Postmenopausal Diseases and Disorders

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Preface

The second half of female life corresponds to the last years of the reproductive phase and postmenopause. During this period, the specific phenomenon of the menopause occurs, as a consequence of ovarian function cessation, converging in parallel with physical aging. Elder women have specific risk features and disease managements that differ from those of elder men. Therefore, it is clear that due to these differences, medical care should be gender-based. Furthermore, gender biases in medical research have been frequent, and many drugs have not been tested in women before coming into the market. Therefore, it is not surprising that adverse drug reactions are more likely to occur in women than in men due to the lack of gender-oriented research.

Science and medicine are continuous processes characterized by the substitution of "old" for "new" evidence. The so-called evidence-based medicine (EBM) refers to clinical decision-making or the indication of interventions based on validated tests or scientific data. Nonetheless, EBM cannot provide answers to all scientific questions or, in many cases, may not provide a sufficient level of quality. Hence, well-designed observational studies may also provide provisional recommendations—and limitations—for clinical interventions until randomized controlled trials offer a higher level of evidence. Thus, management strategies that are based on clinical trials undertaken in younger people or in men may not be appropriate for postmenopausal women.

For much time, physicians and other healthcare providers have accepted as routine care those procedures and treatments that seem consolidated or free of any discussion. However, sooner or later, uncertainties or limitations are detected, even in the most obvious aspects, and everything is subject to revision. Therefore, science is a *perpetuum mobile*, and this book has tried to collect the most rigorous and current scientific information as a starting point to delve into each topic. The aim of this book is to provide a practical, holistic, unbiased, and non-promotional guide for health professionals dealing with women in their post-reproductive years. International authors and opinion leaders cover the wide spectrum of gynecological and non-gynecological conditions affecting post-reproductive health. Evidence-based information, where available, is presented, and clinical recommendations are put into perspective. The book therefore provides an integrated approach to post-reproductive health.

This book includes many topics that are relevant to women's health during their second half of life, written by opinion leaders in their corresponding area of knowledge. Each reader will jump into chapters that are closer to their quotidian area of clinical or research interest and healthcare work. In addition, the book also expects to serve as a consulting reference for those borderline/frontier aspects or topics that are not so close to the daily clinical practice yet need to be reassessed or updated in a given moment.

From time to time, we need to "pause" in order to assess where we are, and where we want to go, to reach the best clinical approach as researchers, academics, and healthcare providers. The authors of the different chapters have performed a great effort in order to provide a critical analysis of the state-of-the-art knowledge, without omitting doubts or controversies. The last years have been a time of progress in diagnosis, treatments, and integration of renovated ideas, which have not been exempt from controversy. This book includes the best evidence possible related to different hot topics in older women's health. Many chapters also put into perspective clinical recommendations, always based on recent meta-analyses.

The editor wants to thank the authors for their dedication and efforts in writing on schedule. I would also like to thank Springer Nature for their excellent and rapid editorial assistance. The editor and the authors look forward to an international readership taking advantage of this book to update their knowledge and improve their clinical practice.

Zaragoza, Spain Faustino R. Pérez-López

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Nicolás Mendoza Ladrón de Guevara
and Miguel Angel Motos Guirao

1.1 Fertility and Aging

1.1.1 Age as a Social Factor of Infertility

If we analyze the demographic progression that took place in Europe in the last century, we observe a clear secular trend toward a decrease in the birth rate and an increase in maternal age. As an explanation of this, it seems that a purely cultural reason stands out: the postponement in the desire for genesis, which, in many cases, occurs for a variety of employment, social, and economic reasons. On the other hand, advances in assisted reproduction allow pregnancy at any age, and we face new ethical and health challenges regarding the question of what is the limit for a woman to become pregnant. It is shown that age decreases fertility due to factors such as [1, 2]:

- A decrease in the number of oocytes
- A decrease in the frequency of intercourse
- A decrease in oocyte quality
- A decreases in sperm quality

1.1.2 Problems in Fertility and Pregnancy Derived from Age

Fertility declines with the passage of time, particularly after 35 years. A decline is seen in both the number and quality of the reserve of ovules, which increases the difficulty for pregnancy and the risk of spontaneous abortions (more than 50%) and of fetuses with chromosomal abnormalities (e.g., Down's syndrome) [3].

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As age itself is the factor that most influences the rate of spontaneous pregnancy and the outcomes of fertility treatments, in people over 35 years of age, it is not recommended to wait a year to see a specialist; instead it is advisable to take matters into their hands after 6 months of trying to conceive. In people aged over 40 years, it is recommended to seek help immediately [4].

The application of assisted reproductive techniques (ARTs) is very common in this age group, with a strong tendency to resort to egg donation. This also prevents the increased risk of fetuses with chromosomal abnormalities (the age of the oocyte is that of the donor), but not that of other pregnancy complications such as gestational diabetes, hypertension, intrauterine growth restriction, placental pathology, and prematurity, which continue to depend on the mother's age. Multiple pregnancies are also more frequent, because of the greater number of embryos transferred. As a consequence, the numbers of operative or instrumental deliveries and perinatal and maternal morbidity/mortality are all increased during perimenopause [5].

1.1.3 Up to What Age Is Pregnancy Allowed with Fertility Treatments?

Progress in reproductive medicine and in obstetrics itself has raised another important debate regarding age: what is the age limit to conceive or to apply an ART? Certain healthy habits and the feeling of staying young and being prepared for all eventualities have triggered the demand for fertility treatments for women over 40. Oocyte donation makes this a possibility even for those who have crossed the border into menopause. Since uterine age does not correspond to ovarian age, the maternity departments are now full of "older" women, an example of how advances in medicine appear to have developed ahead of the necessary and slow process of legislation and ethics. An older woman, even being postmenopausal, may not feel too old to have a child and may offer the infant a better education now that she no longer has the financial or emotional needs of younger women [6].

However, one of the immediate consequences of an increase in pregnancies in older women is the greater demand for medical and psychological assistance, since there are fewer requests for prenatal diagnostic methods, practices to reduce stress, and voluntary interruptions of pregnancy, along with an increase in perinatal and maternal morbidity and mortality, not to mention the concern for raising grandchildren instead of children.

There is an open debate on whether or not a child's upbringing is optimal at these ages. In particular, some people are shocked to see older women breastfeeding their babies in the nonscientific press, while others warn of the high risk of leaving them as orphans at a young age. In the future vision of our own wellbeing, there are even those who argue that it is preferable to have children—regardless of the age at which they are conceived—to increase the birth rate. In their arguments in favor it is pointed out that they will take care of our care when we are elderly. And even

when the argument seems to have tilted on the side of those who accept as logical, and even normal, a pregnancy over 40 years, common sense should still prevail when it comes to putting a cap on this demand. Although there is no clear limit, it seems to be ethical and medically advisable to place this limit before the age of 55, but it is more reasonable to place it at 50 years, given the high risk of cardiovascular morbidity from that age [7].

1.1.4 Social Controversies of Infertility Treatments

Of all the areas of medicine and all the attributes that have conditioned the evolution of our species, it is without doubt that sexuality and reproduction are those that are most loaded with social singularities. In addition, the rapid advance of reproductive technology has introduced significant changes in the conception of families that is sometimes difficult to assimilate within less advanced societies and those most impregnated with extreme conservatism. Some common practices in reproductive medicine have also generated controversies, such as the donation or freezing of gametes and embryos, embryonic reduction, or the costs of these treatments for the health system.

1.1.5 The Sociocultural Acceptance of the New Models of Families that Emerged with ARTs

From the first birth achieved with ART, what appears to have been most scandalous certain groups is the change in the classic conception of family, that is, two-parent, heterosexual, within a religious or civil commitment, and with the transmission of one's genes to the offspring.

We can see then how far the concept of family to which we have become accustomed has shifted in the new millennium. It is now seen as nothing more than cohabitation with single-parent families, those of homosexual couples with no legal ties or where genes other than those of legal parents are transmitted. In this regard, in countries where surrogacy is allowed, it can be possible for a baby to theoretically have five parents: the donor of the ovule, the sperm donor, the woman who has gestated the child in surrogacy, and the legal parents who have requested the treatment. Improvements in laboratory techniques for the cryopreservation of gametes or embryos have even made it possible for one parent to be deceased. There is no doubt that popular fantasies have been triggered and that continued discussion of these issues will cause perplexity.

Now that ARTs are common throughout the world, the medical, legal, moral, and ethical debates unleashed since their inception have been globalized. Some countries, like Spain, have regulated these by taking into account the clinical recommendations, but in other latitudes and within the groups of immigrants with whom we live, there are opinions of a religious nature that prevail in the deemed suitability and use of these methods [8].

1.2 Infertility Generalities

Infertility is a generic term that refers to the problems that reduce human fertility and that, in the strictest sense, is considered a disease. From an epidemiological perspective, infertility is considered a frequent phenomenon. It is estimated that (i) infertility affects some 70–80 million couples around the world, that 15% of those living in Western countries will consult for it, and (ii) that in these more advanced societies, there is a growing group of men and women who already have at least one child but wish to have another. There is a direct relationship between certain social and lifestyle factors and fertility and infertility: age; use of tobacco, alcohol, caffeine, marijuana, cocaine, and other drugs; use of anabolics; obesity; and psychological stress.

1.2.1 Diagnosis of Infertility

1.2.1.1 When to Diagnose Infertility?

In the absence of previous indications, couples who have been trying to become pregnant for more than 1 year should begin testing and therapeutic measures. An exam should be conducted when the woman is over 35 years old or if there is a history of menstrual rhythm disturbances or suspicion of uterine, tubal, or endometriosis pathology, as well as when the male has a history of cryptorchidism or other testicular pathology.

1.2.1.2 What Is the Basic Infertility Test?

This test consists of establishing a complete clinical history, a menstrual history, a general exam, preconceptional advice, and coital counseling. The exam must be given to both members of the couple. During the infertility test, cost-effective measures should be considered, being as minimally invasive as possible and conducted in accordance with the wishes of the two partners. The causes of infertility are varied and, in many cases, are multiple. This almost always involves both members of a couple. The tests included for infertility are gynecological exam and cytology, ultrasound of the uterus and ovaries, basic seminogram, tubal X-ray (hysterosalpingography), and hormone and ovarian reserve study. In cases where another alteration is suspected and other fertility treatments have failed, other tests may be performed, such as advanced hormonal study, cervical or vaginal cultures, hysteroscopy, advanced seminogram and sperm DNA fragmentation test, and study of coagulation disorders.

1.2.1.3 Monitored Anamnesis in Reproductive Medicine

For female patients, evaluation of anamnesis in reproductive medicine considers parity, obstetrical outcomes, age at first menstruation, menstrual formula, dysmenorrhea, contraceptive methods used, number of sexual relationships, length of infertility and previous treatments, previous surgeries and illnesses, gynecological history, allergies to medication, lifestyle habits (such as use of tobacco, alcohol,

drugs, diet, and frequency of exercise), occupation (and any associated stress), and family history. For male patients, anamnesis includes information about children from a previous partner (having other children does not exclude the potential for infertility), length of infertility and results from previous studies and treatments, previous surgeries and illnesses, medication allergies, lifestyle habits (such as use of tobacco, alcohol, drugs), occupation (and any associated stress), and family history.

1.2.1.4 Diagnosis of Ovarian Function and the Hypothalamic-Gonadal Axis

Evaluate ovarian function, menstrual history, basal temperature, cervical mucus, serum progesterone, urinary luteinizing hormone (LH), follicular development, endometrial thickness and appearance, and analysis of androgens, thyroid hormones, prolactin, and gonadotropins. Conduct a transvaginal ultrasound.

1.2.1.5 Study of Ovarian Function

The evaluation of ovulatory function is an important part of the basic infertility test. However, we do not have any evidence that accurately assures us that ovulation has occurred except, obviously, pregnancy. This says a lot about the variability and false-positives of many of the tests that are routinely used in the clinic. A history of regular cycles corresponds to correct ovulation in 97% of cases.

1.2.1.6 The Test of the Ovarian Reserve

Although age is the main prognostic factor of female fertility, in recent decades, motherhood has been possible for older women, which has changed our usual practice in the fertility clinic such that the analysis of the ovarian reserve has become one of the basic pillars upon which an adequate diagnosis and reproductive prognosis can be reached. Parameters for evaluating the ovarian reserve include biochemical markers such as follicle-stimulating hormone (FSH), estradiol (E2), inhibins A and B, and, more recently, the anti-Müllerian hormone (AMH). Ultrasound markers include the ovarian volume, the number of antral follicles, and the flow of the uterine artery. In addition, some dynamic tests have been designed to improve the prognosis of those using drugs commonly used in ovarian stimulation (clomiphene, exogenous FSH, or gonadotropin-releasing hormone (GnRH) analogues). These tests measure the variation of endogenous FSH, estradiol, and inhibin. Although they have been able to improve the sensitivity of the test, the increase is not sufficient to justify the expense and exposure to the established drug. AMH derives its name from its capacity to cause the regression of the conduits of Müller during masculine differentiation. In women, the AMH has a great paracrine power. The function of AMH is to inhibit the growth of nondominant follicles, with its local concentration increasing until reaching maximum levels in the antral follicles. Consequently, the measurement of AMH is a reflection of follicular activity, and as its peripheral blood values do not fluctuate as much as other hormones, it is used as an excellent ovarian reserve marker.

1.2.1.7 Indicators of Ovarian Reserve

Biochemical indicators of ovarian reserve include FSH, estradiol, inhibins A and B, testosterone, and AMH. Indicators observable by ultrasound include the number of antral follicles and the volume of the ovary. Dynamic tests may include clomiphene testing, exogenous FSH ovarian reserve testing, response of inhibin and E2 to exogen FSH, and testing the response of inhibin and E2 GnRH analogues. These various tests comprise the different ovarian reserve indicators. In summary, the most accurate are the ultrasound counts of antral follicles and the measurement of AMH; the least expensive are the ultrasound counts of antral follicles and the basal value of FSH and E2 (between the first and third day of the cycle); dynamic tests do not provide benefits compared with biochemical indicators or ultrasound tests and are expensive while remaining unable to predict the age of menopause presentation. Dynamic tests are only useful for offering a reproductive prognosis in women who plan to undergo fertility treatment.

1.2.2 Causes of Infertility

1.2.2.1 Ovarian Factors

The evaluation of ovulatory function is important as a first measure in basic infertility testing because it corresponds to 15–25% of the causes of infertility. A history of regular cycles corresponds to ovulation in 97% of the cases. A confirmed pregnancy is the only way to establish that ovulation actually occurred due to the great variability and false-positives involved with other tests. When an ovulatory dysfunction is diagnosed and a pharmacological treatment is indicated after 3–6 months without getting pregnant, another possible cause of infertility must be investigated. As a general rule, when the woman has regular cycles, ovulation is likely to be correct. When irregular cycles are presented, we can measure progesterone in the second phase or request a graph of basal temperature.

A prolactin measurement routine is not necessary unless there are menstrual abnormalities, galactorrhea, or suspected pituitary tumor. Similarly, patients with anovulation have a higher proportion of presenting with thyroid disease, but thyroid-stimulating hormone will only be measured when this disease is suspected. The assessment of the ovarian reserve is made in certain cases of patients over 35 years of age or with the intention of providing them with a prognosis or additional information to decide on possible treatments. An FSH lower than 10 mIU/mL with E2 less than 30 pg/mL reflects a normal follicular reserve status.

1.2.2.2 Uterine Factors

The cervical factor is a rare cause of infertility. The postcoital test is the classic test that determines it, but there is great interobserver variability, and it is not necessary to routinely carry this out because it has no prognostic value and is not indicative of any type of therapy. Although uterine malformations are not usually a cause of infertility, examining the uterine cavity should be part of a basic infertility test. This

should be done in an individualized manner, according to other previous findings, and should be based on a transvaginal ultrasound. In case of suspicion of organic pathology (polyps, submucosal fibroids, hyperplasia), a hysterosonography or a hysteroscopy will be requested.

1.2.2.3 Tubal and Peritoneal Factor

Tubal obstruction is responsible for infertility, either as a single cause or accompanied by other causes in 30% of cases. The tubal factor should be investigated when other infertility factors have been ruled out because the test that determines it, called the hysterosalpingography (HSG), is an invasive and often painful technique. Of course, if in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) is planned, HSG is not needed. For the study of tubal factor, the HSG is the least invasive and most cost-effective form, allowing diagnosis of tubal obstructions (proximal or distal) and evaluation of the uterine cavity. It is done in the first phase of the cycle before ovulation. If screening for chlamydial infection has not been done, antibiotic prophylaxis must be carried out. However, it is not precise in detecting peritubal adhesions and for diagnosing a peritoneal endometriosis, in which case it is indicated to perform a laparoscopy if there are strong suspicions of endometriosis, tuboperitoneal adhesions, or important tubal pathology.

1.2.2.4 Male Factor

The minimum evaluation of the male should include a complete medical history, a physical exam, and at least two seminograms separated 3 months from each other that should be initiated before subjecting the woman to any type of invasive exam, such as HSG. The seminogram is the main test in the study of the male factor, and abstinence is recommended for 2–3 days. The seminogram offers basic information on seminal volume, concentration, mobility, and sperm morphology. Unless the laboratory has its own criteria, it is recommended to follow the 2010 WHO guidelines.

1.2.3 Techniques for Assisting Reproduction

1.2.3.1 What Is Artificial Insemination (AI)?

Broadly speaking, AI involves the introduction of semen into the uterus, which is why it is also called intrauterine insemination. We distinguish the conjugal AI (CAI), meaning it is from the male partner, from donor AI (DAI). We have used the word “capacitated,” which is an important part of these ART. Indeed, for a sperm to acquire the ability to cross the membrane that surrounds the ovum and fertilize it, it must first undergo biochemical modifications in the most distal part of its head in a region called the acrosome. This phenomenon occurs naturally when the acrosome passes through the cervix and is imitated in the laboratory before being deposited inside the uterine cavity. Sometimes we use it as a diagnostic method known as a training test, and it helps us assess whether a patient’s semen is valid for proposing a conjugal AI.

1.2.3.2 What Are the Indications of AI?

It can be supposed that all semen qualifies for CAI. In each clinic or unit of human reproduction, there are criteria to decide if the seminogram, as the analysis is called, is normal or has some alteration and also if it is valid or not for a CAI or even IVF or ICSI. Some centers have their own criteria for defining seminograms, and although few do, they must be centers where there is a researcher who has previously published such criteria in specialized journals. For this reason, the majority of reproduction laboratories use the WHO's criteria, which are periodically renewed. The latest revision is available online.

1.2.3.3 What Is IVF and ICSI?

When IVF or an ICSI is proposed, the two gametes (oocytes and sperm) are needed in the reproduction laboratory to perform the fertilization, which is why it is called in vitro. According to the latest data collected by the Spanish Society of Fertility, the pregnancy rate per transfer is close to 40%. These techniques require the training and accreditation of the personnel in charge (gynecologists and embryologists) and are planned in a series of steps:

1. Follicular development: recruitment (rescue) and growth of one or more follicles, the structures of the ovary where the oocytes mature. Development is usually stimulated by a medication that contains gonadotropins, the natural female hormones responsible for follicular development. The process may be controlled with ultrasound and hormonal analysis.
2. Obtaining the oocytes. The vagina is punctured, and the process of obtaining the oocytes is guided by ultrasound. The follicles are punctured, and their liquid content (follicular fluid) is suctioned where the oocytes supernate. Although it can be performed under local anesthesia, sedation of the patient is preferred in many centers so that the patient does not suffer pain from the puncture.
3. In vitro fertilization (IVF). Fertilization itself occurs when the microinjection (ICSI) or its modern variant is performed with the extension of the microscopic vision and the selection of the sperm with better morphology (intracytoplasmic morphologically selected sperm injection).
4. Embryo transfer. Once the oocytes are fertilized, the resulting embryo or embryos are transferred into the uterus in a maneuver similar to that of AI. They are usually scheduled 2–6 days after the follicular puncture, and those that are not chosen for the transfer are cryopreserved for another attempt. The criteria to decide which are transferred and which are frozen are morphological, and each reproduction center usually has its own scale to catalog its quality. The number of embryos to be transferred is controversial and generates uncertainty in patients. The transfer of more than three embryos is not allowed and for ethical reasons it is often recommended to limit this to only one, although this restricts the percentage of pregnancies.

1.2.3.4 What Is Preimplantation Genetic Diagnosis?

Preimplantation genetic diagnosis (PGD) was developed as a technique to find out the sex of embryos with a test that detects the Y chromosome in the selected embryonic cells. Evidently, the determination of sex is not the purpose of this technique, but rather its purpose is the location of genetic defects transmitted by the X chromosome. Since the 1990s then, its use has expanded to other genetic diseases. Undoubtedly, the PGD has proved to be an extraordinary step, both for the knowledge of embryonic development and for the infertility and infertility clinic.

1.3 Genetics in Assisted Reproduction

1.3.1 Genetic Counseling and Consultation of Clinical Genetics

Genetic counseling "is a communication process that deals with the human problems associated with the occurrence, or the risk of occurrence, of a genetic disorder in a family" [9]. It is based on medical, reproductive, and family history and must always be carried out. In assisted reproduction, risk assessment includes not only the embryo and the fetus but also the parent itself. In this way, it is necessary to assess the possibilities of giving birth to a child with congenital malformations or genetic diseases and even their long-term appearance (e.g., genomic imprinting diseases), but for this it is necessary to study thoroughly the causes of infertility of the couple and their genetic, personal, and family clinical history. The information must be obtained in a systematic way, and, although the autonomy of the couple prevails, in cases of doubt, the interests of the future children must be put before them. Genetic counseling is always nondirective and is an essentially medical act, although other health professionals may be involved. Today it is not possible to carry out any genetic study detached from genetic counseling, and, in turn, genetic counseling should not be carried out outside the context of medical consultation. This consultation must be conducted by a clinical geneticist and has a multiple purpose—diagnostic, prognostic, preventive, and therapeutic—since it helps to choose the ideal reproduction technique in each case. The consultation also serves the purpose of performing comprehensive genetic counseling and obtaining informed consent for any genetic measure that is to be adopted. In a structured way, the pretest objectives are as follows:

- Obtaining the genetic medical history
- Report and evaluation of the genetic-reproductive risks of the couple
- Forecast report of future genetic tests
- Evaluation of the results of genetic and complementary tests
- Report of the reproductive genetic counsel
- Genetic eligibility report
- Obtaining the informed consent of genetic tests

Similarly, the posttest objectives are:

- Interpret the results obtained with the genetic analysis carried out pre- and postimplantation (prenatal)
- Establish embryo-fetal viability and the absence of genetic disease in the newborn
- Validate the genetic diagnostic strategy used
- Establish genetic counseling for future pregnancies

In assisted reproduction, pretest genetic counseling falls primarily on the couple and consists of studying the possible genetic etiology of the causes of infertility that have led to it, along with the genetic makeup of the parents. Posttest genetic counseling, in contrast, focuses on the embryo (preimplantation study techniques), fetus (prenatal study techniques), and newborn (postnatal study techniques).

As observed, the work that is carried out in the clinical genetic consultation is extensive and very specialized and is currently considered essential. The various types of genetic reports each fulfill a different but complementary function: genetic risk assessment report, pretest genetic counseling report, posttest genetic counseling report, genetic-reproductive counseling report, estimation report of future genetic tests, and suitability genetic report (in the case in which the carrying out of a preimplantation genetic study is recommended). We must not lose sight of the fact that all these reports are made at the preconception stage. If these genetic reports are not taken into account, this will lead to a situation of poor counseling of couples, a higher failure rate of reproductive techniques, an increase in the number of abortions, and possible clinical and legal repercussions due to the transmission of hereditary diseases, along with an increase in economic spending. It should also be noted that assisted reproduction units are, on many occasions, the first point of contact for a couple with an infertility consultation so, as a first step, the possible genetic etiology of infertility should be studied.

1.3.2 Genetic Diagnosis vs. Preimplantation Genetic Screening

Among the most genuinely "reproductive" genetic diagnostic techniques, there are two available procedures; these are very similar to each other but have very different indications.

The so-called preimplantation genetic test (*PGT*) is a procedure that consists of obtaining one or two blastomeres from an embryo in the stage of 6–8 cells (usually on the 3rd day postfertilization). The cells obtained can be studied genetically by means of different types of tests, and, depending on the outcome of the study, the decision can me made regarding whether or not to transfer the embryo of origin to the patient. The objective of the study is, of course, to avoid the transmission of a genetic disease to offspring and can be carried out from two different and complementary perspectives. If the aim is to avoid transmitting a known genetic disease, we would speak of a clearly diagnostic procedure (*PGD*). In contrast, the preimplantation genetic screening procedure (*PGS*) is a technique similar to the

previous one, whereby the embryo is selected in certain population groups initially "not affected" by a known genetic disease, but with a high risk of having offspring with some type of inherited disease, usually chromosomal abnormalities. The exposed groups are usually women of advanced age, males with different degrees of oligospermia, couples with repeated failures using reproductive techniques, and couples with recurrent miscarriages and normal karyotypes.

This distinction between *PGD* and *PGS* has been losing relevance with changes in molecular diagnostic methods. In a recent review, Harper et al. (2018) have shown that the increasingly frequent use of next-generation sequencing (*NGS*) technology makes it unnecessary to propose a differentiated study between the various chromosomes among themselves or between the different indications of study. Using current terminology we would replace the use of the term *PGT-A* techniques (preimplantation genetic test of aneuploidies) with *PGS*, and *PGT-M* techniques would be replaced with *the PGD* (preimplantation genetic test on Mendelian diseases). The *PGT-M* techniques are no longer reduced to the analysis of a single locus, one or two genes, or a genomic region, but with the use of NGS techniques, it is possible to implement the study of an increasing genomic variability. Even haplotyping techniques, through analysis of *CNVs* (*copy number variations*) and *SNVs* (*single-nucleotide variants*), can be applied to almost any genetic disease [10].

The changes in the embryonic material used for the analysis favor the evolution of the preimplantation diagnosis, since frozen embryos are frequently used with various vitrification techniques, which make more time available for the study. The blastocoel fluid that can genetically represent the internal cell mass is also under investigation, while the study of the trophectoderm cells only represents the extraembryonic tissue. The possibility of studying the DNA present in the embryonic culture media (as a noninvasive source) has even been pointed out, but doubts persist as to whether these culture media are really free of any trace of human DNA or if the presence of cells of the maternal oophore cluster persists in them [11].

One question that has not yet been clarified is whether these embryo selection techniques based on chromosomal screening *(PGT-A*) are really useful, that is, if they have clinical utility. In this context this is measured by their ability to improve clinical outcomes in terms of embryo survival and the birth of children without chromosomal abnormalities in different types of populations (advanced maternal age, infertile, with severe male factors) and with different stages of development (cleavage, blastocyst). This will not be known until enough controlled and randomized clinical trials are published. Therefore, it is preferable to consider these *PGT-A* techniques as a quantitative selection (*ranking tool*) rather than a qualitative selection (*screening tool*) [12].

We have previously warned that no genetic test can be considered outside the context of genetic counseling, particularly these complex preimplantation techniques that require a thorough knowledge of the materials studied, the times in which they are made, the possible techniques to be applied, and the possible results to be obtained, along with the need to explain all of this to the couple in the form of pretest and posttest genetic counseling.

1.3.3 Epigenetic Effects of Assisted Reproduction Techniques

A question of great interest is how can assisted reproduction techniques affect in vitro the epigenome of the developing embryo. The epigenome is the set of chemical processes that affect the genetic material of a cell or organism without altering its sequence, but modifying its expression. The reprogramming moments of the epigenome represent stages that are potentially sensitive to certain effects from outside the embryo. Two stages of reprogramming are clearly distinguished: the period of formation of the reproductive cells (gametogenesis) and postfertilization embryonic development (preimplantation) [13].

Regarding gametogenesis, the mechanisms of epigenetic regulation such as methylation—which can help to stabilize the germline DNA or to silence certain genes—are poorly understood. The degree of methylation in oocytes appears to be half that observed in sperm. Another element of regulation at this stage is the control of the expression of transposons (short and mobile sequences of DNA), which could be involved in the development of some genetic diseases. During initial embryonic development, there are many changes produced by DNA methylation in the form of silencing (or not) of certain genes involved in it. The environmental agents suspected to interfere with this reprogramming are, among others, multiple ovulation [14], the composition of the culture media [15], the vibration to which the embryonic cultures are subjected, light, temperature, and the same genetic manipulation [16]. One of the possible consequences under study is the appearance of genetic diseases in relation to genomic imprinting phenomena, such as the Beckwith-Wiedemann, Prader-Willi, Angelman, and Silver-Russell syndromes. In a recent study on the REMERA (Registre des Malformations en Rhône-Alpes) registry, Uk et al. found up to three times more risk of these diseases among children born by assisted reproduction techniques than those born of natural gestations [17]. Currently, it is too early to establish an unequivocal relationship with these diseases, and the studies carried out are insufficient. The disturbing transgenerational effects that may exist cannot yet be determined until a good number of generations have elapsed. Thus, although in general it could be estimated that the risk is low, no firm conclusions can be drawn until the outcomes of future research are known [18].

1.3.4 Congenital Defects, Population Genetics, and Assisted Reproduction

Currently, it has been accepted that the use of assisted reproduction techniques involves a slight increase in the risk of developing congenital defects, as well as an increase in the genetic causes of infertility in future pregnancies. Although there is evidence for these suggestions, studies that include larger populations and specific designs are necessary to further validate them.

With regard to congenital defects, Chen et al. [19] in a recent review and meta-analysis concluded that there is a significant association between a high prevalence

of congenital defects and single pregnancies achieved after the use of assisted reproduction techniques such as IVF/ICSI (both considered in absolute numbers, as for all categories of congenital defects including musculoskeletal, urogenital, circulatory, digestive anomalies, chromosomal defects, face, neck, eyes, auricular pavilions, cleft lip, cleft palate, respiratory system) except for malformations of the nervous system. These authors concluded that the risk of congenital defects is greater after the ICSI technique than after IVF. With regard to the specific case of cardiac defects, Giorgione et al. [20] also concluded after an extensive review and meta-analysis that cardiac defects are more prevalent (up to 50% more) after obtaining pregnancies with ART techniques. This leads to the recommendation of a systematic echocardiographic study of all pregnancies obtained after the use of these techniques. These results, although very indicative of the high risk of congenital defects following assisted reproduction techniques, should be considered with caution [20]. Further cohort studies and a more uniform methodology are needed in order to confirm this correlation.

Finally, the use of assisted reproduction techniques allows couples with abnormal karyotypes, mutations for cystic fibrosis, and microdeletions of the Y chromosome to achieve pregnancy and potentially transmit these genetic defects to their offspring, which represents an increased risk for the fertility of future generations. Harper et al. [10] ask "Is this a true risk?" Will it matter if, simultaneously, it improves our ability to treat infertility? Again we have to conclude that there is not yet a sufficient time perspective to evaluate these possible transgenerational modifications, but we must be vigilant to assess their possible consequences [10].

1.3.5 Regenerative Medicine

Among the potential genetic uses of assisted reproduction techniques there is regenerative medicine, which consists of curing damaged organs by introducing healthy cells. Current techniques allow human embryonic stem cells to be obtained at the blastocyst stage (5–6 days) or even earlier (3rd day). Surprisingly, we now know that completely differentiated somatic cells (such as fibroblasts) can be reprogrammed into pluripotent cells by means of the induced expression of only four key genes [21], *OCT4*, *KLF4*, *SOX2*, and *C-MYC*, which opens the door to its use as an alternative to embryonic cells, as it is devoid of other ethical and legal considerations. The utility of these non-embryonic cells is confirmed as a possible source of highly differentiated tissues or for research, generating disease models from people affected by unique mutations.

Finally, it should be noted that cultures of pluripotent cells have shown to be at risk of generating genomic instability [22] by developing alterations (trisomies of chromosomes 12 and 17 and small recurrent amplifications of chromosome 20 [23], mitochondrial mutations [24], and epigenomic changes [25]) that could be considered precursors of certain types of cancer, particularly those of germ cells, which requires a thorough study to improve the conditions of the crops.

1.3.6 Genetic Therapy and Assisted Reproduction

We will cite two examples of the possible therapeutic uses of the genetic techniques of assisted reproduction: the prevention of the transmission of mitochondrial diseases and the genomic edition.

It is well known that the mitochondria that accompany the pronuclei are exclusively maternal, which gives rise to a type of inheritance with very specific characteristics, the so-called mitochondrial inheritance. Given that this type of disease is currently incurable, solutions are sought through assisted reproduction. To avoid the transmission of known mitochondrial mutations, three types of techniques have been developed, known as mitochondrial replacement techniques (*TRM*): transmission of the achromatic spindle, transmission of the pronuclei, and transmission of the polar corpuscles. All of these techniques are designed to transmit the genome of an egg/zygote containing the abnormal mitochondria to an egg/zygote with normal (donated) mitochondria. An interesting review of this topic has recently been published [26].

Genomic editing is a procedure that involves the use of molecular scissors, capable of identifying a specific sequence of the genome, cutting it and inserting another DNA sequence into it to repair a damaged DNA or modify its expression. These scissors or tools are diverse, the most outstanding of which include zinc finger nucleases (*ZFN*), transcription activating nucleases (*TALEN*), and the revolutionary nucleases of reverse repeated palindromic sequences (*CRISPR-Cas*) [27]. There are still no safe routes of clinical application of this technique directly on the embryo [28], but nevertheless its application to germ cells—both spermatogonia and mature oocytes—is being investigated. However, the actual indications for its possible application are currently limited. Scientific societies such as the ASHG, the ESHG, and the ESHRE[2] are making recommendations on this matter [29].

1.3.7 Ethical and Legal Issues

There are many ethical issues that arise when we address the genetic aspects within the field of assisted reproduction, and in this chapter, we do not intend to analyze them exhaustively although it seems convenient, at least, to list them to have a perspective of the problems that arise and the need to generate adequate responses to them. We are going to stay with genetic issues without entering into other specific ethical debates (even though these are equally necessary) linked to the use of reproductive techniques.

