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NEWS

Celebrating 30 years since the Gerhard Leyendecker and colleagues' formulation of the hyper-dysperistalsis theory in endometriosis

Paolo Vercellini[1,2] · Beatrice Conca[1,2] · Noemi Salmeri[1,2] · Veronica Bandini[1,2] · Paola Viganò[1,2] · Edgardo Somigliana[1,2]

Background

In recent decades, immense efforts have been devoted to understanding the origin of endometriosis. However, progress has been limited and disappointing overall [1, 2]. Looking back, the hypothesis of Gerhard Leyendecker and his colleagues clearly stands out as one of the few ideas and discoveries that have shaped the general understanding of the disease's etiology. Thirty years after the initial publication describing myometrial hyper- and dysperistalsis in infertile patients with endometriosis [3], we honor the visionary investigators who embarked on a scientific journey to refine their model over time.

While some specific potential mechanistic details of their myometrial dysfunction hypothesis have been criticized [4], seven general and innovative concepts have stood the test of time and have paved the way toward a biologically plausible explanation of the origin of adenomyosis and endometriosis.

✉ Paolo Vercellini
paolo.vercellini@unimi.it

Beatrice Conca
beatrice.conca@unimi.it

Noemi Salmeri
noemi.salmeri@unimi.it

Veronica Bandini
veronica.bandini@unimi.it

Paola Viganò
paola.vigano@policlinico.mi.it

Edgardo Somigliana
edgardo.somigliana@unimi.it

[1] Department of Clinical Sciences and Community Health, Academic Centre for Research on Adenomyosis and Endometriosis, Università degli Studi di Milano, Milan, Italy

[2] Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Via Commenda 12, 20122 Milan, Italy

Here, we revisit these seven aspects confirmed by independent research groups and propose a slightly modified pathogenic outline based on updated evidence.

1. **Hyperperistalsis/dysperistalsis and myometrial hypercontractility are the functional determinants of retrograde menstruation**

   The uterus generates peristaltic waves that originate in the inner myometrium. Wave directionality varies across the menstrual cycle, being cervico-fundal during the follicular phase, to accelerate the transport of spermatozoa toward the salpinges, and fundo-cervical during the menstrual phase to facilitate the orthograde discharge of menstrual debris. The frequency and intensity of out-of-phase retrograde peristaltic waves of the inner myometrium (dysperistalsis/hyperperistalsis) are significantly higher in patients with endometriosis than in individuals without the disease [5]. Moreover, convulsive contractions of the outer myometrium increase the intrauterine hydrostatic pressure, thus creating a gradient between the uterine and abdominal cavities. The combined action of the inner and outer myometrium "squeezes" blood and endometrial fragments through the tubal ostia [6, 7].
2. **Hyperperistalsis/dysperistalsis and myometrial hypercontractility are associated with adenomyosis**

   A few years after formulating the hyper-dysperistalsis hypothesis for endometriosis, Kunz et al. observed that this phenomenon was associated with abnormal thickening of the endo-myometrial junctional zone on MRI [8]. At that time, this sign was proposed as a potential indicator of adenomyosis; today, it is one of the key imaging criteria for its diagnosis. Subsequent studies confirmed adenomyosis as the most frequent anatomical determinant of retrograde menstruation [9].
3. **Adenomyosis is associated with tissue injury and repair (TIAR)**

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Leyendecker and colleagues proposed the TIAR mechanism to explain the development of adenomyosis and, consequently, endometriosis [10]. Several years later, Sun-Wei Guo described adenomyotic lesions as "fundamentally wounds undergoing repeated tissue injury and repair (ReTIAR), which progress to fibrosis through epithelial-mesenchymal transition, fibroblast-to-myofibroblast transdifferentiation, and smooth muscle metaplasia" [11].

4. **The "culprit" is the basal, not the functional, endometrium**

   Leyendecker et al. proposed that the basal endometrium is the source of both adenomyosis and endometriosis. It infiltrates the depth of the myometrial wall, initiating adenomyosis. Additionally, once displaced into the abdominal cavity via retrograde menstruation, it implants and gives rise to endometriosis [12]. This hypothesis is relevant as the basal endometrium is relatively progesterone-resistant, expresses aromatase, and synthesizes estradiol locally [6, 7, 10, 12–14].

5. **Endometriosis and adenomyosis are strictly associated**

   Before Leyendecker and his colleagues published their studies, there was limited awareness of the strict association between adenomyosis and endometriosis. In their series, morphological signs of an abnormal endometrial-myometrial junction, which are compatible with adenomyosis, were found in up to 90% of patients with endometriosis who were evaluated using US and MRI [6, 8, 10, 12]. These findings opened a new line of research and changed the scientific community's perspective on adenomyosis. Until then, adenomyosis was considered a disease of multiparous women in their late reproductive years, if not a para-physiological condition with limited clinical relevance. Bulun et al. argued that adenomyosis and endometriosis share pathogenic mechanisms to the extent that they should be considered "sister entities" [13].

