

Recent Developments in The Transmission of Human Life

19-21 January 2023
Berlin, Germany

What are the outcomes of surgical or medical treatments to cure or treat endometriosis rather than managing it?

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Disclosures: nothing to disclose

Cure of endometriosis <-> persistence - recurrence

- Medical therapy
 - Some lesions inactivate during treatment but no lasting cure
 - and reactivate after
- Surgery: recurrence rates
 - Deep endo excision < 1%
 - Cystic ovarian excision 5%
 - superficial destruction 20%
 - Typical or superficial endo 20%

Misunderstanding – misleading – manipulation

I let you judge

FACTS VIEWS VIS OBGYN, 2022, 14 (3): 225-233

Opinion

Reconsidering evidence-based management of endometriosis

P.R. KONINCKX^{1,2}, A. USSIA³, S. ALSUWAIDI¹, B. AMRO¹, J. KECKSTEIN⁴, L. ADAMYAN⁵, J. DONNEZ⁶, M.C. DAN⁷, A. WATTIEZ^{1,8}

- Understanding statistical inference

Wasserstein RL, Lazar NA. The ASA Statement on p-Values: Context, Process, and Purpose, , 70:2, 129-133,. The American Statistician. 2016;70:129-33.

Traditional statistics

- Hypothesis: no difference
- Calculate the probability that the results can be explained by chance eg less than 5%

Bayesian statistics

- Hypothesis: a difference
- Calculate the probability that the results are true
- Judges the hypothesis

Examples

Google search
weather prediction
medicine

Misunderstanding – misleading – manipulation

I let you judge

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- Evidence in medicine

- Statistical

Some 90% is not true

I Ioannidis JPA. Why most published research findings are false.
PLoS medicine. 2005;2:e124.

- EBM = Grading of applicability and of indirect evidence

By non-experts insubdisciplinesand thus without experience

- Experience based

like cooking

- Opinion based or indirect literature

seems logical

Misunderstanding – misleading – manipulation

I let you judge

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Pathophysiology

- I consider Sampson historical
 - Clearly incomplete and other mechanisms must be involved as
 - > Metaplasia theory, embryonic rests
 - Incompatible with
 - with clonal aspect
 - Biochemical variability of lesions
 - with deep endo starting > 10 years after menopause
 - Does not explain effect of dioxin, radiation
 - Endometriosis in men and in women without a uterus

