PRE-CONGRESS COURSE 7

Fertility-Sparing Surgery in malignant and benign conditions

Special Interest Group Reproductive Surgery
Munich - Germany, 29 June 2014

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SCIENCE MOVING
PEOPLE
MOVING SCIENCE

Fertility-sparing surgery in malignant and benign conditions

Munich, Germany
29 June 2014

Organised by
The ESHRE Special Interest Group Reproductive Surgery

Contents

Course coordinators

Vasilios Tanos (Cyprus), Tin Chiu Li (United Kingdom) and Grigoris Grimbizis (Greece)

Course description

The number of cancer survivors at young reproductive age is increasing. This is due to rising incidence of gynecologic cancer in young patients and the increasing age of first pregnancy. In addition benign diseases such as severe forms of endometriosis and pelvic adhesions also endanger the reproductive integrity during surgery. The management of young patients with early diagnosed gynaecological cancer or severe pelvic pathology who desire further family presents a great challenge since future oncological and obstetrical risks vary. The conflict between fertility preserving treatments and any radical surgery in likelihood of cure most of the times involves big medical and ethical dilemmas. This advanced course aims to educate and give the most recent evidence based update on fertility-sparing surgery (FSS) in benign and malignant cases.

Target audience

Gynaecologists, Gynae-Oncologists, General Surgeons

Course type

Advanced

Scientific programme

Chairmen: Gregoris Grimbizis – Greece and Marco Gergolet - Italy

09:00 - 09:30	Fertility-sparing surgery (FSS) in severe endometriosis and recurrent endometrioma: What is the gold standard approach? ***Stephan Gordts - Belgium***
09:30 - 09:45	Discussion
09:45 - 10:15	Severe adenomyosis: fertility preserving options ***Gregoris Grimbizis - Greece***
10:15 - 10:30	Discussion
10:30 - 11:00	Coffee break
11:00 - 11:30	Giant ovarian and other pelvic tumors and fertility sparing surgery - laparoscopy vs laparotomy ***Vasilios Tanos - Cyprus***
11:30 - 11:45	Discussion
11:45 - 12:15	Preservation of the uterus and endometrium in cases with huge and multiple intramural and/or submucous fibroids ***Tin-Chiu Li - United Kingdom***
12:15 - 12:30	Discussion
12:30 - 13:30	Lunch

Chairmen: Vasilios Tanos – Cyprus and Stephan Gordts - Belgium

13:30 - 14:00	Early, low grade endometrial cancer and fertility sparing surgery ***Kazem Nouri - Austria***
14:00 - 14:15	Discussion
14:15 - 14:45	Early cervical cancer: neoadjuvant chemotherapy and fertility- sparing radical trachelectomy. Pregnancy risks and perinatal outcome ***Andrea Maneo - Italy***
14:45 - 15:00	Discussion
15:00 - 15:30	Coffee break
15:30 - 16:00	Low malignant potential and early stage ovarian cancer: is there a place for FSS? ***Thomas Ind - United Kingdom***
16:00 - 16:15	Discussion
16:15 - 16:45	Ovarian chemio prophylaxis, fertility preservation against the sterilizing effects of chemotherapy and ovarian tissue cryopreservation ***Dror Meirow - Israel***
16:45 - 17:00	Discussion
17:00 - 18:00	SIG Reproductive Surgery business meeting

Fertility-sparing surgery (FSS) in severe endometriosis and recurrent endometrioma: What is the gold standard approach?

Stephan Gordts MD

ESHRE, Munich 2014

Fertility-sparing surgery (FSS)

How to evaluate?

Decreased ovarian reserve (DOR):
may refer to three distinctly, although related, different outcomes

oocyte quality
oocyte quantity
reproductive potential

Testing and interpreting measures of ovarian reserve: a committee opinion
The Practice Committee of the ASRM, Fertil Steril, 2012

Testing and interpreting measures of ovarian reserve: a committee opinion
The Practice Committee of the ASRM, Fertil Steril, 2012

There is mounting evidence to support the use of AMH as a screening test for poor ovarian response, but more data are needed. There is emerging evidence to suggest that a low AMH level (e.g., undetectable AMH) has high specificity as a screen for poor ovarian response but insufficient evidence to suggest its use to screen for failure to conceive.

There is fair evidence to support that a low antral follicle count has moderate to high specificity as a screening test for poor ovarian response and insufficient evidence to support the use of AFC as a screening test for failure to conceive.

What is normal ovarian reserve?
Dillon KE, Gracia CR
Semin Reprod Med. 2013 Nov;31(6):427-36.

"Currently, these biomarkers (AFC, AMH, Inhibine B) are insufficient as predictors of fertility potential or advancement to menopause and no definitive determinations can be made about what constitutes "normal" levels of each measure."

Endometriosis and ovarian reserve

Evaluation of serum anti-Mullerian hormone levels to assess the ovarian reserve in women with severe endometriosis

Pacchiarotti A et al. Eur J Obstet Gynecol Reprod Biol. 2014; 172:62-4 .

	Number	AMH	
Fertile patients	130	1.72 (± 0.63)*	
Endometriosis III -IV	65	0.97 (± 0.59)*	p = 0.001

Endometriosis: damage ovarian reserve
Early sign in young women of advanced ovarian depletion

Endometriomas as a possible cause of reduced ovarian reserve in women with endometriosis
Kitajima et al. Fertil Steril. 2011 Sep;96(3):685-91.

Endometriotic cyst formation and associated structural tissue alterations (fibrosis) in apparently normal ovarian cortex may be a cause of reduced ovarian reserve

Early diagnosis and intervention may be beneficial in women with endometriomas to protect their ovarian function

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Histological assessment of impact of ovarian endometrioma and laparoscopic cystectomy on ovarian reserve.
Kuroda M. et al. Obstet Gynaecol Res. 2012; 38(9):1187-93

Density of follicles in ovarian tissue retrieved at moment of cystectomy

	20 year	30 year	35 y
Reduction with	35.4 %	46.8%	62.7 %

- Ovarian endometriomas have a detrimental impact on follicle reserve in younger patients.
- The resection rate of normal ovarian tissue in cystectomy specimen of the endometriosis group was significantly higher than in the non-endometriotic cyst group ($P < 0.001$).

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Benign cyst and ovarian tissue

Schubert B *et al. Hum Reprod 2005; 20*

density of foll in ovarian tissue surrounding cysts?	*no/mm³*
dermoid (n=7)	*13.04*
endometriosis (n= 13)	*0.31*

Endometriosis invaded the surrounding cortex + fibrotic reaction

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Benign cyst and ovarian tissue

Schubert B *et al. Hum Reprod 2005; 20*

heterogenic distribution of follicles in clusters

median of 8 – 11.4 foll/ mm³

no direct correlation between density and age

after freeze-thawing: normal morphology of follicles preserved in 79 %.

Endometriosis invaded the surrounding cortex + fibrotic reaction

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Benign cyst and ovarian tissue

Maneschi *et al. Am J Obstet Gynecol 1993; 169*

patterns similar to normal ovarian cortex; nl vascular.

dermoid	*92 %*	*84 %*
cystadenoma	*77%*	*78 %*
endometriosis	*19 %*	*22%*

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Surgery and impact on ovaries

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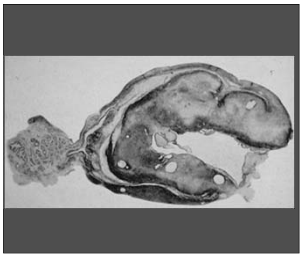
Pathogenesis of ovarian endometrioma

- Superficial endometriotic implants, bleeding and invagination of ovarian cortex.
- Metaplasia of coelomic epithelium
- Involvement of functional ovarian cysts

Pathogenesis of ovarian endometrioma



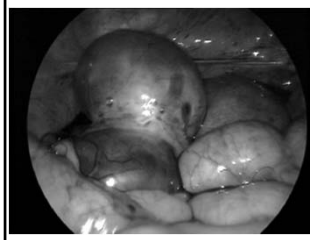
Implantation of regurgitated endometrial cells on ovarian surface.

Adhesion formation

Bleeding at implantation site and invagination cortex

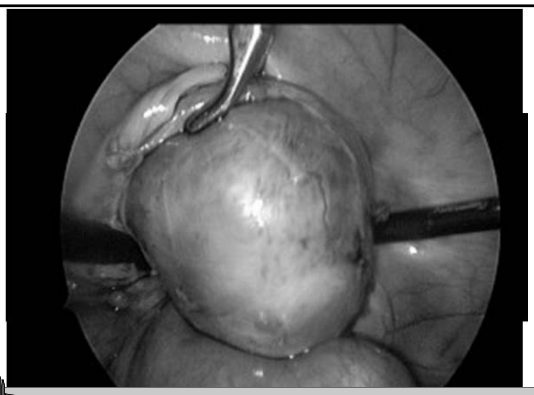
Hughesdon,1957 J Obst.Gynec. 44:481

OVARIAN ENDOMETRIOMA



Pseudocyst

Extra- ovarian localisation



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TECHNIQUES FOR RECONSTRUCTIVE OVARIAN SURGERY IN ENDOMETRIOSIS

Residual ovarian volume after surgery

Endometriosis		Dermoid	
5,1 ±3.2*		6.7 ± 3.3*	
Treated	Control	Treated	Control
4.3±2.3**	9.7±3.9*	7.1±3.5*	8.3±3.1

*p<0.001
*p<0.001
p<0.05

Exacoustos et al. Am J Obst Gynec, 2004,191

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TECHNIQUES FOR RECONSTRUCTIVE OVARIAN SURGERY IN ENDOMETRIOSIS

Residual ovarian volume after surgery

Lack of correlation between residual ovarian volume and cyst diameter…..
Resection of even small endometrioma significant loss of ovarian volume

Exacoustos et al. Am J Obst Gynec, 2004,191

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Decline of AMH after cystectomy for ovarian endometrioma

Characteristics	Overall (n=38)	Unilateral (n=20)	Bilateral (n=18)	P-value
Age	33.8 ±4.7	34.0 ±3.9	33.6 ±5.4	0.830
BMI (kg/m^2)	20.1±2.3	20.4±2.7	19.7±1.7	0.781
Serum AMH				
Pre-operative	3.9±2.5	4.1±2.3	3.6±2.7	0.299
Post-operative	2.1±1.6	2.9±1.6	1.2±1.0	0.001

Hirokawa et al. Hum Reprod 2011; 26, 4

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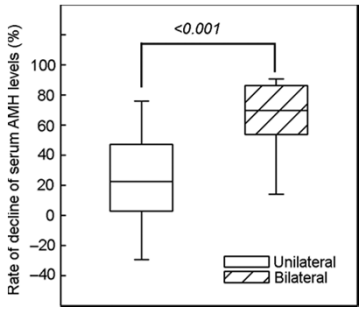
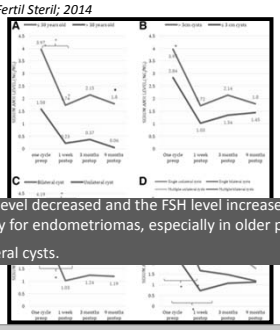
The rate of decline in serum AMH is defined as 100 × [preoperative AMH level – post-operative AMH level]/preoperative AMH level.



Hirokawa W et al. Hum. Reprod. 2011;26:904-910

Human Reproduction

The impact of laparoscopic cystectomy on ovarian reserve in patients with unilateral and bilateral endometriomas.
Alborzi et al. Fertil Steril; 2014



The AMH level decreased and the FSH level increased after laparoscopic cystectomy for endometriomas, especially in older patients and those with bilateral cysts.

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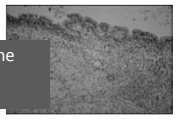
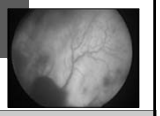
OVARIAN ENDOMETRIOMA



Histologic analysis of endometriomas: what the surgeon needs to know.
Muzzi et al. Fertil Steril 2007, 87: 362-66

Inadvertently excised ovarian tissue: 81%

Endometriotic tissue may cover from 10%- 98%



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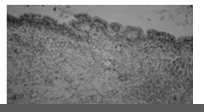
OVARIAN ENDOMETRIOMA



Hachsiguga et al. Hum Reprod 2002

easy removable endom. cyst: prim. follicles 68.9% (1-25)

Muzii et al.Fertil Steril, 2002

endometrioma: ovarian tissue 54%* (1-2 mm thick)
other ovarian cyst: ovarian tissue 6%*
(p<0.005)

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A characterization of the relationship of ovarian reserve markers with age.
Rosen MP. Et al. Fertil Steril. 2012; 97(1):238-43

Age trial conception	N	Med. AFC subfert	Med; Afc Fertil	P value	
<20	35	56	56	.97	
21- 30	171	25	50	.02	
31 - 40	141	25	44.5	.03	
> 40	5	33.5	50	.37	

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Quid fertility preservation?

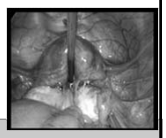
Growing concern:

the serious risk of diminished ovarian reserve up to POF:

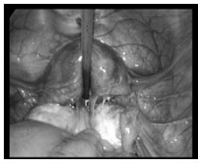
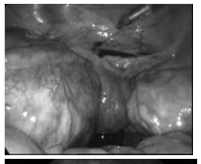
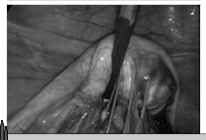
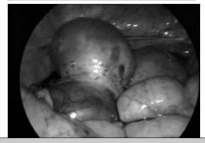
cystectomy: aggressive stripping
extensive and agressive hemostasis

Surgery of ovarian endometrioma: When and how?

HOW ?



FERTILITY PRESERVATION
Ovarian endometrioma

Ovarian endometrioma

TO COMPLEX

AS DISEASE

AS SURGERY

TO REDUCE TREATMENT TO

ABALATION

EXCISION

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Types of endometriomas

Ovarian endometrioma :

type 1: free or loosely fixed, usually small
type 2: densely adherent to pelvic structures in fossa ovarica
type 3: with adenomyosis in adherent tissue

Unilateral/ bilateral

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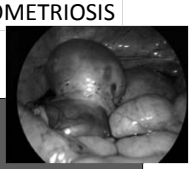
TECHNIQUES FOR RECONSTRUCTIVE OVARIAN SURGERY IN ENDOMETRIOSIS

1. EVERSION



Three steps:

1. Adhesiolysis
2. Wide opening at site of inversion
3. Superficial coagulation endometriotic implants

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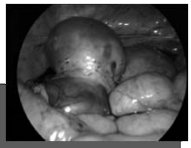
TECHNIQUES FOR RECONSTRUCTIVE OVARIAN SURGERY IN ENDOMETRIOSIS

2. EXCISION



Three steps:

1. Adhesiolysis
2. Wide opening at site of inversion
3. Resection of fibrotic pseudo-capsule

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Eversion/ablation ≠ fenestration

Opening is at site of inversion with resection of fibrotic edges

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OVARIAN ENDOMETRIOMA

Ablation

Lasers: CO_2 lasers, KTP, NdYag …

Current: Bipolar forceps and probe

Plasmajet

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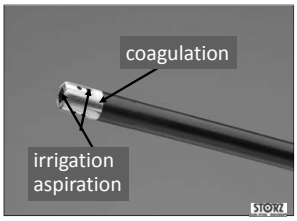
BIPOLAR COAGULATION PROBE



Three in one

Easy handling
Good haemostasis
Helpful dissection
No carbonisation
Minimal cost

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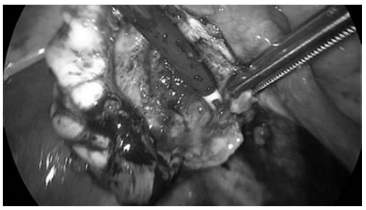

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$$V = \frac{4}{3}\pi r^3$$

diameter (cm)	radius (cm)	volume (cm^3)
1	0,5	0,52
2	1	4,18
3	1,5	14,13
4	2	33,49

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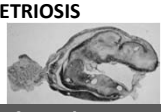
RECONSTRUCTIVE OVARIAN SURGERY IN ENDOMETRIOSIS

		Ablation	Excision
		recurrence rates	
Hemmings	1998	8% *(36)*	12% *(23)*
Saleh	1999	21.9% *(70)*	6.1% *(161)*
Beretta	1998	18.8% *(32)*	6.2% *(32)*
Fayez	1991	33% *(30)*	29% *(66)*

TECHNIQUES FOR RECONSTRUCTIVE OVARIAN SURGERY IN ENDOMETRIOSIS

Ablation versus Excision



Excision: higher incidence adhesion formation
lower recurrence rate ?
Reduced ovarian volume and ovarian reserve
(El-Shawi, 1998; Al-Azemi, 2000; Nargund 1995: Loh, 1999)

Ablation: higher recurrence rates ?

HART RJ, HICKEY M, MAOURIS P, BUCKETT W: EXCISIONAL SURGERY VERSUS ABLATIVE SURGERY FOR OVARIAN ENDOMETRIOMATA
Cochrane review (2005, 2008)

- "*excisional* laparoscopic surgery provides significantly *better* results than draining and destruction of the cyst wall with regard to the *recurrence rate*, both of the endometriotic cyst itself as of its symptoms, but also with regard to the subsequent chance of a spontaneous *pregnancy*. "

HART RJ, HICKEY M, MAOURIS P, BUCKETT W: EXCISIONAL SURGERY VERSUS ABLATIVE SURGERY FOR OVARIAN ENDOMETRIOMATA
Cochrane review (2005, 2008)

- only 3 RCT's were/could be included
- performed in only 2 centres
- on 245 patients
- not multicentric
- include a potential bias since both patient and surgeon were not blinded as to the type of procedure that was going to be performed

DONNEZ J ET AL. MINIMALLY INVASIVE GYNECOLOGIC. CURR.OPIN.OBSTET.GYNECOL., 23, 289-295, 2011

SUMMARY: Some previously published reviews have probably too hastily concluded that excision is a better option than ablation. They failed to analyze the ovarian reserve, which is often significantly decreased after excisional surgery. This manuscript clearly explains the crucial importance of preserving the ovarian blood supply, as well as the ovarian cortex containing all primordial follicles, during surgery.