One of the aspects most questioned from the genetic point of view is the preimplantation diagnosis: Who can access it? There is no closed list of possible genetic conditions, although it is considered reasonable that they are diseases that significantly reduce quality of life. In Spain, the consideration of whether or not to study a disease depends on the respective Autonomic Commission of Assisted Reproduction, and each country deals with its own legislation. It is important to harmonize legislation within the European environment. A second question would

be whether these types of genetic studies should be carried out for predisposing mutations to the development of common long-term diseases, including the genetic predisposition to cancer. Regarding the predisposition to cancer, there are numerous records in many European countries, although the absoluteness of this indication decreases when we refer to other common diseases such as diabetes and hypertension. Digging deeper into this idea, we could arrive at the concept of the *designer baby*, in which we would have excluded all possible mutations (deleterious or predisposing) in order to seek the best possible development, hand in hand with the new massive sequencing technologies (*WES/WGS*). This also occurs with the most commonly accepted baby medication (savior sibling) and the corresponding *HLA* determinations. Derived from this general approach of preimplantation study, new doubts arise as to whether it is ethical to transfer an affected embryo (in the case of not having healthy embryos) in very specific cases or about the use of preimplantation genetic screening.

There is also debate about the necessary genetic studies in gamete donors and their implications, not only referring to the future embryos thus conceived but also to the individuals who donate them.

Genetic cascade studies—offered in a general way to certain families that transmit a genetic trait—may clash with the "right to not know" principle and create a new ethical conflict.

On the other hand, there are ethical questions concerning the possible prevention of mitochondrial diseases that, due to their specific type of transmission, represent an unknown on their expression—yes or no—in offspring and the degree of intensity of mitochondrial diseases.

All these and many others are issues of relevance to which we must respond in a consensual and unitary manner. We must ensure that there are no differences in attention and interpretation in reproductive genetic medicine while also preventing the promotion of inequality, or, where appropriate, the increasing disembarkation of private companies, with their offer of the direct tests offered to the consumer (TDC) and the end of anonymity for gamete donors [30] or the even more recent cases of cross-border reproductive care (transboundary reproductive care) [31].

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Turner Syndrome: Primary Amenorrhea from Adolescence to Aging

2

Camil Castelo-Branco and Iuliia Naumova

Turner syndrome is a chromosomal disease characterized either by the complete absence of one chromosome or by the presence of a defect in one of the X chromosomes, in at least one cell line. The karyotype of such women may be 45X0, mosaicism type 45X/46XX, 45X/46XY, or 45X/46Xq-, isochromosome or ring chromosome. Up to 98–99% of pregnancies with a fetal karyotype of 45X0 result in spontaneous abortions in the early stages. However, Turner syndrome occurs in 1 of 2000 live births; therefore, this rare entity is one of the most common chromosomal abnormalities among life women [1, 2].

2.1 Etiopathogenesis of Turner Syndrome

Half of patients with Turner syndrome show complete absence of one of the X chromosomes, and in these cases, in 70–80% of occasions, the X chromosome of the father is the absent. In the other half of the patients in which one X chromosome is normal, a mosaicism or other anomalies are identified, such as annular chromosomes (consisting of the remaining sections of the short and long chromosomal arm, rX) or isochromosomes (loss of short arm consisting only in the two long arms of the X chromosome (Xq-) [3].

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Depending on the karyotype, the external manifestations of the syndrome may vary from the presence of all typical marks of the clinical picture to the complete absence of those signs [1, 3]. Chromosomal imbalance, observed with Turner syndrome, leads to the appearance of various anomalies of somatic development. A wide spectrum of abnormalities is mainly due to haploinsufficiency of genes, which are usually expressed by both X chromosomes [4].

Key characteristics of TS are low growth, dysmorphic features, and gonadal failure with sterility and insufficient production of sex steroids. Most patients have a delay in puberty and primary amenorrhea, and, in more than a half of patients, it is possible to detect heart and vascular anomalies, which increase the risk of early mortality in a population of women with TS three times compared with the main female population [5, 6]. Congenital malformations of the kidney are nine times more common in subjects with TS [7].

In adult life, patients with Turner syndrome are affected by disorders such as osteoporosis, hypothyroidism, diabetes, dyslipidemia, and non-congenital heart or nephrourologic changes. The morbidity and mortality rates for this condition are higher than in the main population, and the life expectancy is reduced in more than 10 years mainly due to cardiovascular diseases [8–13].

Diagnosing TS is not always easy since only 10% of TS patients have been antenatally diagnosed, 16% in infancy, and 54% in childhood (1–12 years), and up to 20% have the diagnosis just at adolescence (12–18 years) [14]. Therefore, the main attention in providing medical care to such patients should be focused on early diagnosis, detection of prenatal markers of TS, timely administration of growth hormone (GH), adequate hormone replacement therapy, and treatment of associated diseases [7, 9]. Patients with TS from the stage of verification of diagnosis and throughout life should be observed by specialists of various profiles for monitoring and correcting endocrinological and sensorineural abnormalities, identifying coexisting malformations, reproductive counseling, and sexual health. Along with other specialists, the gynecologist has a core position in the management of such patients, maintaining and controlling hormone replacement and referring the patient to another specialist when necessary. A multidisciplinary approach and a well-developed management plan for patients with TS at all age stages are very important for height outcomes, bone health, and psychosocial support.

This chapter discusses possible clinical manifestations, the main aspects of managing patients with TS at different ages, modern approaches to diagnosing the syndrome and associated anomalies, and the specific features of hormone replacement therapy according to the latest guidelines.

2.2 Clinical Features

Most newborn girls with TS have only mild clinical manifestations, but a certain group of babies have lymphatic edema of the hands and feet, as well as skin folds on the posterior surface of the neck. One of the most common anomalies encountered in Turner disease is a short neck with a low level of hair growth and

pterygium neck folds, an enlarged rib cage, weakly developed genitals—small labia, clitoris, and uterus—and widely spaced nipples. Some patients have anomalies in the shape and position of the ears (lop-eared), which are combined in half the cases with deafness [7, 14]. Less common are signs such as multiple pigment nevi or vitiligo, anomalies of the metacarpal and metatarsal bones of the hands and feet, deformations of the elbow and shoulder joints, and hypoplastic narrow nails. The face can have features specific for the syndrome—the jawbones are reduced in size, the soft and hard palate is high, and the ovulation of the eyelids is also observed [2, 7, 14].

Regarding the assessment of the integrity of internal organs, nowadays it is possible to detect cardiovascular abnormalities such as coarctation of the aorta, aorta dissection, disruption of the integrity of the interventricular septum, and a twofold aortic valve. Congenital kidney malformations (horseshoe kidney, kidney agenesis, double pelvis and ureter) and blood vessel anomalies such hemangioma or telangiectasia are also antenatal detectable [14–16].

Short stature and gonadal dysgenesis are the most common clinical stigma in women with TS, which are detected in almost all patients and can be combined with other dysmorphic manifestations [11, 12]. A correlation between karyotype and phenotypic manifestations of TS usually exists, but it is not regular. Thus, external dysmorphology and nephrologic or cardiac malformations are common in the case of pure monosomy [8, 17], while almost 40% of patients with mosaic patterns have spontaneous menarche and less pronounced external manifestations of the syndrome. Subjects with isochromosome in karyotype have sensorineural and immunological disorders, but congenital malformations in such patients are usually not diagnosed.

2.2.1 Short Stature

Short tallness is due to haploinsufficiency of the homeobox containing the gene (SHOX) located in the distal part of the short arm of the X chromosome [18]. The height of adult patients with TS varies between 143 and 147 cm. Mutations in this gene could also explain some skeletal abnormalities in TS, such as Madelung deformity of the wrist, cubitus valgus, or short fourth metacarpal. Additionally, haploinsufficiency of SHOX expression could explain other features such as chronic otitis media, prominent ears, and problems of learning how to suck, blow, eat, or articulate [4, 19]. In patients with TS, partial growth hormone (GH) insensitivity is noted with the preserved secretion of growth hormone by adenohypophysis cells, which leads to a primary bone defect. According to clinical studies, there are positive results in the prescription of recombinant growth hormone therapy as an increase in adult height in patients by 5–8 cm [20–22]. However, the effectiveness of such therapy may vary and depends on a set of factors such as the stature of the patient's parents, the age at which the GH therapy began, the height of the patient at the time of initiation of therapy, and the duration and dose of the prescribed hormone therapy. [23].

Treatment of GH is recommended to start already at the age of 4–6 years; in case of lack of growth, therapy is prescribed earlier to provide adequate duration of therapy before puberty begins [15, 24]. Therefore, patients receiving treatment with GH for a mean of 5.7 years were on average 7.2 cm taller than the control group [25]. It is recommended to begin GH treatment 4 years before estrogen replacement [8].

According to the latest recommendations, the optimal initial dose of GH therapy is 45–50 μg/kg/day with a possible increase in dosage to 68 μg/kg/day in case of insufficient effect. The drug is administered subcutaneously seven times a week, preferably at nighttime [15].

During the treatment, it is recommended to monitor the patient's growth every 3–4 months in the first year of therapy and every 4–6 months thereafter. GH therapy may be discontinued after linear growth is complete (bone age of approximately 13.5 to 14 years; height velocity <2 cm/year).

Potential risks and benefits of GH therapy should be clarified to the family prior to initiation of therapy, and careful monitoring is also needed to identify possible adverse effects. GH therapy is usually well tolerated; however, slipped capital femoral epiphyses, scoliosis, pancreatitis, and a small risk of intracranial hypertension have been described in TS patients [26, 27]. Moreover, evidence exists suggesting that GH therapy may exacerbate the risk of glucose intolerance [28, 29]. According to the latest guidelines, patients with TS need an annual monitoring of hemoglobin A1c regardless of GH therapy and an annual measurement of insulin-like growth factor I (IGF-I) when the GH dose is increased [15].

In cases of insufficient growth in girls older than 10 with GH monotherapy, the addition of oxandrolone, an anabolic steroid, in a dose of 0.03–0.05 mg/kg/day is recommended [15, 30]. Oxandrolone in combination with GH therapy may improve the adult height by 2–5 cm [31]. Possible side effects of oxandrolone therapy include a slight virilizing effect (acne, hirsutism, clitoromegaly); however, when using the drug in a standard dosage, the risk of virilization is extremely low [30].

2.2.2 Ovarian Dysgenesis

Although the gonads in TS differentiate normally until the third month of pregnancy, an accelerated apoptosis of oocytes occurs after this period, with an increase in ovarian stromal fibrosis. Consequently, it's not uncommon that ovarian failure takes place within the first months or years of life.

Routine extraction of oocytes is not recommended for patients under 12 years of age, but young TS women with normal ovarian function should be informed of options for maintaining fertility [15].

Even though primary amenorrhea is usual in TS, the incidence of spontaneous puberty is not uncommon [11, 32]. Concentrations of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are high as early as 5 days of age in infants with TS; although these levels decline afterwards, FSH and LH levels remain higher than in girls with a normal karyotype [12, 33].

In up to 6% of TS patients, the karyotype includes the Y chromosome, which may lead to the development of gonadoblastoma, and malignant neoplasm

composed of stromal and germ cells. Hence, in these cases, early prophylactic excision of the gonads is recommended in TS women, considering that the risk increases with age (from 2% at age 10 to 27.5% at 30 years) [11].

Still, most patients with TS require induction of pubertal and hormone replacement therapy with estrogen-progestational medications for adequate development of the mammary glands and uterus and to get an acceptable peak of bone mass. In these cases for monitoring, it is recommended to check the level of gonadotropins (especially FSH) annually from the age of 11 years to identify hypergonadotropic hypogonadism and timely induction of puberty. It is also recommended in some cases to determine the level of anti-Mullerian hormone (AMH) or inhibin B. A low level of these hormones may indicate a decrease in the ovarian reserve [34, 35].

After induction of puberty, patients with TS require prolonged estrogen replacement therapy. The goal of this therapy is to prevent osteoporosis, reduce the risk of atherosclerosis, and improve cognitive functions [11, 16, 35].

The use of preparations containing natural estrogens per os or in parenteral forms is recommended. Currently, preference is given to the transdermal route in order to elude the first-pass effect in the liver, avoiding many adverse effects of hormone therapy. Transdermal 17β estradiol is recommended to be administered from the age of 11–12 years. The minimum dose of 17β estradiol by transdermal route is 14–25 μg, and the dose can be gradually increased up to adult dosage (50–100 μg/day) at 2–3 years of therapy [15].

Progestagen (oral micronized progesterone or synthetic progestin) must be prescribed in the case of withdrawal bleeding or 2 years after initiation of estrogen therapy to minimize the risk of endometrial cancer [7, 15]. The schedule of progestin administration may be sequential—a minimum of 10 days per month—with menstrual deprivation or as a continuous regimen that prevents menstrual bleeding.

Estrogen deficiency causes bone loss, endothelial dysfunction, decreased insulin production, abnormal lipid pattern, increased central adiposity, and early atherosclerosis. In estrogen-deficient females with TS, replacement therapy improves liver enzyme abnormalities and some cognitive deficits (reaction time, nonverbal processing speed, short-term memory) [36]. Therefore, the use of estrogen replacement up to physiological doses should be maintained until the expected age of menopause. Nonetheless, it is important to emphasize that neither the risk of breast cancer nor that of ovarian or endometrial cancer is higher in these patients than in the general population [12].

2.3 Fertility and Pregnancy

Regarding reproductive function, patients with TS are mostly infertile. In patients with 45X monosomy, spontaneous pregnancy is uncommon and occurs in less than 0.5% of cases. The risk of developing congenital anomalies and chromosomal pathologies in the newborns of such patients is extremely high. Among patients with 45X/47XXX mosaicism, the incidence of spontaneous pregnancies reaches up

to 14%, and the risk of congenital anomalies is less than 5% [37]. In most cases, patients with TS are referred to oocyte donation and in vitro fertilization. However, the risk of first trimester miscarriage is higher, probably due to uterine hypoplasia and some uterine ischemia during pregnancy [33, 38, 39]. Cesarean rates are higher due to cephalopelvic disproportion.

TS is associated with a variety of severe cardiovascular pathologies; therefore, taking a decision on future pregnancy and the use of assisted reproductive technologies and cardiac assessment, including echocardiography and strict blood pressure monitoring, is mandatory to these patients since the risk of death is extremely high. The pregnancy is categorically contraindicated in patients with aortic abnormalities.

Finally, prenatal diagnosis of TS allows the prediction of gonadal insufficiency in women demonstrating early evidence of ovarian function; hence, new techniques of ovarian tissue cryopreservation with the aim of replantation might be suitable for a few selected females with TS.

2.4 Osteoporosis

Patients with TS have low cortical mineral density, osteoporosis, and risk of fractures. These conditions are probably related to a primary defect in bone formation. Although the molecular defect remains to be identified, some genes located in X chromosome are associated with connective tissue changes [40]. In women with TS, the peak in bone mass is reduced by 25% compared to the general population of women. The incidence of fracture in girls and adult women with TS is threefold higher than in normal controls [41]. Girls with TS who have had spontaneous menarche have been found to achieve normal bone mass [42].

The prescription of GH therapy in combination with estrogen replacement therapy before the age of 12 significantly improves bone mineral density.

2.5 Cardiovascular Abnormalities

Cardiovascular abnormalities occur in 50% of patients with TS and are the leading cause of early mortality, which is registered three times more often than in the main female population [5–7, 43]. The life expectancy of such patients is reduced by 13 years [44].

Congenital heart defects, aortic root dilatation and aortic dissection, ischemic heart disease, and cerebrovascular disease contribute nearly 50% to the excess morbidity in TS [45]. Dilatation of the root of the aorta, hypertension, and bicuspid aortic valve have been reported as major cardiovascular concerns in TS [44, 46]. It should also be noted that mortality from ischemic heart disease in patients with TS is seven times higher than that among women in the control group [44].

Figure 2.1 shows the main cardiovascular anomalies associated with TS.

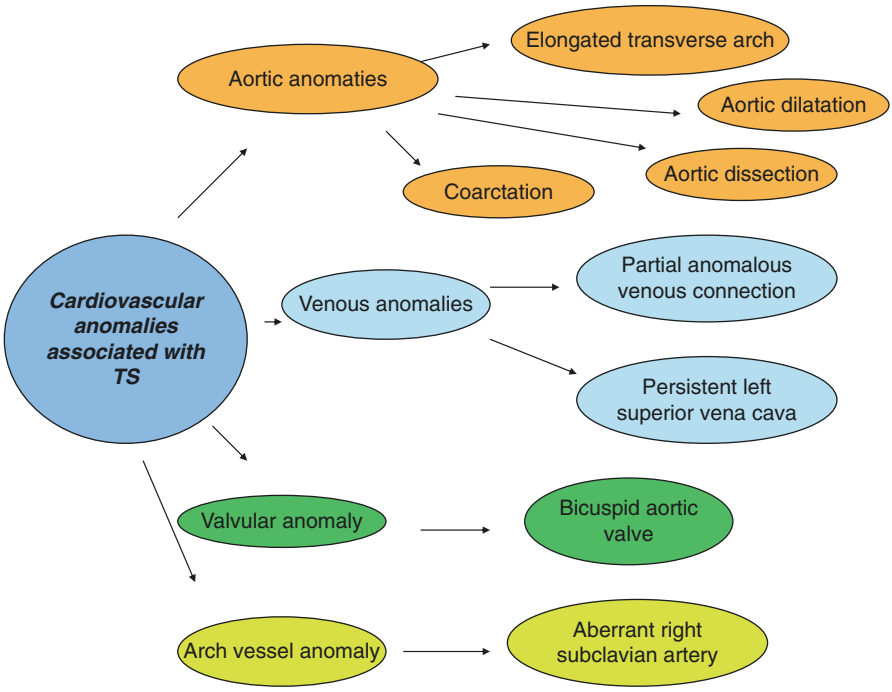

Fig. 2.1 Main cardiovascular complaints associated with Turner syndrome

Cardiovascular complications are related mainly to the hypoestrogenism, but it is believed that differences in X chromosome gene expression can also play a role [47]. Several genes localized in the X chromosome have been described as involved in the control of cardiovascular functions such as the angiotensin type 2 receptor and several kinases and transcription factors [48]. Moreover, the abnormal lipid profile with high level of total and LDL cholesterol in patients with TS is responsible for the high risk of atherosclerosis development and cardiovascular complications [49, 50].

Bicuspid aortic valve is the most common congenital malformation (25–39.2%) [46], and although it is usually an isolated abnormality, it may occur together with other anomalies such as aortic coarctation. This combination may result in progressive valve dysfunction due to calcification in the aortic valve and may cause aortic stenosis or regurgitation in adulthood. Coarctation of the aorta affects 10% of women with TS causing hypertension and seems to be more associated with severe lymphoedema, perhaps due to abnormal lymphatic flow by compression of the ascending aorta [4, 51].

Other abnormalities, such as partial anomalous venous drainage and mitral valve abnormalities are more common among TS women, and left-side cardiac anomalies are associated with endocarditis, with prophylactic antibiotics being essential before surgical procedures.

However, the most serious risk for females with TS is aortic dissection (risk of 36 per 100, 000/TS person year compared to 6 per 100, 000/year in general population), which may occur several decades earlier than in the general female population causing even sudden death [52].

Hypertension, a bicuspid aortic valve, and dilated aortic root (with an age-related increase of the root diameter greater than the normal population) are risk factors for dissection.

Surveillance for aortic root dilatation, treatment for hypertension, and prophylactic medical therapy with timely surgical consultation are essential to reduce the incidence of aortic dissection [18, 53].

Echocardiography should be included in the assessment of TS patients and should be indicated periodically. Electrocardiogram should be carried out along with the imaging studies because conduction or repolarization defects have been reported attributed to neuroautonomic dysfunction [4].

2.6 Neurocognitive, Sexual, and Behavioral Problems

Usually patients with TS have normal intelligence with good verbal skills, although some subjects may have problems in the neurocognitive and psychosocial spheres. The severity of cognitive impairment is supposed to be associated with a karyotype since these disorders are more pronounced in patients with 45X monosomy or rX than in mosaic patterns [10]. It's noteworthy that nearly 10% of girls with TS (especially those with an X-ring karyotype) may exhibit an intellectual impairment [54]. Difficulties can arise with nonverbal training, performance of numerical work, visual-spatial perception, motor coordination, and motor training. Patients with TS have reduced working memory and processing speed; therefore, autism spectrum disorders as well as attention deficit and hyperactivity may be noted [54–58].

Low self-esteem, depression, anxiety, and difficulties in sexual relations are also common among patients with TS [59]. However, most of the series and studies suggest that the high prevalence of depressive symptoms in TS' patients is mainly due to hypogonadism and subsequent hypoestrogenism and is not a direct effect of the absence of the X chromosome. The incidence of depression in patients with TS is comparable to that of women with premature ovarian failure with normal karyotype [60, 61].

Sexual function in women with TS is impaired compared with the general population [62]. In addition, only 50–55% of patients with TS recognize to be sexually active [63, 64], and among patients with regular relationships, a low level of sexual satisfaction is noted [63]. One of the factors that more strongly affect sexual activity is the height of women being sexually inactive patients of a shorter size than sexually active subjects [63].

Early detection of neurocognitive problems and the use of modern principles of rehabilitation help improve achievement and social well-being in children with TS [54, 65].

Therefore, it is recommended that children with TS be screened every year in order to identify behavioral problems and undergo an official neuropsychiatric

testing at the main transitional stages of the child's life [66]. However, as the neuropsychiatric and psychologic problems exist along all the life of these patients, women with TC should have warranted full access to clinical psychologists and psychiatrists for counseling related to anxiety and related conditions [4].

2.7 Sensorineural Disorders

Recurrent otitis media is a common complaint of TS women with a frequency ranging from 61 to 88% of patients upon the different series [67, 68]. Girls with 45X monosomy karyotype are more prone to middle ear problems than those with deletions or mosaicism probably related to altered cranial bone structure [67–69].

Adolescent and young-adult women with TS have a progressive hearing impairment, deteriorating rapidly in adult age. The hearing decline seems to consist of two patterns: a mid-frequency dip and a high-frequency loss resembling age-related hearing impairment [70].

Conductive hearing loss is found in 39–43% of girls under 16 [71, 72], and it persists beyond the age of 20 in around 20% of TS women [68]. This progressive hearing loss seems to be more common in those with a history of recurrent ear infections earlier in life.

The main cause for the infection is the deformity in the pinna, more pronounced in patients with a total deletion of the short arm of the X chromosome, as monosomy 45X0 or isochromosome [68]. Therefore, the conductive loss may have a congenital origin. However, the pathophysiology of sensorineural lesions is not yet fully understood. Some studies indicate that cochlear dysfunction is the cause of the sensorineural impairment and it is possibly influenced by estrogen deficiency [73, 74]. Therefore, regular audiometric checks should be performed referring patients to otorhinolaryngology departments.

2.8 Other Disorders

Congenital renal malformations are ninefold more common in women with TS than in the general population [10]. These abnormalities include horseshoe kidney, duplex systems, and rotated kidneys. Malformations are more common in 45X0 monosomy females, being related to neither hypertension nor other clinical symptoms. Nevertheless, renal ultrasound is recommended at diagnosis and should be repeated at the time of adult transfer.

The most common ocular findings linked to TS are strabismus, ptosis, and amblyopia. All patients should have eye assessment carried out during follow-up if required.

Multiple autoimmune diseases, such as chronic lymphocytic thyroiditis, celiac disease, and inflammatory bowel disease (especially Crohn's disease), are also commonly associated with TS, but the pathophysiologic mechanism of immune alteration remains unclear [75].

Autoimmune thyroid disease with outcome in clinical or subclinical hypothyroidism is detected in approximately 50% of patients. Therefore, regular monitorization of thyroid hormones and antithyroid antibodies is mandatory in women with TS and allows timely initiation of adequate substitution therapy [76].

2.9 Diagnosis

Diagnosis of Turner syndrome is not always simple. Unfortunately, often the syndrome is diagnosed late, and up to 38% of patients learn about their diagnosis in adulthood [77]. However, in some cases, a diagnosis is possible at the prenatal stage. When performing ultrasound, increased nuchal translucency, cystic hygroma, and left-sided obstructive cardiac anomalies (especially coarctation of the aorta) in a fetus can be TS markers [78]. The results of maternal serum screening may also be abnormal; however, prenatal confirmation of the diagnosis requires amniocentesis or chorionic villus analysis. Karyotype is recommended to be repeated in postnatal period [2, 15].

Nowadays, karyotyping is recommended if there is at least one of the following signs: fetal hydrops or cystic hygroma, unexplained short stature, delayed puberty, obstructive left-sided cardiac abnormality such as a bicuspid aortic valve, coarctation, aortic stenosis, hypoplastic left heart syndrome or mitral valve abnormalities, characteristic facial features (such as short broad neck with webbing, narrow palate, micrognathia, low set ears, and down-slanted palpebral fissures with epicanthal folds), or in a couple presenting with infertility. The combination of two or more cardiovascular and/or kidney abnormalities specific for TS, as well as Madelung deformity, dysplastic nails, multiple nevi, neuropsychological issues, and hearing loss associated with short stature, is a clear indication for carrying out karyotyping [15].

2.10 Conclusion

Turner syndrome is a chromosomal abnormality affecting all stages of a woman's life—from intrauterine development to the adult period. The complex of congenital anomalies associated with Turner syndrome is hypogonadism, hypoestrogenism, cardiovascular complications, renal pathology, neurosensory disorders, metabolic disorders, cognitive impairment, and difficulties in social adaptation requiring early diagnosis and timely treatment. The onset of GH therapy in childhood and the timely initiation of pubertal and estrogen replacement therapy in adolescence and adulthood allow patients with TS to have almost normal quality of life indicators and to be psychologically and socially well adapted in society. Subsequently, during adulthood endocrinological-gynecology units might diagnose conditions that may debut later in life, including endocrino-metabolic, immunological, and sensorineural disorders such as diabetes, hypothyroidism, coeliac disease, hearing loss, etc. and refer these patients to other consultants. Only the work of a multidisciplinary team of specialists, including pediatricians, endocrinologists, gynecologists, cardiologists, otolaryngologists, and psychologists, can optimize the management and treatment of such patients (Table 2.1).

Table 2.1 Regular checks in Turner syndrome patients

	Basal	Yearly	3–5 years of monitoring
Weight and stature	x	x	
Tanner	x		
Blood pressure	x	x	
Lab tests			
Hemogram, lipid profile	X	X	
Metabolism (liver enzymes, glucose intolerance)	X	X	
Thyroid assessment (TSH, T4)/thyroidal Ab	X/X	X/X[a]	X/X
FSH, LH	x		
Autoimmunity	X	X[a]	
Karyotype	x		
Echocardiogram, EKG	X	X[a]	X
Abdominal ultrasound	X	X[a]	X
Gynecological ultrasound	X	X	
Bone absorptiometry	X	X[a]	X
Audiometry	X	X[a]	X

[a]When indicated

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Premature Ovarian Insufficiency

3

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3.1 Definition

Premature ovarian insufficiency (POI)—first described in 1942 by Fuller Albright [1] is defined as the loss of ovarian function before the age of 40 years. It's a state of female hypogonadism associated with amenorrhoea, increased gonadotropin levels, and hypoestrogenism [1, 2]. The ESHRE guideline criteria recommend the following diagnosis criteria for POI: oligo-/amenorrhoea for at least 4 months and elevated follicle-stimulating hormone (FSH) level >25 IU/L on two occasion >4 weeks apart [3, 4].

3.2 Etiopathogenesis

Spontaneous causes of POI include genetic abnormalities, autoimmune disorders, infections, enzyme deficiency, metabolic diseases, or very often idiopathic causes [5, 6]. Induced or iatrogenic POI is often a result of oncological treatment: radiotherapy, chemotherapy, and surgery (bilateral ovariectomy) [5, 7, 8].

Approximately 10–12% of women with POI have chromosomal abnormalities. Among them 94% represent X chromosome abnormalities (X structural defects or X aneuploidy), and the rest 6% are autosomal gene defects. In women with POI and primary amenorrhoea, the incidence of karyotype abnormalities is higher (21%) than in women with secondary amenorrhoea (11%) [9, 10].

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Turner syndrome is characterized by 45,X0 karyotype and occurrence of dysgenetic gonads and has an incidence of 1 in 2500 females [11]. 80% patients with Turner syndrome lack paternal X chromosome; in the remaining cases, there is an incorrect chromosome X (isochromosome X), the failure of short arm of chromosome X, or damage to chromosomal segment 2.6 Mb Xp-Yp of pseudoautosomal region [12]. Having two chromosomes X is necessary for full development of the ovary and the correct course of folliculogenesis. In case of absence or abnormal chromosome X, the oocytes cannot properly undergo meiosis and degrade [13]. In some cases of Turner syndrome with mosaicism 45,X0/46,XX, we can observe menarche and the occurrence of menstruations for many years [11]. In a study by Gravholt, 12% of women with Turner syndrome (12 of 114 patients) had Y chromosome and elevated risk of developing gonadal neoplasia (10–30%) [14].

Trisomy X (karyotype 47,XXX), with the incidence of 1:800 born girls, is caused by nondisjunction of the X chromosome during maternal meiosis. It's also connected with POI and development of mental disorders, but the prevalence of POI in this group is unknown [15, 16].

One of the most common genetic contributors to POI is permutation of the fragile X mental retardation 1 (FMR1) gene, which is responsible for up to 13% of familial cases and 0.8–7.5% of sporadic cases of POI [17, 18]. FMR1 gene is located on chromosome X and normally contains 5–44 CGG repeats in a region within the 5′ untranslated region of the gen [19]. Expansion of the triplet to 55–199 repeats is considered a "permutation," and 200 or more repeats provide basis for the diagnosis of full mutation FMR1, which can result in mental retardation but primarily in men [19]. 20% of women who carry this permutation will develop POI, which is a much higher percentage than the 1% among women of the general population [20, 21].

3.2.1 Autosomal Gene Mutations

POI is a heterogeneous condition with no single underlying cause, but a number of autosomal genes were indicated as the cause of premature ovarian function depletion [22]. For some of these genes, the mutations are recognized, while the others are listed as candidate genes with the necessity for future investigation. The genes that could result in POI are genes involved in folliculogenesis (NRA51, NOBOX, FIGLA, and FOXL2), folliculogenesis growth factors (BMP15, GDF9, inhibin A), ovarian steroidogenesis (FSH, FSHR, LH, LHR), or genes identified in syndromes often associated with POI (BLM, WRN, RTS) [23–25].

Galactosemia is a rare autosomal disorder due to a defect in galactose 1-phosphate uridyltransferase (GALT) metabolism. Proper galactose metabolism is required for ovarian function, and without that its metabolites accumulate to toxic levels and accelerate follicular atresia or the glycosylation of gonadotropin subunits leading to biological inactivity [26].

Autoimmune diseases, such as Addison's disease, Hashimoto's thyroiditis, systemic lupus erythematosus, type 1 diabetes mellitus, Sjögren's syndrome, and rheumatoid arthritis, often occur with POI[27]. POI can be a part of the autoimmune polyglandular syndrome (APS) types 1 and 2. Type 1 is characterized by

hypoparathyroidism, adrenal insufficiency, chronic mucocutaneous candidiasis, and the prevalence of POI in 15% cases [28]. Type 2 is associated with adrenal insufficiency, autoimmune thyroid disease, type I diabetes mellitus, and POI with the frequency of 3.6–10% [29]. It has been suggested that autoimmunity explains up to 30% of POI cases [27] [30]. Although coexistence of autoimmune or immune-mediated disorders is frequent in POI, histological examinations on ovarian tissue have documented that signs of oophoritis can be detected only in those women with circulating adrenal or ovarian autoantibodies directed to steroidogenic enzymes (steroid cell autoantibodies (SCA)) [31]. The prevalence of SCA in POI patients is 4–5% [27].

POI is also associated with thyroid autoimmunity; the prevalence of POI among women with Hashimoto's thyroiditis is about 14–27% [31, 32].

Chemotherapy and radiotherapy for treatment of malignant disease are also frequent causes of premature ovarian insufficiency. The risk that oncological treatment will lead to POI increases with age after puberty, with high-dose chemotherapy regimens and with combined chemo- and radiation therapy [33]. Age, radiation field, and dosage of radiation are the most important factors affecting the risk of POI during radiotherapy [34]. Doses of 9 Grays or higher are of high risk of ovarian insufficiency [35]. Chemotherapy affects the structure and function of oocytes and granulosa cells and decreases the number of oocytes in a dose- and drug-dependent manner. The use of anthracycline and alkylating agents has been shown to be most gonadotoxic in childhood and in adulthood [36, 37]. Induced POI could be temporary, but the recovery of ovarian function decreases with patient age [38].

Pelvic surgery has a potential role in early menopause. Laparoscopic excision of bilateral endometriomas leads in 2,4% to premature ovarian insufficiency [39] and ovarian endometrioma surgery is associated with a decline in serum AMH and diminishing the ovarian reserve [40].

Several case reports have indicated the association between various infections, including mumps, HIV, herpes zoster, cytomegalovirus, tuberculosis, malaria, varicella and shigella, and POI [41]. Mumps oophoritis may cause POI, and the incidence of 3–7% has been reported among POI patients [42]. However none of the remaining infectious agents have been able to establish any cause and relationship between the infection and the diagnosis of POI [42].

Smoking has been shown to be associated with earlier menopause, and the suggested pathophysiology is that tobacco smoke contains polycyclic hydrocarbons which are toxic to germ cells [43, 44].

In a significant number of women with POI (up to 90% according the literature), the cause is unknown, and these women are described as having unexplained or idiopathic POI [42, 45].

3.3 Epidemiology

The prevalence of POI is about 1% [46, 47] and is variable depending on the age: 1% of women younger than 40 years, 0.1% under 30 years, and 0.01% under the age of 20 years [48]. There are also ethnic differences ranging from 1.4% in women of African-American and Hispanic descent to 1,0% in Caucasian, 0,5% in Chinese,

and 0,1% in Japanese women [47]. Among women with primary amenorrhoea, the frequency of POI is 10–28% and in those with secondary amenorrhoea 4–18% [49].

3.4 Clinical Features of Premature Ovarian Insufficiency Patients

In particular, women suffering from POI experience abnormalities in menstrual cycle. Secondary amenorrhea or prolonged oligomenorrhea and primary amenorrhea may be the first symptoms and are the most common complains. About 75% of patients suffering from POI may also manifest typical postmenopausal symptoms. Hot flushes and night sweats are most common and appear, respectively, in 59.2% and 41.5% of POI patients. Moreover patients suffer from vaginal dryness (23.8%), vaginal mucus atrophy or dyspareunia, as well as mood disturbances, such as depression, anxiety (20.3%), and low libido (14.8%) [50]. Iatrogenic POI and older age at diagnosis are associated with exacerbation of symptoms [51].

3.5 Diagnostic Evaluation of POI

The diagnosis of POI should be based on the presence of menstrual disturbances and biochemical parameters: 4-month period of oligo-/amenorrhoea and two measurement of elevated FSH >25 IU/L on two occasions >4 weeks [3, 4].

