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A call for new theories on the pathogenesis and pathophysiology of endometriosis

The Endometriosis Initiative Group

Running title: A call for new theories for endometriosis

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Introduction

This group was formed out of the conviction that endometriosis research has not progressed at a pace in proportion to disease severity and the negative impact on women's quality of life. Furthermore, advancement in our understanding of this condition requires a quantum shift based on new theories of disease pathogenesis. With this conviction, this international group calls for new theories that may improve the understanding of this condition, leading to optimized management or even prevention. To facilitate this, a dedicated website serving as a repository where all proposed theories can be reviewed and critiqued by peers will be created.

Back to square one

When preparing for the first World Congress on Endometriosis (WCE) in November 1986, the primary goal of the scientific program committee was to understand the activity of the disease. Why does endometriosis affect some, but not all women? Why does it progress in some, but not all of those affected? At that time, genetic predisposition [1], abnormal peritoneal inflammation [2], altered hormonal responsiveness [3], and altered general immunity [4] were already considered as potential and promising research pathways. Excepting epigenetic aberrations [5, 6], the stem cell hypothesis [7, 8] and somatic mutations in both eutopic and ectopic endometrium [9-11] all the other possible mechanisms proposed to explain the presence of endometrial-like cells outside of the uterine cavity were already published. Yet none of these putative mechanisms, which may occur in every woman, could individually explain why the disease occurs in some women but not others.

Nearly four decades later, minimally invasive surgery is the standard of surgical care, assisted reproductive technology (ART) has transformed the management of infertility, and imaging enabled diagnosis of several subtypes of endometriosis has somewhat reduced the need for laparoscopy for diagnosis. Among 34,508 PubMed-indexed publications on endometriosis to date, the vast majority of them (n=29,601, or 85.8%) were published after 1986 (https://pubmed.ncbi.nlm.nih.gov/?term=endometriosis&sort=date, accessed on January 17, 2024). However, treatment modalities of the disease are still limited to surgical excision, medically induced amenorrhea with or without hypoestrogenism and symptomatic therapies such as non-steroidal anti-inflammatory drugs and pelvic floor therapy. Recently, management based on patient reported outcome measures and experience of the disease was recommended to maximize the clinical benefits of these treatments [12].

Almost one century after Sampson proposed his retrograde menstruation theory [13], few know he also demonstrated the presence of “bits of endometrium” in uterine vessels during menses, already suggesting that a singular mechanism was not able to explain the variable clinical diseases associated with ectopic endometrium [14]. Many alternative hypotheses are proposed [15-20] and although generally based on observations, most are speculative by definition, limiting their wide acceptance.

Where Progress has been made

The Human Genome Project and other large-scale multinational programs have profoundly transformed biomedical research, introducing ever more sophisticated and powerful tools: microarrays, proteomics, metabolomics, metagenomics, next-generation sequencing, and,

recently, single-cell technologies, and spatial transcriptomics. Nearly every aspect of endometriosis has been explored or investigated with these technologies, albeit often with limited sample sizes and confounded controls.

Substantive clinical, cellular, or molecular differences between patients with and without endometriosis are increasingly reported, as well as differences in groups of patients with endometriosis. During the endometriosis meetings held in Edinburgh, Abu Dhabi and Rome in spring of 2023, numerous new findings were presented. These included the identification through genome-wide association studies (GWAS) of some 42 loci predisposing women to endometriosis, a threefold increase from previous studies [21]. Such results hold promise for the development of new diagnostic tools, or newer targets for drug development or repurposing. Despite concerns [22], microRNA-based non-invasive tools are also entering the market, promising to change the way to diagnose endometriosis [23, 24]. The possible role of microbiota in the development of endometriosis has been recently reported, suggesting that the role of infection in disease etiology should be taken seriously and further investigated [25]. These findings are obvious reasons for hope in endometriosis patients throughout the world. They provide the rationale for funding this fast-expanding research field, particularly when more sophisticated and powerful technologies, such as organoids, tissue engineering, and single-cell sequencing, are used increasingly for the studies in endometriosis [26-29].

