Received: 18 August 2021 | Accepted: 17 December 2021

DOI: 10.1002/rmb2.12438

Reproductive Medicine and Biology

WILEY

REVIEW

Age-dependent phenotypes of ovarian endometriomas

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Funding information
Science and Technology Commission of Shanghai Municipality, Grant/Award Number: 2017ZZ01016; National Natural Science Foundation of China, Grant/Award Number: 81771553 and 82071623; Shanghai Shenkang Center for Hospital Development

Abstract

Purpose: To analyze the characteristics of the ovarian endometrioma (OE) across the life span of a woman. In the past, the OE has traditionally been viewed as a single, monolithic disease. Today, there are emerging data indicating that OE phenotypes differ according to the age of the woman.

Method: A narrative review of original articles on OE indexed by PubMed.

Results: When appearing in *infancy and early adolescence*, OE may be the consequence of endometrial cells retrogradely shed with neonatal uterine bleeding. The *postmenarcheal* variant, manifesting itself during full adolescence, is singularly frequent in the presence of vaginal or uterine outflow obstructive anomalies. The typical and most frequent *adult phenotype* is characterized by increasing fibrosis and a tendency to progress; its mere presence exerts a detrimental effect on the surrounding healthy ovarian tissue. In *postmenopause*, an old lesion may be reactivated in the presence of exogenous or endogenous estrogens, or even be produced *ex novo*; rarely, it can spread to a variety of organs and structures and even degenerate causing malignancies.

Conclusions: Given the existence of these variants, it is important to agree on management guidelines that take into consideration these different phenotypes.

KEYWORDS
adolescence, adulthood, neonatal uterine bleeding, ovarian endometrioma, postmenopause, premenarche

1 | INTRODUCTION

Ovarian endometrioma (OE) is the most common subtype of endometriosis.[1,2] OE can occur in human females of almost all ages and can cause harm to the ovarian cortex either by its mere presence, or because of surgery to eliminate it, or both. Its management still poses a great challenge, due, perhaps in no small part, to our limited and often fragmented knowledge of its pathogenesis and pathophysiology. Indeed, the correct approach to mitigate or even eliminate the harm to the ovary because of OE can only be achieved through a better understanding of the mechanisms through which damage is produced.[3]

In this respect, almost a hundred years ago, Blair Bell called for the attention of his British colleagues to a point of great pathological and clinical interest[4]; namely, that the "chocolate" cysts of the ovary contain menstrual fluid discharged by the endometrium lining the inside of the ovarian cyst. In fact, he was the one who coined the word "*endometrioma*" to identify what Sampson a year earlier had named in his original publication "*Perforating hemorrhagic (chocolate) cysts of the ovary*",[5] encouraging his British colleagues to use the new word.

In reviewing the literature, it becomes evident that characteristics of the various phenotypes of endometriosis differ greatly according to the age of the patient.[5] The same seems to apply to the specific issue of changes in the characteristics of OE. For this reason,

we believe that a review of the various features of OE at different stages of a woman's life can yield important insight and help physicians in better understanding and in managing of this condition. In this review, we elaborate these age-dependent phenotypes of OE and their clinical implications.

2 | MATERIALS AND METHODS

2.1 | Search

PubMed was exhaustively searched using the phrase "ovarian endometrioma" or "ovarian endometriomas"; the resultant original articles were retrieved and carefully read, and the resultant information was distilled.

2.2 | Method

All the retrieved original articles were then reviewed and the relevant points summarized in a narrative manner.

3 | HISTORICAL PERSPECTIVE

The general architecture of the OE was first described in 1957 by the pathologist Hughesdon[6] who collected, at the time of hysterectomy, ovaries with the OE *in situ* of 29 women and carried out for the first time a meticulous histological investigation of its *in situ* structure. He used serial sections to obtain a three-dimensional view of the OE and documented its connection with the ovarian cortex. In this way, he was able to prove that in fact the OE is lined by cortex derived from folding-in forming a pseudocyst. An important observation regarded the case of a woman aged 57 years. Normally, at this age there is a sharp contrast between the narrow dark-staining peripheral cortex and the blotchily pale central medulla, with its hyaline vessels and *corpora albicantia*. In this case, as shown in Figure 1, the medulla was displaced, stretched, and distorted by the folding-in from above of nearly half of the cortex, to create and surround the central cavity. The presence of an inner cortex showed that the relation to the surface is primary and not secondary, such as would be implied by Sampson's description.

Almost 40 years later, Brosens et al.[7] used laparoscopic ovariioscopy to investigate the characteristics of the endometrial cyst *in situ* and to locate the implants for selective biopsy. This atraumatic technique allowed the description in young women of the typical features of the inner wall of the OE; it also allowed the localization of active implants for biopsy. With this technique of guided biopsies, endometrial tissue was obtained in 82% of the cases versus 42% when using large, random biopsies.

Among the interesting findings was the fact that, in contrast to the situation in older patients, in young patients red lesions were more prevalent, predominantly located at the site of the invagination

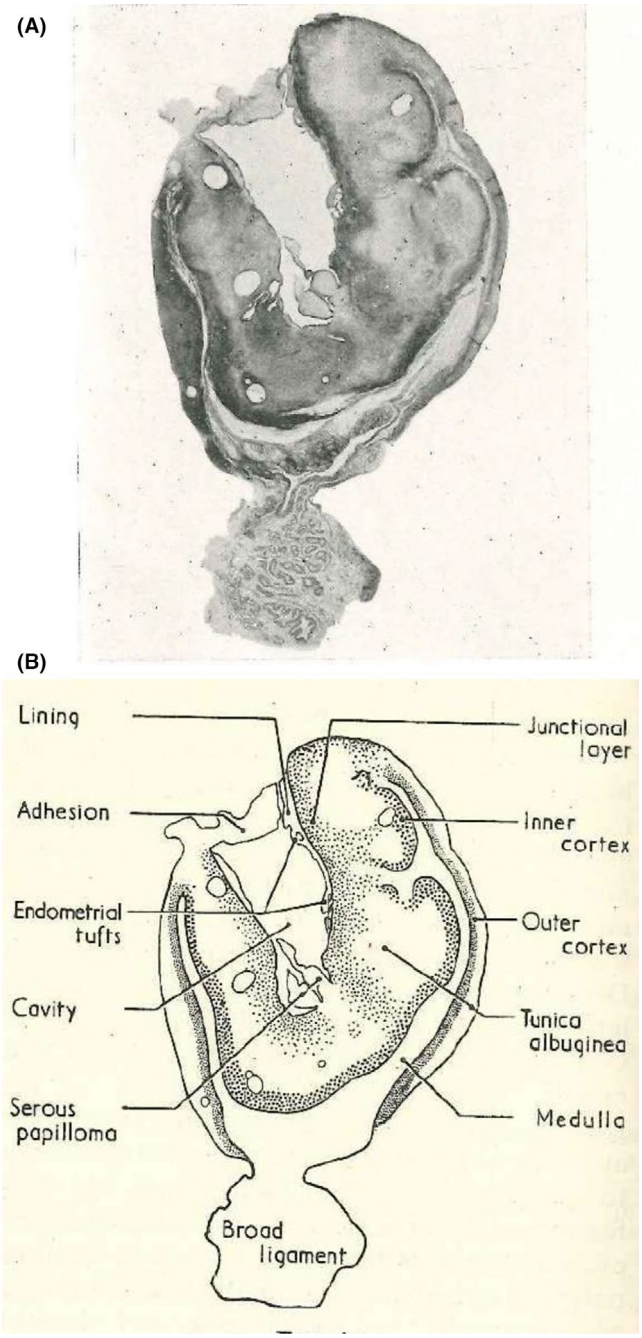

FIGURE 1 Full section of the ovary of a 57-year-old woman with an endometrioma (*left*) and its schematic view (*right*). Adhesions are visible above the cavity; this is surrounded in succession by thickened invaginated cortex, U-shaped medulla, and the remainder of the cortex. Below is the broad ligament. Reprinted with permission from Hughesdon[6]

stigma, and were highly indicative of a mucosa-type implant. Therefore, in most cases the OE is formed by invagination of the cortex and active, vascularized implants are located at the site of invagination. In the younger woman, the invaginated cortex is fully or patchily covered by an angiogenic mucosa. Biopsies of the red mucosal implants yielded significantly more active endometrial-like tissue than biopsies taken at random.

This investigation showed clear and remarkable differences between OE features in young patients and in older ones, prompting us to review the characteristics of the various phenotypes of the OE from its "seeding" in few, selected cases, possibly already around birth, to its formation either during pubertal years, adult life, or even in postmenopause.

This approach is in line with the natural history of endometriosis in general, characterized by three age-related stages[5]:

1. A premenarcheal and adolescent variant, with two distinct phenotypes: the classic one, due to early activation of endometrial debris in retrogradely carried menstrual flow, described since the early days and considered rare[8]; a new possible phenotype caused by activation around menarche of resting stem cells shed at the time of the rarely occurring phenomenon of neonatal retrograde uterine bleeding.[9]
2. The well-known adult variant with its three major phenotypes: superficial peritoneal, ovarian, and deep (or adenomyotic) endometriosis.
3. A postmenopausal variant, developing or being reactivated in the presence, but rarely even in the absence, of exogenous estrogens, that can spread to a variety of organs and structures causing constrictive lesions. Additional evidence on the characteristics of this variant has recently been published.[10]

Applying this approach to the natural history of OE may lead to a better understanding of OE's formation and progression. This is definitely not a new idea since, in 1922, namely 5 years before he identified "endometriosis" as a new pathological entity, Sampson[11] wrote a ponderous review on "*The life history of ovarian hematomas (hemorrhagic cysts) of endometrial (Müllerian) type*," in which he stated that "*the epithelium primarily giving rise to these implantations is derived from, or through the fimbriated end of the fallopian tubes*," thereby proposing that ovarian implants are at the origin of all variants of what he later named "*endometriosis*." Sampson reviewed 56 cases and made a series of important observations: First, "*hemorrhagic cysts*" are unusual in women under thirty years of age, supporting the view that they are "*of developmental and not of acquired origin*." Second, they develop during the menstrual life of the patient, "*when tubal and uterine epithelium would be more likely to escape from, or through the fimbriated end of the tube*." Indeed, in all his cases the tubes were apparently patent. Third, he acknowledged the possibility that the implantation on the ovary may occur before puberty (although he made no reference to neonatal menstruation as a possible source). Fourth, he mentioned the existence of a postmenopausal variant. Finally, he discussed the rare finding of these "*ovarian hematomas*" in pregnancy; in the only case he observed, the "hematoma" was lined by typical decidual tissue that histologically "*was identical with that of the compact layer in the decidua vera of the pregnant uterus*." Glands were not present in the lining of this "ovarian hematoma."

4 | EXISTING THEORIES ON THE PATHOGENESIS OF OE

4.1 | Celomic metaplasia

At the turn of the 20th century, Robert Mayer[12] proposed that endometriosis (at the time known as "adenomyoma") may arise from celomic epithelium; that is, some committed cell type (eg, mesothelium) can be transdifferentiated into an alternative cell type (eg, endometrial epithelium), leading to endometriosis. It should be noted that such a developmental plasticity of celomic epithelial cells is mostly lost in mature reproductive tracts.[13]

The metaplasia theory may explain cases of very early onset of endometriosis, since the metaplastic process might be activated by the increase in estrogen production at the time of thelarche. However, so far there has been no experimental evidence in support for this theory. A recent critical review concluded that, in the context of endometriosis in patients with Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, there is no convincing evidence supporting the existence of an association between uterus/endometrium agenesis and endometriosis.[14] The MRKH syndrome is a disorder that occurs in females and mainly affects the reproductive system; it causes the vagina and uterus to be underdeveloped or absent, although external genitalia are normal. Affected women usually do not have menstrual periods due to the absent uterus. In their view, patients with MRKH syndrome develop endometriosis only when a uterus/endometrium is present, highlighting, but not in conflict with, Sampson's implantation hypothesis.

While the finding of mesothelium in endometriosis has been used as evidence in support for the celomic metaplasia theory,[15] it should be noted that all such inferences were made *post hoc* from observations on patients who have already been diagnosed with endometriosis. Mesothelial epithelial cells can be recruited and transdifferentiated into endometriotic cells through MMT.[16] Indeed, MMT has been documented in a mouse model of endometriosis[17,18] and can be shown in *in vitro* experimentation.[16] It is likely that the lesional presence of peritoneal mesothelial cells observed by Nakamura et al.[15] may be a result of active recruitment of MMT. Taken together, these results seem to suggest that the mesothelial cells found in endometriotic lesions may have been recruited *after*, not *before*, lesions are established. Consequently, in light of modern discovery of the role of MMT in endometriosis, the celomic metaplasia theory should be cast in new light and may require a reappraisal.

4.2 | Embryonic Müllerian rests

The Müllerian rest hypothesis posits that endometrial-like tissues in endometriotic lesions are developed from differentiation and proliferation of embryonic cell rests that are constituted by misplaced cells of primitive endometrial tissue along the migratory pathway of

Müllerian ducts,[19,20] which can be stimulated by ovarian steroids at thelarche.[21] As reviewed recently by Laganà et al.,[22] embryological studies give credence to the presence of Müllerian rests near the normal deep cul-de-sac area, but not in other sites such as the ovary, sigmoid colon, appendix, or more distal sites such as the diaphragm and pleura.[23]

Goldstein et al.[24] presented a case of endometriosis diagnosed five months after menarche that supports this theory. Further support for the theory was subsequently provided by the description of cases in premenarcheal girls.[25,26] In addition, more support has been provided by Signorile et al.[23,27] who autopsied a total of 37 female fetuses at different gestational age and carried out a morphological and immunohistochemical study of their pelvic organs. They found 4 cases that had the presence of endometrium at five different ectopic sites.