The second part of the diagnostic process is to establish a cause of POI. It is necessary to examine karyotype in every woman with POI, and in case of incidence of Y chromosome, gonadectomy should be advised [52, 53]. FMR1 premutation testing is indicated in all women with POI to determine the cause of hypergonadotropic hypogonadism and also because of the risk of developing POI or cases of mental retardation associated with fragile X syndrome in family members [52, 54]. Routine autosomal genetic testing in POI is not recommended, unless the typical phenotype characteristics of type 1 blepharophimosis, ptosis, and epicanthus inversus syndrome (BPES) (dysplasia of the eyelids) are present [55].

According to data from the literature, autoimmunity explains up to 30% of POI cases [27, 30]. The ESHRE Committee recommended screening for 21OH-Ab (or alternatively adrenocortical antibodies (ACA)) in women with POI and to refer the 21OH-Ab/ACA patients to endocrinologist for testing of adrenal function and to rule out Addison's disease [3, 4]. The screening for thyroid peroxidase autoantibodies (TPO-Ab) is also recommended in all women with POI, and in case of positive test, thyroid-stimulating hormone (TSH) should be marked every year to exclude hypo- and hyperthyroidism [3, 4]. There is no evidence to recommend routinely screening for diabetes or for infectious disease in women with POI [3, 4]. Although there is no causal relation between cigarette smoking and POI, women with POI should be advised to stop smoking.

3.6 Consequences of Premature Ovarian Insufficiency for Women's Health

3.6.1 Cardiovascular System

Cardiovascular disease (CVD) seems to be the main cause of death among women. Though there has been an overall decline in CVD mortality over the past 40 years, the mortality in younger women has plateaued since around the year 2000. The incidence of myocardial infarction (MI) in women, although lower than in men, increases dramatically following menopause. The role of menopause itself is not so clear [56].

CVD includes four major areas:

- Coronary heart disease (CHD) clinically manifested by myocardial infarction (MI), angina pectoris, heart failure (HF), and coronary death
- Cerebrovascular disease clinically manifested by stroke and transient ischemic attack
- Peripheral artery disease clinically manifested by intermittent claudication
- Aortic atherosclerosis and thoracic or abdominal aortic aneurysm

It has been postulated that women with POI may be at higher risk for CVD and death due to loss of ovarian function and subsequent deficiency of endogenous estrogens. They present several risk factors for the development of cardiovascular disease: endothelial dysfunction, autonomic dysfunction, abnormal lipid profile, insulin action disturbances, and metabolic syndrome.

Women in the premenopausal period with premature coronary artery disease have significantly lower plasma estradiol levels in comparison to healthy women. Estrogens have effects on ventricular myocyte contractile function and on intracellular Ca^{2+} kinetics in coronary endothelial cells, thus having antiarrhythmic effects in cardiac myocytes. There is also evidence that estrogens decrease insulin resistance and protect against lipid peroxidation. There may be different effects of HRT in younger women (with early menopause starting treatment within 3 years of their last menstrual period in life), compared to older women (with age at menopause higher than 50, starting treatment 10 years after their last menstrual period in life). The difference most probably results from the complexity of estrogen and progestogen receptor systems. A higher expression of the estrogen receptors and higher level of enzymes involved in estrogen metabolism have been found in the vascular smooth muscle cells seen in aortas of women suffered from mild atherosclerosis than in the cells seen in aortas of women with severe atherosclerosis. The abovementioned observations are consistent with experimental data from animal models showing that estrogen administration protects against atherosclerosis only if vessels are healthy without established atherosclerosis. In more advanced stages of atherosclerosis, oral estrogen administration can have negative effects on the cardiovascular system via its prothrombotic effects possibly contributing to plaque instability.

Despite lack of longitudinal outcome data, hormone replacement therapy (HRT) when used early is strongly recommended in women with the diagnosis of POI to control future risk of cardiovascular disease. HRT should be continued at least until the average age of natural menopause [57].

Women with the diagnosis of POI should be advised that HRT may have a role in primary prevention of diseases of the cardiovascular system [58].

Endothelial function, measured as the flow-mediated dilation of the brachial artery, has been demonstrated to be significantly reduced in women with POI. Likewise, the amount of circulating endothelial progenitor cells is decreased and correlated with reduced serum estradiol level [59].

Women with natural POI before the age of 40 years have earlier onset of coronary heart disease and increased CVD mortality [60]. There is an inverse relationship between age at natural menopause and cardiovascular mortality [61].The POI women present an increased carotid intima media thickness and left ventricular diastolic function [62].

Moreover, patients diagnosed with POI present abnormalities in lipid profile, but the results are conflicting regarding particular lipoproteins. Even though there are conflicting data regarding lipid profile and insulin resistance indices, the overall cardiovascular risk in POI women seems to be significantly increased, as the mortality. Especially the risk of mortality from ischemic heart disease is increased approximately 80% in the POI women group compared to women with menopause at 49–55 years [63].

The primary cardiovascular risk factors in women, along with the conditions considered CHD equivalents are: personal history of CHD or other atherosclerotic vascular disease (peripheral arterial, cerebrovascular, and aortic disease), age over 55, family history of premature CHD (first-degree male relative under age 50 or a female under age 60), hypertension, dyslipidemia—high low-density lipoprotein (LDL) and/or low high-density lipoprotein (HDL), diabetes mellitus, metabolic syndrome, chronic kidney disease (CKD), smoking, postmenopausal status, psychological stress (e.g., depression, posttraumatic stress disorder), inflammatory/rheumatic diseases, pregnancy-related complications (e.g., eclampsia, preeclampsia, gestational hypertension, gestational diabetes). All these risk factors and their assessment should be an important component of periodic health examinations [64, 65].

POI women should be advised of risk factors that they can modify through behavioral change (e.g., stopping smoking, taking regular weight-bearing exercise, and maintaining a healthy weight).

Cardiovascular risk should be assessed in women diagnosed with POI. At least blood pressure, weight, and smoking status should be monitored annually with other risk factors being assessed if indicated [66].

POI is an independent though modest risk factor of ischemic heart disease and overall CVD [67].

Women undergoing prophylactic bilateral oophorectomy before the age of 40 consistently showed an increased risk for cardiovascular disease and cerebral infarction [68–70].

Reduced life expectancy, due to cardiovascular disease, is observed among women with untreated POI [71].

Observational data suggest that early menopause may be associated with small increases in total mortality and mortality due to ischemic heart disease and also possibly ischemic stroke. However, at this time, evidence is insufficient to recommend hormone replacement therapy for the sole purpose of preventing cardiovascular disease or stroke [72].

It is said that for each year's delay in menopause, the cardiovascular mortality risk decreased by 2% [73].

3.6.2 Metabolic Health

Data concerning metabolic health among women with POI are conflicting. Women with POI present similar levels of glucose, insulin, HOMA-IR, low-density lipoprotein cholesterol (LDL-C), and triglyceride as the controls, but the incidence of metabolic syndrome is significantly increased [74]. In contrast, other authors detected increased serum glucose, insulin, and the homeostatic model assessment of insulin resistance (HOMA-IR) in POI women ($N = 43$) vs. controls ($N = 33$) [75].

3.6.3 Bone Metabolism

It is well established that prolonged estrogen deficiency exerts negative influence on bone mineral density (BMD) and is well-known risk factor of decrease in BMD. POI patients have on average 2–3% lower BMD at L1–L4 spine, femoral neck, and total hip than healthy age-matched controls [76, 77]. Despite the underlying pathomechanism of POI, either Turner syndrome, other gonadal dysgenesis, chemotherapy, or idiopathic POI, patients are particularly vulnerable to decreased BMD [4]. In the study conducted by Maclaran et al. [51], at the moment of diagnosis, over one third of patients had low BMD (29.7% osteopenia, 5% osteoporosis). Moreover it was noticed that women suffering from idiopathic POI had significantly lower BMD in comparison to iatrogenic POI (respectively, 1.108 g/cm^3 and 1.174 g/cm^3, $p = 0.0043$). In another study percentage of POI women with abnormal BMD reached even 67% [78]. Risk factors, which particularly contribute to the degree of BMD loss, are duration of estrogen deficiency, POI before the age of 20 years, long period before the beginning of the disease, and initiation of HRT, as well as low calcium intake, lack of physical exercise, and low vitamin D3 concentration (<32 ng/mL) [4, 77, 79].

3.6.4 Genitourinary Syndrome

Hypoestrogenism leads to diminished elastin, collagen, and hyaluronic acid content and loss of vascularity in the urogenital region, leading to thinning of vaginal

epithelium and impaired smooth muscle proliferation [80]. Symptoms of urogenital estrogen deficiency known as genitourinary syndrome (GS) include vaginal dryness, dyspareunia, vaginal itching and discharge, lesions, vaginal vault prolapse or vaginal stenosis, and shortening. Urological symptoms of GS are connected with stress urinary incontinence and recurrent urinary tract infections. The patients experience loss of libido and dyspareunia.

Information about genitourinary syndrome in patients with POI is scant. The incidence of genitourinary syndrome probably differs depending on the age of the diagnosis and etiology of the ovarian function depletion (from 10 to 42%) [81]. The West London POI database found lower incidence of vaginal dryness and loss of libido in women younger than 30 years than in the patients of age 30–35 years [81]. Moreover, women with POI as a consequence of malignant disease more frequently experienced vaginal dryness and loss of libido than patients with the cessation of ovarian function without malignant cause [81]. Sexual function of POI patients during estrogen therapy stays within the normal range; however the scores are lower than achieved by control women [82]. Interestingly worse sexual function seems to be more related to the psychological than to physiological aspects such as pain or lubrication [83]. No urodynamic changes before and after oral and vaginal estrogen therapy were found in a small group of patients with POI [84]. The authors concluded that estrogen deficiency alone in the absence of aging and other risk factors for stress incontinence is of minimal significance.

Standard and the most efficacious treatment of genitourinary syndrome is estrogen therapy. It restores vaginal epithelium and vasculature and lowers vaginal pH [85, 86]. Both systemic and vaginal estrogens are effective [87].

Non-hormonal treatment modalities, such as local treatment with lubricants and moisturizers, intravaginal laser therapy, oral selective estrogen receptor modulator – ospemifene, or pelvic floor physical therapy, have not been studied in patients with POI.

3.6.5 Fertility

Fertility in women is determined by numerous factors; however normal function of hypothalamic-pituitary-ovarian axis plays a key role. Dysfunction at each level of this axis can lead to the infertility. Normal ovarian function is of crucial significance for proper ovulation process. Premature ovarian insufficiency (POI) defined as the loss of ovarian function before age 40 has important influence on hypoestrogenism and infertility [88]. This condition is regarded as pathological state in contrast to the menopause which is physiological state. There are numerous factors related to etiopathogenesis of this disorder which were described at the beginning of this chapter [89]. Depending on the causes, ovaries of some POI patients may present activity, particularly at the early stage of this disorder. However chance for spontaneous conception is very limited and ranges from 4.0 to 8.0% [90]. Therefore women diagnosed with this disorder should be informed that there is a small chance of spontaneous pregnancy.

3.6.6 Central Nervous System

Cognitive functions of POI patients are particularly impaired in cases of genetic disorders associated with POI. Fragile X syndrome is an X-linked mutation of the *FMR1* gene leading to mental retardation, especially in males. Women with premutation of *FMR1* are at high risk of developing POI, but they do not suffer from mental retardation. Women with *FMR1* full mutation had a significantly lower IQ when compared to healthy controls; moreover they suffered from weakness on executive function, spatial ability, and visual memory [91]. Trisomy of X chromosome (47,XXX) is anomaly associated with increased prevalence of POI. Moreover women suffering from trisomy X have higher rates of cognitive deficits and learning disabilities in the school-age years with an increased risk of speech and motor delays [92].

It is suspected that early menopause may contribute to increased risk of cognitive impairment and dementia; nevertheless data are not consistent [93]. Earlier age of premature menopause, especially due to oophorectomy, is a risk factor of more rapid cognitive decline [94].

Recently conducted studies indicated that untreated surgical menopause may result in development of Parkinson's disease, while oophorectomy due to nonmalignant pathologies increased the risk of cognitive decline by 64% [95]. Moreover patients after oophorectomy present worse word recall, decreased episodic memory, and semantic memory, which are particularly associated with development of dementia [96, 97]. Moreover earlier menopause contributed to AD neuropathology, particularly to development of neurotic plaques and thus increased risk of Alzheimer's disease [97].

3.6.7 Emotional Health and Sexual Life

It is well estimated that POI patients develop distressing symptoms associated with disturbances in sexual health and quality of life. Taking into consideration Female Sexual Function Index (FSFI), almost all domains of sexual life such as arousal, lubrication, orgasm, satisfaction, and pain are affected [98, 99]. Results from previously conducted studies presented evidence that POI patients are less sexually responsive, have lower libido, and suffer from dyspareunia more often than healthy premenopausal controls [100]. Moreover estrogen deficiency leads to vaginal dryness and difficulties in orgasm achieving and painful intercourse [101]. Lower concentration of androgens associated with POI may also contribute to impaired sexual function; nevertheless data are inconsistent [102]. Problems in sexual life may contribute to loss of self-confidence and self-esteem, increased anxiety, and concerns [101]. Other complications associated with emotional health of POI patients are depression, somatization, sensitivity, hostility, blue mood, despair, depression, and psychological distress [102, 103]. In World Health Organization Quality of Life (WHOQOL-100) questionnaire, physical and psychological health are two main affected domains [103].

3.7 Management of Premature Ovarian Insufficiency Patients

3.7.1 The Role of Hormonal Replacement Therapy

The mainstay of treatment of POI is hormone replacement therapy (HRT) until at least the age of natural menopause [3, 104, 105].

Estrogen replacement therapy has several important goals, such as puberty induction, maintaining the optimal bone mass density, protection against cardiovascular risk, and alleviating the symptoms of hypoestrogenism. 17β-Estradiol, estradiol valerate, conjugated equine estrogens, and synthetic ethinylestradiol are available in many different forms: oral pills, transdermal patches or gels, vaginal rings, or cream.

Progestagen therapy has to be added to systemic estrogen treatment (oral or transdermal) to protect from endometrial cancer. Micronized progesterone is available as oral or vaginal pill, while synthetic progestins are administered in a form of tablets, injections, rings, implants, or an intrauterine device.

Estrogens or progestins can be administered in a separate regimen or can be combined in a form of hormonal replacement therapy intended for postmenopausal women or contraceptive formulations in forms of pills, rings, or patches.

3.7.1.1 Puberty Induction

In prepubertal girls with hypogonadism, small doses of estrogen help to achieve secondary sexual characteristics, induce growth spurt, build maximal bone mass density, and increase the volume and vasculature of the uterus. Natural 17β-estradiol is recommended at the age of 12 at initial doses of 6.25 μg/day transdermally or 0.25 mg/day orally [3]. Then during 2–3 years, the doses are gradually increased reaching at 15–16 years of age doses of 50–100 μg/day transdermally or 1–2 mg/day orally [3]. Cyclic progestagen (for 10–12 days a month) is recommended after 2 years of estrogen treatment or when the breakthrough bleeding occurs [3, 106]. Regular withdrawal bleeding in POI patients provides a sense of normalcy in comparison with their peers.

3.7.1.2 HRT Risk

There is no evidence that risk connected with HRT when used in postmenopausal women can be applied to the younger population of women with POI. Breast cancer is not increased in women treated with HRT before the age of natural menopause; however, HRT is contraindicated in breast cancer survivors [3, 107, 108].

Increased risk of thromboembolism depends on estrogen concentration and type of progestins [109]. Second-generation progestins (levonorgestrel) carry lower risk than third-generation progestins or new progestins (gestodene, desogestrel, cyproterone acetate, drospirenone). Transdermal estrogens have lower risk of venous thromboembolism (VTE) than estrogens administered orally.

3.7.1.3 Androgens

Serum androgen levels are decreased in POI patients [110], and some clinicians recommend testosterone supplementation in order to increase libido [111]. The

effect of testosterone on quality of life and self-esteem in women with POI has not been proven [112]. Available evidence does not support routine replacement of testosterone or dehydroepiandrosterone in patients with ovarian failure [3, 113].

3.7.1.4 Choice of Estrogen/Progestin Regimen

There is no consensus on the optimum regimen of estrogen and progesterone replacement therapy in patients with premature ovarian insufficiency.

Physiological sex steroid replacement (pSSR) including estradiol patches (50–100 μg/day) in regimen with vaginal progesterone (100–300 mg/day for 10–12 days in a month) achieves steroid serum concentrations similar with women with normal ovarian function [107, 113–115]. That treatment regimen in comparison with standard HRT or oral contraceptive pill (OCP) better improves parameters of uterine function [116]; is associated with lower blood pressure, better renal function, and less activation of the renin-angiotensin system [57]; and results in better BMD *z*-scores in lumbar spine region [114].

Transdermal estradiol delivers hormones directly into circulation avoiding first-pass effect on the liver and may be the lowest-risk route of administration of estrogens in women suffering from migraine with aura, hypertension, and obesity or at an increased risk of VTE [3].

Combined oral contraceptive pill containing ethinylestradiol delivers hormones at greater dose than is required for physiological replacement. Some progestins included in standard combined HRT or OCP may have worse influence on lipid profile and carry higher risk of VTE, but they probably offer better endometrial protection than micronized progesterone [1, 13].

Compliance to hormonal therapy in a group of patients with premature ovarian failure is low. The follow-up of the patients shows that around 40% stops the treatment [114, 117]. Main reasons are absence of subjective benefit, adverse effects, fear of breast cancer, and weariness [117]. Therefore, the route, drug, and dose of HRT have to be individualized and adjusted for every patient. The patient's preference for a combined or separate regimen, the need for contraception, and the preferred frequency of withdrawal bleeding should be taken into account. Although the pSSR regimen may seem preferable from the metabolic point of view, combined hormone replacement in a form of HRT or oral contraception pill may appear more convenient and more "peer-friendly" for young patients with POI.

Hormonal replacement therapy should be long term in POI patients; therefore issues of compliance as well as risk-benefit ratio are very important to maximize longer-term health.

3.7.2 Treatment of Other POI Consequences

3.7.2.1 Reproductive Health

Treatment in this field is very difficult and still challenging. There are attempts to use treatment to increase natural pregnancy rate in POI patients [118]. Gonadotropins, estrogens, and corticosteroids present very limited action. van Kasteren and Schoemaker [119] analyzed seven controlled trials of the POI treatment, and they did not find statistically significant increase in the ovulation rate.

Data regarding use of immunosuppression in patients with POI are limited. Patient with colitis ulcerosa with autoimmune premature ovarian failure and Addison's disease underwent azathioprine therapy [120]. This treatment helped to restore normal cycles and fertility.

As a consequence that there is no reliable treatment which can increase ovarian activity in POI patients, other methods are needed. At present oocyte donation is the only proven and recommended treatment for women with POI. The first successful procedure was reported by Lutjen [121]. According to Ameratunga et al. [122], pregnancy rate after an oocyte donation cycle is around 40%, and cumulative pregnancy rates after four cycles reach 70–80%. Oocyte donation pregnancies can be associated with some obstetric risks which are related to the cause of POI.

Apart from oocyte donation, other techniques of fertility preservation in POI patients also can be considered. Fertility preservation can concern cryopreservation of oocytes, embryos, and ovarian tissue. There is a question whether it can be applied, for instance, to the Turner syndrome patients [123]. Fertility preservation in cancer patients still requires new advanced methods. Cryopreservation of ovarian tissue is regarded as a medical challenge which can be very promising for young women with cancer. Broadly considering cryopreservation of ovarian tissue can be also a method for women who have hormone-sensitive malignancies and also women anticipating hematopoietic stem cell transplantation for the treatment of benign hematologic diseases (sickle cell anemia, thalassemia major, aplastic anemia) [124]. The biggest worldwide report on ovarian transplantation tissue was published in 2016. It includes 95 orthotopic transplantation in 74 women of ovarian tissue after cytotoxic treatment in a fertility preservation network (16 centers in Europe) [125]. Twenty-one pregnancies and 17 deliveries were reported. Although this study presents good results of described procedures, the ovarian tissue cryopreservation and transplantation is still regarded as experimental. Additional progress in this field is referred to the new method known as in vitro activation of dormant follicles developed by Kawamura [126]. It presents new perspectives for POI patients.

Treatment of infertility in POI patients presents one of the most important issues of the POI management. It requires professional, modern, and interdisciplinary medical knowledge and also very good communication with the patient.

3.7.2.2 Mood and Sexual Impairment

First-line treatment for mood disturbances is HRT; nevertheless data are inconsistent whether it influences mood or psychological aspect of sexual life. In previously conducted studies, it was suggested that HRT did not improve quality of life of POI patients [83]. Nevertheless in a recent review, it was estimated that it improves results achieved by POI patients in Psychological General Well-Being (PGWB) scale. Moreover patients reported improved self-esteem and increase in the overall McCoy Sex Scale score and in interest in sex [112, 127]. It is also necessary to highlight that additional administration of testosterone did not influence neither quality of life nor self-esteem [127].

3.7.2.3 Genitourinary Health

POI patients treated with oral estrogen show no differences in vaginal pH, cytology of epithelium cells, or vaginal microflora in comparison to healthy patients [85], but still report worse lubrication and higher prevalence of pain during intercourse [86]. Local therapy with estrogens is the most effective and brings the fastest relief of the symptoms of genitourinary syndrome, but does not reduce the risk of osteoporosis or manage vasomotor symptoms. Vaginal estradiol and conjugated equine estrogens or estriol are available in the form of tablet, pessary, ring, or cream. According to Cochrane review, all forms of vaginal estrogens appear to be equally effective for the symptoms of vaginal atrophy [87]. Treatment with estriol seems to be safer, because it is less potent than estradiol, is cleared more quickly, and is not inverted to estradiol.

3.7.2.4 Bone Health

Bone mass density is decreased in patients with premature ovarian insufficiency comparing to their peers [117, 128]. Around 30% of POI patients have osteopenia and 8% osteoporosis at the time of diagnosis [117]. Hormonal replacement therapy improves BMD in POI patients but has not been proven to be completely effective in prevention of osteoporosis [113, 114, 129–131].

3.7.2.5 Central Nervous System

It seems that HRT protects POI patients against early dementia and deprivation of cognitive function [97]. Estrogens protect particularly healthy neurons, while pathologically changed neurons show acceleration in their demise when exposed to estrogens [93]. On the other hand, some studies indicated that women after surgical menopause, who underwent HRT, had significantly worse long-term episodic memory and mental flexibility when compared to controls without HRT [132]. It is necessary to highlight the influence of timing of HRT initiation. Postmenopausal patients, who underwent HRT in early age (50–60 years), experienced beneficial and neuroprotective effect of estradiol supplementation. Conversely, HRT in older postmenopausal patients caused increased risk of dementia and cognitive impairment [133].

3.7.2.6 Cardiovascular System

POI patients are at higher risk of cardiovascular disease [3]. Endothelial function is impaired in women with premature ovarian insufficiency, and normalization of the parameters was observed after 6 months of hormonal replacement therapy [134]. Although there is lack of strong evidence, it is generally recommended to initiate HRT in POI patients early and continue until the age of natural menopause to control the risk of cardiovascular disease [3, 105].

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Human Papillomavirus Infection and Cancer Risk in Peri- and Postmenopausal Women

4

Pedro Vieira-Baptista, Mario Preti, and Jacob Bornstein

4.1 Introduction

The most commonly acknowledged complication of human papillomavirus (HPV) infection is invasive cervical cancer (ICC), to which this infection is a *sine qua non* condition. However, the burden of disease associated with HPV is much higher than that of ICC and its precursor lesions (high-grade squamous intraepithelial lesions [HSIL] encompassing cervical intraepithelial neoplasia [CIN] 2 and 3) and not limited to women. Besides benign diseases, even if distressing (genital warts, recurrent respiratory papillomatosis, low-grade squamous intraepithelial neoplasia [LSIL]), HPV infection is regarded as a necessary cause of a variety of preinvasive/invasive lesions of the vulva and vagina, penis, anus/perianus, and oral cavity and oropharynx [1].

The risk of cancer and of squamous intraepithelial lesions is related to the HPV genotype and infection persistence. However, it is still up to debate if a persistent infection implies continuous detection of the virus or can include latent periods—translating into a very relative definition of "transient" and "persistent" infection [2, 3]. HPV is the most prevalent sexually transmitted infection (STI) in the world, with more than 80% of the sexually active women being infected during their lifetime with at least one genotype [4]—a situation that will definitely change in the future, as the effects of HPV vaccination start to be noticed. Several factors must interplay,

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as only a minority of infected people develops disease (HPV genotype, age, smoking, other STIs, vaginal microbiome, immunosuppression, hormonal and genetic factors, etc.).

While HPV infection is more common in younger women, the serious complications tend to occur at later ages (in the peri- or postmenopause). According to that, politics of cervical cancer/precancer screening and treatment tend to take that into account and ponder the risk of being too aggressive (starting screening at young age, treating CIN2 in women younger than 30 years old), with serious impact on obstetrical outcomes (for instance, preterm labor or premature rupture of membranes) against that of missing or not treating significant disease.

As we start anticipating the end of screening, derived from massive vaccination [5], it must not be forgotten that, even in developed countries, there will be extensive cohorts of unvaccinated women for three or four decades more, which cannot be neglected by the euphoria of the anticipated elimination of ICC.

Some older women may consider they are not at risk at this stage, as they already had several screening tests or because they have lost their partners or are in a monogamous relationship.

4.2 HPV Epidemiology

Despite the significant geographical variations, global prevalence of cervical high-risk HPV in young women can be as high as 50% in the early twenties, dropping to about 10–15% after the age of 25–30 [6]. After that, in developed countries, there is a slight decrease until the fifth or sixth decades of life, when a new peak is encountered [7–9]. This peak may be even more pronounced for non-oncogenic (low-risk) HPV genotypes, which may be explained, in part, by its higher tropism for the mature squamous epithelial cells, rather than for the transformation zone (TZ) [10]. In less developed countries, the prevalence tends to be higher, and the second peak is typically absent [11]. One study has clearly shown that the risk of having a positive HPV test, 3 years after a negative one, is similar between women aged 51 years and younger ones [12].

The prevalence of HPV16 and HPV18 seems to be stable after the age of 35 years old, but, at least in some countries, they are responsible for significantly less cervical high-grade lesions than in premenopausal women; less aggressive genotypes seem to play a more important role in older women [13, 14].

While the first peak, in young women, can be attributed to the onset of sexual debut, the second one may be due to new sexual partners (especially after divorce or widowing), "Viagra effect," and hormonal milieu (and consequent associated microbiome changes) or just a consequence of a waning of the immune system (immunosenescence). In the second peak, besides newly acquired infections, there may be a role for reactivation of older, latent infections. Having had two or more sexual partners, after a negative HPV test, in postmenopausal women, was associated with an odds ratio of 3.9 (95% CI = 1.2–12.4) of having a subsequent positive test—highlighting the role of acquisition of new infections for the second peak of prevalence of HPV infection. In

this same study, having had two or more sexual partners in the past was associated with a 1.7-fold (95% CI 1.1–2.5) higher likelihood of having a positive HPV test later in life [10]. In a study by Gravitt et al [9], it was found that women with a higher number of sexual partners (≥5) during their lives were at a greater risk of being HPV positive later in life—thus supporting the hypothesis of reactivations of HPV infections. Women entering now the menopause lived their youth after the sexual revolution and, thus, are likely to have had more sexual partners than the previous generation. This may translate into higher rates of HPV infections and cervical intraepithelial neoplasia than what has been usually encountered in postmenopausal women.

As we have previously discussed, there is now enough evidence that previous infections can be reactivated, thus women cannot discontinue screening, even in the absence of a (new) sexual partner [15]. This concept is important and may be worth explaining to patients, as it can help, in some cases, to overcome suspicion of infidelity or feelings of guilt. On the same way, it can be explained that a negative test is not always synonymous of absence of the virus but rather that the viral load is below the defined risk threshold.

The risk of reactivation of HPV at older ages, associated with a lower performance of diagnostic tests (discussed ahead), has led some authors to theorize that in well-screened populations, this will translate into a proportional increase in the diagnosis of ICC, rather than HSIL [9].

4.3 The Interaction of Aging, Hormones, Vaginal Microbiome, and HPV

In general, 90% of HPV infections clear within a year. There are contradictory data concerning clearance of HPV in older women, but apparently, the time for clearance of new HPV infections does not seem to be increased [8, 10, 16]. On the contrary, regression of cervical intraepithelial neoplasia seems to decrease with the advance of age: a recent meta-analysis has shown that for every 5 years of age, the odds for regression decrease 21%, while those of progression increase. These tendencies were shown to be independent of the grade of the lesion and the presence or not of a high-risk HPV infection ($p < 0.001$) [17]. Adding to the effect of age on the immune system, there is some evidence that the hormonal changes of menopause, namely, estrogen deprivation, can also contribute to the attenuation of the immune response and an increase in the inflammatory markers [18, 19]. Despite this, the CD4 T-lymphocytes population, which has a key role in the regression of intraepithelial lesions, along with CD8+ and CD56+ macrophages, is diminished. The same is true for B lymphocytes (which contributes to explain the lower efficacy of vaccines in older women), as well as for the activity of NK cells [20–22]. It has been demonstrated that women with a lower immunological response to a challenge with HPV16 virus-like particles are at higher risk of developing an HPV infection [15].

Despite the immunosuppression associated with age, the risk of HSIL associated with a newly identified positive HPV test does not seem to be higher in older women [23].

Several studies have associated the use of combined oral contraceptives with increased risk of HSIL and ICC, assumed to be due to transactivation of viral oncogenes [24]. Postmenopausal hormone therapy has not been associated with increased prevalence of HPV nor with increased viral replication, despite a potential role in modulating the immune response [20, 25]. The EPIC cohort study found a decreased risk of ICC in women who ever used menopausal hormone therapy (HT) (HR = 0.5, 95%CI 0.4–0.8); longer duration of its use also had a trend toward lower risk [26]. The interpretation of these findings is not straightforward, as women who took HT are more likely to have attended more routine gynecological appointments and, thus, more often screened and treated for cervical cancer precursors.

The unopposed use of estrogen was associated with a higher risk of CIN3/CIS [26] and HPV infection [27]. There is evidence that estrogen receptors α (ERα) are essential in the initiation of the invasive process. This led to the theory that selective estrogen receptor modulators (SERMs), namely, raloxifene, can play a role in the prevention of the progression of HSIL to invasive cancer and even that it can be used as an adjuvant treatment of ICC [24, 28].

In one observational study, however, the use of intravaginal estrogen cream, isolated or associated with other modalities of treatment, was associated with rates of regression of vaginal intraepithelial neoplasia (VaIN) [29]. It should be emphasized that its use is usually recommended before other treatments, to increase the thickness and elasticity of the vaginal mucosa.

Given the current knowledge, HPV infection or cervical dysplasia should not affect the decision to start or discontinue menopause HT, contrary to what has been previously suggested [30].

In recent years, a staggering amount of information is being gathered showing that vaginal flora or microbiome plays a key role in the acquisition and persistence of HPV infection, as well as on the development and persistence of CIN. We are, however, far from the full understanding of the picture.

Increased vaginal pH, a surrogate for abnormal vaginal flora (AVF) (absent/severely depleted number of lactobacilli—usually bacterial vaginosis [BV] or aerobic vaginitis [AV]) has been associated with a 30% increased risk of HPV infection and abnormal Pap test, especially in women younger than 35 or older than 65 years [31]. Data linking BV and mixed flora (most likely AV) to persistence of HPV infection has led some authors to recommend its screening and treatment, even if asymptomatic [32, 33]. BV is encountered more frequently in women with a Pap test worse than LSIL (20.5% vs. 13.2%, $p = 0.09$); moderate/severe forms of AV are significantly more common in women with these results (16.9% vs. 7.2%, $p = 0.009$) [33].

Given that the prevalence of BV seems to steadily increase after menopause, and persistence/recurrence seems to be very common, this can be another factor posing these women at risk for HPV acquisition, persistence, or reactivation, as well as development and progression of intraepithelial neoplasia [34]. It is, however, indissociable from the complex relation between vaginal microbiome and hormones.

Recently, it has even been shown that 3 months after loop electrosurgical excision procedure (LEEP) for HSIL, there is a decrease in species diversity and that vaginal microbiome shifts from *Prevotella*, *Leptotrichia*, and *Clostridium* to a *L. iners* dominance [35].

4.4 Vaccination

The anti-HPV vaccines have been proven to be highly efficacious in the prevention of the infection, genital warts, abnormal Pap tests, and the development of intraepithelial neoplasia and adenocarcinoma in situ (AIS). Although a significant impact is also expected to be seen in terms of cervical cancer (carcinoma and adenocarcinoma), there are not yet studies with enough duration to prove it [36].

Most studies have focused on the impact of the vaccines in women under the age of 26 years old. The few studies enrolling older women (>25 years old) demonstrated that the efficacy is lower than in younger ones. A recent Cochrane review concluded that in women 24–45 years old, the rate of CIN2+ associated with HPV16/18 and any CIN2 is equivalent between vaccinated and unvaccinated women (RR 0.74 [0.52 to 1.05] and RR 1.04 [0.83 to 1.30], respectively); no conclusions could be drawn for CIN3 or AIS. If women are selected according to HPV16/18 status, those who are DNA negative still benefited from the vaccine (RR 0.30 [0.11 to 0.81]) for CIN2 associated with these specific genotypes [36].

Previous exposure to HPV and a lower immunological response can explain the decrease in vaccine impact. It is still not proven that newly diagnosed HPV infections in older women are indeed associated with a significant increase of relevant disease [10].

The available data does not allow recommending systematic vaccination of postmenopausal women. However, to those who request it, it is reasonable to offer the vaccine, as the existing data are reassuring in terms of safety and the potential benefits seem to last at least for 10 years [37]. Some countries have not licensed the vaccine for women older than 26 (i.e., USA) or 45 years old (i.e., Canada), thus making its use beyond these ages off-label eventhough reasonable [38].

Three doses of vaccine should be administred, as in any individual older than 15 years old.

The vaccines have proven to decrease the risk of vulvar and vaginal HSIL, when given to young girls, an effect that is expected to lead to significant decrease of these diseases in the future. The impact of vaccination of older women in these conditions remains unknown [39]. There is no clinical evidence that HPV vaccination will lower the number of head and neck cancers. However, salivary antibodies have been identified in the majority of people following vaccination [40, 41].