Type of surgery and impact on ovaries

Type of surgery and impact on ovaries

Every kind of ovarian surgery performed for ovarian endometriosic cysts will have a negative impact upon the ovarian reserve.

Decline of AMH after cystectomy for ovarian endometrioma

Characteristics	Overall (n=38)	Unilateral (n=20)	Bilateral (n=18)	P-value
Age	33.8 ±4.7	34.0 ±3.9	33.6 ±5.4	0.830
BMI (kg/m^2)	20.1±2.3	20.4±2.7	19.7±1.7	0.781
Serum AMH				
Pre-operative	3.9±2.5	4.1±2.3	3.6±2.7	0.299
Post-operative	2.1±1.6	2.9±1.6	1.2±1.0	0.001

Hirokawa et al. Hum Reprod 2011; 26, 4

Unilateral Endometrioma and frequency of ovulation after laparoscopic cystectomy

	Ovulation before	Ovulation after
< 4cm (n=15)	41.0% (±8.0)	19.8% (±6.7)
>4cm (n=13)	26.8% (±10.9)	13.5% (±5.8)
Total	34.4% (±6.6)	16.9% (±4.5)

J assisted reprod genet 2008 25: 239-44

Horikawa T, 2008

Endometriosis and frequency of ovulation after laparoscopic cystectomy for

	Operated site	Intact site
Pregnancy cycles/ Ovulation cycles	2/34	12/156
	8.8%	5.8%

Laparoscopic cystectomy reduces the frequency of ovulations, but maintains the pregnancy rate per ovulation.

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Horikawa T, 2008

OVARIAN RESERVE

	AFC		AMH	
	BEFORE	AFTER	BEFORE	AFTER
GROUP I STRIPPING	2,0 (±0.8)	2.4 (±0.8)	3.9 (±0.4)	2.9 (±0.2)
GROUP 2 3-STEP	1.3 (±0.5)	4.3 (±0.8)	4.5 (±0.4)	3.9 (±0.6)

Pados et al. Hum Reprod 2010

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The effect of laparoscopic ovarian cystectomy versus coagulation in bilateral Endometriomas on ovarian reserve as determined by antral follicle count And ovarian vomume: a prospective randomized study
Var T. Et al Fertil Steril 2001; 95: 2247-50.

Parameter	Cystectomy	cauterization	P-value
Basal follicles nr.	3,67±1,26	4,75±0,60	.001
Ov. volume	6,27±1,95	9,87±2,01	.005
Domin. foll	4,38±0,95	5,05±0,91	.03
Retrieved ooc.	3,08±0,79	3,86±0,88	.01

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OVARIAN RESERVE

	Ablation plasmajet N = 15		Cystectomy N= 15	
	Non operated	operated	Non operated	operated
volume	7 (±2.7)	5.2 (±2.5)	8.8 (±4.2)	3 (±1.6)
AFC	6.8 (±3.5)	5.5 (±3.9)	8 (±5.3)	2.9 (±2.4)

Roman H Fertil Steril, 2011

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Why surgery ?

When surgery?

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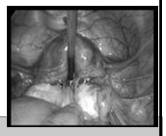
Surgery of ovarian endometrioma

WHY SURGERY ?

POSITIVE APECTS:

1. *creates possibility of spontaneous pregnancy !!*
2. *relief of pain*



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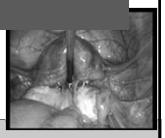
Surgery of ovarian endometrioma

WHY SURGERY ?

NEGATIVE APECTS:

- *Complexity of endometriosis is not resolved by surgery alone*
- *Impact on ovarian reserve*



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Surgery endometrioma and pregnancy rates

Daniell	1991	32	ablation	38%
Mars	1991	23	laser ablation	30.4%
Donnez	1996	814	ablation	51%
Sutton	1997	66	ablation	45%
Bateman	1994	21	stripping	42.8%
Montanino	1996	21	stripping	45%
Busacca	1999	57	stripping	57,5%
Milingos	1999	32	stripping	53%
Hemmings	1998	84	stripping/coagul	50/60%
Beretta	1998	64	stripping/coagul	66/23%

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Endometriosis
Probability of spontaneous conception?

Minimal endometriosis

Marcoux et al.	18 %
Parazzini et al.	22 %
Adamson et al.	37.4 %

Moderate and severe (III-IV)

Adamson et al.	3.1 %
P. Barri et al.	11%

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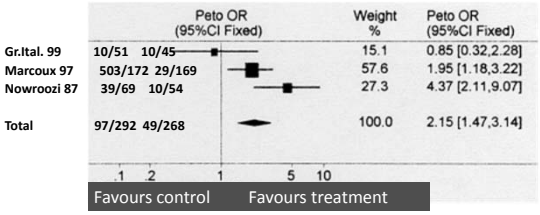
Laparoscopic surgery for subfertility associated with endometriosis - live birth



Cochrane Review - Jacobson, Barlow & Koninckx

ENDOMETRIOSIS- Associated CPP

Prospective, randomized, double-blind trial of laser laparoscopy *(Sutton, Fertil Steril 1994)*

Relief	rAFS 1	rAFS 2-3
Placebo	25%	20%
Laser	46%	74%

TECHNIQUES FOR RECONSTRUCTIVE OVARIAN SURGERY IN ENDOMETRIOSIS

Ovarian response

Canis et al. 2001	not reduced
Donnez et al. 2001	no difference
Geber 2002	reduced
Somigliana 2003	reduced
Barnhart 2002	reduced (meta analysis)
Garcia- Velasco 2004	no difference

ENDOMETRIOSIS-Associated INFERTILITY

Comparison of Pregnancy Rates
(Adamson, Sem Reprod Endocrin 1997)

	Stage of disease	
	Mini/Mild	Severe
Expectant	37,4%	3,1%
Surgical	51,7%	41,3%

Adenomyosis
BE: Endometriosis

Conflict of interest: cons. Storz

Pregnancy rates after surgery and/or IVF

	< 35 y (n= 483)	35 y (n= 144)	Total (n=173)
I= surgery	61 %	29.7%	54.2%
II= surg + IVF	34.3%	25.9%	30.4%
III = IVF first	35.7%	25%	32.2%

P.N. Barri RBMonline 2010

Pregnancy rates after surgery and/or IVF

Pregn after surgery	262	262		
Pregn IVF after surg		56		
Pregn after IVF			68	
No treatment				20
Total pregn.	262	318	68	20
Final % pregn	54.2%	65.8%	32.2%	11.8%

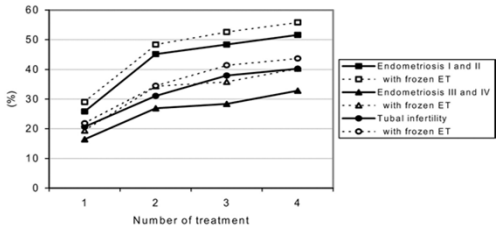
P.N. Barri RBMonline 2010

The effect of endometriosis on in vitro fertilization outcome: A systematic review and meta-analysis
Harb H, Gallos I, et al; BJOG 2013; 120: 1308-20

27 observational studies	n= 8984 patients
Fertilization rates stage I/II:	reduced (RR=0.93, 95% CI p= 0.03
Implantation rate	reduced (RR=0.79, 95%CI, P=0.006
Clinical pregnancy rate	reduced (RR= 0.79, 95% CI, P= O.0008

The presence of endometriosis (III/IV) is associated with poor implantation and clinical pregnancy rates in women undergoing IVF treatment

Cumulative live birth rates (%) with and without frozen embryo transfer



Kuivasaari, P. et al. Hum. Reprod. 2005 20:3130

Cumulative life birth rate
Tummon et al. 1991

Stage I	33%
Stage II	22%
Stage III	15%
Stage IV	13%

Stage of endometriosis and IVF outcome

Meta-analysis

	rAFS I-II	rAFS III-IV	
Mean Nb ooc	8.19	6.70	p<0.001
Peak E_2	5813.38	1447.73	p<0.001
Fertil.%	58.38%	74.47%	p<0.001
Pregn %	21.12%	13.84%	p<0.001
Implant%	11.31%	10.23	0.003

Barnhart et al. Fertil Steril 2002, 77

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Results of pregnancy rates in donation programs

- Women with endometriosis, even those with grade III or IV disease, did not experience a reduced pregnancy rate if the oocytes were donated from healthy women without endometriosis as shown in *all* studies (Kunz et al.,RBMonline).
- On the other hand Pellicer et al. and Shulman et al. (1994, 1999) demonstrated that oocytes donated by women with endometriosis to women with an ovarian insufficiency resulted in a significantly reduced pregnancy rate as compared to donators without endometriosis.

Adenomyosis
BE.
Endometriosis

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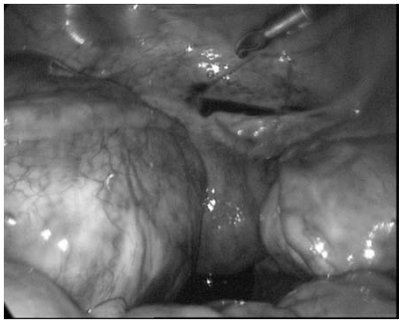
Endometriosis Association Survey

- 10.000 questionnaires mailed
- 4.000 questionnaires entered in analysis

average time between first symptoms and diagnosis is 9.3 years !

- 4.7 years before first medical consult
- 4.6 years before final diagnosis

www.endometriosisassn.org



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Prevalence of endometriosis in adolescents

	Nr	I	II	III	IV	
Goldstein 1980	66	58%	38%	0%	4%	US
Vercellini 1989	18	67%	33%	0%	0%	It
Davis 1993	36	28%	22%	19%	31%	US
Reese 1997	49	80%	12%	6%	2%	US
Laufer 1997	42	77%	23%	0%	0%	US
Emmert 1998	37	92%	8%	0%	0%	Germ
Bai 2002	20	10%	44%	28%	18%	Korean
Ventolini 2005	52	14%	39%	43%	4%	It
Stavroulis 2006	11	45%		55%		UK
Vicino 2010	38	18%	13%	24%	34%	It
Roman 2010	20	40%	45%	5%	10%	N. Zeal
Yang 2012	63	8%	3%	52%	37%	China

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Prevalence of endometriosis in adolescents

rAFS I	8% - 92%
rAFS II	3% - 45%
rAFS III	0% - 52%
rAFS IV	0% – 37%

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Prevalence of endometriosis in adults

Parazzini 2006		I	II	III	IV
Endo	195	51%	22%	20%	7%
Pain	185	37%	24%	30%	10%
Roman 2010		29%	40%	15%	25%

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Ovarian endometrioma

Accuracy of US

	Nr	Size (mm)	Sens.	Spec.
Kurjak	**113**	**18-160**	**84**	**97**
Guerriero	**29**	**40 (SD:10)**	**84**	**95**
Alcazar	**27**	**?**	**89**	**91**
Guerriero	**58**	**40 (SD:16)**	**81**	**96**

QUID ENDOMETRIOMA < 2CM ?

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564 consecutive infertile women, 169 of whom show endometriosis at TVE

Detection of small endometriomas at TVS & TVE
in 169 patients with endometriosis (15-16% of all TVE)

size	TVS +	TVE +	TVS sensitivity
≤ 15 mm	5	11	45 %
> 15 mm	11	11	100 %
total	16	22	16/22 (73%)

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Ovarian endometrioma

Transvaginal sonography

TVS is useful, if diameter of cyst is 15 mm or more

TVS is the preferred method of diagnosing an asymptomatic endometrioma, but cannot exclude the presence of endometriosis.

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The Transvaginal endoscopy

– Hydrolaparoscopy offers the ideal inclination angle to explore the ovarian fossa

– TVE allows for the detection of endometriomas that may be invisible at TVS (<10-12 mm)

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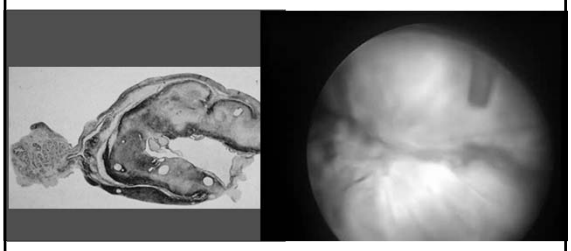

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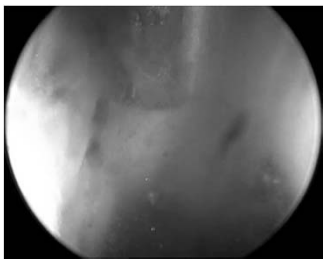

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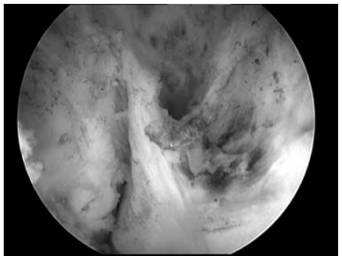

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Advantages of the transvaginal laparoscopic approach

- Minimal invasive
- Early detection of endometriosis
- When indicated early treatment

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TVE and small endometrioma

- We need to focus on the ***early detection*** of the small endometrioma in the young female patient (TVS, MRI, CA-125, TVE)
- We can't make a *distinction* between the small endometrioma with a good prognosis and the one that will continue to grow towards the more destructive stages of the disease.
- Treat when surgery is feasible & efficient, with distinct cleavage planes, minimal fibrosis.
- ~ maximal preservation of healthy ovarian tissue, i.e. functional prognosis (↓ postop adhesion formation) and reproductive potential of the affected ovary

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Recurrence of endometriotic cyst

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Recurrence of endometriosis

Reoperation and CPR

Cheewadhanaraks, 2004	n=32	20.5% (12m)
Wheeler, 1983	n=62	47% (36m)
Pagidas, 1996	n=18	24.4% (9m)
Bussaca, 1998	n=81	45-54% (24m)
Candiani, 1991	n=42	30.7% (27m)

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Endometriosis rAFS III – IV
Re-operation versus ART

	IVF	Re-operation
Number	23	18
Age	32.5	31.6
CPR	33.3%*	24.4%

* 1 cycle

Pagidas et al. 1996 Fertil Steril,65

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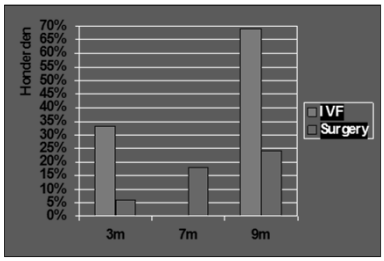
Endometriosis III – IV
CPR: Re-operation versus ART



Pagidas et al. 1996 Fertil Steril,65

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Recommendations in case of recurrence ovarian endometrioma

IVF : first choice
- < 5 cm, unilateral ?
- patients at age,
- combined male pathology
- GnRha down regulation

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Recommendations in case of recurrence ovarian endometrioma

Re operation

- in case of cysts larger 5 cm, bilateral
- pain
- experienced surgeons
- GnRha for 2 – 3 months as preparation for IVF

Informed consent

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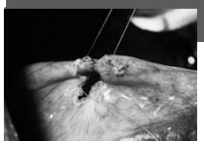
FERTILITY PRESERVATION AND ENDOMETRIOSIS

ABLATION OR EXCISION TECHNIQUE:
IN WOMEN AT REPRODUCTIVE AGE

SURGERY SHOULD BE CARRIED OUT BY EXPERIENCED SURGEONS



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FERTILITY PRESERVATION AND ENDOMETRIOSIS

Patients with endometriosis: surgery first treatment option

If not pregnant after 6m *(>35 y)* -12m *(<35y)*: IVF

Individualized treatment: severity (uni- / bilateral)
pain
intestinal involvement
other fertility impairing factors

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- Do not destroy the ovary
  - By missing the plane of cleavage
  - By excessive coagulation especially at the hilus
  - By operating in one time large cysts
- Decreased ovarian reserve
  - Blame the surgeon

FERTILITY PRESERVATION AND ENDOMETRIOSIS

Growing concerns on ovarian reserve:

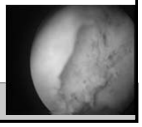
Ablative surgery less impact on follicular reserve; higher recurrence rate?

Cysts > 5 cm: 2 step operative procedure protect the hilus (Donnez et al FS 2008,)

<u>Conclusions:</u>

No indication for ovarectomy in case of benign or endometriotic ovarian cyst.

Endometrioma (extra-ovarian) is different from other cyst with potential danger of reduced follicular reserve after cystectomy.



CONCERNS

Endometriomas in spontaneous pregnancies are rare, but a fourfold increase has been reported in recent years making it today the most common adnexal mass detected during pregnancy

Ueda, Y., Enomoto, T., Miyatake, T., Fujita, M., Yamamoto, R., Kanagawa, T., Shimizu, H., Kimura, T., 2010. A retrospective analysis of ovarian endometriosis during pregnancy Fertil. Steril. 94, 78-84.

CONCERNS

The endometrioma may not be large and although benign, may cause significant complications at any stage during gestation (Gregora and Higgs, 1998). Recently, Reif et al. (2011) presented a case of acute haemoperitoneum caused by a ruptured endometrioma in a late twin pregnancy.