However, closer scrutiny of these seemingly exciting discoveries leaves significant concerns. Firstly, the reports of microRNA-based biomarkers and the putative causal link between microbial agents and endometriosis are yet to be independently validated [22]. Second, despite years of work involving tens of thousands of patients, the 42 loci identified only explain approximately 2% of disease variance [21], meaning the vast majority of causes (>98%) are not accounted for by hereditary factors, although improved understanding of disease risk according to

sub-phenotypes might offer promise. Regardless, research requires reconciliation of genetic susceptibility and increasingly evident mismatch between evolutionary legacy and modern society [30-33], and for the contribution of *in utero* developmental factors and environmental insults to disease pathogenesis and pathophysiology [34]. Such technological advancements provide incremental knowledge and may possibly significantly improve patients' lives in the future, but to date have not led to a sweeping and revolutionary breakthrough in insight into endometriosis pathophysiology, leaving our understanding of the disease still limited.

We need fundamental changes in the ways we observe and interpret clinical, imaging, surgical and pathological data as well all research (whatever the research technique used) data that are acquired. In our opinion, if there is no change in the way we conceptualize the disease, no matter how much more data we accumulate and or how we acquire these data, it will add little to our understanding. We may not need to understand the disease causality to find new treatments, drugs or diagnostic tools. For instance, placebo-controlled studies of laparoscopic surgery informed us that recurrence of pain within 6 months probably has nothing to do with the development of *de novo* lesions but rather signifies the end of the placebo effect [35, 36]. Therefore, repeated surgery shortly after a previous unsuccessful one is unjustified with multiple medical and surgical RCTs [37], reporting very similar results in this regard.

A time for reflection and re-examination

Any and all new research theories regarding endometriosis should be developed, discussed and scrutinized at the outset, since no matter how fast a car travels, it will never reach its destination if going in the wrong direction. The beginning of the genomic era 20 years ago brought with it great hope and anticipation [38], especially with the reporting of the first genome-

wide study [39]. This approach is particularly attractive, since disease pathogenesis does not need to be known and it was predicted that it would radically transform diagnosis and treatment. Unfortunately, it turned out to be far more complicated than anticipated.

To date, basic science research has been too scant to substantively improve clinical outcomes in endometriosis, due, at least in part, to historically poor funding of this field. Both clinicians and patients are frustrated by the repeated failure of clinical trials involving non-hormonal drugs and even anti-estrogenic compounds - some rather surprisingly and unexpectedly [40, 41]. Compared with over 100 drugs approved for cancer since 1990, a paltry three (namely GnRH agonists, dienogest and GnRH antagonists) have been approved for endometriosis. Furthermore, none of these drugs that induce amenorrhea, were based on modern molecular and/or genomic approaches with specific targets identified. The disappointing stagnation in drug development is palpable among clinicians [42], as well as patients who often voice considerable dissatisfaction with the currently available hormonal drugs to treat endometriosis [43].

We recognize that major breakthroughs in science or medicine are unpredictable and do not occur overnight, with the translation of basic science discoveries to tangible clinical benefits often long and arduous. Hence, these frustrations may not be fully justified, since the field is progressing, and 40 years may still be considered too short to achieve desirable improvements.

Drawing from the roller-coaster experience during these 40 years, it is the conviction of this group that to transform the science around endometriosis, we need alternatives to the commonly accepted hypotheses and or new ways to investigate the current ones. This must be accompanied by more expeditious, well planned, and well-funded clinical trials for safety and efficacy. An alternative to the hand-waving saying that “endometriosis is a chronic, inflammatory, multifactorial, progesterone resistant, and complex disease” is urgently needed. Since the adjective “complex”, means “hard to separate, analyze, or solve” (Webster Dictionary),

using the word “complex” may be a tacit concession that we are unlikely to find an explanation for the cause of the disease and to significantly improve our care for symptomatic patients.

