



Universiteit  
Leiden  
The Netherlands

## Tailoring therapy in endometrial and cervical cancer

Gent, M.D.J.M. van

### Citation

Gent, M. D. J. M. van. (2017, June 20). *Tailoring therapy in endometrial and cervical cancer*. Retrieved from <https://hdl.handle.net/1887/51101>

Version: Not Applicable (or Unknown)

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/51101>

**Note:** To cite this publication please use the final published version (if applicable).

Cover Page



Universiteit Leiden



The handle <http://hdl.handle.net/1887/51101> holds various files of this Leiden University dissertation

**Author:** Gent, M.D.J.M. van

**Title:** Tailoring therapy in endometrial and cervical cancer

**Issue Date:** 2017-06-20



# CHAPTER 2

## **No Surgery for Low-Grade Endometrial Cancer in Women with a desire to Preserve Fertility**

Mignon van Gent  
Marjolein Kagie  
Baptist Trimbos

*Journal of gynecological surgery 2012 Oct; volume 28 (issue 6): 398-398*

## **CHAPTER 2**

### **No Surgery for Low-Grade Endometrial Cancer in Women with a desire to Preserve Fertility**

- 2.1 Abstract
- 2.2 Introduction
- 2.3 Objectives
- 2.4 Materials and methods
- 2.5 Results
- 2.6 Discussion
- 2.7 Authors' conclusions
- 2.8 References

## 2.1 ABSTRACT

### Objective

The treatment of endometrial cancer is total hysterectomy including bilateral salpingo-oophorectomy. Standard treatment takes away the possibility for fertile women to conceive. This review studies the effectiveness and safety of conservative/hormonal therapy for stage I grade 1 and 2 endometrial cancer.

### Materials and Methods

We searched Pubmed for publications from January 1968 to November 2008. Publications included retrospective studies, case reports, multicenter Phase II study, and literature reviews describing conservative treatment for women with type I endometrial cancer.

### Results

Fifty-five studies described 245 patients with stage I endometrial cancer. The median age of the patients was 30.3 years. Two hundred and thirty-two patients had grade 1 disease, and 16 had grade 2 or more. Grading was unknown for five patients. Patients were treated with different progestatives. Three out of 245 patients did not receive any treatment for their disease. The mean number of months of treatment was 7 months. One hundred and ninety-three of the 245 patients responded initially to therapy. Progesterone receptor status was known in 86 of 245 patients. Seventy-seven patients (90%) were progesterone receptor positive. The mean follow-up was 47 months. No patient died of endometrial cancer. One hundred and twenty-seven pregnancies and 109 living births were described.

### Conclusions

Conservative treatment of endometrial cancer may be considered in a well-selected group of patients: stage I, grade 1 and 2 endometrial cancer in women who want to preserve their fertility. The patients have to be treated according to a well-defined, pre-set protocol. The process should be well documented to improve the safety and effectiveness of the conservative treatment.

## **2.2 INTRODUCTION**

The standard treatment for patients with endometrial cancer is total hysterectomy including bilateral salpingo-oophorectomy. However, this standard approach takes away the possibility for fertile women to conceive. We undertook this review to determine the effectiveness and safety of conservative/hormonal therapy for stage I grade 1 and 2 endometrial cancer.

## **2.3 OBJECTIVES**

Conservative (hormonal) treatment of early stage endometrial cancer has been advocated as an alternative method of treatment in exceptional cases for young women who wish to preserve their fertility. The objectives of this review are (1) to determine the effectiveness and safety of conservative therapy for stage I grade 1 and 2 endometrial cancer, and (2) to formulate a protocol to save fertility in young patients with endometrial cancer.

## **2.4 MATERIALS AND METHODS**

We searched Pubmed for publications from January 1968 to November 2008. Publications included retrospective studies, case reports, multicenter Phase II study, and literature reviews describing conservative treatment for women with type I endometrial cancer. Because of a lack of prospective studies, we collected all data available on the subject. Two investigators abstracted the data. Studies that were not available online were hand searched.

## **2.5 RESULTS**

Literature on conservative treatment of endometrial cancer in women who want to preserve fertility is inconclusive with regard to the best treatment modality. There are many case reports, retrospective observational studies, some prospective studies, and many reviews. Jadoul <sup>1</sup> reported 38 patients being treated with progestagens. Rackow <sup>2</sup> studied 90 patients. Gotlieb <sup>3</sup>, Ramirez <sup>4</sup> and Boing 2006 <sup>5</sup> have written the most complete and clear reviews. Chiva has used most of this information and completed it with the last available data and described 133 patients. <sup>6</sup> We offer the most recent and complete review of the available literature. Receptor status and methods of therapy were previously not described as clearly as they are in this review. Table 1 shows all case reports and prospective observational studies published from 1986 to the end of 2008. <sup>1, 3, 6-58</sup>

### **Number of patients**

We found 55 studies describing conservative treatment of endometrial cancer. We checked for double registration, and 245 patients remained. The median age of the patients is 30.3 years.

### **Grading**

Two hundred and thirty-two patients with stage I endometrial cancer had grade 1 disease, and 16 patients had grade 2 or more. Grading was unknown for five patients.

### **Treatment**

Patients were treated with medroxyprogesterone acetate (MPA), megestrol acetate (MA), hydroxyprogesterone caproate (OH-prog), norethisterone acetate (NA), dihydrosterone (DH), and norethindrone (NE). Three of 245 patients did not receive any treatment for their disease. Most patients were treated with MPA varying from 5 to 800mg per day. The duration of the treatment varied between 1 and 37 months. The mean duration was 7 months. One hundred and ninety-three out of 245 patients responded to therapy. Histology results for 143 patients were grade 1, five were grade 2, one was grade 3, and 21 were either grade 1 or 2, not specified by the authors.

### **Receptor status**

Progesterone receptor status was only known in 86 of 245 patients. Seventy-seven (90%) were progesterone receptor positive. Nine patients were receptor negative. Receptor status for all other cases was unknown.

