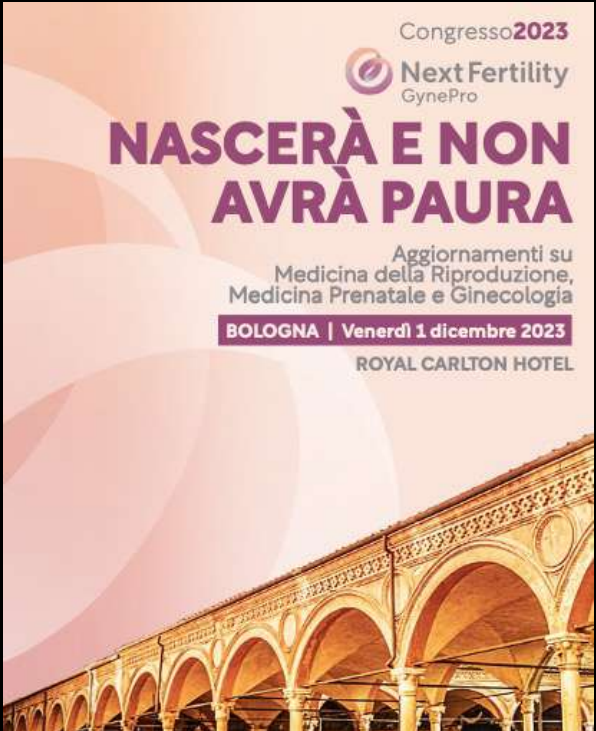


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SANT'ORSOLA



ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA



Paolo Casadio

Gynecology and Physiopathology
of Human Reproduction
Prof. Renato Seracchioli
University of Bologna



Bologna 1 Dic 2023

Fertility Sparing in pazienti con neoplasia endometriale



ENDOMETRIAL CANCER (EEC)

- The most frequent gynecological cancer in developed countries
- >80% of EC occurs after 50 years of age. Among women with an EC diagnosis, approximately 20% are in premenopausal age and 5% are under 40 years of age
Duska et al. 2001



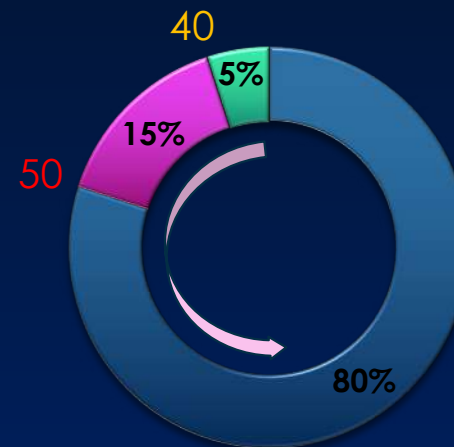
Delayed childbearing

Endometrial cancer diagnosed before the first pregnancy



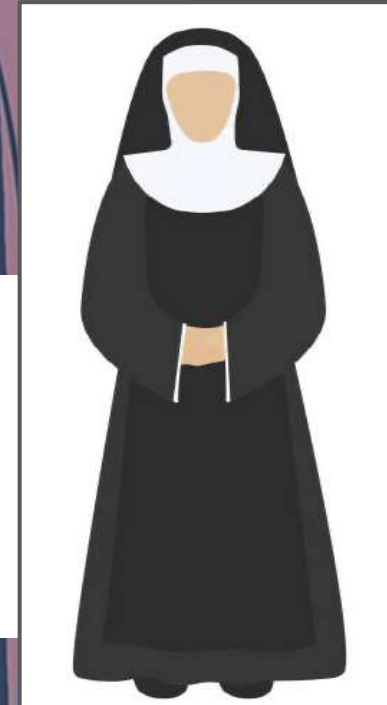
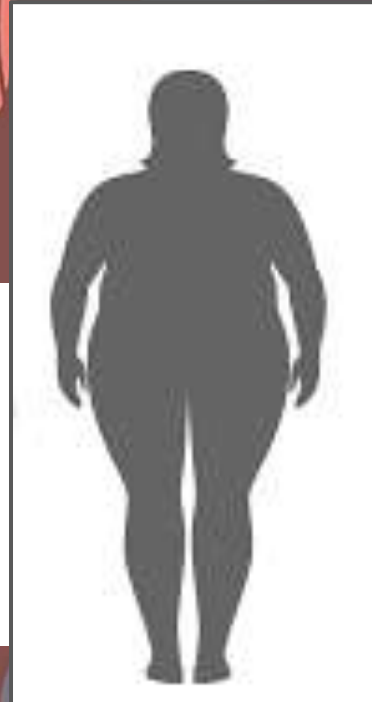
MORE ATTENTION TO CONSERVATIVE TREATMENT

INCIDENCE

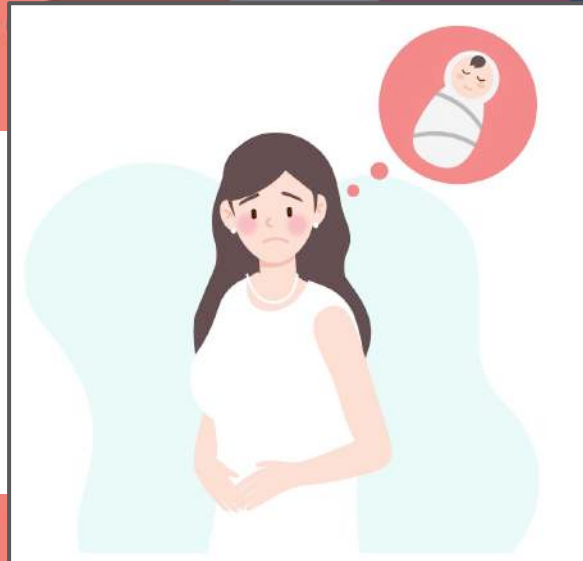


■ menopause ■ premenopause ■ ≤40 years

STEREOTYPE

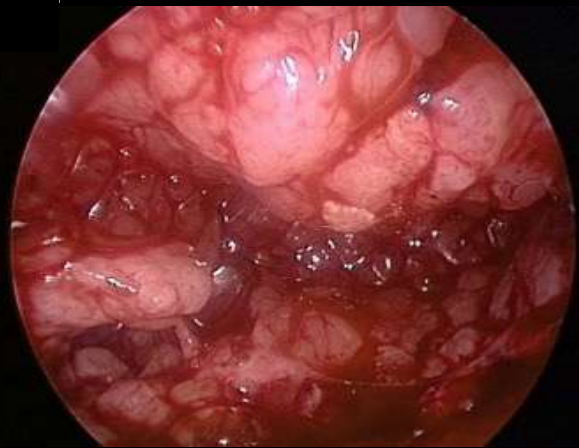


STEREOTYPE



BMI = 22
Normopeso





GOLD STANDARD



Hysteroscopic Surgery

Courtesy of Di Spiezio Sardo Attilio

ENDOMETRIAL CANCER (EEC)

