

ENDOMETRIOSI: UNA VISIONE NUOVA



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Struttura Complessa di Ostetricia e Ginecologia
Direttore Dr. Felice Repetti

- Tra le adolescenti con **dolore pelvico** severo è stata stimata una prevalenza di endometriosi del 53%.
- E' inoltre la prima causa di ricovero ospedaliero ginecologico nelle donne di età compresa fra i 15 e 44 anni.
- Frequentemente la prima diagnosi è tra i 20 ed i 35 anni.
- Dati recenti riportano che nell'Unione Europea l'endometriosi interessa circa 14 milioni di ragazze e giovani donne.
- Il 25-35% delle donne con **problemi riproduttivi** ed il 20-40% delle donne con dolore pelvico cronico presenta lesioni di tipo endometriosico.

Endometriosis and infertility

The Practice Committee of the American Society for Reproductive Medicine

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The current clinical opinion is that a surgical procedure such as laparoscopy is required for definitive diagnosis of endometriosis. Given this state of clinical practice, an important question is when to perform laparoscopy to determine if endometriosis is present. A history and physical examination can yield a number of significant findings, including affected first degree relatives, chronic pelvic pain and dysmenorrhea, retroverted uterus, adnexal masses, cul de sac nodularity and uterosacral ligament thickening and tenderness, but none is diagnostic. Ultrasound can help the clinician establish a presumptive diagnosis of ovarian involvement with endometriosis, but laparoscopy is necessary to confirm the diagnosis. Endometriosis is a heterogeneous

- Le stime di prevalenza configurano l'endometriosi come una **priorità** nell'ambito dei programmi di tutela della salute pubblica.
- La carenza di **informazione** diffusa, **l'assenza di protocolli terapeutici univoci** e condivisi e la attuale **scarsa disponibilità di servizi territoriali** adeguati sono fattori che creano forte aspettativa e rendono complessa la definizione e l'attuazione di programmi efficaci di prevenzione, di **diagnosi precoce** e di cura.
- I recenti dati internazionali indicano un **ritardo diagnostico di oltre nove anni** nonché frequenti diagnosi sbagliate dovute alla mancanza di consapevolezza e comprensione dei sintomi.

OBIETTIVI

- **Diagnosi** di endometriosi.
- **Informazione** esaustiva di cos'è l'endometriosi.
- **Valutazione pre-operatoria** comprensiva di localizzazione e quantificazione del dolore e, quando necessario, di indagini quali RMN / CLISMA-TC al fine di pianificare una equipe operatoria selezionata al caso (es. Ginecologo + Chirurgo Generale nei casi con interessamento intestinale).
- Sistematica stadiazione intraoperatoria della malattia endometriosa secondo la “ASRM Revised Classification of Endometriosis” al fine di potere personalizzare la terapia medica per ogni caso immediatamente dopo la chirurgia.

OBIETTIVI

- **Follow-up** delle Pazienti operate di Endometriosi.
- Immediato trasferimento dati al **Centro di Diagnosi e Terapia dell'Infertilità** per quelle Pazienti con desiderio di maternità alle quali sia stata diagnosticata sterilità da endometriosi.
- **Monitoraggio epidemiologico** del fenomeno endometriosi e conduzione di idonee **campagne informative** di prevenzione nell'area di pertinenza della A.S.L.
- Sviluppo di protocolli di **ricerca** di base e clinica nel campo dell'endometriosi.

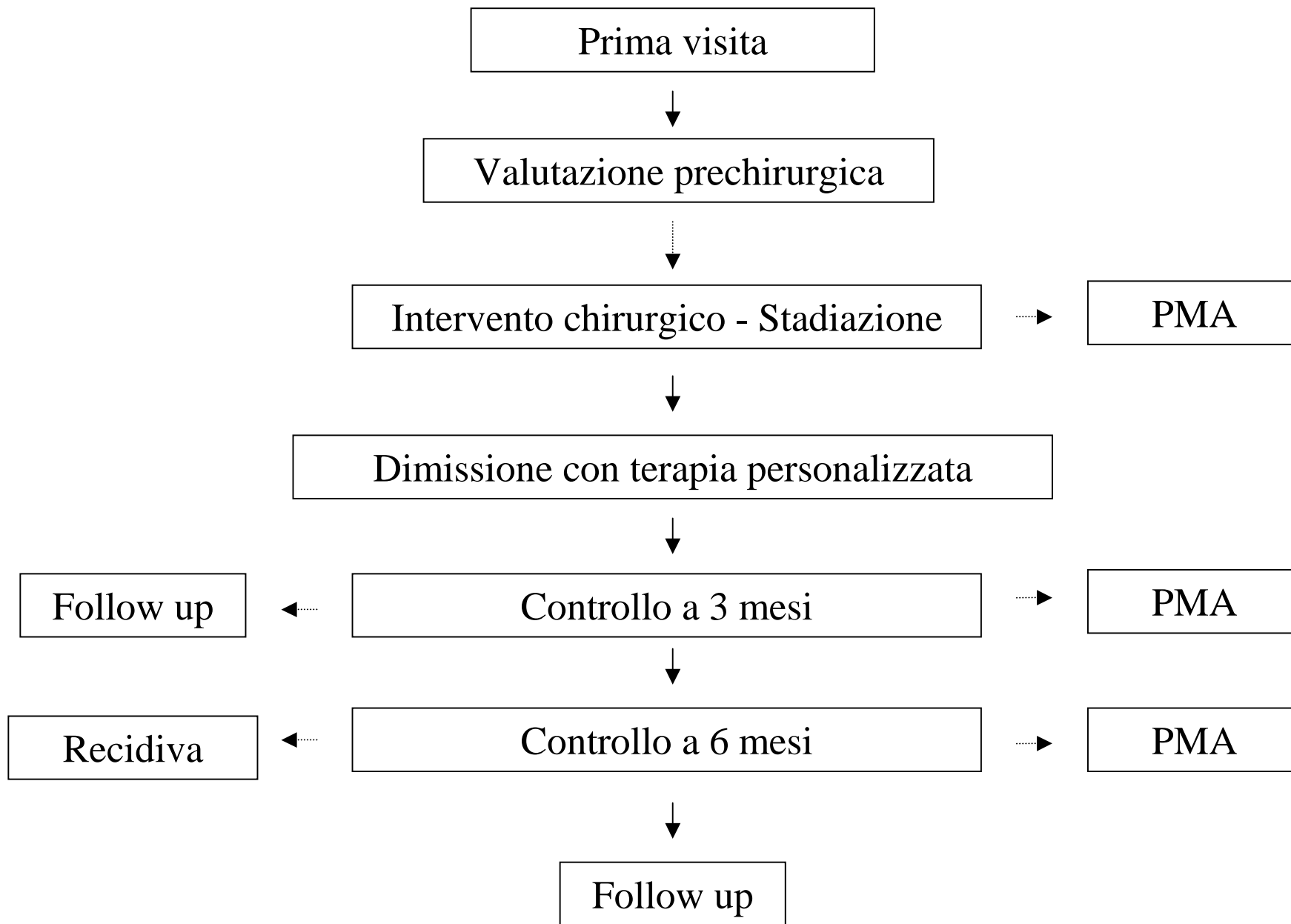
Recependo la delibera 30/2004 del 19-4-2004 del Parlamento Europeo

**il 18/1/2006 il Senato ha chiuso il tavolo tecnico
dichiarando l'Endometriosi "Malattia Sociale"**

Organizzazione di **percorsi diagnostico-terapeutici specifici** per le pazienti
affette.

Istituzione della Giornata Nazionale dell'Endometriosi, ossia un "Awareness day"
nell'intento di accrescere le conoscenze su tale condizione debilitante.

Istituzione di fondi per la prevenzione e la ricerca nel campo di tale patologia.



- L'opinione clinica dominante è infatti che la diagnosi definitiva di endometriosi sia chirurgica e riteniamo che la laparoscopia sia in questi casi oltrechè diagnostica / operativa soprattutto “**prognostica**”.
- Dati come la stadiazione della endometriosi pelvica e lo stato delle tube, infatti, sono assolutamente necessari per formulare un piano terapeutico che porti a significative percentuali di gravidanza.
- Una delle molte sfide che i fertilologi si trovano dunque ad affrontare è quella di decidere **quando eseguire la laparoscopia** al fine di diagnosticare l'endometriosi.

- Una delle possibili soluzioni a questo problema è quello di **standardizzare, computare e analizzare in maniera obiettiva e riproducibile tutti i dati generati dal percorso diagnostico-terapeutico** con approccio multidisciplinare che le pazienti affrontano quando vi sia il sospetto clinico di endometriosi.
- Nel nostro centro abbiamo creato un software capace di calcolare in tempo reale 35 indicatori clinici derivanti dall'auto-valutazione della paziente, dalla visita e dalla diagnostica.

Creazione di software dedicato al percorso diagnostico –terapeutico per endometriosi

Valutazione del dolore

Valutazione del dolore

Intensità del Dolore Mestruale (IDM)

Intensità del Dolore Pelvico (IDP)

Dolore Rapporti Sessuali (DRS)

NESSUN DOLORE

MASSIMO DOLORE

IDM-IDP-DRS : 6,25

ISTRUZIONI ALLA COMPILAZIONE

Traslate l'indicatore visuale per indicare nella scala l'entità del dolore pelvico.

La valutazione ripetuta nel tempo deve rigorosamente essere auto-stimata dalla paziente alla quale sono mostrate le valutazioni precedenti se esistenti.

