2° ORNELLA SIZZI
Women's Surgeons Day
Benign Uterine Pathologies and Endometriosis
Rome,June 22,2019

ADOLESCENT ENDOMETRIOSIS

ANASTASIA USSIA MD
ROME,ITALY

GRUPPO ITALO BELGA FOR ENDOMETRIOSIS
AND ADVANCED
PELVIC SURGERY
WWW.GYNSURGERY.ORG
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ENDOMETRIOSIS IN THE ADOLESCENT

- What do we know about endo in adolescent
- What is the pathophysiology and natural history ?

When to do a clinical exam - ultrasound ?

- If negative
- If endometrioma
- If deep endometriosis
- When to start treatment : medical or laparoscopy & surgery
- What are the benefits and risks?

Sampson's Theory is today historical speculation

Whether considered as retrograde menstruation, as stem cells, as pale cells……..

- Does not explain metaplasia
- Does not explain progression to typical, cystic or deep endometriosis

- Cannot explain hereditary aspect
- Is incompatible with clonal aspect
- Does not explain effect of dioxin, radiation etc;

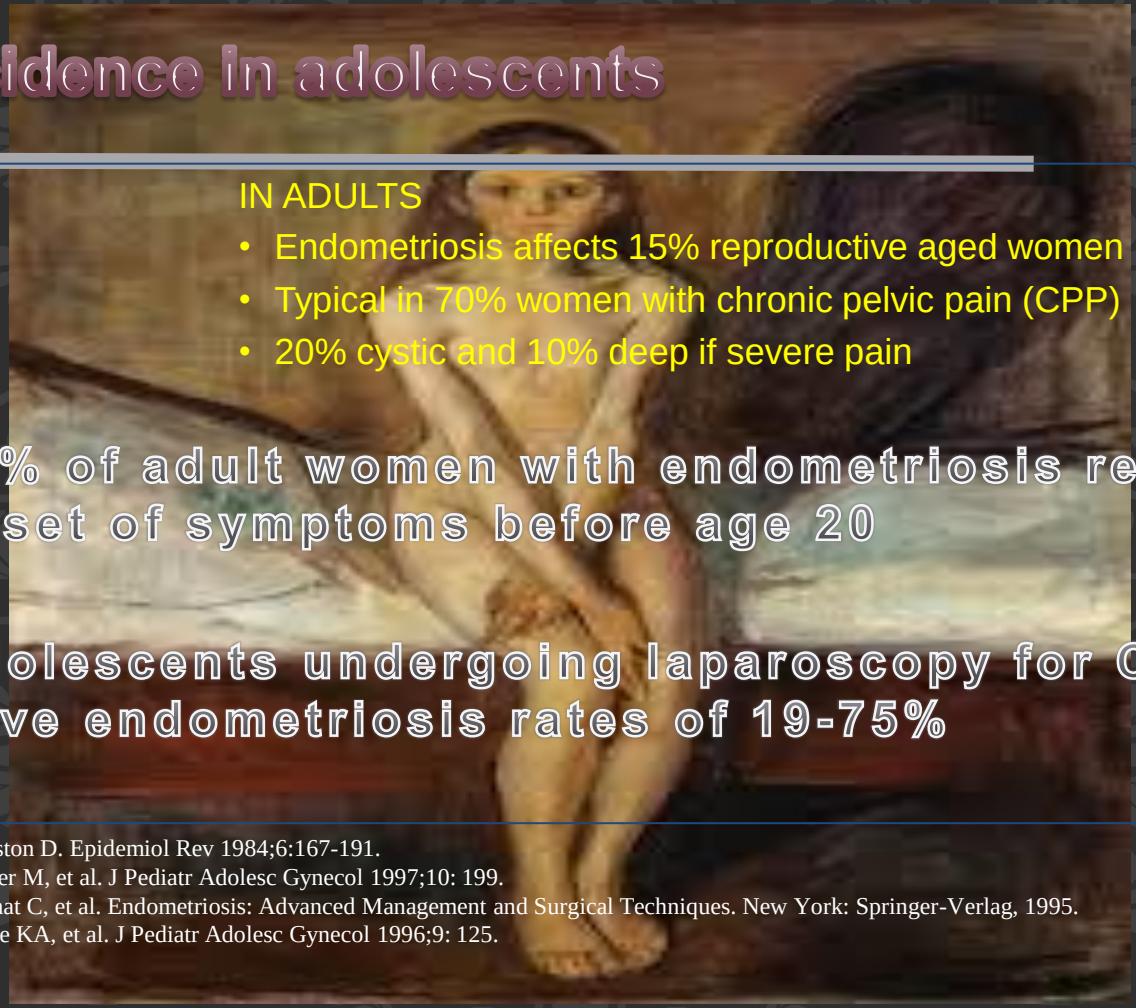
THE ISSUE

"Doctors just kept on telling me it was normal..."

"It is terrible to watch your child in pain
and feel completely helpless to her."

"*I was evaluated for lactose intolerance,
Crohn's disease, sexual abuse,
sexually transmitted diseases... everything .....
except endometriosis.*"

Incidence in adolescents



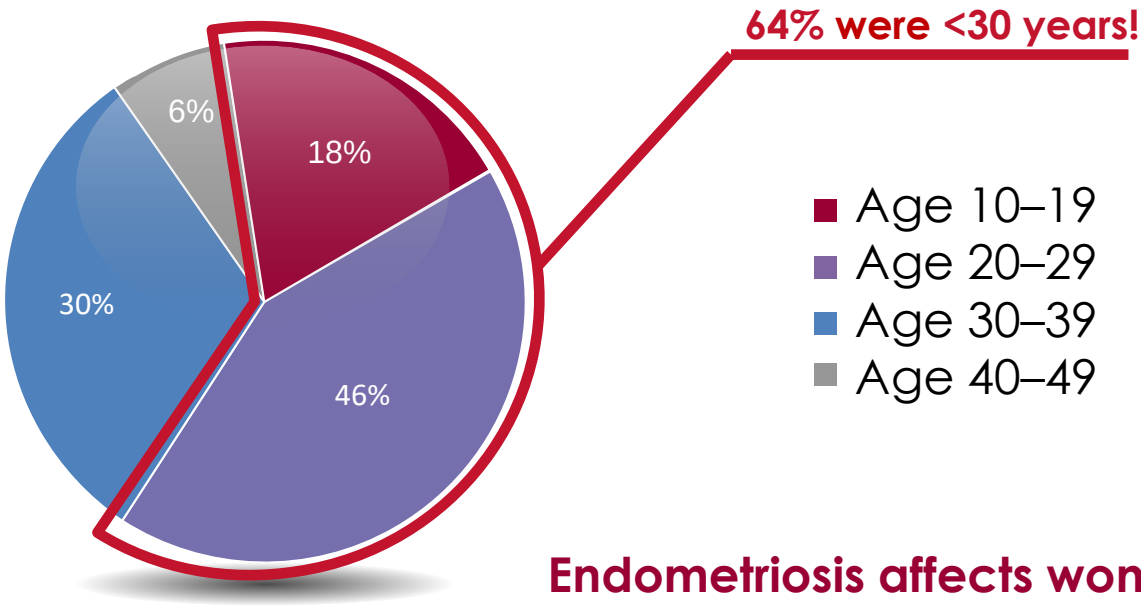
IN ADULTS

- Endometriosis affects 15% reproductive aged women
- Typical in 70% women with chronic pelvic pain (CPP)
- 20% cystic and 10% deep if severe pain

- 66% of adult women with endometriosis report onset of symptoms before age 20
- Adolescents undergoing laparoscopy for CPP have endometriosis rates of 19-75%

Houston D. Epidemiol Rev 1984;6:167-191.
Laufer M, et al. J Pediatr Adolesc Gynecol 1997;10: 199.
Nezhat C, et al. Endometriosis: Advanced Management and Surgical Techniques. New York: Springer-Verlag, 1995.
Reese KA, et al. J Pediatr Adolesc Gynecol 1996;9: 125.

Age of endometriosis symptoms



Endometriosis affects women during their prime years!

Nnoaham et al, Fertil Steril 2011

Severity of endometriosis in adolescents with chronic pelvic pain (publications 2000-2013)

	Number	Age	Stage I	Stage II	Stage III	Stage IV
Bai (2002)	39	14-21	10%	44%	**28%**	**18%**
Ventolini (2005)	28	12-18	14%	39%	**43%**	**4%**
Vicino (2010)	38	15-21	18%	13%	**34%**	**34%**
Roman (2010)	20	14-20	40%	45%	**5%**	**10%**
Yang (2012)	63	12-20	8%	3%	**52%**	**37%**

Adolescent endometriosis - RECURRENCE

Study	Nb	Diagn	duration	findings	age
Tandol et al 2011	57	Biopsy	2000-2005	Recurrence 56%	≤21
Doyle et al 2009	90	Visual	1995-2007	Progression: 10% Persistent: 70 %	12 24
Yeung et al 2011	20	Biopsy	1999-2007	47.1% recurrence symptoms No endometriosis	12 19
Audebert et al 2015	50	visual/biopsy	1998-2013	23 % resolution 34% recurrence of pain 50 % recurrence/new	12 19

Adolescent Endometriosis
Incidence ovarian endometrioma and DE

Table I. Incidence of Ovarian Endometrioma and Deep or Rectovaginal Endometriosis in Adolescents or Young Women With Advanced Stage Pelvic Endometriosis.