Gold standard treatment of an early stage well differentiated EC is

TH + BSO

(with sentinel lymph node biopsy)

→ Excellent 5-year overall survival



National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 1.2022
Endometrial Carcinoma



European
Society for
Gynaecological
Endoscopy

**Fertility sparing treatment for
endometrial carcinoma**

2022

GUIDELINES

Medical treatment and uterine sparing management is now accepted as a reasonable short-term alternative to definitive surgical management in patients with a histological diagnosis of

**grade 1
endometrioid EC**

**pre-malignant
disease such as EIN**



Hysteroscopic Surgery



EARLY ENDOMETRIAL ENDOMETRIOID CANCER

FERTILITY SPARING TREATMENT

in young patients with childbearing desire

ONLY if EEC grade 1 non-invasive

a) **Continuous progestin-therapy** (MPA, NA, MA, LNG-IUS) + Follow-up

b) **HYSTEROSCOPY** + **Continuous progestin-therapy** + Follow-up

MEDICAL TREATMENT

HORMONE THERAPY: Progestins

- **Medroxyprogesterone acetate** (400-600 mg/die)
- **Megestrol acetate** (160-320 mg/die)
- **LNG-IUS**

Effects: Secretory differentiation, estrogen receptor function inhibition, endometrial cell mitosis inhibition, antiangiogenic effects

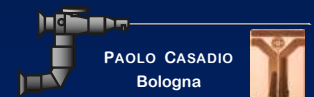
Saegusa, Cancer 1998

Average treatment time: 6-9 months

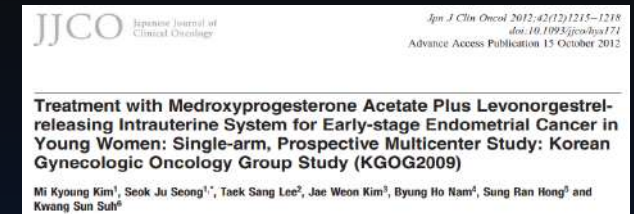
(response must be complete in the first 6 months)

Outcomes: Complete response in 76% - Recurrence in 24%

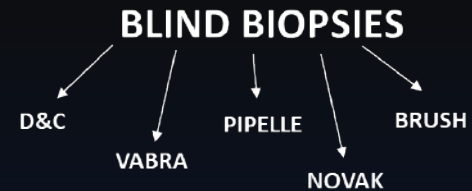
Chiva, Gynecol Oncol 2008



Hysteroscopic Surgery

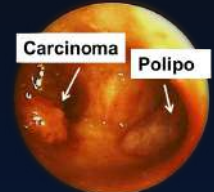


HYSTEROSCOPY - Oncology



1980 - 2023

**From the
Diagnosis**



To in-Office Surgery



Hysteroscopic Surgery

Courtesy of M. Franchini - Firenze

THERAPY



AGE



CONSERVATIVE HYSTEROSCOPIC TREATMENT



FERTILITY SPARING

Conservative hysteroscopic strategies with encouraging outcomes in women with endometrial cancer of childbearing age and desiring pregnancies

The Oncologist **2018**
Fertility-Sparing Treatment of Endometrial Cancer with Initial Infiltration of Myometrium by Resectoscopic Surgery: A Pilot Study
PAOLO CASADIO,^a FRANCESCA GUASINA,^a ROBERTO PARADISI,^a CONCETTA LEGGIERI,^a GIACOMO CAPRARA,^b RENATO SERACCHIOLI^a
^aDepartment of Obstetrics, Gynecology, and Reproductive Biology and ^bDepartment of Pathology, DIMEC, S. Orsola Hospital, University Alma Mater Studiorum of Bologna, Bologna, Italy
Disclosures of potential conflicts of interest may be found at the end of this article.



2020



Article

Fertility Sparing Treatment of Endometrial Cancer with and without Initial Infiltration of Myometrium: A Single Center Experience

Paolo Casadio ¹, Mariangela La Rosa ¹, Andrea Alletto ^{1,*}, Giulia Magnarelli ^{1,*}, Alessandro Arena ¹, Enrico Fontana ¹, Matilde Fabbri ¹, Kevin Giovannico ¹, Agnese Virgilio ¹, Diego Raimondo ¹, Francesca Guasina ², Roberto Paradisi ¹ and Renato Seracchioli ¹

Hysteroscopic resection (H)+ Progestin (P) vs P alone

Fertility and Sterility 

Conservative surgical management of stage IA endometrial carcinoma for fertility preservation

Di Spiezio Sardo A. et al, **2008**
Mazzon I. et al, **2010**

2020



Fertility-sparing treatment for intramucous, moderately differentiated, endometrioid endometrial cancer: a Gynecologic Cancer Inter-Group (GCIG) study

Francesca Falcone ¹, Umberto Leone Roberti Maggiore ², Violante Di Donato ³, Anna Myriam Perrone ⁴, Luigi Frigerio ⁵, Giuseppe Bifulco ⁶, Stephan Polterauer ⁷, Paolo Casadio ⁸, Gennaro Cormio ⁹, Valeria Masciullo ¹⁰, Mario Malzoni ¹¹, Stefano Greggi ¹

CONSERVATIVE HYSTEROSCOPIC TREATMENT

Hysteroscopic resection

+

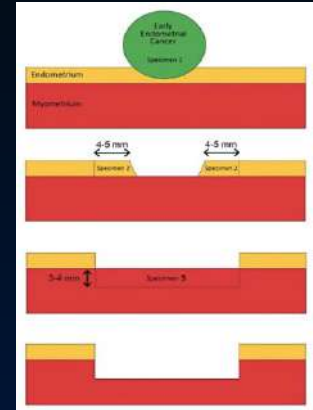
Progestin



Good oncological outcomes

Good reproductive outcomes

Mazzon I. et al, 2005
Di Spiezio Sardo A. et al, 2008
Mazzon I. et al, 2010



RESULTS

Hysteroscopic resection + Progestin

VS

Progestins alone



Pregnancy rate: 66% vs 33%



Hysteroscopic Surgery

MEDICAL TREATMENT- RESULTS

Sparing fertility in young patients with endometrial cancer

Luis Chiva *, Fernando Lapuente, Lucia González-Cortijo, Natalia Carballo, Juan F. García, Alejandro Rojo, Antonio Gonzalez-Martín