Gregora, M., Higgs, P., 1998. Endometriomas in pregnancy. Aust. N. Z. J. Obstet. Gynaecol. 38:106-109.
Reif. P., Schöll. W., Klaritsch. P., Lang. U.. 2011. Rupture of endometriotic ovarian cyst causes acute hemoperitoneum in twin pregnancy. Fertil. Steril. 95:2125

Severe Adenomyosis: Fertility-Sparing Surgical Options

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Medical School
Aristotle University of Thessaloniki

Declaration of Interests

- ***None (commercial)***

-Member of the Executive Committee of ESHRE

-Member of the advisory board of ESGE

- Member of the Executive Committee of the Hellenic Society of Obstetrics & Gynecology

-Member of the Executive Committee of the Hellenic Society of Gynecological Endoscopy

Adenomyosis

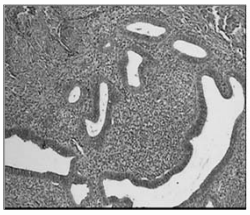
- *Definitions and Classification*
- *Diagnosis and mapping*
- *Symptoms and aims of treatment*
- *Uterus sparing surgical treatment*
- *Safety options*

Adenomyosis

- Definitions and classification
- Diagnosis and mapping
- Symptoms and aims of treatment
- Uterus sparing surgical treatment
- Safety options

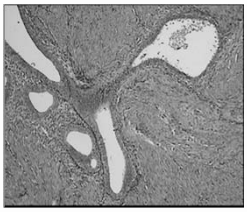
Adenomyosis: Definitions

- *As adenomyosis is defined the presence of heterotopic endometrial glands and stroma in the myometrium with adjacent smooth muscle hyperplasia*
- *Adenomyosis can be either diffuse or focal, taking the form of adenomyoma or adenomyotic cyst*
  - *Ademomyomas are grossly circumscribed nodules of hypertrophic and distorted endometrium and myometrium usually embedded within the myometrium*
- *Histologically, it could range from mostly solid to mostly cystic*



Endometrial glands of varying shapes embedded in abundant endometrial stroma are surrounded by smooth muscle bundles (hematoxylin & eosin, X 50)

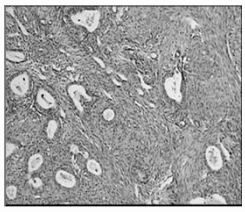
Histological characteristics of adenomyosis



Surgical/histological classification of adenomyosis

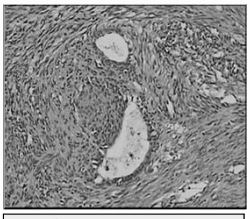
Diffuse adenomyosis	*1. Smooth muscle hyperplasia with ectopic endometrium (⇧ junctional zone)* *2. Micro-dilated ectopic endometrial glands throughout hyperplastic myometrium*
Focal adenomyosis	*1. Adenomyomas* *2. Cystic adult adenomyosis* *2a. Juvenile cystic adenomyosis*
Polypoid adenomyosis	*1. Typical polypoid adenomyomas* *2. Atypical polypoid adenomyomas*
Special categories	*1. Adenomyomas of endocervical type* *2. Retroperitoneal adenomyosis or rectovaginal endometriosis*

Grimbizis et al, Fertil Steril, advance access online, 2013



Multiple endometrial glands are found between smooth muscle bundles / Most glands are tubular, while some of them are haphazardly shaped / They somehow give an impression of an infiltrative growth pattern. (hematoxylin & eosin, X 50)

Atypical polypoid adenomyosis Histological characteristics



No nuclear atypia or significant mitoses are observed in higher magnification (hematoxylin & eosin, X 100)

Adenomyosis

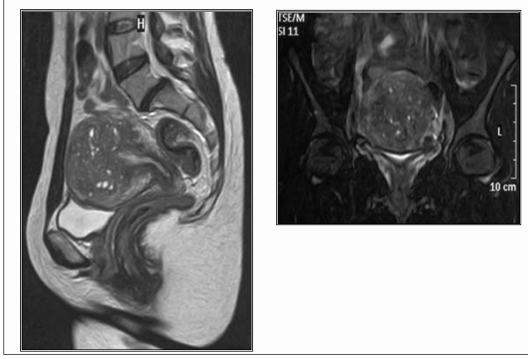
- *Definitions and Classification*
- ***Diagnosis and mapping***
- *Symptoms and aims of treatment*
- *Uterus sparing surgical treatment*
- *Safety options*

Adenomyosis: Spectrum of MRI findings

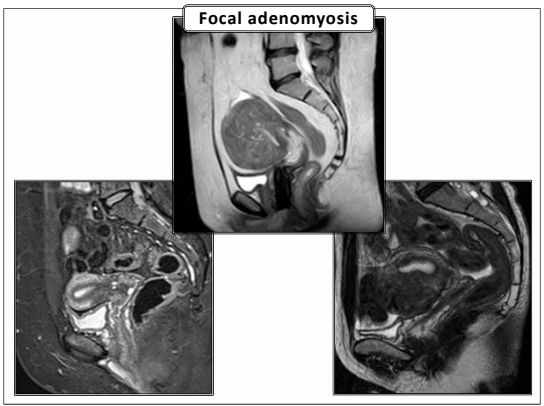
- *Diffuse or focal thickening of the junctional zone (max >12mm) with low T2 signal intensity*
- *Ill defined myometrial nodule of low T2 signal intensity within myometrium (adenomyomas)*
- *Punctuate foci of high intensity within the myometrium or within the low intensity lesions*
- *HighT2 signal intensity linear striations radiating out of the endometrium (pseudo-widening of the endometrium)*

Tamai et al, Best Pract Res Clin Obstet Gynecol, 20: 583-602, 2006

Diffuse adenomyosis



Focal adenomyosis



Diagnostic accuracy of MRI for adenomyosis

Study	Design / Patients	Sensitivity	Specificity	PPV	NPV	AUC
Stamatopoulos et al / 2012	Prospective (N=135)	46.15	99.08	92.31	88.52	0.726 (0.643 – 0.799)
Moghadam et al / 2006	Retrospective (N=153)	38.71	90.98	52.17	85.38	0.648 (0.567 – 0.724)
Dueholm et al / 2001	Prospective (N=106)	63.64	88.10	58.33	90.24	0.759 (0.666 – 0.836)
Bazot et al / 2001	Prospective (N=120)	77.50	92.50	83.78	89.16	0.850 (0.773 – 0.909)
Reinhold et al / 1996	Prospective (N=119)	85.71	85.71	64.86	95.12	0.857 (0.781 – 0.914)
Ascher et al / 1994	Prospective (N=20)	88.24	66.67	93.75	50.00	0.775 (0.535 – 0.927)

- *High Overall Diagnostic performance of MRI: Area Under the Curve (AUC) >0.75*
- *High specificity (& high PPV): the possibility of adenomyosis found in MRI to be correctly diagnosed is very high (>90%)*

Stamatopoulos et al, JMIG, 19:620-626 , 2012

Correlation of MRI findings with histology

Low T2 intensity lesions *(junctional zone)*	*Smooth muscle hyperplasia associated with ectopic endometrium* *(Differential diagnosis: hyperplasia of myometrium / normal variant)*
High T2 intensity foci within low intensity lesions	*Ectopic endometrial glands cystically dilated*
High T2 intensity linear striations into myometrium	*Benign invasion of basal endometrium within adjacent myometrium*
High T2 intensity cystic lesion within myometrium	*Adenomyotic cyst*

Adenomyosis

- *Definitions and variants*
- *Diagnosis and mapping*
- *Symptoms and aims of treatment*
- *Uterus sparing surgical treatment*
- *Safety options*

Symptoms and aims of treatment

Abnormal Uterine Bleeding	• ***Reduction of Bleeding***
Pelvic pain ***Dysmenorrhea, dyspareunia, chronic pelvic pain***	• ***Reduction of pain***
Poor reproductive outcome ***Infertility & poor pregnancy outcome***	• ***Achievement and evolution of pregnancy***

Treatment options in patients with adenomyosis

- **Non-surgical medical and/or interventional options**
  - *Hormonal treatment: GnRH-a / LNG-IUS*
  - *Uterine artery embolization*
  - *Magnetic Resonance guided Focused Ultrasound Surgery (MRgFUS)*
- **Uterus sparing surgical options**
  - *Complete adenomyomectomy*
  - *Partial adenomyomectomy*
  - *Non-excisional techniques*
- **Total hysterectomy**

Adenomyosis

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Uterus sparing surgical treatment of adenomyosis

Rationale and basis for classification of the techniques

Excision or destruction of the diseased tissue with concomitant maintenance of the healthy myometriun is the goal of any surgical conservative treatment

Adenomyosis/adenomyomas infiltrate myometrium and, thus, adenomyomectomy is always associated with concomitant removal of some amount of myometrial tissue

Classification of surgical techniques should be based on:

1. Extent of removal of adjacent healthy myometrium and,

2. Preservation of the integrity (and subsequently the functionality) of the uterine wall

Grimbizis et al, Fertil Steril, advance access online, 2013

Classification of Surgical Techniques

1. Complete excision of adenomyosis

complete removal of all the clinically recognizable, non-microscopic lesions with maintenance of uterine wall integrity

2. Partial excision of adenomyosis / cytoreductive surgery

partial removal of the clinically recognizable non-microscopic lesions. complete removal would lead to "functional" hysterectomy due to the concomitant excision of a critical amount of healthy myometrium

3. Non-excisional techniques

interventions where removal of adenomyotic tissue is not included

Grimbizis et al, Fertil Steril, advance access online, 2013

Classification of uterus sparing techniques and their variants
Excisional techniques

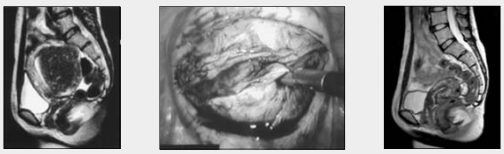
Surgical category	Techniques	Described variant
Complete excision	*Adenomyomectomy*	*1. **Classical technique** (Hyams, 1952; Grimbizis et al, 2008; Wang et al, 2009) / plus intraoperative ultrasound guidance (Nabeshima et al, 2003; Nabeshima et al, 2008)* *Modifications:* *⊙ **U-shaped suturing** (Sun et al, 2011)* *⊙ **Overlapping flaps** (Tacheshi et al, 2006)* *2. **Triple flap method** (Osada et al, 2011)*
	Cystectomy	*Classical technique*
Partial excision (cytoreductive surgery)	*Partial Adenomyomectomy*	*1. **Classical technique** (Fujishita et al, 2004)* *2. **Transverse H incision** (Fujishita et al, 2004)* *3. **Wedge resection** of the uterus (Sun et al, 2011)* *4. **Asymmetric dissection** of the uterus (Nishida et al, 2010)*

Grimbizis et al, Fertil Steril, advance access online, 2013

The beginning of the story ……

Laparoscopic Excision of Myometrial Adenomyomas in Patients with Adenomyosis Uteri and Main Symptoms of Severe Dysmenorrhea and Hypermenorrhea

Mineto Morita, M.D., Yasuyuki Asakawa, M.D., Masahito Nakakuma, M.D., and Harumi Kubo, M.D.



Morita et al, J Am Assoc Gynecol Laparosc, 11: 86–89, 2004

"Classical" Technique

REPRODUCTIVE SURGERY

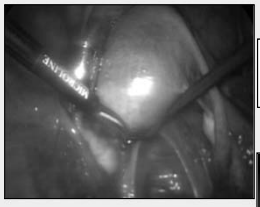
Laparoscopic excision of uterine adenomyomas

Grigoris F. Grimbizis, M.D., Ph.D.,[a,b] Themistoklis Mikos, M.D., M.Sc.,[a] Leonidas Zepiridis, M.D., Ph.D.,[a,b] Theodoros Theodoridis, M.D., Ph.D.,[a,b] Dimosthenis Miliaras, M.D., Ph.D.,[a] Basil C. Tarlatzis, M.D., Ph.D.,[a] and John N. Bontis, M.D., Ph.D.[a,b]

Laparoscopic adenomyomectomy has the same operative steps as myomectomy

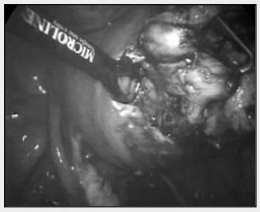
Differences
(i) not clearly defined surgical borders
(ii) excision into the neighboring healthy myometrium
(iii) grasping and traction very difficult
(iv) rich vascularization

Grimbizis et al, Fertil Steril, 89: 953-961, 2008

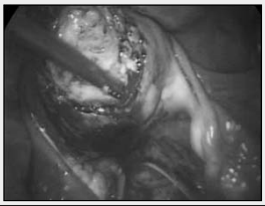


Adenomyoma
Careful inspection for recognition of the ill defined borders

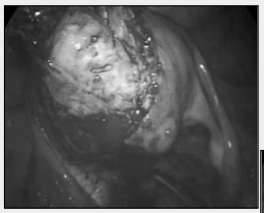
Longitudinal incision of the uterine serosa along the lesion



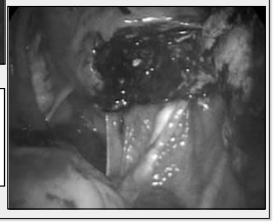
Dessection of the adenomyoma with the use of scissors / Attention to secure hemostasis



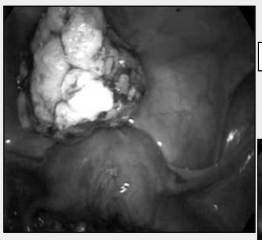
Difficulties in grasping and traction with tearing of the adenomyotic tissue



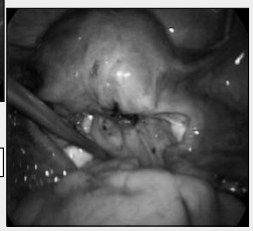
Dissection of the adenomyotic lesion with excision into the neighboring healthy myometrium



Uterine wall after the removal of the adenomyotic tissue: normal myometrium with rich vascularization



Adenomyotic tissue



Closure of the uterine wall

"Classical" Technique: Overlapping flaps

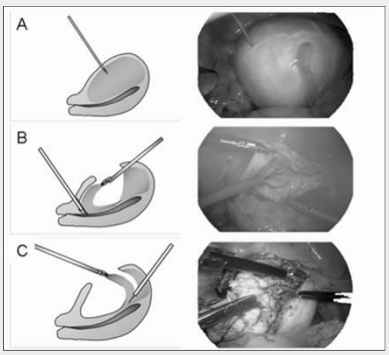
Laparoscopic adenomyomectomy and hysteroplasty: A novel method

Hiroyuki Takeuchi, MD, Mari Kitade, MD, Iwaho Kikuchi, MD, Hiroto Shimanuki, MD, Jun Kumakiri, MD, Takamitsu Kitano, MD, and Katsuyuki Kinoshita, MD

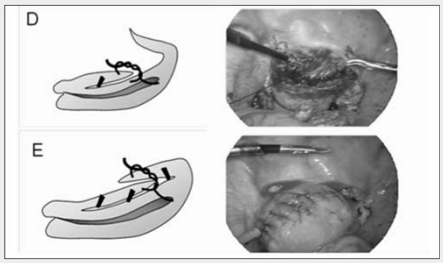
Operative steps

(i) Local injection by diluted vasopressin solution
(ii) Transverse incision in the adenomyotic tissue up to the endometrium
(iii) Surgical removal of the adenomyotic tissue with a monopolar needle
(iv) The normal muscle layer on the serosal membrane side was left as an upper and lower serosal flap
(v) Overlapping of the flaps were overlapped and sutured to counteract the lost muscle layer to reconstruct the uterus.