Normal GT	Age (years)	Stage III-IV (n)	Endometrioma	Deep or RV
Vicino[38]	≤ 21	26	26 (100%)	0 (0%)
Yang[39]	≤ 21	48	40 (83%)	18 (40%)
Lee[40]	≤ 20	35	35 (100%)	0 (0%)
Smorgick[41]	≤ 22	20	14 (70%)	1 (5%)
Audebert[42]	12-19	24	18 (75%)	6 (25%)
GT obstruction	**Age**	**Number**	**Endometrioma**	**Deep or RV**
Yang[39]	≤21	15	14 (93%)	2 (13%)
Tong[35]				
Complete	< 20	10	10 (100%)	0 (0%)
Incomplete	< 37	8	8 (100%)	0 (0%)

Abbreviations: GT: genital tract; Deep or RV: deep or rectovaginal endometriosis.

I. Brosens et al Reprod Sciences 2016, Vol. 23(10) 1282-1288

COMPARISON ADOLESCENT VERSUS ADULT

ADOLESCENT ENDOMETRIOSIS		ADULT ENDOMETRIOSIS	
SYMPTOMS :	-Severe Primary Dysmenorrhea -frequently resistant to	**SYMPTOMS**	-Moderate Dysmenorrhea
LAPAROSCOPY:	rASRM I-II+++ 77% rASRM III-IV 32%	**LAPAROSCOPY**	rASRM STAGE I/II + RASRM STAGE III/IV+++
PERITONEAL	Red , clear or vascular imp Minimal fibrosis	**PERITONEAL**	-Black intraperitoneal implants White fibrotic
OVARY:	Endometrioma Adhesions +++ DIE +	**OVARY**	Endometrioma adhesion+++ Fibrosis+++ Adenomayotic lesion DIE+++
CYSTOSCOPY	Neoangiogenesis+++ Inflammation+++ Endometrial implants + White delineation	**CYSTOSCOPY**	Neoangiogenesis+ Iinflammation+ Endometrial implants+ White brown delineation
CONCOMITANT PATHOLOGY	Mullerian anomalies	**CONCOMITANT PATHOLOGY**	Rectal and bladder endometriosis Adenomyosis

STUDY OBJECTIVE

To describe the prevalence of endometriosis, time to diagnosis, and referral patterns of adolescent girls with pelvic pain

Perper MM, Nezhat F, Goldstein H, Nezhat CH, Nezhat C. Dysmenorrhea is related to the number of implants in endometriosis patients. Fertil Steril. 1995 Mar;63(3):500-3.

RESULTS: MULTIPLE DOCTORS OVER YEARS

Mean time from onset of symptoms to diagnosis of endometriosis was 22.8 months (range 1-132 months)

Average number of physicians seen for evaluation of pelvic pain was 2.7 physicians (range 0-12)

Prior to referral to our practice, 60% saw one or more gynecologists, 36% saw a gastroenterologist, 16% saw an internist, 16% saw a urologist, 8% saw a general surgeon

Other specialists seen prior to the diagnosis of endometriosis include: pediatric surgery, infectious disease, pain specialist, psychiatry and orthopedic surgery

RESULTS: OTHER DIAGNOSES

Prior to the diagnosis of endometriosis other diagnoses considered included:

PID (12%)

irritable bowel syndrome (12%)

ovarian cysts (12%)

Crohn's Disease (8%)

appendicitis (8%)

orthopedic issue (8%)

Intersitial cystitis (8%)

renal colic (4%)

CONCLUSIONS

Adolescents with pelvic pain and no other radiologic evidence of pathology have a high rate of endometriosis.

Incorrect diagnoses continue to result in delays in diagnosis and management, as well as evaluation by various subspecialists.

Endometriosis should be considered in these patients and this population should have timely referral to a gynecologist who is experienced with laparoscopic diagnosis of endometriosis.

human reproduction

OPINION

Endometriosis in adolescents is a hidden, progressive and severe disease that deserves attention, not just compassion

I. Brosens[1,*], S. Gordts[1], and G. Benagiano[2]

ABSTRACT: Endometriosis in the adolescent has, in recent years, been discovered to be a challenging problem in gynaecology. Although the pain may start at a young age, even before the onset of menstruation, the diagnosis by laparoscopy is almost always postponed for several years, by which time destructive lesions have affected the tubo-ovarian structures and severely compromised fecundability. Several factors may play a role, but one important reason for this disease progression is likely to be the delay in diagnosis. Therefore, transvaginal ultrasounds and transvaginal access with a less invasive needle endoscopy are recommended for exploration of the pelvis, diagnosis of endometriosis and treatment at an early stage before severe lesions develop.

Key words: endometriosis / adolescence / adult / pathogenesis / laparoscopy

Adolescent endometriosis

Pathogenesis

Clinical aspects

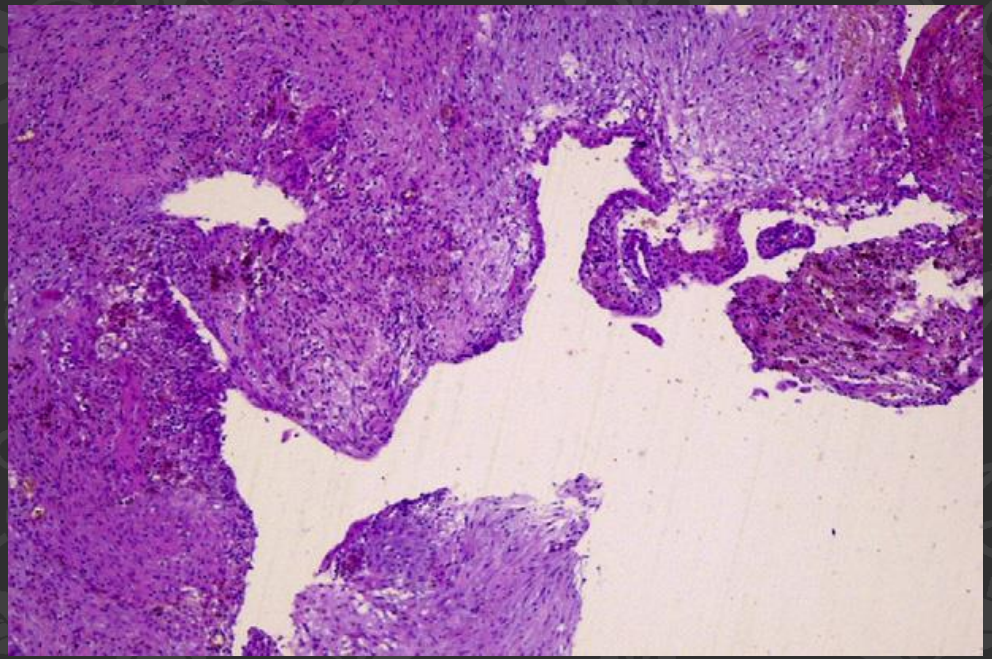
Treatment

Conclusions

FACT : Onset can beshortly before Menarche

Ovarian endometrioma in a premenarcheal girl Gogacz 2013

- An 11-y-old girl underwent an emergency operation for left ovarian endometrioma.
- Menarche occurred spontaneously 6 months later.



