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Running title: Evidence based medicine and endometriosis treatment

Evidence based medicine: Pandora's Box of medical and surgical treatment of endometriosis.

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Precis

Pandora's Box of evidence based medical and surgical therapy of endometriosis.

Abstract

Evidence based medical and surgical therapies of endometriosis remain debated. A discussion of their limitations and pitfalls might help the clinician.

Statistical evidence, including the RCT, is the probability that the means of 2 populations or therapies are different. Since the accuracy of the estimation of the mean increases with sample size, significance increases with sample size. Mathematical significance however may not indicate clinical usefulness since this requires some magnitude of the effect. In addition, results are valid only for the group investigated as defined in inclusion and exclusion criteria.

Solid evidence on the treatment of pain associated with endometriosis is limited. Indeed double blind trials are needed for endpoints as pain and well-being because of the placebo effect and the observer bias. This unfortunately is not possible for medical therapies when menstruation is affected or for surgery for ethical reasons.

For endometriosis therapy, publication bias is huge and quality of information is low. For medical therapy the main problems are the non-published trials and the huge commercial interest in trial outcome. For surgery the main problem is the limited numbers of interventions by surgeon, the variability in surgical techniques, in surgical skills and in complexity. A single center trial therefore risks not having sufficient power whereas a multicenter trial risks evaluating rather the surgeon not the intervention. Information on accidents and rare events and are limited to case reports and observations.

In conclusion it seems wise to reconsider the evidence for the treatment of endometriosis knowing the limitations of non-blinded trials for pain and the variable quality of surgery

Keywords : endometriosis; medical therapy; surgery endometriosis; endometriosis therapy

Introduction

In the absence of an adequate animal model, endometriosis remains a poorly understood disease. Its pathophysiology and epidemiology are debated, the natural history is unknown and the treatment remains controversial(1). "Endometrial glands and stroma located outside the uterus" as definition of endometriosis may not always represent a pathological condition(2). Therefore the disease causing pain and/or infertility and other symptoms needs other definitions. The prevalence and epidemiology are unclear because a laparoscopy is needed to make the diagnosis and because of the variable inclusion of subtle lesions (3). Although Sampson's theory remains the widely accepted theory explaining the pathophysiology, evidence obtained during the last decade permits us to postulate that genetic or epigenetic changes are required for symptomatic endometriotic disease to develop while the original cells are less important. These can be adult or neonatal endometrium, stem cells or bone marrow derived cells(4). The type of genetic or epigenetic changes will determine the progression to typical, cystic ovarian, deep pelvic or extra-pelvic lesions; these can be considered as different diseases. However, all types of endometriosis continue to be perceived as one disease, because of the concept of retrograde menstruation with implantation and progression of these normal endometrial cells due to their presence in an abnormal environment.

The medical or surgical treatments of endometriosis are hampered by the poor correlation between the severity of symptoms and the severity of lesions. Trials are usually performed with 1 type of therapy. Also, during meetings alternative therapies are generally presented by 2 different speakers, this often organized as a debate. The strengths of the evidence of each therapy are judged by statistical evidence and by the quality of the study design and the conclusions are summarized in evidence based medicine (EBM) guidelines. We should realize that this conglomerate of many little pieces of evidence suits our Western world's Cartesian thinking that believes: "understanding improves by dissecting a problem in small parts."

Clinical medicine is different from research and requires a holistic approach of the person, which unfortunately is practically impossible to mimic in a huge comprehensive trial. Research on pathophysiology, diagnosis and treatment of endometriosis provides data, which are

obviously useful to know. Clinical medicine is not limited to the results of specific trials but comprises all women and pathologies including those with multi-morbidities. The necessary translation of research data into clinical medicine requires clear awareness of the limitations of evidence produced by trials. It requires an understanding of statistical significance and of the absence of evidence together with an awareness of the limitations of each trial design, which balances between ideal and realistic, due to the human bias confronted with massive information. We do indeed judge the available data, with our educational background during the (limited) time available to us, and probably colored by our beliefs. The conscious awareness of how each of these elements are influencing our judgment might help to understand better the medical and surgical treatment of endometriosis which has recently be called a 100 years' war (1).

