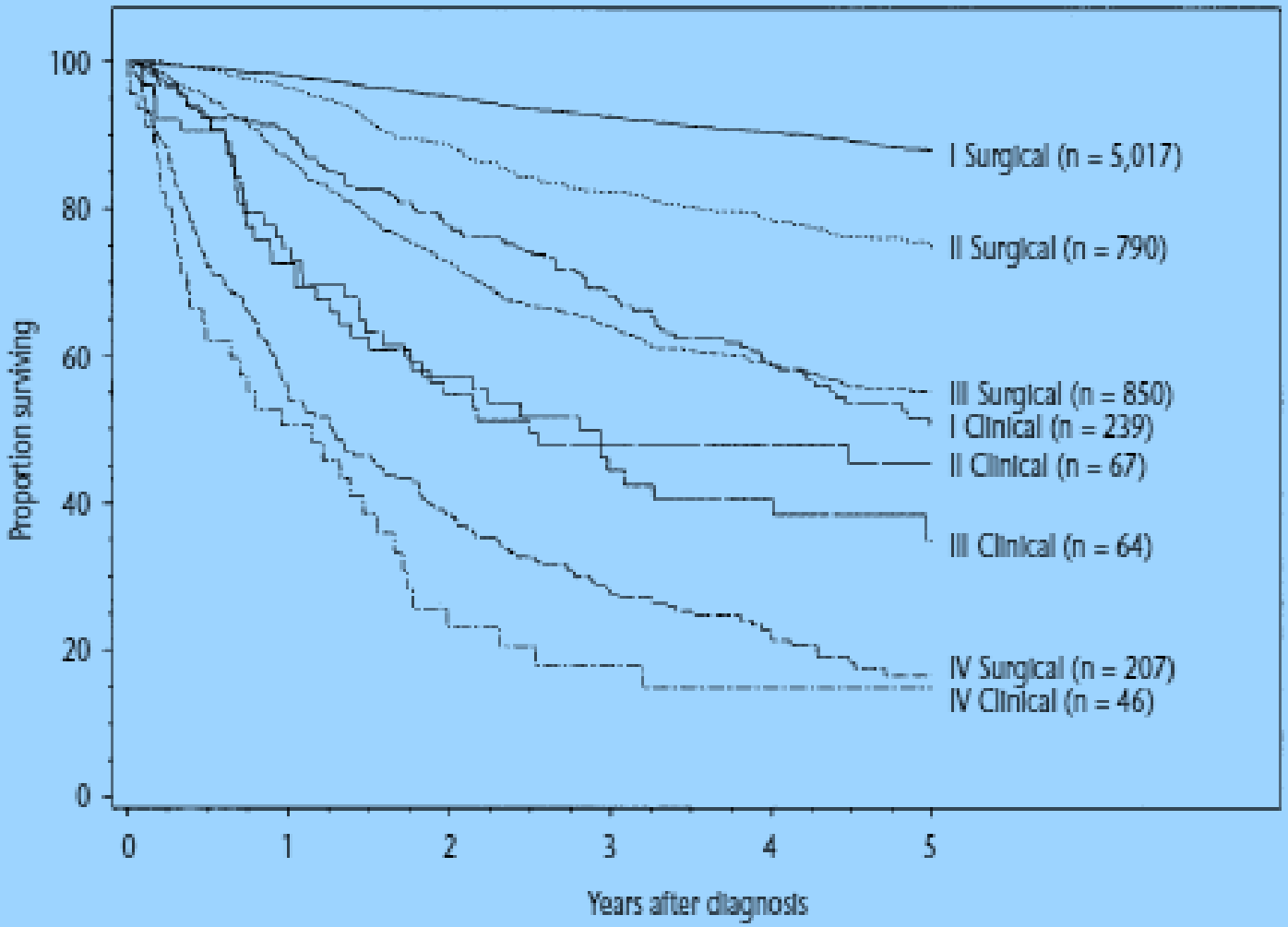


Figure 1. Carcinoma of the corpus uteri, patients treated 1996–1998. Survival by mode of staging, N = 7,280. (Reprinted from Int J Gynaecol Obstet, Vol. 83 (Suppl 1), Creasman WT, Odicino F, Maisonneuve P, Beller U, Benedet JL, Heintz AP, et al. Carcinoma of the corpus uteri. p. 79–118. Copyright 2003, with permission from the International Federation of Gynecology and Obstetrics.)

Relationship between Depth of Myometrial Invasion and Five-Year Survival Rate (Stage I)

- Tumors limited to the endometrium: 90,8%

- Tumors invading the deep myometrium: 85,4%

Morice P, et al. Endometrial cancer. Lancet.2016

Maximal Invasion and Node Metastasis

Maximal invasion (n)	Pelvic nodes (%)	Aortic nodes (%)
Endometrium only (87)	1 (1)	1 (1)
Superficial muscle (279)	15 (5)	8 (3)
Intermediate muscle (116)	7 (6)	1 (1)
Deep muscle (139)	35 (25)	24 (17)

Modified from Creasman WT et al: Cancer 60:2035, 1987

Frequency of Pelvic and Para-Aortic Nodal Disease

Depth of invasion	Grade		
	I (n=180)	II (n=288)	III (n=153)
Endometrial only (n=86)	0%/0%	3%/3%	0%/0%
Inner one-third (n=281)	3%/1%	5%/ 4%	9%/4%
Middle one-third (n=115)	0%/5%	9%/0%	4%/0%
Outer one-third (n=139)	11%/6%	19%/14%	34%/23%