4.5 Cervical Intraepithelial Neoplasia (CIN) and Cervical Cancer

Cervical cancer (Fig. 4.1) is the seventh most common cancer among women in developed countries and the second one in developing countries. Among the 527,000 estimated new cases per year, 444,500 occur where the efficacious preventive tools (screening, vaccines, treatment of HSIL) are still lacking. This cancer is responsible for the death of 230,000 women die every year [42]. This, however, is expected to change if massive vaccination of girls is implemented in those countries—even in the absence of well-organized screening programs [43, 44]. Several low-income countries have already shown that high-coverage vaccination is feasible [45].

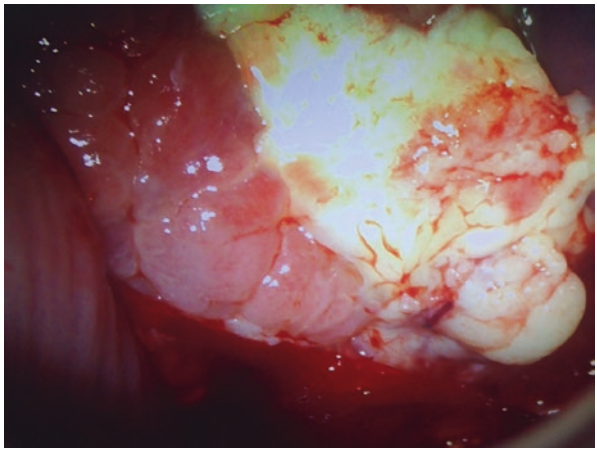

Fig. 4.1 Locally advanced cervical cancer

In countries without an effective screening program, the incidence of cervical cancer has a sudden rise in the perimenopause years; after that, the incidence keeps rising with advancing age. In those countries with effective screening, the distribution is usually bimodal: one peak around 35 years old and a latter one around 65 years old [13, 46] (Table 4.2).

In less developed countries, as the toll of deaths attributable to other infectious diseases reduces (namely, with the available treatments for human immunodeficiency virus [HIV]), the number of cervical cancers in older women is expected to increase.

4.5.1 Particularities of Screening

The aging of western countries' population will lead to a substantial number of screened women for cervical cancer being postmenopausal. On the other hand, with mass anti-HPV vaccination, disease will become less prevalent in younger women, leading to postponing of the age of beginning of the screening programs. In practical terms, during the next years, there will be an apparent shift of the peak of HSIL [47].

Primary high risk (HR)HPV test for screening is widely acknowledged as the best way to perform cervical cancer screening, in women older than 25–30 years old. A few studies have evaluated specifically how Pap test compares to HR-HPV test in postmenopausal women. The increased rate of parabasal cells, with a higher nucleus-cytoplasm ratio, along with more or less severe inflammation, partially explains the increased difficulty in the assessment of the Pap test in hypoestrogenic women. A Swedish study has shown that screening with Pap test alone misses more than half of the high-grade lesions detected using HR-HPV test [14]. On the other hand, as the positive predictive value of the Pap test seems to be lower in older women, some authors consider that triage with HR-HPV tests of ASC-H and even HSIL Pap tests can be a useful approach in this age group [48, 49]. Besides the

added difficulties for Pap test in postmenopausal women (atrophy, inflammation, regression of the transformation zone to the endocervix [type 3 transformation zone] [50, 51]), it must be taken into account that the Pap test is highly operator dependent—in other settings the results could have been dramatically different [52]. A short course of intravaginal estrogens can improve the performance of the Pap test [53].

Postmenopausal women are more likely to have Pap test without representation of the transformation zone and/or the glandular epithelium. While some clinicians feel uncomfortable with these results, studies have shown that as long as it was classified as negative (NILM), there is no increased risk of missing disease. In the case of absence of representation of the transformation zone, it is, however, preferable to perform an HR-HPV test. The result of this test is not at all influenced by the lack of representation of the transformation zone [54–56].

Cuzick et al., in 2013, presented data showing that HPV triage of LSIL Pap test is an effective measure to avoid unnecessary referrals for colposcopy. After the age of 40, only half these tests are HR-HPV positive; HR-HPV negativity successfully predicted the absence of HSIL [55, 57]. Employing triage of LSIL Pap tests in postmenopausal women can safely reduce to half the number of colposcopies, which is highly significant, given the limitations of this exam in this population. Additionally, in case of positivity, a better risk stratification can be made. The cases that test negative should be reassessed at 12 months, and if either one or both of the tests (Pap test or the HR-HPV test) are positive, the patient should be referred for colposcopy [55].

There is no consensus among different societies on the age to discontinue screening. Most societies recommend, for previously well-screened women, without history of HSIL (CIN2/CIN3) or adenocarcinoma *in situ*, to discontinue it at 65 years old [55, 58]. Some women, however, will be uncomfortable with that or will feel that the system is giving up on them, because of their age. In opportunistic (personalized) screening, the benefits of continuing the screening must be considered and discussed with the woman. A Pap test ASC-US, even if the HPV test is negative, does not allow stopping the screening [55]. Interestingly, there are data suggesting that maintaining screening up to the age of 79 years old could lead to a reduction in ICC of 77–79% in the USA [59]. It has also been shown that long-term survival is higher, also in older women, if the diagnosis of ICC is made in the sequence of a screening test, rather than a clinical diagnosis [60]. These issues must be taken into account, especially with the increase in life expectancy.

According to ASCCP and ACOG guidelines, women with a previous diagnosis of HSIL or AIS should continue routine screening for 20 years after the treatment or regression of the lesion, independently of the age at which it occurred and the presence or not of the cervix [55, 58].

4.5.2 Colposcopy and Treatment of Lesions

Colposcopy is a true challenge in postmenopausal women. Lack of estrogens leads to thinning of the vaginal and cervical mucosa and capillary fragility (Figs. 4.2 and 4.3)

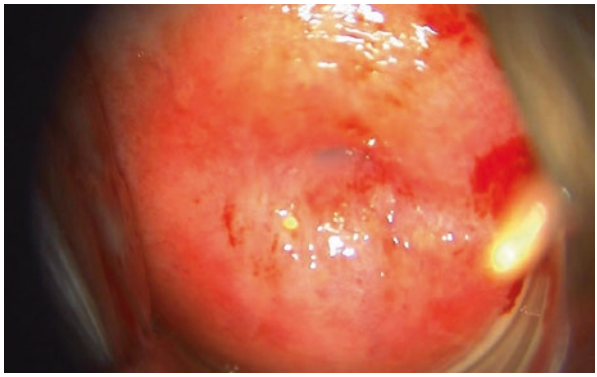

Fig. 4.2 Colposcopy of a postmenopausal woman, before the application of acetic acid. Note the presence of petechiae and easy bleeding upon touch

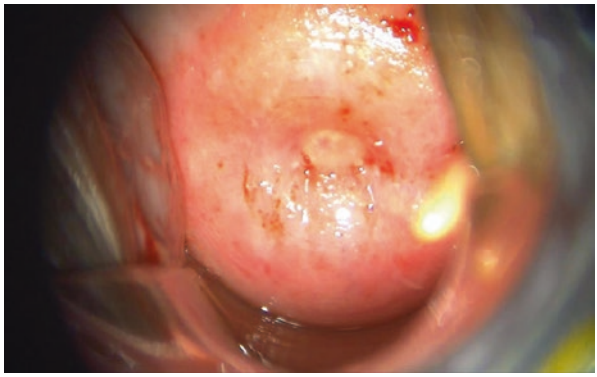

Fig. 4.3 Same woman as in Fig. 4.2, after the application of acetic acid

that can lead to discomfort/pain during sexual intercourse and gynecological examination and easy bleeding upon speculum placement.

As previously referred, it is uncommon to find an active TZ readily visible in the ectocervix in these women; the rate of poor visibility colposcopies is thus higher. Up to 44% of the CIN lesions are endocervical in postmenopausal women—and, in accordance, the rate of positive endocervical curettages is also higher in this age group [61, 62]. There are limited and sometimes contradictory data on the role of misoprostol or vaginal estrogens to reduce the number of inadequate colposcopies in hypoestrogenic women. Short courses (3–6 weeks) of intravaginal estrogens seem to be more efficacious and associated with a lower rate of adverse effects [53, 63–66].

The role of endocervical sampling and the best way to perform it are controversial. There is evidence that the use of endocervical brushes has a similar sensitivity and specificity to that of curettage (Fig. 4.4). The former is associated with less discomfort and lower number of insufficient samples (0–7.6% vs. 0–22%), but, on the other hand, grading of the lesions is more difficult, due to the lack of an organized tissue sample [67–69]. The role of this procedure is debatable, with studies finding it to be positive in the range of 1.4–17.9% in women with a good visibility

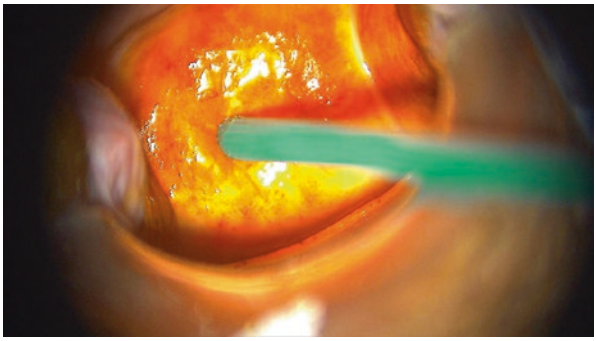

Fig. 4.4 Sampling of the endocervix with a cervical brush, due to nonvisible squamous columnar transition. Notice the diffuse lack of staining with iodine solution

of the TZ and up to 57.3% if visibility is poor. Most studies do not favor its use if the squamous columnar junction is fully visible [69]. It has also been reported that endocervical curettage can miss 45% of cases of HSIL while having a 25% false-positive rate [70]. Its role in the study of glandular abnormalities is less debatable, even though performance may be below the desirable [69].

The lack of an active TZ and the fact that the epithelium is usually thinner (Fig. 4.3) imply that any acetowhite lesion must be valued in this age group. Some lesions are not apparent without previous estrogen treatment. Sometimes, in women taking oral or transdermal HT, that may not be enough for proper vaginal epithelium maturation and topical treatment may be needed for a proper valuation of the lesions.

The use of Lugol's iodine solution (Schiller's test) is of more limited value in postmenopausal women, especially in those without estrogen HT: the lack of glycogen in the vaginal cells leads to a diffuse light brown to yellow coloration (Fig. 4.4) that can be mistaken as a negative iodine response.

Like in premenopausal women, excision of the transition zone (TZ) is the definite treatment for HSIL, significantly decreasing the risk of progression to ICC (estimated in some series to be as high as 40%, for untreated CIN3 [17]). The risk of failure of LEEP is usually inferior to 10% [71]. Ablation is usually not considered as an option in postmenopausal women, given the frequency of inadequate colposcopies and the significant rate of invasive disease only diagnosed with the excisional procedure (up to 4.3%) [72].

Usually, given the characteristics of the TZ, the height of the cone needs to be bigger than in premenopausal women [73]—and also there is no concern with the risk of excessive excision and obstetric outcomes. Even though, the likelihood of positive endocervical margins is higher in postmenopausal women [73, 74].

In case of positive margins, expectant management and a new excision of the TZ are the recommended options. Expectant management implies a compliant patient and, preferably, visible squamous columnar junction (even though this may be a minor issue if HR-HPV test is being used for follow-up and it is negative). A small study reported that after repeated excision of the TZ, the rate of residual disease can be as high as 52.3% [75]. However we can theorize that the rate of positivity probably decreases with time elapsed between the first and second procedure. Some

support the performance of hysterectomy, on the basis that residual disease is common when it is performed in postmenopausal women, following excision of the TZ, independently of the status of margins (67.6%) [76]. This, however, does not seem to correlate with daily practice. It must be kept in mind that long-term follow-up is recommended in women with history of HSIL, even after hysterectomy, because of the increased risk of multicentric HPV lesions [77].

In a systematic review and meta-analysis, Arbyn et al. found that the risk of CIN2+ after an excisional procedure was 0–8% if a follow-up HPV test was negative and 3–7% if margins were free [78]. These figures leave some room for expectant management in the presence of positive margins, especially if the SCJ is totally visible post-procedure.

In hypoestrogenic women, cervical stenosis after excision of the transformation zone is common, thus making the follow-up more complicated. The local use of estrogens may reduce this complication, with some supporting that it should be kept for at least 1 year after the procedure [79, 80]. Except for stenosis, the rate of complications seems to be comparable between pre- and postmenopausal women [73].

As in premenopausal women, hysterectomy should not be performed for isolated treatment/exclusion of HSIL. Besides being a much more complex procedure, with a much higher rate of associated complications, there is the risk of an undiagnosed invasive cancer (better managed with more radical surgery).

Follow-up after treatment of HSIL is better accomplished with HPV test, like in premenopausal women. It is useful to have knowledge of the HPV status prior to the treatment, namely, because of the uncommon cases of HSIL lesions that test negative for HPV—in this setting, a negative test would be a false reassurance. The American Society of Colposcopy and Cervical Pathology (ASCCP) recommends follow-up to be performed using co-testing (HPV and Pap test) at 12 and 24 months. After two consecutive negative tests, they recommend that the woman can be discharged for routine screening [55]. Some studies suggest that one single negative HR-HPV test after treatment, as early as 4–6 months, may be considered a test of cure: the risk of HSIL is similar to that of an HR-HPV-negative woman from the general population [81–83]. Earlier testing, however, may be associated with a higher positivity of tests, not necessarily significant. Older women (>67 years) appear to be at higher risk of subsequent CIN2+, probably deserving a more careful and longer follow-up [81].

A recent paper from the Dutch nationwide registry of histopathology and cytopathology found that the 89.018 women with a previous diagnosis of CIN3 had an increased risk of HR-HPV-associated high-grade lesions and carcinomas of the vulva, vagina, anus, and oropharynx when compared with 89.018 control subjects. In particular, the incidence rate ratios were higher for vulvar cancer, 13.66 (93% CI, 9.69 to 19.25); vulvar HSIL, 86.08 (95% CI, 11.98 to 618.08); and vaginal cancer, 25.65 (95% CI, 10.50 to 62.69).

As long-term follow-up still showed increased risk, new strategies for screening of HPV-related neoplasia, other than cervical ones, must be investigated, validated, and adopted in this increased risk group of patients [84].

4.6 Other Lesions

4.6.1 Vagina

High-grade vaginal intraepithelial neoplasia (VaIN) (VaIN2 and VaIN3) is considered the malignant precursor of vaginal cancer. It is usually asymptomatic and HPV-related, mostly with HPV16 (>50% of the cases) [85]. Although its incidence has been reported to be increasing in the last decades, especially in younger women, it is still a rare lesion—100 times less frequent than CIN [86, 87]. That increase, however, may not be real, but rather just translating better screening methods, more awareness, and higher compliance with screening guidelines (for instance, maintenance of follow-up in hysterectomized women with a diagnosis of HSIL). Screening for VaIN or vaginal cancer should not be kept in hysterectomized women, without a previous history of HSIL.

Vaginoscopy, independently of the presence or absence of the cervix, is more complicated than colposcopy, more time consuming, and associated with more discomfort. Previous treatment with topical estrogens is mandatory before performing vaginoscopy in postmenopausal women. Typical patterns of LSIL or HSIL are difficult to establish, implying that, in doubt, a biopsy is needed. VaIN is located in the upper third of the vagina 80% of the time and usually is multifocal [88]. Vaginoscopy should be performed by experienced colposcopists [89].

The risk of progression of vaginal HSIL to invasion is low (3%), and vigilance rather treatment seems to be a relatively safe option [90]. The use of vaginal imiquimod seems to be an efficacious and relatively safe choice, but further studies are needed before it can be assumed as a first-line option for treatment [91, 92]. However, independently of the chosen treatment modality, recurrence is very common, especially in women with multifocal disease [88].

Primary vaginal cancer is one of the rarest gynecologic malignancies, representing 2% of the total number of it. Its incidence is of around 7:1.000.000 women/year [93, 94]. At least 50% of the vaginal cancers of squamous origin are HPV-related, especially with HPV16; HPV18 seems to play a minor role in this neoplasia. A history of previous cervical cancer and/or pelvic irradiation is also common. Other studies have linked previous hysterectomy (in some series in up to 40% of women) and surgical menopause to this neoplasia [85, 93, 95]. Those with a VaIN history following a hysterectomy tend to be older [85].

4.6.2 Vulva

4.6.2.1 Warts

Genital warts or *condyloma acuminata* are not exclusively found in the vulva, but this location is the most common and is associated with higher levels of psychological suffering [96]. It affects less than 1% of the whole population. It is more prevalent in young people (peaking at the age of 20–24 years old) and rare in postmenopausal women [97–99].

Their presence is frequently asymptomatic but can also manifest by itching and burning or, less frequently, by bleeding. Most frequently, it presents as a cauliflower-like, skin-colored to pink tumor. Lesions are usually multiple and can involve multiple organs; it can measure a few millimeters or, especially in immunosuppressed patients, can measure several centimeters.

The use of acetic acid in the vulva to identify warts is controversial, as it is non-specific of HPV infection. Its use by practitioners who are not aware of this frequently leads to overdiagnosis and overtreatment [100], with potential psychological and physical consequences.

Most of the cases are caused by low oncogenic risk HPV genotypes—HPV6 and HPV11 are responsible for at least 80% of the cases. HPV16 can be involved in up to 10% of cases—which could partly explain the decrease in genital warts noticed in adolescents vaccinated with the bivalent vaccine [101, 102].

Especially in older women, a biopsy may be needed to exclude intraepithelial or invasive disease. Screening for other STIs should be performed, and investigation of immunosuppression should be considered in older women.

4.6.2.2 Vulvar Intraepithelial Neoplasia and Cancer

Vulvar cancer accounts for approximately 3–5% of all gynecological malignancies, with an incidence rate of 2.4 new cases per 100,000 women per year, and represents 0.4% of all new cancers in the USA [103]. The most common histology (almost 90%) is squamous cell carcinoma of the vulva. Other rare histotypes include melanoma, adenocarcinoma, invasive Paget disease, basal cell carcinoma, and sarcoma [104]. Similar incidence rates have been observed in western countries, following a slight preference for white race compared to black and Asian race [105]. Several authors have reported an increase in the overall incidence rate in many countries. Specifically, in Germany, Buttmann-Schweiger et al. observed a doubling in the incidence rate from 1.7 to 3.6 new cases per 100,000 women per year from 1999 to 2011 [106]. In Denmark, a 1.97% per year increase in the incidence rate between 1978 and 2007 has been reported [107]. This trend has been confirmed also in the USA: a 1.0% per year increase in the incidence between 1973 and 2004 [108, 109]. Some authors noticed that this increase has been more pronounced in women below 50 years. Especially in Germany and Denmark, but also in Australia, there was a significant 84% increase in patients below 60, with a substantial stable rate in those older than it; however in the USA, such a pattern was not noticed [106, 107, 109, 110].

These epidemiological data underline the importance of the ISSVD (International Society for the Study of Vulvovaginal Disease) in vulvar disease terminology [111]. Since its foundation in 1970, the ISSVD set the terminology of preneoplastic vulvar lesions as one of its missions, with dedicated committees composed by gynecologists, pathologists, dermatologists, and other specialists. It is clear from the different ISSVD vulvar disease's classifications that not only preneoplastic lesions must be distinguished from nonneoplastic ones, but also that in the former there are different origins (squamous and non-squamous epithelial origin). As a final point, among vulvar squamous intraepithelial lesions (VSIL), ISSVD always underlined the two different precursor lesions of invasive squamous cell carcinoma of the vulva [112].

The most recent ISSVD classification has been published accordingly with these points: VHSIL (vulvar high-grade squamous intraepithelial lesion) is the precursor of HPV-related vulvar squamous cell carcinomas (VSCC), and differentiated VIN (vulvar intraepithelial lesion) is the precursor of non-HPV-related VSCC [113] (Table 4.1). The VSIL classification includes VLSIL (vulvar low-grade squamous intraepithelial lesion), and it clearly underlines that it includes flat condyloma or HPV effect and it is not precancerous and does not need to be treated, unless symptomatic.

The two types of VSCC and its precursors differ in epidemiology, clinical presentation, histopathology, and molecular profile.

HPV-unrelated VSCC (Fig. 4.5) accounts for more than 70% of the cases, while its underdiagnosed precursor, differentiated VIN (DVIN) (Fig. 4.6), represents less than 10% of all diagnosed VSIL [114]. These neoplasms occur at an older age, in patients with a long-lasting history of itching and burning, in a background of chronic dermatologic disease, in most instances lichen sclerosus or lichen planus. HPV-unrelated VSCC and DVIN will not be prevented by HPV vaccination. Only

Table 4.1 2015 ISSVD Terminology of vulvar SILs (from Bornstein et al. [113])

LSIL of the vulva (vulvar LSIL, flat condyloma, or HPV effect)
HSIL of the vulva (vulvar HSIL, VIN usual type)
DVIN

SIL squamous intraepithelial lesion; *LSIL* low-grade SIL; *HPV* human papillomavirus; *HSIL* high-grade SIL; *VIN* vulvar intraepithelial neoplasia; *DVIN* differentiated-type VIN

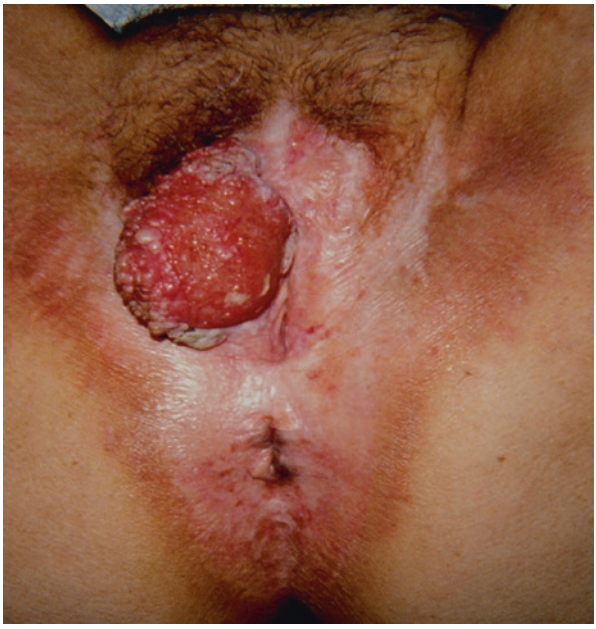

Fig. 4.5 Vulvar cancer. Notice the background of lichen sclerosus

an appropriate examination of the vulva, and biopsy with no delay in suspect cases, can increase DVIN diagnoses, reducing the incidence of invasive cancer.

VHSIL, on the other hand (Fig. 4.7), occurs at younger ages: van de Nieuwenhof et al. found in a series of 1,893 cases of VSIL a median age of 47.8 years (Table 4.2). In this same study, it was described that the incidence almost doubled (from 1.2/100.000 to 2.1/100.000) from 1992 to 2005 [115]. Increasing age in VHSIL

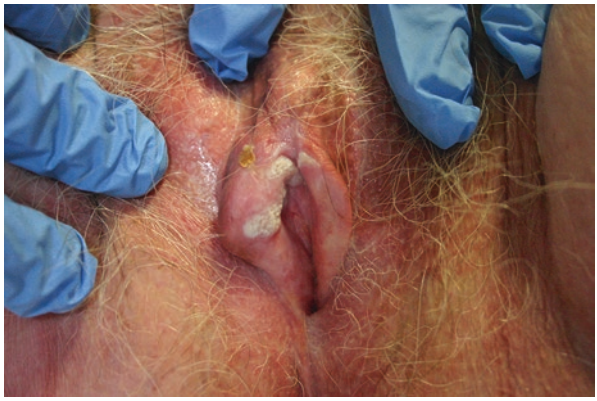

Fig. 4.6 Differentiated VIN, in a background of lichen sclerosus

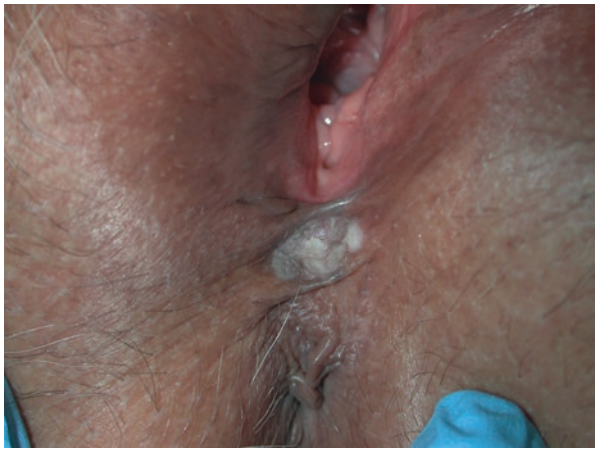

Fig. 4.7 Vulvar high-grade squamous intraepithelial neoplasia

Table 4.2 Age of diagnosis of intraepithelial lesions and invasive cancer

	HSIL (-IN2 or IN3)	Invasive cancer
Cervix [17, 154, 155]	25–41 years old	35–55 years old (>15% in women older than 65 years old)
Vagina [88, 93, 94]	VaIN2—47.2 years old VaIN3—61.8 years old	65–80 years
Vulva [39]	40–44 and >55 years old	55–75 years
Anus [142, 145, 156, 157]	43–49 years old	55–65 years old

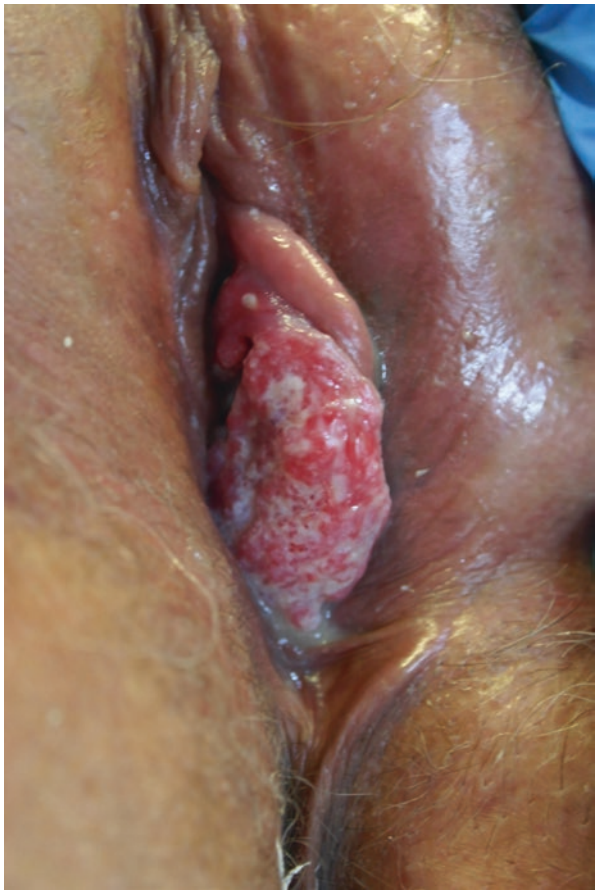

Fig. 4.8 Vulvar squamous cell cancer, HPV-related

patients is associated with higher risk of subsequent diagnosis of VSCC (2.7% if <29 years vs. 8.5% if>75 years) and shorter time of progression (50 months for the <29-year group vs. 25 months for the >75-year group) (Fig. 4.8) [116].

Older age is statistically associated with increased prevalence of stromal invasion in patients undergoing surgical excision after an office biopsy of VHSIL (4.2% in patients younger than 42 years, 10.8% in patients between 43 and 62 years, and 18.3% if older than 62 years) [117].

VHSIL can be located around the introitus, often involving the labia minora and majora. They are usually elevated, sharply defined lesions with normal surrounding skin/mucosa. Lesions can be brownish, white, or red (Fig. 4.5).

HPV16 is the most prevalent HPV type in VHSIL (about three-quarters of all HPV-positive cases), followed by HPV 33 and HPV18 [114] confirming the potential of nine-valent HPV vaccine to eradicate the majority of VHSIL [5].

Multifocality (more than one lesion on the vulva) and multicentricity (involvement of vagina, cervix, and/or anus as well as the vulva) are common and indicate a decreased immune response to HPV infection, with the same HPV type involved in

all the lesions [116]. Younger patients have a higher risk of multifocal lesions (59% in women aged 20–34 and 10% in patients >50 years of age), but older patients have more often intraepithelial lesions at uncommon sites (vagina, anus, and periurethral region) [118].

Treatment of DVIN must be surgical excision, as it has a high potential of progression and it can occur in a very short time. These women must have a close follow-up, as there is a high risk of recurrence [119–121].

Therapy of VHSIL has to take into account (1) characteristics of the lesion (size, configuration, location, multifocality, and multicentricity); (2) characteristics of the patient (age, general condition, symptomatology, associated disease, psychologic issues, work environment, and reliability to follow-up); and (3) available resources and medical skills [122].

Surgery still represents the standard of treatment, with similar results and recurrence rate independent of the technique used (cold knife, LASER, radiofrequency surgery). Many medical treatments have been attempted to avoid surgery in these women. To date, no medications are approved by the Food and Drug Administration (FDA) for this purpose. Several randomized trials have shown imiquimod to be a promising therapy in selected patients [123, 124]. Anyway when, in controlled studies, conservative treatments of VHSIL are chosen, it is of utmost importance to exclude the presence of foci of stromal invasion that exposes patients at risk for metastatic spread to lymph nodes (higher risk if older patients or periclitoral localization) [117].

In the treatment of invasive VSCC that typically occurs in the seventh decade, when comorbidity is common, various conservative and individualized approaches have been proposed to reduce the risk of mutilating en bloc surgery while maintaining oncological radicality and not compromising patients' recurrence-free survival [125–127].

Based on the 1983 definition proposed by the ISSVD, FIGO stage Ia or superficially invasive carcinoma identifies tumors invading the stroma to a depth no greater than 1 mm, with extremely low risk of lymph nodes metastases. These are the only cases where surgical assessment of nodal status can be omitted [128].

For stages higher than Ia, separate incisions for vulva and groins are now considered a standard approach. Radical removal of the tumor can be achieved through a local excision, removing 1–1,5 cm of clinically clear surgical margins in extension and a depth reaching the perineal membrane; the results of this approach are comparable to those of total vulvectomy [129].

Lymph node status is the single most important predictive factor for survival; and nodal recurrence is lethal within 2 years in most patients [130]. The different approaches to inguinofemoral lymphadenectomy must match correct nodal assessment and reduced immediate and long-term morbidity [131].

Sentinel lymph node dissection (SLND) seems to be reliable and safe in early disease [132]. This technique requires specific equipment, a multidisciplinary team (medical physicists and nuclear medicine physicians), and a learning curve for the surgeon. As a consequence, SLND should not be routinely employed by surgeons outside referral centers.

In locally advanced disease [133], new regiments of chemotherapy combined with radio/brachytherapy are promising therapies for this group of patients that usually has a very poor 5-year survival rate [134–137].

There is increasing evidence that HPV-associated VSCC are less aggressive. Recent studies are focusing on p16 overexpression as a prognostic biomarker in VSCC [138]. Other studies showed significant association between p16 expression and improved survival [139, 140].

These promising results have no current impact in the treatment of HPV-associated and HPV-independent VSCC [141], and further cooperative studies are needed to establish HPV status as prognostic factor as in patients with oropharyngeal, anal, and cervical cancers.

4.6.3 Other

4.6.3.1 Anus

Anal cancers are rare (2:100,000 women), but its incidence, and especially that of anal HSIL, has been rising in last decades. Around 90% of anal cancers are HPV-related, having anal HSIL (anal intraepithelial neoplasia [AIN]2-3) as its precursor [142–145]. Anal and cervical cancer share several features, including the existence of a transformation zone, highly susceptible to HPV infection.

While its prevalence is higher in men who have sex with men and immunosuppressed people, the higher number of diagnosis is performed in women—most of them postmenopausal [146]. Women with history of another HPV-related cancer have a three times higher risk of developing an anal cancer [143]. Screening strategies for anal cancer are not yet widespread. In women, the following are likely to benefit from anal cancer screening: HIV patients, organ transplant recipients, past or current history of other intraepithelial neoplasia or cancer (cervical, vaginal, vulvar, or multiple) [142].

Anal cytology seems to be a good option to perform screening in high-risk populations; its low sensitivity precludes its use in low-risk populations. Sampling can be done using a moistened Dacron swabs or cervical brushes. For an optimal specimen, it should be introduced about 4–5 cm into the anal canal and rotated. Classification of the specimens is made according to the Bethesda classification for cervical cytology [142]. The threshold for high-resolution anoscopy is ASC-US.

4.6.3.2 Head and Neck

The list of risk factors for head and neck cavity cancers has included, as most relevant, smoking and alcohol consumption. However, cancers from the oropharynx (tonsils and base of the tongue) do not share these risk factors but rather are HPV-related—especially with HPV16—which is the isolated genotype in 90% of the cases. They have a better prognosis and a better response to chemotherapy and radiotherapy [147, 148]. The relation between HPV and oral cavity cancers in other sites is less clear [149].

While the incidence of other head and neck cancers has been decreasing, in parallel with the decrease in smoking, the ones possibly associated with HPV infection are on the rise. Currently, the latter may represent at least half of the cases [150].

The prevalence of HPV in the mouth ranges between 2 and 8%, with HPV16 being the most prevalent. The infection is less prevalent in women and more frequent in those who engage in oral-genital sex, who are immunosuppressed, or smokers [149]. The reservoir for the infection seems to be the gingival junction [149, 151].

Woon et al., in line with the terminology used for the anus and lower genital tract, have recommended the use of the designation "HPV-associated oral intraepithelial neoplasia" for the dysplastic changes related to HPV and found in the mouth and associated with increased risk for invasive cancer [152].

Currently, there is no recommendation to screen for oral HPV, and no HPV tests have been approved by the FDA for that effect. In a systematic review of studies involving HPV-positive head and neck cancers, the sensitivity of HPV tests was limited (72%, 95% CI 45–89%) [153].

4.7 Conclusion

The burden associated with HPV infection goes far beyond that of cervical cancer. There are lots of suffering—both physical and psychological—associated with this infection. A simple positive HR-HPV test, even in the absence of lesions, can raise several questions and doubts. The practitioner must be prepared to give these answers, finding balance between tranquilizing the patient and, at the same time, not missing relevant disease.

Older women may feel not to be at risk for HPV infections, if they are on a monogamous relationship or have no sexual partner. However, the role of latent and reactivated infections is more and more acknowledge and precludes stopping the screening, even in these patients.

