The Art and Science of Endometriosis:
Standardizing the Measurement of Pain and Diagnostic Criteria

New Orleans, October 20th 2006

CORRELATION BETWEEN LESIONS AND PAIN

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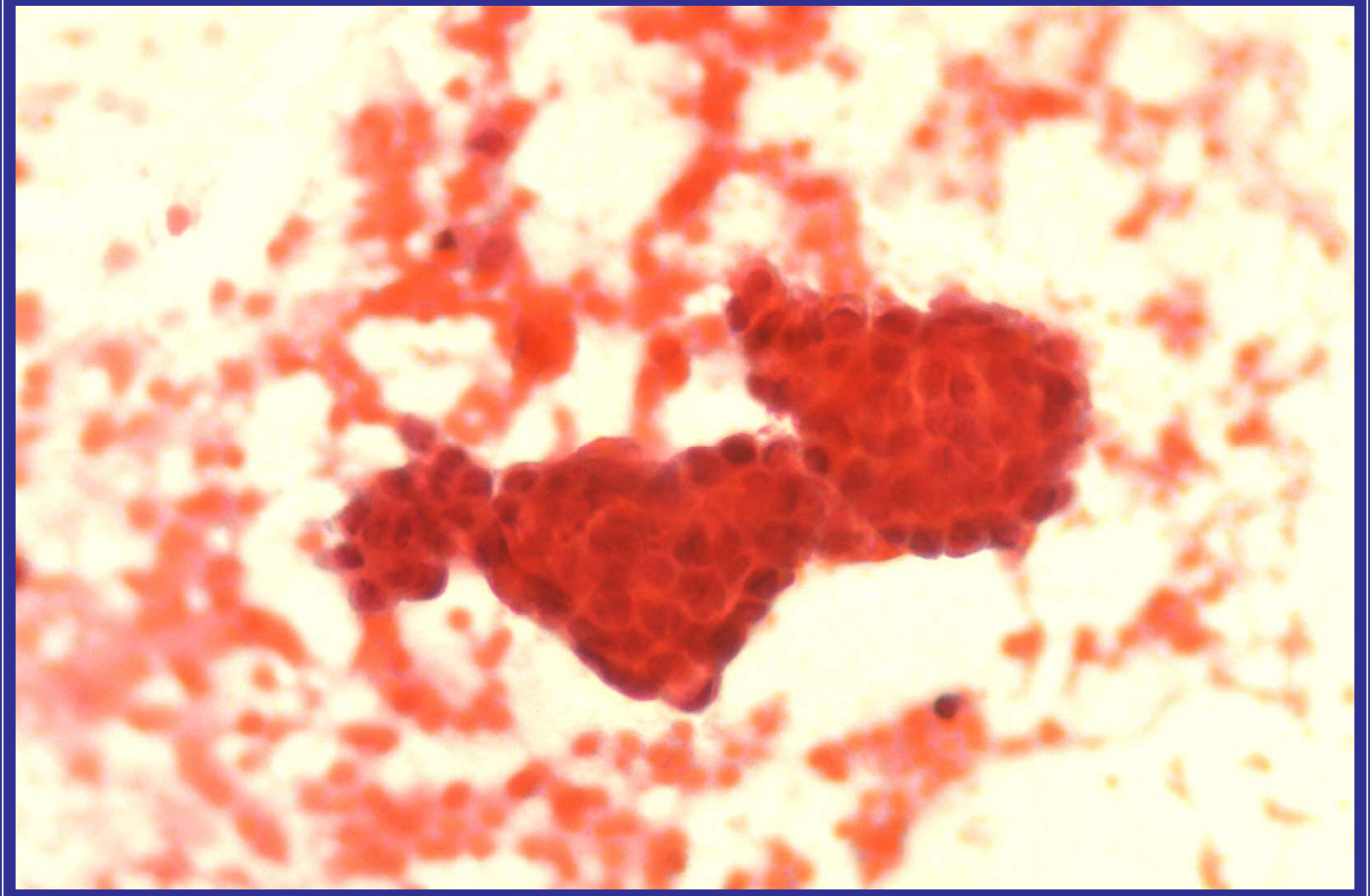
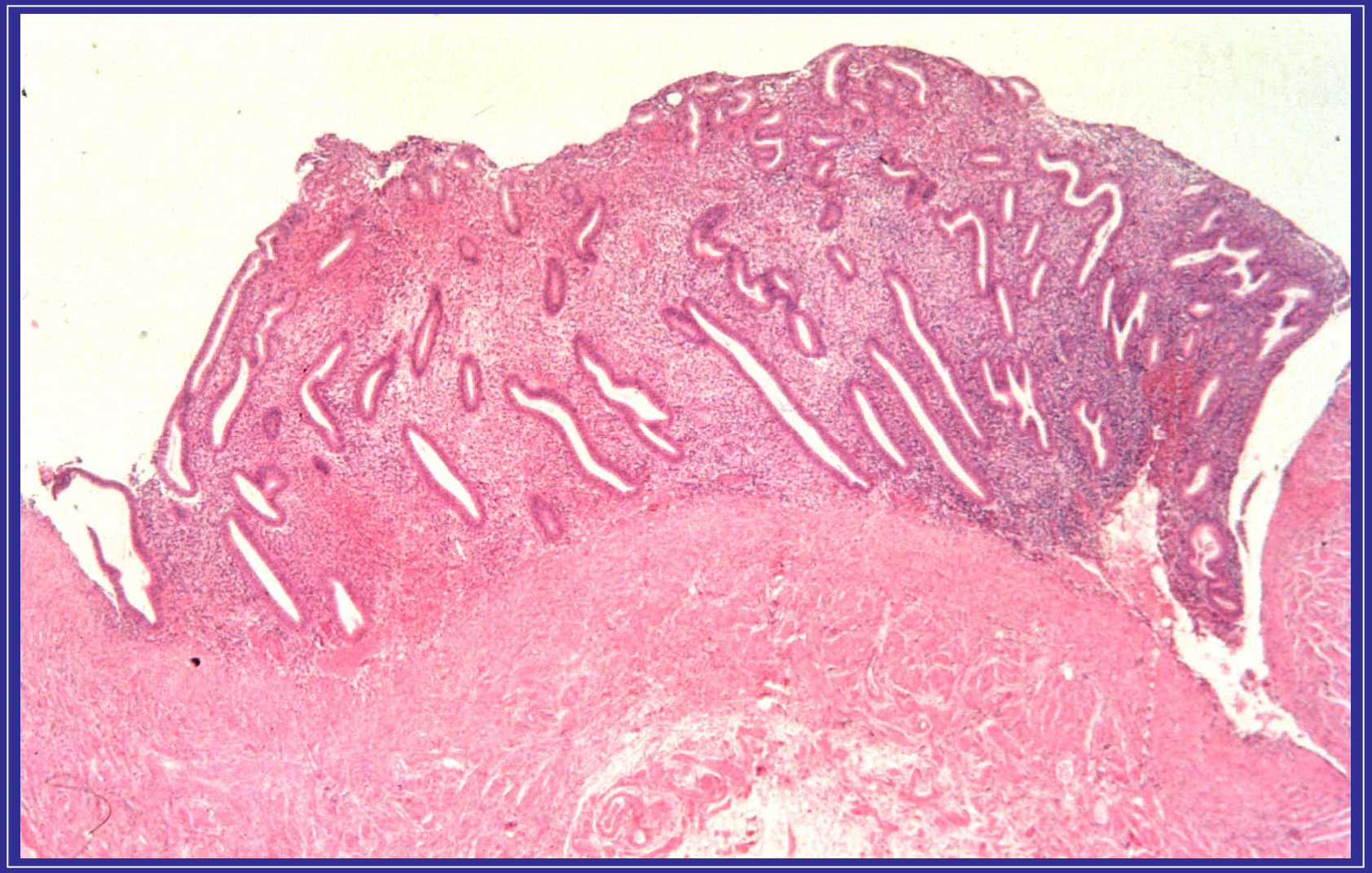
