# ENDOMETRIOSI: NUOVI OPZIONI DIAGNOSTICHE E TERAPEUTICHE

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VIEWS AND REVIEWS

# Introduction:
# Management of endometriosis: moving toward a problem-oriented and patient-centered approach

2015

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Department of Clinical Sciences and Community Health, Università degli Studi di Milano and Fondazione Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

## What's in a name?

Endometriosis is anything.

It may be considered a histologic diagnosis,

a disease of the female genital apparatus,

a disorder that manifests itself under very different forms, from a few superficial endometrial implants to infiltrating lesions involving several organs with loss of function.

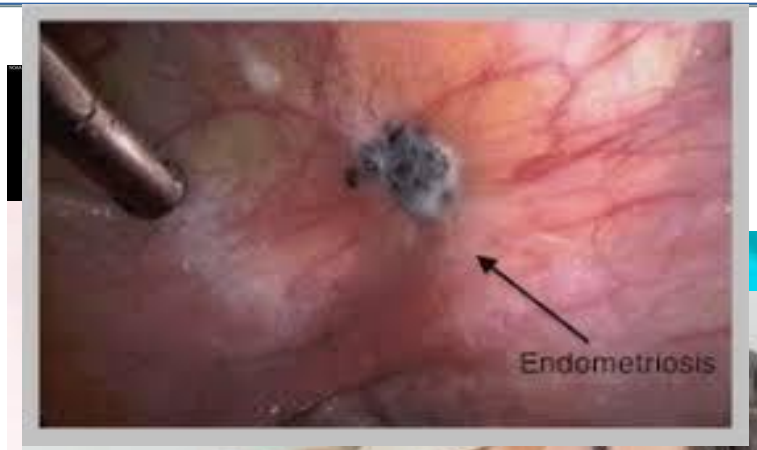
Endometriosis may be asymptomatic or be associated with pain so severe that it greatly limits health-related quality of life.

Endometriosis may allow natural conception or impede reproduction forever.

Endometriosis may be selflimiting or require repeated surgical procedures and prolonged medical treatments.

Endometriosis may afflict a woman for a limited period of time or until menopause ensues.

**Therefore, different clinical conditions require specific and sometimes very different therapeutic approaches.**








# ENDOMETRIOSI_Perché ?

## LE DIMENSIONI DEL PROBLEMA



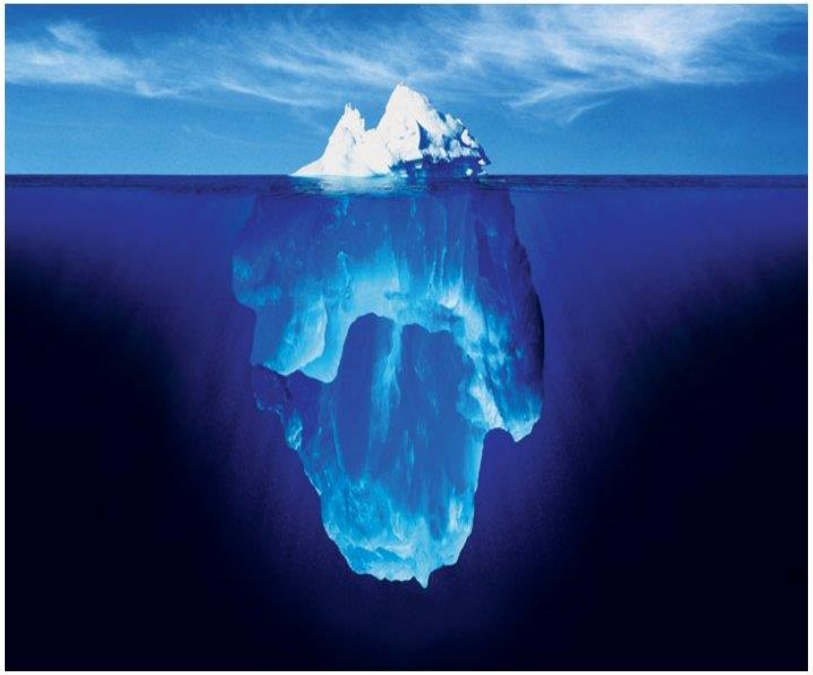
**176 milioni**
**le donne** colpite nel mondo.

**10-20%**
**delle donne in età riproduttiva**

*Luisi et al. Endometriosis in Italy: from cost estimates to new medical treatment. Gynecol Endocrinol. 2009, Nnoham et al. Impact of endometriosis on quality of life and work productivity: a multicenter study across ten countrie. Fertil & Steril 2011*

# ENDOMETRIOSI_Perché ?

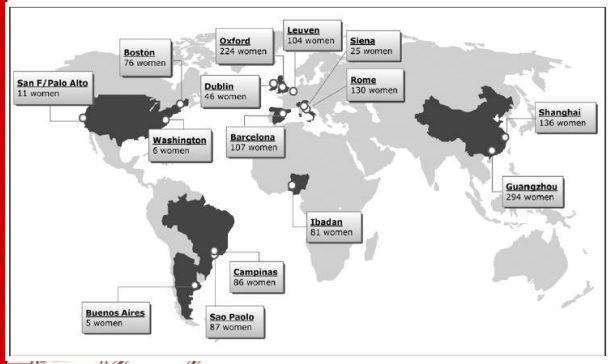
## LE DIMENSIONI DEL PROBLEMA



**3 milioni**
**le donne** colpite in italia

Tra l'insorgenza dei sintomi e la diagnosi passano in media **9 anni**

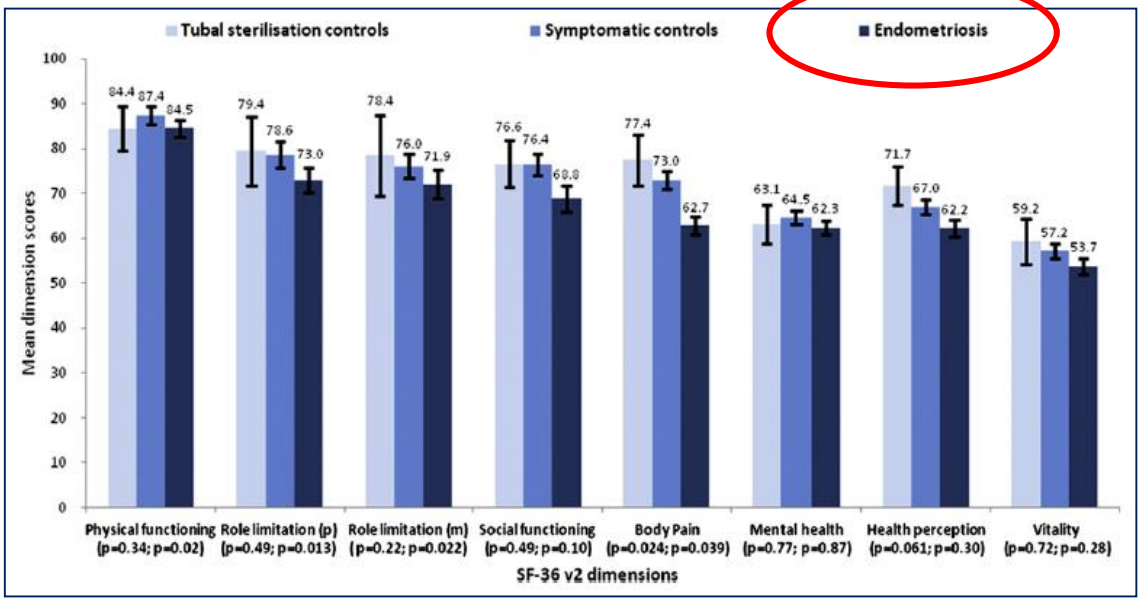
*Luisi et al. Endometriosis in Italy: from cost estimates to new medical treatment. Gynecol Endocrinol. 2009, Nnoham et al. Impact of endometriosis on quality of life and work productivity: a multicenter study across ten countrie. Fertil & Steril 2011*




# Impact of endometriosis on quality of life and work productivity: a multicenter study across ten countries

*Kelechi E. Nnoaham, M.D.,[a,b] Lone Hummelshoj,[c] Premila Webster, M.D.,[a] Thomas d'Hooghe, M.D.,[d] Fiorenzo de Cicco Nardone, M.D.,[e] Carlo de Cicco Nardone, M.D.,[e] Crispin Jenkinson, D.Phil.,[f] Stephen H. Kennedy, M.R.C.O.G.,[b] and Krina T. Zondervan, D.Phil.,[b,g] on behalf of the World Endometriosis Research Foundation Global Study of Women's Health consortium*

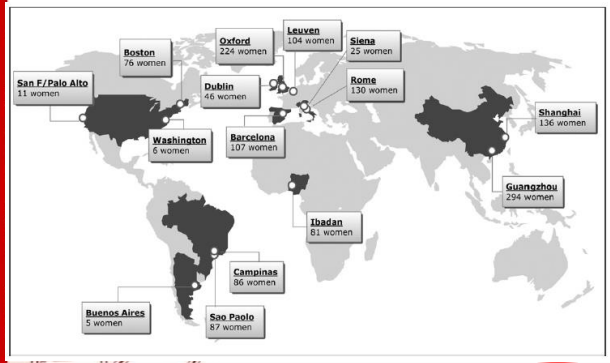
*Nnoaham. Endometriosis, quality of life and work. Fertil Steril 2011.*






**Gruppo endometriosi ha una riduzione significativa di qualità di vita, nella funzione fisica psichica e mentale**

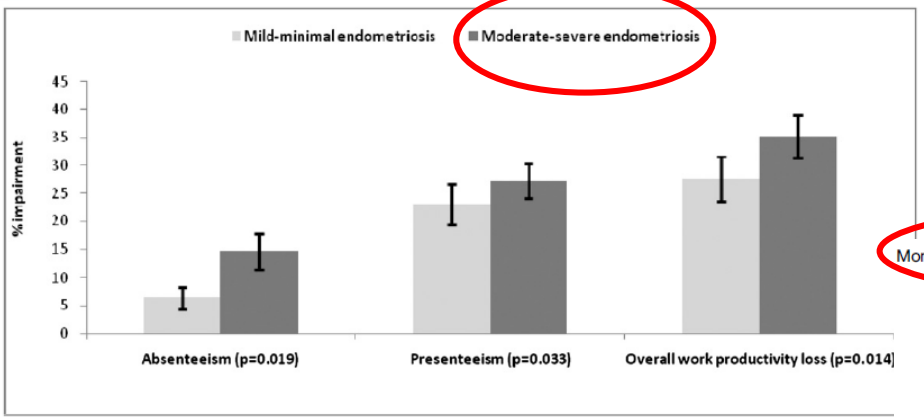

IL PRESENTE MATERIALE È RISERVATO AL PERSONALE DELL'UNIVERSITÀ DI BOLOGNA E NON PUÒ ESSERE UTILIZZATO AI TERMINI DI LEGGE DA ALTRE PERSONE O PER FINI NON ISTITUZIONALI



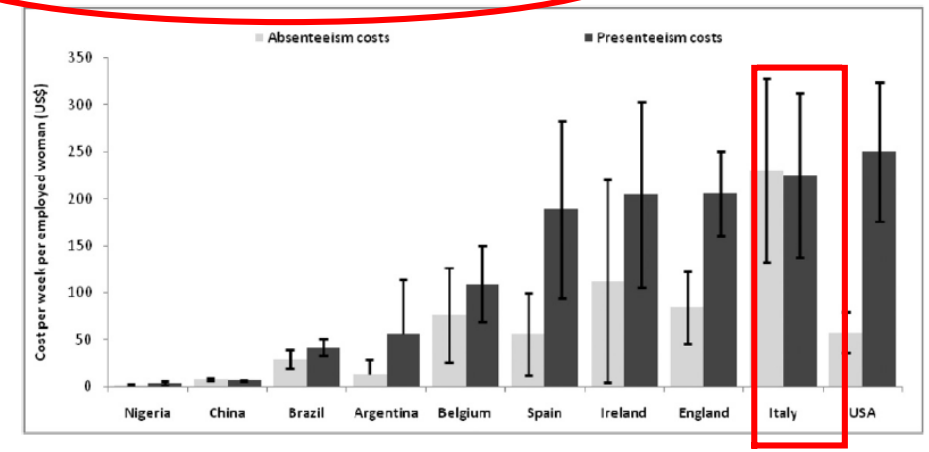

# Impact of endometriosis on quality of life and work productivity: a multicenter study across ten countries

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Monetary loss from endometriosis-associated work absenteeism and presenteeism.