Epigenetics

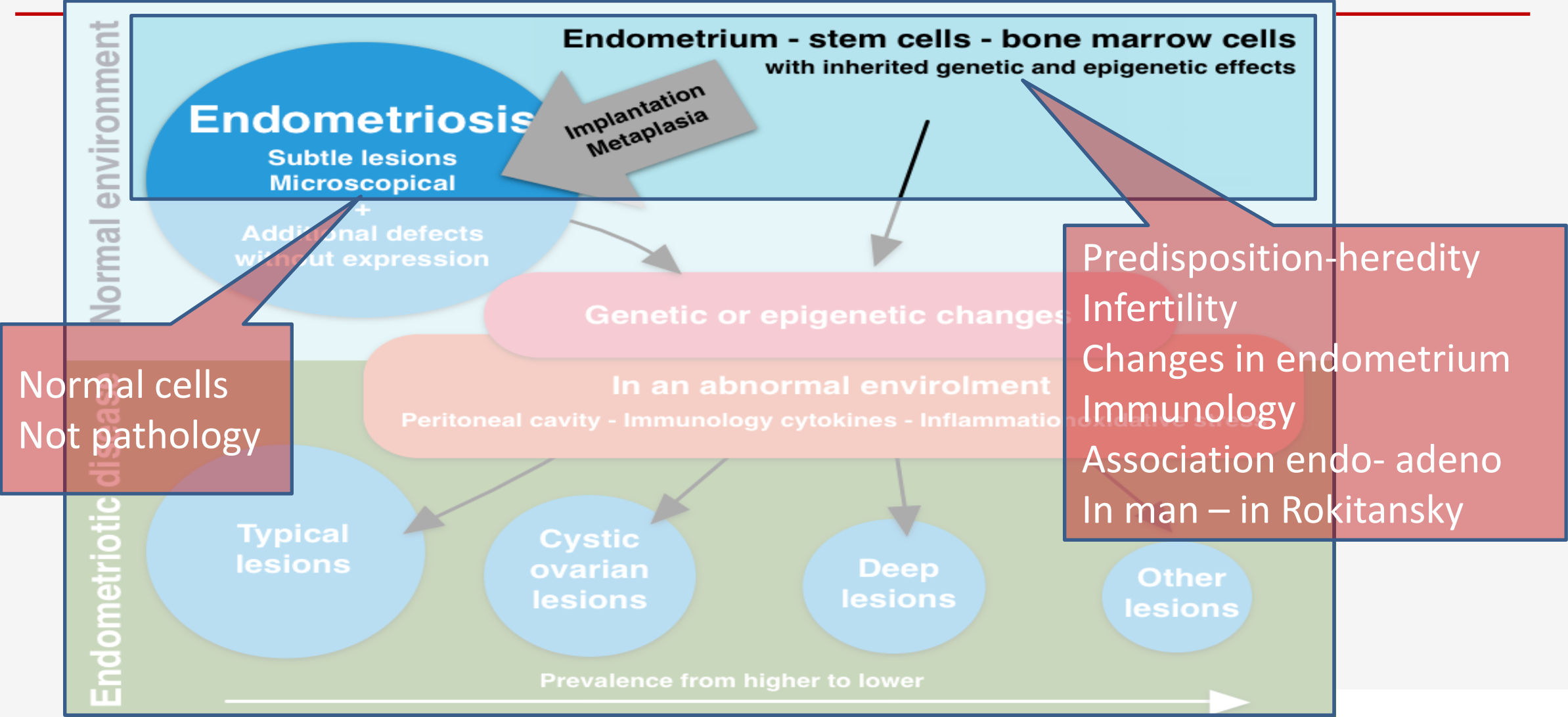
reversible - irreversible

Genetic-epigenetic changes

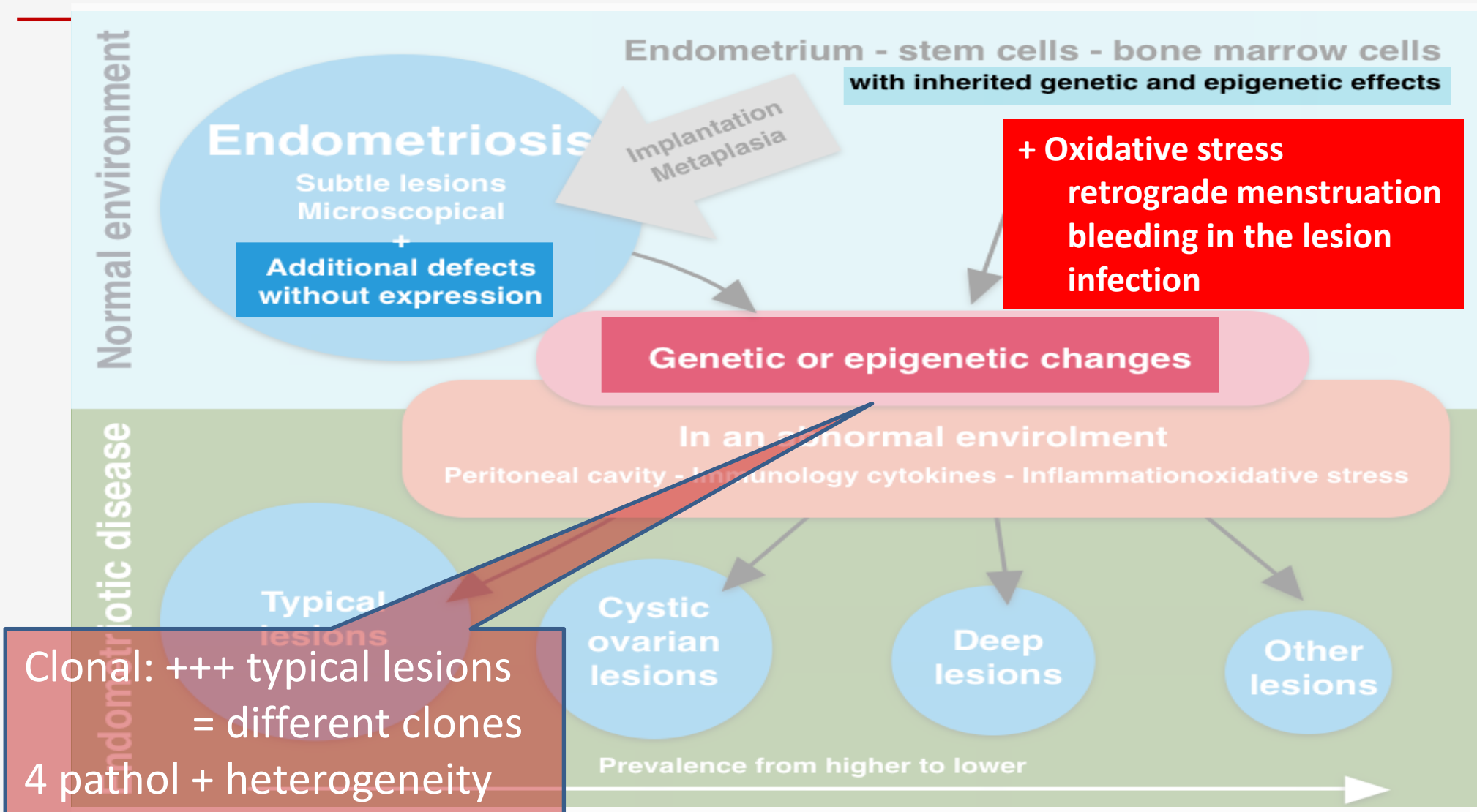
Think

metaplasia and embryonic rests

The original cell

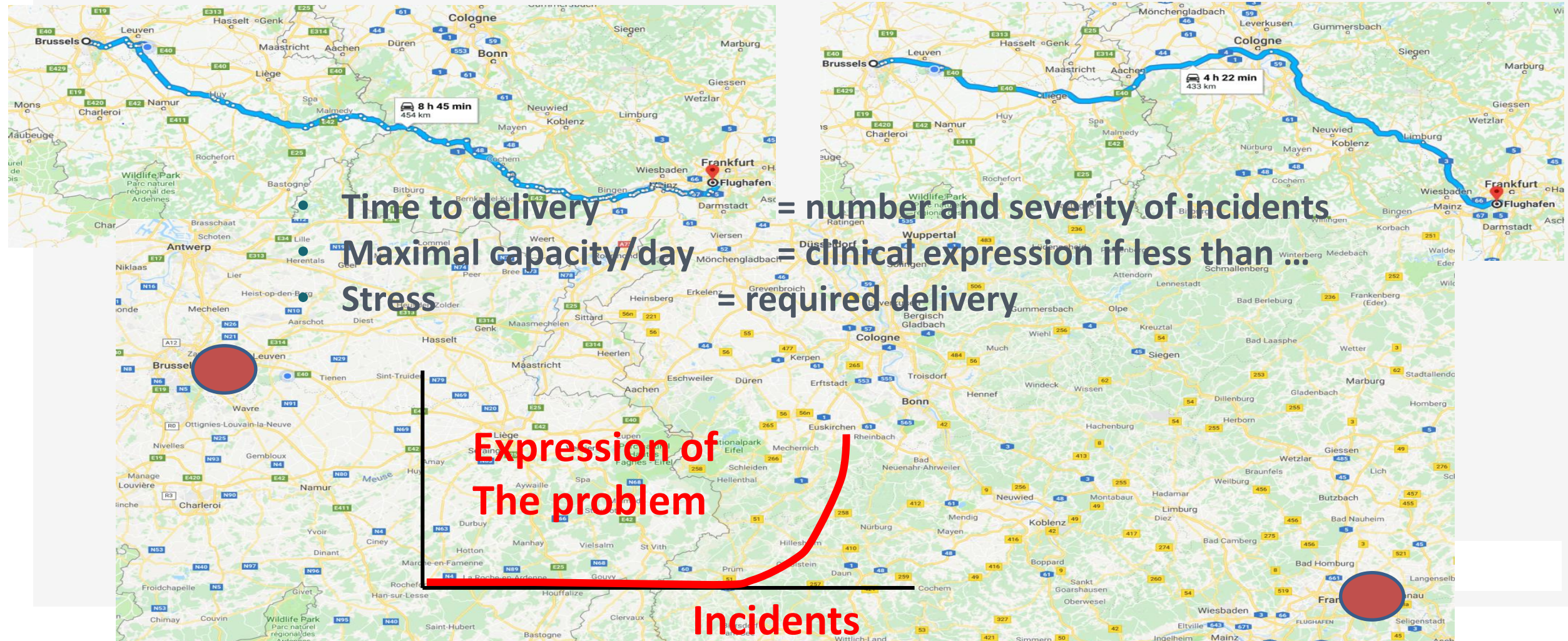


Cumulative incidents



Genetics and epigenetics : redundancy

consider molecular biology as the delivery of goods



The cumulative genetic – epigenetic incidents

Inherited defects

- Endometriosis risk
- Endometrium
- Infertility
- pregnancy
- immunology

+1

+1

+1

- Radiation
- Pollution
- Oxidative stress
 - Blood
- infection

Adenomyosis lesion
Endometriosis lesion
With a specific set of defects

variability

types of endo-adeno
estrogen production
progesterone resistance
ReTIAR – bleeding - trauma

recurrence risk

Infection as a potential cofactor in the genetic-epigenetic pathophysiology of endometriosis: a systematic review

FACTS VIEWS VIS OBGYN, 2019, 11 (3): 209-216

P.R. KONINCKX^{1,2,3,4}, A. USSIA^{3,5}, M. TAHLAK¹, L. ADAMYAN^{6,7}, A. WATTIEZ^{1,8}, D.C. MARTIN^{9,10,11}, V. GOMEL¹¹

- More infections
 - Lower genital tract
 - Endometritis
 - PID
- Altered microbiome
 - Endometrium
 - Menstrual fluid
 - Peritoneum
 - Bowel
- In endometriosis
 - HPV and mollicutes

