



REGIONE AUTONOMA FRIULI VENEZIA GIULIA

ISTITUTO DI RICOVERO e CURA  
a carattere scientifico  
Burlo Garofolo di Trieste



Endometriosi alle porte del nuovo decennio  
Trieste 13/12/2019

PAIN

# IL DOLORE NELL'ENDOMETRIOSI

Giovanni Di Lorenzo

10% Of Women Of Reproductive Age

Infertility

Pain

# Pain

An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage

# Pain effects

PERSONAL

PATIENTS

SOCIAL

FAMILIES

ECONOMIC

THEIR PARTNERS

## Pain characteristics

- **Severity**
- **Quality** (e.g. burning, stabbing etc.)
- **Interference** with physical or emotional function or quality of life in general

## Pain characteristics

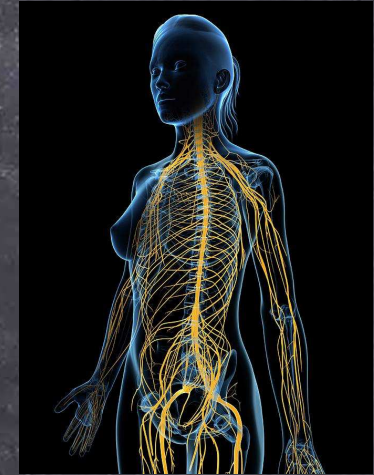
The use of an appropriate **combination** of such **tools** can give a much more clinically meaningful assessment of the pain experience **than a single descriptor of pain severity**

TYPE	DEFINITION	ENDOMETRIOSIS SETTING	DIAGNOSIS AND TREATMENT
Inflammatory pain	Pain <u>associated with active inflammation</u> (falls in the category of nociceptive pain)	<ul style="list-style-type: none"> <li>Endometriotic implants cause a local inflammatory reaction, irritating nerve endings.</li> <li>Active role of nerve fibres by secreting proinflammatory neuromediators (<b>neurogenic inflammation</b>)</li> </ul>	Responds best to Non-Steroidal Anti-inflammatory drugs ( <b>NSAIDS</b> ). COX2 drugs are newer and have a different safety profile.
Nociceptive pain	Pain that <u>arises from damage to non-neural tissue</u> . Due to the <b>activation</b> of <b>nociceptors</b> . It can be divided into visceral and superficial.	<b>Visceral nociceptive C-fibres</b> activated by noxious stimuli from cells in target organs have been implicated as mediators of noxious stimulus intensity	<b>NSAIDS</b> . Opiates should be avoided except for acute flares of pain. Visceral pain may be harder to treat than somatic.
Neuropathic pain	Pain <u>caused by a lesion or disease of the somatosensory nervous system</u> . It is a clinical description not a diagnosis requires a demonstrable lesion or a disease	<ul style="list-style-type: none"> <li>Small proportion of women with endometriosis-associated pelvic pain have definite neuropathic pain.</li> <li><u>More than half may have a mixed nociceptive-neuropathic picture</u></li> </ul>	Although there is no evidence in endometriosis specifically, it responds to <b>adjunctive analgesics</b> including amitriptyline, gabapentin, pregabalin and duloxetine

Modified by: M. Morotti et al. / European Journal of Obstetrics & Gynecology and Reproductive Biology 209 (2017) 8–13

