3rd ASGO Workshop

ASGO
Asian Society of Gynecologic Oncology

Session II : Special Issues I

Fertility Preservation In Endometrial Cancer

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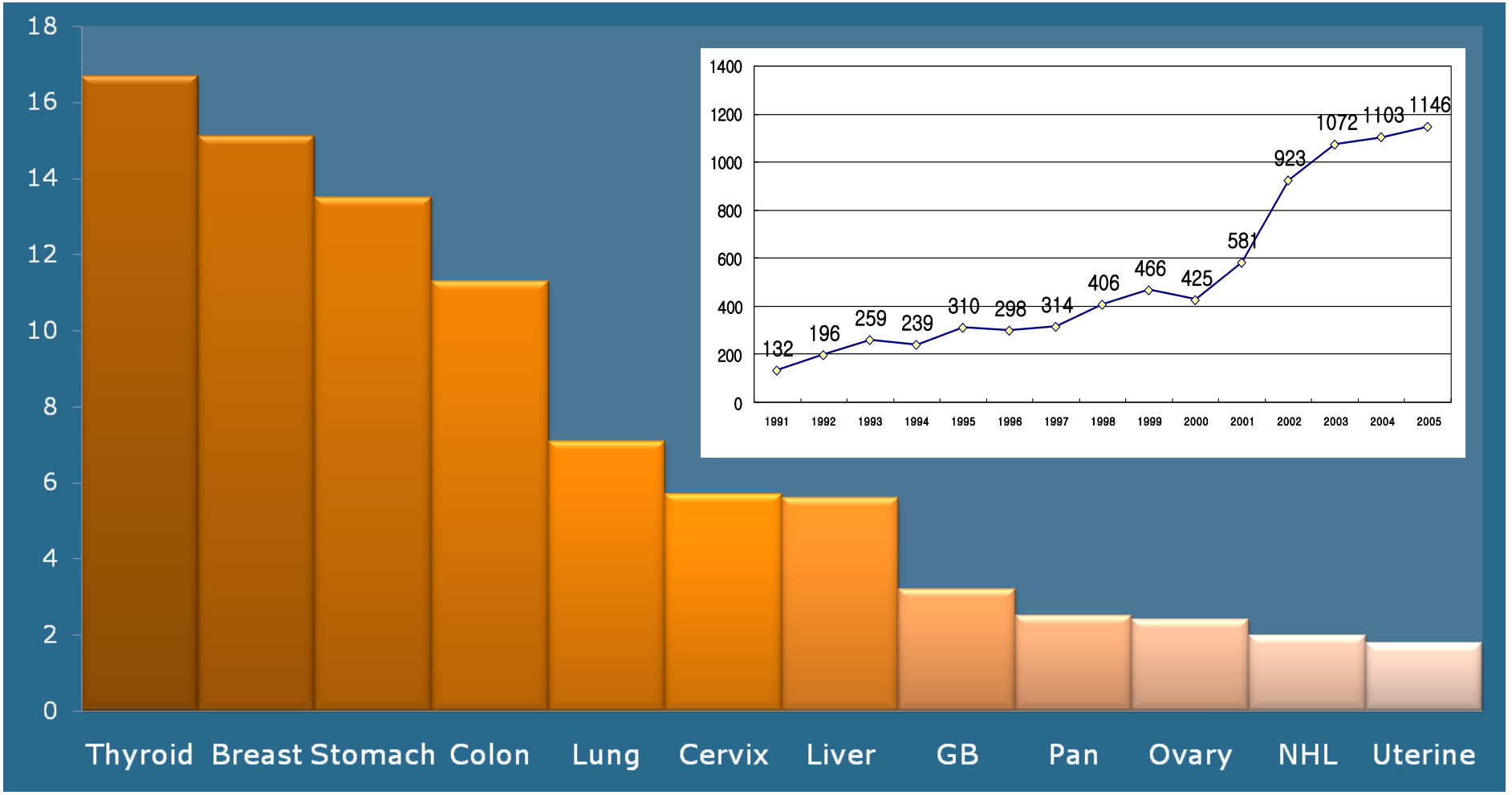
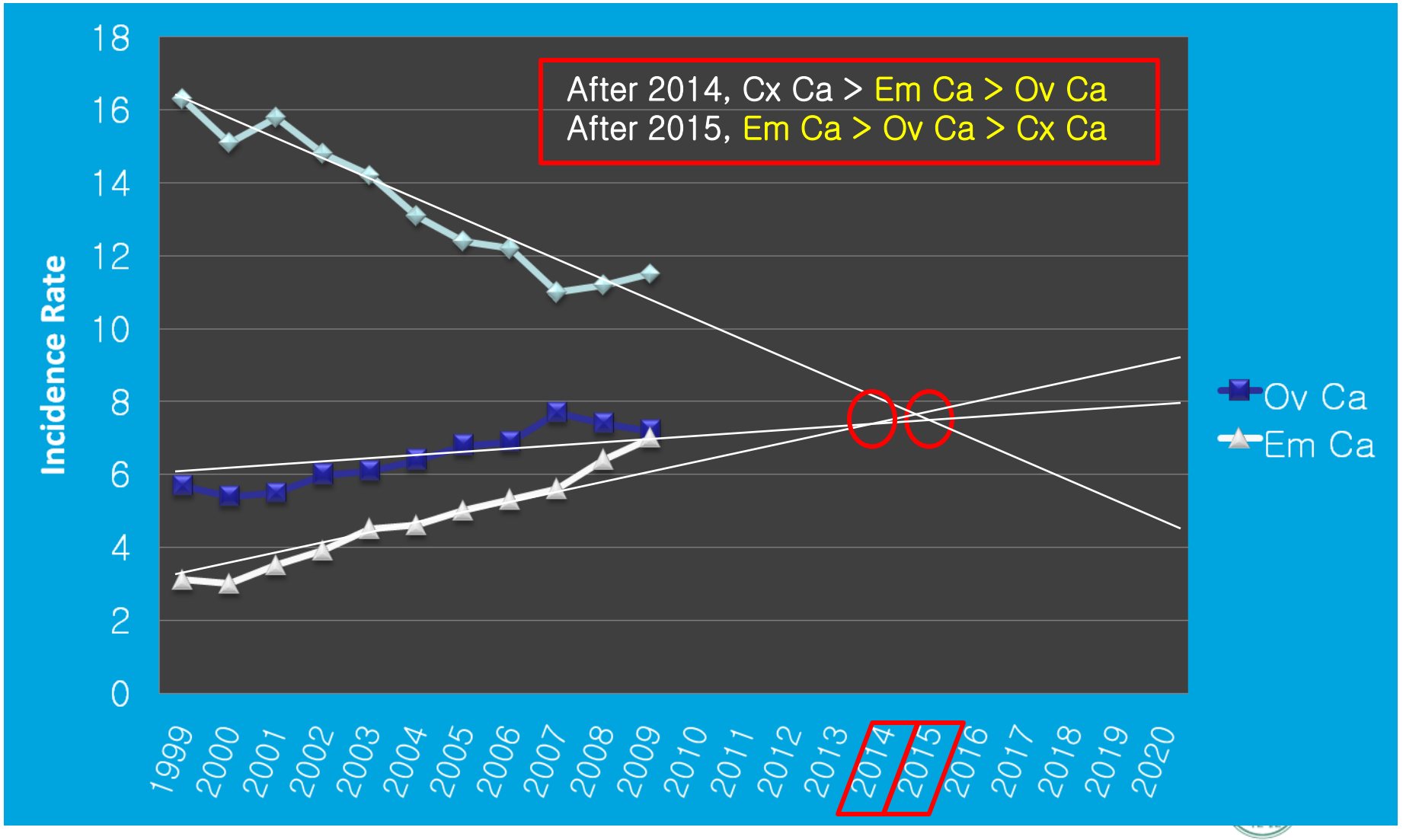
Endometrial Cancer in Korea