Materials and Methods

A systematic review of each of the over 40.000 articles in the literature is realistically impossible and the result would be clinically irrelevant because of the many opposite opinions. To restrict the number of articles according to whatever predefined elements of quality, as done in most reviews and meta-analysis or guidelines, is not a solution since occasional accidents, complications and case reports will be missed. We therefore shaped this article as a critical appraisal of the clinical practice of each of the authors in treating women with endometriosis as developed by reading the literature, attending congresses and mainly after many hours of discussion.

Statistical evidence and the population

A law of physics is evidence, since based on repeatable observations without a single exception in the given circumstances. The often-heard statement that there is no 'evidence' for a parachute or for a guillotine therefore does not take into account that this evidence belongs to this type of law-evidence.

Statistical evidence of an effect is based upon the probability that an observed difference is true. This statistical evidence known as "significance" remains a probability, comprising spurious significances and a (small) probability of error. Significance increases with the number

of observations. Therefore absence of statistical difference does not permit a conclusion. Conclusions are limited to the group of subjects investigated, i.e. matching exactly the inclusion and exclusion criteria as age, blood pressure, weight etc. The extrapolation of results to the entire population is always hazardous and based on judgment. To judge the effect of a therapy, a statistical or mathematical significant difference although being an obvious prerequisite, is not sufficient for clinical usefulness since this requires some magnitude of the effect. More subtle is the clinical usefulness of diagnostic tests. Their value is evaluated statistically by their sensitivity and specificity for a given population, whereas their clinical usefulness of these values has to be judged clinically. Clinical judgment indeed has to decide whether a test with 10% false positives and 10% false negatives, i.e. with 90% sensitivity and 90% specificity, is clinically useful. Statistical differences should not be inverted as useful predictors: although men are significantly taller than women, height is a poor predictor of sex. Clinical usefulness of a test often needs clinical stratification of prediction. Indeed, that 'ultrasound highly accurately predicts the presence of a deep endometriosis nodule' has limited clinical usefulness. Although true for all nodules taken together, it is not necessarily true for all sizes of nodules and does not permit to judge the lower detection limit. A third limitation is that any investigated population may hide a smaller subpopulation with a different or opposite effect. An example taken from deep endometriosis is that it took 20 years before we realized that a small sub-group had bowel perforations during pregnancy, (5) which is the opposite of the regression expected during pregnancy. The limitations of evidence, clinical usefulness and statistical significances hold true for all forms of statistics. The many pitfalls of statistics include the subtle and probably not intended misuse of statistical analysis (6-8). In conclusion statistical evidence of differences is very useful in research, but does not necessarily permit a judgment of clinical importance, which is mainly based on the magnitude of the (significant) effect and on specificity and sensitivity of a specific diagnostic question.

A prerequisite for statistical evidence are identical populations and the absence of a bias in observation. Population bias requires strict randomization. For easily measurable endpoints as height and weight or pregnancy observation bias is minimal. For endpoints as pain and well-being observation biases can be strong. These are known as placebo effects and observer bias.

Therefore double blind trials are mandatory to obtain evidence for these endpoints. Statistical analysis cannot make up for poor data collection since the level of a river cannot rise above its source.

The EBM pyramid of evidence is mathematically fully valid with the confirmed double blind randomized controlled trial on top of the pyramid. Unfortunately the many restrictions are rarely highlighted. A first obvious restriction is that a significance of 0.05 means 95% probability of being true but also a 5% probability of being wrong. A second restriction is that the most perfect randomization of the population cannot ascertain a homogeneous effect since a small hidden population with a different/opposite effect will not be detected. A third major problem is that rare events need huge trials to be detected. Indeed an event occurring in 1% requires a prospective trial of some 3000 women to find 30 events, which is the numbers needed for meaningful statistics. The fourth and most important problem is that endometriosis and its therapy has so many important variables that a trial permitting to take each of them into consideration becomes unrealistic. This problem is similar to multi-morbidity, which is not suited for a RCT.