An alternative is also needed to the very often used proposition that “common sense tells us that endometriosis should be a progressive disease beginning with menarche and menstrual bleeding” [44], since age and the severity of the disease are unrelated [44]. Retrograde menstruation, stem cells, embryological remnants and/or metastases could occur or possibly occur in all women, yet endometriosis does not. Consequently, we need accurate mechanistic explanations rather than merely a “just-so” story, to understand why and how the disease begins and progresses to find effective therapeutic interventions.

To achieve this goal, we may need to move away from our “comfort zone” and not become complacent.

New and innovative theories/hypotheses are needed

Hopefully, new theories/hypotheses will be able to fully answer at least one of the questions as listed (Table 1).

(Table 1 about here)

Obviously, more questions will be added to this initial list. We suggest that a proposed theory/hypothesis would be summarized in 2000 words with one page for references and one page for proposed clinical and or basic research studies, designed to either confirm or refute the hypothesis.

All endometriosis researchers are encouraged to focus on addressing one or more of the questions listed above when conceiving, designing, and executing endometriosis studies and to collaborate with those in related and non-related disciplines to broaden the lens through which disease is seen.

Prerequisites for a good theory

While there is no shortage of hypotheses or speculations on the pathogenesis and pathophysiology of endometriosis, what is truly needed must be novel, innovative, and perhaps disruptive theories that may provide an explicit explanation of the causes of endometriosis. As Werner Heisenberg has stated, "what we observe is not nature itself, but nature exposed to our method of questioning".

A good theory should satisfy at least three basic requirements [45].

1. The theory should explain most, if not all, existing observations about the pathogenesis of endometriosis in at least a substantial and identifiable subset of patients; the theory may also account for why groups of patients may be different.
2. The theory ought to be falsifiable, meaning that it can be proven or refuted by experimentation. This requirement distinguishes a theory from a dogma. Indeed, a theory, however good or comprehensive, should be amenable to scientific tests and scrutiny even if this is not immediately accessible, as illustrated the case of the quantum mechanics studies performed by the 2022 physics Nobel prize laureates that confirmed hypotheses proposed several decades before. Medical examples include the finding of causative relationships between Helicobater pylori infection and stomach

cancer [46] and the more recently determined causation of prior infection with Epstein-Barr virus and the development of multiple sclerosis [47, 48].

3. The theory should be able to make useful predictions that can be used to guide our future scientific query, development of new therapies or clinical management.

Making endometriosis history

This group cordially invites everyone to join us in collectively solve all the many unanswered questions. Despite decades of research, endometriosis is still enigmatic. This is unsatisfactory, and stressful to every patient. Innovative, even disruptive and risky, ideas, together with worldwide collaborations are essential to change this situation. If there is no change, there is the real and unsettling prospect that the current questions will remain unsolved in 2 decades from now. Our patients deserve greater incremental progress than has been made up to the present.

We must state that we have genuine and deep respect for the tremendous, highly original and long-term research efforts that have been conducted in the last 40 years. The results of these efforts, and the technological advancements they have promoted, have laid a foundation for the future. Could these efforts have paid off more profitably if guided by different and or more structured theories? That will always be unknown, but perhaps it is high time for a drastic change in the thinking we have employed when generating new hypotheses.

Challenges ahead

Any new approach should take into account that not all the patients have the same disease, as suggested by the large standard deviations reported in many studies. Hypotheses that generate