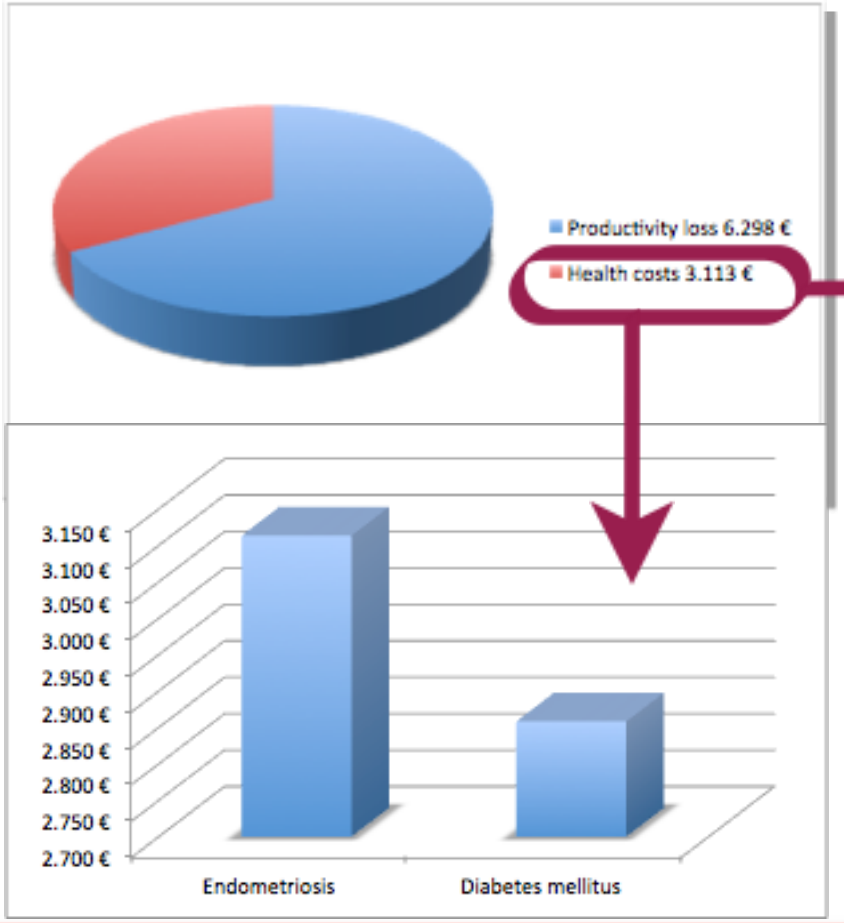


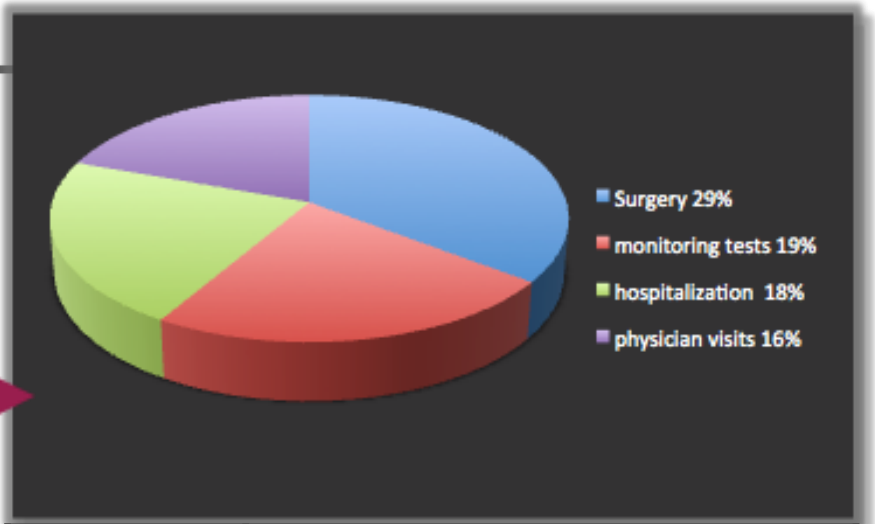

**DPC e la SEVERITA della malattia sono cause > di minor produttività**


IL PRESENTE MATERIALE È RISERVATO AL PERSONALE DELL'UNIVERSITÀ DI BOLOGNA E NON PUÒ ESSERE UTILIZZATO AI TERMINI DI LEGGE DA ALTRE PERSONE O PER FINI NON ISTITUZIONALI

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

Simoens et al. Human Reproduction, Vol.27, No.5 pp. 1292–1299, 2012



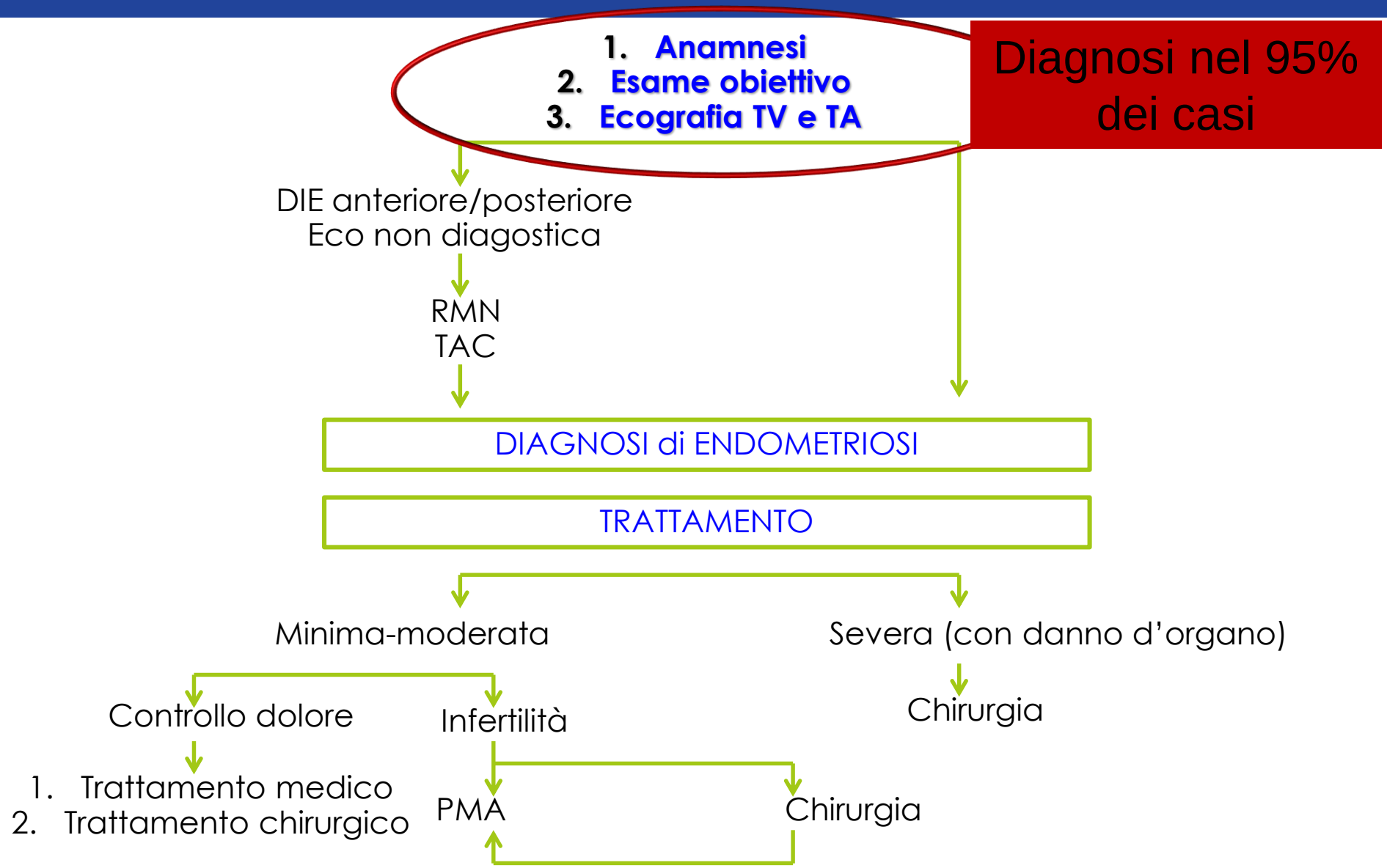

| Country | Total annual societal burden in BILLION € |
|---|---|
| Switzerland | 1.3 |
| Hungary | 1.6 |
| Belgium | 1.7 |
| Netherlands | 2.6 |
| Italy | 9.3 |
| France | 9.5 |
| U.K | 9.9 |
| Germany | 12.5 |
| USA | 49.6 |

ALMA
IL PRESENTE MATERIALE È RISERVATO AL PERSONALE DELL'UNIVERSITÀ DI BOLOGNA E NON PUÒ ESSE




# ENDOMETRIOSI: NUOVI OPZIONI DIAGNOSTICHE

# Algoritmo diagnostico-terapeutico



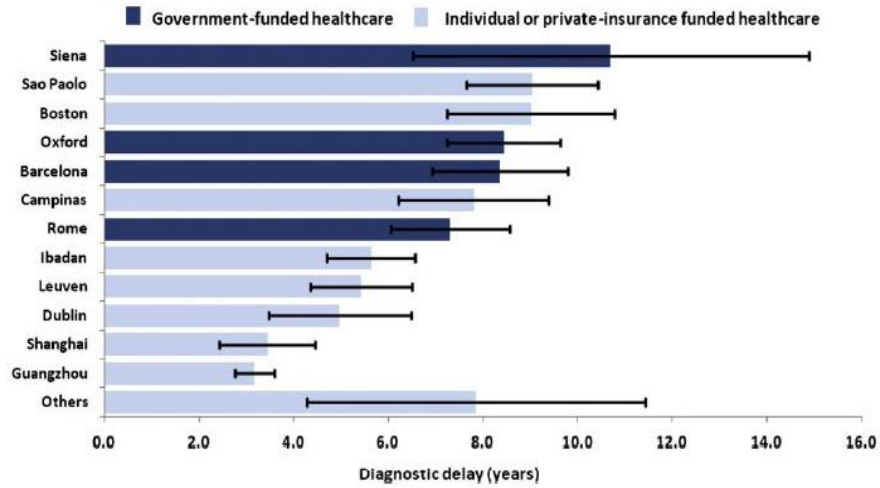
Prevenzione primaria
Diagnosi precoce

E’ possibile una prevenzione primaria?

Diagnosi precoce.

# Don't be late!

Tempo medio di diagnosi in Italia: **7-10 aa**




Nnoaham. Endometriosis, quality of life and work. Fertil Steril 2011.