# Endometriotic pain alteration

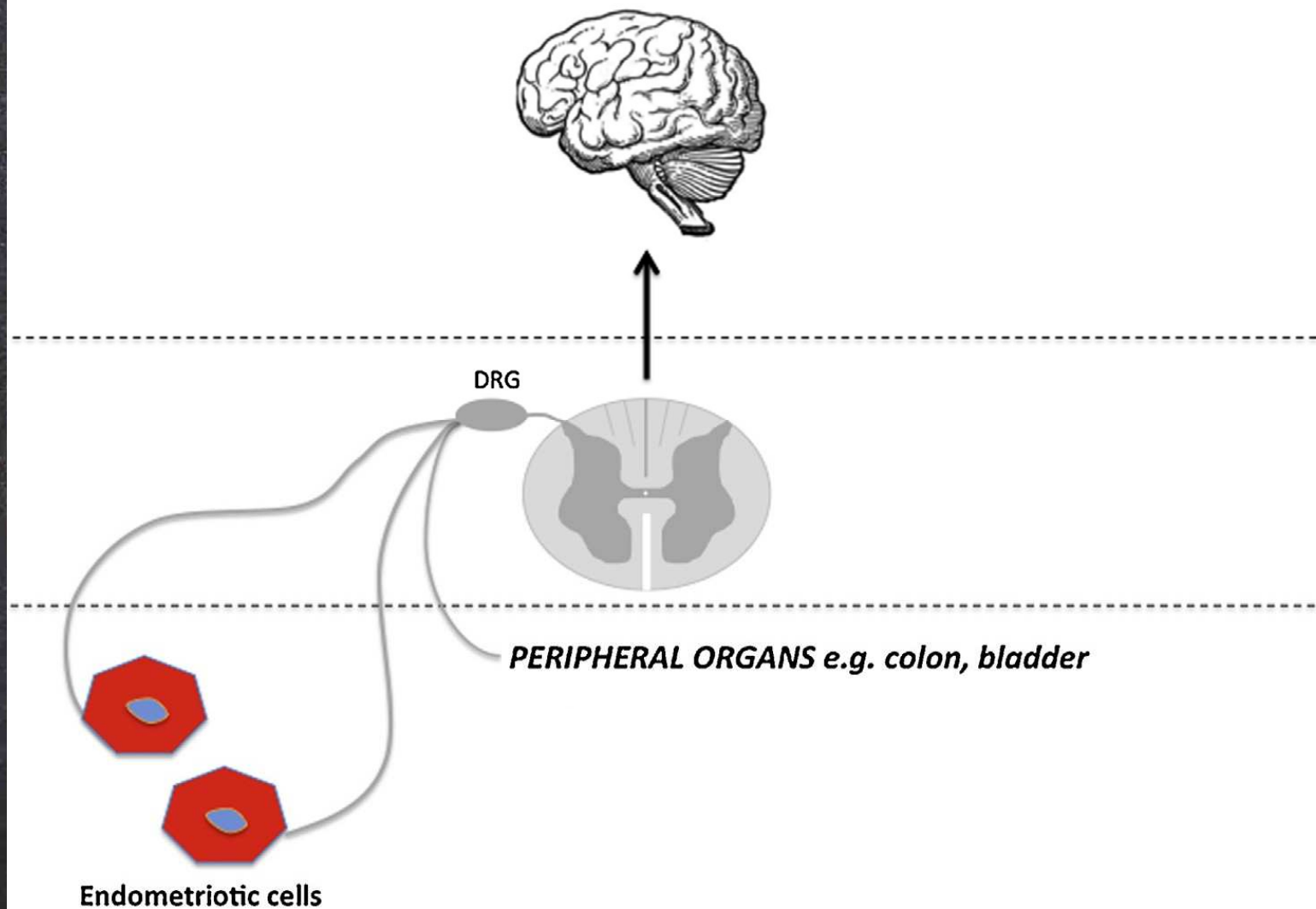
Peripheral nervous  
systems



Central nervous systems



## CENTRAL NERVOUS SYSTEM

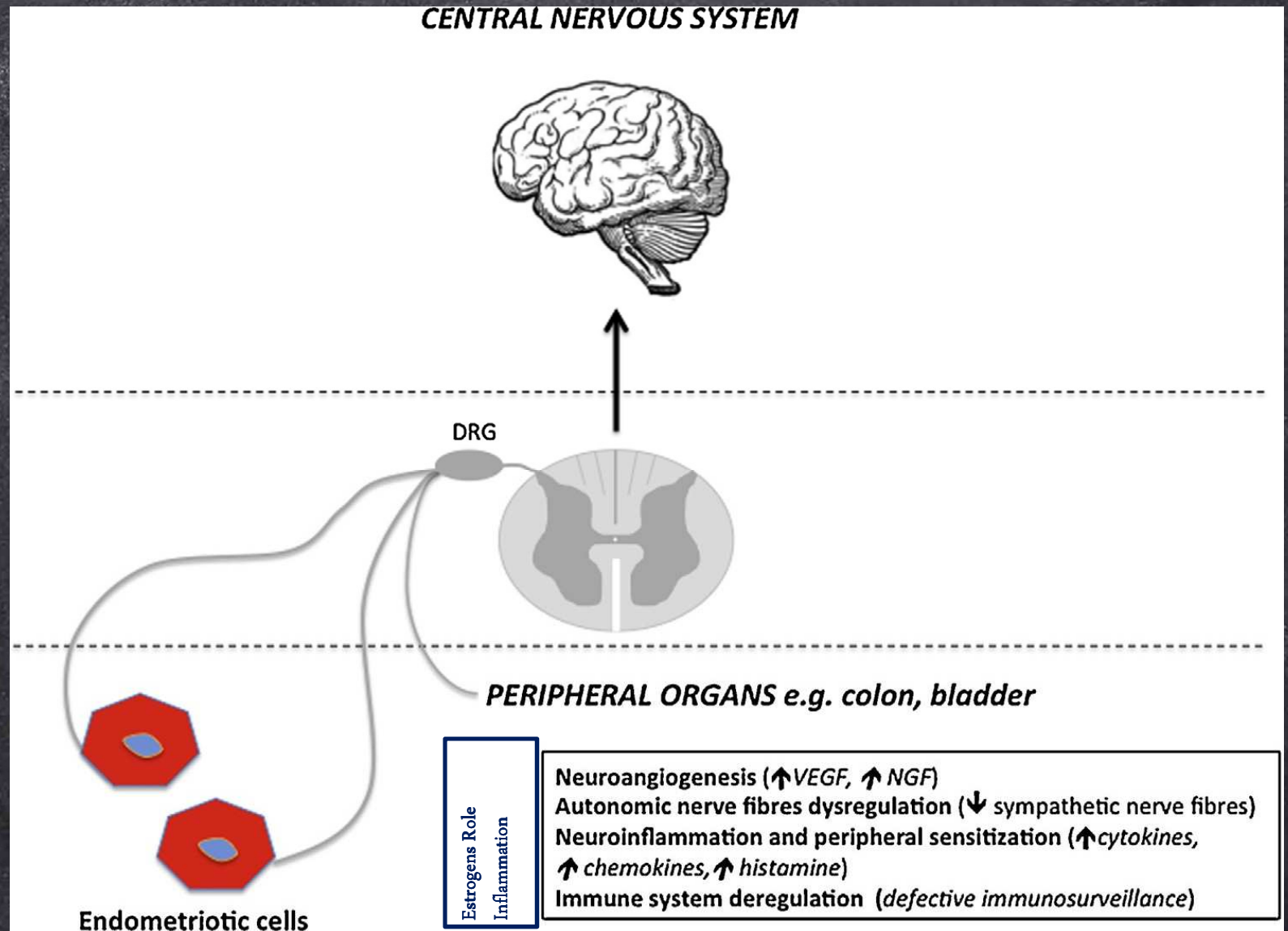
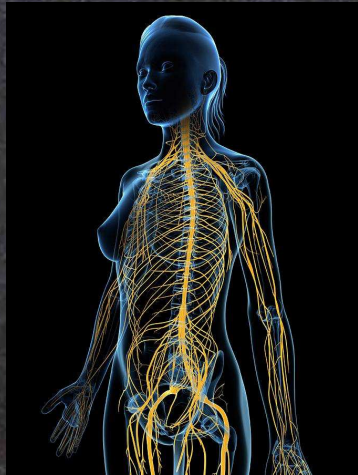


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# PERIPHERAL NERVOUS SYSTEMS

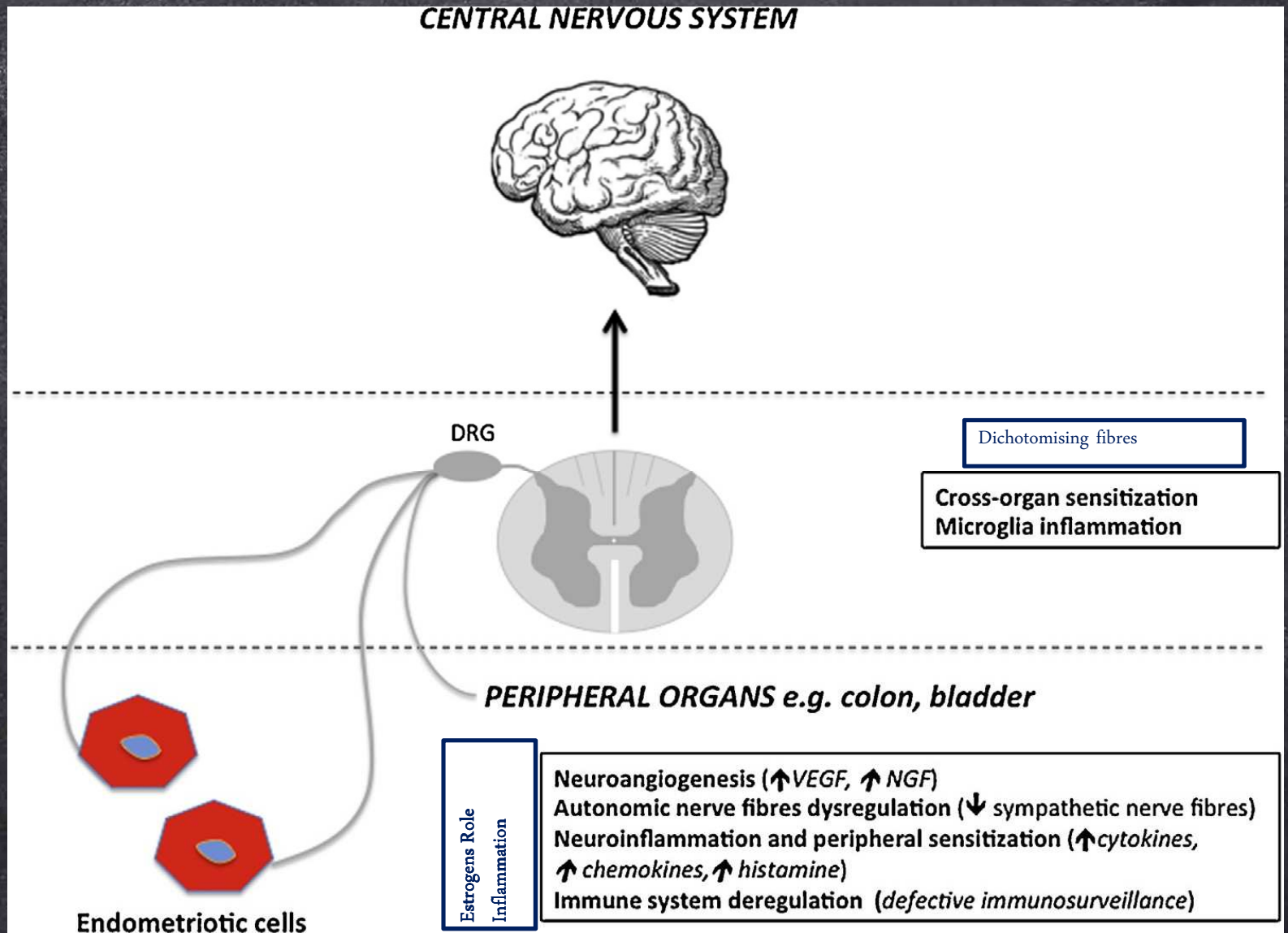
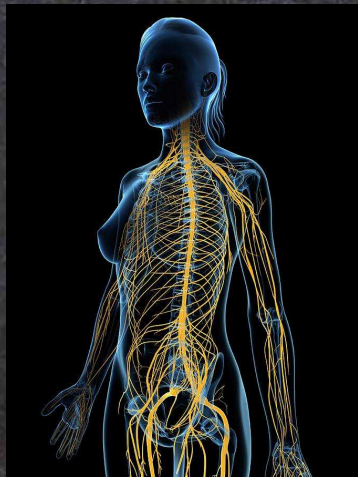


Peripheral nervous systems



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Peripheral nervous systems



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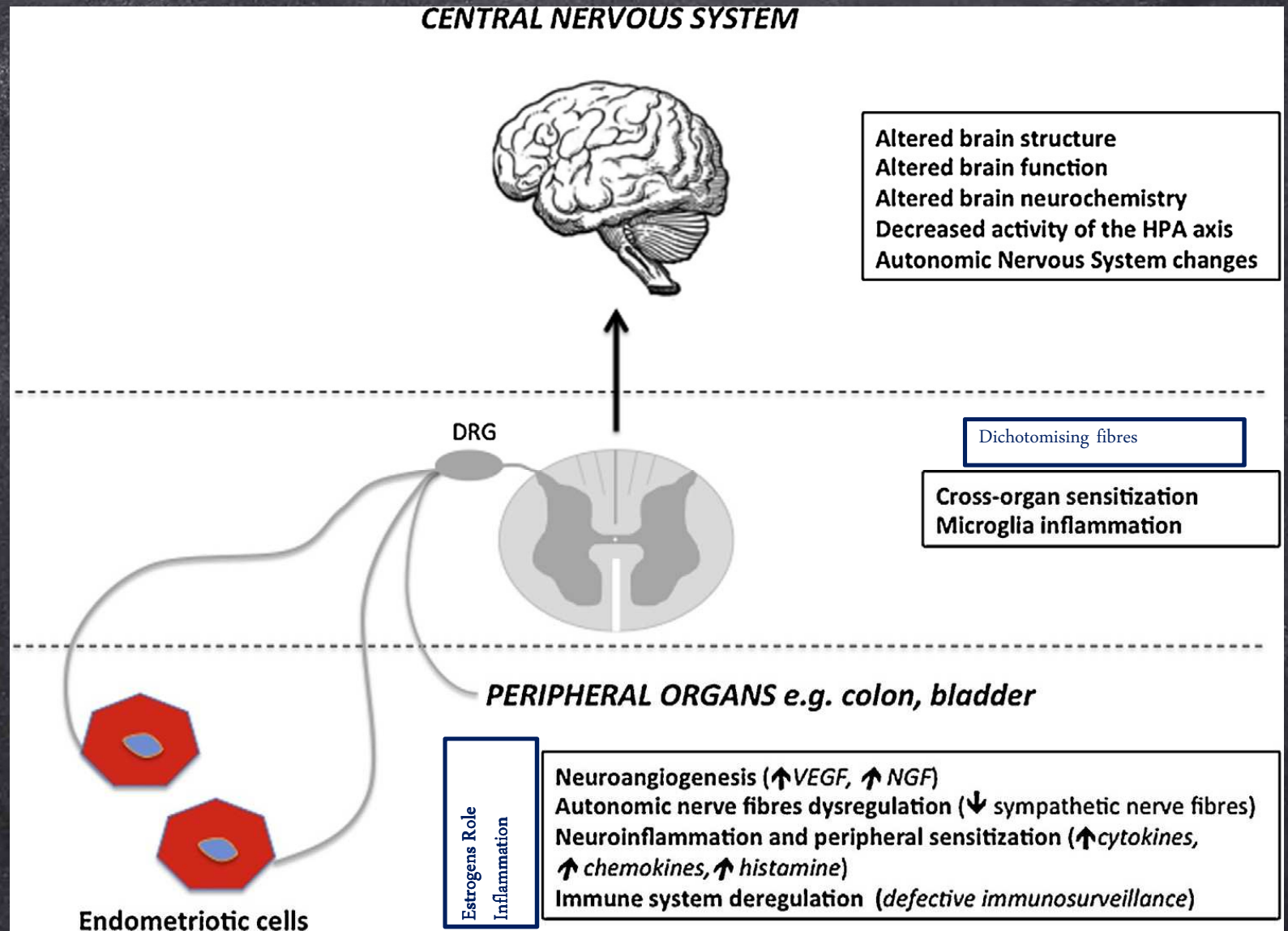
# CENTRAL NERVOUS SYSTEMS