Takeuchi et al, J Min Invas Gynecol, 13: 150–154, 2006

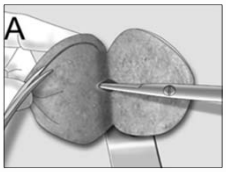


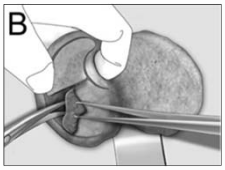
Takeuchi et al, J Min Invas Gynecol, 13: 150–154, 2006

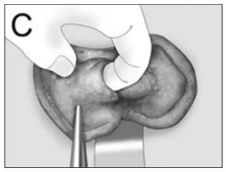


Takeuchi et al, J Min Invas Gynecol, 13: 150–154, 2006

Triple flap technique



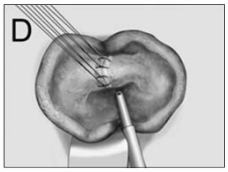


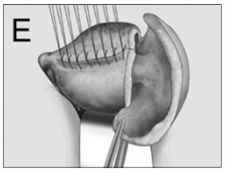


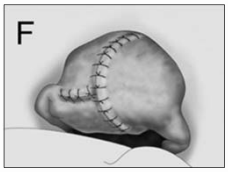
(A) Bisection of the uterus & Opening of the cavity
(B & C) Excision of adenomyotic tissue leaving myometrial flaps from the serosa and endometrium

Osada et al, RBM Online, 22: 94–99, 2011

Triple flap technique





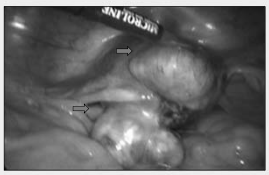


(D) Closure of the endometrium

(E & C) Closure of the uterine wall with the characteristic triple flap technique (overlapping of the two sutured flaps with the third one)

Osada et al, RBM Online, 22: 94–99, 2011

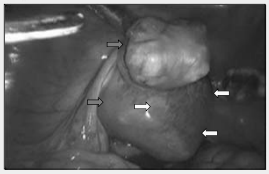
Partial adenomyomectomy & myomectomy

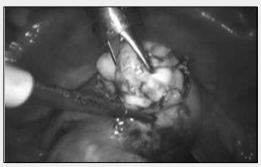


-Patient's age: 46 years
-Abnormal uterine bleeding / Severe anemia
-Myomas & adenomyoma
Wishing pregnancy with oocyte donation

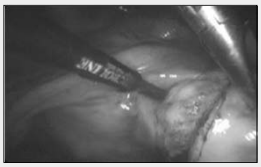
Myoma ➡

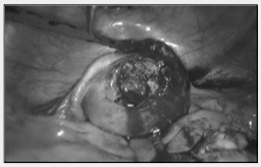
Adenomyoma ⇨

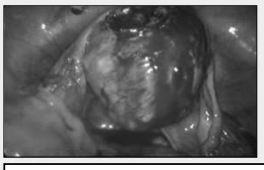


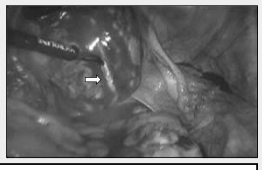


Laparoscopic myomectomy

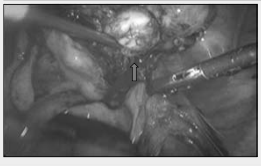


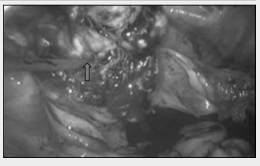


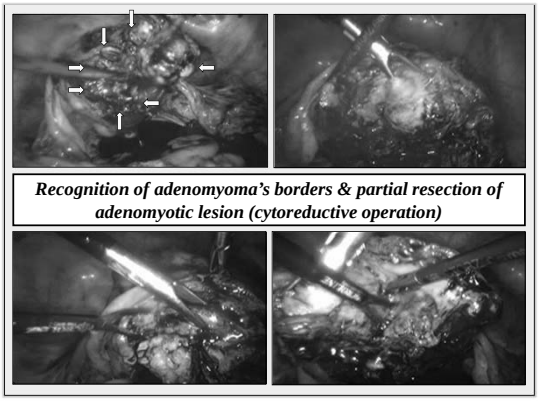




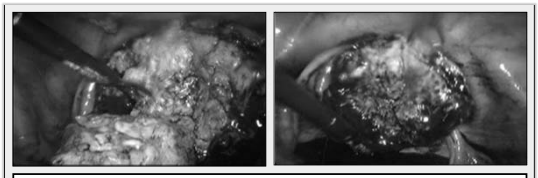
Incision of uterine wall and removal of intramural myoma of the posterior wall



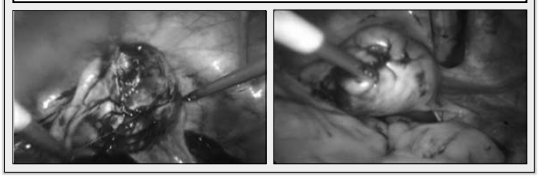




Recognition of adenomyoma's borders & partial resection of adenomyotic lesion (cytoreductive operation)



Partial adenomyomectomy ("cytoreductive" resection)
Suturing of the uterine wall



Adenomyomectomy under US trans-trocar control

Successful Total Laparoscopic Cystic Adenomyomectomy After Unsuccessful Open Surgery Using Transtrocar Ultrasonographic Guiding

Hiroshi Nabeshima, MD, PhD*, Takashi Murakami, MD, PhD, Mitsuo Nishimoto, MD, Noboru Sugawara, MD, and Naoko Sato, MD, PhD

(a) MRI: a cystic adenomyoma was present, (b) Small-diameter (10 mm) ultrasonographic (USG) probe used for laparoscopy. Uterine shape is roughly normal and cystic lesion is not identifiable, (c) USG view obtained intraoperatively showing location of cystic adenomyoma (yellow arrow)

Nabeshima et al, J Min Invas Gynecol 15: 227–230, 2008

Classification of uterus sparing techniques and their variants
Non-excisional techniques

Non-excisional techniques	***Combined with excisional***	***Uterine artery ligation together with adenomyomectomy*** *(Kang et al, 2009)*
	Non excisional only	***1. Uterine artery ligation*** *(Wang et al, 2002)* ***2. Electrocoagulation of myometrium*** *(Wood, 1998; Phillips, 1996)*
	Hysteroscopic	***1. Endometrial resection*** *(Wood, 1998; Fernandez et al, 2007; Kumar et al, 2007; Maia et al, 2007)* ***2. Endometrial ablation*** *(Preuthhupan et al, 2010)* ***3. Hysteroscopic cystectomy***
	Others	***1. High frequency ultrasound (HIFU)*** *(Yang et al, 2009),* ***2. Alcohol instillation*** *for cystic adenomyosis (Furman et al, 2007),* ***3. Endometrial non-hysteroscopic ablation*** ⊙ ***Radiofrequency*** *(Ryo et al, 2006)* ⊙ ***Microwave*** *(Kanaoka et al, 2004)* ⊙ ***Balloon*** *(Chan et al, 2001)*

Grimbizis et al, Fertil Steril, advance access online, 2013

…… electrocoagulation of the myometrium

Laparoscopic Bipolar Coagulation for the Conservative Treatment of Adenomyomata

Douglas R. Phillips, M.D., FACOG, Howard G. Nathanson, M.D., FACOG, Steven J. Milim, M.D., FACOG, and Joan S. Haselkorn, M.D., FACOG

Operative steps

(i) Use of a 32-cm-long myoma bipolar coagulation instrument with two distal, parallel, 5cm-long needles
(ii) Systematic perforation and slow coagulation of the adenomyomas at 5- to 10-mm intervals through the serosal surface to its base, forming parallel cylinders of desiccated and denatured tissue
(iii) The end point of the procedure was paling and blanching of the entire over-lying serosal surface.

Phillips et al, J Am Assoc Gynecol Laparosc, 4: 19–24, 1996

Laparoscopic Uterine Artery Ligation for Treatment of Symptomatic Adenomyosis

Chin-Jung Wang, M.D., Chih-Feng Yen, M.D., Chyi-Long Lee, M.D., and Yung-Kuei Soong, M.D.

Study population: 20 patients
Parameters: uterine volume, bleeding control, pain control

Overall satisfaction: 3/20
Hysterectomy: 3/20, Consider hysterectomy: 5/20,
Stationary: 9/20
Overall estimation: poor results

Wang et al, J Am Assoc Gynecol Laparosc, 9: 293–296, 2002

Uterus sparing operative treatment for adenomyosis. A systematic review

Grimbizis et al, Fertil Steril, advance access online, 2013

	Criteria for study evaluation		Grading
	Selection		
1.	Type of Study design	(a) Prospective	1
		(b) Retrospective	0
2.	No of patients	(a) >25	1
		(b) <25	0
3.	Is the definition of the extend of the adenomyosis adequate?	(a) MRI or US and Clinical	1
		(b) Clinical / Not reported	0
	Is the definition of the type of adenomyosis adequate?	(a) Yes	1
			0
4.	Representativeness of the cases		es of cases 1
			0
	Exposure		
5.	Ascertainment of surgical technique		1
		(b) Written self report of medical record only	0
		(c) No description	0
	Is there a detailed description of the surgical technique?	(a) Yes	1
		(b) No	0
	Outcome		
6.	Outcome evaluation	(a) Structured questionnaire	1
		(b) Self report / No description	0
7.	Was follow-up long enough for outcomes to occur?	(a) >24 months	1
		(b) <24 months	0
8.	Adequacy of follow-up of cohorts	(a) Complete follow-up / all subjects accounted for	1
		(b) Subjects lost to follow-up unlikely to introduce bias – small number lost	1
		(c) Inadequate follow-up rate	0
		(d) No statement	0
9.	Statistical analysis	(a) Existence of statistical analysis	1
		(b) Absence of statistical analysis	0
	Maximum Grading		9/9

High Quality: Score >5

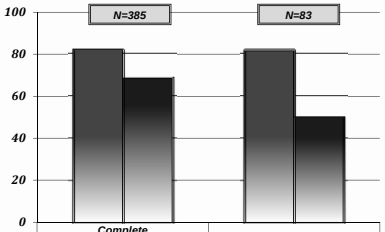
Uterus sparing operative treatment for adenomyosis. A systematic review

Grimbizis et al, Fertil Steril, advance access online, 2013

Author, year	Study Design	No of Patients	Modality of initial diagnosis / Definition of extent of the disease		Follow up/ Adequate length	Total Grade
Complete adenomyomectomy						
Dai et al, 2012	Pro	38	U/S	Focal adenomyosis (adenomyoma)	24/12	9
Osada et al, 2011	Pro	104	U/S, MRI	Diffuse/focal adenomyosis	24/12	9
Wang et al, 2009	Pro	165	U/S	Focal adenomyosis (adenomyoma)	24/12	9
Takeuchi et al, 2006	Pro	14	MRI	Focal adenomyosis (adenomyoma)	N/A	6
Al Jama et al, 2011	Retro	18	U/S, MRI	Focal adenomyosis (adenomyoma)	36/12	6
Koo et al, 2011	Retro	18	U/S	Focal adenomyosis (adenomyoma)	9/12	6
Sun et al, 2011	Retro	40	N/A	Focal adenomyosis (adenomyoma)	27/12	5
Grimbizis et al, 2008	Retro	6	U/S	Focal adenomyosis (adenomyoma)	13/12	5
Fedele et al, 1993	Retro	18	Histology	Focal adenomyosis (adenomyoma)	53/12	4
Partial excision of adenomyosis / Partial adenomyomectomy						
Sun et al, 2011	Retro	13	N/A	Focal adenomyosis (adenomyoma)	20/12	4
Nishida et al, 2010	Retro	44	MRI	Diffuse adenomyosis	12/12	6
Wang et al, 2009	Retro	28	U/S	Diffuse adenomyosis	36/12	8
Fujishita et al, 2004	Retro	11	U/S, MRI	Diffuse adenomyosis	36/12	6
Wood, 1998	Retro	25	N/A	Diffuse/focal adenomyosis	24/12	4
Cystic Adenomyomas and Juvenile Cystic Adenomyomas						
Takeuchi et al, 2010	Retro	9	U/S, MRI	JCA	35/12	8
Kriplani et al, 2011	Retro	4	U/S, MRI	JCA	18/12	5
Non excisional techniques						
Kang et al, 2009	Retro	37	U/S	Diffuse/focal adenomyosis	12/12	7
Wang et al, 2002	Pro	20	U/S, MRI	Unclear description of lesion	8/12	6
Wood, 1998	Retro	11	N/A	Diffuse/focal adenomyosis	24/12	3
Philips et al, 1996	Pro	10	MRI	Unclear description of lesion	25/12	4
Preutthupan et al, 2010	Retro	190	U/S	Diffuse/focal adenomyosis	60/12	7
Maia et al, 2003	Retro	95	U/S	Unclear description of lesion	12/12	5
Wood, 1998	Retro	18	N/A	Diffuse/focal adenomyosis	24/12	3

Adenomyomectomy: post-operative results

Reduction of pain and bleeding

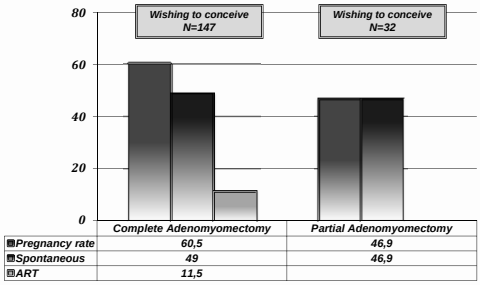


	Complete Adenomyomectomy	Partial Adenomyomectomy
Reduction of Pain	82	81,8
Reduction of Bleeding	68,8	50

Grimbizis et al, Fertil Steril, advance access online, 2013

Adenomyomectomy: post-operative results

Pregnancy rates: spontaneous and/or ART



	Complete Adenomyomectomy	Partial Adenomyomectomy
Pregnancy rate	60,5	46,9
Spontaneous	49	46,9
ART	11,5	

Grimbizis et al, Fertil Steril, advance access online, 2013

Is the surgical approach beneficial to subfertile women with symptomatic extensive adenomyosis?

Peng-Hui Wang, Jong-Ling Fuh, Hsiang-Tai Chao, Wei-Min Liu, Ming-Huei Cheng and Kuan-Chong Chao

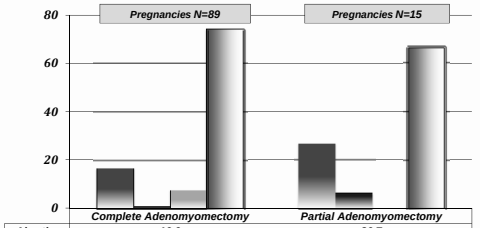
Patients	Pregnancy rates Delivery rates
Group A (n=28) Conservative surgery ± GnRH a	13/28 – 46,4% 9/28 – 32,1%
Group B (n=37) GnRH a only (6 months)	4/37 – 10,8% 3/37 – 8,1%

P<0,05

Wang et al, J Obstet Gynaecol Res, 35: 495–502, 2009

Adenomyomectomy: post-operative results

Pregnancy outcome



	Complete Adenomyomectomy	Partial Adenomyomectomy
Abortions	16,9	26,7
Ongoing	1,1	6,6
Preterm	7,9	
Term	74,1	66,7

Grimbizis et al, Fertil Steril, advance access online, 2013

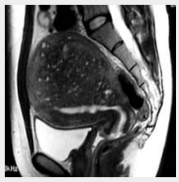
Adenomyosis

- Definitions and variants
- Diagnosis and mapping
- Symptoms and aims of treatment
- Uterus sparing surgical treatment
- **Safety options**

…… safety aspects

Spontaneous uterine rupture of a twin pregnancy after a laparoscopic adenomyomectomy: A case report

Shin-ichiro Wada, MD, Masataka Kudo, MD, and Hisanori Minakami, MD

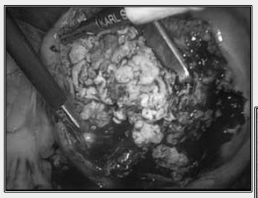


Spontaneous rupture at 30th week of gestation

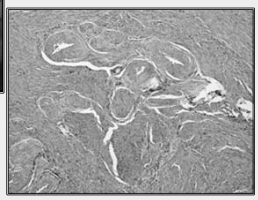
Laparoscopically assisted vaginal excision
Incision of the vaginal posterior wall after laparoscopic removal of the uterosacral ligaments and seperation of the vagina from the rectum / Uterus extraction and turning over to a vaginal approach

Wada et al, J Am Assoc Gynecol Laparosc, 13: 166–168, 2006

…… safety aspects

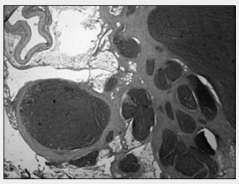


Important: histology of the lesion!!!



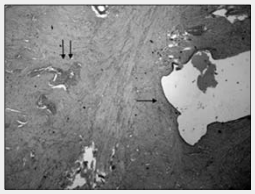
Angioleiomyoma resembling adenomyosis

…… *safety aspects*



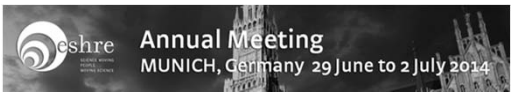
Endometrial stromal sarcoma resembling adenomyosis

Important: histology of the lesion!!!



Conclusions

- ***Adenomyosis represents a clinical challenge due to its various histological forms and to the fact that it infiltrates myometrium***
- ***MRI is an extremely useful tool with high diagnostic accuracy and excellent correlation of MRI findings with histology***
- ***Uterus sparing surgical treatment is feasible and it is associated with a significant reduction of symptoms and an improved reproductive outcome***



Giant ovarian and other pelvic tumors and fertility sparing surgery Laparoscopy versus Laparotomy

Pre Congress Course -Reproductive Surgery

Vasilios Tanos MD, PhD
Prof. Obstetrics & Gynaecology

St George's University of London
UNIVERSITY OF NICOSIA Medical School

Ovarian masses

- corpus luteum cysts
- functional / simple cysts and complex masses
- endometriomas and implants
- dermoid cysts
- Ovarian tumors LMP and EOC
- Pelvic masses due to PID / Abscess
- Adhesion conglomerates

Functional ovarian cysts and Oral Contraceptives treatment

- common gynecological problem of reproductive age worldwide
- when large, persistent, or painful, may require operations
- treatment with oc common practice since 70s

- 7 RCTs from 4 countries - 500 women.
- with cysts that occurred spontaneously and /or after ovulation induction
- Results: most cysts resolved without treatment within a few cycles
- persistent cysts tended to be endometrioma or para-ovarian cyst

- Conclusion: Combined oc has no benefit in ovarian cyst resolution

Cochrane Database of Systematic Reviews 2006
DA Grimes et al. 2009

Benign ovarian cysts in US

Prospective Observational longitudinal study

- 323 women, 19-50 y old, with ovarian cysts
- 120 study group, 6-12 months follow up

- Endometriomas 3.3cm (SD 1.5)
- Simple cyst 4.1cm (SD 1.6)
- Dermoid cyst 3.2cm (SD 1.4)
- Haemorrhagic cyst 3.5cm (SD1.2)
- Follow up median 42 months (18 -94 months)
- 8.3% disappear during follow up
- Non developed to ovarian Ca

- Conclusion: Conservative management is recommended for Bg ovarian cysts / masses until final possible diagnosis

J L Alcazar et al. 2005 Hum Reprod

Ovarian reserve is damaged after excision of ovarian masses

- gonadal damage is at least partly caused by the presence of an ovarian mass per se preceding surgery
- laparoscopic / laparotomy by
- stripping or excision or
- electrosurgical coagulation /bipolar /monopolar causes

- local inflammation
- vascular compromise following
- lack of local fibrinolytic response and
- creation of adhesions and
- destruction of microvascularization

Reduced ovarian reserves after Surgery

- 20 w Bg ovarian cysts – lappic cystectomy
- AMH & ovarian volume by US
- AMH level recovered to 65% of the preop level 3 months pop
- AMH level was higher 1 week pop in endometriosis as compared to non endometriotic cysts

H J Chang et al 2010 - Fertil Steril

Ovarian cyst in Adolescence

- Incidence ovarian cysts 2-5 / 100,000 girls / year
- Major symptom is abdominal pain
- 0.2% of all pediatric surgery
- Tumor Markers – Ca 125, alfa-fetoprotein, beta hCG,
- TAU - all, TVU - 40%, CTS - 21%, MRI – 20%
- Malignant - 1% of all cancers in children and adolescents Benign functional cysts 30% and cystic teratomas 26%
- Fertility sparing surgery – preserve ovarian hilus and avoid destruction of mesosalpings, ie microvascularization

Cass DL et al J Paediat Surg 2001
Templeman C et al Obst Gynecol 2000,
Bristow RE J Adolesc Health 2006

Ovarian cysts pathological findings and incidence

Pathology	%	Pathology	%
I. Benign	46	**II. Neoplastic Benign**	
Follicular cysts	83	Mature cystic teratoma	
Corpus Luteum cyst		Serous Cystadenoma	
Paraovarian cysts		Mucinus Cystadenoma	
Endometriosis		Fibroma	
Salpingo- oophoritis		Serous Cystadenofibroma	
		III. Malignant	1
		Yolk Sac Tumor	
		Sex Cord stromal Tumors	

Giant Ovarian cysts and pelvic tumors Any relations to the large size ??

