Review Article

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2024.58.009214

Endometriosis: A Century of Unresolved Pathogenesis – It's Time for Decisive Action

Francesco Maria Bulletti[1], Maurizio Guido[2], Antonio Palagiano[3], Maria Elisabetta Coccia[4] and Carlo Bulletti[5]*

[1]*CHUV Lausanne - Département D'hôpital Maternité / Gynécologie et obstétrique, Switzerland*

[2]*Full Professor Obstetrics and Gynecology, MeSVA department, University of L'Aquila, Italy*

[3]*Chief Consultant in Fertility and Sterility – CSA, Italy*

[4]*Associate Professor SSD: MEDS-21/A – University of Florence, Italy - Ginecologia e Ostetricia Dipartimento di Scienze Biomediche, Sperimentali e Cliniche 'Mario Serio, Italy*

[5]*Associate Professor Adjunct, Department Obstetrics, Gynecology and Reproductive Science, Yale University New Haven (Ct) USA, and Director of Help Me Doctor a Worldwide Platform for 1st and 2nd medical Opinions. Cattolica (Rn), Italy*

***Corresponding author:** Carlo Bulletti, Associate Professor Adjunct, Department Obstetrics, Gynecology and Reproductive Science, Yale University New Haven (Ct) USA, and Director of Help Me Doctor a Worldwide Platform for 1st and 2nd medical Opinions. Cattolica (Rn), Italy

ARTICLE INFO

Received: September 16, 2024

Published: September 26,2024

Citation: Francesco Maria Bulletti, Maurizio Guido, Antonio Palagiano, Maria Elisabetta Coccia and Carlo Bulletti. Endometriosis: A Century of Unresolved Pathogenesis – It's Time for Decisive Action. Biomed J Sci & Tech Res 58(5)-2024. BJSTR. MS.ID.009214.

ABSTRACT

Endometriosis affects around 10% of reproductive-age women, causing severe pain, infertility, and various other symptoms. Traditional treatments, like hormonal therapies and surgeries, often provide temporary relief with significant side effects, The disease's heterogeneity and varied responses to treatment necessitate a personalized approach. The leading hypothesis for endometriosis onset and recurrence is retrograde menstruation, influenced by factors like uterine position, tubal filtering function by its length and opening sizes, and specific uterine contractility profiles. This hypothesis suggests that only some women are predisposed due to these factors, leading to endometrial cell regurgitation into the pelvic cavity. Advances in biophysical and biochemical markers (proteomics and metabolomics) offer insights into disease activity and treatment response, enabling real-time monitoring and personalized care. Targeted therapies, including angiogenesis inhibitors and drugs/devices modulating hormonal and inflammatory pathways, and uterine content outflow through adequate cervical/tubal openings and uterine contractions control, promise to enhance outcomes and quality of life.

Keywords: Endometriosis; Pathogenesis; Theory; Epidemiology

Introduction

Background Information

Endometriosis is characterized by the growth of tissue resembling the lining of the uterus in areas outside the uterus, such as the ovaries, fallopian tubes, bladder, intestines, or peritoneum. It can less commonly affect areas outside the pelvis, like the diaphragm, pleura, abdominal wall, or nervous system [1,2]. This condition causes severe pelvic pain and can make it difficult to conceive. About 10% of women and girls of childbearing age worldwide, around 190 million people, are affected by endometriosis. The economic impact is significant, with costs exceeding 80 billion USD annually [1-4]. It manifests as a chronic ailment with symptoms that can be debilitating, such as severe menstrual pain, discomfort during sex, difficulties with bowel movements or urination, dysuria, ongoing pelvic pain, bloating, constipation, painful bowel movements, nausea, exhaustion, and in some cases, depression and anxiety [1,3,4]. Approximately 40-50% of women with infertility issues have endometriosis [3-5]. Although various mechanisms have been suggested to explain infertility linked to endometriosis, there is no conclusive evidence of its association with endometrial receptivity. A recent study found a slight decrease in live birth rates among women with a history of endometriosis, suggesting that minor impairments in uterine receptivity might contribute to infertility in these women [6].

On the other hand, the condition distorts pelvic anatomy, causes adhesions and fallopian tube scarring, and leads to local inflammation and hormonal regulation disruptions [3-5]. These symptoms can significantly affect a person's quality of life, education, career, and relationships [1-5]. This article offers a comprehensive overview of the current understanding and recent advancements in the theories of endometriosis pathogenesis, with our opinion on the need for a few RCTs designed to confirm the pathogenesis. An extensive literature search was performed using databases such as PubMed, Scopus, and Web of Science, employing keywords including "endometriosis," "pathogenesis," "theory," and "epidemiology." The aim of synthesizing these findings is to provide a wide-ranging perspective on endometriosis pathogenesis, emphasizing potential areas for future research.

Endometriosis can present a wide range of symptoms that significantly impact the quality of life and emotional well-being, including pain, fatigue, heavy menstrual bleeding, and mood swings. These symptoms can affect education, career, and intimate relationships [1-8]. The condition can start with the first menstrual period and continue in varying patterns until menopause. Starting menstruation after age 14 is significantly correlated with a lower risk of developing endometriosis. Currently, there is no known way to prevent the disease, and while it cannot be cured, symptoms can be managed through medication or surgery [4,9,10]. Endometriosis manifests in three main forms: superficial peritoneal endometriosis, ovarian endometriomas, and deep infiltrating endometriosis (DIE) [1,2,4,10-12]. DIE penetrates organs in the pelvic area and often requires surgical treatment. The disease can progress in 37% of cases, remain stable in 50%, and regress in 17% (10). Surgery for DIE carries a risk of major complications (3-4%) and minor complications (10-15%) [12]. Gaining a full grasp of the complex processes behind endometriosis is essential for advancing treatment options, which are presently inadequate [2,5,12]. A recent large-scale, web-based survey revealed that women with endometriosis endure a lengthy and challenging journey before receiving a diagnosis and effective treatment, highlighting the urgent need to reduce diagnostic delays. On average, seven years elapse between the onset of symptoms (at 23.8 ± 10.2 years) and diagnosis (31.0 ± 8.9 years). Women reported an average of 4.6 ± 2.3 symptoms, with 82% experiencing severe pain (pain scores between 7 and 10). After diagnosis, 66% of women received medical treatment, primarily hormonal (45%), which significantly reduced pain intensity (VAS scores after treatment = 4.9 ± 2.7, $p < 0.001$). Additionally, 62% had undergone surgery, with 22% undergoing laparotomies. The survey highlighted significant impacts on daily life, particularly in sexual, psychological, and physical areas, with an overall quality of life score averaging 4.3 ± 2.6 out of 1013.