**Table IV** Relationships between psychosocial/clinical characteristics and diagnostic delay.

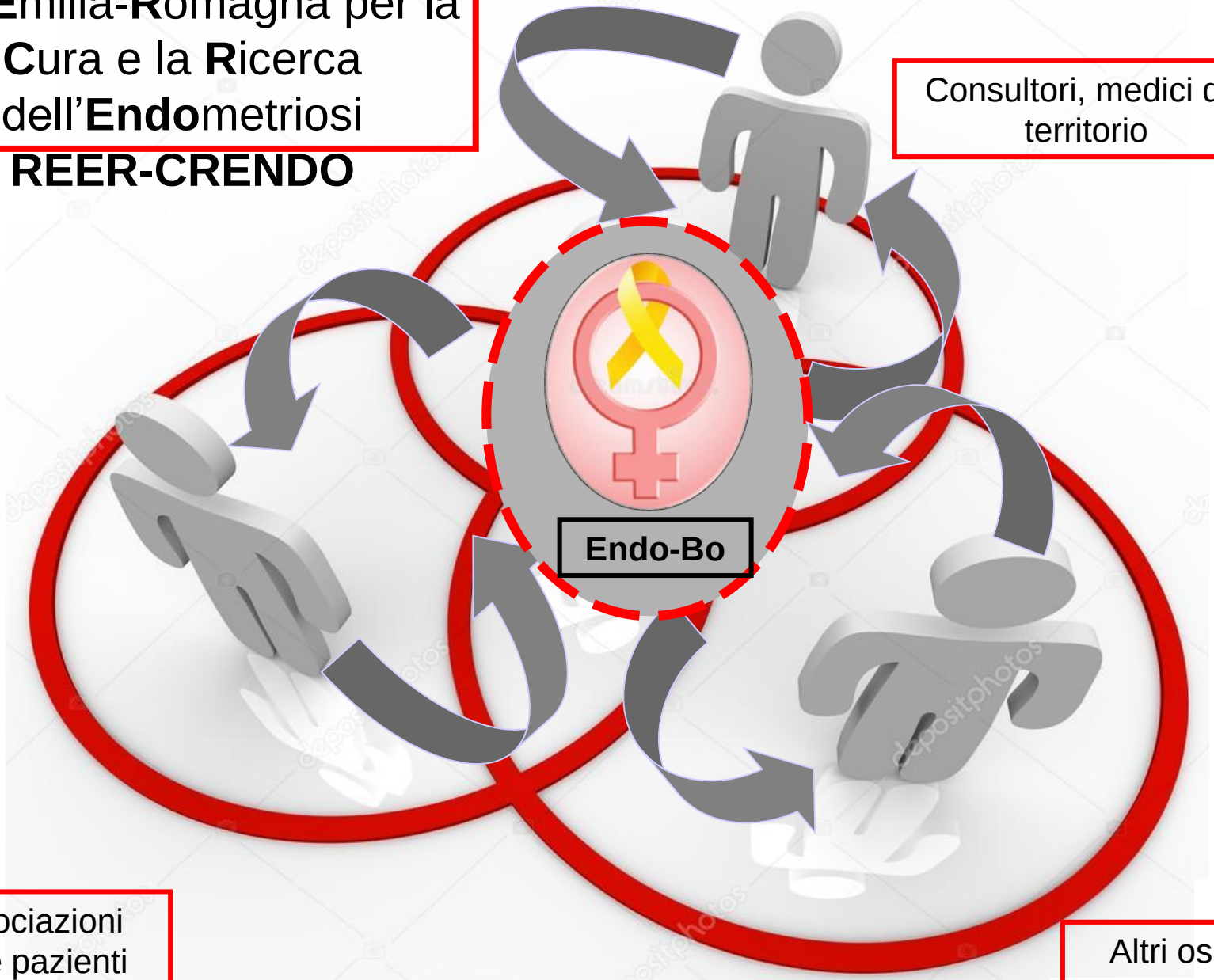
| Variable | Median (years) | SD | P |
|---|---|---|---|
| Mother regarded menstruation positive | 9.7 | 7.9 | <0.01* |
| Mother regarded menstruation negative | 14.6 | 6.6 | |
| Patient regarded menarche positive | 9.9 | 7.1 | 0.28 |
| Patient regarded menarche negative | 11.2 | 8.7 | |
| No/some menstrual cramps during adolescence | 9.0 | 7.3 | 0.03* |
| Severe menstrual cramps during adolescence | 11.6 | 8.2 | |
| Normalization of pelvic pain/ dysmenorrheal | 11.3 | 7.5 | 0.04* |
| No normalization of pelvic pain/ dysmenorrheal | 8.5 | 8.4 | |
| Misdiagnosis | 11.5 | 8.2 | <0.01* |
| No misdiagnosis | 7.4 | 6.3 | |
| Hormonal therapy use | 10.8 | 7.7 | 0.39 |
| No hormonal therapy use | 9.6 | 8.6 | |
| Analgesic medication use | 11.1 | 7.9 | 0.11 |
| No analgesic medication use | 9.0 | 8.0 | |
| Superficial/peritoneal endometriosis | 10.5 | 8.0 | 0.87 |
| Deep infiltrating endometriosis | 10.3 | 7.8 | |
| Subfertility | 9.9 | 8.2 | 0.69 |
| Pelvic pain | 10.5 | 7.9 | |
| Gynecologist took pain intensity not seriously | 11.5 | 8.0 | 0.02* |
| Gynecologist took pain intensity seriously | 8.6 | 7.5 | |

- Sintomi aspecifici
- Decorso sub-clinico
- Scarsa conoscenza medica e sociale della malattia

Nnoaham et al., 2011; Hudelist et al., 2012

**Re**te **R**egionale dell'**E**milia-**R**omagna per la **C**ura e la **R**icerca dell'**Endo**metriosi

**REER-CRENDO**




Consultori, medici del territorio

Associazioni delle pazienti

Altri ospedali non specializzati

**Re**te **R**egionale dell'**E**milia-**R**omagna per la **C**ura e la **R**icerca dell'**Endo**metriosi

**REER-CRENDO**

## Obiettivi Specifici REER-CRENDO

- Superare le disomogeneità territoriali, a livello di servizi sanitari e prestazioni erogate;

Garantisce alle donne equità e pari opportunità di accesso alla diagnosi tempestiva ed alle cure, in quanto favorisce lo scambio di esperienze e competenze tra gli operatori sanitari che fanno parte della rete.

- identificare precocemente la paziente con endometriosi complessa e la presa in carico della paziente da parte del centro specialistico dedicato implica i seguenti vantaggi:
  - tempestività degli interventi;
  - interdisciplinarità del piano di cura.

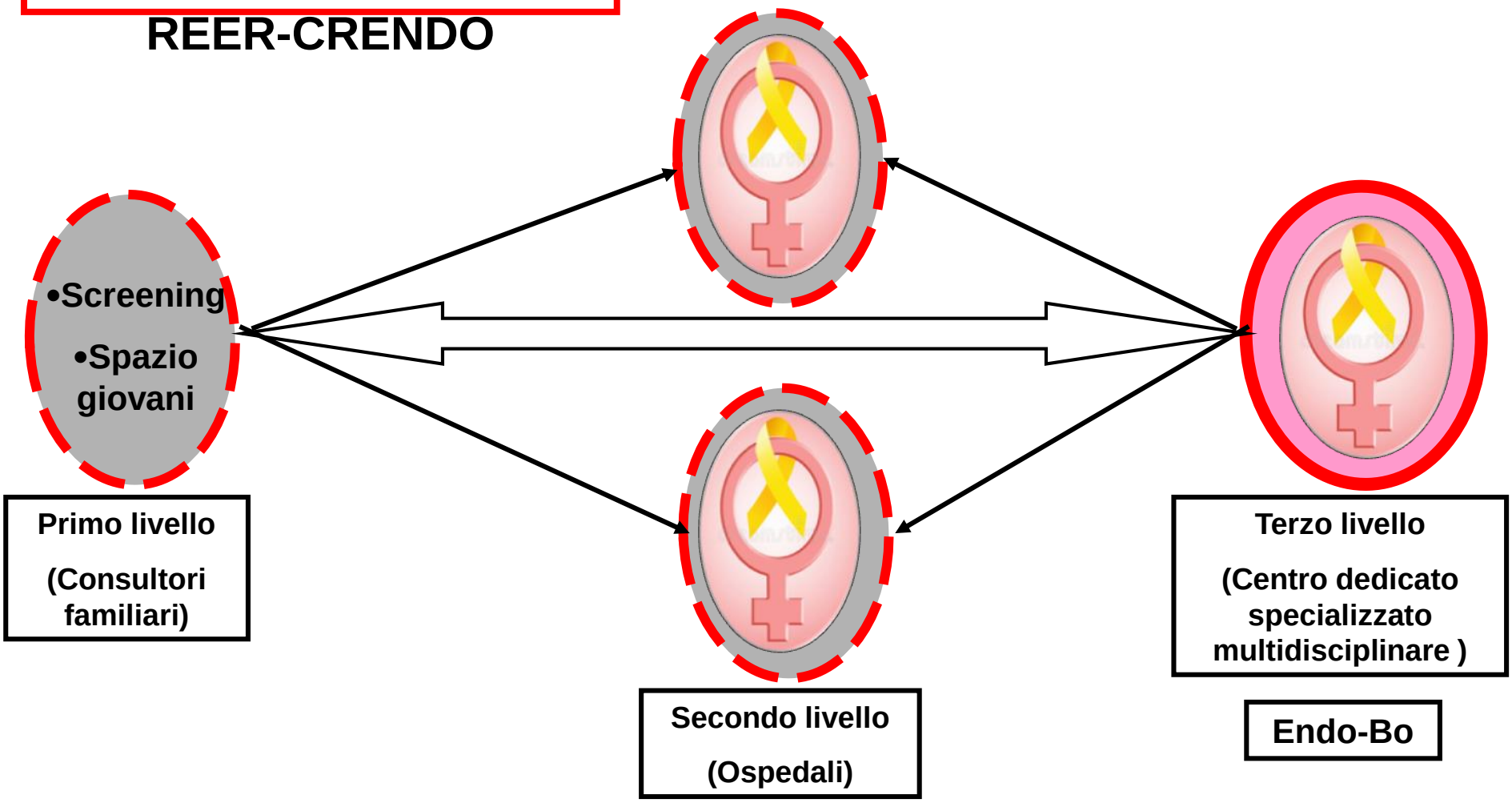
- raggiungere standard di trattamento sempre più elevati;

- semplificare le fasi di accesso ai servizi, da parte del paziente, e lo sviluppo dei percorsi diagnostico-terapeutici e assistenziali regionali uniformi e coerenti

