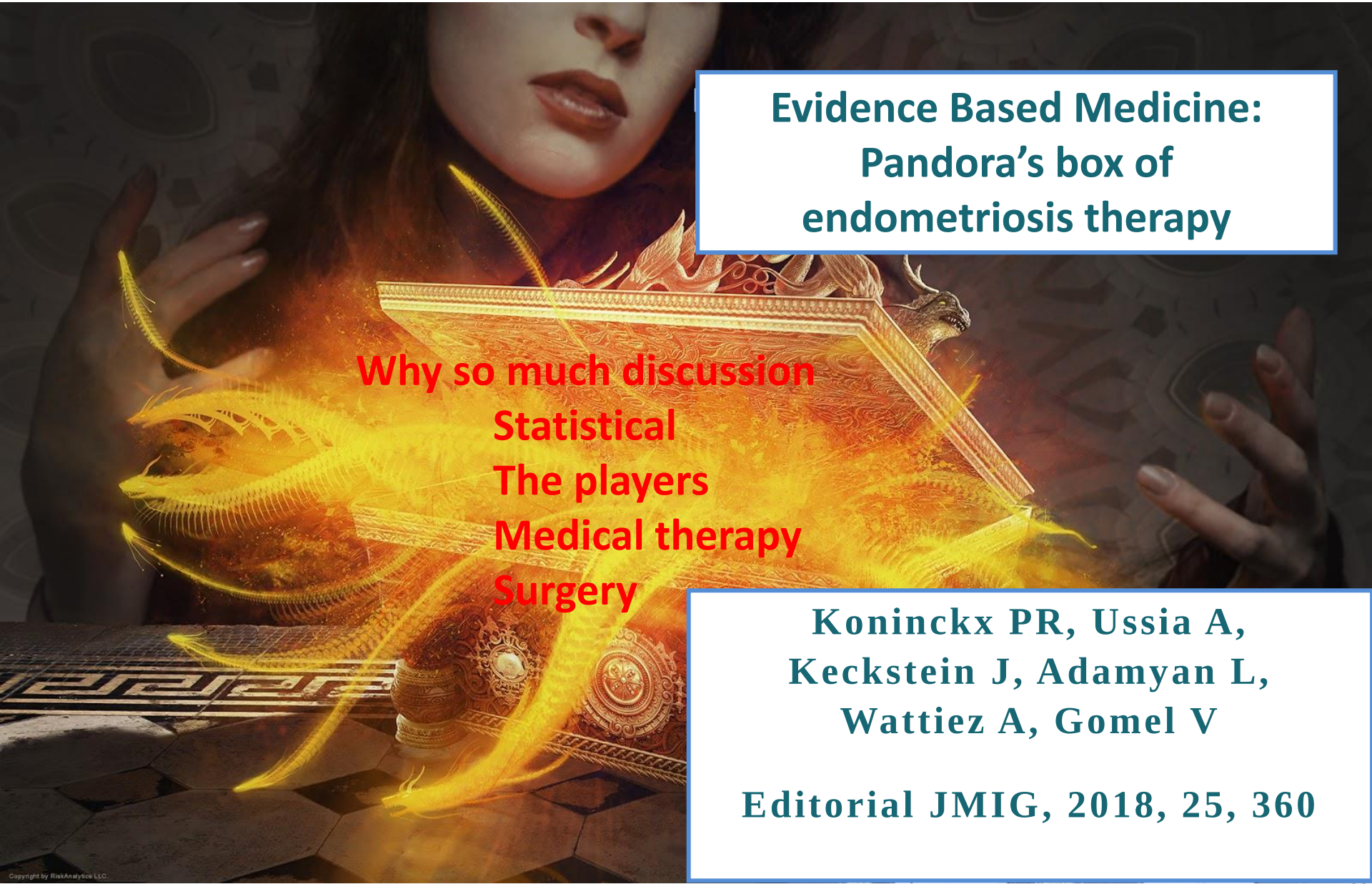
Moscow
28/1/2018

Evidence Based Medicine: Pandora's box of endometriosis therapy



Koninckx PR, Ussia A, Keckstein J, Adamyan L, Wattiez A, Gomel V

Editorial JMIG, 2018, 25, 360

ELSEVIER

JMIG The Journal of Minimally Invasive Gynecology

AAGL

Editorial

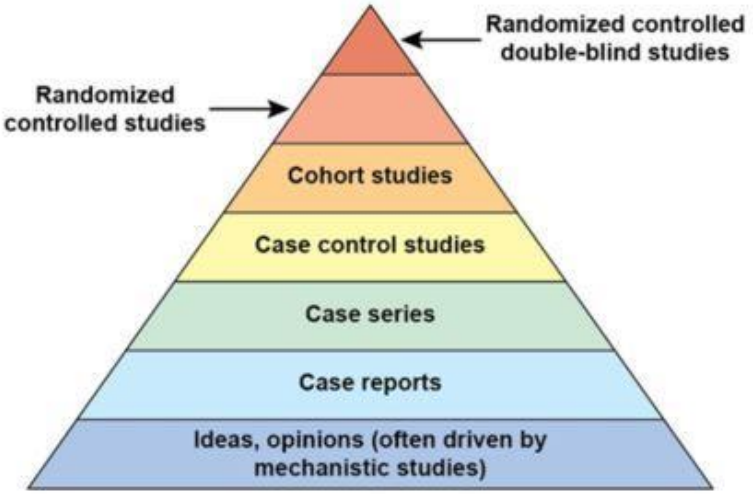
Evidence-Based Medicine: Pandora's Box of Medical and Surgical Treatment of Endometriosis