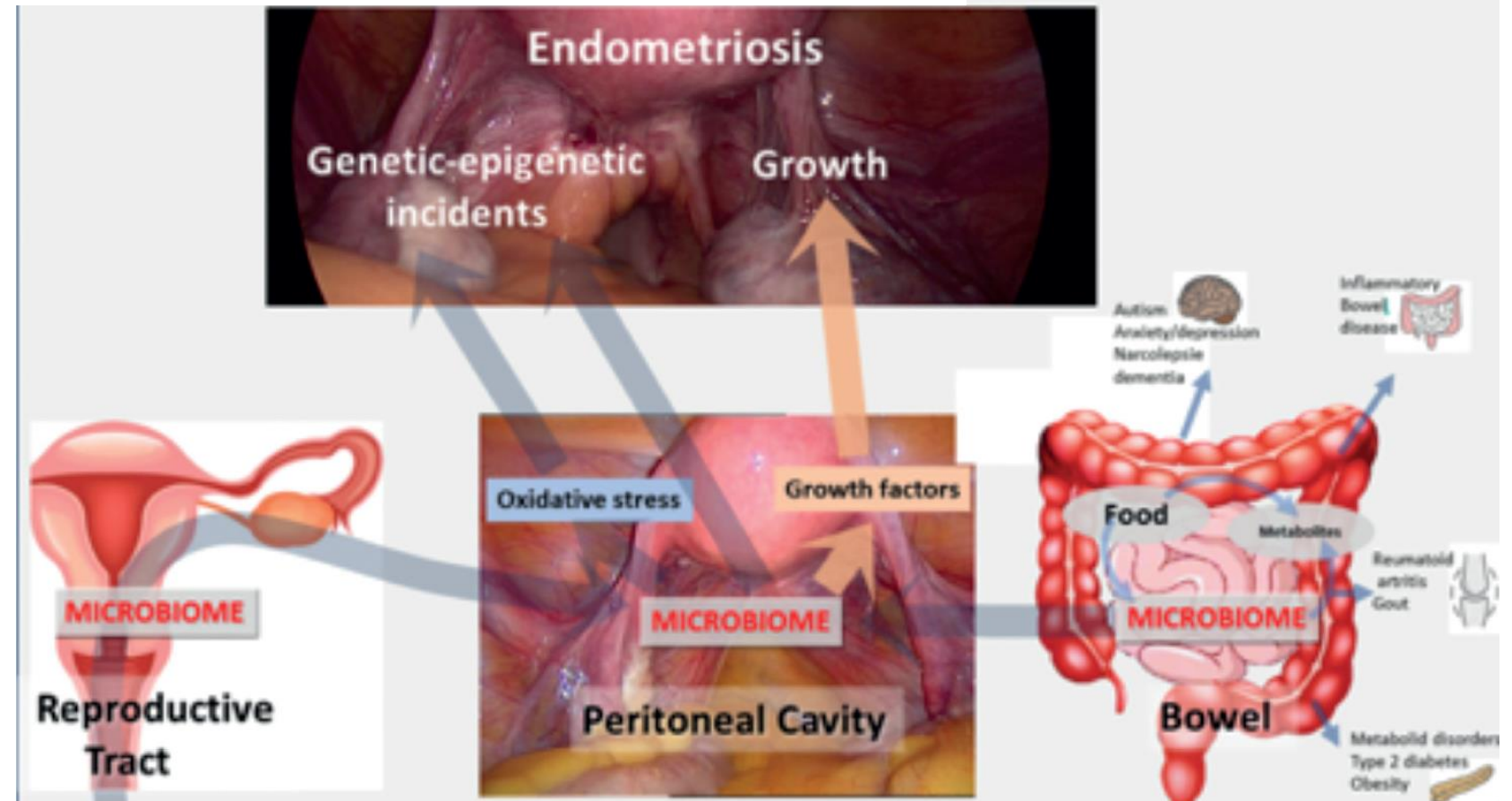
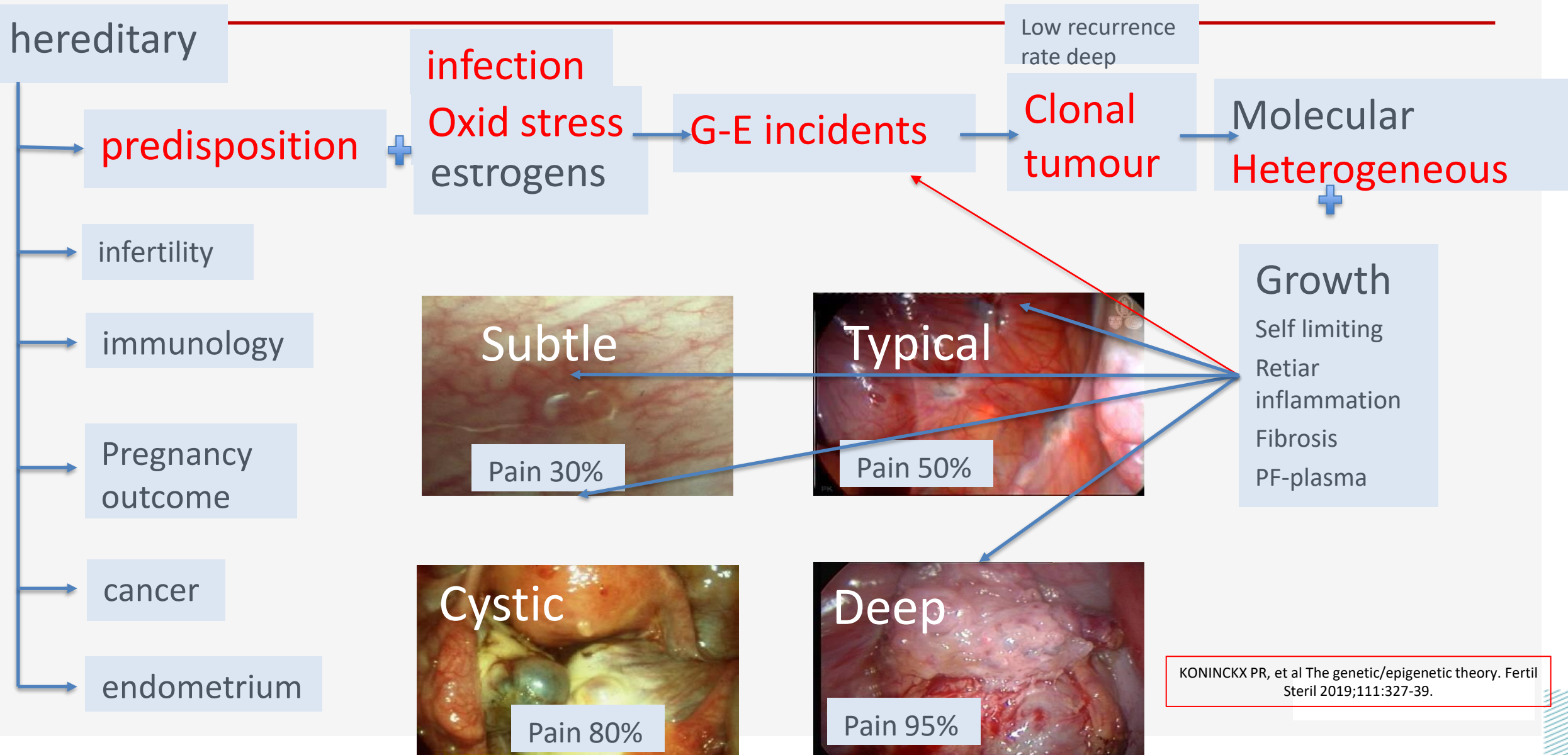


Figure 1: The peritoneal microbiome results from the uterine and upper-genital tract microbiome and the gut microbiome. The peritoneal microbiome can cause endometriosis by inducing genetic epigenetic incidents either directly or by increasing the oxidative stress. The peritoneal microbiome also can increase endometriosis growth through growth factors and immunologic changes. This explains why the gut microbiome, which is influenced by food intake and exercise, can influence the induction and growth of endometriosis, besides many other effects.

Endometriosis model : initiation and growth

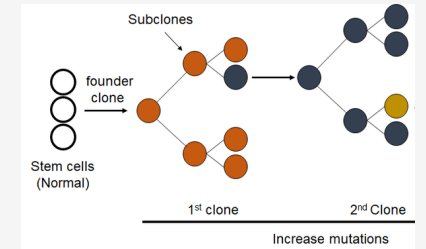


Growth of endometriosis lesions

Koninckx PR, Martin DC, Donnez J. Do we need to separate initiation and growth to understand endometriosis? *Fertility and Sterility* 2020;114:766-7

G-E set

+ evt other G-E incidents bleeding, microbiome



In peritoneal fluid

Koninckx PR, Heyns W, Verhoeven G, Van Baelen H, Lissens WD, De Moor P et al. Biochemical characterization of peritoneal fluid in women during the menstrual cycle. *J Clin Endocrinol Metab* 1980;51:1239-44.