The observation that the four young girls diagnosed between thelarche and menarche with histologically confirmed endometriosis,[25,26] in conjunction with the macroscopic and microscopic findings in a female infant who died of sudden infant death syndrome,[28] provides a tantalizing piece of evidence for the Müllerian rest theory. In addition, in the aforementioned 4 premenarcheal girls, the interval between thelarche and diagnosis appears to be too short to account for symptomatic endometriosis resulting from metaplasia of pelvic peritoneum. However, that same short interval may be quite sufficient to account for the pelvic pain resulting from estrogen stimulation of preexisting embryonic Müllerian rest endometriosis.

Therefore, the Müllerian rest theory may account for certain early forms of endometriosis, but not for all forms.

4.3 | Genetic susceptibility

One popular theory for the pathogenesis of endometriosis is the genetic susceptibility theory. This theory postulates that there are genes or genetic polymorphisms that confer susceptibility and predispose women to endometriosis. It is based on studies that purportedly show that endometriosis is hereditary.

In retrospect, most evidence for a hereditary component for endometriosis comes from family studies published since 1980 when Simpson et al. reported a prevalence of endometriosis in 5.9% of sisters of affected probands and 8.1% in their mothers, as compared to 1% in the first-degree female relatives of the probands' husband.[29] Unfortunately, many such studies suffer from various biases, such as ascertainment bias and reporting bias. In fact, most family studies showing an increased prevalence of endometriosis in cases than that in controls fail to control one important parameter: the number of sisters that the case or control has.[30] All published results of heritability, however, hinge critically on overly simplified mathematical models that assume no gene-environment interactions and time constancy.

To varying degrees, almost all human diseases have a tendency to familial aggregation. In fact, some non-genetic diseases such as scurvy, kuru, and the sudden infant death syndrome were once proven to be familially aggregated and thus suspected to have a genetic component that later proved to be untrue. Indeed, familial aggregation of disease is not necessarily synonymous with the existence of a hereditary component, since risk factors, such as diet, cultural belief, and lifestyle, also tend to aggregate in families.[31-33] As such, it is extremely challenging to tease out "nature versus nurture," which are often intimately intertwined. In addition, it is biologically plausible that some genetic polymorphisms that are known to be risk factors for endometriosis, such as early onset of menarche, may be indirectly linked, by association studies, to the risk of developing endometriosis,[30,34] as has been shown recently.[35] But this does not qualify the polymorphism to be the genetic variant that predisposes women to endometriosis.

It is perhaps not surprising to see that, despite well over thirty years of active research, the search for genes predisposing to endometriosis has only yielded a handful of genetic variants that contribute, individually or collectively, to the minute proportion of variability of endometriosis risk,[36] providing another example of "missing heritability" as in many other complex diseases.[37]

From the evolutionary standpoint, endometriosis is now viewed as being driven, proximately, by relatively low levels of prenatal and postnatal testosterone,[38] highlighting the notion that pre- and postnatal developmental environment may exert far more important effect than genetic composition on the risk of developing endometriosis. This is akin to Barker's hypothesis, which postulates that adverse living and nutritional conditions in utero and in early infancy may influence the risk of metabolic diseases in adult life.[39]

In light of the current state of the genetic research on endometriosis, it may be time to take stock of what has been achieved, reappraise data showing familial aggregation of endometriosis, and critically scrutinize the notion of genetic predisposition.

5 | EMERGING VIEWS ON THE NATURAL HISTORY OF LESIONS

Remarkably, these historical perspectives are broadly consistent with the molecular and cellular characterization of the natural history of endometriotic lesions, which views them, first and foremost, as wounds undergoing repeated tissue injury and repair (ReTIAR).[40-42] In a nutshell, endometriotic lesions, once established, experience epithelial-mesenchymal transition (EMT), fibroblast-to-myofibroblast transdifferentiation (FMT), and smooth muscle metaplasia (SMM), ultimately culminating in fibrosis.[42] Of note, endometriotic lesions can recruit various cells, including endothelial and mesothelial cells, into the lesions through endothelial-mesenchymal transition (EndoMT) and mesothelial-mesenchymal transition (MMT).[16,43] In addition, the lesional microenvironment, as a nexus of lesion and host, as well as a transducer of lesional signals and of host lifestyle, is of vital importance, dictating the tempo and pace of lesional progression and determining the fate and destiny of lesions.[44] Looking through this prism of ReTIAR, it can be understood as why there are a hyperestrogenism[45,46] and aberrant

expression of estrogen receptor β (ERβ),[47] why there is a reduced cytotoxicity of natural killer (NK) cells[48,49] in endometriosis, and why there is histological difference, as documented by Brosens et al.,[7] in OE between younger and older patients or between OE and deep endometriosis (DE).[44,50,51] Above all, we can understand why OE is a progressive disease if unimpeded[52] (Figure 2).

This perspective can not only help us understand the age-dependent features of various OE phenotypes but may also help us devise better management strategies.

6 | INFANCY AND EARLY ADOLESCENCE

This variant, although rare, is well documented today, and more than one theory has been proposed. We note that some of the theories elaborated below are *not* specific to OE or even endometriosis for this age group *per se*, and in fact is proposed for endometriosis in all age groups in general.

6.1 | Dissemination of stem/progenitor cells at birth through neonatal uterine bleeding

In 2006, Starzinski-Powitz et al.[53] argued that endometrial cells in retrograde menstruation have inherent developmental properties, since they represent a mixture of various cellular stages, including rather undifferentiated cells capable of self-renewal. These, in turn, may represent the cellular source of primary endometriotic lesions.

Based on this hypothesis, a new theory has been proposed to explain pre- and early post-menarcheal endometriosis,[9,54] given that neonatal endometrium can, in a small number of cases, display secretory activity around the time of birth and even changes analogous to adult menstruation,[55] indicating that it is capable of shedding. The presence of a functional barrier plugging of the endocervical canal in the neonate[56] may in turn promote retrograde flux of endometrial cells contained in menstrual debris.

In all fairness, the validity of this hypothesis hinges on a number of assumptions. First, that the bloodshed during neonatal uterine bleeding (NUB) can regurgitate into the pelvic cavity. Since neonates spend most of their time in a supine position, as opposed to a standing position in adulthood, this assumption would need further validation. Second, that the fallopian tubes in neonates are patent without any barrier for retrograde NUB. Third, and perhaps most importantly, that the blood should contain stem or progenitor cells. So far, there have been no data on this, and as such, this assumption would require further scrutiny. Finally, it is not known whether these progenitor cells possess estrogen receptors (ERs) and progesterone receptors (PRs). At the same time, it is still biologically possible that they could be somehow "incubated" and activated by gradually rising estrogen levels during thelarche.

As of today, there are no data showing that in patients with NUB, blood is present in the peritoneal cavity; however, blood has been observed in the peritoneal dialysis catheter of adult women

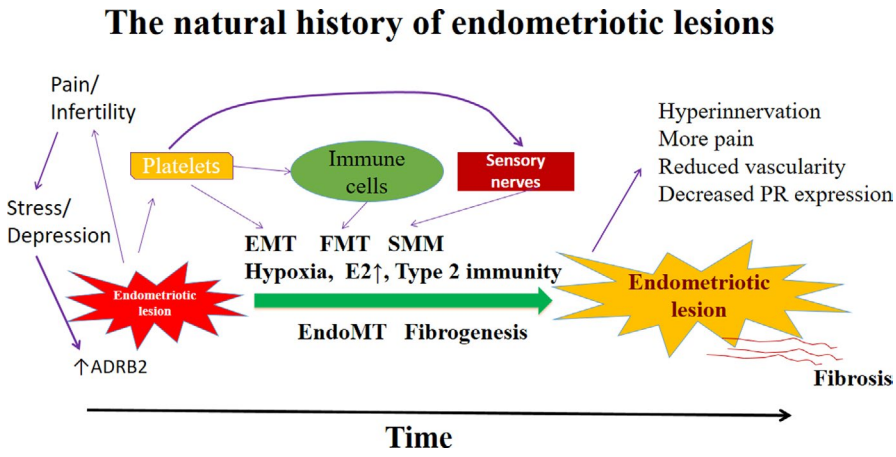

FIGURE 2 Natural history of endometriotic lesions (adapted from[167]). This diagram sketches, in broad strokes, the progression of endometriotic lesions, which interact with various mediators and players in their microenvironment, such as estrogen (E2), hypoxia, platelets, various immune cells, and sensory nerve fibers, through epithelial-mesenchymal transition (EMT), endothelial-mesenchymal transition (EndoMT), fibroblast-to-myofibroblast transdifferentiation (FMT), mesothelial-mesenchymal transition (MMT), smooth muscle metaplasia (SMM), and type 2 immunity, leading ultimately to fibrosis. In addition, pain or infertility resulting from endometriosis may also induce stress, depression, and anxiety, resulting in the activation of the hypothalamic-pituitary-adrenal (HPA) and sympatho-adreno-medullary (SAM) axes, which, in turn, release copious amount of catecholamines. When these catecholamines reach the endometriotic lesions, adrenaline β2 receptor (ADRB2) would be activated, causing further progression of endometriosis. The progression of endometriosis would cause increased nerve fiber density within or surrounding the lesions (hyperinnervation) and as the fibrogenesis progresses, result in reduced vascular density and progesterone receptor (PR) expression, causing more pain and making lesions resistant to drug treatment. Note that all these players in the lesional microenvironment could engage in crosstalk through various mechanisms (the arrows). ADRB2, adrenaline β2 receptor; E2, estrogen; EMT, epithelial-mesenchymal transition; EndoMT, endothelial-mesenchymal transition; FMT, fibroblast-to-myofibroblast transdifferentiation; MMT, mesothelial-mesenchymal transition; PR, progesterone receptor; SMM, smooth muscle metaplasia

with severe renal failure prior to menstruation.[57] In addition, a "cyclical blood staining of peritoneal dialysis fluid" was observed "prior to any vaginal bleeding" in three girls who reached menarche while undergoing peritoneal dialysis.[58] Finally, endometrial implantation in the bowel of a newborn with hydrometrocolpos has been documented.[59]

Assuming that these assumptions will all prove to be correct, then these data suggest that endometriosis, in children and young adolescents, may originate from retrograde uterine bleeding soon after birth. This hypothesis is strengthened by the finding that endometrial stem/progenitor cells are present in adult menstrual blood, and therefore, they may also be shed during NUB. Supported by niche cells, they can survive and likely become dormant in the pelvic cavity for years in the absence of circulating estrogens: During thelarche, under the influence of surging estrogen levels (and perhaps other factors, yet to be identified, as well), endometrial stem (ESC)/progenitor cells would be reactivated, and proliferate, establishing the ectopic lesions characteristic of endometriosis.[60] This is akin to the legendary "sleeping beauty," awaken miraculously by the kiss of a handsome and charming prince, after years of slumbering. After all, all cells within a person have identical genomes, and as such, the viable cells in the NUB regurgitated into the pelvic cavity contain all the ER and PR machinery, which can be activated given the right moment and activators.

NUB occurs predominantly in the presence of chronic fetal distress (ie, in association with preeclampsia, fetal growth restriction, and ABO incompatibility) (Table 1), a condition apparently capable of accelerating endometrial maturation, decreasing or eliminating the well-known phenomenon of "*ontogenetic progesterone resistance*",[61] first documented by Ober and Bernstein[55] in an autopsy investigation of premature and term neonates.

Cases of premenarcheal OE have been published; possibly the first was that reported by Clark[62] in a 11-year-old girl in whom, 8 months before menarche, at laparotomy, an ovarian chocolate cyst, measuring 6.5 × 3 × 3 cm and attached to the left horn of a bicornuate uterus, was observed. The second, published over 60 years later by Gogacz et al.,[63] consisted of a similar case with an OE in the left ovary in an 11-year-old adolescent. She underwent an emergency operation for the left OE, and her menarche occurred spontaneously 6 months after surgery.

The potential role of endometrial stem cells in the pathogenesis of endometriosis has been summarized by Sasson and Taylor,[64] whereas, more recently, Cousins and Gargett[65] examined neonatal ESC in early OE formation. They explained that cyclical regeneration of human endometrium is likely to be mediated by these cells, representing a diverse group including $CD140b^{+}CD146^{+}$ or $SUSD2^{+}$ endometrial mesenchymal stem cells, N-cadherin+endometrial epithelial progenitor cells, and a heterogeneous cell population, predominantly comprising endothelial cells. ESCs may contribute to the pathogenesis of endometriosis by their retrograde shedding either after menarche or as a result of NUB.

7 | POST-MENARCHE AND FULL ADOLESCENCE

During the early phases of reproductive life, OE, whether originated through neonatal or cyclic retrograde shedding of endometrial fragments, possesses specific features that require detailed description.

7.1 | The wall of the early OE in the adolescent

In the adolescent, the physical barrier between the cyst contents and the normal ovarian tissue consists of a thin wall composed of the ovarian cortex itself. The absence of fibro-reactive tissue, due mainly to the lack of sufficient time for progression, may explain the relatively larger size of some OE in adolescents[25] (Table 2).

The already-mentioned comparison of adolescent *vs*. adult variants[52] identified specific differences in the OE wall between the two groups; adolescents showed significantly higher E-cadherin staining levels in the epithelial component ($p = 0.0004$), and significantly higher staining levels of α-smooth muscle actin (α-SMA), desmin, and neurokinin receptor 1 (NK1R). On the contrary, levels of adrenergic receptor β2 (ADRB2) were not different. These observations led to the conclusion that, with age (and thus with more time for the development of the lesion), there is a progression in the three classic paradigms of endometriosis: EMT (as shown by the lowering with age of E-cadherin staining in the epithelial component); FMT (characterized by higher α-SMA staining in the stromal component); and SMM (visualized by a higher desmin, as well as oxytocin receptor (OTR) staining in the stromal component). These time-dependent changes document a significantly less fibrotic content in the OE's wall in adolescent patients.