So much we know , ain't so

- Misuse of Statistics
  - Diagnosis : sensitivity and specificity
  - Results : significant versus clinical useful
  - Limitations of RCT -rare events-extrapolation multimorbidity
- The subspecialist – the industry
- Medical therapy : not one blinded RCT
- Surgery of endometriosis : no quality control

Evidence based medicine : Therapy

- The best available evidence



- RCT
  - Randomised to avoid inclusion bias
  - Double blind to avoid

    Placebo effect

    Observer bias

Double blind randomised trial is mathematically perfect

but

- Blinding is not always feasible

  eg medical treatment of endo

- Only valid for the population investigated

  inclusion/exclusion criteria

  Subgroups are not detected

  Not suited for complex multi-morbidity

- Not suited for rare events

1% = RCT of 6000

Limitations of the RCT

- "EBM has become considered a movement in crisis with the realization that …."
  - clinical guidelines have become unmanageable
  - that statistically significant may have little clinical relevance
  - that EBM poorly maps on complex multimorbidity[2]
  - That EBM is not suited for rare events

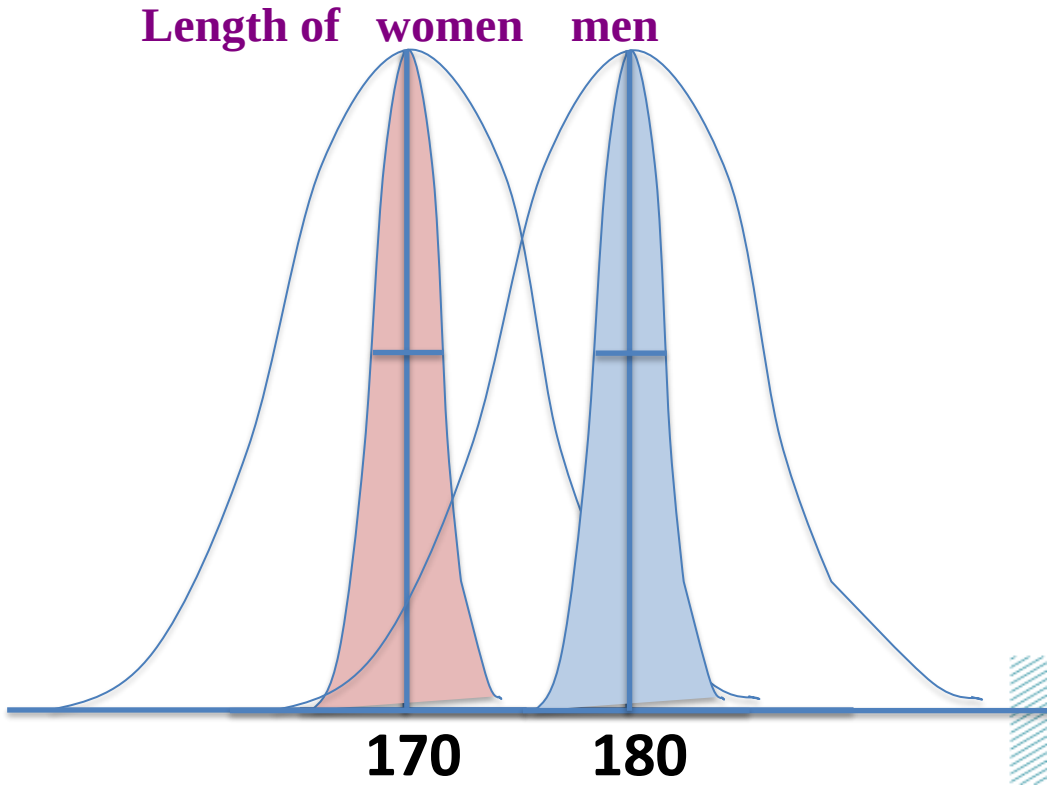
  Greenhalgh T, Howick J, Maskrey N. Evidence based medicine: a movement in crisis? Bmj 2014; 348:g3725

- What s the value of a not perfect RCT ?
  - Eg when blinding is impossible as medical treatment of endo