An ovarian exudate

Steroid hormones draining from the ovary

In the bowel wall

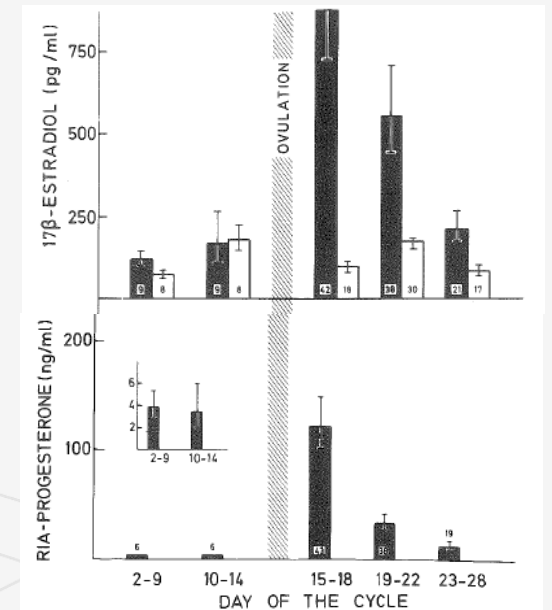
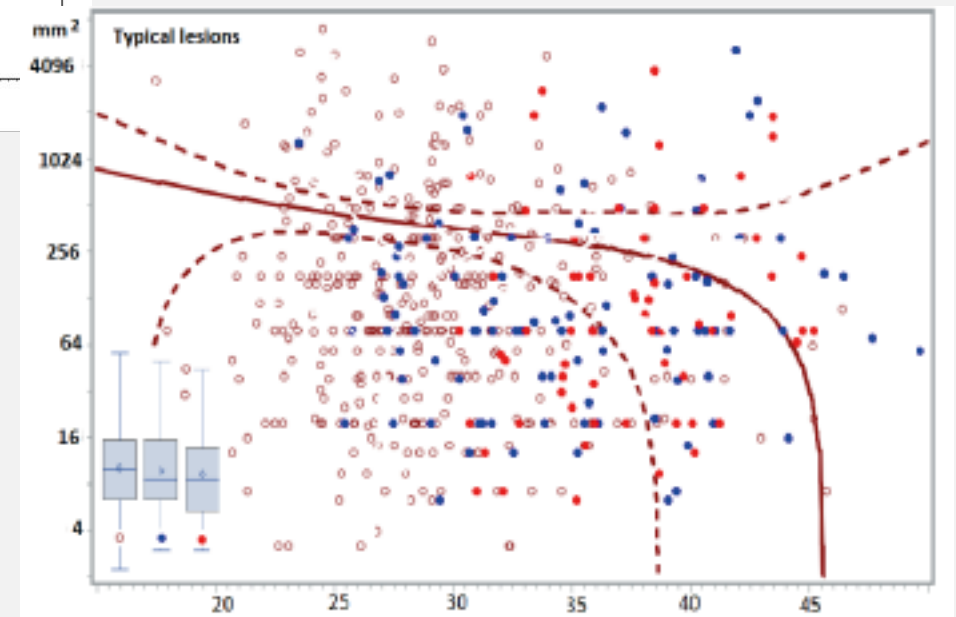
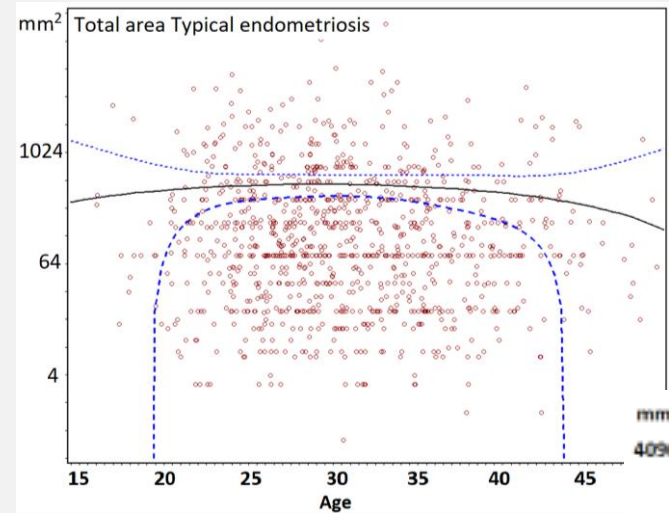
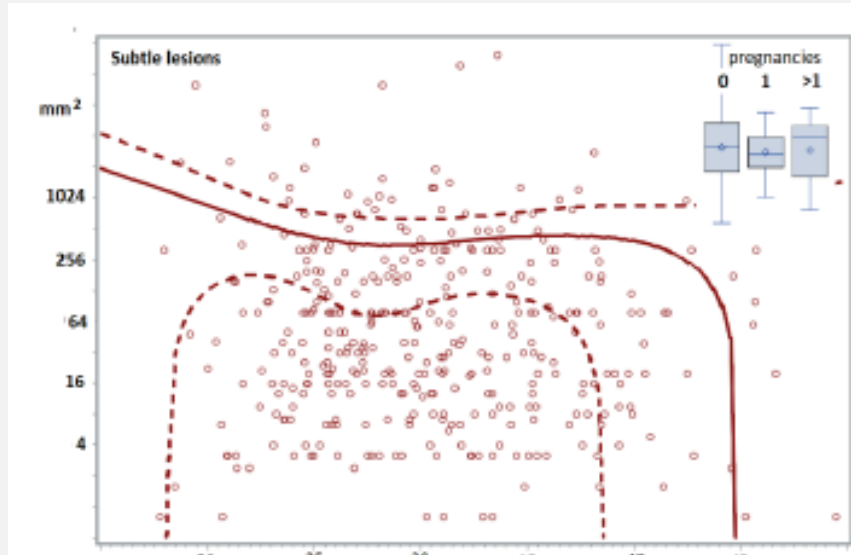


FIG. 1. Concentrations of 17β-estradiol and progesterone, assayed by CPB and RIA, in peritoneal fluid (■) and paired plasma samples (□). The mean_± SE and the number of determinations are indicated.

A self-limiting growth

Koninckx PR, Ussia A, Wattiez A, Adamyan L, Martin DC, Gordts S. The severity and frequency distribution of endometriosis subtypes at different ages: a model to understand the natural history of endometriosis based on single centre/single surgeon data. FVVOG 2021;



- No increase with age
- Fibrosis = war of trenches
- Decrease of subtle with age



Fibrosis = end point

PR Koninckx, R Fernandes, A Ussia, L Schindler, A Wattiez, S Al-Suwaidi, B Amro, B Al-Maamari, Z Hakim, M Tahlak Pathogenesis based Diagnosis and Treatment of endometriosis, *Frontiers in Endocrinology*, 2021

- Fibrosis (Guo, Vigano)

- A war of trenches

- Inflammation, immunology

- Belongs to the body

- Stops growth ?