Creazione di software dedicato al percorso diagnostico –terapeutico per endometriosi

Caratterizzazione del dolore e limitazioni

Caratterizzazione del Dolore (CDD)

	nessuno	lieve	moderato	severo		
Pulsante	◀				▶	■
Trafitivo	◀				▶	■
Crampiforme	◀				▶	■
Bruciore	◀				▶	■
Pesantezza	◀				▶	■
Gonfiore	◀				▶	■

CDD : 2,57

Limitazioni da dolore

Limitazione delle attività fisiche

Limitazione delle attività intellettive

Limitazione del sonno

LDD : 8,00

Creazione di software dedicato al percorso diagnostico –terapeutico per endometriosi

Disfunzioni indotte

Alterazioni alvo sincrono con il ciclo

stitichezza/diarrea	<input type="range"/>	<input type="range"/>
tenesmo	<input type="range"/>	<input type="range"/>
stitichezza	<input type="range"/>	<input type="range"/>
diarrea	<input type="range"/>	<input type="range"/>
ematochezia	<input type="range"/>	<input type="range"/>

Alterazioni urinarie sincrono con il ciclo

stranguria	<input type="range"/>	<input type="range"/>
tenesmo vescicale	<input type="range"/>	<input type="range"/>
pollachiuria	<input type="range"/>	<input type="range"/>
disuria	<input type="range"/>	<input type="range"/>

Mal di testa sincrono con il ciclo

<input checked="" type="checkbox"/> cefalea	<input type="range"/>	<input type="range"/>
<input checked="" type="checkbox"/> emicrania	<input type="range"/>	<input type="range"/>
<input checked="" type="checkbox"/> cefalea a grappolo	<input type="range"/>	<input type="range"/>

SPA: 2,64

Creazione di software dedicato al percorso diagnostico –terapeutico per endometriosi

Valutazione medica

Visita ginecologica

Utero fisso	◀		▶	■
Cisti ovarica	◀		▶	■
Compromissione Douglas	◀		▶	■
Nodulo vaginale	◀		▶	■

VM : 3,30

Indagini strumentali

<input type="checkbox"/> CA-125	POS
<input checked="" type="checkbox"/> ECO - Ecografia	<input checked="" type="checkbox"/>
<input checked="" type="checkbox"/> CA-19.9	<input type="checkbox"/>
<input type="checkbox"/> RMN - Risonanza Magnetica	<input type="checkbox"/>
<input checked="" type="checkbox"/> TC - Tomografia computerizzata	<input checked="" type="checkbox"/>
<input type="checkbox"/> Colonscopia	<input type="checkbox"/>

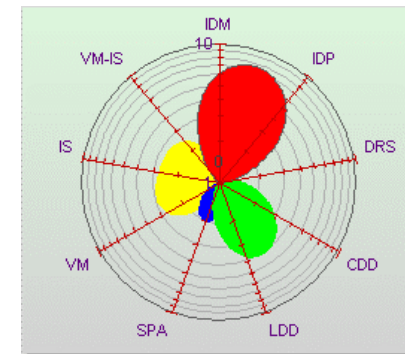
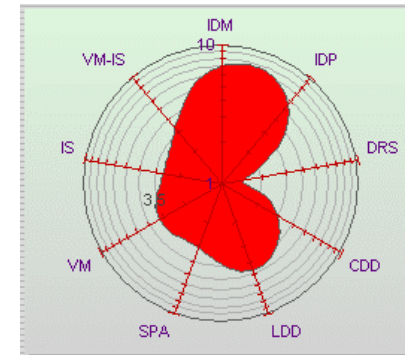
IS : 2,50

VM-IS : 3,00

Le variabili e i parametri clinici, analizzati secondo la fattorizzazione ad unico dominio (Reina S et al. 2005), sono espressi da un punteggio normalizzato capace di fornire un livello sia qualitativo che quantitativo di patologia:

l'Indice di Patologia Endometriosi (IPE)

Indici normalizzati dei punteggi-collezione		SEZIONI
Valutazione del dolore (IDM + IDP + DRS + CDD)		36,94
Limitazioni alle funzioni e alle attività (LDD)		81,70
Sintomi patologici e alterazioni (Alvo/urinarie) (SPA)		21,50
Medico alla visita ginecologica (VM)		9,85
Diagnostica e referti strumentali (IS)		41,67
Indice di endometriosi :		38,10



Pannelli
 Collezioni di indicatori
 Indicatori

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Simple Records Matching Method for diagnostic and clinical datasets of patient's records

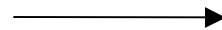
Salvo Reina, *Institute of Microbiology School of Medicine University of Genoa, Italy*

Vito M. Reina, *ICT Freelance in Rome*

Eugenio A. Debbia, *University of Genoa, Italy*

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MODELLO
BILANCIATO

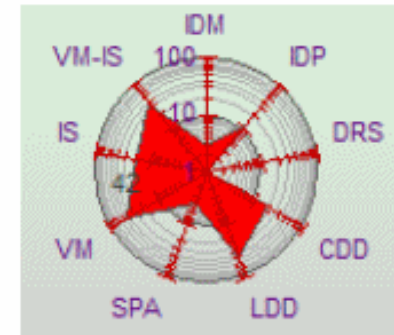
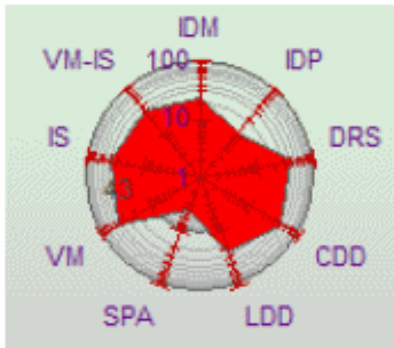


DOL (AUTO) VALUTAZIONE DOLORE
LDD LIMITAZIONI QUALITA' DELLA VITA
SPA SINTOMATOLOGIA INDOTTA
GIN VALUTAZIONE GINECOLOGICA
IS INDAGINI STRUMENTALI E DIAGNOSTICA

Indice Endometriosi > Fase II

65 Pazienti affette da endometriosi

35 casi appaiati per IE (Pre/Post)



STAGE IV (SEVERE)



Univariate statistics

	AGE	EIPRE	EIPOST	DELTA	ASRM	DOLPRE	DOLPOST
N	32	32	32	32	32	32	32
Min	25	14,18	0	39,7674	3	6,03	0
Max	46	58,77	20,72	100	92	81,68	28,37
Mean	34,4063	32,8319	9,54313	68,9833	39,5625	39,9725	7,74813
Std. error	1,05862	2,1402	0,794964	2,48163	4,20755	3,48187	1,4891
Variance	35,8619	146,574	20,223	197,072	566,512	387,949	70,9574
Stand. dev	5,98848	12,1068	4,497	14,0382	23,8015	19,6964	8,42362
Median	34	31,42	8,54	70,7117	39,5	37,35	5,135
Skewness	0,393749	0,381122	0,494212	-0,196176	0,365601	0,193585	1,19163
Kurtosis	-0,726268	-0,753595	0,107758	-0,269493	-0,692565	-0,709264	0,166352

Univariate statistics

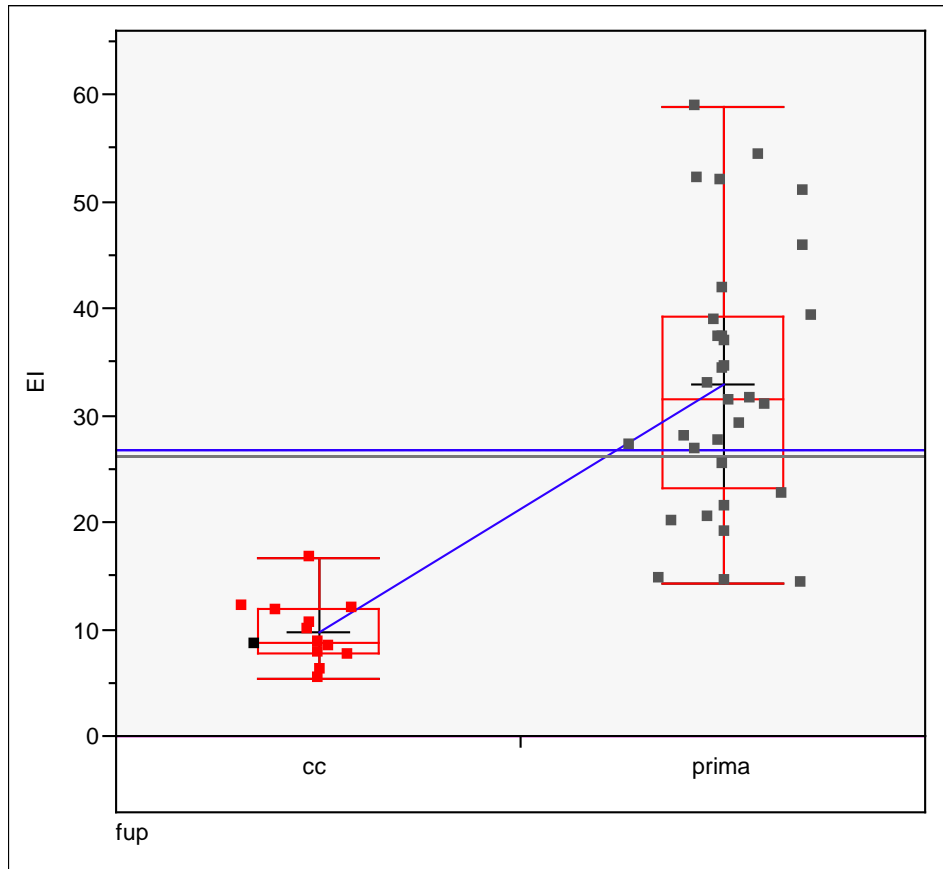
	LDDPRE	LDDPOST	SPAPRE	SPAPOST	GINPRE	GINPOST	ISPRE	ISPOST
N	32	32	32	32	32	32	32	32
Min	0	0	0	0	0	0	0	0
Max	95	48,3	41	7	51,69	16,62	75	58,33
Mean	30,9063	4,86125	9,04688	1,375	17,9816	2,57594	48,6972	35,6788
Std. error	4,9217	1,67911	1,75279	0,390151	2,1497	0,688173	3,41097	2,18947
Variance	775,141	90,2217	98,3122	4,87097	147,879	15,1546	372,311	153,4
Stand. dev	27,8414	9,49851	9,91525	2,20703	12,1606	3,89289	19,2954	12,3855
Median	25,32	1	6,75	0	13,54	0	58,33	41,67
Skewness	0,685053	3,14716	1,21406	1,17783	0,955015	1,649	-1,05453	-1,32802
Kurtosis	-0,712297	11,0693	1,2474	-0,192854	0,0957324	2,80092	0,470857	1,86287