Modified from Creasman WT et al: Cancer 60:2035, 1987

Molecular data and mechanism of action

Molecular basis: dualistic model of endometrial tumorigenesis

TYPE 1

- 70-80%
- Endometrioid
- Unopposed estrogen
- Low grade- superficial
- PTEN- mTOR mutated pathway
- Frequent positive hormone receptors ER- PR- AR

TYPE 2

- 10-20%
- Serous- clear cell
- Unrelated to estrogen exposure
- Early spread
- Poor prognosis
- Aneuploid
- p53- p16- Her-2/neu

P. Tsikouras et al. / European Journal of Obstetrics & Gynecology and Reproductive Biology In Press (2013)

Patients selection criteria

Selection criteria

- A well-differentiated carcinoma
- The tumor does not deeply invade the myometrium, demonstrated by MRI, TVUS, HSC
- Absence of suspicious pelvic or preaortic nodes
- Obesity remains a significant risk factor of endometrial transformation even after primary treatment (approximately 50% of ≥25 BMI patients recur)

L. Chiva et al. / Gynecologic Oncology 111 (2008) S101–S104
P. Morice et al. / Gynecologic Oncology 96 (2005) 245–248
Gotlieb et al., Obstet Gynecol 2003;102:718 –25
G. Laurelli et al. / Gynecologic Oncology 120 (2011) 43–46

Selection criteria (2)

- Absence of synchronous ovarian tumor : Ca 125, abdomino-pelvic US, pelvic MRI (consider diagnostic laparoscopy + peritoneal cytology).
  Risk of occult synchronous ovarian tumour in stage I: 1-5%

- No contraindications for medical treatment

- The patient understands and accepts that this is not standard treatment

- The patient should show her desire to complete the follow-up protocol

L. Chiva et al. / Gynecologic Oncology 111 (2008) S101–S104
P. Morice et al. / Gynecologic Oncology 96 (2005) 245–248
Gotlieb et al., Obstet Gynecol 2003;102:718 –25
G. Laurelli et al. / Gynecologic Oncology 120 (2011) 43–46

Positive diagnosis: imaging and surgery

Diagnosis and pre-treatment evaluation: imaging

- MRI is slightly more sensitive than ultrasound for the evaluation of myometrial invasion (86%–89% vs 66%–79%)
- Combination of both transvaginal sonography and MRI could be more accurate in detecting myometrial invasion.
- MRI : sensitivity of 80% and specificity of 100% in diagnosing cervical invasion.
- Lymph node greater than 1cm in short axis or with central necrosis is considered to be suspicious on MRI

Rodriguez-Trujillo A, et al. Int J Gynecol Cancer. 2016
Savelli L, et al.. Ultrasound Obstet Gynecol 2008
Mazzon. Fertility preservation in endometrial cancer. Fertil Steril 2010.
Manfredi R et al. Radiology. 2004
Vasconcelos C et al ., J Obstet Gynaecol. 2007

Diagnosis and pre-treatment evaluation: biopsy

D&C and pipelle biopsies most used

- source of diagnostic challenges (artifacts)
- myometrial invasion can't be detected
- Interinstitutional discrepancies of surgical pathological diagnoses have been reported

S.M. Jacques et al., Interinstitutional surgical pathology review in gynecologic oncology. I. Cancer in endometrial curettings and biopsies, Int. J. Gynecol. Pathol. 17 (1998)

Diagnosis and pre-treatment evaluation: biopsy (continued)

- Trimble et al.: atypical endometrial hyperplasia on pipelle biopsy **upgraded in 42.6%** of cases to endometrial cancer on final specimen.

- Leitao et al: D&C only **8.7%** of patients were upgraded in the final specimen vs **17.4%** with pipelle biopsy ($p < .007$)

- BUT Dilatation and curettage **still incorrectly** graded approximately 25% of the patients, with higher grade tumor being missed in about 10%.

Trimble CL et al. : a Gynecologic Oncology Group study. Cancer. 2006
Leitao , et al. Gynecol Oncol 2009
Larson DM et al., Obstet Gynecol 1995;

Diagnosis and pre-treatment evaluation: biopsy

- **Hysteroscopy** is the most accurate way for biopsy and evaluation of the cavity
- Excludes cervical involvement (NPV 100%, low Sp), complementary to MRI.
- Best procedure to estimate the extent of the cancerous spread within the uterine cavity (>50% prognostic factor)
- Indirectly predictive of tumoral size (independent prognostic factor of lymph node spread and disease-free survival)
- Complication rate of 3%, with 1% of uterine perforation
- No prognostic significance for migrant cells outside the cavity

Rose PG. Endometrial carcinoma. N Engl J Med 1996
Toky T et al., Br J Obstet Gynaecol 1998
Garuti et al., Gynecol Oncol 2001
Touboul C. et al. Anticancer Res 2014
Lo KW et al. Gynecol Oncol 2002

The Oncologist 2015;20:270–278

- laparoscopic evaluation of the:
  - adnexa
  - lymph node
  - peritoneal cavity
- not recommended **unless imaging studies suggest** a suspicious involvement of these regions in tumor spread.