Developing new interventions to prevent both the occurrence and recurrence of endometriosis is crucial. The exact cause of endometriosis is not definitively known, but several theories offer insights into its potential origins and guide research toward innovative treatments [2,3,8,9,12]. These theories include metastatic dissemination, surgical transplantation, genetic factors, coelomic metaplasia, immune dysregulation, embryonic cell origin, endometrial stem cell involvement, hormonal imbalance, bone marrow stem cells, and retrograde menstruation [1-10]. Recent research also suggests the possible role of microbiota in the development of endometriosis, indicating that the role of infection in disease etiology should be further investigated14. Despite these theories, questions remain about why certain women are affected, the varied progression of the disease, and its resistance to progesterone treatment [1-8].

Literature Review

While the Sampson theory on endometriosis is supported by numerous facts [1-4,8,9], it seems to leave some questions unanswered. However, a careful, deep analysis can provide answers to these questions:

Variability in Affected Women

Endometriosis affects certain women and not others due to differences in the amount and frequency of endometrial debris transported through the fallopian tubes and subsequently implanted in the pelvic cavity (Figure 1) [1-4].

Disease Progression

The progression of endometriosis in some women, while remaining stable in others, is influenced by individual combinations of chemical-physical factors. These factors determine the capacity for leakage and accumulation of endometrial debris (Figures 1A-1C) [1-4,8,9].

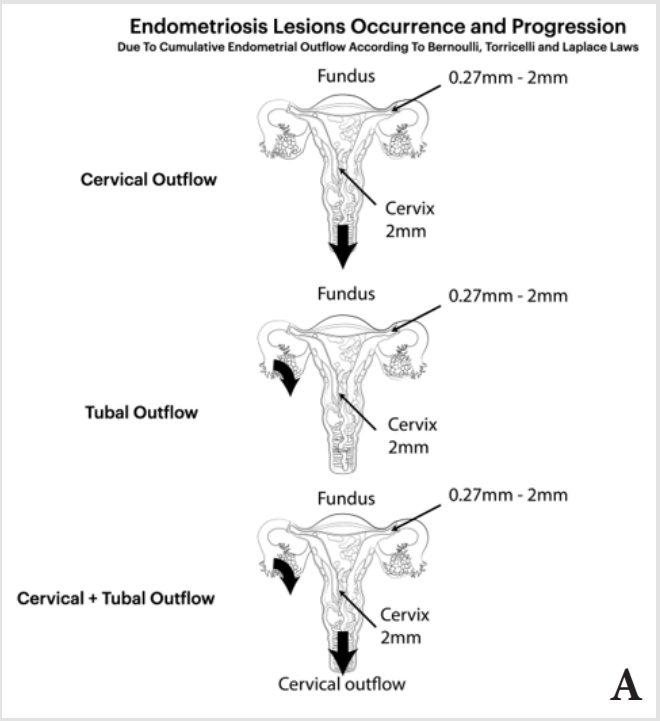
Beyond Oversimplified Views

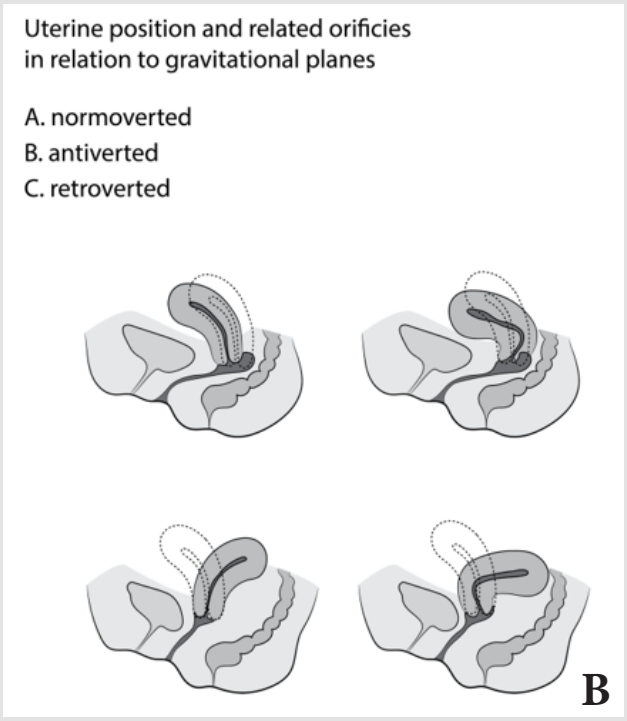
Viewing endometriosis as merely a chronic, inflammatory, multifaceted disease that resists progesterone treatment is an oversimplification. The Sampson theory emphasizes that the chronic nature, inflammation, and complexity of the disease result from the continued presence of endometrial tissue outside the uterus [1-4,8,9].

Mechanical Aspects

Understanding the mechanical aspects of how endometriosis begins and advances is crucial. Detailed explanations are needed to guide the creation of targeted and effective treatments rather than relying on general theories [1-4,8,9]. Physical and chemical factors such as the size of the cervical canal, the dimensions of the tubal ostia, the configuration of the tubal portion within the uterine wall, the length of the tubes, the functioning of the junction between the uterus and tubes, the volume of menstrual flow, the personal placement of the uterus, the size of its openings, and the frequency and intensity of myometrial contractions significantly contribute to the likelihood of developing endometriosis (Figures 1A-1C) [1-4,8,9]. These factors particularly affect individuals with obstructive Müllerian anomalies 25. The principles laid out by Bernoulli, Torricelli, and Laplace [8,13,14] underpin the variation in quantities from person to person (Figures 1A-1C).