Indice Endometriosi

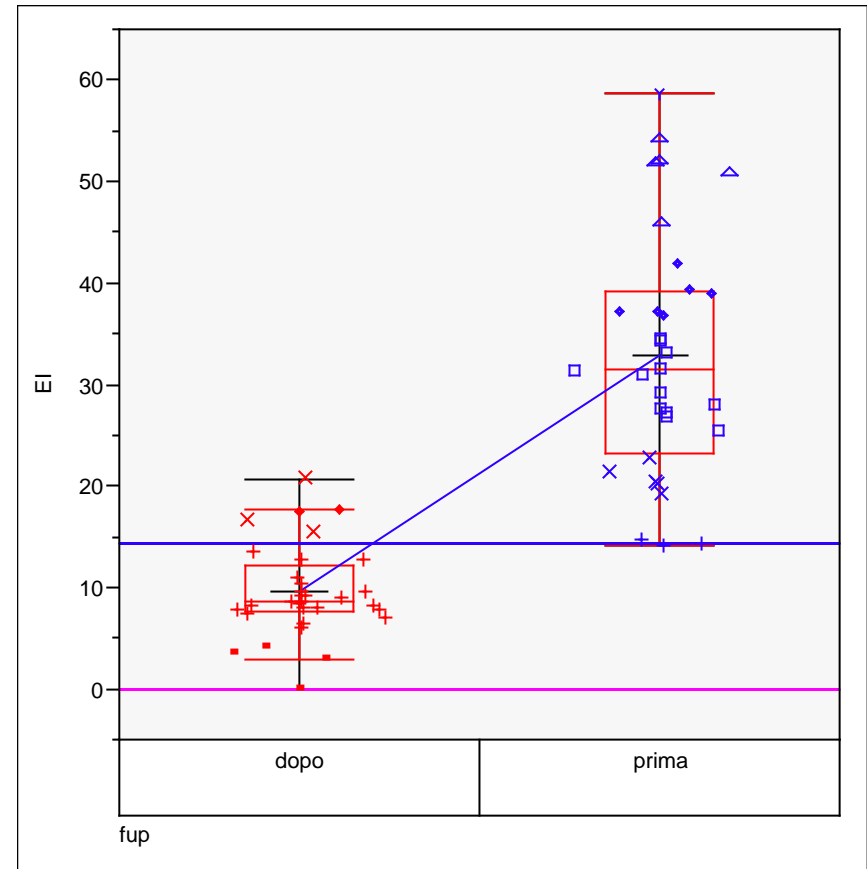
controlli

Univariate statistics							
	eta	El	dol	ldd	spa	gin	is
N	13	13	13	13	13	13	13
Min	30	5,34	3,16	0	0	0	25
Max	46	16,56	23,34	6	3	12,31	41,67
Mean	34,3846	9,62769	8,33769	1,17846	1,46154	1,32538	37,8231
Std. error	1,23277	0,826885	1,55206	0,560268	0,351104	0,960197	2,02751
Variance	19,7564	8,8886	31,3155	4,0807	1,60256	11,9857	53,4402
Stand. dev	4,44482	2,98138	5,59602	2,02007	1,26592	3,46204	7,31028
Median	34	8,76	5,46	0	2	0	41,67
Skewness	1,19371	0,660069	1,35245	1,21494	-0,148078	2,4384	-1,13343
Kurtosis	0,863502	-0,155528	1,17815	-0,0312833	-1,80069	4,82918	-0,756213