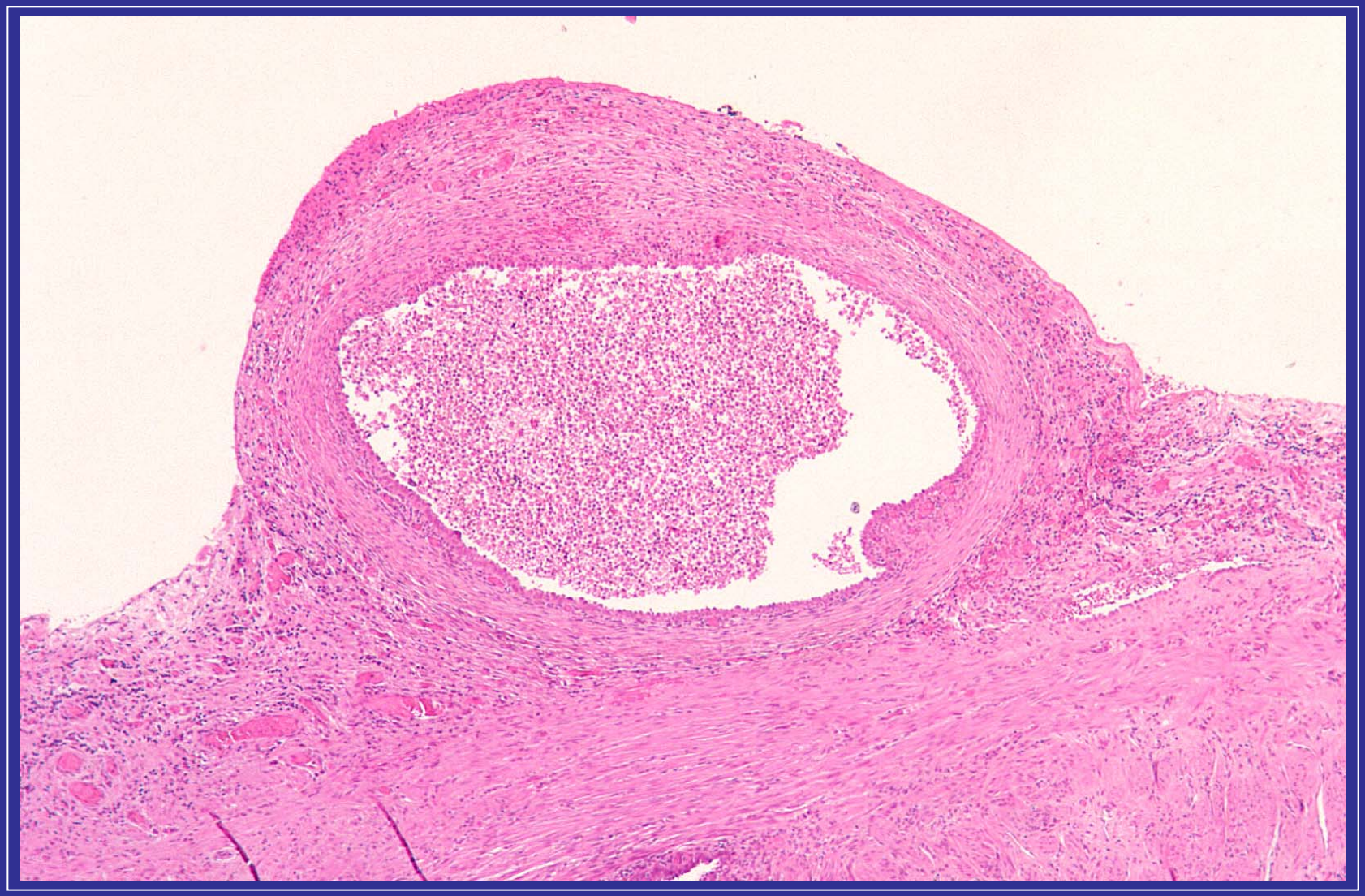
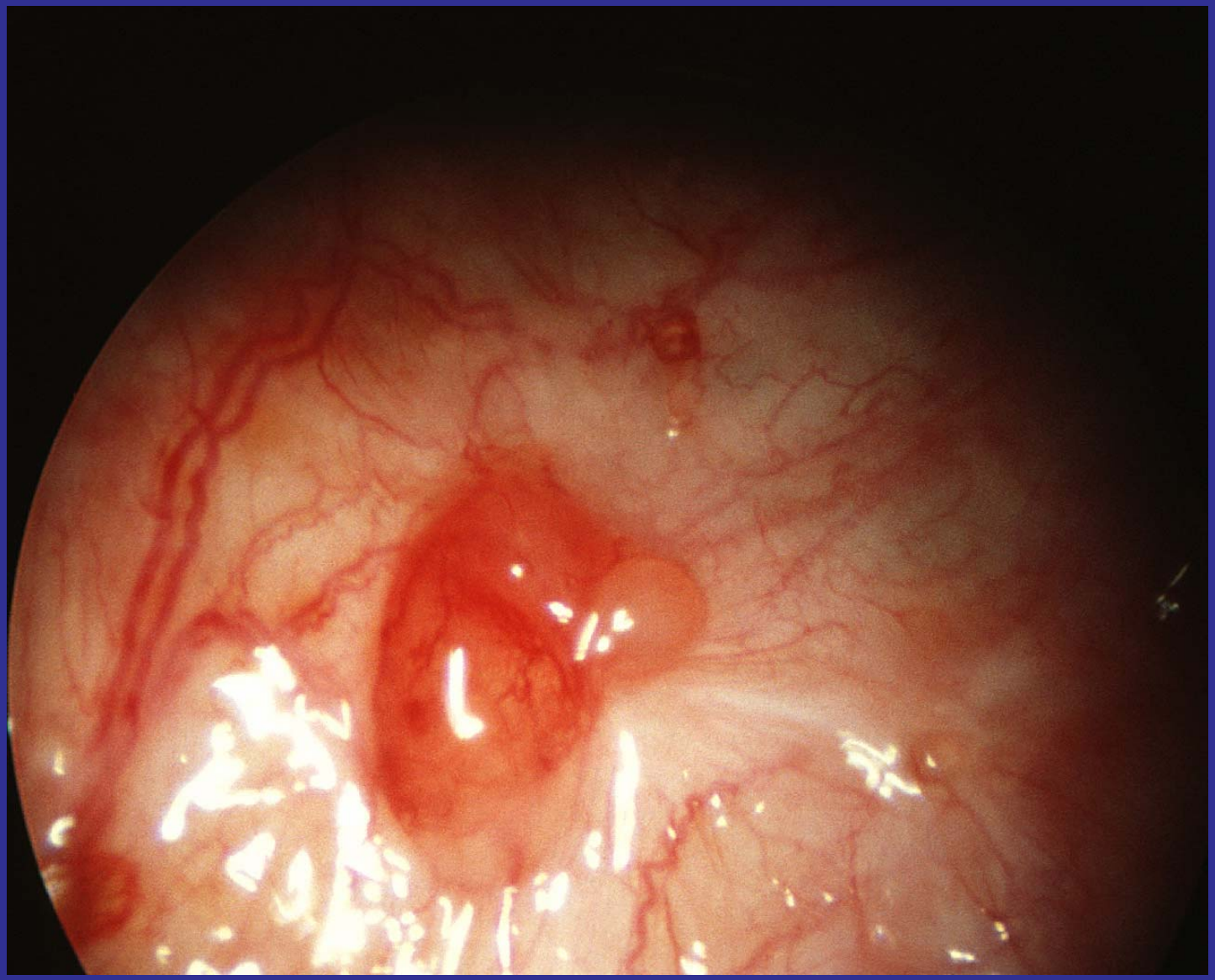
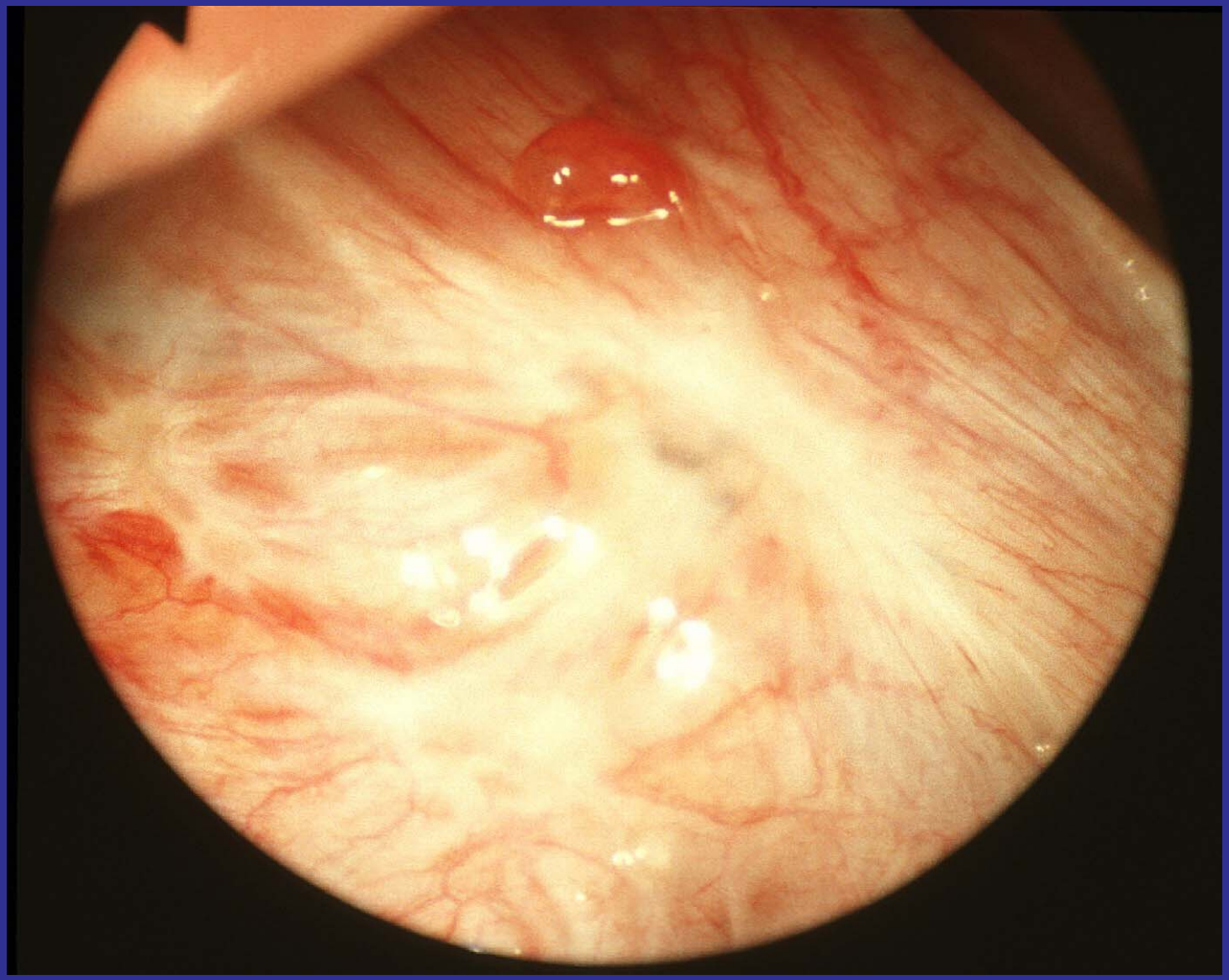
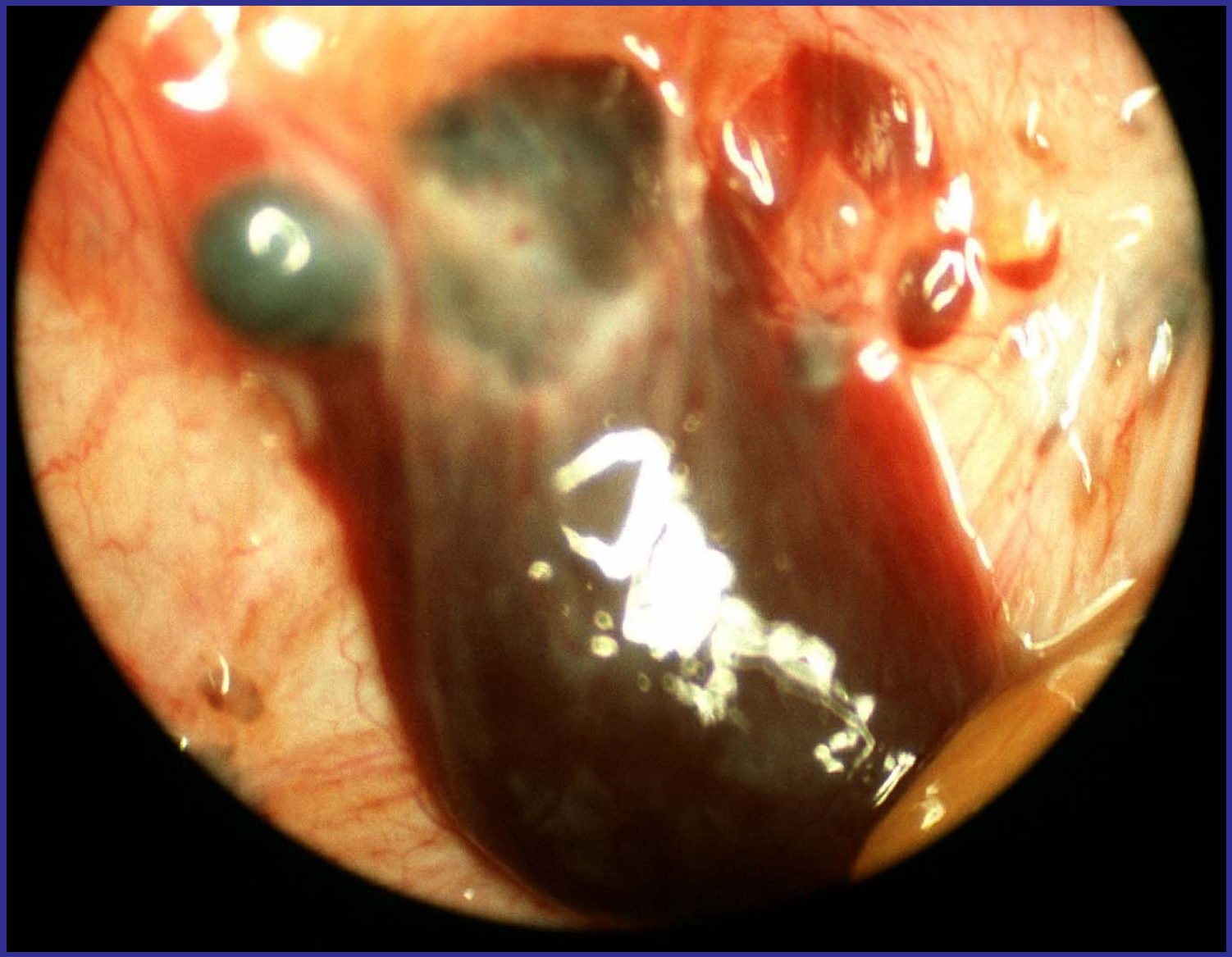