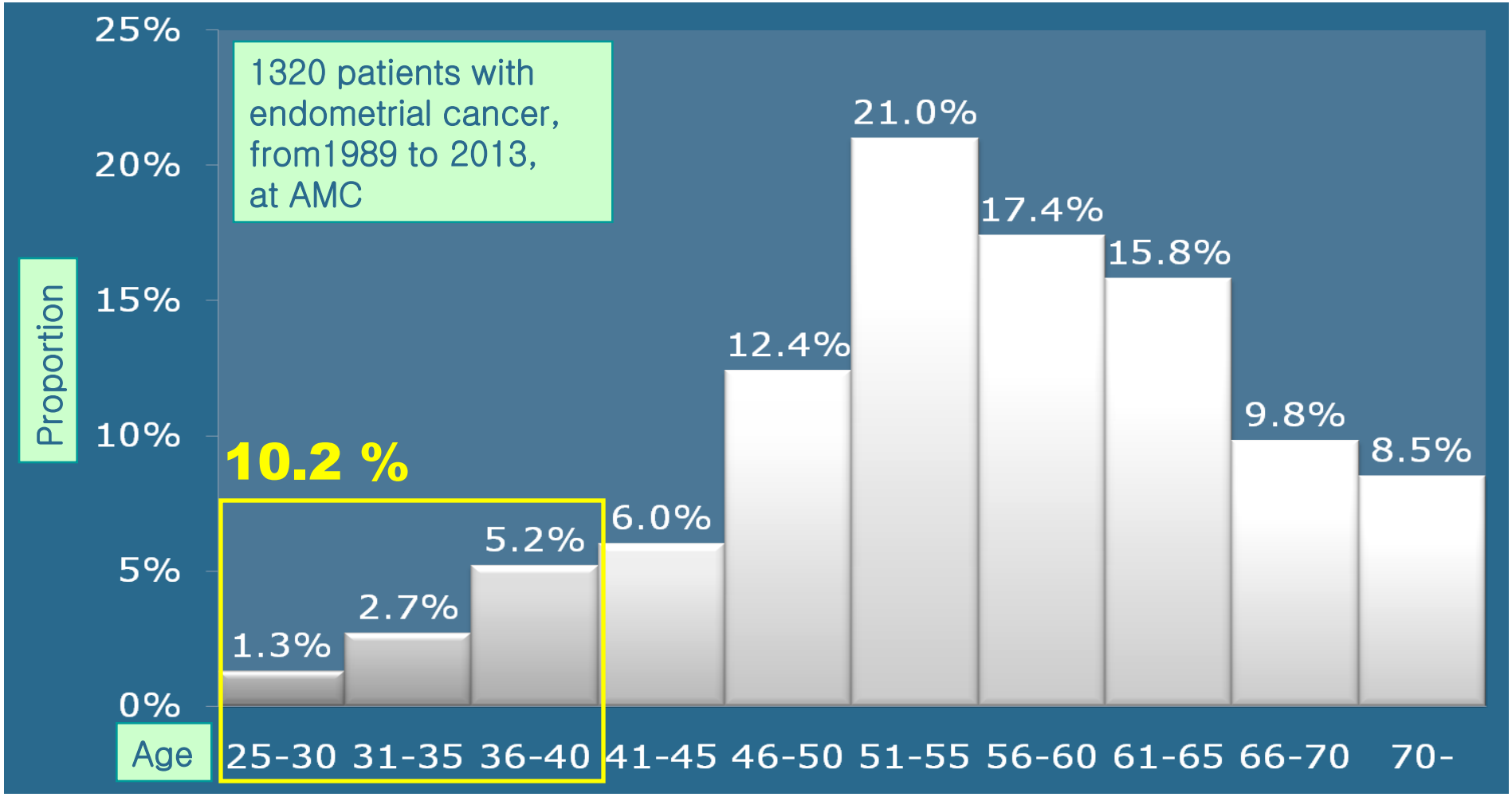


Future Incidence Rate Estimation

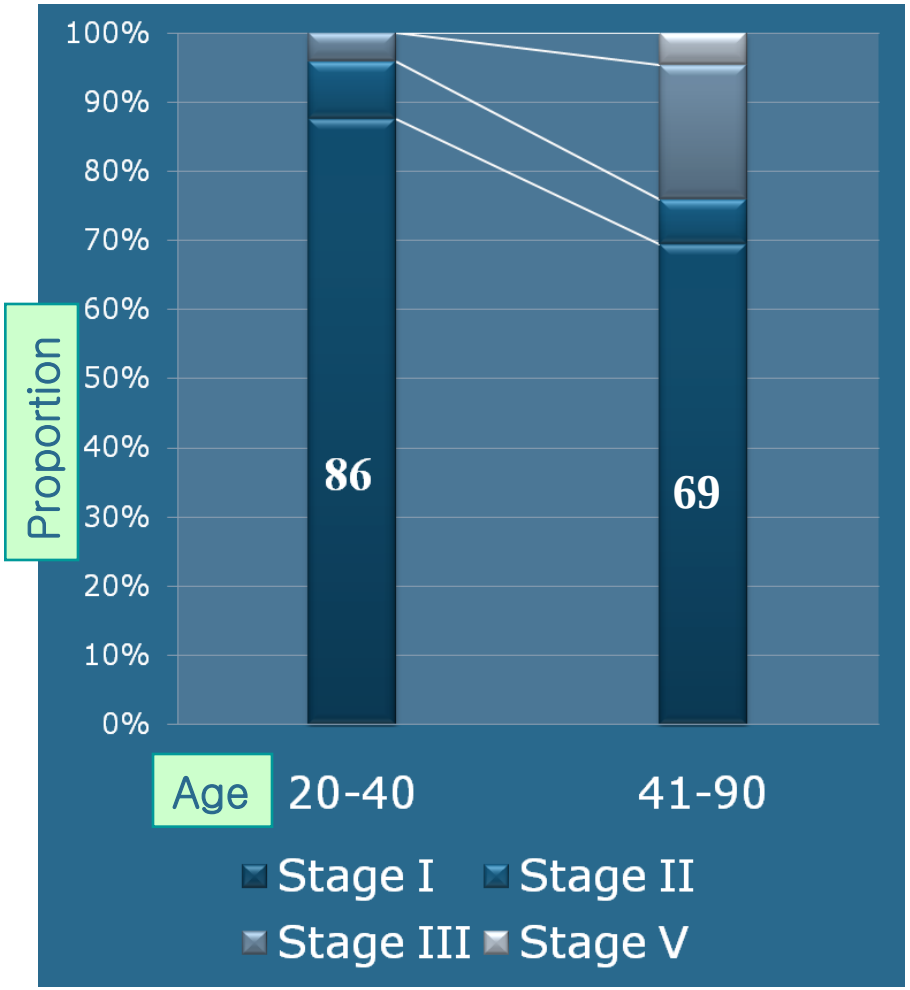
(cases/100,000)

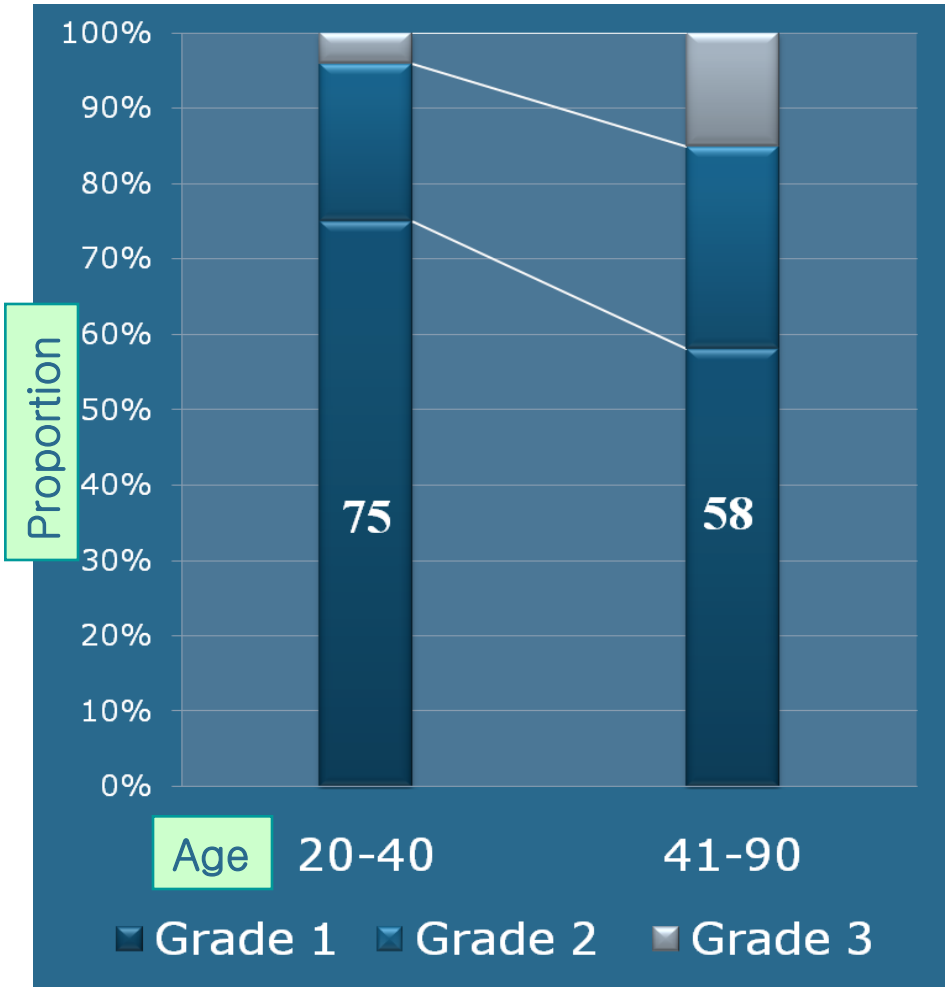


Age Distribution of Endometrial Cancer at AMC



Stage & Grade Distribution by Age at AMC





Endometrial Cancer in the Young

- Typically associated with good prognosis because of early stage & high tumor differentiation

  ⇒ 5 year survival ; >90%

Ota T, etal . Int J Gynecol Cancer 2005;15:657–62.
Cormio G, et al. Int J Gynecol Cancer 2006;16:2044–8.

Type I	Type II
Hyperestrogenic setting	Hypoestrogenic setting
40-60 years (rarely in 20s)	Elderly
Obesity (+)	Obesity (-)
Nulliparous	Multiparous
Chronic anovulation, HRT	No history of hyperestrogenism
Well differentiated	High grade
Stage I	Advanced stage
Non-myoinvasive	Deep myoinvasion
Endometrial hyperplasia	Non-noeplastic enometrium, atrophic
ER (+), PR (+), p53 (-), low Ki-67	ER (-), PR (-), p53 (+), high Ki-67
Endometrioid	UPSC, ECCC
Favorable prognosis	Poor prognosis

First suggested by Bokhman et al. Gyneol Oncol 1983;15:10-7

Fertility-sparing Management

Conventional treatment

Staging operation including hysterectomy &BSO
Radiotherapy

- Definitive sterilization
- Surgical menopause
- Loss of sexuality

- Fertility preservation
- Ovary preservation
- Sexuality preservation

→ Quality of life ↑

Fertility-sparing Treatment

- Current fertility-sparing treatment modalities mainly comprise hormonal therapies involving
  - ✓ Progestins
  - ✓ Progestin-releasing intrauterine devices
  - ✓ Natural progesterone
  - ✓ Oral contraceptives
  - ✓ Selective estrogen receptor modulators
  - ✓ Gonodotropin-releasing hormone agonist
  - ✓ Aromatase inhibitor

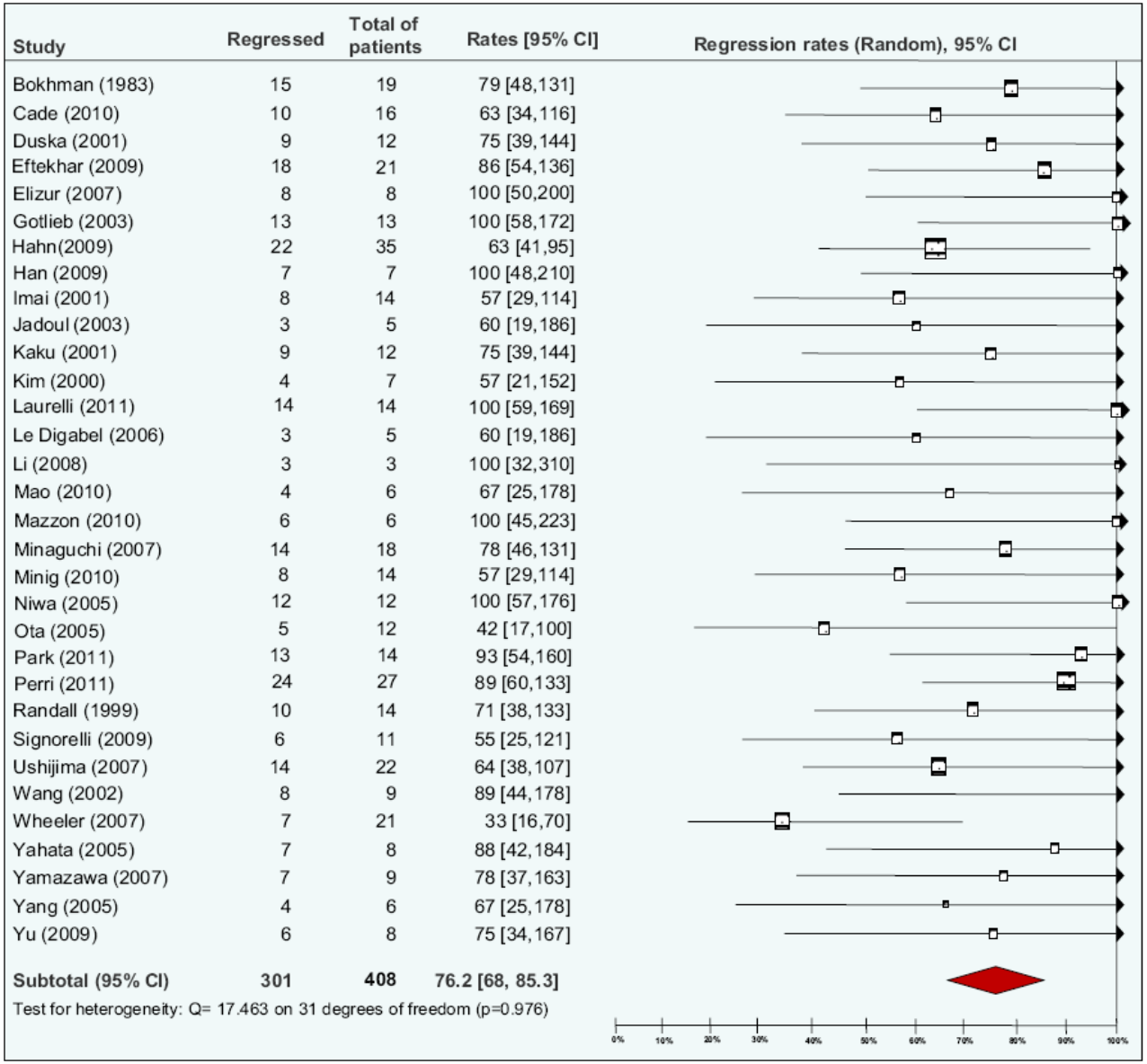
Progestin Therapy

- The most common conservative therapy
- Progesterone receptor
  - Often positive in EM cancer
  - The level of PR ↑
    ⇒ Differentiation ↑, stage↓
  - As independent prognostic factor
- Progesterone effect
  - Antagonistic to estrogen-mediated cell proliferation
  - Down-regulation of estrogen receptor concentration
    □ ↓active estrogen concentration
  - Antagonizing the action of ER at the molecular level
    a) sequestration of transcription factors
    b) direct dominant-negative effects on estrogen receptor