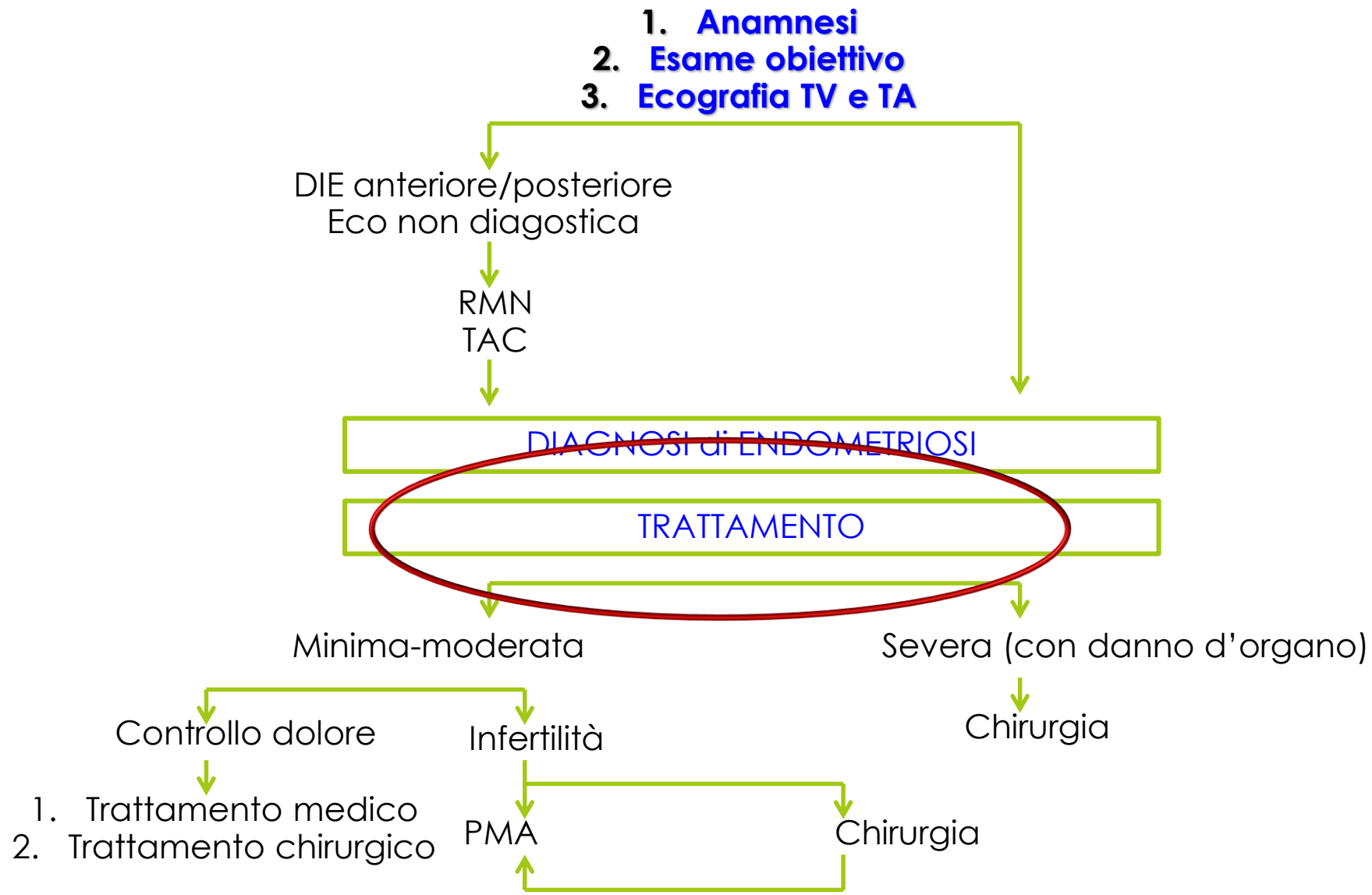
- accompagna la paziente lungo i percorsi di diagnosi e di terapia sia prima che dopo l'intervento chirurgico, offrendo modalità di cura multidisciplinari e assistenza continua da parte dei centri dedicati ( II e III livello)

**Rete Regionale dell'Emilia-Romagna per la Cura e la Ricerca dell'Endometriosi**

**REER-CRENDO**



# Algoritmo diagnostico-terapeutico



# Consensus on current management of endometriosis

Neil P. Johnson[1,2,3,*] and Lone Hummelshoj[1], for the World Endometriosis Society Montpellier Consortium[†]

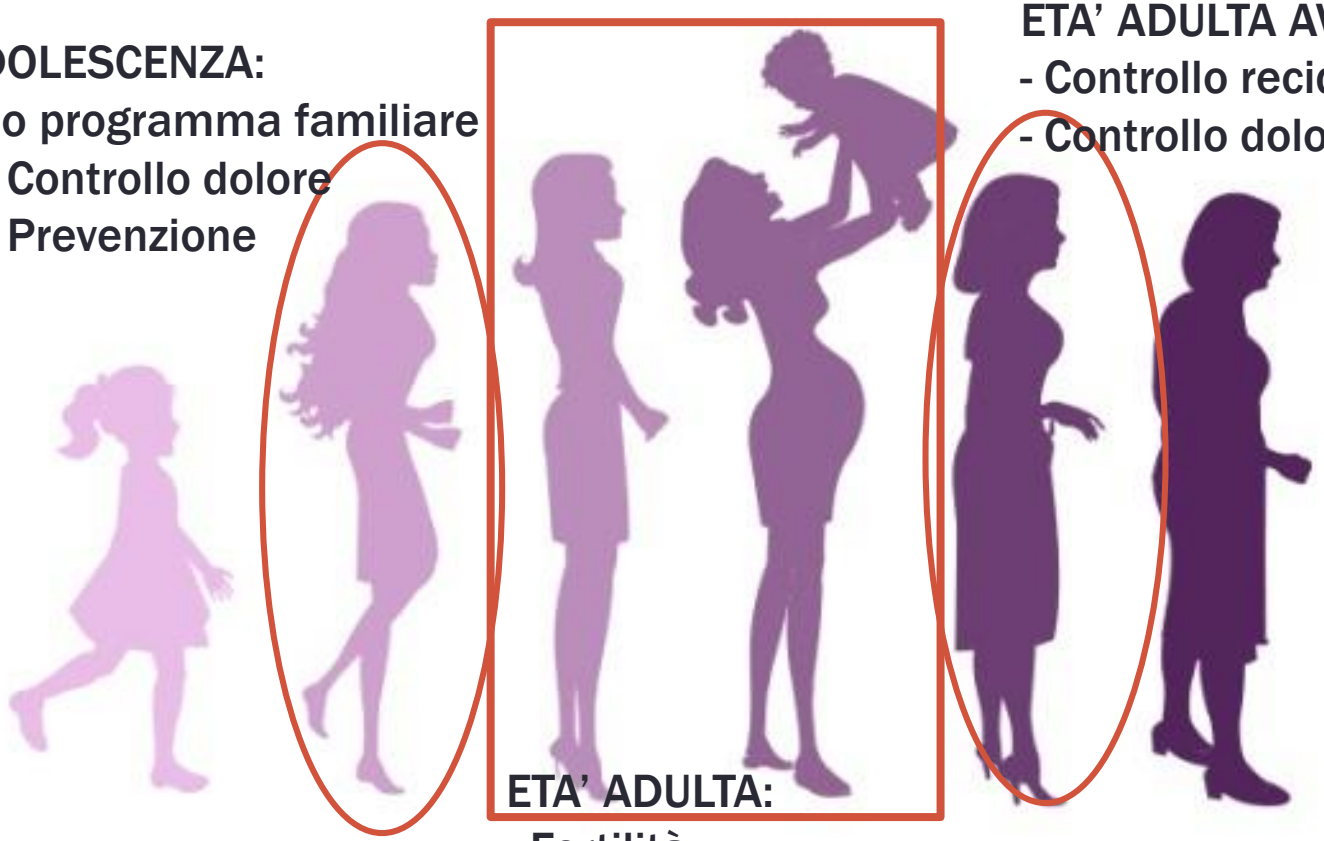
| | *Consensus grading* |
|---|---|
| Women with endometriosis require **individualised care over a long-term period**, where priorities may change owing to the type and severity of symptoms, impact of these symptoms, current or future fertility wish and lifestyle factors (strong GPP). | **A** (more than 80% agreed without caveat and fewer than 5% disagreed) |
| Individualised care benefits from a **multi-disciplinary network of experts** sufficiently skilled in providing advice on and treatment of endometriosis and its associated symptoms, based on the best available knowledge, their extensive experience and their transparent record of success rates (strong GPP). | **B** (fewer than 5% disagreed but fewer than 80% agreed without caveat) |

**Johnson** NP, Hummelshoj L; World Endometriosis Society Montpellier Consortium. Consensus on current management of endometriosis. *Hum* Reprod. 2013 Jun;28(6) 1552-68.