Treatment modalities

- HORMONAL:

- Megestrol acetate
- Medroxyprogesterone acetate
- Levonorgestrel IUD

- HYSTEROSCOPIC Tumor Resection and Progesterone therapy

Literature review on hormonal treatment

Ramirez 2004

- Review 1961-2003
- 81 patients in 27 articles
- MPA or MA
- 76% response with a median time of 12 weeks
- 24% recurrence (19 months)
- Mean duration of treatment
  - In responders 24 months
  - In non-responders 12 months

Chiva 2008

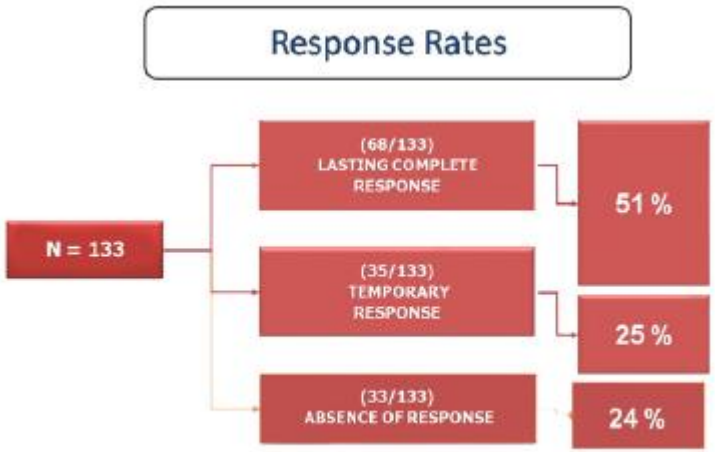


Fig. 2. Outcome of patients after conservative management.

- 30% of patients who recurred → second course of progestins → 80% response
- Half of recurrence were understaged (stage III in 6 patients)
- 4 patients died (3: carcinomatosis)
- 80 nulliparous. 53 pregnancies, 35 through ART
- 70 hysterectomies after gestation: 3 residual carcinomas, 1 ovarian carcinoma

L. Chiva et al. / Gynecologic Oncology 111 (2008) S101–S104

Gunderson 2012

- Review 2004→ 2011.
- 45 studies, 391 subjects, only 5 prospective studies

Table 4
Composite oncologic and reproductive outcomes.

	Initial response	Complete response	Complete response with recurrence	Persistent/ progressive disease	Proportion achieving pregnancy	Number of live births
CAH	85.6%	65.8%	23.2%	14.4%	28/111 (41%)	28
EC	74.6%	48.2%	35.4%	25.4%	86/280 (34.8%)	89
p-value	0.03	0.002	0.03	0.02	0.39	n/a

CAH: complex atypical hyperplasia.
EC: endometrial carcinoma.

Park 2012

- Retrospective Korean study
- 148 patients
- Mean Complete Response (CR) rate: 77.7%
- Durab[illegible] at 5 years

BMI, MPA, maintenance, pregnancy

- BMI >25 kg/m2 was the only significant factor associated with a failure to achieve CR
- BMI < 25 kg/m2, MPA (compared to MA), maintenance treatment and pregnancy were significantly associated with a lower risk of recurrence on multivariate analysis

J.-Y. Park et al. / European Journal of Cancer 49 (2013) 868–874

LNG-IUD

Gallos ID 2010:

- systemic analysis of 189 EAH patients from 14 studies,
- higher pooled regression rate compared with oral progestogens (pooled rate, 90% vs. 69%; p=0.03)

Pal N 2018:

- retrospective study
- 80% response rate in EAH
- 67% in EEC G1

Leone Roberti Maggiore U (2019):

- Retrospective study
- 28 EAH, 16 EEC G1 and 4 EEC G2
- long follow-up period (82.6±47.2 months)
- CR rate of 89.3% (25/28) in EAH patients, 81.3% (13/16) in EEC G1 patients, and 75% (3/4) in EEC G2 patients

Gallos ID, et al. Am J Obst Gyn 2010
Pal N et al. Obst Gyn 2018
Maggiore J Gynecol Oncol 2019

LNG-IUD

- LNG-IUD more effective in EAH
- RCOG: LNG-IUD first line treatment in EAH
- NCCN includes it in the options for conservative treatment of EEC g1
- **LNG-IUS alone should be used carefully in patients with enlarged uterine cavity :** progesterone reaches the adjacent endometrium
- Consider addition of an oral progestin
- *Several ongoing clinical trials*

Dhar KK et al., Gynecol Oncol 2005
C.C. Gunderson et al. / Gynecologic Oncology 125 (2012)

Koskas 2012

- Compare the survival of patients with grade 1 intramucous endometrial adenocarcinoma according to the extent of surgery