Well-known Indications

- 1. Histologically confirmed endometrioid type endometrial adenocarcinoma
- 2. Well-differentiated tumor (FIGO grade 1)
- 3. Disease confined to the endometrium (FIGO stage IA)
- 4. No evidence of myometrial invasion on imaging study
- 5. No clinical evidence of extrauterine spread of disease
- 6. Strong desire to preserve fertility
- 7. Age (≤ 40 years); relative indication
- 8. No contraindication for medical treatment
- 9. Informed consent with the understanding that this is not a standard treatment and carries a higher risk of recurrence

Complete Response Rate



Study	Regressed	Total of patients	Rates [95% CI]
Bokhman (1983)	15	19	79 [48,131]
Cade (2010)	10	16	63 [34,116]
Duska (2001)	9	12	75 [39,144]
Eftekhar (2009)	18	21	86 [54,136]
Elizur (2007)	8	8	100 [50,200]
Gotlieb (2003)	13	13	100 [58,172]
Hahn(2009)	22	35	63 [41,95]
Han (2009)	7	7	100 [48,210]
Imai (2001)	8	14	57 [29,114]
Jadoul (2003)	3	5	60 [19,186]
Kaku (2001)	9	12	75 [39,144]
Kim (2000)	4	7	57 [21,152]
Laurelli (2011)	14	14	100 [59,169]
Le Digabel (2006)	3	5	60 [19,186]
Li (2008)	3	3	100 [32,310]
Mao (2010)	4	6	67 [25,178]
Mazzon (2010)	6	6	100 [45,223]
Minaguchi (2007)	14	18	78 [46,131]
Minig (2010)	8	14	57 [29,114]
Niwa (2005)	12	12	100 [57,176]
Ota (2005)	5	12	42 [17,100]
Park (2011)	13	14	93 [54,160]
Perri (2011)	24	27	89 [60,133]
Randall (1999)	10	14	71 [38,133]
Signorelli (2009)	6	11	55 [25,121]
Ushijima (2007)	14	22	64 [38,107]
Wang (2002)	8	9	89 [44,178]
Wheeler (2007)	7	21	33 [16,70]
Yahata (2005)	7	8	88 [42,184]
Yamazawa (2007)	7	9	78 [37,163]
Yang (2005)	4	6	67 [25,178]
Yu (2009)	6	8	75 [34,167]
Subtotal (95% CI)	**301**	**408**	**76.2 [68, 85.3]**

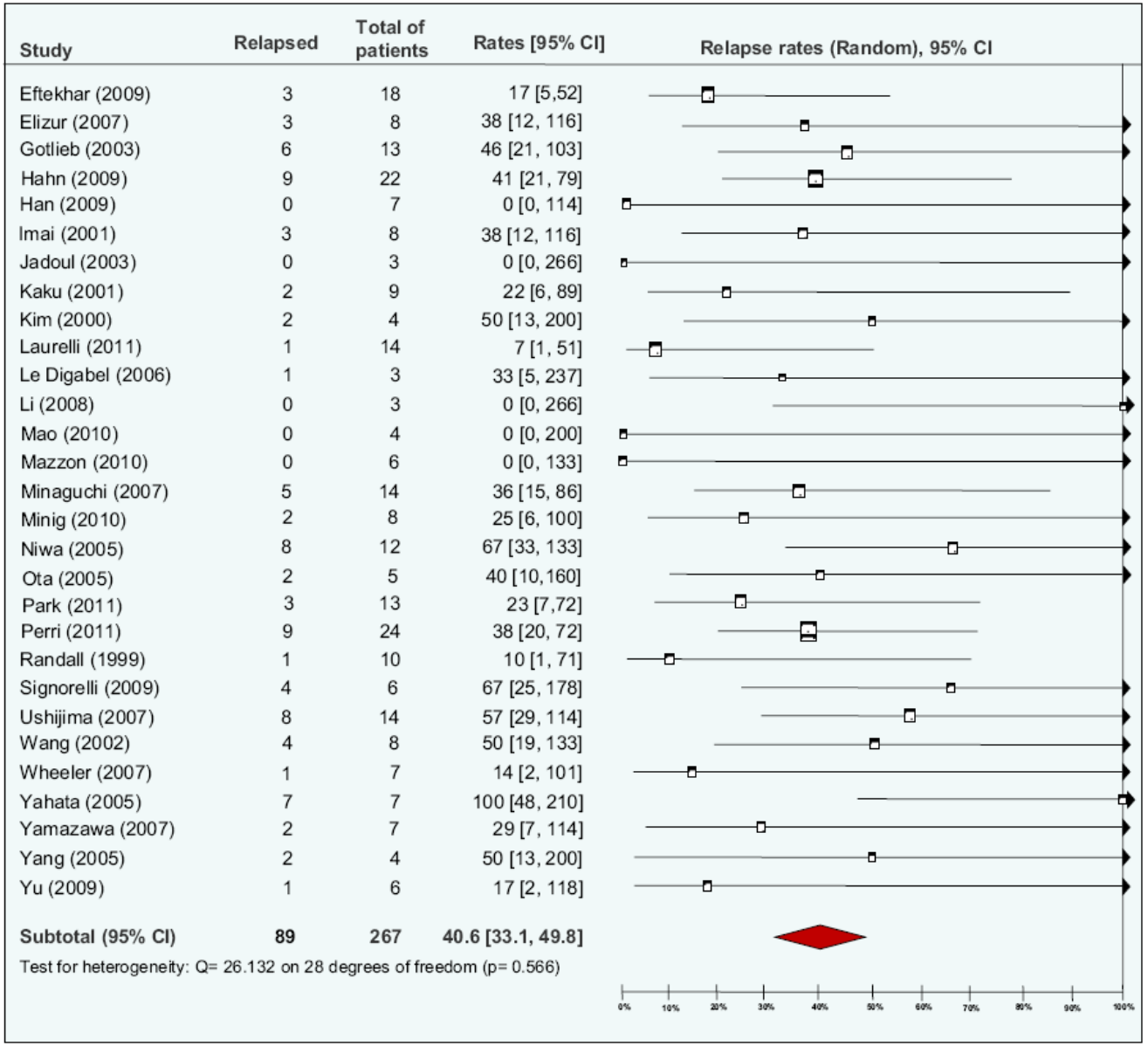
Test for heterogeneity: Q= 17.463 on 31 degrees of freedom (p=0.976)

Conservative Management of Endometrial Cancer

Regression
= 76.2%
(98-85.3%)

AJOG 2012;207:266.e1-12.

Recurrence Rate



Study	Relapsed	Total of patients	Rates [95% CI]
Eftekhar (2009)	3	18	17 [5,52]
Elizur (2007)	3	8	38 [12, 116]
Gotlieb (2003)	6	13	46 [21, 103]
Hahn (2009)	9	22	41 [21, 79]
Han (2009)	0	7	0 [0, 114]
Imai (2001)	3	8	38 [12, 116]
Jadoul (2003)	0	3	0 [0, 266]
Kaku (2001)	2	9	22 [6, 89]
Kim (2000)	2	4	50 [13, 200]
Laurelli (2011)	1	14	7 [1, 51]
Le Digabel (2006)	1	3	33 [5, 237]
Li (2008)	0	3	0 [0, 266]
Mao (2010)	0	4	0 [0, 200]
Mazzon (2010)	0	6	0 [0, 133]
Minaguchi (2007)	5	14	36 [15, 86]
Minig (2010)	2	8	25 [6, 100]
Niwa (2005)	8	12	67 [33, 133]
Ota (2005)	2	5	40 [10,160]
Park (2011)	3	13	23 [7,72]
Perri (2011)	9	24	38 [20, 72]
Randall (1999)	1	10	10 [1, 71]
Signorelli (2009)	4	6	67 [25, 178]
Ushijima (2007)	8	14	57 [29, 114]
Wang (2002)	4	8	50 [19, 133]
Wheeler (2007)	1	7	14 [2, 101]
Yahata (2005)	7	7	100 [48, 210]
Yamazawa (2007)	2	7	29 [7, 114]
Yang (2005)	2	4	50 [13, 200]
Yu (2009)	1	6	17 [2, 118]
Subtotal (95% CI)	**89**	**267**	**40.6 [33.1, 49.8]**

Test for heterogeneity: Q= 26.132 on 28 degrees of freedom (p= 0.566)

Conservative Management of Endometrial Cancer

Relapse
= 40.6%
(33.1-49.8%)

AJOG 2012;207:266.e1-12.

European Journal of Cancer (2013) 49, 868–874

Available at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.ejcancer.info

Long-term oncologic outcomes after fertility-sparing management using oral progestin for young women with endometrial cancer (KGOG 2002)

Jeong-Yeol Park [a], Dae-Yeon Kim [a], Jong-Hyeok Kim [a], Yong-Man Kim [a], Kyu-Rae Kim [b], Young-Tak Kim [a], Seok Ju Seong [c], Tae-Jin Kim [d], Jae Weon Kim [e], Seok Mo Kim [f], Duk-Soo Bae [g], Joo-Hyun Nam [a,*]

- To estimate ***long-term survival outcomes*** after fertility-sparing management using oral progestin in young women (≤ 40 years) with FIGO stage IA, grade 1, endometrioid type endometrial cancer
- To analyze ***the predictive factors for response and recurrence***

Inclusion Criteria

- Young women who desire to preserve fertility (Age≤40years)
- Endometrioid type
- Well differentiated carcinoma (Grade 1)
- No myometrial invasion (stage IA)
- No synchronous ovarian malignancy

Patients' characteristics (n=148)

Characteristics		N (%)
Age	Mean (range), years	31.3 (21-40)
	≤ 30 years	68 (45.9)
	> 30 years	80 (54.1)
Body mass index	Mean (range), kg/m^2	24.98 (15.06-38.20)
	< 25 kg/m^2	89 (60.1)
	≥ 25 kg/m^2	59 (39.9)
Medical co-morbidity*	No	127 (86.5)
	Yes	20 (13.5)
Marital status at diagnosis	Unmarried	53 (35.8)
	Married	95 (64.2)
Parity	0	139 (93.9)
	1	7 (4.7)
	2	2 (1.4)
Polycystic ovary syndrome	No	125 (84.5)
	Yes	23 (15.5)