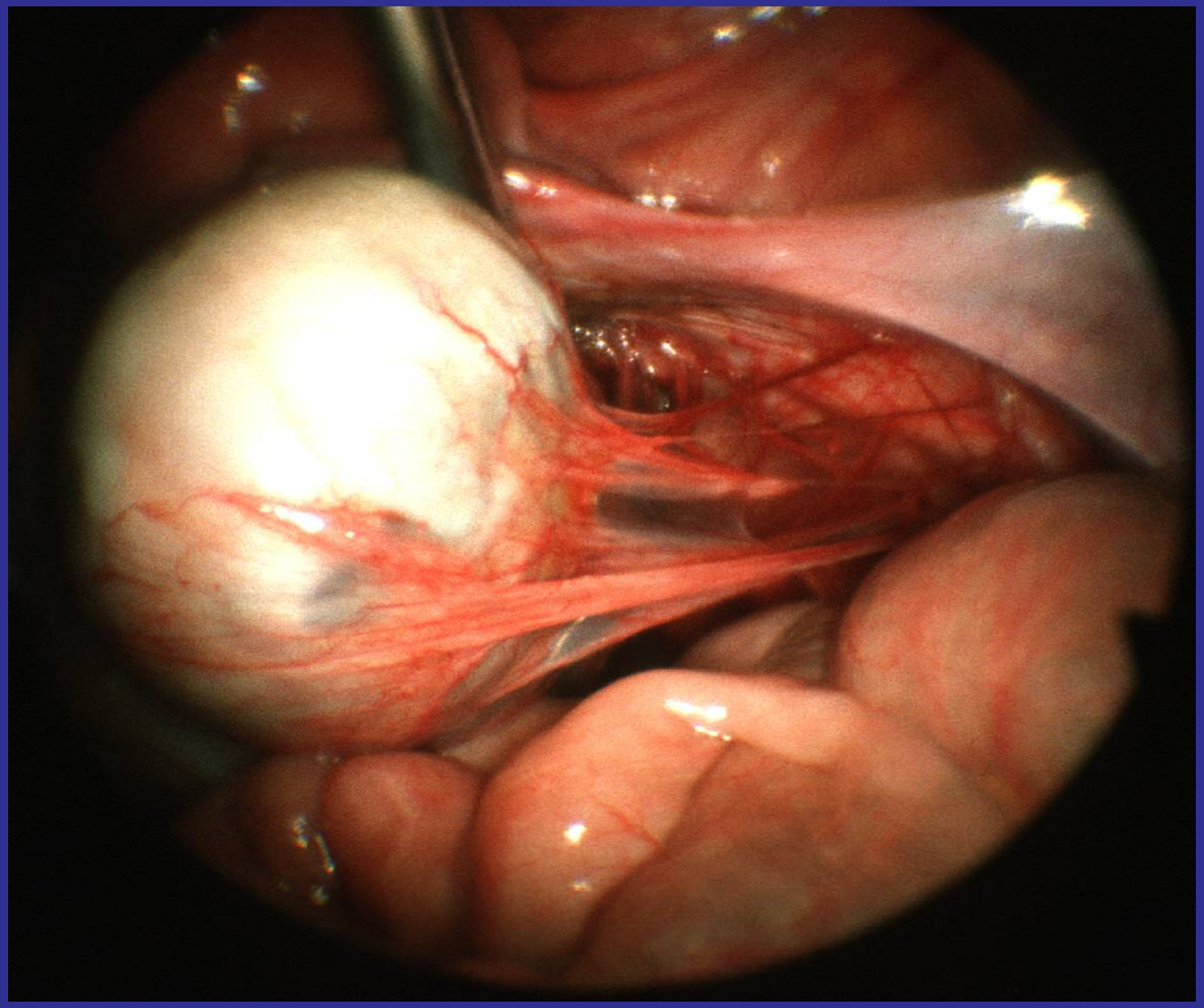




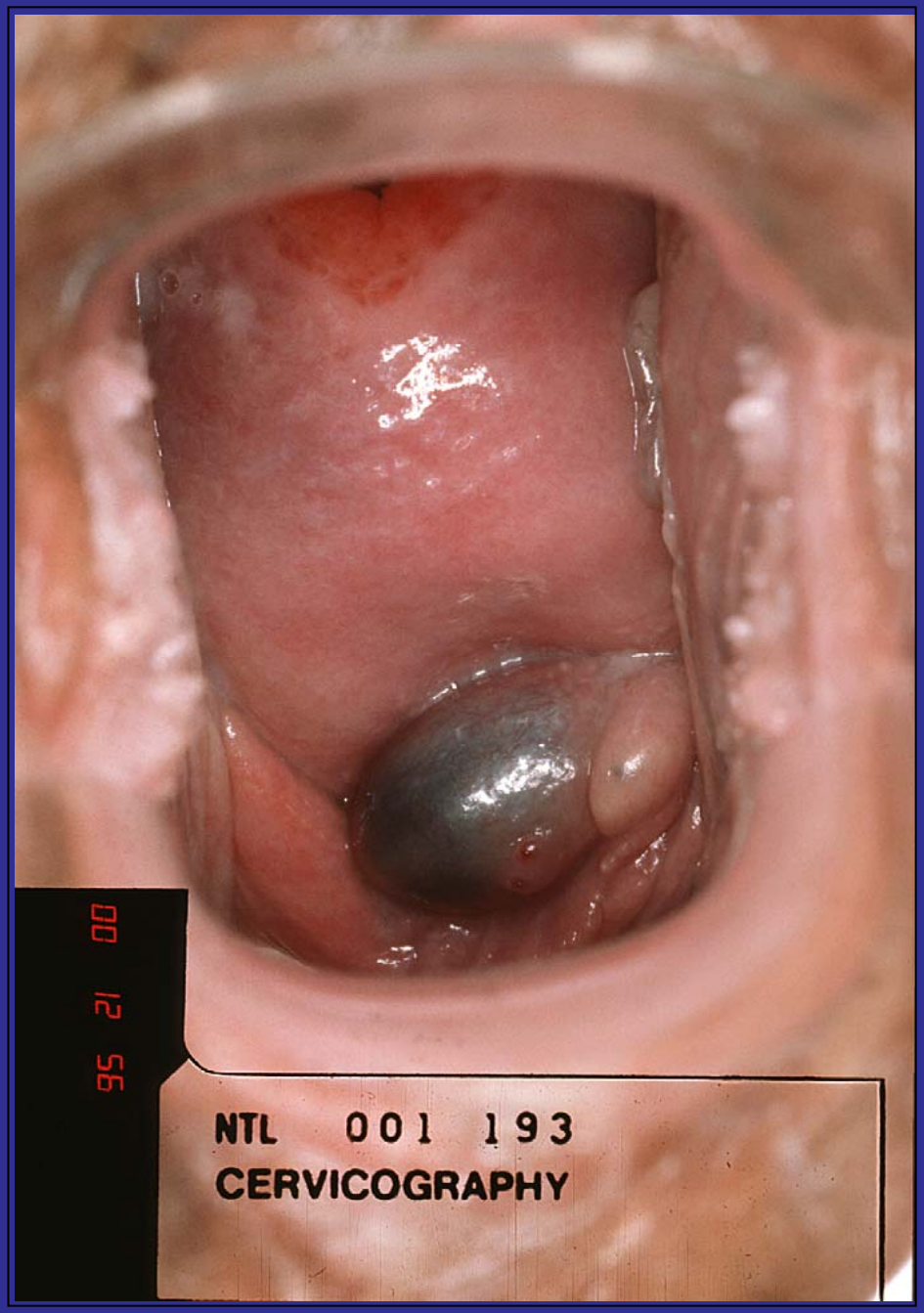








Colposcopic appearance of the posterior fornix with reddish vegetations and a bluish nodule