DOI: 10.26717/BJSTR.2024.58.009214





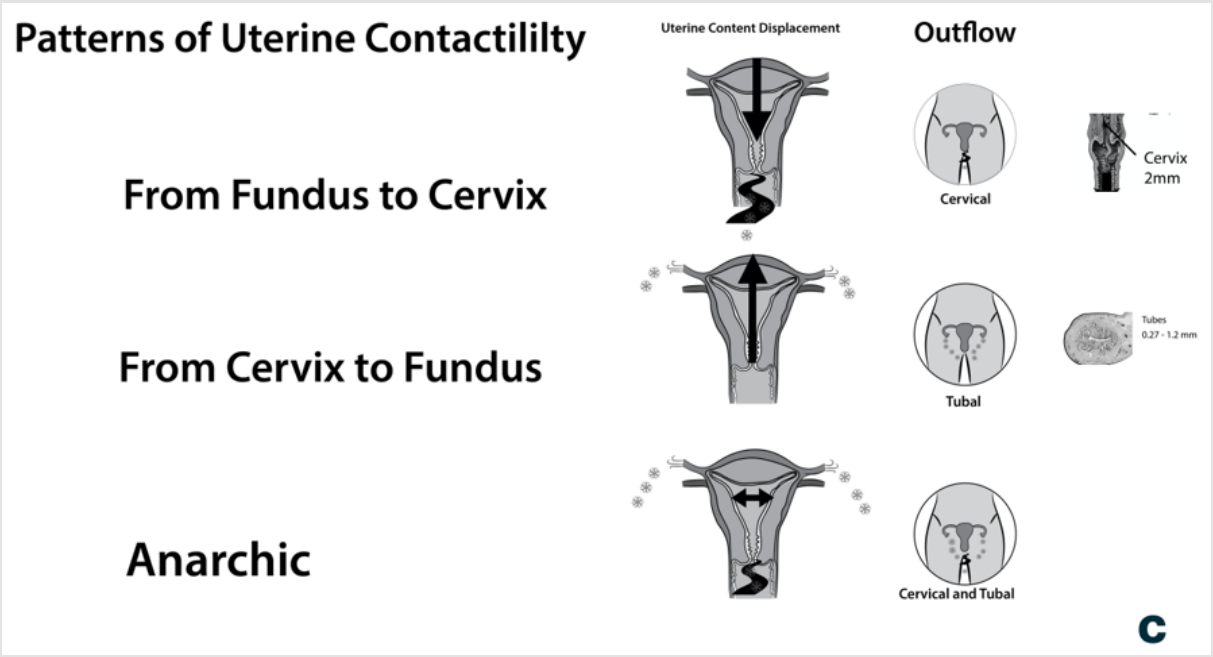


Figure 1:

A. Endometrial Shedding: Debris exits through the cervix and tubes, with the tubes acting as filters. Uterine contractions and anatomy affect this process. The cumulative regurgitation of endometrial debris through the tubal opening into the pelvic cavity is governed by Bernoulli, Torricelli, and Laplace Laws, which is responsible for the progression and regression of the disease (Figure 1A). The individual length and internal size of cervical and tubal openings filter the endometrial debris from the lumen content to the pelvic cavity.

B. Uterine Position: Normoverted, Anteverted, and Retroverted. Different uterine positions influence the flow of endometrial debris through the cervix and tubes. This may explain the varying occurrences of endometriosis (Figure 1B).

C. Uterine Contractions: Contraction patterns influence the displacement of uterine content, with estrogen increasing and progesterone decreasing contraction frequency. This introduces three different patterns and related directions of displacement through the cervical os, tubal openings, or both (Figure 1C).

Statement of Opinion

The retrograde menstruation theory (Sampson)15,16suggests that during menstruation, some endometrial tissue may backflow through the fallopian tubes into the abdominal cavity, potentially leading to the formation of endometriotic lesions [12,15-18] (Figures 1A-1C). Recurrent endometrial accumulation infiltrates deeper structures or appears outside the peritoneal cavity, where lymphatic dissemination has been implicated 2-9. Risk factors such as short menstrual cycles, extended menstrual periods, and uterine obstructions are associated with the development of the disease in women with open fallopian tubes 1-4

A - Endometrial Shedding

Debris exits through the cervix and tubes, with the tubes acting as filters. Uterine contractions and anatomy affect this process. The cumulative regurgitation of endometrial debris through the tubal opening into the pelvic cavity is governed by Bernoulli, Torricelli, and Laplace Laws, which is responsible for the progression and regression of the disease (Figure 1A). The individual length and internal size of cervical and tubal openings filter the endometrial debris from the lumen content to the pelvic cavity.

B - Uterine Position

Normoverted, Anteverted, and Retroverted. Different uterine positions influence the flow of endometrial debris through the cervix and tubes. This may explain the varying occurrences of endometriosis (Figure 1B).

C - Uterine Contractions

Contraction patterns influence the displacement of uterine content, with estrogen increasing and progesterone decreasing contraction frequency. This introduces three different patterns and related directions of displacement through the cervical os, tubal openings, or both (Figure 1C).

Discussion

Endometriosis as a Systemic Disease?

Endometriosis is considered a systemic disease, evidenced by the presence of extra-pelvic endometriosis, including thoracic endometriosis. Retrograde menstruation is a potential mechanism but does not fully explain the disease's pathophysiology [19]. There may be a genetically predisposed condition [20-23] that, when combined with retrograde menstruation, leads to endometriosis. Although most cases (>98%) are not hereditary, understanding disease risk according to subphenotypes could be promising. Retrograde menstruation is an intrinsic part of the overall predisposition, potentially influenced by abnormal myometrial contractions [4,10,24-26]. Adolescents with obstructive Müllerian anomalies are more prone to developing endometriosis and hematosalpinx [27]. Both endogenous and exogenous stem cells may also play a role, with bone marrow-derived stem cells potentially colonizing the endometrium [28,29]. Endometriosis is a chronic inflammatory disease, and while chronic inflammation has long-term consequences, the pathogenesis may still be rooted in retrograde menstruation.