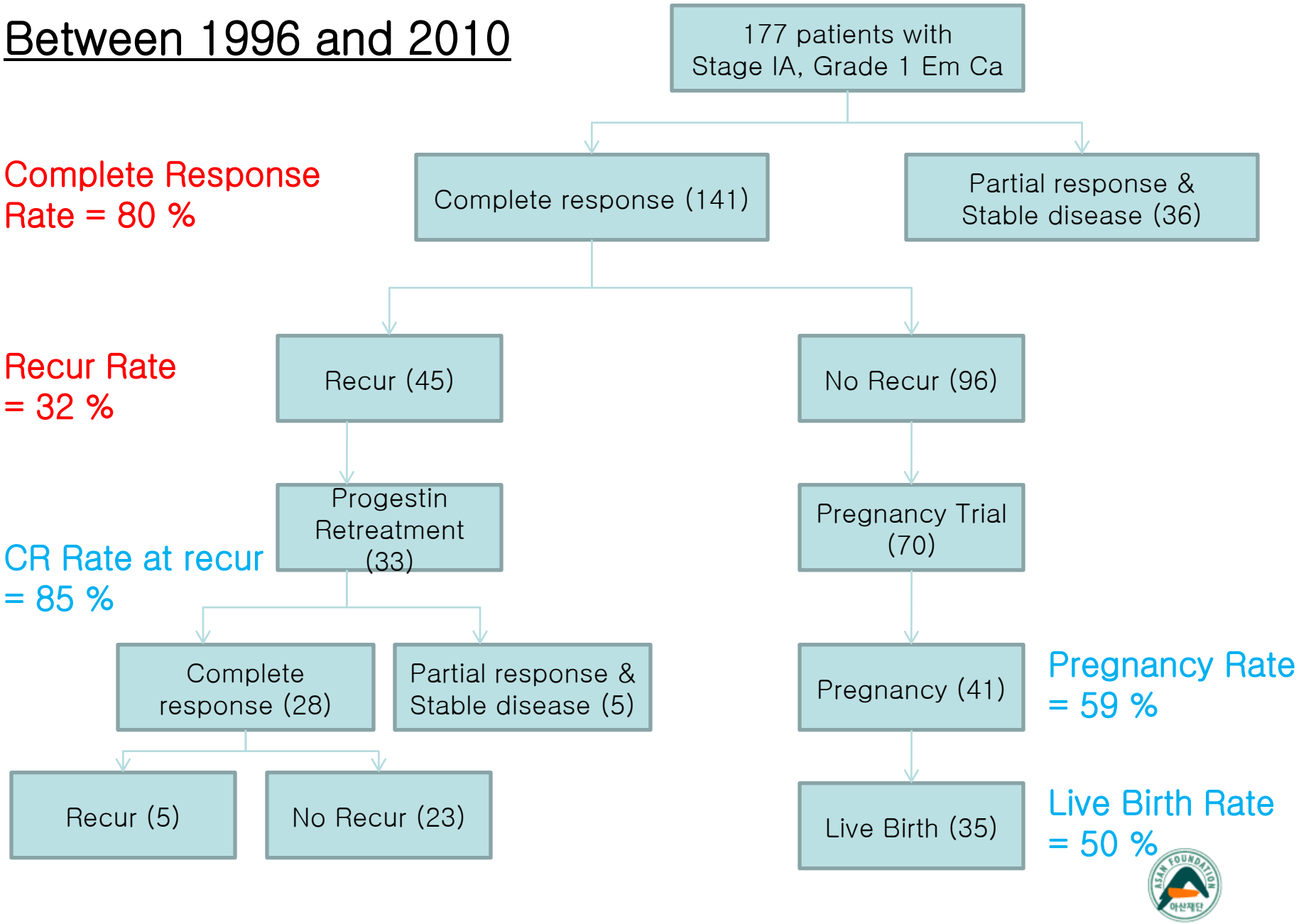
* Hypertension, diabetes mellitus, hypothyroidism, valvular heart disease, IgA nephropath

Treatment summary

Characteristics		Variable (n=148)
Progestin type	Medroxyprogesterone acetate	91 (61.5%)
	Megestrol acetate	57 (38.5%)
Progestin dose, mean (range)	Medroxyprogesterone acetate	500 mg/day (30-1500)
	Megestrol acetate	160 mg/day (40-240)
Patients who achieved **complete remission**		115 (**77.7%**)
Mean time interval to complete remission (range), weeks		18 (8-55)
Mean duration of treatment (range), months		8 (2-31)

Complete remission:
No evidence of hyperplasia or carcinoma on endometrial biopsy

Between 1996 and 2010



Factors predicting CR to progestin treatment (n=148)

Characteristics		Total, n	Complete response, n (%)	p-value
Age	≤ 30 years	68	52 (76.5)	0.740
	> 30 years	80	63 (78.8)	
Body mass index	< 25 kg/m^2	89	79 (85.4)	0.006
	≥ 25 kg/m^2	59	39 (66.1)	
Medical co-morbidity*	No	128	101 (78.9)	0.374
	Yes	20	14 (70)	
Parity	0	139	108 (77.7)	0.999
	1-2	9	7 (77.8)	
Polycystic ovary syndrome	No	125	98 (78.4)	0.635
	Yes	23	17 (73.9)	
Progestin type	Medroxyprogesterone acetate	57	45 (78.9)	0.773
	Megestrol acetate	91	70 (76.9)	
Progestin dose	< 500 mg	73	56 (76.7)	0.775
	≥ 500 mg	75	59 (78.7)	

CI, confidence interval; CR, complete remission

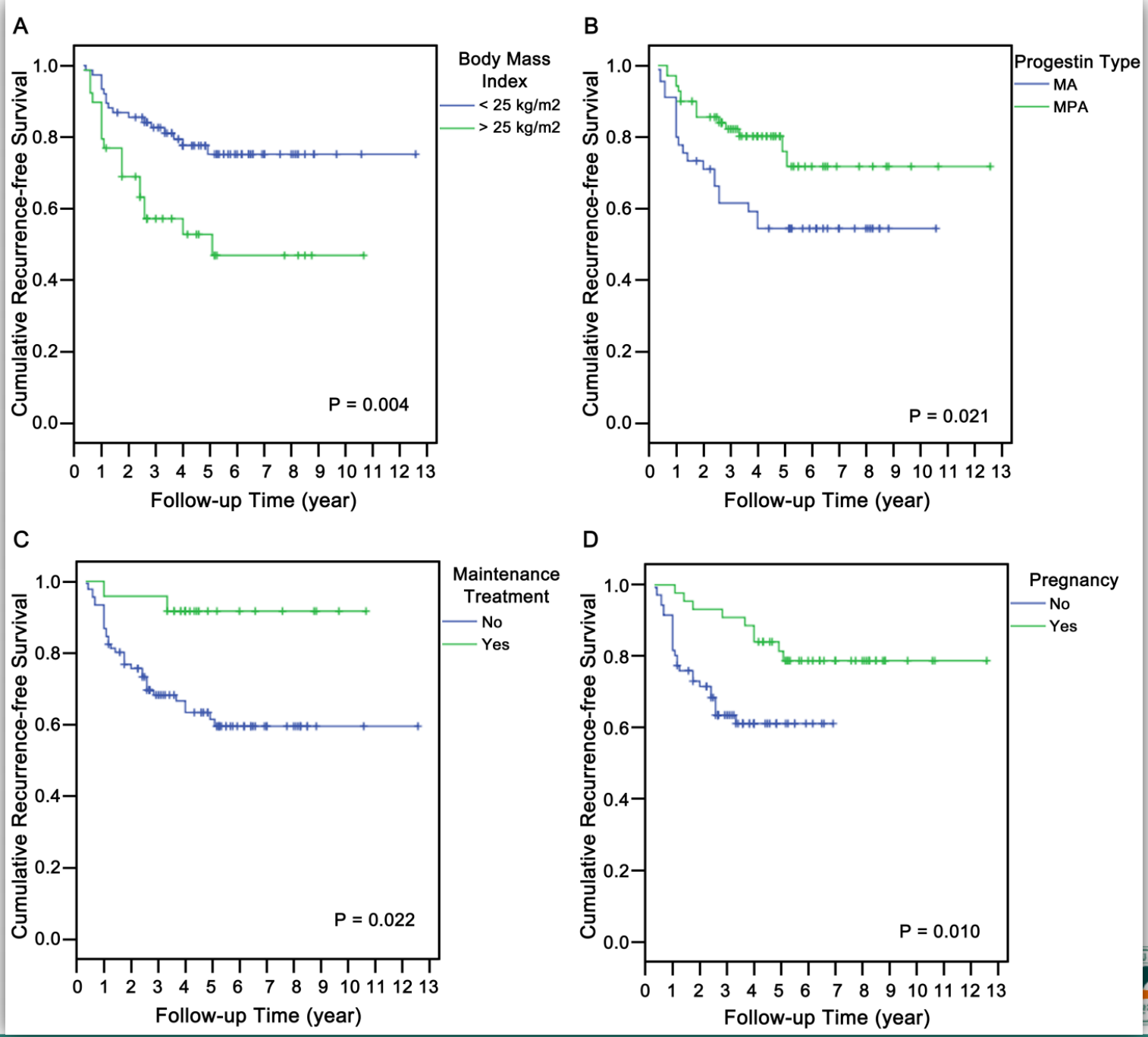
* Hypertension, diabetes mellitus, hypothyroidism, valvular heart disease, IgA nephropathy

Follow-up after treatment

- Recurrence after complete remission
  - ✓ After median follow-up time of 66 months (range, 14-194 months), **35 (30.4%)** of 115 patients who achieved complete remission experienced recurrence.
  - ✓ The median time interval to recurrence was 15 months (range, 4-61 months).
  - ✓ 5-year recurrence free survival rate was 68%.
  - ✓ At the time of recurrence, no one had clinical progression of disease.

Factors predicting recurrence-free survival after complete remission (n=115)

