L'endométriose de la jeune fille

UNIVERSITÉ PARIS DESCARTES

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You'll Never Walk Alone

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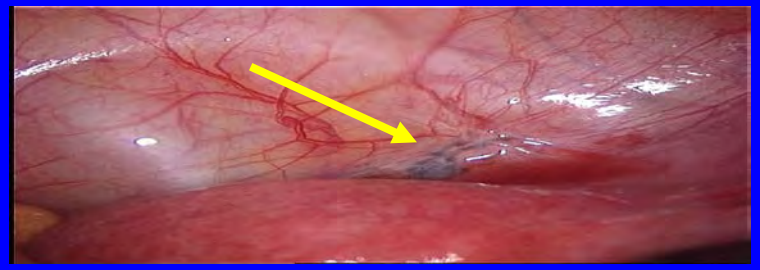
Endometriosis: Anatomical lesions

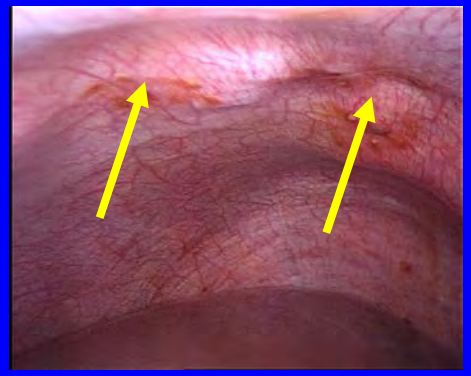


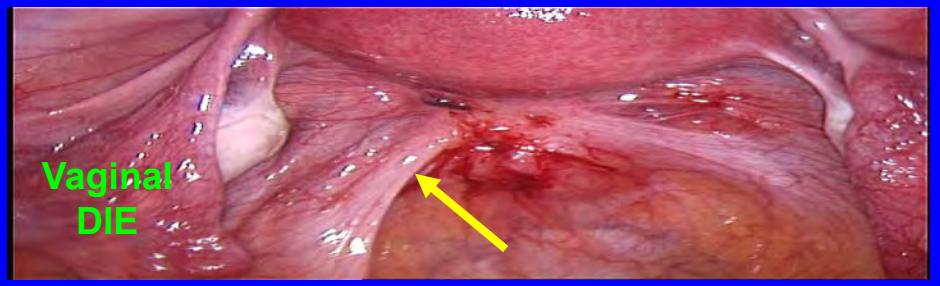
Superficial endometriosis

Ovarian endometriomas

Endometriosis

Deep infiltrating endometriosis





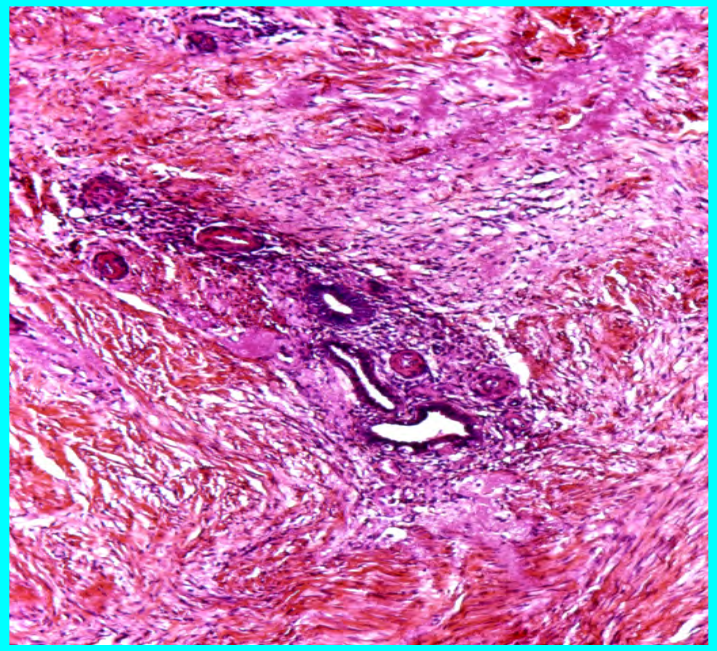
Bladder endometriosis:

Frequency of extravesical OSIS *(n = 58)*

Forms of the disease	n	%	95%CI
Superficial peritoneal	34	58.6	45.2-71.2
Ovarain endometriomas	26	44.8	32.2-58.2
Pelvic adhesions	47	81.0	68.4-89.6
Deep peritoneal implants	16	27.6	16.7-40.8
Overall	51	87.9	76.7-94.3

Somigliana - Chapron *et al.*, Fertil Steril (2007)

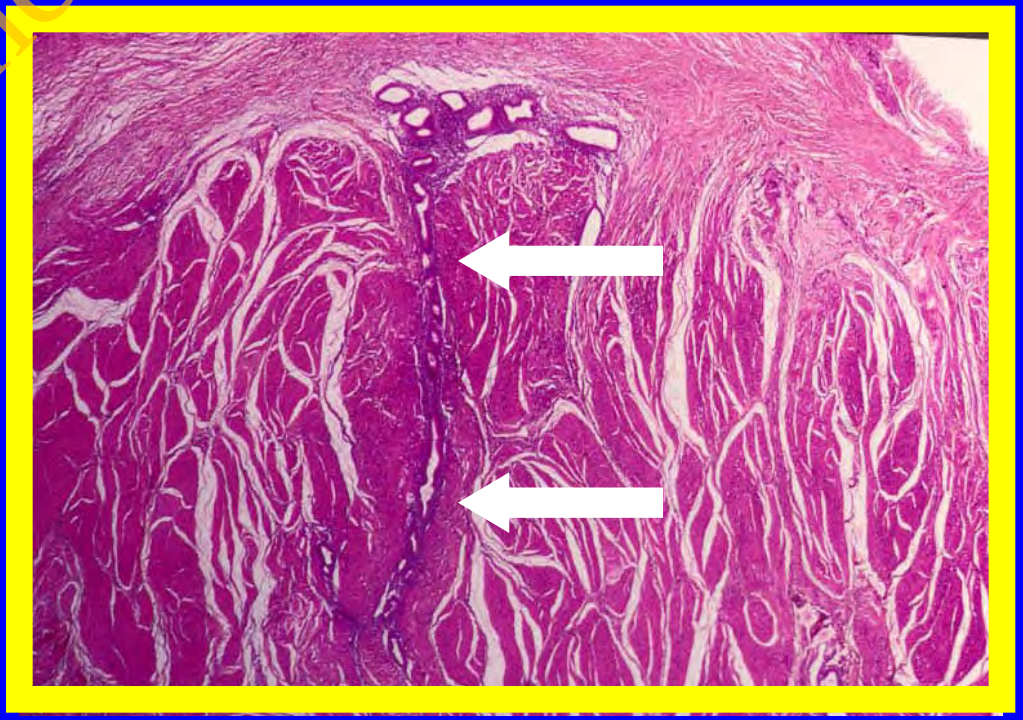
Endometriosis: Définitions



ENDOMETRIOSIS IS DEFINED BY THE PRESENCE OUTSIDE OF THE UTERUS OF ENDOMETRIAL TISSUE:

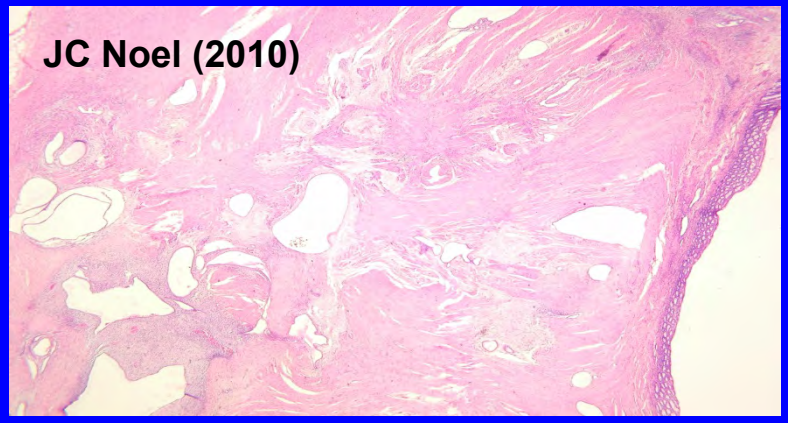
- Endometrial glands
- Stroma

DIE IS ARBITRARLY DEFINED AS LESIONS EXTENDING MORE THAN 5MM UNDERNEATH THE PERITONEUM



Koninckx *et al.*, Fertil Steril (1991)

Deep endometriosis: Définitions



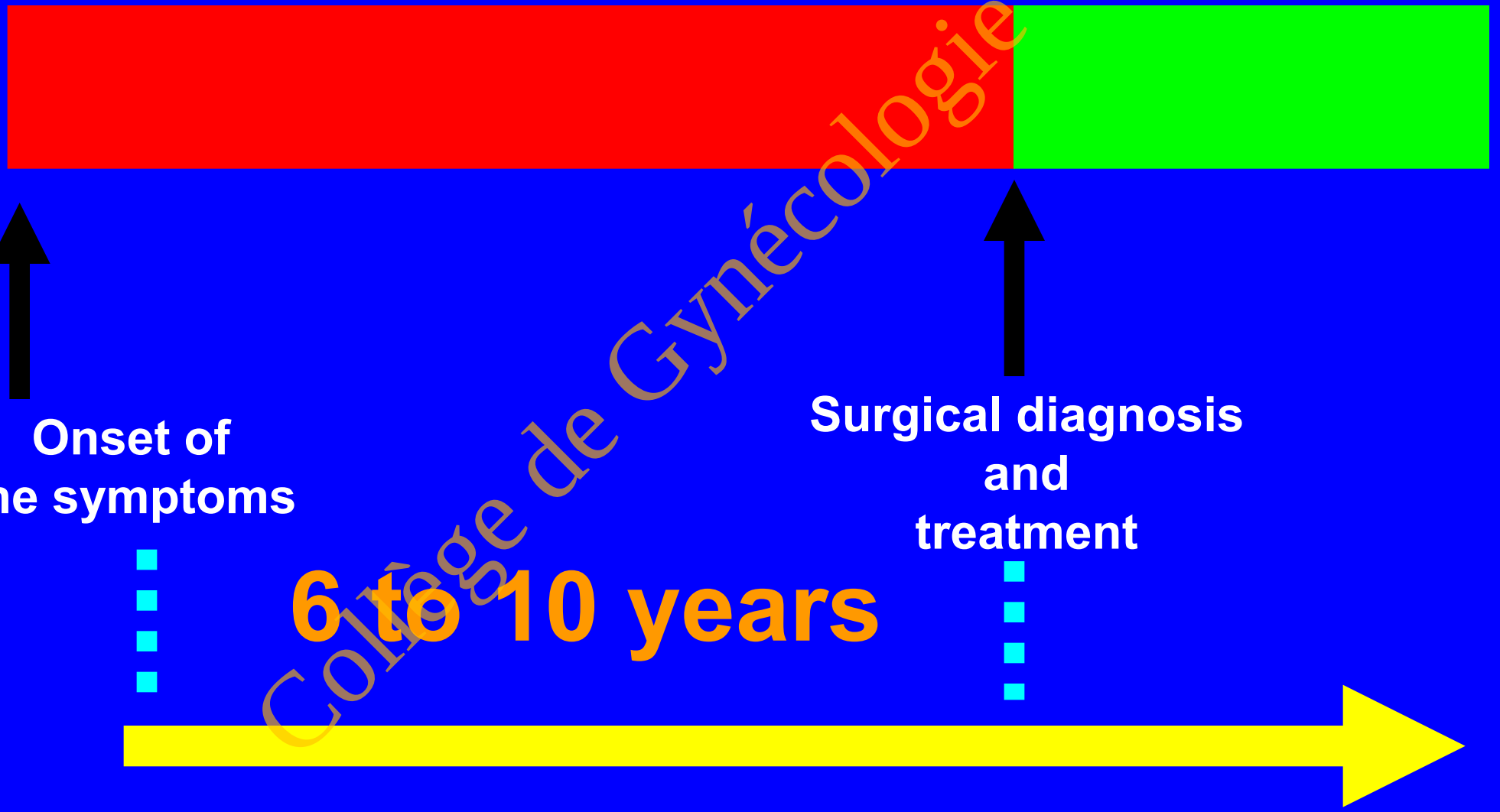
Invasion of the *muscularis propria*

Surgery for bladder endometriosis: long-term results and concomitant management of associated posterior deep lesions

Hum Reprod (2010)

Charles Chapron[1,2,3,*], Antoine Bourret[1], Nicolas Chopin[1], Bertrand Dousset[4], Mahaut Leconte[4], Delphine Amsellem-Ouazana[5], Dominique de Ziegler[1], and Bruno Borghese[1,2,3]

Endometriosis: Diagnosis process



Endometriosis: Diagnosis process

	N	Country	Delay in diagnosis
Hadfield *et al., (1996)*	134	UK	7.9
Hadfield *et al.*, (1996)	84	USA	11.7
Sinaii *et al.*, (2002)	3 680	UK	10.0
Husby *et al.*, (2003)	-	Norway	6.7
Ballard *et al.*, (2006)	32	UK	8.5
Arruda *et al.*, (2003)	200	Brazil	7.0
Ballweg (2004)	4 000	USA	9.3
Matzusaki *et al.*, (2006)	95	France	6.6
Sinaii *et al.*, (2008)	940	UK	7.8
Greene *et al.*, (2009)	4 334	USA	9.3

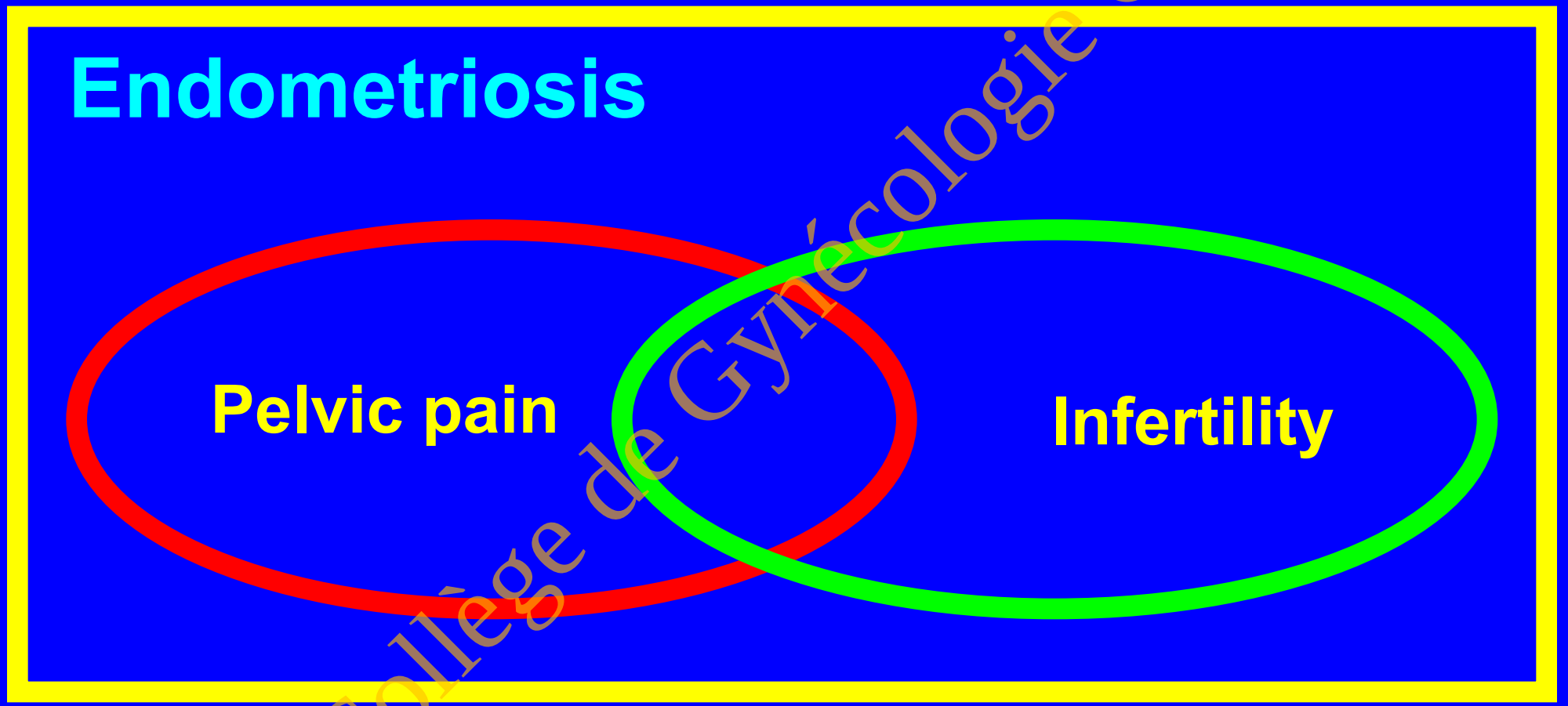
Deep endometriosis: *Diagnostic delay*

(n = 95 DIE patients)

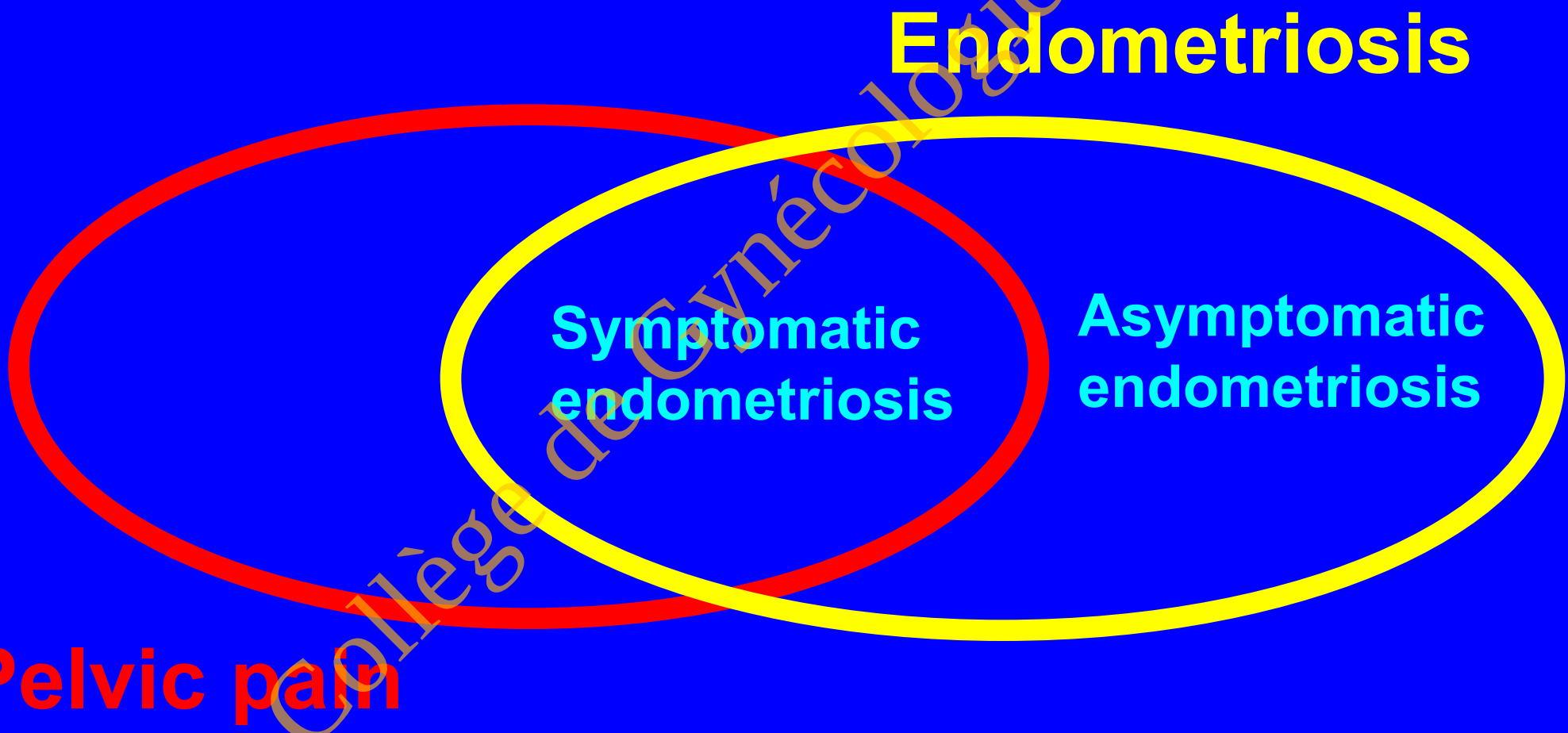
rAFS stages	N	Diagnostic delay (years)	p
I	30	3.5 ± 3.4	< 0.0001
II	23	6.7 ± 5.8	< 0.003
III	15	5.5 ± 5.0	< 0.003
IV			
Score ≤ 70	12	6.3 ± 4.6	< 0.005
Score > 70	15	14.4 ± 5.7	