Gynecologic
Oncology

PREGNANCY

33%

Response
76%

No recurrence
66%

Long-term response
51%

Recurrence
34%

Short-term response
25%

Non-response
24%

Non-response
24%



Hysteroscopic Surgery

HYSTEROSCOPIC RESECTION + HORMONAL THERAPY - RESULTS

Fertility and Sterility 

Conservative surgical management of stage IA endometrial carcinoma for fertility preservation

Mazzon I. et al, 2005
Di Spiezio Sardo A. et al, 2008
Mazzon I. et al, 2010

Response
91,7%

Non-response
8,3%

No recurrence
91%

Recurrence
9%

PREGNANCY
60%

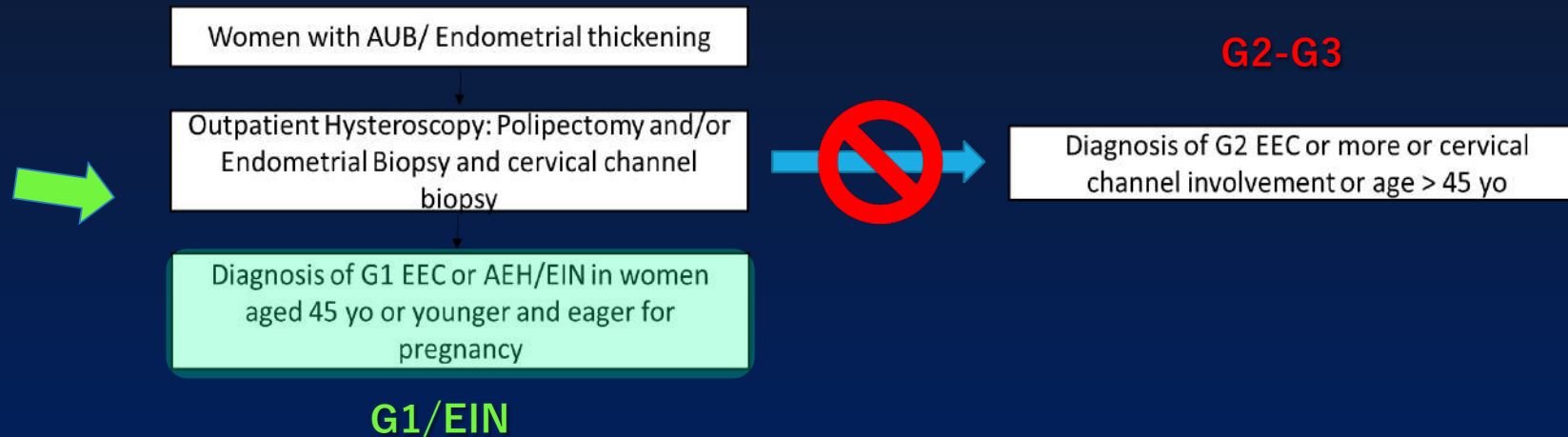
Long-term response
83,4%

Short-term response
8,3%

Non-response
8,3%


OUR EXPERIENCE

Inclusion and exclusion criteria

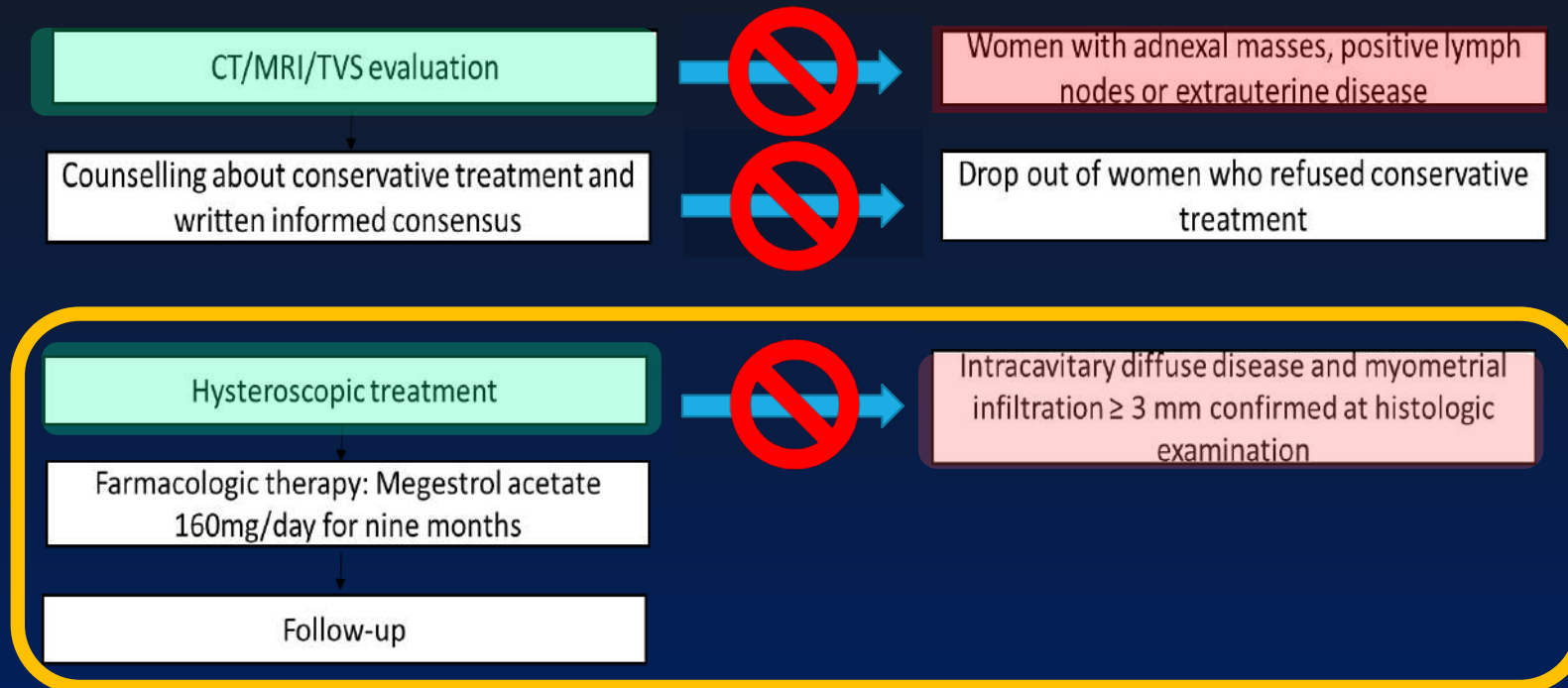


OUR EXPERIENCE

Inclusion and exclusion criteria Selection of patients!