CPP IS OFTEN ASSOCIATED WITH NEGATIVE COGNITIVE, BEHAVIOURAL, SEXUAL AND EMOTIONAL CONSEQUENCES, POTENTIALLY FURTHER EXACERBATING THE PAIN EXPERIENCE.

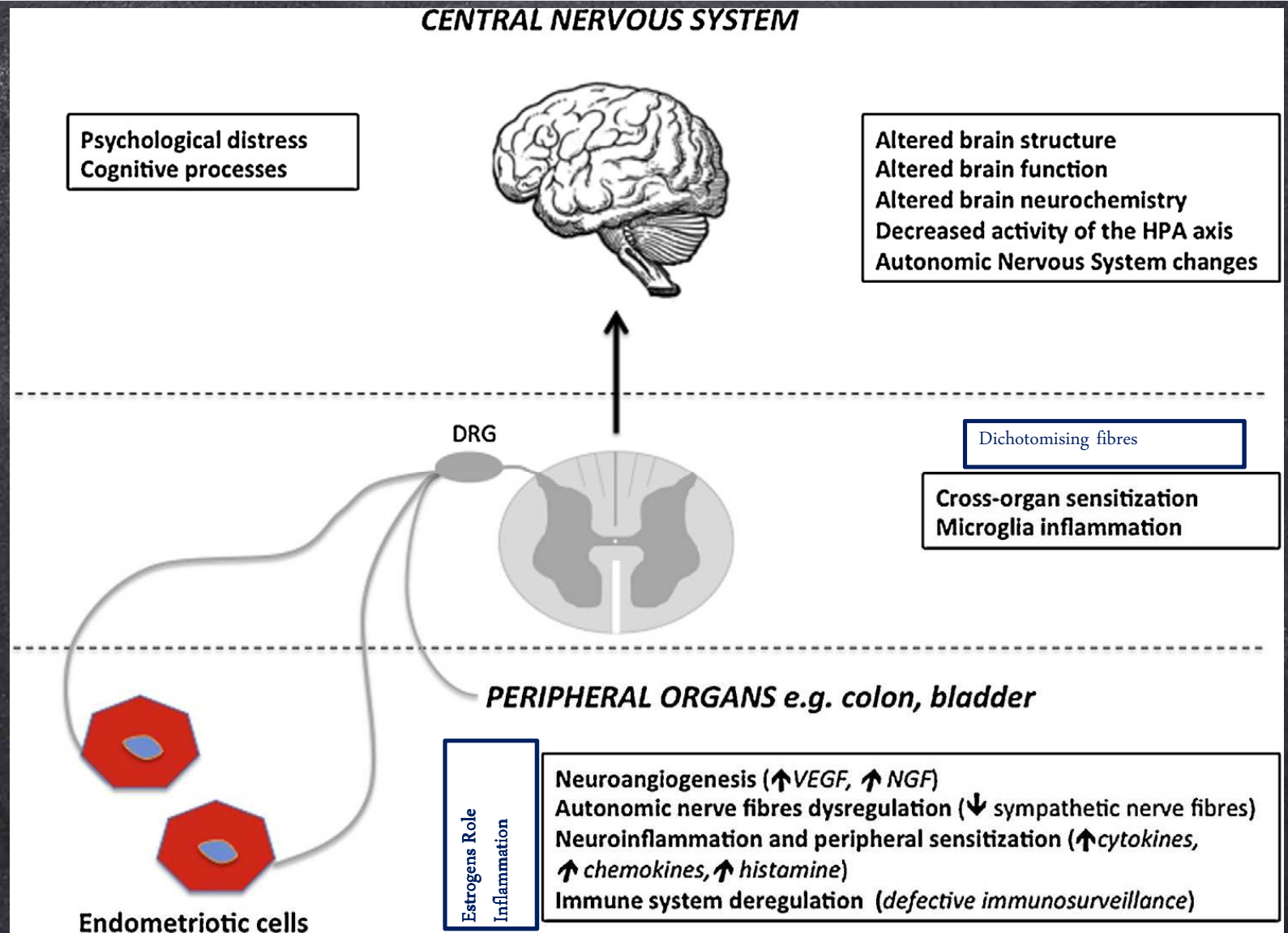
Daniels et al. Bmj 2010

Central nervous systems



Modified by: M. Morotti et al. / European Journal of Obstetrics & Gynecology and Reproductive Biology 209 (2017) 8–13

# Central nervous systems



Modified by: M. Morotti et al. / European Journal of Obstetrics & Gynecology and Reproductive Biology 209 (2017) 8–13

## CENTRAL NERVOUS SYSTEMS

Central changes associated with endometriosis may explain why **therapies** directed at the periphery **fail** to (sufficiently) relieve pain, and pain becomes increasingly difficult to treat



Central changes contribute to the well-established **disparity** between the extent of disease observed at **laparoscopy** and the **pain** experienced and to the persistence of pain despite adequate surgical **treatment**



# Pain cognition versus pain intensity in patients with endometriosis: toward personalized treatment

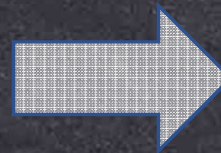
Fertility and Sterility 2017

Mieke A. W. van Aken, M.D.,<sup>a,b,c</sup> Joukje M. Oosterman, Ph.D.,<sup>d</sup> C. M. van Rijn, M.D., Ph.D.,<sup>d</sup> Magdalena A. Ferdek, M.Sc.,<sup>d,e</sup> G  S. F. Ruigt, Ph.D.,<sup>f</sup> B. W. M. M. Peeters, Ph.D.,<sup>a</sup> Didi D. M. Braat, M.D., Ph.D.,<sup>c</sup> and Annemiek W. Nap, M.D., Ph.D.<sup>b</sup>

Multidimensional approach to treating endometriosis-related pain

Adding

Cognitive behavioral therapy for women who tend to experience a negative pain cognition.



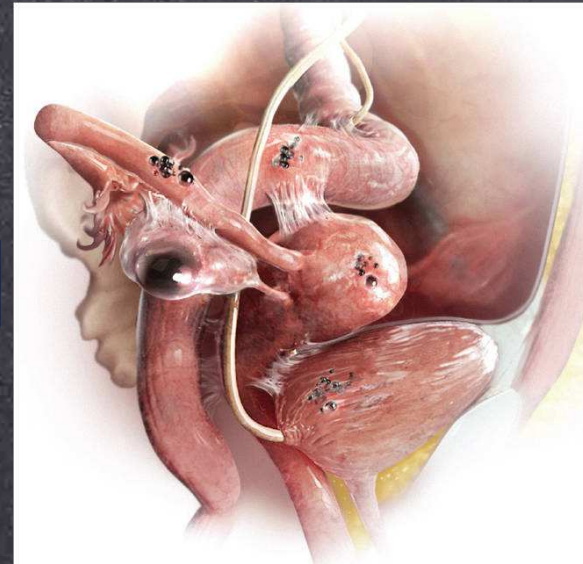
PAIN COGNITION IS AN INDEPENDENT FACTOR INFLUENCING THE HRQOL OF ENDOMETRIOSIS PATIENTS.

An adequate screening for pain cognition in patients with poor treatment outcomes could help to identify the patients who might benefit from cognitive behavioral therapy.