Misuse of statistical significance

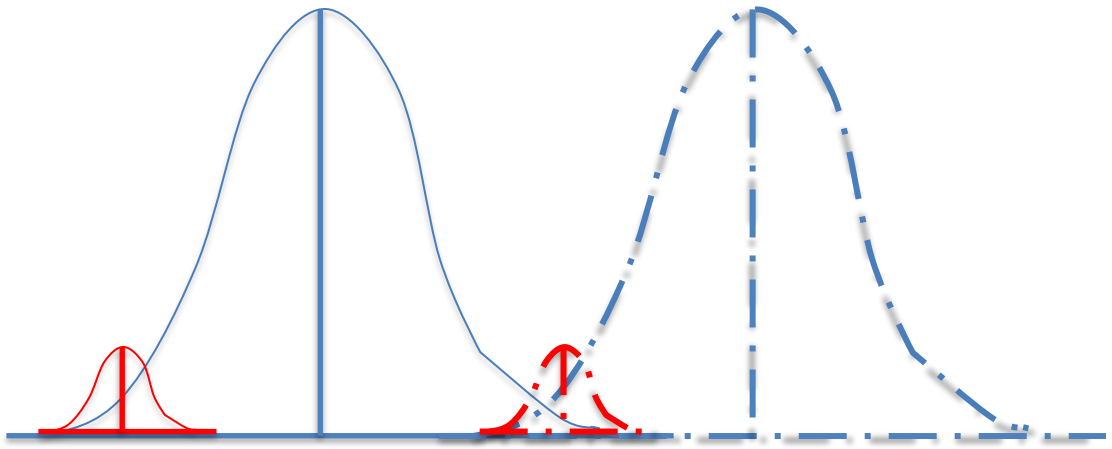
- T-test = significance
  - What is the probability that there is no difference
  - Varies with the real difference and with **N or SEM**

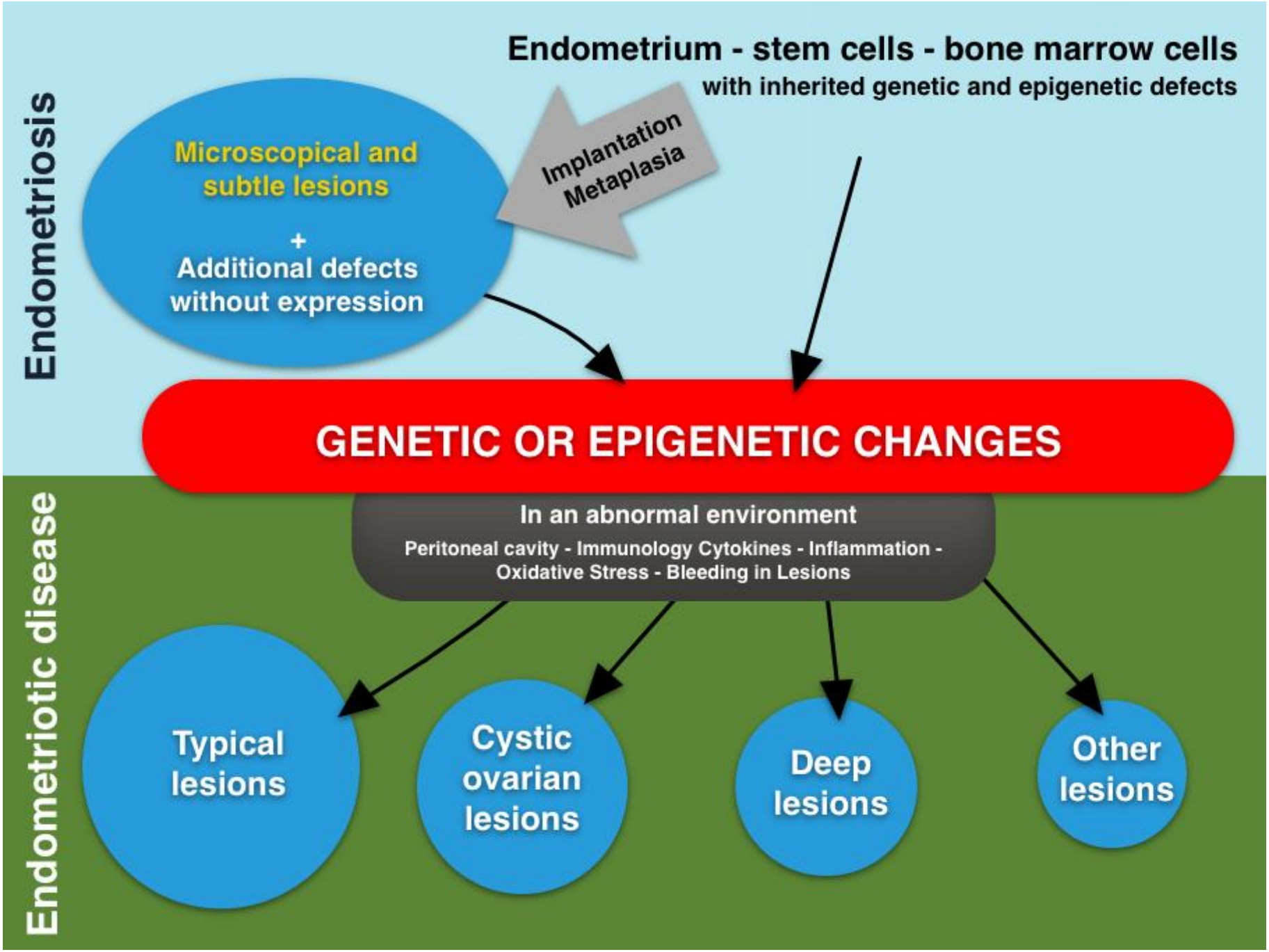
In very large groups
Minor differences
Become significant