 *cancers* Casadio 2020 

Article
Fertility Sparing Treatment of Endometrial Cancer
with and without Initial Infiltration of Myometrium:
A Single Center Experience



OUR EXPERIENCE

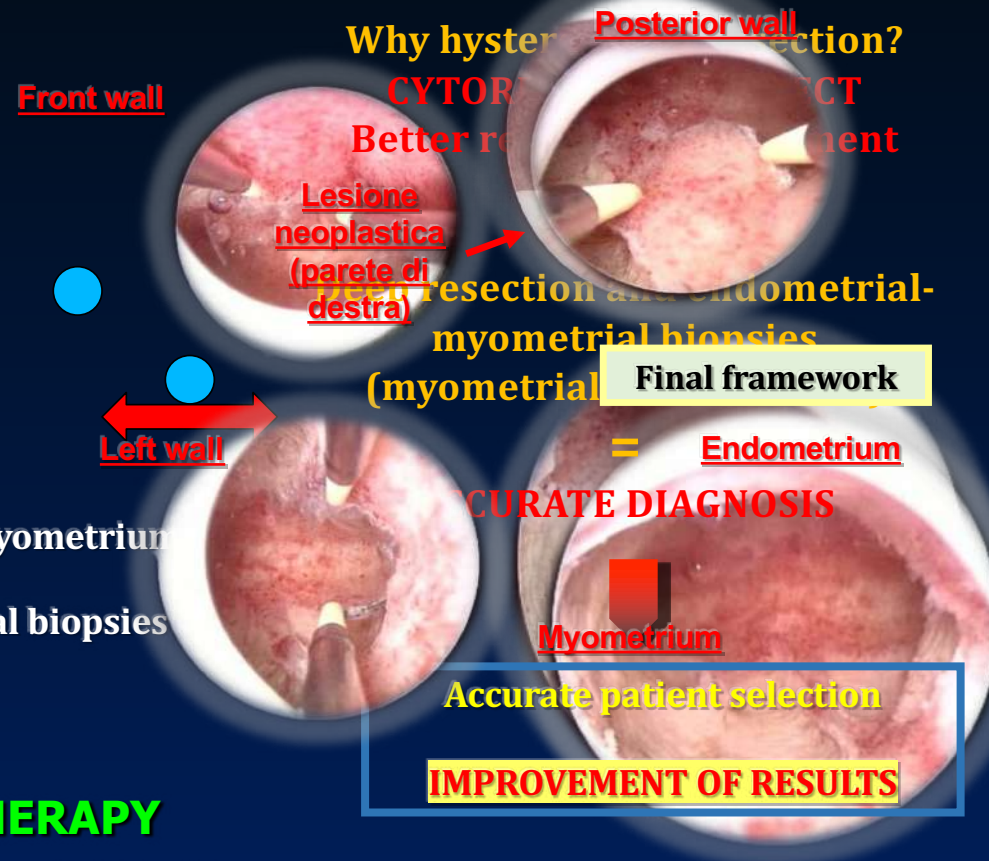
Fertility sparing treatment: suggested management

- Resection of the focal lesion
- Widening of the resection
- Resection of 4 mm underlying myometrium
- Random endometrial-myometrial biopsies

+

HORMONAL THERAPY

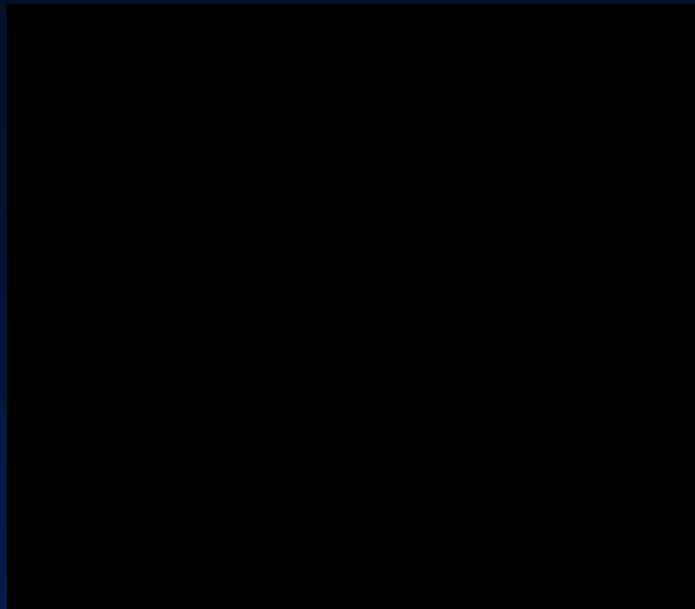
3-monthly follow-up (ISC+Bx)



Patients with FOCAL EIN/EEC G1 and childbearing desire





Resectoscopic Surgery

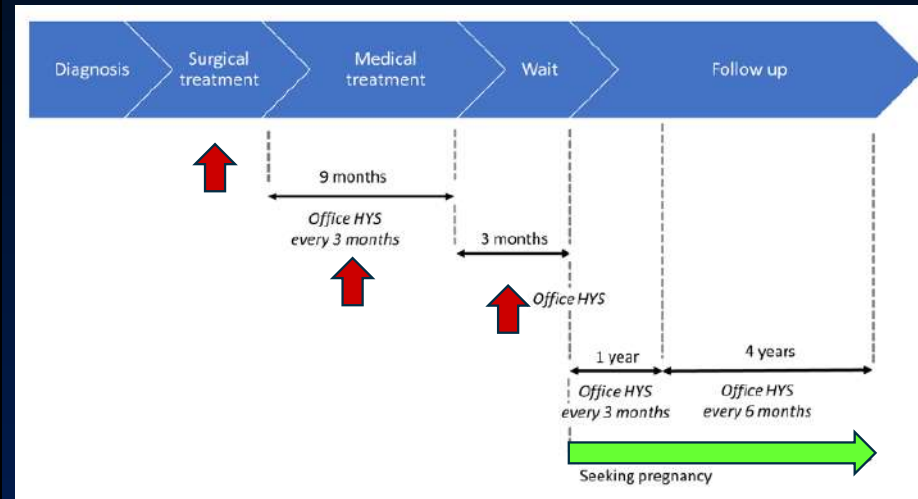


Histologic examination: EIN/EEC G1 (< 3 mm myometrium invasion)

Fertility sparing treatment: suggested management

 **cancers** Casadio et al. - 2020 

Article
Fertility Sparing Treatment of Endometrial Cancer with and without Initial Infiltration of Myometrium: A Single Center Experience



The Oncologist Brief Communications

Fertility-Sparing Treatment of Endometrial Cancer with Initial Infiltration of Myometrium by Resectoscopic Surgery: A Pilot Study

PAOLO CASADIO,¹ FRANCESCA GUASINA,² ROBERTO PARADISI,³ CONCETTA LEGGIERI,³ GIACOMO CAPRARA,³ RENATO SERACCHIOU³
¹Department of Obstetrics, Gynecology, and Reproductive Biology and ²Department of Pathology, DIMEC, S. Orsola Hospital, University Alma Mater Studiorum of Bologna, Bologna, Italy
Disclosures of potential conflicts of interest may be found at the end of this article.