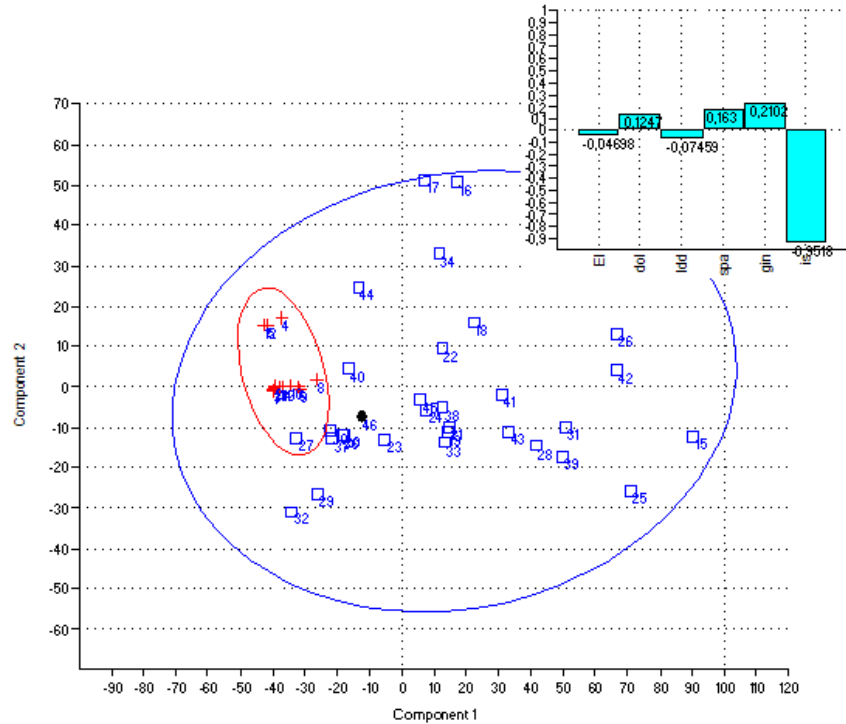
IE - Indicazione



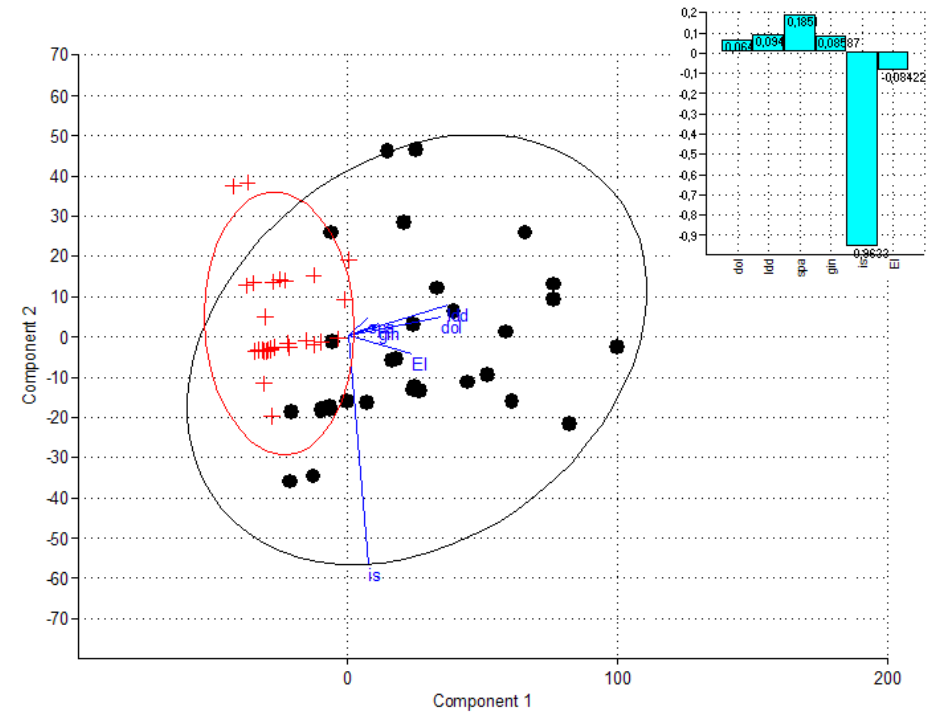
IE - Chirurgia



ANALISI COMPONENTI CTRL / PRE



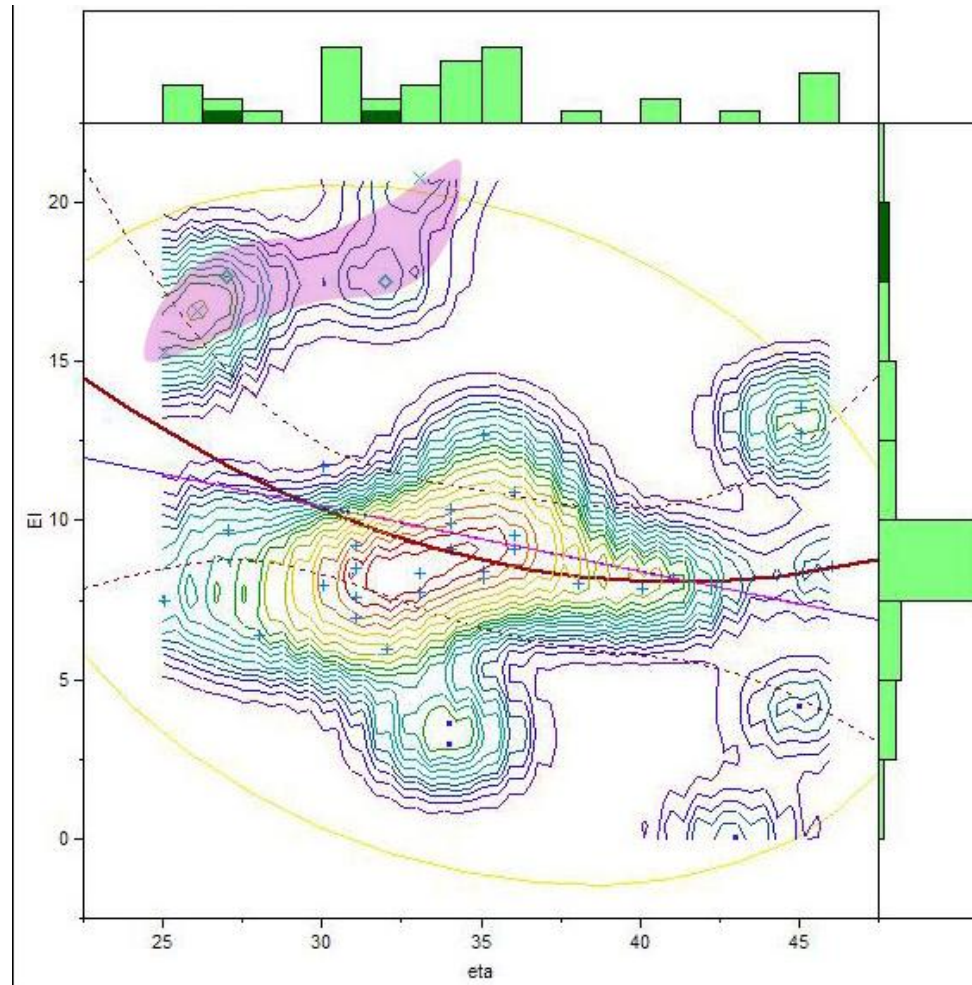
ANALISI COMPONENTI POST / PRE



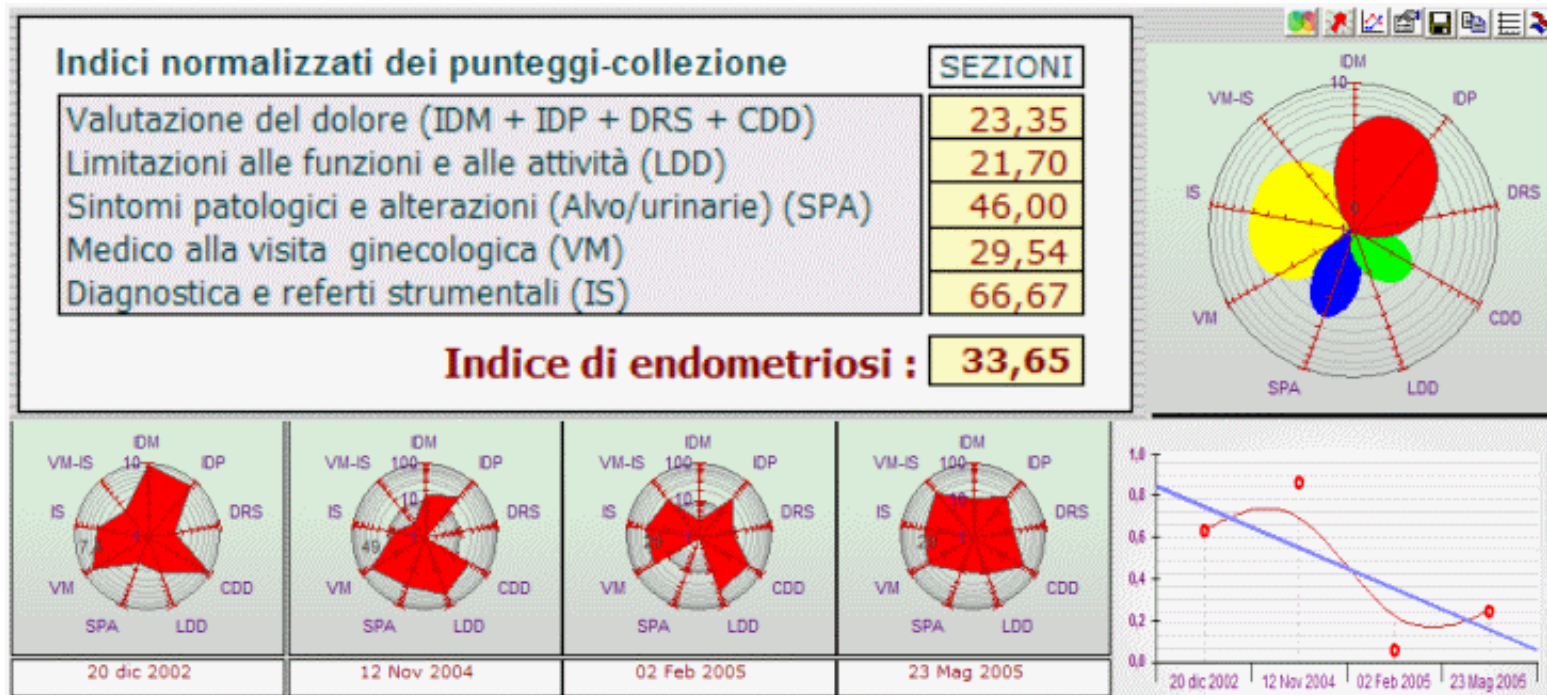
dopo la chirurgia le pazienti sono ricondotte dal nostro modello ad una distribuzione statisticamente confrontabile con quella di donne senza endometriosi

IE

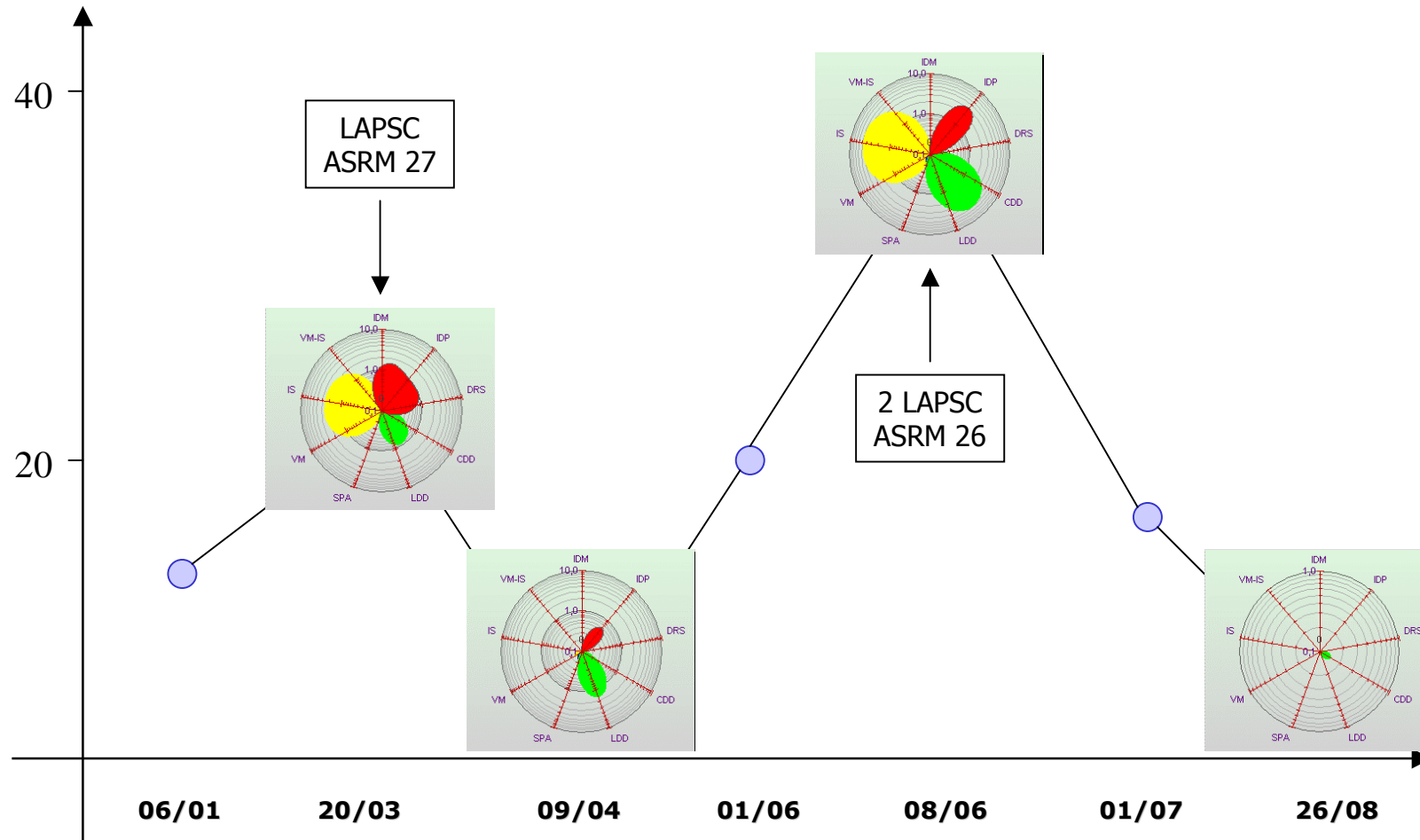
INDICATORE PROGNOSTICO / INDICATORE STATO PATOLOGICO



Dal momento che i valori dell'IPE sono discreti ed oggettivi la loro analisi può determinare **l'indicazione alla chirurgia**, suggerire la **ricidiva di malattia** e fornire sia dati prognostici che epidemiologici.



indicatore dello status patologico > recidiva



PREVENZIONE > CONOSCENZA PATOGENESI

- “MALATTIA SCONOSCIUTA”
- PATOLOGIA “RICORRENTE” —————> RICERCA
- “NON ESISTE UNA CURA”

