Uterine Peristaltic Activity and the Development of Endometriosis

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ABSTRACT: Peristaltic activity of the nonpregnant uterus serves fundamental functions in the early process of reproduction, such as directed transport of spermatozoa into the tube ipsilateral to the dominant follicle, high fundal implantation of the embryo, and, possibly, retrograde menstruation. Hyperperistalsis of the uterus is significantly associated with the development of endometriosis and adenomyosis. In women with hyperperistalsis, fragments of basal endometrium are detached during menstruation and transported into the peritoneal cavity. Fragments of basal endometrium have, because of their equipment with estrogen and progesterone receptors and because of their ability to produce estrogen, an increased potential of implantation and proliferation, resulting in pelvic endometriosis. In addition, hyperperistalsis induces the proliferation of basal endometrium into myometrial dehiscencies. This results in endometriosis-associated adenomyosis with a prevalence of approximately 90%. Adenomyosis results in impaired directed sperm transport and thus constitutes an important cause of sterility in women with endometriosis. Our own data and that from the literature strongly suggest that the principal mechanism of endometriosis/adenomyosis is the paracrine interference of endometrial estrogen with the cyclical endocrine control of archimyometrial peristalsis exerted by the ovary, thus resulting in hyperperistalsis.

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INTRODUCTION

The nonpregnant uterus is actively involved in the early processes of reproduction not only by providing the site of implantation but also by actively transporting of spermatozoa into the tube ipsilateral to the dominant follicle. 1-3 This directed transport is provided by retrograde uterine peristaltic contractions 1,4,5 that are controlled by the ovaries. 5,7 Also high-fundal implantation of the embryo and retrograde menstruation are considered to result, at least in part, from this peristaltic function.

The peristaltic activity of the nonpregnant uterus is drastically altered in infertile women with endometriosis. Because there is strong circumstantial evidence that peritoneal endometriosis is caused by transtubal dissemination of endometrial tissue as first proposed by Sampson, 9 the physiological mechanism of retrograde uterine peristaltic activity and its dysfunction may be causally involved in the development of the disease. In this article, data on the peristaltic activity of the nonpregnant uterus are reviewed. Furthermore, the evidence that uterine peristalsis and its dysfunction constitute very early steps in the events that finally lead to pelvic endometriosis and also uterine adenomyosis is summarized.

CONTRACTILITY OF THE NONPREGNANT UTERUS

Rhythmic contractions of the nonpregnant uterus and rapid sperm transport within minutes from the vagina to the fallopian tubes have long been recognized in many species including humans. Because the velocity of spermatozoal movement could not account for covering such a long distance through the female genital tract within a few minutes, rapid sperm transport was considered a passive phenomenon and had been ascribed to the uterine contractile activity. 9 Recently, the availability of videohysteroscopy of uterine peristalsis (VHSP) 1-5 and hysterosalpingography (HSSG) 1,10-13 made it possible to study uterine peristaltic activity and uterotubal transport in vivo without stress and injury. In HSSG, technetium-labeled albumin macrospheres of spermatozoal size are placed into the posterior vaginal fornix, and the ascension of these particles within the female genital tract can be documented by serial scintigrams.

CHARACTERIZATION OF UTERINE PERISTALTIC ACTIVITY

By means of videohysteroscopy of uterine peristalsis, three major types of contractions may be distinguished from each other (Fig. 1): cervicofundal contractions (type A); fundocervical contractions (type B); and isthmical contractions (type C). Although contractions of type A and B travel as peristaltic waves over the whole distance from the cervix to the fundal region and from the fundus to the cervical region,
FIGURE 1. Histogram demonstrating the frequency of the uterine peristaltic waves during menstruation, the early, mid-, and late follicular, and mid- and late luteal phases of the cycle, respectively, as obtained from video sonography of uterine peristalsis in healthy women. The relative distribution of cervicofundal (type A) versus fundocervical (type B) and isthmical (type C) contractions is also shown. The graph demonstrates the increase of the frequency of type A contractions with the progression of the follicular phase reaching a maximum during the late follicular phase and the decrease during the luteal phase of the cycles. With the progression of the menstrual cycle, type B contraction waves almost disappear. Type C contractions prevail during the luteal phase. These contractions do not extend beyond the isthmic or lower corporal part of the uterus, rendering the fundocervical part of the uterus a zone of relative peristaltic quiescence during the period of embryo implantation (top panel). Uterine peristaltic activity obtained in hypogonadal women treated sequentially with estradiol and estradiol plus progesterone, yielding physiological ovarian steroid hormone levels in blood (bottom panel).
respectively, isthmic peristaltic waves (type C) extend only from the uterine isthmus to the lower midcervical region.