### **Follow-up**

The mean follow-up was 47 months. One hundred and twenty-seven pregnancies and 109 living births were described. Six studies did not mention pregnancy rates, and the rest of the studies were incomplete. It was not stated if all patients wished to conceive. Not all of the studies report all pregnancies (including miscarriages). Three patients died after being treated conservatively: two died of ovarian cancer and one died of liver cirrhosis. A description of the mortality is provided.

**Table 1.** Studies on Conservative Treatment of Endometrial Cancer From 1986 Till 2008.

Author Year	N	Grade	Treatment/day	Duration treatment ‡	Response
Kempson 1968 <sup>6</sup>	3	2-3 1-2	progestagen (2) none (1)	>1	1/2
O'neill 1970 <sup>7</sup>	1	1	NE 2mg/mo Mestranol 0.1 mg	2.5	1/1
Eddy 1978 <sup>8</sup>	1	1	OH-prog 1000 mg 3/wk, MPA cycle	2	1/1
Greenblatt 1982 <sup>9</sup>	1	uk	uk	uk	0/1
Bokhman 1985 <sup>10</sup>	19	1 (15) 2 (4)	OH-prog 25-83 gram + chemo	3.6	12/19
Thornton 1985 <sup>11</sup>	1	uk	NA 20mg 21/28 days +NA 5mg	13 6	1/1
Fahri 1986 <sup>12</sup>	4	1	Progestogen	uk	3/4
Muechler 1986 <sup>13</sup>	1	1	MPA	15	1/1
Lee 1989 <sup>14</sup>	2	uk	uk	uk	1/2
Paulson 1990 <sup>15</sup>	1	1	MA 160mg	6	1/1
Kimmig 1995 <sup>16</sup>	1	1	MPA 200mg	2	1/1
Lai 1994 <sup>17</sup>	1	uk	uk	6	1/1
Kim 1997 <sup>18</sup>	7	1	MA 160mg	3	4/7
Kung 1997 <sup>19</sup>	1	1	Tamoxifen 30 mg +MA 160 mg	6	1/1
Randall 1997 <sup>20</sup>	12	1	MA 40-160mg +MPA or Tamoxifen or Platinum bromocriptine 10 mg	9	9/12
Salha 1997 <sup>21</sup>	1	1	MPA 60 mg	9	1/1
Zanetta 1997 <sup>22</sup>	1	1	MPA 5 mg	3	1/1
Sardi 1998 <sup>23</sup>	3	1	MPA 200-500 mg	4	3/4 (grade 1)
	1	2			
Schammel 1998 <sup>24</sup>	3	uk	none (1) progesterone (2)	6	2/3
Zuckerman 1998 <sup>25</sup>	1	2	MPA 600 mg	5,5	1/1
Kowalczyk 1999 <sup>26</sup>	1	1	uk	6	1/1
Vinker 1999 <sup>27</sup>	1	1	MPA 400 mg/day	2.5	0/1
Shibahara 1999 <sup>28</sup>	1	1	None	uk	1/1



No surgery for low-grade endometrial cancer

Recurrence	Mean Age	Receptor status	Follow up mean (mo)	Gravity/ parity
none	27,3	uk	24	G2 P uk
none	17	uk	19	G1 P1
none	21	uk	50	G1 P1
none	31	uk	uk	uk
uk	28	uk	36-108	uk
none	23	uk	21	uk
none	17,5	uk	45 3 -120 1 LTFU	G2 P2
none	31	uk	54	G2/P1/A1
uk	19	uk	30	G1/P1
none	35	uk	15	G2/P1/A1
none	28	uk	21,5	G1/P1+2
uk	31	uk	30	G1/P1
2/4	32,4	uk	12,9	G uk/P0
none	22	+	uk	uk
1/9	30,5	uk	46	G9 P7 A2
1/1	32,0	uk	uk	G0
none	30	uk	52	G2/P2
none	31,8	uk	41	G3 P3
none	35	uk	39	G4 P4
none	26	uk	18	G3/P1+1
none	28	uk	18	G1
none	33	uk	48	G0
none	32	+	11	G1

2

**Table 1.** Continued

<b>Author Year</b>	<b>N</b>	<b>Grade</b>	<b>Treatment/day</b>	<b>Duration treatment ‡</b>	<b>Response</b>
Jobo 1999 <sup>29</sup>	2	1	MPA 600 mg	6,5	2/2
Mitsushita 2000 <sup>30</sup>	1	1	MPA 400 mg, 4mo MPA 600 mg, 6mo	12	1/1
Ogawa 2000 <sup>31</sup>	1	1	MPA 400 mg	3	1/1
Kaku 2001 <sup>32</sup>	12	1 (10) 2 (2)	MPA 200-800 mg	2-14	9/12 8 CR 1 PR
Pinto 2001 <sup>33</sup>	1	1	MA 40 mg	uk	1/1
Imai 2001 <sup>34</sup>	12	1	MPA 400-800 mg	>3	8/15
	1	2			
	2	a			
Duska 2001 <sup>35</sup>	12	1	Progestin	uk	10/12
Wang 2002 <sup>36</sup>	9	1	MA 30 mg tamoxifen gnRHa	>6	8/9
Lowe 2003 <sup>37</sup>	2	1	MA 80 mg	3 6	2/2
Gotlieb 2003 <sup>3</sup>	13	1 (11) 2 (2)	MA 160mg (8) MPA 200-600 mg OH-prog2-3gr/wk NA 5 mg	12.7 (3-37 mo)	13/13
Jadoul 2003 <sup>1</sup>	5	1	endometrium resection + GnRH agonist	3-6	5/5 3 CR 2 PR
Burnett 2004 <sup>38</sup>	2	1	MPA 160 mg + arimidex 1 mg	8-....	2/2
Nakao 2004 <sup>39</sup>	2	1	MPA 400 mg	7-9	2/2
Yarali 2004 <sup>40</sup>	1	1	MA 160 mg	6	1/1
			MPA 10 mg	6	
Niwa 2005 <sup>41</sup>	12	1	MPA 400-600 mg	6-10	12/12
Ota 2005 <sup>42</sup>	12	1	MPA 600 mg	uk	5 /12 CR
Ferrandina 2005 <sup>43</sup>	1	1	DH 20 mg CD15-25	2	1/1