Hidden subgroups

- RCT cannot detect or exclude a smaller subgroup with a different effect




Endometriosis
Endometrium - stem cells - bone marrow cells
with inherited genetic and epigenetic defects
Microscopical and subtle lesions
+
Additional defects without expression
Implantation
Metaplasia
GENETIC OR EPIGENETIC CHANGES
In an abnormal environment
Peritoneal cavity - Immunology Cytokines - Inflammation - Oxidative Stress - Bleeding in Lesions
Endometriotic disease
Typical lesions
Cystic ovarian lesions
Deep lesions
Other lesions

Clinical evidence

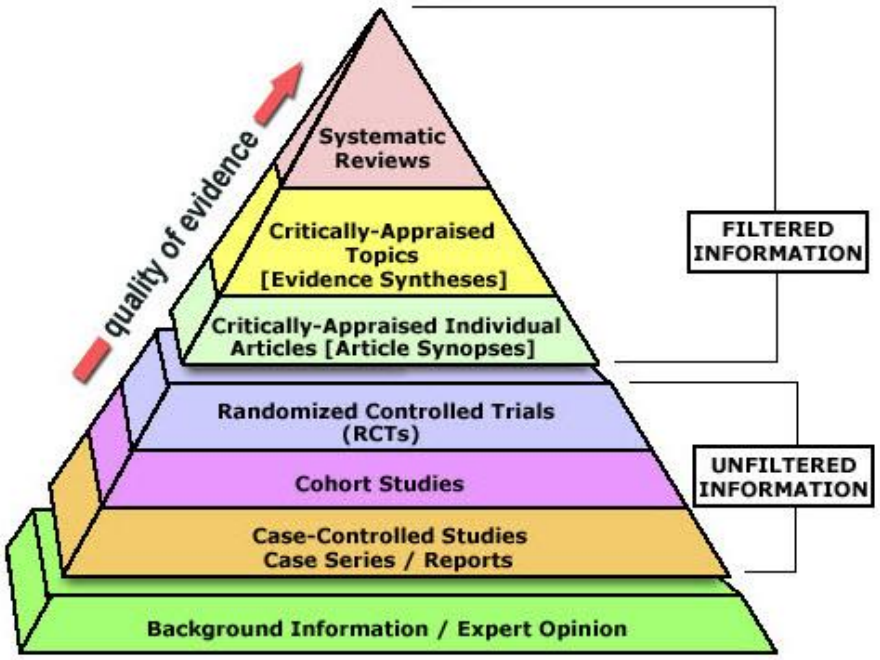
JMIG The Journal of Minimally Invasive Gynecology

Koninckx PR, Ussia A, Zupi E, Gomel V
2017: 24(5): 692-694.

Perspective

Evidence-Based Medicine in Endometriosis Surgery: Double-Blind Randomized Controlled Trial Versus the Consensus Opinion of Experts

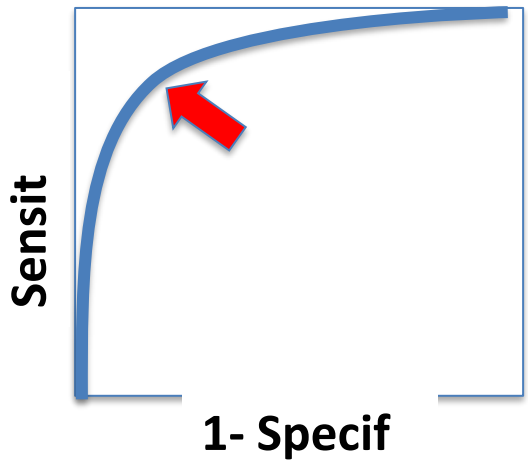
1. Clinical observation
2. Opinion- common sense
3. Consensus opinion
4. When unclear
   do a trial
   if possible

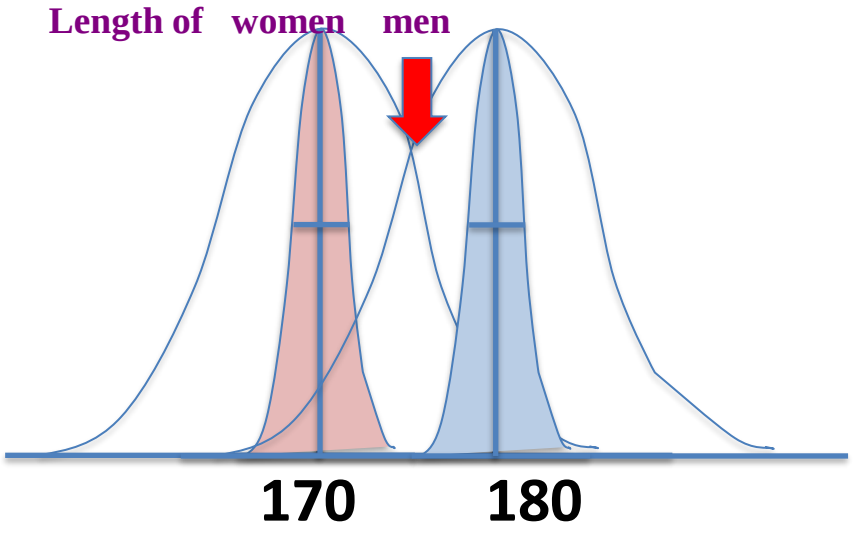


Diagnosis

- Although significant
- Not clinically useful

- Sensitivity : independent of N
- Specificity : independent of N
- ROCurve





		Test +	Test -
Disease	+	Sensit	
	-		Specif
		Total +	Total -

Ask clinical questions

- Clinically Wrong question
  - What is the diagnostic accuracy of ultrasound for deep endometriosis
- Clinically right question
  - What is the diagnostic accuracy of ultrasound

    for a nodule of 0,5 cm, 1cm…. = Stratification by size

    At the level of the sigmoid, the rectosigmoid …. = stratification by localization