6. **Endometriosis is an epiphenomenon of adenomyosis**

   Twenty-five years ago, Leyendecker stated that adenomyosis and endometriosis represent a unique entity, also based on the MRI findings of Kunz et al. [8]. He also wrote that "*adenomyosis and its early manifestations constitute the primary lesion, with pelvic endometriosis being merely a sequel*" and "*the aetiology of endometriosis is primarily the aetiology of adenomyosis*" [15]. In our opinion, this represents a revolution in pathogenic research because the focus shifted from the peritoneum of the pelvic cavity to the uterine wall as the source of endometriosis [8]. Leyendecker and his colleagues further identified embryologically distinct myometrial structures, attributing different functions to the inner (archi-myometrium) and outer (neo-myometrium) myometrium. The latter would actively contribute to uterine auto-traumatization via hypercontractility and "*compression by contractions*" of the former, and to the development of adenomyosis [6, 7].

7. **Repetitive ovulatory menstruations trigger TIAR**

   Habiba et al. wonder what the "*primum movens*" for the hyper-dysperistalsis is, what triggers TIAR, and if and how these processes can be prevented or mitigated [4]. Leyendecker et al. suppose that "*in most cases of endometriosis/adenomyosis, a causal event early in the reproductive period of life must be postulated leading rapidly to uterine hyperperistalsis*" [10]. They also pointed out that "*in the wild and also in archaic human societies non-conceptive cycles and menstruation were and still are rather infrequent incidences*" and that "*non-conceptional cycles, uterine hypercontractility, spontaneous decidualization, and menstruation constitute central aspects in the pathophysiology of the disease process*" [7]. In this regard, adolescents who experience the onset of regular ovulatory menstrual cycles in the early postmenarcheal period are evolutionarily advantaged, as this indicates reproductive health, sexual maturity, and readiness to conceive. However, if dysmenorrhea (an indicator of incipient uterine auto-traumatization) is also present and conception is delayed, they would be exposed to a higher risk of developing adenomyosis [7].

Prospectus

Habiba et al. maintain that "*there are no data to show that hyper- or dys-peristalsis indeed preceeds adenomyosis*". Thus, adenomyosis may be the cause rather than the result of myometrial dysfunction [4]. Since temporality has not been demonstrated, the sequence of events indicated by Leyendecker may be based on reverse causality bias. The directionality may be from adenomyosis to hyper-dysperistalsis and hypercontractility, instead of the reverse. Myometrial dysfunction would result from damage to the normal tissue structure and function caused by endometrial infiltration, chronic inflammation, and eventual fibrosis. If so, then prolonged periods of repetitive ovulatory menstruation, uninterrupted by pregnancies and lactational amenorrhea [13, 14], could trigger the TIAR mechanism, rather than primary uterine auto-traumatization and biomechanical stress. Accordingly, Leyendecker and colleagues' general concepts can be used to reinterpret the origin of adenomyosis and endometriosis, but with a slightly different initial temporal sequence based on considerations from Guo [10], Habiba et al. [4], Bulun et al. [13], Bulun [14], and Vercellini et al. [9], among others (Fig. 1). However, not all women with adenomyosis will develop endometriosis, because the