Matsuzaki *et al.*, Fertil Steril (2006)

Endometriosis: Clinical symptoms



Endometriosis: Relationship between osis and chronic pelvic pain

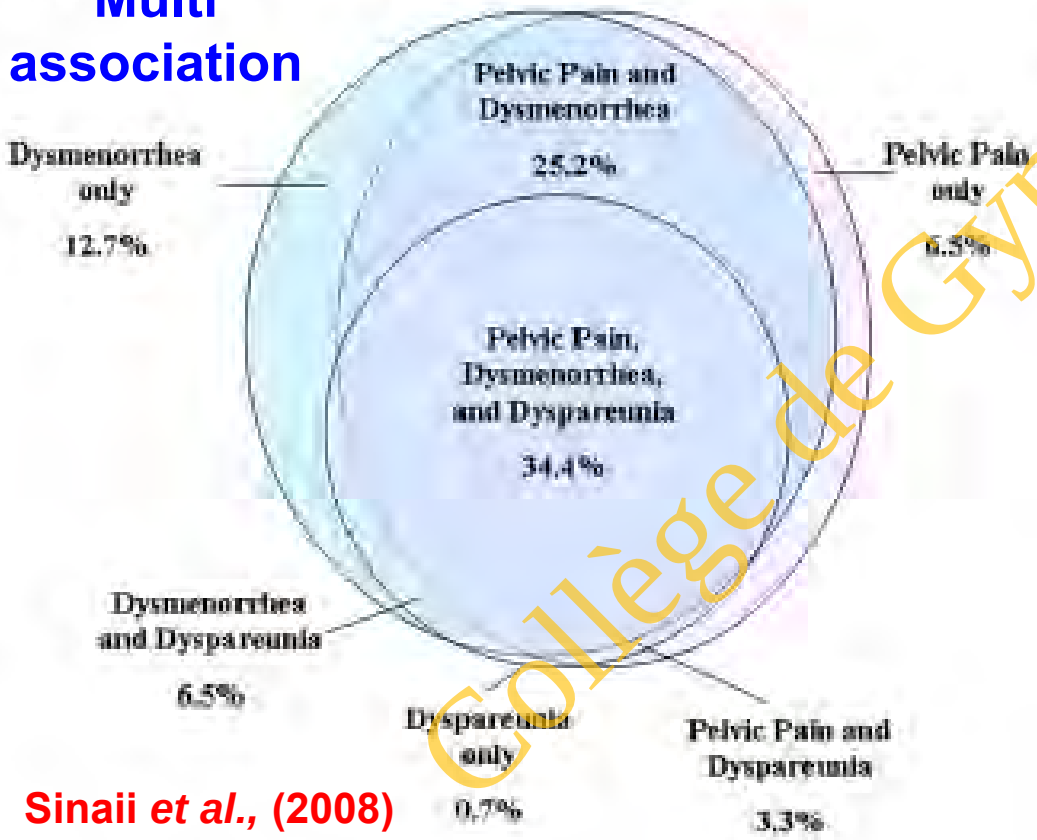


Adaptated from Hurd Obstet Gynecol (1998)

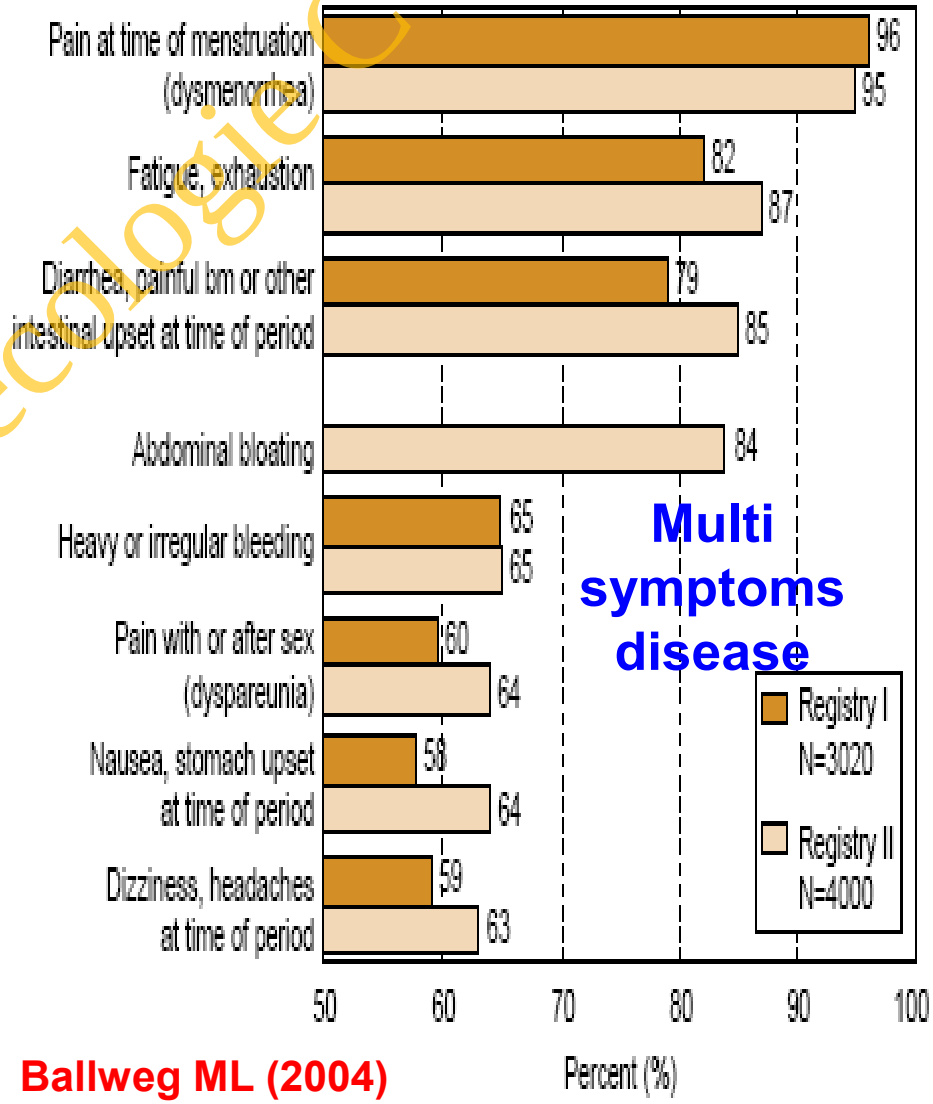
Endometriosis: Diagnosis process

Prevalence and overlap of gynecologic pain symptoms that led to the surgical diagnosis of 940 women with endometriosis who participated in the OXEGENE study. Footnote: 10.7% of women did not report any gynecologic pain symptoms.

Multi association



Sinaii *et al.*, (2008)



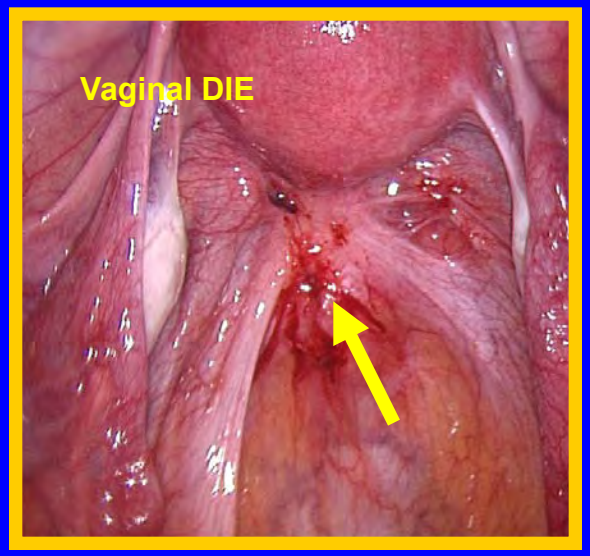
Multi symptoms disease

Ballweg ML (2004)

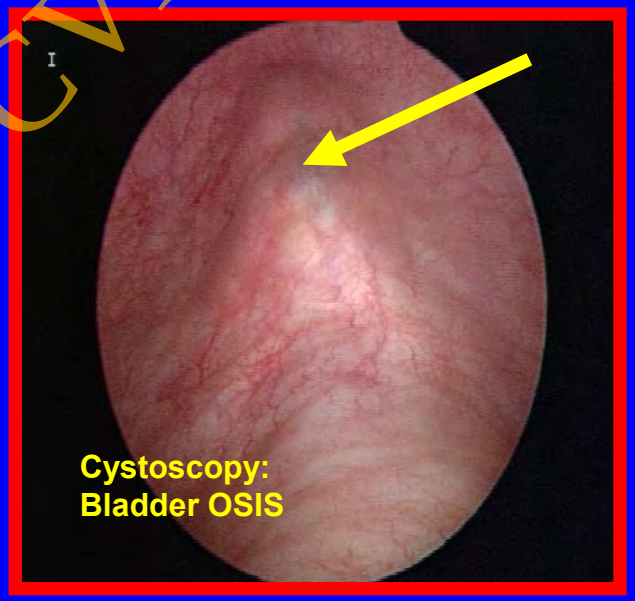
Pelvic Pain and Endometriosis

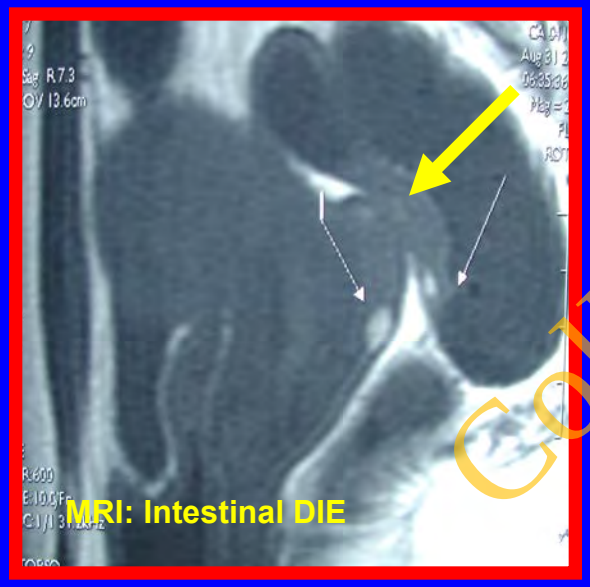
Painful symptoms		Anatomical lesions		Mecanisms
DM DP CPP Intestinal FS Urinary FS Others	??? ⟷	Superficial: P and O OMA Adhesions DIE Associations	??? ⟷	Inflammation Adhesions Location Depth Neurial pathol. - Fibrosis - Invasion

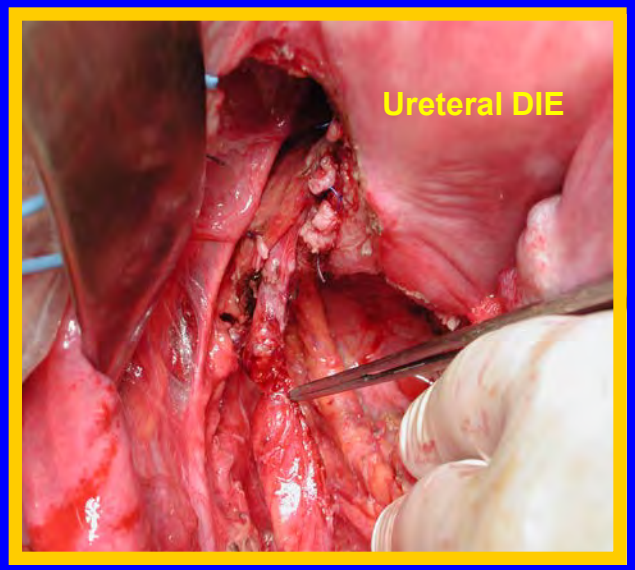
Adolescent endometriosis



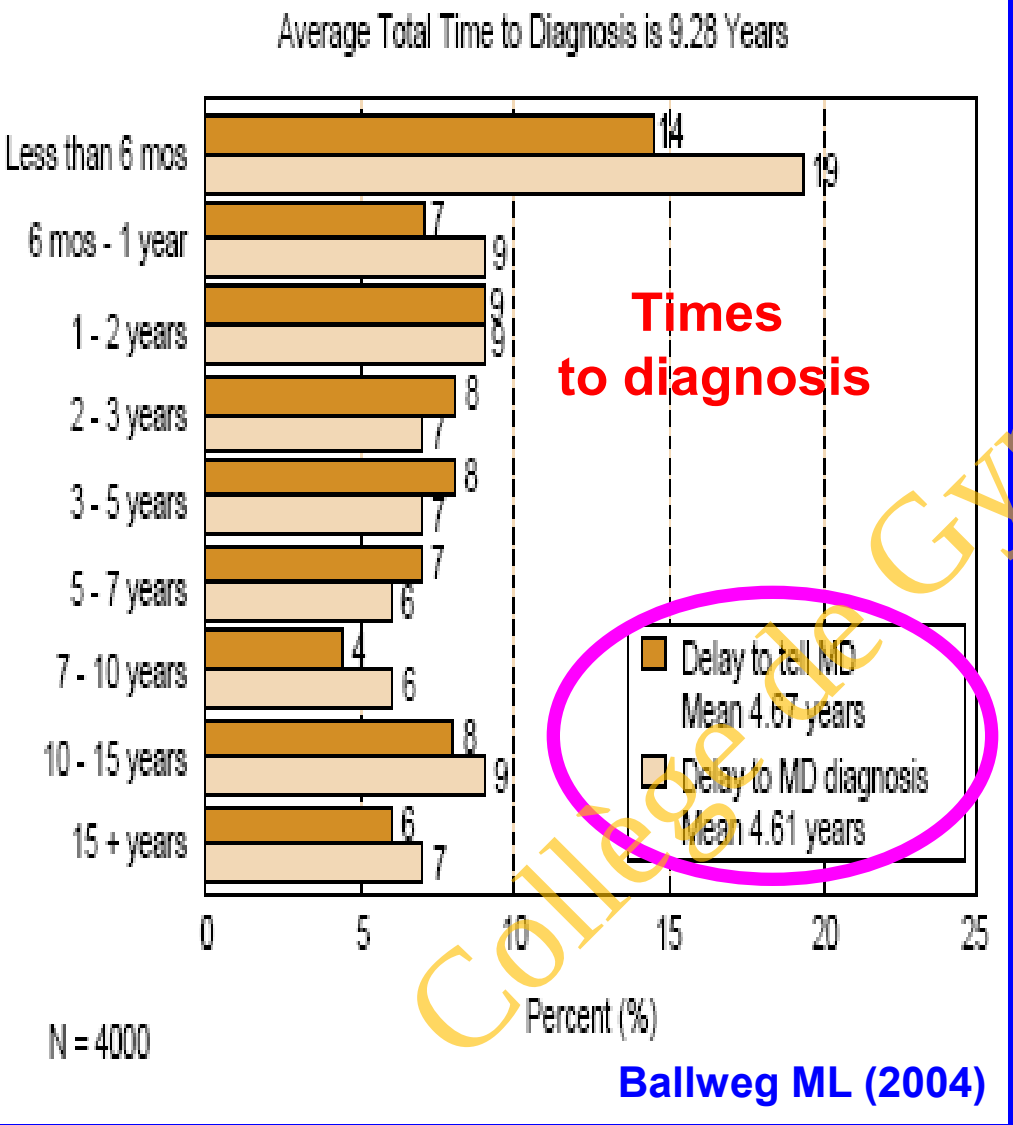
What are the main characteristics of this enigmatic disease ?



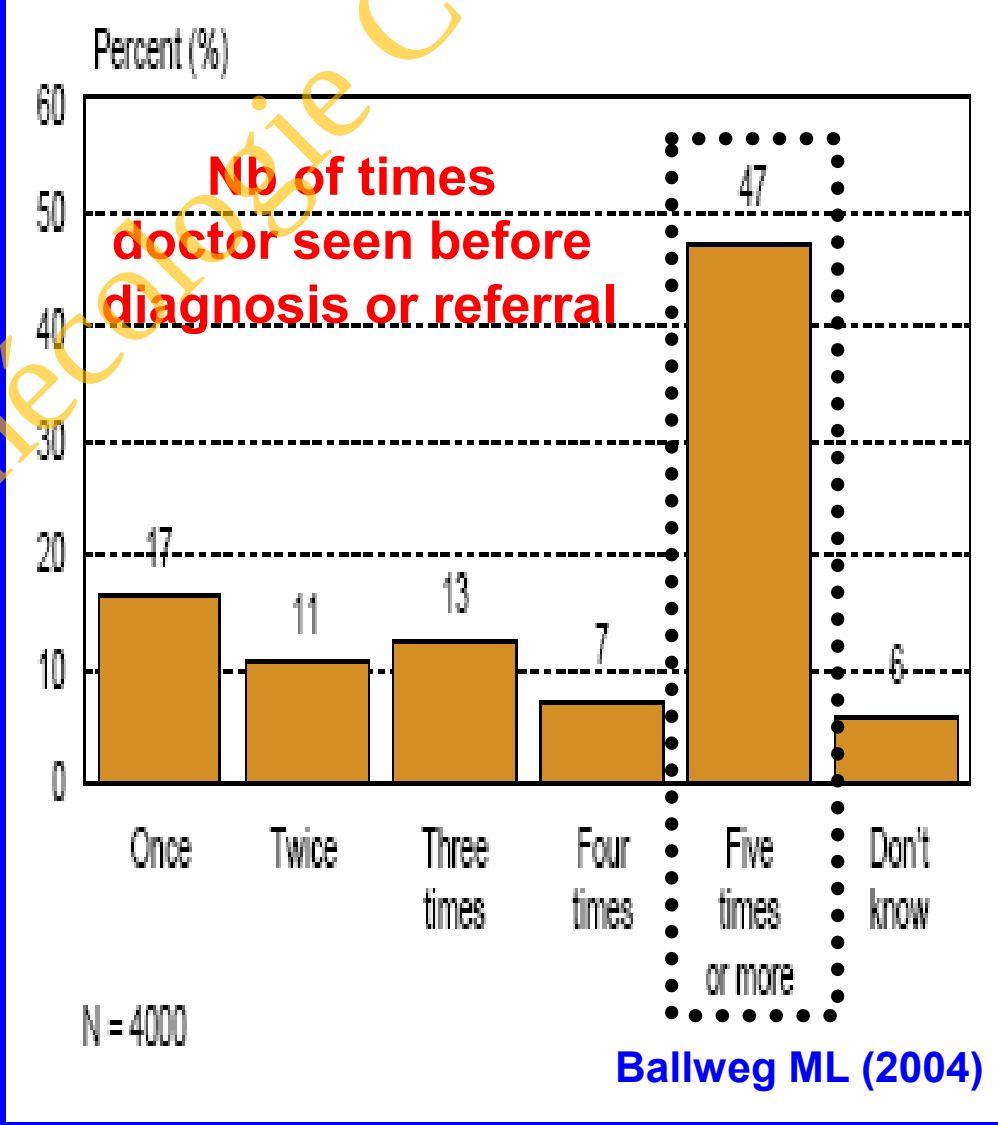




Endometriosis: Diagnosis process

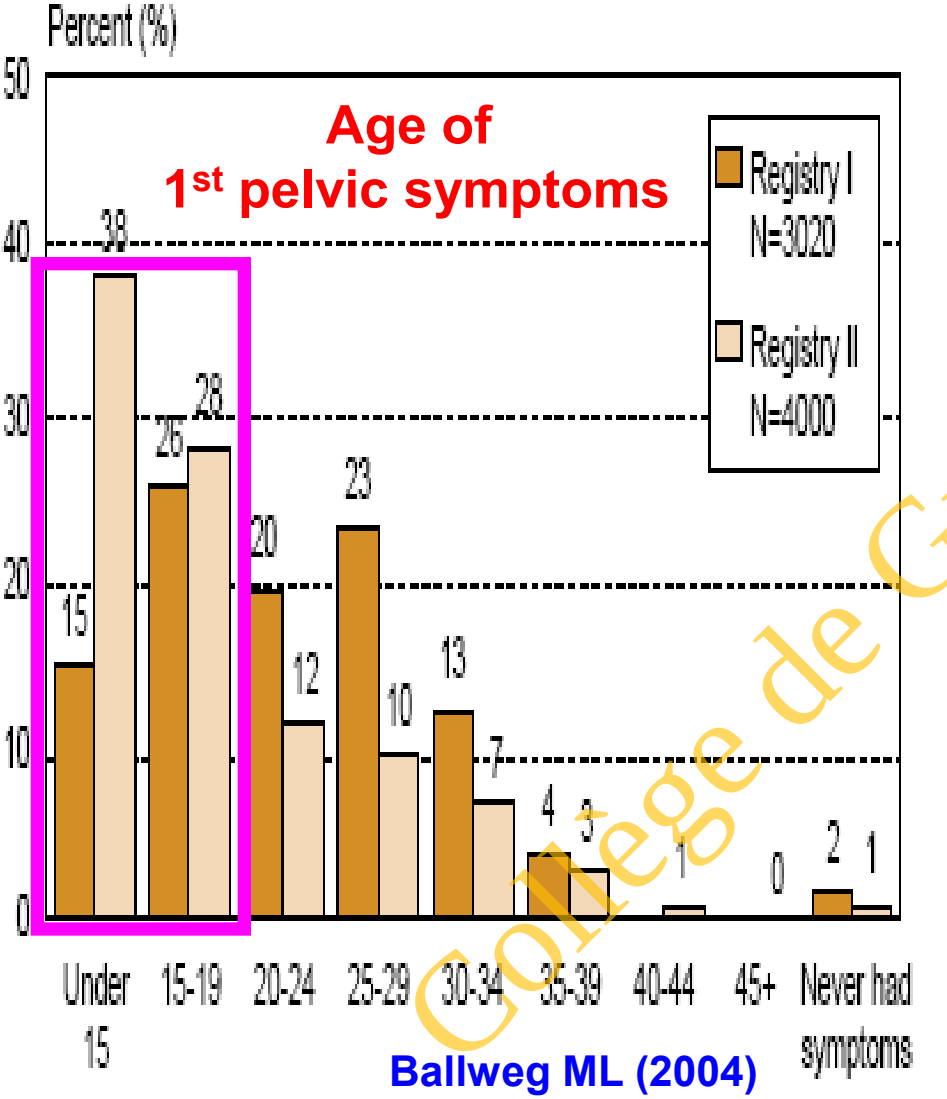


Ballweg ML (2004)