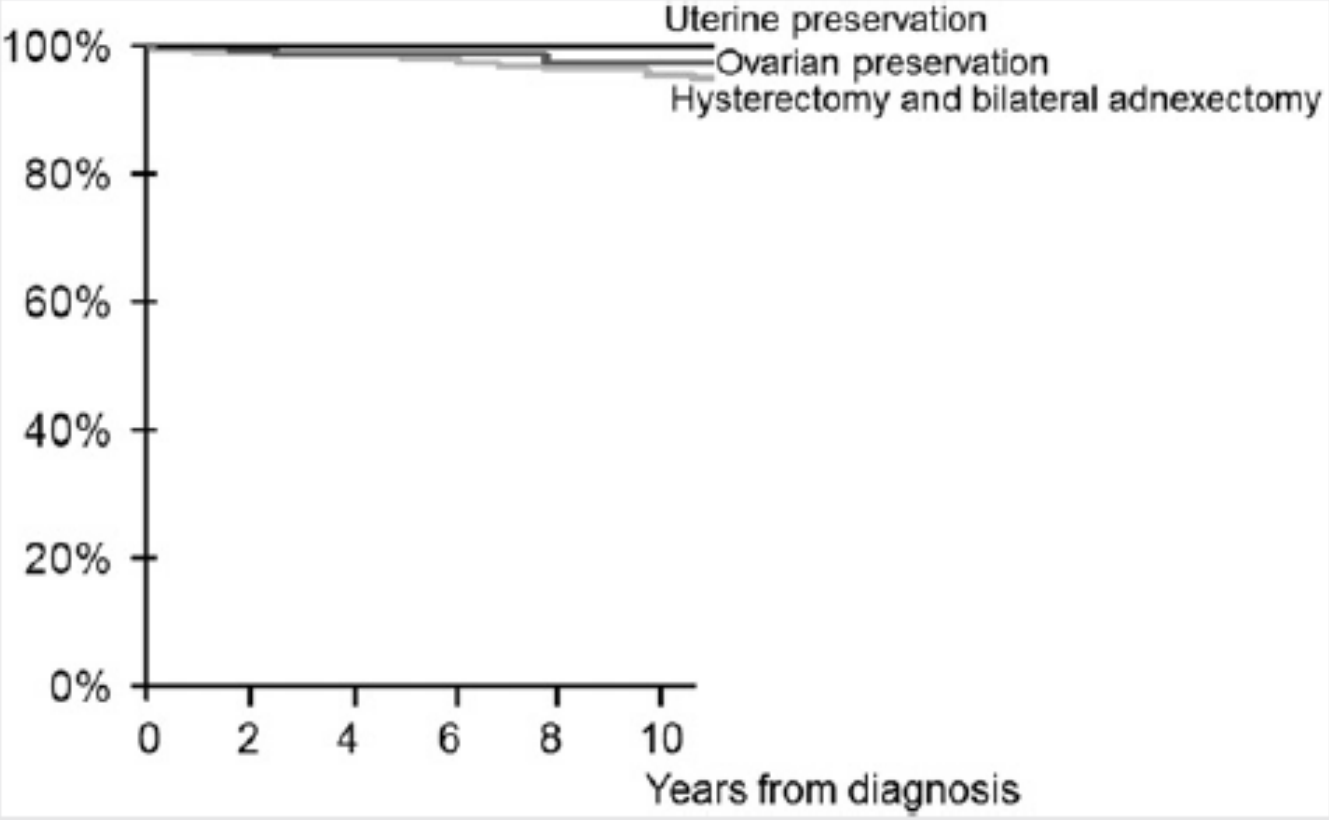
Conservation not associated with an increase in all causes and cancer-related-mortality in univariate and multivariate analysis

preservation, 184 patients who underwent ovarian preservation, and 204 patients who underwent hysterectomy with oophorectomy

- Conservation not associated with an increase in cancer-related-mortality in univariate and multivariate analysis