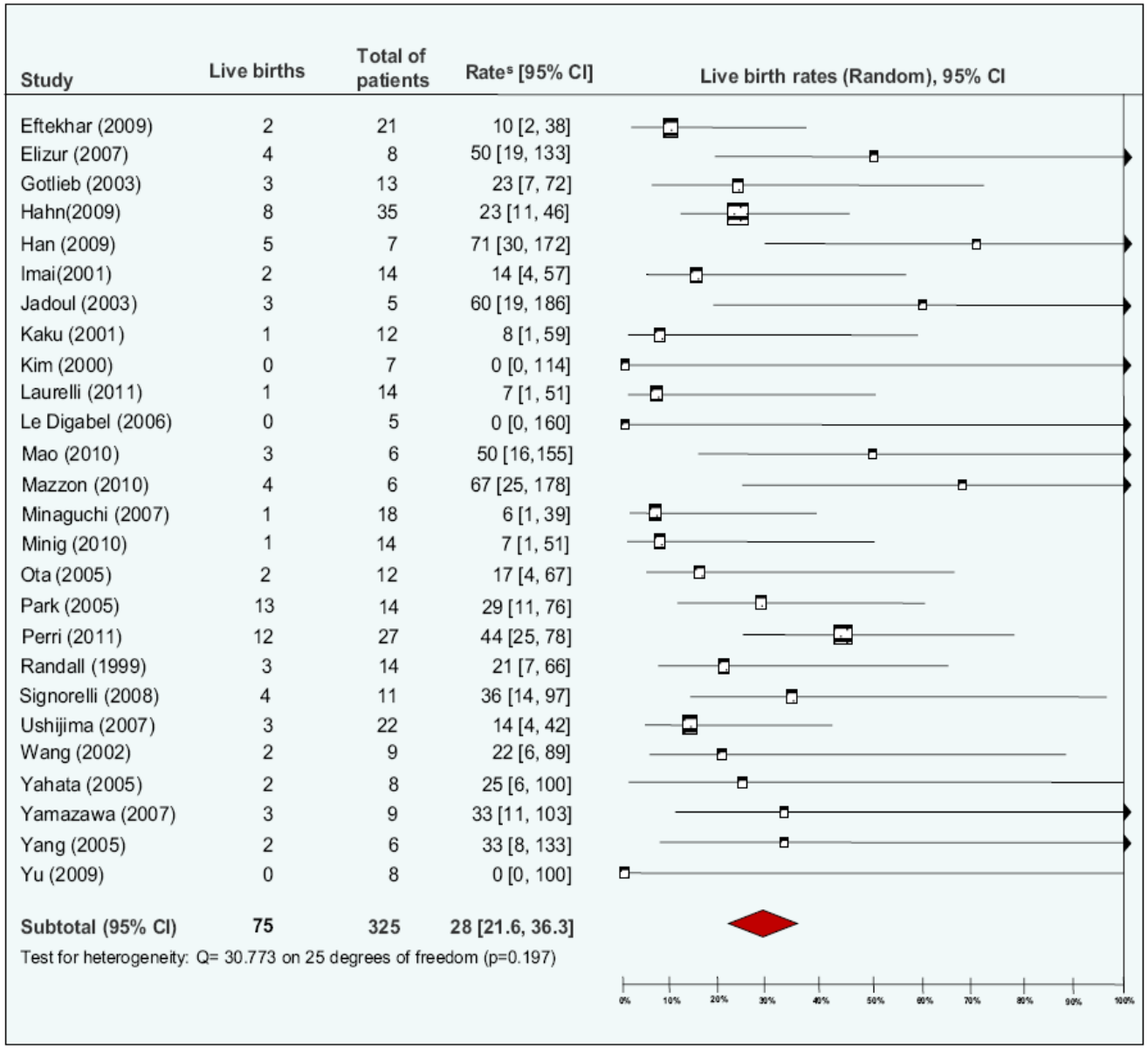
Characteristics		Total, n	Recur, n (%)	5 year RFS (%)	Univariate analysis		Multivariate analysis	
					Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Age	≤ 30 years	52	18 (34.6)	64	1		-	
	> 30 years	63	17 (27)	71	0.77 (0.40-1.50)	0.450	-	-
BMI	< 25 kg/m^2	76	17 (22.4)	75	1		1	
	≥ 25 kg/m^2	39	18 (46.2)	53	2.64 (1.35-5.13)	0.004	2.14 (1.06-4.31)	0.033
Medical co-morbidity*	No	101	31 (30.7)	68	1		-	
	Yes	14	4 (28.6)	63	0.94 (0.33-2.67)	0.910	-	-
Parity	0	108	33 (30.6)	67	1		-	
	1-2	7	2 (28.6)	71	0.93 (0.22-3.88)	0.920	-	-
Polycystic ovary syndrome	No	98	23 (26.6)	72	1		-	
	Yes	17	9 (52.9)	47	2.01 (0.94-4.29)	0.072	-	-
Progestin type	MA	45	20 (44.4)	54	1		1	
	MPA	70	15 (21.4)	76	0.45 (0.23-0.89)	0.021	0.44 (0.22-0.88)	0.021
Progestin dose	< 500 mg	56	22 (39.3)	60	1		-	
	≥ 500 mg	59	13 (22)	75	0.55 (0.28-1.10)	0.089	-	-
Time interval to achieve CR	≤ 18 weeks	64	24 (37.5)	59	1		-	
	> 18 weeks	51	11 (21.6)	78	0.55 (0.27-1.13)	0.105	-	-
Treatment duration	≤ 8 months	56	16 (28.6)	71	1		-	
	> 8 months	59	19 (32.2)	65	1.14 (0.59-2.21)	0.695	-	-
Maintenance treatment after CR	No	91	33 (36.3)	61	1		1	
	Yes	24	2 (8.3)	92	0.19 (0.05-0.78)	0.022	0.22 (0.05-0.94)	0.042
Pregnancy	No	71	26 (36.6)	61	1		1	
	Yes	44	9 (20.5)	81	0.36 (0.17-0.78)	0.010	0.25 (0.11-0.56)	0.001


A
Cumulative Recurrence-free Survival
1.0
0.8
0.6
0.4
0.2
0.0
0 1 2 3 4 5 6 7 8 9 10 11 12 13
Follow-up Time (year)
P = 0.004
Body Mass Index
< 25 kg/m2
> 25 kg/m2
B
Cumulative Recurrence-free Survival
1.0
0.8
0.6
0.4
0.2
0.0
0 1 2 3 4 5 6 7 8 9 10 11 12 13
Follow-up Time (year)
P = 0.021
Progestin Type
MA
MPA
C
Cumulative Recurrence-free Survival
1.0
0.8
0.6
0.4
0.2
0.0
0 1 2 3 4 5 6 7 8 9 10 11 12 13
Follow-up Time (year)
P = 0.022
Maintenance Treatment
No
Yes
D
Cumulative Recurrence-free Survival
1.0
0.8
0.6
0.4
0.2
0.0
0 1 2 3 4 5 6 7 8 9 10 11 12 13
Follow-up Time (year)
P = 0.010
Pregnancy
No
Yes

Summary

- Fertility-sparing management using daily oral MPA or MA was highly effective & safe
- BMI < 25 kg/m^2, MPA (compared to MA), maintenance treatment and pregnancy were a/w higher possibility of long-term success

Live Birth Rate



Study	Live births	Total of patients	Rates [95% CI]
Eftekhar (2009)	2	21	10 [2, 38]
Elizur (2007)	4	8	50 [19, 133]
Gotlieb (2003)	3	13	23 [7, 72]
Hahn(2009)	8	35	23 [11, 46]
Han (2009)	5	7	71 [30, 172]
Imai(2001)	2	14	14 [4, 57]
Jadoul (2003)	3	5	60 [19, 186]
Kaku (2001)	1	12	8 [1, 59]
Kim (2000)	0	7	0 [0, 114]
Laurelli (2011)	1	14	7 [1, 51]
Le Digabel (2006)	0	5	0 [0, 160]
Mao (2010)	3	6	50 [16,155]
Mazzon (2010)	4	6	67 [25, 178]
Minaguchi (2007)	1	18	6 [1, 39]
Minig (2010)	1	14	7 [1, 51]
Ota (2005)	2	12	17 [4, 67]
Park (2005)	13	14	29 [11, 76]
Perri (2011)	12	27	44 [25, 78]
Randall (1999)	3	14	21 [7, 66]
Signorelli (2008)	4	11	36 [14, 97]
Ushijima (2007)	3	22	14 [4, 42]
Wang (2002)	2	9	22 [6, 89]
Yahata (2005)	2	8	25 [6, 100]
Yamazawa (2007)	3	9	33 [11, 103]
Yang (2005)	2	6	33 [8, 133]
Yu (2009)	0	8	0 [0, 100]
Subtotal (95% CI)	**75**	**325**	**28 [21.6, 36.3]**

Test for heterogeneity: Q= 30.773 on 25 degrees of freedom (p=0.197)

Conservative Management of Endometrial Cancer

Live Birth
= 28%
(21.6-36.3%)

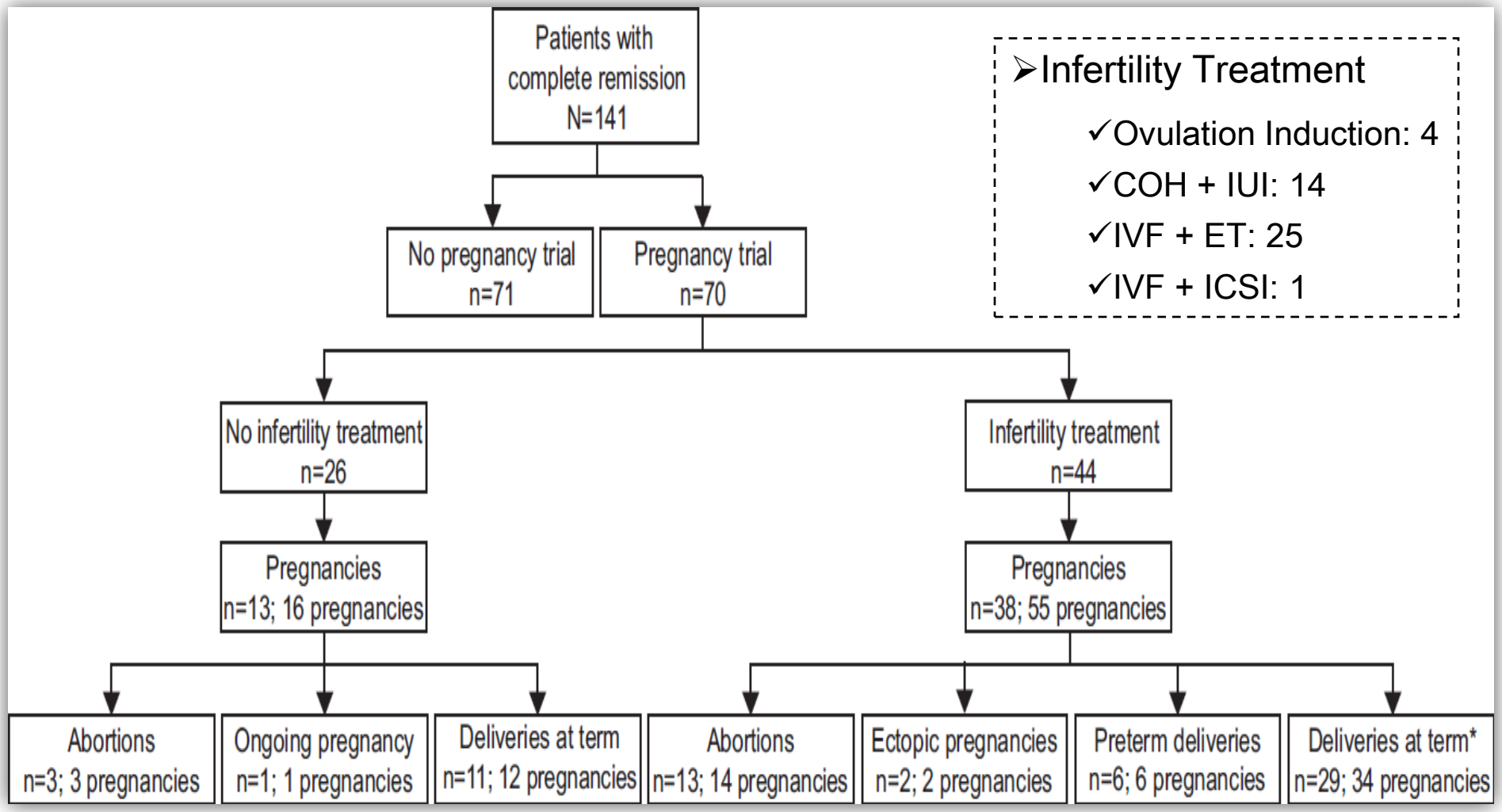
AJOG 2012;207:266.e1-12.