Pathophysiology : Sampson Theory

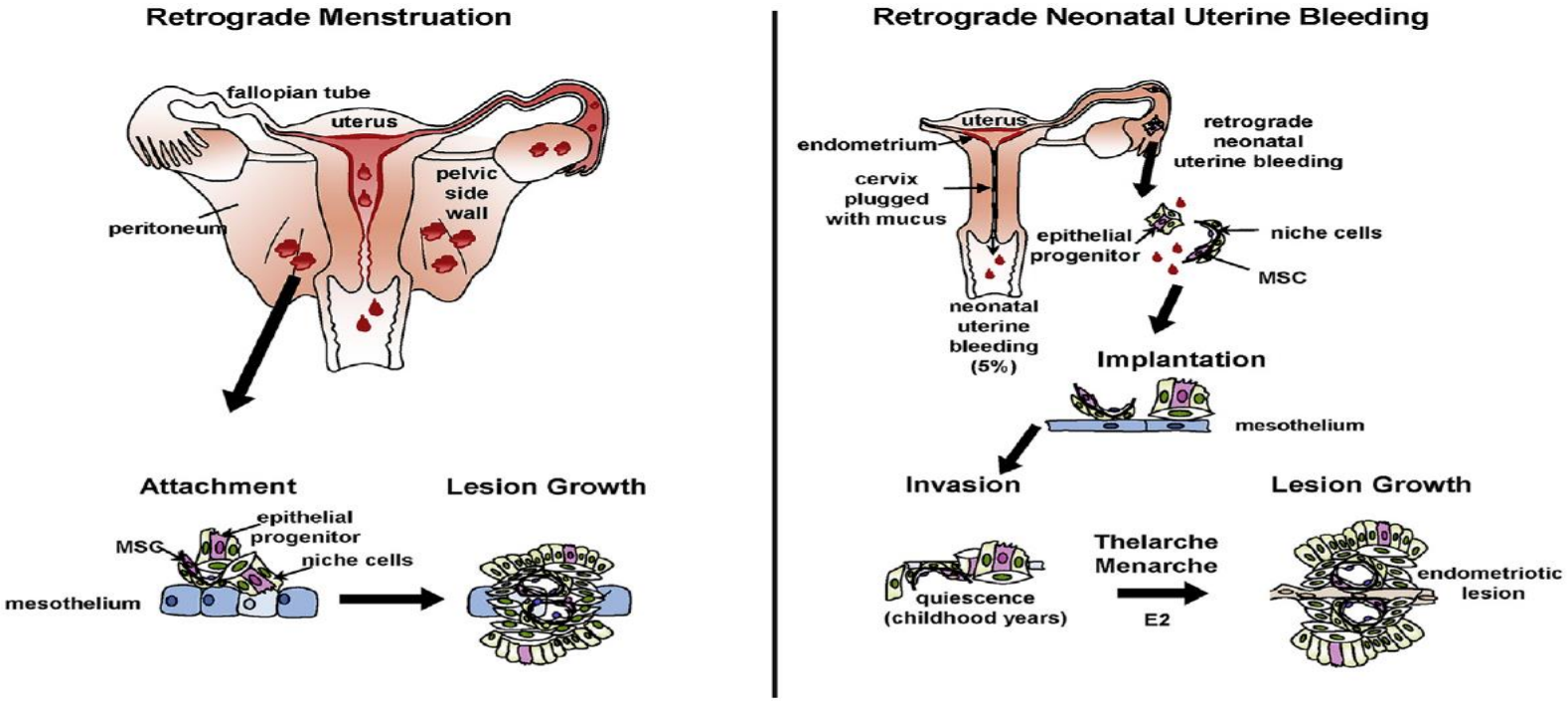


Fig. 2. Retrograde menstruation of endometrial stem/progenitor cells. A. Retrograde menstruation; menstrual debris flows backward through the fallopian tubes and enters the peritoneal cavity where it attaches to pelvic organs and the pelvic side wall. Fragments containing endometrial mesenchymal stem cells (eMSCs) and endometrial epithelial progenitor cells attach to the mesothelium and initiate lesion growth. B. Retrograde neonatal uterine bleeding; At birth, differentiated neonatal endometrium sheds in response to withdrawal of maternal progesterone in 5% of infants. Flow of these fragments through the vagina is hindered by thick cervical mucus in a long cervix. It is postulated that fragments flow backward through the fallopian tubes and invade the mesothelium where they remain dormant until increasing estrogen levels associated with thelarche and menarche reactivate neonatal eMSCs and epithelial progenitors to initiate growth of endometriotic lesions. Adapted from Ref. [58] with permission from Oxford Univeristy Press.

Neonatal Uterine Bleeding (NUB)

NUB	Incidence	Reference
Visible	4.7%	Levy (1964)
	5.3%	Kaiser and Grässel (1974)
	3.3%	Huber (1976)
Occult (Hb test)	61.3%	Kaiser and Grässel (1974)
	25.4%	Huber (1976)

Neonatal Uterine Bleeding (NUB)

NUB Increased incidence in

pre-eclampsia
post maturity
blood incompatibility
low birth weight (<2500 kg)

Levy et al (1963)

Mechanism : ??
Intra uterine hypoxia seems to accelerate maturation of fetal endometrium

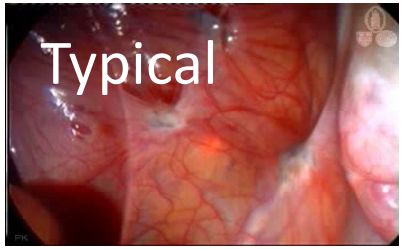
Pathogenesis of endometriosis: the genetic/epigenetic theory

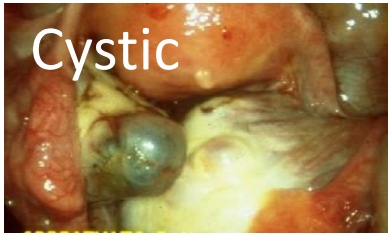
Philippe R. Koninckx, M.D., Ph.D.,[a,b,c,d] Anastasia Ussia, M.D.,[b,d] Leila Adamyan, M.D., Ph.D.,[e] Arnaud Wattiez, M.D., Ph.D.,[c,f] Victor Gomel, M.D.,[g] and Dan C. Martin, M.D.[h]

Fertil Steril, February 2019

Observations on endometriosis

"Endometrium like glands + stroma outside the uterus"





PK, AU, LA, AW, VG, DM Fertil steril, 2019

Clinical Observations on endometriosis

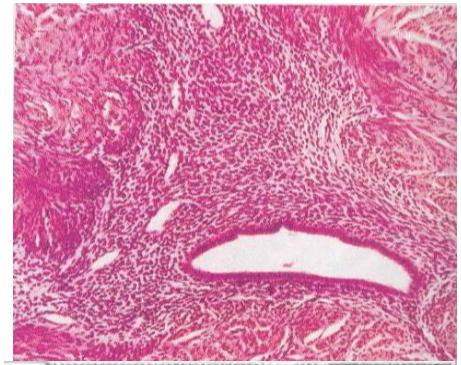
1. Variable appearance (subtle-typical-cystic-deep)
2. Occurs also in women without endometrium and in men
3. An hereditary disease and predisposition
4. Natural history
   - most subtle lesions do not progress
   - most typical-cystic-deep lesions are not progressive after diagnosis
   - most typical-cystic-deep lesions are not recurrent after surgery
5. Epidemiology of endometriosis
6. An heterogeneous disease
7. Endometriosis is associated with
   - Pain and infertility
   - Adenomyosis
   - Changes in plasma
   - Changes in peritoneal fluid
   - Changes in endometrium
   - Changes in pregnancy outcome
   - Pelvic infections
   - Cancer risk
   - Total body radiation and dioxin intake

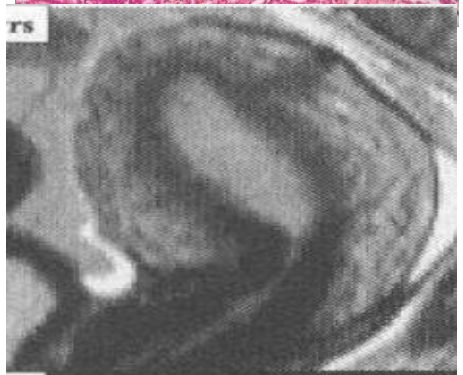
The endometriosis lesion

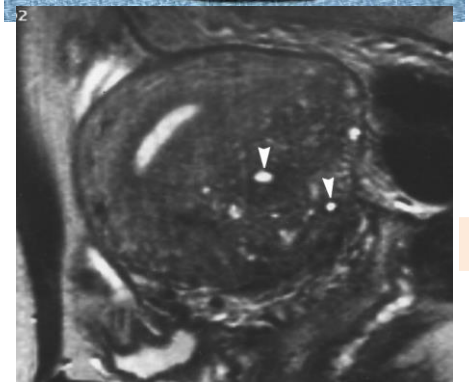
8. Clonal
9. Altered biology: estrogen production – progesterone resistance etc.