- End stage

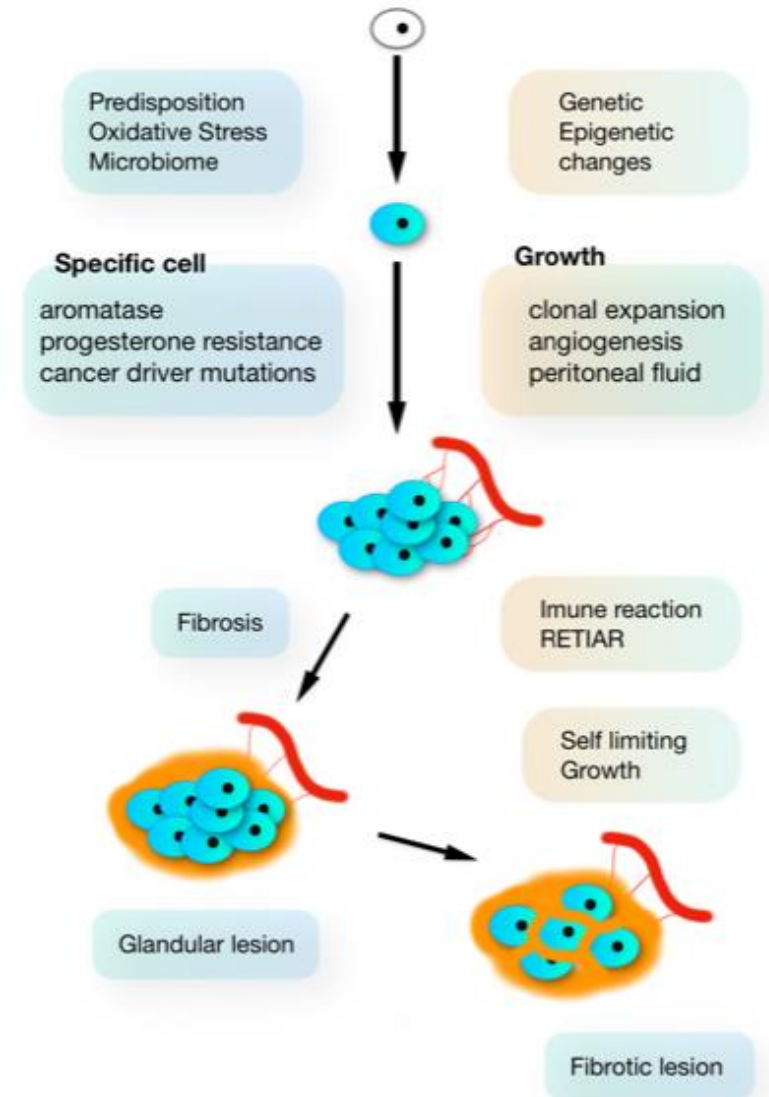


- Subtle lesions are $\pm 100\%$ prog resistant

- Migration of endometriotic cells

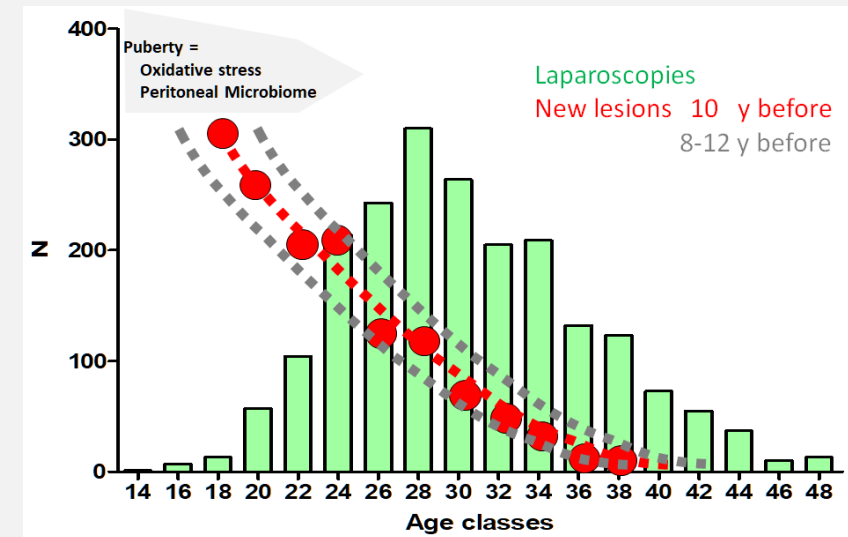
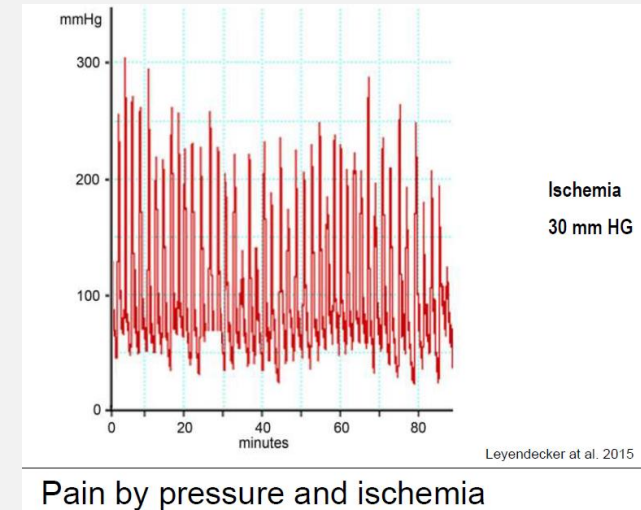
- Invasiveness of endometrium

- Immunology, MET



Adolescence

- Primary dysmenorrhoea
 - Quid diagnosis?
 - Cause or consequence
- Higher risk of initiating endometriosis



Pain at distance

Pain Mapping of Endometriosis

Prevalence of Endometriosis and Peritoneal Pockets in Women with Infertility and/or Pelvic Pain

Philippe R. Koninckx, MD, PhD;^{1,2,3,4,5,6} Anastasia Ussia, MD;^{4,6} Jörg Keckstein, MD, PhD;^{7,8} Leila Adamy, MD, PhD;^{9,10} Arnaud Wattiez, MD, PhD;^{1,11} Dan C. Martin, MD^{12,13}



Endometriosis Can Cause Pain at a Distance

Philippe R. Koninckx, MD, PhD;^{1,2,3,4,5} Anastasia Ussia, MD;^{4,6} Roy Mashiach, MD;⁷ George Vilos, MD;⁸ Dan C. Martin, MD^{9,10}

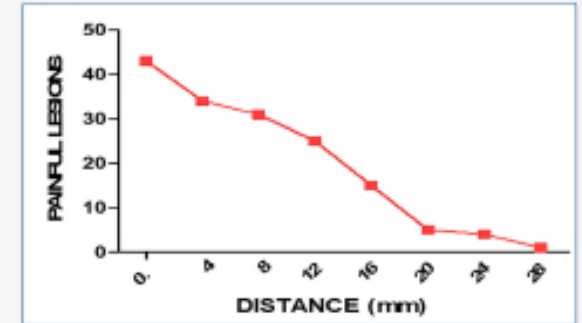
After surgery, 20/25 sciatalgia solved

Quid exploration large somatic nerves

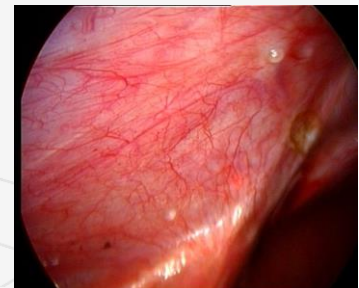
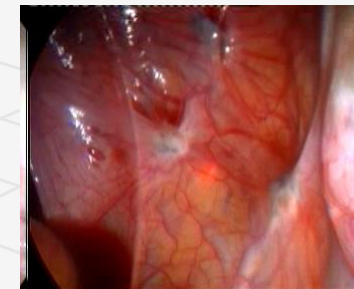
Type of lesion :

Type of lesion	%
Clear Lesion	32
Red Vascular Lesion	37
White Scar Lesion	20
Black Lesion	11

Pain at distance



Adapted from Demco L. Review of pain associated with minimal endometriosis. *JSLLS* 2000;4: 5-9.