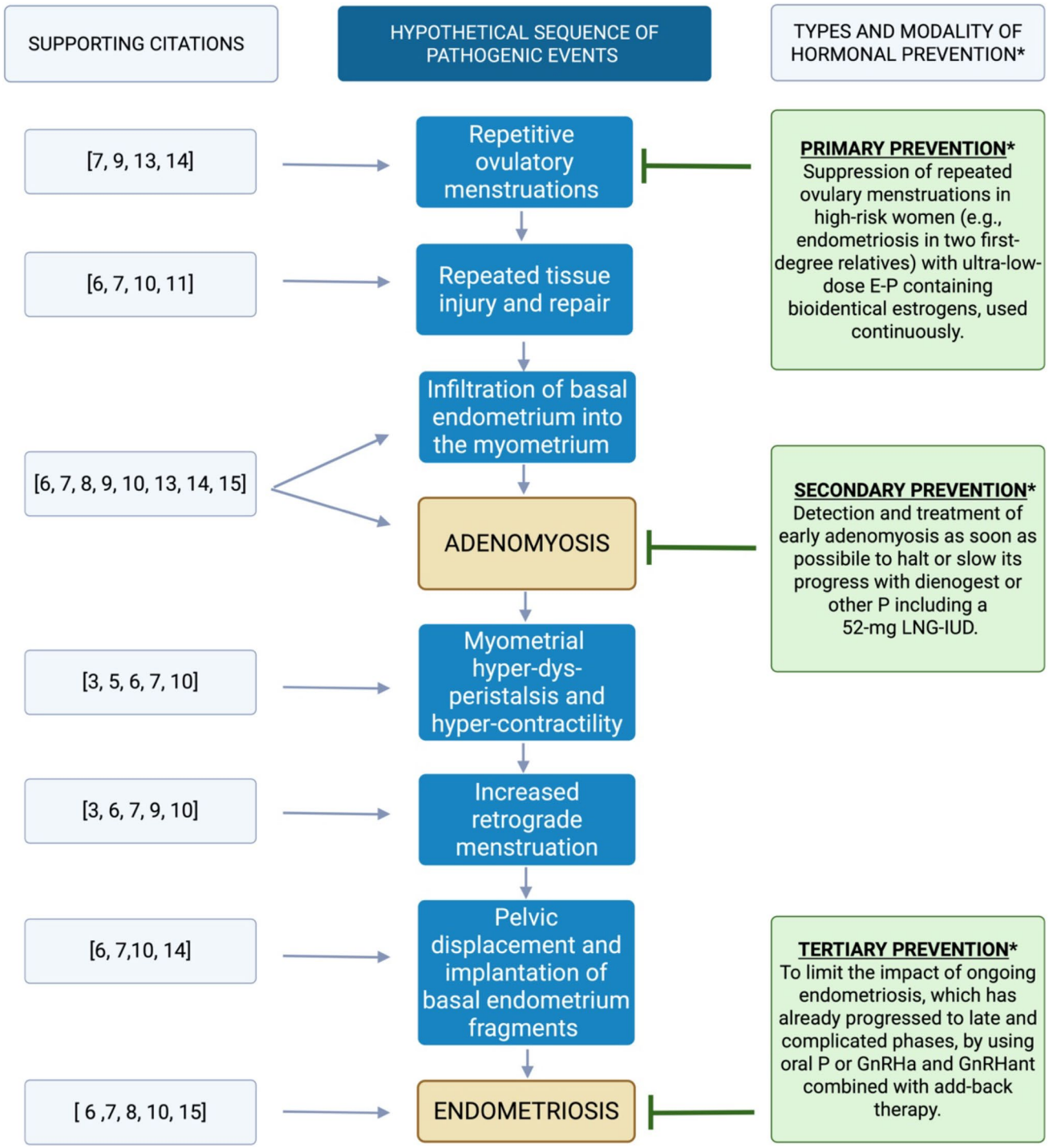

Fig. 1 The various steps of the pathophysiological path leading to endometriosis are based on the findings and theory of Leyendecker and colleagues [3, 6–8, 10, 12, 15], but the hypothetical sequence of initial events has been modified based on the results and interpretations of Bulun [14], Bulun et al. [13], Guo [11], Habiba et al. [4], Salmeri et al. [5], and Vercellini et al. [9]. *The proposal for primary prevention in high-risk subpopulations is not based on evidence and only constitutes a working hypothesis. The hormonal medications indicated for secondary and tertiary prevention are a limited selection of the available compounds, and relevant publications are not included in the reference list. *E–P* estrogen–progestogen combinations, *P* progestogen monotherapies, *LNG-IUD* levonorgestrel-releasing intrauterine device, *GnRHa* gonadotropin-releasing hormone agonists, *GnRHant* gonadotropin-releasing hormone antagonists

sequence of pathogenic events may not inevitably progress to the final stage. Conversely, almost all patients with endometriosis should have even a mild form of adenomyosis, possibly reflecting a clinical or subclinical endometrial-myometrial interface dysfunction [6, 7].

Future validation of this hypothetical model would have important practical implications. If unphysiological, repetitive ovulatory menstruations cause the iterative uterine TIAR process that leads to adenomyosis, then the ideal secondary prevention strategy for severely symptomatic young women should be pursuing ovariostasis and amenorrhea (Fig. 1) [9, 13, 14]. Indeed, Bulun is surprised that clinicians and researchers have not yet explicitly addressed this issue [14].

Author contributions P.Ve. and B.C. conceived the text and drafted the original version of the letter. N.S., V.B., P.Vi. and E.S. participated in conceiving and drafting part of the letter and critically revising it. All authors approved the final version of the manuscript.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest P.Ve. is a member of the Editorial Board of Human Reproduction Open, the Journal of Obstetrics and Gynaecology Canada, and the International Editorial Board of Acta Obstetricia et Gynecologica Scandinavica; has received royalties from Wolters Kluwer for chapters on endometriosis management in the clinical decision support resource UpToDate; and maintains both a public and private gynaecological practice. P.Vi. is Co-editor-in-Chief of the Journal of Endometriosis and Uterine Disorders. E.S. is Editor-in-Chief of Human Reproduction Open; discloses payments from Ferring and Theramex for research grants and personal honoraria from Merck-Serono, Ibsa, and Gedeon-Richter; and maintains both a public and private gynaecological practice. B.C., N.S., and V.B. declare they have no conflict of interest.

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