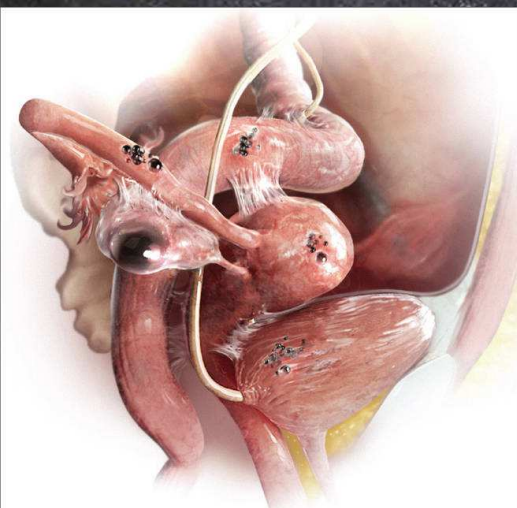
# Pain and type of endometriosis

Endometrioma

Superficial endometriosis



Deep endometriosis



Human Reproduction Update, Vol.11, No.6 pp. 595–606, 2005

Advance Access publication September 19, 2005

doi:10.1093/humupd/dmi029

## Endometriosis and pelvic pain: epidemiological evidence of the relationship and implications

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A.Fauconnier<sup>1,2</sup> and C.Chapron<sup>3,4</sup>

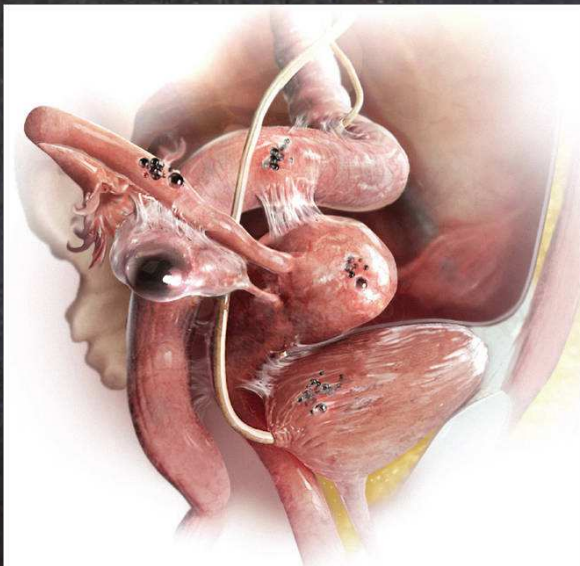
RATHER THAN THE PRESENCE OF ENDOMETRIOSIS ITSELF, IT IS THE CHARACTERISTICS OF THE LESIONS AND THEIR EXTENT THAT WOULD EXPLAIN THE CHRONIC PELVIC PAIN SYMPTOMS

# Deep infiltrating endometriosis(DIE)

DIE is the only macroscopic type of lesion for which the relationship with chronic pelvic pain symptoms appears to be well understood

Those diagnosed with DIE suffered from the most severe painful symptoms

Explained by compression or infiltration of the sub-peritoneal nerve fibres by DIE implants (Anaf et al., 2000). DIE is a distinct entity



These symptoms are related to the involvement of specific anatomical locations (i.e. dyspareunia) or specific organs (i.e. urinary tract signs).

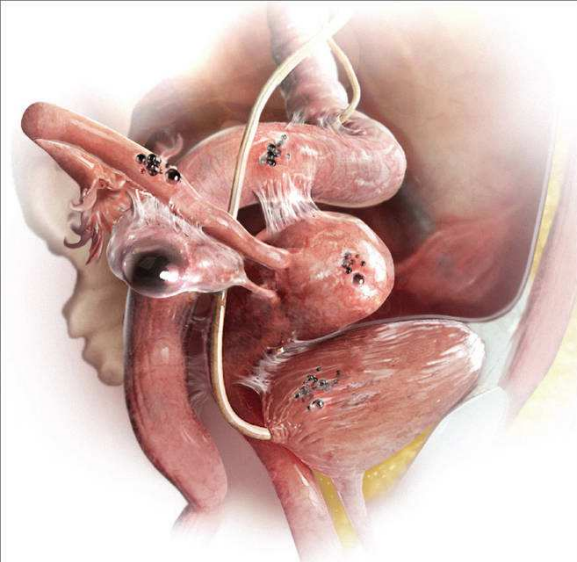
**Location indicating pain.**

# Endometrioma

The relationship between chronic pelvic pain symptoms and cystic ovarian endometriosis is a subject of debate

One of the hypotheses that we make, along with other authors, is that apart from severe dysmenorrhoea, the existence of painful symptoms in a woman with an endometrioma may be caused by associated DIE lesions (Bowel and Ureteral) which should be sought for and treated

*Koninckx et al., 1991; Vercellini, 1997*



Ovarian endometriomas are adherent to the surrounding pelvic structures in more than 90%

Periovarian adhesions contain endometrial and inflammatory cells which may generate painful symptoms (*Jirasek et al., 1998*)

Endometriosis

QoL

## Physical pain and emotion regulation as the main predictive factors of health-related quality of life in women living with endometriosis

Gabriella Márki<sup>1,2,\*</sup>, Attila Bokor<sup>3</sup>, János Rigó<sup>3</sup>, and Adrien Rigó<sup>2</sup>

54.79% presented with anxiety  
20.3% with depressive symptoms

### HRQoL

- Directly related to severe physical pain
- Indirectly related to difficulties in emotion regulation

**Table II** Correlations of HRQoL, pain symptoms and psychological variables.

	HRQoL	Physical HRQoL	Mental HRQoL
Health measure, pain during...			
first day of menstruation	-0.31 <sup>***</sup>	-0.34 <sup>***</sup>	-0.20 <sup>*</sup>
additional bleeding days of the menstrual cycle	-0.41 <sup>***</sup>	-0.57 <sup>***</sup>	-0.19 <sup>*</sup>
bleeding-free days	-0.35 <sup>***</sup>	-0.43 <sup>***</sup>	-0.23 <sup>**</sup>
sexual intercourse (dyspareunia)	-0.36 <sup>***</sup>	-0.41 <sup>***</sup>	-0.28 <sup>***</sup>
urination (dysuria)	ns	-0.18 <sup>*</sup>	ns
bowel movement (dyschesia)	-0.40 <sup>***</sup>	-0.35 <sup>***</sup>	-0.31 <sup>***</sup>
Psychological measure			
HADS–depression	-0.54 <sup>***</sup>	-0.33 <sup>***</sup>	-0.62 <sup>***</sup>
HADS–anxiety	-0.60 <sup>***</sup>	-0.42 <sup>***</sup>	-0.70 <sup>***</sup>
PSS	-0.55 <sup>***</sup>	-0.34 <sup>***</sup>	-0.64 <sup>***</sup>
DERS	-0.38 <sup>***</sup>	-0.17 <sup>*</sup>	-0.52 <sup>***</sup>

Note: HADS = Hospital Anxiety and Depression Scale; PSS = Perceived Stress Scale; DERS = Difficulties in Emotion Regulation Scale; \* $P < 0.05$ ; \*\* $P < 0.01$ ; \*\*\* $P < 0.001$ ; ns = not significant

## Personality in women with endometriosis: temperament and character dimensions and pelvic pain

Federica Facchin<sup>1,\*</sup>, Giusy Barbara<sup>2</sup>, Emanuela Saita<sup>1</sup>,  
Stefano Erzegovesi<sup>3</sup>, Riccardo Maria Martoni<sup>3</sup>, and Paolo Vercellini<sup>4</sup>

PAINFUL ENDOMETRIOSIS

VS

HEALTHY PATIENTS AND NON

PAINFUL ENDOMETRIOSIS

- higher harm avoidance
- lower exploratory excitability
- lower responsibility
- higher fatigability

- lower novelty seeking
- Higher harm avoidance and lower self-directedness were associated with a greater severity of chronic pelvic pain

Treatment of endometriosis requires an integrated approach combining medical and psychological interventions



# Endometriosis and pain costs

Human Reproduction, Vol.27, No.5 pp. 1292–1299, 2012  
Advanced Access publication on March 14, 2012 doi:10.1093/humrep/des073

human  
reproduction

ORIGINAL ARTICLE *Gynaecology*

## The burden of endometriosis: costs and quality of life of women with endometriosis and treated in referral centres

Steven Simoens<sup>1</sup>, Gerard Dunselman<sup>2</sup>, Carmen Dirksen<sup>3</sup>,

AVERAGE TOTAL ANNUAL COSTS AMOUNTED TO  
€9579 PER WOMAN

Dominated by **indirect costs** of productivity loss (mean: €6298 per woman; **66% of total costs**)

Direct costs:

- health care costs (€3113 per woman; 95% of direct costs)
- non-health care costs (€168; 5% of direct costs)

# QoL and health care costs

QUALITY OF LIFE REPRESENTS THE MOST IMPORTANT PREDICTOR OF TOTAL COSTS AND OF DIRECT HEALTH CARE COSTS

## REGARDING HEALTH-RELATED QUALITY OF LIFE:

1. 56% reported problems with **pain/discomfort**
2. 36% reported problems with **anxiety/depression** at the beginning of the study
3. 29% reported problems with usual activities
4. 16% of women reported (some or major) problems with mobility
5. 3% reported problems with self-care

## REGARDING HEALTH CARE COSTS:

Surgery (29% of health care costs)  
Monitoring tests (19%)  
Hospitalization (18%)  
Physician visits (16%)  
Medication accounted for 10% of health care costs

# QoL and health care costs

QUALITY OF LIFE REPRESENTS THE MOST IMPORTANT PREDICTOR OF TOTAL COSTS AND OF DIRECT HEALTH CARE COSTS

The total annual societal burden of endometriosis-associated symptoms can be extrapolated to

1. €0.8 million in Denmark
2. €1.3 billion in Switzerland
3. €1.6 billion in Hungary
4. €1.7 billion in Belgium
5. €2.6 billion in the Netherlands
6. **€9.3 billion in Italy**
7. €9.5 billion in France
8. €9.9 billion in the UK
9. €12.5 billion in Germany
10. €49.6 billion in the USA

# Classification tools for endometriosis



Contents lists available at ScienceDirect

Best Practice & Research Clinical  
Obstetrics and Gynaecology

journal homepage: [www.elsevier.com/locate/bpobgyn](http://www.elsevier.com/locate/bpobgyn)



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Endometriosis classification according to pain symptoms: can the ASRM classification be improved?