As we anticipate the end of cervical cancer, as a consequence of HPV vaccination, in the next decades we will still have large cohorts of unvaccinated women. Any future programs must take this into consideration.

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Sporadic Ovarian and Fallopian Tube Cancer in Postmenopausal Women

5

Faustino R. Pérez-López

Abbreviations

AMH	Anti-Müllerian hormone
BMI	Body mass index
COCs	Combined oral contraceptives
EOCs	Epithelial ovarian carcinomas
EPIC	European Prospective Investigation into Cancer and Nutrition
HR	Hazard ratio
IGF	Insulin growth factor
IGFBP	Insulin growth factor binding protein
MHT	Menopausal hormone therapy
MRI	Magnetic resonance imaging
NSAIDs	Nonsteroidal anti-inflammatory drugs
OC3	Ovarian Cancer Cohort Consortium
OCs	Oral contraceptives
PCOS	Polycystic ovary syndrome

5.1 The Burden of Ovarian Cancer

Ovarian cancer is the female genital malignancy that causes the majority of deaths in developed countries. Its high mortality is largely related to its late diagnosis basically due to the lack of presenting early symptoms and the low effectiveness of screening methods [1–4]. Furthermore, the screening of asymptomatic women

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without a genetic predisposition does not decrease mortality. In fact, it increases risks in healthy women who undergo unnecessary surgery [2], which itself can increase morbidity and mortality [5, 6].

The incidence of ovarian cancer has decreased during recent years in countries in which there have been changes in reproductive-related factors. Indeed, for instance, more women have used oral contraceptives (OCs) for long periods [7]. On the other hand, knowledge regarding the pathogenia of serous carcinomas has improved. Pathology assessment has included the study of the fallopian tube, which has implications related to the incidence, management, and prevention of ovarian cancer [8]. In addition, the introduction of updated therapeutical strategies has been associated to a slight decrease in ovarian cancer mortality rate [9]. However, worldwide, the frequency of the different types of ovarian cancer (with different prognosis and risk factors) varies amply, and this may influence survival estimations for all combinations of ovarian cancer [10, 11].

This chapter will examine the evidence regarding protective and risk factors for sporadic ovarian cancer in postmenopausal women as well as risk-reducing strategies.

5.2 Fallopian Tube, Ovarian, and Peritoneal Carcinogenesis

Ovarian cancer is a heterogeneous group of malignancies more frequently encountered in peri- and postmenopausal women. Ovarian cancer types include (1) epithelial ovarian carcinomas (EOCs) (90%), usually observed in postmenopausal women; (2) germ cell carcinomas (4%), more frequent in adolescents and women in their early 20s, although they may also develop at any age; (3) stromal carcinomas (teratomas, dysgerminomas, and endodermal sinus tumors), generally diagnosed at early stages; (4) and other primitive and metastatic malignant tumors, which are less common.

EOCs derive from the epithelium of the ovarian surface; nevertheless, new evidence suggests that they may arise from endometrial tissue or the epithelium of the fallopian tube. This new paradigm has set changes in the classification of cancer extension, in terms of tumor rupture or surgical spilling and abdominal dissemination [12].

There are currently two types of EOCs in terms of clinical and molecular characteristics. Type I includes low-grade serous, clear-cell, low-grade endometrioid, mucinous cancers and Brenner tumors, which have relatively stable molecular and genetic properties. Type II includes high-grade epithelial serous, high-grade endometrioid, and undifferentiated cancers and mixed mesodermal malignancies. These have allowed genetic stability and a high frequency of p53 mutations and are initiated from extra-ovarian tissue, mostly the fallopian tubes [12–15].

Magnetic resonance imaging (MRI) may characterize ultrasound-indeterminate adnexal masses and differentiate benign versus malignant masses [16, 17]. In addition, MRI has been suggested for the early diagnosis of primary fallopian tube cancer and to differentiate from primary ovarian cancer, although typical images are not always present [18, 19].

Nearly a 10% of ovarian cancers are related to genetic factors, mostly being related to mutations of the BRCA1 and BRCA2 genes. Other mutations (PTEN mutation of the Cowden syndrome, Lynch syndrome, and Peutz-Jegher syndrome) are less frequent. The Lynch syndrome increases lifetime risk by 4.3% for ovarian cancer [20]. The majority of women with risk of hereditary cancer are managed with surgical interventions (bilateral oophorectomy with or without hysterectomy and salpingectomy) that are carried out in young women during the premenopausal years, in their late 30s or early 40s. Therefore, they are usually treated early, before the appearance of cancer.

5.3 Age and Familial Risks

With few exceptions, ovarian cancer risk increases with age. Presentation is dominated by two age profiles. The *first* corresponds to cancers that originate from germ cells and stromal tissue; this type of presentation is generally observed in adolescents and young women (<30 years). The *second* corresponds to EOCs that appear in postmenopausal women, often in their 70s or 80s [21].

A family history of ovarian cancer (and related syndromes) is the most prominent risk factor. Hence, the presence of an ovarian cancer in one first-degree relative increases women's lifetime risk by 5%; the risk increases up to 7% if there are two such relatives [22]. The risk is also high in families with hereditary breast and ovarian cancer syndromes in association with autosomal dominant mutations of the BRCA1 and BRCA2 genes.

The preventive management of gynecological cancer risk in gene-mutated syndromes includes bilateral salpingo-oophorectomy; basically in the majority of consenting women who have achieved reproductive aims. In some particular syndromes, in which endometrial cancer risk is increased, hysterectomy is added to salpingo-oophorectomy.

5.4 Reproductive Factors

5.4.1 Menarche and Menopause

Some reproductive factors are non-modifiable. Age at menarche, age at first full-term pregnancy, and spontaneous and induced abortion have a small or nil effect over the risk of ovarian cancer [23]. The results of the European Prospective Investigation into Cancer and Nutrition (EPIC) study and a large Korean prospective cohort failed to find an association between age at menarche and ovarian cancer risk [23, 24]. However, a meta-analysis of case-control studies reported an inverse association between age at menarche and ovarian cancer risk [25].

Reports indicate that there may be a relationship between a late onset of menopause and ovarian cancer risk [26]. The number of menstrual cycles may correlate with ovarian cancer risk. Thus, older age at menopause onset was a risk factor for

ovarian cancer in both the EPIC study [27] and a Korean prospective cohort [24]. It has been suggested that women who have a longer exposure to ovarian hormones (menstrual cycles ≥40 years) have an increased risk of ovarian cancer.

The anti-Müllerian hormone (AMH) is a marker of ovarian reserve, and in experimental conditions, it inhibits the growth of ovarian tumors. Nevertheless, in nine cohorts of premenopausal women, AMH levels were not associated with ovarian cancer risk. Indeed, ovarian cancer risk was similar when comparing the highest with the lowest quartile of AMH levels (there was no inverse association between pre-diagnostic AMH levels and ovarian cancer risk) [28]. It seems that hormones involved in the menstrual cycle have limited influence in carcinogenesis. The current view regarding ovarian cancer is that its origin is from multiple cell types and that many malignant precursors are outside the ovaries (see Sect. 5.2 about Carcinogenesis), with several steps occurring many years after the menstrual cycles are over. This evidence seems to reduce the importance of hormones in the origin of malignant ovarian tumors.

5.4.2 Pregnancy and Breastfeeding

In a case-control study of women living in Massachusetts or New Hampshire, multiparity (≥3 vs. 0 children) had a strong and inverse association with an increased risk of type I ovarian cancers [29]. Wentzensen et al. [30] reported a detailed analysis regarding reproductive factors in relation to the histologic subtypes from the large Ovarian Cancer Cohort Consortium (OC3), including 1.3 million women from 21 studies. This study reported that a higher parity was associated with a lower relative risk for endometrioid and clear-cell carcinomas.

A recent Australian population-based study reported that increased parity was associated with a reduced risk of high-grade serous ovarian cancer in women without a personal history of breast cancer; however, the "protective" factor was not present in women with a history of a previous breast cancer [31].

A history of gestational diabetes mellitus has been related to a higher risk of female malignancies, including ovarian cancer [32]. Studies indicate that prepregnancy obesity yields a higher cumulative risk of ovarian cancer after adjusting for different confounding factors, including gestational diabetes and maternal age [33].

Women who breastfeed for more than a year have a reduced ovarian cancer risk [34]. A meta-analysis of observational studies found a protective effect of breastfeeding against EOCs as compared with never breastfeeding; in addition, there was a 0.5-fold decreased risk [35].

5.4.3 Hormone Contraception

OCs reduce the risk of any cancer, and the protective effect is strengthened for both ovarian and endometrial cancers when duration is taken into account [7, 8, 36, 37]. In the large (46,022 women) UK Royal College of General Practitioners' Oral

Contraception Study, with four decades of follow-up, the incidence risk ratio was significantly reduced with OC use [36]. Combined oral contraceptives (COC) reduce the risk of EOC.

A meta-analysis of case-control and cohort studies reported a significant reduction in ovarian cancer risk whenever-users are compared to never users. In addition, there is a reduction of more than 50% in the incidence when use is 10 or more years [38]. However, COCs do not seem to reduce the incidence of mucinous tumors [39], and the use of progestin-only contraceptive pills does not seem to provide protection against ovarian cancer risk [40].

The protective effect of OCs is closely related to the dose of estrogen and treatment duration, although there is no accumulative effect of estrogen intake [40], and the protective effect is not reduced with increasing attained age [41]. COC use before the first full-term pregnancy has a protective effect on the risk of EOC. A case-control study of invasive EOCs in parous women aged 40 or more years reported a 9% risk reduction in those who had used combined contraceptives before their first birth, suggesting a protective effect long after hormones were used [42].

There is also a significant inverse association between BRCA-related ovarian cancer risk and the use of COCs. This effect is similar when women are analyzed separately among carrying BRCA1 or BRCA2 mutations [43].

As mentioned above, the use of progestogen-only contraceptive pills does not seem to provide protection against ovarian cancer risk [40]. Despite this, the levonorgestrel-releasing intrauterine system decreases the risk of mucinous, endometrioid, and serous ovarian carcinomas [44].

5.4.4 Menopause Hormone Therapy

The incidence of EOC has been related to the use of menopausal hormone therapy (MHT). The worldwide reduction in the prevalence of ovarian cancer during the last decade has been linked with the decline in MHT use, although no causal relationship between MHT use and ovarian carcinogenesis has been demonstrated [45–47].

New publications are now focused on the controversy related to the link between menopause hormone treatments (with interactions with other factors) and ovarian cancer risk. A population-based study addressed the issue regarding long-term MHT use in women aged 50–64 years [48]. In this study, female ovarian cancer risk was increased in long-term MHT users, suggesting a role for hormones in the carcinogenesis that should be considered at the time of prescribing MHT.

A population-based Finnish National study evaluated all women aged over 50 during the period 1995–2007 (receiving menopause hormone therapy) with EOC by histologic subtype, comparing one case with three controls matched for age and place of residency and excluding controls with oophorectomy. The use of estradiol alone for 5 years or more was associated with a significant higher risk of serous ovarian cancer subtype, but with a reduced risk of the mucinous subtype. The sequential treatment of estradiol-progestin for 5 years or more was associated with

an increased risk of overall cancer risk, especially increasing the endometrioid subtype. On the contrary, the use of continuous estradiol-progestin, estradiol + intrauterine levonorgestrel intrauterine system, or tibolone had no significant effect on overall ovarian cancer risk [49]. Therefore, only sequential use of estradiol + progestin increases the overall risk of ovarian cancer.

A subsequent study from the same research group reported the incidence of primary fallopian tube cancer and the use of hormone therapy in women aged 50 or older, which was identified from the Finnish Cancer Registry, excluding cases with a previous salpingectomy [50]. The use of 5 years or more of estradiol combined with the levonorgestrel-releasing intrauterine system and the use of sequential estradiol and progestin treatment were both associated with an increased risk of fallopian tube cancer. On the contrary, the treatment with only estradiol or continuous estradiol and a progestin did not increase the risk of the cited cancer.

5.4.5 Assisted Reproductive Technology

There is controversy regarding any possible increase in ovarian cancer risk in women subject to assisted reproductive technology. It is likely that medication used for fertility treatments may increase the risk of borderline ovarian tumors [51, 52]. However, results seem to depend on the fact of achieving or not pregnancy. It seems that women who are successfully treated for infertility and give birth do not display an increased ovarian cancer risk, when compared to those that remain nulliparous. The latter women have a higher risk of EOCs. Another explanation could be that infertility, *per se*, and not the used treatment, be the cause of an increased ovarian cancer risk [53].

5.4.6 Tubal Ligation, Salpingectomy, and Hysterectomy

Fallopian tube ligation and hysterectomy (if performed before age 35) reduce the risk of EOC, particularly non-serous cancers [54, 55]. An Australian Cancer Study, a Danish register-based case-control study, the OC3, and the Million Women Study reported that tubal ligation has different preventive effects according to histologic types, with protection being higher for high-risk serous, endometrioid, and clear-cell carcinomas, while results are controversial regarding mucinous carcinomas [29, 30, 56–58].

The effect of salpingectomy on ovarian cancer risk has been compared to that achieved with tubal ligation. Madsen et al. [57] and Falconer et al. [59], respectively, reported that salpingectomy reduced EOC in the Danish register-based case-control study and in a national US population-based study. Results suggest that opportunistic bilateral salpingectomy, aimed at removing the site where ovarian cancer might originate, should be recommended when women are hysterectomized due to benign conditions and among those seeking tubal ligation [14, 60].

Opportunistic salpingectomy should be encouraged instead of tubal ligation or performed at the time of hysterectomy in order to reduce the risk of future fallopian

and ovarian cancers. However, data of large prospective studies are not available to confirm the value of opportunistic salpingectomy in the prevention of ovarian cancer. On the other hand, there are ongoing trials comparing the effect of salpingectomy (without oophorectomy) with delayed oophorectomy in BRCA mutation carriers [61].

Reports indicate that hysterectomy in young women due to benign conditions, with conservation of the fallopian tubes and the ovaries, may also reduce the risk of ovarian cancer [29, 54, 55]. However, there is no sense of performing a hysterectomy while preserving the fallopian tubes, if childbearing is over. Therefore, it is recommendable that hysterectomy be carried out with concomitant opportunistic salpingectomy. In addition, surgery for pelvic floor disorders treated by hysterectomy can include vaginal opportunistic salpingectomy excision [62–64]. Opportunistic distal salpingectomy can also be performed during a cesarean section in women who are sure they have completed their family [65].

The safety of opportunistic salpingectomy has been confirmed in large cohorts [66]. However, the confirmation of the real value of opportunistic salpingectomy in the prevention of ovarian cancer may require a 20–30-year follow-up. On the other hand, salpingectomy has also been challenged as a risk-reducing intervention [67].

5.5 Anthropometric Variables

5.5.1 Body Weight

Birth weight has not been associated with ovarian cancer risk [68]. Prospective studies assessing the effects of body fat at ages 5 and 10, body mass index (BMI) at age 18, and other anthropometric measures have reported a small relationship between height and EOC risk [69].

Data from the large prospective EPIC cohort indicate that obesity (BMI $\geq$30.0 kg/m^2 vs. <25 kg/m^2) is associated with an increased EOC risk, although the association was weaker in pre- versus postmenopausal women. Height, weight gain, and fat distribution were not associated with an increased risk, although waist-hip ratio was associated with a higher risk of mucinous tumors [70]. Results from the Nurse's Health and Women's Health Initiative (WHI) cohorts failed to demonstrate any influence of obesity over ovarian cancer risk [71, 72]. A recent study among African American women pointed out that ovarian cancer risk was significantly elevated in women with a BMI $\geq$40 kg/m^2 as compared with those with a BMI <25, and there was an association between this cancer risk and weight gain after age 18 comparing the highest versus the lowest quartile. In postmenopausal women (MHT users and nonusers), ovarian cancer risk increased by 15% per 5 kg/m^2 increase of BMI or 6% per 5 kg of weight gain [73].

Despite this, a later meta-analysis of 47 studies reported a 12% increase in EOC risk for obese women (>30 kg/m^2), after adjusting for different confounding factors such as MHT use [74]. Furthermore, a more recent meta-analysis of prospective studies found a non-linear increase in ovarian cancer for each 5 units of BMI

increase. This rise started with a BMI of 28 kg/m^2 and higher. In addition, there was no association between ovarian cancer and weight gain, hip circumference, or waist-hip ratio [75]. It is important to note that obesity does not seem to increase the risk of the most aggressive (or lethal) cancers and that associations are similar among MHT users and nonusers [76].

Adult weight gain has been related to female endocrine-related cancers, particularly among non-MHT users. Thus, a meta-analysis found that for each 5 kg increase in adult weight, ovarian cancer risk increased in postmenopausal women, both in low MHT and non-MHT users [77]. These results suggest the importance of preventing weight and obesity in young women.

The links between obesity and higher ovarian cancer risk are probably mediated by alterations in sex steroid hormones, insulin- related alterations and inflammation. Excessive weight has been related to invasive endometrioid, low-grade invasive serous, and invasive mucinous ovarian carcinomas as well as borderline serous tumors. In addition, the risk is similar in postmenopausal MHT users and nonusers.

These studies provide evidence that excessive body weight is a modifiable risk factor for ovarian cancer, especially among postmenopausal women.

5.5.2 Height

It has been suggested that altered insulin growth factor (IGF) 1 levels may influence early-life body size and adulthood cancer risk. In the two cohorts of the Nurses' Health Study, height was associated with an increased relative risk of EOC [69]. A pooled analysis of 12 prospective cohorts that collectively included more than a half million women from North America and Europe reported that taller women (>1.69 m vs. <1.60 m) have an increased EOC risk (both pre- and postmenopausal), while there was no statistical difference observed between those with increased BMI compared to those with a normal BMI (BMI >29.9 kg/m^2 vs. 18.5–23 kg/m^2) [78].

A meta-analysis of case-control studies found that IGF-1 and IGF binding protein-3 levels were lower in patients with ovarian cancer [79]. Another meta-analysis (of prospective studies) reported that there was no significant influence of IGF-1/IGF binding protein-3 on the ovarian cancer risk [80].

5.6 Diet, Physical Activity, and Other Modifiable Lifestyle Factors

5.6.1 Diet

Some diets have been postulated to protect against cancer. For example, the Mediterranean diet might decrease the incidence of various cancers by genomic actions and by increasing levels of the sex hormone-binding globulin [81, 82]. However, there is no significant evidence demonstrating that the adherence to the Mediterranean diet reduces ovarian cancer risk [83].

A potential link between the dietary inflammatory index and the risk of EOC was analyzed among African American women. A 10% increase in EOC risk was observed for each unit change in the energy-adjusted dietary inflammatory index, and this association was higher in women aged over 60 [84].

In a randomized controlled trial of postmenopausal women, the adherence to a low-fat diet for 4 years decreased ovarian cancer risk [85]. One meta-analysis found that egg consumption was related to ovary cancer, although the dose-response was unclear. A significant effect of egg intake on ovarian cancer has been reported in case-control studies, but not in cohort studies [86].

Studies related to the vitamin D endocrine system and carcinogenesis have produced controversial results. In vitro studies suggest that vitamin D may have a role in cancer prevention. Results from observational clinical studies are masked by confounding factors. However, Ong et al. [87] reported a significant association between decreased vitamin D levels in Europeans and ovarian cancer risk. They used a Mendelian randomization assessment to overcome the usual statistical errors observed in conventional studies. However, further studies are needed before recommendations can be proposed regarding vitamin D supplementation and ovarian cancer risk.

Studies analyzing the association between dietary intake of acrylamide and EOC risk have not been able to demonstrate any effect [88]. In a large prospective Japanese cohort, no association was observed between acrylamide and ovarian cancer [89]. Other dietary components have not been associated with ovarian cancer risk, including the intake of fiber or of curcumin or a high-starch diet, although there might be several confounding factors that have not been taken into account.

5.6.2 Physical Activity

The effect of recreational physical activity on ovarian cancer risk is inconclusive or controversial [90]. The protective effect of recreational physical activity is more consistent among case-control studies, while benefits have been reported in some cohort studies [91]. Nevertheless, recent evidence shows that physical inactivity is independently associated with an increased risk of some particular histologic subtypes of EOC [92]. A prospective study assessing the effect of physical activity on ovarian cancer risk found that in premenopausal women risk increased with low to high levels of cumulative physical activity, while physical activity was not associated with ovarian cancer in postmenopausal women [93]. These investigations, not completely comparable, provide controversial results that do not currently allow providing recommendations regarding the preventive effect of physical activity on ovarian cancer risk.

5.6.3 Perineum Exposure to Body Powder and Vaginal Douching

There is some evidence from case-control studies that the use of powder on the perineum (genital powder) is associated with an increased EOC risk, but the data are

conflicting. The modest increased risk seems to be for invasive serous, endometrioid, and clear-cell carcinomas and borderline tumors in genital but not in non-genital powder users [94]. The same study found no significant trend in the risk with increasing number of lifetime applications of genital powder. Despite this, a case-control study of Afro-American women showed a dose-response effect for duration and the lifetime number of applications of genital powder and EOC risk. In addition, non-genital powder use was linked to non-serous EOC [95]. A recent meta-analysis of case-control and cohort studies reported that perineal talc use increases ovarian cancer risk. In addition, this increased risk was significant for serous and endometrioid subtypes, although not for mucinous or clear-cell subtypes [96].

The prospective cohort Sister Study (involving 50,884 women with a sister with breast cancer) found little association between baseline perineal talc use and subsequent ovarian cancer. Douching was more common among talc users, and douching at baseline was associated with an increased subsequent risk of ovarian cancer. The authors of the Sister Study concluded that douching, but not talc use, was associated with an increased ovarian cancer risk [97].

5.6.4 Alcohol, Coffee, and Tea Consumption

Alcohol consumption does not seem to influence ovarian cancer risk [98, 99]. However, low alcohol consumption may reduce the risk of ovarian cancer, but this may depend on the type of alcohol and the age at which it was consumed [100]. Red wine consumption protects against ovarian cancer risk as compared with nonconsumption, but the consumption of white wine, beer, or spirits does do not confer protection. The protection conferred by red wine is greatest when consumption is initiated before the age of 50 [101].

It seems that coffee or tea consumption may not reduce EOC risk [102]. However, higher black tea intake may have a protective effect against several cancer variants [103]. A Danish case-control study reported that coffee consumption and total caffeine consumption (combination of tea and coffee) were associated with a small reduction in ovarian cancer risk [104]. However, a Canadian study did not find any effect of coffee, tea, and caffeine intake on the ovarian cancer risk [105].

5.6.5 Cigarette Smoking

Cigarette smoking has been associated with certain histologic subtypes of ovarian cancer [106]. The large Norwegian-Swedish Women's Lifestyle and Health cohort analyzed national registries according to different measures of smoking exposures and adjusted for confounding factors. This study found that women who smoked for more than 20 years had three times the risk of developing borderline EOCs as compared to never smokers, and there was an almost significant relation for mucinous

tumors. In addition, there was also a significant dose-response effect with smoking intensity and duration for both borderline and serous tumors [107].

The same authors reported new information from the Norwegian cohort regarding smoking and primary invasive and borderline tumors by histologic types [108]. Current smokers who had smoked for more than 10 years had a very much higher risk of developing mucinous ovarian cancers than never smokers, but smoking was not associated with serous or endometrioid ovarian cancers. The OC3 reported that smoking 20 packs/year was associated with an increased risk of mucinous cancers and a decreased risk for clear-cell cancers [30].

In Afro-American women, smoking was associated in a higher degree to serous ovarian cancer than for all types of ovarian cancers. In addition, compared to never smokers, serous ovarian cancer risk was increased in lifetime ever smokers, in former smokers who quit within 0–2 years of diagnosis, and in relation to total pack-years smoked among lifetime smokers. In addition, smoking was not associated with mucinous ovarian cancer [109].

5.6.6 Nonsteroidal Anti-Inflammatory Drugs and Analgesic Treatment

Nonsteroidal anti-inflammatory drugs (NSAIDs) and some analgesics may have chemopreventive actions against cancer from different organs. Pooled data from population-based and case-control studies of ovarian cancer reported that aspirin use was associated with a lower ovarian cancer risk, while non-aspirin NSAIDs and acetaminophen use was not. In addition, the reduction of cancer risk was strong with daily aspirin use as compared with other dosages, while for non-aspirin NSAIDs, the risk reduction was strong for high-dose use [110]. The same authors also reported a prospective analysis of the OC3 regarding analgesic use and ovarian cancer risk. They analyzed data from 13 studies, finding that women who use aspirin daily have a slightly lower risk of developing ovarian cancer than infrequent/nonusers [111]. This result was similar to the risk reduction observed in case-control analyses.

Low-dose aspirin (150 mg/day for ≥5 years) may reduce the risk of EOCs in terms of histological types, the strongest inverse associations observed for mucinous and endometrioid tumors [112].

The African American Cancer Epidemiology Study on the EOC risk analyzed the effect of aspirin and non-aspirin NSAIDs and acetaminophen use on ovarian cancer risk [113]. The study found that NSAIDs (aspirin and non-aspirin) significantly reduced this risk, while acetaminophen had no protective effect. It is likely that ovarian follicle rupture during ovulation releases fluid containing prostaglandins and other compounds that induce inflammation [114], which can potentially be neutralized by NSAIDs. Therefore, small doses of NSAIDs may be a preventive intervention for women at high risk of ovarian cancer. In addition, it seems that

anti-inflammatory drugs may improve ovarian cancer prognosis when used along with chemotherapy [115].

5.6.7 Occupation Risk Factors for Ovarian and Primary Fallopian Tube Cancer

The risk of EOC was examined according to occupation in a Canadian population-based case-control study, adjusting for confounders (BMI, OC use, menopause hormone therapy, previous genital surgery, among others). The authors reported an increased risk of EOC for teaching and related occupations, bookkeepers and accounting clerks, and educational service and noninstitutional health service employees [116].

An Australian population-based case-control study assessed the association of lifetime environment ultraviolet radiation exposure and both invasive and borderline ovarian cancers in women aged 18–79 years. Women in the highest tertile of daily average of environment radiation exposure were at the lowest risk of EOCs than those in the lowest tertile [117]. This study suggests that there is an inverse association between ovarian cancer risk and ultraviolet exposure.

In a Scandinavian study, correlation between occupation and the risk of primary fallopian tube cancer was reported among 2206 cases and more than 50 occupations [118]. The authors found that the risk of primary cancer was significant among smelting workers, artistic workers, hairdressers, packers, nurses, shop workers, and clerical workers. These findings were sustained for the different included countries. The risk was significantly low for farm-working women, painters, and chemical process workers.

5.7 Comorbidity and Ovarian Cancer Risk

5.7.1 Endometriosis

Women who had endometriosis during their reproductive years are at a higher risk of developing endometrioid and clear-cell tumors (type I EOC) [29]. The older a woman is when ovarian endometriosis is diagnosed, the higher the risk of ovarian cancer [119]. An international collaborative investigation comprising 13 case-control studies reported an association between a history of endometriosis and an increased risk of clear-cell, low-grade serous, and endometrioid invasive cancers, while there was no association with the risk of mucinous or high-grade serous invasive ovarian cancers or borderline serous and mucinous tumors [120].

There is evidence for shared genetic risk between endometriosis and almost all histologic types of ovarian cancer. The strongest correlation is between endometriosis and clear-cell carcinoma and endometrioid and low-grade serous carcinomas,

while high-grade serous carcinoma (which often arises from the fallopian tubes) had a weaker genetic correlation with endometriosis [121]. These findings suggest shared genetic susceptibility factors.

A meta-analysis reported that endometriosis was associated with an increased risk of EOC, and tubal ligation had a protective effect [80]. In that review, hysterectomy did not have any significant effect on ovarian cancer risk in women with endometriosis. The relationship between endometriosis and malignant transformation to ovarian cancer may be related to epigenetic factors exerting effects over the ectopic endometrium [122].

To date, the protective role of opportunistic bilateral salpingectomy among women with previous endometriosis has not been specifically addressed.

5.7.2 Pelvic Inflammatory Disease

Pelvic inflammatory disease/salpingitis increases the risk of serous borderline and invasive ovarian cancers [123–125]. An Australian population-based study reported an increased risk of high-grade serous ovarian carcinoma associated with pelvic inflammatory disease, but not with infertility or the diagnosis of endometriosis [31]. This data support the participation of inflammatory processes in the carcinogenesis of some epithelial ovarian cancers.

Although there are no reports addressing the value of salpingectomy in women with inflammatory adnexal processes, salpingectomy might exert the same protective role as it does in women without an inflammatory process.

5.7.3 Long Menstrual Cycles and Polycystic Ovary Syndrome

Long and irregular menstrual cycles and polycystic ovary syndrome (PCOS) were not initially related to ovarian cancer risk; however, when histologic subtypes were taken into account in the analysis, menstrual cycle irregularities among women who had never used oral contraceptives and those who were overweight were associated with a reduced risk of high-grade serous EOCs and an increased risk of serous borderline tumors [126].

The association between lifetime number of ovulatory cycles and epithelial ovarian cancer risk has been reported, supporting the hypothesis that incessant ovulation contributes to the pathogenesis of ovarian cancer [84]. Women with menstrual cycle intervals of more than 35 days have a lower risk of invasive ovarian cancer in comparison with those reporting cycle lengths of $\leq$35 days. Also women with irregular menstrual cycles have a lower risk of invasive ovarian cancer as compared to those women with regular cycles [127].

A meta-analysis of few observational studies in women <55 years suggests that PCOS did not increase ovarian cancer risk [128]. Ovarian cancer risk does not seem to be increased in women with PCOS [127].

5.7.4 Epithelial Ovarian Borderline Tumors

A significant number of epithelial ovarian borderline tumors are diagnosed at early stages, and fertility-sparing surgery can be used in women without children and those with localized tumors [129, 130]. However, tumor recurrence may affect 10–18% of patients who retain ovarian tissue [131, 132], and it seems that mucinous tumors have a higher recurrence risk than serous types [128]. Therefore, pregnancy should be attempted as soon as possible, in women who wish to do so. However, there is no clear evidence that radical treatment, hysterectomy, or bilateral salpingectomy reduces the risk of recurrence or malignant progression.

5.7.5 Previous Malignant Diseases

Girls and women who had suffered a germ cell tumor are more prone to have a second malignant ovarian cancer [133]. An Australian population study reported that breast cancer increases the rate of high-grade serous ovarian cancer threefold [31].

5.8 Conclusions

To date, ovarian cancer screening and early diagnosis are not feasible. There are some general recommendations (Table 5.1) from the current knowledge based on risk and protective factors. The use of combined oral contraceptives for more than 5 years, salpingectomy, and hysterectomy may reduce the risk of ovarian cancer. Prevention of obesity and weight gain may also contribute at reducing ovarian cancer risk. Reproductive factors, such as parity and breastfeeding are individual

Table 5.1 Risk and protective factors for ovarian cancer

Risk factors	Protective factors
Increased age	Breastfeeding (>1 year)
Family history (first degree) of ovarian cancer: BRCA1-2 mutations; Cowden syndrome, Lynch syndrome	Multiparity (>3 births)
Height (taller women)	Combined oral contraceptives
Obesity (>29.9 kg/m^2) but more important ≥40 kg/m^2	Fallopian tube ligation or salpingectomy
Increase in adult body mass index (>5 kg/m^2)	Hysterectomy
Diet with a high inflammatory index	Low-fat diet for at least 4 years
Physical inactivity	Red wine
Exposure to talc powder	Black tea
Smoking	Nonsteroidal anti-inflammatory drugs (aspirin and non-aspirin)
Endometriosis	
Pelvic inflammatory disease	
Previous history of epithelial ovarian borderline tumor	

elections. Factors related to healthy lifestyles such as physical activity, alcohol consumption or smoking, body talc use, and moderate red wine and NSAIDs consumption may be a part of general health recommendations. Patients with a history of endometriosis, pelvic inflammatory disease, and ovarian borderline tumors should be appropriately treated and followed up.

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Vulvar Dermatoses and Menopause

6

Joana Lyra and Pedro Vieira-Baptista

6.1 Introduction

Vulvar dermatoses are inflammatory conditions, frequently associated with itching and burning. Concomitant extragenital involvement may also be present in some cases. The diagnosis is usually clinical. Occasionally, there can be superimposed or associated conditions, such as lichen simplex chronicus and lichen sclerosus, which can add to the diagnostic challenge [1].

Vulvovaginal symptoms such as pruritus, pain, and dyspareunia are a common cause for gynaecological referral. They are estimated to affect, approximately, one in five women [2]. Considering that these symptoms are often chronic, with a gradual onset and persistence over time, one must always consider the presence of dermatologic conditions as a cause. The initial approach to these complains should always include a systematic physical examination and an inquiry about symptoms onset, duration, location, aggravating and alleviating factors, as well as possible precipitating or known risk factors [3]. Although the diagnosis may be complex, mainly when different conditions coexist, a systematic evaluation of the symptoms may simplify this process. The challenge of diagnosis in postmenopausal women is aggravated, as the signs and symptoms of vulvovaginal atrophy can overlap with those of a dermatosis—and both situations often coexist. More recently, the creation of the "genitourinary syndrome of menopause" increased the risk that vulvar diseases will be missed or ignored and thus not receive appropriate management [4].

Vulvar dermatoses can be subdivided in nonscarring, e.g. atopic and contact dermatitis and lichen simplex chronicus, and scarring dermatosis, e.g. lichen sclerosus

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and lichen planus. The International Society for the Study of Vulvovaginal Diseases (ISSVD), in 2006, divided vulvar dermatoses into eight different histological patterns: spongiotic, acanthotic, lichenoid, dermal homogenization/sclerosis, vesiculobullous, acantholytic, granulomatous, and vasculitic [5]. This classification was aimed at being clinically practical and transversal to all medical specialities working in the field. When the clinician is able to directly make a diagnosis, there is no need to resort to the classification. When that is not the case, a biopsy can be taken, and two new scenarios arise: either the pathologist provides a diagnosis or he is unable to do so and categorizes it into one of those patterns. In the latter case, the clinician evaluates again the clinical aspects inside that pattern and may reach a diagnosis [6].

In 2011, a new ISSVD terminology was approved, based on clinical findings (colour, type of dermatological lesion [pustules, patches, ulcers, etc.], surface, margination, and configuration). This approach leads to eight morphological groups (skin-coloured lesions, red lesions [patches and plaques], red lesions [papules and nodules], white lesions, dark-coloured lesions, blister, erosions and ulcers, and oedema), narrowing the diagnostic options [7]. In our opinion, both documents are useful and complimentary in daily clinical practice.

