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 interest4; 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,

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
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 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. used laparoscopic ovarioscopy 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 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:

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; 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.
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.

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 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 proposed that endometriosis (at the time known as "adenomyoma") may arise from endometrial 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.

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. 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, 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. Indeed, MMT has been documented in a mouse model of endometriosis and can be shown in in vitro experimentation. It is likely that the lesional presence of peritoneal mesothelial cells observed by Nakamura et al. 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 endometrioid-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,\textsuperscript{19,20} which can be stimulated by ovarian steroids at thelarche.\textsuperscript{21} As reviewed recently by Laganà et al.,\textsuperscript{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.\textsuperscript{23}

Goldstein et al.\textsuperscript{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.\textsuperscript{25,26} In addition, more support has been provided by Signorile et al.,\textsuperscript{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,\textsuperscript{25,26} in conjunction with the macroscopic and microscopic findings in a female infant who died of sudden infant death syndrome,\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 familiallly 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.\textsuperscript{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,\textsuperscript{30,34} as has been shown recently.\textsuperscript{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,\textsuperscript{36} providing another example of “missing heritability” as in many other complex diseases.\textsuperscript{37}

From the evolutionary standpoint, endometriosis is now viewed as being driven, proximately, by relatively low levels of prenatal and postnatal testosterone,\textsuperscript{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.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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).\textsuperscript{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.\textsuperscript{44} Looking through this prism of ReTIAR, it can be understood as why there are a hyperestrogenism\textsuperscript{45,46} and aberrant
expression of estrogen receptor β (ERβ), why there is a reduced cytotoxicity of natural killer (NK) cells in endometriosis, and why there is histological difference, as documented by Brosens et al., in OE between younger and older patients or between OE and deep endometriosis (DE). Above all, we can understand why OE is a progressive disease if unimpeded (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. 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, 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, indicating that it is capable of shedding. The presence of a functional barrier pluging of the endocervical canal in the neonate 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.
with severe renal failure prior to menstruation. 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. Finally, endometrial implantation in the bowel of a newborn with hydrometrocolpos has been documented.

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. This is akin to the legendary “sleeping beauty,” awoken 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”, first documented by Ober and Bernstein in an autopsy investigation of prematurity and term neonates.

Cases of premenarcheal OE have been published; possibly the first was that reported by Clark in a 11-year-old girl in whom, 8 months before menarche, at laparotomy, an ovarian chocolate cyst, measuring 6.5 x 3 x 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., 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, whereas, more recently, Cousins and Gargett 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 (Table 2).

The already-mentioned comparison of adolescent vs. adult variants 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 sympathetic-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, 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, since menstruation facilitates ReTIAR, and thus EMT, FMT, SMM, and fibrogenesis.

Brosens et al. 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).
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.

Boruh 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-Wunderlich syndrome, another six had imperforated hymen, two had a transverse vaginal septum, and one each had cervico-vaginal atresia, unicorne 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 hema- tosalpinx 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 uterus 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,
| 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 | 2–4                  | Endometrial     | More active implant           |                 |
| Hughesdon (1957)\(^{6}\)    | Ovariectomy     | NA        | n = 29               | Endometrial (83%) fibrotic | NA                | SMM             |
| Maneschi et al. (1993)\(^{348}\) | 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)\(^{49}\) | Large           |           |                     |                 |                               |                 |
| Donnez et al. (1996)\(^{50}\) | Large           |           |                     |                 |                               |                 |
| Hemmings et al. (1998)\(^{51}\) |                |           |                     |                 |                               |                 |
| Fukunaga (2000)\(^{152}\)   | HSO             | 26–70 years | n = 265              | SMM             |                               | SMM in 18.9% (photographs) |
| Anaf et al. (2000)\(^{553}\) | biopsy n = 9) ovarietomy (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) ovarietomy (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                | Follies related to age |
| Retto et al. (2011)\(^{160}\) | Stripping       | n = 36    | 5.2 cm (range: 3–10 cm) |                 |                               | ??              |
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\(^7^8\) 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.\(^7^9\) 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.\(^7^9\)

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.\(^7^9^\) 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.\(^8^0^\)\(^–^\)\(^8^3^\) In traditional Chinese medicine, the treatment used for hundreds of years for endometriosis- or adenomyosis-like symptoms has always been antiplatelet/thrombotic.\(^8^4^\)\(^–^\)\(^8^6^\)

### 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 devascularized. 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.  

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 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 with specific consequences, especially in terms of response to treatment. Indeed, a recent investigation by Sroyra et al. 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, 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, which has been documented in OE lesions.  

While eutopic or even normal endometrium can also harbor Kras mutation, the microenvironment of ectopic endometrium would be more conducive to somatic mutations, 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. concluded that there is sufficient molecular and histomorphological 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. As OE lesions in adolescent and adult patients display different fibrotic content, 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, suggesting that adolescent patients with OE may be more responsible to NSAID treatment.

Ding et al. 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.\textsuperscript{99} 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.\textsuperscript{99} As documented by adolescent disease, the initial stages of an OE are not characterized by fibrosis; rather, they involve neo-angiogenesis.\textsuperscript{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.”\textsuperscript{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.\textsuperscript{101}

In this respect, Fauconnier and Chapron\textsuperscript{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.,\textsuperscript{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.\textsuperscript{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.\textsuperscript{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,\textsuperscript{106} and for this reason, this issue has been extensively investigated by Leiserowitz\textsuperscript{107} who stressed that morphological criteria exist to accurately distinguish benign cysts from malignant conditions. Subsequently, Leiserowitz et al.\textsuperscript{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.\textsuperscript{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.,\textsuperscript{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.\textsuperscript{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\textsuperscript{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\textsuperscript{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 decidualosis). 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.\textsuperscript{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\textsuperscript{113} who found mention by Guy\textsuperscript{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.\textsuperscript{115} Then, Punnonen et al.\textsuperscript{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.\textsuperscript{117}

Morotti et al.\textsuperscript{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\textsuperscript{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.\textsuperscript{120} The recent review by Ladanyi et al.\textsuperscript{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.\textsuperscript{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 \(>50\) years. They analyzed 91 cases, between 50 and 59, and 6 \(>60\) years. 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.\textsuperscript{123} 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).\(^{127}\)

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...
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.

They may also respond to therapies that target the EP2 and/or EP4 receptors. In contrast, OE lesions in adults may not respond well to either NSAID treatment or therapies that target the EP2 and/or EP4 receptors, especially when the lesions are highly fibrotic.

The answer to the recent concern of Somigliana et al. 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. To speed up the identification of an OE in a young woman, Zannoni et al. 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) 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) technique, can be applied.

In this respect, Hung et al. 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...
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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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,    | NUB, obstructive anomaly,     | NUB, obstructive anomaly,   | Preexisting or residual lesions |
|                         | celomic metaplasia, embryonic    | retrograde menstruation, celomic | menstruation, celomic metaplasia, embryonic rests, genetic susceptibility, and environmental or lifestyle factors |
|                         | Müllerian rests, genetic       | metaplasia, embryonic Müllerian rests, genetic susceptibility, and environmental or lifestyle factors |
| Size                    | $6.5 \times 3 \times 3 \text{ cm}^{63}$ | Mean cyst size $75 \pm 29 \text{ mm}^{165}$ | Up to the size of a grapefruit$^{166}$ | Up to $3.121g^{128}$ |
| 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/          | Cystic                         | Cystic                        | Various, can be cystic and fibrotic | Cystic |
| Histological appearance|                               |                               |                  |               |
| 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     | Not described                  | ??                            | ??               | Not described |
| aberration              |                               |                               |                  |               |

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