Of note, expression of the cell membrane-spanning ADRB2 in the lesion, along with the duration of dysmenorrhea, can be correlated with the extent of fibrosis in the wall—a proxy for disease progression, suggesting that, in addition to time, the presence of pain can also promote progression through the activation of the hypothalamic-pituitary-adrenal (HPA) and sympatho-adrenomedullary (SAM) axes, forming a vicious cycle in the development of the lesion. This may explain why the progression of *asymptomatic* rectal nodules is unlikely to occur,[66] or may be much slower, because no such a vicious cycle exists. Also, this also explains why there is a risk of progression of *symptomatic* deep endometriotic nodules infiltrating the recto-sigmoid, especially in menstruating women,[67] since menstruation facilitates ReTIAR, and thus EMT, FMT, SMM, and fibrogenesis.[42]

Brosens et al.[68] have described and illustrated how the endoscopic inspection of an ovarian cyst can document changes in its appearance in adolescents and mature women. Indeed, in recently formed OE, ovarioscopy often shows a marble-white or pigmented invaginated cortex lined by endometrial-like tissue. In older patients, this is gradually replaced by dark pigmented fibrotic tissue (Figure 3).

TABLE 1 Obstetrical disorders causing an increased frequency of neonatal uterine bleeding (NUB)

	No. of newborns	NUB Numbers and frequency
Controls	1207	57 (4.7%)
Newborns after a normal term pregnancy		
Born after preeclampsia	65	27 (41.5%)*
Born postmature	13	7 (54%)

Note: From Lévy et al.[146]
*$p < 0.001$.

The typical highly vascularized appearance of an OE in young women is shown in Figure 4.

7.2 | OE in patients with Müllerian anomalies

In 2008, Balci et al.[69] described the case of a 17-year-old girl with MRKH syndrome, the absence of pubertal stages and primary amenorrhea, and a 6 × 11 cm-sized cyst on the right adnexal area. At pathology examination, this was identified as a large hemorrhagic endometriotic cyst. More recently, another case of the coexistence of an OE and with MRKH syndrome in a 15-year-old girl has been also published.[70] These cases suggest that in patients with MRKH syndrome an early OE can be produced through dislocation of primitive endometrial tissue outside the uterine cavity during organogenesis.[71] Indeed, the occurrence of endometriosis in these patients seems to suggest metaplasia as the cause of endometriosis. However, a recent critical reevaluation of the literature on this issue carried out by Konrad et al.[14] indicates that most often only MRI diagnoses were available, and in the rare instances when histological confirmation was obtained, the presence of endometriosis was invariably associated with the presence of uterine remnants with endometrium.

Finally, in a retrospective study of 92 patients with MRKH syndrome, Wang et al.[72] correlated the anatomical features and clinical settings with patterns of uterine involvement. They concluded that the anatomical key point was that the presence of rudimentary uteri, especially bilateral rudimentary uteri, was quite common in MRKH syndrome; these uterine remnants can be relatively large, especially the unilateral rudimentary uterus. This entails that the existence of an active endometrium and of complications stemming from it (such as an OE) is more frequent in the presence of a unilateral rudimentary uterus.

Boruah et al.[70] have described the presence of vaginal or uterine outflow obstructive anomalies with hematocolpos or hematometra in a hospital-based prospective MRI study of 17 adolescent female patients. Six of these young patients had Herlyn-Werner-Wünderlich syndrome, another six had imperforated hymen, two had a transverse vaginal septum, and one each had cervico-vaginal atresia, unicornuate uterus, and a communicating rudimentary uterine horn. MRI revealed hematocolpos in 15 patients (88.2%), hematometra in 13 (76.5%), endometriotic ovarian cysts in 6 (35.3%), and hematosalpinx in 3 (17.6%). The authors recommended early imaging diagnosis to guide adequate surgical management, which, if undertaken promptly, will help avoiding complications, such as an OE, due to reflux from vaginal or uterine outflow obstruction. In this series, also the incidence of the presence of endometrium (100% vs. 22%, $p < 0.001$), hematometra (56% vs. 3%, $p < 0.001$), and OE (22% vs. 3%, $p < 0.01$) was significantly increased in the group with unilateral rudimentary uteri compared with the group of bilateral uterine remnants. This confirmed the findings of Wang et al.[72] that complications due to the presence of endometrium are more frequent in unilateral anomalies and that pelvic pain seems more common in individuals with unilateral rudimentary uterus than in those who had no (56% vs. 5%, $p < 0.01$) or bilateral uterine remnants (56% vs. 14%, $p < 0.05$).

7.3 | Symptomatology

A correct evaluation of symptoms associated with the presence of an OE is of fundamental importance to aid in the diagnosis. Unfortunately, no study has so far specifically addressed the issue of symptoms associated with the presence of OE alone.

In general, the prevailing symptom reported in most studies of early-onset endometriosis is a chronic and persistent pelvic pain (dysmenorrhea, acyclic chronic pain) not modified by classic medical treatment. Occasionally, it can manifest itself as acute abdominal pain.[73] In a cohort of young women (≤21 years), Staal et al.[74] cataloged the following complaints: dysmenorrhea (64%), menorrhagia (44%), abnormal or irregular uterine bleeding (60%), gastrointestinal symptoms (56%), and genitourinary symptoms (52%).

It seems that also the incidence of migraine is increased with a linear relationship between its severity and the probability of the presence of endometriosis.[75] In terms of severity, a review of cases of early-onset endometriosis up to 2013[76] identified 12 manuscripts for a total of 437 adolescents with laparoscopy-proven endometriosis. They found that the more recent studies clearly showed that endometriosis in the adolescent is no longer a disease of subtle superficial lesions, but is also characterized by severe stages, including the presence of extensive adhesions and OE.

A subsequent large, systematic review evaluated a total of 1243 adolescents with persistent pelvic pain, 64% of whom were found to have endometriosis.[77] Thirteen studies categorized disease severity using the rAFS/ASRM classification. Among these,

TABLE 2 Pathology findings in ovarian endometriomas in adults and adolescents

Author (Year of publication)	Specimen Number Age group	Cyst diameter (in cm)	Cyst lining wall	Adhesion site: implant, adherence	Endometrioma bed
Sampson (1921)[147]	HSO 30–50 year *n* =?	2–4	Endometrial	More active Implant	
Hughesdon (1957)[6]	Ovariectomy NA *n* = 29		Endometrial (83%) fibrotic	NA	SMM
Maneschi et al. (1993)[148]	Cystectomy <38 years		Cortical (19%), devascularised	NA	Less follicles
Brosens et al. (1994)[7]	Selective biopsy by ovarioscopy 21–46 years *n* = 51		Endometrial cortical, fibrous	Active implant with outgrowths Cortical retraction	NA
Brosens et al. (1996)[149]	Large				
Donnez et al. (1996)[150]	Large				
Hemmings et al. (1998)[151]					
Fukunaga (2000)[152]	HSO 26–70 years *n* = 265		SMM		SMM in 18.9% (photographs)
Anaf et al. (2000)[153]	biopsy (*n* = 9) ovariectomy (*n* = 3) 20–43 years		SMM		
Muzii et al. (2000)[154]	Stripping 21–35 years				Ovarian tissue 1–2 mm in 54%
Scurry et al. (2001)[155]	Cystectomy (*n* = 27) ovariectomy (*n* = 2) <35 years		Endometrial tissue covering cortical (34%), fibrous (48%), or destructed tissue (18%)	NA	NA
Muzii et al. (2005)[156]	Stripping vs coagulation and cutting *n* = 48		Endometrial, fibrous, and less follicles	NA	Ovarian tissue
Dilek et al. (2006)[157]	Laparoscopic cyst excision *n* = 46		??		
Muzii et al. (2007)[158]	Stripping *n* = 59		Endometrial, cortical 10–98%		Invasion depth of 2 mm
Romualdi et al. (2011)[159]	Cystectomy <40 years		Fibrous common in older and size	NA	Follicles related to age
Retto et al. (2011)[160]	Stripping *n* = 36	5.2 cm (range: 3–10 cm)		??	

TABLE 2 (Continued)

Author (Year of publication)	Specimen Number Age group	Cyst diameter (in cm)	Cyst lining wall	Adhesion site: implant, adherence	Endometrioma bed
Kuroda et al. (2012)[161]	Biopsy of ovary after stripping <35 years		NA	NA	Higher impact on follicle reserve in younger
Gogacz et al. (2012)[63]	Cystectomy 11 years	8 × 5	Endometrial		
Palmara et. al. (2012)[*162]	Cystectomy $n = 4$ Adolescents	4.5–10	Endometrial		Up to 1 mm
Lee et al. (2013)[163]	Cystectomy ≤20 years	6.1 × 2.6			
Kitajima et al. (2014)[164]	Cortical biopsy <40 years	≤4			Fibrosis and "follicle burnout"

Note: According to Scurry et al.,[155] specimens obtained by oophorectomy are more likely to provide an accurate distinction between the possible types of endometriomas, but are also more prone to miss the site of inversion of the cortex.

Abbreviations: HSO, hystero-salpingo-oophorectomy; SMM, smooth muscle metaplasia; NA, not applicable.

[a]Laparotomy *vs* laparoscopy in adolescents. No recurrence at 12- and 18-month follow-up by sonography.

53% of participants (201/381) had stage I, 28% (105/381) had stage II, 20% (76/381) had stage III, and 13% (49/381) had stage IV disease.

7.4 | Possible association with von Willebrand disease

Mitri and Casper[78] have pointed out that, while no systematic investigation of bleeding disorders in women with endometriosis has been carried out, there is clinical evidence suggesting that in these patients, bleeding may be increased. Attention has been focused on Von Willebrand disease (vWD), a condition characterized by the absence or reduction of the so-called "von Willebrand factor" (vWF), a protein involved in the coagulation cascade that binds to factor VIII (FVIII), a helper in the formation of the platelet plug. It is characterized by heavy and prolonged menstrual bleeding, and it was first observed in the form of catamenial hemoptysis in a young patient with histologically proven pulmonary endometriosis.[79] Recently, the case has been reported of a 17-year-old adolescent with vWD who was diagnosed with multiple OEs and underwent repeated surgery because of a suspicious appearance upon imaging evaluation. The authors advanced the hypothesis that vWD may increase the risk of developing severe endometriosis.[79]

While the seemingly increased risk of endometriosis in women with bleeding disorders may be conveniently explained by the increased tendency of distribution and dissemination of endometrial debris due to Sampson's retrograde menstruation theory, there is actually a deeper underlying connection. vWF is required for platelet adhesion to the subendothelium exposed by a vascular injury and also in mediating platelet-platelet interactions together with fibrinogen, thus enhancing the hemostatic process. Furthermore, VWF is the carrier of coagulation FVIII, driving it to the site of vascular damage and modulating its proteolytic degradation. It has been reported that infusion of FVIII or FVIII plus vWF concentrates, surgery, pregnancy, and desmopressin infusion could be risk factors for thrombosis in patients with vWD.[79] The infusion of FVIII or FVIII plus vWF could help to generate a hypercoagulable state.

Indeed, women with endometriosis, including OE, have been reported to be in a hypercoagulable state.[80-83] In traditional Chinese medicine, the treatment used for hundreds of years for endometriosis- or adenomyosis-like symptoms has always been antiplatelet/thrombotic.[84-86]

7.5 | Preventive management in the adolescent

A problem that effectively permits the progression of the disease before any treatment is installed is the almost inevitable delay in diagnosis. In spite of the fact that symptoms attributable to the presence of an OE will often start at a young age, even before menarche, a correct evaluation may not be completed for years. In this way, young women risk serious damage and impairment of future fertility