Observations on adenomyosis & endometriosis

"Endometrium like glands + stroma outside the uterus"







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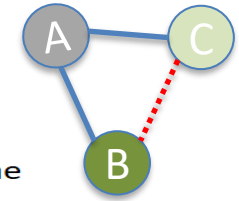

The endometriosis lesion

8. Clonal
9. Altered biology: estrogen production – progesterone resistance etc.

In men and in women without an uterus
An hereditary disease

- Familial clustering — Humans: Kennedy et al (1995) J Assist Reprod Genet 12, Rhesus: Hadfield et al (1997) Hum Reprod Update 3, 109
- Twin studies : MZ >> DZ — Moen (1994) Acta Obstet Gynecol Scand 73, 59; Hadfield et al (1997) Fertil Steril 68, 941; Treloar et al (1999) Fertil Steril 71, 701
- Heredity
  - symptom onset age in non-twin sisters — Kennedy et al (1996) Hum Reprod 11, 101
  - 6-9x increased prevalence in 1st degree relatives — Simpson et al (1980) Am J Obstet Gynecol 137, 327; Coxhead & Thomas (1993) J Obstet Gynaecol 13, 42; Moen & Magnus (1993) Acta Obstet Gynecol Scand 72, 560
  - 15% prevalence in 1st degree relatives (using MRI) — Kennedy et al (1998) Lancet 352, 1440

- Genome wide scanning and linkage analysis
  - 5-15 loci
  - All in regulatory regions

Clonality in endometriosis

Genetic damage to single progenitor cell

Monoclonal neoplasm

- Cystic ovarian endometriosis
  - Jimbo et al (1997) *Am J Pathol* 150, 1173 ;21 samples from 11 endometriomas 21/21 samples monoclonal
  - Tamura et al (1998) *Lab Invest* 78, 213 ;25 epithelial cells from 25 archival endometriomas ; Controls = 25 matched ovarian stroma tissue ; Marker = X-linked *PGK* gene 10/25 samples informative (all 10 monoclonal)
- Deep endometriosis *Mayr D, Amann G, Siefert C, Diebold J, Anderegg B. A clonal analysis of lasermicrodissected tissue. FASEB J 2003;17:693–5.*
- Several typical lesions
  - Wu, Y., et al. (2003). "Resolution of clonal origins for endometriotic lesions using laser capture microdissection and the human androgen receptor (HUMARA) assay." Fertil. Steril 79 Suppl 1: 710-717.
  - Mayr, D., et al. (2003). "Does endometriosis really have premalignant potential? A clonal analysis of laser-microdissected tissue." FASEB J 17(6): 693-695.

Heterogeneity of lesions

Bowel complications of deep endometriosis during pregnancy or in vitro fertilization

António Setúbal, M.D.,[a] Zacharoula Sidiropoulou, M.D., M.Sc.,[b] Mariana Torgal, M.D.,[c] Ester Casal, M.D.,[c] Carlos Lourenço, M.D.,[b] and Philippe Koninckx, M.D.[d]

Vigano P, Corti L, Berlanda N. Beyond infertility: obstetrical and postpartum complications associated with endometriosis and adenomyosis. Fertil Steril. 2015;104:802-812.

Sampson's Theory is today historical speculation

Whether considered as retrograde menstruation, as stem cells, as pale cells ……..

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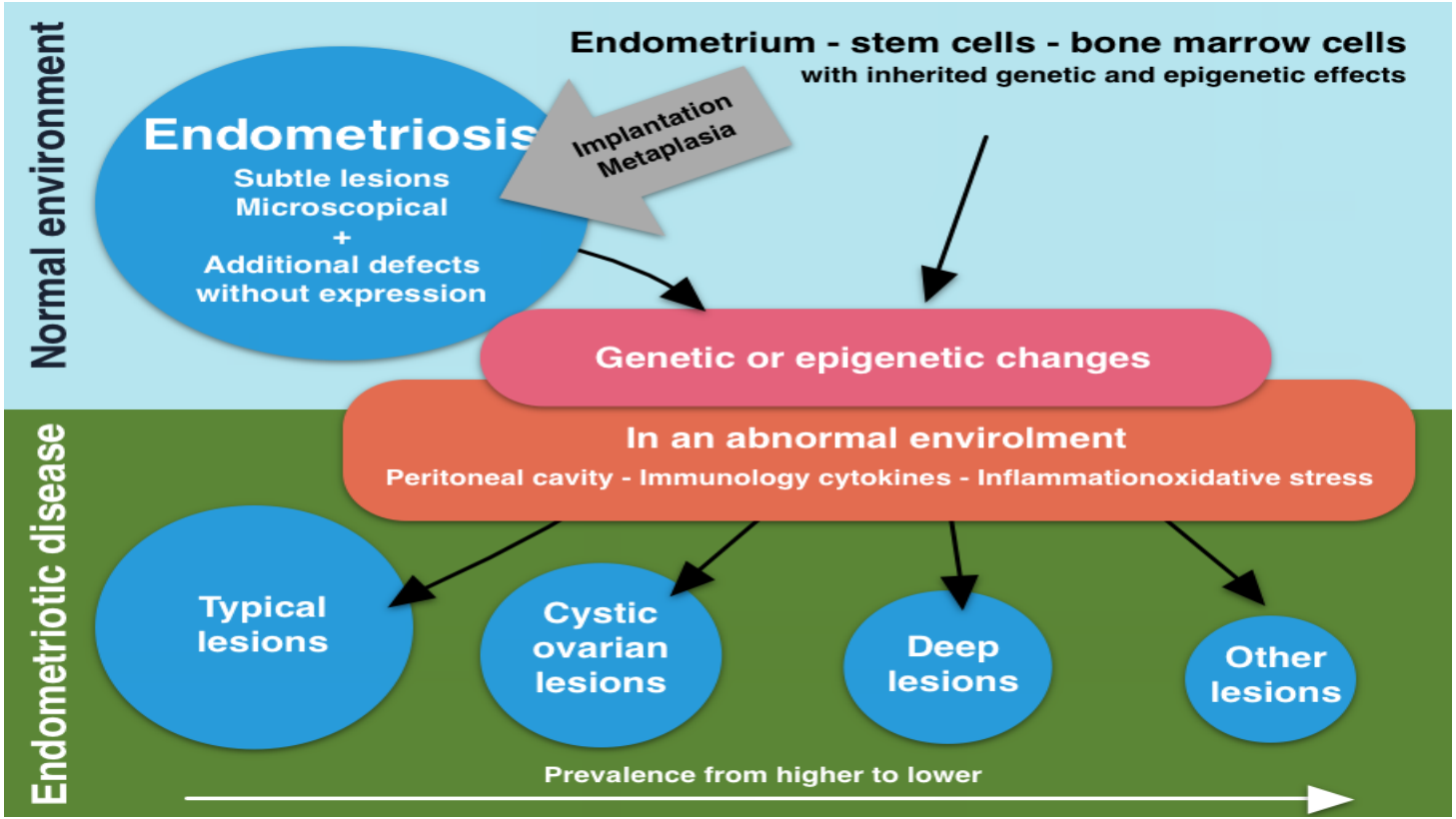
The genetic epigenetic theory



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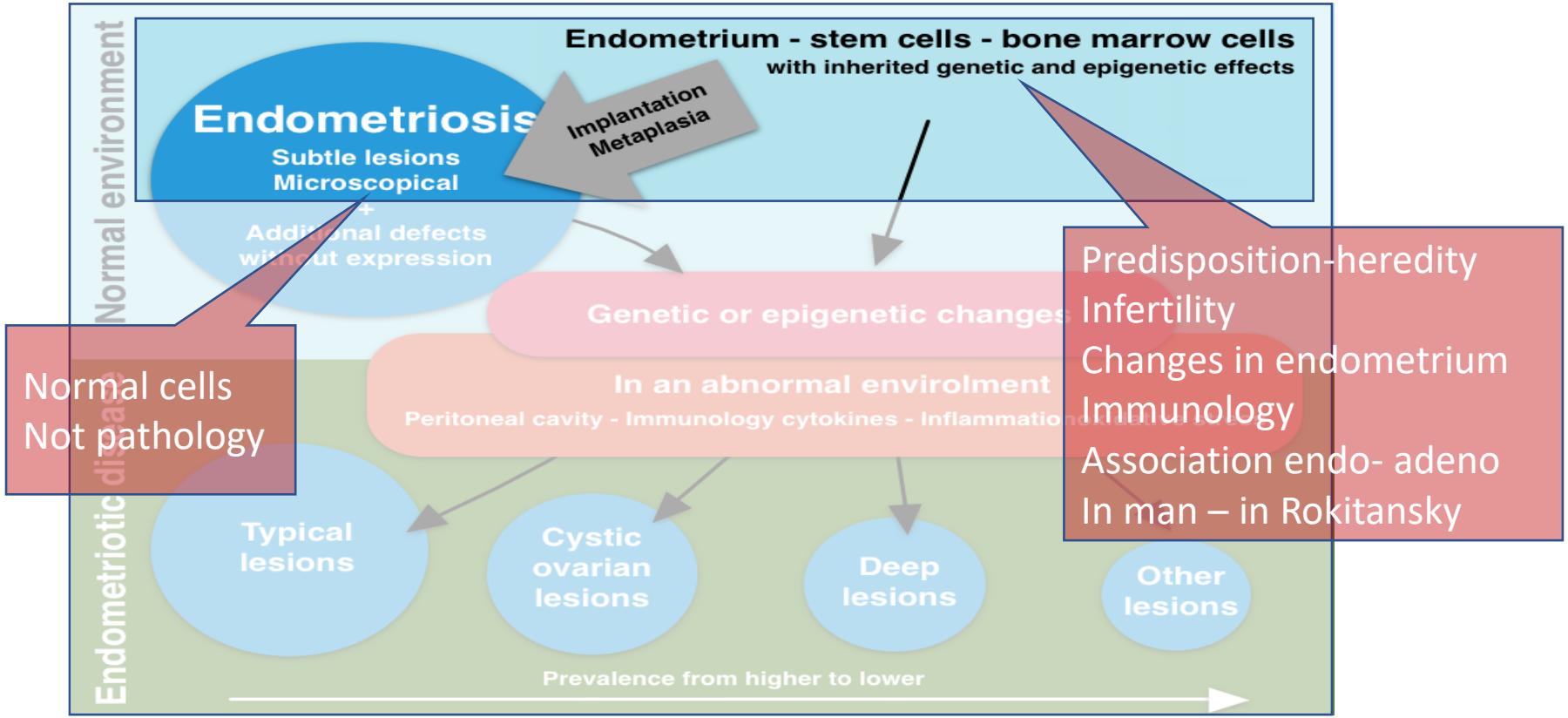
The original cell