- Related to pathological classification
- Time of existence
- Age
- Any other factors
- Inherited
- Relation to infertility
- Management options

Persistent Corpus Luteum Cysts

- Clinical manifestations
- Discomfort and pain due to compression
- Ovarian / adnexal Torsion
- Ruptured CL cyst

Laparoscopic cystectomy

Ovarian cyst in torsion during adolescence carries high risk for a torsion to the contralateral side

Detorsion and Expectant management
Avoid oophorectomy or salpingoophorectomy

Giant ovarian cysts can be treated laparoscopicaly
Aspiration of the cysts can be performed under US guidance to reduce the size and then to perform laparoscopy

Germ cell tumours

- Derived from primitive germ cells of embryonic gonad
- Account for 2-10% of all ovarian tumours
- Most common in young women < 35
- Often curable with high survival rates
- Usually present as a rapidly enlarging abdominal mass, which causes considerable pain.
- They often rupture or undergo torsion.
- Dysgerminoma is the most common type and has an excellent prognosis for Stage I tumours.
- Types of germ cell tumours are:
  - Dysgerminoma, Endodermal sinus tumours, Teratoma.
  - Embryonal carcinoma, Choriocarcinoma, Sarcomas

Sex cord-stromal tumors

Derive from connective tissue cells
Less than 5% of all ovarian tumours

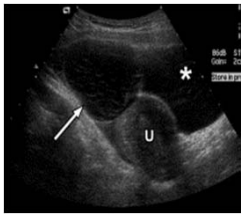
- Fibroma.
- Fibrosarcoma.
- Sertoli-Leydig tumours.
- Granulosa cell tumours.

Dermoid cysts
Patients' Age & US findings

- dermoid cysts registered in 20 tertiary and secondary hospitals
  multicentric review 2000 and 2005 RS 306 cases
- Results: - patients' mean age 32 and median age 30
- Average size 7cm (2-30cm)
- Mostly Cystic (solid in 1/3)
- Bilateral 8.5%

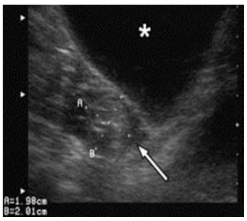
M Arab et al J Gyn Surgery 2010

24y with abdominal pain
Abd US longitudinal pelvic US
bladder (asterisk)
uterus (U)
multiseptated, cystic mass (arrow)
Dg: hemorrhagic ovarian cyst
US follow-up showed
complete resolution



17y, Lt ovarian dermoid of 2cm
heterogenous, echogenic mass
(cursors and arrow)
Stable for 1 year and later growth

A hemorrhagic cyst would have
been resolved after this period of
time



Dermoid spill facts

- Spillage in laparoscopy 15-100% and Spillage in laparotomy 4-13%

- 26 laparoscopic dermoid cysts excision 1999 - 2005
- 31 cysts with mean diameter 7.5cm,
- 28 dermoid cysts – treated with conservative cystectomy
- Encountered 14 spillages. The chemical peritonitis risk was (1/14) 0.2%

- Review of 14 studies
- 470 laparoscopic dermoid cystectomies and Spillage in 310 cases (66%)
  The incidence of chemical peritonitis was 0.2%
- Only 1 case, 9 months post op developed granulomatous peritonitis

- NS differences in complications noted between the spillage and non spillage groups.

O Shawki et al 2007

Mg transformation in ovarian dermoid cyst

- 10 centers in Australia, Canada, Germany, and Austria.
- 33 patients mean age 49, followed between 1979 – 2007
- frequency of Mg transformation was 1% to 2%

Results:
15 pts at S I and most of S II and S III were optimally debulked.
Platinum-based regimens most commonly used
Chemotherapy after surgery was not effective

- 4 S I had fertility-sparing surgery (FSS) with good outcomes
- 2 pts had a sustained remission after second surgery for relapsed disease
- S I pts had a good outcome 2 alive and well at 12 months of follow-up

Conclusions:
FSS may be an option in Stage I young patients willing to have a child
Patients with advanced disease do poorly, regardless of treatment

M Gainford et al. International Journal of Gynaecological Cancer 2010

Pregnancy outcome with dermoid and other benign ovarian cysts (1)

- 93 occurred in patients with benign ovarian cysts
- benign cystadenoma 41.9%, adenofibroma 1.8%, dermoid cyst 36.7%

- 12.9% were diagnosed during pregnancy by US
- 10.8% were diagnosed before pregnancy

- The mean diameter at diagnosis was
  9.05 ± 7.6 cm for cystadenoma
  6.09 ± 3.0 cm for dermoid cyst
  4.55 ± 4.1 cm for adenofibroma.

L Katz et al Archives of Gynecology, 2010

Pregnancy outcome with dermoid and other benign ovarian cysts (2)

Results:

- Only 3 cases of ovarian torsion were noted (3.2%), and 15 cases hospitalized due to abdominal pain (16.2%).
- Pregnancy and perinatal outcome with dermoid and other Bg ovarian cysts is favorable.
- The cysts should be managed conservatively with routine US follow up during the pregnancy since complications are extremely rare

L Katz et al Archives of Gynecology, 2010

Classification of Mg Ovarian Germ Cell Tumors

I. Primitive germ cell tumors

A. Dysgerminoma,
B. B. Yolk sac tu
C. Embryonal carcinoma
D. Polyembryoma
E. Nongestational choriocarcinoma
F. Mixed germ cell tumor, specify components

II. Biphasic or triphasic teratoma

A. Immature teratoma
B. Mature teratoma
1. Solid
2. Cystic, dermoid cyst
3. Fetiform teratoma, homunculus

III. Monodermal teratoma and somatic-type tumors associated with biphasic or triphasic teratoma

A. Thyroid tumor group
B. Carcinoid group
C. Neuroectodermal tumor group
D. Carcinoma group
E. Melanocytic group
F. Sarcoma group
G. Sebaceous tumor group
H. Pituitary-type tumor group
I. Retinal anlage tumor group
Others

Borderline tumours (tumors of low malignant potential)

10-15% of ovarian tumours

managed primarily by surgery and do not respond well to chemotherapy

- Borderline serous - the most common.
- Borderline mucinous.
- Borderline endometrioid

ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (2013)

Epithelial ovarian tumours

- Arise from the ovarian epithelium
- Most common type, 85-90% of all ovarian cancers
- Most commonly in women >50
- Serous - most common subtype, > 50% of epithelial Tu
- Occur in women between 40-60 years of age

- Clear cell tumours, 5-6% of epithelial tumours
- Affect ages 40-80, often associated with endometriosis

- Mucinous tumours, 10% of epithelial tumours
- Most commonly affect ages 30-50

Metastatic tumours

Ovarian secondary tumours may arise from

- Breast
- GIT
- haemopoietic system
- uterus
- cervix

OC - Epidemiology

- Ovarian cancer is 5th most common Ca in women
- lifetime risk of around 2% for women in EU
- it is the leading cause of death from gyn cancer

  NICE Clinical Guideline, April 2011
- Incidence rate 17.1 per 100,000 women

  (NCIN)/Trent Cancer Registry report, Nov 2012
- 61% mortality rate (OC Statistics) Cancer Research UK

Risk factors (1)

- Increasing age,
- lifestyle (21%) Parkin DM et al. Br J Cancer. 2011
- Smoking (2%) Parkin DM BJC 6;105 Suppl 2 2011
- Lack of exercise
- Obesity during menopause
- Infertility and fertility drugs (cc)
- Nulliparity
- Early menarche
- Late menopause

Risk factors (2)

- FBOC Syndrome 3-4 times risk of developing OC
- only 10% of cases arise in women with a positive family history (Gavther SA, Pharoah PD Curr Opin Genet Dev. 2010)
- BRCA1 and 2 genes mutations (Melin A, Sparen P, Bergqvist A. Hum Reprod. 2007)
- Endometriosis and link - ov endometriosis and clear-cell oc - mutation of the ARID1A gene (Wiegand KC et al NEJM 2010)

Symptoms of Ovarian Tumors

- women of 50 with recent IBS history (rarely 1st time at this age)
- unexplained fatigue, weight loss or change in bowel habit
- abdominal distension (often described as 'bloating')
- early feeling of fullness whilst eating (satiety) and/or loss of appetite
- pelvic or abdominal pain
- Urinary frequency or urgency

Clinical evaluation and Lab workup

- **Clin Exam:** ascites and/or a pelvic/abdo mass
- **Laboratory:** Raised Ca 125, CEA, LFTs
- **Imaging:** TVU, Abd US, CTS, MRI

- **Treatment:**
  - Neoadjuvant therapy
  - Surgery
  - Chemotherapy

Ovarian cancer types most appropriate for fertility sparing surgery

- Borderline ovarian tumors
- Invasive Epithelial OC (Stage 1A)
- Malignant Ovarian Germ Cell Tumors
- Ovarian Sex Cord-Stromal Tumors

  Granulosa -Cell Tumors and

  Sertoli - Leydig Cell Tumors

FSS for epithelial ovarian cancer Safety and Reproductive outcomes (1)

- EOC young patients frequently want to preserve their fertility
- 62 patients underwent FSS,
- (preservation of ovarian tissue in one or both adnexa and the uterus)
- 1990 – 2006, retrospective review
- 36 - S IA, 2 –S IB, 21 S - IC, and 1 - S IIB, 1- S IIIA, 1 - S IIIC;
- 48 - G I, 5 - G II, and 9 - G III
- 48 - platinum-based chemo (mean 4.6 cycles, range 1–9 cycles)

JY Park, et al. 2008

FSS for epithelial ovarian cancer Safety and Reproductive outcomes (2)

Results:

- median follow-up of 56 months (range, 6–205 months),
- 11 –with tumor recurrence, 6 died of disease, 2 were alive with disease
- 54 alive without disease
- Patients with stage > IC ($p = 0.0014$) or grade III ($p = 0.0002$) tumors had significantly poorer survival.
- 19 attempted to conceive, 22 - term pregnancies, with no congenital anomalies in any of the offspring.

Conclusion:

Fertility-sparing surgery in young patients with EOCs at Stage IA–C and G I–II who desire to preserve their fertility seems to be acceptable

JY Park, et al. 2008

Conclusion

The size of pelvic cysts should not be an obstacle to laparoscopic surgery

Oophorectomy should be avoided in young women without completed family planning

FSS for certain types of ovarian malignancies , at early stage and low grade, is possible once an extensive and detailed workup of the disease has been performed

Huge & Multiple Fibroids

Preservation of the uterus and endometrium in cases with huge and multiple intramural and /or submucous fibroids

Professor T C Li
Professor of Reproductive medicine & Surgery
Sheffield, England

29 June 2013

Outline

- Avoiding loss of uterus
- Protecting endometrial function

Huge fibroids

Surgical challenges

- Laparotomy often required
- Often increased vascularity, blood loss could be rapid
- Uterus often grossly distorted, risk of cavity being occluded after reconstruction
- Increase risk of hysterectomy

COMPLICATIONS OF MYOMECTOMY

1-2% risk of hysterectomy due to uncontrolled bleeding

Outline

- Avoiding loss of uterus
  1. peri-operative loss
  2. delayed loss
- Protecting endometrial function

Managing Blood loss

A. Pre-operative

- X-match
- Competent assistant
- Experienced anaesthetist
- GnRH or progesterone receptor blockade
- Consent re increased risks
- Preparation - Cell saver, Foley catheter for tourniquet

Managing Blood loss

B. Immediate Pre-operative

- Team brief
- Vasopressin
- Tourniquet
- Cell saver

Team Brief

Cell Saver

Managing Blood loss

C. Intra-operative

- Vasopression
- One incision at a time
- Slick but effective haemostatic sutures
- Drain?

Vasopressin Injection

CASE HISTORY

- Two cases of cardiac arrest immediately following vasopressin injection prior to myomectomy in Sheffield over a 20 year period

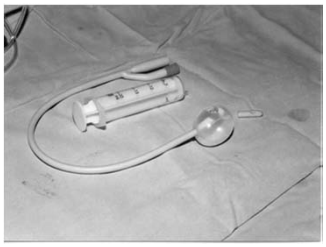
USE OF VASOPRESSIN safety guidelines

- Correct dose - 6 units (minimum effective dose)
- Correct dilution – 20 units in 20 ml normal saline
- Correct location – midline, not close to cornua or broad ligament (vessel there)
- Correct technique – before injection, apply suction to ensure tip of needle not in a vessel
- Correct protocol – ensure anaesthetist is alert (wake up the anaesthetist)

Bleeding after Hysterocopic resection of submucus fibroid

Bleeding after Hysterocopic resection of submucus fibroid

Foley tamponade



Does it work?

Yu D, Xia E, Li TC, Huang X, Zheng J (2006)

A prospective randomised controlled trial on the effectiveness of routine Foley Balloon Tamponade on the reduction of bleeding after hysteroscopic resection of myoma.

Gynae Surgery 3: 93-96

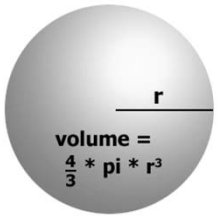
Volume of balloon?

Volume of balloon?

The same volume as the fibroid

Volume of balloon?

- The same volume as the fibroid



Volume of balloon?

- The same volume as the fibroid

diameter	volume
2cm	4.2ml
3cm	14ml
4cm	34ml
5cm	65ml

How long for?

6 hours or so

Managing Blood loss

D. Post-operative

- Close monitoring
- Quick response to any sign of bleed

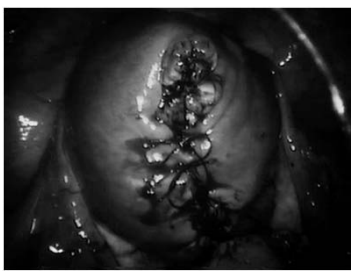
CASE HISTORY

- 28 year old women underwent myomectomy
- Operation performed by trainee supervised by a consultant
- 3 hours post-op urine output low
- 5 hour post-op drop in BP, given colloid
- 7 hour post-op haemoglobin 3.7
- Immediate laparotomy, haematoma in uterus, hysterectomy

Outline

- Avoiding loss of uterus
  1. peri-operative loss
  2. delayed loss
- Protecting endometrial function

Laparoscopic Myomectomy



Scar rupture leading to delayed loss of uterus

Risk factors for uterine rupture after laparoscopic myomectomy

Parker et al, 2010
Journal Minim Invasive Gynecol 17:551

1. Excessive use of electro-cautery
2. Poor suturing technique (16/19 cases had single layered suture)

Report of 7 uterine rupture cases after laparoscopic myomectomy: update of the literature

Pistofidis et al 2012

J Minim Invasive Gynecol 19:762

1. Excessive use of electro-cautery (6/7 cases)
2. Poor suturing technique (6/7 cases had single layered suture)

Delayed Mortality
Rupture Gravid Uterus

How to prevent?

1. Use minimal amount of diathermy
2. Proper suturing, in layers

Delayed Mortality
Rupture Gravid Uterus

How to prevent?