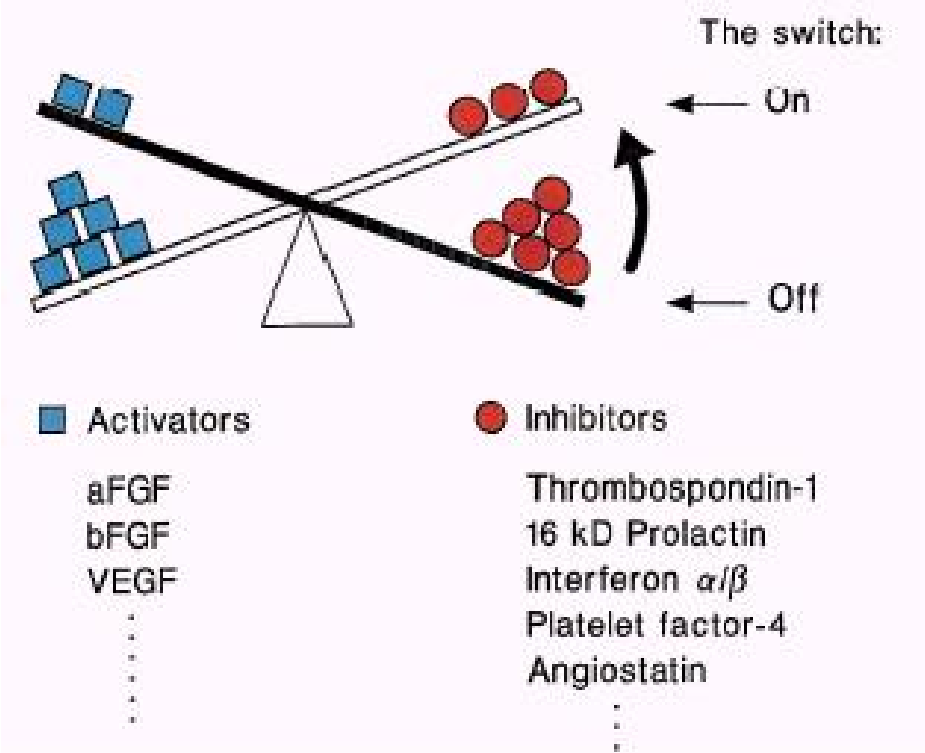
DIAGNOSI PRECOCE

- IDENTIFICAZIONE DELLE PAZIENTI CON ENDOMETRIOSI A STADI I / II



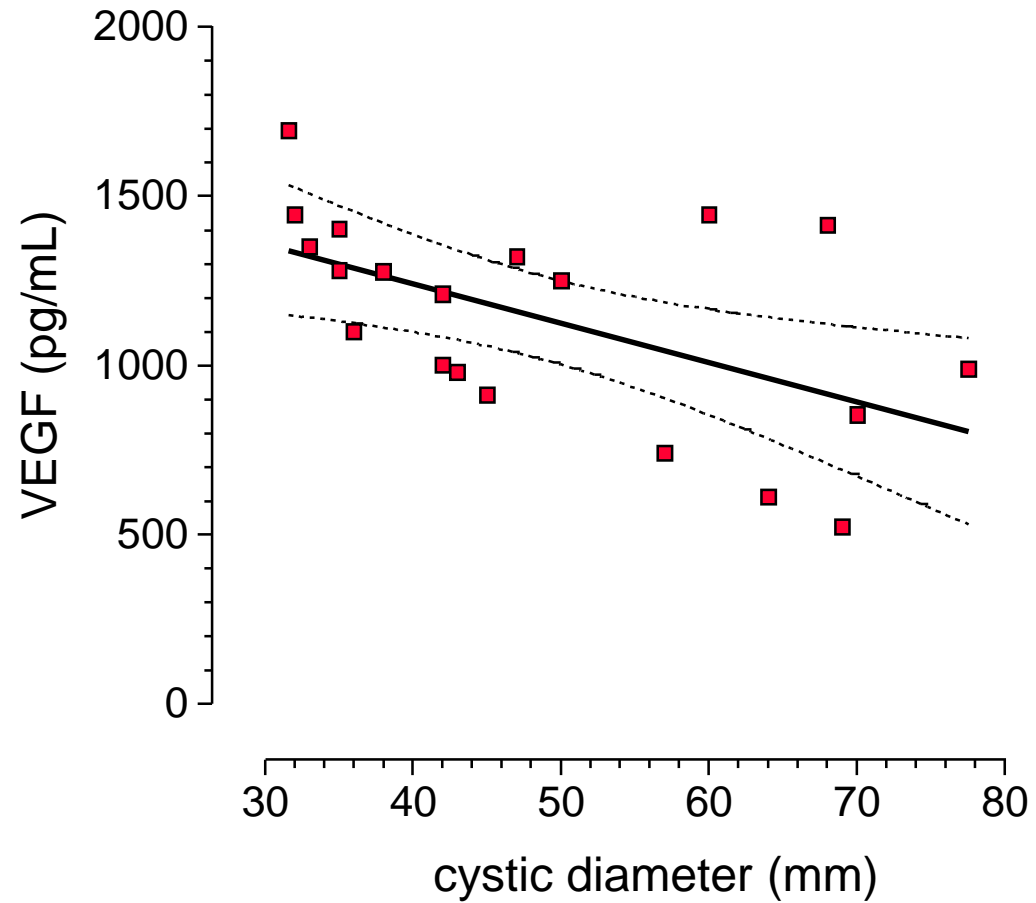
IPE

ENDOMETRIOSIS - ANGIOGENESIS

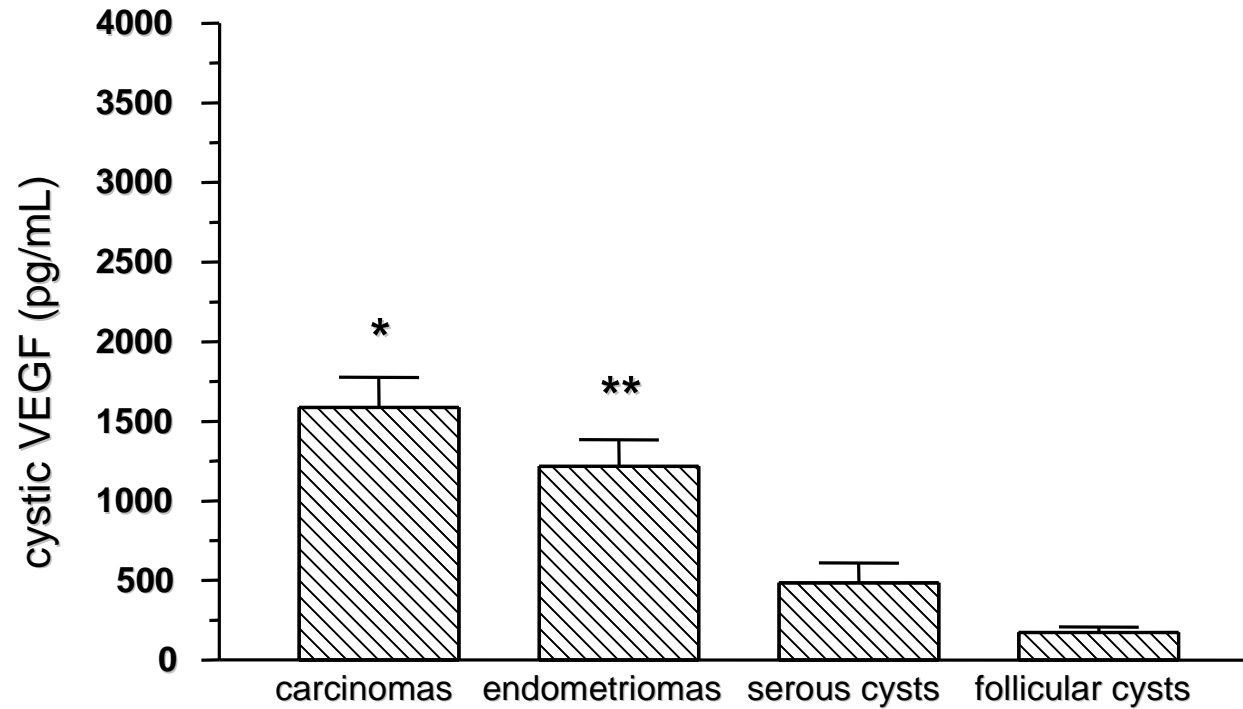


**THE VEGF CYSTIC FLUID CONCENTRATIONS ARE INVERSELY CORRELATED
TO THE DIAMETER OF THE OVARIAN ENDOMETRIOMATA**

(n = 20, r = 0.32, P = 0.162)



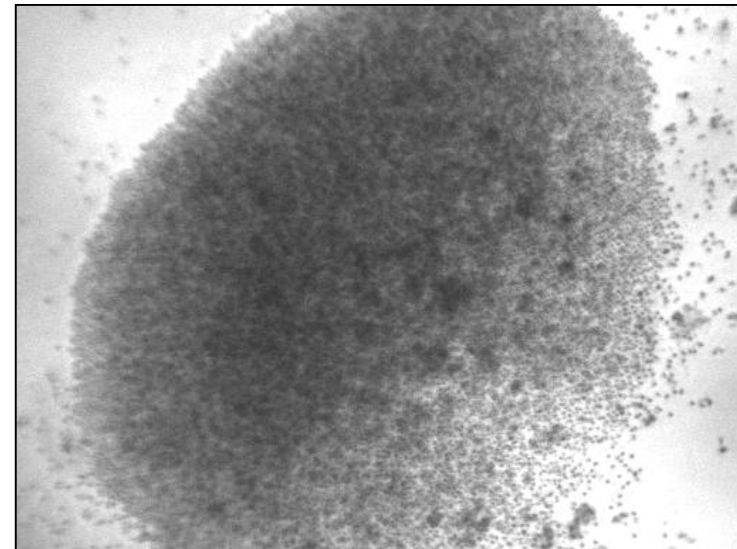
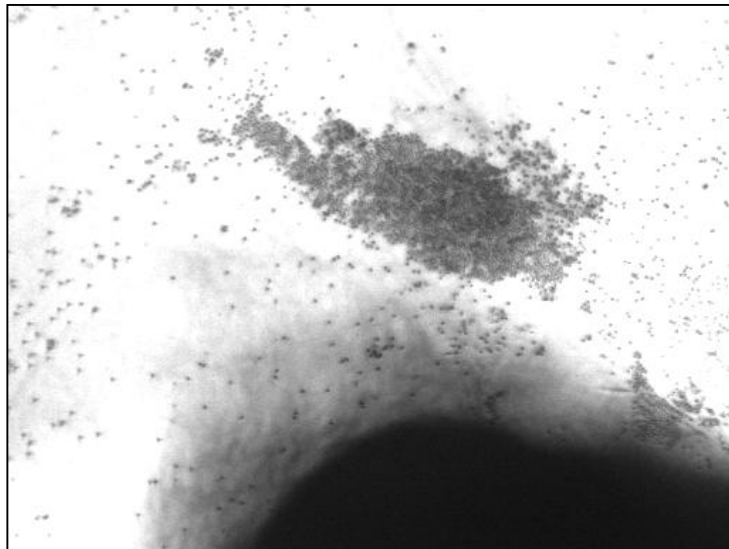
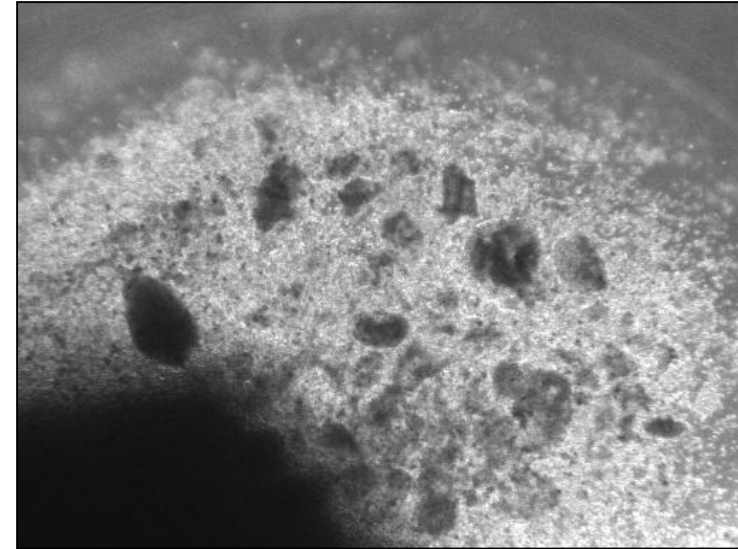
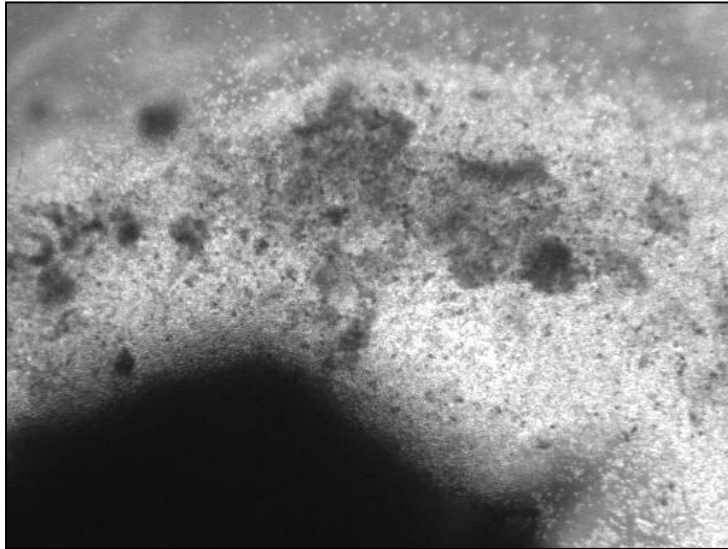
CYSTIC FLUID VEGF CONCENTRATIONS IN THE DIFFERENT HISTOLOGIC TYPES OF ADNEXAL MASSES