Pregnancy Outcomes After Fertility-Sparing Management in Young Women With Early Endometrial Cancer

Jeong-Yeol Park, MD, PhD, Seok Ju Seong, MD, PhD, Tae-Jin Kim, MD, PhD, Jae Weon Kim, MD, PhD, Seok Mo Kim, MD, PhD, Duk-Soo Bae, MD, PhD, and Joo-Hyun Nam, MD, PhD

Obstet Gynecol 2013;121:136-42

Pregnancy Outcomes



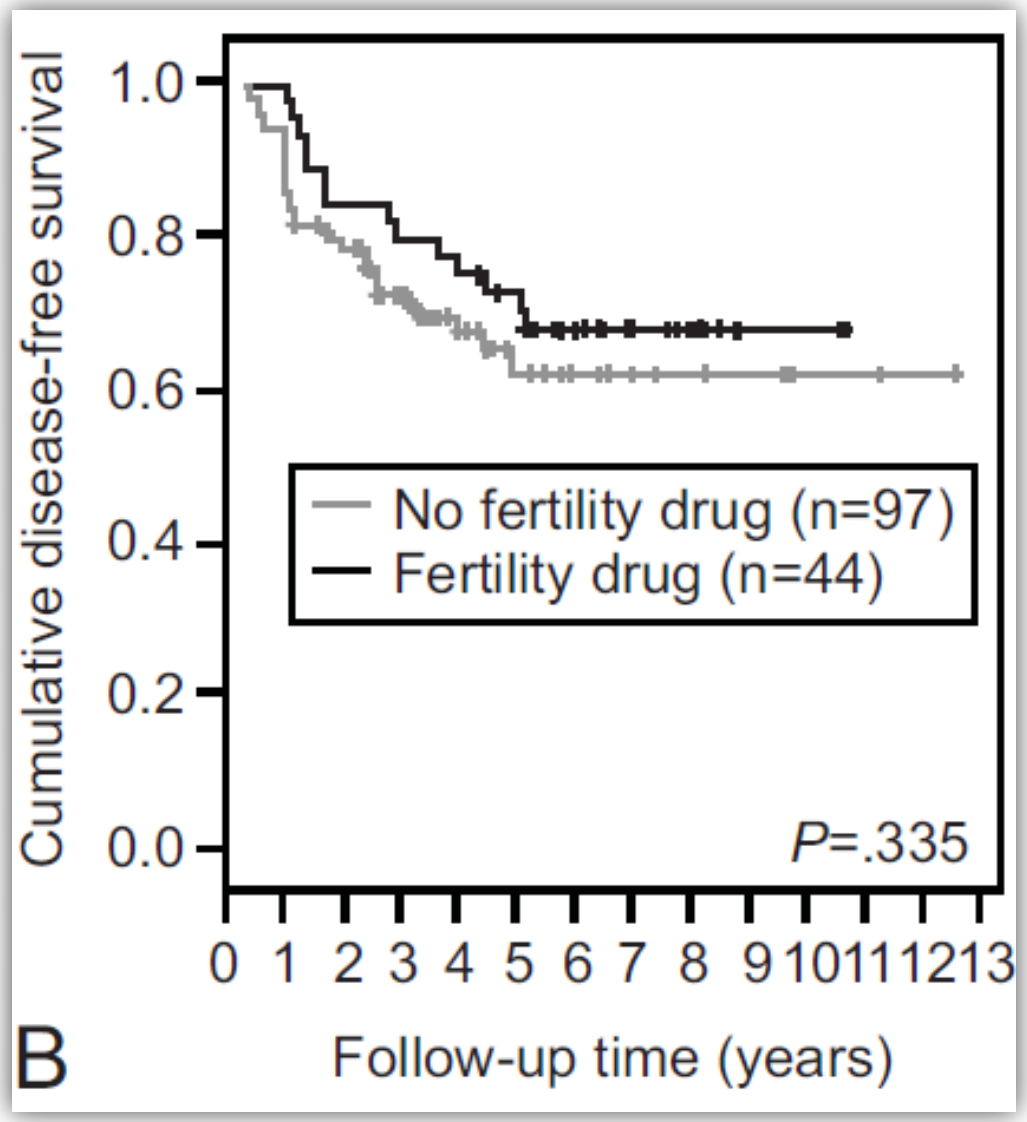
Pregnancy Outcomes

	Total	Infertility treatment -	Infertility treatment +	General population
Pregnancy rate	73% (61%-82%)	50%*	86.4%*	
Live birth rate	66% (54%-76%)	42.3%*	70.5%*	
Spontaneous abortion **	24% (15%-35%)	18.8%	25.5%	15-20%
Ectopic pregnancy	2.8% (0.2%-10.3%)	0%	3.6%	2%
Preterm delivery	11.5% (5%-52.3%)	0%	10.9%	10%

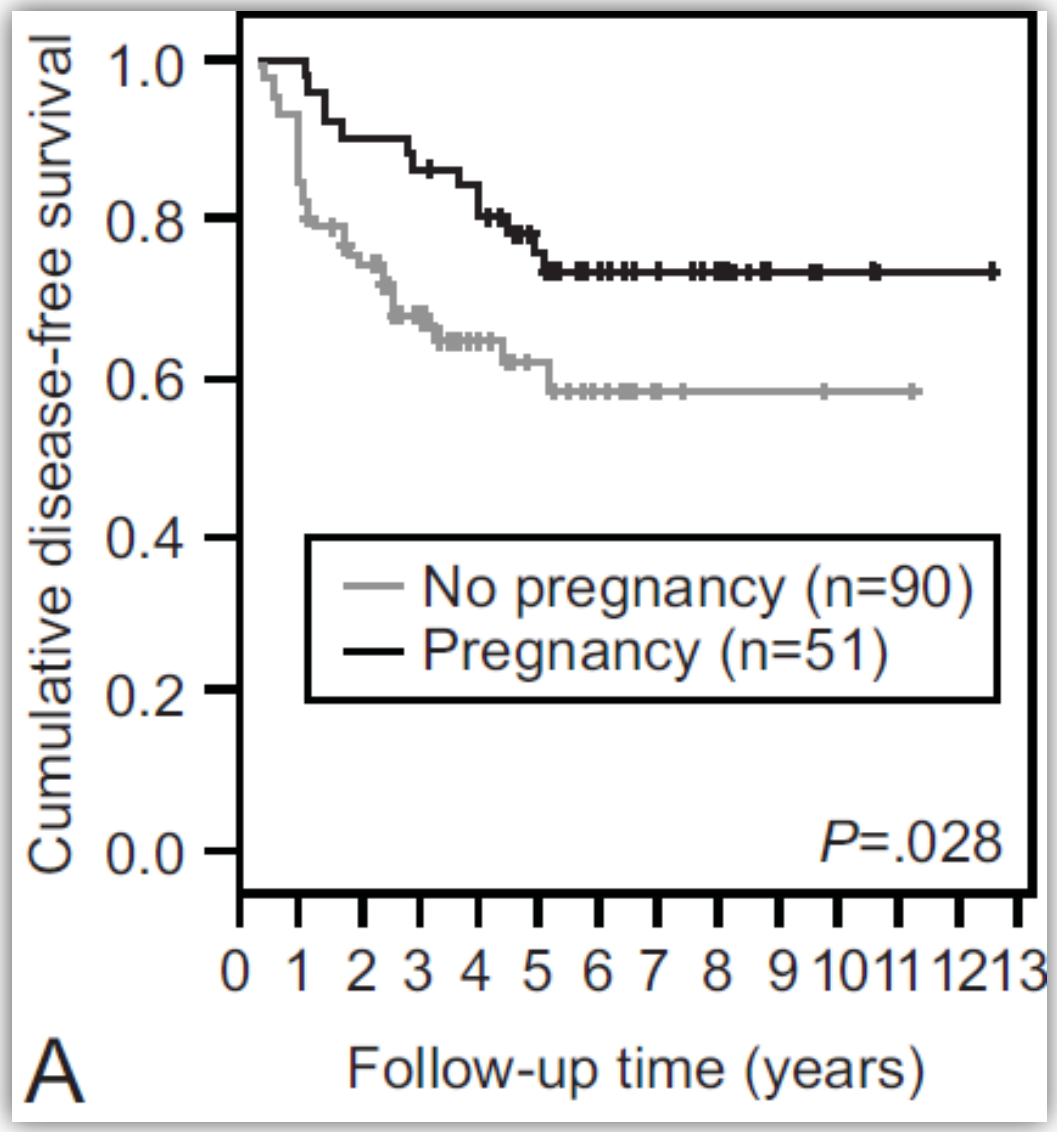
*P < 0.05

** *< 35 year vs. ≥ 35 years = 22.5% vs. 63.6% (P = 0.023)*

Fertility drug vs Recurrence



Pregnancy vs Recurrence



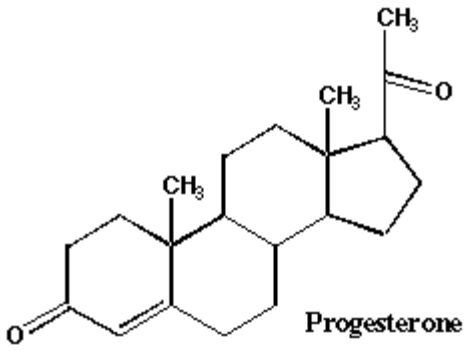
Summary

- Although the proportion of our current patients with a history of subfertility or infertility was high, the pregnancy outcomes following the use of assisted reproductive technology are very promising.
- Importantly, the use of fertility drugs in our present cohort was not found to be associated with a higher incidence of endometrial cancer recurrence.

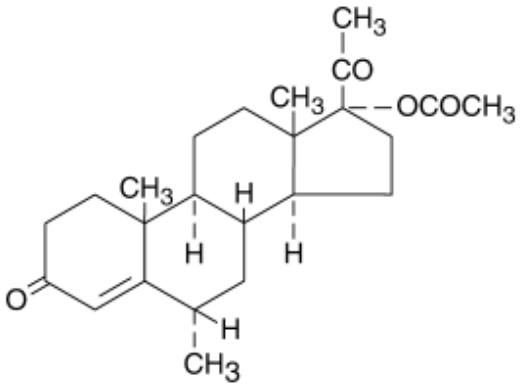
Controversial Issues

- Type of progestin (preferred progestin?)
- Dose of progestin
- Duration of progestin therapy
- Consolidation and maintenance therapy
- Progestin therapy for more advanced disease
- Progestin therapy for recurrent disease

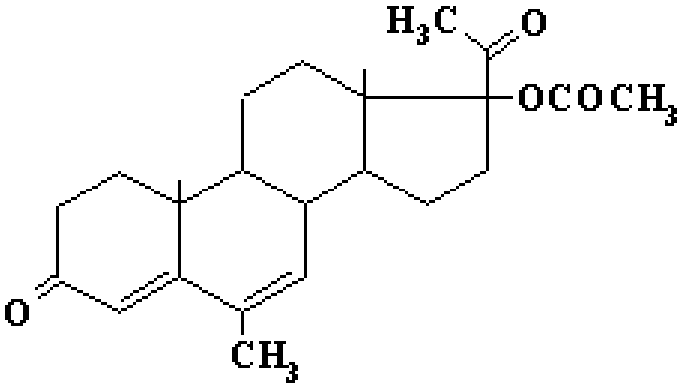
Progestin Agents



Progesterone



Farlutal® 500mg/1T
(medroxyprogesterone acetate)



Megace®
40mg/1T
(megestrol acetate)

Type of Progestin Agent

Progestin	N (81)	%
Medroxyprogesterone acetate	36	44
Megestrol acetate	28	35
17α-Hydroxyprogesterone	5	5
Oxyprogesterone acetate	3	4
Hydroxyprogesterone acetate	3	4
Norethindrone	2	3
Unspecified progesterone	2	3
Norethindrone and mestranol	1	1
Medrogestone	1	1

Ramirez et al. Gynecol Oncol 2004;95:133-138

Optimal dose of Progestin Agent

Study and year [reference]	*n*	Treatment protocol	Duration of treatment	Tumor regression (*n*)	Tumor recurrence (*n*)	Tumor progression (*n*)	Pregnancy (*n*)
Ota *et al.* 2005 [28•]	12	MPA 600 mg/day	3–12 months	5	3	5	4
Niwa *et al.* 2005 [25••]	12	MPA	6–10 months	12	8	1	5
Yang *et al.* 2005 [33•]	6	Megestrol acetate 160 mg/day	2–5 months	4	2	4	2
Jadoul and Donnez 2003 [21]	5	Endometrial resection + GnRHa	3–6 months	5	0	0	4
Gotlieb *et al.* 2003 [20]	13	Megestrol acetate or MPA	2–8 months	13	6	0	3 (several pending)
Wang *et al.* 2002 [17]	9	Megestrol acetate ± tamoxifen ± GnRHa	At least 8 weeks	8	4	0	4
Kaku *et al.* 2001 [22]	12	MPA	1–12 months	9	2	1	2
Kim *et al.* 1997 [23]	7	Megestrol acetate 160 mg/day	3 months	4	2	0	0
Randall and Kurman 1996 [5]	12	Megestrol acetate or MPA	3–18 months	9	1	0	4

MPA, medroxyprogesterone acetate.