    After previous surgery and fibrosis = stratification by previous surgery

- Clinically **Wrong** question
  - Are men taller than women
- Clinically **right** question
  - Which race ? Which country ? When in history ?

Pandora's box : statistical problems

- **Therapy : at least statistical significance**
  - Statistical evidence is only a probability
  - Statistical significant does not mean clinically useful

    Increases with N = magnitude of effect
  - Realise the limitations of a trial

    Non blinded trials on pain or well being have little value

    The problems of Extrapolation

    Rare events and subgroups
- **Diagnosis = sensitivity and specificity**
  - Statistical significant cannot judge a diagnostic test
  - Value of a diagnostic test = clinical judgment
  - Clinical stratification

The player bias

- 3 different (sub) specialist with their biases
  - Infertility specialist

    Medical treatment specialist

    Surgeon
- Subtle manipulation
  - Data eg Intention to treat analysis (removal of outlyers)
  - Study design : non-inferiority design, comparator drug
- Industry
  - drug therapy : almost all studies industry organised
  - surgical therapy : almost no industry organised trial

Pandora's box : the player bias

- **3 different specialist**
  - 3 specialists with their biases

    Diagnosis of endometriosis without a laparoscopy

    Missing endometriosis at laparoscopy
- **Subtle manipulation**
  - No intention to treat analysis
  - Study design, comparator drug
- **Industry**
  - Industry support for congresses and individuals
  - Industry support of medical trials – not of surgical trials
  - Non favourable trials are not published : publication bias

Diagnosis of endometriosis

- Superficial endometriosis : only by laparoscopy
- Cystic ovarian endometriosis = US
- Deep endometriosis
  - Clinical suspicion

    10-50% are diagnosed clinically

    Ultrasound

      Accurate diagnosis when larger

      Unclear value for smaller lesions

No test can exclude endometriosis

Endometrioma by ultrasound

Age & diameter

<1 **1-3** **3-6** **> 6**

No symptoms

either wait

- how long ?
- if not growing
- age

or laparoscopy

- excision
- ablation

Infertility

IVF without full fertility work-up

Is not recommended

Pain

laparoscopy

diagnosis

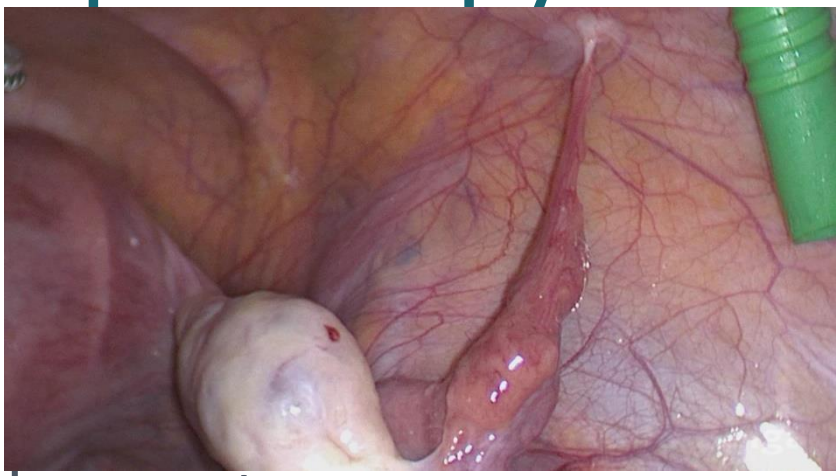
treatment

- 2 step
- ovariectomy

Evidence Based medicine <-> Evidence based clinical medicine

we do not treat endometrioma's we treat patients

Infertility : when a laparoscopy ?



- Yes
  - if associated pain
  - If big cystic endometriosis
- ? When infertility is the only symptom
  - Calculated risk : overtreatment
    missing treatable pathology
  - The exact place of THL is still unclear
- No when IVF is anyway indicated

Neither clinical exam nor imaging can exclude pelvic pathology
adhesions and or endometriosis

During Diagnostic laparoscopy (THL ?)