The peristaltic activity of the uterus in the different phases of the cycle is characterized by a varying composition with respect to these three types of contractions as well as by a varying frequency and intensity of the specific contractile activity. In general, cervicofundal contraction waves (type A) prevail during the follicular as well as the luteal phase of the cycle (Fig. 1). The frequency of these contractions is low during the late menstrual period and increases gradually during the proliferative phase with a maximum frequency during the preovulatory phase. In parallel, type B contraction waves (fundocervical peristalsis) decrease progressively during the late menstrual period and disappear nearly completely at midcycle. Thus, practically all peristaltic activity around ovulation is cervicofundal in character.

During the luteal phase, uterine peristaltic activity is composed of type A and type C contraction waves. The frequency of cervicofundal contractions (type A) decreases from 1 contraction per minute on the average in the midluteal phase to 0.4 contractions per minute during the late luteal phase, whereas isthmic contractions (type C) decrease from 2 contractions per minute in the midluteal phase to 1.6 contractions per minute in the late luteal phase, respectively. Thus, only 50% of the contractions started in the isthmocervical region reach the fundal region during the midluteal phase and only 25% in the late luteal phase. This renders, during the midluteal and late luteal phases of the cycle, the fundal part of the uterus a region of relative peristaltic quiescence (Fig. 1).

**FIGURE 2.** (Left) A schematic representation of the endometrial-subendometrial unit ("archimetry") within the human uterus based on immunocytochemical results and the morphological and ontogenetic data, respectively. The endometrial-subendometrial unit is composed of the glandular (green) and the stromal part of the endometrium and the stratum subvasculare of the myometrium with predominantly circular muscular fibers (yellow). Ontogenetically, the endometrial subendometrial unit is derived from the paramesonephric ducts (green) and their surrounding mesenchyme (yellow). The bulk of the human myometrium does not originate from the paramesonephric ducts (blue). It consists of the stratum vasculare with a three-dimensional meshwork of short muscular bundles and the stratum supravasculare with predominantly longitudinal muscular fibers. The stratum vasculare is the phylogenetically most recent acquisition and, in contrast with the endometrial-subendometrial unit, both the stratum vasculare and supravasculare develop late during ontogeny. The stratum vasculare and supravasculare surround the uterine corpus and extend caudally only to the uterine isthmus. There is a transitory zone within the stratum vasculare adjacent to the stratum subvasculare where muscular fibers of the two layers blend (yellow margin of the stratum vasculare). The endocervical mucosa is the most caudal structure derived from the paramesonephric ducts. The underlying circular muscular fibers, which are progressively diminishing in caudal direction, and the accompanying connective tissue blend with vaginal tissue elements (red) to form the vaginal portion of the cervix. The primordial uterus of the 23rd week of pregnancy is composed of the elements of the archimetra, such as endometrium and archimymometrium (specific actin staining) (top right). The "halo" in transvaginal sonography represents the archimymometrium (middle right) as does the "junctional zone" in MRI (bottom right).
THE MORPHOLOGICAL BASIS OF UTERINE PERISTALSIS

Videosonography reveals that the uterine peristaltic waves are confined to the subendometrial myometrium. Anatomically, this is the stratum subvasculare of the myometrium or archimyometrium and is characterized by a predominantly circular arrangement of the muscular fibers. The other of two layers of the myometrium are the stratum supravasculare with a predominantly longitudinal arrangement of the muscular fibers and the stratum vasculare as the middle layer, being composed of a three-dimensional mesh of short muscular bundles that constitute the bulk of the human myometrium.\textsuperscript{14-16}

The archimyometrium is the muscular component of the archimeta, of which the others are the epithelial and stromal endometrium.\textsuperscript{3,14,16,17} It extends from the lower part of the cervix through the uterine corpus into the cornua, where it continues as the muscular layer of the fallopian tubes.\textsuperscript{14,15} In high-resolution sonography and