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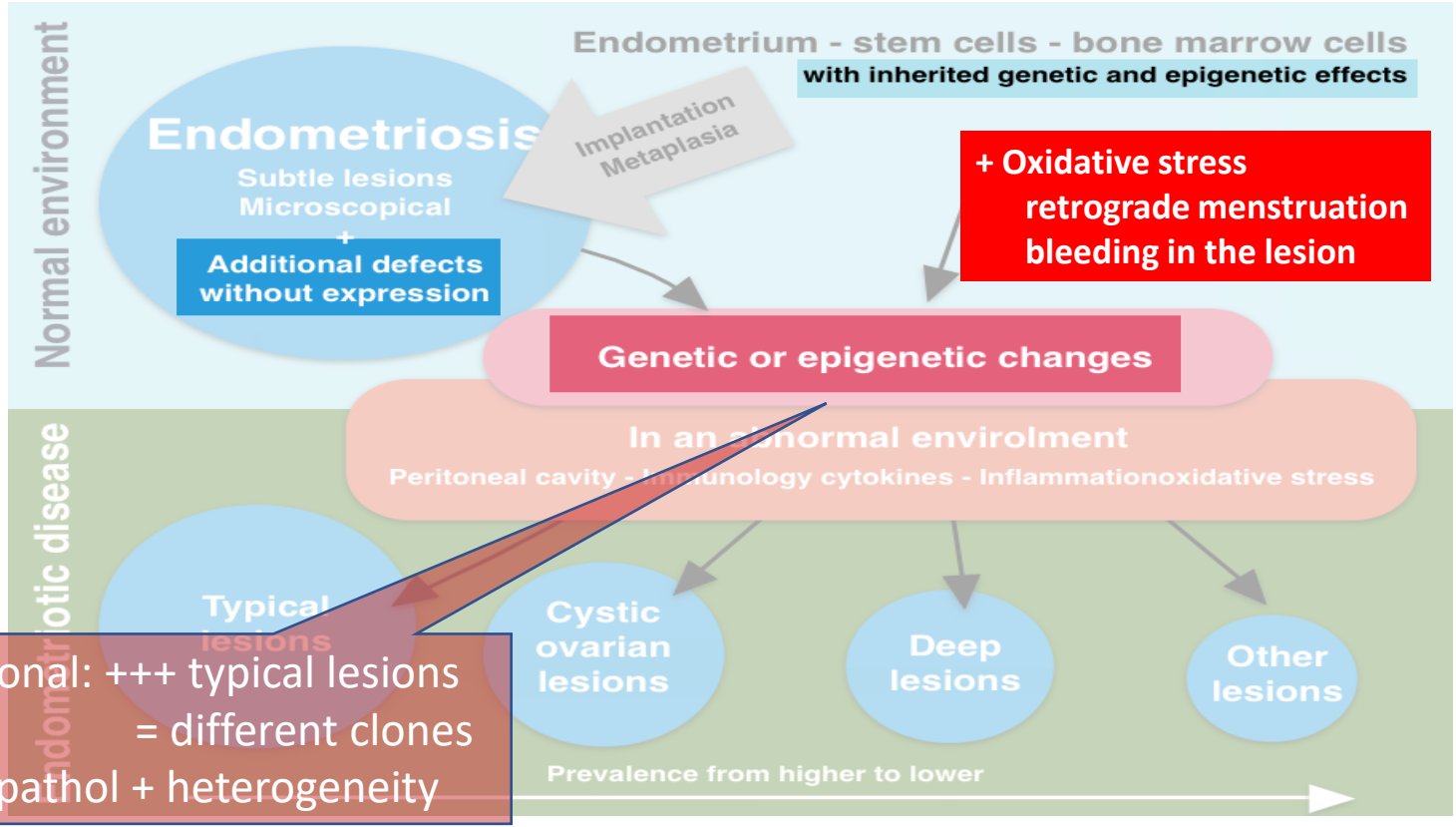
Cumulative incidents



Clonal: +++ typical lesions
= different clones
4 pathol + heterogeneity

PK, AU, LA, AW, VG, DM Fertil Steril, 2019

The cumulative genetic – epigenetic incidents

Inherited defects

- Endometriosis risk
- Endometrium
- Infertility
- pregnancy
- immunology

+1 +1 +1

- Radiation
- Pollution
- Oxidative stress
  - Blood
- infection

Endometriosis lesion

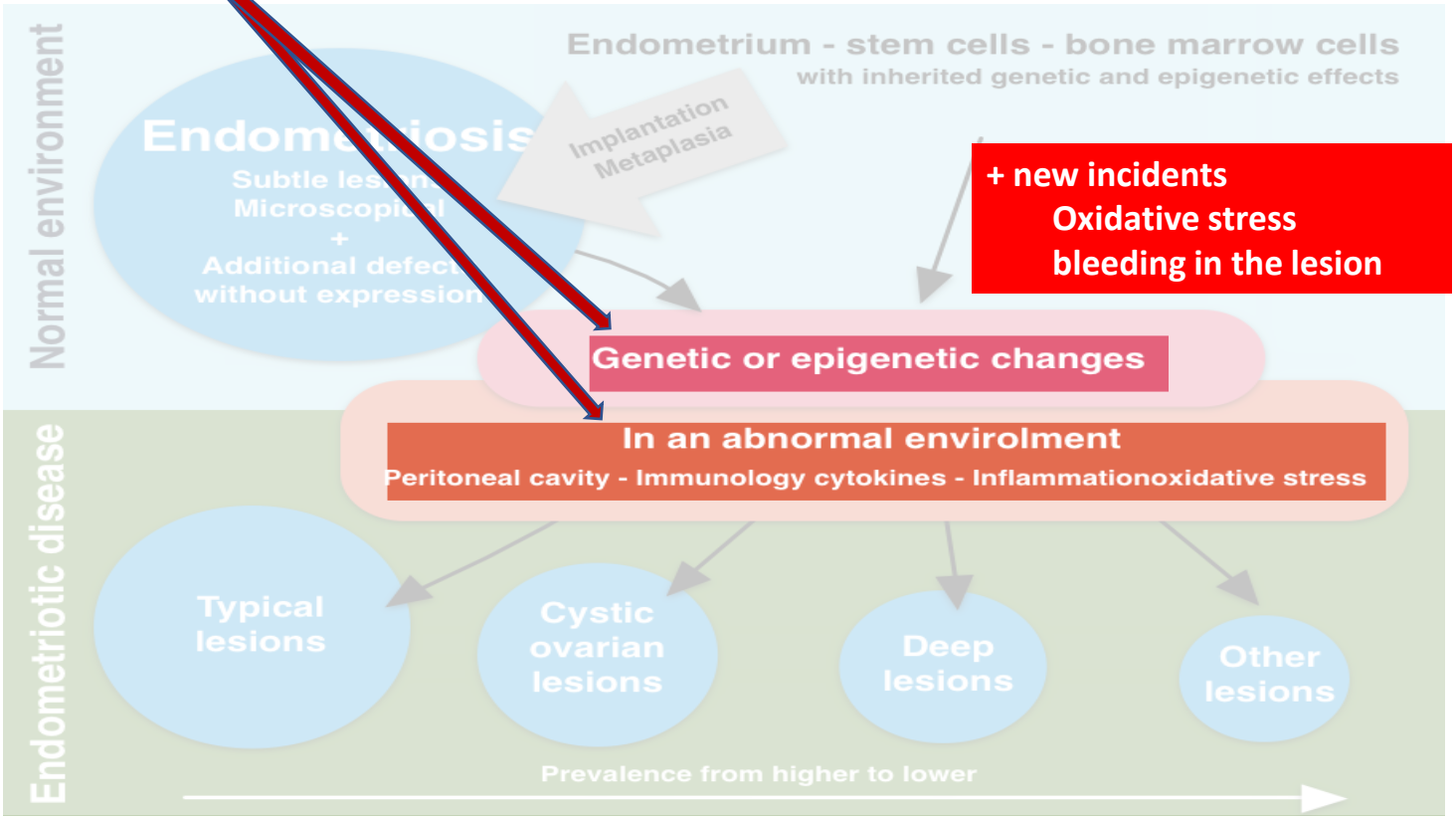
With a specific set of defects

variability

types of endometriosis
estrogen production
progesterone resistance
ReTIAR - bleeding