Ballweg ML (2004)

Endometriosis: Diagnosis process

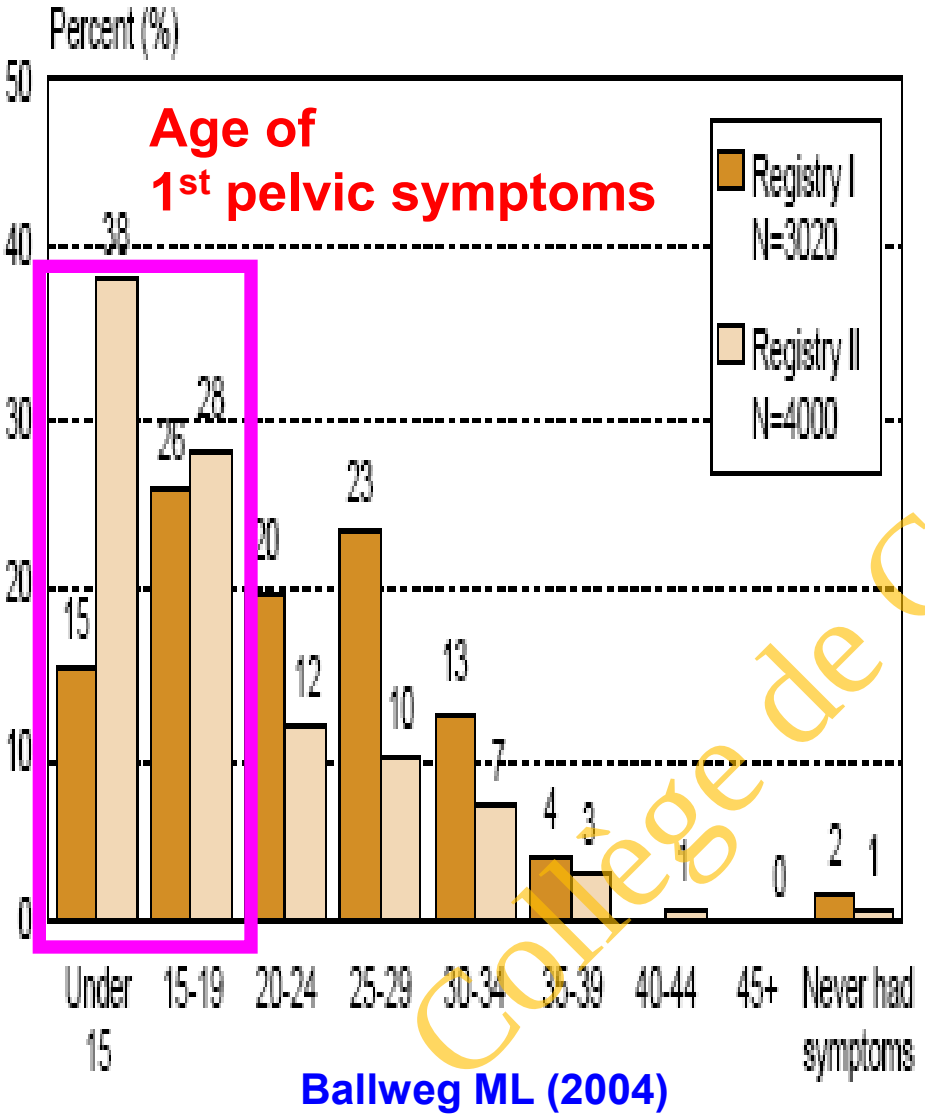


Onset of symptoms

Adolescents	67.1%
Adults	39.2%

Greene *et al.*, Fertil Steril (2009)

Endometriosis: Diagnosis process

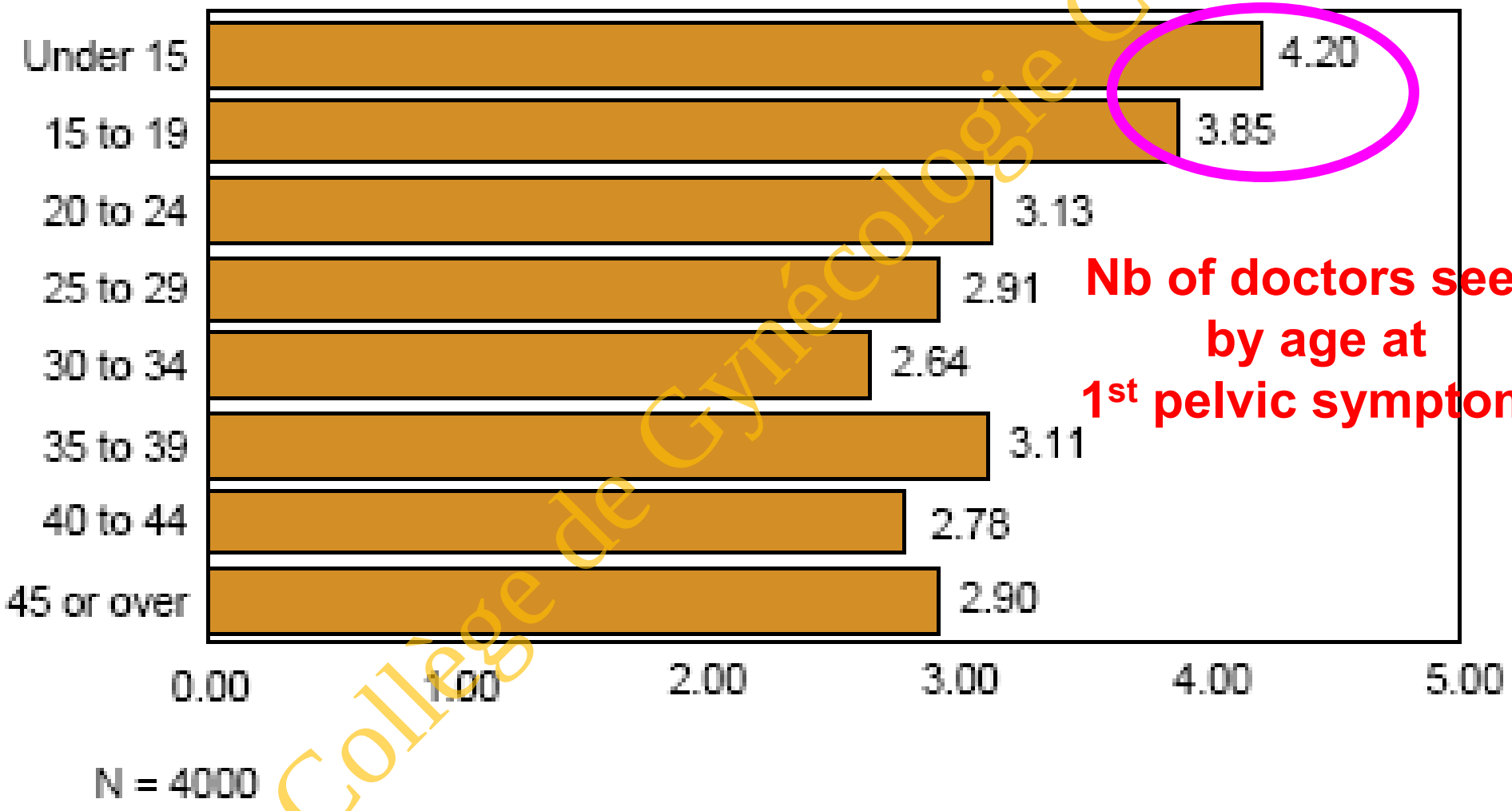


Ballweg ML (2004)

Onset of symptoms	Time from seeking medical attention to diagnosis
Adolescents	6.0 ± 0.2 years
Adults	2.0 ± 0.3 years

Greene *et al.*, Fertil Steril (2009)

Endometriosis: Diagnosis process



Ballweg ML (2004)

Endometriosis: Diagnosis process

	Type of physician seen 1st		
	Gynecol	Generalist	Total
	n = 2 180	*n = 1 955*	*n = 4 334*
Onset of symptoms			
Adolescent	63.4	70.9*	67.1
Adult	35.8	29.1*	32.9
Age at diagnosis	29.5 ± 0.1	29.3 ± 0.1	29.6 ± 0.1
Time from symptoms to			
Medical attention	4.0 ± 0.1	3.8 ± 0.2	4.6 ± 0.1
Diagnosis	3.6 ± 0.1	4.7 ± 0.2*	4.7 ± 0.1

Greene *et al.*, Fertil Steril (2009)

Endometriosis: Diagnosis process

Nb of physicians seen before diagnosis	Type of physician seen 1st: Gynecol *n = 2 180*	Generalist *n = 1 955*	Total *n = 4 334*
1 – 2	50.4	31.9	41.3
3 – 4	31.9	38.3	35.2
5 - 9	14.1	22.6	18.3
≥ 10	3.6	7.2	5.2

Greene *et al.*, Fertil Steril (2009)

Endometriosis: Progressive disease ?

Age and incidence of endometriotic lesions

	Age					
	20 to 25 (n = 79)	26 to 30 (n = 228)	31 to 35 (n = 206)	36 to 40 (n = 92)	41 to 45 (n = 21)	Probability value[b]
With endometriosis	62	75	71	71	76	NS[c]
Subtle lesions SUP	53.1	54.0	49.6	35.4	37.5	0.006
White vesicles	10.2	11.1	6.8	6.2	25.0	NS
Red vesicles	26.5	24.6	19.1	7.7	0.0	0.0001
Polypoid	30.6	33.9	31.3	21.5	12.5	0.03
Allen and Masters	8.2	9.9	6.8	6.2	6.2	NS
Typical lesions	57.1	56.7	61.2	64.6	75	NS
Solitary black puckered spots	46.9	40.9	44.9	38.5	25	NS
Black puckered plots in white plaques	22.5	26.3	27.9	35.4	62.5	0.0009
Endometrioma OMA	22.5	27.5	36.7	36.9	37.5	0.018
Deep infiltration (>6 mm) DIE	14.5	13.2	20.9	24	41.7	0.02

Koninckx *et al.*, Fertil Steril (1991)

Surgery for intestinal DIE

n = 100 patients; Minimum of follow-up: 5 years

Predictive factors for transient neurogenic bladder

Parameters	Transient neurogenic bladder				
	Yes *(n = 16)*		No *(n = 84)*		p
	n	%	n	%	
Age ≥ 35	6	37	28	33	NS
BMI > 25	4	25	16	19	NS
Multiple previous surgery	10	62	38	45	NS
Additional intestinal resction	2	12	7	8	NS
Coloanal anastomosis	9	56	7	8	< 0.001
Associated hysterectomy	4	25	4	5	< 0.01
N DIE lesions ≥ 4	11	69	44	52	< 0.05

Dousset and Chapron Ann Surg (2010)

Deep intestinal endometriosis:

Previous surgical history for endometriosis

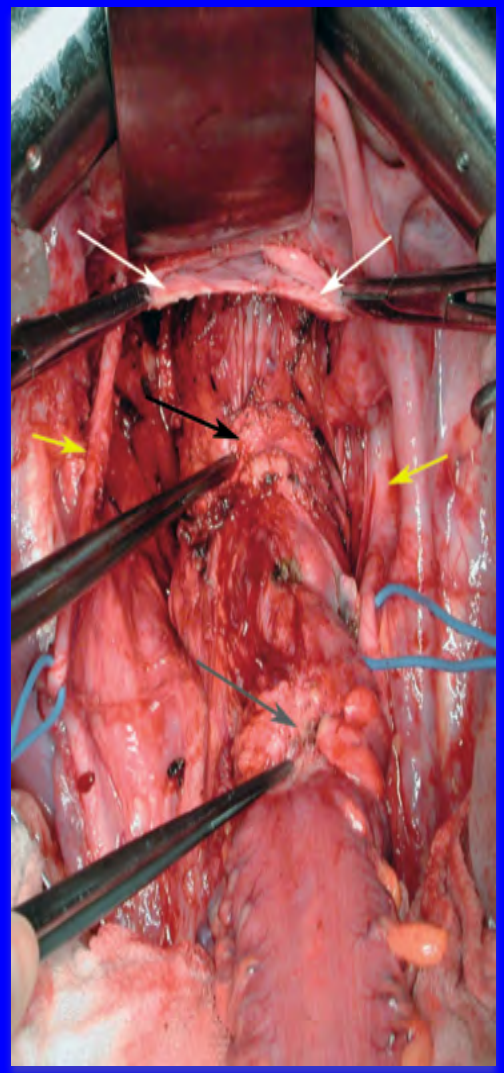
Complete Surgery for Low Rectal Endometriosis

Long-term Results of a 100-Case Prospective Study

Ann Surg (2010)

Bertrand Dousset, MD, Mahaut Leconte, MD,* Bruno Borghese, MD,† Anne-Elodie Millischer, MD,‡ Gilles Roseau, MD,§ Sylviane Arkwright, MD,¶ and Charles Chapron, MD†*

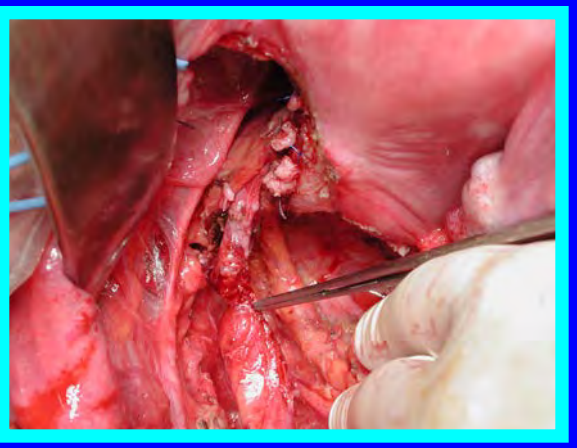
Previous surgery for Osis	82%
Operative laparoscopy	59%
Open surgery	29%
Multiples procedures	48%
Hysterectomy	5%



DIE with colorectal involvement

Bowel resection anastomosis	Previous therapeutic surgery	
N	n	%
1 607	948	59.0

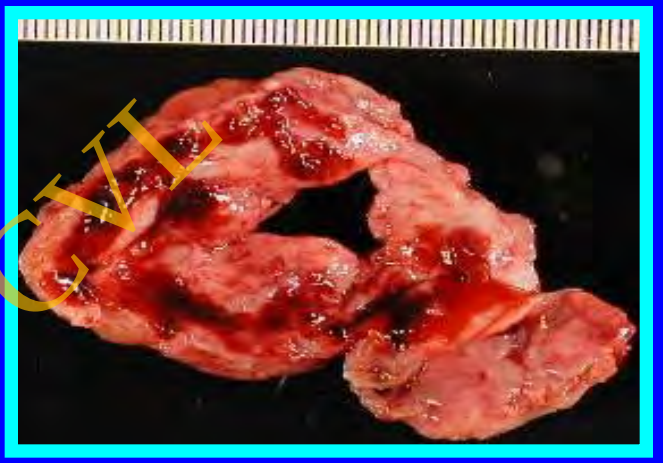
Meuleman *et al.*, Hum Reprod Update (2011)



Severe ureteral endometriosis

Delay for diagnosis

(n = 52 patients)

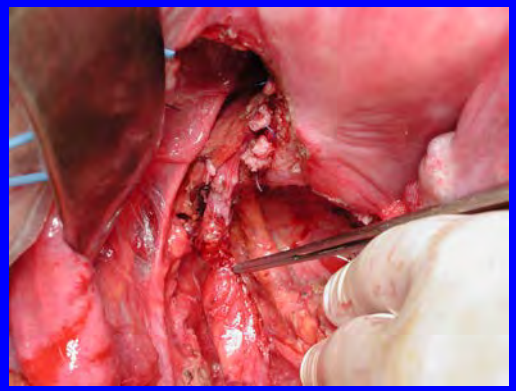


	Patients	
	N	%
Nephrectomy	11	21.1

!!!!!!