FIGURE 3. Modified original drawing from Werth and Grusdew,\textsuperscript{14} showing the architecture of the subendometrial myometrium (archimyometrium) in a human fetal uterus. The specific orientation of the circular fibers of the archimyometrium results from the fusion of the two paramesonephric ducts forming a fundocornual raphe in the midline (dashed rectangle). The peristaltic pump of the uterus, which is continuously active during the menstrual cycle, is driven by coordinated contractions of these muscular fibers. Directed sperm transport into the dominant tube is made possible by differential activation of these fibers. By the time muscular distentions at the fundocornual raphe result in the formation of gaps, endometrial proliferation into these dehiscences results.
FIGURE 4. The distribution pattern of uterine peristalsis with respect to the absence (dotted line) \((n = 36)\) or presence (solid line) \((n = 31)\) of endometriosis. Data of the midfollicular and the midluteal phases, respectively, of the cycle were used. The peristaltic frequency was normalized to the mean frequency in women without endometriosis as 100%. In women with endometriosis, the grade according to the revised AFS classification (American Society for Reproductive Medicine) is indicated in addition (from Leyendecker et al.\(^2\) with permission).
According to the data obtained by applying hysterosalpingoscintigraphy with labeled albumin microspheres of sperm size, the following concept of the dynamics of rapid sperm ascension within the female genital tract could be developed.\(^1\) Rapid sperm ascension occurs immediately after deposition of the ejaculate at the external os of the cervix. As early as 1 minute thereafter, spermatozoa have reached the intramural and isthmic part of the tube. Quantitatively, however, the extent of ascension increases with the progression of the follicular phase. Although only a few spermatozoa enter the uterine cavity and even fewer enter the tubes during the early follicular phase, the proportion of spermatozoa that enters the uterine cavity increases drastically during the midfollicular phase with still a limited entry into the tube. During the late follicular phase, there is a considerable ascension of spermatozoa into the tubes.

In these normal females with proven tubal patency, there were no indications that the albumin microspheres entered the peritoneal cavity to a large extent. In contrast, they were rather retained in the isthmic part of the tube. Electron microscopic studies have demonstrated significant morphological and, by inference, functional changes of the tubal epithelium during the menstrual cycle.\(^23\)–\(^25\) During the preovulatory phase, secretory cells appear in the isthmic part of the tube, being responsible for the development of an isthmic mucous plug during this phase of the cycle.\(^25\) This plug is probably responsible for the isthnotubal arrest of passive sperm ascension and may serve, following the cervical mucus and crypts, as a secondary tubal sperm reservoir.\(^9\)

Furthermore, the HSSG revealed the preferential direction of rapid sperm transport into the tube ipsilateral to the dominant follicle, which corresponds with findings during surgery that the number of sperm around ovulation was higher in the tube ipsilateral to the dominant follicle than on the other side.\(^1\),\(^26\) This directed passive transport of sperm (microspheres) into the "dominant" tube constitutes a genuine uterine function and results from both the specific structure of the archimyometrium with its fundocornual bipartition of the circular fibers and the effects of the uteroovarian counter-current system that provide a higher input of stimulatory signals from the ovary into the uterine cornual region ipsilateral to the dominant ovarian structure.\(^6\),\(^14\),\(^20\)

**Fundocornual Implantation**

The uterine peristaltic pump is significantly active also during the luteal phase of the cycle. The specific quality of the contractile activity, however, renders the fundocornual region a zone of relative peristaltic quiescence, presumably minimizing mechanical irritation of the process of implantation.

HSSG, however, revealed that the few peristaltic waves that reach the fundal part of the uterus still exhibit significant transport capacity.\(^27\) It is possible that these contractions directed toward the "dominant" tube assure high fundocornual implantation of the embryo ipsilateral to the corpus luteum. In ART cycles with fresh embryo transfer directed in one of the uterine cornua, most of the chorionic sacs were found at the site of transfer.\(^28\) After directed transfer of frozen-thawed embryos in artificial cycles with exogenous steroids and without a dominant ovarian structure, this correlation, however, was not found.\(^28\) After spontaneous conception, most of the chorionic sacs were found in the cornual region ipsilateral to the corpus luteum, indicating
that there is no major migration of the blastocyst within the uterine cavity before implantation. Interestingly, in cases of missed abortion a significant number of embryonal sacs were located on the side contralateral to the corpus luteum.\textsuperscript{28}

\textbf{Retrograde Menstruation}

As toward the end of pregnancy, the number of oxytocin receptors is increasing toward the end of the luteal phase within the neometral myometrium, with the highest expression in its fundal part.\textsuperscript{29} The discharge of menstrual debris might be facilitated by contractions of the neometra induced by the activation of these receptors by endometrial oxytocin.\textsuperscript{21} Anterograde menstruation may be further supported by archimymetrical fundocervical peristaltic contractions that decrease with the progression of the early follicular phase.