# ETA’

# L'ETA' COME PUNTO CARDINE

**ADOLESCENZA:**
- No programma familiare
- Controllo dolore
- Prevenzione



**ETA' ADULTA:**
- Fertilità
- Controllo dolore

**ETA' ADULTA AVANZATA:**
- Controllo recidiva
- Controllo dolore

# L'ETA' COME PUNTO CARDINE



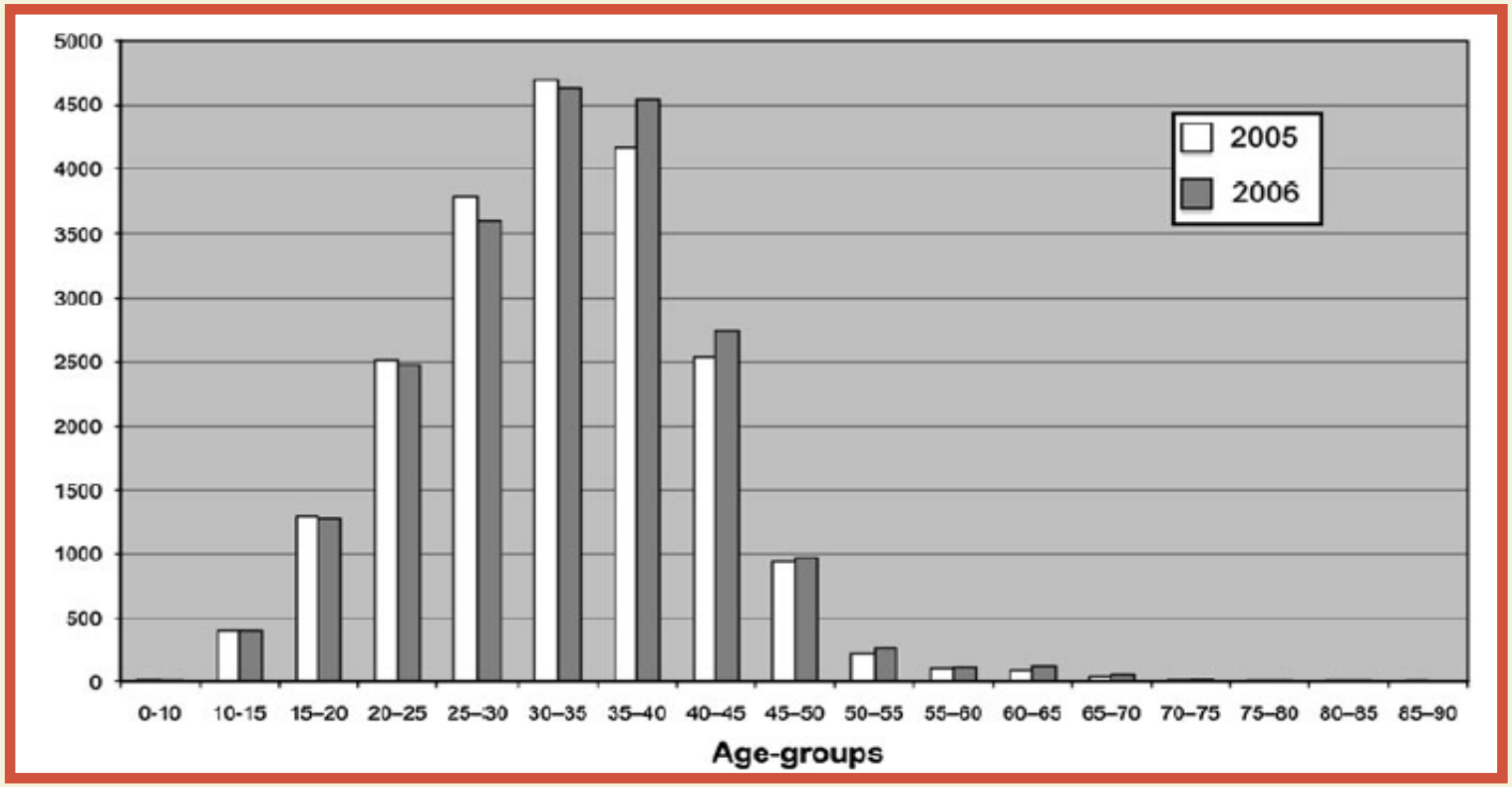
Prevenzione

Terapia medica

Terapia chirurgica

Fecondazione assistita

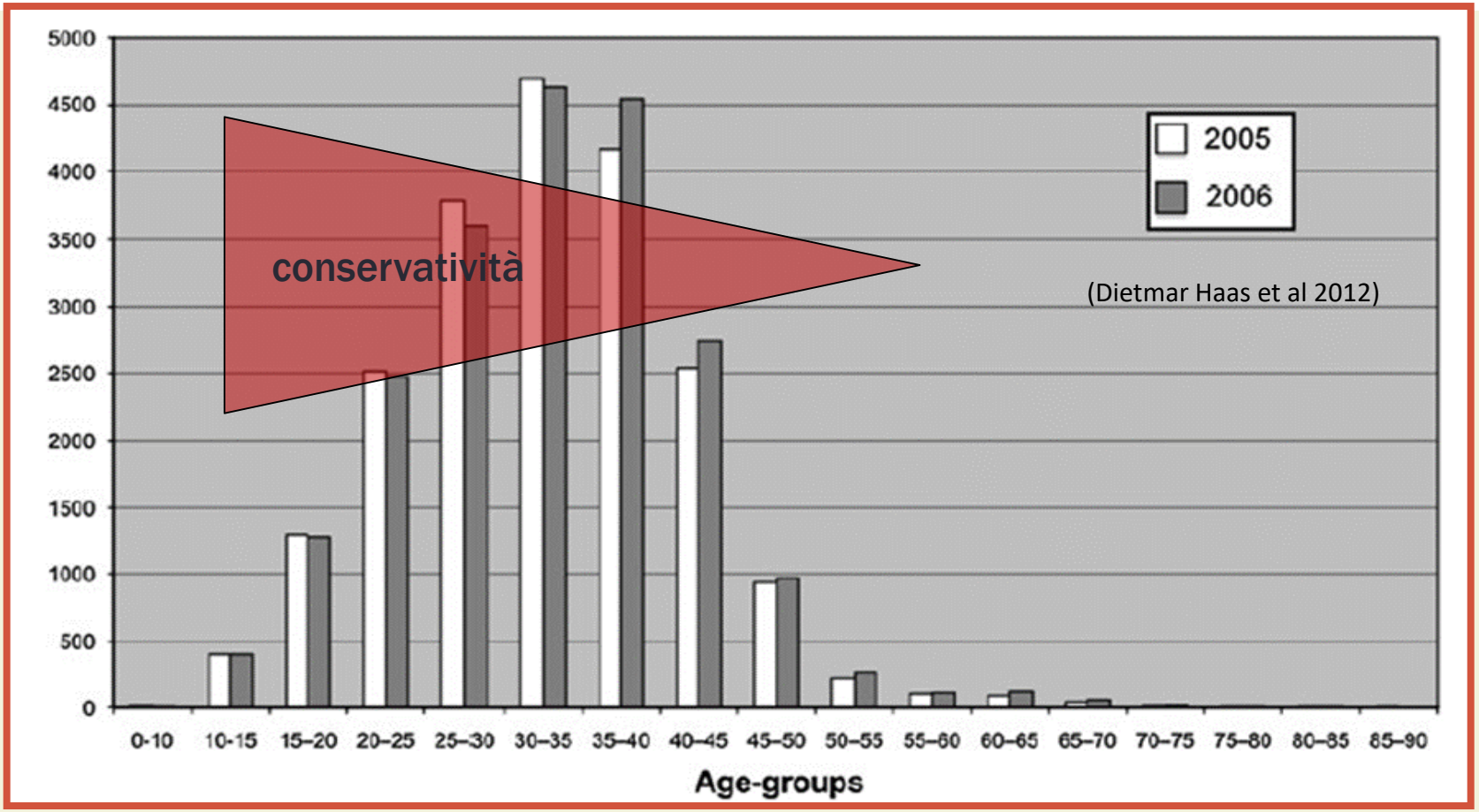
# L'ETA' COME PUNTO CARDINE




**Differenti incidenze nella sua storia naturale**

(Dietmar Haas et al 2012)

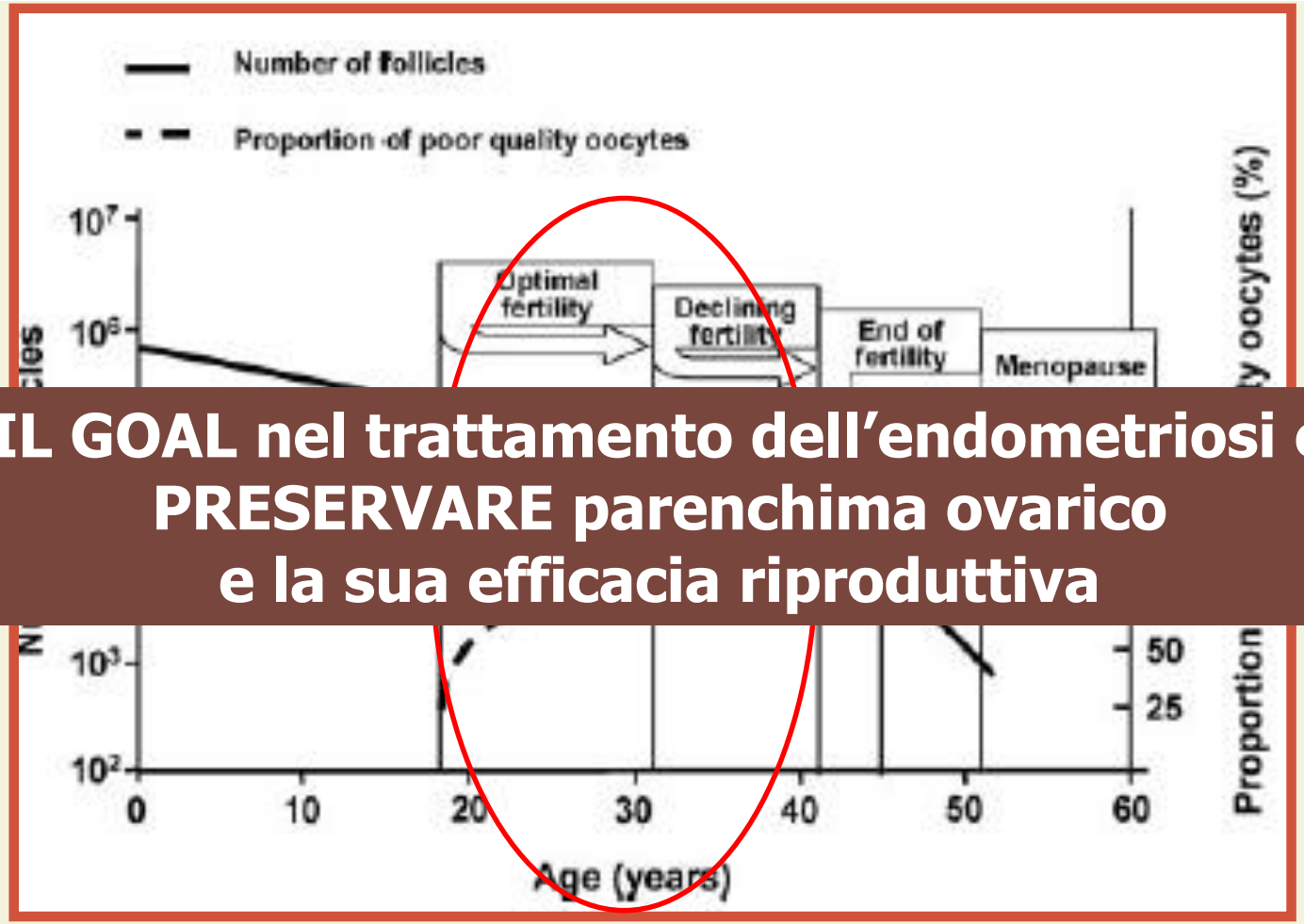
# L'ETA' COME PUNTO CARDINE




Diverso approccio medico

# Preservazione fertilità

# L'ETA' COME PUNTO CARDINE




**IL GOAL nel trattamento dell'endometriosi è PRESERVARE parenchima ovarico e la sua efficacia riproduttiva**

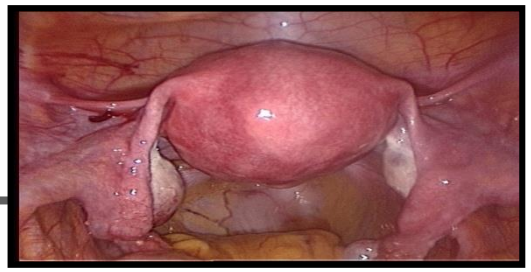
Differenti outcome di fertilità

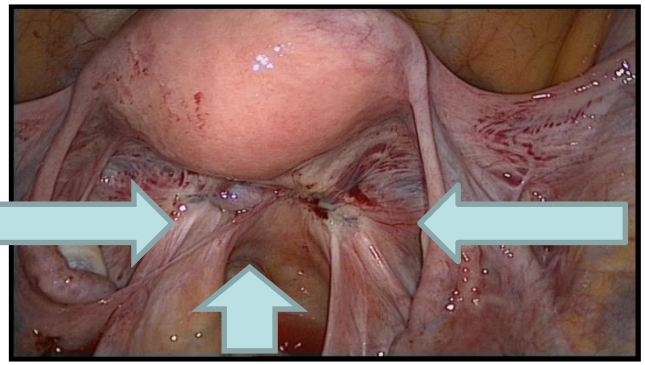
(Dietmar Haas et al 2012)

# Novità terapeutiche: chirurgia

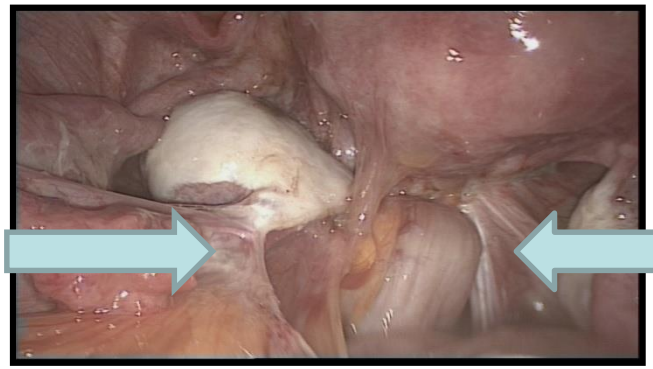
# 1) Understanding the disease
# Posterior DIE