recurrence risk

Growth of the lesions



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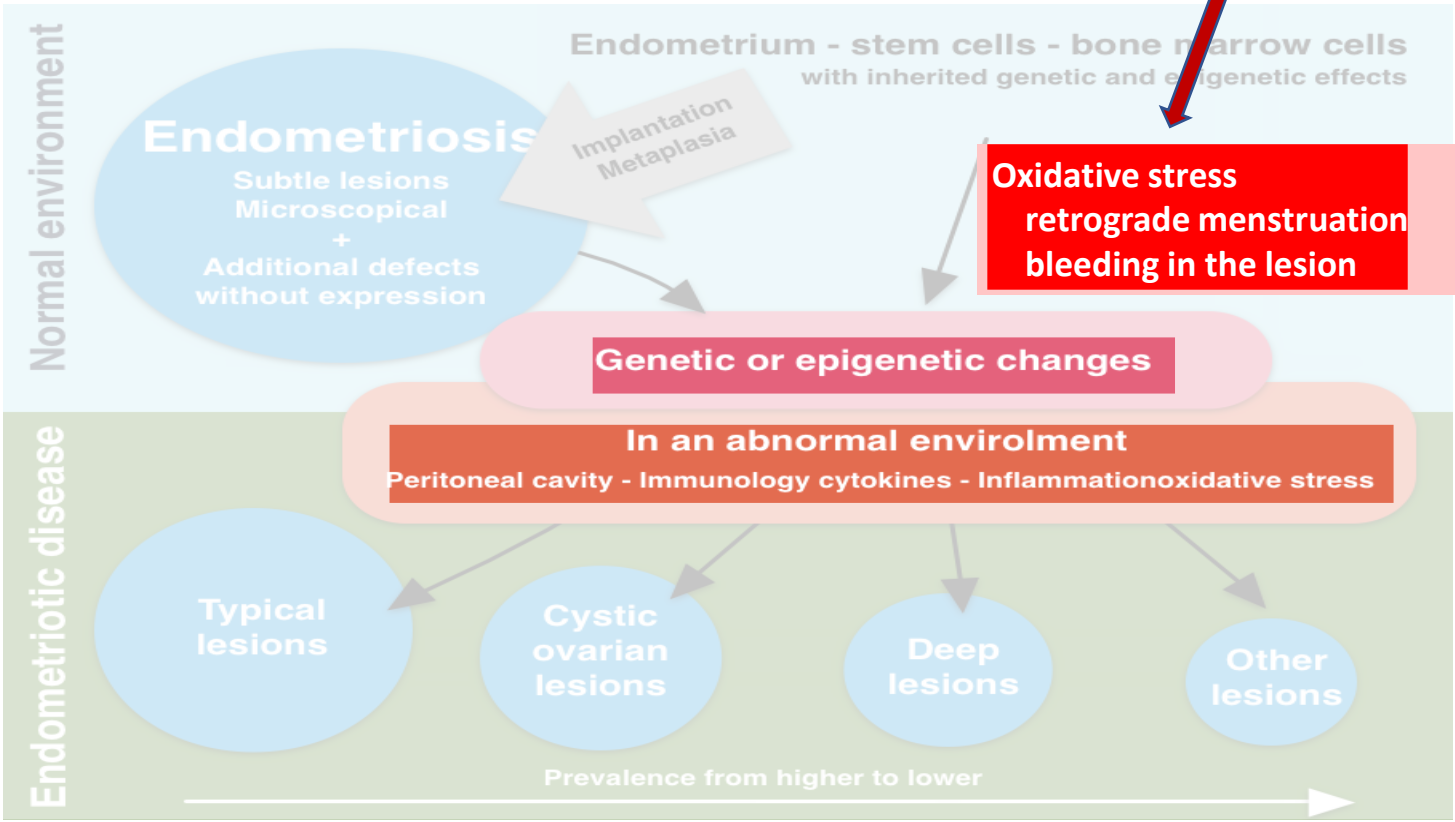
Recurrences

New lesions



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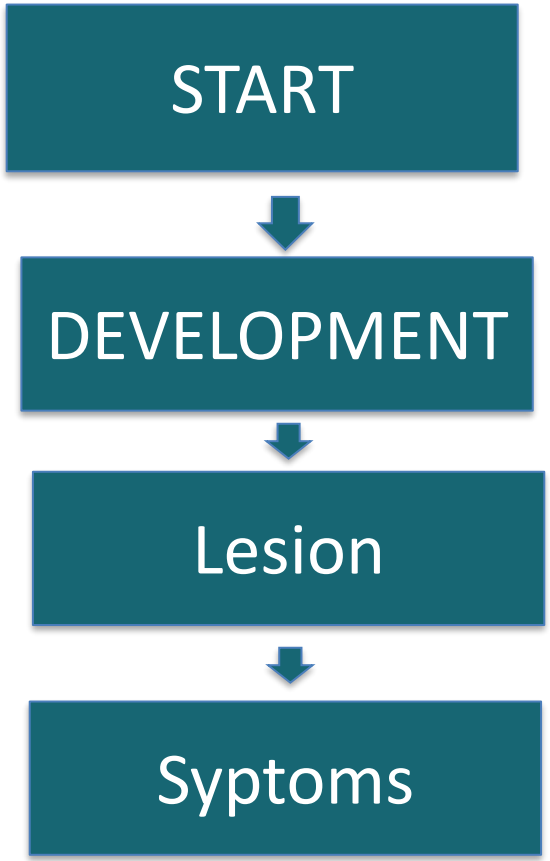
Importance of Pathophysiology



Genetic –epigenetic incident
Driven by … oxidative stress, environment, infection
In an abnormal environment without JZ

- Prevention & Prevention of recurrences

- Medical therapy and heterogeneity
- Completeness-radicality of Surgery

Prevention of endometriosis - incidents

- **Reduce pollution**
  - **Investigate deep lesions**

Gynecol Surg (2016) 13:457–467
DOI 10.1007/s10397-016-0970-4

REVIEW ARTICLE

Epidemiology of subtle, typical, cystic, and deep endometriosis: a systematic review

Philippe R. Koninckx[1,2,3,4,5,6] · Anastasia Ussia[3,5] · Jörg Keckstein[7,8] · Arnaud Wattiez[9] · Leila Adamyan[4]

- **Prevention of oxidative stress**
  - **Less blood in peritoneal cavity and in the endometriosis**
    = no withdrawal bleeding eg continuous OC
    early surgery – no delay in diagnosis
  - **Anti-oxidants food intake**
  - **CO2 pneumoperitoneum**

- **Infection**

NATURAL HISTORY OF ADOLESCENT ENDOMETRIOSIS

- **Growth of endometriosis in adolescence**
  - No solid data but between onset and adult endometriosis growth must occur
  - Clinical observation suggests heterogeneity
    - In most women growth is self limiting : typical and deep are no longer progressive when diagnosed - mecahnism unknown
    - In some progression seems to continue
    - In some progression during pregnancy and under OC (?)
- **Pain**
  - Many women with deep endo report pain since menarche
  - Pain can increase progressively over time
  - In some women pain suddenly had become worse before first consultation
- **Infertility**
  - No data in adolescents since fertility is not an issue yet
  - Volume of cystic ovarian endo seems to increase over time
    - by repetitive bleeding ?
    - With increasing ovarian damage ?