The Pandora's box of EBM and endometriosis treatment comprises all forms of incorrect use of evidence (6-8) and of ignoring the limitations of trials. Accidents as someone falling over cables in the OR causing an electrical black-out with injury to the patient is a rare event with solid evidence of a causal relationship between cause and effect. However, this will not be picked up in a RCT. Randomization to achieve comparable populations and double blinding for pain or well-being trials are important for medical and surgical therapy. The value of a non-blinded trial for pain or well-being as endpoints is questionable. Rare events and complications or accidents will only be picked up by observational medicine. Moreover, surgical trials inherently comprise important additional variables that are the surgeon and the quality of surgery.

The 'Player' and the endometriosis bias

The all-round gynecologist educated in and mastering both advanced surgery and basic endocrinology no longer exists, as a consequence of sub-specialization and the sheer amount of data. Even those of us trained initially in one aspect of the discipline will rapidly become less up

to date after moving to another one. Like a woman loves her children we all have the biases of our interests.

The 'non spoken' reality is that each of the many factors as environment, ambition, work, hazard, publications, grants, congress presentations etc. matter for our careers. Affiliated to University or industry, young or old, researchers and academics have common interests in patents, publications and presentations. This translates in grants for research, travel grants, visibility and in publications that ultimately help for promotions and/or private practice.

Endometriosis has 2 specific biases. The severity of disease often becomes fully apparent only during surgery. The absence of a validated classification hampers comparison of results.

Pandora's Box of endometriosis includes the margin of error when the diagnosis is made without resort to a laparoscopy and the absence of a validated classification system. The player's bias contains all forms of imperfect data and their interpretation due to personal interests. Since data manipulation can be insidious and since the 'honest' removal of outliers can be subjective, intention to treat analysis was introduced. Both surgical and drug companies assist individuals and societies with research and travel grants, and provide support to congresses. The budgets of surgical companies are relatively small and they are rarely directly involved in trials. On the contrary all major trials of medical treatment of endometriosis were organized by the pharmaceutical industry. Although these trials were scrupulously randomized and monitored, the subtle manipulations of trial design is rarely discussed. Examples are the choice of the comparator drug and non-inferior analysis. A much bigger problem is that many trials with unfavorable results are either stopped after interim analysis, or not published as evident by the analysis of registered RCT's (9). This difference in support provided by the surgical industry is a reason why surgical trials are smaller and often poorly monitored. Fortunately, the overall integrity of both medical and surgical gynecologists is high.

Medical therapy revisited

For infertility medical therapy of endometriosis is not useful (10). To the best of our knowledge the TNFa trial (11) was the only double blind RCT that evaluated pain associated with

endometriosis. Remarkably, in this trial there was a very strong placebo effect. Indeed with placebo infusions some women who previously needed monthly morphine injections became almost pain free. All trials affecting menstruation unfortunately were not blinded since the women were aware of their menstruation. Another specific bias of all major endometriosis trials is the inclusion criteria, which used to be 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.

However, this statement does not completely invalidate the many observations that medical treatment decreases endometriosis associated pain (12-14). A decrease in pain indeed seems logic since in the absence of estrogens and/or presence of progestogens the endometrium stops to grow and decidualizes. Less well documented are the long-term effects (15) as to the prevention of progression or recurrence. Data are limited to a slightly lower incidence of typical lesions after years of treatment with oral contraceptives and on lower recurrence rates of cystic ovarian endometriosis during treatment. There are no data that permit the conclusion that medical treatment prevents the onset of endometriosis or the progression of subtle lesions or of deep endometriosis or extra-genital endometriosis. There are no data that progression is prevented in all women as suggested by the occasional women with severe endometriosis after more than 10 years of medical treatment (personal observations).

It is surprising that no attention was paid to the effect of medical therapy on the steroid hormone concentrations in peritoneal fluid, a space in which peritoneal endometriosis grows.