Retrograde menstruation appears to be a physiological phenomenon. It is observed in nearly all menstruating women with patent tubes\textsuperscript{30–33} and may be caused by the increased uterine tone during menstruation and also by cervicofundal peristalsis that is already present during the menstrual period and increases during the early follicular phase.\textsuperscript{2} Because cervicofundal peristalsis constitutes a potential risk of infection of the genital tract and sperm transport that early during the proliferative phase is unlikely to result in pregnancy,\textsuperscript{34} retrograde menstruation must provide significant evolutionary benefit. It had been suggested that cervicofundal contractions increasing in number with the progression of the menstrual period enable, by retrograde menstruation, the preservation of iron content of the body.\textsuperscript{33,35} This might be of particular importance in juvenile dysfunctional bleeding with persistent follicles and high endogenous estradiol levels that stimulate the uterine peristaltic pump.

\textbf{ENDOMETRIOSIS AND ADENOMYOSIS AS DYSFUNCTIONS AND DISEASES OF THE ARCHIMETRA}

In various publications, we have presented data corroborating the view that endometriosis constitutes primarily a uterine disease and that the development of endometriosis is closely related to the genuine uterine function of peristaltic activity and retrograde transport. The evidence for a uterine cause of endometriosis is circumstantial but is supported by various findings that are significantly associated with endometriosis. These include uterine hyperperistalsis and dysperistalsis, the desquamation of basal endometrium during menstruation, and the parallel development of adenomyosis.

\textbf{Uterine Hyperperistalsis and Dysperistalsis with Impeded Sperm Transport}

Women with endometriosis show a significant increase in uterine peristaltic activity compared with women free of disease\textsuperscript{2,35} (Fig. 4). During the early and midfollicular phases of the cycle, the frequency of the peristaltic waves is doubled compared with normal.\textsuperscript{2} The cyclical pattern of peristaltic activity in women with endometriosis is similar to that obtained in normal women with high endogenous estrogen levels during controlled ovarian hyperstimulation and with intravenous bolus injections of oxytocin.\textsuperscript{3} At midcycle, in women with endometriosis, peristaltic ac-
tivity becomes dysperistaltic. The regular contractions are replaced by more convulsive uterine activity. Moreover, in women with endometriosis, the intrauterine pressure is increased compared with women without the disease.

This change in the contractile activity of the uterus in women with endometriosis has a profound effect on the uterine retrograde transport capacity. In HSSG, the transport of labeled inert particles is drastically increased during the early and midfollicular phases of the cycle, but the directed transport of the particles into the tube ipsilateral to the dominant follicle is absent in the periovulatory phase. With respect to the fundamental mechanisms in the early processes of reproduction, these findings allow the conclusion that in women with endometriosis directed sperm transport is severely impaired. Astonishingly, this aspect is not recognized as a possible mechanism of subfertility in women with endometriosis and patent tubes.

Dislocation of Basal Endometrium

Immunohistochemical studies revealed that immunostaining for the estradiol receptor (ER), progesterone receptor (PR), and P450 aromatase (P450 A) becomes negative in all of the functionalis and spongiosa but not in the basalis toward the end of the cycle. This discrepancy of the immunostaining between basalis and functionalis at the end of the cycle was utilized to identify endometrial fragments of the basalis and the functionalis, respectively, in menstrual blood. It could be shown that in 80% of women with endometriosis and in only 10% of women without endometriosis fragments of basal endometrium could be detected in the respective menstrual blood specimen (P < 0.05).