Chapron – Dousset (2011)

Severe ureteral endometriosis



	Intrinsic ureteral DIE		
	N	n	(%)
Patients with radical ureteral surgery[a]			
N patients	21	11	52.4
N ureters	24	13	54.2

Author(s)	Patients, N	Intrinsic ureteral DIE, n (%)	Radical ureteral surgery,[a] n (%)	Real intrinsic ureteral DIE,[b] n (%)
Nezhat et al. (1996)	21	4 (19)	11 (52)	4 (36)
Donnez et al. (2002)	18	2 (11)	2 (11)	2 (100)
Antonelli et al. (2004)	13	5 (38)	13 (100)	5 (38)
Ghezzi et al. (2006)	33	1 (3)	2 (6)	1 (50)
Frenna et al. (2007)	54	0 (0)	0 (0)	0 (0)
Seracchioli et al. (2008)	30	4 (13)	8 (27)	4 (50)
Present study (2009)	29	11 (38)	21 (72)	11 (52)
Total	198	27 (14)	57 (29)	27 (47)

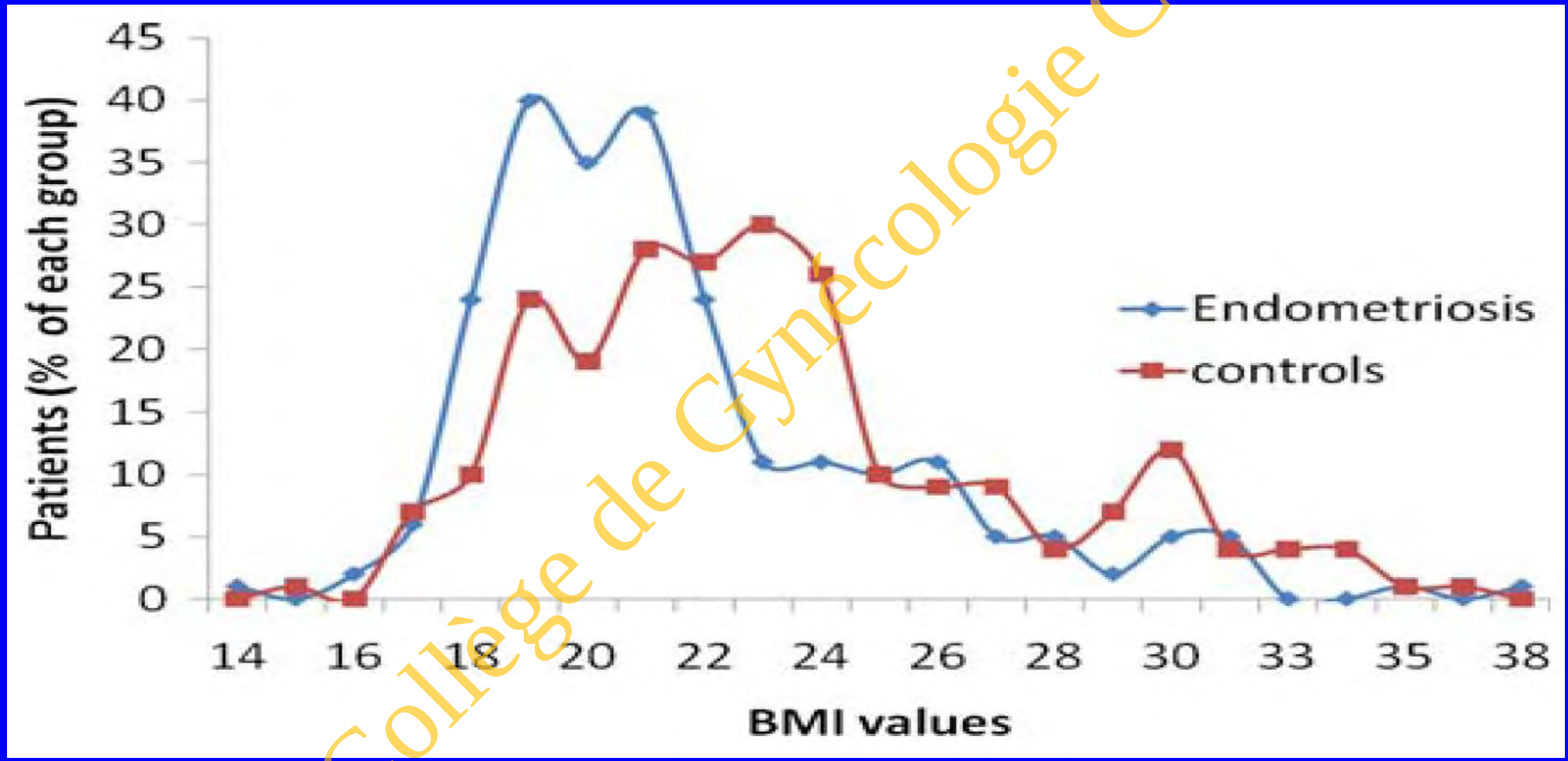
Chapron et al., Fertil Steril (2010)

Endometriosis: *Management options*

Future:

How to get
a quicker diagnosis ?

Endometriosis: Body Mass Index



Lafay Pillet, Chapron *et al.*, Hum Reprod (2012)

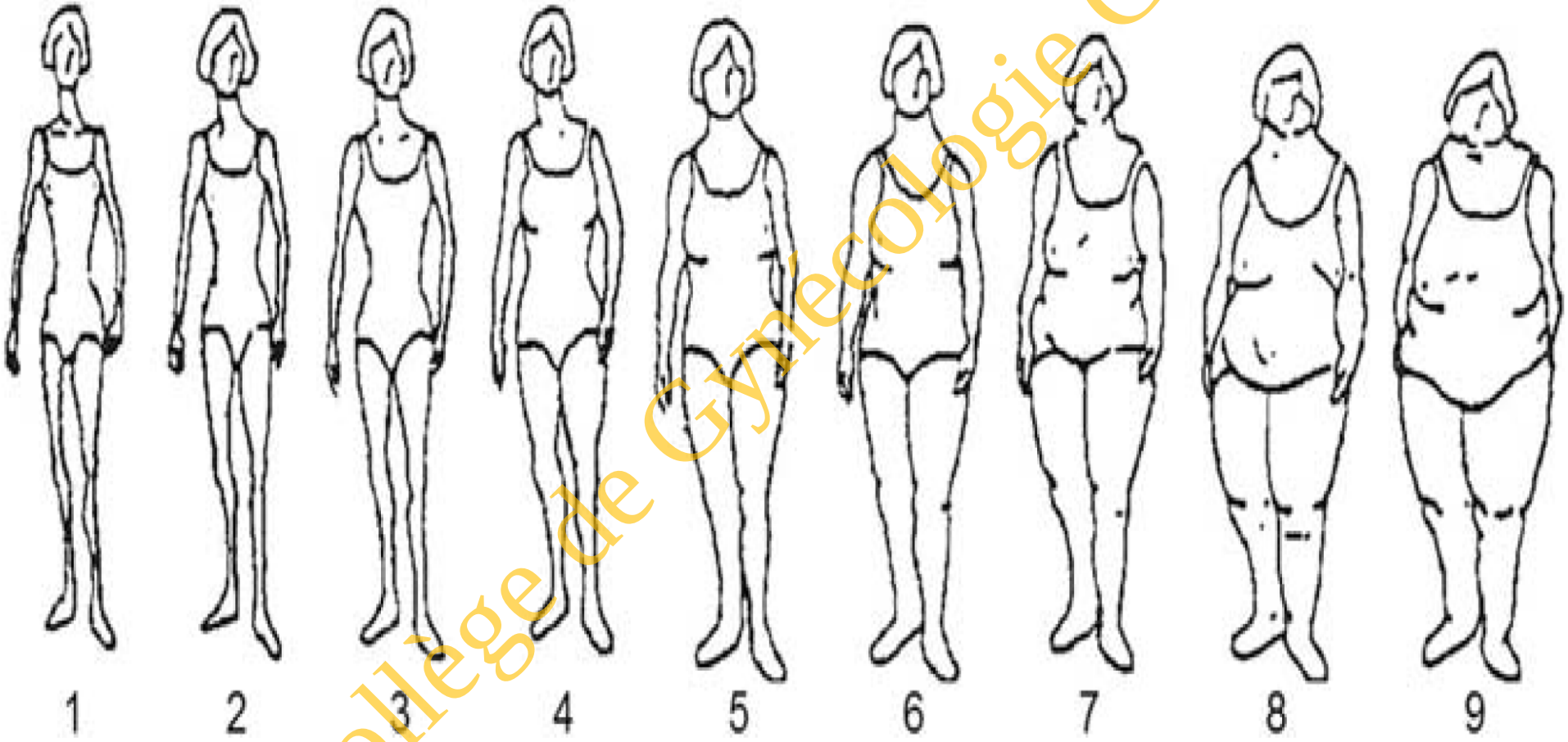
Endometriosis: Body Mass Index

A prospective study of body size during childhood and early adulthood and the incidence of endometriosis

Human Reproduction
2010

Allison F. Vitonis[1,*], Heather J. Baer[2], Susan E. Hankinson[3], Marc R. Laufer[4], and Stacey A. Missmer[5]

Endometriosis: Body Mass Index



Vitonis *et al.*, Hum Reprod (2010)

Endometriosis: Body Mass Index

	All women (no past infertility)			
	Cases	Person-years	Age-adjusted RR[b]	MV RR (95% CI)[c]
Figure at age 5				
1	504	196 367	1.23	1.23 (1.08, 1.40)
2	564	268 816	0.98	0.99 (0.87, 1.13)
3	428	202 963	1.00	1.00
4	206	107 550	0.91	0.88 (0.74, 1.04)
≥5	115	56 214	0.98	0.90 (0.73, 1.11)
				$P_{trend} < 0.0001$
Figure at age 10				
1	360	148 773	1.12	1.14 (0.99, 1.32)
2	572	258 668	1.00	1.02 (0.90, 1.16)
3	422	192 175	1.00	1.00
4	259	132 966	0.89	0.86 (0.74, 1.01)
≥5	204	99 328	0.95	0.88 (0.74, 1.04)
				$P_{trend} = 0.0004$
Average childhood figure (ages 5–10 years)				
1	333	137 283	1.15	1.18 (1.02, 1.36)
1.5–2	583	258 173	1.05	1.08 (0.95, 1.22)
2.5–3	454	212 703	1.00	1.00
3.5–4.5	350	172 605	0.96	0.93 (0.80, 1.07)
≥5	97	51 145	0.90	0.82 (0.66, 1.02)
				$P_{trend} = 0.0002$
Figure at age 20				
1	90	33 663	1.36	1.32 (1.06, 1.65)
2	456	211 910	1.04	1.04 (0.92, 1.18)
3	672	319 455	1.00	1.00
4	406	176 226	1.09	1.05 (0.93, 1.19)
≥5	193	90 655	1.01	0.87 (0.74, 1.03)
				$P_{trend} = 0.04$

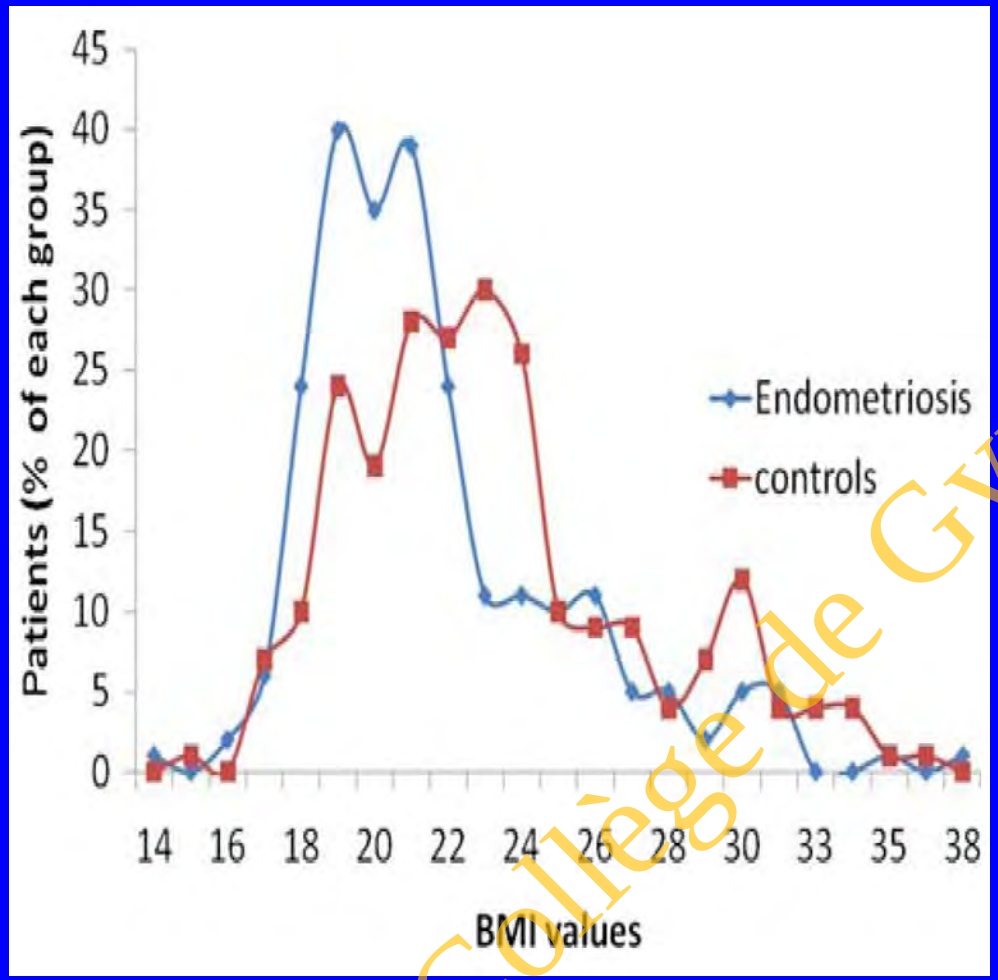
Vitonis *et al.*, Hum Reprod (2010)

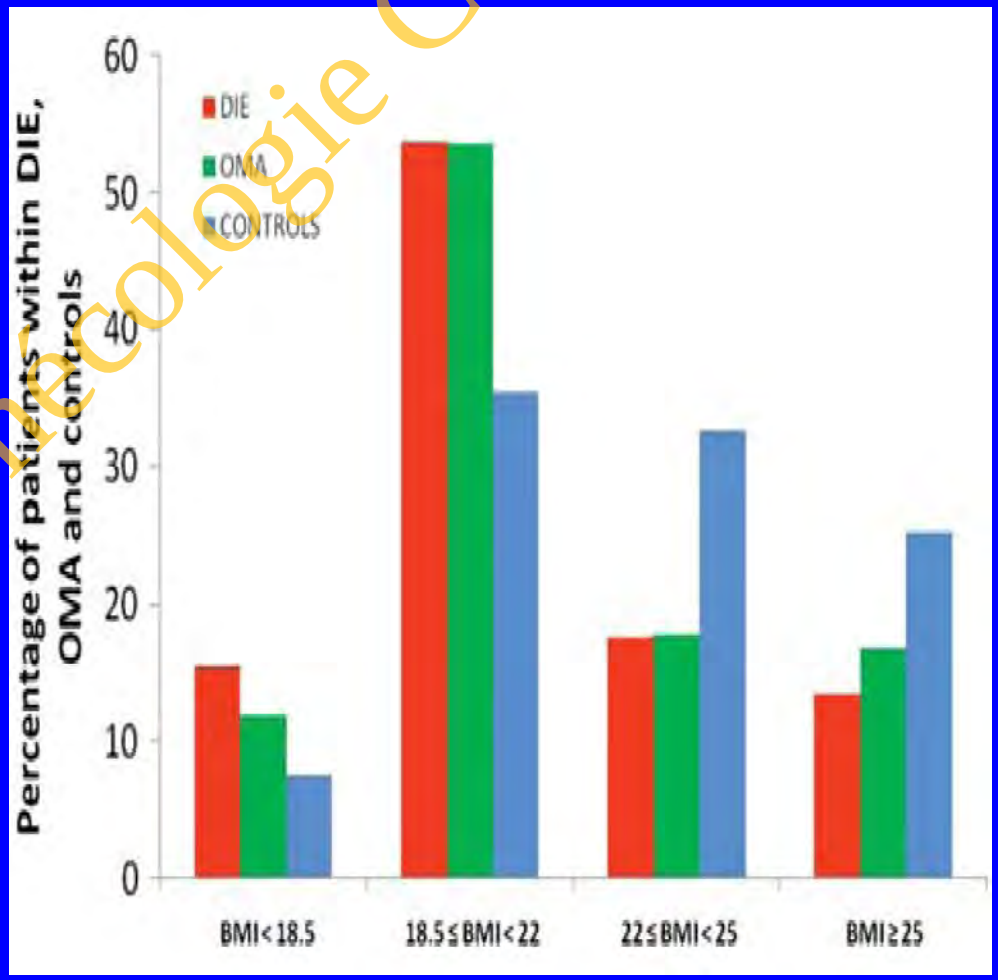
Endometriosis: Body Mass Index

	Cases	Person-years	Age-adjusted RR[a]	MV RR (95% CI)[b]	MV RR (95% CI)[c]
Change from ages 5–10 years					
Decreased	100	48 041	0.99	0.97 (0.79, 1.19)	1.08 (0.88, 1.34)
No change	1223	574 263	1.00	1.00	1.00
Increased 1 level	371	155 297	1.12	1.09 (0.97, 1.23)	1.07 (0.95, 1.21)
Increased 2 or more levels	123	54 308	1.07	1.02 (0.85, 1.23)	0.98 (0.81, 1.18)
Change from ages 10–20 years					
Decreased	312	146 908	1.07	1.05 (0.91, 1.20)	1.17 (1.00, 1.37)
No change	556	280 438	1.00	1.00	1.00
Increased 1 level	697	310 055	1.10	1.12 (1.00, 1.25)	1.05 (0.94, 1.18)
Increased 2 or more levels	252	94 508	1.29	1.22 (1.05, 1.42)	1.13 (0.96, 1.32)
Change from ages 5–20 years					
Decreased	228	107 618	1.09	1.07 (0.91, 1.25)	1.21 (1.02, 1.43)
No change	492	255 098	1.00	1.00	1.00
Increased 1 level	690	306 368	1.14	1.14 (1.02, 1.28)	1.07 (0.94, 1.21)
Increased 2 or more levels	407	162 826	1.25	1.19 (1.04, 1.36)	1.06 (0.92, 1.23)

Vitonis *et al.*, Hum Reprod (2010)

Endometriosis: Body Mass Index





Lafay Pillet, Chapron *et al.*, Hum Reprod (2012)

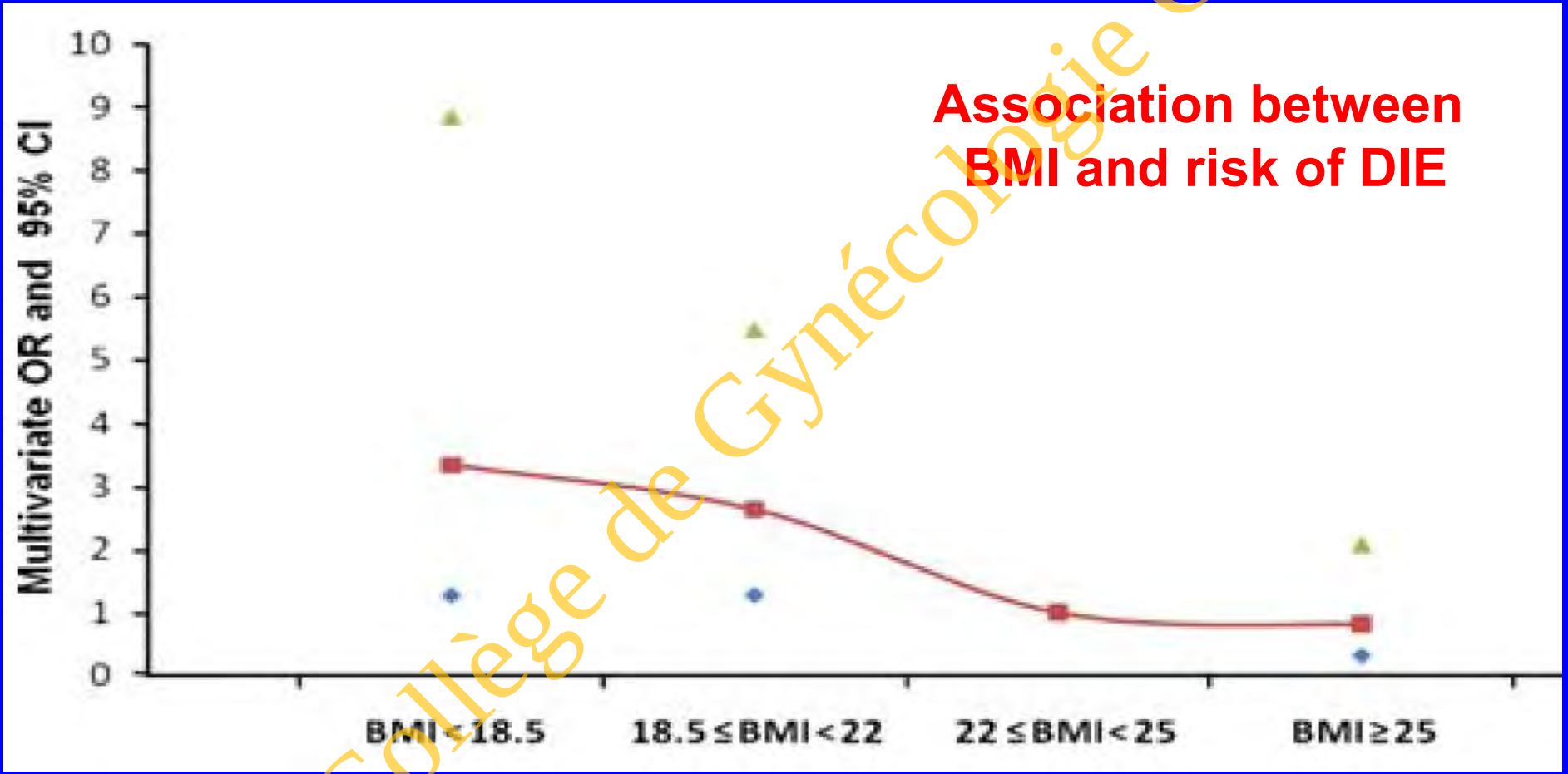
Endometriosis: Body Mass Index

BMI	<18.5	18.5–21.9	22–24.9	≥25
All endometriosis	*n* = 33	*n* = 126	*n* = 40	*n* = 39
Univariate OR (95% CI)	3.4 (1.7–6.9)	2.9 (1.8–4.6)	Reference	1.3 (0.7–2.2)
Multivariate OR (95% CI)	3.3 (1.6–6.8)	2.7 (1.6–4.4)		1.2 (0.7–4.4)
DIE	*n* = 15	*n* = 52	*n* = 17	*n* = 13
Univariate OR (95% CI)	3.7 (1.6–8.8)	2.8 (1.5–5.2)	Reference	1 (0.4–2.0)
Multivariate OR (95% CI)	3.3 (1.3–8.8)	2.6 (1.3–5.5)		.8 (0.3–2.1)
OMA	*n* = 12	*n* = 54	*n* = 18	*n* = 17
Univariate OR (95% CI)	2.8 (1.12–6.9)	2.7 (1.5–5.1)	Reference	1.2 (0.6–2.6)
Multivariate OR (95% CI)	2.7 (1.1–6.1)	2.9 (1.5–5.4)		1.2 (0.6–2.6)