No surgery for low-grade endometrial cancer

Recurrence	Mean Age	Receptor status	Follow up mean (mo)	Gravity/ parity
none	34	+	41,5	G2/P2+1
1/1	28	+	uk	G1 P1
none	31	uk	>9	G1/P1
2/9	31	uk	31,5 10-133	G2 P1
none	29	uk	6	G1/P1+2
3/8	30,2		59	G2 P2+1
3/12	31	uk	uk	G uk/P5
4/8	32	7 + 1 - 1 weak +	69	G6 P3+2 EUG 2/A1
none	32,5	uk	44	G2 P3+2
5/13	31	uk	82 6-258	G12 P9 A1 pregnant 2
uk	33,4	uk	6-72	G4 P3+1 A1
none	29,0	uk	19	uk
none	36	+	32,5	G2/P2
none	32	uk	uk	G1 P1
8/9 (long term follow up)	28,5	+	18	G7  P5+1/A1 IUFD 22 wks
1/12	30,9	11 +	52,7	G5/P3/Apla 1 p.i. 22 wk
1/1	30	+ (prim tumour) - (recurrence)	uk	G1 P1

2

**Table 1.** Continued

Author Year	N	Grade	Treatment/day	Duration treatment ‡	Response
Huang 2005 <sup>44</sup>	1	1	MA 160 mg	1	0/1
			>1 mo tamoxifen	4	
			no response		
Mazzon 2005 <sup>45</sup>	1	1	MA 160 mg	10	1/1
Yang 2005 <sup>46</sup>	6	1	MA 160 mg	uk	4/6
Chang 2006 <sup>47</sup>	1	1	MPA 500 mg twice/wk	6	1/1
Park 2006 <sup>48</sup>	1	1	MA 600 mg	2	1/1
			400 mg	1	
			320 mg	3	
Sparac 2006 <sup>49</sup>	1	1	MPA 400 mg	3	1/1
Yahata 2006 <sup>50</sup>	8	1	MPA 1800 mg	22	7/8
Gurgan 2007 <sup>51</sup>	1	1	uk	uk	0/1
Minaguchi 2007 <sup>52</sup>	19	1	MPA 400-600 mg	2-12	15/19
Shamshirsaz 2007 <sup>53</sup>	1	1	MA 160 mg	6	1/1
			MPA 20 mg		
			14days/mo	6	
			MPA 30 mg		
			14/days/mo	continued	
Ushijima 2007 <sup>54</sup>	22	1	MPA 600 mg	6.5	12/22 CR
			+ 81 mg aspirin		7/22 PR
Yamazawa 2007 <sup>55</sup>	9	1	MPA 400 mg	>6	9/9
					7 CR
					2 PR
Hurst 2008 <sup>56</sup>	1	1	MA 160 mg	6	1/1
Takahashi 2008 <sup>57</sup>	1	1	MPA 600 mg+E37	4.5	1/1
Wu 2008 <sup>58</sup>	1	1	MA 160 mg	2 x 6 mo	1/1

N, number of of patients; ‡ Month; MPA, medroxyprogesterone acetate; MA, megestrol acetate; OH-prog. Hydroxyprogesterone caproate; NA, norethisterone acetate; DH, dihydrosterone; NE, norethindrone; a, adenocanthoma; LTFU, lost to follow up.

No surgery for low-grade endometrial cancer

Recurrence	Mean Age	Receptor status	Follow up mean (mo)	Gravity/ parity
none	36	-	uk	G0
none	31,0	+	33	G1/P1
2/4	33	4 +	48,8	G4
		2 -		P2
none	35	uk	12	uk
none	36	+	24	G1 P1
none	30	uk	uk	G1/P1
7/7	31,9	7	76,5	G7
		-1		P2
none	39	uk	uk	G0
5/15	30,6	17 +	40,7	G10
		1 -	2-109	P 6+1
		1 doubt		A4
1/1	21	uk	9	G0
7/19	31,7	uk	47,9	G12 P7+2/A5
2/9	36	7 + (CR)	39	G4
		2 - (PR)		P3
				A1
1/1	31	uk	uk	G0
1/1	39	+	uk	G0
1/1	35	+	24	G0

2

### Recurrence

Fifty-nine out of 193 patients had recurrent disease after first responding (partially or completely) to the treatment. Recurrence was noted by hysteroscopy and biopsy or mini-curettage. Of all 59 patients with recurrences after complete or partial response, 45 hysterectomies with bilateral salpingo-oophorectomy were performed. Eleven patients were retreated with progestatives and responded completely to treatment. One study describing three patients did not give any further information about their pathology results. Of the 45 patients who underwent hysterectomy, no evidence of disease was seen in three patients. Definitive pathology results were not described for 11 patients with recurrence. One patient had hyperplasia with atypical cells. Thirty-three patients were diagnosed with endometrial cancer, as detailed in Table 2.

**Table 2.** Patients with endometrial cancer at recurrence

		Grade				
		1	2	3	unknown	
Stage	I	-	-	-	-	3
		a	5	-	-	2
		b	7	-	-	-
		c	3	-	-	-
	II	a	-	1	-	-
		b	-	-	-	-
		c	-	-	-	-
	III	a	7	-	-	2
		b	-	-	-	-
		c	-	1	-	1
IV		-	1	-	-	

### Details

#### Mortality

The first death was described by Ota.<sup>42</sup> A patient died after not responding to conservative treatment, choosing abdominal hysterectomy without bilateral salpingo-oophorectomy. She was treated with 600mg MPA. Twenty months after initial surgery, a site of recurrence was found in one of the ovaries. Surgery was performed where bilateral salpingo-oophorectomy, pelvic lymphadenectomy, and omentectomy was performed. She was treated with chemotherapy. The patient died 71 months after primary treatment with MPA. The second death is discussed by Ushijima.<sup>59</sup> After 26 weeks, the patient was in complete remission. She was treated with 600mg MPA and 81mg aspirin a day. She had three more treatments with MPA for repeated recurrences. Two years after initial MPA treatment, she got peritoneal carcinomatosis and grade 2 endometrioid adenocar-

cinoma in her ovary. She died 4 months after surgery. It is speculated that it must have been a secondary primary malignancy (endometrial cancer and ovarian cancer) because no signs of endometrial malignancy were found at hysteroscopy 3 months before development of peritoneal lesions. The third patient died of liver cirrhosis not expected to be due to this treatment, and one patient had progressive disease but showed no evidence of disease after hysterectomy and bilateral salpingo-oophorectomy.<sup>60</sup>