Indian & Chinese food supplements - diet - exercise

- ? Anti-oxidants
- ? Immune response
- ? Intestinal microbioma

Front-line prescription

Patient Name: _____ Date: _____
Address: _____

R_x

- berberine
- casein-free
gluten-free diet
- zinc 30+ mg
- **NAC** 2000+ mg

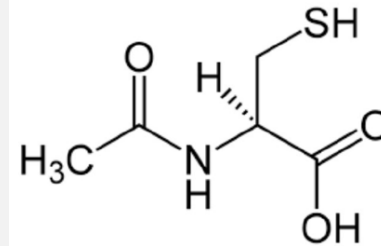
MD: _____
Signature: _____



Curcumin

- Downregulates **NF-κB** and promotes **apoptosis** [PMID: 22227273]
- Suppresses local production of **estrogen** [PMID: 24639774]
- Inhibits **angiogenesis** [PMID: 17569210]
- Supports **glutathione** [PMID: 16433888] and **Treg cells** [PMID: 19839007]

N-acetyl cysteine



- Downregulates **NF-κB** and reduces inflammatory cytokines.
- Precursor to **glutathione** which upregulates activity of NK cells and Treg cells.
- Reduces oxidative stress.
- May influence apoptosis and angiogenesis. [PMID: 28367412]

A Promise in the Treatment of Endometriosis: An Observational Cohort Study on Ovarian Endometrioma Reduction by N-Acetylcysteine

Maria Grazia Porpora,¹ Roberto Brunelli,¹ Graziella Costa,² Ludovica Imperiale,¹ Ewa K. Krasnowska,² Thomas Lundeberg,³ Italo Nofroni,¹ Maria Grazia Piccioni,¹ Eugenia Pittaluga,² Adele Ticino,¹ and Tiziana Parasassi²

Conclusion: it seems likely

- >1 disease heterogeneous ... clonal GE
- Self limiting growth after initiation
- Impact on pregnancy is independent of endometriosis lesion, rather predisposition
- Variable progesterone resistance, and estrogen production = G-E
- Reversible and irreversible genetic-epigenetic changes
 - Consider metaplasia and embryologic rests
 - Inherited predisposition
 - + more incidents -> **abnormal cell** in and abnormal environment and immunology -> more immunologic changes
 - **Normal cell** in and abnormal environment and immunology -> **abnormal epigenetics** and behaviour

Subtle differences but finally an epigenetically abnormal cell, and often genetically

Medical therapy

- GN-RH, oestro-progestogens, progestogens
 - Cannot be blinded
 - Placebo effect +++++ e.g. the anti-TNF- α trial

Human Reproduction Vol.23, No.9 pp. 2017–2023, 2008
Advance Access publication on June 12, 2008

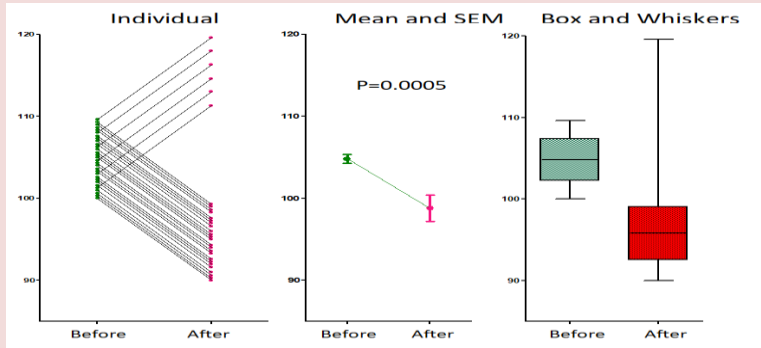
doi:10.1093/humrep

Anti-TNF- α treatment for deep endometriosis-associated pain: a randomized placebo-controlled trial

P.R. Koninckx^{1,2,4}, M. Craessaerts¹, D. Timmerman¹, F. Cornillie³ and S. Kennedy²

Variability of endometriosis and respons to MT

Heterogeneity of



KONINCKX PR, USSIA A, ADAMYAN L, WATTIEZ A, GOMEL V, MARTIN DC. Heterogeneity of endometriosis lesions requires new approaches to research, diagnosis and treatment. FVVO 2019;11: 263.

M+SD: inadequate



Advances in the medical management of bowel endometriosis

Paolo Vercellini, M.D.^{a,b,*}, Greta Sergenti, M.D.^a, Laura Buggio, M.D.^b, Maria Pina Frattaruolo, M.D.^b, Dhouha Dridi, M.D.^{a,b}, Nicola Berlanda, M.D.^b

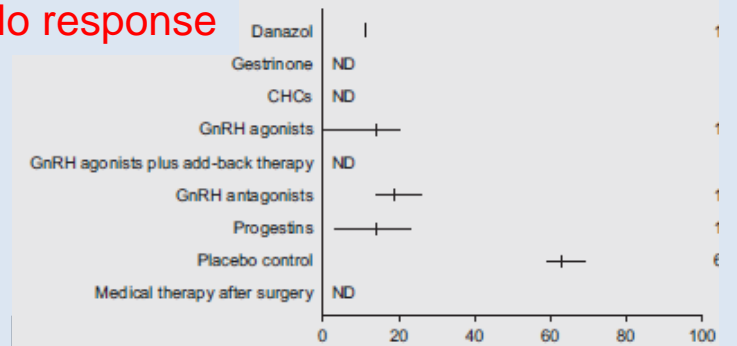
Practice points

- Medical treatment is a valuable therapeutic option that could be proposed in selected women with bowel endometriosis.
- About two-thirds of the patients with rectosigmoid endometriosis and three-fourths of those with rectovaginal lesions can be managed successfully with hormonal drugs, provided strict selection criteria are fulfilled.
- Endometriotic bowel lesions should be checked periodically with imaging techniques to identify possible nodule progression during medical treatment despite symptom relief.

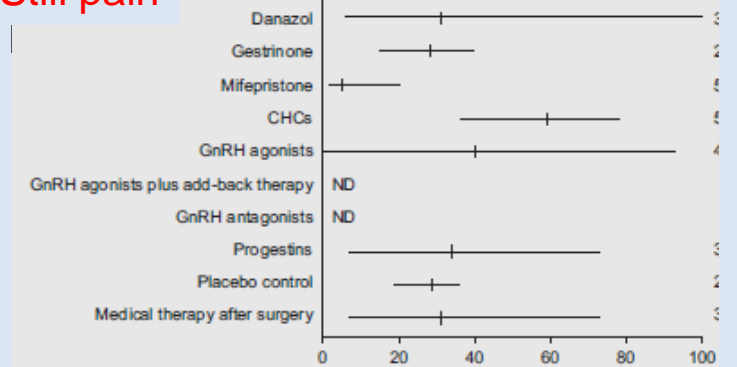
Medical therapy deep reduces pain in 2/3
Some lesions progress

Becker CM, Gattrell WT, Gude K, Singh SS. Reevaluating response and failure of medical treatment of endometriosis: a systematic review. Fertil Steril 2017;108:125-36

No response



Still pain



Medical therapy

- Can inactivate lesions and can decrease pain
- Some lesions continue to grow during medical therapy
 - Experience based in 10.000 treatments judged >80% VAS 8-10/10
- To be discussed
 - Mean and SD cannot judge medical therapy
 - Unclear whether effect the effect of MT is on the lesion
 - Unclear whether a different effect by different progestogens
 - All GnRH agonists and antagonist have the same effect on ovary /estrogen

Koninckx PR, Ussia A, Adamyan L, Gomel V, Martin DC. Peritoneal fluid progesterone and progesterone resistance in superficial endometriosis lesions. Human Reproduction. 2022;28:209-19.

Surgery is logical if benign tumour

- Deep and ovarian endometriosis: not suited for RCT
 - Variable severity + duration + adhesions + completeness
 - Variable ovarian damage and bowel and ureter complications
 - Recurrences of deep endometriosis are rare
 - Recurrences of ovarian endometriosis are rare after excision 5%
 - Recurrences of ovarian endometriosis are rare during medical therapy
 - The singer or the song
- Pain relief, quality of life
- Fertility

Surgery for superficial endometriosis

- 20% recurrence rates
 - Implantation or GE theory: logical
 - Completeness of surgery is doubtful
- Decrease in pain
 - RCTs inadequate
- Fertility
 - Endocan study

Cystic ovarian endometriosis

- Technique
 - Excision
 - Superficial destruction
 - Excision and hilus vaporisation
- Size and 2 step
- Localisation
- Ovarian reserve
- Recurrences
- Fertility: 60 % CPR within 1 year