Association between BMI and Osis

Lafay Pillet, Chapron *et al.*, Hum Reprod (2012)

Endometriosis: Body Mass Index



Lafay Pillet, Chapron *et al.*, Hum Reprod (2012)

DIE: Importance of questionning

Parameters	Group A No DIE (n = 131)	Group B DIE (n = 98)	p	OR 95%CI
Family history of Osis	6 (4.6%)	13 (13.3)	0.02	3.2 (1.2 - 8.8)

Chapron *et al.*, Fertil Steril (2011)

Endometriosis: Familiy history

Incidence of osis among first-degree relatives

		Mothers	Sisters	All	Controls
Simpson *et al., (1980)*	USA	5.9	8.1	6.9	0.9
Lamb *et al., (1986)*	USA	6.2	3.8	4.9	2
Moen *et al., (1993)*	Norway	3.9	4.8	4.3	0.6
Coxhead *et al., (1993)*	UK	-	-	5.5	0.8
dos Reis *et al., (1999)*	Brazil	-	-	8.6	0.0
Stefansson *et al., (2002)*	Iceland	-	5.2	-	-
Kashima *et al., (2004)*	Japan	-	8.8	5.7	1.5
Metalliotakis *et al., (2003)*	USA	3.9	5.5	9.4	1.0

DIE: Importance of questionning

Parameters	Group A No DIE (n = 131)	Group B DIE (n = 98)	p	OR 95%CI
Absenteeism from school during menstruation	33 (25.2%)	37 (37.7%)	0.04	1.7 (1 - 3)

Chapron *et al.*, Fertil Steril (2011)

DIE: Importance of questionning

Parameters	Group A No DIE (n = 131)	Group B DIE (n = 98)	p	OR 95%CI
Prescription of OCPs because of severe primary dysmenorrhea	15 (25.9%)	29 (58.0%)	0.001	4.5 (1.9 – 10.4)
Age *(years)*	18.1 ± 3.2	16.5 ± 2.4	0.07	
Duration of use *(years)*	5.1± 3.8	8.4 ± 4.7	0.02	

Chapron *et al.*, Fertil Steril (2011)

Questioning patients about their adolescent history can identify markers associated with deep infiltrating endometriosis

Fertil Steril *(2011)*

Charles Chapron, M.D.,[a,b,c] *Marie-Christine Lafay-Pillet, M.D.,*[a] *Elise Monceau, M.D.,*[a] *Bruno Borghese, Ph.D.,*[a,b,c] *Charlotte Ngô, Ph.D.,*[a,d] *Carlos Souza, M.D.,*[a,e] *and Dominique de Ziegler, M.D.*[a]

Characteristic	Group A No DIE (n = 131)	Group B DIE (n = 98)	*P* value	OR 95% CI
Preoperative painful symptoms scores[a]				
VAS >7				
Dysmenorrhea	44 (35.6)	55 (56.1)	.0001	2.8 (1.6–4.6)[b]
Deep dyspareunia	12 (9.2)	20 (20.4)	.015	2.5 (1.2–5.5)[b]
Noncyclic chronic pelvic pain	5 (3.8)	12 (12.2)	.016	3.5 (1.2–10.3)[b]
Gastrointestinal symptoms	6 (4.6)	28 (28.6)	.0001	8.6 (3.4–21.7)[b]
Lower urinary tract symptoms	0 (0)	15 (15.3)	.0001	–
Prescription of OC pills because of severe primary DM				
Age <18 y	8 (6.1)	21 (21.4)	.001	4.2 (1.8–10.0)[c]

Take home messages

Questioning patients about their adolescent history can identify markers associated with deep infiltrating endometriosis

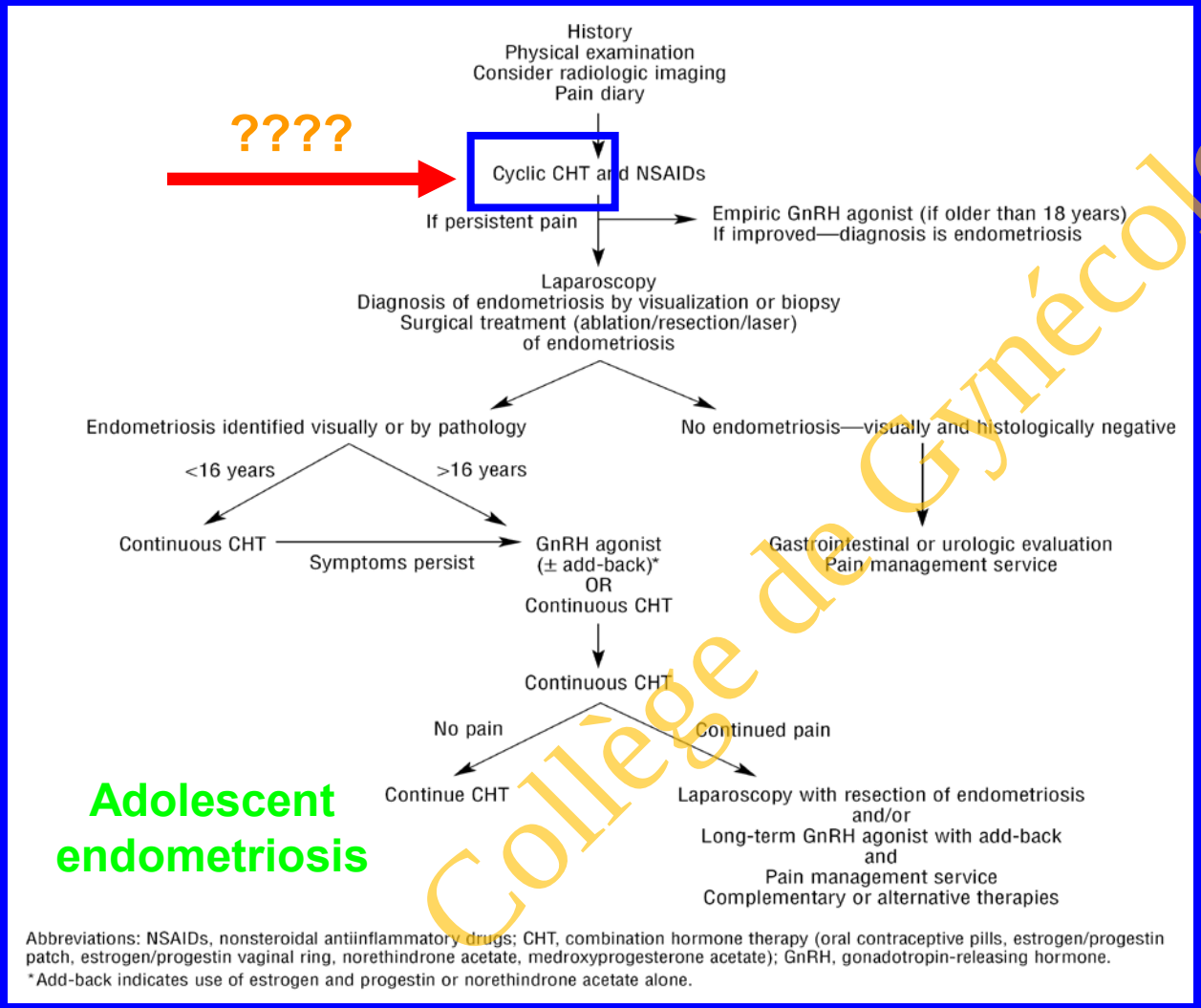
Fertil Steril (2011)

Charles Chapron, M.D.,[a,b,c] *Marie-Christine Lafay-Pillet, M.D.,*[a] *Elise Monceau, M.D.,*[a]
Bruno Borghese, Ph.D.,[a,b,c] *Charlotte Ngô, Ph.D.,*[a,d] *Carlos Souza, M.D.,*[a,e] *and Dominique de Ziegler, M.D.*[a]

For the first time +++

This study identifies the links existing between certain peri-menarchal symptoms and the development of deep infiltrating endometriosis

Take home messages



Adolescent endometriosis

ACOG Committee on Adolescent Health Care

2005

ACOG Committee Opinion

Non-contraceptive prescription of OCPs

to treat severe primary DM

after failure of NSAIDs

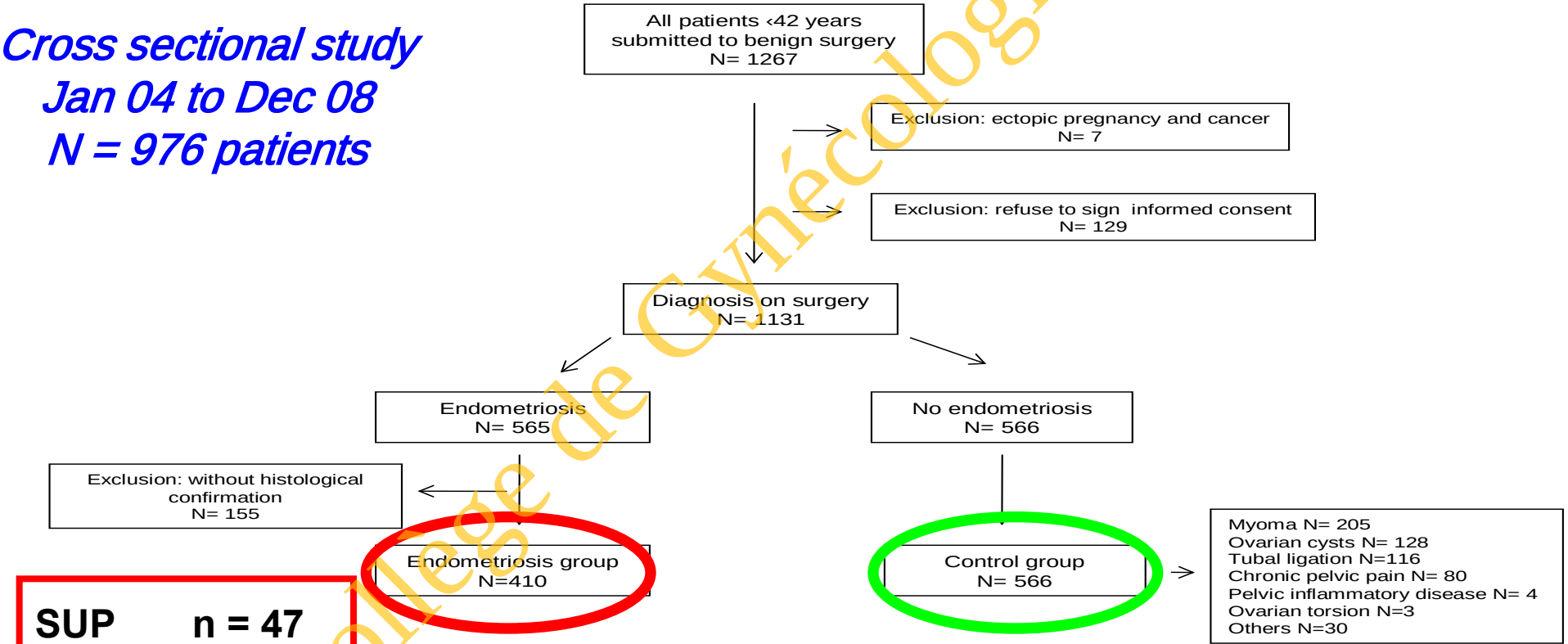
seems not to be

a satisfactory therapeutic option.

Oral contraception and endometriosis:

Flow chart showing longitudinal of the study population

Cross sectional study
Jan 04 to Dec 08
N = 976 patients



SUP	**n = 47**
OMAs	**n = 120**
DIE	**n = 243**

Chapron *et al.*, Hum Reprod (2011)

Oral contraception and endometriosis:

Logistic regression analysis

OC user	Ad OR 95% CI	p
Never user	Reference	
Ever user	2.17 (1.19 – 3.95)	p = 0.012
Current user	1.22 (0.6 - 2.52)	p = NS
Past user	2.79 (1.74 – 5.12)	p = 0.002

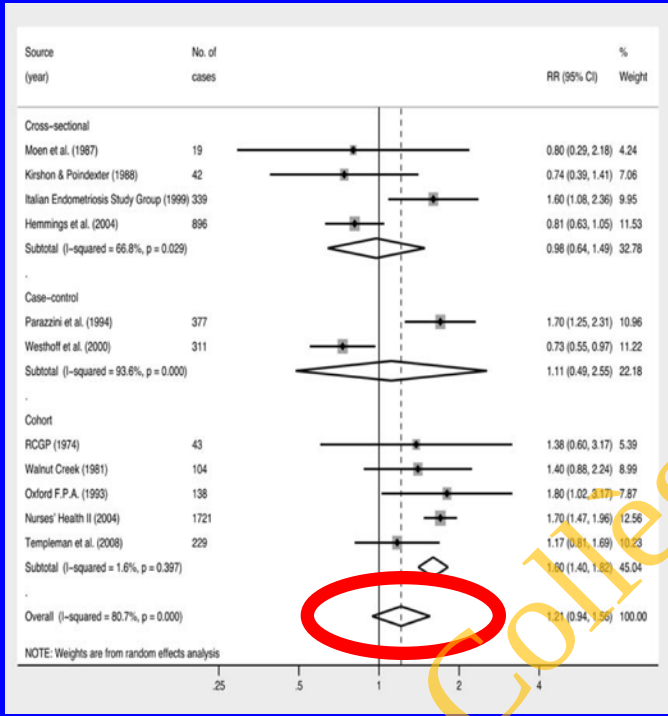
Chapron *et al.*, Hum Reprod (2011)

human reproduction update

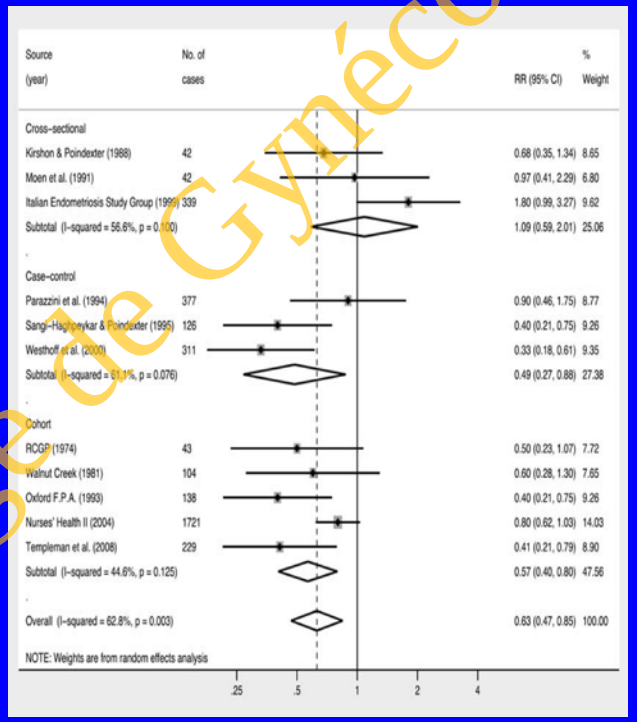
Oral contraceptives and risk of endometriosis: a systematic review and meta-analysis

(2011)

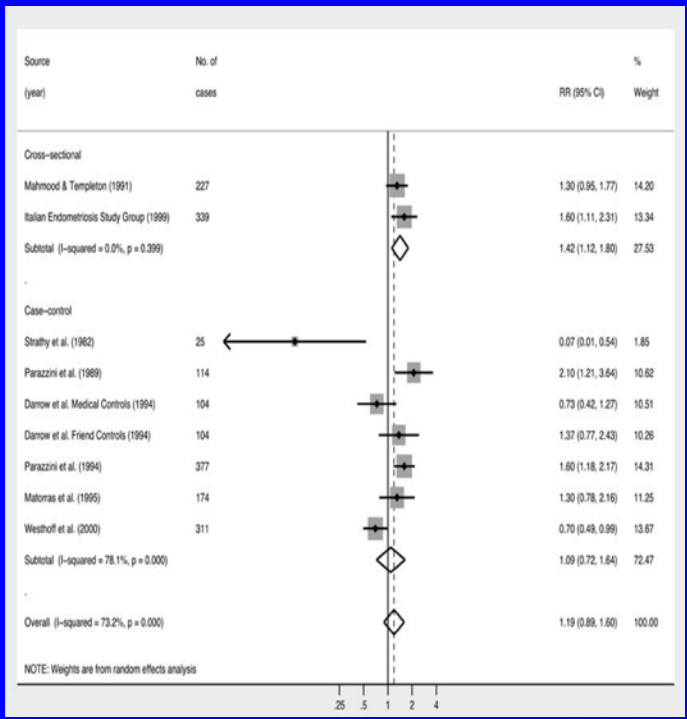
Paolo Vercellini[1,2,*], Brenda Eskenazi[3], Dario Consonni[4], Edgardo Somigliana[1,2], Fabio Parazzini[1], Annalisa Abbiati[1,2], and Luigi Fedele[1]



Past users



Current users



Ever users

Oral contraception and endometriosis

According to the type of endometriotic lesions:

Logistic regression analysis

OC user	Ad OR 95% CI SUP	OMAs	DIE
Never user	Reference		
Ever user	2.59 (1.11 - 6.03)	1.37 (0.84 - 2.23)	4.2 (1.54 - 11.2)
Current user	2.7 (0.98 - 7.47)	0.95 (0.5 - 1.7)	1.98 (0.65 - 6.07)
Past user	2.56 (1.07 - 6.09)	1.65 (0.99 - 2.75)	5.7 (2.1 - 15.7)

Chapron *et al.*, Hum Reprod (2011)

Oral contraception and endometriosis:

According to the indication for OC use prescription

Logistic regression analysis

Previous OC use	Group A Controls (n = 566)		Group B Osis (n = 410)	Ad OR 95% CI
No	160	(28.3%)	46 (11.2%)	
Yes				
- To treat severe primary DM	37	(6.5%)	78 (19.0%)	5.6 (3.2 - 9.8)
- Other indications	369	(65.2%)	286 (69.8%)	2.6 (1.8 - 4.1)

Chapron *et al.*, Hum Reprod (2011)

Oral contraception and endometriosis

According to the indication for OC use prescription and the type of endometriotic lesions: :

Logistic regression analysis

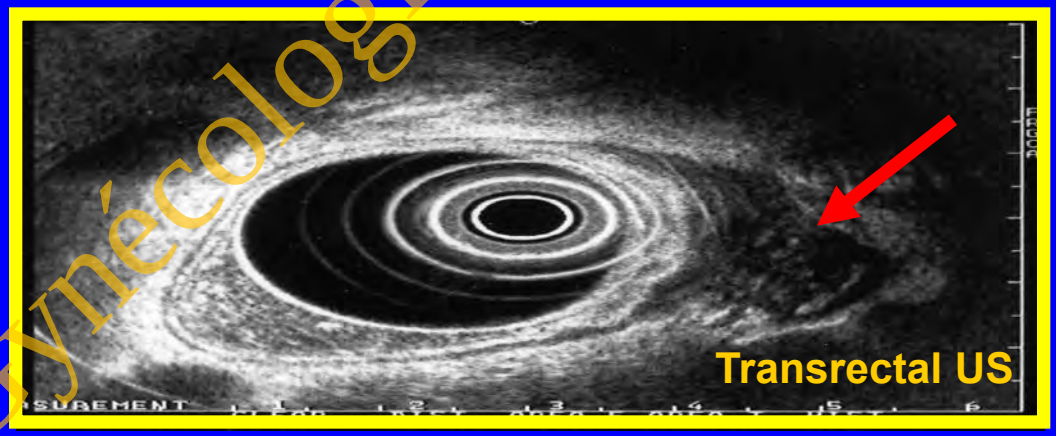
Previous OC use		Ad OR 95% CI SUP	OMAs	DIE
No			Reference	
Yes	To treat severe 1st DM	3.5 (0.9 - 13.5)	1.9 (0.8 - 4.3)	16.2 (7.8 - 35.3)
	Other indications	2.8 (1.1 - 7.1)	1.3 (0.8 - 2.1)	6.4 (3.2 - 13.7)