* Adenocarcinomas vs. Follicular and vs. Serous cysts ($P < 0.05$)

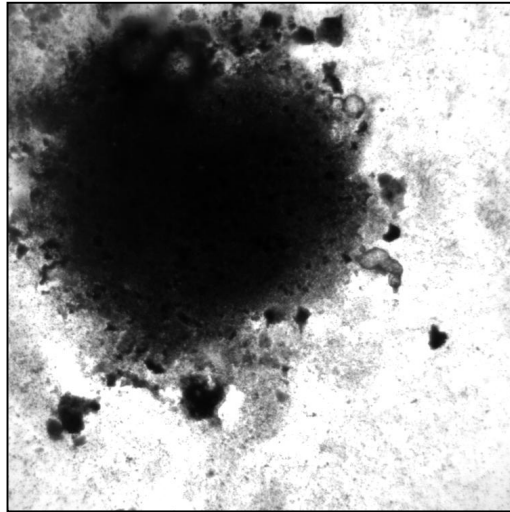
** Endometriomas vs. Follicular and vs. Serous cysts ($P < 0.05$)

**3D CULTURE OF ENDOMETRIUM TO MIMIC
THE EARLY STEPS OF ITS GROWTH**

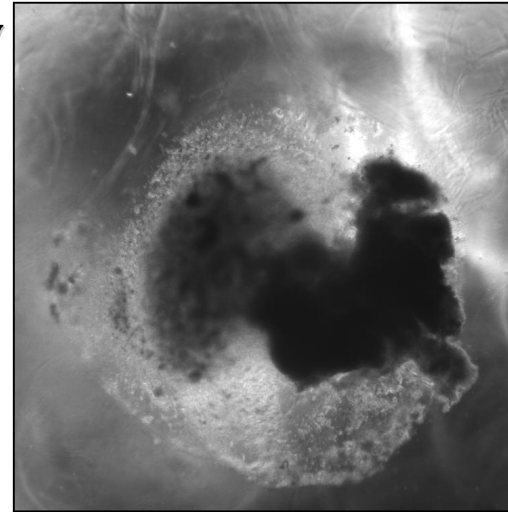


**3D CULTURE OF ENDOMETRIUM TO MIMIC
THE EARLY STEPS OF ITS GROWTH**

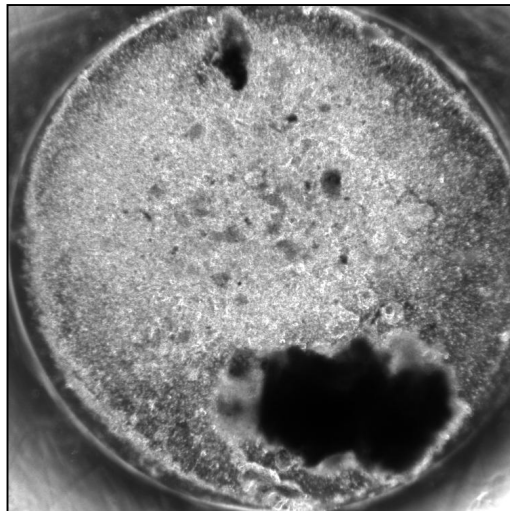
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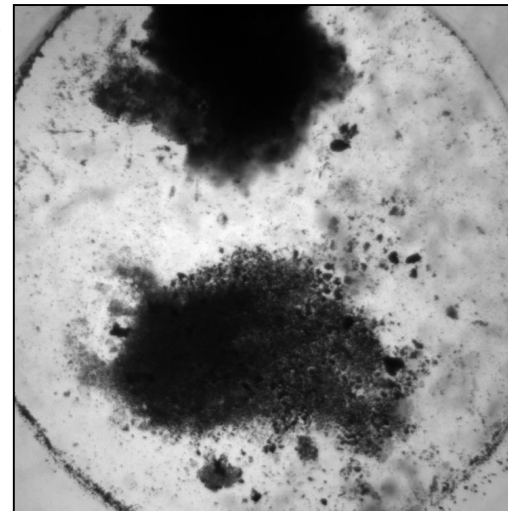
2nd w