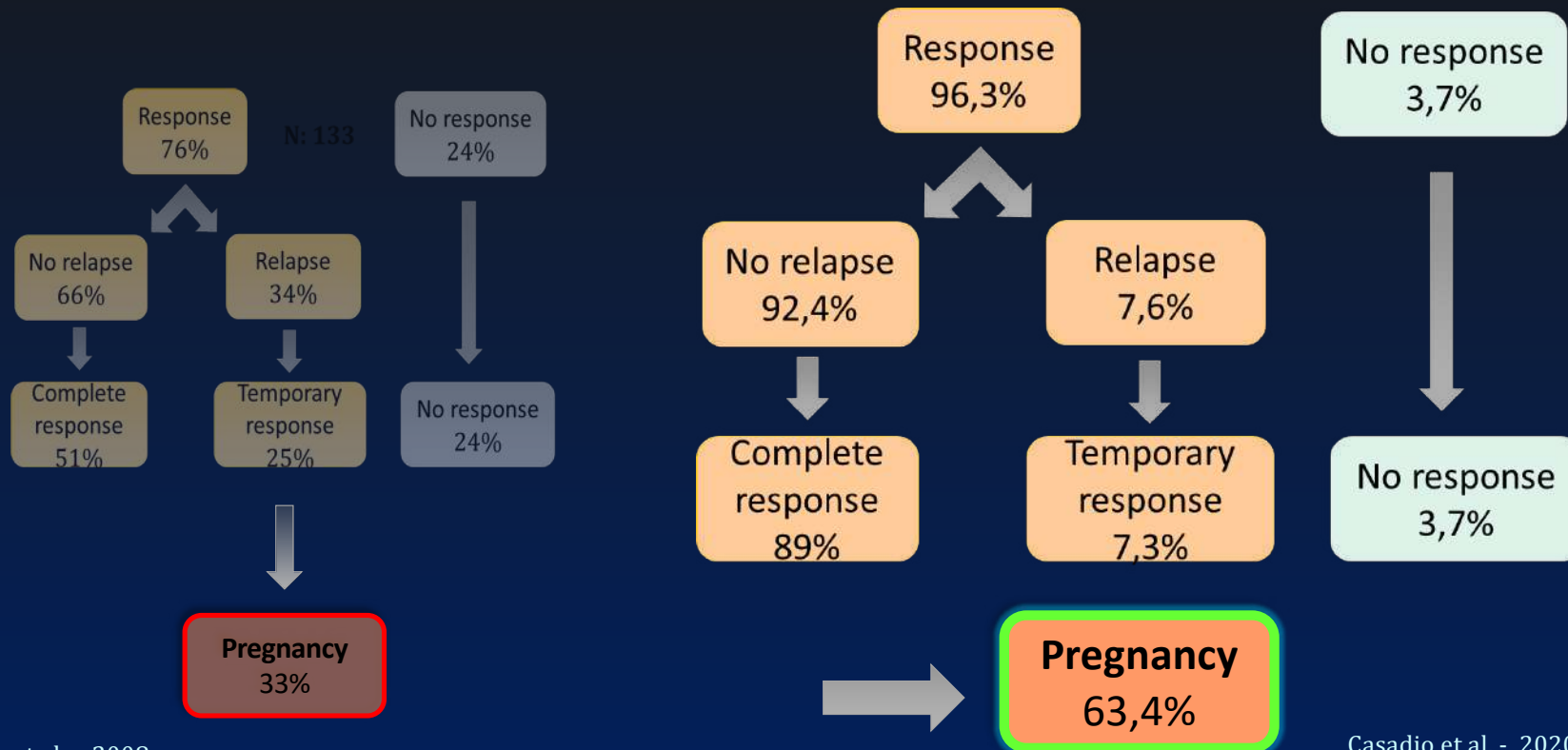
Casadio et al. - 2018

OUR EXPERIENCE

The Oncologist
 Brief Communications
Fertility-Sparing Treatment of Endometrial Cancer with Initial Infiltration of Myometrium by Resectoscopic Surgery: A Pilot Study
 PAOLO CASADIO,¹ FRANCESCA GUARNA,² ROBERTO PARABISI,³ CONCETTA LOSIBILI,⁴ GIACOMO CAPRARA,⁵ RENATO SIRACCHESI⁶
¹Department of Obstetrics, Gynecology, and Reproductive Biology and ²Department of Pathology, IRMEG, S. Orsola Hospital, University Alma Mater Studiorum of Bologna, Bologna, Italy
 Disclosures of potential conflicts of interest may be found at the end of this article. **Casadio et al. - 2018**

cancers Casadio 2020 MDPI
 Article
Fertility Sparing Treatment of Endometrial Cancer with and without Initial Infiltration of Myometrium: A Single Center Experience