#### *Receptor status*

Only 18 studies described the receptor status; 37 did not. In the prospective studies of Yang<sup>46</sup>, Minaguchi<sup>60</sup> and Yamazawa<sup>61</sup> the receptor status was known. Yang treated six patients with 160mg MA per day. Four patients showed response, but two had recurrent disease. The two non-responders and the two patients with recurrent disease underwent a hysterectomy and bilateral salpingo-oophorectomy. Histological findings were twice stage IIa, twice stage Ic, and once grade 2 endometrial cancer. All four specimens showed ovarian cancer. Two samples were proven to be a second primary tumor, but the other two were inconclusive. The two responders were receptor positive, and two other patients were receptor positive: one had recurrence and one failed any response. The two patients with a negative receptor status were a non-responder and a patient with recurrence. Minaguchi treated 19 patients with 400 to 600mg MPA per day for 2-12 months.<sup>60</sup> Seventeen patients were receptor progesterone receptor positive, one negative and one inconclusive. Fifteen patients responded, and five had recurrent disease, all of whom were receptor positive. Yamazawa included nine patients, all grade 1, with 400mg MPA, for at least 6 months.<sup>61</sup> All patients showed response—seven complete responses and two partial responses. Progesterone receptor was positive in the complete response group and negative in the specimen of the two patients with partial response. One patient underwent an additional 9-month treatment with chemotherapy after not showing remission after 6 months. Two patients with recurrent disease were treated surgically and both showed grade 1 ovarian cancer.

#### *Side effects therapy*

Ushijima et al. treated their patients with 81mg aspirin in addition to 600mg MPA per day to avoid thrombo-embolic complications that can be theoretically expected.<sup>59</sup> No study proves a significant higher chance of thrombo-embolic or cardiovascular problems with varying amounts of progesterone. Only two authors described a side effect of progesterone. Park described a weight gain of 15 kg during treatment with 600mg MA (2 months), 400mg MA (1 month), and 320mg MA (3 months).<sup>48</sup> Complaints of nausea made one patient choose to stop the treatment in Randall's study.<sup>20</sup> This patient was not treated maximally with medication to diminish the emesis.

## 2.6 DISCUSSION

Two hundred and forty-five patients were treated conservatively with progestagens. Mostly they were treated with MPA. The recurrence rate was high: 31% of all 193 patients that (partially) responded to the treatment. However, the mortality rate was low—3 out of 245 patients—and no patient died of endometrial cancer. We conclude that there is still insufficient evidence to compare the conservative treatment of endometrial cancer with the gold standard. At the same time, there is an increasing demand for conservative treatment of many cancers. Patients demand a better quality of life by keeping the possibility of being able to conceive. The aim of the study was to provide a protocol for gynecologists to treat their patients uniformly and to clarify the conservative treatment of endometrial cancer. In addition, data were collected prospectively to improve the effectiveness and safety of this method further.

### **The Safety of Non-invasive Staging**

Surgical-pathological staging is the gold standard. FIGO staging for endometrial cancer is done by observing myometrial invasion of the endometrium, intra-peritoneal growth, and adnexal metastasis. In our protocol, surgical staging cannot be done, so clinical judgment for staging has to be done as accurately as possible. Tran investigated that more than 50% myometrial invasion is seen in 24% of young patients versus 49% of older patients.<sup>62</sup> Approximately 7% to 10% of the patients with grade 1 endometrial cancer have deep myometrial invasion.<sup>63,64</sup> The chance of myometrial invasion is small for patients with grade 1 endometrial cancer. During the development of our protocol, we considered the fact that a stage Ic has a less favorable prognosis than a stage Ia, and the diagnostic tools to judge the myometrial invasion are limited. The most accurate way of imaging the myometrial invasion is by (contrast-enhanced) magnetic resonance imaging. The accuracy varies between 68% and 82%.<sup>65</sup> Contrast MRI is the only possibility to approach the accuracy of surgical staging. However, because the accuracy varies between 68% and 82% and there is only a small chance of deep myometrial invasion in low-grade tumors of 7% to 19%, we decided to include all assumed stage I tumors and not leave out stage Ic.<sup>62,63,64</sup> The essence of performing a pre-treatment laparoscopy can be discussed. Twenty-two studies described recurrences, and 29 stated that no recurrences were noticed at follow-up. Four studies did not mention recurrences. In the first group, only one study described performing a laparoscopy. In the second group without recurrences, laparoscopy had been performed in 10 out of 29 studies, and one study described pre-treatment staging by laparotomy. No patients were excluded from treatment because of laparoscopic findings. We could suggest laparoscopy has been performed more often during fertility analyses before discovering endometrial cancer. However, it has not been recorded. In conclusion, from this review, we cannot conclude



whether a laparoscopy is necessary. However, if lesions are suspected by vaginal ultrasound or MRI, laparoscopy is mandatory.

### **Grading**

Endometrioid adenocarcinoma is the most common histological type of endometrial cancer in young patients. Other histological types are papillary serous and clear cell carcinoma. These are high-grade tumors and are not included in our protocol. Transitional cell, squamous cell, mucinous, and small cell cancers account for fewer than 2% of all endometrial cancers and are also excluded.