The Pandora box of medical therapy is that in non-blinded medical trials with GNRH, progestins or estro-progestins the placebo effect was poorly investigated if not ignored. Also observer bias was not investigated. Inclusion criteria of most trials make it questionable that the pain these women were experiencing was due to endometriosis after having been surgically removed. This contrasts sharply with the widely held belief of efficacy and the recommendations of life long treatments to treat pain and to prevent progression. Another

major problem is the frequent use of medical therapy for longer periods of time in women with pain, suspected of endometriosis, but without a documented diagnosis.

Surgical therapy revisited: individual experience

A laparoscopy is needed to diagnose superficial endometriosis, during which typical lesions can be excised, vaporized or coagulated(16). The proof of efficacy of this treatment is limited to one double blind randomized trial for pain (17). This trial moreover demonstrates a huge placebo effect for several months whereas the magnitude of effect is highly variable. Surgical treatment of superficial endometriosis to increase infertility is unclear. Indeed the "Gruppo Italiano" did not find an increase in fertility. The Endocan trial on the contrary was not blinded (18) and it is unclear whether pregnancy rates increased after surgery, or whether pregnancy rates decreased in the control group as a result of the stress caused by the awareness that the endometriotic lesions had not been removed. . However, in view of the low surgical risks associated with the procedure not to treat would not be an option.

Cystic ovarian endometriosis is diagnosed by ultrasound. After surgery, - excision or vaporization- spontaneous cumulative pregnancy rates are 50% to 60% and recurrence rates vary from 5% to 20%. To undertake a trial designed to evaluate whether surgical treatment and adhesiolysis affects progression, would ethically be questionable. The outcome of a surgical intervention seems to vary with the surgeon (19). A special problem is the small cystic ovarian endometrioma especially in young girls (20). Indeed, since both an endometrioma and surgery can damage oocyte reserve, and considering a recurrence rates between 5% and 20% the decision to perform surgery balances between the risk that the cyst become bigger and the risk of repetitive surgery. Although poorly defined, deep endometriosis is associated with severe pain in most women and severe bowel and ureter problems in some. The natural history is not known but clinical observation suggests that most lesions are no longer progressive, when the diagnosis is made. However, some such lesions may progress rapidly. The added value of ultrasound and MRI for the diagnosis and the radicality of surgical excision or the need of bowel resection remains debated. Notwithstanding the reported postoperative 20% to 50% spontaneous cumulative pregnancy rates it is unclear whether surgery improves fertility. Pain

relief is well documented albeit not in randomized controlled trials (21), the feasibility and ethical aspects of which would obviously be questionable. The recurrence rate of deep endometriosis nodules is rare (less than 1%) as observed by deep endometriosis surgeons, whereas recurrence of pain and of subsequent surgery is at least 20%. Deep endometriosis surgery is difficult and complication prone.

Besides the technical aspects the 'experience' of the surgeon and his knowledge of the disease endometriosis are important. The symptoms of the patient, findings of preoperative imaging and the patient's expectations as revealed by preoperative counseling, modulate the specific type of intervention performed. Although all surgeons are strongly aware of this aspect, it cannot be found in publications. Moreover, this aspect would not be compatible with a randomized controlled trial.

Pandora's Box of surgical treatment of endometriosis is the absence of quality control. Indeed without video-registration neither the diagnosis, nor the completeness of excision especially from the bowel or the ureter, nor the ovarian damage caused, nor the skills of the surgeon can be judged (22). The latter has become even more important since we know that duration of surgery and the extent of manipulation are key factors in adhesion formation (23). That preoperative findings will influence choices made during surgery is an element to consider in multidisciplinary approaches.

Sequential therapy

Surgical therapy can be followed by medical therapy. Although this is widely used in order to prevent progression of disease data are limited. Any data moreover are hampered by the absence of information about the completeness of surgical diagnosis and surgical treatment without video registration.

Medical therapy can be followed by surgery. Clinical observation of very severe endometriosis after many years of medical therapy in women with increasing symptoms suggest that endometriosis has been progressive in these women. Also a frozen pelvis is a common observation after repetitive IVF cycles in women with deep endometriosis. In young symptomatic women it is unclear how to balance early diagnosis and surgery versus medical treatment. In the absence of data this discussion seems

based on the belief whether endometriosis is a recurrent disease after complete excision. If not early surgery seems preferable; otherwise it seems wise to postpone surgery as much as possible.