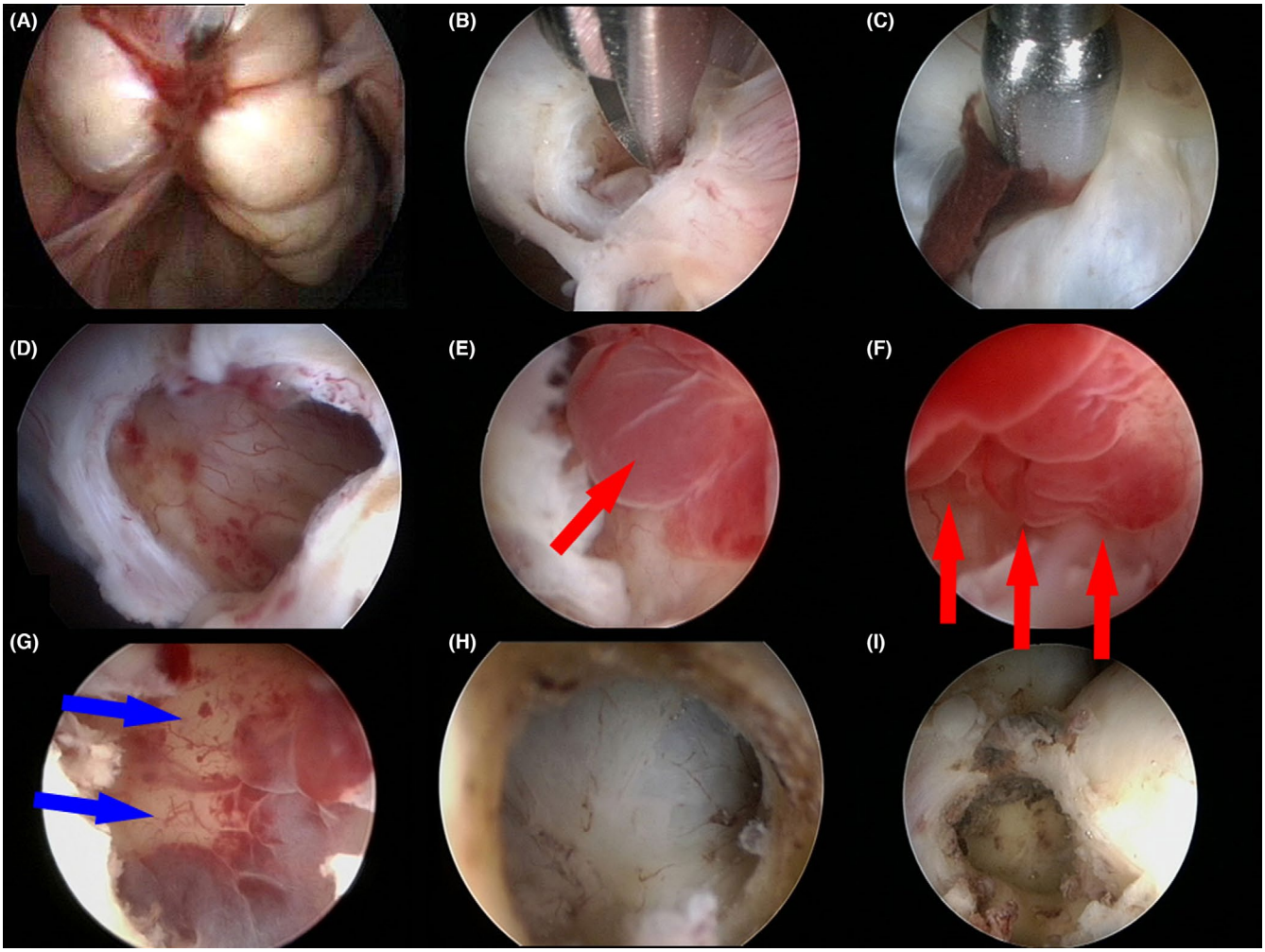

FIGURE 3 Hydrolaparoscopic approach to the ovarian endometrioma. Transvaginal hydrolaparoscopy for reconstructive surgery of non-fibrotic ovarian endometrioma up to 3 cm in diameter. (A) Disconnection of adhesions between ovary and pelvic side wall at the site of invagination; (B) Ovariolysis and exploration of what lies beneath the surface with sharp microscissors; (C) The "chocolate" content appears, clearly indicating the presence of an underlying endometrioma; (D) The endometrioma is further incised with the use of a bipolar needle to an opening of approximately 15 mm in diameter. Image taken after washing out the chocolate content; (E, F) Inside view, clearly showing the presence of red cobblestone-like ectopic endometrium, well differentiated at pathology (red arrows) and concentrated mostly behind the site of invagination and retraction. With a 5-Fr biopsy forceps, biopsies can easily be taken under direct visual control; (G) Endometriotic implants (blue arrows) inside the endometrioma superficially spread on a white background of inverted ovarian cortex; (H & I) End result of a conservative "minimally invasive" ablative surgery with a 5-Fr bipolar probe or a 1000 fiber of a 15-W diode laser under direct visual control, minimizing the damage to the cortex, that is, preserving ovarian reserve to a maximal extent. Reprinted with permission from Benagiano et al[87]

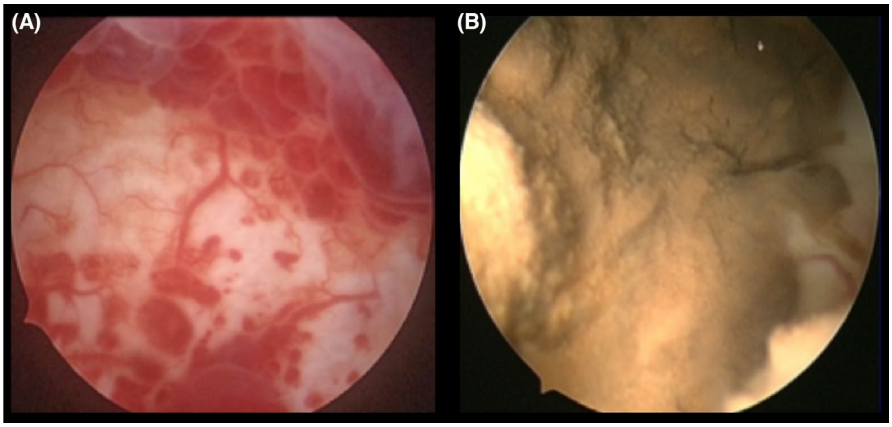

FIGURE 4 Assessment of ovarian endometriomas by ovarioscopy. (A) In younger women, the wall of the endometriotic cyst has the same marble-white or yellowish appearance as the outer cortex and is lined by a thin highly vascularized mucosa. (B) By contrast, the lining of older cysts typically appears darker, fibrotic, and devascularised. Reprinted with permission from Brosens et al[68]

since, if the lesions are rapidly progressing, they can severely affect pelvic organs and distort anatomical structure, even in the absence of serious symptoms. Given this predicament, great attention must be paid to symptomatology that is often non-specific, justifying a search for new, simple, non-invasive markers of the ovarian pathology. Appropriate use of modern imaging techniques will aid considerably in screening for the presence of early-onset endometriosis and particularly of OE.[87]

Finally, if we accept the evidence pointing to a progressive nature of at least some phenotypes of endometriosis, early intervention appears to be of vital importance. In view of the close correlation between the expression of ADRB2 in the lesions and the progression, an early intervention aimed at alleviating pain seems to be justified and warranted in order to break the vicious cycle and, hopefully, slow down progression.

Appropriate management in adolescents has been recently reviewed by Mama[88] who stressed the importance of early diagnosis and of a better understanding of the complex proinflammatory pathways underlying its progression. This may lead to tailored medical or combined medico-surgical treatment.

8 | ADULT LIFE

The majority of OE cases are observed during adult, fertile life, a phenomenon that, given their dependence on circulating steroid hormones, should not surprise. Our knowledge of adult OE is largely based on the inspection of the lesions in the abdominal cavity in women with infertility or pelvic pain. Then, following surgery, histopathology has provided vital and more revealing knowledge on the structure of disease in adults. In recent years, the picture has been expanded by comparison of the ectopic endometrium with its eutopic counterpart and by high-definition imaging of the lesions.

8.1 | Differences between adolescent and adult OE

The most characteristic difference between juvenile and adult OE consists of the progressive fibrotic process that involves the wall of OE in mature patients.

The study of ovaries with the endometrioma *in situ* has shown progressive SMM and fibrosis of the cortical layer as the main ovarian lesion in adult women[87] with specific consequences, especially in terms of response to treatment. Indeed, a recent investigation by Sroyrya et al.[89] evaluated comparatively the expression of ERα and ERβ and progesterone receptors (PR-A and PR-B) in eutopic endometria and cyst walls of women with OE with a size ≥3 cm, in patients treated or not with depot medroxyprogesterone acetate (DMPA). They observed that expression levels of ERα and ERβ, their corresponding mRNAs, and number of immunoreactive cells in stroma and glands of endometria of the DMPA group were significantly lower than those of the untreated groups. In contrast, following the use of DMPA, levels of PR-A and PR-B expression and numbers of positive cells in stroma and endometrial glands were significantly increased. Interestingly, the expression levels of both receptors in ectopic endometrium were low and DMPA treatment did not significantly change them, leading to the conclusion that DMPA can upregulate the expressions of PR-A/B and downregulate ERα and ERβ in eutopic endometria, but not in an OE cyst wall. The latter is very likely due to the silencing of PR-B because of hypermethylation,[90] which cannot be easily rectified by hormonal treatment. Alternatively, the promoter hypermethylation at both PR-A and PR-B loci may be caused by Kras mutation,[91] which has been documented in OE lesions.[92] While eutopic or even normal endometrium can also harbor Kras mutation,[92,93] the microenvironment of ectopic endometrium would be more conducive to somatic mutations,[94] and as such, the difference in ER/PR changes after the DMPA treatment.

In a review of the literature on the cellular structure and features of the endometriotic cyst, Sanchez et al.[95] concluded that there is sufficient molecular and histo-morphological evidence to support a deleterious effect of the OE on the adjacent ovarian cortex, independent of the mere mechanical stretching owing to its size. It also has been reported that over half of cortical samples from ovaries with OE showed fibrosis and concomitant loss of cortex-specific stroma, not observed in contralateral normal ovaries, suggesting that OE formation and associated structural tissue alterations, especially fibrosis, in apparently normal ovarian cortex may be a cause of reduced ovarian reserve.[96] As OE lesions in adolescent and adult patients display different fibrotic content,[52] older women with OE may have more reduced ovarian reserve. In addition, compared with adolescent patients, OE lesions in adult patients display reduced prostaglandin E2 (PGE2) signaling as manifested as expression of COX-2, EP2, and EP4, concomitant with increased extent of lesional fibrosis,[97] suggesting that adolescent patients with OE may be more responsible to NSAID treatment.

Ding et al.[83] conducted a cross-sectional study of 100 women with laparoscopically and pathologically diagnosed OE and another 100 women without any form of endometriosis. The platelet count, platelet activation rate, maximum platelet aggregation rate, plasma levels of D-dimer, fibrinogen, fibrin degradation products (FDPs), plasma-soluble P-selectin (sP-sel), and prothrombin fragment 1+2 (F1+2), prothrombin time, thrombin time (TT), and activated partial thromboplastin time were measured before surgery and 3 months after it, and clinical data were recorded. These measurements were also performed in control patients. They found that, compared with controls, women with OE had a significantly higher platelet activation rate and platelet aggregation rate, elevated plasma D-dimer, fibrinogen, FDPs, sP-sel, and F1+2 levels, as well as shortened TT. Remarkably, TT was prolonged, and all the other coagulation measurements, except plasma fibrinogen level, were significantly reduced 3 months after surgical removal of endometriotic lesions. Thus, their study provides another piece of evidence that endometriosis is a hypercoagulable disease, and anticoagulation therapy may hold promises in treating it.

Given the new information, it should not surprise that, since the presence of a smooth muscle component and fibrosis represents

consistent features of all variants of endometriosis, Viganò et al.[98] have now proposed to redefine endometriosis as *"A fibrotic condition in which endometrial stroma and epithelium can be identified."* They believe that the new definition will help in reorienting current research efforts toward more effective therapies, developing more adequate animal models for endometriosis, and improving patient care. The idea has merit, although there is a conceptual issue underlying this redefinition; while it correctly focuses attention on the "*fibrotic condition*," it ignores the basic fact that the disease is caused by the heterotopic presence of endometrial cells and stroma. Indeed, the best available evidence indicates that peritoneal endometriosis and ovarian endometriosis are caused by the retrograde, ectopic, and presence of endometrial cells and stroma; fibrosis and muscle metaplasia are almost ubiquitous but secondary phenomena.[99] As documented by adolescent disease, the initial stages of an OE are not characterized by fibrosis; rather, they involve neo-angiogenesis.[100] An alternative may be represented by defining endometriosis as *"a condition that starts with the ectopic deposition of endometrial epithelium and stroma, which undergo cyclic bleeding and thus repeated tissue injury and repair, resulting in gradual and progressive smooth muscle metaplasia and fibrogenesis"*.[42] By highlighting the dynamic nature of lesional progression, this definition has the advantages of being capable to explain as why adolescent and adult patients may respond differently to NSAIDs and/or hormonal treatment.

8.2 | Diagnosis

Most reports on symptoms associated with the presence of endometriosis in adult patients do not specifically mention those present in the ovarian variant. This should not surprise when considering that in a very recent retrospective study of 310 medical records randomly chosen from 1,054 patients treated for OE, this variant was present alone (ie, without extra-ovarian endometriosis and/or adhesions), in only 2.3% of the cases.[101]

In this respect, Fauconnier and Chapron[102] stressed over 15 years ago that randomized trials indicated that in more than half of confirmed cases of endometriosis, pelvic pain was the prevailing symptom, making a causal association very probable. An important point is that the association is independent of the macroscopic variant of the condition or of the anatomical location. In fact, pain may be related to recurrent cyclic microbleeding in the implants and/or to the presence of adhesions.

Further light on the symptomatology of OE was provided by Khan et al.,[103] who investigated the relationship between OE and pain symptoms in 350 cases of laparoscopically confirmed cases. Peritoneal endometriotic (PE) lesions coexisted in some 77% of the patients, and in this group, some 85% of the women experienced pelvic pain. In contrast, among the 81 women with isolated OE, pelvic pain was present only in some 38% of the cases. The difference between the 2 groups was statistically significant ($p < 0.01$).

Finally, they observed that CD68-immunoreactive macrophage infiltration and tissue expression of COX-2 and $PGF_{2\alpha}$ were significantly higher in both the eutopic and ectopic endometria in women with peritoneal endometriosis than in tissues of women with OE.

While the co-occurrence of PE lesions in patients with OE sounds reasonable, it should be pointed out that most, if not all, women underwent surgery due to OE, not PE. Findings of PE lesions, incidental or otherwise, are already included within the rASRM scoring system.

DiVasta et al.[104] carried out a cross-sectional study to try to identify differences between symptoms present in adolescents and mature women. Overall, 90% of participants experienced moderate-to-severe menstrual pain. More adolescents than adults reported pain (in the prevalence of non-cyclic nature) starting at menarche ($p = 0.002$) and nausea accompanying pain (69% vs. 53%, $p = 0.01$).

In conclusion, it is possible that pelvic pain in women with OE is mostly due to the concomitant presence of the other variants.