### **Receptor status**

Positive ER and PR receptor status is of great importance to the response to progesterone. Type I tumors are typically low-grade endometrioid carcinomas, with positive estrogen (ER) and progesterone receptors (PR) in 92% of cases. A dose-response study of the Gynecologic Oncology Group showed a response rate of 37% in PR receptor positive patients and 8% in PR receptor negative patients. Likewise, ER receptor positive patients had a 26% response rate and only 7% for ER receptor negative patients.<sup>66</sup>

2

### **Ovarian cancer**

Ulbricht writes that simultaneous presence of an ovarian tumor with the same histology is present in 8% of endometrial cancers.<sup>67</sup> The risk of synchronous primary ovarian cancer is approximately 5% for intrauterine disease.<sup>68</sup> The ovarian tumour should be considered as metastatic when it is small, bilateral, or multinodular with surface implants and angiolymphatic invasion in the ovarian cortex.<sup>67</sup>

### **Hereditary predisposition**

Endometrial cancer originates in high endogenous or exogenous estrogen levels or genetic predisposition like type II Lynch syndrome. Type I is estrogen dependent, hormone sensitive, and low stage with a very good prognosis, and type II, the minority, is associated with endometrial atrophy, being high grade, and having a high rate of recurrence.<sup>69</sup> Lynch II syndrome is an autosomal-dominant inherited cancer susceptibility mainly associated with colorectal cancer or endometrial cancer.<sup>70</sup> Patients have a risk of approximately 20% of developing endometrial cancer before the age of 50.<sup>69</sup> The lifetime risk of getting ovarian cancer for this group is more than 12%.<sup>71</sup> Women diagnosed with endometrial cancer at a fertile age should be referred to a genetic counselor.

### **Biological factors**

Exposure to either endogenous or exogenous excess of estrogens instigates an increased risk of developing endometrial carcinoma. Among the risk factors are obesity,

early menarche, late menopause, no pregnancies, and genetic disorders. The literature suggests that endometrial carcinoma in young women is less aggressive and biologically different from that of older women.<sup>4,5,7</sup> The fact that obese women have a higher chance of a miscarriage is of secondary value and can be considered for inclusion in the counselling but will not be part of the standard work up.

### **Therapy**

Most studies used MPA as their treatment. Eighteen of these studies used a low dose of  $\leq 200$  mg, 11 studies about 400 mg, and 7 studies a high dose of 600mg or more. A study comparing the effects of MPA, NE, and norethynodrel on the endometrium showed a more intense response to progestin than to NE and norethynodrel.<sup>72</sup> MPA is free of estrogen action. Studies in recurrent endometrial cancer have shown 200mg of MPA to be superior to the higher dose of 1,000mg per day. It is less toxic and equally effective.<sup>73</sup> There is a 5-17% chance of thrombophlebitis while using MPA.<sup>74,75</sup> A higher dose leads to an increased chance of adverse effects. Considering these arguments, we have proposed the use of 200mg per day for our protocol.

### **Fertility**

Before starting the conservative treatment, normal work up for endometrial cancer should be performed, including contrast enhanced MRI. Most patients start conservative treatment because of a wish for offspring. For this reason, fertility analysis of the patient and her partner (if applicable) should be performed before starting the protocol.

### **Outcome**

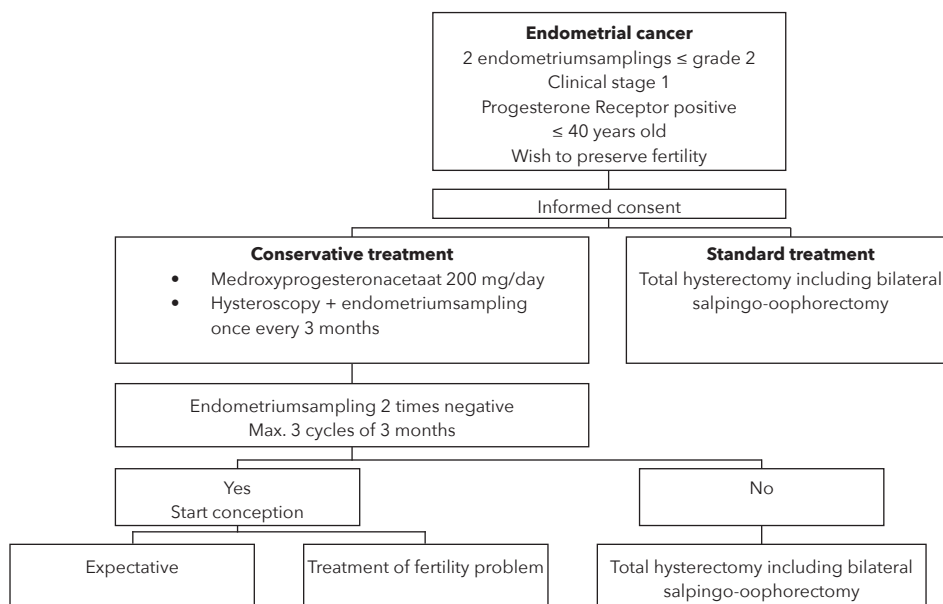
Three out of 245 patients died during the mean follow-up of 47 months: two died of ovarian cancer and one died of liver cirrhosis. No patient died of endometrial cancer. The low mortality rate might be because when patients are treated conservatively, the follow-up is strict and the possibility of switching to surgery is always available. Most patients showing recurrent disease were treated surgically. While looking at the results, the influence of publication bias should always be considered. We are supported in this idea, while looking at the data we can see a recurrence rate of 31% compared to 47% in the article of Ushijima and 40.9% in a more recent study by Hahn.<sup>8,75</sup>