Martin Koskas et al., Fertil Steril 2012

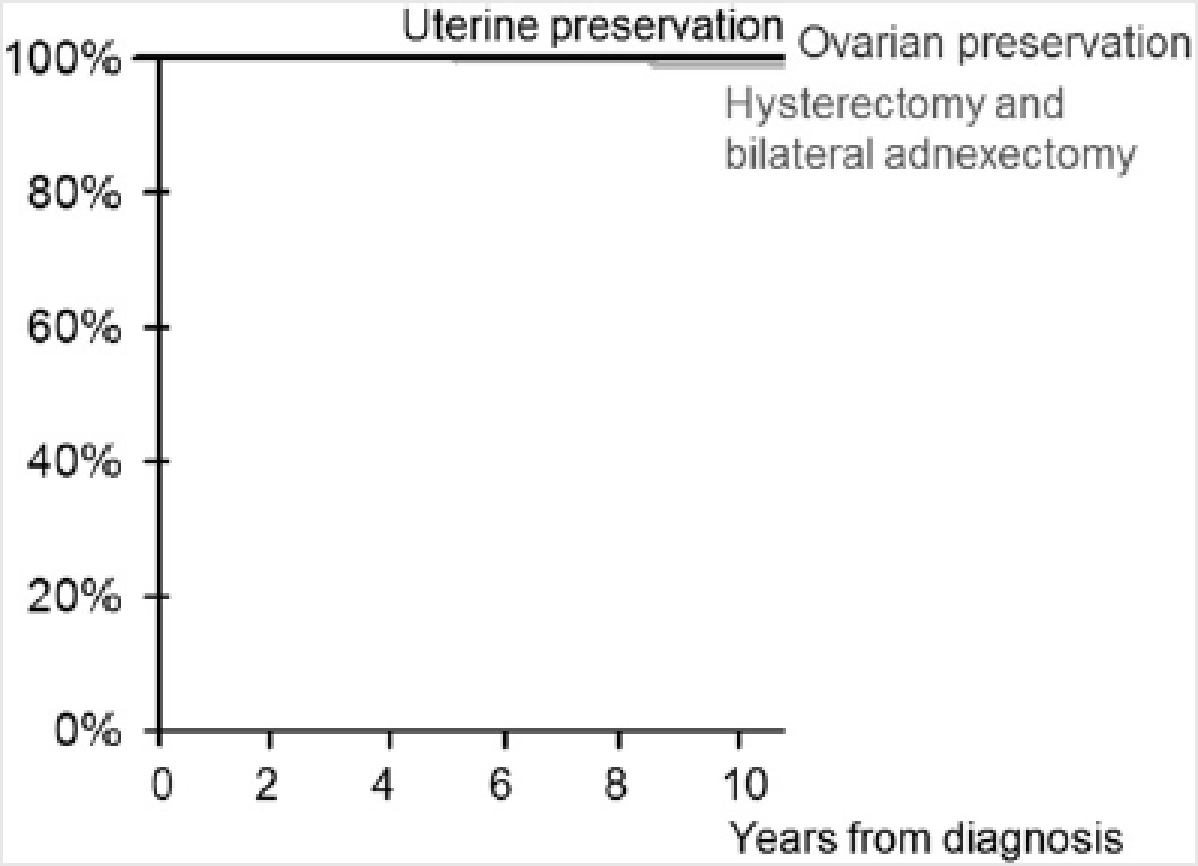
FIGURE 1



Kaplan-Meier analysis of overall survival (*P*=.07) of patients with grade 1 endometrial adenocarcinoma that was limited to the endometrium stratified by uterine preservation, ovarian preservation, and radical surgery.

Koskas. Fertility preservation in endometrial cancer. Fertil Steril 2012.

FIGURE 2



Kaplan-Meier analysis of cancer-related survival (*P*=.49) of patients with grade 1 endometrial adenocarcinoma that was limited to the endometrium stratified by uterine preservation, ovarian preservation, and radical surgery.

Koskas. Fertility preservation in endometrial cancer. Fertil Steril 2012.

Greenwald 2017

- Population-based cohort of patients with low grade endometrial cancer younger than 45 years.
- no differences in all-cause mortality and cancer-specific mortality after a 15-year follow-up between:

-161 patients who received initial hormonal therapy

VS

- 6178 who received primary surgery

Greenwald ZR, et al.Cancer. 2017;123:1545–1554.

Literature review on hysteroscopic resection followed by progesterone

Resectoscopic treatment/evaluation

- Laurelli et al., 2011: hysteroscopic resection of the endometrial lesion and a small layer of the myometrium below.
- Progestin treatment if no evidence of myometrial involvement. 14 patients. 1 relapse. 40 months mean follow-up
- HSC: more accurate, therapeutic + diagnostic

Resectoscopic treatment/evaluation (continued)

- Mazzon 2010: three-step technique in which each step is characterized by a pathologic analysis:
  - removal of the tumor (step 1)
  - removal of the endometrium adjacent to the tumor (step 2)
  - removal of the myometrium underlying the tumor (step 3)
- 6 patients. No relapse with 50.5 months mean follow-up

Hysteroscopic resection treatment

J Gynecol Oncol. 2017 Jan;28(1):e2
https://doi.org/10.3802/jgo.2017.28.e2
pISSN 2005-0380·eISSN 2005-0399

JOURNAL OF GYNECOLOGIC ONCOLOGY

Original Article

Check for updates

OPEN ACCESS

Fertility preserving treatment with hysteroscopic resection followed by progestin therapy in young women with early endometrial cancer

Francesca Falcone,[1,2] Giuseppe Laurelli,[1] Simona Losito,[3] Marilena Di Napoli,[4] Vincenza Granata,[5] Stefano Greggi[1]

- 15-years institutional experience of fertility-sparing treatment
- 27 patients had 3 steps hysteroscopic treatment followed by MA (160 mg) or LNG-IUD
- 26 patients had CR
- 2 relapses
- 14 pregnancies, 13 live births
- Follow up : 6-172 months

Atallah D., El Kassis N. et al.
The Use of Endometrectomy in the Conservative Treatment of Early Endometrial Cancer in Fertile Women

- 10 patients, having AEH or EC had total superficial endometrial resection:

  -resection at the tumor or thickness site with underlying myometrium
  -sampling and superficial resection of the rest of the endometrial cavity

- Allowing evaluation of the whole endometrium and staging of tumor, and reducing the risk of missing high grade lesions

- Guided with suprapubic ultrasound

- With hysteroscopic biopsies every 3 months during treatment with progesterone (160mg of) (BETTOCCHI® without dilation) , until pregnancy

- Permission for pregnancy attempt was given after 2 X 12 Weeks of negative controls

Patient	Histology at initial diagnosis	Grade	Nb of successful pregnancies	Hysterectomy	Recurrence
1	C Atypical hyperplasia	_	1 (7 months)	_	_
2	C Atypical hyperplasia	_	1 (3 years)	_	_
3	synchronous endometrioid ovarian and endometrial carcinoma	I	1 (12 months)	_	_
4	Endometrioid carcinoma	I	2 (3 yrs; 5.5 yrs)	_	_
5	Endometrioid carcinoma	I	1 (12 months)	_	_
6	C Atypical hyperplasia	_	_	yes	_
7	Endometrioid carcinoma	II	_	yes	Yes (3 months)
8	Endometrioid carcinoma	I	_	yes	Yes (12 months)
9	Endometrioid carcinoma	I	Lost to follow-up		
10	Endometrioid carcinoma	I	Lost to follow-up		

Our Results

- Mean age = 36 years old
- Mean BMI = 24 kg/m^2
- All had megestrol acetate and GnRH analog
- Mean follow-up time 40 months
- 2 patients lost to follow up
- No residual disease on follow-up by all grade I patients
- Recurrence in 2 Patients (20%)
- 6 spontaneous pregnancies, 50% pregnancy rate
- The average time from end of treatment till pregnancy was 20 months

Simultaneous early ovarian and endometrial cancer treated conservatively with spontaneous pregnancy

David Atallah[1*], Joelle Safi[1], Nadine el Kassis[1], Roman Rouzier[2] and Georges Chahine[3]

Abstract

Introduction: Young cancer patients increasingly request fertility sparing alternatives to their cancer treatments, which they should be offered when allowed so by the risk-benefit balance and after obtaining informed consent.