FIGURE 5. Immunohistochemistry of estrogen receptors in the endometrium of the late proliferative phase. The basal endometrium is positively stained, whereas there was no estrogen receptor expression in the spongiosa and functionalis. The basalis is broader in women with endometriosis than in those without the disease.
FIGURE 6. Transvaginal sonography (TVS) and magnetic resonance imaging (MRI) of the uterus of a 32-year-old woman with moderate endometriosis. In TVS, the “halo” is broadened in the posterior wall of the uterus. In MRI, the junctional zone is broadened in both the anterior and posterior wall of the uterus with the typical “patchy” appearance.
On the basis of these findings, it was suggested that it is the retrograde transport of fragments of basalis rather than of functionalis that leads to pelvic endometriosis. Up to now, there is no direct proof available for this assumption. Evidence, however, may be derived from the fact that, at the end of the cycle, the basal layer of the endometrium constitutes very active tissue with an increasing mitotic rate and increasing expression of ER and PR both in the epithelium and stroma and with the persistent expression of P450 aromatase, whereas the functionalis is destined to cell death. Moreover, all endometriotic lesions form peristromal muscular tissue. The potential to form Müllerian muscular tissue fibers by stromal metaplasia, however, is, during ontogeny and during the menstrual cycle, confined to the basal stroma.39

Immunostaining of the whole uterine wall for ER, PR, and P450 showed no differences in the cyclical immunoreactive scores (IRSs) for the different uterine layers including the basalis in women with and without endometriosis. It was, however, observed that the basal endometrium was significantly thicker in women with endometriosis than in those without the disease (0.8 vs. 0.4 mm)39 (Fig. 5).

Parallel Development of Adenomyosis

During studies on uterine peristalsis in women with and without endometriosis, significant structural abnormalities of the uterine wall became apparent in women with endometriosis. As judged from the data of transvaginal sonography (TVS) and magnetic resonance imaging (MRI), respectively, there was a significant association between uterine adenomyosis and peritoneal endometriosis40 (Fig. 6). In a more recent extended study with MRI scans of the uterus in 160 women with endometriosis and in 67 controls, the posterior junctional zone (JZ) was significantly thicker in women with endometriosis (11.5 mm) than in healthy controls (8.5 mm). In patients with endometriosis and normal sperm count of the partners, the diameter of the posterior JZ was 14.0 mm, which was significantly larger than the respective diameter in women with endometriosis and partners with low sperm counts. In women with endometriosis as the only recognizable cause of infertility of the couple as judged from a normal sperm count, the prevalence of adenomyosis amounted up to 90% (G. Kunz, P. Huppert, D. Beil, G. Leyendecker, in preparation). Dysperistalsis and impeded sperm transport of women with endometriosis might result from the adenomyotic destruction of the functional architecture of the archimyometrium as the myometrial layer responsible for directed sperm transport.

A UNIFYING CONCEPT OF THE DEVELOPMENT OF ENDOMETRIOSIS AND ADENOMYOSIS

The data just presented provide strong circumstantial evidence that endometriosis results from the transtubal dislocation and implantation of basal endometrium. Likewise, from a mere topographical point of view, it is evident that uterine adenomyosis results from the infiltration of basal endometrium into the underlying myometrium. Both endometriotic and adenomyotic lesions form peristromal muscular tissue that has, with respect to the ER and PR expression, the immunohistochemical characteristics of the archimyometrium. Both lesions with all their components, such as glandular and stromal endometrium and peristromal muscular tissue, mimic with respect
to the cyclical pattern of the IRS of ER and PR expression the respective cyclical pattern of the basal endometrium and the archimyometrium. It therefore was suggested that dislocated fragments of basal endometrium have “stem cell potential” and, when implanted on, for example, peritoneal surfaces, resume their embryonal growth program to form all components of the archimetra including muscular tissue. The ectopic endometrial lesions therefore can be considered as microprimordial uteri or “microarchimetras.”

The association of endometriosis with adenomyosis and vice versa has been discussed frequently in the literature. In the last century, the lesions were described to occur in the uterus and in the peritoneal cavity. Also, Sampson described “primary endometriosis” as the uterine variant of the disease.\(^8\) His scientific interest, however, was directed toward the development of peritoneal variety, and it was his theory that finally resulted in the separation of peritoneal endometriosis from uterine adenomyosis as different disease entities and by confinement of research to the pelvic endometriotic lesion.\(^41\)

THE BASAL ENDO METRIUM AS AN ENDO CRINE GLAND

Archimetral Hyperestrogenism

Uterine hyperperistalsis is one of the predominant uterine findings in endometriosis. Because its extent is independent of the severity of the disease, it was suggested that hyperperistalsis constitutes the primary and that endometriosis constitutes the secondary phenomenon.\(^5\)

Hyperperistalsis can be induced by increased peripheral levels of estradiol in blood. In women with endometriosis and hyperperistalsis, however, the mean peripheral estradiol and also progesterone levels during the menstrual cycle did not differ from those of women without the disease.