Hysteroscopic + Medical treatment Results



Chiva et al. - 2008

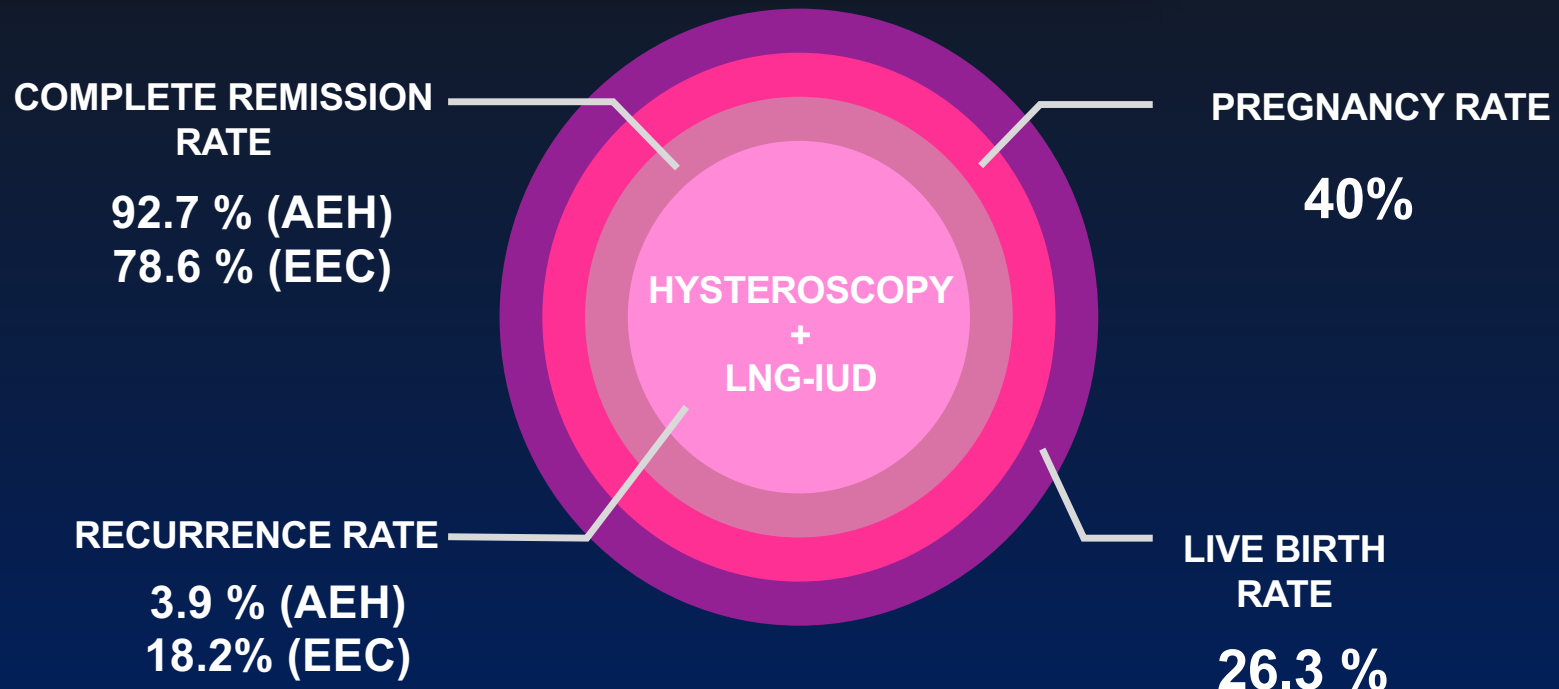
Casadio et al. - 2020

Hysteroscopic Endometrial Focal Resection followed by Levonorgestrel Intrauterine Device Insertion as a Fertility-Sparing Treatment of Atypical Endometrial Hyperplasia and Early Endometrial Cancer: A Retrospective Study

Pierluigi Giampaolino, MD, PhD, Attilio Di Spiezio Sardo, MD, PhD, Antonio Mollo, MD, PhD, Antonio Raffone, MD, Antonio Travaglino, MD, Antonio Boccellino, MD, Brunella Zizolfi, MD, Luigi Insabato, MD, PhD, Fulvio Zullo, MD, PhD, Giuseppe De Placido, MD, PhD, and Giuseppe Bifulco, MD, PhD



2019



Courtesy of Di Spiezio Sardo Attilio



PUBLISHED JANUARY 2021

Fertility preservation

Work-up for fertility preservation treatments

A

Patients who are candidates for fertility-preserving treatment must be referred to specialized centers. Fertility-sparing treatment should be considered only in patients with AH/EIN or grade 1 endometrioid endometrial carcinoma without myometrial invasion and without genetic risk factors.

A

In these patients, endometrial biopsy, preferably through hysteroscopy, must be performed.

A

AH/EIN or grade 1 endometrioid endometrial carcinoma must be confirmed/diagnosed by a pathologist experienced in gynecological pathology.

B

Radiologic imaging to assess the extension of the disease must be performed. An expert ultrasound examination can substitute pelvic MRI scan.

A

Patients must be informed that fertility-sparing treatment is not a standard treatment. Only patients who strongly desire to preserve fertility should be treated conservatively. Patients must be willing to accept close follow-up and be informed of the need for future hysterectomy in case of failure of treatment and/or after pregnancies.

- Well-differentiated (grade 1) endometrioid adenocarcinoma on dilation and curettage (D&C) confirmed by expert pathology review
- Disease limited to the endometrium on MRI (preferred) or transvaginal ultrasound^h
- Absence of suspicious or metastatic disease on imaging
- No contraindications to medical therapy or pregnancy
- Patients should undergo counseling that fertility-sparing option is NOT standard of care for the treatment of endometrial carcinoma



Today

THE GOLD STANDARD



Courtesy of Di Spiezio Sardo Attilio

OUR EXPERIENCE

The
Oncologist[®]

2018

Fertility-Sparing Treatment of Endometrial Cancer with Initial Infiltration of Myometrium by Resectoscopic Surgery: A Pilot Study

PAOLO CASADIO,^a FRANCESCA GUASINA,^a ROBERTO PARADISI,^a CONCETTA LEGGIERI,^a GIACOMO CAPRARA,^b RENATO SERACCHIOLI^a

^aDepartment of Obstetrics, Gynecology, and Reproductive Biology and ^bDepartment of Pathology, DIMEC, S. Orsola Hospital, University Alma Mater Studiorum of Bologna, Bologna, Italy

Three women with a well-differentiated grade 1 endometrioid adenocarcinoma of the endometrium with minimal myometrial infiltration were treated with hysteroscopic resection and hormone therapy. The presence of myometrial infiltration has often been mentioned as an exclusion criterion for conservative management in young patients because of worsening cancer prognosis. The subsequent 5-year follow-up and the pregnancies achieved may confirm the choice of this temporary treatment and indicate a new option for fertility-sparing treatment in highly motivated patients. *The Oncologist* 2018;23:478–480



Hysteroscopic Surgery

OUR EXPERIENCE

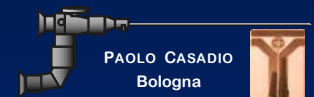
Fertility-sparing treatment for intramucous, moderately differentiated, endometrioid endometrial cancer: a Gynecologic Cancer Inter-Group (GCIG) study



2020

Francesca Falcone ¹, Umberto Leone Roberti Maggiore ², Violante Di Donato ³,
Anna Myriam Perrone ⁴, Luigi Frigerio ⁵, Giuseppe Bifulco ⁶,
Stephan Polterauer ⁷, Paolo Casadio ⁸, Gennaro Cormio ⁹, Valeria Masciullo ¹⁰,
Mario Malzoni ¹¹, Stefano Greggi ¹

In conclusion, fertility-sparing treatment seems to be feasible even in a higher than G1 risk category of EC patients. Although the population sample is very limited, the rates of CR, recurrence, and duration of response are similar to those observed in G1 patients, with less than 2% risk of unfavourable outcome. Caregivers, however, should apply caution with the potential pathological undergrading or non-endometrioid histology misdiagnosis. The low rate of attempt to conceive and the disappointing compliance to definitive surgery underline the role for a 'global' counselling including psychological support extended to the follow-up period. Routine MMR IHC analyses should be recommended while ProMisE application may be adopted for a better risk stratification.