This condition allows blood and endometrial cells to pass through the fallopian tubes, causing persistent inflammation. Endometriosis has been linked to diseases such as atherosclerosis, migraines, and Raynaud's syndrome, as well as a tendency towards a hypercoagulable state [30]. The inflammatory response affects cytokine cascade metabolites, increasing uterine contractions [13]. It remains unclear whether vascular endothelial damage [17] is a cause or consequence of the inflammation, and whether this is specific to endometriosis or common to general inflammation. Given these complexities, the question remains: how do we stop the disease? Should we slow down estrogen pressure or engage in radical surgeries, or can we engage in prevention? The inflammatory cells release cytokines and chemokines, causing further inflammation. Interestingly, progesterone acts not only as an antiproliferative agent but also as an immune modulator [31]. Chronic inflammation in endometriosis suggests it may also be an autoimmune disease. Traditional treatments often yield partial results. Interventions aimed at reversing key causal phenomena, such as retrograde menstruation, should be prioritized, alongside early diagnostic tools [32,33]. Preventing the retrograde transit of endometrial debris could reduce the disease's incidence and complications. Sub-classifications of endometriosis that predict prognosis and enhance treatment prioritization are essential [32,33]. Recent studies identifying genetic alterations, such as APOBEC3B deletion, might help in better diagnosing and treating endometriosis [20].

Theoretical Framework

Retrograde menstruation can cause endometrial tissue to exit through the fallopian tubes [17,18,34] under specific conditions (Figures 1A-1C). Ovarian hormones and chronic inflammation promote the adhesion and growth of endometrial tissue in the pelvic cavity [1-4,7], where undifferentiated mesenchymal cells in the peritoneum act as progenitors of endometrial stromal cells.

Supporting Evidence

Recurrent menstrual cycles exacerbate inflammation and tissue damage, progressing endometriosis [1-4,8,9]. Genetic, hormonal, lifestyle [35], and environmental factors contribute to the disease. Endometrial ablation and levonorgestrel IUDs can reduce recurrence and alleviate pain [8,9]. Postpartum cervical changes in parous women decrease endometriosis risk by promoting cervical outflow [14]. Reduced periods of amenorrhea, due to fewer pregnancies and less frequent breastfeeding in modern times, may increase the risk of endometriosis and adenomyosis among young women.

Interpretation of Facts

Normally, inflammation from menstruation is temporary and non-damaging. However, repeated menstrual cycles may lead to ongoing inflammation [1,5] increased production of utero-contracted prostaglandins, sequential increases in tubal debris outflow [17,18,27,28] and scarring, potentially contributing to conditions like adenomyosis.

Comparison with Existing Literature

Recurrent menstrual cycles cause repeated stress on the uterine lining and may result in basal endometrium fragments being dislodged into the pelvic area [1-8] and myometrium. This could lead to damage from excess iron and resistance to cell death40, promoting lesion progression and fibrosis.

Limitations

Despite the acceptance of this pathophysiological hypothesis, specific randomized studies are lacking and therefore it remains the hypothesis with the highest presumption of correspondence to the real pathophysiology of its genesis but not yet included in the evidence.

Conclusion

Over a century since the initial pathogenetic hypothesis of endometriosis, the disease remains a significant challenge, affecting millions of women without a definitive cure. Despite numerous treatment strategies, the scientific community is at an impasse, partly due to the hesitation to invest in and validate the most credible theories. This hesitation has hindered progress in developing effective treatments.

Symptom Variability and Impact

Endometriosis significantly impairs quality of life, causing symptoms such as pain, fatigue, heavy bleeding, and emotional distress. These symptoms can start from the first menstrual period and continue until menopause, impacting education, career, and personal relationships. Women who begin menstruating after age 14 have a lower risk of developing endometriosis.

Types and Progression

There are three main types of endometriosis: superficial peritoneal, ovarian endometriomas, and deep infiltrating endometriosis (DIE). DIE often invades pelvic organs and typically requires surgical intervention. Endometriosis can progress in 37% of cases, remain stable in 50%, and regress in 17%. Surgery for DIE carries a 3-4% risk of major complications.

Diagnostic Challenges

Women with endometriosis often face long delays in diagnosis and treatment, averaging seven years from symptom onset to diagnosis. Common symptoms include severe pain, with 82% of women reporting pain scores between 7 and 10. Post-diagnosis, 66% receive hormonal treatment, significantly reducing pain, and 62% undergo surgery.

Need for New Interventions

New interventions are urgently needed to prevent the occurrence and recurrence of endometriosis.

Theories of Origin

The exact cause of endometriosis remains unknown. Theories include metastatic dissemination, genetic factors, coelomic metaplasia, immune dysregulation, embryonic cell origin, involvement of endometrial stem cells, hormonal imbalance, and retrograde menstruation. Recent research suggests a potential role for microbiota in disease development.

Sampson Theory and Unanswered Questions

While the Sampson theory of retrograde menstruation explains some aspects of endometriosis, it leaves several questions unanswered, such as why some women develop the disease and others do not, and why the disease progresses in some cases but not others. This variability may be due to differences in the amount and frequency of endometrial debris transported through the fallopian tubes and individual biochemical and biophysical factors [36-38].

Mechanical and Chemical Influences

Factors such as the size of the cervical canal, the dimensions of the tubal ostia, the configuration of the tubal portion within the uterine wall, menstrual flow volume, uterine placement, and myometrial contractions significantly influence the development of endometriosis. These factors affect the volume of blood and endometrial cells regurgitate each cycle, contributing to the likelihood of developing the disease.

Genetic and Mechanical Contributions

Genetic predisposition and physical dynamics (such as principles of Bernoulli, Torricelli, and Laplace) explain variations in disease prevalence among individuals, especially those with obstructive Müllerian anomalies. While retrograde menstruation is common, not all women develop endometriosis or adenomyosis, suggesting protective mechanisms are at play. Variations in the amount of endometrial debris, its passage through the cervix or fallopian tubes, uterine contractions, and the filtering ability of the tubes could explain discrepancies in disease development (Figures 1A-1C).