## **2.7 AUTHORS' CONCLUSIONS**

From the results of our literature review, we can conclude that for a selected group of patients, following clear guidelines and protocols, conservative treatment with progesterone is a save method to treat endometrial cancer. Using the information we extracted from the literature, we propose the following protocol. The inclusion criteria

are patients with stage I grade 1 and 2 endometrial cancer, under the age of 40 years, progesterone receptor positive, wishing for offspring, and whose informed consent has been obtained for the treatment advice of total hysterectomy including bilateral salpingo-oophorectomy. The exclusion criteria are patients with recurrent endometrial cancer, endometrial cancer more than stage one and/or grade two, and high-risk cell types. Patients are treated with 200mg MPA per day for at least 6 months and no more than 12 months. The minimum duration of treatment is a 3-month-long treatment course and a 3-month-long consolidation course. Three monthly check-ups with hysteroscopy and endometrial sampling are performed to investigate the effectiveness. If a suspicious lesion is seen, it is resected. In cases of irregular bleeding, a hysteroscopy will be performed directly. After two negative endometrial samplings, conception may be pursued. Follow-up starts after two negative endometrial samplings. During a period of 5 years, a hysteroscopy with endometrial sampling will be performed every 6 months. After this period, check-ups are done yearly. Factors that must be reported in future case reports are: receptor status, drug use, body mass index, attempts for pregnancies, fertility problems, follow-up, and histology results. Treatment is stopped if (1) histology results show endometrial cancer after three cycles of 3 months of therapy; (2) one of the samplings shows endometrial cancer grade 3; or (3) imaging shows extra-uterine disease. If a patient is excluded from the protocol, she receives a total hysterectomy including bilateral salpingo-oophorectomy. The protocol is shown in Figure 1.

2



**Figure 1.** Flow chart showing conservative treatment of endometrial cancer

## 2.8 REFERENCES

1. Jadoul P, Donnez J. Conservative treatment may be beneficial for young women with atypical endometrial hyperplasia or endometrial adenocarcinoma. *Fertil Steril*. 2003;80(6):1315-24.
2. Rackow BW, Arici A. Endometrial cancer and fertility. *Curr Opin Obstet Gynecol*. 2006;18(3):245-52.
3. Gotlieb WH, Beiner ME, Shalmon B, Korach Y, Segal Y, Zmira N, et al. Outcome of fertility-sparing treatment with progestins in young patients with endometrial cancer. *Obstet Gynecol*. 2003;102(4):718-25.
4. Ramirez PT, Frumovitz M, Bodurka DC, Sun CC, Levenback C. Hormonal therapy for the management of grade 1 endometrial adenocarcinoma: a literature review. *Gynecologic oncology*. 2004;95(1):133-8.
5. Boing C, Kimmig R. Fertility-preserving treatment in young women with endometrial cancer. *Gynäkologisch-geburtshilfliche Rundschau*. 2006;46(1-2):25-33.
6. Kempson RL, Pokorny GE. Adenocarcinoma of the endometrium in women aged forty and younger. *Cancer*. 1968;21(4):650-62.
7. O'Neill RT. Pregnancy following hormonal therapy for adenocarcinoma of the endometrium. *Am J Obstet Gynecol*. 1970;108(2):318-21.
8. Eddy WA. Endometrial carcinoma in Stein-Leventhal syndrome treated with hydroxyprogesterone caproate. *Am J Obstet Gynecol*. 1978;131(5):581-2.
9. Greenblatt RB, Gambrell RD, Jr., Stoddard LD. The protective role of progesterone in the prevention of endometrial cancer. *Pathology, research and practice*. 1982;174(3):297-318.
10. Bokhman JV, Chepick OF, Volkova AT, Vishnevsky AS. Can primary endometrial carcinoma stage I be cured without surgery and radiation therapy? *Gynecol Oncol*. 1985;20(2):139-55.
11. Thornton JG, Brown LA, Wells M, Scott JS. Primary treatment of endometrial cancer with progestagen alone. *Lancet*. 1985;2(8448):207-8.
12. Farhi DC, Nosanchuk J, Silverberg SG. Endometrial adenocarcinoma in women under 25 years of age. *Obstet Gynecol*. 1986;68(6):741-5.
13. Muechler EK, Bonfiglio T, Choate J, Huang KE. Pregnancy induced with menotropins in a woman with polycystic ovaries, endometrial hyperplasia, and adenocarcinoma. *Fertil Steril*. 1986;46(5):973-5.
14. Lee KR, Scully RE. Complex endometrial hyperplasia and carcinoma in adolescents and young women 15 to 20 years of age. A report of 10 cases. *Int J Gynecol Pathol*. 1989;8(3):201-13.
15. Paulson RJ, Sauer MV, Lobo RA. Pregnancy after in vitro fertilization in a patient with stage I endometrial carcinoma treated with progestins. *Fertil Steril*. 1990 54(4):735-6.

16. Kimmig R, Strowitzki T, Muller-Hocker J, Kurzl R, Korell M, Hepp H. Conservative treatment of endometrial cancer permitting subsequent triplet pregnancy. *Gynecol Oncol.* 1995;58(2):255-7.
17. Lai CH, Hsueh S, Chao AS, Soong YK. Successful pregnancy after tamoxifen and megestrol acetate therapy for endometrial carcinoma. *Br J Obstet Gynaecol.* 1994;101(6):547-9.
18. Kim YB, Holschneider CH, Ghosh K, Nieberg RK, Montz FJ. Progestin alone as primary treatment of endometrial carcinoma in premenopausal women. Report of seven cases and review of the literature. *Cancer.* 1997;79(2):320-7.
19. Kung FT, Chen WJ, Chou HH, Ko SF, Chang SY. Conservative management of early endometrial adenocarcinoma with repeat curettage and hormone therapy under assistance of hysteroscopy and laparoscopy. *Hum Reprod.* 1997;12(8):1649-53.
20. Randall TC, Kurman RJ. Progestin treatment of atypical hyperplasia and well-differentiated carcinoma of the endometrium in women under age 40. *Obstetrics and gynecology.* 1997;90(3):434-40.
21. Salha O, Martin-Hirsch P, Lane G, Sharma V. Endometrial carcinoma in a young patient with polycystic ovarian syndrome: first suspected at time of embryo transfer. *Hum Reprod.* 1997;12(5):959-62.
22. Zanetta G GA, Losa G, Cappellini A, Mangioni C. conservative management of endometrial carcinoma with prolonged preservation of the uterus in a young patient. *Int J Gynecol Cancer.* 1997;7:332-4.
23. Sardi J, Anchezar Henry JP, Paniceris G, Gomez Rueda N, Vighi S. Primary hormonal treatment for early endometrial carcinoma. *Eur J Gynaecol Oncol.* 1998;19(6):565-8.
24. Schammel DP, Mittal KR, Kaplan K, Deligdisch L, Tavassoli FA. Endometrial adenocarcinoma associated with intrauterine pregnancy. A report of five cases and a review of the literature. *Int J Gynecol Pathol.* 1998;17(4):327-35.
25. Zuckerman B LO, Neumann M, et al. Endometrial carcinoma Stage I-Grade II. Conservative treatment followed by a healthy twin pregnancy. *Int J Gynecol Cancer.* 2002;8(2):172-4.
26. Kowalczyk CL, Malone J, Jr., Peterson EP, Jacques SM, Leach RE. Well-differentiated endometrial adenocarcinoma in an infertility patient with later conception. A case report. *J Reprod Med.* 1999;44(1):57-60.
27. Vinker S, Shani A, Open M, Fenig E, Dgani R. Conservative treatment of adenocarcinoma of the endometrium in young patients. Is it appropriate? *Eur J Obstet Gynecol Reprod Biol.* 1999;83(1):63-5.
28. Shibahara H, Shigeta M, Toji H, Wakimoto E, Adachi S, Ogasawara T, et al. Successful pregnancy in an infertile patient with conservatively treated endometrial adenocarcinoma after transfer of embryos obtained by intracytoplasmic sperm injection. *Hum Reprod.* 1999;14(7):1908-11.