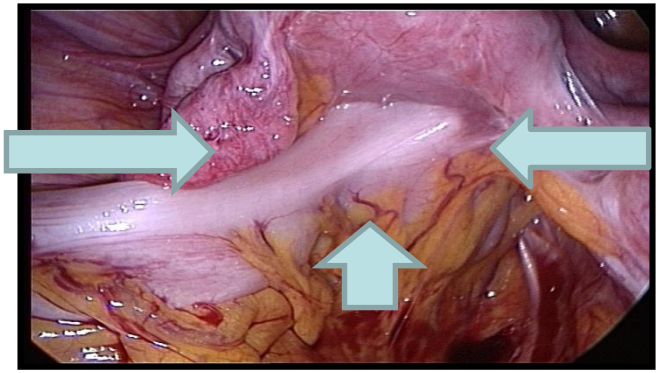
## Anatomical Consequences



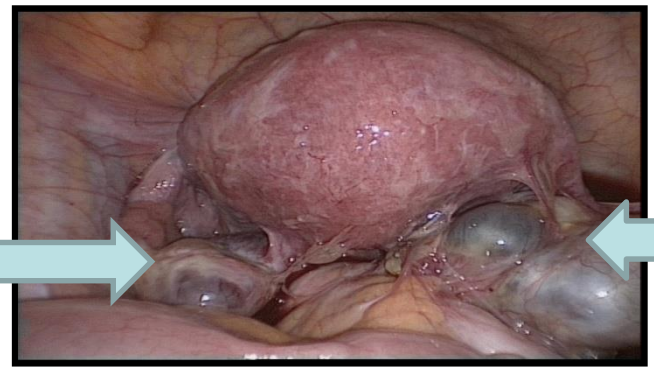


**Pelvic anatomy alteration**





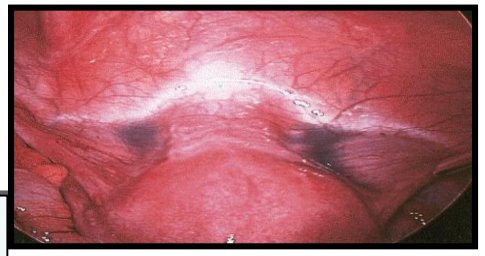
**Multiorgan involvement**



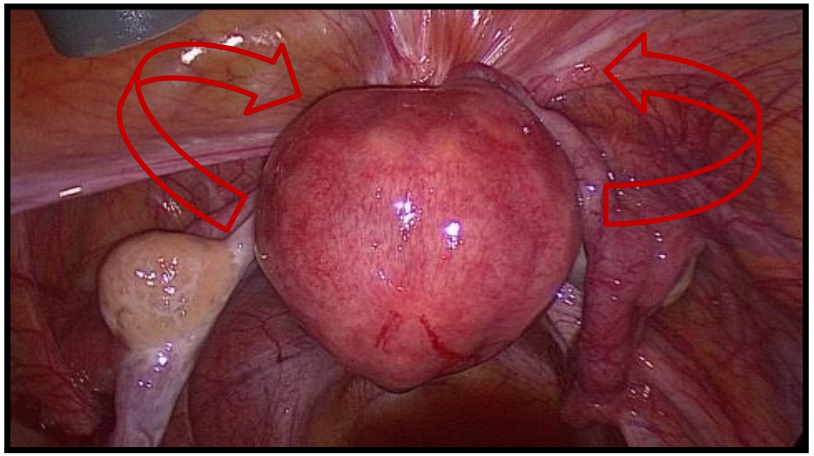
**Adhesions**

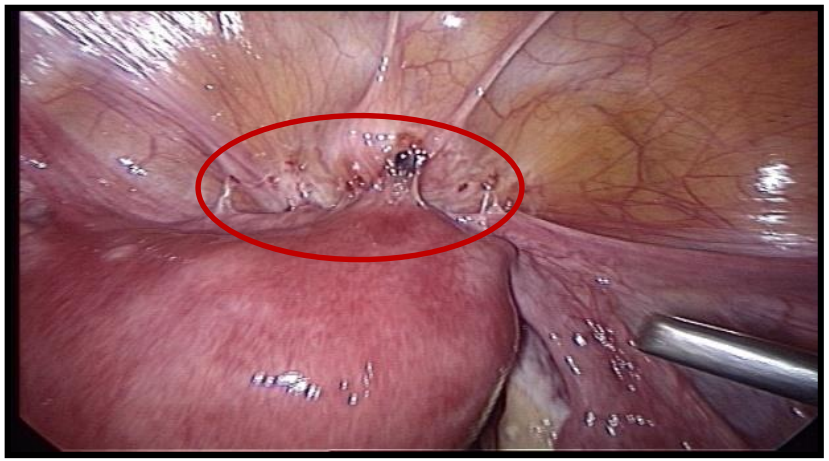
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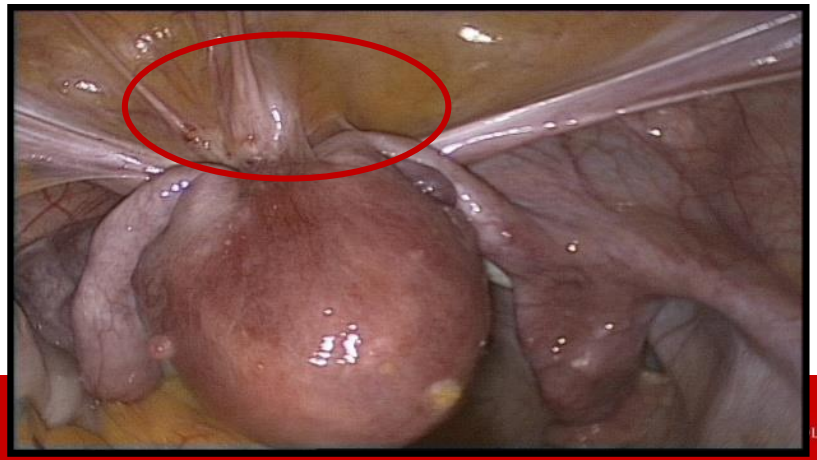
# 1) Understanding the disease
# Anterior DIE

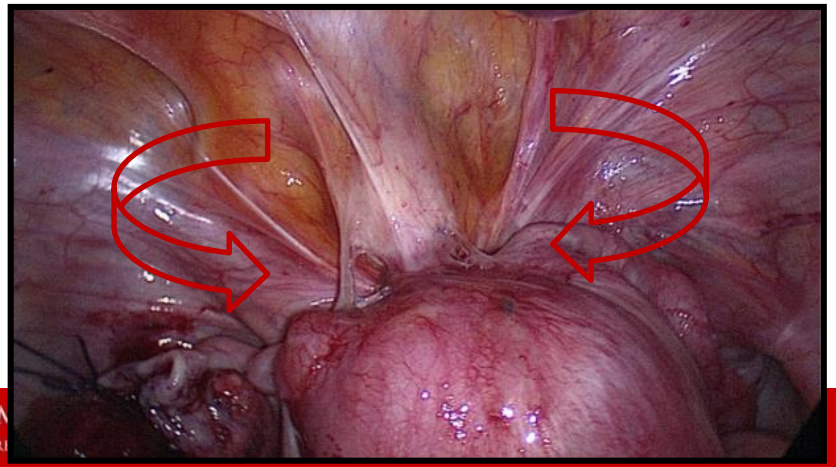


## Anatomical Consequences



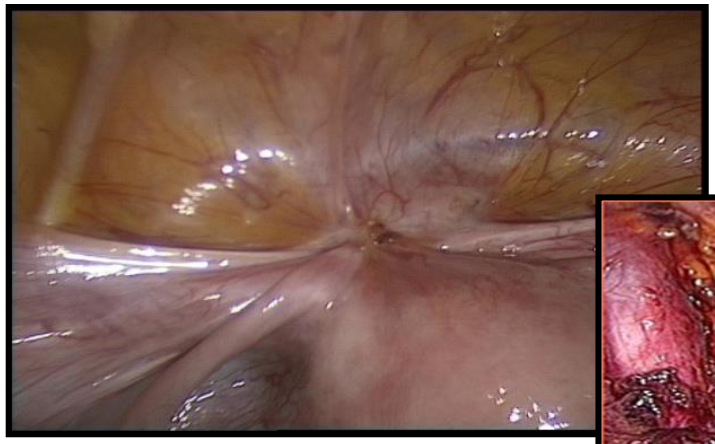






# 1) Understanding the disease
# Parametrial DIE

## Anatomical Consequences

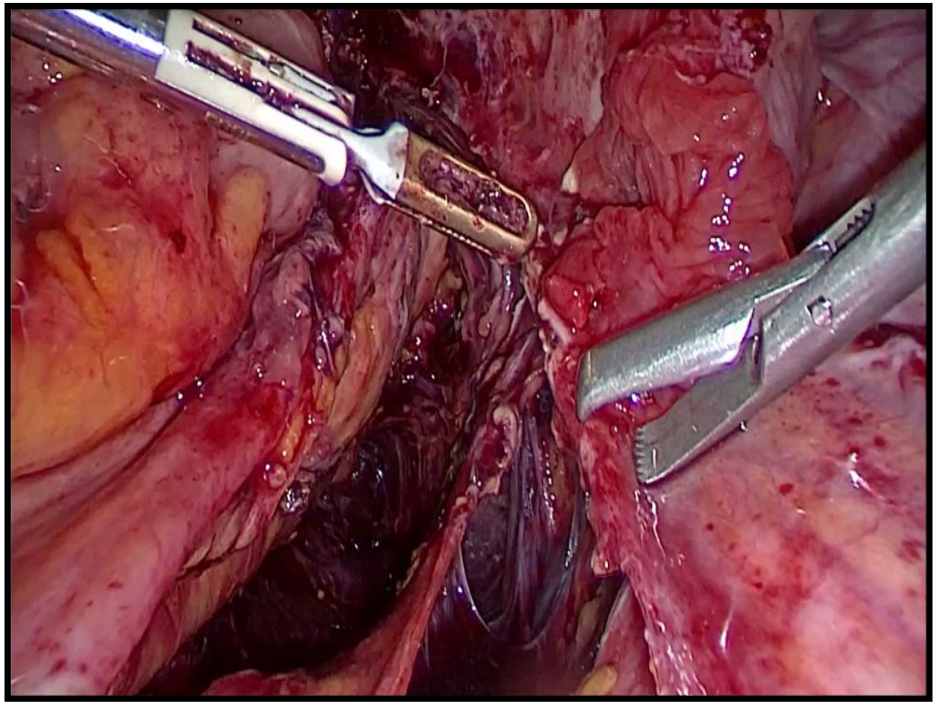


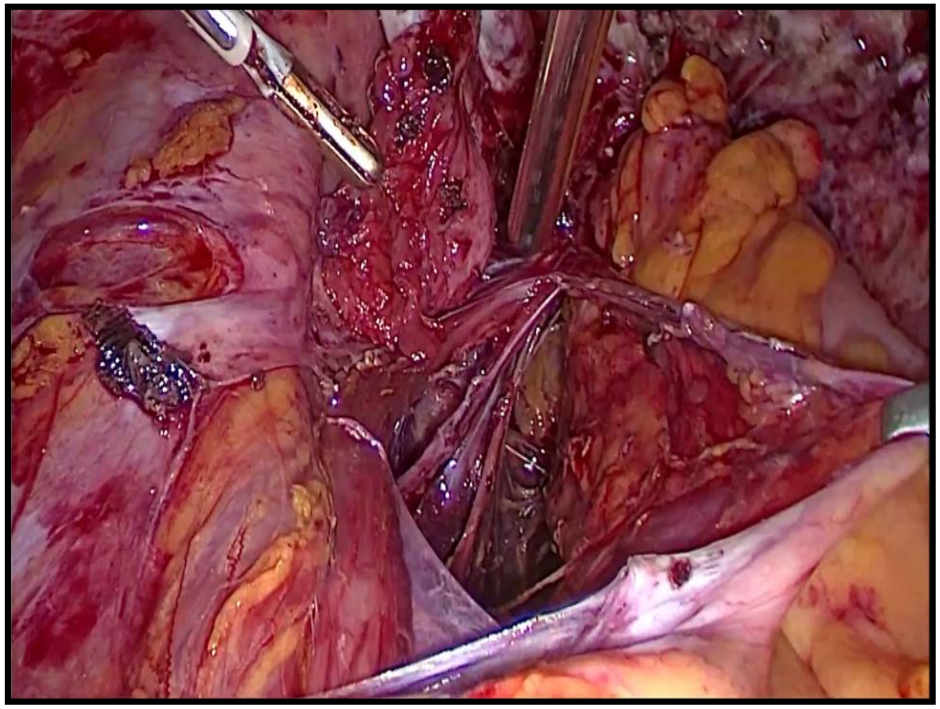




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# Surgical challenge





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# Novità terapeutiche: terapia medica