Case presentation: Here, we report the case of a 25 year-old nulliparous patient who presented with a synchronous endometrioid ovarian and endometrial carcinoma. She was able to conduct a full-term spontaneous pregnancy after conservative surgical treatment followed by adjuvant chemotherapy and hormonal treatment. Fertility sparing treatment is feasible in selected cases of synchronous ovarian and endometrial cancers. Thorough follow-up remains mandatory.

Conclusion: This case demonstrates some interesting and unique features of synchronous ovarian and endometrial cancers since it resulted in a spontaneous pregnancy and normal delivery.

Keywords: Conservative treatment, Endometrial, Ovarian cancer, Pregnancy, Synchronous

- Fertility sparing treatment is feasible in selected cases of synchronous ovarian and endometrial cancers
- Follow-up remains mandatory

J Ovarian Res. 2013

Recurrence rate

Table 4. Response rates: relapse and result.

	Median follow-up (months)	Recurrence	Persistent disease	Time to recurrence	Hyperplasia without atypia	Atypical hyperplasia
Laurelli [11]	40 (range 13–79)	1/14 (7%)	-	5 months	1/14 (7%)	0
Mazzon [10]	50.5 (range 21–82)	0%	-	-	3/6 (50%)	1/6 (16.6%)
Shan [12]	34.7 (range 15–66)	2/14 (14.2%)	3/14 (21%)	10 and 12 months	2/14 (14%)	1/14 (7.1%)
Marton [14]	11 and 22 months	½ 50%		22 months	-	½ 50%
Total	40 (range 11–82)	4/36 (11.1%)		12.2 months	6/36 (16.6%)	3/36 (8.3%)

- **Recurrence rate = 11.1% (in patients with EC)**
- *Hysteroscopic resection before hormonal treatment*
- *Shan: hysteroscopy then curetage*

***Alonso S** ecancer 2015, 9:505*

Recurrence rate

Gynecologic Oncology 125 (2012) 477–482

Contents lists available at SciVerse ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Review

Oncologic and Reproductive outcomes with progestin therapy in women with endometrial hyperplasia and grade 1 Adenocarcinoma: A systematic review

Camille C. Gunderson [a,*], Amanda Nickles Fader [a,b], Kathryn A. Carson [c], Robert E. Bristow [d]

- **Recurrence rate = 35.4% (in patients with EC)**
- *treated with progestin alone*

Recurrence factors

Table 3
Relevant factors associated with recurrence after complete response to progestin treatment (n = 39).

Variables	Recurrence[a]	*P* value
Age, y		0.009
≥35	6/10 (60)	
<35	4/29 (14)	
Body mass index[b]		0.003
≥30	4/4 (100)	
<30	6/35 (17)	
Polycystic ovary syndrome		0.109
Yes	5/11 (46)	
No	5/28 (18)	
Family history of cancer		0.156
Yes	2/3 (67)	
No	8/36 (22)	
Pathology		1.000
Complex endometrial hyperplasia	3/12 (25)	
Endometrial carcinoma	7/27 (26)	
Progestin type		0.282
Megestrol acetate	6/17 (35)	
Medroxyprogesterone acetate	4/22 (18)	
Time to complete response, mo		<0.001
≤6	1/24 (4)	
>6	9/15 (60)	
Consistent infertility after progestin treatment		0.024

International Journal of Gynecology and Obstetrics 132 (2016) 34–38

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www.figo.org

CLINICAL ARTICLE

Oncologic and reproductive outcomes after fertility-sparing management with oral progestin for women with complex endometrial hyperplasia and endometrial cancer

Ming Chen [a,b], Ying Jin [a], Yan Li [a], Yalan Bi [c], Ying Shan [a], Lingya Pan [a,*]

ELSEVIER

JMIG The Journal of Minimally Invasive Gynecology

Original Article

Hysteroscopic Resection in Fertility-Sparing Surgery for Atypical Hyperplasia and Endometrial Cancer: Safety and Efficacy

Patrizia De Marzi, MD*, Alice Bergamini, MD, Stefania Luchini, MD, Micaela Petrone, MD, Gian Luca Taccagni, MD, Giorgia Mangili, MD, Gabriella Colombo, MD, and Massimo Candiani, MD

From the Department of Obstetrics and Gynecology, San Raffaele Hospital, Milan, Italy (all authors).

23 patients ; mean follow-up = 25 months

NO intrauterine adhesions

J Minim Invasive Gynecol. 2015

Fertility-Preserving Treatment in Young Women With Grade 1 Presumed Stage IA Endometrial Adenocarcinoma

A Meta-Analysis

Zunpan Fan, MD, Hui Li, MD,† Rui Hu, MD,* Yuling Liu, MD,* Xinyu Liu, MD,* and Liping Gu, MD**

	Number of patients	Complete Remission Rate (CRR)	Recurrence Rate (ReR)	Pregnancy Rate (PregR)
Progestin only	456	**76.3 %**	**30.7 %**	**52.1 %**
Hysteroscopic resection followed by progestin therapy	73	**95.3 %**	**14.1 %**	**47.8 %**
Intrauterine progestin therapy	90	**72.9 %**	**11.0 %**	**56.0 %**

Int J Gynecol Cancer. 2018

Optimal duration of treatment

- Unclear and no consensus
- Minimum 3 months, median 9 months
- Anovulatory and obese patients need longer treatments and follow-up
- Individually tailored (response time is variable, depending on underlying physiology).