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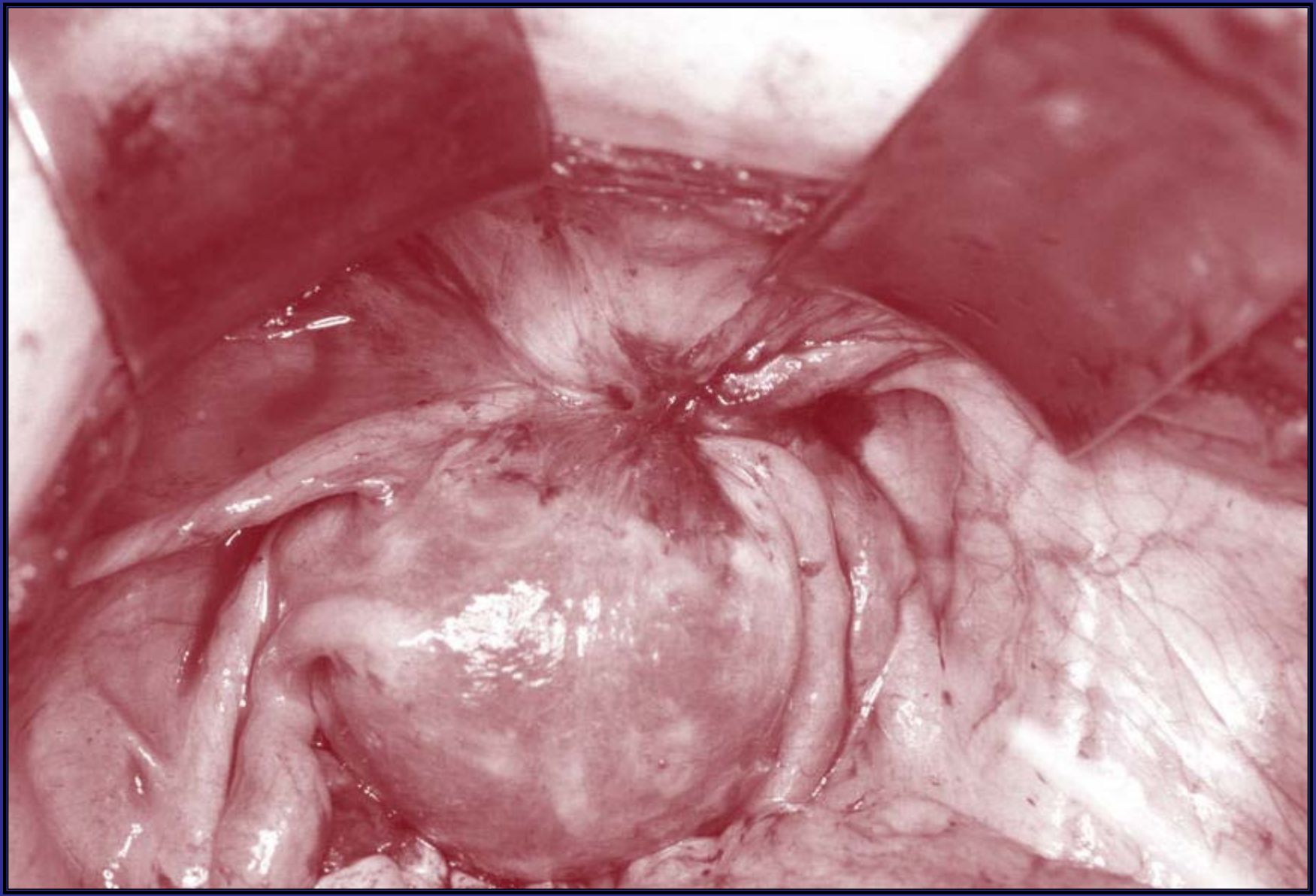
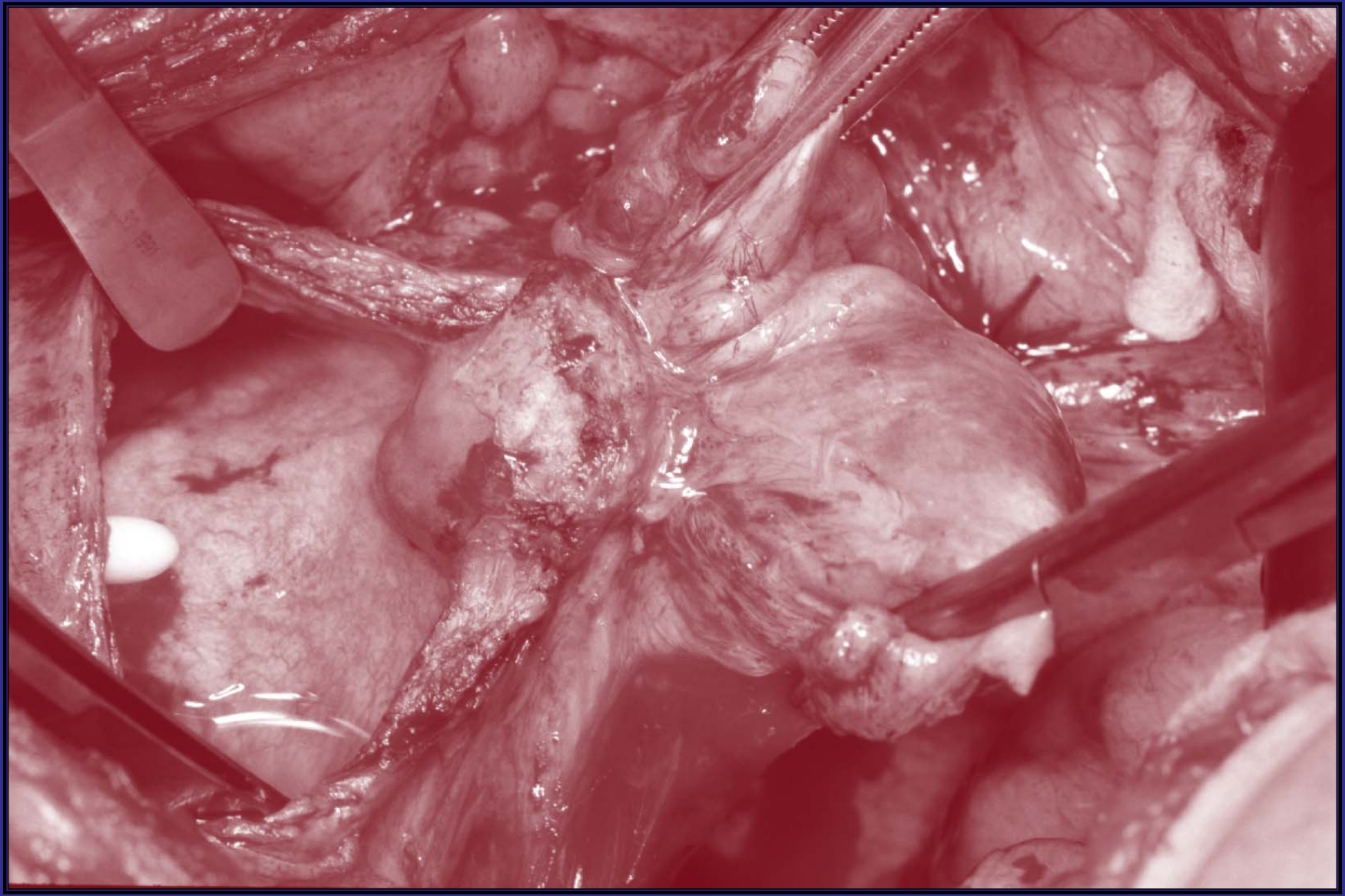




Relationship between endometriosis lesions or stage according to the revised American Fertility Society classification and severity of pain symptoms. (Literature data, 1990 – 2006)

Source	No. of patients	Indication for surgery	Association between lesions or stage and pain symptoms
Fedele *et al*., 1990	160	Infertility, pain, pelvic mass	No (stage:frequency and severity of pain symptoms)
Cornillie et al., 1990	179	Infertility, pain	Yes (depth of endometriosis : pelvic pain)
Koninckx *et al*., 1991	452	Infertility, pain	Yes (volume and depth of endometriosis:pelvic pain)
Mahmood et al., 1991	201	Various	No (stage : frequency of pain symptoms)
Marana et al., 1991	206	Infertility, pain, pelvic mass	No (stage, type and site of lesions : severity of pain)
Ripps & Martin, 1991	59	Infertility, pain, mass	Yes (deep lesions : pain) No(stages:frequency and severity of pain symptoms)
Stout et al., 1991	102	Various	No (stages : severity of pain symptoms)
Vercellini et al., 1991	73	Pain	Yes (typical lesions : deep dyspareunia) No (stages:frequency and severity of pain symptoms)
Fedele et al.,1992	124	Infertility	Yes (stages III-IV:dysmenorrhoea,non-menstrual pain)
Perper *et al*., 1995	53	Infertility, pain	Yes (number of implants : severity of dysmenorrhoea) No (location of implants : severity of dysmenorrhoea)
Matorras et al., 1996	174	Infertility	No (stage : frequency of pain symptoms)

Relation between endometriosis lesions or stage according to the revised American Fertility Society classification and severity of pain symptoms. (Literature data, 1990 – 2006) (continued)

Source	No. of patients	Indication for surgery	Association between lesions or stage and pain symptoms
Vercellini *et al*., 1996	244	Pain	Yes (deep vaginal lesions : dyspareunia) No (stage : frequency and severity of pain symptoms)
Muzii *et al*., 1997	65	Infertility, pain, mass	Yes (AFS score : severity of dysmenorrhea)
Stovall *et al*., 1997	48	Pain	Yes (stage : severity of pain symptoms at follow-up)
Porpora *et al*., 1999	90	Infertility, pain, mass	Yes (deep lesions and adhesions : severity of pain) No (stage : frequency and severity of pain symptoms)
Parazzini et al., 2001	469	Pain	No (stage, site, type : frequency and severity of pain)
Fauconnier *et al*., 2002	225	Pain	Yes (site of deep lesions : specific types of pain)
Chapron *et al*., 2003	209	Pain	Yes (rectovaginal lesions and adhesions : severity of dysmenorrhea)
Ferrero *et al*., 2005	309	Infertility, pain, mass	Yes (deep uterosacral ligament lesions : dyspareunia)
Szendei *et al*., 2005	181	Pain	No (stage : severity of pain symptoms)
Parazzini et al., 2006	574	Pain	No (endometriosis associated adhesions:severity of pain symptoms)
Milingos et al., 2006	95	Pain	Yes (AFS score:frequency and severity of dysmenorrhea and deep dyspareunia)