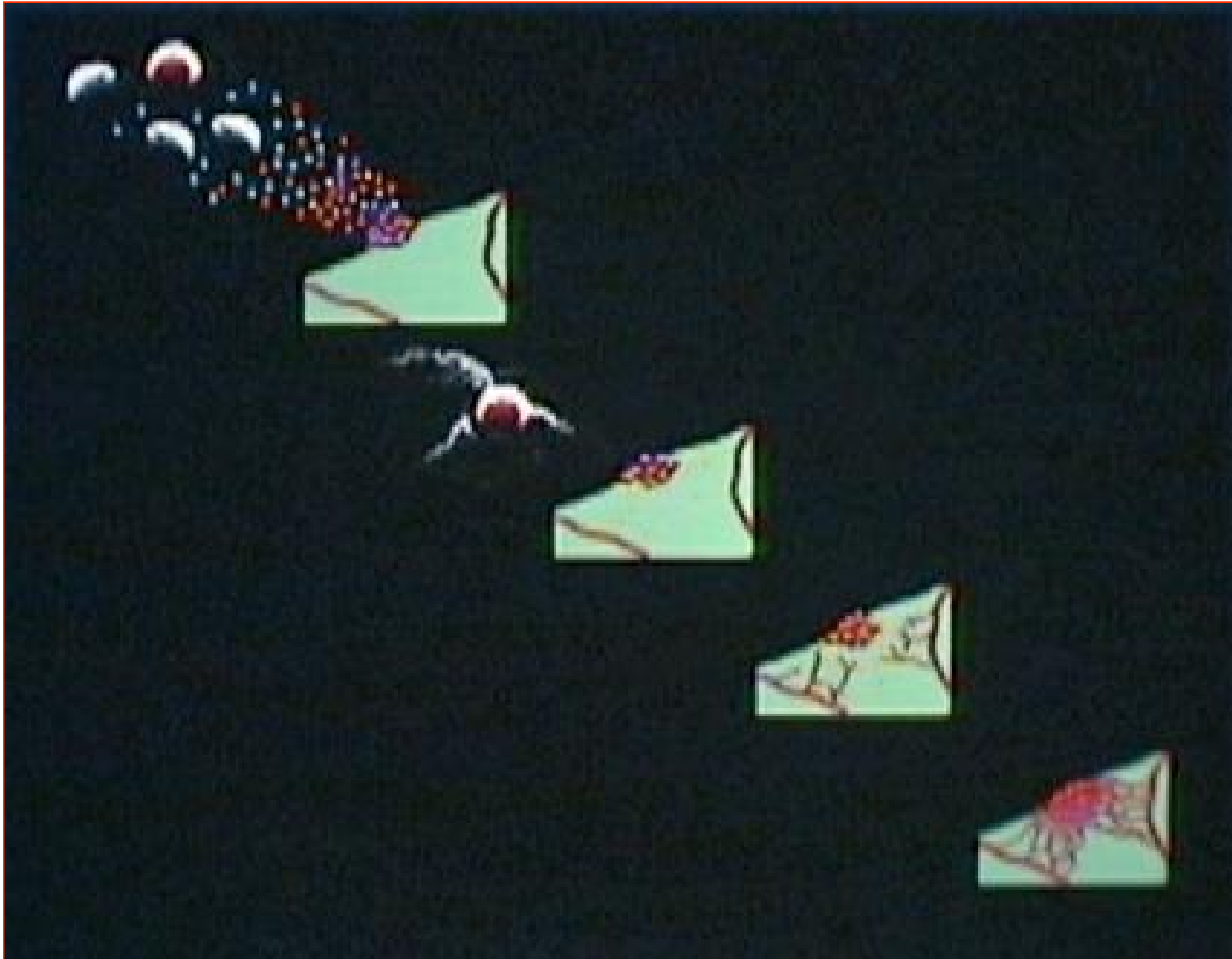
3rd w



4th w



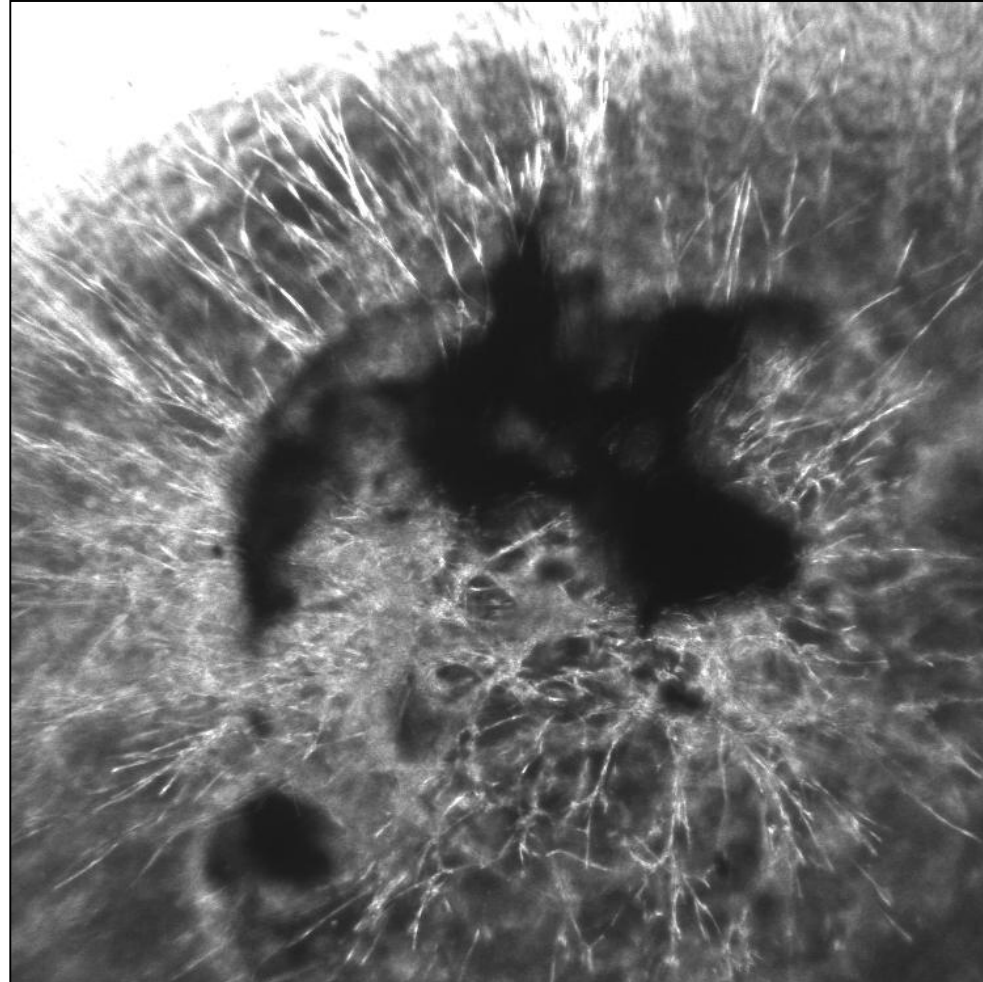
ENDOMETRIOSIS - ANGIOGENESIS



**3D CULTURE OF ENDOMETRIUM TO MIMIC
THE EARLY STEPS OF ITS GROWTH**



**3D CULTURE OF ENDOMETRIUM TO MIMIC
THE EARLY STEPS OF ITS GROWTH**



Recently, the induction of an angiogenic phenotype in human endometriotic cells has been shown *pari passu* by the establishment of their ability to implant.

The endometrial fragments, similarly to tumour metastases, follow two basic steps to generate endometriosis:

1. implantation
2. acquisition of a new blood supply through angiogenesis.

However, because of the inability to identify patients with early stage disease, mechanisms that control the implantation and growth of the ectopic implants remain elusive.

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Three-dimensional in vitro culture of endometrial explants mimics the early stages of endometriosis

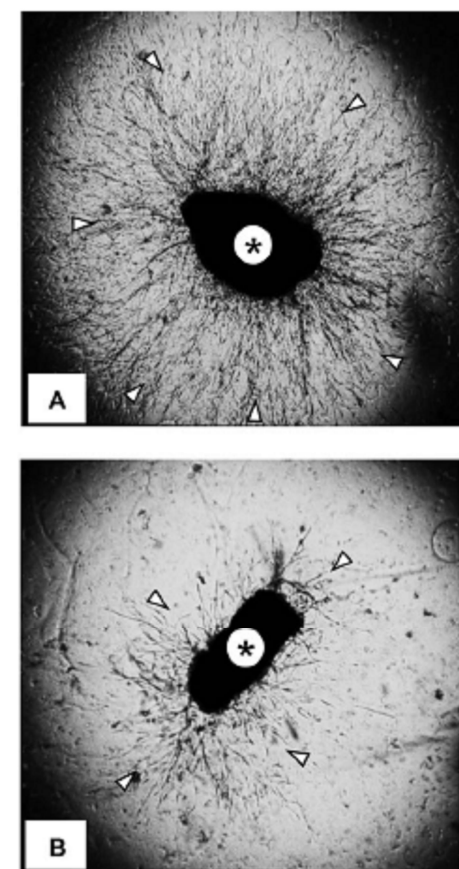
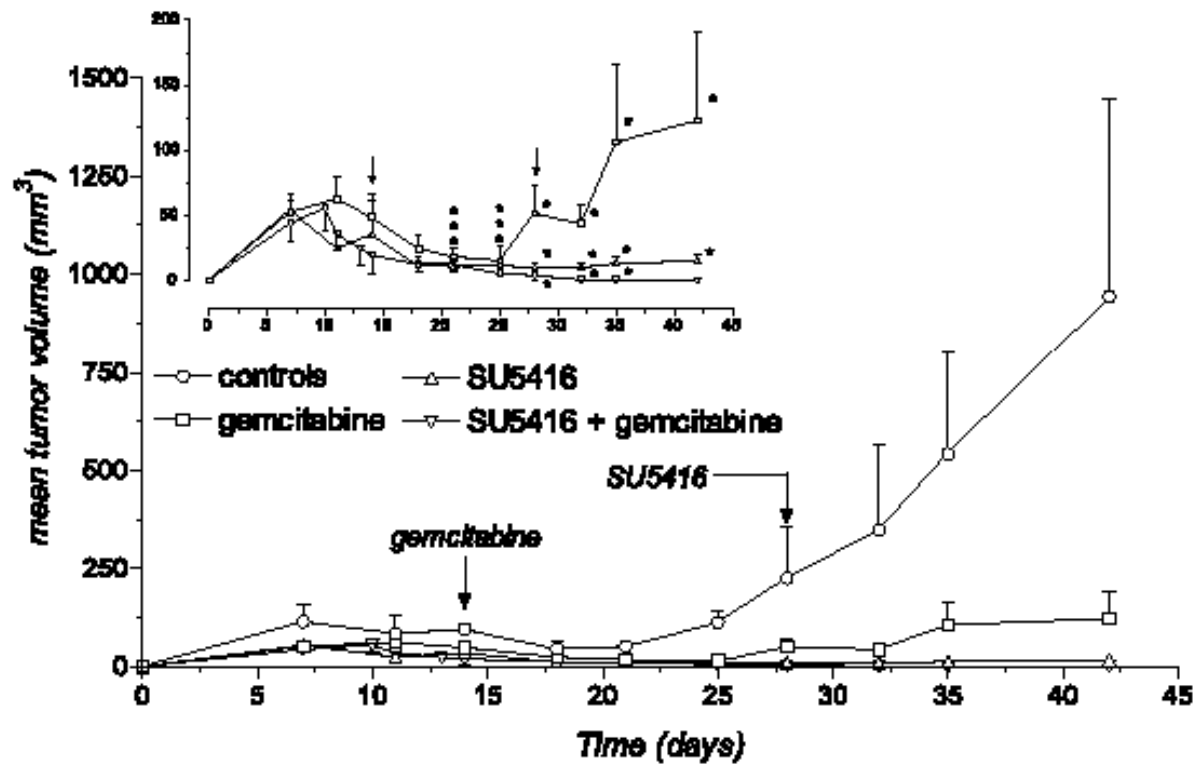
*Alessandro Fasciani, M.D.,^a Guido Bocci, M.D.,^b Jing Xu, M.D., Ph.D.,^a
Ryszard Bielecki, D.V.M.,^a Ellen Greenblatt, M.D.,^a Nicholas Leyland, M.D.,^a and
Robert F. Casper, M.D.^a*

*Department of Obstetrics and Gynecology, Samuel Lunenfeld Research Institute, Mount Sinai Hospital,
University of Toronto, Toronto, Ontario, Canada*