# Trattamento medico – **controllo del dolore**

**TRATTAMENTO MEDICO**

***…chronic disease***

***GTA: Trattamento della remissione da malattia***

***The Practice Committee of the American Society for Reproductive Medicine (2014)***

- ✓ Massimizzare l'**uso del trattamento medico**
- ✓ Evitare la ripetizione di interventi chirurgici

# TERAPIA MEDICA & ENDOMETRIOSI
# QUALE

## ESTROPROGESTINICI

## PROGESTINICI

- MEDROSSIPROGESTERONE
- NORETHISTERONE
- DESOGESTREL
- LEVONORGESTREL
- LNG IUS
- CIPROTERONE
- DIENOGEST

## … altri

- INIBITORI TNF-alfa
- INIBITORI AROMATASI
- ELAGOLIX

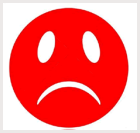


## ANALOGHI GnRH

- LEUPRORELINA
- BUSERELINA
- TRIPTORELINA

## DERIVATI DEL TESTOSTERONE

- DANAZOLO
- GESTRINONE

| | LNG-IUS | COC | GNRH agonisti | GNRH antagonisti | Danazolo |
|---|---|---|---|---|---|
| PRO  | - Compliance<br>- Lungo termine<br>- < effetti metabolici sistemici | - ↓ LH e FSH<br>- Decidualizzazione endometrio (→ atrofia) | Completa inibizione R ormonali → Ottimo effetto sintomatologico | Rispetto agli agonisti: Effetto più rapido e reversibilità più veloce alla sospensione | - Inibisce steroidogenesi<br>- ↑ androgeni |
| CONTRO  | - Costo<br>- Rischio PID (1,5%)<br>- Spotting (65%)<br>- Cisti ovariche semplici (55%) | - Cefalea<br>- ↑ peso<br>- Vampate<br>- ↓ libido<br>- Spotting<br>- Edemi<br>- Mastodinia<br>- Alterazioni umore | Sintomi menopausali<br>- ↓ Massa ossea<br>- Insonnia<br>- Depressione | Ancora in fase di studio | - Irsutismo<br>- Abbassamento di voce<br>- Alterazione funz epatica<br>- Vampate<br>- Cefalea |



Molto efficace per dismenorrea, dispareunia e DPC



Regimi:
- Continuo
- Ciclico (21+7)
- Ciclico esteso (24+4, 26+2)




ADD-BACK THERAPY



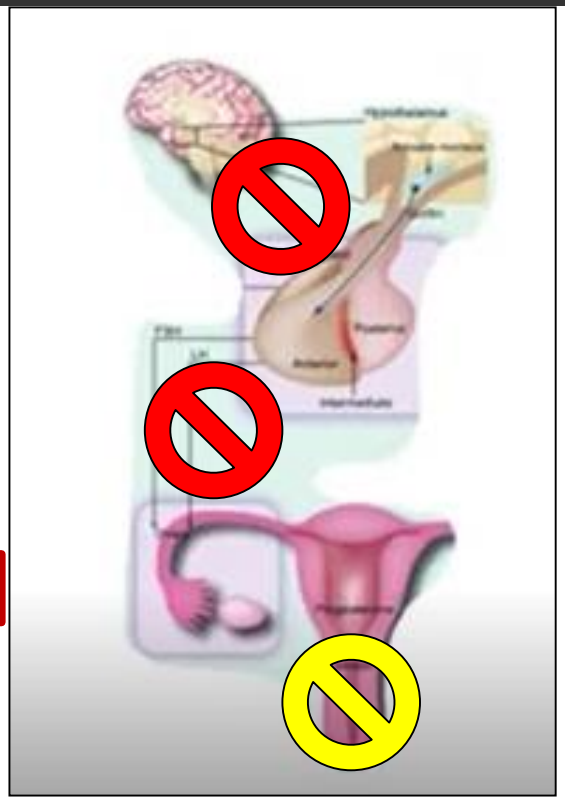



# LO SCOPO DELLA TERAPIA

**Lo scopo della terapia per endometriosi, in definitiva, è agire sull'asse ipotalamo-ipofisi-ovaia ed inibire a vari livelli a seconda del farmaco utilizzato, la produzione di estrogeni, l'alimentatore dei foci endometriosici**

**Diverse possibilità di azione**:

- Soppressione ovarica: COC,Progestinici, GnRh - a etc
- Diminuire l'esposizione locale all'estrogeno: intracrinologia
- Blocco dei R-estrogenici (usato in oncologia, non ancora utilizzato per l'endometriosi)



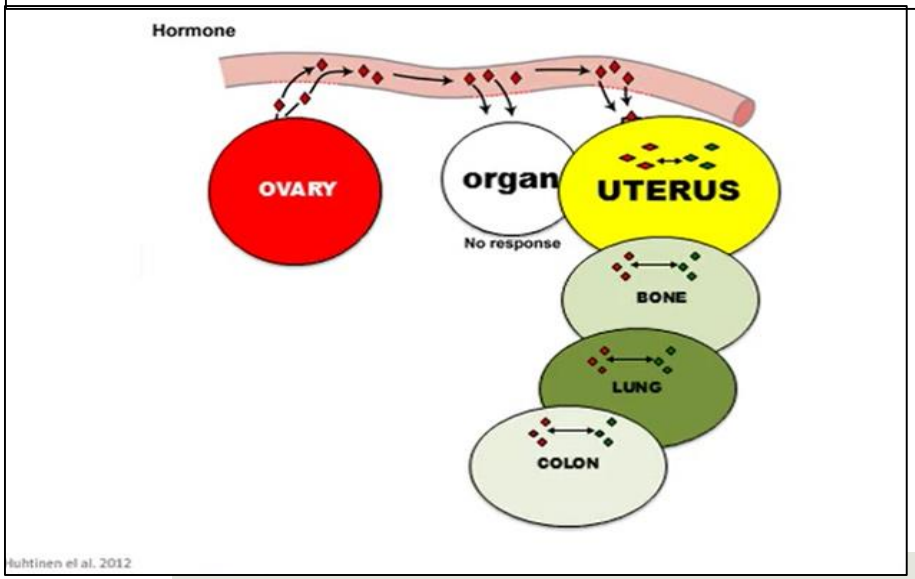
# INTRACRINOLOGIA

## Nuova frontiera, in via di sperimentazione clinica

A large proportion of androgens in men(40%), and the majority of estrogens in women (75% before menopause and close to 100% after menopause), are synthesized in peripheral target tissues from preursor steroids of adrenal origin.

The genes encoding the enzymes responsible for the formation and metabolism of androgens and estrogens are expressed in a large series of peripheral tissues, thus providing the basis for a promising new era in hormone action, namely **intracrinology.**

These steroidogenic and steroid metabolizing enzymes should become a major target of novel therapies for steroid-sensitive diseases, particularly breast and prostate cancer.



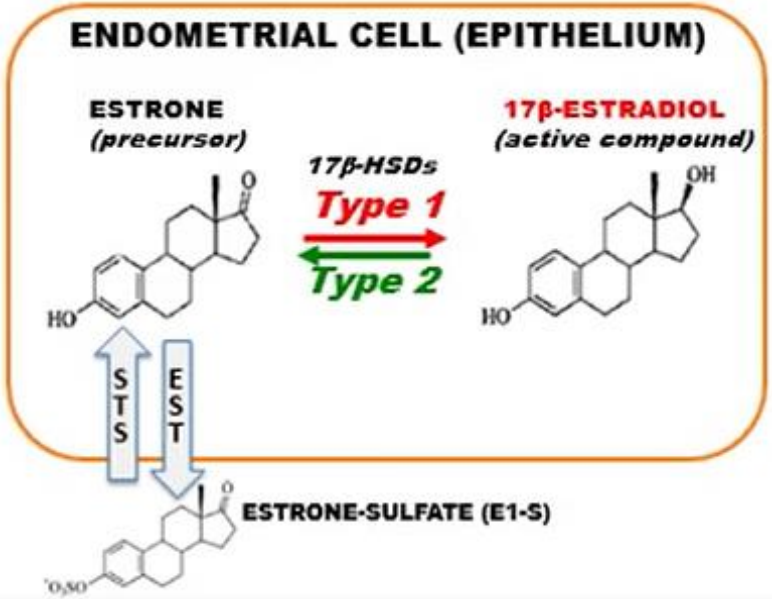

**La codifica del meccanismo di azione intracellulare degli ormoni sulle diverse cellule dell'organismo ha permesso di individuare un nuovo target di terapia: gli enzimi cellula-specifici interessati dal processo fisiopatologico.**

# INTRACRINOLOGIA

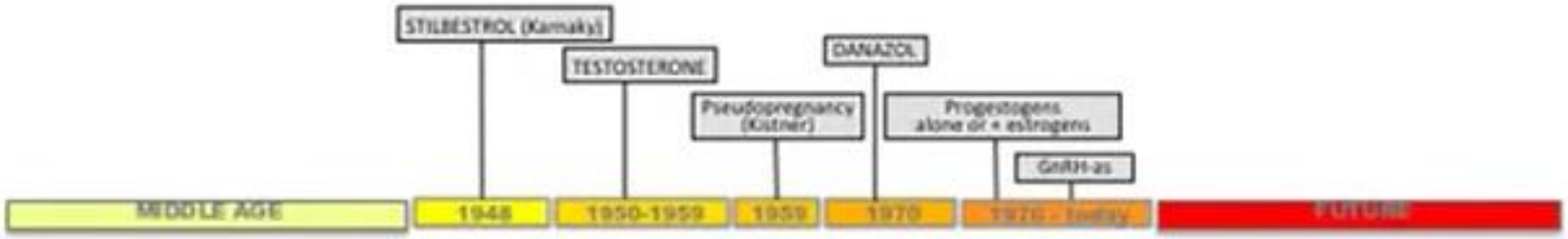
## Nuova frontiera, in via di sperimentazione clinica

**17 beta idrossisteroido-deidrogenasi** nuovo target da combattere??

- 17B-HSDs redox balance is relevant in endometrium
- 17B-HSD-1 is elevated in endometriosis and can be a drug target
- STS can decrease estrogen intracellularisation