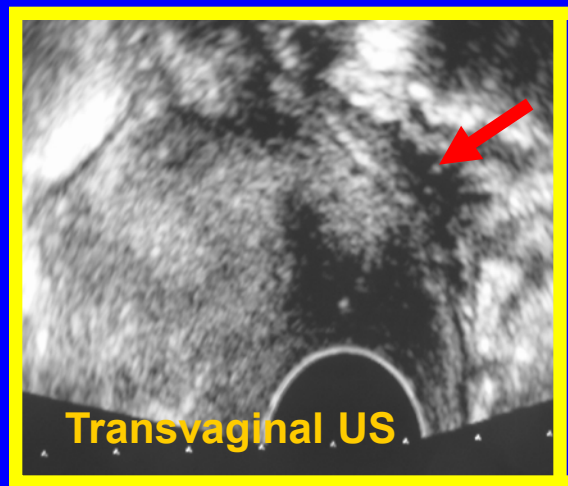
Chapron *et al.*, Hum Reprod (2011)

Deeply infiltrating endometriosis:
Diagnosis of the rectum wall infiltration:
Comparaison between TRUS et TVUS

	TRUS	TVUS
Se	82	95
Sp	88	100
VPP	94	100
VPN	64	89

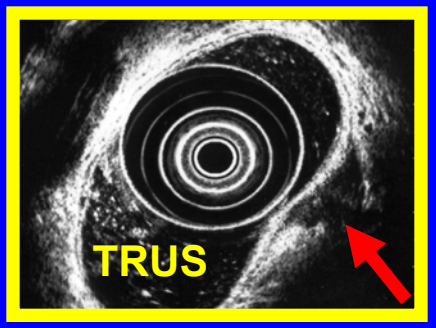
Bazot *et al.*, Hum Reprod (2003)

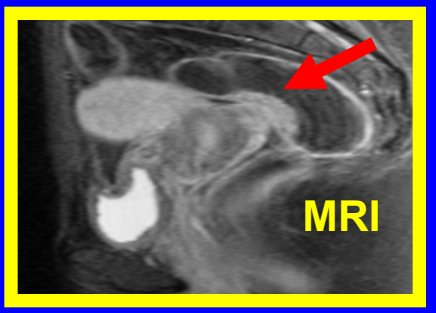


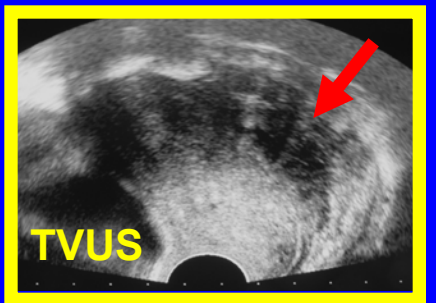


Deep endometriosis: Rectal wall infiltration

	N	Se	Sp	PPV	NPV
TRUS					
Chapron *et al., (2004)*	81	97	89	87	98
Bazot *et al., (2007)*	81	89	93	96	81
Piketty - Chapron *(2009)*	134	96	100	100	95
MRI					
Chapron *et al., (2004)*	81	76	98	96	85
Abrao *et al., (2007)*	104	83	98	97	84
Bazot *et al. (2007)*	88	83	93	96	79
TVUS					
Abrao *et al. (2007)*	104	98	100	100	98
Bazot *et al., (2007)*	81	93	100	100	87
Piketty – Chapron *(2009)*	134	90	96	97	89







Deep endometriosis: preoperative diagnosis

human reproduction ORIGINAL ARTICLE *Gynaecology*

Preoperative work-up for patients with deeply infiltrating endometriosis: transvaginal ultrasonography must definitely be the first-line imaging examination

Hum Reprod (2009)

Mathilde Piketty[1], Nicolas Chopin[1], Bertrand Dousset[2], Anne-Elodie Millischer-Bellaische[3], Gilles Roseau[1], Mahaut Leconte[2], Bruno Borghese[1,4,5], and Charles Chapron[1,4,5,6]

Table IV Sensitivity, specificity, positive and negative predictive value of TVUS and TRUS in the diagnosis of rectal involvement for patients presenting with DIE (n = 134)

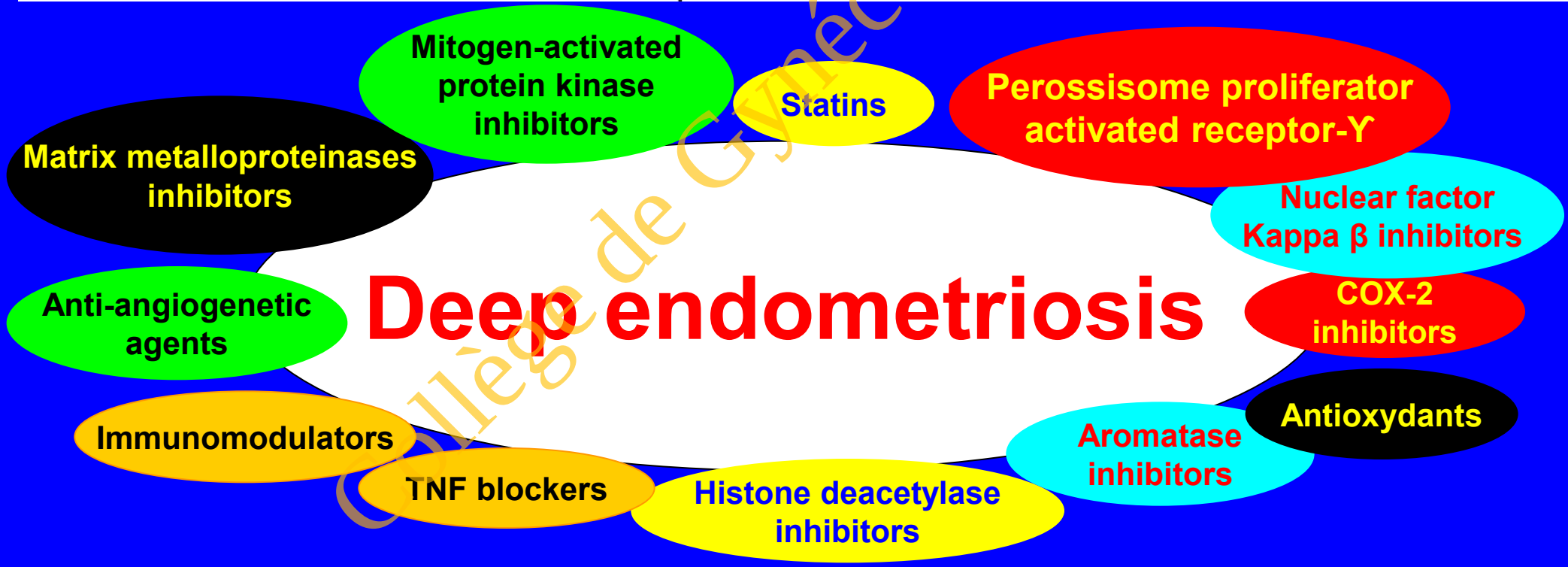
	TVUS		TRUV	
	% (n)	95% CI	% (n)	95% CI
Sensitivity	90.7% (68/75)	0.84/0.97	96.0% (72/75)	0.92/1.00
Specificity	96.5% (56/58)	0.92/1.01	100% (59/59)	1.00/1.00
PPV	97.1% (68/70)	0.93/1.01	100% (72/72)	1.00/1.00
NPV	88.9% (56/63)	0.81/0.97	95.2% (59/62)	0.90/1.01

Endometriosis: *New non hormonal medical options*

New treatment strategies and emerging drugs in endometriosis

Expert Opin Emerging Drugs (2012)

Isabelle Streuli†, Dominique de Ziegler, Bruno Borghese, Pietro Santulli, Frédéric Batteux & Charles Chapron



Endometrisois:

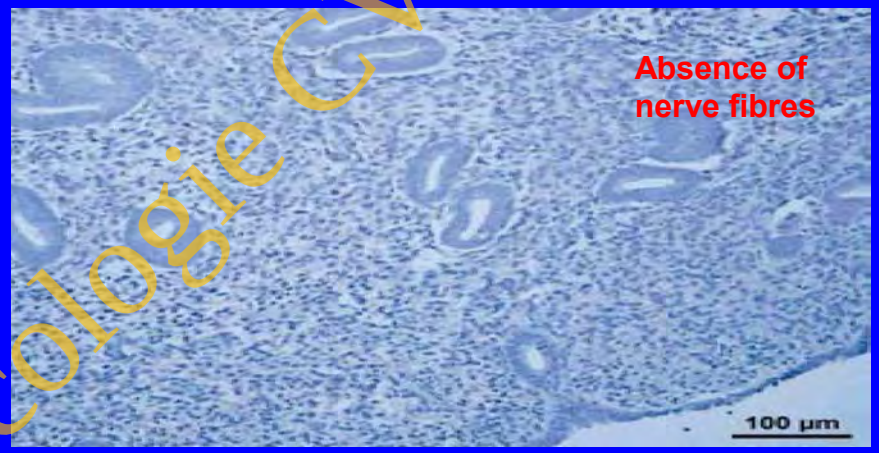
Future management ????

Future options for earlier diagnosis

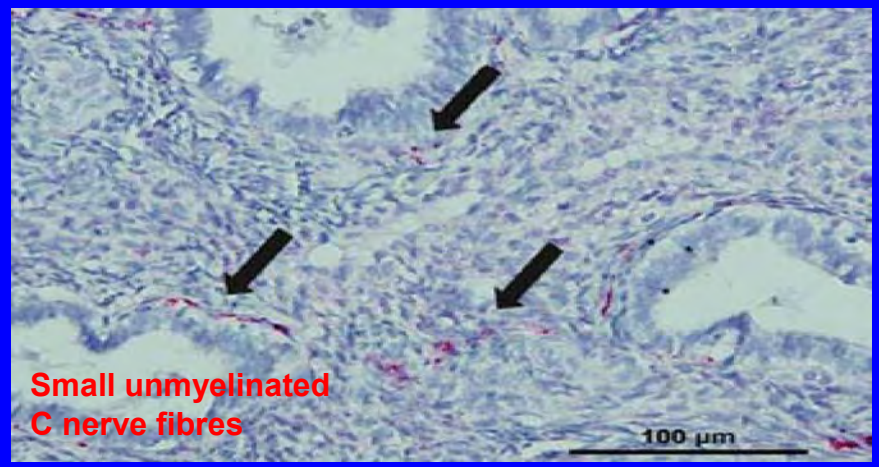
Endometriosis diagnosis: Endometrial biopsy

Endometrial biopsy	Osis at laparoscopy Yes (n = 64)		No (n = 35)	
Endometrial nerve fibers				
Yes	63	98%	6	17%
No	1	2%	29	83%

Specificity	83%	(66 - 93%)
Sensitivity	98%	(90 - 99%)
PPV	91	(81 - 96%)
NPV	96	(81 - 99%)

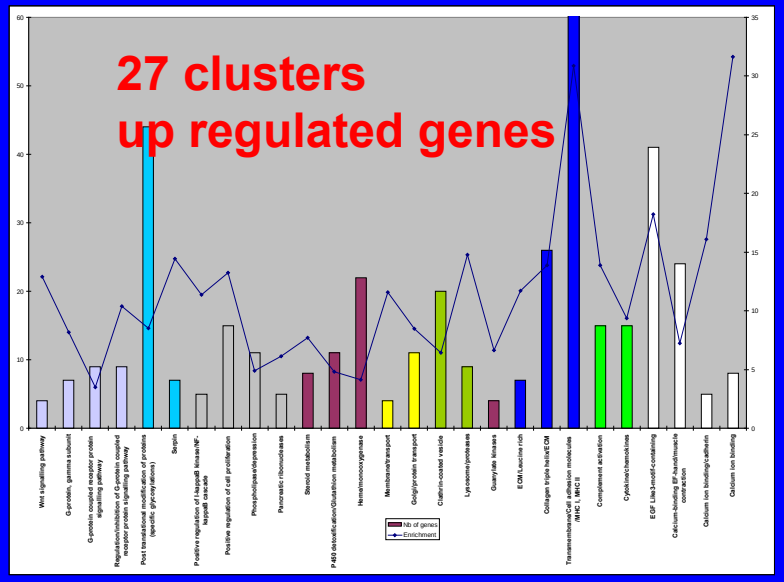


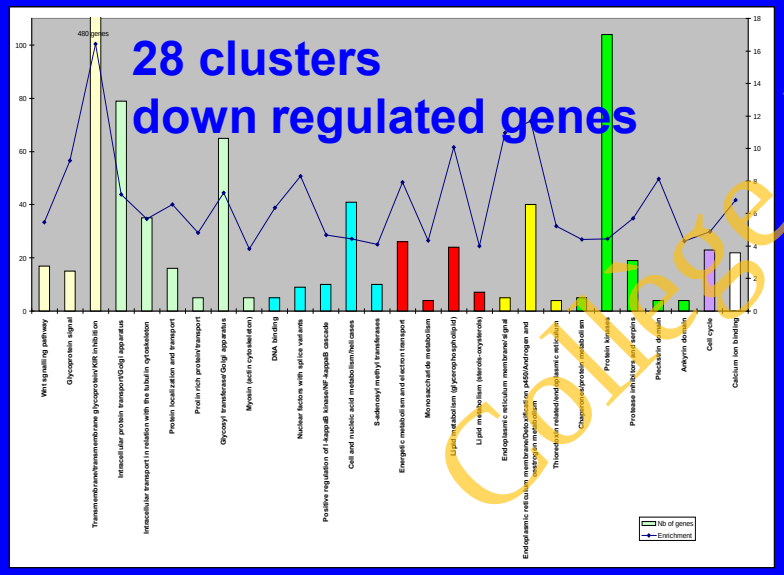
Functional layer of endometrium



Al - Jefout *et al.*, Hum Reprod (2009)

Endometriosis: Gene signature





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Molecular Endocrinology 22(11):2557–2562
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doi: 10.1210/me.2008-0322

RESEARCH RESOURCE

Gene Expression Profile for Ectopic *Versus* Eutopic Endometrium Provides New Insights into Endometriosis Oncogenic Potential

Bruno Borghese, Françoise Mondon, Jean-Christophe Noël, Isabelle Fayt, Thérèse-Marie Mignot, Daniel Vaiman, and Charles Chapron

Genes

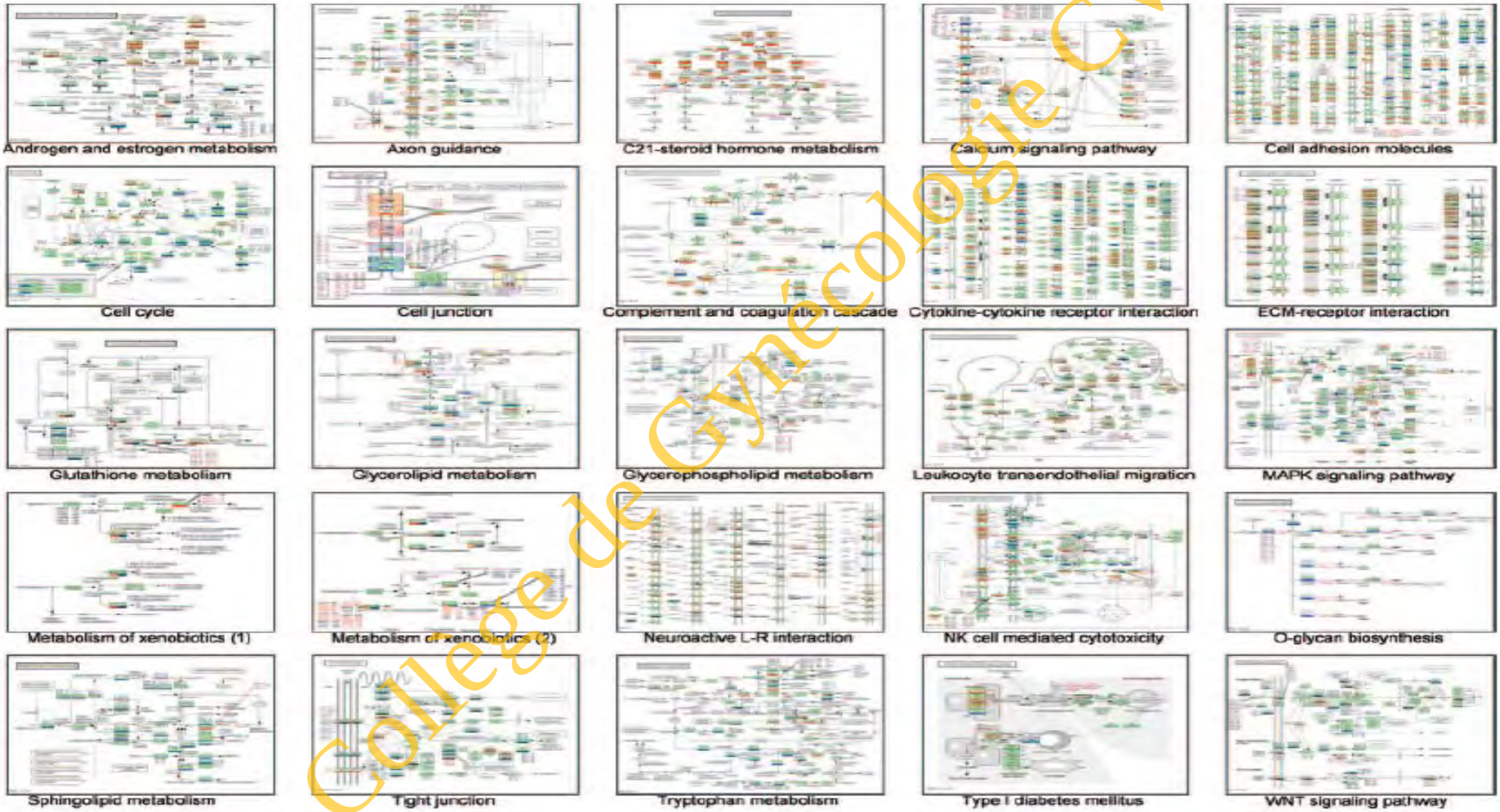
Up regulated

CYP17A1	+ 368	*Streoid synthesis*
INL 3	+ 226	
GATA 4	+ 123	*Transcriptional factor*

Down regulated

MMP 26	- 330	*Metalloproteinase*

Endometriosis: Gene profile analysis



B Borghese, D Vaiman, C Chapron Mol Endocrinol (2008)

0888-8809/08/$15.00/0
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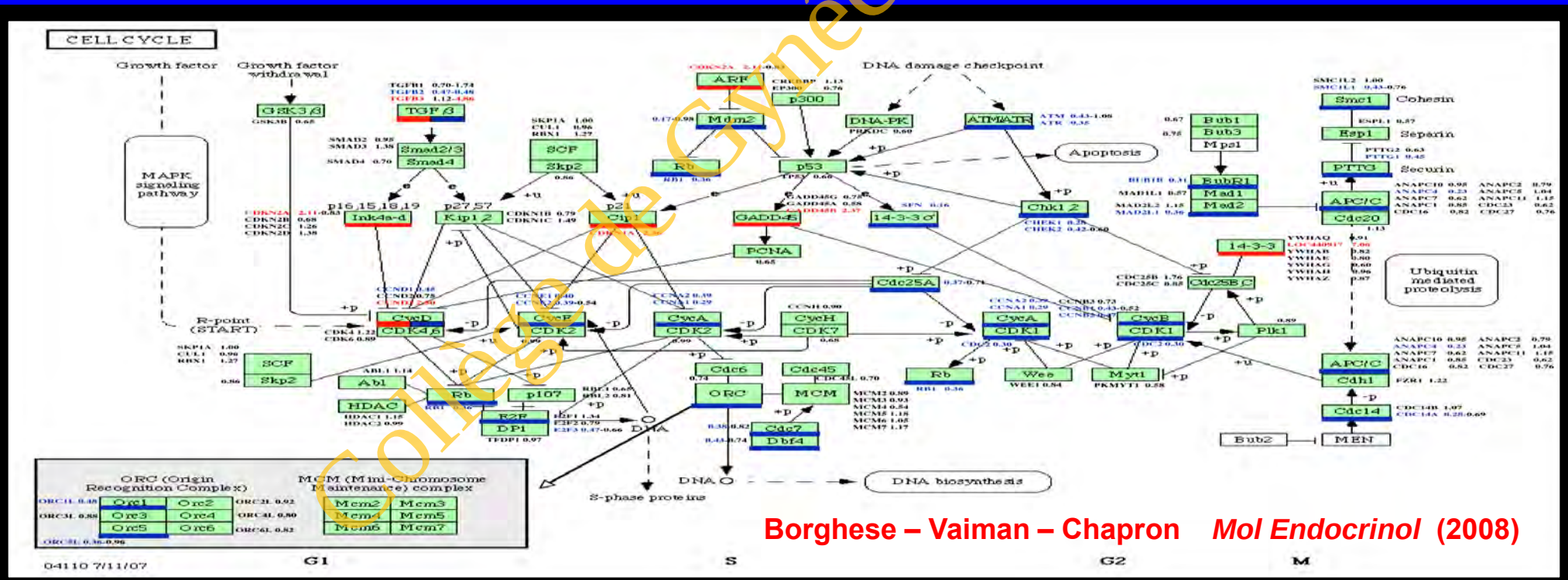
Endometriosis: Pathogenesis