Hysteroscopic Surgery

ESGO/ESHRE/ESGE Guidelines for the fertility-sparing treatment of patients with endometrial carcinoma*†

A. RODOLAKIS¹, G. SCAMBA², F. PLANCHAMP³, M. ACIEN⁴, A. DI SPIEZIO SARDO⁵, M. FARRUGIA⁶, M. GRYNBERG^{7,8,9}, M. PAKIŽ¹⁰, K. PAVLAKIS^{11,12}, N. VERMEULEN¹³, G. ZANNONI¹⁴, I. ZAPARDIEL¹⁵, K. L. TRYDE MACKLON¹⁶



European
Society for
Gynaecological
Endoscopy

**Fertility sparing treatment for
endometrial carcinoma**

GUIDELINES

2023

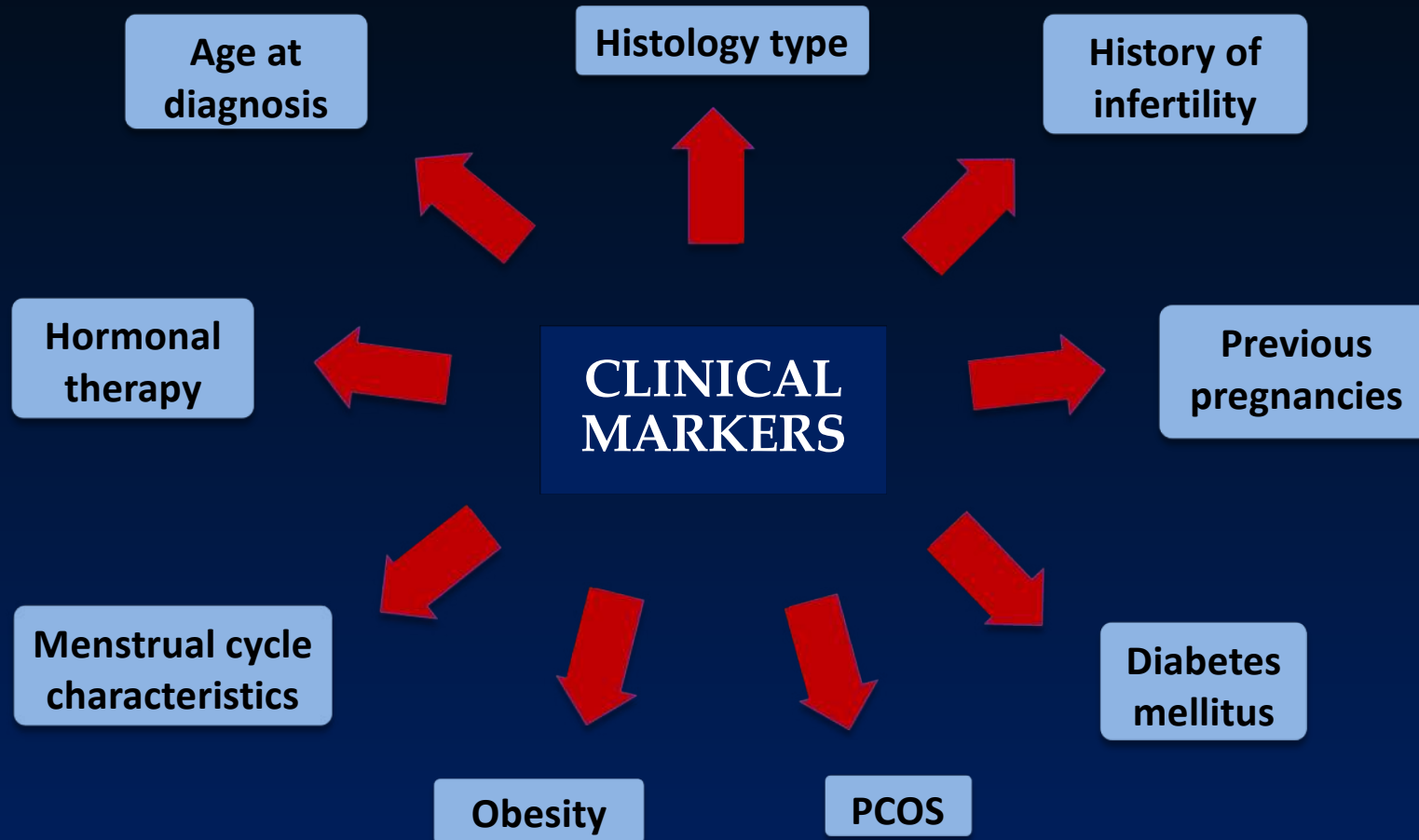


Combined approach consisting of hysteroscopic tumour resection, followed by oral progestins and/or LNG-IUD, is the most effective fertility-sparing treatment both in terms of highest complete response rate and live birth rate compared to other treatment options [II, B].

FUTURE PROSPECTIVES

FUTURE PROSPECTIVES

Predictive markers of response



Kostas et al, Fertil Steril. 2014

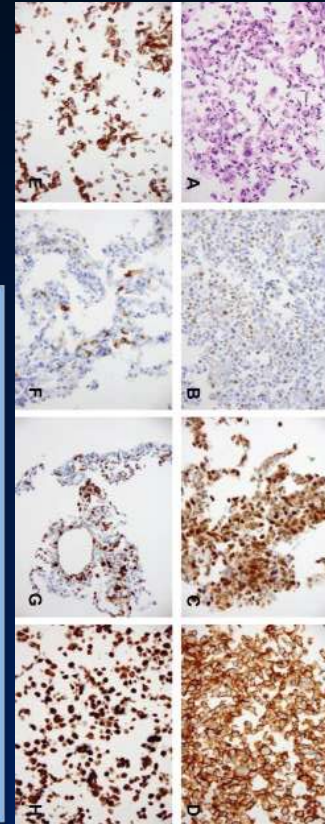
FUTURE PROSPECTIVES

Predictive markers of response

IMMUNOHISTOCHEMICAL MARKERS

41 IHC markers

PR, PRA, PRB, ER, ER α , ER β , PTEN, Ki67, Bcl2, PAX2, BAX, surviving, Nrf2, MMR, MLH1, Fas, p-AKT, p-Mtor, NCoR, Dusp6, GRP78, HE4, AKR1C1, SPAG9, 17 β -HSD2, FasL, AR, p53, IGF1R, p27, SRC1, p300/CBP, SMRT, caspase-3, MT, aromatase, ssDNA, COX2, FOXO1, B-catenin, 17 β -HSD1



FUTURE PROSPECTIVES

Predictive markers of response

CLINICAL MARKERS

Regression



Previous pregnancy (OR: 2,7)

Infertility (OR: 2,26)

Treatment with megestrol acetate (OR: 2,7)

Kostas et al, Fertil Steril 2014

Treatment failure
(no regression
or recurrence)



Infrequent menstrual bleeding

Longer menstrual cycles (OR: 2,1, p=0.042)

Diagnosis of EEC instead of AEH (OR: 4,54, p=0,3)

Raffone et al, J Adolesc Young Adult Oncol. Under revision.