Rackow et al. Curr Opion Obstet Gynecol 2006

MPA 200-800mg/day
or Megestrol acetate 40-400mg/day

- A high daily dose of oral progestin is typically used in clinical practice, but it is not clear whether low- or high-dose progestin is more effective.

Optimal dose of Progestin Agent

- In a previous Gynecologic Oncology Group randomized trial of advanced and recurrent endometrial cancer, the response rate and progression-free survival outcome following MPA therapy was higher in low dose group (200 mg/day) than in high dose group (1000 mg/day).

- In KGOG 2002, the response rate and recurrence rate in endometrial cancer patients did not differ between low dose (MPA or MA, < 250 mg/day) and high dose (MPA or MA, > 250 mg/day) fertility-sparing treatment groups.

Optimal Treatment Duration

- The median time interval to a complete response is 12 weeks (range, 4-60 weeks) and median total treatment duration was 6 months (range, 3-36 months).
- The impact of progestins on endometrial cancer cells becomes apparent as early as 10 weeks after the start of treatment.
- An initial exposure period of at least 12 weeks should be allowed before response is evaluated (a reasonable time point for the first pathologic response evaluation is 3 months after the start of treatment).
- If the patient has persistent disease without progression at this time point, further treatment with progestin can be performed to 9-12 months because many instances of a complete response after 9-12 months have been reported.

Consolidation or Maintenance

- It is not yet clear when progestin therapy should be discontinued in patients who achieve a complete response.
- The benefit of additional high-dose progestin therapy for several months after a complete response was not clear in a previous study.
- Long-term maintenance treatment using low-dose cyclic progestin, oral pill or progestin-containing IUD was associated with lower recurrence rate in previous studies.

Original Research

Hormonal Therapy for Women With Stage IA Endometrial Cancer of All Grades

Jeong-Yeol Park, MD, PhD, Dae-Yeon Kim, MD, PhD, Tae-Jin Kim, MD, PhD, Jae Weon Kim, MD, PhD, Jong-Hyeok Kim, MD, PhD, Yong-Man Kim, MD, PhD, Young-Tak Kim, MD, PhD, Duk-Soo Bae, MD, PhD, and Joo-Hyun Nam, MD, PhD

Obstet Gynecol 2013;122:7-14

- To estimate the oncologic and pregnancy outcomes after oral progestin treatment of young women with endometrial adenocarcinoma of ***grade 2-3*** *and/or* ***superficial myometrial invasion***.

Results

- 48 patients had stage IA, grade 2-3 or superficial myometrial invasion.
- Classification of patients
  - ✓ ***Group 1***: Stage IA, grade 2-3, without superficial myometrial invasion (n=17)
  - ✓ ***Group 2***: Stage IA, grade 1, with superficial myometrial invasion (n=23)
  - ✓ ***Group 3***: Stage IA, grade 2-3, with superficial myometrial invasion (n=8)

Superficial myometrial Invasion:
Myometrial invasion < ½ in pretreatment MRI

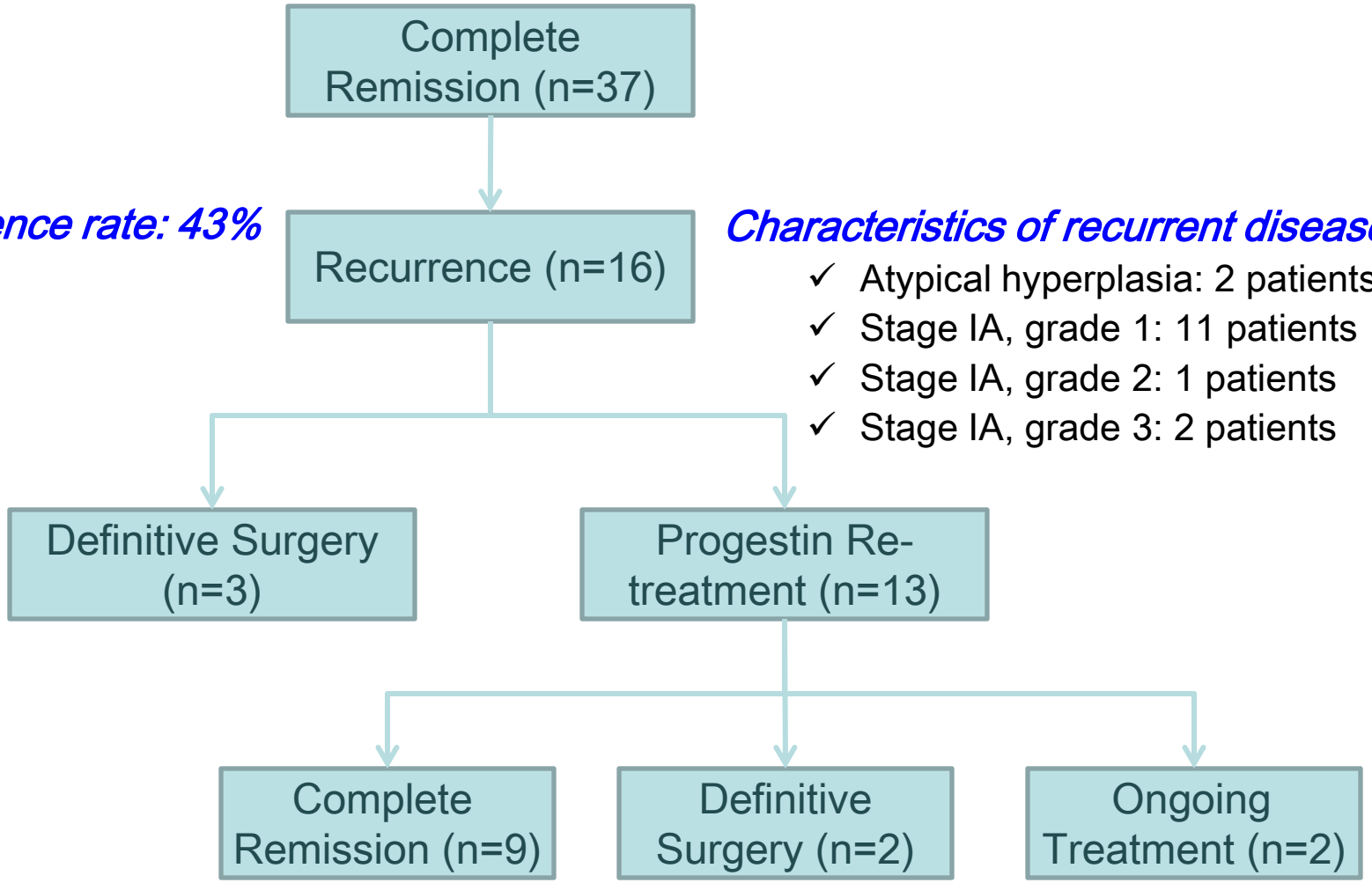
Response to Progestin Treatment (n=48)

	Group 1 (n=17)	Group 2 (n=23)	Group 3 (n=8)	Total (n=48)
Complete Response	13 (76.5%)* (52.2-91%)	17 (73.9%)* (53.2-87.7%)	7 (87.5%)* (50.8-99.9%)	37 (77.1%) (63.3-86.9%)
Partial Response	0 (0%)	1 (4.3%) (0.01-22.7%)	0 (0%)	1 (2.1%) (0.01-11.9%)
Stable Disease	4 (23.5%) (9.1-47.8%)	5 (21.7%) (9.2-42.3%)	1 (12.5%) (0.1-49.2%)	10 (20.8%) (11.5-34.4%)
Progressive disease	0 (0%)	0 (0%)	0 (0%)	0 (0%)

"The median time to CR was 17 weeks (range, 9-51weeks)."

- Data are n (%) (95% confidence interval).
- * $P = 0.731$
- Group 1: Stage IA, grade 2-3, without superficial myometrial invasion (n=17)
  Group 2: Stage IA, grade 1, with superficial myometrial invasion (n=23)
  Group 3: Stage IA, grade 2-3, with superficial myometrial invasion (n=8)

Recurrent Disease (n=16)



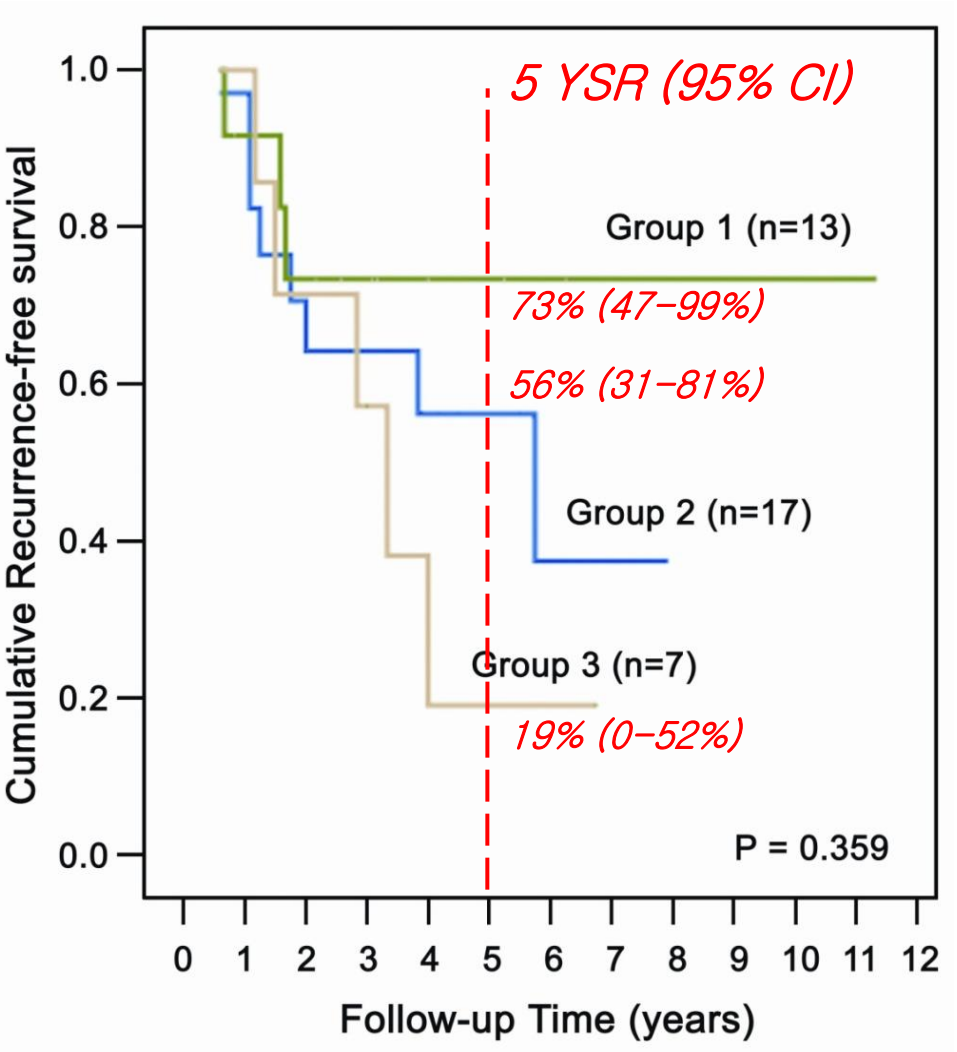
Recurrence after CR (n=37)