8.3 | Pregnancy and its management

An investigation of variations in the morphology and size of OE diagnosed during pregnancy was undertaken by Pateman et al.[105] who, in an investigation of their behavior during pregnancy, found a poor vascularization on Doppler examination, with a tendency to a decrease in size; in a few cases, there were sonographic features suggestive of decidualization (thick and irregular inner wall, papillary projections, and highly vascular images on Doppler). The discovery of the presence of an OE during pregnancy may pose diagnostic problems, due to the difficulty of reaching a definite diagnosis at ultrasound,[106] and for this reason, this issue has been extensively investigated by Leiserowitz[107] who stressed that morphological criteria exist to accurately distinguish benign cysts from malignant conditions. Subsequently, Leiserowitz et al.[108] carried out a population-based study that identified 9375 women with a diagnosis of an ovarian mass associated with pregnancy and concluded that ovarian cancers, including low-grade tumors, are rare (a rate of 0.93% malignancies per total number of ovarian masses).

A complicating factor is represented by the major increase in circulating progesterone levels during pregnancy that may cause decidualization of the ectopic endometrial tissue in the OE. A few cases in which such a modification had occurred have been described: Fruscella et al.[106] characterized one such case through transvaginal ultrasound, color Doppler examination, magnetic resonance characteristics, tumor marker longitudinal evaluation during the first trimester of pregnancy, and a final histological description. Then, Pateman et al.,[105] after examining 24 pregnant patients with a total of 34 OE, found sonographic features suggestive of decidualization in 4/34 (11.8%, 95% CI 1.0–22.6); such features consisted of thick and irregular inner wall, papillary projections, and highly vascular appearance on Doppler examination. Finally, Taylor et al.[109] described a case and also reviewed the literature on the patient, identifying 14 articles reporting on additional 26 cases; 19 (70%) were managed surgically and eight conservatively.

Although it is expected that regression and involution after pregnancy may improve the situation, a recent review[110] of 11 publications measuring OE during pregnancy and the postpartum period concluded that there is no evidence that pregnancy can generally reduce the size and number of endometriotic lesions. Overall, fewer beneficial effects than previously reported were found; nonetheless, in several cases regression of the OE occurred. Unfortunately, the aging factor has not been taken into account in investigating decidual changes in pregnancy, and moreover, all studies have been performed on OE as seen in the adult woman and none in the adolescent.

A rare, but severe, complication in pregnant women with endometriosis is the occurrence of a spontaneous hemoperitoneum. A recent systematic review[111] reported that in four cases, bleeding occurred in one ovary and that in all cases where a biopsy of the bleeding site was obtained, decidualization was documented, even in the absence of visible endometriosis (a phenomenon called *deciduosis*). Its severity or incidence seems to be increased in controlled ovarian hyperstimulation for *in vitro* fertilization (IVF).

In this connection, the question arises whether assisted reproduction techniques (ART) can affect the outcome of pregnancy. In 2015, Hamdan et al.[112] carried out a systematic review on the impact of assisted reproduction techniques on pregnancy and its outcome. They concluded that, when compared to women without the disease, patients with OE had a lower mean number of oocytes retrieved (MNOR) [standard mean deviation (SMD) −0.23; 95% confidence interval (CI) −0.37, −0.10] and a higher cycle cancelation rate [OR 2.83; 95% CI 1.32, 6.06]. Clinical pregnancy rates (CPR) were similar [OR 1.17; 95% CI) 0.87, 1.58], as well as live birth rates (LBR) [OR 0.98; 95% CI 0.71, 1.36]. Hamdan et al. also evaluated the effect of surgically treating the OE before an ART and found similar MNOR [SMD −0.17; 95% CI −0.38, 0.05], CPR [OR 0.97; 95% CI 0.78, 1.20], and LBR [OR 0.90; 95% CI 0.63, 1.28].

9 | POSTMENOPAUSAL OE

The history of postmenopausal endometriosis has been reconstructed by Inceboz[113] who found mention by Guy[114] of a first report published in 1942 by Haydon, followed by a large series of 136 cases published by Kemper in 1960; in this series, out of 41 postmenopausal women, 25 had OE.[115] Then, Punnonen et al.[116] reported on 903 patients with adenomyosis or endometriosis; among them, 20 (2.2%) were at least 2 years postmenopausal: 11 had ovarian endometriosis, eight adenomyosis, and one both diseases. Symptomatology included metrorrhagia and abdominal pain; in one patient, a distorted OE caused an acute abdomen necessitating emergency surgery. In 9 out of the 12 cases, the cyst was lined with endometrial-like stroma and glands, and in eight, the wall of the cyst was heavily fibrotic.

9.1 | Symptoms and morphology

The symptomatic presence of an OE in menopause is rare, and based on limited information, it shows a clinical picture significantly different from that in women of fertile age. This variant appears to have a greater predisposition to malignant change, may have a greater tendency to spread to extragonadal organs, and may develop into constrictive and/or obstructive lesions; for these reasons, it should be preferably treated surgically.[117]

Morotti et al.[118] examined the records of 72 postmenopausal women with endometriosis (only two were using hormonal replacement therapy [HRT]) who underwent surgery at the median age of 58.5 years and found that the most frequent location was the ovary. Among these patients, 35% had different grades of metaplasia, hyperplasia, atypia, and endometrioid carcinoma arising out of the endometriotic tissue.

9.2 | Pathophysiology

Potential mechanisms for postmenopausal endometriosis have been evaluated by Bendon and Becker[119] who stressed that several cases described in the literature could be linked to the presence of premenopausal disease, although not all cases could be explained this way.

In terms of pathogenetic mechanisms, besides HRT, importance must be given to extra-ovarian estrogen production by the skin and adipose tissue, giving a role to obesity in its pathogenesis. Such extra-ovarian sites of estrogen neosynthesis have been identified in several cases. In addition, locally produced estrogens may play a significant role.[120] The recent review by Ladanyi et al.[121] stresses that, although no unifying theory has been satisfactorily proposed, "*estrogen dependence is central to the pathophysiological process*," since recent studies confirmed the presence in endometriotic lesions of the enzymes necessary for estrogen synthesis; thus, this local source represents a likely pathogenic contributor.

Cumiskey et al.[122] investigated morphological and immunohistochemical characteristics of pre- and postmenopausal endometriosis by reviewing all cases that occurred in their department from 1990 and 2007 in women aged >or =50 years. They analyzed 91 cases <50, 8 between 50 and 59 and 6 > or =60. In older women, they found that the disease is less common, is present in smaller volumes, and is less active, although there was no statistical difference in the proportions of epithelium or stroma. In addition, older women showed a statistically significant lower incidence of hemorrhage, but no significant difference in immune-histochemical profile.

An important issue is whether the presence of an OE in postmenopause carries a significant risk of malignant transformation. A recent meta-analysis by Giannella et al.[151] systematically reviewed existing literature on malignant transformation of postmenopausal endometriosis, without making distinction between the various phenotypes. They retrieved 90 cases, with a mean age of 55.8 ± 8.5 years. Two-thirds of the patients used HRT, in the majority of cases (75%), estrogen-only treatment. Histopathology indicated that some 70% of the patients had endometrioid adenocarcinoma or clear cell carcinoma. Follow-up outcome, available for 61 women, showed a survival rate of 78.7%, a recurrence rate of 9.8%, and a death rate

of 11.5%. In conclusion, the identified risk factors include recurrence of endometriosis, previous hysterectomy, with or without bilateral salpingo-oophorectomy before menopause, and estrogen-only HRT for a relatively long time.

9.3 | Management

Streuli et al.[123] believe that symptomatic postmenopausal endometriosis should be managed surgically because of the risk of malignancy, with medical treatments limited to cases with pain recurrence after surgery. This may be sensible or justifiable, since the detrimental impact of either OE lesions or surgery on ovarian cortex no longer matters any more for postmenopausal women. In contrast, the risk of malignancy cannot be dismissed lightly, since the chance of acquiring new lesions after menopause is low and since the lesions are likely already in existence prior to the menopause. As such, they may be in existence for a long time, likely to have acquired certain cancer-associated mutations (CAMs) already. If they have acquired enough number and type of CAMs, malignancy transformation ensues.[94]

9.4 | Association with hormone replacement therapy

For decades, active OE in postmenopause has been associated with HRT[124,125]; a systematic Cochrane review carried out ten years ago on the effect of HRT in postsurgical menopause in women with endometriosis concluded that it could result in pain and disease recurrence, although the evidence was not strong.[126]

In 2007, another systematic review identified some 32 case reports on postmenopausal endometriosis in patients who took HRT, especially estrogen-only therapy, and identified the ovaries as the most common location.[127] The authors concluded that the condition is rare, but it infers a risk of recurrence and malignant transformation, possibly higher when only estrogens are administered. One such case is worthy of mention, because it occurred in a 54-year-old in whom a total abdominal hysterectomy for uterine leiomyomata with left ovarian cystectomy had been performed 7 years previously and an estradiol transdermal patch had been prescribed. At surgery, the remaining right adnexa contained a smooth surfaced, non-adherent, cystic OE weighing 3121 g.[128] Finally, the case has been published recently by Jeon et al.[129] of a 51-year-old woman who took HRT for 5 years in whom imaging suggested the presence of a left OE. Following surgery, pathology examination confirmed that it was an ovarian endometriotic cyst.

There is a report of the presence of ectopic decidua in several pelvic and para-aortic lymph nodes in a postmenopausal woman treated for 5 years with HRT, who underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, and lymphadenectomy for a clear cell ovarian carcinoma. The ectopic decidua consisted of layers of loosely cohesive, large, uniform round cells with eosinophilic cytoplasm and a few inactive endometrial glands; decidual cells tested positive for CD10, vimentin, estrogen, and progesterone receptors.[130]

A recent review by Ladanyi et al.[121] placed the frequency at 2.5% of postmenopausal women, but stressed that knowledge of prevalence, pathogenesis, and treatment options is limited. In their opinion, all suspected cases should be surgically excised for optimization of treatment and prevention of malignant transformation. In this respect, Cope et al.[131] stressed that guidelines describing appropriate imaging surveillance in postmenopausal women are lacking.

9.5 | Cases in untreated postmenopausal women

In recent years, a few reports of large OE in untreated postmenopausal women have been described in detail.[132-134] Of particular relevance is the case described by Bailey et al.[135] with a retroperitoneal endometriotic mass plus a secondary one involving the small bowel mesentery. Intriguingly, cystic OE was found in the right kidney and right distal ureter, but no residual ovarian tissue was identified. This case is supportive of the theory of an autocrine estradiol synthesis.

OE in untreated postmenopausal women may even mimic metastatic ovarian carcinoma[136] and, on fluorodeoxyglucose PET/CT, show peritoneal dissemination and gross ascites (Figure 5).[137]

Finally, Sasson and Taylor[138] described a case of a patient with no history of pelvic endometriosis who had an abdominal wall well-encapsulated, multiloculated cyst diagnosed as a benign hemorrhagic cyst that recurred twice. At first recurrence, exploration of the cyst revealed multiple locations with chocolate fluid. The cyst wall presented scattered foci of endometrial glands and stroma. The second recurrence occurred 10 months later, and following surgery, the patient was successfully treated with an aromatase inhibitor.

A recent systematic review of the literature between 1995 and the beginning of 2018 has been carried out by de Almeida Asencio et al.,[11] who found only 29 cases in the literature and added seven new of their own, including two patients in whom symptoms increased progressively in the absence of increased estrogen secretion or intake. They consisted exclusively of either OE or deep infiltrating endometriosis. It seems that the severity of symptoms and localization are highly variable, and in some, two thirds of the patients' symptoms started more than 10 years after menopause.

The authors concluded that clinically progressive, symptomatic endometriosis after menopause in the absence of increased systemic estrogen production or intake on average starts more than 10 years after menopause. They suggested that "a genetic and/or epigenetic incident caused estrogen-independent progression."