Diabetes mellitus does not affect the outcome of conservative treatment [OR=1.20 (95% CI, 0.58–2.48)] (p= 0.62)

Raffone et al, Gynecol Endocrinol. 2019



Hysteroscopic Surgery

FUTURE PROSPECTIVES

Predictive markers of response

IMMUNOHISTOCHEMICAL MARKERS – ABNORMAL EXPRESSION

PR & ER



Conflicting results

PR & ER
isoforms



Best results (in particular PRB)

MMR, Dusp6, GRP78 & PTEN
combined with phospho-AKT
or phospho-mTOR



Significant results, but
assessed in only one
study each

Nrf2 and survivin



Most significant markers in in the
follow-up phase

Fas, NCoR, AKR1C1, HE4,
PAX2 and SPAG9



Need for further
studies

FUTURE PROSPECTIVES



Fertility sparing treatment for
endometrial carcinoma

Molecular Profiling of Early-onset Endometrial Carcinoma and Correlation with Response to Treatment

- Performing the ProMisE molecular classifier in all young patients with grade 1, low-stage endometrial carcinoma who wish to preserve fertility is encouraged, although available data do not allow clinical applicability (Level of evidence IV, grade B).
- Immunohistochemistry for the identification of mismatch repair-deficient tumours is mandatory in order to identify patients at high risk for Lynch syndrome (Level of evidence III, grade A).
- If a Lynch syndrome is identified, patients should have an appropriate counselling on the risk of developing additional cancers (Level of evidence III, grade A).



Visual dilation and curettage for the fertility-sparing treatment of atypical endometrial hyperplasia/endometrial intra-epithelial neoplasia: an easy to perform in-office technique

Paolo Casadio,¹ Antonio Raffone ,^{2,3} Paolo Salucci ,³ Diego Raimondo,¹ Renato Seracchioli,^{1,3} Jose Carugno,⁴ Attilio Di Spiezio Sardo²

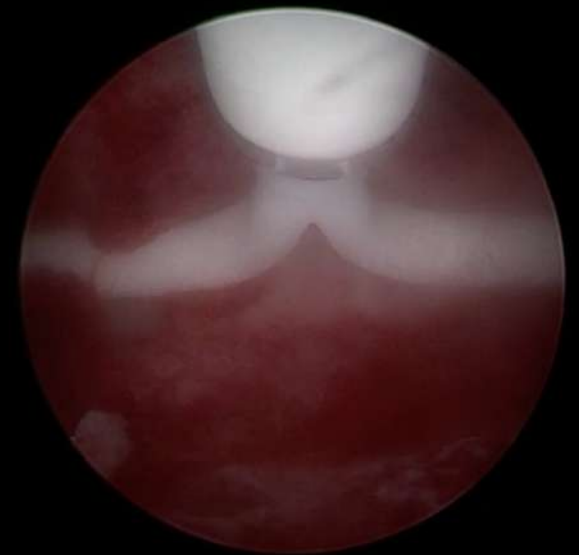
Almost there!



Intervention

Fertility-sparing treatment was performed in the office setting and consisted of hysteroscopic endometrial resection using the Hysteroscopic Tissue Removal System followed by the insertion of a levonorgestrel-releasing intrauterine device

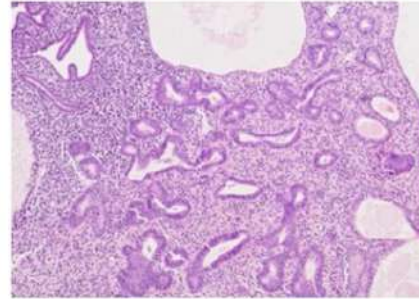
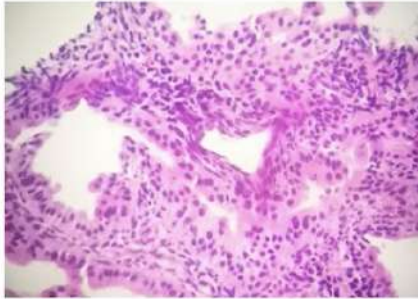
The patients were scheduled for close follow-up every 3 months with ultrasound evaluation and serial endometrial biopsies to assess the response to the treatment





Further advantages

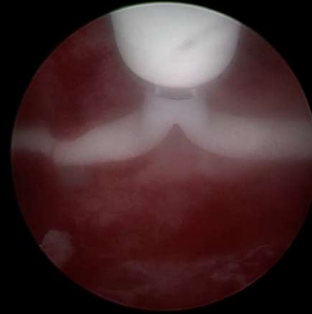
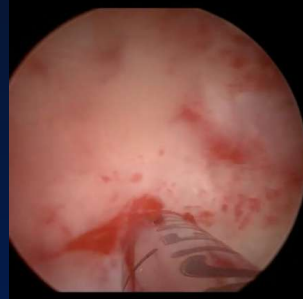
Short learning curve of the use of the Hysteroscopic Tissue Removal System



Higher quality of specimens for histological examination, not subject to thermal damage*



INTERNATIONAL JOURNAL OF
GYNECOLOGICAL CANCER

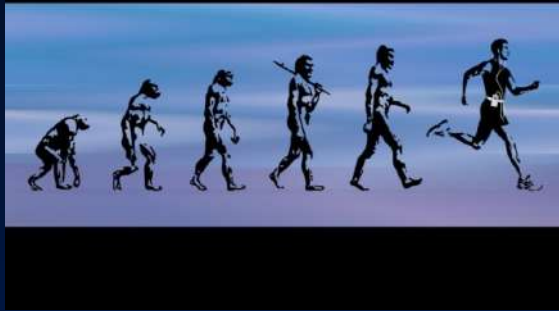


- Office setting
- Speed of the procedure
- Safety
- Ease of use
- Reproducibility
- Quality of specimens for histological examination



ONCOLOGICAL HYSTEROSCOPIC CULTURE

Evolution of Technique and Technology



Multidisciplinary
Oncology Team and
Diagnostic
Integration



Careful
patient
selection



Experience,
Comparison,
Research and
Organization



Thank
you