Gotlieb et al., Obstet Gynecol 2003
Randall TC, Kurman RJ. Obstet Gynecol 1997

Other treatment options

- GNRH agonists
- Aromatase inhibitors (reduction of estrogen concentrations. Small studies with letrozole or anastrozole in advanced or recurrent)
- Metformin
- Combined

Emons G, Heyl W. Hormonal treatment of endometrial cancer. J Cancer Res Clin Oncol 2000;126:619–23.

Adverse events

- Well tolerated
- Adverse events less than 5%
- Thromboembolic events have been reported as a complication in a number of studies, in addition to weight gain and hypertension

Pandya KJ et al. Megestrol and tamoxifen in patients with advanced endometrial cancer: an Eastern Cooperative Oncology Group Study (E4882). Am J Clin Oncol 2001;24:43– 68.

Thigpen JT et al. Oral medroxyprogesterone acetate in the treatment of advanced or recurrent endometrial carcinoma: a dose-response study by the Gynecologic Oncology Group. J Clin Oncol 1999;17: 1736– 44.

Reproductive outcome

- Pregnancy rate of 33% in 400 candidates with EAH or EEC treated conservatively after a mean follow-up of >40 months

- *Young women who develop endometrial carcinoma are typically also affected by other factors that affect fertility, such as obesity, polycystic ovarian syndrome, and chronic anovulation.*

Koskas M, et al. Bull Cancer 2012
P.T. Ramirez et al. / Gynecologic Oncology 95 (2004)

Reproductive outcome

- **No data on optimal time from completion** of progesterone therapy to attempting pregnancy
- Lack information on the safety of intrinsic hormonal changes that take place during pregnancy and on the long-term effects of the medications used during ART
- Assisted reproductive techniques do not appear to worsen the prognosis (increases the chances of successful conception and decrease the interval to conception)

P.T. Ramirez et al. / Gynecologic Oncology 95 (2004)

Table 4
Composite oncologic and reproductive outcomes.

	Initial response	Complete response	Complete response with recurrence	Persistent/ progressive disease	Proportion achieving pregnancy	Number of live births
CAH	85.6%	65.8%	23.2%	14.4%	28/111 (41%)	28
EC	74.6%	48.2%	35.4%	25.4%	86/280 (34.8%)	89
p-value	0.03	0.002	0.03	0.02	0.39	n/a

CAH: complex atypical hyperplasia.
EC: endometrial carcinoma.

Follow-up

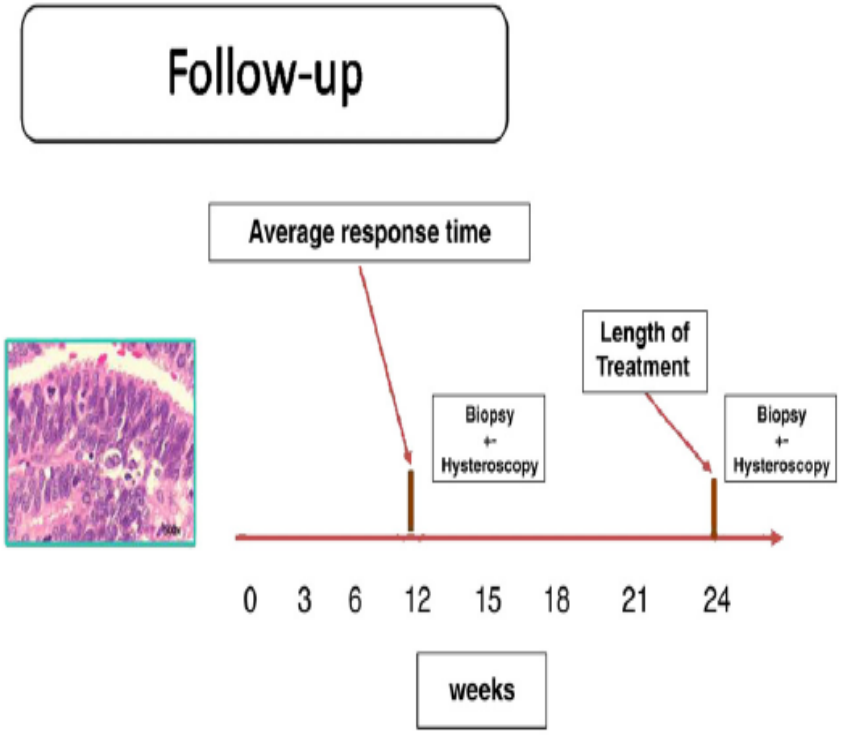

Fig. 3. Proposed follow-up during hormonal treatment.

- First biopsy after 12 weeks of hormonal treatment (average response time)
- If positive → another 12 weeks treatment
- Second biopsy after 24 weeks of treatment (average length of treatment reported in the literature)
- If positive → standard surgical approach
- If negative → encourage conception
- Advisable to do intermittent biopsies in the preovulatory part of the cycle every 3 or 4 months

L. Chiva et al. / Gynecologic Oncology 111 (2008) S101–S104

Maintenance therapy: suggestions

- Maintenance therapy with **ongoing progestagens is necessary** until childbearing is wanted.