10 | CONCLUSIONS

As alluded to above, age-dependent phenotypic variations in OE are discernable. These variations, summarized in Table 3, may have

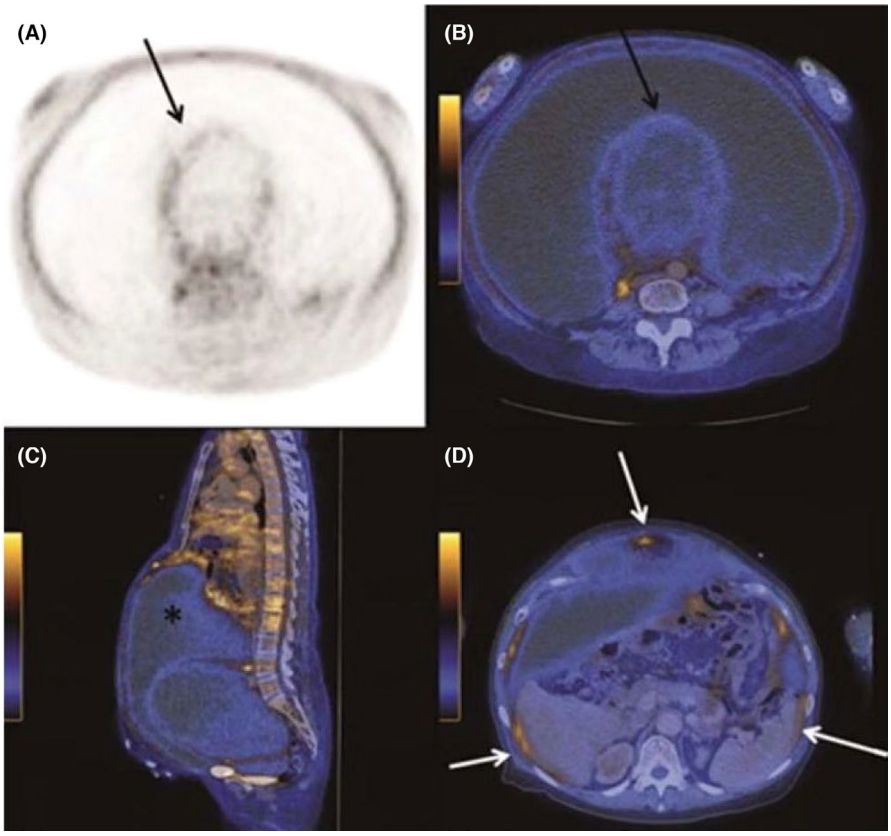

FIGURE 5 Appearance at positron emission tomography-computed tomography (PET/CT) with [^{18}F]-fluorodeoxyglucose (FDG) of an abdominal mass found in a 69-year-old woman. The four images show a predominantly cystic mass arising from the pelvis. (A) Axial view. (B) Same axial image as appearing at fused FDG PET-CT. (C) Fused sagittal FDG PET-CT image. (D) Fused axial FDG PET-CT image. Initially, a diagnosis was posed of a primary ovarian malignancy with ascites and diffuse peritoneal carcinomatosis. At surgery, however, a large tumor (25 cm in diameter) containing a solid area and chocolate-like material was found. At histology, bilateral endometriomas were found, but no malignant cells. Peritoneal deposits consisted of a florid histiocytic reaction, with foreign body-type giant cells and cholesterol clefts. Reprinted with permission from Agarwal Sharma et al[137]

important implications in ascertaining their pathogenesis and devising strategies for intervention or even prevention. They may also have important implications in management. For example, on average the OE lesions in adolescents would be more likely to be cystic and less fibrotic than those in adults, which would mean that these patients would be more likely to respond to non-steroid anti-inflammatory drugs (NSAIDs) therapy since the PGE2 signaling is less likely to be attenuated.[97] They may also respond to therapies that target the EP2 and/or EP4 receptors.[139] In contrast, OE lesions in adults may not respond well to either NSAID treatment[97] or therapies that target the EP2 and/or EP4 receptors,[139] especially when the lesions are highly fibrotic.

The answer to the recent concern of Somigliana et al.[140] about damage that both the OE and surgery can produce is clearly related to the present delay of diagnosis and to the poor understanding of the complex pathophysiology of the ectopic endometrial cells.

This is a serious issue, since a number of investigations have shown that OE can substantially affect the quality of life on an adolescent.[141] To speed up the identification of an OE in a young woman, Zannoni et al.[142] have suggested a number of practical ways to diagnose it as early as possible. The first suggestion is to never underestimate the pain symptom; this means that a physician should always consider endometriosis as a possible cause of severe cyclic pain. Pain should be immediately treated with hormonal therapies and analgesics; if the symptom persists, imaging technology should be employed without delay; however, it is important to obtain a detailed and accurate history before performing clinical evaluation and pelvic sonography. Finally, for these patients, frequent follow-up visits to reevaluate the situation should be planned.

What needs to be stressed is that, given the life cycle of the OE as shown here, guidelines for its treatment, as produced by the European Society of Human Reproduction and Embryology (ESHRE), the European Society for Gynecological Endoscopy (ESGE), and the World Endometriosis Society (WES)[143] should not be indiscriminately the same for the treatment of the condition when presenting in the adolescent, the adult, and the postmenopausal patient.

Indeed, the OE in the adolescent has a thin cortical lining, which explains the frequently observed large sizes. Therefore, wall thickness should be determined by ultrasound, together with the presence or absence of signs of mucosal aging. In case of a large OE with a thin inner cortex, it is logical to first reduce the size of the OE by aspiration to allow involution of the pseudo-cystic structure. When the size has been reduced to 4cm or less, then minimally traumatic approaches, such as the transvaginal hydrolaparoscopy (THL)[144] technique, can be applied.

In this respect, Hung et al.[145] carried out a retrospective population-based analysis of the Nationwide Inpatient Sample (part of a family of databases and software tools developed for the Healthcare Cost and Utilization Project, most comprehensive source of hospital care data in the USA). They evaluated patients aged 9–25 years, diagnosed with adenomyosis, endometriosis, or chronic pelvic pain, with a median age at diagnosis of 22 years, and observed an overall inpatient intervention rate of 45.0% (18.6% for excision/ablation; 15.7% for hysterectomy; 9.5% for diagnostic laparoscopy; and 1.2% for biopsy). Interestingly, the rate of hysterectomy

TABLE 3 Comparison of ovarian endometriomas in different age groups

	Infancy and early adolescence	Post-menarche and adolescence	Adulthood	Postmenopausal
Possible source/ origin	NUB, obstructive anomaly, celomic metaplasia, embryonic Müllerian rests, genetic	NUB, obstructive anomaly, retrograde menstruation celomic metaplasia, embryonic Müllerian rests, genetic susceptibility, and environmental or lifestyle factors	NUB, obstructive anomaly, retrograde menstruation, celomic metaplasia, embryonic Müllerian rests, genetic susceptibility, and environmental or lifestyle factors	Preexisting or residual lesions
Size	6.5 × 3 × 3 cm[62] 9 cm in diameter[63]	Mean cyst size 75 ± 29 mm[165]	Up to the size of a grapefruit[166]	Up to 3121 *g*[128]
Cyst wall lining	Endometrial epithelium, stroma, and hemosiderin-laden macrophages, but no glandular structures	A thin wall composed of the ovarian cortex itself.	Progressive smooth muscle metaplasia leading to fibrosis	Different grades of metaplasia, hyperplasia, atypia; endometrioid carcinoma may arise out of the endometriotic wall tissue.
Morphological/ Histological appearance	Cystic	Cystic	Various, can be cystic and fibrotic	Cystic
Pattern of pain	Acute (?)	Absent or cyclic	Usually, cyclic	Persistent
Pattern of vascularity			Reduced vascularity concomitant with increased fibrosis	Statistically significant lower incidence of hemorrhage
Extent of fibrosis	Absent	Largely absent	Increasingly fibrotic	Presence of constrictive and/ or obstructive lesions
Epigenetic/ genetic aberration	Not described	??	??	Not described

Notes: ?, unknown/unclear; NUB, neonatal uterine bleeding.

increased in the late 2000s while rates of all other interventions decreased. Rates of intervention differed according to geographic location, race, insurance status, and type of hospital. They concluded that there is a need for "data-driven" treatment guidelines for the management of young patients with chronic pelvic pain to ensure appropriate application of surgical treatments and expand high-value surgical care.

Unfortunately, the delay of diagnosis is not likely to change as long as the possible new marker of an increased risk of early-onset endometriosis represented by the occurrence of NUB is not widely recorded and therefore validated or discarded. In the absence of any registration of NUB on a birth certificate, it can be proposed to use obstetrical information of chronic fetal distress, such as preeclampsia or fetal growth restriction. Since they have been linked to a higher incidence of NUB, they can be considered as potential predictors of neonatal menstruation; it may be possible through these means to indirectly determine whether NUB carries an increased risk of early onset of endometriosis during adolescence.

Finally, it must be stressed that hydroflotation, as used in THL, can detect the early stage of angiogenesis in endometriotic lesions, thereby avoiding both excessive ovarian surgery and the future loss of fertility.

ACKNOWLEDGMENTS

This research was funded in part by grants 81771553 (SWG) and 82071623 (SWG) from the National Natural Science Foundation of China, an Excellence in Centers of Clinical Medicine grant 2017ZZ01016 (SWG) from the Science and Technology Commission of Shanghai Municipality, and Clinical Research Plan Grant SHDC2020CR2062B from Shanghai Shenkang Center for Hospital Development (SWG).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

1. Jenkins S, Olive DL, Haney AF. Endometriosis: pathogenetic implications of the anatomic distribution. *Obstet Gynecol*. 1986;67(3):335-338.
2. Gylfason JT, Kristjansson KA, Sverrisdottir G, Jonsdottir K, Rafnsson V, Geirsson RT. Pelvic endometriosis diagnosed in an entire nation over 20 years. *Am J Epidemiol*. 2010;172(3):237-243.
3. Somigliana E. Ovarian reserve, endometriomas, and surgery: research must go on. *Fertil Steril*. 2018;110(5):856-857.
4. Blair BW. Endometrioma and endometriomyoma of the ovary. *J Obstetr Gynaecol Brit Emp*. 1922;29:443-446.
5. Brosens I, Puttemans P, Benagiano G. Endometriosis: a life cycle approach? *Am J Obstet Gynecol*. 2013;209(4):307-316.
6. Hughesdon PE. The structure of endometrial cysts of the ovary. *J Obstet Gynaecol Brit Emp*. 1957;64:481-487.
7. Brosens IA, Puttemans PJ, Deprest J. The endoscopic localization of endometrial implants in the ovarian chocolate cyst. *Fertil Steril*. 1994;61(6):1034-1038.
8. Meigs JV. Endometriosis. *Ann Surg*. 1948;127(5):795-809.
9. Brosens I, Benagiano G. Is neonatal uterine bleeding involved in the pathogenesis of endometriosis as a source of stem cells? *Fertil Steril*. 2013;100(3):622-623.
10. de Almeida Asencio F, Ribeiro HA, Ayrosa Ribeiro P, et al. Symptomatic endometriosis developing several years after menopause in the absence of increased circulating estrogen concentrations: a systematic review and seven case reports. *Gyncol Surg*. 2019;16.
11. Sampson JA. The life history of ovarian hematomas (hemorrhagic cysts) of endometrial (Müllerian) type. *Am J Obstet Gynecol*. 1922;3:451-512.
12. Meyer R. Ueber eine adenomatose. Wucherung der serosa in einer Banchuabe. *Zeit Geburt Gynak*. 1903;49:32-41.
13. Kurita T. Normal and abnormal epithelial differentiation in the female reproductive tract. *Differentiation*. 2011;82(3):117-126.
14. Konrad L, Dietze R, Kudipudi PK, Horne F, Meinhold-Heerlein I. Endometriosis in MRKH cases as a proof for the coelomic metaplasia hypothesis? *Reproduction*. 2019;158(2):R41-R47.
15. Nakamura M, Katabuchi H, Tohya T, Fukumatsu Y, Matsuura K, Okamura H. Scanning electron microscopic and immunohistochemical studies of pelvic endometriosis. *Hum Reprod*. 1993;8(12):2218-2226.
16. Yan D, Liu X, Xu H, Guo SW. Mesothelial cells participate in endometriosis fibrogenesis through platelet-induced mesothelial-mesenchymal transition. *J Clin Endocrinol Metab*. 2020;105(11):e4124-e4147.
17. Hull ML, Escareno CR, Godsland JM, et al. Endometrial-peritoneal interactions during endometriotic lesion establishment. *Am J Pathol*. 2008;173(3):700-715.
18. Yan D, Liu X, Guo SW. The establishment of a mouse model of deep endometriosis. *Hum Reprod*. 2019;34(2):235-247.
19. Lauchlan SC. The secondary Mullerian system. *Obstet Gynecol Surv*. 1972;27(3):133-146.
20. Batt RE, Smith RA, Buck Louis GM, et al. Mullerianosis. *Histol Histopathol*. 2007;22(10):1161-1166.
21. Batt RE, Smith RA. Embryologic theory of histogenesis of endometriosis in peritoneal pockets. *Obstet Gynecol Clin North Am*. 1989;16(1):15-28.
22. Laganà AS, Garzon S, Götte M, et al. The pathogenesis of endometriosis: molecular and cell biology insights. *Int J Mol Sci*. 2019;20(22):5615.
23. Signorile PG, Baldi F, Bussani R, D'Armiento M, De Falco M, Baldi A. Ectopic endometrium in human foetuses is a common event and sustains the theory of mullerianosis in the pathogenesis of endometriosis, a disease that predisposes to cancer. *J Exp Clin Cancer Res*. 2009;28:49.
24. Goldstein DP, deCholnoky C, Leventhal JM, Emans SJ. New insights into the old problem of chronic pelvic pain. *J Pediatr Surg*. 1979;14(6):675-680.
25. Reese KA, Reddy S, Rock JA. Endometriosis in an adolescent population: the Emory experience. *J Pediatr Adolesc Gynecol*. 1996;9(3):125-128.
26. Marsh EE, Laufer MR. Endometriosis in premenarcheal girls who do not have an associated obstructive anomaly. *Fertil Steril*. 2005;83(3):758-760.
27. Signorile PG, Baldi F, Bussani R, et al. New evidence of the presence of endometriosis in the human fetus. *Reprod Biomed Online*. 2010;21(1):142-147.
28. Redwine DB. Is "microscopic" peritoneal endometriosis invisible? *Fertil Steril*. 1988;50(4):665-666.
29. Simpson JL, Elias S, Malinak LR, Buttram VC Jr. Heritable aspects of endometriosis. I. Genetic studies. *Am J Obstet Gynecol*. 1980;137(3):327-331.
30. Di W, Guo SW. The search for genetic variants predisposing women to endometriosis. *Curr Opin Obstet Gynecol*. 2007;19(4):395-401.
31. Guo SW. Sibling recurrence risk ratio as a measure of genetic effect: caveat emptor! *Am J Hum Genet*. 2002;70(3):818-819.
32. Guo SW. Does higher concordance in monozygotic twins than in dizygotic twins suggest a genetic component? *Hum Hered*. 2001;51(3):121-132.
33. Guo SW. Familial aggregation of environmental risk factors and familial aggregation of disease. *Am J Epidemiol*. 2000;151(11):1121-1131.
34. Guo SW. Recurrence of endometriosis and its control. *Hum Reprod Update*. 2009;15(4):441-461.
35. Ponomarenko I, Reshetnikov E, Polonikov A, et al. Candidate genes for age at menarche are associated with endometriosis. *Reprod Biomed Online*. 2020;41(5):943-956.
36. Lee SH, Harold D, Nyholt DR, et al. Estimation and partitioning of polygenic variation captured by common SNPs for Alzheimer's disease, multiple sclerosis and endometriosis. *Hum Mol Genet*. 2013;22(4):832-841.
37. Guo SW. Chapter 6. The quest for genetic sequence variants conferring risk of endometriosis. In: Garcia-Velasco JA, Seli E, eds. *Human reproductive genetics: Emerging technologies and clinical applications*. Academic Press; 2020:91-104.
38. Dinsdale N, Nepomnaschy P, Crespi B. The evolutionary biology of endometriosis. *Evol Med Public Health*. 2021;9(1):174-191.
39. Barker DJ. The fetal and infant origins of adult disease. *BMJ*. 1990;301(6761):1111.
40. Zhang Q, Duan J, Liu X, Guo SW. Platelets drive smooth muscle metaplasia and fibrogenesis in endometriosis through epithelial-mesenchymal transition and fibroblast-to-myofibroblast transdifferentiation. *Mol Cell Endocrinol*. 2016;428:1-16.
41. Zhang Q, Duan J, Olson M, Fazleabas A, Guo SW. Cellular changes consistent with epithelial-mesenchymal transition and fibroblast-to-myofibroblast transdifferentiation in the progression of experimental endometriosis in baboons. *Reprod Sci*. 2016;23(10):1409-1421.
42. Guo SW. Fibrogenesis resulting from cyclic bleeding: the Holy Grail of the natural history of ectopic endometrium. *Hum Reprod*. 2018;33(3):353-356.
43. Yan D, Liu X, Xu H, Guo SW. Platelets induce endothelial-mesenchymal transition and subsequent fibrogenesis in endometriosis. *Reprod Biomed Online*. 2020;41(3):500-517.
44. Yan D, Liu X, Guo SW. Neuropeptides substance P and calcitonin gene related peptide accelerate the development and fibrogenesis of endometriosis. *Sci Rep*. 2019;9(1):2698.
45. Qi Q, Guo S-W, Liu X. Activated platelets induce hypoxia-inducible factor-1α expression likely through transforming growth factor-β1 in human endometrial stromal cells. *Reprod Dev Med*.. 2019;3(2):69-76.