Estradiol inducing hyperperistalsis might come from the endometrium itself. By virtue of the expression of the P450 aromatase that also persists during the whole luteal phase within the basalis, the basal endometrium constitutes an endocrine gland that produces estrogen from androgenic precursors. In women with endometriosis and adenomyosis, the concentration of estradiol in menstrual blood was higher than that in healthy women, whereas the respective peripheral levels were the same.\(^42\) In our recent study,\(^39\) the basalis as measured during the luteal phase and distant from adenomyotic lesions was twice as thick as the basal endometrium in healthy women, probably increasing drastically the amount of estrogen in the endometrium with its paracrine effects in the chain of events that result in hyperperistalsis. It remains to be shown whether there is an increased production of estrogen in the basal endometrium per volume of tissue of women with endometriosis compared with controls.

This concept of nonovarian archimetral hyperestrogenism as one of the initial events in the development of endometriosis may be pertinent to the ongoing discussion of the role of environmental factors such as endocrine disruptors and food intake. In an animal experiment, dioxin increased tubal peristaltic activity, and it was active via the oxytocin receptor.\(^43\) In a study aimed at examining the hereditary component of endometriosis in colonized rhesus monkeys, only a history of treatment
with estrogen patches (in addition to a history of trauma by hysterotomy) showed a significant association with endometriosis.\textsuperscript{44} Taken together, our own and data from the literature strongly suggest that the principal mechanism of endometriosis/adenomyosis is the paracrine interference of endometrial estrogen with the cyclical endocrine control of archimyometrial peristalsis exerted by the ovary.

FIGURE 7 summarizes our present concept of the development of endometriosis and adenomyosis, which is an extension of the concept proposed earlier.

The archimyometrium is stimulated by locally increased levels of estradiol and by a cascade of events that may include the endometrial oxytocin and its receptor. The primary event or events that lead to archimetal hyperestrogenism currently are not known. Archimetal hyperestrogenism results in uterine hyperperistalsis and increased uterine pressure.

Hyperperistalsis constitutes a mechanical trauma resulting in desquamation of fragments of basal endometrium and, in combination with an increased retrograde uterine transport capacity, in enhanced transtubal dissemination of these fragments. By chance, these fragments might implant somewhere in the peritoneal cavity with certain sites of predilection dependent on the pelvic topography. After the process of implantation, spontaneous healing might be possible but also proliferation and infiltrative growth depending on the proliferative potential of the seeded basal fragments. The pleomorphic appearance of pelvic endometriosis is largely caused by the long causal chain between the primary disturbance on the level of the archimeta and the eventually established individual endometriotic lesion.

In adenomyosis, this chain of events is shortened. Hyperperistalsis and increased intrauterine pressure might result in myometrial dehiscenices that are infiltrated by
basal endometrium with the secondary development of peristromal muscular tissue. Diffuse or local adenomyosis of various extent ensues. Adenomyotic foci usually are localized in the anterior and/or posterior wall with preference in the posterior wall and practically never in the lateral walls of the uterine corpus (G. Kunz, P. Huppert, D. Beil, G. Leyendecker, in preparation). The lesions usually present close to the "fundocornual raphe" of the archimyometrium (Fig. 3), underlining the primarily mechanical or traumatic character of their development.

With their muscular component, adenomyotic lesions might contribute to the increased intrauterine pressure. More important, however, the lesions destroy the functional architecture of the archimyometrium and are, with their myometrial component, responsive to the stimuli that control regular peristaltic activity. Thus, dysperistalsis and impaired directed sperm transport ensue.

As ectopic archimetras, endometriotic and adenomyotic lesions possess the biochemical potential of the parent basal endometrium. Thus, the lesions are able to produce estrogen and therefore may be able to sustain their benign proliferative potential. That is why infiltrative endometriosis and adenomyosis may constitute progressive diseases, in rare cases even beyond menopause.\textsuperscript{45}

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