Marina Paula Andres <sup>a, b</sup>, Giuliano Moysés Borrelli <sup>a</sup>,  
Mauricio Simões Abrão <sup>a, b, \*</sup>

**Ideal classification system:**

- provide information on the severity and type of endometriosis
- correlate with the severity and type of symptom including pain and infertility
- accessible, reproducible, and easy to perform
- provide information about the prognosis of the disease



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 \_\_\_\_\_  
 Laparoscopic Treatment \_\_\_\_\_  
 Prognosis \_\_\_\_\_

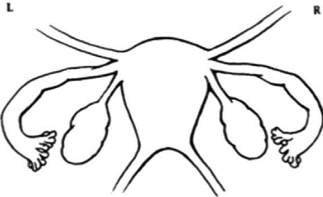
PERITONEUM	ENDOMETRIOSIS	<1 cm	1-3 cm	>3 cm
		Superficial	1	2
	Deep	2	4	6
OVARY	R Superficial	1	2	4
	Deep	4	16	20
	L Superficial	1	2	4
	Deep	4	16	20
POSTERIOR CULDESAC OBLITERATION		Partial	Complete	
		4	40	
OVARY	ADHESIONS	< 1/3 Enclosure	1/3-2/3 Enclosure	> 2/3 Enclosure
	R Filmy	1	2	4
	Dense	4	8	16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

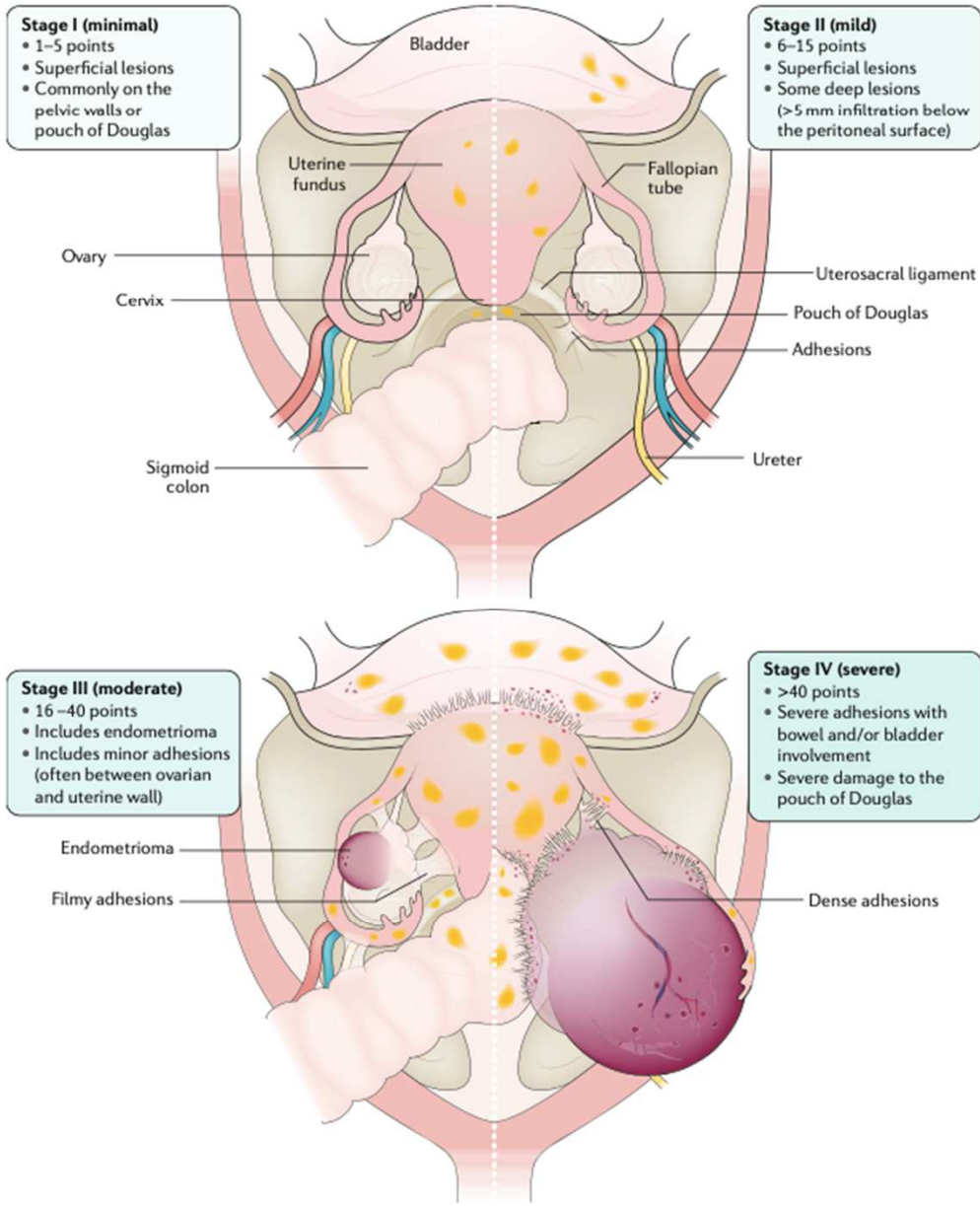
Additional Endometriosis: \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_

Associated Pathology: \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_

To Be Used with Normal Tubes and Ovaries



To Be Used with Abnormal Tubes and Ovaries



The biggest challenge of classifying endometriosis is to correlate the staging of disease with infertility and pain

rASRM scoring system lacks on those two issues

Enzian 2012  
Classification of deeply infiltrating endometriosis  
(according to the Endometriosis Research Foundation,SEF)

**Sacrouterine ligaments**  
**Cardinal ligaments**  
**Pelvic sidewall**  
**External ureter**

Rectovaginal space  
Vagina  
Compression  
Rectum

Compartment  
A, B, or C

Level 1  
< 1 cm

Level 2  
1-3 cm

Level 3  
> 3 cm

(A) (B) (C)  
(A1) (B1) (C1)  
(A2) (B2) (C2)  
(A3) (B3) (C3)

**Uterine and other types of extragenital deep infiltration endometriosis**

Adenomyosis  
Bladder  
Ureter, intrinsic

(FA) (FB) (FU)

Intestine, others (sigmoid, caecum, appendix and ileum)  
Other regions of localisation

(FI) (FO)

● Lung  
● Diaphragm  
● Inguinal region, e.g.

© Keckstein

## ENDOMETRIOSIS FERTILITY INDEX (EFI) SURGERY FORM

### LEAST FUNCTION (LF) SCORE AT CONCLUSION OF SURGERY

Score	Description	Left	Right
4	= Normal		
3	= Mild Dysfunction		
2	= Moderate Dysfunction		
1	= Severe Dysfunction		
0	= Absent or Nonfunctional		

Fallopian Tube

Fimbria

Ovary

Lowest Score  +  =

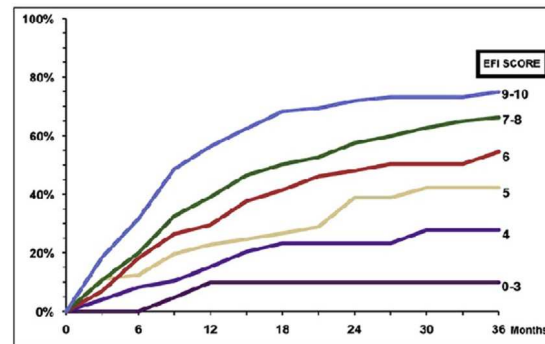
Left Right LF Score

To calculate the LF score, add together the lowest score for the left side and the lowest score for the right side. If an ovary is absent on one side, the LF score is obtained by doubling the lowest score on the side with the ovary.