In this chapter, the most common vulvar dermatoses (Table 6.1) encountered in postmenopausal women will be discussed, including lichen simplex chronicus, lichen sclerosus, lichen planus, psoriasis, and atopic and contact dermatitis.

6.2 Vulvar Dermatoses

6.2.1 Lichen Simplex Chronicus

Lichen simplex chronicus (LSC) is a nonscarring, chronic inflammatory skin disorder, representing the most common symptomatic vulvar condition. It is considered a localized variant of atopic dermatitis, and in 65–75% of patients, a history of an allergic condition can be identified [3]. LSC accounts for up to 35% of patients' visits to vulvar specialty clinics, but its prevalence remains unknown. It can be found at any age, but it is typically more common in mid- to late adult life [8].

The cardinal symptom is intense pruritus, worsening during the night and that may disturb sleep [1]. It can first be triggered by a wide variety of initiating processes that cause skin irritation, such as environmental factors (e.g., clothing, chemical, heat, perspiration), infections (e.g. candidosis), and other vulvar dermatoses (e.g. lichen sclerosus), as well as neurological and psychiatric disorders that promote repetitive scratching. In any case, an itch-scratch cycle is promoted which leads to skin thickening and additional irritation. Besides pruritus, women usually complain about pain associated with the excoriations from the scratching process [3]. Scratching is described as relieving or even pleasuring—but inevitably followed by worsening.

On physical examination we can observe (Fig. 6.1) erythematous or white lichenified plaques with irregular borders, with or without excoriations, that

Table 6.1 Comparison of vulvar dermatosis in menopause

	Presentation	Lesion characteristics	Histopathologic pattern (ISSVD 2006)	Treatment
Lichen simplex chronicus	Intense pruritus, worsening during the night, pain Sometimes asymmetrical	Erythematous or white lichenified plaques and/or excoriations in labia majora Hypopigmented areas that can become hyperpigmented	*Acanthotic pattern*	1. Avoidance of irritants, barrier protection 2. High potency topical corticosteroids 3. Antihistamines, tricyclic antidepressants, or selective serotonin reuptake inhibitors 4. Calcineurin inhibitors
Lichen sclerosus	Pruritus and/or burning in the vulvar and perianal area Pain, soreness, dyspareunia, and dysuria	Reddish papules/ivory patches, hyperkeratosis Fissures, erosions, ulcerations, oedema, hypo-/hyperpigmentation "Figure of 8" or "key hole sign" Introital stenosis, phimosis, fusion and resorption of the labia minora	*Lichenoid pattern* *Dermal homogenization/ sclerosis pattern*	1. Avoidance of irritants, barrier protection 2. High potency topical corticosteroids 3. Calcineurin inhibitors 4. Antihistamines, tricyclic antidepressants 5. Systemic treatments: steroids + methotrexate, retinoids methotrexate alone and cyclosporine
Lichen planus	Dyspareunia, burning, vaginal discharge, and postcoital bleeding	White, reticulate, lacy, or fernlike striae (Wickham striae) adjacent to erythematous epithelium Pruritic, purple, shiny papules Vaginal involvement Synechiae, obliteration of the vagina	*Lichenoid pattern*	1. High potency topical corticosteroids 2. Calcineurin inhibitors, systemic steroids, immunomodulators, methotrexate, and retinoids

(continued)

Table 6.1 (continued)

	Presentation	Lesion characteristics	Histopathologic pattern (ISSVD 2006)	Treatment
Psoriasis	Chronic pruritus Usually there are typical lesion in other anatomical areas	Bright red, sharply demarcated lesions Silver scales are often absent and can only be apparent in the mons pubis	*Acanthotic pattern*	1. Low and medium potency topical steroids 2. Emollients, topical vitamin D analogues, and calcineurin inhibitors
Atopic and contact dermatitis	Acute or chronic pruritus	Acute eczema: erythema, oedema, vesicles/papules Chronic eczema: excoriations and dry scaly lichenification of the vulva	*Spongiotic pattern*	Elimination of irritants and/or allergens
Vulvovaginal atrophy	Dryness, irritation, dyspareunia, dysuria, and vaginal discharge	Loss of vaginal rugae, shortened vaginal length and width Increases the laxity of the introitus, reduction in the width of labia minora, preserving its length	–	1. Avoidance of contact irritants 2. Vaginal moisturizers and low-dose vaginal oestrogen preparations

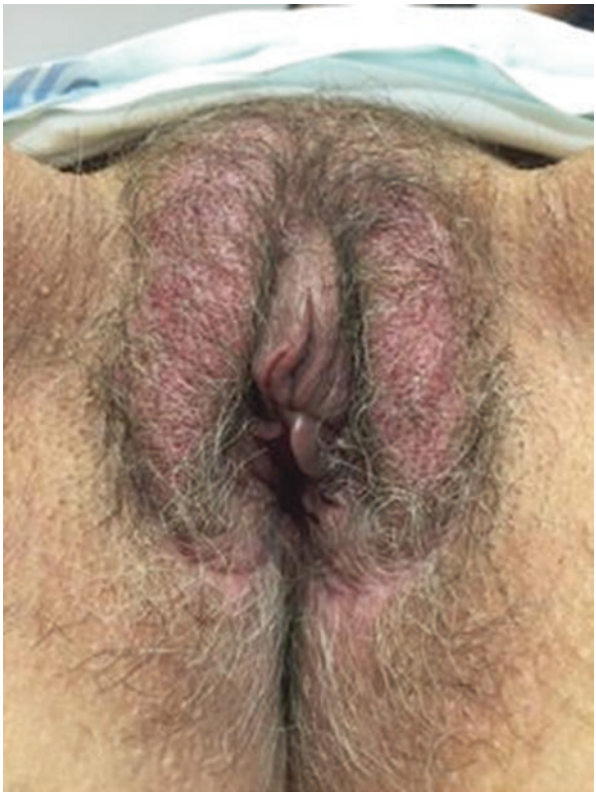

Fig. 6.1 Lichen simplex chronicus. Bilateral involvement of the labia majora

commonly involve the labia majora and are mostly asymmetric (usually more pronounced on the dominant side) (Fig. 6.2). It can also present as hypopigmented areas that can later may become hyperpigmented, as consequence of the inflammatory process in long-standing disease. The diagnosis is based on clinical presentation, leaving the biopsy for exceptional cases. Because LSC can disrupt the normal skin barrier, there may be superimposed infections, namely, fungal.

The treatment should involve a multitargeted approach with removal of irritating factors, repair of the skin's barrier function, reduction of inflammation, and disruption of the itch-scratch cycle [1]. Concerning genital hygiene, avoidance of irritants and use of barrier protection (e.g. zinc oxide ointment) should be advised. Considering pharmacological options, moderate to high potency topical corticosteroids in an ointment base are the cornerstone of the treatment, such as clobetasol propionate (applied daily while the symptoms are intense and then for 1 more month). In severe cases the use of calcineurin inhibitors can be considered. For disruption of the itch-scratch cycle and to improve sleep quality, a combination of antihistamines (hydroxyzine), tricyclic antidepressants (amitriptyline), or selective serotonin reuptake inhibitors (fluoxetine, paroxetine) can be used.

As this may be a recurrent disease, maintained treatment may be needed in some cases. Eviction of triggers is of utmost importance to avoid recurrences.

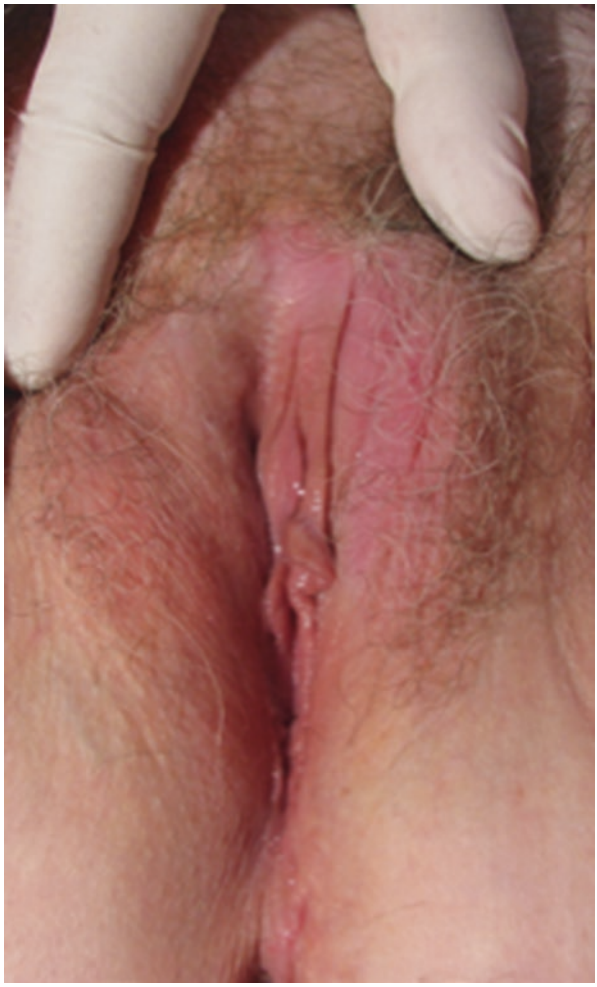

Fig. 6.2 Lichen simplex chronicus, predominantly on the left side

6.2.2 Lichen Sclerosus

Lichen sclerosus (LS) is a chronic inflammatory disease that affects the genital and perianal areas. Extragenital lesions can be found in about 11–20% of patients (mainly in the chest, upper back, arms, neck, and buttocks) [9]. The true prevalence of LS remains unknown, but recent data showed that it is more common than previously described, with a prevalence of 1:60 [10], and when considering older populations, it can be as high as 1:30 [11]. It can be seen at any age, but usually the distribution of prevalence has two peaks: one prepubertal (7–15% of all cases) and the other at the fifth and sixth decades of life, comprising the majority of cases [12].

While there are several risk factors and conditions known to be linked to LS, its aetiology is still not completely understood [1]. Its association with autoimmunity is well recognized, particularly with thyroid disease (until 30%), but also other disorders,

such as alopecia areata, pernicious anaemia, morphea, vitiligo, diabetes mellitus, inflammatory bowel disease, celiac disease, and psoriasis. Autoantibodies are frequently positive—extracellular matrix 1 protein, anti-basement membrane, and antithyroid antibodies. There is also a genetic association, with a positive familial history in 17% of cases. The hormonal milieu has also been implicated, with hypoestrogenism and a diminished number of androgenic receptors considered to be possible contributing factors—however, lack of response to hormonal treatments (such as oral contraceptives and menopausal hormone therapy) gives no consistency to this theory [13]. The presence of traumatic lesions induced by burning, friction, and scars is a frequent target to the appearance of LS lesions—Köbner or isomorphic phenomenon [12].

The most common symptomatology is vulvar pruritus and/or burning sensation in the vulvar and perianal area, worsening at night time. Some women also refer pain, soreness, dyspareunia, and dysuria. They may present scratching habits, but they do not refer relief with it, contrary to what happens in LSC. They can, however, develop LSC secondary to the repetitive scratching. It is important to recognize that at least 15–40% of the women are asymptomatic [10, 14].

Physical examination may reveal reddish papules or ivory patches, with hyperkeratosis that can coalesce and form plaques, usually symmetrical. It is also common to find fissures, petechiae, purpura, erosions, ulcerations, oedema, hypo- and hyperpigmentation, and "cigarette paper wrinkling" aspect of the skin (Fig. 6.3).

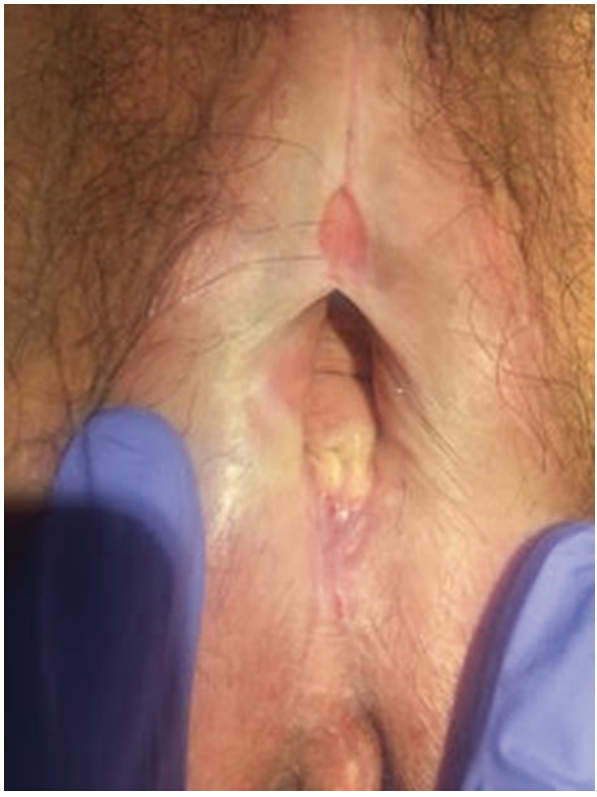

Fig. 6.3 Lichen sclerosus. Atrophy of the labia minora, phimosis, cigarette paper wrinkling, and hypopigmentation

The lesions are typically confined to hairless vulvar areas (inner portion of labia majora, labia minora, vestibule, clitoral hood) and frequently (30%) perianal area. When there is simultaneous involvement of vulva and perianal area, a "figure of 8" or "key hole sign" is the characteristic observed feature (Fig. 6.4). In cases of long-standing disease, radical anatomical changes can occur, such as introital stenosis, phimosis, fusion (Fig. 6.5), and resorption of the labia minora, with both a reduction in width and length (in senile atrophy of the labia minora, usually the length is preserved), and all these alterations can be asymmetrical. Vaginal involvement is exceptional and seems to be associated with vaginal walls prolapse (Fig. 6.6) [15].

Sexual dysfunction is common among women with LS. Dyspareunia and symptoms derived from distortion of the vulvar anatomy are frequently referred. The phimosis and consequent burying of the clitoris can lead to the formation of smegmatic pseudocysts that can become enlarged, painful, and infected. Also, the formation of synechiae over the urethral meatus or the fusion of labia minora can cause urinary stream alterations and recurrent urinary tract infections (Fig. 6.5).

The most fearful complication of LS is vulvar intraepithelial neoplasia (VIN) and vulvar cancer. Although LS is not considered a premalignant condition, it has

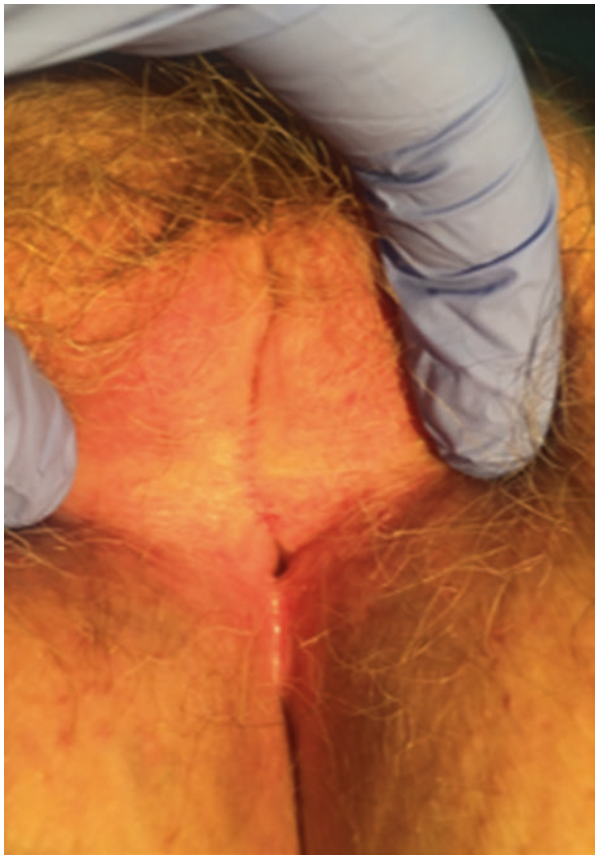

Fig. 6.4 Lichen sclerosus. "Figure of 8" or "key hole sign"

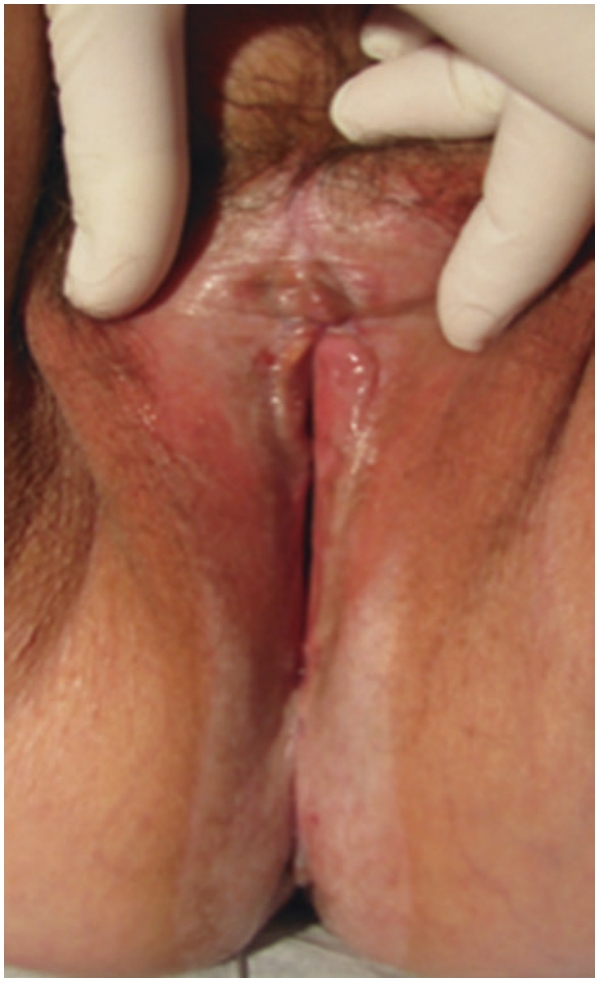

Fig. 6.5 Lichen sclerosus. Almost complete fusion of the labia minora

been associated with an increased risk of keratinized vulvar squamous cell carcinoma (2.6–6.7%) [12, 16]. The truly premalignant lesion associated with LS is VIN, differentiated type (dVIN). It is much rarer (2–10%) [17] than the HPV-associated vulvar high-grade squamous intraepithelial neoplasia (HSIL), but it is responsible for the majority of vulvar cancers. Those are indolent lesions, with a 10-year risk of progression estimated in 18% [12].

The diagnosis of LS is clinical. While some authors recommend routine biopsy in all cases, most disagree and recommend it only in cases of treatment failure, when second-line therapy is needed, or to exclude dVIN or cancer. Suspicious lesions that should prompt a biopsy are erosions/ulcers, hyperkeratosis, or pigmented areas. It is important to note that biopsy does not guarantee a final diagnosis of LS, especially in patients already under steroid treatment. Of note, the same area or lesion may have to be biopsied along the time, if suspicion persists [12].

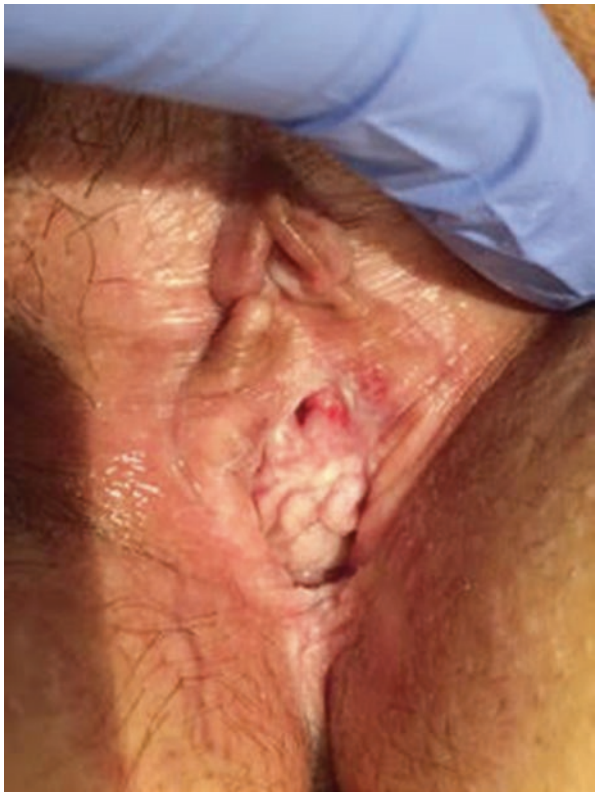

Fig. 6.6 Lichen sclerosus. Unusual case of LS with involvement of the anterior vaginal wall

As part of the autoimmune diseases workout, we recommend routine testing of thyroid function, including T4, TSH, and thyroid antibodies [12].

The treatment aims to control the symptoms, prevent anatomical distortion, and diminish the risk of malignancy. In about one-fifth of the cases, total remission can be observed [18]. Women compliant to the prescribed treatments are less likely to develop vulvar cancer, reinforcing the importance of treating even asymptomatic women and leading to the discussion on the need of maintenance therapy in asymptomatic women [1, 18, 19].

1. General care: it is essential to break the itch-scratch cycle to minimize all possible trauma to the genital area. As so, it is important to advise against multiple washing and use of irritating products (soaps) and to avoid factors that can worsen the symptoms (urinary incontinence, menstruation).
2. Topical treatments: ultra-potent topical steroids are the mainstay of the treatment for LS. Clobetasol propionate (CP) ointment 0.05% is the most used one, and its efficacy is due to anti-inflammatory, vasoconstrictor, and antipruritic proprieties. The authors advocate a scheme of application of CP once a day for 4 weeks, followed by once every other day for another 4 weeks, and finally twice a week for another 4 weeks, completing 3 months of initial treatment. Afterwards, it should

be used the lowest dose possible for symptomatic control (application 2–3 times a week), with a maximum dosage of 60–120 g/year. Everyday schemes for more than 3–4 weeks are not advised, not only because of the risk of complications but also due to that of tachyphylaxis [20]. As second-line topical treatment—when topical steroids are not well tolerated or there is no response—calcineurin inhibitors can be considered, starting by applying one to two times daily and then reducing the frequency for long-term maintenance. Those are immunomodulators agents that block the release of inflammatory cytokines from T lymphocytes and are efficient in controlling the signs and symptoms of the disease. Moreover, CP is faster in controlling the symptoms and is associated with higher likelihood of achieving complete remission [21].

3. Systemic treatments: reserved for severe LS, nonresponsive to topical treatments. Options include a combination of steroids plus methotrexate, retinoids (acitretin, isotretinoin, or etretinate), methotrexate alone, and cyclosporine. In any case, before initiating one of these options, it is mandatory to have a histological diagnosis. Oral tricyclic antidepressants (amitriptyline, 10 mg), antihistaminic drugs, or local anaesthetics may be used to control the symptoms.
4. Surgical treatment: it should be reserved for the treatment of complications, such as urinary obstruction, introital stenosis, synechiae causing symptoms, and symptomatic smegmatic pseudocysts, or treatment of premalignant or malignant lesions. It is important to note that disease tends to relapse in scars and even in grafted tissue [12].

   A close follow-up is necessary, with the first visit after beginning the treatment no later than 3 months and the following one no longer than 6 months. The goal of treatment should be controlling the symptoms and normalization of skin colour and texture [22]. There is a risk of vulvar cancer throughout the woman's life, which signifies that the follow-up must be kept indefinitely, independently of being symptomatic or not—at least every 6–12 months.

   Recently, there have been some papers suggesting the use of adipose-derived stem cells and platelet-rich plasma and even LASER for the treatment of LS. Up to now, the available evidence does not sustain those claims, and development of LS has even been associated with Nd:YAG LASER therapy for hair removal [23, 24]. In our opinion, and in line with the ISSVD and International Continence Society position, these treatments should be avoided and only used in the context of clinical trials [25].

6.2.3 Lichen Planus

Lichen planus (LP) is an inflammatory disorder that affects mucocutaneous tissues. Vaginal involvement is common, as well as that of other non-genital regions, including the oral mucosa (Fig. 6.7), skin, nails, oesophagus, and conjunctiva. Among women with oral disease, up to 75% have genital involvement [26]. Vulvovaginal LP can be divided in three forms: erosive LP, papulosquamous LP, and hypertrophic LP. Erosive LP is the most common variant that affects the vulva. The prevalence of

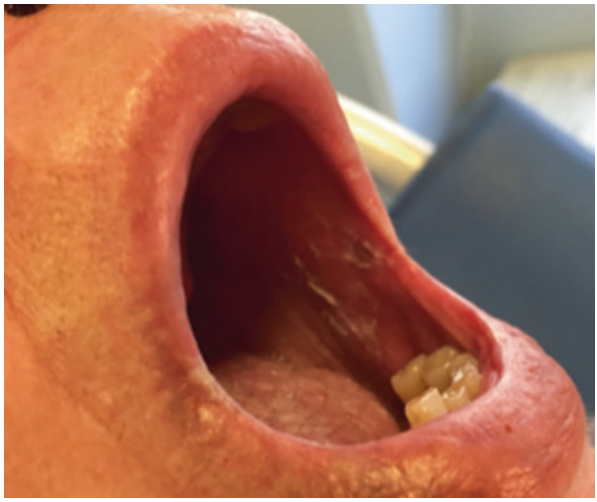

Fig. 6.7 Lichen planus. Oral involvement in a woman who also has vulvar LP

LP is estimated to be of 0.5–3.7% [27], and it mostly affects women between 30 and 60 years old.

LP is considered an autoimmune disease with a T-cell-mediated pathogenesis, and the interaction with some exogenous factors (nonsteroidal anti-inflammatory and antihypertensive drugs and, in oral LP, hepatitis C virus [28]) may also play a role. However, the exact aetiology remains unclear, and despite the associations described, recommendations for screening are lacking in asymptomatic women [1].

The symptoms are similar to those described for LS, namely, dyspareunia and burning. Vaginal discharge and postcoital bleeding are also common complains. On physical examination, the presence of white, reticulate, lacy, or fernlike striae (Wickham striae) adjacent to erythematous epithelium is typical, and they often affect the medial aspect of the labia minora and the vulvar vestibule (Figs. 6.8 and 6.9) [29]. Also, the presence of pruritic, purple, shiny papules may be seen, but they are dusky pink in colour, without an apparent scale and less well demarcated than on other areas of the body. Contrary to LS, vaginal involvement is frequent, and the epithelium can have an erythematous, eroded, and acutely inflamed aspect. The use of wet mount microscopy can be useful to evaluate vaginal involvement and monitor the response to treatment (Fig. 6.10). In the posterior vestibule and labia minora, deep, painful, erythematous erosions may be apparent, and they result in a resorption of labial architecture (Fig. 6.9). These erosive lesions are extremely friable, and, over the time, the surfaces may adhere resulting in synechiae and, eventually, complete obliteration of the vagina [3]. The examination of the oral cavity is mandatory, and in woman with genital LP, up to 70% have oral disease (Fig. 6.7) [30]. There are some cases of asymptomatic disease, but it seems to be rare [31]. The diagnosis is clinical, and biopsy is considered for dubious cases in which it is necessary to rule out neoplastic conditions, in which there is no response to treatment, or when a diagnosis of some autoimmune blistering diseases is also being considered [1].

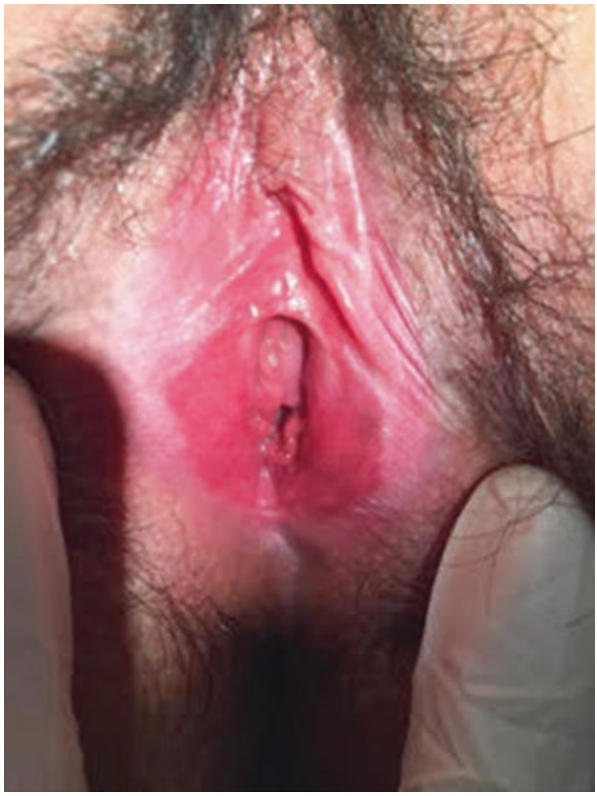

Fig. 6.8 Lichen planus. Erythema of the vestibule and partial resorption of the labia minora

General care management measures are similar to those previously described for LS. If these patients are taking nonsteroidal anti-inflammatory or antihypertensive drugs, if possible, it should be stopped temporarily, to check if there is improvement. The first-line treatment is, as in LS, the ultra-potent topical steroids, and the application scheme could be the same proposed for the treatment of LS. Second-line options include calcineurin inhibitors, systemic steroids, immunomodulators, methotrexate, and retinoids. The use of vaginal dilators may be considered to prevent vaginal adhesions derived from the coaptation of the inflamed vaginal mucosa. It can be coated with a corticosteroid ointment and oestrogen vaginal cream. Usage can be daily or every other day, according to the response [32]. Surgery is reserved to restore the vaginal vault.

The follow-up schedule is similar to that described for LS. In patients with LP, the risk of cancer of the lip, tongue, oral cavity, oesophagus, and larynx is increased [33], but the occurrence of neoplastic transformation for vulvar LP is controversial. The standardized incidence ratio of vulvar cancer in women has been estimated to double in women with LP [33], and these cancers seem to be more aggressive and more likely to recur [34]. A recent study, however, did not observe any case of HPV-independent vulvar squamous cell carcinoma in women with LP [35]. Of note, Preti et al. have associated higher risk of recurrence of vulvar HSIL in women with

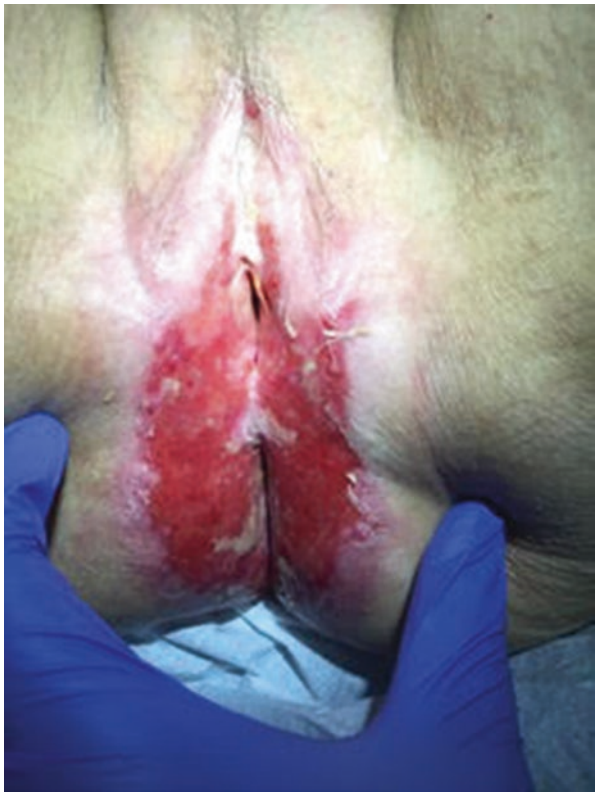

Fig. 6.9 Lichen planus. Extensive involvement of the perianal area

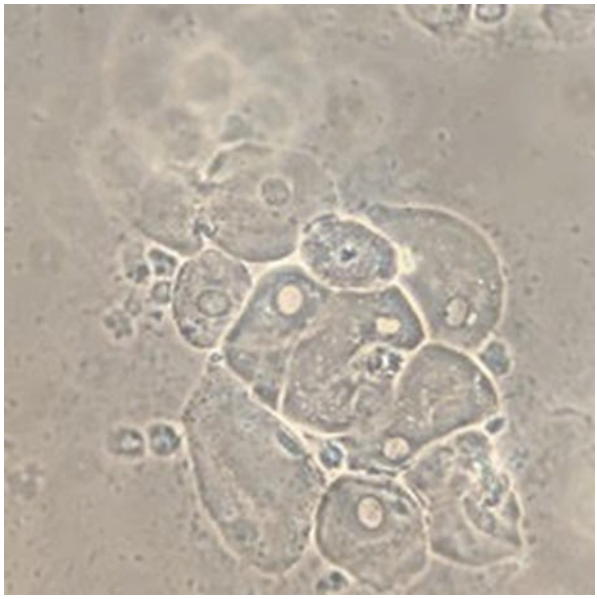

Fig. 6.10 Vaginal involvement by LP in a premenopausal woman. Note the presence of inflammation and parabasal cells (phase contrast microscopy, 400×)

concurrent steroid-treated LP [36], thus highlighting that these women may have increased risk of vulvar cancer through the two pathways (dermatoses and HPV).

6.2.4 Psoriasis

Psoriasis is a chronic inflammatory skin disease with a prevalence of approximately 2% in the general population. This disease has a bimodal onset, but vulvar manifestations can occur in patients of all ages [37].

On physical examination, bright red, sharply demarcated lesions can appear above the surrounding normal skin (Fig. 6.11). Differently from the typical lesions of psoriasis in other areas, the silver scales are often absent and can only be apparent in the mons pubis [38]. The presence of psoriatic lesions on other areas (knees, elbows, gluteal cleft, scalp) suggests the diagnosis. Köebner or isomorphic phenomenon can also be apparent in genital psoriasis. The biopsy should be considered only in difficult cases without a typical presentation and to exclude malignant lesions.