Endometriosis is not a cancer

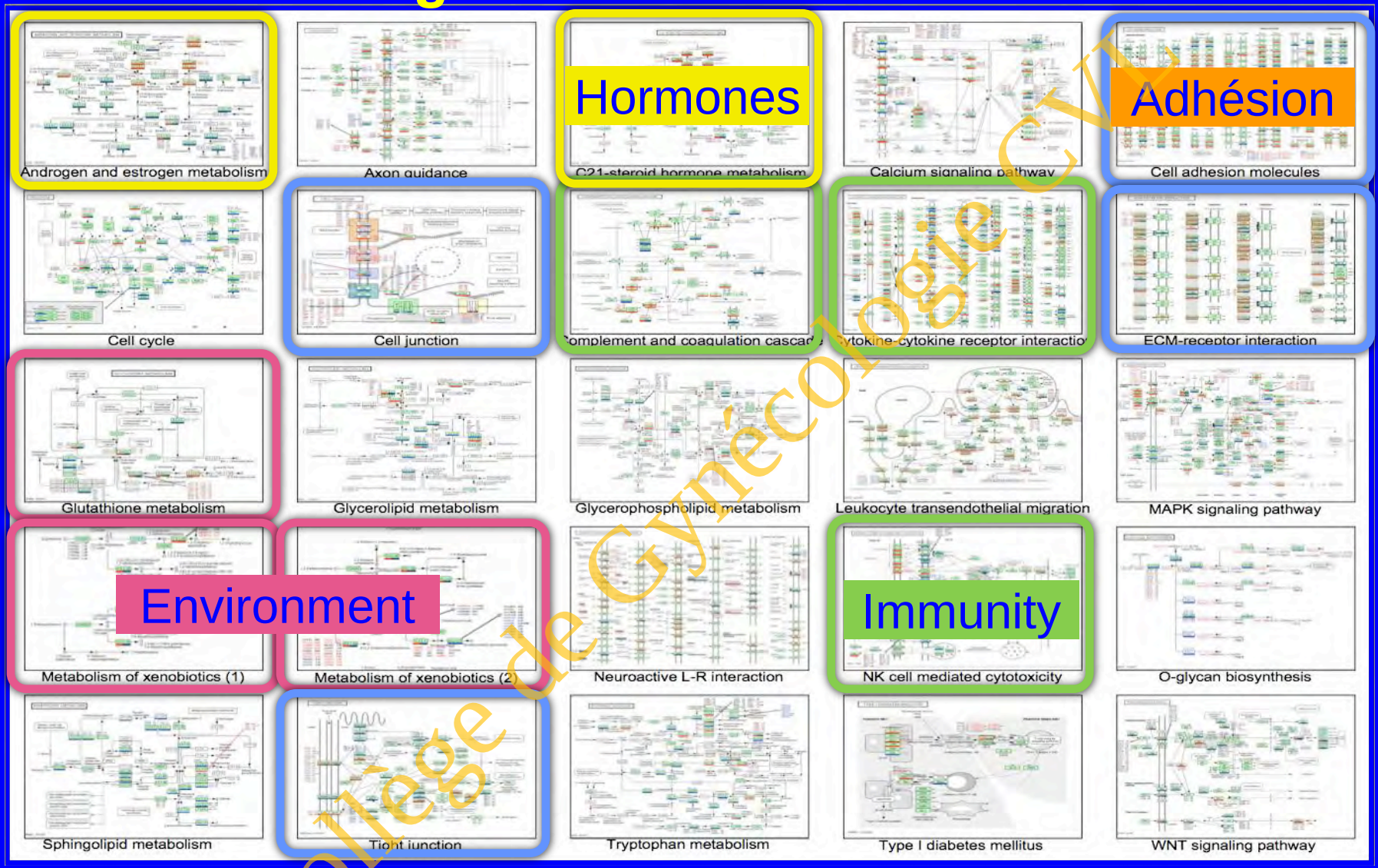
The cell cycle pathway is modified in an univocal way +++

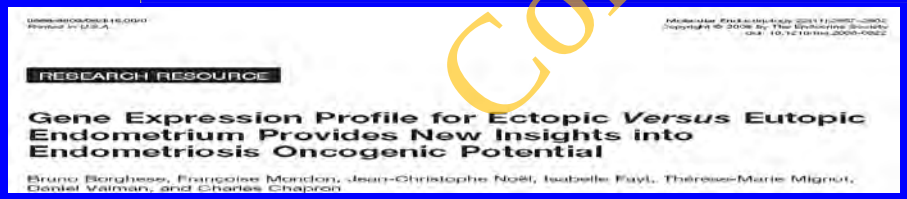
There is a systematic down regulation of genes involved in the cell cycle ++++



Borghese – Vaiman – Chapron *Mol Endocrinol* (2008)

Massive gene alterations in endometriosis





RESEARCH RESOURCE

Gene Expression Profile for Ectopic *Versus* Eutopic Endometrium Provides New Insights into Endometriosis Oncogenic Potential

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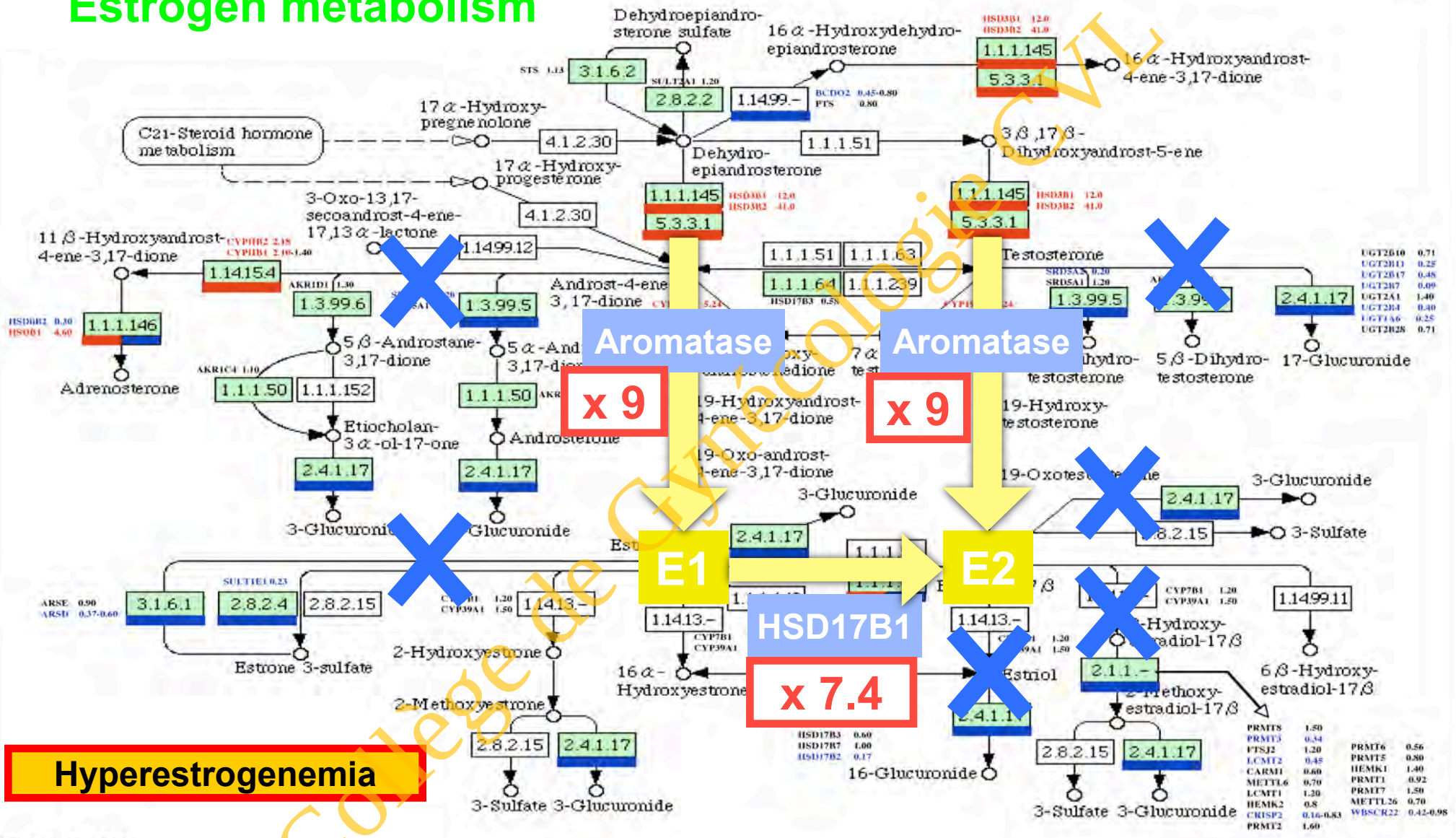
Borghese – Vaiman – Chapron ***Mol Endocrinol*** **(2008)**

Estrogen metabolism



B Borghese, D Vaiman, C Chapron Mol Endocrinol (2008)

Endometriosis: Gene profile analysis

Specific modifications of genes of the four HOX clusters in endometriosis

Induction ratio	Genome[a]	HOX clusters[a]				
		All	*HOX-A*	*HOX-B*	*HOX-C*	*HOX-D*
< 0.5	4174	30	14	13	0	3
0.5 - 2.0	39623	17	5	4	3	5
> 2.0	3836	17	0	0	12	5
P-value[b]		< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

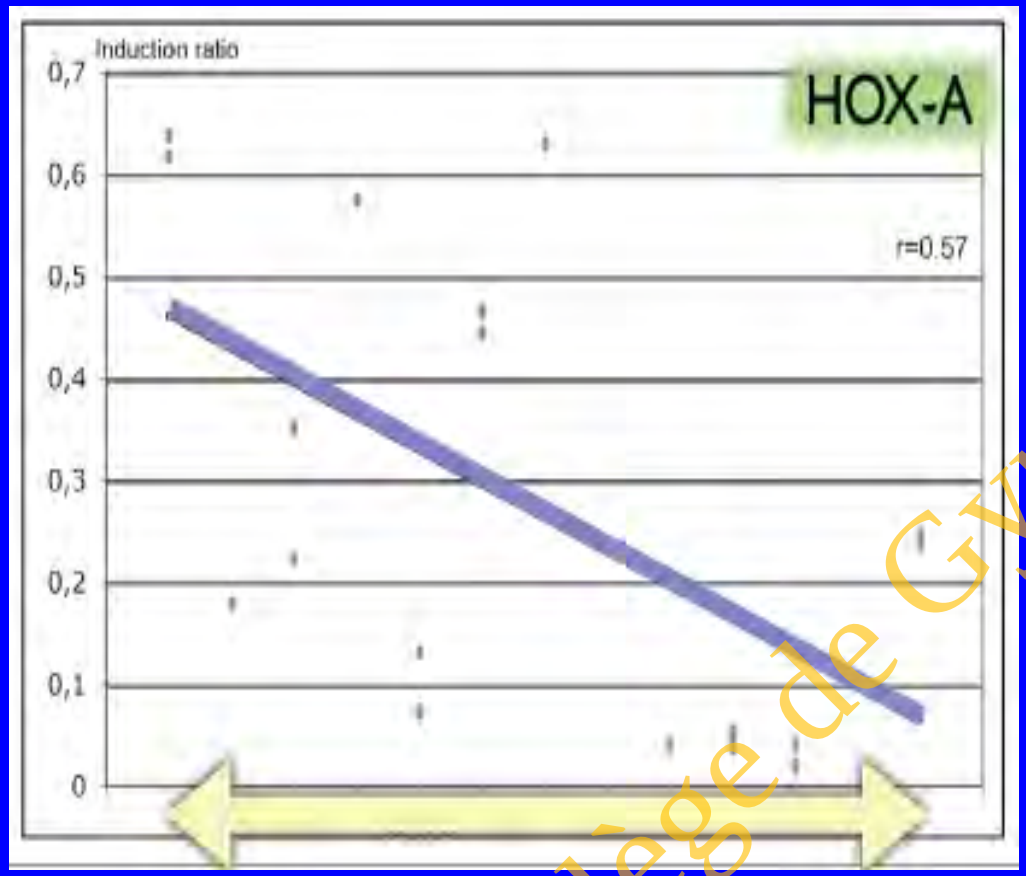
[a]number of tags on NimbleGen™ microarray

[b]chi-square test for comparison between genome and each HOX cluster

Systematic dysregulation of HOX genes opposite of breast and ovarian K

B Borghese, D Vaiman, C Chapron Mol Endocrinol (2008)

Endometriosis: Gene profile analysis

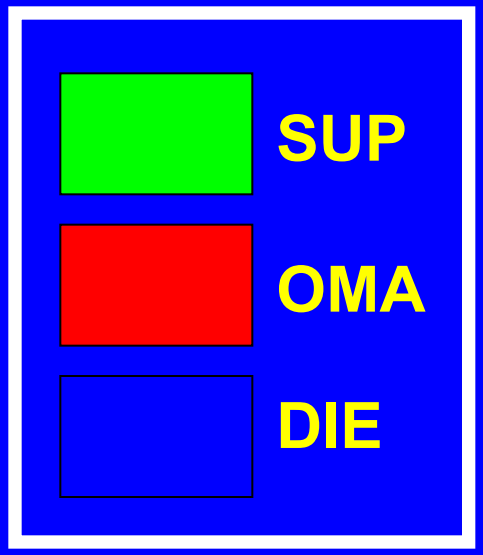


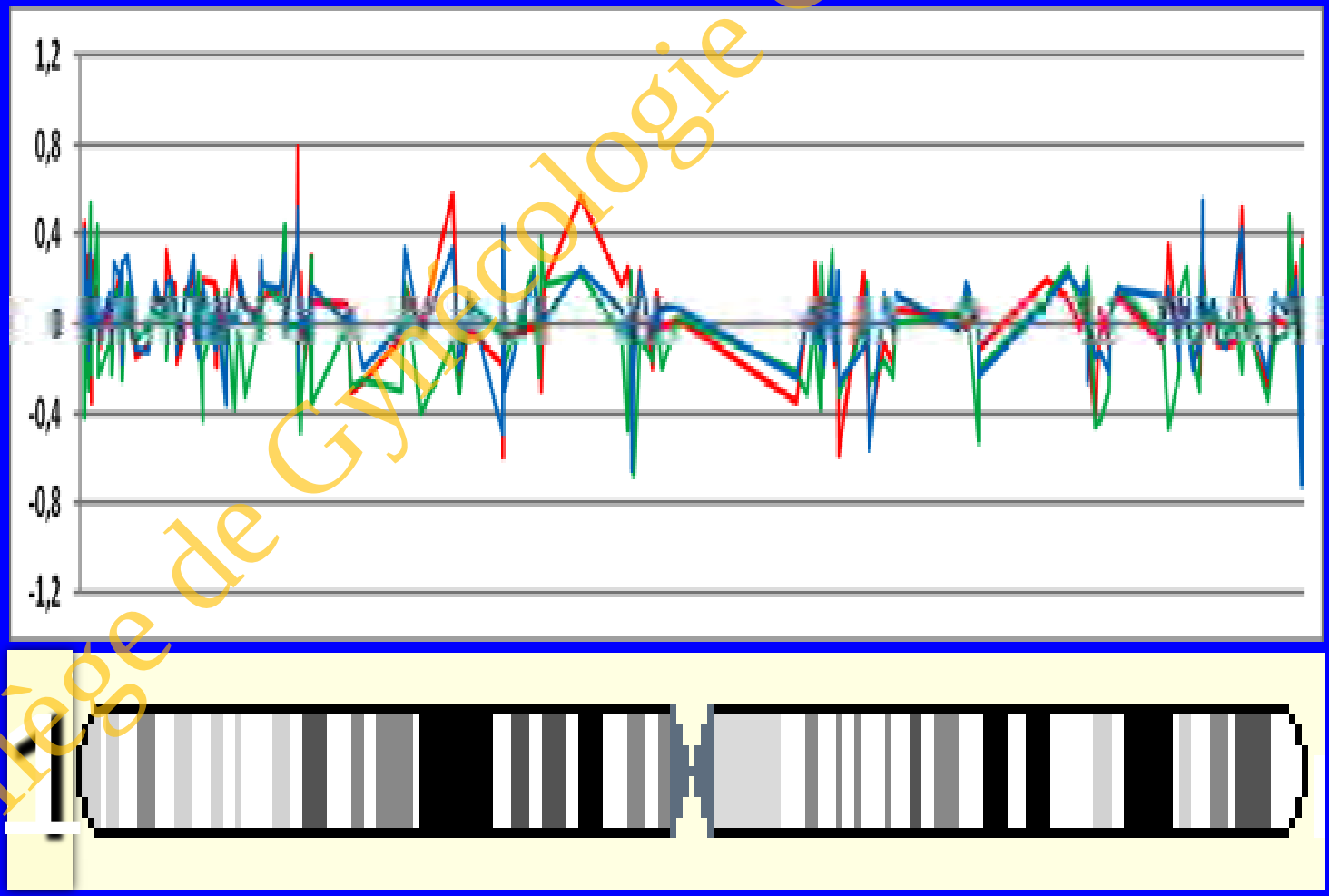
Gene expression is linearly dysregulated according to the position on HOX-genes

B Borghese, D Vaiman, C Chapron Mol Endocrinol (2008)

Endometriosis: Epigenetic changes

Chromosal locations of methylation alterations



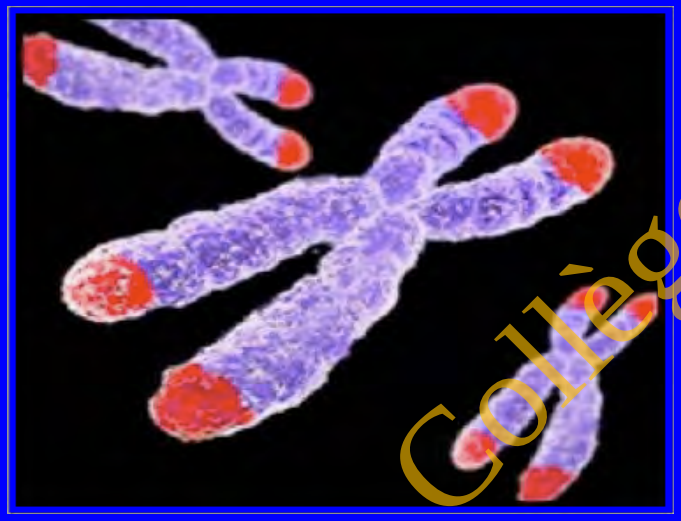


B Borghese, C Chapron, D Vaiman Mol Endocrinol (2010)

Endometriosis: Epigenetic changes

Chromosal distribution of methylated and demethylated promoter regions

Threshold (% of chromosomal ends)	OMA		SUP		DIE	
	demethylated	hypermethylated	demethylated	hypermethylated	demethylated	hypermethylated
10%	NS	< 0.01	NS	NS	NS	< 0.01
5%	NS	< 0.01	0.05	< 0.01	NS	< 0.01
2%	NS	< 0.01	NS	< 0.01	NS	< 0.01