Future Directions

New strategies for prevention and relapse should include hormonal changes, biochemical agents affecting uterine muscle movements, introducing uterine pacemakers [31,39] and altering retrograde menstruation to flow through the cervical opening, potentially by enlarging its internal uterine opening [17]. Retrograde menstru-

ation, stem cells, embryologic remnants, and/or metastases could occur in all women, yet endometriosis does not develop universally. Therefore, we need precise mechanistic explanations rather than simplistic "just-so" stories to understand why and how the disease begins and progresses, to identify effective therapeutic interventions. To achieve this goal, we must step out of our "comfort zone" and avoid complacency [36-38,40]. We require fundamental changes in our interpretation of clinical, imaging, surgical, and pathological data. In our opinion, if we do not alter our conceptualization of the disease, accumulating more data, regardless of how it is obtained, will contribute little to our understanding. We must embark on a path of treatment experimentation based on the most credible pathogenetic theory after 100 years. This is essential to prevent the onset, progression, and recurrence of the disease. This path is now obligatory [41,42] (Table 1).

Table 1: The table reports the proposal of 4 RCTs aimed at strengthening the pathogenic hypothesis of endometriosis with more robust evidence that lays the foundation for treatments consistent with this physiopathology. Two of the four studies establish two potential intervention tools that are the result of this hypothesis.

Randomized Controlled Trials (RCT) Proposal			
Study Question 1: The Role of Endometrial Debris Tubal Outflow in Causing and Developing Endometriosis?		**Study Question 2: The Effectiveness of Reversing Tubal to Cervical Outflow of Endometrial Debris in Reducing Occurrence and Recurrence of Endometriosis.**	
Study 1	**Study 2**	**Study 3**	**Study 4**
Endometriosis and Uterine Contractility **Overview**: This study aims to explore the relationship between uterine contractility and the occurrence and recurrence of endometriosis through a carefully designed randomized controlled trial. Uterine contractility, particularly during menstruation, is believed to play a key role in the development and progression of endometriosis, a chronic gynecological condition that affects a significant percentage of reproductive-age women. The trial will assess both clinical outcomes and physiological parameters related to uterine contractility. **Study Population:** 400 women of reproductive age will be enrolled and divided into two groups. Group 1: 200 women with adequate uterine contractility displacement during their menstrual period. Group 2: 200 women with inadequate uterine contractility, as measured by displacement during the menstrual period. Participants will be recruited based on well-defined inclusion and exclusion criteria ensuring proper classification into their respective groups. **Primary Objective:** Assess the Occurrence and Recurrence of	**Endometriosis and Family History** **Overview:** This randomized controlled trial aims to investigate the relationship between family history, delivery method, and the occurrence and recurrence of endometriosis. Additionally, the study will explore the role of uterine contractility during menstruation and its correlation with endometriosis. The study will compare two groups of women: those with a family history of endometriosis and a control group without such history, further subdivided by mode of previous delivery (vaginal vs. cesarean section). **Study Population:** 400 women of reproductive age will be enrolled in two groups: **Group 1:** 200 women with a family history of endometriosis. **Group 2 (Control Group):** 200 women without a family history of endometriosis. These groups will be further stratified based on previous childbirth method: vaginal deliveries versus cesarean sections. **Primary Objective.** Evaluate the Occurrence and Recurrence of Endometriosis: • The trial will examine the incidence and recurrence of endometriosis, comparing the role of family history and the impact of previous delivery method (vaginal vs. cesarean). • The study will also utilize ultrasound measurements of the internal os of the cervix to assess any potential anatomical correlation with the occurrence and recurrence of endometriosis.	**Impact of Periodic Cervical Os Dilation on Endometrial Debris Outflow and Endometriosis Occurrence** **Study Design:** This is a double-blind, randomized controlled trial (RCT) aimed at investigating the impact of periodic cervical os dilation on the quantity of cervical endometrial debris outflow and its effect on the incidence and recurrence of endometriosis. **Participants will be randomly assigned to two groups:** One undergoing regular cervical dilation, and A control group with no intervention. **Participants:** The study will include 400 women, aged 18–45, divided into two equal groups of 200 each: **Intervention Group (n=200):** Women will undergo periodic cervical os dilation at predetermined time intervals. The dilation will be performed by a trained clinician using a standardized protocol. **Control Group (n=200):** These women will receive no cervical os dilation or any related intervention. All participants will have a history of menstrual-related symptoms or risk factors for endometrial debris retention, but none will have a prior confirmed diagnosis of endometriosis. **Inclusion Criteria:** Women aged 18-45 Regular menstrual cycles No prior diagnosis of endometriosis No history of cervical surgery or interventions	**Efficacy of a Physical Pacemaker in Managing Dysmenorrhea in Women with Endometriosis: A Randomized Controlled Trial** **Study Design:** This is a randomized controlled trial (RCT) aimed at evaluating the efficacy of a phtysical pacemaker implanted in the uterine fundus in reducing dysmenorrhea and managing endometriosis. The study will compare outcomes between women receiving the pacemaker and those who do not. **Participants:** The study will involve 400 women diagnosed with endometriosis, all of whom report severe dysmenorrhea (painful menstrual periods). The participants will be divided into two groups: Intervention Group (n=200): Women will have a physical pacemaker surgically implanted in the uterine fundus to induce fundus-to-cervix contractions during menstruation. Control Group (n=200): These women will not receive a pacemaker but will be monitored under the same protocol as the intervention group. **Inclusion Criteria:** Women aged 18–45 with a confirmed diagnosis of endometriosis Severe dysmenorrhea, measured using a validated pain scale. Regular menstrual cycles. No prior uterine surgeries. **Exclusion Criteria:** Pregnant or breastfeeding women. Previous uterine surgery or pacemaker implantations. Concurrent treatment for endometriosis beyond standard medical management

Endometriosis:
The trial will primarily focus on evaluating the incidence of new endometriosis cases and the recurrence of previously diagnosed endometriosis in the two groups over a defined follow-up period.