The clinical reality of endometriosis treatment

The clinical reality of endometriosis begins with the frequent delay in diagnosis, either because endometriosis is not considered when clinical examination and ultrasound findings are negative, or to avoid a diagnostic laparoscopy, especially in young women (24). This reluctance is moreover fueled by the perception that the quality of surgery is variable; that surgery can ovarian damage, that the skills to treat an unsuspected severe endometriosis are not always present and that the quality of surgery is difficult to evaluate.

Surgery of superficial pelvic endometriosis is considered mainstream. Surgery of cystic ovarian endometriosis is technically difficult (25) although ovarian cysts were erroneously considered by bodies as the RCOG as the first level of surgery. The technical difficulty of larger deep endometriotic lesions is creating a shift towards pelvic surgeons and to technically skilled oncologists and abdominal surgeons with limited knowledge of the disease.

Medical therapy is widely used in women suspected of having endometriosis in order to avoid surgery and/or to prevent progression. It is widely used after surgery to prevent recurrences or because of incomplete surgical excision.

The increased success rate of IVF has led to frequent use of IVF even before undertaking a diagnostic laparoscopy.

The end result is that the information to the patient and the therapy given vary widely with the background of the doctor. The cost of treatment only recently began to be addressed (22).

Pandora's Box of clinical reality is that endometriosis specialist care is spread over fertility specialists, medical treatment specialists and surgeons. Referrals occur, but less frequently than necessary. A major problem is that the available evidence does not permit clear conclusions. Each of the three type of specialists noted above are undoubtedly honest, notwithstanding their differing opinions and forms of treatment.

Conclusions

The available results of endometriosis treatment unfortunately are not very clear. The perception that medical versus surgical treatment of endometriosis is a 100 year war is caused by the fact that the weaknesses and limitations of each type of therapy are rarely addressed in the title and abstract of original articles but at best discussed and thus hidden in the discussion.

The limitations of the noninvasive diagnosis of minor forms of endometriosis remain a major problem. Symptoms not always reflect severity of the disease and biochemical markers and imaging still are not very useful. For cystic ovarian and for deep endometriosis the combination of complete anamnesis, ultrasound investigation with high-resolution machines and MRI by well trained radiologists may give us information for the choice of further therapeutic steps.

All various surgical techniques should be available in the same institution to avoid a bias due to lack of surgeons with proper training and expertise. An option could be to create centers of excellence with expertise in every aspect of the disease: diagnosis, both medical and surgical treatment and proper follow up of the patients.

It would be useful if we could focus on what we agree upon, without being polemic. This could become the basis of the information given to women with pelvic pain, infertility or endometriosis. Available evidence permits us to make following statements. 1. A woman with pain and/or infertility has a 50% (26) probability of having typical endometriosis or worse. 2. Medical treatment of endometriosis over long periods without a diagnosis is not recommended. 3. Superficial endometriosis can only be diagnosed by laparoscopy. 4. Medical therapy of endometriosis can reduce pain but is ineffective for infertility and for cystic ovarian endometriosis. 5. It is unknown whether medical therapy prevents progression of deep endometriosis 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 treat the disease as part of the diagnostic laparoscopy. 8. Quality control of surgery is only possible with video-registration of the entire intervention. 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.