	Group 1 (n=13)	Group 2 (n=17)	Group 3 (n=7)	Total (n=37)
Recurrence	3 (23.1%)* (7.5-50.9%)	8 (47.1%)* (26.2-69%)	5 (71.4%)* (35.2-92.4%)	16 (43.2%) (28.7-59.1%)
Median FU time (months)	38 (7-136)**	49 (22-95)**	76 (36-99)**	48 (7-136)
Median time to recur (months)	19 (8-20)***	18 (7-69)***	34 (14-48)***	20 (7-69)

- Data are n (%) (95% confidence interval) or n (range).
- * $P = 0.104$ / ** $P = 0.326$ / *** $P = 0.515$
- Group 1: Stage IA, grade 2-3, without superficial myometrial invasion (n=17)
  Group 2: Stage IA, grade 1, with superficial myometrial invasion (n=23)
  Group 3: Stage IA, grade 2-3, with superficial myometrial invasion (n=8)

Recurrence-free Survival (n=37)

- 5-year recurrence-free survival rate: 52% (95% CI, 34-71%)
- Median recurrence-free survival: 69 months (95% CI, 32-106 months)



Group 1: Stage IA, grade 2-3, without superficial myometrial invasion (n=17)

Group 2: Stage IA, grade 1, with superficial myometrial invasion (n=23)

Group 3: Stage IA, grade 2-3, with superficial myometrial invasion (n=8)

Literature Review

Author	Year	Case	Age (yrs)	Grade	Myometrial invasion	Treatment	Treatment duration, mos	Response	Recur	Pregnancy	Follow-up time, mos	Status
Sardi et al.	1998	Case 1	32	2	no	Oral MPA, 50mg/day	4	no	—	no	20	NED
Zuckeman et al.	1998	Case 2	26	2	no	Oral MPA,	2	CR	no	Twin (IVF)	—	NED
Imai et al.	2001	Case 3	—	2	no	Oral MPA, 600mg/day	9	CR	Yes	no	7	FU loss
		Case 4	—	2	no	Oral MPA, 600mg/day	3	no	—	no	47	NED
Kaku et al.	2001	Case 5	30	2	no	Oral MPA, 800mg/day	4	CR	no	NFD	19	NED
		Case 6	33	2	no	Oral MPA, 600mg/day	6	no	—	no	22	NED
Gotlieb et al.	2003	Case 7	25	2	no	Oral MPA, 200mg/day*	3	CR	Yes	NFD	94	NED
		Case 8	35	3	no	Oral MPA, 600mg/day	5	CR	no	no	18	NED
		Case 9	26	3	no	Oral MA, 160mg/day	3	CR	no	no	16	NED
Koskas et al.	2011	Case 10	41	2	no	Oral NES, 20mg/day	3	CR	Yes	no	12	AWD
		Case 11	32	2	no	Oral MA, 160mg/day	6	CR	—	Twin	24	NED
		Case 12	35	2	no	Oral NG, 5mg/day	5	CR	Yes	no	60	NED
		Case 13	42	3	no	GnRHa	6	no	—	no	23	NED
Brown et al.	2012	Case 14	18	2	no	LNG-IUD	3	CR	no	no	13	NED

71% 40%

- * for 14 days, every 4 weeks, then LNG-IUD for 37 months as maintainance treatment
- MPA, medroxyprogesterone acetate; NED, no evidence of disease; CR complete resonse; IVF, in vitro fertilization; FU, follow-up; NFD, normal full term delivery; MA, megestrol acetate; NES, norethisterone; AWD, alive with disease; NG, nomegestrol; GnRHa, gonodotropin-releasing hormone agonist; LNG-IUD, levonorgestrel-releasing intrauterine device

Summary

- Conservative management with oral progestin can be a reasonable treatment option for

  - ✓ Patients with stage IA, grade 2-3 differentiation without superficial myometrial invasion

  - ✓ Patients with stage IA, grade 1 differentiation with superficial myometrial invasion

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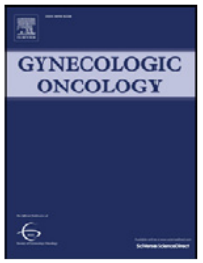
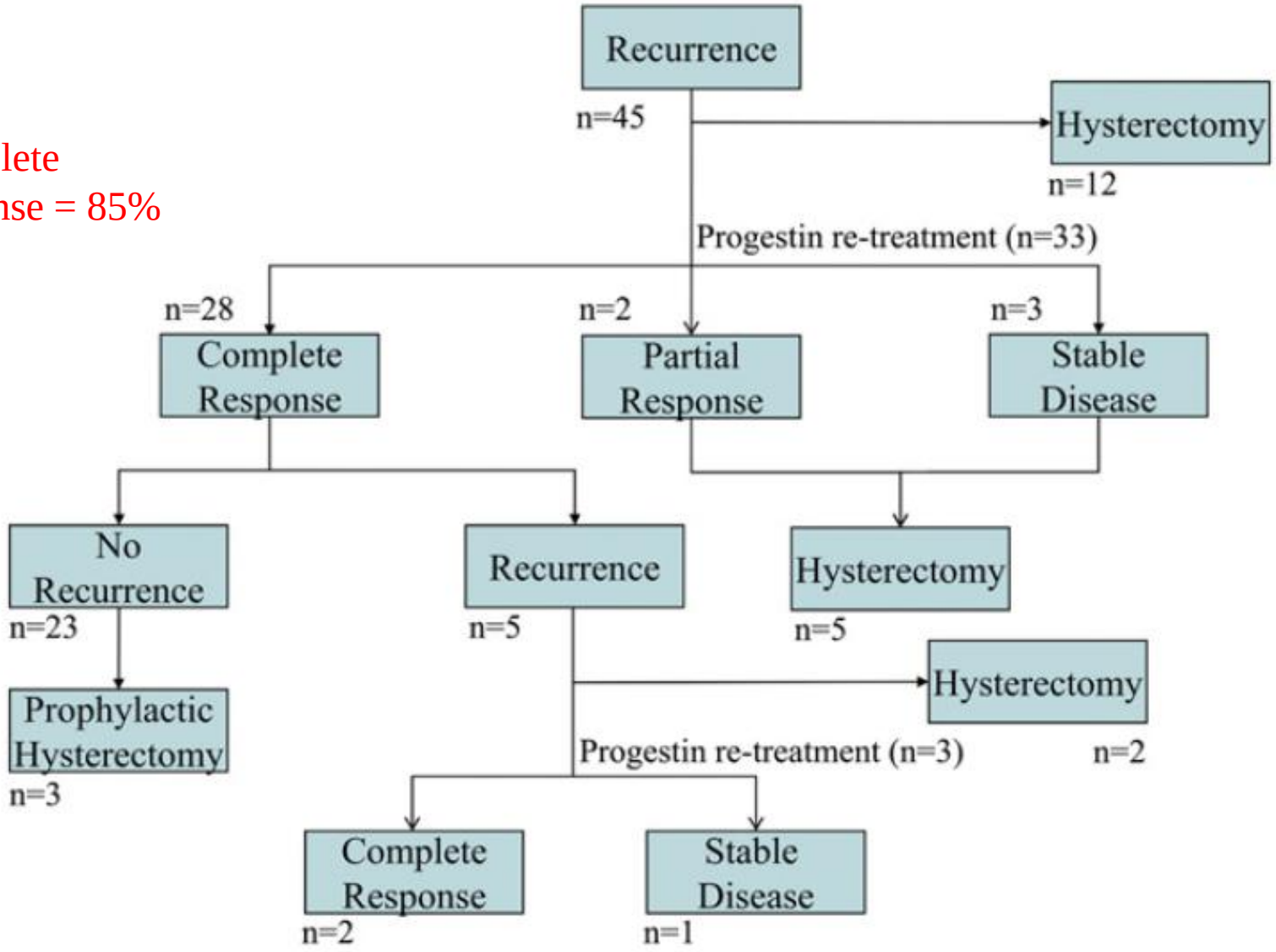


Progestin re-treatment in patients with recurrent endometrial adenocarcinoma after successful fertility-sparing management using progestin

Jeong-Yeol Park [a], Sang-Hun Lee [b], Seok Ju Seong [c], Dae-Yeon Kim [a], Tae-Jin Kim [d], Jae Weon Kim [e], Jong-Hyeok Kim [a], Yong-Man Kim [a], Young-Tak Kim [a], Duk-Soo Bae [f], Joo-Hyun Nam [a,*]

Complete response = 85%



Literature Review

Authors	Year	Recurrent disease					
		Recurrence, n (%)	Time to recurrence (months)[a]	Progestin retreatment, n	Complete response, n (%)	Re-recurrence, n (%)	Follow-up time (months)[a,b]
Gotlieb et al. [16]	2003	6 (50)	40 (19–357)	4	4 (100)	0	40 (39–50)
Ushijima et al. [17]	2007	8 (57) 6 (43)	34.6 44.2	)8	)6 (75)	)5 (83)	)NA
Yu et al. [18]	2009	1 (20) 3 (21)	30 11 (6–16)	0 2	NA 1 (50)	NA 0	NA 12
Eftekhar et al. [19]	2009	3 (17)	36 (24–72)	3	2 (67)	0	NA
Perri et al. [20]	2011	15 (62)	NA	11	11 (100)	5 (45)	NA (22–43)

Summary

- Progestin re-treatment in patients with recurrent endometrial cancer was effective and safe.
- This can be recommended for young women who still want to preserve fertility at recurrence after complete response to progestin.

Conclusion

- Fertility-sparing progestin therapy is highly effective in selected young women with primary and recurrent endometrial cancer.
- The selection of appropriate patients through comprehensive pretreatment evaluations is of paramount importance to achieve the best outcomes without compromising survival outcomes.
- Because of the high rate of recurrence after successful fertility-sparing management, close surveillance is mandatory and prophylactic hysterectomy is the best option after a successful pregnancy.
- Pregnancy outcomes are very promising in these cases with the aid of assisted reproductive technologies.
- Continuous daily oral MPA or MA is the preferred progestins for fertility-sparing therapy. However, future studies should be performed to determine the optimal dose and treatment duration of these agents.


Thank you for your attention !!