Deep endometriosis

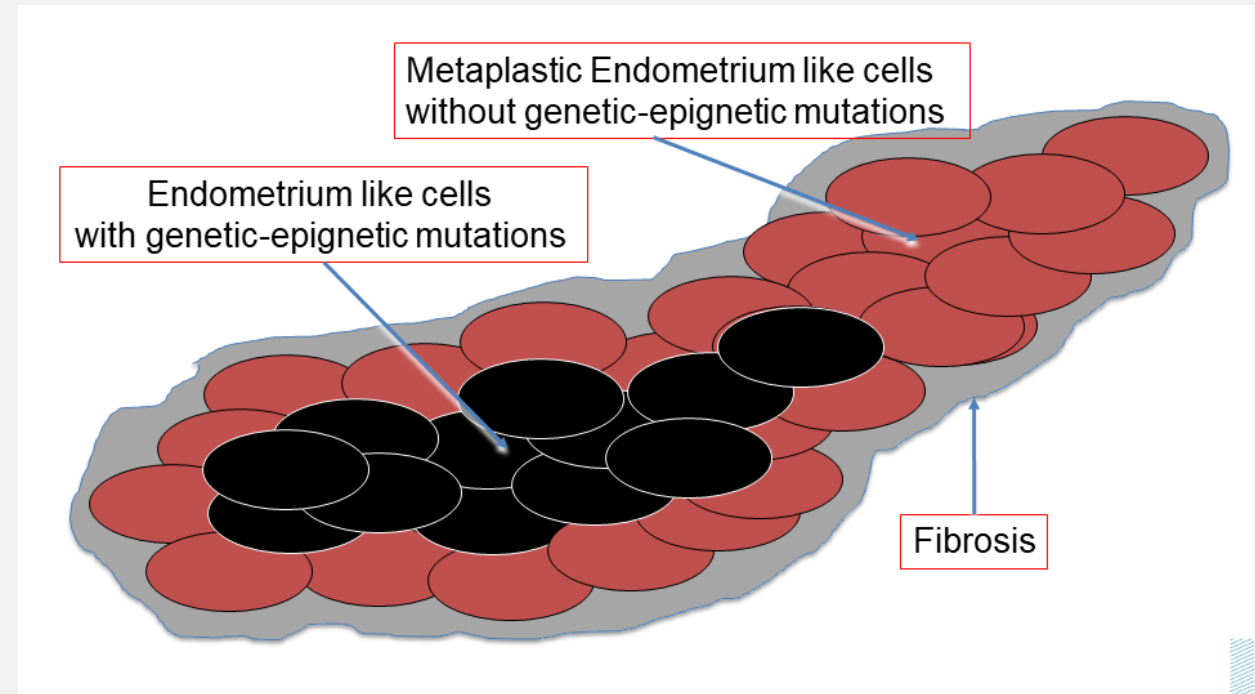
- Technique
 - Excision
 - Discoid
 - Bowel resection
- Ureter
- Fertility
- Pain

Surgery & understanding the disease

- Fibrosis belongs to the body
 - Superficial treatment of ovarian endometriosis
 - Deep endometriosis: more conservative surgery
 - leave a rim of fibrosis
 - if periphery is rather metaplasia

Reversible metaplasia

- Looks endometriosis but reversible
 - Another argument to be conservative
- ### Arguments
- Endometriosis in lymph nodes
 - Endo in bowel at distance
 - Congenital malformations: regression after removing obstruction



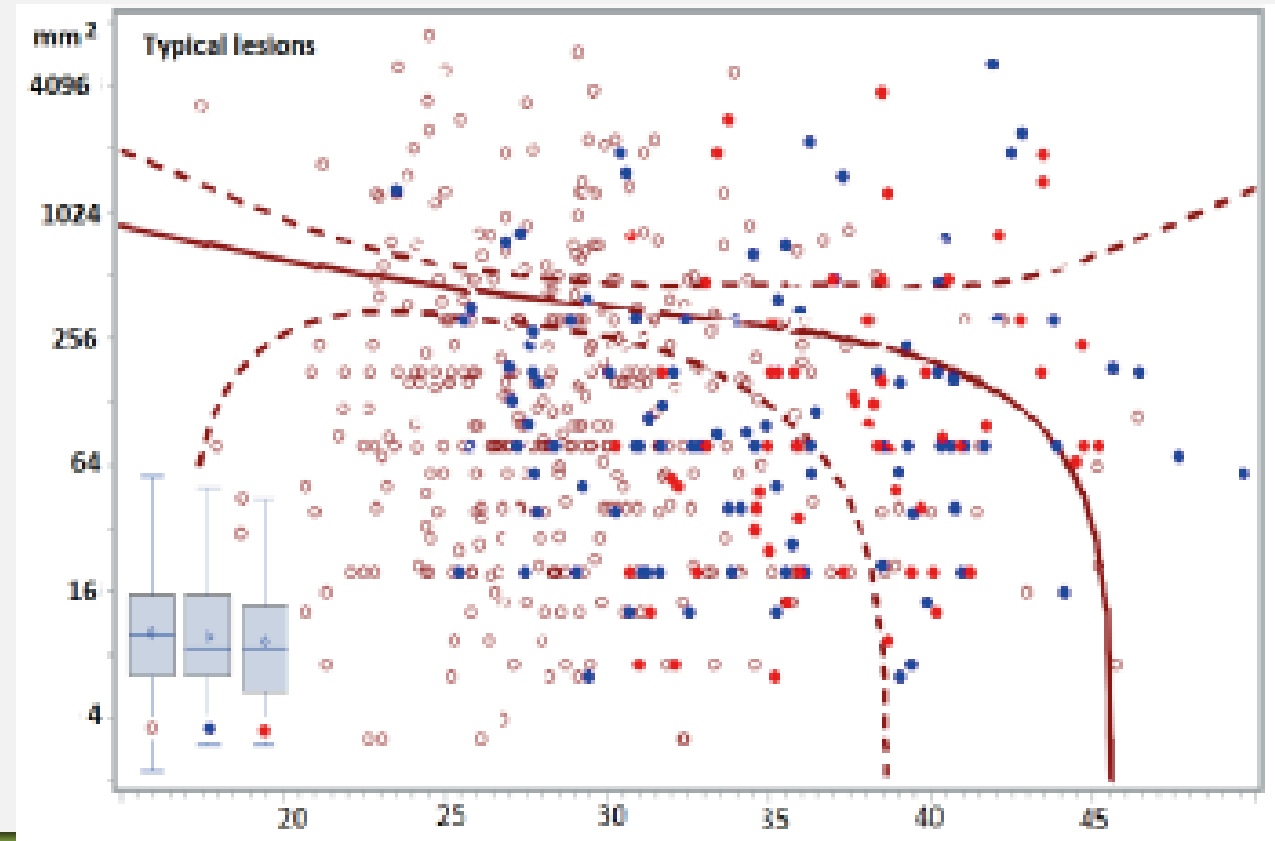
PR Koninckx, A Ussia, S Al-Suweidi, B Amro, H Gharbi, M. Tahlak, L. Adamian, A Wattiez. Conservative surgery for deep bowel endometriosis Ferrero S and Ceccaroni M (eds) Clinical Management of Bowel Endometriosis. 2020. Springer pp. 119-134

Clinical management of endometriosis

- First the diagnosis
 - absence of non-invasive diagnosis
 - Symptoms + clinical exam + ultrasound
 - superficial lesions: not useful
 - Cystic ovarian ++++ performant
 - Deep ????? Considering PPV and prevalence, no data stratified by size
- Practically
 - Pain and a suspicion : indication for a MT trial
 - Also in adolescence
 - ? When to continue
 - Some lesions keep growing

Delay in diagnosis

- Should we prevent or is it already too late
- Especially if self-limiting growth



Prevention of endometriosis = G-E incidents

- Reduce pollution
- Reduce oxidative stress
 - Reduce blood in peritoneal cavity
 - Reduce blood in the endometriosis lesions
 - Anti-oxidants food intake
- Peritoneal microbiome (and upper genital tract)
 - Genital Infections
 - Intestinal microbiome
 - Food intake & exercise

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 Wattiez⁹ · Leila Adamyán⁴

Hypotheses

- (Continuous) oral contraception
- Anti-oxidants ?
- Food intake ?
- Exercise ?