1. Use minimal amount of diathermy
2. Proper suturing, in layers
3. Avoid full thickness cut

Avoid full thickness cut
in the management of intramural fibroid

Avoid full thickness cut
in the management of intramural fibroid

Avoid full thickness cut
in the management of intramural fibroid

Outline

- Avoiding loss of uterus
  1. peri-operative loss
  2. delayed loss
- Protecting endometrial function

Preserving the endometrium

- Avoid intra-cavity adhesions
- Incise, not excise endometrium
- Prophylaxis against infection

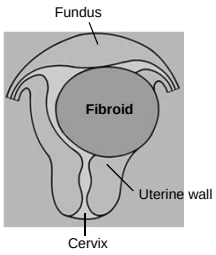
CASE HISTORY

- 32 year women
- Became amenorrhoea after myomectomy
- FSH normal, oestradiol normal
- Progestogen challenge test negative

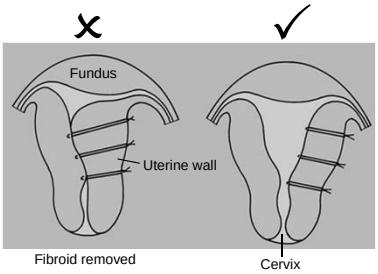
CASE HISTORY

- 32 year women
- Became amenorrhoea after myomectomy
- FSH normal, oestradiol normal
- Progestogen challenge test negative
- HSG ‘not possible’ because there was no uterine cavity

Fibroids



Fibroids



Anatomical Reconstruction

Intra-operative

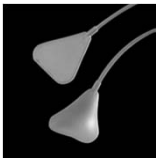
- Foley in uterine cavity
- Check carefully if cavity entered
- First layer – interrupted sutures

Risk of intra-uterine adhesion

Higher in multiple submucosal fibroid

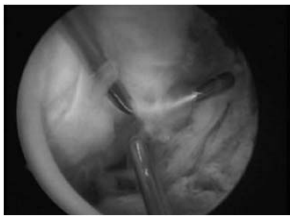
Removal of multiple submucosal fibroids

- High risk of intra-cavity adhesions formation
- Consider removing fibroids in stages
- Intra-uterine balloon



Does cold loop hysteroscopic myomectomy reduce intrauterine adhesions? A retrospective study

Ivan et al 2013
Fertility & Sterility



Does the shaver help to preserve the endometrium?

Resection of Submucus fibroid

Incision of the endometrium

Pre-op treatment to shrink fibroid

UAE impairs wound healing and increases risk of intra-cavity adhesion

Pre-op treatment to shrink fibroid

GnRH or P receptor blockade better

Pre-op treatment to shrink fibroid

GnRH or P receptor blockade better

Cervical dilatation more difficulty

Pre-op treatment to shrink fibroid

GnRH or P receptor blockade better

Cervical dilatation more difficulty

Cervical priming to reduce trauma to cervix during dilatation (Yu et al 2006)

cervical pretreatment

– Misoprostol – 1000 microgram 12 hours pre-op
– laminara

52

THANK YOU

Early, low grade endometrial cancer and fertility sparing surgery

K. Nouri

Medical school of Vienna
Department for gynecological Endocrinology and reproductive medicine

MEDIZINISCHE UNIVERSITÄT WIEN

Die menschliche Größe

I certify that there is **no conflict of interest** with any financial organization regarding the material discussed in presentation.

Learning objectives

1- To review the basic about the endometrial cancer and its epidemiology with focus on the young age patients

2- To discuss the feasibility and efficacy of conservative therapy options of endometrial cancer in women who desire fertility preservation.

3- To analyze the different ART options in Endometrium cancer patients after conservative therapy.

Epidemiology

Endometrial cancer is the most common gynecologic malignancy in the United States, with over 40,000 cases diagnosed each year, typically in the postmenopausal women.

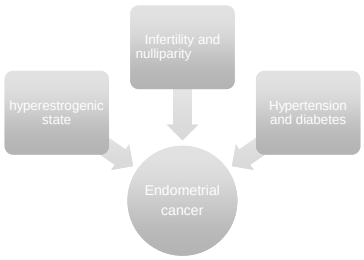
25% of cases affect premenopausal women.

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

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

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

Risk factors !



Tran BN, Connell PP, Waggoner S, et al. Characteristics and outcome of endometrial carcinoma patients age 45 years and younger. Am J Clin Oncol 2000; 23:476–480.

hyperestrogenic state

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

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

hyperestrogenic state

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

Endometrial sampling !!

Duska LR, Garrett A, Rueda BR. Endometrial cancer in women 40 years old or younger. Gynecol Oncol 2001; 83:388–393 .

Key Symptoms

1. Abnormal bleeding !
2. Prolonged anovulation

Duska LR, Garrett A, Rueda BR. Endometrial cancer in women 40 years old or younger. Gynecol Oncol 2001; 83:388–393 .

other malignancy

Ovarian malignancy
Young women with endometrial cancer are at significant risk for concomitant adnexal disease:
1- Synchronous primary ovarian tumors (10-29,4 %)
2- Endometrial metastases to the ovary (5%)

Lynch/HNPCC

Gitsch G, Hanzal E, Jensen D, et al. Endometrial cancer in premenopausal women 45 years and younger. Obstet Gynecol 1995; 85:504–508.
Walsh C, Holschneider C, Hoang Y. Coexisting ovarian malignancy in young women with endometrial cancer. Obstet Gynecol 2005; 106:693–699
Morice P, Fourchotte V, Sideris L. A need for laparoscopic evaluation of1 patients with endometrial carcinoma selected for conservative treatment. Gynecol Oncol 2005; 98:245–248

Good prognosis

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

Fertility Preservation !

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

Staging FIGO 2010

Carcinoma of the Endometrium

IA	Tumor confined to the uterus, no or < ½ myometrial invasion
IB	Tumor confined to the uterus, > ½ myometrial invasion
II	Cervical stromal invasion, but not beyond uterus
IIIA	Tumor invades serosa or adnexa
IIIB	Vaginal and/or parametrial involvement
IIIC1	Pelvic node involvement
IIIC2	Para-aortic involvement
IVA	Tumor invasion bladder and/or bowel mucosa
IVB	Distant metastases including abdominal metastases and/or inguinal lymph nodes

Grade

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

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

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

Staging of endometrial carcinoma

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

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

Hysteroscopy with D&C

1-Hysteroscopy with directed biopsies and D&C
2-Following the lesion during the course of therapy

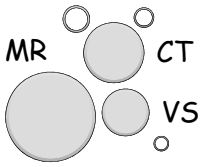
Huang SY, Jung SM, Ng KK, et al. Ovarian metastasis in a nulliparous3 woman with endometrial adenocarcinoma failing conservative hormonal treatment. Gynecol Oncol 2005; 97:652–655 .

Hysteroscopy with D&C

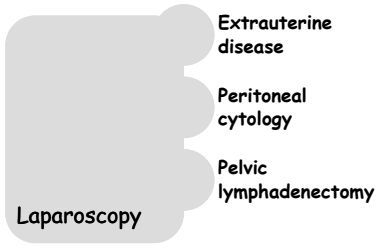
Fluid based hysteroscopy could cause retrograde seeding of the peritoneal cavity with malignant cells, the prognostic significance of positive peritoneal cytology in clinical stage I endometrial adenocarcinoma remains controversial

Bradley WH, Boente MP, Brooker D. Hysteroscopy and cytology in endo- metrial cancer. Obstet Gynecol 2004; 104:1030–1033.
Egarter C, Kreistan C, Kurz C. Abdominal dissemination of malignant cells with hysteroscopy. Gynecol Oncol 1996; 63:143–144.
Revel A, Tsafrir A, Amsby SO, Shushan A. Does hysteroscopy produce intra- peritoneal spread of endometrial cancer cells? Obstet Gynecol Surv 2004; 59:280–284.

Imaging ?



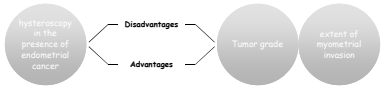
The Role of Laparoscopy



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

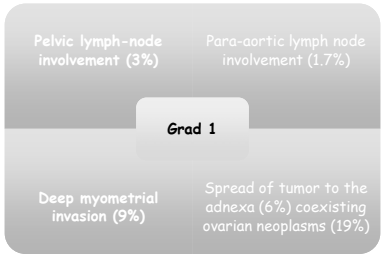
Morice P, Fourchotte V, Sideris L. A need for laparoscopic evaluation of patients with endometrial carcinoma selected for conservative treatment. Gynecol Oncol 2005; 96:245–248.

Hysteroscopy and direct resection



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

Grade 1 Endometrial carcinoma

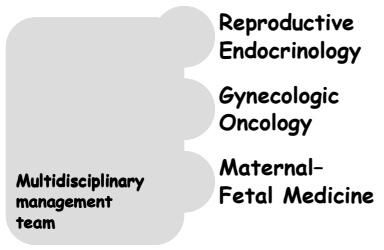


Risk of Disease Progression

The risk of disease progression during conservative management of grade 1 endometrial carcinoma : 6%

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

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



Conclusiones

1- Detailed informed consent

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

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

Thank you for your attention !

Azienda Ospedaliera Bolognini Seriate

Early cervical cancer : neoadjuvant chemotherapy and fertility-sparing radical trachelectomy.
Pregnancy risks and perinatal outcome.

Andrea Maneo, MD, Ph.D

Gynecologic Oncology Unit
Azienda Ospedaliera Bolognini
Seriate (Italy)

No commercial relationships or conflicts of interest are present

eshre European Society of Human Reproduction and Embryology

Azienda Ospedaliera Bolognini Seriate

Learning objectives

- main fertility-sparing strategies in cervical cancer
- oncologic and obstetrics outcomes of each policy
- current trends towards conservative therapies with less morbidity

No commercial relationships or conflicts of interest are present

eshre European Society of Human Reproduction and Embryology

Radical trachelectomy Selection criteria

- Fertility - preservation desire
- No apparent reason of sterility
- Stage IA2 - IB1
- T size < 2 cm.
- Limited endocervical extension (colposcopy)
- Negative nodes

Roy and Plante 1998; Dargent 2000

Azienda Ospedaliera Bolognini Seriate

Radical trachelectomy

Oncologic results

Author		pts.	no residual mean tumor	FUP	relapses
Steed	2003	93	0	30	7
Mathevet	2003	95	0	76	4
Plante	2004	72	60 %	60	3
Ungar	2005	30	NA	32	0
Hertel	2006	100	NA	29	3
Shepherd	2006	112	63 %	45	3

Radical trachelectomy

Obstetric results

Author		pts. desiring offspring	% pregnant (pregnancies)	miscarriages 1° trim	miscarriages 2° trim	births ≤ 32 w.
Steed	2003	42 %	46 % ( )	2	2	NA
Mathevet	2003	44 %	81 % (56)	14	8	5
Plante	2004	47 %	43 % (50)	8	2	3
Ungar	2005	17 %	60 % (3)	1	0	0
Hertel	2006	NA	18 % (18)	1	NA	NA
Shepherd	2006	63 %	41 % (55)	14	7	8

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Radical trachelectomy

Patients' selection

Author		pts.	% IB1	% N+	% adenoca.
Steed	2003	93	34 %	1 %	52 %
Mathevet	2003	108	74 %	3 %	20 %
Plante	2004	82	63 %	5 %	42 %
Ungar	2005	33	70 %	6 %	13 %
Hertel	2006	108	64 %	4 %	31 %
Shepherd	2006	123	98 %	6 %	29 %

Vaginal radical trachelectomy
Oncologic results

Author		pts.	fertility	relapses
		no preservation		
Lanowska	2011	225	6 %	3.8 %
Shepherd	2012	208	11 %	3.8 %
Covens	2013	180	9 %	2.7 %
Plante	2011	140	11 %	4.8 %
Marchiolè	2007	135	13 %	5.7 %
Kim	2012	51	18 %	3.9 %
Total		924	10 %	4.4 %

Vaginal radical trachelectomy
Obstetrical outcome

Author		1 trimester pts.	2 trim. miscarriage	3 trim. delivery	delivery
Shepherd	2012	125	22 %	14 %	45 %
Plante	2011	106	20 %	3 %	75 %
Covens	2013	86	16 %	8 %	66%
Speiser	2011	60	8 %	5 %	60%
Mathevet	2003	56	16 %	14 %	85 %
Kim	2012	19	5 %	0 %	60 %
Total		452	17 %	8.6 %	64 %

Radical trachelectomy
Different approaches

Plante Int J Gynecol Cancer 2013

Author		pts.	Recurrence	Pregnancies	
VRT	2003-13	924	4.4 %	452	49%
ART	2008-12	337	3.7 %	44	13%
LPS	2003-12	120	7 %	8	7 %
Robotic	2008-12	36	0	5	14%

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Vaginal radical trachelectomy Obstetric results

Boss et al. Gynecol. Oncol. 2005

16 studies 1998-2005 355 patients

- **43% attempted to conceive**
- **70% became pregnant (161 pregnancies)**
- **30% showed infertility**
- **21% losses 1st trimester, 8% 2nd trimester**
- **29% preterm deliveries (≤ 36 weeks)**

Obstetrical outcome after conisation for early cervical lesions

Kyrgiou et al. Lancet 2006

Method	pts.	RR
LLETZ		
Premature labor	3141	1,70
Caesarean section	2463	0,88
pPROM	1943	2,69
LASER conisation		
Premature labor	1488	1,71
Caesarean section	908	1,16
pPROM	729	2,18
Cold-knife conisation		
Premature labor	28378	2,59
Caesarean section	1020	3,17
pPROM	-	-

Expanding RVT/ART with tumor > 2 cm

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29 patients

Adenocarcinoma 41 %
RVT 20% ART 80%

Positive margins 24 %
Positive nodes 45 %

Fertility preservation: 31 %
One recurrence

Wethington et al Int J Gynecol Cancer 2012

Expanding RVT/ART with tumor > 2 cm

	Papers	range	pts	>2 cm	recurrences
RVT	11	2003-08	766	67	16 (24%)
ART	9	2005-11	221	40	5 (12%)

Ribeiro Cubal et al IJSO 2012

Parametrial involvement by tumor diameter (stage IB1)

Primary radical surgery 1982 - 2010 at S. Gerardo Hospital - Monza

Tumor size (cm)	pts.	Parametrial involvement	RR	Node involvement	RR
≤ 1	190	9 (5 %)	1	18 (9%)	1
1.1 – 2	212	21 (10 %)	2	29 (14%)	1.5
2.1 – 3	201	42 (21 %)	4.2	38 (20%)	2.2
3.1 – 4	122	33 (27 %)	5.4	39 (32 %)	3.5
Total	725	105 (14 %)		124 (17%)	

Treatment schedule

Initial evaluation :

Colposcopy, hysteroscopy, PAP, biopsy (optionally LEEP)

Neoadjuvant chemotherapy :

Paclitaxel (175 mg/sqm)
Cisplatin (75 mg/sqm)
Ifosfamide (5 g/sqm) or Epirubicin (80 mg/ sqm)
every 3 weeks for 3 courses

Intraoperative evaluation:

massive cervical residue → radical surgery
pCR or microresidue → cold knife conisation + PLND

Neoadjuvant chemotherapy Literature

Azienda Ospedaliera Bolognini Seriate

Author		preserved /total	histotype squamous	+ adeno	Cons. surgery ≤ 2	+ > 2 cm
Plante	2006	3 / 3	3	0	0	3
Kobayashi	2006	1 / 1	1	0	0	1
Landoni	2007	3 / 3	0	3	0	3
Maneo	2008	19 / 24	9	10	15	4
Rob	2008	12 / 15	8	4	3	9
Liu	2008	1 / 1	1	0	1	0
Marchiolè	2011	7 / 7	4	3	0	7
Palaia	2011	1 / 1	1	0	0	1
Tsubamoto	2012	3 / 7	3	0	0	3
Vercellino	2012	6 / 6	2	4	0	6
Maneo	unpubl.	1 / 2	0	1	1	0
TOTAL		57 / 70	56%	44%		64%

Neoadjuvant chemotherapy Oncologic and obstetric results

Azienda Ospedaliera Bolognini Seriate

Author		CR or PR1 /total	Relapses	Pregnant	Miscarriage patients	Newborns ≤ 32 + >32
Plante	2006	3 / 3	0	2	0	0 + 3
Kobayashi	2006	1 / 1	0	1	0	0 + 1
Landoni	2007	2 / 3	0	3	0	0 + 3
Maneo	2008	18 / 24	0 (5 CIN)	10	3	2 + 11
Rob	2008	9 / 15	3	7	0	1 + 6
Liu	2008	1 / 1	0	1	0	0 + 1
Marchiolè	2011	4 / 7	0	1	0	0 + 1
Palaia	2011	1 / 1	0	0	-	-
Tsubamoto	2012	3 / 7	0	0	-	-
Vercellino	2012	4 / 6	0	1	0	0 + 1
Maneo	unpubl.	1 / 2	1 (ovary)	0	-	-

Pregnancy outcomes by method of conservative therapy

Azienda Ospedaliera Bolognini Seriate

		Pregnant women	Odds ratio	p
Vaginal T	483	30 %	1	
Abdom. T	194	15 %	0.4	< 0.0001
Simple T	32	53 %	2.6	0.01
NACT	26	50 %	2.3	0.05

		Deliveries	Odds ratio	p
Vaginal T	621	30 %	1	
Abdom. T	194	10 %	0.3	< 0.0001
Simple T	32	37 %	1.4	0.4
NACT	26	61 %	3.3	0.002

Modified from Rob et al Lancet Oncology 2011

Trachelectomy vs. conization
Pros and cons

Trachelectomy	Chemo - conization
Tumor size up to 2 cm.	Tumor size up to 3 cm.
Histologic evaluation of parametria	Sterilisation of micrometastases and LVSI
No chemotherapy	Well known technique
Permanent cerclage set up at the time of surgery	
Major obstetric risk	

Azienda Ospedaliera Bolognini Seriate

Final proposal
Stage IB1 tumors

Azienda Ospedaliera Bolognini Seriate

≤ 1 cm	1 - 2 cm	2-3 cm (4?)
Simple T or conization	Radical T or NACT + conization	NACT + conization NACT + radical T

Decision also depending on:

- **obstetric outcomes**
- **risk of parametrial and nodal involvement**
- **patient's acceptance of chemotherapy**

Low malignant potential and early stage ovarian cancer: is there a place for FSS?