Secondary Objectives:

Evaluate Menstrual Cervical Outflow. Cervical outflow will be measured during menstruation in both groups to investigate any potential correlation between contractility patterns and menstrual fluid expulsion through the cervix.

Ultrasound Assessment of the Internal Os:

High-resolution ultrasound will be employed to examine the internal os of the cervix, assessing its structure, patency, and any potential abnormalities. This will help establish any relationship between cervical anatomy and uterine contractility.

Examination of Liquid Collection in the Douglas Pouch:

The presence of fluid in the Douglas pouch (rectouterine pouch) will be evaluated via ultrasound. Accumulation of fluid here could serve as an indicator of retrograde menstrual flow, which is a hypothesized contributing factor to the development of endometriosis.

Methodology:

Baseline Assessment:

All participants will undergo baseline screening, including a detailed gynecological history, pelvic examination, and ultrasound imaging to assess uterine contractility and any pre-existing endometriosis.

Randomization:

Participants will be randomized into two arms based on their uterine contractility displacement (adequate vs. inadequate) during menstruation.

Intervention and Follow-Up:
Both groups will be followed for a period of 12 to 24 months, with regular assessments of endometriosis symptoms, recurrence, and ultrasound measurements.

Secondary Objective.

Establish the Pattern of Uterine Contractility During Menses:
• This objective involves identifying patterns of uterine contractility during menstruation in both groups. By comparing contractility in women with and without a family history of endometriosis, the study aims to identify potential predictive markers or risk factors for the development or recurrence of endometriosis.

Methodology:

Baseline Assessment:
Participants will undergo a detailed medical history, physical examination, and initial ultrasound assessment of the internal os of the cervix. Uterine contractility will be evaluated using ultrasound during menstruation in both groups.

Randomization and Stratification:
Participants will be randomly assigned to either the family history or control group. Each group will then be further divided into those who have had vaginal deliveries versus cesarean sections.

Follow-Up and Data Collection:
Participants will be followed over a period of 12-24 months, with assessments for the occurrence or recurrence of endometriosis. Ultrasound imaging will be performed at regular intervals to monitor changes in the internal os and uterine contractility patterns.

Outcome Measures:
Primary Outcome: Incidence and recurrence rates of endometriosis based on family history and mode of delivery.
Secondary Outcomes:
Contractility patterns during menstruation in both groups and their correlation with endometriosis. Anatomical variations in the internal os and their potential link to endometriosis.

Exclusion Criteria:
Pregnant or breastfeeding women

History of cervical abnormalities
Hormonal treatments affecting menstruation in the past six months

Intervention:
The intervention group will receive cervical os dilation at regular intervals throughout the menstrual cycle, timed to coincide with key phases of the cycle (e.g., pre-menstrual and post-menstrual).
The dilation will be performed using a standardized dilator to a set dilation size, ensuring consistency across participants. Each participant will undergo dilation five times over a six-month period.
The control group will receive standard care without any cervical dilation interventions but will be monitored on the same schedule for comparison.

Primary Objectives:
Cervical Endometrial Debris Outflow: The primary aim is to measure the quantity of cervical endometrial debris expelled following each menstrual cycle. This will be quantitatively assessed through fluid and tissue samples collected at specific time intervals after menstruation.
Incidence and Recurrence of Endometriosis: The study will also track the incidence of newly diagnosed endometriosis in both groups over the course of 12 months. In women with pre-existing symptoms, recurrence rates will be documented. Diagnosis of endometriosis will be confirmed through clinical evaluation and, if necessary, laparoscopic investigation.

Outcome Measures:

Primary Outcome:
Quantity of endometrial debris outflow, assessed through cytology and histology at specified intervals.
Incidence and recurrence rates of endometriosis, as determined through clinical follow-up and imaging.
Secondary Outcomes:
Change in menstrual symptoms such as pain, flow, and duration.
Quality of life as measured by validated questionnaires (e.g., SF-36).

Intervention:

The intervention group will undergo a surgical procedure for the insertion of a physical pacemaker in the uterine fundus. The device will be programmed to generate rhythmic contractions of the uterus from the fundus to the cervix, mimicking natural contractions but enhancing outflow of menstrual contents. The goal is to reduce uterine congestion and improve the clearance of endometrial debris, potentially alleviating pain and lowering the risk of endometriosis recurrence.
The control group will not receive any pacemaker but will be closely followed for comparison.

Primary Objectives:

Pain Intensity (Dysmenorrhea):
The primary objective is to assess the intensity of dysmenorrhea using a validated pain score (e.g., Visual Analog Scale, VAS) before and after the intervention in both groups.

Occurrence and Recurrence of Endometriosis: The secondary objective is to evaluate the impact of pacemaker-induced contractions on the incidence of new or recurrent endometriosis. This will be tracked over a 12-month follow-up period using clinical evaluations, imaging, and potentially laparoscopy.

Outcome Measures:
Primary Outcome:
Change in dysmenorrhea pain scores, assessed monthly over a 12-month period, using VAS or similar pain assessment tools.
The occurrence and recurrence of endometriosis, measured by clinical symptoms and confirmed through imaging or surgical exploration.
Secondary Outcomes:
Menstrual flow characteristics (volume and duration)
ü Quality of life, measured by validated questionnaires (e.g., SF-36)
Adverse events related to pacemaker insertion or function