The treatment should stop the itch-scratch cycle, as it contributes to more inflammation. Low to medium potency topical steroids, in combination with steroid-sparing agents, are often used to reduce the inflammation. Second-line treatments

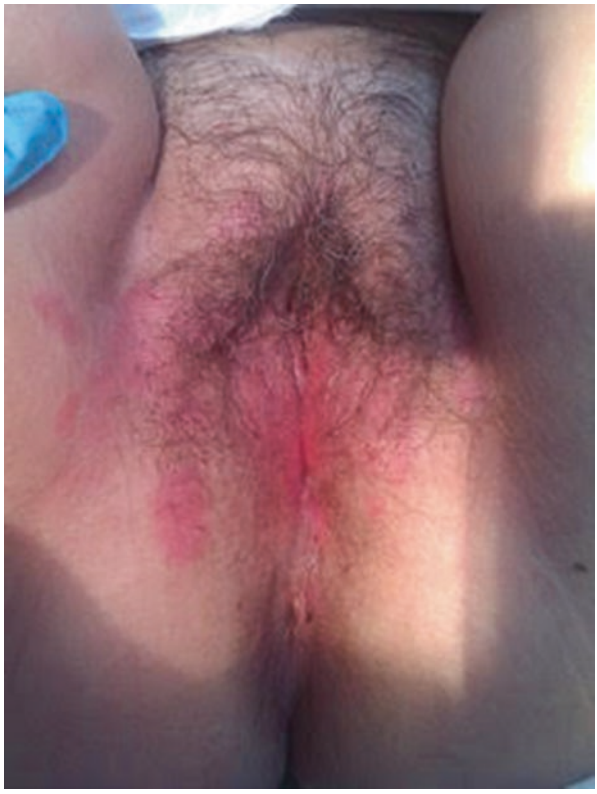

Fig. 6.11 Psoriasis

include emollients, topical vitamin D analogues, and calcineurin inhibitors [38]. In severe cases systemic therapy, including immunosupressants and biologics, may be considered.

6.2.5 Atopic and Contact Dermatitis

Dermatitis or eczema is a poorly demarcated, erythematous, and usually itchy rash that can be found in 20–60% of patients with chronic vulvar symptoms [39].

Atopic dermatitis (AD) is a chronic pruritic skin disorder with multiple clinical presentations according to the age, but the vulvar involvement can be seen both in children and adult women. The true prevalence of vulvar AD is not known. A history of other atopic diseases, such as asthma, can be present. Vulvar manifestations arise from a combination of factors that make this area particularly sensitive to eczema or irritant contact dermatitis when exposed to irritants, such as a deficient skin barrier function and a thin epidermis. The principal symptom referred is pruritus. On physical examination, acute eczema is characterized by erythema, oedema, and vesicles/

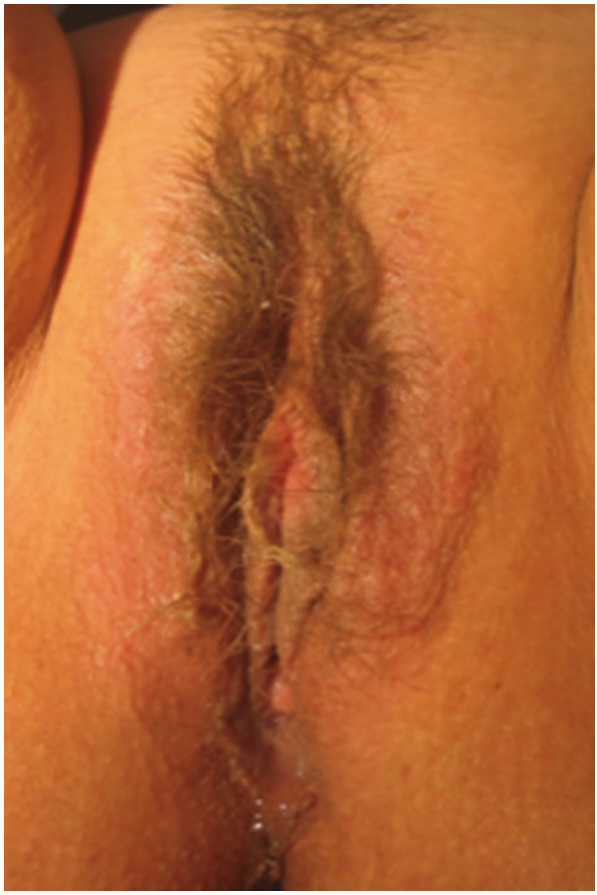

Fig. 6.12 Atopic dermatitis

papules (Fig. 6.12), whereas in chronic eczema, there are excoriations and dry scaly lichenification of the vulva. The presence of typical atopic eczema in other areas suggests the diagnosis. The diagnosis is clinical. Regarding the treatment, median potency topical steroids are the first option. Calcineurin inhibitors may also be used.

Contact dermatitis (CD) may be associated with repeated contact with an irritant or due to sensitization and contact allergy to a specific allergen. A flare-up of the rash after specific exposure should raise the diagnostic suspicion. The main symptoms are pruritus and pain. On physical examination, erythema, vesicles, oedema, and erosions can be found.

Irritant contact dermatitis is the most frequent form of CD, and several factors (e.g. urinary incontinence, detergents, surfactants) have been implicated in causing vulvar eczema. Women with AD are at increased risk for contact dermatitis. One frequent form of irritant contact dermatitis, in middle-age women, is intertrigo. It is caused by increased moisture and friction in the intertriginous areas and that may affect the vulva. Obesity, sweating, poor hygiene, and urinary incontinence are some of the factors associated with it. Intermittent symptomatic treatment with topical corticosteroids is advised.

Allergic contact dermatitis could be nonsystemic or systemic. In the nonsystemic form, many allergens are implicated, and the identification requires a dermatological evaluation with patch testing. Women with vulvar dermatosis have a higher risk of secondary contact sensitization due to locally applied medications (including topical steroids (Fig. 6.13)) and can react with a flare-up vulvar eczema due to contact with products containing the allergen. The systemic form is an allergic type IV reaction in women previously sensitized to a specific allergen, when it is inhaled or injected, resulting in an eczematous reaction. Some of these identified allergens are nickel, chromium, and cobalt that are present in food products as oats, soy, chocolate, nuts, and cocoa.

The therapy for both irritant and allergic contact dermatitis is based on eliminating irritants and/or allergens [40].

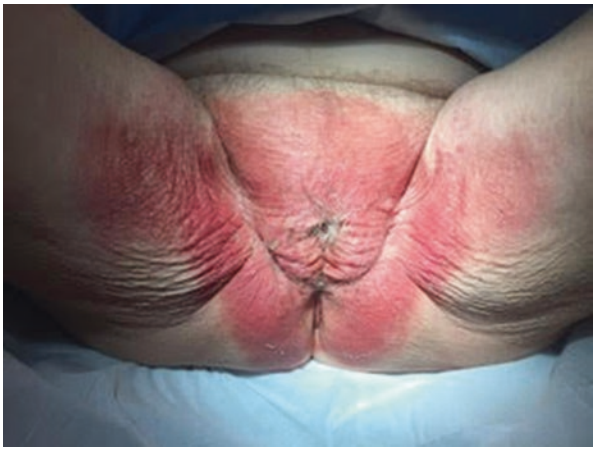

Fig. 6.13 Allergic contact dermatitis (clotrimazole + dexamethasone cream)

6.3 Menopause and Vulvar Atrophy

The urogenital tract is dramatically affected by the hormonal changes that characterize menopause. With lower levels of oestrogens, not only the vagina but also the vulva suffers many changes. In the vagina, mucosal thinning, loss of vaginal rugae, reduced vaginal discharge, shortened vaginal length and width, and elevated vaginal pH (associated with a marked decrease in lactobacilli and an increased diversity of species) can be observed. In the vulva, the skin and vestibular mucosa become thinner, subcutaneous fat decreases, the introitus becomes more lax, sensitivity diminishes, and there is a reduction in the width of the labia minora, with preserved length—contrary to what can be seen in lichenoid dermatosis, in which there is a reduction of both width and length [4].

Some of these changes may also be seen in women with vulvar dermatosis, and, on the other hand, the latter are more common in postmenopausal women [14]. Altogether, this makes the differential diagnosis between vulvar dermatosis and natural changes due to menopause a difficult task.

One of every two postmenopausal women will have vulvovaginal symptomatology attributable to menopause, such as dryness, irritation, dyspareunia, dysuria, and noninfectious vaginal discharge. Those symptoms can appear long after other menopausal symptoms have resolved, and 10–25% of women using systemic hormone therapy can still have urogenital symptoms [41].

Treatment may be initiated according to patient preferences and severity of the symptoms. Avoidance of contact irritants, use of vaginal moisturizers, and low-dose vaginal oestrogen preparations can be used. Vaginal oestrogen application (daily for 1–2 weeks and then two times weekly) has been shown to be safe and effective in the relief of genital symptoms than oral formulations [42].

Conflict of Interest No conflicts of interest to declare.

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Bladder Pain Syndrome/Interstitial Cystitis

7

Rui Almeida Pinto

7.1 Bladder Pain Syndrome/Interstitial Cystitis Introduction

Bladder pain syndrome/interstitial cystitis (BPS/IC) is a chronic visceral painful condition of unknown etiology that affects millions of people worldwide. Symptoms can be so severe that patients with BPS/IC may have quality of life with lower scores than those treated for end-stage renal disease [1].

It was previously known as interstitial cystitis, later as painful bladder syndrome, and since 2008 as bladder pain syndrome/interstitial cystitis in an attempt to include and classify all patients with pain related to the bladder, not necessarily with inflammation coursing the bladder. The European Society for the Study of Interstitial Cystitis (ESSIC) and the Bladder Pain Syndrome Committee of the International Consultation on Incontinence defined BPS/IC as chronic (more than 6 months) pelvic pain, pressure, or discomfort perceived to be related to the bladder, accompanied by at least one other urinary symptom such as persistent urge to void or increased daytime and nighttime voiding frequency, with the exclusion of confusable diseases, namely, infection [2, 3]. The term interstitial cystitis (IC) should be reserved for patients that have typical cystoscopic findings like Hunner's lesions and glomerulations as well as histological evidence of bladder inflammation [2, 3].

Patients with the non-ulcerative phenotype, traditionally viewed as more benign, tend to be younger, have lower urinary frequency, and have shorter duration of symptoms before diagnosis. Pain is frequently described in the literature as more intense in patients with ulcerative phenotype, the more aggressive form. Although attractive it is yet to be shown that the ulcerative form of BPS/IC represents a progression of the non-ulcerative disease or a distinct disease within BPS/IC [4–6].

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7.2 Bladder Pain Syndrome/Interstitial Cystitis Epidemiology

Based on population studies, the prevalence of BPS/IC shows enormous variations. These variations have been attributed to different factors such as definition used, diagnostic tools applied, and population surveyed [3].

The prevalence of BPS/IC ranges between 0.57 and 12.6% depending upon the use of the O'Leary-Sant (OLS) or Pain and Urgency/Frequency (PUF) questionnaires, respectively [7]. BPS/IC has also 30–50 times higher prevalence with these screening tools/questionnaires than with confirmed physician medical history and physical examination [8].

Using OLS questionnaire, prevalence between countries varies, being so low as 20–30 per 100,000 women in Japan and the Netherlands and 300–450 per 100,000 in Austria, Taiwan, Finland, and the USA [9, 10]. Up to 12% of women experience some symptoms during their lifetime [3]. Typically, BPS/IC age of onset is bimodal: between 21–45 and 66–75 years old [8]. Expert opinion leans to accept an average prevalence of 300 per 100,000 women [3]. The prevalence among first-degree relatives of BPS/IC patients can be 17 times higher than in non-related individuals [11].

7.3 Bladder Pain Syndrome/Interstitial Cystitis Pathogenesis

Etiology remains unknown and pathophysiology is probably multifactorial. Up to 50% of BPS/IC patients exhibit chronic inflammation on bladder biopsy [12]. Typical histological findings include abundant inflammatory infiltrates in the bladder urothelium with thinning or erosion, detrusor mastocytosis, granulation tissue, and intrafascicular fibrosis [2]. The presence of mast cell migration is one of the diagnostic criteria for BPS/IC from the National Institute of Diabetes and Digestive and Kidney Disease (NIDDK).

The hypotheses for etiologies of BPS/IC range from unknown infection, immunologic abnormality, autonomic dysfunction, to pelvic floor dysfunction and even sexual abuse [12].

Since the early 1920s and 1930s, bacterial infection was and still is thought to be a significant cause of the changes observed in BPS/IC. However, until now, studies failed to confirm one of the putative bacteria [13].

There is an association of systemic lupus erythematous and Sjogren syndrome with BPS/IC. This fact strengthens the autoimmune disorder as the initial insult [14]. An abnormal expression of HLA-DR molecules by the urothelium and activation of T-helper lymphocytes in patients with BPS/IC may enable these cells to cause destruction of the urothelium [15]. However, no consistent profile of immune activity has been reported.

BPS/IC patients also have increased resting heart rates [16] and increased sensitivity to ischemia [17]. This autonomic dysfunction can be explained by the raise of sympathetic tone without corresponding activation of the hypothalamic-pituitary-adrenal axis

[18]. Moreover, BPS/IC patients have been shown to exhibit high levels of urinary catecholamines and an increase in the number of sympathetic fibers coursing the bladder [19, 20].

BPS/IC patients are often found to have an increased prevalence of conditions such as allergies (up to 70% higher in BPS/IC patients), Sjogren syndrome, or even other somatic or visceral pain syndromes, namely, irritable bowel syndrome, fibromyalgia, dyspareunia, pelvic floor dysfunction, chronic pelvic pain, vulvodynia, and complex regional pain syndrome [21, 22]. The incidence of inflammatory bowel disease was found to be 30 times more common in BPS/IC patients with Hunner's lesions than in general population.

BPS/IC also has been associated with psychiatric illness such as panic disorder. Recently, attention has been drawn to the high prevalence of child abuse in patients with BPS/IC. This is a life event known to be linked with chronic pain development [23].

Higher prevalence of previous pelvic surgery has also been demonstrated among BPS/IC patients [24]. It is therefore possible that, in many patients, surgeries or other unrecognized pelvic insults may be the trigger mechanism to initiate the dysfunction of the pelvic region, mainly in postmenopause patients.

After the initial insult, pathophysiology of BPS/IC involves several modifications. Although histological evidence of edema has never been documented, urothelium suffers several changes, namely, altered permeability, decreased tight junction formation, decreased proliferation, and increased apoptosis [12]. The glycosaminoglycan (GAG) layer is disrupted, thus allowing the adherence of microorganisms and the contact of urinary noxious elements with the urothelium, generating pain [25]. Altered bladder permeability is commonly attributed to reduced tight junction formation. Decreased proliferation and reduced tight junction formation are usually related to increased urinary levels of antiproliferative factor (APF) [26]. In addition, increased apoptosis was also reported, mostly due to an upregulation of inflammatory signals mediated by p38 and TNF-α [27].

Proliferation of sensory nerve fibers also occurs in BPS/IC. In fact, some authors suggested that inflammation and tissue injury generate a significant peripheral sprouting of peptidergic, sympathetic, and parasympathetic fibers, which could be the mechanism responsible for sensitization of the bladder, potentiating pain [28–30]. These phenomena could be correlated with the high levels of vascular endothelial growth factor (VEGF) and nerve growth factor (NGF) found in BPS/IC patients [31].

7.4 Bladder Pain Syndrome/Interstitial Cystitis Assessment

As previously stated, BPS/IC is a condition characterized by chronic pelvic pain, pressure, or discomfort perceived to be related to the bladder. Associated symptoms could be persistent urgency and increased daytime and nighttime voiding frequency. Pain is believed to be the driving symptom for other lower urinary tract symptoms that commonly afflict BPS/IC patients like frequency and nocturia [2]. Pain could be described as a pressure, burning, discomfort, feeling of fullness/distension, soreness, sharp, stabbing, spasm, or dull sensation related to the bladder. Usually related

to the bladder, pain may radiate to the vulva, clitoris, vagina, rectum, perineum, or sacrum and is relieved by voiding. Patients often report numerous pain sites outside the bladder/pelvic region. Visual analog scale (VAS) is a useful tool to grade pain. Cognitive, behavioral, emotional, and sexual consequences of the pain syndrome must also be evaluated. Other pain syndromes associated with BPS/IC such as irritable bowel syndrome, fibromyalgia, and chronic fatigue syndrome should be investigated. Increased numbers of body pain sites are associated with poorer patient outcomes [32]. A general medical history should give special emphasis to previous pelvic operations or radiation treatment, urinary tract infections, and autoimmune or other urologic diseases.

BPS/IC patients usually complain of frequency and nocturia. A 3-day voiding diary with volume intake and output is typically used to assess urinary frequency and maximum functional bladder capacity.

Two questionnaires have been used to assess symptoms and problems of these patients: O'Leary-Sant (OLS) and Pain and Urgency/Frequency (PUF). These questionnaires address urgency, frequency, nocturia, pain, as well as the bothersomeness for those symptoms [33]. The OLS symptom and problem score has been recognized as the most reliable and valid instrument [12]. These questionnaires can be supplemented with the assessment of the quality of life.

Physical examination should be performed, including the lower abdomen for bladder tenderness and mapping pain during inspection. Special attention should be given to the presence of kyphosis, scars, hernia, abduction/adduction of the hips, and hyperesthetic areas.

Bacterial cultures for *Chlamydia trachomatis*, *Ureaplasma urealyticum*, *Mycoplasma hominis*, *Mycoplasma genitalium*, *Corynebacterium urealyticum*, *Candida* species, and *Mycobacterium tuberculosis* should be performed.

BPS/IC patients usually disallow cystoscopy at outpatient clinic. However, cystoscopy with hydrodistension under anesthesia should be carried out to exclude other identifiable causes. Nevertheless, there is no consensus about when it should be performed, immediately at diagnosis [2] or later if patients are refractory to standard management [34]. Bladder signs of BPS/IC are glomerulations and Hunner's lesions. Glomerulations are described as punctate/petechial hemorrhages after hydrodistension. Hunner's lesions are most often recognized on the lateral walls using bladder distension. Before hydrodistension resemble a circumscript inflammatory reaction with radiating small vessels and central scar with fibrin deposit. After distension, Hunner's lesions look like a mucosal rupture with waterfall-like bleeding [12]. Hydrodistension under anesthesia also gives important information about potential functional capacity [12].

Bladder biopsies can be performed during cystoscopy under anesthesia. They are helpful to characterize histologically each BPS/IC patient and to exclude confusable diseases, for example, carcinoma in situ. Common findings include epithelial denudation, submucosal inflammation, granulation tissue, and hemorrhage. More specific findings such as mast cell infiltration and bladder wall fibrosis might also give information about disease severity and prognosis [35]. Up to 50% of BPS/IC patients have normal biopsies [12].

ESSIC, in an attempt to clarify this disease, proposed a classification based on findings during cystoscopy with hydrodistension (presence of Hunner's lesions/glomerulations) and morphological findings in bladder biopsies (presence of inflammatory infiltrates and/or detrusor mastocytosis and/or granulation tissue and/or intrafascicular fibrosis).

Imaging with ultrasound or computed tomography and urodynamics are rarely necessary in BPS/IC.

Potassium sensitivity test or Parson's test consists on instilling a 0.4 Mol solution of potassium chloride (KCL) into the bladder [36]. This test is no longer recommended because of the long-lasting pain persisting after the procedure and its positivity in both healthy and idiopathic overactive bladder patients at this concentration. This test also does not give any information regarding efficacy of treatment and outcome [37].

7.5 Bladder Pain Syndrome/Interstitial Cystitis Management

There is no cure for BPS/IC. Thus the main goal of available treatments is to decrease the intensity of lower urinary tract symptoms, in particular pain. There is a 50% incidence of temporary remission unrelated to therapy, with a mean duration of 8 months. Therefore, a step-by-step approach is recommended (Fig. 7.1).

Stress reduction, exercise, warm tub baths, and efforts by the BPS/IC patient to maintain a normal lifestyle all contribute to improving overall quality of life. Biofeedback, soft tissue massage, acupuncture, and other physical therapies may aid in muscle relaxation of the pelvic floor [38].

Many patients find that their symptoms are adversely affected by specific diets. Nevertheless, diets should be introduced on an individual basis. Triggering food may include caffeine, alcohol, artificial sweeteners, hot pepper, and beverages like cranberry juice that might acidify the urine.

Long-term use of analgesic medications represents a fundamental part of the treatment of a chronic pain condition like BPS/IC. Concerning more specific oriented therapies, few of the oral drugs commonly used have been supported by unequivocal evidence of efficacy in large, multicenter, randomized controlled clinical trials (RCTs). There is little or no evidence that any therapy changes the natural history of the disease. Pentosan polysulfate sodium (PPS) is a heparin-like macromolecule that resembles urothelium GAG and remains the only oral therapy approved by the Food and Drug Administration (FDA). PPS is postulated to act by replacement of the GAG layer as well as by inhibition of mast cell degranulation [39]. However, PPS showed efficacy in 30% of BPS/IC patients after 6 months of medication in its first study [40]. Amitriptyline, a tricyclic antidepressant, has anticholinergic and sedative properties by decreasing 5-hydroxytryptamine reuptake. It stabilizes mast cells and blocks the actions of histamine [41]. Nevertheless, all RCTs conducted with amitriptyline were negative. Only the subanalysis of the RCT conducted by the Interstitial Cystitis Collaborative Research Network (ICCRN) for

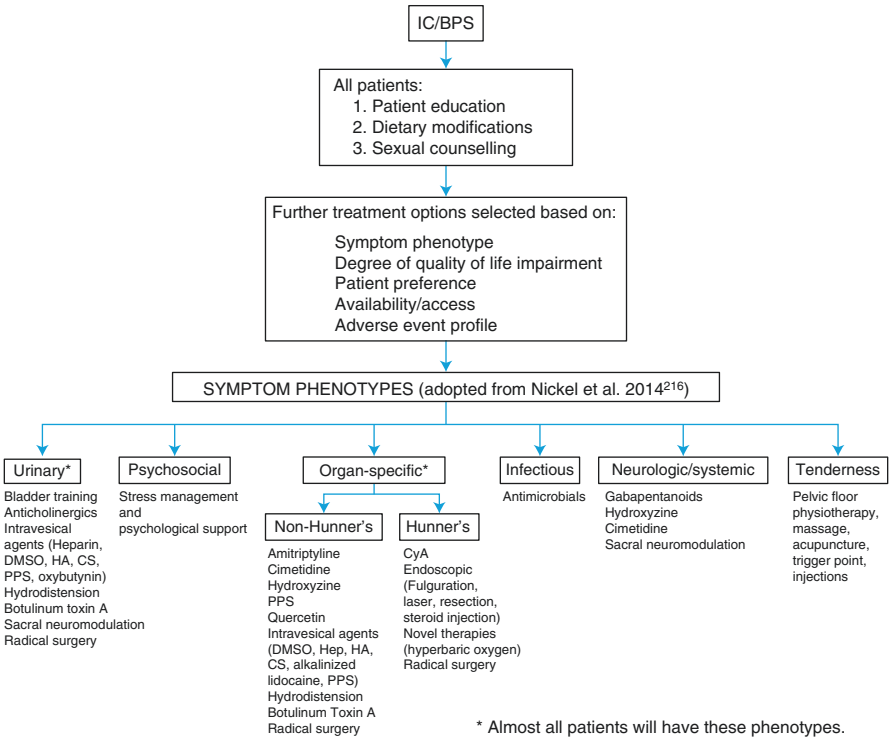

Fig. 7.1 Recently proposed management paradigm for the treatment of IC/BPS according to the Canadian Urological Association

doses above 50 mg/day showed efficacy, however with increased risk of side effects [41]. Hydroxyzine is a H1-receptor antagonist that inhibits mast cells by blocking serotonin release in the bladder. At dosages of 25–50 mg daily, it was suggested to decrease the severity of the symptoms in 40% of patients. In patients that had personal history of allergies, the success rate reached 55% [42]. Again, all RCTs conducted with hydroxyzine were negative [43]. Tanezumab is a humanized anti-NGF monoclonal antibody that binds with high affinity and specificity to NGF, preventing it from interacting with receptors on nociceptive neurons. Tanezumab was investigated for the treatment of BPS/IC pain in a phase 2 RCT against placebo. The modest efficacy (only 50% of patients having a 30% or greater reduction of pain score) and the serious adverse events do not suggest tanezumab as a promising treatment for BPS/IC [44]. Other drugs being tested for BPS/IC include micro-RNA manipulation, APF antagonists, selective cannabinoid type-1 receptor agonists, and phosphodiesterase type 5 inhibitors. APF antagonists revert tight junction damage in laboratory models [45]. Micro-RNA manipulation may mediate downregulation of NK-1 receptor in BPS/IC [46]. Selective cannabinoid type-1 receptor agonists

significantly decrease inflammatory activity in the urothelium [47]. Daily low-dose sildenafil also proved to be an easy, well-tolerated, and effective treatment [48].

Intravesical therapy is another important treatment option. It opens the possibility to directly apply higher drug doses or even to deliver substances that orally are impossible to use. Dimethyl sulfoxide (DMSO) is the only intravesical therapy approved by the FDA for BPS/IC. DMSO is an organic solvent, a by-product of the paper pulp industry, which has analgesic and anti-inflammatory properties, muscle relaxant, and collagen-dissolution effects [49]. DMSO alone currently holds an evidence grade C recommendation for BPS/IC, which can be explained by the inexistence of any positive RCT [12]. Moreover, BPS/IC patients frequently feel a typical garlic body odor, when they receive more than 50 mL of 50% DMSO per week. DMSO is often combined in intravesical cocktail solutions (lidocaine, heparin, and/or sodium bicarbonate) that are administered weekly or biweekly. There is no study to conclusively show that these preparations are any more effective than DMSO alone [50]. Intravesical lidocaine or its alkalinized form has shown value in the management of pain and urgency in BPS/IC [51]. Alkalinized lidocaine had a significantly immediate effect on mean pain score, which lasted for 8 days after the instillation [52]. Another molecule that can be instilled is PPS. Through this route it can achieve higher concentrations near urothelium than when given orally. In a recent RCT, simultaneous oral and intravesical PPS showed significant advantage of use over placebo or oral PPS alone [53]. GAG layer restitution has also been attempted with chondroitin sulfate and hyaluronic acid. Nevertheless, RCTs against placebo of intravesical sodium chondroitin sulfate or hyaluronic acid were negative or showed high recurrence rate during the first year [54]. Sensory type C fibers are responsible for pain transmission in BPS/IC. Thus, desensitizing TRPV1 receptor and inactivating C fibers can be an alternative approach. Several studies showed a beneficial effect of resiniferatoxin (RTX) applied intravesically [42]. Nevertheless, the only large RCT conducted with RTX against placebo was negative [55]. Other RCT examined the effect of the intravesical instillation of bacillus Calmette-Guérin (BCG) and concluded that it has no clinical effect on BPS/IC [56].

Hydrodistension under anesthesia in addition to being a diagnostic tool can be also used as a treatment for BPS/IC. After the initial cystoscopic examination, the physician "hydrodistend" the bladder by filling it with fluid at low pressure (60–80 cm) and keeping it full for 1–5 min before letting the fluid out. Long-term symptom-free periods may follow the procedure. Exactly why this procedure has therapeutic benefits for some patients is still unknown. A recently conducted study examined patients with BPS/IC who were treated with hydrodistension and subsequent bladder training. Of the 361 patients recruited into this uncontrolled study, only 13.4% described urgency symptoms 8 weeks after hydrodistension, and more than 80% of patients showed improvement in their BPS/IC flares of pain associated with menstruation and sexual intercourse [57]. Nevertheless, long-term results are not so encouraging [12].

Surgical fulguration of Hunner's lesions with LASER/resection was shown to be effective in relieving symptoms for up to 12 months or more in BPS/IC patients [58]. The drawback of this option is that it is only effective in the subset of ulcerated patients.

Neuromodulation is a procedure in which the S3 sacral nerve or the pudendal nerve roots are stimulated by a mild electrical current. Several studies have shown its safety and efficacy in the management of refractory BPS/IC, with good long-term results [59]. Nevertheless, it is an expensive treatment with frequently reported side effects, namely, bleeding, infection, program malfunction, or lead displacement [59]. Posterior tibial nerve stimulation is designed to deliver stimulation to the sacral nerve via the posterior tibial nerve at the medial malleolus, being less invasive than neuromodulation. However, its efficacy in BPS/IC was never proved [60].

A relatively new technique for refractory BPS/IC patients is the use of hyperbaric oxygen therapy. It has been shown that there is increased expression of $HIF_{1\alpha}$ and VEGF in patients with BPS/IC, supporting the use of hyperbaric oxygen therapy for the treatment of BPS/IC [61]. This treatment allows hyperoxia of the urothelium, resulting in leucocyte activation and promotion of healthy granulation tissue growth. However, there is no RCT supporting this procedure in BPS/IC.

Pain relief remains very difficult to achieve with standard treatment, leading several investigators to use onabotulinum toxin A (OnaBotA). The toxin impairs nociceptive fibers by preventing neurotransmitter release [62]. Intravesical OnaBotA administration also decreases urinary NGF [63] and VEGF [64], two important molecules in the pathophysiology of BPS/IC. Altogether, these facts indicate a strong antinociceptive effect of OnaBotA in the bladder. Since 2008, some authors showed that 100 U OnaBotA improve symptoms in refractory BPS/IC patients, independently of their initial ESSIC classification or phenotype [65–68]. Two major questions around intravesical OnaBotA are the controversy around which should be the best local of administration and which should be the ideal dose. In a recent randomized placebo-controlled trial, intra-trigonal injections of 100 U significantly improved bladder symptoms and quality of life [69].

Urinary diversion with bladder conservation, supratrigonal cystectomy with enterocystoplasty, subtrigonal cystectomy, or radical cystectomy including excision of the urethra with urinary diversion should be the last resort. Refractory patients with Hunner's lesions and smaller bladder capacities under anesthesia are probably the candidates [70]. Unfortunately, urinary diversion or cystectomy cannot guarantee a pain-free result [71].

7.6 Bladder Pain Syndrome/Interstitial Cystitis Conclusions

Nowadays, the traditional structured monotherapy approach should not be considered the best standard of care for BPS/IC patients (Fig. 7.2). A tailor-made treatment plan directed toward the patient's unique clinical phenotype will ultimately lead to a better outcome.

Offer sub-type and phenotype-oriented therapy for the treatment of Bladder Pain Syndrome (BPS).
Multimodal behavioural, physical and psychological techniques should always be considered alongside oral or invasive treatments of BPS.
Administer amitriptyline for use in BPS.
Offer oral pentosane polysulphate for the treatment of BPS.
Treatment with oral pentosane polysulphate plus subcutaneous heparin is recommended especially in low responders to pentosane polysulphate alone.
Administer intravesical lidocaine plus sodium bicarbonate prior to more invasive methods.
Administer intravesical pentosane polysulphate before more invasive treatment alone or combined with oral pentosane polysulphate.
Administer submucosal injection of Botulinum toxin type A (BTX-A) plus hydrodistenstion if intravesical installation therapies have failed.
All ablative organ surgery should be the last resort and undertaken by experienced and BPS knowledgeable surgeons only.
Offer intravesical hyaluronic acid before more invasive measures.
Offer intravesical chondroitin sulphate before more invasive measures.
Offer transurethral resection (or coagulation or laser) of bladder lesions, but in BPS type 3 C only.
Offer neuromodulation before more invasive interventions.
Offer dietary advice.
Offer intravesical heparin before more invasive measures alone or in combination treatment.
Offer intravesical bladder wall and trigonal injection of BTX-A if intravesical instillation therapies have failed.
Corticosteroids are not recommended for long-term treatment.
Bladder distension is not recommended as a treatment of BPS.

Fig. 7.2 European Guidelines for treatment of IC/BPS

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Overactive Bladder

8

Visha K. Tailor and G. Alessandro Digesu

8.1 Introduction

Overactive bladder (OAB) has been defined by the International Continence Society (ICS)/International Urogynecological Association (IUGA) as urinary urgency with or without urge urinary incontinence, usually accompanied by frequency and nocturia in the absence of a urinary tract infection or other pathology [1]. The symptoms can be distressing affecting all aspects of a woman's quality of life (QoL) including social, work-related, emotional and sexual function [2].

OAB has a reported overall prevalence of 16.9% in women which increases with age. Women under 25 have a prevalence of 4.8% increasing to 30.9% in women over 65 [3]. Prevalence has separately been reported as high as 38% in postmenopausal women [4].

8.2 Pathogenesis

OAB is a symptom-based diagnosis with an aetiology that is still poorly understood. It can be associated with detrusor overactivity which is diagnosed by urodynamic studies. Spontaneous or provoked involuntary contractions of the detrusor muscle during the filling stage of micturition can be observed.

OAB is more prevalent in postmenopausal women with symptoms of genitourinary syndrome of menopause (GSM). Symptoms include vaginal dryness, burning, dyspareunia and urinary tract infections. The aetiology can be linked with genitourinary atrophy which can be attributed to oestrogen deficiency during the menopause with reduced oestrogen receptors in tissues such as vaginal epithelium and the bladder trigone [5]. This is also thought to contribute to urinary symptoms

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because of the increased contact of sensitive nerve endings with urine due to bladder atrophy [6].

There is emerging research suggesting that OAB in some patients may be linked to chronic bladder infection, although the mechanism of how bacterial colonisation causes OAB is unclear. Newer technologies such as RNA sequencing or extended culture techniques have shown different groups of microbiota cultured from patients with or without OAB. This will have an impact on future emerging treatment options [7].

8.3 Assessment of Women

A full clinical history is important to explore factors that can contribute to OAB symptoms and influence ongoing management. Discuss lower urinary tract symptoms divided into storage problems (frequency, urgency, nocturia, incontinence), voiding symptoms (hesitancy, straining, poor and intermittent flow), post-micturition symptoms (sensation of incomplete emptying, post-micturition dribble) and other symptoms (nocturnal enuresis, dysuria). Enquire into menopausal symptoms to explore GSM.

Lifestyle questions exploring fluid intake, type of fluids preferred (e.g. carbonated drinks, caffeinated drinks) and pad usage to assess for modifiable habits and severity of disease.

Past gynaecological and obstetric history is useful to identify if the patient is known to have a fibroid uterus that may compress the bladder causing urinary urgency and frequency or risk factors for vaginal prolapse, for example.

Relevant medical history such as diabetes or neurological symptoms should be assessed to identify co-morbidities that may produce or worsen OAB symptoms. If pharmacotherapy for OAB is being considered, conditions such as prolonged QT interval, uncontrolled hypertension, functional gastrointestinal pathology, myasthenia gravis and uncontrolled narrow-angle glaucoma, as well as renal and liver impairment will influence treatment choice [8].

Previous surgical history, for example, hysterectomy or vaginal prolapse surgery, may have influenced symptoms.

Current medication history may identify medications contributing to worsening of symptoms such as diuretics and sympathomimetics or if any medications will interact with medical treatment of OAB.