Thomas Ind

Gynaecological Surgeon

St George's & Royal Marsden Hospitals

Royal Marsden Hospital

St George's Hospital

FIGO & WHO – 1973

Imprecisely defined tumours which show intermediate behaviour between benign and malignant

- Borderline
- Low Malignant Potential

Royal Marsden Hospital

St George's Hospital

1973

Royal Marsden Hospital

St George's Hospital

1973

1973

1973

Willy Brandt

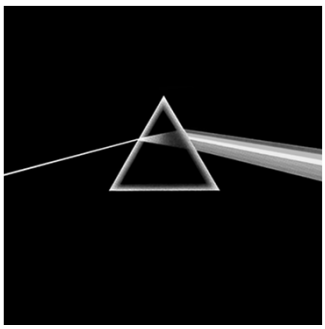
1973

Georges Pompidou

1973

1973

1973



1973

Ovarian Tumour Panel RCOG - 1983

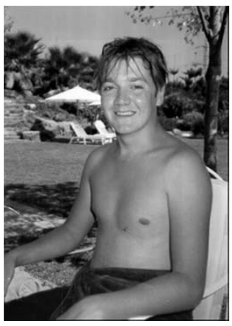
"…epithelial component shows some, or all, of the characteristics of malignancy but in which there is no stromal invasion."

1983

1983

1983

1983



Every unit had a published series

- Recurrence rates for stage 1 borderline tumours – Ind & Shepherd 2002 *
  - Tazelar et al 1985 3/20 (15.0%)
  - Lim-Tan el al 1988 4/33 (12.1%)
  - Bell & Scullly et al 1990 1/13 (7.7%)
  - Rice et al 1990 0/30 (0.0%)
  - Sawada et al 1991 1/5 (20.0%)
  - Manchul et al 1992 0/15 (0.0%)
  - Casey et al 1993 0/7 (0.0%)
  - Trope et al 1993 0/14 (0.0%)
  - Chao et al 1996 0/23 (0.0%)
  - Chow et al 1996 0/24 (0.0%)
  - Darai et al 1996 4/16 (15.4%)
  - Kennedy & Hart 1996 2/18 (11.1%)
  - Sykes et al 1997 0/15 (0.0%)
  - Chambers et al 1998 2/10 (20.0%)
  - TOTAL 17/227 (7.5%)

Not a single entity

No such thing as a BOT

Just borderline pathologists

Flow cytometry

- Haploid
- Diploid
- Aneuploid

Bethesda Classification 2006

- Serous
  - Serous cystadenoma
  - S-BOT
  - MPSC
  - S-BOT with microinvasion
  - S-BOT with extra-ovarian lesions
    - Peritoneal endosalpingiosis
    - Non-invasive peritoneal implants
    - Invasive peritoneal implants
    - S-BOT associated with serous epithelium in lymph nodes
- Mucinous
  - Mucinous cystadenoma
  - M-BOT gastro-intestinal type
  - (pseudomyoma peritonei)
  - M-BOT endo-cervical like type (AKA Müllerian & mixed epithelial)
  - M-BOT with intra-epithelial carcinoma (CIS)
  - M-BOT with microinvasion
- Others (Endometrioid, Clear Cell, & Brenner)

Dilemma – **Ovarian cyst on ultrasound**

- Radical Surgery
- Tentative Radical Surgery
- Conservative Surgery
- Observation

PROD

Conservative surgery

Presentation

- Suspicious for borderline on USS or MRI
  - Predominantly cystic with a few papillary projections and a normal or marginally raised CA125.
- Suspicious for borderline on frozen section.
- Diagnosis of borderline on final paraffin section after surgery for suspected benign disease.

Dilemma

- Adequate treatment and staging of cancer
- Adequate treatment of other conditions
- Curing symptoms
- Maintaining fertility
- Maintaining ovarian function

Radical Surgery

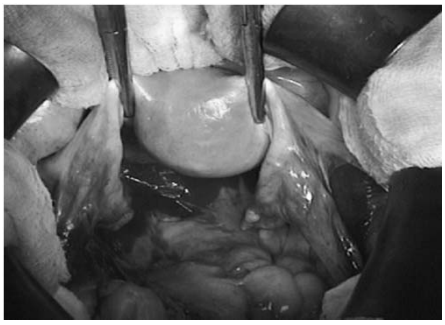
- PROD

Primary Radical Ovarian Debulking Procedure

Hysterectomy (Womb, tubes, & cervix)
Omentectomy
If cancer removal of cancer
    Colectomy +/- stoma
    Splenectomy
Staging laparotomy
Pelvic lymphadenectomy
Para-aortic lymphadenectomy

ULTRARADICAL PERITONEECTOMY
BOWEL RESECTIONS

PROD



TEntative Radical Ovarian Surgery

- TEROS

- Surgery determined by frozen sections
- Midline Operation
  - Frozen section to determine if hysterectomy and contra lateral ovary removed
  - Frozen section to determine if full staging and lymphadenectomy is performed

Conservative surgery

- Unilateral oophorectomy
- Unilateral salpingo-oophorectomy
- Ovarian cystectomy

- No place for cyst aspiration

Conservative surgery

- Pfannensteil (bikini line) incision
- Laparoscopic surgery

Observation

- Repeat scan in 3/12 +/- cyclical suppression
  - ? Discharge
  - ? Intervene
  - ? Continue observation

Bethesda Classification 2006

- Serous
  - Serous cystadenoma
  - S-BOT
  - MPSC
  - S-BOT with microinvasion
  - S-BOT with extra-ovarian lesions
    - Peritoneal endosalpingiosis
    - Non-invasive peritoneal implants
    - Invasive peritoneal implants
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  - (pseudomyoma peritonei)
  - M-BOT endo-cervical like type (AKA Müllerian & mixed epithelial)
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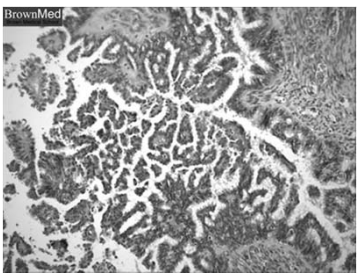
  - M-BOT with microinvasion
- Others (Endometrioid, Clear Cell, & Brenner)

1700 evening talk

1700 evening talk



1700 evening talk

No just thing as BOT

S-BOT

- THEY ARE BENIGN (not borderline)
- Cystedenomas with atypical proliferative
- Survival 100% for Stage I
- Three time more likely to die from treatment than cancer
- Can have invasive implants but probably another cell line

No just thing as BOT

MPSC

- THEY ARE MALIGNANT
- Often associated with advanced disease
  - 60% ten year survival
- THE PROGNOSIS IS NOT GOOD

No just thing as BOT

S-BOT

- Invasive implants represent MALIGNANCY
- Non-invasive implants and endosalpingiosis can occur in conjunction with S-BOT and behave in a BENIGN manner

No just thing as BOT

M-BOT (gastro-intestinal type)

- All advanced forms probably associated with PMP and Appendiceal tumours
- All others are probably BENIGN

No just thing as BOT

M-BOT (PMP)

- Probable appendiceal CANCER
- Refer to Basingstoke

No just thing as BOT

M-BOT (Endocervical / Mullerian)

- Mixed epithelial borderline tumours
- Can have a sero-mucinous
  - Atypical proliferative sero-mucinous tumours
- Can even MPSC component in which case MALIGNANT

Having identified that no such thing as a BOT how do we manage equivocal cysts

Risk of Malignancy Indices (RMI)

- Histological diagnosis only adequate one
  - No good imaging technique
  - No good tumour marker
- RMIs help differentiate between low and high risk cysts
- Also low & high risk populations

An RMI

- U x M x Ca125
  - U = Number of ultrasound features
    - U = 0 – None
    - U = 1 – One
    - U = 3 – More than one
  - CA125 = Ca125 concentration in IU
  - M = Menopausal status
    - M = 1 – Premenopausal
    - M = 3 – Postmenopausal (or equivocal)
- HE4 & ROMA

Ultrasound features

- Includes
  - Solid elements
  - Bilaterality
  - Multiple septae
  - Ascites
  - Papillary projection
- Does not include
  - Dopplers (not universally available)
  - Size (a poor indicator)

RMI groups

♦ <25	Population risk
♦ 25 – 200	Increased risk
♦ >200	High risk

Other Risk Tools

- Other RMIs
- ROMA (HE4 + CA125)
- IOTA criteria

Other tests

- CT scan (not as good as USS)
  - Good for spread
- MRI
- Radio-immunoscan
- Place for PET still undetermined

RCOG guidelines

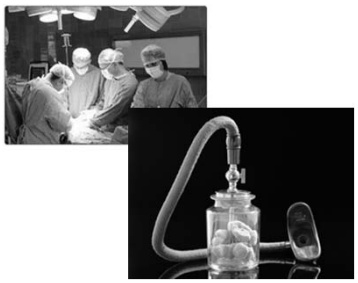
- Population risk
  - Conservative management
    - Observation & ovarian suppression
    - Discharge
- Increased risk
  - Short term observation
  - Conservative surgery
- High Risk
  - PROD or TEROS by 'sub-specialist based in a cancer centre'

Frozen sections

- Borderline tumour at Frozen section
  - 20% invasive
- 20% of Borderline tumours
  - Benign at Frozen section
- Is a second operation really all that bad

Second operations

Second operations



Post-op Diagnosis of 'BENIGN' Borderline

- Salpingo-oophorectomy
  - Unless only one ovary
- Hysteroscopy
- Assessment of contra lateral ovary
- Omentectomy
- Appendicectomy

- LAPAROSCOPIC

Post-op Diagnosis of 'MALIGANT' Borderline

- Fertility sparing surgery still acceptable
- Salpingo-oophorectomy or TAH BSO
- Hysteroscopy
- Assessment of contralateral ovary
- Omentectomy
- Appendicectomy
- Pelvic and para-aortic lymphadenectomy

- LAPAROSCOPIC OR ROBOTIC

Laparoscopic para-aortic LN

Robotic pelvic LN

Sub-specialist in gynaecological cancer

Laparoscopic surgeon

Laparoscopic surgeon

ROYAL COLLEGE
OF
OBSTETRICIANS AND GYNAECOLOGISTS

LEVEL THREE CERTIFICATION IN LAPAROSCOPIC SURGERY

This is to certify that

THOMAS ING

has satisfactorily completed an approved minimal access surgery training programme and preceptorship at level 3 in Laparoscopy as outlined by our College

Professor R Garry
Chairman
MAS Training Sub-Committee

Professor W Dunlop
Chairman
Specialist Training Committee

Date: 24 July 1999

Conclusion

- Medical independence is the last refuge of the medically incompetent

Title:
Ovarian chemo prophylaxis, fertility preservation against chemotherapy sterilizing effects and ovarian tissue cryopreservation.

Dror Meirow Disclosure:
Nothing to disclose.

Ovarian chemo prophylaxis,
Fertility preservation against
chemotherapy sterilizing effects
And ovarian tissue cryopreservation

Dror Meirow
Fertility Preservation Center
Sheba Medical Center
Sackler school of medicine, Tel- Aviv University, Israel.

Fertility-Sparing Surgery in malignant and benign conditions

Learning Objectives

- Effects of chemotherapy on female reproduction.
- Effects of chemotherapy on the ovary.
- Chemo-protective agents.
- Mechanism of protection.
- Ovarian tissue freezing & transplantation results.
- Comparison with other fertility preservation methods.
- Future roll in benign conditions.

Chemo Drugs According to Gonadotoxicity

High Risk
- Cyclophosphamide
- Chlorambucil
- Melphalan
- Busulfan
- NitrogenMustard
- **Procarbazine**

Intermediate Risk
- Cisplatin
- Adriamycin

Low Risk
- Methotrexate
- 5-Fluorouracil
- Vincristine
- Bleomycin
- ActinomycinD

Unknown Risk
- Oxaliplatin
- Irinotecan

Pre-pubertal gonad is not protected

S. Lee et al. ASCO Guidelines 2006

Ovarian function in patients treated for Hodgkin's disease

Ref.	No.	Follow up	parameter	treatment	Results %
Behringer 05	405	3.2 years	amenorrhea	ABVD	3.9
				advanced *	23-51
Decanter 07	30	1 year	AMH	ABVD	Normal
Brusamolino 07	67	10 years	fertility	ABVD	preserved
Kiserud 07	91	10 years	parenthood	Low dose	55
				advanced *	22-27

Ovarian failure risk – treatment related
- 1st line chemo – very low
- Advanced chemo – significant

Harel S. et al 2011

Ovarian damage after Cy. protocols for breast cancer

Reference	Age/ treatment		%
Lower E.E 1999	Pre menopause		**45%**
Meirow D 1999	<44 years		**50%**
Goodwin P. 1999	**CMF**	38-48	**65%**
Burstein H. 2000	**CMF**	30-39	**30-40%**
	CAF	30-39	**10-25%**
	AC	30-39	**13%**
Jonat W. 2001	Pre menopause		**60%**
Petrek 2006	35-39		**39-55%**

Failure

D. Meirow 2010

		Mean	P value
AFC	Controls	11	**0.0042**
	Survivors	5	
AMH	Controls	1.8	**0.0004**
	Survivors	0.6	
FSH	Controls	8.0	**0.02**
	Survivors	11.6	

Damage

A. Partridge 2010

Ablative Chemotherapy &
Bone Marrow Transplantation

	No.	Age	% failure
Sanders 96	73	mean 38	99
Teinturier 98	21	2 - 17	72
Thibaud 98	31	3.2 - 17	80
Meirow 99	63	mean 29	79
Grigg 2000	19	mean 30	100

Ovarian failure risk - very high.

Meirow, Anderson, Wallace 2010

Premature ovarian Failure
in Childhood Cancer Survivors

Disease	Odds ratio (patients)
Hodgkin's D.	3.8 (66 / 487)
Non- Hodgkin's Ly.	3.2 (19 / 168)
Sarcoma	2.6 (27 / 290)
Wilm's tumor	3.0 (35 / 329)
Leukemia	1.0 (43 / 1088)

W. Chemaitilly et. Al. 2006

Our studies on chemotherapy effects
on the ovaries enabled:

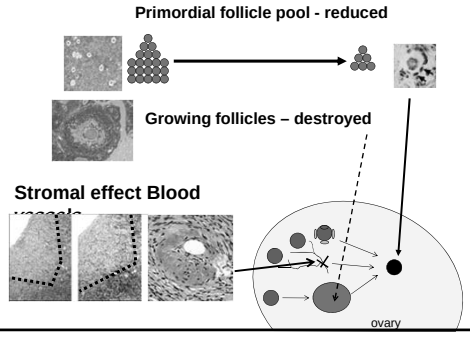
- Understand Follicle dynamics and reveal universal mechanism of follicle loss.
- Selection of effective & safe Fertility preservation procedures.
- Search for protective agents.

Effects of cytotoxic drugs on the ovary:

Cell Type		Action	Outcome	Drug Class
Growing follicles	Oocyte	Apoptosis Aneuploidy DNA damage Cell cycle arrest	Cell death Embryonic & fetal malformations mortality	Alkylating agents [1,5] Anthracycline antibiotics [1-5] Cisplatin[1,4,5] Taxanes [1,5] Vinca alkaloids[1,5]
	Granulosa cells	Apoptosis DNA damage	Cell death	Alkylating agents [1,4,5] Anthracycline antibiotics (Utsunomiya[1-5]5] Taxanes[1,4]
Dormant follicle		Activation Apoptosis*	Follicle growth Cell death	Alkylating agents [1-4] Anthracycline antibiotics [2, 3,4] Multiagent [2,5]
Blood vessels		Narrowing and hyalinization of small blood vessels	Ischemia, focal fibrosis Neovascularisation Decreased blood flow	Anthracycline antibiotics[1,5] Multiagent [2,5]
Stroma		Alterations in collagen structure	Fibrosis Necrosis	Anthracycline antibiotics[1,5] Multiagent [2,5]

Study type: 1. Rodent, 2. Human, 3. Xenograft, 4. In-vitro, 5. In-vivo

Chemotherapy effects on the ovary



Effects of chemotherapy

on resting primordial follicles

Lab Experiments

What is the mechanism

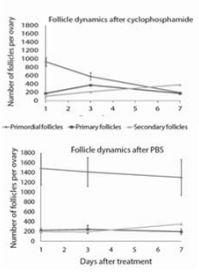
Clinical implications

Cyclophosphamide triggers follicle activation causing ovarian reserve 'burn out'

Science Translational Medicine AAAS

Kalich Philosoph et al 2013

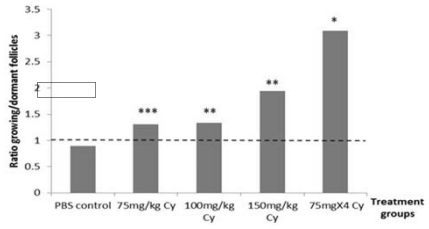
Cy causes PMF activation



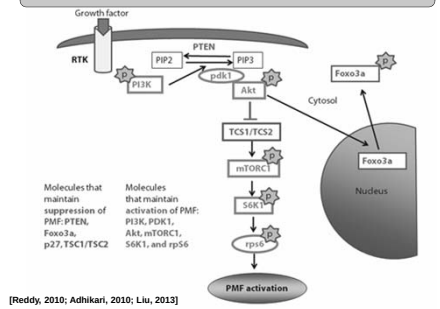
- Loss of PMFs
- No apoptosis of PMFs
- Apoptosis only in growing follicles
- But no decrease in growing follicles?
- Increase in early growing follicles
- Increase in proliferation of transitional follicles

PMF activation

Ratio of growing/non growing follicles with different doses of Cy



What triggers the activation?