- If surgery is indicated
  - Perform surgery if skilled
  - Otherwise refer

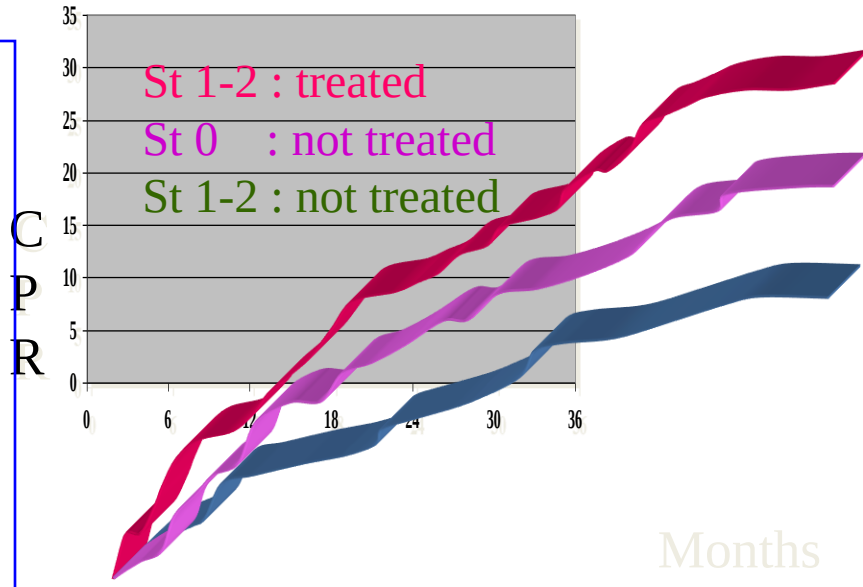
- 3 Groups
  - Surgery indicated for reasons other than fertility
    - Very severe pain + deep endometriosis, cystic ovarian endo, frozen pelvis
    - Symptomatic myoma
  - Surgery indicated beyond reasonable doubt
    - Hysteroscopic polypectomy, small myomectomy, septum
    - Superficial endometriosis
    - Filmy peritubal-peri-ovarian adhesions
  - Unclear indications Surgery<->IVF
    - Ovarian drilling (under water) for PCO
    - Deep endometriosis without pain, asymptomatic severe adhesions
    - Smaller cystic ovarian endo
    - Tubal occlusion : hydrosalpinx , cornual block

Results of treatment

- Infertility
  - Surgical treatment : Endocan study (R. Maheux et al)

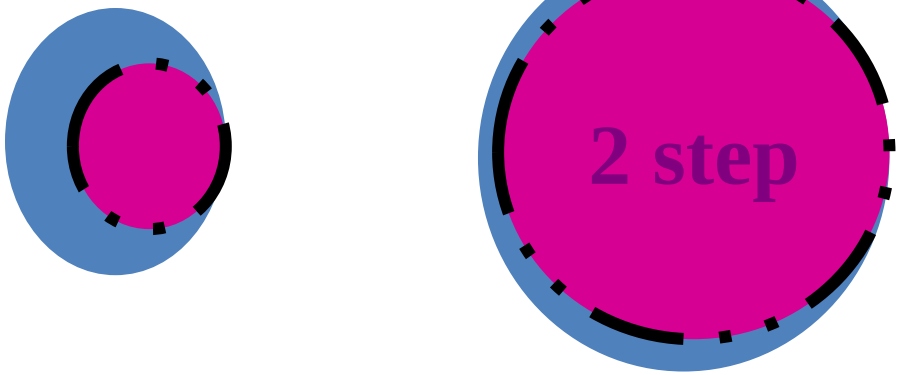
    Stage I and II and no other infertility factor

- **Discussion**
  - **Patient not blinded to treatment**
  - **Increase in treatment or**
  - **decrease in non treatment ?**
  - **LUF and stress**
  - **Trait anxiety and fertility**

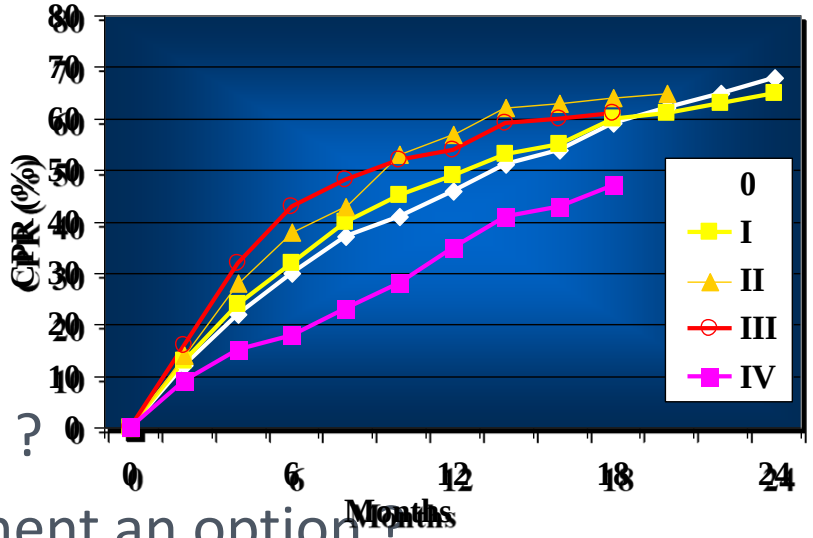


Cystic ovarian endometriosis

- > 6 cm = 2 step



- Smaller
  - Excise
  - Do not destroy the ovary
  - Fertility : CPR 60%



- The Questions are
  - Judgment without a laparoscopy ?
  - During laparoscopy : is no treatment an option ?
  - Unclear : smaller and recurrences

Deep Endometriosis and infertility

- Huge variability in techniques
- Poorly documented fertility explorations
- Series too small for meaningful analysis eg size
- spontaneous pregnancy rates of 25-60%

- Indication for surgery is pain not fertility

- Data suggest a negative effect of deep endometriosis on fertility without treatment

Surgery for endometriosis

Pain and infertility

- 1 double blinded RCT on superficial endometriosis& pain
- Many observational studies for cystic ovarian endometriosis or deep endometriosis
  - Strong evidence of pain relief by postop clinical exam
  - Strong evidence of improved fertility after cystic ovarian endo

Recurrence rate

- 5-15% for cystic ovarian endometriosis
- 1% for deep endometriosis

Prevention of progression

- ??