- Progestin treatment should be followed immediately by downregulatory therapy with GnRHa in order to prevent reinduction of the menstrual cycles and unnecessary prolonged exposure to estrogens

Rackow B & Arici A. Curr Opin Obstet Gynecol 2006; 18: 245–252.
Gotlieb W et al., Obstet Gynecol 2003; 102: 718–725
Plante M. Curr Opin Oncol 2000
Park JC et al., J Korean Med Sci 2006

Rationale for post-fertility hysterectomy

- Successful pregnancy does not automatically exempt a coexisting endometrial carcinoma: case report by Mistsuhita et al. of carcinoma remaining after term pregnancy post MPA treatment

- Most authors agree that **consolidation hysterectomy** should be advisable after completion of family planning.

Mitsushita J et al., Gynecol Oncol. 2000;79:129–132
Jadoul P et al., Fertil Steril 2003

Conservative medical treatment: hormone therapy

- **ESGO & IGCS 2015:**

-MPA (400 to 600 mg/d)and MA (160 to 320 mg/d) are equivalent , LNG-IUD role still to be elucidated

-Duration of Treatment: at least 6 months

-follow-up: first D&C to check for response 6 months after initiation of treatment and not before.

-Maintenance treatment is advisable if immediate pregnancy is not pursued.

-In case of recurrence, repeat progestin therapy

-Due to a high recurrence rate, hysterectomy is advisable once family planning has been completed.

-early pregnancy is recommended (1 month after complete response)

IGCS &ESGO 2015:Clinical Recommendations for Fertility-Sparing Management in Young Endometrial Cancer Patients

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Endometrial Carcinoma

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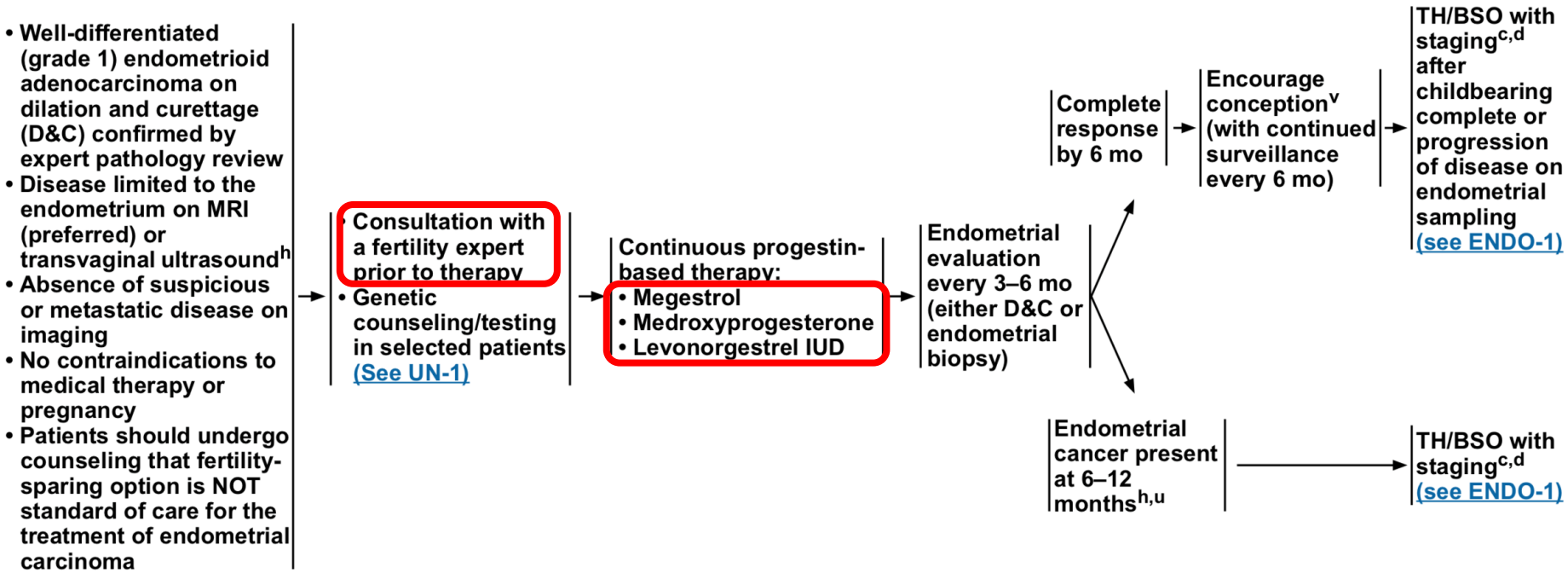

Take home messages

- Hormonal management/hysteroscopic resection are safe and effective

- There is an increased likelihood of response with progestin treatment of complex atypical hyperplasia compared with treatment of endometrial carcinoma

- Treatment with progestin, or HSC may allow for reasonable fecundity

Take home messages

- Careful oncologic, psychotherapeutic, genetic and reproductive counseling is advised before offering a non-standard treatment strategy to young endometrial cancer patients.
- Documentation of informed consent should reflect these discussions and patient understanding
- Conservative management can also be useful for inoperable patients
- Lack of prospective, randomized controlled and appropriately powered trials

Thank you!

QUESTIONS?