ENDOMETRIOSIS AND PELVIC PAIN

Fresh, metabolically active, intraperitoneal implants may cause functional pain sympoms such as dysmenorrhea, whereas infiltrating, nodular and fibrotic lesions are resposible for organic-type pain such as deep dyspareunia

Vercellini et al., J Reprod Med 1991; Fertil Steril 1996; Semin Reprod Med 1997

ENDOMETRIOSIS AND PELVIC PAIN

Patients with vaginal endometriosis had a significantly increased risk of deep dyspareunia compared with those whose lesions were at other sites

(OR, 2.55; 95% C.I., 1.21-5.39)

Stage was not correlated with frequency and severity of pain symptoms

Vercellini et al., Fertil Steril 1996

ENDOMETRIOSIS AND PAIN
LOGISTIC REGRESSION ANALYSIS OF 1054 PATIENTS

Covariates included in the regression equations:

- Age at surgery
- BMI
- Parity
- r-AFS classification stage
- r-AFS classification score for implants
- r-AFS classification score for adhesions
- Uterine position
- Lesions of the anterior cul-de-sac
- Lesions of the posterior cul-de-sac
- Diameter of the right and left ovarian endometriomas
- Rectovaginal lesions

From Vercellini et al., Hum Reprod 2006

DISTRIBUTION OF 1054 CONSECUTIVE WOMEN OPERATED FOR ENDOMETRIOSIS, ACCORDING TO AGE, PARITY AND REVISED AMERICAN FERTILITY SOCIETY (AFS) CLASSIFICATION STAGE

	n	%
Age		
< 20	103	9.8
20-24	72	6.8
25-30	300	28.5
31-35	313	29.7
36-40	167	15.8
> 40	99	9.4
Primary indication		
Chronic pain	329	31.2
Pelvic mass	313	29.7
Infertility	312	29.6
Mixed	100	9.5
AFS stage		
I	319	30.3
II	139	12.3
III	292	27.7
IV	304	28.8

DISTRIBUTION OF PAIN SYMPTOMS ASSOCIATED WITH ENDOMETRIOSIS ACCORDING TO DISEASE STAGE

	Absent/mild		Moderate/severe	
	n	%	n	%
Dysmenorrhea				
r-AFS stage				
I	153	50.0	153	50.0
II	49	36.3	86	63.7
III	123	44.9	151	55.1
IV	106	37.6	176	62.4
Total	431	43.2	566	56.8

r-AFS, revised American Fertility Society

From Vercellini et al., Hum Reprod 2006

DISTRIBUTION OF PAIN SYMPTOMS ASSOCIATED WITH ENDOMETRIOSIS ACCORDING TO DISEASE STAGE

	Absent/mild		Moderate/severe	
	n	%	n	%
Deep dyspareunia				
r-AFS stage				
I	195	85.5	33	14.5
II	68	71.6	27	28.4
III	179	83.6	35	16.4
IV	145	69.7	63	30.3
Total	587	78.8	158	21.2

r-AFS, revised American Fertility Society

From Vercellini et al., Hum Reprod 2006

DISTRIBUTION OF PAIN SYMPTOMS ASSOCIATED WITH ENDOMETRIOSIS ACCORDING TO DISEASE STAGE

	Absent/mild		Moderate/severe	
	n	%	n	%
Non-menstrual pain				
r-AFS stage				
I	176	74.6	60	25.4
II	65	64.4	36	35.6
III	166	72.8	62	27.2
IV	143	65.0	77	35.0
Total	550	70.1	295	29.9

r-AFS, revised American Fertility Society

From Vercellini et al., Hum Reprod 2006

ENDOMETRIOSIS AND DYSMENORRHEA
LOGISTIC REGRESSION ANALYSIS OF 1054 PATIENTS

Variable	Wald χ^2	*P*	O.R.	95% C.I.
Age at surgery	31.64	0.0001	0.93	0.91 – 0.95
r-AFS stage	5.14	0.02	1.33	1.04 – 1.71
Right cyst diameter (cm)	4.70	0.03	0.87	0.77– 0.97

From Vercellini et al., Hum Reprod 2006

ENDOMETRIOSIS AND DEEP DYSPAREUNIA
LOGISTIC REGRESSION ANALYSIS OF 1054 PATIENTS

Variable	Wald χ^2	*P*	O.R.	95% C.I.
Age at surgery	8.15	0.004	0.95	0.92 – 0.98
Douglas pouch lesion	17.00	0.0001	2.64	1.68 – 4.24

From Vercellini et al., Hum Reprod 2006

ENDOMETRIOSIS AND NON-MENSTRUAL PELVIC PAIN LOGISTIC REGRESSION ANALYSIS OF 1054 PATIENTS

Variable	Wald χ^2	*P*	O.R.	95% C.I.
Age at surgery	26.03	0.0001	0.92	0.89 – 0.95
r-AFS stage	5.63	0.018	1.01	1.00 – 1.03
Douglas pouch lesions	5.88	0.015	1.58	1.09 – 2.30
Left cyst diameter (cm)	5.92	0.014	0.84	0.72 – 0.96

From Vercellini et al., Hum Reprod 2006

DETERMINANTS OF SEVERITY OF DYSMENORRHEA IN 209 WOMEN WITH DEEP INFILTRATING ENDOMETRIOSIS

Indipendent variable	Adjusted O.R.	95% C.I.
Rectal lesions	2.5	1.1- 5.9
Vaginal lesions	4.1	1.6-10.2
Recto-vaginal lesions	4.3	1.7-10.7
Extensive adnexial lesions	1.9	1.1- 3.5

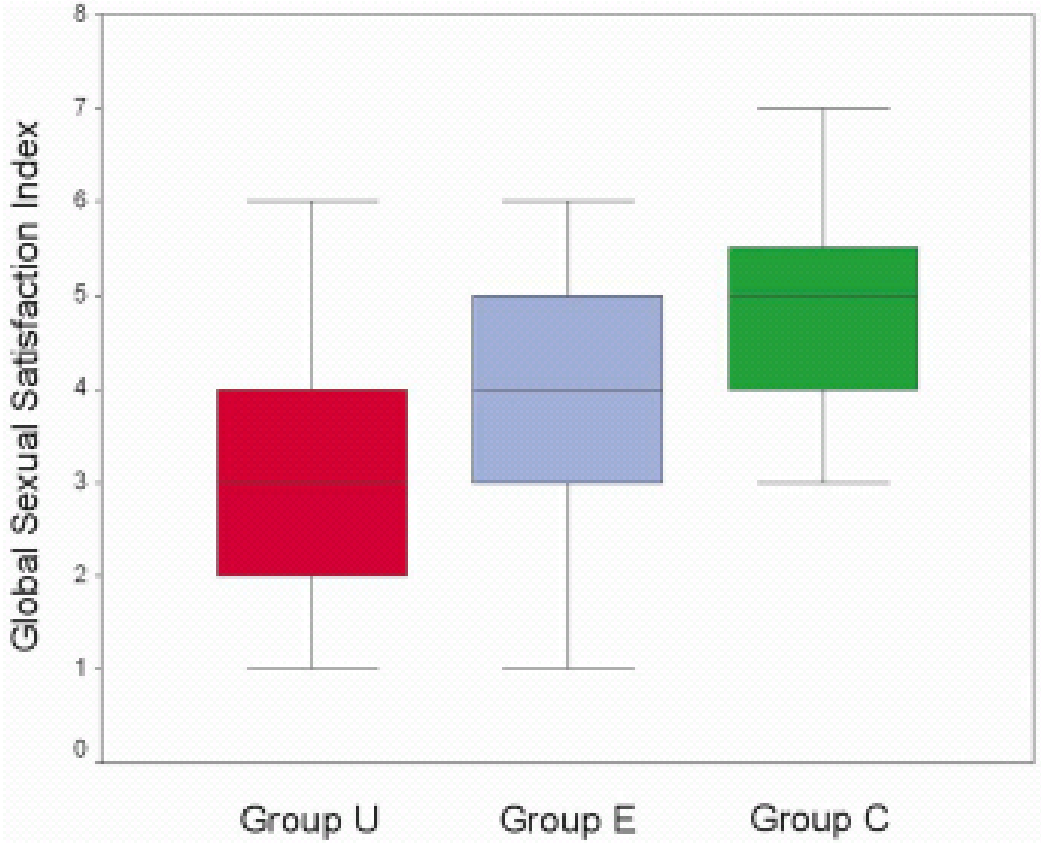
From Chapron et al., Hum Reprod 2003

PAIN SYMPTOMS AND ANATOMIC LOCATION OF DEEP INFILTRATING ENDOMETRIOSIS LOGISTIC REGRESSION ANALYSIS OF 225 WOMEN

Pain Symptom	Indipendent variable	O.R.	95% C.I.
Dysmenorrhea			
	Douglas obliteration	5.0	1.8 - 13.7
	Parity ≥ 2	0.2	0.1 - 0.7
Deep dyspareunia			
	USL infiltration	3.4	1.4 - 8.2
Non-cyclic pain			
	Bowel lesions	10.6	3.6 - 30.8
	Infertility	0.3	0.2 - 0.6
Dyschezia			
	Vaginal lesions	2.9	1.5 - 5.7
Bladder symptoms			
	Bladder lesions	51.8	13.6 - 197.7
GI Symptoms			
	Bowel lesions	4.4	1.7 - 11.4
	Vaginal lesions	3.1	1.4 - 6.7