Reference List

1. Vercellini P, Vigano P, Buggio L, Somigliana E. THE HUNDRED YEARS' WAR BETWEEN EXPERTS OF SURGICAL AND MEDICAL TREATMENT FOR SYMPTOMATIC DEEP ENDOMETRIOSIS. JMIG 2017;in press
2. Koninckx PR, Donnez J, Brosens I. Microscopic endometriosis: impact on our understanding of the disease and its surgery. Fertil Steril 2016;105:305-6.
3. Koninckx PR, Ussia A, Keckstein J, Wattiez A, Adamyan L. Epidemiology of subtle, typical, cystic, and deep endometriosis: a systematic review. Gynaecol Surgery 2016;13:457-67.
4. Gordts S, Koninckx PR, Brosens I. Pathophysiology of deep endometriosis. Fertil Steril 2017;in press.
5. Setubal A, Sidiropoulou Z, Torgal M, Casal E, Lourenco C, Koninckx P. Bowel complications of deep endometriosis during pregnancy or in vitro fertilization. Fertil Steril 2014;101:442-6.
6. A R. Statistics done wrong. San Francisco: William Pollock, No starch press, 2015.
7. J C. How to lie with statistics. LLC: Unlimited Press Works 2015.
8. D H. How to lie with statistics New York, London: WW Norton & company, 1982.
9. Guo SW. An overview of the current status of clinical trials on endometriosis: issues and concerns. Fertil Steril 2014;101:183-90 e4.
10. Hughes E, Fedorkow D, Collins J, Vandekerckhove P. Ovulation suppression for endometriosis. Cochrane Database Syst Rev 2003:CD000155.
11. Koninckx PR, Craessaerts M, Timmerman D, Cornillie F, Kennedy S. Anti-TNF-alpha treatment for deep endometriosis-associated pain: a randomized placebo-controlled trial. Hum Reprod 2008;23:2017-23.
12. Casper RF. Introduction: A focus on the medical management of endometriosis. Fertil Steril 2017;107:521-2.
13. Bedaiwy MA, Allaire C, Yong P, Alfaraj S. Medical Management of Endometriosis in Patients with Chronic Pelvic Pain. Semin Reprod Med 2017;35:38-53.
14. Bedaiwy MA, Allaire C, Alfaraj S. Long-term medical management of endometriosis with dienogest and with a gonadotropin-releasing hormone agonist and add-back hormone therapy. Fertil Steril 2017;107:537-48.
15. 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.
16. Gizzo S, Conte L, Di Gangi S, Leggieri C, Quaranta M, Noventa M *et al.* Could surgeon's expertise resolve the debate about surgery effectiveness in treatment of endometriosis-related infertility? Arch Gynecol Obstet 2015;292:217-23.
17. Sutton CJG, Ewen SP, Whitelaw N, Haines P. Prospective, randomized, double-blind, controlled trial of laser laparoscopy in the treatment of pelvic pain associated with minimal, mild, and moderate endometriosis. Fertil Steril 1994;62:696-700.
18. Marcoux S, Maheux R, Berube S. Laparoscopic surgery in infertile women with minimal or mild endometriosis. Canadian Collaborative Group on Endometriosis [see comments]. N Engl J Med 1997;337:217-22.
19. Muzii L, Miller CE. The singer, not the song. J Minim Invasive Gynecol 2011;18:666-7.

20. Gordts S, Puttemans P, Gordts S, Brosens I. Ovarian endometrioma in the adolescent: a plea for early-stage diagnosis and full surgical treatment. Gynecol Surg 2015;12:21-30.
21. Donnez J, Squifflet J, Pirard C, Jadoul P, Wyns C, Smets M. The efficacy of medical and surgical treatment of endometriosis-associated infertility and pelvic pain. Gynecol Obstet Invest 2002;54 Suppl 1:2-7.
22. Van Voorhis BJ, Sparks AET, Allen BD, Stovall DW, Syrop CH, Chapler FK. Cost-effectiveness of infertility treatments: A cohort study. Fertil Steril 1997;67:830-6.
23. Koninckx PR, Gomel V, Ussia A, Adamyan L. Role of the peritoneal cavity in the prevention of postoperative adhesions, pain, and fatigue. Fertil Steril 2016;106:998-1010.
24. Saridogan E. Adolescent endometriosis. Eur J Obstet Gynecol Reprod Biol 2017;209:46-9.
25. Muzii L, Tucci CD, Feliciantonio MD, Galati G, Verrelli L, Donato VD *et al.* Management of Endometriomas. Semin Reprod Med 2017;35:25-30.
26. Koninckx PR, Meuleman C, Demeyere S, Lesaffre E, Cornillie FJ. Suggestive evidence that pelvic endometriosis is a progressive disease, whereas deeply infiltrating endometriosis is associated with pelvic pain. Fertil Steril 1991;55:759-65.