29. Jobo T, Imai M, Kawaguchi M, Kenmochi M, Kuramoto H. Successful conservative treatment of endometrial carcinoma permitting subsequent pregnancy: report of two cases. *Eur J Gynaecol Oncol.* 2000;21(2):119-22.
30. Mitsushita J, Toki T, Kato K, Fujii S, Konishi I. Endometrial carcinoma remaining after term pregnancy following conservative treatment with medroxyprogesterone acetate. *Gynecol Oncol.* 2000;79(1):129-32.
31. Ogawa S, Koike T, Shibahara H, Ohwada M, Suzuki M, Araki S, et al. Assisted reproductive technologies in conjunction with conservatively treated endometrial adenocarcinoma. A case report. *Gynecol Obstet Invest.* 2001;51(3):214-6.
32. Kaku T, Yoshikawa H, Tsuda H, Sakamoto A, Fukunaga M, Kuwabara Y, et al. Conservative therapy for adenocarcinoma and atypical endometrial hyperplasia of the endometrium in young women: central pathologic review and treatment outcome. *Cancer Lett.* 2001;167(1):39-48.
33. Pinto AB, Gopal M, Herzog TJ, Pfeifer JD, Williams DB. Successful in vitro fertilization pregnancy after conservative management of endometrial cancer. *Fertil Steril.* 2001;76(4):826-9.
34. Imai M, Jobo T, Sato R, Kawaguchi M, Kuramoto H. Medroxyprogesterone acetate therapy for patients with adenocarcinoma of the endometrium who wish to preserve the uterus-usefulness and limitations. *Eur J Gynaecol Oncol.* 2001;22(3):217-20.
35. 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(2):388-93.
36. Wang CB, Wang CJ, Huang HJ, Hsueh S, Chou HH, Soong YK, et al. Fertility-preserving treatment in young patients with endometrial adenocarcinoma. *Cancer.* 2002;94(8):2192-8.
37. Lowe MP, Cooper BC, Sood AK, Davis WA, Syrop CH, Sorosky JI. Implementation of assisted reproductive technologies following conservative management of FIGO grade I endometrial adenocarcinoma and/or complex hyperplasia with atypia. *Gynecol Oncol.* 2003;91(3):569-72.
38. Burnett AF, Bahador A, Amezcua C. Anastrozole, an aromatase inhibitor, and medroxyprogesterone acetate therapy in premenopausal obese women with endometrial cancer: a report of two cases successfully treated without hysterectomy. *Gynecol Oncol.* 2004;94(3):832-4.
39. Nakao Y, Nomiya M, Kojima K, Matsumoto Y, Yamasaki F, Iwasaka T. Successful pregnancies in 2 infertile patients with endometrial adenocarcinoma. *Gynecol Obstet Invest.* 2004;58(2):68-71.
40. Yarali H, Bozdag G, Aksu T, Ayhan A. A successful pregnancy after intracytoplasmic sperm injection and embryo transfer in a patient with endometrial cancer who was treated conservatively. *Fertil Steril.* 2004;81(1):214-6.
41. Niwa K, Tagami K, Lian Z, Onogi K, Mori H, Tamaya T. Outcome of fertility-preserving treatment in young women with endometrial carcinomas. *BJOG.* 2005;112(3):317-20.

42. Ota T, Yoshida M, Kimura M, Kinoshita K. Clinicopathologic study of uterine endometrial carcinoma in young women aged 40 years and younger. *Int J Gynecol Cancer*. 2005;15(4):657-62.
43. Ferrandina G, Zannoni GF, Gallotta V, Foti E, Mancuso S, Scambia G. Progression of conservatively treated endometrial carcinoma after full term pregnancy: a case report. *Gynecol Oncol*. 2005;99(1):215-7.
44. Huang SY, Jung SM, Ng KK, Chang YC, Lai CH. Ovarian metastasis in a nulliparous woman with endometrial adenocarcinoma failing conservative hormonal treatment. *Gynecol Oncol*. 2005;97(2):652-5.
45. Mazzoni 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(5):974-8.
46. Yang YC, Wu CC, Chen CP, Chang CL, Wang KL. Reevaluating the safety of fertility-sparing hormonal therapy for early endometrial cancer. *Gynecologic oncology*. 2005;99(2):287-93.
47. Chang WH, Chen CH, Yu MH. Conservative therapy of stage I endometrial adenocarcinoma and atypical endometrial hyperplasia for the preservation of fertility. *Int J Gynaecol Obstet*. 2006;92(2):137-8.
48. Park JC, Cho CH, Rhee JH. A successful live birth through in vitro fertilization program after conservative treatment of FIGO grade I endometrial cancer. *Journal of Korean medical science*. 2006;21(3):567-71.
49. Sparac V, Ujevic B, Ujevic M, Pagon-Belina Z, Marton U. Successful pregnancy after hysteroscopic removal of grade I endometrial carcinoma in a young woman with Lynch syndrome. *Int J Gynecol Cancer*. 2006;16 Suppl 1:442-5.
50. Yahata T, Fujita K, Aoki Y, Tanaka K. Long-term conservative therapy for endometrial adenocarcinoma in young women. *Hum Reprod*. 2006;21(4):1070-5.
51. Gurgan T, Bozdogan G, Demiroglu A, Ayhan A. Preserving fertility before assisted reproduction in women with endometrial carcinoma: case report and literature review. *Reproductive biomedicine online*. 2007;15(5):561-5.
52. Minaguchi T, Nakagawa S, Takazawa Y, Nei T, Horie K, Fujiwara T, et al. Combined phospho-Akt and PTEN expressions associated with post-treatment hysterectomy after conservative progestin therapy in complex atypical hyperplasia and stage Ia, G1 adenocarcinoma of the endometrium. *Cancer Lett*. 2007;248(1):112-22.
53. Shamshirsaz AA, Withiam-Leitch M, Odunsi K, Baker T, Frederick PJ, Lele S. Young patients with endometrial carcinoma selected for conservative treatment: a need for vigilance for synchronous ovarian carcinomas, case report and literature review. *Gynecol Oncol*. 2007;104(3):757-60.