### ENDOMETRIOSIS FERTILITY INDEX (EFI)

Historical Factors			Surgical Factors		
Factor	Description	Points	Factor	Description	Points
Age	If age is ≤ 35 years	2	LF Score	If LF Score = 7 to 8 (high score)	3
	If age is 35 to 39 years	1		If LF Score = 4 to 6 (moderate score)	2
	If age is ≥ 40 years	0		If LF Score = 1 to 3 (low score)	0
Years Infertile	If years infertile is ≤ 3	2	<b>AFS Endometriosis Score</b>		
	If years infertile is > 3	0	If AFS Endometriosis Lesion Score is < 16	1	
Prior Pregnancy	If there is a history of a prior pregnancy	1	If AFS Endometriosis Lesion Score is ≥ 16	0	
	If there is no history of prior pregnancy	0	<b>AFS Total Score</b>		
<b>Total Historical Factors</b>			<b>Total Surgical Factors</b>		
EFI = TOTAL HISTORICAL FACTORS + TOTAL SURGICAL FACTORS:			EFI Score		

### ESTIMATED PERCENT PREGNANT BY EFI SCORE



Pain scores is relevant in endometriosis.

None of the endometriosis classification systems currently in use includes this information.

Efforts should be made to **improve** the available systems or to **develop** a new system

# Pain therapy

**Table 1** Currently available medical therapies for endometriosis-related pain in the United States

Medical therapy	Mechanism of action	Medication	Route
Nonsteroidal anti-inflammatory drugs	Inhibits production of prostaglandins	Ibuprofen	Oral
		Naproxen	Oral
		Ketorolac	Oral intramuscular, intranasal
		Celecoxib	Oral
		Aspirin	Oral
		Diclofenac	Oral
Combined hormonal contraceptives	Decidualization and atrophy of endometrial tissue	Oral contraceptive pill	Oral
		Ethinyl estradiol/etonogestrel vaginal ring	Intravaginal
		Norelgestromin/ethinyl estradiol transdermal patch	Transdermal
Progestins	Decidualization and atrophy of endometrial tissue Inhibition of inflammatory pathways Suppression of matrix metalloproteinases Inhibition of angiogenesis	Norethindrone acetate MPA	Oral
		DMPA	Intramuscular
		Etonogestrel	Subdermal implant
		Levonorgestrel – Intrauterine device	Intrauterine
GnRH agonists	Downregulation of pituitary GnRH receptors and suppression of gonadotropins, leading to anovulation, hypogonadism, amenorrhea, and endometrial atrophy	Leuprolide	Intramuscular Subcutaneous
		Leuprorelin	Intramuscular Subcutaneous
		Goserelin	Intramuscular Subcutaneous
		Triptorelin	Intramuscular
GnRH antagonists	Downregulation of pituitary GnRH receptors and suppression of gonadotropins, leading to anovulation, hypogonadism, amenorrhea, and endometrial atrophy	Elagolix	Oral
		Nafarelin	Intranasal
Aromatase inhibitors	Block the peripheral conversion of androgens to estrogens	Anastrozole	Oral
		Letrozole	Oral
		Exemestane	Oral
Danazol	Suppresses FSH and LH production, creating a high androgen and low estrogen environment resulting in atrophy of endometrial tissue	Danazol	Oral

Abbreviations: DMPA, depot-medroxyprogesterone; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; MPA, medroxyprogesterone acetate.

# Patient Preferences for Endometriosis Pain Treatments in the United States

VALUE HEALTH. 2019; 22(6):728-738

Christine Poulos, PhD,<sup>1,\*</sup> Ahmed M. Soliman, MS, PhD,<sup>2</sup> Cheryl L. Renz, MD,<sup>2</sup> Joshua Posner, BA,<sup>1</sup> Sanjay K. Agarwal, MD<sup>3</sup>

WOMEN WITH ENDOMETRIOSIS ARE WILLING TO ACCEPT RISKS TO ACHIEVE IMPROVEMENTS IN  
ENDOMETRIOSIS-ASSOCIATED PAIN

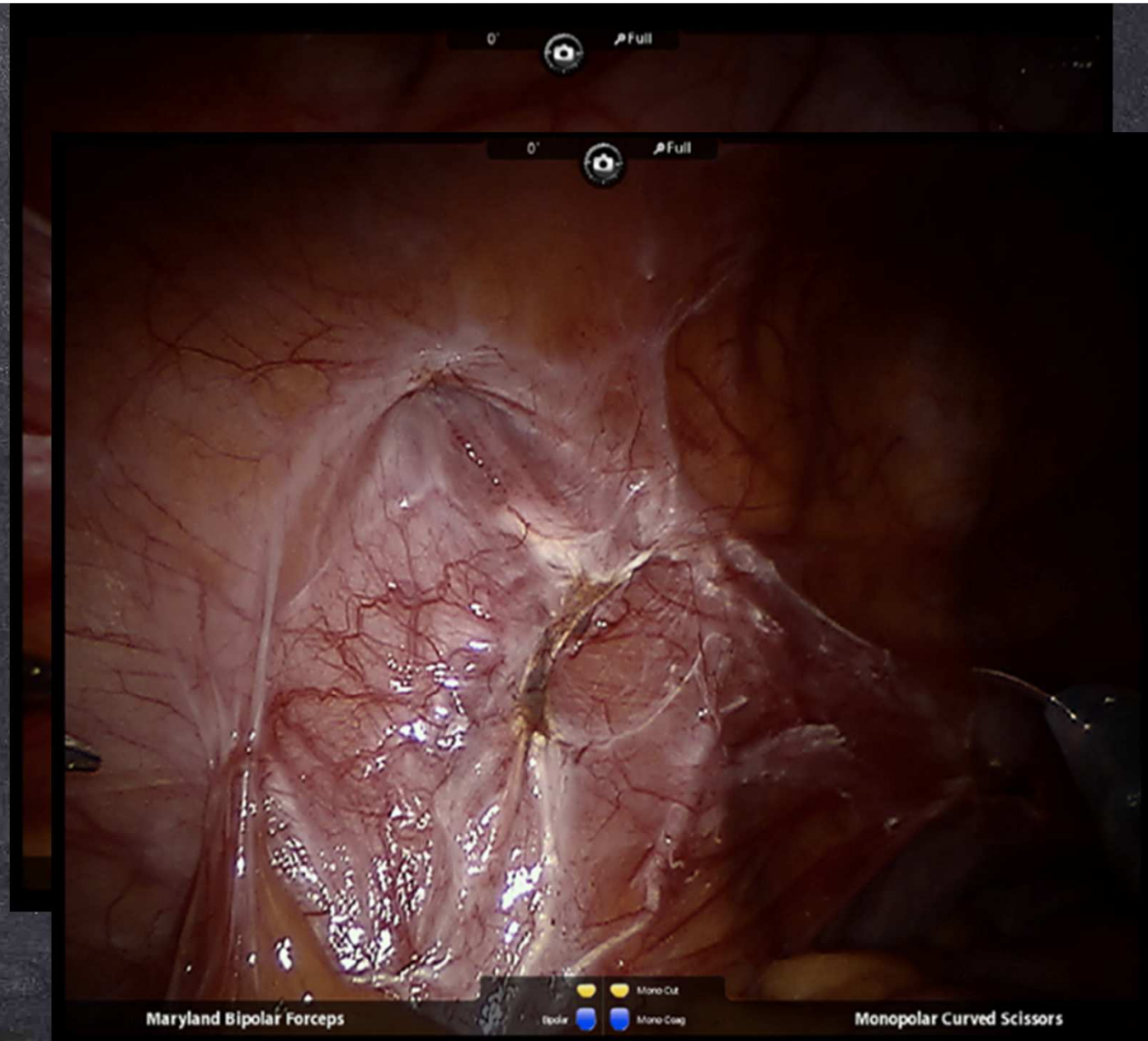
Risk of moderate to severe **hot flashes** was most important attribute

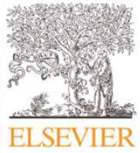
Risk of bone fracture was the least important attribute

Most important improvements taken in account were dyspareunia, NMPP, and dysmenorrhea



Post-menopausal  
endometriosis pain





**Chronic Pelvic Pain Caused by Postmenopausal Endometriosis**

Megan N. Wasson, DO

*From the Department of Gynecologic Surgery, Mayo Clinic Arizona, Phoenix, Arizona*

2018

Limited therapy options:

- aromatase inhibitors can be effective;
- gonadotropin-releasing hormone agonists, progestins, and danazol are ineffective;
- the first-line treatment should be surgical excision

- Endometriosis diagnosis
- 2%—5% of all cases
- In women with previous subsequent surgery with
- Although endometriosis this disease process has without HRT

POSTMENOPAUSAL ENDOMETRIOSIS SHOULD BE EVER CONSIDERED IN SURGICALLY, MEDICALLY, AND NATURALLY MENOPAUSAL WOMEN PRESENTING WITH CHRONIC PELVIC PAIN AND SYMPTOMS CONSISTENT WITH ENDOMETRIOSIS

effective in relieving pain

# Pelvic pain in adolescent

## GYNECOLOGICAL CONDITIONS:

- Endometriosis
- pelvic inflammatory disease
- ovarian cysts
- obstruction of the reproductive tract

## NONGYNECOLOGIC CONDITIONS:

- irritable bowel syndrome
- interstitial cystitis
- myofascial pain

## ENDOMETRIOSIS APPEARS TO BE A COMMON CAUSE OF DYSMENORRHEA AND CHRONIC PELVIC PAIN IN ADOLESCENTS.

Contrary to the past more recent studies described **advanced stage endometriosis in adolescent:** endometrioma, DIE, cul-de-sac obliteration in **30 to 40% cases**

Jansen et al 2013; Smorgick et al 2014; Smorgick 2018.