In adolescents with endo symptoms

- Diagnosis
  - Can clinical exam and/or imaging prevent a diagnostic lap.
  - If not
- Treatment

- After treatment: Prevention of recurrences

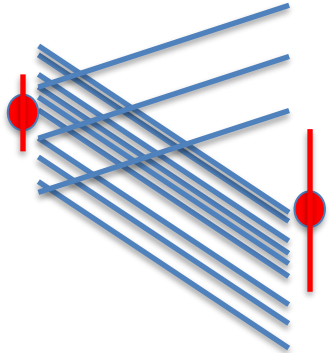
In adolescents with endo symptoms
The dilemma

- Avoid surgery
  - Avoid repeat surgery
  - Avoid adhesion
  - Avoid ovarian damage
- Therefore
  - Medical therapy
  - Risk of continued growth

- Early diagnosis & surgery
  - To avoid progression
  - To avoid infertility
- Risk
  - Repeat surgery

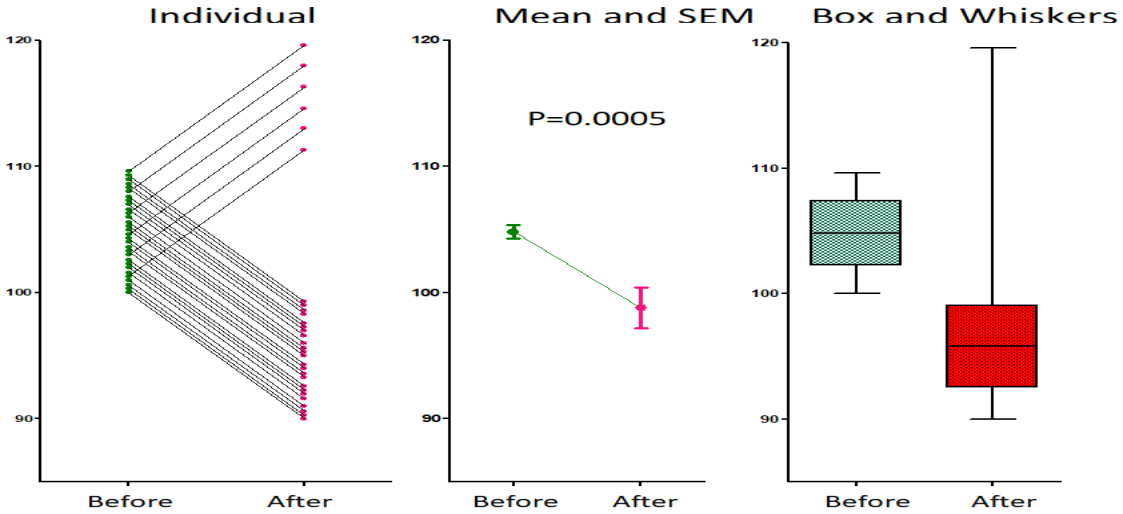
Heterogeneity = Individualisation of therapy

- **Individualisation of medical therapy**
  - **If no effect after 1-2 months = stop therapy**
- **In Nodules with 100% progesterone resistance , oestro progestins stimulate**
- **Surgery**
  - **No surgery in the absence of growth or symptoms**
  - **Delay of surgery and more ReTIAR is probably wrong**
  - **(Unclear what is disease versus surrounding metaplasia and fibrosis)**



Individualisation of therapy

- **Heterogeneity of lesions means that classical statistics are inappriopriate**
  - **Means and SD to evaluate therapy is wrong (basic assumptions are not met : an homogeneous normally distributed population)**
  - **We have to look at individual data**
  - **Guidelines have to be revised: only valid for the standard woman**



Impact on management

- We begin to understand
  - Heredity-Pregnancy-infertility
  - Blood and oxidative stress
  - Recurrence risk
- Endometriosis is a benign tumour
  - 5 different diseases
- Adolescent endometriosis
- Prevention
- Medical therapy
  - Heterogeneity of lesions
  - OC may stimulate some lesions
- A surgical disease
  - Subtle
  - Arguments to be less radical ?
  - Nerve pain at distance and nerve dissection
  - After surgery : Medical therapy to reduce bleeding and prevent recurrences

Pathogenesis of endometriosis: the genetic/epigenetic theory

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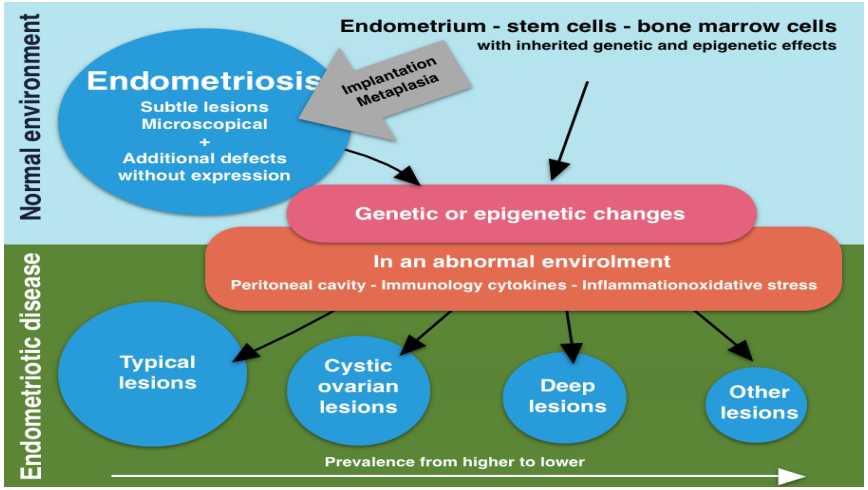


Clinical options

- **Considering that**
  - Only a laparoscopy can diagnose superficial endometriosis
  - Diagnostic absence of data about diagnostic accuracy of clinical exam and of ultrasound is unknown for pubertal deep endometriosis
  - Absence of data that medical treatment prevents progression in all women
- **Rule 1 A diagnostic laparoscopy - THC before starting treatment**
  - If treatment is necessary for severe pain or persisting severe pain under OC
  - Never start long term medical treatment without a diagnosis,
- **Rule 2 After diagnosis consider the treatment options**
  - Either complete surgery of typical, cystic and deep endometriosis
  - Either postpone surgery as long as possible and start with medical therapy
  - Or minimal surgery followed by medical therapy
- **Which evidence we have for each option ?**

Pro and cons of medical therapy

- **Pro**
  - Avoids surgery and its complications as ovarian damage
  - Avoids repetitive surgery
- **Contra**
  - No data that medical therapy prevents progression in all women
  - No data that medical therapy prevents ovarian damage

Considerations considering little evidence available

- Medical therapy is based on Sampson's theory
  - Endometriosis is progressive and recurrent by definition
  - Subtle lesions are important
- Endometriotic disease theory
  - Endometriosis is heterogeneous
  - Subtle lesions are not yet pathology

Pro and contra of adolescent surgery

- **Pro**
  - Recurrence rate of deep endometriosis after excision is rare :1 %
  - Recurrence rate of cystic ovarian endometriosis is 5% to 20 %

- **Contra**
  - Ovarian damage during surgery
  - Adhesion formation after repeat surgery
  - And thus maybe an increased risk of infertility

Practical conclusions

- **A diagnostic laparoscopy**
- **Surgery during this laparoscopy**
  - If available
- **After surgery**
  - Wise to give medical therapy to prevent recurrences of cystic ovarian endometriosis
  - But not mandatory if too much side effects
- **Quid THL ?**

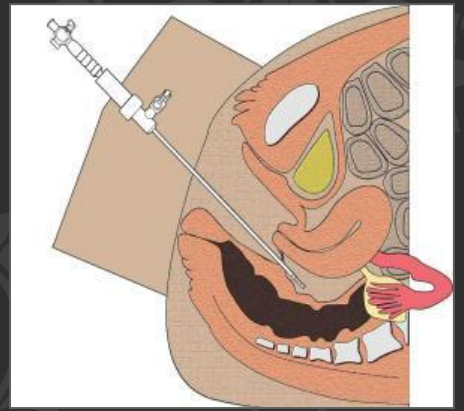
Adolescent endometriosis - *Clinic*

Early endometriosis characterized by neo-angiogenesis

- Red lesions
- Ovarian endometrioma
- Adhesion formation

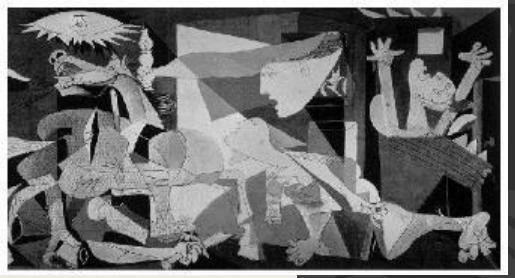
Adolescent endometriosis - *Treatment*

In adolescents with chronic pelvic pain and/or dysmenorhea, TVL is offering a minimal invasive way of diagnosis and early treatment.



Tale of the weeping ovary

by Stephan Gordts



- In my very early days I'm invaded by nasty cells, and most of you don't know it!
- When I am sick, still being young, you are not paying attention and it is not considered important.
- When you finally detect my disease you prefer most frequently not to treat me because my lesion is too small.
- When you finally decide to treat me, my disease became more severe and you are becoming very aggressive

GRAZIE

Endometriomas as a possible cause of reduced ovarian reserve in women with endometriosis
Kitajima et al. Fertil Steril. 2011 Sep;96(3):685-91.

Endometriotic cyst formation and associated structural tissue alterations (fibrosis) in apparently normal ovarian cortex may be a cause of reduced ovarian reserve

Early diagnosis and intervention may be beneficial in women with endometriomas to protect their ovarian function

Endometriomas less than 4 cm!!!