46. Qi Q, Liu X, Zhang Q, Guo S-W. Platelets induce increased estrogen production through NF-κB and TGF-β1 signaling pathways in endometriotic stromal cells. *Sci Rep*. 2020;10(1). 10.1038/s41598-020-57997-6
47. Zhang Q, Ding D, Liu X, Guo SW. Activated platelets induce estrogen receptor beta expression in endometriotic stromal cells. *Gynecol Obstet Invest*. 2015;80(3):187-192.
48. Du Y, Liu X, Guo SW. Platelets impair natural killer cell reactivity and function in endometriosis through multiple mechanisms. *Hum Reprod*. 2017;32(4):794-810.
49. Guo SW, Du Y, Liu X. Platelet-derived TGF-beta1 mediates the down-modulation of NKG2D expression and may be responsible for impaired natural killer (NK) cytotoxicity in women with endometriosis. *Hum Reprod*. 2016;31(7):1462-1474.
50. Liu X, Zhang Q, Guo SW. Histological and immunohistochemical characterization of the similarity and difference between ovarian endometriomas and deep infiltrating endometriosis. *Reprod Sci*. 2018;25(3):329-340.
51. Liu X, Yan D, Guo SW. Sensory nerve-derived neuropeptides accelerate the development and fibrogenesis of endometriosis. *Hum Reprod*. 2019;34(3):452-468.
52. Ding D, Wang X, Chen Y, Benagiano G, Liu X, Guo S-W. Evidence in support for the progressive nature of ovarian endometriomas. *J Clin Endocrinol Metab*. 2020;105(7):2189-2202.
53. Starzinski-Powitz A, Zeitvogel A, Schreiner A, Baumann R. Endometriosis–a stem cell disease? *Zentralbl Gynakol*. 2003;125(7–8):235-238.
54. Brosens I, Brosens JJ, Benagiano G. The potential perinatal origin of placentation disorders in the young primigravida. *Am J Obstet Gynecol*. 2015;212:580-585.
55. Ober WB, Bernstein J. Observations on the endometrium and ovary in the newborn. *Pediatrics*. 1955;16:445-460.
56. Terruhn V. A study of impression moulds of the genital tract of female fetuses. *Arch Gynecol*. 1980;229:207-217.
57. Blumenkrantz MJ, Gallagher N, Bashore RA. Retrograde menstruation in women undergoing chronic peritoneal dialysis. *Obstet Gynecol*. 1981;57:667-670.
58. Turner G, Coulthard MG. Premenarchal endometrial shedding revealed by peritoneal dialysis. *Arch Dis Childhood*. 1995;73:88-89.
59. Arcellana RC, Robinson TW, Tyson RW, Joyce MR. Neonatal fellowship. McKusick-Kaufman syndrome with legal complications of hydrometrocolpos and congenital endometriosis. *J Perinatol*. 1996;16(3 Pt 1):220-223.
60. Gargett CE, Schwab KE, Brosens JJ, Puttemans P, Benagiano G, Brosens I. Potential role of endometrial stem/progenitor cells in the pathogenesis of early-onset endometriosis. *Mol Hum Reprod*. 2014;20(7):591-598.
61. Brosens I, Benagiano G. Progesterone response in neonatal endometrium is key to future reproductive health in adolescents. *Womens Health*. 2016;12:279-282.
62. Clark AH. Endometriosis in a young girl. *J Am Med Assoc*. 1948;136(10):690.
63. Gogacz M, Sarzyński M, Napierała R, Sierocińska-Sawa J, Semczuk A. Ovarian endometrioma in an 11-year-old girl before menarche: a case study with literature review. *J Pediatr Adolesc Gynecol*. 2012;25:e5-e7.
64. Sasson IE, Taylor HS. Stem cells and the pathogenesis of endometriosis. *Ann N Y Acad Sci*. 2008;1127:106-115.
65. Cousins FL, O DF, Gargett CE. Endometrial stem/progenitor cells and their role in the pathogenesis of endometriosis. *Best Pract Res Clin Obstet Gynaecol*. 2018;50:27-38.
66. Fedele L, Bianchi S, Zanconato G, Raffaelli R, Berlanda N. Is rectovaginal endometriosis a progressive disease? *Am J Obstet Gynecol*. 2004;191(5):1539-1542.
67. Netter A, d'Avout-Fourdinier P, Agostini A, et al. Progression of deep infiltrating rectosigmoid endometriotic nodules. *Hum Reprod*. 2019;34(11):2144-2152.
68. Brosens I, Gargett CE, Guo S-W, et al. Origins and progression of adolescent endometriosis. *Reprod Sci*. 2016;23(10):1282-1288.
69. Balci O, Karatayli R, Capar M. An incidental coexistence of Mayer-Rokitansky-Kuster-Hauser syndrome with pelvic ectopic kidney and perirenal endometrioma. *Saudi Med J*. 2008;29(9):1340-1341.
70. Boruah DK, Sanyal S, Gogoi BB, et al. Spectrum of MRI appearance of Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome in primary amenorrhea patients. *J Clin Diagn Res*. 2017;11(7):TC30-TC5.
71. Brosens I, Gordts S, Puttemans P, Benagiano G. Pathophysiology proposed as the basis for modern management of the ovarian endometrioma. *Reprod Biomed Online*. 2014;28(2):232-238.
72. Wang Y, Lu J, Zhu L, et al. Evaluation of Mayer-Rokitansky-Kuster-Hauser syndrome with magnetic resonance imaging: Three patterns of uterine remnants and related anatomical features and clinical settings. *Eur Radiol*. 2017;27(12):5215-5224.
73. Shim JY, Laufer MR. Adolescent endometriosis: an update. *J Pediatr Adolesc Gynecol*. 2020;33(2):112-119.
74. Staal AH, van der Zanden M, Nap AW. Diagnostic delay of endometriosis in the Netherlands. *Gynecol Obstet Invest*. 2016;81(4):321-324.
75. Miller JA, Missmer SA, Vitonis AF, Sarda V, Laufer MR, DiVasta AD. Prevalence of migraines in adolescents with endometriosis. *Fertil Steril*. 2018;109(4):685-690.
76. Brosens I, Gordts S, Benagiano G. Endometriosis in adolescents is a hidden, progressive and severe disease that deserves attention, not just compassion. *Hum Reprod*. 2013;28(8):2026-2031.
77. Hirsch M, Dhillon-Smith R, Cutner AS, Yap M, Creighton SM. The prevalence of endometriosis in adolescents with pelvic pain: a systematic review. *J Pediatr Adolesc Gynecol*. 2020;33(6):623-630.
78. Mitri F, Casper RF. Endometriosis and mild bleeding disorders. *Fertil Steril*. 2015;103(4):886-7 e1.
79. Rizzello F, Ralli E, Romanelli C, Coccia ME. Severe recurrent endometriomas in a young woman with congenital von Willebrand disease. *Gynecol Endocrinol*. 2019;35(12):1040-1042.
80. Wu Q, Ding D, Liu X, Guo SW. Evidence for a hypercoagulable state in women with ovarian endometriomas. *Reprod Sci*. 2015;22(9):1107-1114.
81. Vigano P, Ottolina J, Sarais V, Rebonato G, Somigliana E, Candiani M. Coagulation status in women with endometriosis. *Reprod Sci*. 2018;25(4):559-565.
82. Ding S, Lin Q, Zhu T, et al. Is there a correlation between inflammatory markers and coagulation parameters in women with advanced ovarian endometriosis? *BMC Womens Health*. 2019;19(1):169.
83. Ding D, Liu X, Guo SW. Further evidence for hypercoagulability in women with ovarian endometriomas. *Reprod Sci*. 2018;25(11):1540-1548.
84. Guo SW, Ding D, Liu X. Anti-platelet therapy is efficacious in treating endometriosis induced in mouse. *Reprod Biomed Online*. 2016;33(4):484-499.
85. Zhu B, Chen Y, Shen X, Liu X, Guo SW. Anti-platelet therapy holds promises in treating adenomyosis: experimental evidence. *Reprod Biol Endocrinol*. 2016;14(1):66.
86. Zhao RH, Sun WW, Liu Y, Dai ZQ. Chinese medicine in management of chronic disease endometriosis. *Chin J Integr Med*. 2020;26(2):88-91.
87. Benagiano G, Guo SW, Puttemans P, Gordts S, Brosens I. Progress in the diagnosis and management of adolescent endometriosis: an opinion. *Reprod Biomed Online*. 2018;36(1):102-114.
88. Mama ST. Advances in the management of endometriosis in the adolescent. *Curr Opin Obstet Gynecol*. 2018;30(5):326-330.
89. Sroyraya M, Songkoomkrong S, Changklungmoa N, et al. Differential expressions of estrogen and progesterone receptors in endometria and cyst walls of ovarian endometrioma from women with endometriosis and their responses to depo-medroxyprogesterone acetate treatment. *Mol Cell Probes*. 2018;40:27-36.