54. 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. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2007;25(19):2798-803.
55. Yamazawa K, Hirai M, Fujito A, Nishi H, Terauchi F, Ishikura H, et al. Fertility-preserving treatment with progestin, and pathological criteria to predict responses, in young women with endometrial cancer. *Hum Reprod*. 2007;22(7):1953-8.
56. Hurst SA, Hartzfeld KM, Del Priore G. Occult myometrial recurrence after progesterone therapy to preserve fertility in a young patient with endometrial cancer. *Fertil Steril*. 2008;89(3):724 e1-3.
57. Takahashi N, Hirashima Y, Harashima S, Takekuma M, Kawaguchi R, Yamada Y, et al. A patient with stage 1a endometrial carcinoma in whom a solitary recurrent lesion was detected in the external iliac lymph node after MPA therapy. *Arch Gynecol Obstet*. 2008;278(4):365-7.
58. Wu HM, Lai CH, Huang HY, Wang HS, Soong YK. A successful live twin birth by in vitro fertilization after conservative treatment of recurrent endometrial cancer. *Chang Gung medical journal*. 2008;31(1):102-6.
59. 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(19):2798-803.
60. Minaguchi T, Nakagawa S, Takazawa Y, Nei T, Horie K, Fujiwara T, et al. Combined phospho-Akt and PTEN expressions associated with post-treatment hysterectomy after conservative progestin therapy in complex atypical hyperplasia and stage Ia, G1 adenocarcinoma of the endometrium. *Cancer letters*. 2007;248(1):112-22.
61. Yamazawa K, Hirai M, Fujito A, Nishi H, Terauchi F, Ishikura H, et al. Fertility-preserving treatment with progestin, and pathological criteria to predict responses, in young women with endometrial cancer. *Human reproduction (Oxford, England)*. 2007;22(7):1953-8.
62. Tran BN, Connell PP, Waggoner S, Rotmensch J, Mundt AJ. Characteristics and outcome of endometrial carcinoma patients age 45 years and younger. *American journal of clinical oncology*. 2000;23(5):476-80.
63. Boronow RC, Morrow CP, Creasman WT, Disaia PJ, Silverberg SG, Miller A, et al. Surgical staging in endometrial cancer: clinical-pathologic findings of a prospective study. *Obstetrics and gynecology*. 1984;63(6):825-32.
64. Larson DM, Connor GP, Broste SK, Krawisz BR, Johnson KK. Prognostic significance of gross myometrial invasion with endometrial cancer. *Obstetrics and gynecology*. 1996;88(3):394-8.
65. Ben-Shachar I, Vitellas KM, Cohn DE. The role of MRI in the conservative management of endometrial cancer. *Gynecologic oncology*. 2004;93(1):233-7.



66. Thigpen JT, Brady MF, Alvarez RD, Adelson MD, Homesley HD, Manetta A, et al. Oral medroxyprogesterone acetate in the treatment of advanced or recurrent endometrial carcinoma: a dose-response study by the Gynecologic Oncology Group. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 1999;17(6):1736-44.
67. Ulbright TM, Roth LM. Metastatic and independent cancers of the endometrium and ovary: a clinicopathologic study of 34 cases. *Human pathology*. 1985;16(1):28-34.
68. Creasman WT, Morrow CP, Bundy BN, Homesley HD, Graham JE, Heller PB. Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group Study. *Cancer*. 1987;60(8 Suppl):2035-41.
69. Amant F, Moerman P, Neven P, Timmerman D, Van Limbergen E, Vergote I. Endometrial cancer. *Lancet*. 2005;366(9484):491-505.
70. Sorosky JI. Endometrial cancer. *Obstetrics and gynecology*. 2008;111(2 Pt 1):436-47.
71. Prat J, Ribe A, Gallardo A. Hereditary ovarian cancer. *Human pathology*. 2005;36(8):861-70.
72. Moyer DL, Felix JC. The effects of progesterone and progestins on endometrial proliferation. *Contraception*. 1998;57(6):399-403.
73. Amant F, Leunen K, Neven P, Berteloot P, Vergote I. Endometrial cancer: predictors of response and preferred endocrine therapy. *Int J Gynecol Cancer*. 2006;16 Suppl 2:527-8.
74. Evans-Metcalf ER, Brooks SE, Reale FR, Baker SP. Profile of women 45 years of age and younger with endometrial cancer. *Obstetrics and gynecology*. 1998;91(3):349-54.
75. Bafaloukos D, Aravantinos G, Samonis G, Katsifis G, Bakoyiannis C, Skarlos D, et al. Carboplatin, methotrexate and 5-fluorouracil in combination with medroxyprogesterone acetate (JMF-M) in the treatment of advanced or recurrent endometrial carcinoma: A Hellenic cooperative oncology group study. *Oncology*. 1999;56(3):198-201.