Management is more complex:

- both the adolescent and her parents are counseled and addressed
- her long-term emotional and physical health
- Fertility
- Sexuality are considered
- association with depression and anxiety

## Clinica Ginecologica e Ostetrica dell'Università di Trieste

(Direttore Prof. G. Ricci)

### Ambulatorio di Endometriosi e Dolore Pelvico Cronico

Scheda di valutazione sintomatologia endometriosi

Nome: \_\_\_\_\_ Cognome: \_\_\_\_\_ data di nascita: \_\_\_\_\_

Ultima Mestruazione: \_\_\_\_\_

Terapia Medica Si/No (specificare quale tp e se in continuo).....

Segni con una X per ogni sintomo se presente e con intensità di dolore da 1 a 10 secondo la scala descritta sotto\*.

Sintomo	Presente in terapia		Presente senza terapia	
	si	no	si	no
Ipermenorrea (Flussi abbondanti)				
Perdite fuori da mestruazione				
Dolore ovulatorio				
	Intensità*:		Intensità*:	
Dolore precedente al flusso				
	Intensità*:		Intensità*:	
	Totale giorni:		Totale giorni:	
Algie pelviche non correlate al flusso o all'ovulazione				
	Intensità*:		Intensità*:	
Dismenorrea (dolore durante flusso)				
	Intensità*:		Intensità*:	
Disparesunia (dolore durante rapporti)				
	Intensità*:		Intensità*:	
Dischezia (dolore alla defecazione)				
	Intensità*:		Intensità*:	
Disuria (dolore alla minzione)				
	Intensità*:		Intensità*:	



-Inizio attività sessuale: Si/No

-Sede del dolore mestruale: \_\_\_\_\_

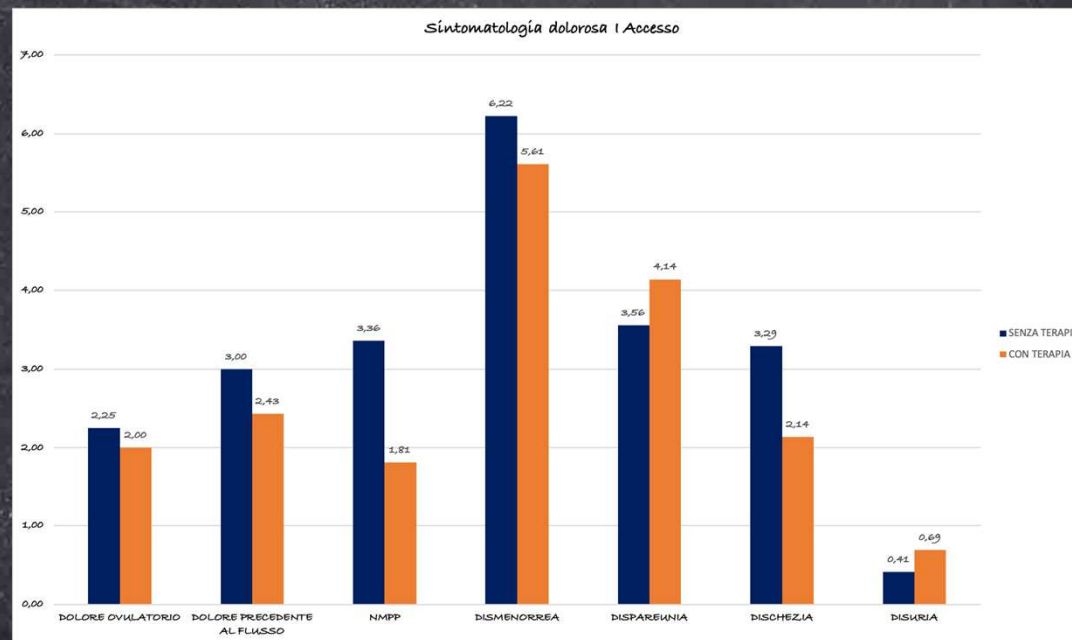
-Irradiazione del dolore in sede: \_\_\_\_\_

-Risposta ad antidolorifici: Si/No, nome farmaco: \_\_\_\_\_ per \_\_\_\_\_ ore

-Desiderio di Gravidanza: Si/No

Data: \_\_\_\_\_ Firma: \_\_\_\_\_

# Our data



# Conclusion



Central nervous sistem



HRQoL and its costs



Stadiation tools



Fertil life extremity

GRAZIE PER  
L'ATTENZIONE





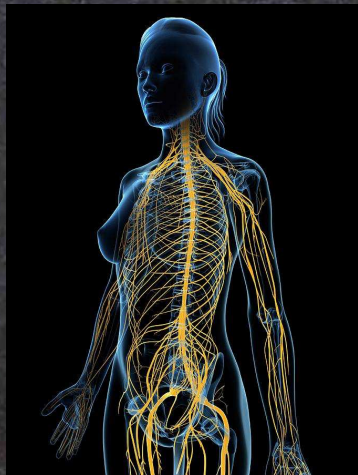
Buone  
Feste



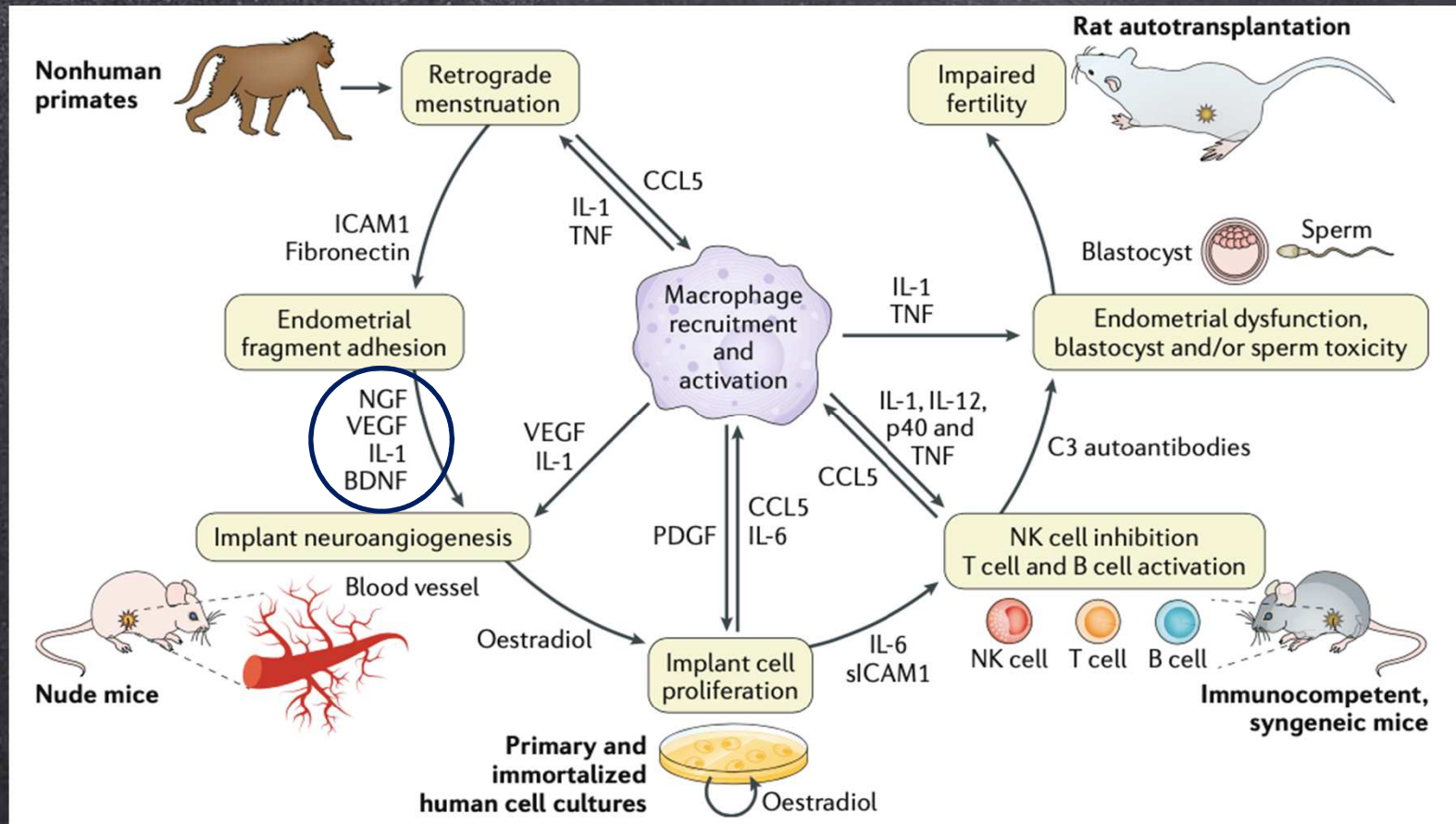




# Peripheral nervous systems



## ENDOMETRIOSIS MODELS AND MEDIATORS



Zondervan et al 2018 Nature review

The use of an appropriate **combination** of such **tools** can give a much more clinically meaningful assessment of the pain experience **than a single descriptor of pain severity**

## Pain characteristics

Dimensions of pain examined in questionnaires used in endometriosis research.