90. Wu Y, Strawn E, Basir Z, Halverson G, Guo SW. Promoter hypermethylation of progesterone receptor isoform B (PR-B) in endometriosis. *Epigenetics*. 2006;1(2):106-111.
91. Inoue S, Yoshida E, Fukui Y, et al. KRAS mutations in uterine endometrium are associated with gravidity and parity. *Cell Death Dis*. 2020;11(5):347.
92. Suda K, Nakaoka H, Yoshihara K, et al. Clonal expansion and diversification of cancer-associated mutations in endometriosis and normal endometrium. *Cell Rep*. 2018;24(7):1777-1789.
93. Suda K, Nakaoka H, Yoshihara K, et al. Different mutation profiles between epithelium and stroma in endometriosis and normal endometrium. *Hum Reprod*. 2019;34(10):1899-1905.
94. Guo SW. Cancer-associated mutations in endometriosis: shedding light on the pathogenesis and pathophysiology. *Human Reprod Update*. 2020;26(3):423-449.
95. Sanchez AM, Vigano P, Somigliana E, Cioffi R, Panina-Bordignon P, Candiani M. The endometriotic tissue lining the internal surface of endometrioma: hormonal, genetic, epigenetic status, and gene expression profile. *Reprod Sci*. 2015;22(4):391-401.
96. Kitajima M, Defrère S, Dolmans M-M, et al. Endometriomas as a possible cause of reduced ovarian reserve in women with endometriosis. *Fertil Steril*. 2011;96(3):685-691.
97. Huang Q, Liu X, Guo SW. Higher fibrotic content of endometriotic lesions is associated with diminished prostaglandin E2 (PGE2) signaling. *Reprod Med Biol*. 2021;21(1):e12423.
98. Vigano P, Candiani M, Monno A, Giacomini E, Vercellini P, Somigliana E. Time to redefine endometriosis including its profibrotic nature. *Hum Reprod*. 2018;33(3):347-352.
99. Brosens I, Puttemans P, Benagiano G. Which cell defines endometriosis? *Hum Reprod*. 2018.
100. Brosens I, Benagiano G. Endometrioma in adolescents and future reproductive health. *J Endometr Pelvic Pain Disord*. 2017;9:9-16.
101. Piriyev E, Schiermeier S, Romer T. Coexistence of endometriomas with extraovarian endometriosis and adhesions. *Eur J Obstet Gynecol Reprod Biol*. 2021;263:20-24.
102. Fauconnier A, Chapron C. Endometriosis and pelvic pain: epidemiological evidence of the relationship and implications. *Hum Reprod Update*. 2005;11(6):595-606.
103. Khan KN, Kitajima M, Fujishita A, et al. Pelvic pain in women with ovarian endometrioma is mostly associated with coexisting peritoneal lesions. *Hum Reprod*. 2013;28(1):109-118.
104. DiVasta AD, Vitonis AF, Laufer MR, Missmer SA. Spectrum of symptoms in women diagnosed with endometriosis during adolescence vs adulthood. *Am J Obstet Gynecol*. 2018;218(3):324.e1-e11.
105. Pateman K, Moro F, Mavrelos D, Foo X, Hoo WL, Jurkovic D. Natural history of ovarian endometrioma in pregnancy. *BMC Womens Health*. 2014;14:128.
106. Fruscella E, Testa AC, Ferrandina G, et al. Sonographic features of decidualized ovarian endometriosis suspicious for malignancy. *Ultrasound Obstet Gynecol*. 2004;24(5):578-580.
107. Leiserowitz GS. Managing ovarian masses during pregnancy. *Obstet Gynecol Surv*. 2006;61(7):463-470.
108. Leiserowitz GS, Xing G, Cress R, Brahmbhatt B, Dalrymple JL, Smith LH. Adnexal masses in pregnancy: how often are they malignant? *Gynecol Oncol*. 2006;101(2):315-321.
109. Taylor LH, Madhuri TK, Walker W, Morton K, Tailor A, Butler-Manuel S. Decidualisation of ovarian endometriomas in pregnancy: a management dilemma. A case report and review of the literature. *Arch Gynecol Obstet*. 2015;291(5):961-968.
110. Leeners B, Damaso F, Ochsenbein-Kolble N, Farquhar C. The effect of pregnancy on endometriosis-facts or fiction? *Hum Reprod Update*. 2018;24(3):290-299.
111. Brosens IA, Lier MC, Mijatovic V, Habiba M, Benagiano G. Severe spontaneous hemoperitoneum in pregnancy may be linked to in vitro fertilization in patients with endometriosis: a systematic review. *Fertil Steril*. 2016;106(3):692-703.
112. Hamdan M, Dunselman G, Li TC, Cheong Y. The impact of endometrioma on IVF/ICSI outcomes: a systematic review and meta-analysis. *Hum Reprod Update*. 2015;21(6):809-825.
113. Inceboz U. Endometriosis after menopause. *Womens Health*. 2015;11(5):711-715.
114. Guy JM. Edgar Haydon (1859–1942): general practitioner and radium pioneer. *J Med Biogr*. 2009;17(3):127-134.
115. Kempers RD, Dockerty MB, Hunt AB, Symmonds RE. Significant postmenopausal endometriosis. *Surg Gynecol Obstet*. 1960;111:348-356.
116. Punnonen R, Klemi PJ, Nikkanen V. Postmenopausal endometriosis. *Eur J Obstet Gynecol Reprod Biol*. 1980;11(3):195-200.
117. Tan DA, Almaria MJG. Postmenopausal endometriosis: drawing a clearer clinical picture. *Climacteric*. 2018;21(3):249-255.
118. Morotti M, Remorgida V, Venturini PL, Ferrero S. Endometriosis in menopause: a single institution experience. *Arch Gynecol Obstet*. 2012;286(6):1571-1575.
119. Bendon CL, Becker CM. Potential mechanisms of postmenopausal endometriosis. *Maturitas*. 2012;72(3):214-219.
120. Bulun SE, Yang S, Fang Z, Gurates B, Tamura M, Sebastian S. Estrogen production and metabolism in endometriosis. *Ann N Y Acad Sci*. 2002;955:75–85; discussion 6–8, 396–406.
121. Ladanyi C, Boyd S, Sticco P, Mohling S. Postmenopausal endometriosis, where are we now? *Curr Opin Obstet Gynecol*. 2019;31(4):267-278.
122. Cumiskey J, Whyte P, Kelehan P, Gibbons D. A detailed morphologic and immunohistochemical comparison of pre- and postmenopausal endometriosis. *J Clin Pathol*. 2008;61(4):455-459.
123. Streuli I, Gaitzsch H, Wenger JM, Petignat P. Endometriosis after menopause: physiopathology and management of an uncommon condition. *Climacteric*. 2017;20(2):138-143.
124. Goodman HM, Kredentser D, Deligdisch L. Postmenopausal endometriosis associated with hormone replacement therapy. A case report. *J Reprod Med*. 1989;34(3):231-233.
125. Goh JT, Hall BA. Postmenopausal endometrioma and hormonal replacement therapy. *Aust N Z J Obstet Gynaecol*. 1992;32(4):384-385.
126. Al Kadri H, Hassan S, Al-Fozan HM, Hajeer A. Hormone therapy for endometriosis and surgical menopause. *Cochrane Database Syst Rev*. 2009(1):CD005997.
127. Oxholm D, Knudsen UB, Kryger-Baggesen N, Ravn P. Postmenopausal endometriosis. *Acta Obstet Gynecol Scand*. 2007;86(10):1158-1164.
128. Bellina JH, Schenck D. Large postmenopausal ovarian endometrioma. *Obstet Gynecol*. 2000;96(5 Pt 2):846.
129. Jeon DS, Kim TH, Lee HH, Byun DW. Endometriosis in a postmenopausal woman on hormonal replacement therapy. *J Menopausal Med*. 2013;19(3):151-153.
130. Kim HS, Yoon G, Kim BG, Song SY. Decidualization of intranodal endometriosis in a postmenopausal woman. *Int J Clin Exp Pathol*. 2015;8(1):1025-1030.
131. Cope AG, VanBuren WM, Sheedy SP. Endometriosis in the postmenopausal female: clinical presentation, imaging features, and management. *Abdom Radiol*. 2020;45(6):1790-1799.
132. García Manero M, Royo P, Olartecoechea B, Alcázar JL. Endometriosis in a postmenopausal woman without previous hormonal therapy: a case report. *J Med Case Reports*. 2009;3:135.
133. Matsushima T, Asakura H. Huge ovarian endometrioma that grew after menopause: case report. *J Obstet Gynaecol Res*. 2016;42(3):350-352.
134. Filipescu GA, Clim N, Niculiu C, Mitran M, Boiangiu AG. Voluminous endometrioma in a postmenopausal woman without previous hormonal therapy. Case report. *Ginecol Eur*. 2017;13:75-77.

135. Bailey AP, Schutt AK, Modesitt SC. Florid endometriosis in a postmenopausal woman. *Fertil Steril*. 2010;94(7):2769.e1-2769.e4.
136. Suchonska B, Gajewska M, Zygula A, Wielgos M. Endometriosis resembling endometrial cancer in a postmenopausal patient. *Climacteric*. 2018;21(1):88-91.
137. Agarwal Sharma R, Lee EY, Vardhanabhuti V, Khong PL, Ngu SF. Unusual case of postmenopausal diffuse endometriosis mimicking metastastic ovarian malignancy. *Clin Nucl Med*. 2016;41(2):e120-e122.
138. Sasson IE, Taylor HS. Aromatase inhibitor for treatment of a recurrent abdominal wall endometrioma in a postmenopausal woman. *Fertil Steril*. 2009;92(3):1170.e1-1170.e4.
139. Huang Q, Liu X, Guo S-W. Changing prostaglandin E2 (PGE2) signaling during lesional progression and exacerbation of endometriosis by inhibition of PGE2 receptor EP2 and EP4. *Reprod Med Biol*. 2021;21(1):e12426.
140. Somigliana E, Vigano P, Benaglia L, Busnelli A, Paffoni A, Vercellini P. Ovarian stimulation and endometriosis progression or recurrence: a systematic review. *Reprod Biomed Online*. 2019;38(2):185-194.
141. Zannoni L, Giorgi M, Spagnolo E, Montanari G, Villa G, Seracchioli R. Dysmenorrhea, absenteeism from school, and symptoms suspicious for endometriosis in adolescents. *J Pediatr Adolesc Gynecol*. 2014;27(5):258-265.
142. Zannoni L, Forno SD, Paradisi R, Seracchioli R. Endometriosis in adolescence: practical rules for an earlier diagnosis. *Pediatr Ann*. 2016;45(9):e332-e335.
143. Dunselman GA, Vermeulen N, Becker C, et al. ESHRE guideline: management of women with endometriosis. *Hum Reprod*. 2014;29(3):400-412.
144. Gordts S, Campo R, Rombauts L, Brosens I. Transvaginal hydrolaparoscopy as an outpatient procedure for infertility investigation. *Hum Reprod*. 1998;13(1):99-103.
145. Hung YC, Westfal ML, Chang DC, Kelleher CM. Lack of data-driven treatment guidelines and wide variation in management of chronic pelvic pain in adolescents and young adults. *J Pediatr Adolesc Gynecol*. 2020;33(4):349-353.e1.
146. Levy JM, Rosenthal R, Dellenbach P, Pequenot JP. Crise ge´nitale du nouveau-ne´. Re´percussion de certains facteurs maternels ou gravidiques sur la fre´quence des me´trorragies ne´onatales. [Genital crisis in the newborn. Repercussion of certain maternal or pregnancy factors on the frequency of neonatal metrorrhagia]. *Arch Fr Pediatr*. 1964;21:819-827.
147. Sampson JA. Perforating hemorrhagic (chocolate) cysts of the ovary. Their importance and especially their relation to pelvic adenomas of the endometrial type ("adenomyoma" of the uterus, rectovaginal septum, sigmoid, etc.). *Arch Surg*. 1921;3:245-323.
148. Maneschi F, Marasa L, Incandela S, Mazzarese M, Zupi E. Ovarian cortex surrounding benign neoplasms: a histologic study. *Am J Obstet Gynecol*. 1993;169(2 Pt 1):388-393.
149. Brosens IA, Van Ballaer P, Puttemans P, Deprest J. Reconstruction of the ovary containing large endometriomas by an extraovarian endosurgical technique. *Fertil Steril*. 1996;66(4):517-521.
150. Donnez J, Nisolle M, Gillet N, Smets M, Bassil S, Casanas-Roux F. Large ovarian endometriomas. *Hum Reprod*. 1996;11(3):641-646.
151. Hemmings R, Bissonnette F, Bouzayen R. Results of laparoscopic treatments of ovarian endometriomas: laparoscopic ovarian fenestration and coagulation. *Fertil Steril*. 1998;70(3):527-529.
152. Fukunaga M. Smooth muscle metaplasia in ovarian endometriosis. *Histopathology*. 2000;36(4):348-352.
153. Anaf V, Simon P, Fayt I, Noel J. Smooth muscles are frequent components of endometriotic lesions. *Hum Reprod*. 2000;15(4):767-771.
154. Muzii L, Marana R, Caruana P, Catalano GF, Margutti F, Panici PB. Postoperative administration of monophasic combined oral contraceptives after laparoscopic treatment of ovarian endometriomas: a prospective, randomized trial. *Am J Obstet Gynecol*. 2000;183(3):588-592.
155. Scurry J, Whitehead J, Healey M. Classification of ovarian endometriotic cysts. *Int J Gynecol Pathol*. 2001;20(2):147-154.
156. Muzii L, Bellati F, Palaia I, et al. Laparoscopic stripping of endometriomas: a randomized trial on different surgical techniques. Part I: Clinical results. *Hum Reprod*. 2005;20(7):1981-1986.
157. Dilek U, Pata O, Tataroglu C, Aban M, Dilek S. Excision of endometriotic cyst wall may cause loss of functional ovarian tissue. *Fertil Steril*. 2006;85(3):758-760.
158. Muzii L, Bianchi A, Bellati F, et al. Histologic analysis of endometriomas: what the surgeon needs to know. *Fertil Steril*. 2007;87(2):362-366.
159. Romualdi D, Franco Zannoni G, Lanzone A, et al. Follicular loss in endoscopic surgery for ovarian endometriosis: quantitative and qualitative observations. *Fertil Steril*. 2011;96(2):374-378.
160. Retto G, Santoro G, Sturlese E, et al. Efficacy of laparoscopic stripping for ovarian cysts: histological and clinical findings. *J Obstet Gynaecol Res*. 2011;37(6):547-552.
161. Kuroda M, Kuroda K, Arakawa A, et al. Histological assessment of impact of ovarian endometrioma and laparoscopic cystectomy on ovarian reserve. *J Obstet Gynaecol Res*. 2012;38(9):1187-1193.
162. Palmara V, Sturlese E, Romeo C, et al. Morphological study of the residual ovarian tissue removed by laparoscopy or laparotomy in adolescents with benign ovarian cysts. *J Pediatr Surg*. 2012;47(3):577-580.
163. Lee DY, Kim HJ, Yoon BK, Choi D. Factors associated with the laterality of recurrent endometriomas after conservative surgery. *Gynecol Endocrinol*. 2013;29(11):978-981.
164. Kitajima M, Dolmans MM, Donnez O, Masuzaki H, Soares M, Donnez J. Enhanced follicular recruitment and atresia in cortex derived from ovaries with endometriomas. *Fertil Steril*. 2014;101(4):1031-1037.
165. Lee SY, Kim ML, Seong SJ, Bae JW, Cho YJ. Recurrence of ovarian endometrioma in adolescents after conservative, laparoscopic cyst enucleation. *J Pediatr Adolesc Gynecol*. 2017;30(2):228-233.
166. Zondervan KT, Becker CM, Koga K, Missmer SA, Taylor RN, Vigano P. Endometriosis. *Nat Rev Dis Primers*. 2018;4(1):9.
167. Guo SW. Cancer driver mutations in endometriosis: variations on the major theme of fibrogenesis. *Reprod Med Biol*. 2018;17(4):369-397.

How to cite this article: Benagiano G, Guo S-W. Age-dependent phenotypes of ovarian endometriomas. *Reprod Med Biol*. 2022;21:e12438. doi:10.1002/rmb2.12438