Promoter regions

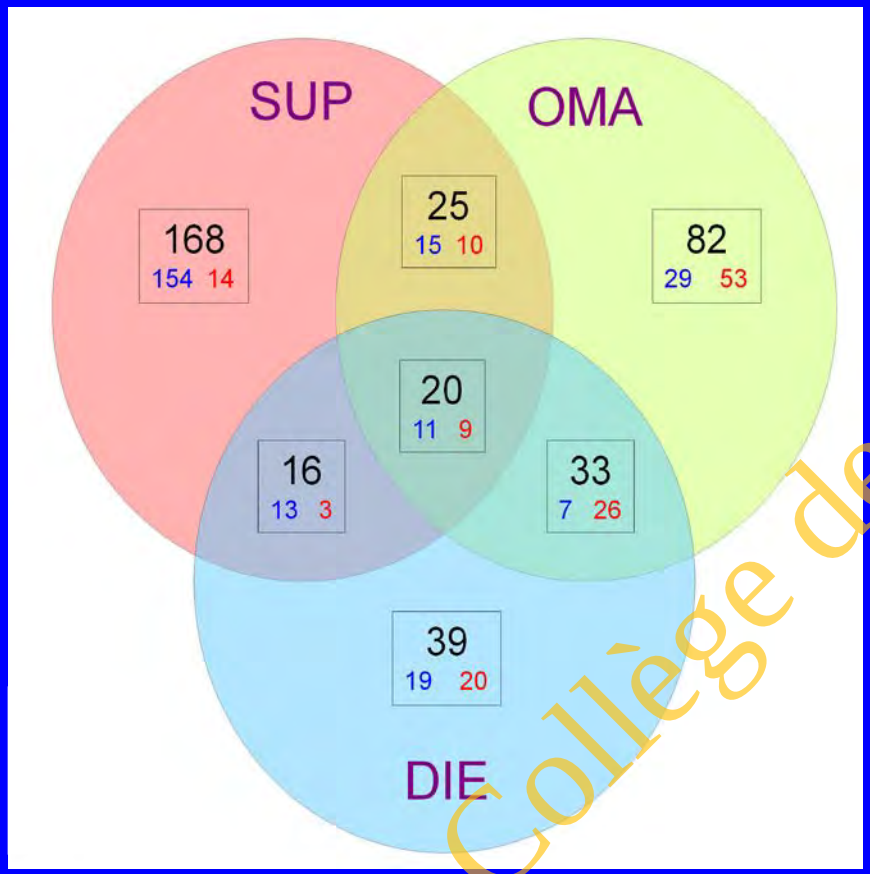
Demethylated: **uniformly distributed**

Methylated: **Subtelomeric**

B Borghese, C Chapron, D Vaiman Mol Endocrinol (2010)

Endometriosis: Epigenetic changes

Common and specific active regions between different endometriotic lesions



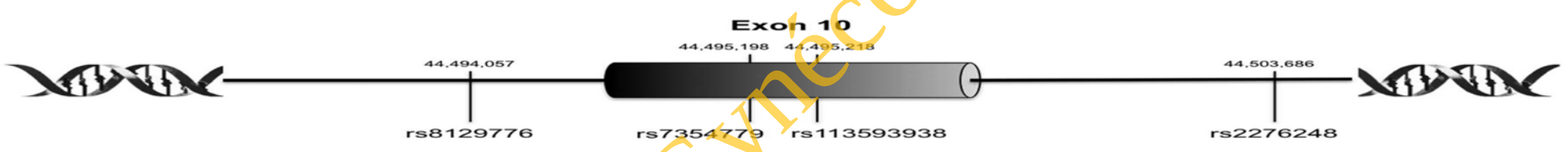
Liste of 20 active regions common to SUP, OMA and DIE.

Chromosome	#Active Region	Start	Lengh	Ratio OMA/EE	Ratio SUP/EE	Ratio DIE/EE	Gene list	Gene name
7	2186	55207807	8821	1,61	1,54	1,91		
7	2263	156232815	1524	3,06	3,10	2,16	NOM1	nucleolar protein with MIF4G domain 1
10	224	44815659	252	2,19	2,05	1,82	RASSF4	ras association (RalGDS/AF-6) domain family member 4
10	224	44815659	252	2,19	2,05	1,82	C10orf25	chromosome 10 open reading frame 25
10	224	44815659	252	2,19	2,05	1,82	ZNF22	zinc finger protein 22 (KOX 15)
11	310	520194	1229	2,58	1,69	1,83	HRAS	v-Ha-ras Harvey rat sarcoma viral oncogene homolog
11	310	520194	1229	2,58	1,69	1,83	LRRC56	leucine rich repeat containing 56
13	556	112809520	1027	2,47	1,83	2,03	F7	coagulation factor VII (serum prothrombin conversion accelerator)
13	561	113114606	556	2,44	2,30	1,52	DKFZp451A211	DKFZp451A211 protein
13	561	113114606	556	2,44	2,30	1,52	ADPRHL1	ADP-ribosylhydrolase like 1
16	735	1250431	492	1,59	1,57	1,67	TPSD1	tryptase delta 1
16	815	31142886	513	1,71	1,63	1,64	PYDC1	PYD (pyrin domain) containing 1
19	1136	617852	1086	1,85	2,38	1,58	RNF126	ring finger protein 126
19	1136	617852	1086	1,85	2,38	1,58	FSTL3	follistatin-like 3 (secreted glycoprotein)
2	1466	242661047	1477	0,29	0,52	0,59	FLJ38379	hypothetical protein FLJ38379
2	1467	242662876	1138	0,40	0,62	0,39	FLJ38379	hypothetical protein FLJ38379
2	1470	131249876	565	0,36	0,43	0,41	DEFB125	defensin, beta 125
3	1728	122953778	587	0,59	0,60	0,60	GOLGB1	golgin B1, golgi integral membrane protein
5	1896	763481	1315	0,65	0,37	0,60		
5	1999	170219671	206	0,62	0,44	0,59		
5	1911	1669770	393	0,35	0,55	0,52		
6	2091	138477515	243	0,60	0,66	0,57	PERP	TP53 apoptosis effector
9	2396	17261249	762	0,65	0,64	0,60	CNTLN	centlein, centrosomal protein
17	986	54115047	229	0,56	0,51	0,66	TEX14	testis expressed 14
17	986	54115047	229	0,56	0,51	0,66	RAD51C	RAD51 homolog C (S. cerevisiae)
X	2538	37114623	597	0,55	0,53	0,58	FTHL19	ferritin, heavy polypeptide-like 19

B Borghese, C Chapron, D Vaiman Mol Endocrinol (2010)

Endometriosis: Epigenetic changes

Genetic Polymorphisms of *DNMT3L* Involved in Hypermethylation of Chromosomal Ends Are Associated with Greater Risk of Developing Ovarian Endometriosis **Borghese, Vaiman, Chapron Am J Pathol (2012)**



Haplotype	OMA/ controls	OR	95% CI	Global *P* value
ACCT	14/6	5.99	2.17–16.52	0.0002
ACCC	2/0	7.15*	2.63–19.44*	
GTCT	13/48	0.44	0.21–0.89	
ATCT	30/67	0.85	0.46–1.58	
ATCC	0/3	NA	NA	
GCCT	1/0	NA	NA	

Take home messages

CONCLUSIONS

Endometriosis: Diagnosis process

Future objective = Earlier diagnosis

Necessity to improve:
- Questioning
- Imaging process

Epidemiological data

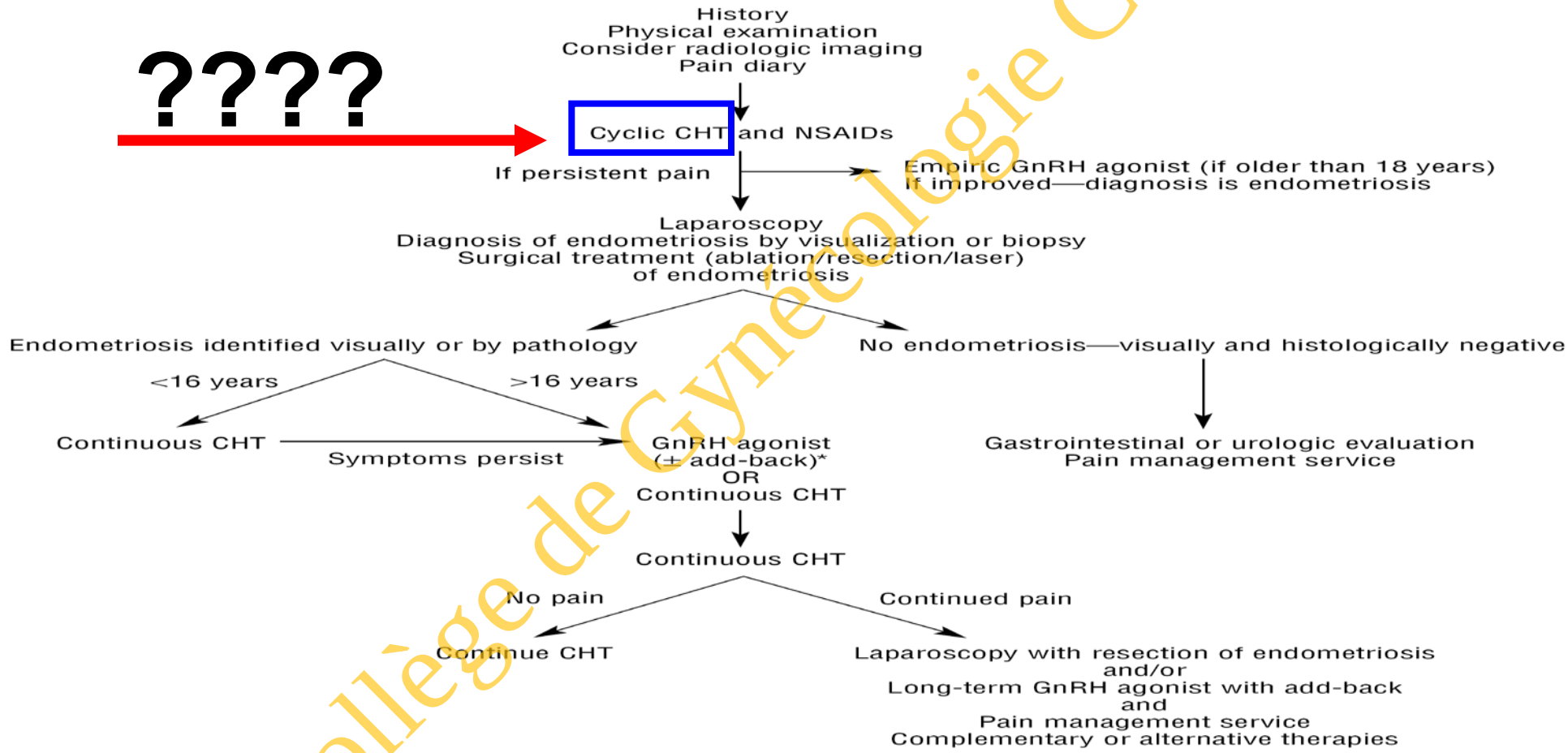
Prospective databae

Clinical and epidemiological research

Adolescent endometriosis:

Modern management

????



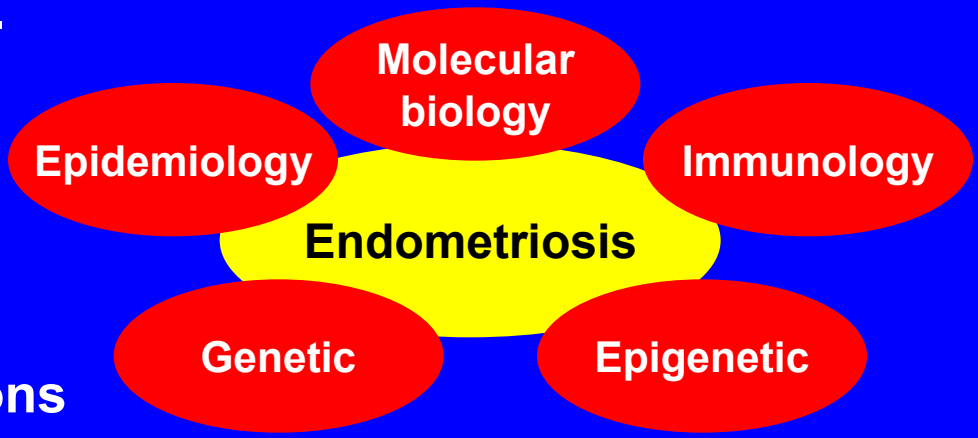
Abbreviations: NSAIDs, nonsteroidal antiinflammatory drugs; CHT, combination hormone therapy (oral contraceptive pills, estrogen/progestin patch, estrogen/progestin vaginal ring, norethindrone acetate, medroxyprogesterone acetate); GnRH, gonadotropin-releasing hormone.
*Add-back indicates use of estrogen and progestin or norethindrone acetate alone.

ACOG Committee Opinion, 2005

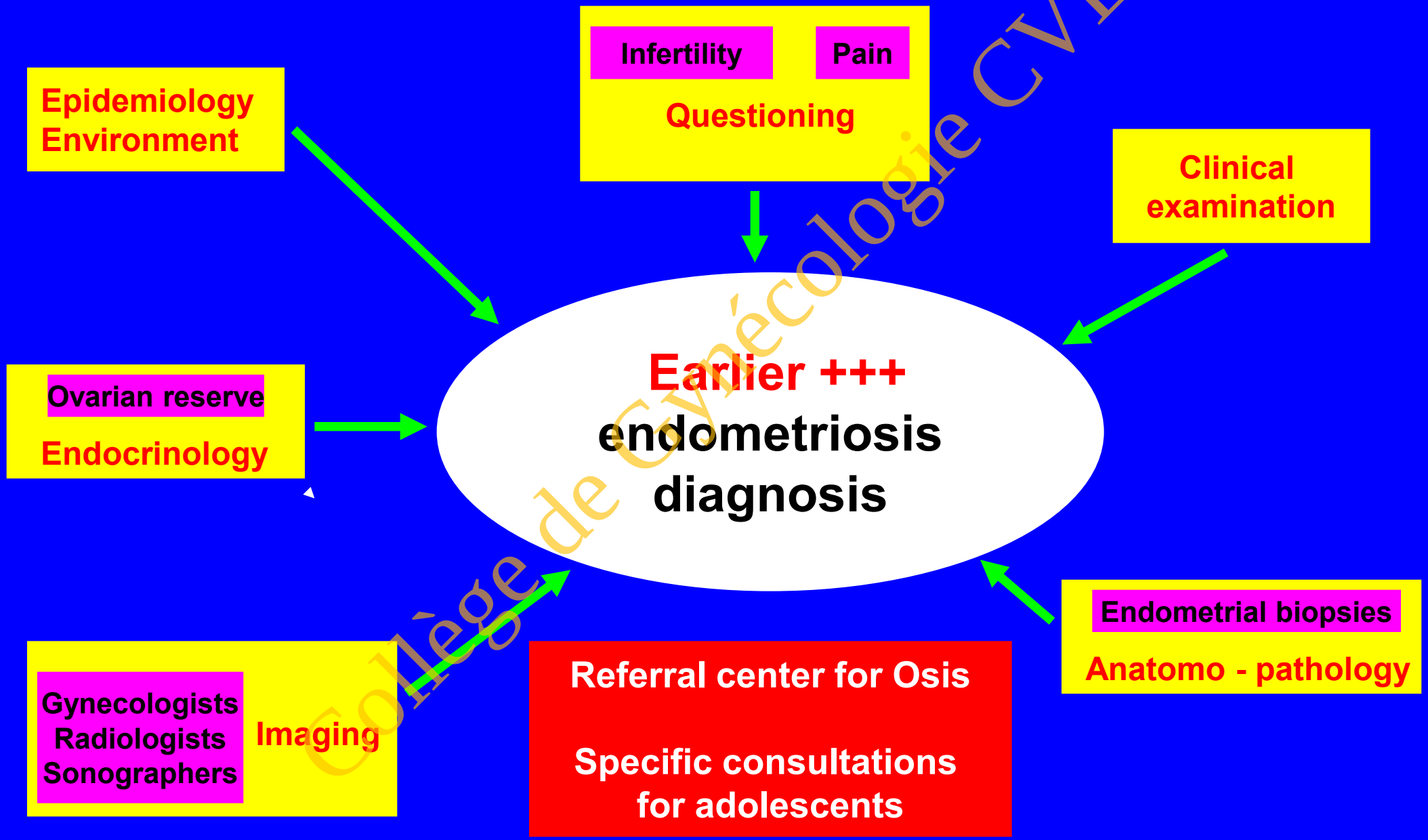
Adolescent endometriosis:

Modern management

- Knowledge of epidemiologic risk factors:
  - Previous family history of Osis
  - Body mass index
  - Absenteeism from school
  - Severity of primary DM
  - Failure of NSAIDs for primary DM
- No OCPs systematic prescrition if NSAIDs are inefficient.
- Complete initial surgery, if indicated.
- Profile of patients at risk of Osis:
- New non hormonal therapeutic options

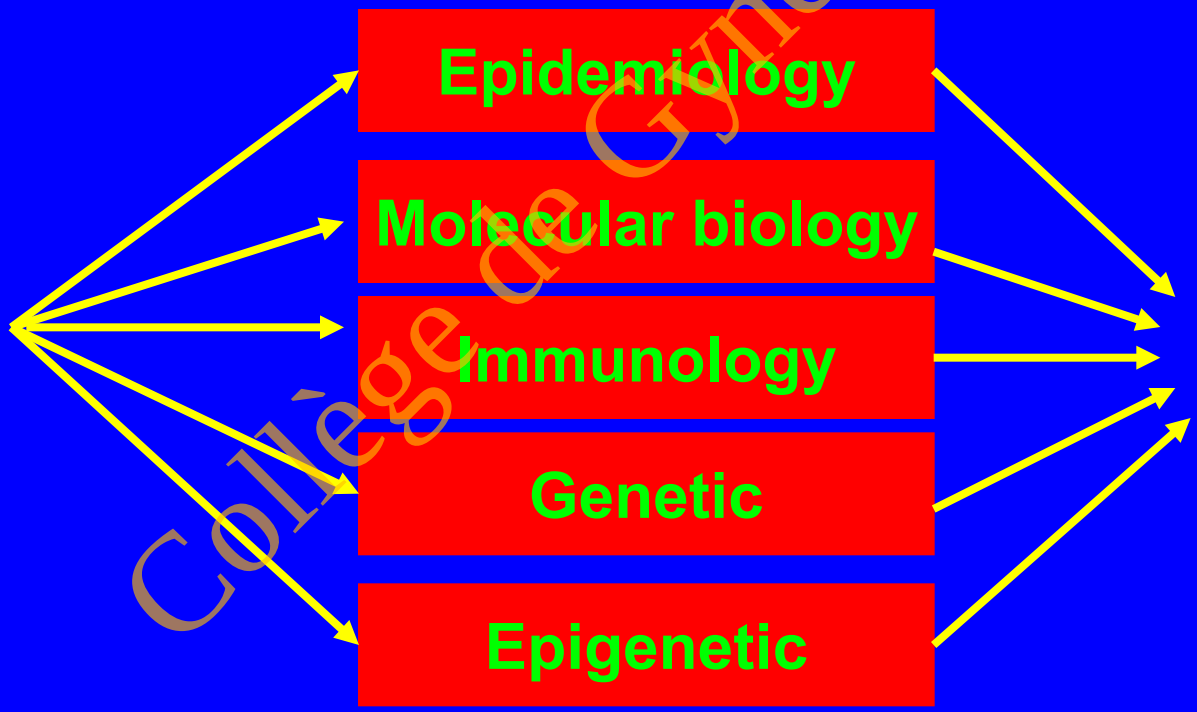


Deep endometriosis: *Multidisciplinary approach*



Take home messages

- Earlier diagnosis +++

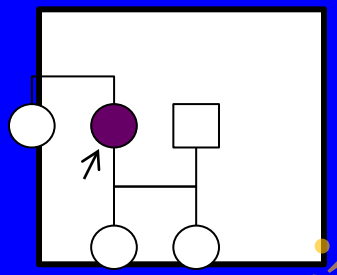


The future for endometriosis treatment

Blood

Osis lesions

Endometrium: Endometrial biopsy ?



Phenotype +++

Polymorphisms
Proteomics
Gene profiling
Epigenetic profiling

Individualized treatment +++

- Screening the relatives
- Preventive treatment ?

- Sensibility to medics
- Risk of malignancy
- Risk of recurrence