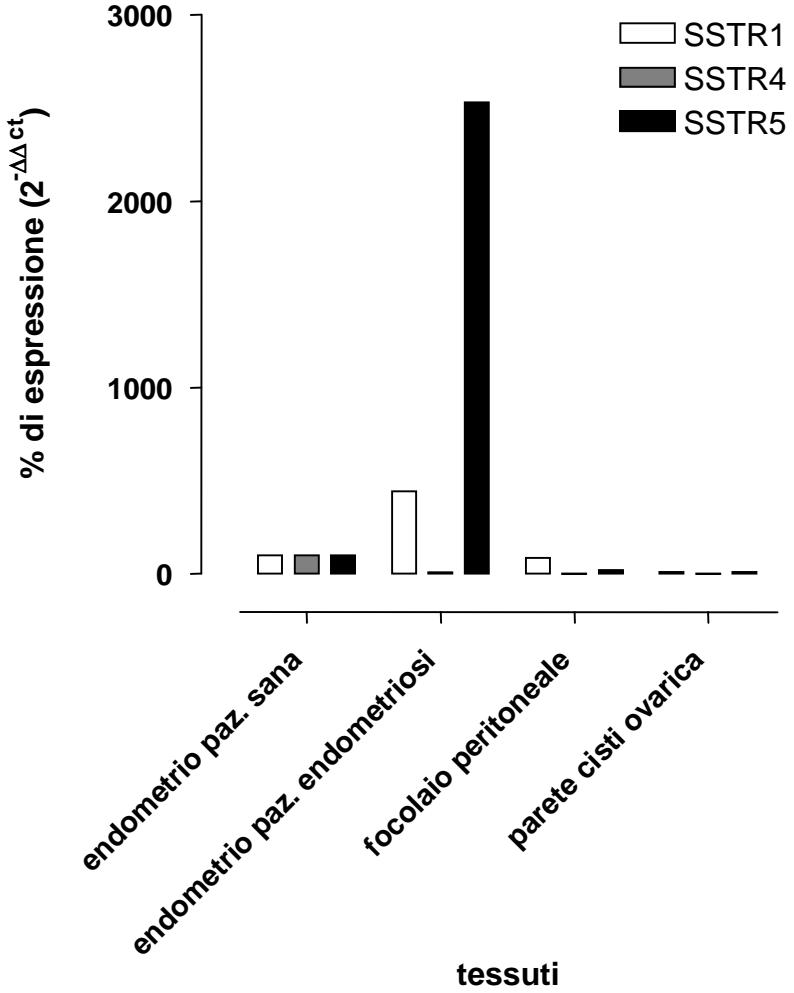
This system may recapitulate the very earliest development of endometriosis and may prove to be useful for screening new drug strategies for the treatment/prevention of endometriosis.

Antiangiogenic versus cytotoxic therapeutic approaches to human pancreas cancer: an experimental study with a vascular endothelial growth factor receptor-2 tyrosine kinase inhibitor and gemcitabine

3.2. Inhibition of endothelial cell culture from placental blood vessel by SU5416



PCR QUANTITATIVA



GRAZIE

Dr. Repetti
Dr. Costa
Prof. Dagna Bricarelli

Dr. Reina

Dr. Colia
Dr. Moneta
Dr. Bottazzi
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Endometriosis and infertility

The Practice Committee of the American Society for Reproductive Medicine

Birmingham, Alabama

quently, a clinical staging system is necessary to allow clinicians to communicate effectively regarding prognosis and treatment. The American Society for Reproductive Medicine revised classification system for endometriosis (ASRM 1996) is the most widely accepted staging system (19).

Unfortunately, the staging system does not correlate well with a woman's chance of conception following therapy. This poor predictive ability is related to the arbitrary assignment of a point score for the observed pathology and the arbitrary cut-off points chosen to establish the stage of disease. The ASRM 1996 classification system might be enhanced by including a description of the morphologic subtype of disease or other biological markers (20). It is unlikely that any accurate staging system will be introduced until we have a better understanding of the pathophysiology of endometriosis-associated infertility.



AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE
REVISED CLASSIFICATION OF ENDOMETRIOSIS

Patient's Name _____ Date _____
 Stage I (Minimal) - 1-5
 Stage II (Mild) - 6-15
 Stage III (Moderate) - 16-40
 Stage IV (Severe) - >40
 Total _____
 Laparoscopy _____ Laparotomy _____ Photography _____
 Recommended Treatment _____
 Prognosis _____

PERTONEUM	ENDOMETRIOSIS	< 1cm	1-5cm	> 5cm
	Superficial	1	2	4
Deep	2	4	6	
OVARY	R Superficial	1	2	4
	Deep	4	16	20
	L Superficial	1	2	4
	Deep	4	16	20
POSTERIOR CULDESAC OBLITERATION	Partial	4		Complete
		4		40
OVARY	ADHESIONS	< 1/3 Enclosure	1/3-2/3 Enclosure	> 2/3 Enclosure
	R Filmy	1	2	4
	Dense	4	8	16
	L Filmy	1	2	4
	Dense	4	8	16
	TUBE	R Filmy	1	2
Dense		4	8	16
L Filmy		1	2	4
Dense		4	8	16

*If the fimbriated end of the fallopian tube is completely enclosed, change the point assignment to 16.
 Denote appearance of superficial implants types as red (R), red, red-pink, flame-like, vesicular blots, clear vesicles; white (W), opacifications, peritoneal defects, yellow-brown; or black (B) black, hemosiderin deposits, blue. Denote percent of total described as R____%, W____% and B____%. Total should equal 100%.

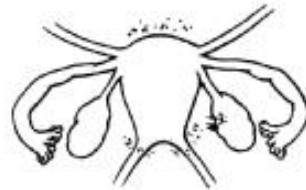
Additional Endometriosis: _____

Associated Pathology: _____



EXAMPLES & GUIDELINES

STAGE I (MINIMAL)



PERITONEUM		
Superficial Endo	- 1-3cm	- 2
R. OVARY		
Superficial Endo	- < 1cm	- 1
Filmy Adhesions	- < 1/3	- 1
TOTAL POINTS		<u>4</u>

STAGE II (MILD)



PERITONEUM		
Deep Endo	- > 3cm	- 6
R. OVARY		
Superficial Endo	- < 1cm	- 1
Filmy Adhesions	- < 1/3	- 1
L. OVARY		
Superficial Endo	- < 1cm	- 1
TOTAL POINTS		<u>9</u>

STAGE III (MODERATE)



PERITONEUM		
Deep Endo	- > 3cm	- 6
CULDESAC		
Partial Obliteration		- 4
L. OVARY		
Deep Endo	- 1-3cm	- 16
TOTAL POINTS		<u>26</u>

STAGE III (MODERATE)



PERITONEUM		
Superficial Endo	- > 3cm	- 4
R. TUBE		
Filmy Adhesions	- < 1/3	- 1
R. OVARY		
Filmy Adhesions	- < 1/3	- 1
L. TUBE		
Dense Adhesions	- < 1/3	- 16*
L. OVARY		
Deep Endo	- < 1 cm	- 4
Dense Adhesions	- < 1/3	- 4
TOTAL POINTS		<u>30</u>

STAGE IV (SEVERE)



PERITONEUM		
Superficial Endo	- > 3cm	- 4
L. OVARY		
Deep Endo	- 1-3cm	- 32**
Dense Adhesions	- < 1/3	- 8**
L. TUBE		
Dense Adhesions	- < 1/3	- 8**
TOTAL POINTS		<u>52</u>

*Point assignment changed to 16

**Point assignment doubled

STAGE IV (SEVERE)



PERITONEUM		
Deep Endo	- > 3cm	- 6
CULDESAC		
Complete Obliteration		- 40
R. OVARY		
Deep Endo	- 1-3cm	- 16
Dense Adhesions	- < 1/3	- 4
L. TUBE		
Dense Adhesions	- > 2/3	- 16
L. OVARY		
Deep Endo	- 1-3cm	- 16
Dense Adhesions	- > 2/3	- 16
TOTAL POINTS		<u>114</u>

Determination of the stage or degree of endometrial involvement is based on a weighted point system. Distribution of points has been arbitrarily determined and may require further revision or refinement as knowledge of the disease increases.

To ensure complete evaluation, inspection of the pelvis in a clockwise or counterclockwise fashion is encouraged. Number, size and location of endometrial implants, plaques, endometriomas and/or adhesions are noted. For example, five separate 0.5cm superficial implants on the peritoneum (2.5 cm total) would be assigned 2 points. (The surface of the uterus should be considered peritoneum.) The severity of the endometriosis or adhesions should be assigned the highest score only for peritoneum, ovary, tube or culdesac. For example, a 4cm superficial and a 2cm deep implant of the peritoneum should be given a score of 6 (not 8). A 4cm

deep endometrioma of the ovary associated with more than 3cm of superficial disease should be scored 20 (not 24).

In those patients with only one adenexa, points applied to disease of the remaining tube and ovary should be multiplied by two. **Points assigned may be circled and totaled. Aggregation of points indicates stage of disease (minimal, mild, moderate, or severe).

The presence of endometriosis of the bowel, urinary tract, fallopian tube, vagina, cervix, skin etc., should be documented under "additional endometriosis." Other pathology such as tubal occlusion, leiomyomata, uterine anomaly, etc., should be documented under "associated pathology." All pathology should be depicted as specifically as possible on the sketch of pelvic organs, and means of observation (laparoscopy or laparotomy) should be noted.

Diagnosis of pelvic endometriosis with use of macroscopic versus histologic findings

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Objective: To obtain histologic confirmation of lesions suspected of endometriosis at laparoscopy.

Design: Prospective clinical study.

Setting: Patients in an academic hospital.

Patient(s): Women of reproductive age who complained of chronic pelvic pain.

Intervention(s): A total of 122 biopsies were obtained from 54 patients undergoing laparoscopy, after exclusion of other potential causes of pelvic pain.

Main Outcome Measure(s): Lack of consistency between laparoscopic and histologic diagnosis of endometriosis, in particular for minimal/mild stages.

Results: Endometriosis was confirmed by histology in 54% of the excised lesions. Diagnosis was more often confirmed among classic lesions than for all atypical lesions considered together. The histologic diagnosis of fibrosis was the most common among those biopsies, which lacked the presence of endometriosis. The revised American Fertility Association (AFS) scores before and after histologic confirmation differed significantly. In particular, 20 patients in either revised AFS class I or II were down-graded to stage 0. No single anatomical site turned out to be particularly prone to misdiagnosis at laparoscopy, in comparison to the other sites.

Conclusion(s): These results confirm the need of histologic confirmation to obtain a diagnosis of endometriosis.

However, the clinical impact of such findings remains a matter of debate. (*Fertil Steril*® 2005;84:12–5. ©2005 by American Society for Reproductive Medicine.)

Key Words: Pelvic endometriosis, diagnosis, laparoscopy, histology