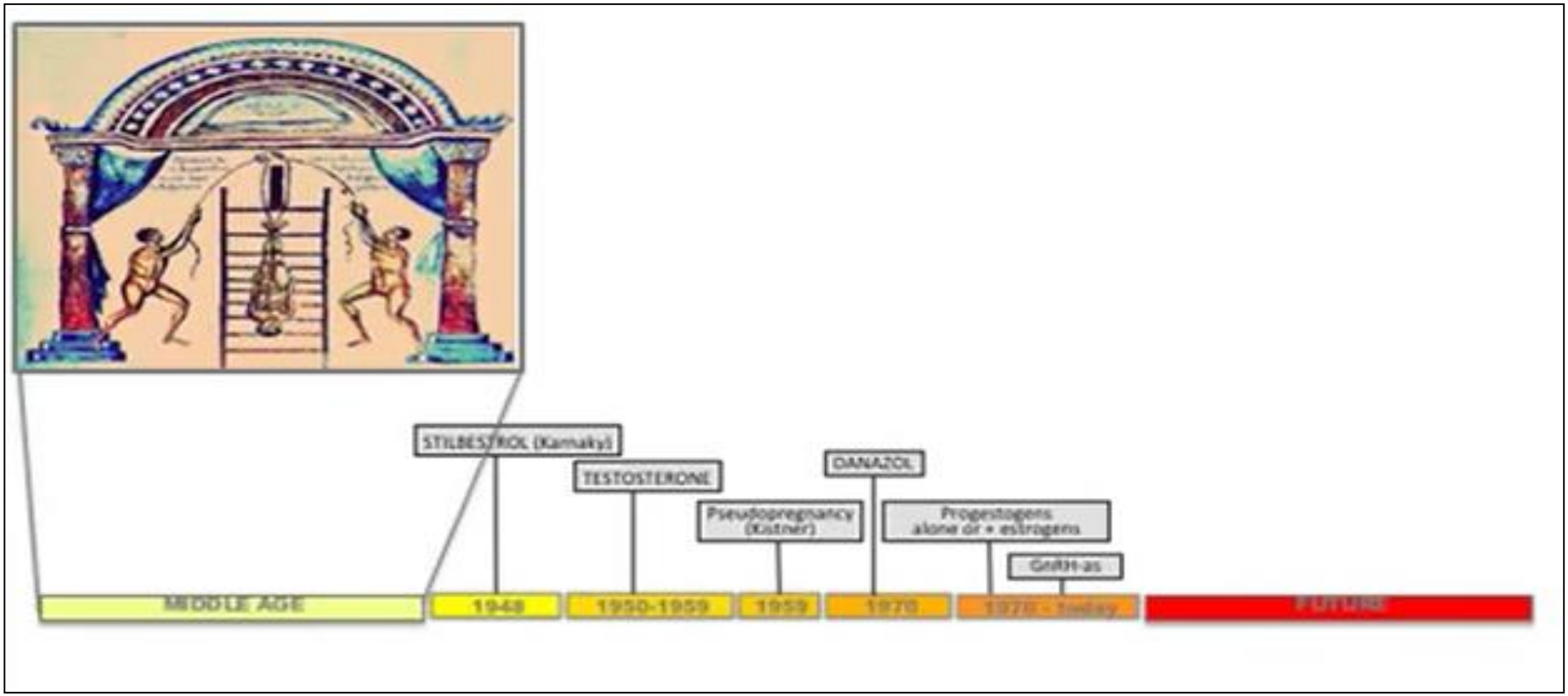


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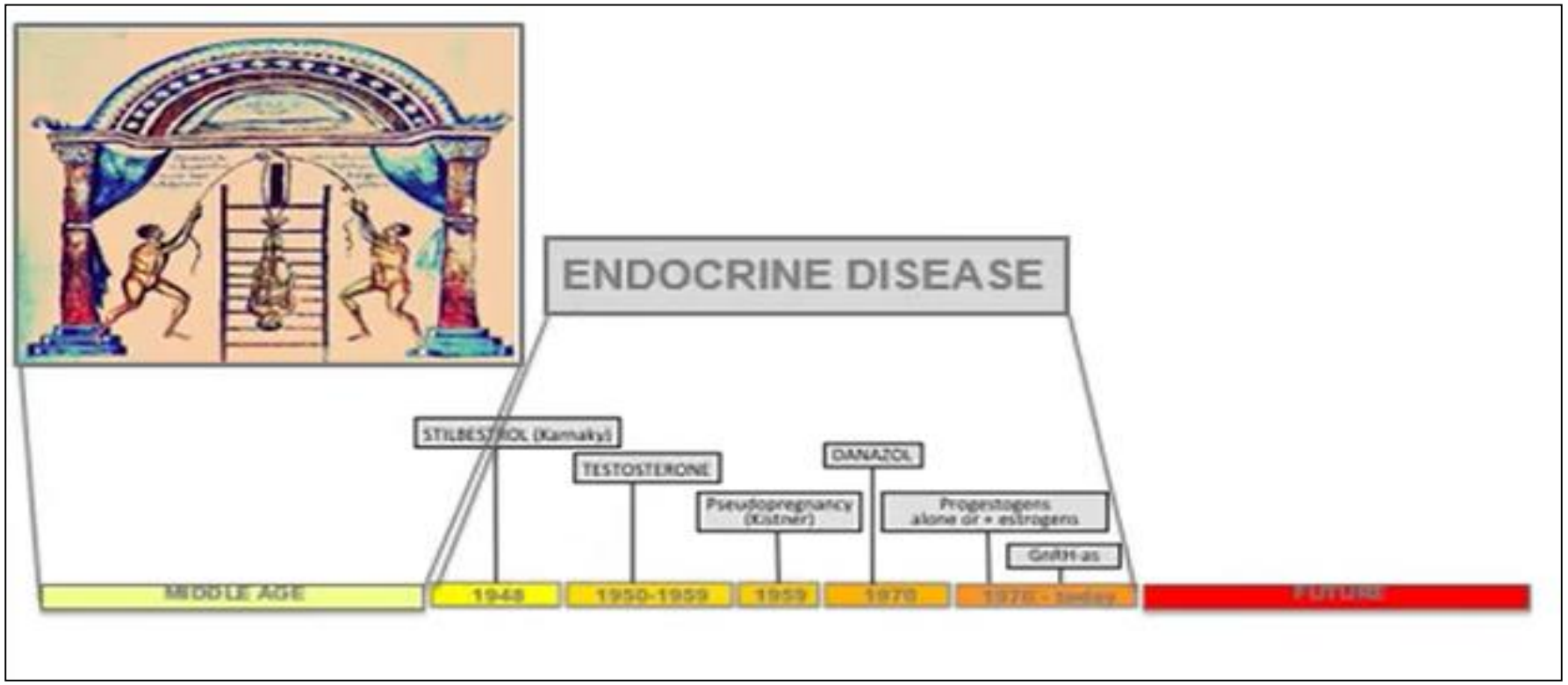

**THE WAY WE TREAT PATIENTS IS BASED ON OUR UNDERSTANDING**

# INTRACRINOLOGIA



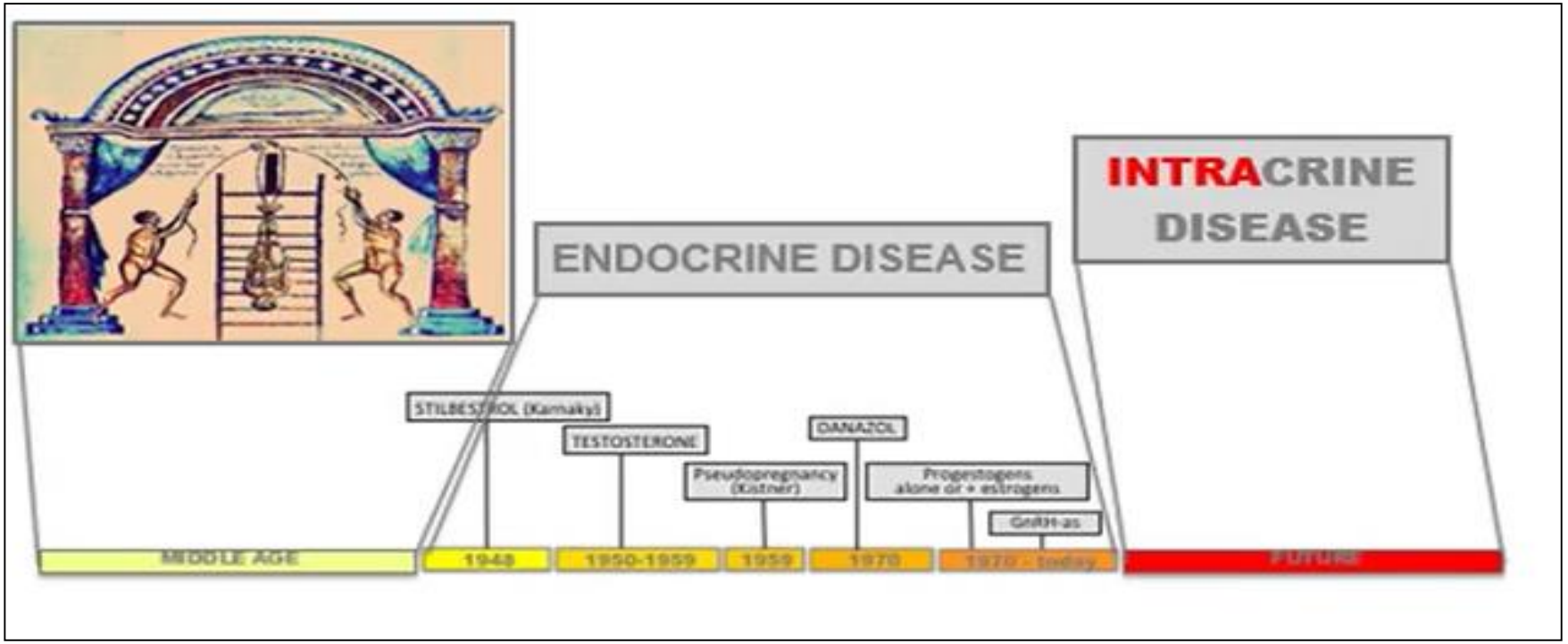

**THE WAY WE TREAT PATIENTS IS BASED ON OUR UNDERSTANDING**

# INTRACRINOLOGIA




**THE WAY WE TREAT PATIENTS IS BASED ON OUR UNDERSTANDING**

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**THE WAY WE TREAT PATIENTS IS BASED ON OUR UNDERSTANDING**

# Thank you for the attention!





# GRAZIE

VIEWS AND REVIEWS

# Introduction:
# Management of endometriosis: moving toward a problem-oriented and patient-centered approach

2015

Paolo Vercellini, M.D.
Department of Clinical Sciences and Community Health, Università degli Studi di Milano and Fondazione Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

## What's in a name?

Endometriosis is anything.

It may be considered a histologic diagnosis,

a disease of the female genital apparatus,

a disorder that manifests itself under very different forms, from a few superficial endometrial implants to infiltrating lesions involving several organs with loss of function.

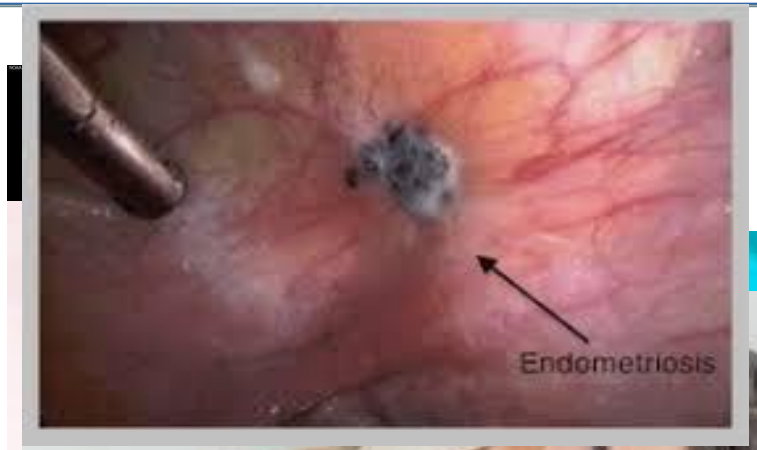
Endometriosis may be asymptomatic or be associated with pain so severe that it greatly limits health-related quality of life.

Endometriosis may allow natural conception or impede reproduction forever.

Endometriosis may be selflimiting or require repeated surgical procedures and prolonged medical treatments.

Endometriosis may afflict a woman for a limited period of time or until menopause ensues.

**Therefore, different clinical conditions require specific and sometimes very different therapeutic approaches.**








VIEWS AND REVIEWS

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