	Sensory	Emotional	Quality	Periodicity	Functional interference	Psychological wellbeing	Quality of life
EHP	No	Yes	No	No	Yes	No	Yes
SF-36	Yes	Yes	No	No	Yes	No	Yes
EQ-5D	Yes	No	No	No	No	No	Yes
McGill pain questionnaire	Yes	Yes	Yes	No	No	No	No
Brief pain inventory	Yes	No	Yes (long form only)	No	Yes	No	No
VAS	Yes	No	No	No	No	No	No
WHYMPI	Yes	Yes	No	No	Yes	Yes	No
painDETECT	Yes	No	Yes	Yes	No	No	Yes

Abbreviations: EQ-5D, European Quality of Life–5 dimensions; SF-36, short-form 36; VAS, visual analogue scale; WHYMPI, West Haven–Yale Multidimensional Pain Inventory.

**Table II Annual costs of endometriosis-associated symptoms (in euro) (n = 909).**

Item	Mean	Standard deviation	Minimum	Maximum	95% CI of the mean
Direct health care costs	3113.1	13244.1	0	290420.4	2251.0–3975.3
Physician visits	513.3	1331.9	0	12906.0	426.6–600.0
Medication	320.3	1364.2	0	23843.3	231.5–409.1
Monitoring tests	596.4	2087.7	0	31224.0	460.5–732.3
Surgery	899.3	10801.1	0	167426.0	196.2–1602.4
Other treatments	153.2	741.1	0	15114.7	104.9–201.4
Informal care	84.0	623.2	0	11610.0	43.4–124.5
Hospitalization	546.7	3614.1	0	53644.2	311.5–782.0
Direct non-health care costs	167.8	481.5	0	5983.2	136.5–199.2
Transportation	102.4	321.0	0	5983.2	81.5–123.3
Support household activities	65.4	350.3	0	5310.6	42.6–88.2
Direct costs	3281.0	13336.4	0	292286.4	2412.9–4149.1
Indirect costs	6298.3	7262.6	0	39120.0	5825.6–6771.1
Total costs	9579.3	15666.8	0	298584.7	8559.5–10599.1

## Central nervous systems



### DYSMENORRHOEA:

- Brain metabolism differences during menstruation between women with dysmenorrhoea compared with those whose periods were not painful
- Women with dysmenorrhoea were more sensitive to noxious stimuli, probably due to increased activation of particular CNS regions (e.g. the entorhinal cortex), even when not experiencing pain

Tu et al, 2009; Vincent et al 2011

### CENTRAL SENSITISATION:

- Patient becomes more sensitive to peripheral stimuli.
- Central sensitisation may become independent of peripheral stimuli via neural mechanisms, this may be a reason why pain can persist despite treatment of all identified peripheral pathology

Ren et al 2007

### BRAIN STRUCTURE AND FUNCTION:

- Several volumetric modifications in thalamus, insula, putamen, etc. compared to pain-free women .
- Women with endometriosis but without CPP had an increase in the volume of their periaqueductal grey (PAG), a key region in the descending pain modulatory pathways. Maybe women with endometriosis who do not suffer pain still generate the peripheral noxious stimuli associated with the condition but have such good descending pain inhibitory activity that they do not experience pain.

Eippert et al, Nat neurosci 2014

## Central nervous systems



### EXCITATORY NEUROTRANSMITTERS

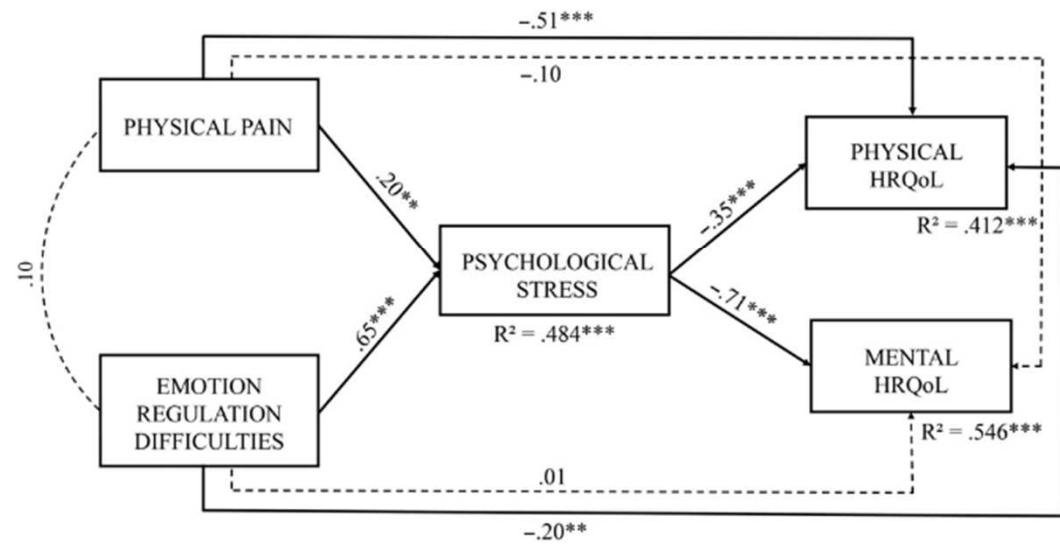
- Increased concentrations of excitatory neurotransmitters in the anterior insula and greater intrinsic connectivity to the medial prefrontal cortex
- Support the use of therapies targeting the CNS as opposed to (or in combination with) those focussing on peripheral endometriotic lesions

As-Sanie et al 2015; RCOG 2015 Scientific Impact Paper No. 46

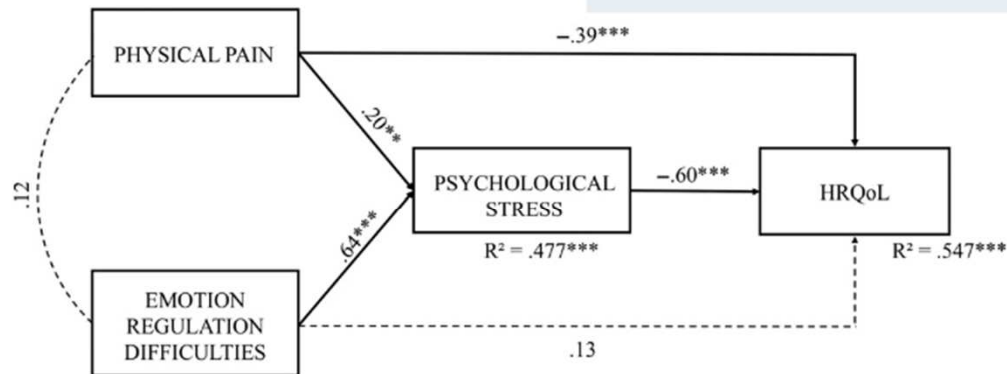
### DYSFUNCTION OF THE HYPOTHALAMIC–PITUITARY–ADRENAL (HPA) AXIS:

- Women with dysmenorrhea and endometriosis have significantly lower serum cortisol levels
- Low basal levels of cortisol represent “burnout” of the system.
- It could well be harmful in inflammatory conditions exacerbating the peripheral burden but suppression of HPA axis activity may protect an individual from the negative consequences of chronic over-activity of the system
- Cortisol levels were negatively related to the duration of symptoms supporting the burnout theory

Vincent et al 2011; Fries et al 2005



**Figure 2** The comparison mediation model for physical and mental HRQoL with standardized path coefficients and explained variance of the variables (R-squared). All variables shown are the observed variables. HRQoL = health-related quality of life. Note:  $*P < 0.05$ ;  $**P < 0.01$ ;  $***P < 0.001$ ; solid line = significant path; dashed line = non-significant path.



**Figure 1** Mediation model for HRQoL with standardized path coefficients and explained variance of the variables (R-squared). All variables shown are the observed variables. Note: HRQoL = health-related quality of life;  $**P < 0.01$ ;  $***P < 0.001$ ; solid line = significant path; dashed line = non-significant path.



## ENDOMETRIOSIS APPEARS TO BE A COMMON CAUSE OF DYSMENORRHEA AND CHRONIC PELVIC PAIN IN ADOLESCENTS.

### Endometriosis-related pain in adolescents:

- dysmenorrhea
- noncyclical pain
- bowel movement
- dyspareunia in

#### Management is more complex:

- both the adolescent and her parents are counseled and addressed
- her long-term emotional and physical health
- Fertility
- Sexuality are considered
- association with depression and anxiety

on of pelvic pain

eatment

Contrary to the past more recent studies described **advanced stage endometriosis in adolescent:** endometrioma, DIE, cul-de-sac obliteration in **30 to 40%** cases

Jansen et al 2013; Smorgick et al 2014; Smorgick 2018.

1. ~~Parte sensoriale \*~~
2. ~~(differenze nei diversi tipi di endometriosi **Chapron**)~~
3. ~~QoL & psiche~~
4. ~~Risvolti del dolore (soldi)~~
5. ~~Cambiare classificazione su dolore?~~
6. ~~Preferenza terapia~~
7. ~~Adolescenti~~
8. ~~Post menopausa~~