Recurrence of endometriosis will be confirmed through laparoscopy if clinically indicated. **Outcome Measures:** **Primary Outcome:** Incidence and recurrence rates of endometriosis in both groups. **Secondary Outcomes:** Quantitative and qualitative analysis of cervical outflow. Structural and functional assessment of the internal os. Presence and volume of fluid in the Douglas pouch. **Significance of the Study:** This randomized controlled trial will provide valuable insights into the potential role of uterine contractility in the pathogenesis and recurrence of endometriosis. The findings could pave the way for new therapeutic interventions aimed at improving uterine contractility, potentially offering novel approaches to the management and prevention of this debilitating condition. The combination of clinical observations with advanced imaging techniques (ultrasound) adds rigor and depth to the study, offering a comprehensive evaluation of the mechanisms behind endometriosis development.This format should clearly illustrate the proposed study design and its relevance, ensuring that the research objectives are presented in a structured and convincing manner.	**Significance of the Study:** This study will provide insights into the role of family history and previous delivery method (vaginal vs. cesarean) in the development and recurrence of endometriosis. By investigating uterine contractility patterns and correlating them with the occurrence of endometriosis, the study could lead to improved understanding of the underlying mechanisms and risk factors. Additionally, the use of ultrasound measurements of the internal os offers a novel approach to examining potential anatomical contributions to endometriosis. This research could ultimately contribute to better prediction, prevention, and management strategies for women at risk of endometriosis. This format clearly presents the objectives and design of the second study, providing a comprehensive and structured overview.	**Data Collection and Analysis:** **Baseline Assessments:** All participants will undergo a detailed baseline assessment, including a medical history, gynecological examination, and pelvic ultrasound. **Follow-up Visits:** Participants will attend follow-up visits at regular intervals for monitoring, sample collection, and assessments. **Statistical Analysis:** Data will be analyzed using appropriate statistical methods (e.g., t-tests, chi-square tests) to compare the intervention and control groups for primary and secondary outcomes. A p-value of <0.05 will be considered statistically significant. **Ethical Considerations:** Informed consent will be obtained from all participants. The study will adhere to the ethical guidelines set forth by relevant regulatory authorities, ensuring participant safety and privacy. An independent Data Safety Monitoring Board (DSMB) will oversee the trial. **Conclusion:** This RCT will provide important insights into the role of periodic cervical os dilation in enhancing endometrial debris outflow and its potential in preventing or reducing the recurrence of endometriosis. If successful, this intervention could represent a novel, non-invasive strategy for managing endometrial health and reducing the burden of endometriosis.	**Data Collection and Analysis:** **Baseline Assessments:** All participants will undergo a baseline assessment including medical history, gynecological examination, and pain evaluation. **Follow-up Visits:** Monthly follow-up visits will be conducted for pain assessment, menstrual flow evaluation, and pacemaker performance (for the intervention group). **Statistical Analysis:** Data will be analyzed using appropriate statistical methods (e.g., paired t-tests, chi-square tests) to compare the two groups. A p-value of <0.05 will be considered statistically significant. • **Ethical Considerations:** Informed consent will be obtained from all participants. The study will adhere to ethical guidelines ensuring participant safety and privacy. A Data Safety Monitoring Board (DSMB) will oversee the trial, particularly in monitoring any adverse effects related to the pacemaker. **Conclusion:** This RCT aims to determine whether the use of a physical pacemaker to induce fundus-to-cervix uterine contractions can effectively reduce dysmenorrhea and manage endometriosis. The findings could potentially introduce a novel treatment approach for women suffering from severe pain and recurrent endometriosis.

Authors Contribution

- Francesco Maria Bulletti and Carlo Bulletti contributed equally to this article in terms of conceptualization and the first draft of the manuscript. Francesco Maria Bulletti wrote the last version of the manuscript
- Antonio Palagiano and Maurizio Guido provided to search and first selection of the studies required and remarked the more realistic pathogenetic concept reported
- Maria Elisabetta Coccia revised the second and third draft
- Ethical Considerations are not applicable.

References

1. Becker CM, Bokor A, Heikinheimo O, Horne A, Jansen F, et al. (2022) ESHRE guideline: endometriosis. Hum Reprod Open.
2. Horne AW, Missmer SA (2022) Pathophysiology, diagnosis, and management of endometriosis. BMJ, pp. 379.
3. De Ziegler D, Borghese B, Chapron C (2010) Endometriosis and infertility: pathophysiology and management. Lancet 376(9742): 730-738.
4. Vercellini P, Bandini V, Viganò P, Di Stefano G, Merli CEM, et al. (2024) Proposal for targeted, neo-evolutionary-oriented secondary prevention of early-onset endometriosis and adenomyosis. Part I: pathogenic aspects. Hum Reprod 39: 1-17.
5. Taylor HS, Kotlyar AM, Flores VA (2021) Endometriosis is a chronic systemic disease: clinical challenges and novel innovations. Lancet 397(10276): 839-852.
6. Alessio Paffoni 1, Maíra Casalechi, Dominique De Ziegler, Ettore Cicinelli, Edgardo Somigliana, et al. (2024) Live Birth After Oocyte Donation In Vitro Fertilization Cycles in Women with Endometriosis: A Systematic Review and Meta-Analysis. JAMA Netw Open 7(1): e2354249.
7. Bulun SE, Yildiz S, Adli M, Chakravarti D, Parker JB, et al. (2023) Endometriosis and adenomyosis: shared pathophysiology. Fertil Steril 119(5): 746-750.
8. Bulletti C, DeZiegler D, Stefanetti M, Cicinelli E, Pelosi E, et al. (2001) Endometriosis: absence of recurrence in patients after endometrial ablation. Hum Reprod 16(12): 2676-2679.