From Fauconnier et al., Fertil Steril 2002

Global Sexual Satisfaction Index (GSSI). GSSI asks subjects to self-rate their overall level of sexual satisfaction on a scale of 0 to 8. The *boxes* delimit scores falling between the 25th and the 75th percentiles, and the *horizontal lines* refer to median scores. The GSSI was significantly lower in women with deep endometriosis infiltrating the uterosacral ligament (group U) than in controls (group C) ($P<.05$). There was a trend for women with endometriosis without deep infiltrating lesions of the uterosacral ligament (group E) to have a lower GSSI than group C, but the difference was not statistically significant.



From Ferrero et al., Fertil Steril 2005

ADHESIONS AND PAIN IN 574 WOMEN WITH FIRST DIAGNOSIS OF ENDOMETRIOSIS

- No overall association between the presence of adhesions and the degree of pain

- The association between adhesions and pain observed in women with ovarian and stage I - II endometriosis was no longer significant after correction for multiple comparisons

Parazzini & Gruppo Italiano per lo Studio dell'Endometriosi,
J Minim Invasive Gynecol 2005

PREOPERATIVE PATIENTS' CHARACTERISTICS AND RESULTS OF SURGERY FOR DEEP INFILTRATING ENDOMETRIOSIS

- Age
- Gravidity/parity
- BMI
- Preoperative medical treatment
- Number and location of deep infiltrating endometriosis (USL, vagina, bladder, intestine)
- Revised AFS classification stage

had no significant influence on postoperative pain variation in 132 highly symptomatic patients

From Chopin et al., J Minim Invasive Gynecol 2005

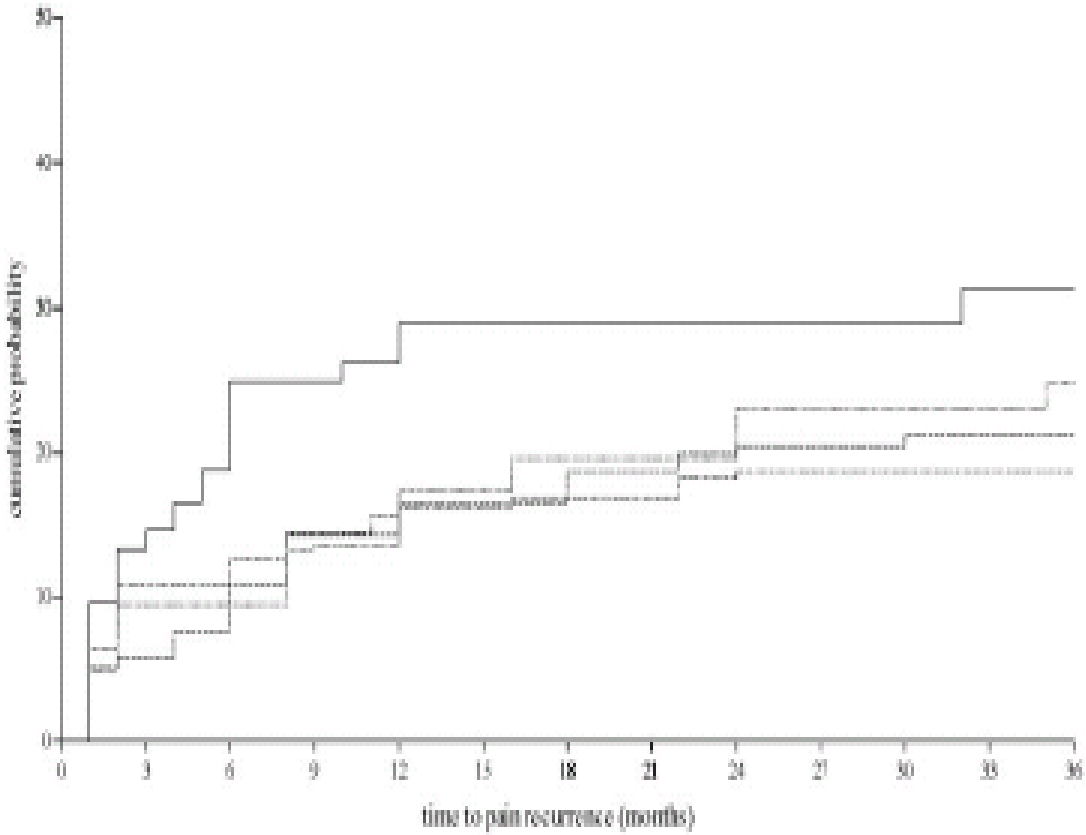


Figure 2. Cumulative 36-month probability of recurrence of moderate or severe dysmenorrhoea by disease stage in 425 symptomatic women who underwent conservative surgery for endometriosis (——, stage I; ——, stage II; ------, stage III; -·-·-·-, stage IV).

From Vercellini et al., Hum Reprod 2006

FOLLOW-UP RESULTS OF SURGERY FOR SYMPTOMATIC ENDOMETRIOSIS MULTIVARIATE REGRESSION ANALYSIS OF 729 WOMEN

Pain symptom	Covariate	Wald χ^2	*P*	R.R.	95% C.I.
Dysmenorrhea					
	Age at surgery	6.81	0.009	0.95	0.91-0.99
	r-AFS stage	0.00	0.95	1.01	-------

From Vercellini et al., Hum Reprod 2006

A QUANTITATIVE ASSESSMENT OF THE DENSITY OF DIFFERENT TYPES OF NERVE FIBRES IN PERITONEAL ENDOMETRIOTIC LESIONS

	Normal peritoneum	Peritoneal endometriotic lesion
Number of specimens	36	40
Total nerve fibre density (mean ± SD/mm^2) (stained with PGP9.5)	2.5 ± 1.3	16.3 ± 10.0
Total nerve fibre density (mean ± SD/mm^2) (stained with NF)	1.0 ± 0.8	6.7 ± 3.7

PGP9.5, protein gene product

NF, neurofilament

From Tokushige et al., Hum Reprod 2006

DISTRIBUTION OF NERVE FIBERS AMONG PATIENTS WITH OVARIAN ENDOMETRIOMAS

Groups	No.	Size of the cyst (cm)	Presence of nerve fibers (%)	Presence of pelvic pain (%)
EC	11	3.2 ± 0.3	0	45.5
EO	11	4.6 ± 1.0	0	63.6
DC	11	5.3 ± 0.5	12	9.1
DO	9	6.1 ± 1.1	22.2	11.1