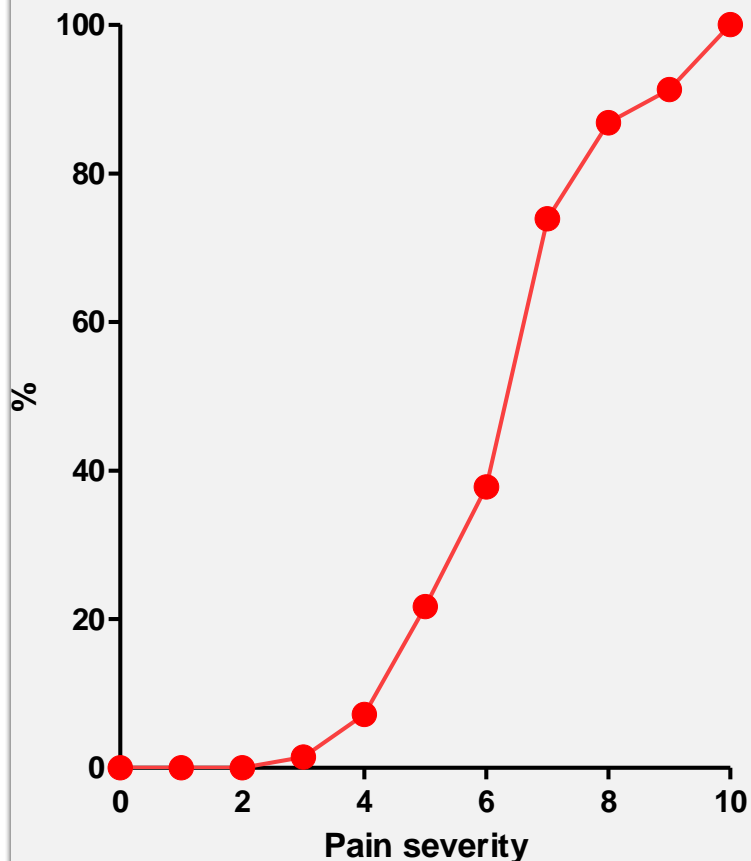
The future prevention ?

- After surgery
- Before initiation

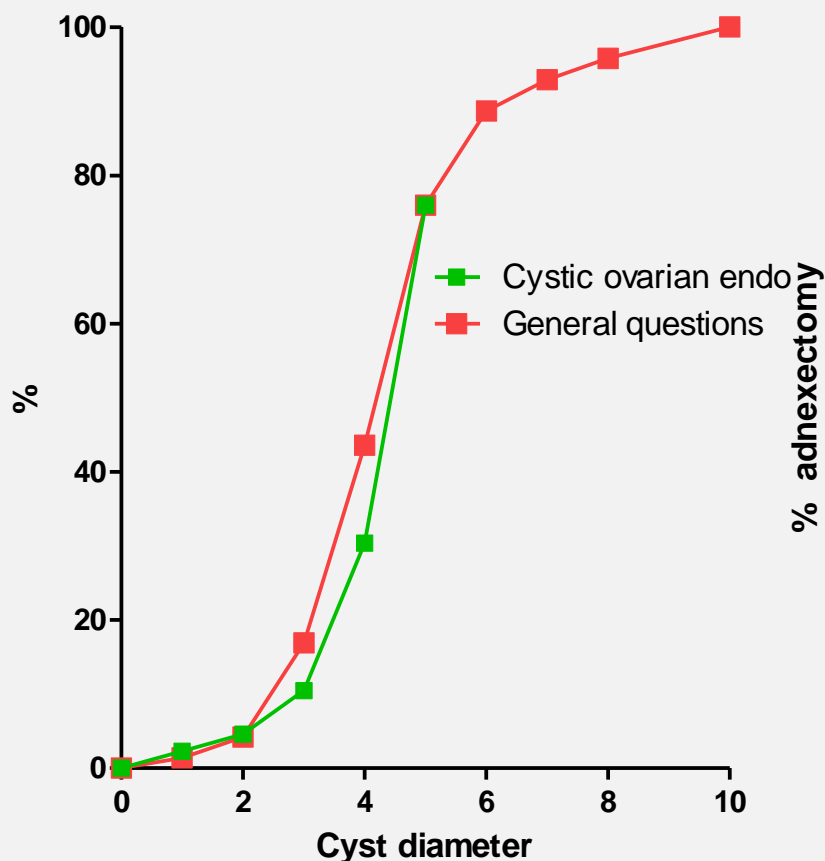
Surgery

- Recognition
- Multivariate not suited for RCT

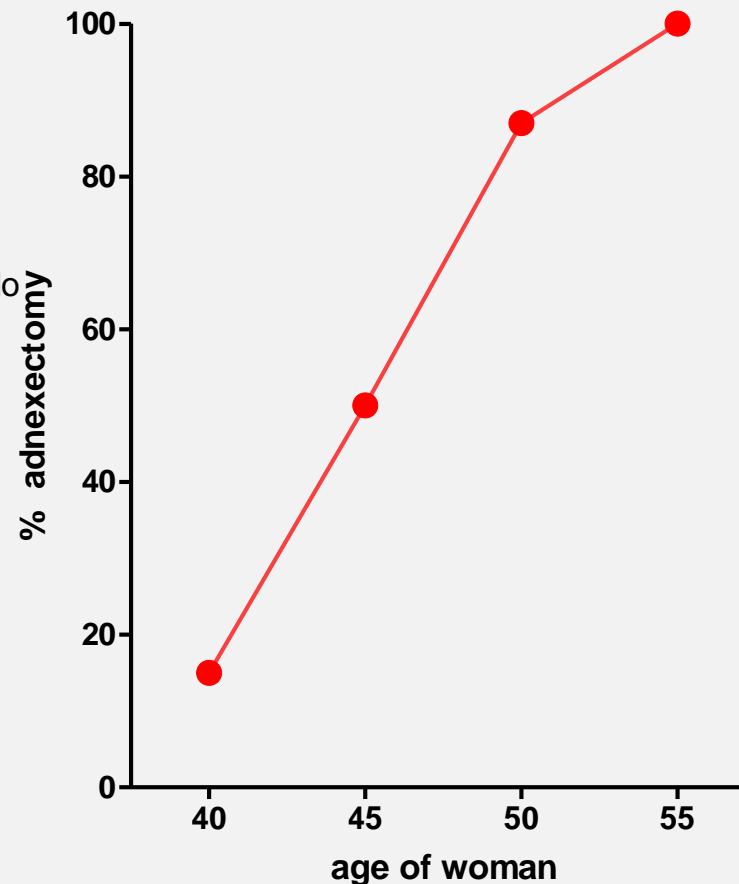
Indication for surgery of cystic ovarian endometriosis multivariate – not suited for RCT



Severity of pain



+ cyst diameter



+ age + fertility

Surgery : multivariate & low numbers-> little RCT data

- Each management is an experiment with an Outcome: continuous Bayesian update ... like cooking
 - When
 - Who
 - How
- Results of a poll reflecting 10.000 managements
 - Surprising agreement on experience based aspects
 - Variable answers for non-experience, but literature based opinions

Adhesions Conclusions



- Individualise
 - ? Risk ? Vaginal infection – vaginoses
 - Blood and fibrin
- No more saline -> Better rinsing liquid
- No dessication
- No warming but cooling
- Add 10% of N2O
- A good surgeon= Gentle tissue handling + fast
- Thinner sutures (especially if knots are safe)

- Idem for anaesthesia, postoperative fatigue

Conclusions

- Evidence based covers less than 5% of what we do
- Experience based fills the gaps – complement evidence
- Opinion – research based variable implementation

Thank you for listening

Statistics: e.g. men are a taller than women

Traditional statistics

- Hypothesis: no difference
- Calculate the probability that the results can be explained by chance eg less than 5%

Bayesian statistics

- Hypothesis: a difference
- Calculate the probability that the results are true