9. Vercellini P, Frontino G, De Giorgi O, Aimi G, Zaina B, et al. (2003) Comparison of a levonorgestrel-releasing intrauterine device versus expectant management after conservative surgery for symptomatic endometriosis: a pilot study. Fertil Steril 80(2): 305-309.
10. Vercellini P, Bandini V, Viganò P, Ambruoso D, Cetera GE, et al. (2024) Proposal for targeted, neo-evolutionary-oriented secondary prevention of early-onset endometriosis and adenomyosis. Part II: medical interventions. Hum Reprod 39(1): 18-34.
11. Knez J, Bean E, Najjar S, Tellum T, Chaggar P, et al. (2023) Natural progression of deep pelvic endometriosis in women who opt for expectant management. Acta Obstet Gynecol Scand 102(10): 1298-1305.
12. Leborne P, Huberlant S, Masia F, de Tayrac R, Letouzey V, et al. (2022) Clinical outcomes following surgical management of deep infiltrating endometriosis. Sci Rep 12: 21800.
13. Bulletti C, DeZiegler D, Polli V, Del Ferro E, Palini S, et al. (2002) Characteristics of uterine contractility during menses in women with mild to moderate endometriosis. Fertil Steril 77(6): 1156-1161.
14. Bulletti C, Montini A, Setti PL, Palagiano A, Ubaldi F, et al. (2010) Vaginal parturition decreases recurrence of endometriosis. Fertil Steril 94(3): 850-855.
15. Bourdon M, Maignien C, Giraudet G, Estrade JP, Indersie E, et al. (2024) Investigating the medical journey of endometriosis-affected women: Results from a cross-sectional web-based survey (EndoVie) on 1,557 French women, Journal of Gynecology Obstetrics and Human Reproduction 53(2).
16. Ayako Muraoka, Miho Suzuki, Tomonari Hamaguchi, Shinya Watanabe, Kenta Iijima, et al. (2023) Fusobacterium infection facilitates the development of endometriosis through the phenotypic transition of endometrial fibroblasts. Sci Transl Med 15: eadd1531.
17. Sampson JA (1927) Metastatic or Embolic Endometriosis is due to the Menstrual Dissemination of Endometrial Tissue into the Venous Circulation. Am J Pathol 3(2): 93-110.
18. Sampson JA (1927) Peritoneal endometriosis due to menstrual dissemination of endometrial tissue into the peritoneal cavity. Am J Obstet Gynecol 14: 422-469.
19. Tulandi T, Vercellini P (2024) Growing evidence that endometriosis is a systemic disease RBMO 49(3): 104292.
20. Vaishnavi B, Saravan R, Swaroop S S, Rajendran S, Joseph LD, et al. (2024) Genetic alteration of mRNA editing enzyme APOBEC3B in the pathogenesis of ovarian endometriosis Reproductive BioMedicine Online 104111.
21. Nilufer Rahmioglu, Sally Mortlock, Marzieh Ghiasi, Peter L Møller, Lilja Stefansdottir, et al. (2023) The genetic basis of endometriosis and comorbidity with other pain and inflammatory conditions. Nat Genet 55: 423-436.
22. Moustafa S, Burn M, Mamillapalli R, Nematian S, Flores VHS (2020) Accurate diagnosis of endometriosis using serum microRNAs. Am J Obstet Gynecol 223: 557.
23. Sofiane Bendifallah, Stéphane Suisse, Anne Puchar, L a Delbos, Mathieu Poilblanc, et al. (2022) Salivary MicroRNA Signature for Diagnosis of Endometriosis. J Clin Med 11.
24. Mumusoglu SHsueh AJW (2024) Is endometriosis due to evolutionary maladaptation? Reprod Biomed Online.
25. Guo SW (2023) How do women get endometriosis? Reprod Biomed Online.
26. Natalie Dinsdale, Pablo Nepomnaschy, Bernard Crespi (2021) The evolutionary biology of endometriosis. Evol Med Public Health 9: 174-191.
27. Takahashi N, Harada M, Kanatani M, Wada-Hiraike O, Hirota Y, et al. (2024) The Association between Endometriosis and Obstructive Müllerian Anomalies. Biomedicines 12(3): 651.
28. Blau HM, Brazelton TR, Weimann JM (2001) The evolving concept of a stem cell: entity or function? Cell 105(7): 829-841.
29. In-Sun Hong (2023) Endometrial stem/progenitor cells: Properties, origins, and functions, Genes & Diseases 10(3): 931-947.
30. Viganò P, Ottolina J, Sarais V, Rebonato G, Somigliana E, et al. (2018) Coagulation Status in Women with Endometriosis. Reproductive Sciences 25(4): 559-565.
31. Bulletti C, Bulletti FM, Sciorio R, Guido M (2022) Progesterone: The Key Factor of the Beginning of Life. Int J Mol Sci 23(22): 14138.
32. Horne AW, Missmer SA (2022) Pathophysiology, diagnosis, and management of endometriosis. BMJ 379: e070750.
33. Tao Liu (2023) Potential Benefits and Risks of Interim Analyses in Clinical Studies, NEJM Evidence 2(7).
34. Yovich JL, Rowlands PK, Lingham S, Sillender M, Srinivasan S (2020) Pathogenesis of endometriosis: Look no further than John Sampson. Reprod Biomed Online 40(1): 7-11.
35. Hearn-Yeates F,Horne AW, O'Mahony SM, Saunders PTK (2024) The impact of the microbiota–gut–brain axis on endometriosis-associated symptoms: mechanisms and opportunities for personalized management strategies Reproduction and Fertility 5: e230085.
36. Huang E, Wang X, Chen L (2024) Regulated Cell Death in Endometriosis. Biomolecules 14(2): 142.
37. Bulletti C, de Ziegler D, Polli V, Diotallevi L, Del Ferro E, et al. (2000) Uterine contractility during the menstrual cycle. Hum Reprod Suppl 1: 81-89.
38. Salmeri N, Di Stefano G, Viganò P, Stratton P, Somigliana E, et al. (2024) Functional determinants of uterine contractility in endometriosis and adenomyosis: a systematic review and meta-analysis Fertility and Sterility.
39. Bulletti C, Prefetto RA, Bazzocchi G, Romero R, Mimmi P, et al. (1993) Electromechanical activities of human uteri during extra-corporeal perfusion with ovarian steroids. Hum Reprod 8(10):1558-1563.
40. Savaris RF, Nichols C, Lessey BA (2014) Endometriosis and the enigmatic question of progression. J Endometriosis Pelvic Pain Disord 6: 121-126.
41. Liuqing He, Haofei Xu, Min Liu, Ying Tan, Shiyu Huang, et al. (2024) The ignored structure for female fertility: fallopian tube cilia, Reproductive Bio Medicine Online.
42. P Vigano, M Candiani, A Monno, E Giacomini, P Vercellini, et al. (2018) Time to redefine endometriosis including its pro-fibrotic nature, Human Reproduction 33(3): 347-352.

ISSN: 2574-1241

DOI: 10.26717/BJSTR.2024.58.009214

Carlo Bulletti. Biomed J Sci & Tech Res

Submission Link: https://biomedres.us/submit-manuscript.php