Pandora's box : Surgical therapy

- **Only 1 valid double blinded RCT for pain**
  - **Huge placebo effect in the control group**
- **Absence of quality control of surgery**
  - Indication – severity of endometriosis
  - Skill of the surgeon
  - Videoregistration
- **Solid evidence for**
  - **Pain relief of cystic and deep**
  - **Improved fertility of cystic**

Medical treatment of endometriosis

- For infertility : not useful
- For pain :
  - therapy affecting menstruation cannot be blinded
  - Inclusion criteria for pain trials are pain and ‘laparoscopic and/or histologically proven endometriosis in the last 1, 2 or 3 years’.

“However, during this diagnostic laparoscopy necessary to confirm endometriosis all visible superficial and cystic lesions of endometriosis are generally excised or coagulated. In such cases it would be questionable whether the remaining pain is still caused by endometriosis.

  - Direct and indirect evidence that medical therapy decreases pain in some women

Human Reproduction Vol.23, No.9 pp. 2017–2023, 2008
Advance Access publication on June 12, 2008
doi:10.1093/humrep/den177

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

P.R. Koninckx[1,2,4], M. Craessaerts[1], D. Timmerman[1], F. Cornillie[3] and S. Kennedy[2]

- Huge placebo effect

Pandora's box : Medical therapy

- **No blinded RCT for pain**
  - **No study of placebo effect**
  - **No study on observer bias**
- **Inclusion criteria of 'proven endometriosis'**
  - Unclear whether endometriosis causes persisting pain
- **Unproven assumptions and extrapolations**
  - Life long treatment

    ?? medical treatment prevent progression

    ?? Lower recurrence rates
  - In all women

    An heterogeneous disease
- **Medical therapy without a diagnosis**

Sequential therapy

Infertility

- Surgery followed by IVF
- IVF followed by surgery

Reproductive surgery in the 21th century

Philippe R Koninckx MD. PhD.*, Anastasia Ussia MD. **, Leila Adamyan MD. PhD. *, Victor Gomel MD. ****

In press in : Global reproductive health

Pain

- Surgery followed by medical treatment
  - To prevent progression ?
- Medical treatment followed by surgery
  - Risk to miss lesions

The clinical reality

- Delay in diagnosis
- Laparoscopy is avoided
  - Variable quality of surgery
  - Ovarian damage
  - Complications
  - Surgery during laparoscopy not available
- IVf without a laparoscopy
  - Surgery+IVF versus IVF
- Limited referrals between the different specialists

Suggestions for improvement

‘Centers’ should have all 3 specialists

Focus on what we agree upon

1. A woman with pain and/or infertility has a 50% probability of typical endo.
2. Medical treatment over long periods without a diagnosis is not recommended.
3. Superficial endometriosis can only be diagnosed by laparoscopy.
4. Medical therapy can reduce pain but is ineffective for infertility and for cystic ovarian endometriosis.
5. It is unknown whether medical therapy prevents progression in all women
6. Diagnostic laparoscopy should be recorded to permit subsequent confirmation of diagnosis and of completeness of diagnosis.
7. It is preferable to have the possibility to do surgery during diagnostic laparoscopy
8. Quality control of surgery is only possible with video-registration
9. Informed consent requires the patient to be given correct information on the indication, planned intervention and level of experience of the surgeon.
10. EBM should be based upon the best evidence available. This includes rare events and the limitation of RCT’s.
11. Our actual clinical management based on experience should be kept unless proven otherwise

Basics of endometriosis lesions

	Prevalence	Pain	Infertility
• Subtle :	80%	no	no
• Typical :	25%	in 50% +	?
• Cystic :	10%	in 80% +++	++++
• Deep :	2-3%	in 95% ++++	???