E= endometriomas C= cystectomy D=dermoid cyst O=oophrectomy

Modified from Al Fozan et al., Fertil Steril, 2004

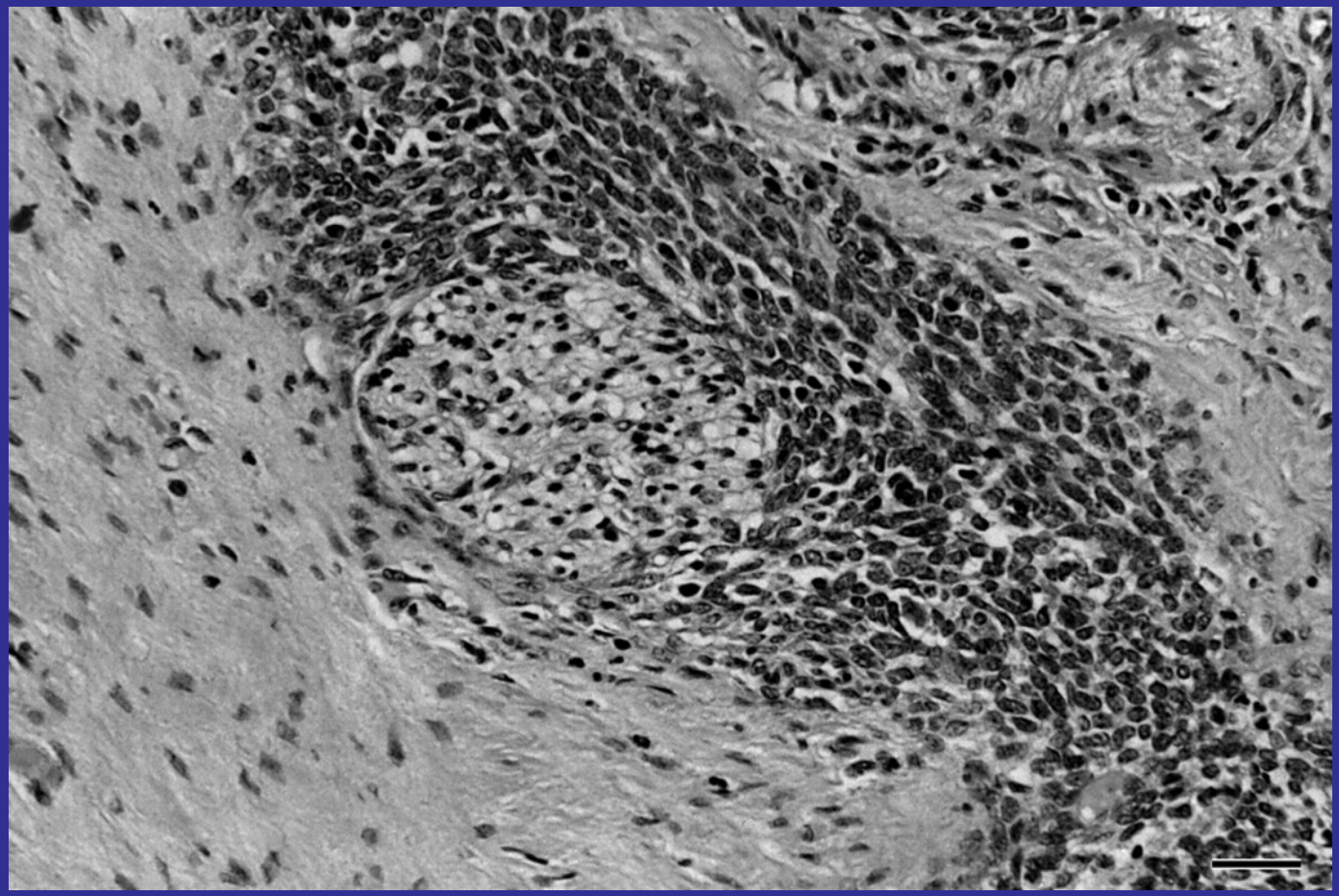
RELATIONSHIP BETWEEN ENDOMETRIOTIC FOCI AND NERVES IN RECTOVAGINAL ENDOMETRIOTIC NODULES : HISTOLOGICAL AND IMMUNOLOGICAL RESULTS FOR 28 PATIENTS ACCORDING TO THE PREOPERATIVE PAIN SCORES

	Dysmenorrhea		Deep dyspareunia	
	Group1 (n=19)	Group2 (n=9)	Group1 (n=21)	Group2 (n=7)
Lesion diameter (mm)	22.6±1.8	22.9 ±2.0	23.0 ±1.9	22.6 ±1.9
No.of nerves per X40 hpf	18.2 ±1.2	17.7 ±0.7	18.0 ±1.4	17.1 ±0.8
No.of lesions per X40 hpf	7.5 ±1.0	7.5 ±1.2	7.4 ±1.0	7.6 ±1.3
Intrafibrotic nerves (%)	40.5 ±6.5	23.4 ±4.3[a]	39.4 ±8.0	22.8 ±4.0[a]
Intraglandular nerves (%)	38.6 ±6.9	26.1 ±5.3[a]	37.6 ±8.0	27.0 ±4.9[a]
Perineurial invasion (% of intra-endometriotic nerves)	29.0 ±6.0	13.5 ±7.3[a]	27.4 ±7.5	13.1 ±7.0[a]
Endoneurial invasion (% of intra-endometriotic nerves)	35.0 ±8.5	11.5 ±6.0[a]	33.5 ±10.6	12.2 ±6.0[a]

Group 1: pain score > 7, Group 2: pain score ≤ 7

a = $P < 0.01$

Modified from Anaf et al., Hum Reprod 2000



Perineurial invasion by endometriotic stroma in rectovaginal septum endometriotic nodule section.
The nerve appears grey in the centre of the photograph.
(haematoxylin and eosin staining; scale bar = 100 μm)

From Anaf et al.,Hum Reprod,2000

NGF EXPRESSION H-SCORES IN ENDOMETRIOSIS AND ENDOMETRIUM

	n	Glands	Stroma
Eutopic endometrium (proliferative)	8	85 ± 15	70 ± 13
Eutopic endometrium (secretory)	8	20 ± 10	30 ± 14
Peritoneal endometriosis (proliferative)	10	110 ± 7	100 ± 9
Peritoneal endometriosis (secretory)	15	65 ± 9	35 ± 13
Ovarian endometriosis (proliferative)	10	140 ± 9	125 ± 5
Ovarian endometriosis (secretory)	11	85 ± 3	85 ± 3
Deep endometriotic nodule (proliferative)	12	226 ± 18	204 ± 21
Deep endometriotic nodule (secretory)	11	181 ± 32	173 ± 28

Modified from Anaf et al.,Hum Reprod, 2002

HYPERALGESIA AND NEUROPATIC PAIN

Hyperalgesia is defined as an exacerbation of pain when a non-painful stimulus is applied

It is characterized by a deplacement to the left of the curve stimulus/response which induces an increase in the pain sensation associated with lower threshold of pain perception and an increased sensitivity of nociceptors

Hyperalgesia is a major characteristic of “neuropathic pain”, which corresponds to a pain sensation that is out of proportion with the intensity of nociceptors stimulation

From Anaf et al., Hum Reprod 2002 and Fertil Steril 2006

PATHOGENESIS OF PAIN IN ENDOMETRIOSIS

OVULATION

⇩

Estrogen synthesis

⇩

Retrograde menstruation

⇩

Endometrial cell implantation

⇩

INFLAMMATION

1 → ↑NGF; ↑NGFRp75; ↑Trk-A

2 → Degranulation of mast cells;
↑PGs; ↑ ILs; ↑ TNF α; ↑ TGFα1; ↑ H; ↑ 5HT

↑NGF; ↑NGFRp75; ↑Trk-A ↔ Degranulation of mast cells; ↑PGs; ↑ ILs; ↑ TNF α; ↑ TGFα1; ↑ H; ↑ 5HT

↑NGF; ↑NGFRp75; ↑Trk-A → Activation/sensitization of sensory nerve fibers

Ingrowth of nerve fibers in endometriotic lesions (neurotrophism) → **HYPERALGESIA**

Activation/sensitization of sensory nerve fibers → **HYPERALGESIA**

ENDOMETRIOSIS AND PAIN

CONCLUSIONS I

The ASRM classification stages are not associated with pain severity

The ASRM classification is not predictive of postoperative results and of symptomatic recurrence

Ovarian endometriomas are not related to pain severity

Deep infiltrating endometriosis is consistently associated with pelvic pain

Distance between nerve fibers and implants, number of intralesional nerve fibers and degree of endometriotic infiltration are consistently associated with pain

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ENDOMETRIOSIS AND PAIN
CONCLUSIONS II

Pain severity is inversely related with age

Disease aggressivness may spontaneously decrease over time

Relevant information should be included in patient's counselling and treatment options should be tailored accordingly

ENDOMETRIOSIS AND PELVIC PAIN CONCLUSIONS III

Future staging systems in women with symptomatic endometriosis should include specific scores for infiltration of parametria, vagina, rectum and bladder

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