Adolescent endometriosis - *Treatment*

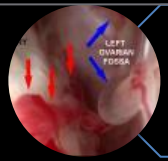
Surgery in adolescents: double-edged sword in adolescents

- Increased in risk of premature ovarian failure due to removal of ovarian follicles
- Minimal invasive
- Performed by experienced surgeons

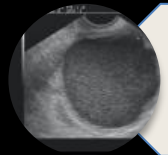
TVE AND SMALL ENDOMETRIOMA

- We need to focus on the ***early detection*** of the small endometrioma in the young female patient (TVS, MRI, CA-125, TVE)
- We can't make a *distinction* between the small endometrioma with a good prognosis and the one that will continue to grow towards the more destructive stages of the disease.
- Treat when surgery is feasible & efficient, with minimal fibrosis.
- Maximal preservation of healthy ovarian tissue

Adolescent endometriosis



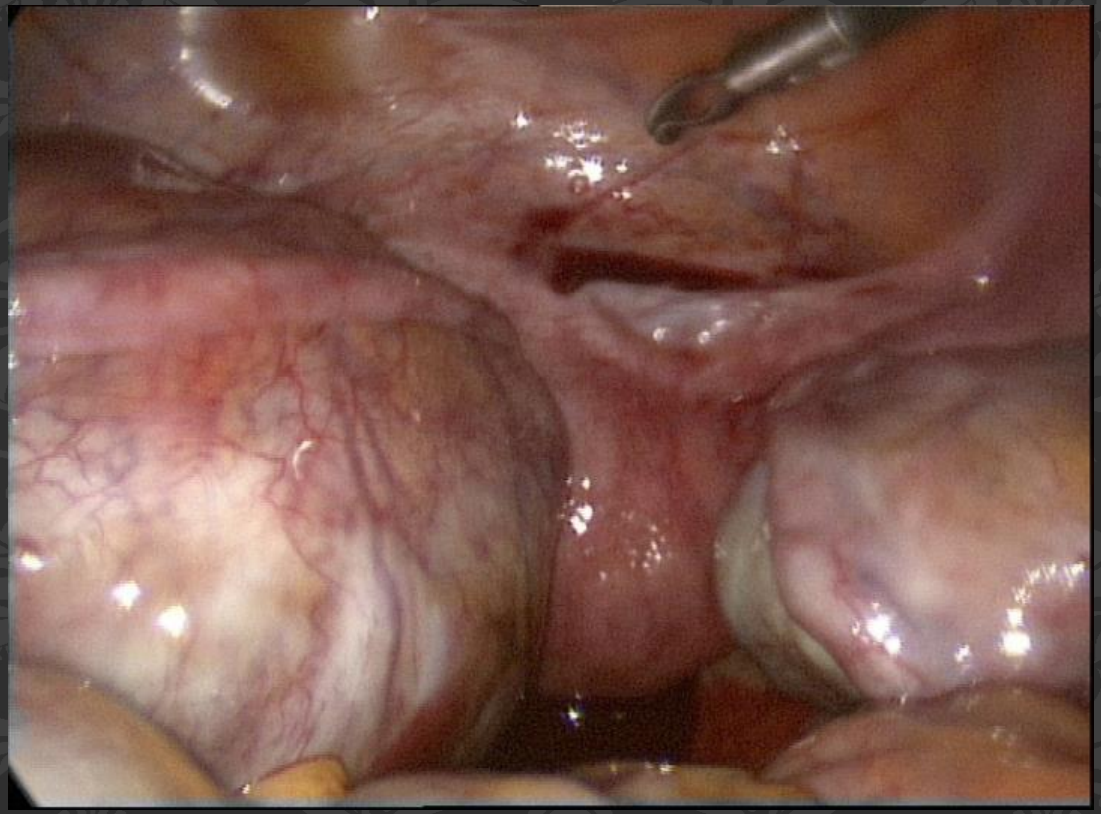
Pathogenesis



Clinical aspects

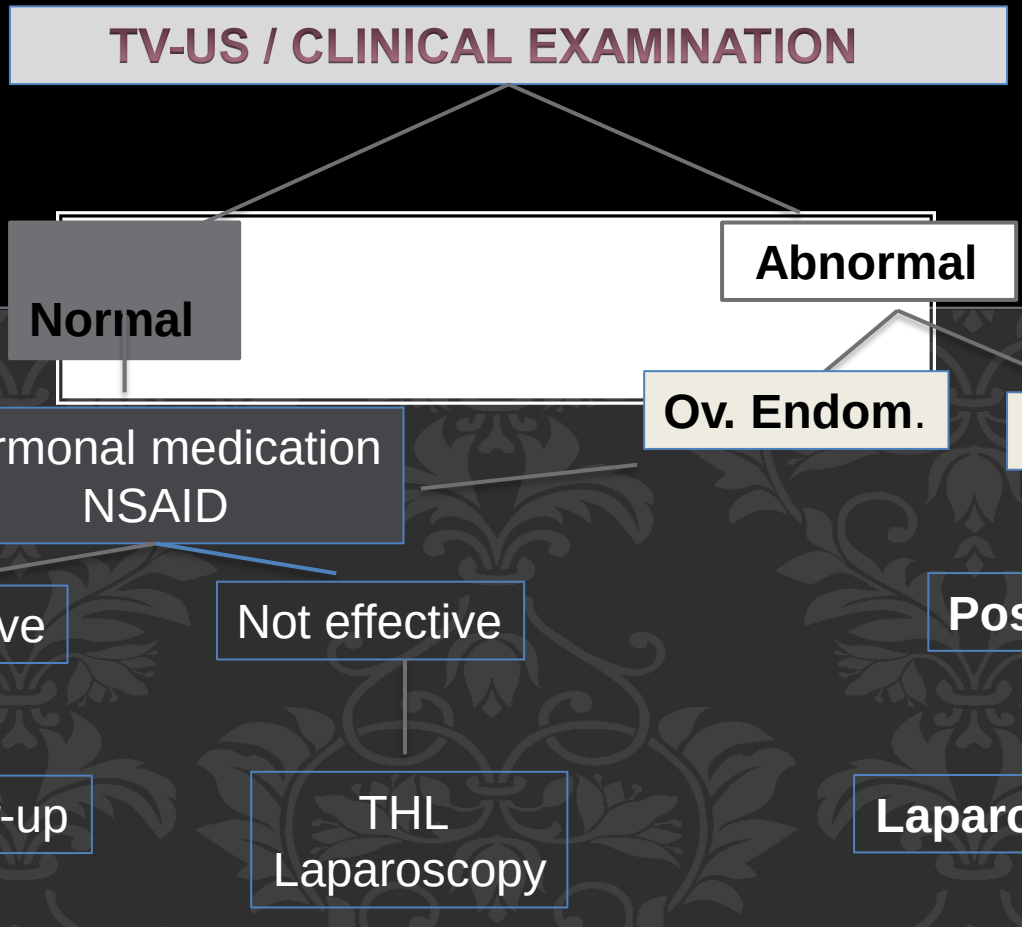
Treatment

Conclusions

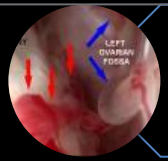


Adolescent endometriosis - *Treatment*

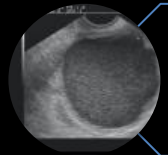
If dysmenorrhea does not improve within 6 months of treatment with NSAIDs and COC, a laparoscopy is indicated to look for endometriosis”


TV-US / CLINICAL EXAMINATION
Normal
Abnormal
Ov. Endom.
DIE
Hormonal medication
NSAID
Effective
Not effective
Positive
Follow-up
THL
Laparoscopy
Laparoscopy

Adolescent endometriosis



Pathogenesis



Clinical aspects

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Adolescent endometriosis - *Treatment*

The ESHRE Guidelines for the Diagnosis and Treatment of Endometriosis, under ‘Endometriosis in adolescents’ state (ESHRE, 2016):
“Laparoscopy should be considered if adolescents with chronic pelvic pain who do not respond to medical treatment (NSAIDs, OCPs) since endometriosis is very common under these circumstances”.

Adolescent endometriosis - *Conclusions*

Endometriosis is still a certain point a progressive disease

Absence of markers to predict progressivity

Prevalence and severity of stage increase with age

Goals of early diagnosis:

- Decrease morbidity
- Limit disease progression
- Reduce risk of infertility

Nezhat C, et al. Endometriosis: Advanced Management and Surgical Techniques. New York: Springer-Verlag, 1995
Koninckx PR, et al. Fertil Seril 1991; 44: 759-65.
D'Hooghe TM, et al. Fertil Steril 1996;65: 645-49.

Conclusions

- Ovarian endometriosis is a cause of reduced ovarian reserve
- Early diagnosis and intervention may be beneficial in women with endometriomas to protect their ovarian function

Surgery for ovarian endometriosis

- results in a spontaneous pregnancy rate of approx. 50%
- results in reduced ovarian reserve; more detrimental effect of cystectomy than ablative surgery.
- in case of large endometrioma: two step procedure is recommended.