[Reddy, 2010; Adhikari, 2010; Liu, 2013]

TOR is a central controller of cell growth

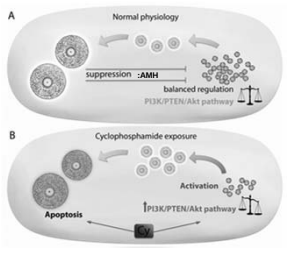
M. Hall 1991

Rapamycin 1965

TOR

arrest program (G_0)	growth program
▪ autophagy	▪ protein synthesis
▪ apoptosis	▪ nucleotide synthesis
▪ protein turnover	▪ lipid synthesis
▪ RNA degradation	▪ ribosome biogenesis
▪ gluconeogenesis	▪ glycolysis
▪ G_0 transcription	▪ transcription

The mechanism for Cy-induced follicle loss is two fold:



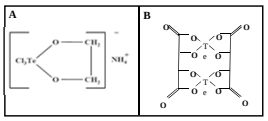
1. **Activation** and growth of the primordial follicles via PI3K pathway. Once recruited, the follicles develop, die, resulting in loss of ovarian follicle reserve.
2. Direct **apoptosis** in growing follicles

loss of suppression

Potential preventive agents (H. Roness et. Al. 2014)

Protective Agent	Mechanism of action on ovary	Studies demonstrating protective effect in vivo	Studies demonstrating no effect	Interactions with cytotoxic treatments
GnRH-a	Unclear. Suppression of pituitary-gonadal axis	**Rodent**: Meirow, 2004, Li, 2013 **Primate**: Ataya, 1995 **Human**: Badawy, 2009; Sverrisdottir, 2009; Del Mastro, 2011; Demeestere, 2013*	**Human**: Gerber, 2011; Munster, 2012; Elgindy, 2013; Demeestere, 2013*	Does not interfere with treatment drugs
S1P	Inhibition of sphingomyelin apoptotic pathway	**Rodent**: Morita, 2000**; Jurisicova, 2006; Hancke, 2007; Kaya *et al.*, 2008** **Primate:** Zelinski *et al.*, 2011** **Human xenograft**: Zelinski *et al.*, 2011**	**Rodent**: Kaya, 2008	May interfere with apotosis action of chemotherapy drugs
Imatinib (GNF-2)	Inhibition of c-ABl kinase apoptotic pathway	**Rodent**: Gonfloni, 2009	**Rodent**: Kerr, 2012	May interfere with apotosis action of chemotherapy drugs
Thalidomide	Unclear: Inhibition of angiogenic factors, suppression of pituitary-gonadal axis	**Rodent**: Ochalski, 2011		Anti-tumor effects
Tamoxifen	Antioxidant via IGF-1 axis, possibly via gonadal suppression	**Rodent:** Ting, 2010; Mahran, 2013 **	**Human:** Sverrisdottir, 2009	Adjuvant treatment
G-CSF	Unclear: neovascularisation	**Rodent:** Skaznik-Wikiel, 2013		Does not interfere with treatment drugs
AS101	Modulation of PI3K/PTEN/Akt follicle activation pathway	**Rodent**: Kalich-Philosoph, 2013		Does not interfere with and may have additive/synergistic interaction with treatment drug.

The immuno-modulator AS101

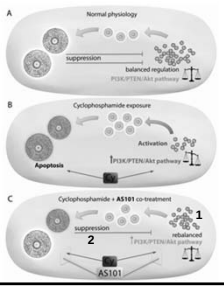


Tellurium based compound developed by us.

Immunomodulator – decrease in IL-10 and IL-1β.

Non-toxic to cancer patients, minimal side effects.

AS101 restores the balance of negative regulation



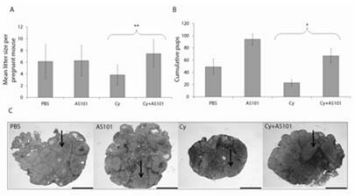
1. **Activation** and growth of the primordial follicles via PI3K pathway.

DIRECT PATHWAY

2. Direct **apoptosis** in growing follicles

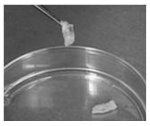
LOSS OF INHIBITION

AS101 improves fertility outcomes



- Increased litter size and cumulative pups
- Increased pregnancy rate
- Increased ovarian volume & number of corpus lutei.

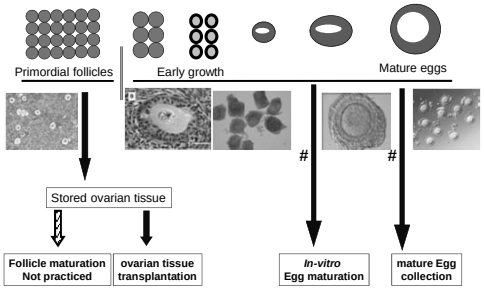
Ovarian tissue storing



and transplantation

Different approaches for fertility preservation

Currently used & experimental



Tissue harvesting “Primum Non Nocere”

- Safety of laparoscopic procedure in sick cancer patients.
- Not delay in cancer treatment.
- No mechanical infertility.
- If not sterilized post cancer treatment high spontaneous pregnancy rate (60-70%).

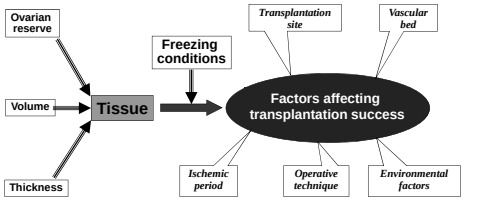
H. Wallace & Kelsey 2012

Transportation of ovarian tissue prior to Cryopreservation

Author	Transport time	Temp.	Live birth	Study
Rosendahl M. et al. Rep.Med.Online 2011	4-5 h	On ice	>2	Xeno transplantation
Dittrich R. et.al. Fertil. Steril. 2012	20 h	5-8^{o}C	1	
Isachenko et.al. Fertil Steril 2009	<26 h	4^{o}C		In vitro growth

Ovarian tissue can be safely transported from one clinic to a highly specialized center.

Factors affecting procedure success



Most follicles are lost immediately post transplantation

Meirow D, Anderson R, Wallace H. 2010

Location: Grafting to the ovary

Sub cortical pockets
Meirow D. Dor J. *et.al* NEJM 2005

Sub cortical pockets
Andersen C.Y. *et.al*. Hum Reprod. 2008

cortical replacement
Donnez J. *et.al*. 2008

cortical replacement
Silber S. Meirow D. 2010

Location: Orthotopic Surgical grafting

Publications: Donnez, Demeestere, Azem, Revel, Pellicer, Muller

- Additional space
- No ovary
- Fibrosis of vascular bed

Additional approaches to improve grafting And prevent follicle loss

- Thin micro organ ovarian fragments prepared prior to transplantation (Revel A. *et al* 2011).
- Double procedure preparation of transplantation site (Donnez J. *et al 2008*).
- Double procedure- two steps transplantation (Piver P. *et al* 2010).
- Agents to improve neovascularization and prevent ischemia. (Abir R. *et al* 2012).

The "Burn-Out" mechanism
Follicle activation and destruction

Universal route of follicle loss
post chemotherapy
post transplantation

H. Roness et.al. 2013

CellCycle

Volume 12 • Issue 20 • October 15, 2013

Primordial follicle activation

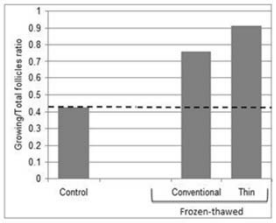
Depletion of growing follicles.

Can it cause

Reduced inhibition and activation?

Ovarian tissue transplantation model

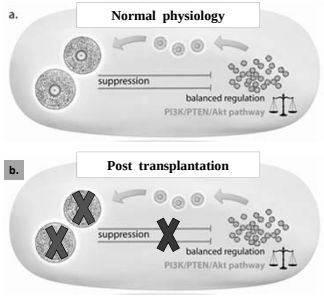
Post transplantation follicle activation the effect of graft thickness.



Thin prepared grafts significantly more follicle loss.

Z. Gavish et.al. 2013

The "Burn-Out" mechanism post transplantation



Most follicles are lost post transplantation.

Not only due to transplantation technique.

Important factor is the 'Burn-Out' effect.

To improve tissue transplantation it is important

to find add factors that prevent 'Burn-Out' .

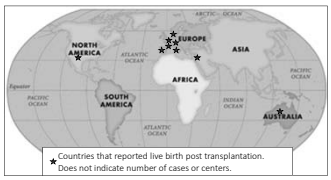
Function of frozen / thawed ovarian tissue transplantation

	site	cases	Ovarian function Menstruation / hormonal	ovulation
Denmark Rigshospitalet	ovary	21/25	100%	+
	peritoneum	9/25		+
Spain La Fe	Ovary +	21/22	94%	+
	peritoneum	8/22		+
Russia Ava- Peter	arm	4/17	76%	No
	abdomen	11/17		No
Belgium St Luc	ovary	8/13	77%	+
	peritoneum	7/13		+
Israel Sheba	Ovary +	10/10	100%	+

- AMH – not predictive usually low. Janse F. et.al. 2011
- Endocrine function – most of patients – years. Andersen CY et.al. 2012
- Ovulation - Not in heterotopic transplantations.

Transplantation of stored ovarian tissue works

- Live birth post OTCP & transplantation. *Donnez et al. Lancet 2004.*
- Live birth, sterilized patient, post OTCP & transplantation & IVF. *Meirow et.al.* NEJ Med *2005.*
- Dozens of babies born post OTCP & transplantation until now. Raanani H. et.al. 2014



Live birth post OTCP & Transplantation after bilateral oophorectomy

	Author	Journal	Age	Diagnosis / indication	Years cryo.	IVF
1.	Callejo J.	BMJ 2012 Ovarian Research 2013	21	Mature teratoma	10	1 cycle
2.	Donnez J.	Fertil Steril 2012	19	Tubo ovarian abscess	7	5 cycles

1. Posterior leaflet broad ligament

2. Anterior leaflet broad ligament

To practice OTCP routinely

To improve technique results

we should first show- procedure success rate.

However, many centers, sporadic cases!

Approach:

1. Collecting world's data.
2. Report total results from single centers.

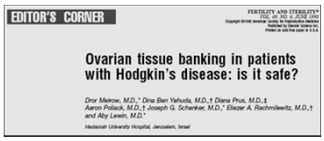
Transplantation results - Sheba

RESULTS

- Spontaneous menstruation returned in all patients,
- AMH, FSH & E2 not predictive .
- Long term graft survival in most patients.
- IVF cycles -modified natural protocol in all cycles.
- Empty follicles – only a few after first cycles.
- No. of embryos post transplantation **HIGHER** Number of embryos stored prior to chemotherapy.

Cryopreservation/transplantation of ovarian tissue works and is effective.

Safety data - Detection of cancer cells


EDITOR'S CORNER

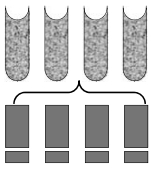
Ovarian tissue banking in patients with Hodgkin's disease: is it safe?

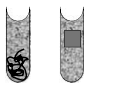
Transmission of donor-related malignancy by organ transplantation is recognized.

Meirow et.al. Fertil Steril 1998

Tissue handling for cancer cells evaluation

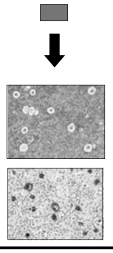
Storing tissue **Future evaluation** **Fresh cortex**





medulla **cortex**

Store for future minimal residual disease evaluation.



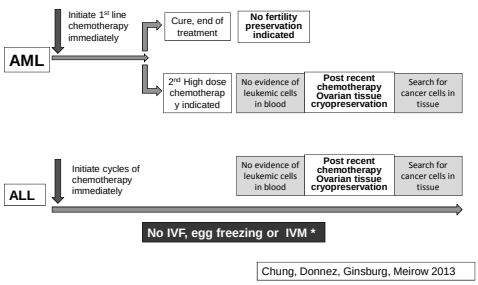
Minimal residual disease detection in cryopreserved ovarian cortex using molecular markers

- **Leukemia and Lymphoma patients** (Meirow et al. 2008, 2013)
  - BCR-ABL (1/3 pt.)
  - T-cell receptor and immunoglobulin rearrangement genes (0/2 pt.)
- **leukemia patients** (Rosendahl et al. 2010)
  - BCR-ABL (4/6 pt.)
  - TEL-AML1 (1/1 pt.)
  - CBFB-MYH11 type A (1/1 pt.)
- **Acute lymphoblastic leukemia** (Dolmans et al. 2010)
  - BCR-ABL (2/6 pt.)
  - T-cell receptor and immunoglobulin rearrangement genes (7/10 pt.)
- **Ewing sarcoma** (Abir et al. 2011)
  - EWS-FLI1 (1/5 pt.)
- **Leukemia** (Greve et al. 2012)
  - CML,ALL,AML (4/12 pt.)

Xenotransplantation studies

Reference	Malignancy	Disease	No. of pt.	Transp. period	Rec.
Greve T. Blood 2012	**Leukemia**	AML, ALL, CML	25	20 w	**0**
Kim S.S. Hum Reprod 2001	**Lymphoma**	HD NHL	18	16 w	**0/13** **3/5**
Dolmans M.M. Blood 2010	**Leukemia**	CML ALL	18	6 mo	**0/6** **4/12**
Lots L. Fertil & Steril 2011	**Ovarian cancer**	Epithelial Germinal Border line	10	24 w	**0**

The "Road map" of fertility preservation in young female patients with acute leukemia.

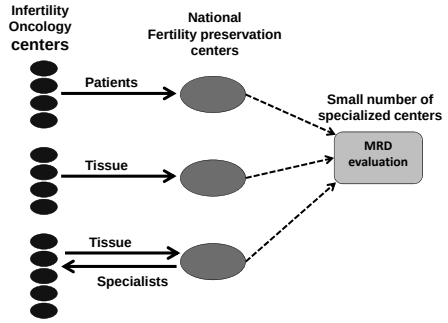


Chung, Donnez, Ginsburg, Meirow 2013

However
the applicability of sensitive molecular markers
methods varies
by the specific disease subtype

- CML, ALL > 90%
- AML < 50%
- Solid tumors < 10%

Personalized molecular markers discovery



Comparison with IVF
for Fertility preservation in cancer Patients

Reference	Eggs		2PN		P
	cancer	controls	cancer	controls	
Oktay 2005	12.3		5.3		
Knopman 2009	14 ± 9	12 ± 7			NS
Quintero 2010	13	11.5	7.4	**6.8**	NS
Robertson 2010	12 ± 8	14 ± 9	6 ± 5	**7 ± 6**	NS
Lawrenz 2011	11.6 ± 7.7		7		
Domingo 2012	**10.5 (9.5-11.6)**	**12.4 11.2-13.6**			0.02
Meirow 2012 <35	**11**		7.1		
>35	**9.2**		6		

The mean number of eggs 12-14, embryos 5-7.

Chung, Donnez, Ginsburg, Meirow 2013

Conclusive remarks

- Ovarian tissue cryo/transp. works– natural & IVF pregnancies.
- Post transplantation IVF results indicate effectiveness.
- Technical improvements and standardization will continue.
- Specialized Fertility preservation centers are recommended.
- Small number of highly specialized centers to evaluate MRD.

Cryopreservation/transplantation of ovarian tissue should no longer considered experimental strategy for fertility preservation in severe diseases.

Future roll in benign conditions

- Endometriosis
- Genetic- mosaic Turner, Galactozemia
- Ovarian operations – large cysts?
- BRCA prophylactic procedures
- Social freezing?

Fertility preservation center and Research laboratory

Dr. Roness Hadassa
Dr. Gavish Zohar
Dr. Rannani Hila
Dr. Kalich-Philosoph Lital
Dr. Pe'er Gil
Dr. Yoram Cohen
Sioni Noa
Elmaleh Lital
Derech Haim Sanaz
Shapira Moran
Oren Kashi
Prof. Orvieto Raoul

Collaborations:

Bar Ilan University
Prof. Benjamin Sredni

Sheba Medical Center
Dr. Ido Wolf
Dr. Hannah Kanety
Prof. Gideon Rechavi,
Dr. Sarit Aviel

UPCOMING ESHRE EVENTS

// ESHRE CAMPUS EVENTS

ESHRE's 30th Annual Meeting

www.eshre2014.eu

Munich, Germany
29 June - 2 July 2014

Epigenetics in reproduction

www.eshre.eu/lisbon

Lisbon, Portugal
26-27 September 2014

Endoscopy in reproductive medicine

www.eshre.eu/endoscopyoct

Leuven, Belgium
15-17 October 2014

Making OHSS a complication of the past: State-of-the-art use of GnRH agonist triggering

www.eshre.eu/thessaloniki

Thessaloniki, Greece
31 October-1 November 2014

From gametes to blastocysts – a continuous dialogue

www.eshre.eu/dundee

Dundee, United Kingdom
7-8 November 2014

Controversies in endometriosis and adenomyosis

www.eshre.eu/liege

Liège, Belgium
4-6 December 2014

Bringing evidence based early pregnancy care to your clinic

www.eshre.eu/copenhagen

Copenhagen, Denmark
11-12 December 2014

An update on preimplantation genetic screening (PGS)

www.eshre.eu/rome

Rome, Italy
12-13 March 2014

For information and registration: www.eshre.eu/calendar
or contact us at info@eshre.eu

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