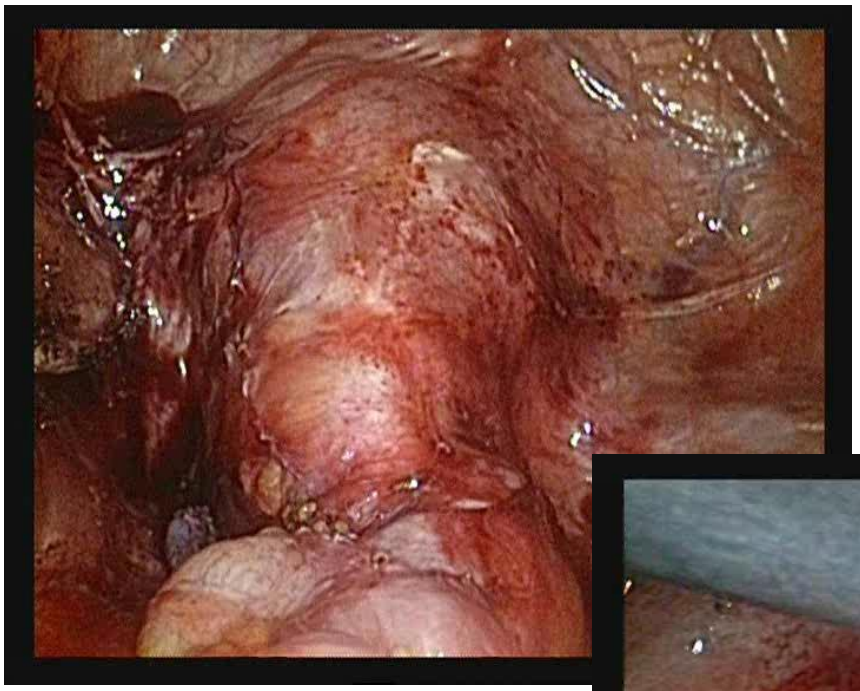
- Adenomyosis
- Peritoneal pockets – Müllerianosis - Choristoma

Expertise required

pain ++

perineal

Radiation



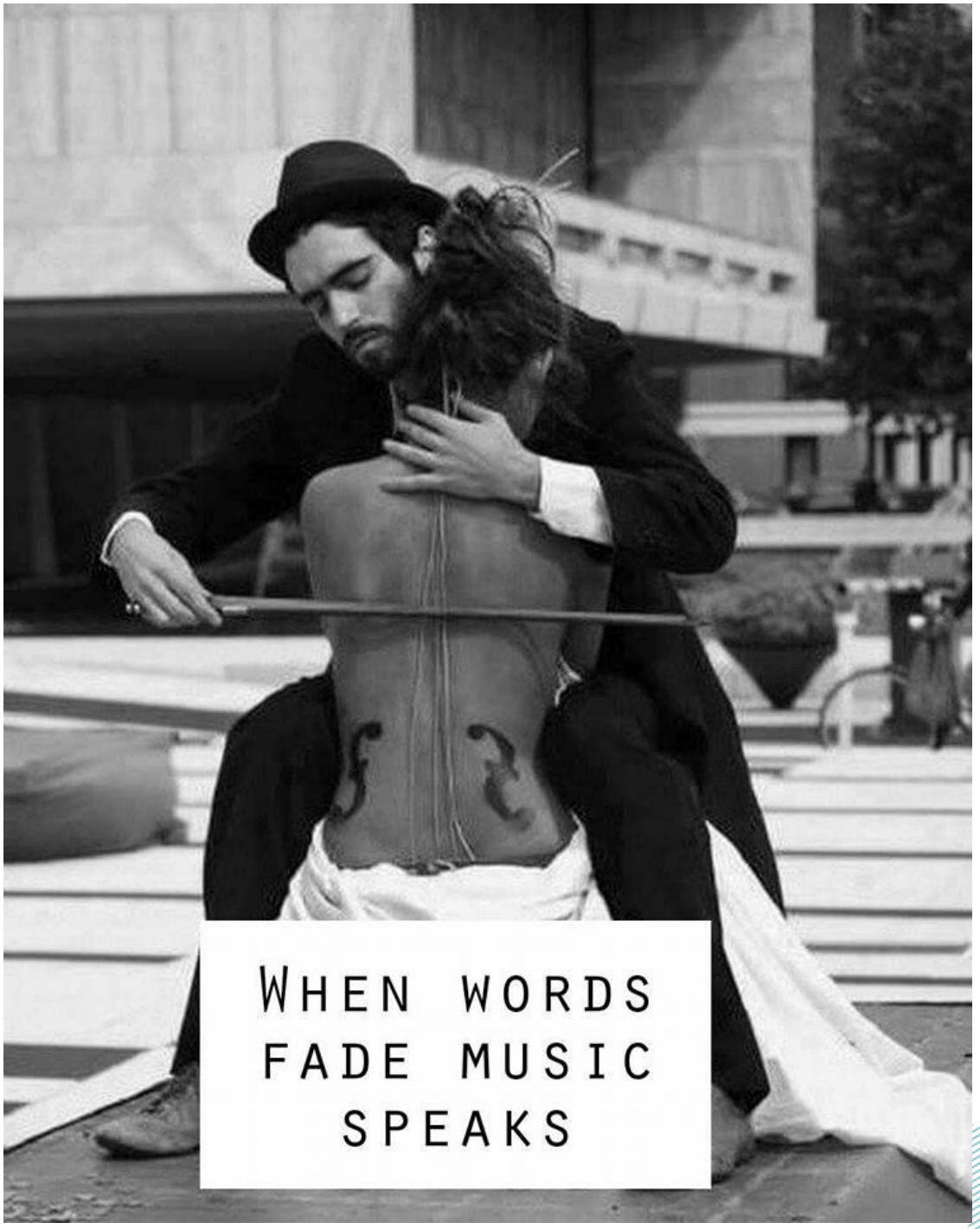
All exams Negative

Clinical, MRI, contrast enema

hysterectomy

Surgery

is like

music

Quality control