studies could be based on clinically, imaging, surgically and or histologically confirmed endometriosis cases, preferably with longitudinal follow-up incorporating metadata to investigate the association of emerging results with better characterized detailed disease phenotypes, including minimal or even occult disease. Challenges acknowledged include the evidence that the rising number of genetic loci that collectively account for only a minuscule portion of disease variance, but may impact on specific disease forms. In addition, many women without endometriosis may carry one or more risk alleles, making the diagnosis, screening, or drug development more challenging. Similarly, environmental contributions to the disease---be it *in utero*, neonatal or developmental---are challenging to investigate because of their complexity, but cannot be ignored as future possibilities for disease modification or even prevention. The detailed anatomical classifications, clearly defined measures and comprehensive approaches for gathering, collecting, and evaluating specific signs and symptoms, association with co-morbidities should be used whenever possible as suggested in the World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonization Project [49]. Multiple classifications and measures will likely be needed since none of those that are currently available appears universally applicable. There are currently significant limitations to our ability to recognize all endometriotic lesions and their progression/regression over time [50]. Control groups should consequently also be carefully evaluated, with comparisons performed according to the criteria used to define the population.

In conclusion, this group proposes that radically different approaches are needed. Indeed, using again and again the same approach, which has provided at best limited success, and hoping things will get better is counterintuitive if not futile. Moreover, imagination will be an absolute necessity, when conceiving novel and impactful theories on endometriosis accounting for all the data and knowledge currently available.

Following the publication of this call, a dedicated repository website (https://endo-theories.org) will be created to publish all submitted theories and also provide a forum for open discussion, capitalizing on the fact that a less formal publication site is more open to new ideas and new theories and can be a chat room for open discussion to more physicians and or scientists. This website, accessible by everyone, will be designed and maintained by the Endometriosis Initiative Group that will be in charge of reviewing the proposed theories and will moderate the discussions about the proposals. The endometriosis Initiative Group will be open to any researcher interested to join the initiative. Anonymous comments or proposals will not be accepted. All are invited to contribute so that future generations of clinicians do not continue to mouth the platitudes that have plagued us for decades. The initial website design and hosting expenses are covered by one of the authors (MC), with future crowd funding proposed to cover future website maintenance costs.

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KAB is an associate editor of *Biology of Reproduction* and has received research funding from Ferring

MC is the president elect of AAGL. He receives travel expenses coverage from AAGL. He also received travel expenses coverage for the 2023 WCE meeting from Gedeon Richter

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DCM was paid an honoraria and was reimbursed for expenses for a presentation at the American Society for reproductive Medicine annual meeting in 2021; had expenses paid for a presentation at the 6th European Endometriosis Congress, Bordeaux, had expenses paid for a presentation at the EndoFound annual meeting 2023; had expenses paid for the American College of Ob Gyn annual meeting 2023 to represent the Endometriosis Foundation of America; had expenses paid for the AAGL 2023 annual meeting as a past president and to represent the Endometriosis

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Table 1. List of questions by category.

Category	Questions
Etiology/pathogenesis	What causes endometriosis?
	When, how, and why does the disease begin?
	Where do endometriosis cells originate?
	What is/are the cell(s) of origin of endometriosis?
	Is endometriosis a singular disease entity or should it be considered as a syndrome?
Natural history	Is the disease progressive?
	If progressive, how can this be quantified and what factors contribute to disease progression?
	Is endometriosis a continuous disease state or can it occur intermittently?
	Does presence of endometriosis have an underlying permanent disease state?
	Can the various phenotypes (clinical, anatomical, histological…) observed be explained?
	Are all lesions observed in a patient related to the same cause ?
	Why are symptoms so variable between women?
	Could or should the clinical management be adapted according to the disease phenotypes (clinical and or surgical) found in a particular patient?
Pathophysiology	How does endometriosis cause or relate to pain and or associated symptoms, subfertility, and pregnancy outcomes?
	How do different subtypes of endometriosis impact pain and or

	associated symptoms severity, subfertility, and pregnancy outcomes?
	What are the mechanisms underlying persistence or recurrence?
	Is there any novel way to prevent endometriosis, or at least to mitigate the risk of the disease and of recurrence?
Clinical management	
	Could or should the clinical management be adapted according to the disease phenotypes (clinical and or surgical) found in a particular patient?
Miscellaneous; Outcome measures	What are the core outcome measures for successful management of endometriosis?