Assessment is completed with physical examination. Abdominal examination and bimanual vaginal examination should be carried out to assess for pelvic masses. Vaginal examination is important to assess pelvic organ prolapse (POP) and the integrity of the vaginal mucosa and identify atrophic change. If neurological symptoms are elicited from the history, carry out neurological examination with attention to the sacral neuronal pathways from S1 to S4 with the assessment of perineal sensation, rectal sphincter tone and ability to contract the anal sphincter [8].

8.4 Investigations

8.4.1 Urinalysis and Mid-stream Urine

Urinalysis should be carried out to identify urinary tract infection which may exacerbate symptoms or masquerade as OAB. Overall however urine dipstick analysis has a low sensitivity of 44% and a specificity of 87% for identification of a urinary tract infection when compared to urine cultured from a catheter sample in women with OAB [9]. Detection of blood can suggest infection, stones or cancer. Presence of protein is in keeping with infection or renal impairment; glucose can be identified in patients with diabetes mellitus, especially when not well controlled.

Microbiology culture and sensitivity of a mid-stream urine specimen are recommended for women with symptoms of a urinary tract infection with either a positive or negative urine dipstick or if the urine dipstick test is positive for leucocytes/nitrites. An acute presentation or exacerbation of symptoms may have an infective aetiology.

If urine sampling is consistently positive for blood, cystoscopy and renal ultrasound are indicated.

8.4.2 Bladder Diary

Bladder diary or frequency volume charts can provide an objective assessment of a patient's fluid input and urinary output. It can provide information on a patient's drinking patterns as well as the number of voids and incontinence episodes through the day. This assessment allows review of symptom severity in the everyday situation. Most current practice recommends completing a diary for 3–5 days covering variations in the women's usual activities, such as both working and leisure days.

The bladder diary itself however does not reliably correlate with urodynamic diagnoses [10].

8.4.3 Quality of Life Questionnaire

OAB symptoms are known to have a negative impact on quality of life. Patients with anxiety and depression report a greater severity in their OAB symptoms, poor quality of life and more psychosocial difficulties compared to OAB patients without anxiety [11]. Women with climacteric symptoms (hot flushes, night sweats, vaginal dryness and dyspareunia) are more likely to report anxiety and/or depressive symptoms although a direct causal link between menopause and anxiety and depression has not been clearly found [12].

Clinical trials acknowledge that improvement in quality of life should be considered an endpoint of successful treatment. With a similar principle, routine assessment of OAB symptoms and their impact on QoL can provide women with a manner of tracking their expectations and/or satisfaction with treatment [13].

There are many available validated questionnaires for this purpose. For example, the Overactive Bladder Questionnaire (OAB-q) includes an 8-item symptom bother scale and 25 quality of life items. It is a validated disease-specific questionnaire that assesses symptom bother and health-related quality of life (HRQL) in people with OAB [13]. The King's Health Questionnaire is also widely used and translated patient acceptable and valuable disease-specific questionnaire designed to assess the impact of urinary incontinence on quality of life (QoL) in women through 21 questions [14]. The Bristol Female Lower Urinary Tract Symptoms (B-FLUTS) assessment and International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF) are alternatives.

8.4.4 Urodynamic Investigation

Urodynamic studies describe several investigations that allow functional assessment of the bladder and urethra. It allows abnormalities of storage and voiding to be identified and detrusor overactivity or concomitant stress urinary incontinence to be confirmed. It is recommended in the investigation of OAB after unsuccessful conservative treatment.

Uroflowmetry is the measurement of urine flow rate. The patient is asked to void onto the flow metre with a comfortably full bladder. This part of the study excludes outflow tract obstruction or a hypotonic bladder.

Multichannel cystometry or subtracted cystometry allows measurement of rectal pressure to represent intra-abdominal pressure and intra-vesical pressure to calculate the detrusor pressure. Cystometric bladder capacity, contractility, compliance, presence of provoked or unprovoked detrusor activity or urodynamic stress incontinence can be determined by this investigation. Sixty-four percent of patients with OAB symptoms have detrusor overactivity detected by urodynamic studies. Conversely 84% of patients with urodynamically proven detrusor overactivity have symptoms of OAB [15].

8.4.5 Cystoscopy

Cystoscopy allows direct visualisation of the bladder using a flexible or rigid cystoscope under local or general anaesthesia, respectively. It can be considered after failure of medical management of overactive bladder or where there is a history of haematuria or recurrent urinary tract infections. Biopsies can be taken to investigate pathology as needed.

8.5 Management

The aim of OAB treatments is to improve control of micturition (behavioural and lifestyle interventions) or to modify detrusor contractility (pharmacological and surgical treatments). There are a variety of treatments available for OAB showing that

none are universally successful. We discuss treatments specifically for OAB further.

To note women with coexisting pelvic organ prolapse and OAB symptoms who undergo surgical correction of prolapse experience improvement in OAB symptoms after surgery in 60–80% of cases. Women with more severe prolapse however may be at a higher risk of persistent frequency or urge incontinence [16].

8.5.1 Lifestyle Modifications

Lifestyle modifications with avoidance of tea (including green tea), coffee, alcohol, carbonated drinks (particularly diet soft drinks) and smoking and dietary advice to avoid constipation are recommended. Following a healthy lifestyle with weight loss encouraged in those who are overweight is the advice of the ICI guidelines [17].

8.5.2 Bladder Retraining

Behavioural modifications include bladder retraining. Bladder retraining focuses on timed voiding aiming to lengthen the intervals between voiding. Patients are asked to void every hour at the start, even if no desire to void, and then progressively increase the voiding interval each week. Bladder retraining is effective for both overactive bladder symptoms and mixed urinary incontinence symptoms. A cure on improvement in symptoms in 59% of women has been reported in a retrospective study [18] of few adverse side effects. It is therefore recommended as first-line therapy with lifestyle modifications.

8.6 Pharmacological Management

Most medications prescribed to treat OAB have anti-muscarinic effects. However antidepressants, vasopressin analogues and alpha-adrenoceptor antagonists and beta-adrenoceptor agonists are also used. There is no ideal medication and treatments can be limited by side effects.

8.6.1 Anti-muscarinic Drugs

Detrusor contraction is mediated by the neurotransmitter acetylcholine binding to muscarinic receptors. Anticholinergic medication targeting M2 and M3 receptors has been the traditional first-line pharmacological treatment. The medication blocks the parasympathetic acetylcholine pathway to reduce the intensity of detrusor muscle contraction. Action via the sensory pathway allows the anticholinergic agent to modulate afferent innervations in the urothelium, thereby altering sensory feedback during filling phase [19].

Popular agents include oxybutynin, tolterodine, trospium, solifenacin, darifenacin and fesoterodine. All agents have shown a statistically significant improvement in OAB symptoms when compared to placebo.

Anti-muscarinic medication, however, can lack bladder specificity with muscarinic receptors in other organs such as the exocrine glands, the nervous system and the heart also interacted with. The most common side effect as a result is dry mouth in 16–28% of patients and as high as 80% with unmodified oxybutynin. Blurred vision, constipation, tachycardia and drowsiness can also occur. Use of extended-release preparations of oxybutynin, tolterodine and fesoterodine or patch or gel formulation of oxybutynin can lower the incidence of dry mouth and constipation [20]. Solifenacin and darifenacin are M3-selective receptor antagonists, in theory more bladder-specific with reduced tendency for anticholinergic side effects, however higher incidence of constipation (9–14%).

Adverse central nervous system side effects include disorientation, hallucinations, convulsions and cognitive impairment. These side effects can be compounded by the total anticholinergic burden contributed to by other regular medication taken by patients, for example, antispasmodic, antipsychotic and tricyclic antidepressants and anti-Parkinson medication [19]. Such side effects limit compliance as well as limit treatment availability for older women with established cognitive impairment.

Contraindications for anti-muscarinic use include hyperthyroidism, myasthenia gravis, narrow-angle glaucoma, hiatus hernia with reflux oesophagitis, heart failure and tachyarrhythmia.

It is good practice to advise patients prior to prescribing this medication of common side effects and that full benefits may take 4 weeks. Prescribe the lowest recommended dose of the medication, and ideally review in 4 weeks to assess symptoms and acceptability of treatment [21].

8.6.2 β3-Adrenoceptor Agonist

Mirabegron, the first β3-adrenoceptor agonist to enter clinical practice, is a selective β3-adrenoceptor agonist. In the human lower urinary tract, β3-adrenoceptors can be found in the bladder detrusor but also in the urothelium. Stimulation of β3-adrenoceptors leads to detrusor relaxation and increased bladder capacity. Mirabegron is a well-tolerated new medication associated with significant improvements in incontinence episodes and micturition frequency. Benefits of treatment were observed in patients with no previous pharmacotherapy for OAB as well as women who have previously trialled and discontinued anti-muscarinic treatment [22].

Combination therapy of mirabegron with solifenacin has also demonstrated significant improvements in mean volume voided (primary endpoint), micturition frequency and number of urgency episodes, without increasing the bothersome adverse effects associated with anti-muscarinic therapy (with the possible exception of constipation).

Reported adverse side effects include hypertension, nasopharyngitis and urinary tract infection. Contraindications to the medication include severe uncontrolled hypertension, severe renal impairment (i.e. GFR 15–29 mL/min/1.73 m^2) or in those with moderate hepatic impairment.

8.6.3 Desmopressin

Desmopressin is a synthetic analogue of vasopressin. Used at night it can reduce nocturnal urine production by up to 50% and can be used to treat nocturnal enuresis or nocturia in adults or children. The drug should be used with care in the elderly however due to a risk of hyponatraemia [23].

8.6.4 Oestrogen

Although oestrogen deficiency has been implicated in the aetiology of OAB by epidemiological studies, the role of oestrogen replacement treatment remains controversial. A Cochrane review has found low-quality evidence that intra-vaginal oestrogen preparations can improve the symptoms of vaginal atrophy and urinary incontinence in postmenopausal women when compared to placebo [24, 25]. It is widely thought that local oestrogen therapy for OAB however may be of benefit.

A randomised placebo-controlled trial (*n*-1612) reports 25 μg of micronised 17beta-oestradiol administered locally improved maximal cystometric capacity (290 mL vs. 200 mL, $P = 0.023$) and volume at which there was a strong desire to void (170 mL vs. 130 mL, $P = 0.045$) with a decrease in uninhibited bladder contractions from baseline pretreatment values [26]. There was no reported endometrial thickening or rise in serum oestrogen level as a result of treatment. Evidence supports a subjective improvement in symptoms of OAB with a better quality of life as assessed by short form-36 [27].

Conversely studies with higher doses of oestrogen, e.g. 25 mg oestradiol implants, have shown adverse effects such as vaginal bleeding with need for investigation and treatment including hysterectomy [28]. Systemic therapy with unopposed or combined hormone treatment has been shown to worsen urinary incontinence and frequency symptoms at 1 year [24] and should not be recommended for lower urinary tract symptoms.

8.6.5 Tricyclic Antidepressants

Although these agents are sometimes used for the treatment of OAB, they are not approved for this indication, nor is there any clinical trial evidence supporting this use [20]. Tricyclic antidepressants (TCAs) are potent inhibitors of muscarinic, a-adrenergic and histamine H1 receptors and inhibit norepinephrine and serotonin

reuptake at nerve terminals. Imipramine or amitriptyline is the most commonly used and may be useful for patients particularly bothered by nocturia or bladder pain [29].

The side effects of TCAs predominantly reflect their anti-muscarinic properties. Caution should be exercised in the context of combination therapy with anticholinergic agents, due to the risk of cumulative side effects, for example, urinary retention, confusion or QT prolongation [23].

8.7 Refractory OAB

Despite conservative and medical management, treatment outcomes may not provide optimal improvement in symptoms for 25–40% of patients [30], and second-line therapies may be sought. Although no standardised definition exists, we describe this as refractory OAB. Treatment options include intra-vesical Botox injections, neuromodulatory treatments or surgery. Before further invasive therapy, it is good practice to discuss the patient with a multidisciplinary team and explain the advantages and disadvantages of all treatment options.

8.7.1 Intra-vesical Treatment with Botulinum Toxin

Botulinum toxin is a neurotoxin produced by the bacterium *Clostridium botulinum*, of which seven (A to G) serotypes have been identified. The use of botulinum A toxin (Botox) to treat a neurogenic OAB was first described in 1999 by Schurch et al. [31]. Injection of botulinum toxin acts presynaptically and prevents fusion of neurotransmitter-containing vesicles, leading to a decrease of acetylcholine release across the neuromuscular junction. The resultant muscle paralysis with a likely additional effect on the sensory afferent pathway mediates an improvement in OAB symptoms [32].

The botulinum toxin product is administered via cystoscopic injection using either a flexible or rigid cystoscope with local or general anaesthesia. There are no current recommendations for standardised administration and dose of the toxin or long-term safety data; however few side effects or complications are reported. Urine retention and the need to carry out clean intermittent self-catheterisation (ISC) have been reported as 5–15% with a risk of urinary tract infection as 5–31% [32, 33]. The risk of urine retention can increase with age and could develop as late as 2 weeks following injection. As such it is recommended that all women should be taught to carry out ISC prior to the procedure and followed up at 2 weeks following the procedure to assess post-void residual volumes.

8.7.2 Neuromodulation

Neuromodulation aims to achieve inhibition of detrusor activity by continuous neural stimulation through peripheral (via the posterior tibial nerve) or central (dorsal sacral nerve roots S2, 3, 4) nerves.

Posterior tibial nerve stimulation (PTNS) is the least invasive method of neuromodulation. It can be carried out in the outpatient setting, usually with 12 weekly sessions. This nerve has mixed fibres originating from L4 to S3 spinal cord segments, in common with bladder and pelvic floor innervation. The technique, first described in 1983, involves passing an electrical current through a 34-gauge needle electrode placed next to the PTN approximately three finger breadths cephalad to the medial malleolus. Subjective improvement in OAB symptoms occurs in about 60% of the patients with 47–56% improvement in frequency voiding charts [34].

The treatment is safe with few side effects (bruising, discomfort, slight bleeding); however without top-up treatments, effectiveness may decrease over time [34]. In a small study, 77% of patients maintained a moderate to marked improvement in their OAB symptoms after 3 years. It is recommended when intra-vesical botulinum A toxin injection treatment to the bladder or sacral neuromodulation is not acceptable or suitable for patients [35].

Central neuromodulation can be carried out using an implantable, programmable medical device with a tined lead electrode that is typically passed through the S3 sacral foramen to lie next to the sacral and pudendal nerves. The battery device delivers continuous electrical stimulation. Originally designed to treat neurogenic bladder disease, the treatment has been shown to be effective in treating overactive bladder, neurogenic bladder symptoms, urinary retention as well as faecal incontinence and chronic pain.

Insertion of the device requires a two-stage procedure. The first implants an external device with a wire or tined electrode for 2 weeks to ensure effectiveness of the product before a subcutaneous permanent device is inserted with a tined electrode. Studies have shown a reduction in improvement in incontinence episodes, leakage severity, voiding frequency and pad use with treatment benefits persisting in 68% of patients at 5 years [33].

Adverse effects must be discussed when offering this treatment modality. The procedure has an overall reported reoperation rate of 33% for pain, lead migration or infection at the implant site or battery change after 5–7 years depending on the device and usage settings. Nine percent of patients required complete removal of the device [36].

Miniature wireless implant devices for pretibial nerve stimulation and rechargeable devices for sacral neuromodulation are currently being developed and trialled for the treatment of OAB which may provide promising treatment alternatives for the future.

8.8 Surgery

Surgical treatment for OAB remains a last resort for those who have failed the above treatment modalities or find them unacceptable. Patients often have a low-capacity, poorly compliant bladder with refractory OAB symptoms. The two most commonly carried out procedures include clam ileocystoplasty or urinary diversion. Both are considered major and complex surgical procedures, and patient selection and comorbidities need to be considered before offering this treatment. The traditional approach to this surgery is through open abdominal surgery; however through

equipment advances, laparoscopic and robotic methods can also be employed in experienced hands [37].

8.8.1 Clam Cystoplasty

Clam cystoplasty aims to turn a high-pressure system into a low-pressure one through the anastomosis of a bowel segment to the bladder. The most commonly used intestinal segment is the ileum in an ileocystoplasty. Bladder capacity is therefore increased, detrusor pressure is reduced, upper tracts are protected and any concurrent ureteric reflux can resolve. Satisfactory outcomes from this procedure are reported in up to 88% of patients.

Common side effects or complications long term include the need to carry out ISC for 10–75% of patients. Metabolic disturbances can contribute to vitamin B12 deficiency and hyperchloraemic acidosis with resulting bone demineralisation with osteoporosis. Others include bacteriuria, urinary tract stones (15–40% of patients), mucous retention in the bladder, spontaneous bladder perforation, incontinence and carcinoma. The chronic exposure of the ileal mucosa to urine can lead to malignant change in 1.2% of patients. As a result, long-term yearly cystoscopic and biopsy monitoring after 10 years post-procedure is advised [37, 38].

8.8.2 Urinary Diversion

As a last-resort treatment modality who cannot carry out ISC, with uncompromised renal function, a urinary diversion to an ileal stoma or various segments of the intestinal tract (most commonly the appendix or ileum) creates a continence reservoir that requires catheterisation to empty the urine. Low incontinence rates of 2–16% [38] have been reported following this procedure.

Key Points

- Overactive bladder is prevalent in postmenopausal women and prevalence increases with age.
- OAB can have a significant impact on quality of life, improvement of which is considered a treatment outcome.
- Lifestyle changes and medical management remain first-line treatment options.
- Treatment with topical oestrogen may be of benefit, although synergistic benefits with pharmacotherapy are unclear.
- Refractory overactive bladder symptoms can occur in 25–40% of patients.
- Multidisciplinary management with patient counselling of treatment options and expected outcomes with written information is essential in the management of refractory OAB.
- Intra-vesical botulinum A toxin injections, posterior tibial nerve stimulation (PTNS) or sacral neuromodulation can provide effective second-line treatment.

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Management of Female Stress Urinary Incontinence

9

Giampiero Capobianco, Pier Luigi Cherchi, and Salvatore Dessole

9.1 Introduction

Urinary incontinence is defined as a condition of involuntary loss of urine [1]. The three most common types of urinary incontinence are the following: stress urinary incontinence (SUI), characterized by an inadvertent loss of urine occurring as a result of an increase of intra-abdominal pressure due to effort or exertion or on sneezing or coughing; urge urinary incontinence (UUI), denoting involuntary leakage arising for no apparent reason and associated by urgency; and mixed urinary incontinence (MUI), when both are occurring. According to Hunskaar et al. [2], the prevalence and distribution of the types of urinary incontinence in noninstitutionalized women are 49%, 21% and 29%, respectively.

SUI has a prevalence between 10 and 40% of the female population, especially in the postmenopausal age, and has a negative impact on the quality of social, working and affective life of the patients [2]. The wide prevalence range of urinary incontinence, in general, depends on the definitions used in clinical studies (if the loss of involuntary urine takes several times in a day or week or if you consider the last 12 months), from the methodology (telephone interviews, questionnaires shipped at home) and in differences between the populations considered in the world.

The objective of this chapter is to report the current state of the art and new therapies on the management of female stress urinary incontinence.

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9.2 Methods of Search Strategy

A detailed literature research on MEDLINE, Cochrane Library, EMBASE, NLH, ClinicalTrials.gov and Google Scholar databases was done up to July 2017 with restriction to English language about articles regarding SUI, medical therapy, surgical therapy and most recent treatment options. The keywords used for this review were female stress urinary incontinence, midurethral sling, tension-free vaginal tape (TVT) and transobturator tape (TOT, TVT-O). Original articles, reviews and meta-analysis were included. Studies including exclusively devices no longer available on the market at the date of the review were excluded. Disagreements among authors as to the studies to include were solved by discussion. In cases of duplication, the study with the most recent data was included. In case of cohort studies with multiple publications, the last dataset on efficacy was used.

9.3 Pathogenesis of Stress Urinary Incontinence

Urinary continence is the result of the synergy between the structures that constitute the pelvic floor and the sympathetic nervous component, parasympathetic and the motor fibres of the pudendal nerves. An alteration of one or both components leads to an inability of the urethra to counteract increases in abdominal pressure resulting in loss of urine during physical exercises, even minimal in the most severe cases.

Factors that may promote the onset of the SUI are age, parity, especially vaginal delivery and obesity as they can facilitate the onset of a weakening of the pelvic floor support structures resulting in urethral hypermobility. The nerve component may affect both bladder and urethral innervation. Even in this case, advanced age, previous pregnancy and parity may influence this mechanism of urinary continence following the stretching or compression of nerves during the passage of the foetus in the birth canal [3, 4].

9.4 Assessment and Investigation of Female Urinary Incontinence

The initial clinical evaluation is the categorization of the woman's urinary incontinence (UI) as SUI, mixed UI or urgency UI/overactive bladder (OAB) because the initial treatment starts on this basis. According to NICE guidelines, if stress incontinence is the predominant symptom in mixed UI, we should discuss with the woman the benefit of conservative management including OAB drugs before offering surgery [5].

Before the use of supervised pelvic floor muscle training for the treatment of UI, routine digital assessment to confirm pelvic muscle contraction is mandatory. Women with UI who have symptomatic prolapse that is visible at or below the vaginal introitus should be referred to a specialist [5].

All women with UI should undertake a urine dipstick test to detect the presence of blood, glucose, protein, leucocytes and nitrites in the urine. If a woman does not

have symptoms of urinary tract infections (UTI) and her urine tests are negative for either leucocytes or nitrites, a urine sample for culture is not necessary because she is unlikely to have UTI [5].

Women should complete a minimum of 3-day bladder diaries covering variations in their usual activities, such as both working and leisure days [5].

Assessment of post-void residual urine by bladder scan or catheterization in women with symptoms suggestive of voiding dysfunction or recurrent UTI is good clinical practice as initial evaluation.

In women with UI, the indications for consideration for referral to a specialist service include persistent bladder or urethral pain, clinically benign pelvic masses, associated faecal incontinence, suspected neurological disease, symptoms of voiding difficulty, suspected urogenital fistulae, previous continence surgery, previous pelvic cancer surgery and previous pelvic radiation therapy [5].

9.5 Conservative Treatment of Stress Urinary Incontinence

Figure 9.1 shows the first management of urinary incontinence in women and Fig. 9.2 the specialized management according to the European Association Urology (EAU) guidelines [6]. Recently, among the main care options are included exercises aimed at restoring the strength and muscle tone of the pelvic floor and oestrogenic therapy with the possibility to also associate the administration of *Lactobacillus acidophilus* in a triple therapy that has proven to be effective as the first therapeutic step [7]. Figure 9.3 shows the care pathway of SUI in women. Multichannel urodynamic testing (MUT) should not be performed before starting conservative management [5].

Lifestyle interventions regard reduction of caffeine intake in women with OAB and advise women with UI, who have BMI >30, to lose weight. Adsorbent products, urinals and toileting aids should not be considered as a treatment for UI but should be used only as an adjunct to ongoing therapy and long-term management of UI only after treatment options have been explored.

We should offer pelvic floor muscle training to women in their first pregnancy as preventive strategy for UI [5].

A multidisciplinary team (MDT) for urinary incontinence should include at least the following healthcare professionals: a urogynaecologist, a urologist with a subspecialist interest in female urology, a specialist nurse, a specialist physiotherapist and a colorectal surgeon with a subspecialist interest in functional bowel problems. The MDT should inform any woman wishing to consider surgical treatment for UI on the benefits and risks of non-surgical and surgical options and their provisional plan [5].

9.5.1 Drugs for Stress Urinary Incontinence

Duloxetine has been approved in Europe for treatment of SUI. The adverse effects include mental health problems and suicidality. Duloxetine was effective for SUI in women, but the rates of associated harms outweighed the benefits [8].

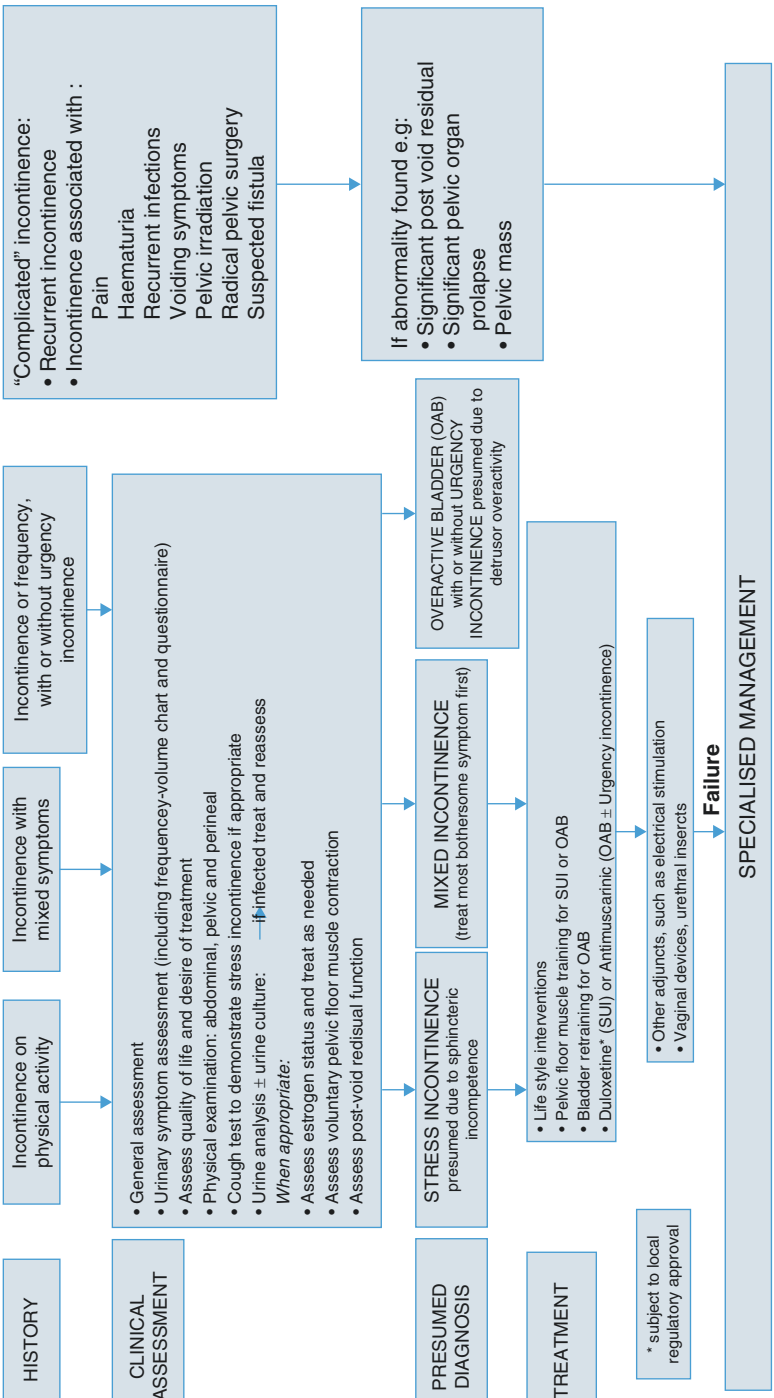

Fig. 9.1 First management of urinary incontinence in women [6]

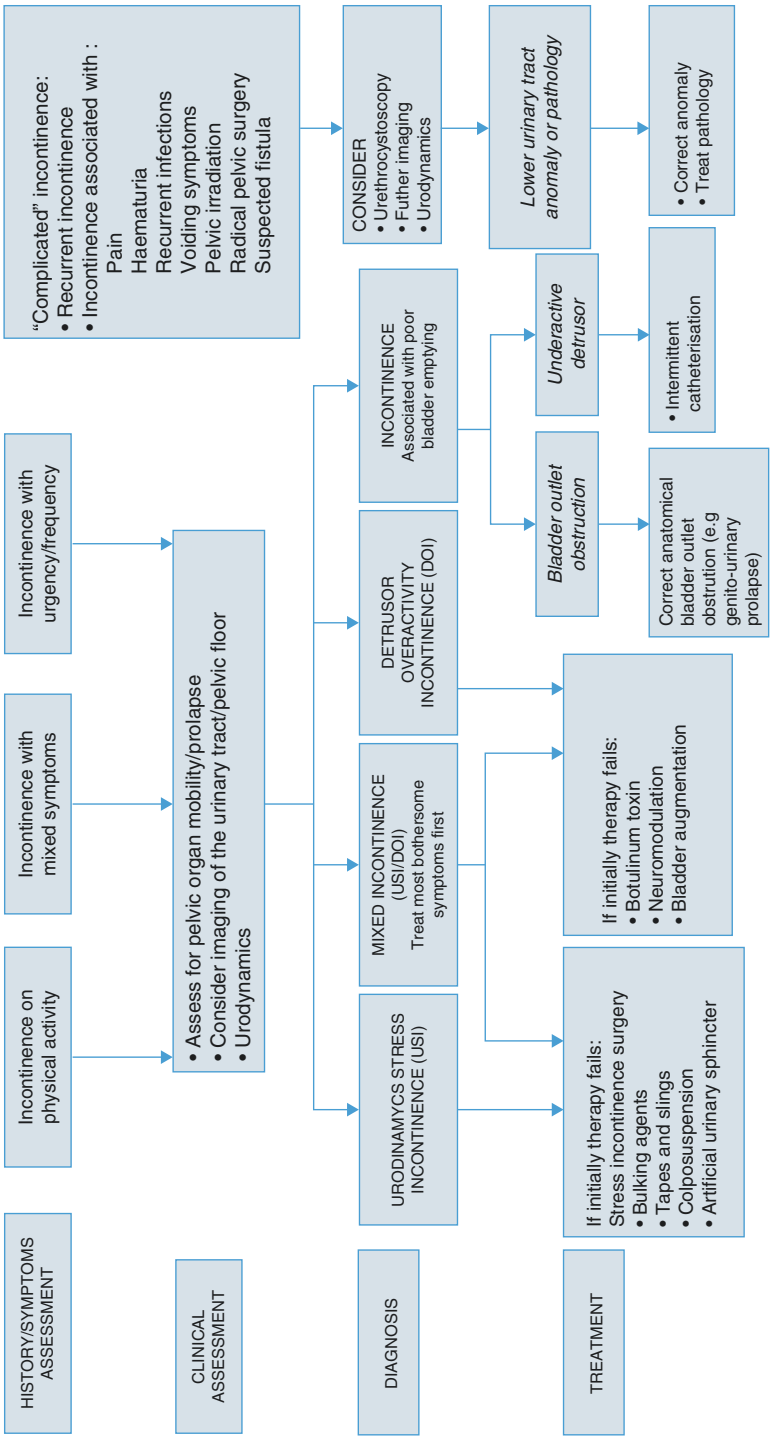

Fig. 9.2 Specialized management of urinary incontinence in women [6]

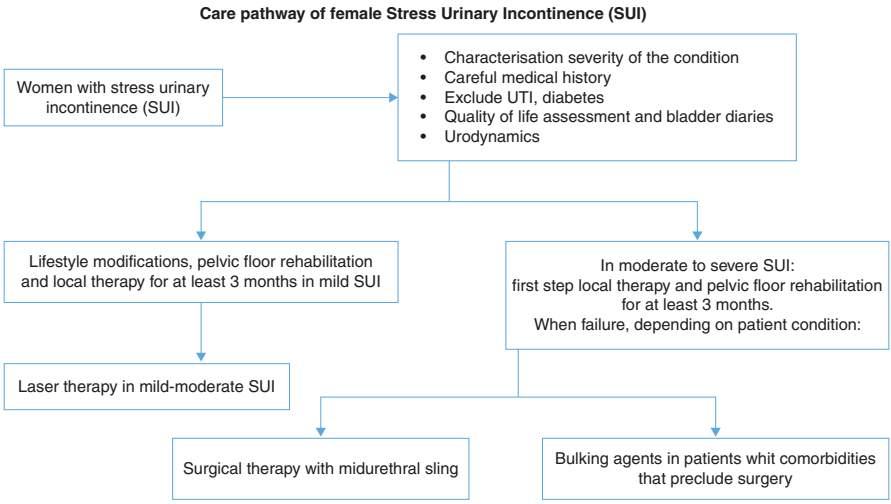

Fig. 9.3 Care pathway of female stress urinary incontinence

Furthermore, the UK National Institute for Health and Care Excellence guideline states that duloxetine should not be used as a first-line treatment or routinely offered as a second-line treatment for stress urinary incontinence, given that pelvic floor muscle training is more effective and less costly than duloxetine and that surgery is more cost-effective than duloxetine [5].

9.5.2 Laser Therapy

Now, laser therapy has been introduced in the non-invasive treatment of the SUI, already used in the gynaecological field for the treatment of vaginal disorders typically associated with menopause (vaginal atrophy). The lasers used in the gynaecological field are mainly of two types, the CO_2 laser and the vaginal erbium ER:YAG laser (VEL) (so-called because it uses an erbium-doped yttrium-aluminium-garnet medium, (YAG)), which, although not having a microablative function as CO_2 lasers, can induce changes in genital tissues that can induce benefit both in cases of vaginal dryness and dyspareunia and in the treatment of mild and moderate SUI. This type of laser can be used in the SUI therapy with a significant reduction of the symptoms reported by the patients [9–12]. The mechanism of action is attributed to the remodelling, which occurs due to a thermogenic effect of the collagen that constitutes the pelvic floor; with menopause a drastic reduction in the amount produced occurs thus resulting in the decrease of its physiological function of support causing not only urinary incontinence but also facilitating the onset or aggravation of the prolapse of the genital organs. The thermogenic effect is such that it induces in the target tissues a neoangiogenesis, neoformation of collagen, increased epithelial thickness and the content of cellular glycogen thus ensuring greater support for the

urethra. All these changes of the tissues are detectable for at least 6 months after treatment [10]. The first studies on laser therapy in the SUI are due to Fistonic et al. [11] who evaluated through the questionnaire "Incontinence Questionnaire—Urinary Incontinence Short Form" (ICIQ-UI SF) the efficacy and safety of the ER:YAG showing that even in severe SUI, there was a significant improvement in symptomatology, without any particular adverse events being recorded. The efficacy of the treatment is already visible after a single session, further increasing after three sessions with benefits lasting for at least the next 6 months [11]. Although there are not currently enough studies investigating the efficacy of the use of laser in the long term, it appears clear that this represents a therapeutic option that can be developed in the future, minimally invasive for the patient, and with objective benefits demonstrated, not only with regard to the SUI but the whole spectrum of symptoms of the genitourinary syndrome of menopause (GSM). A study of Gambacciani et al. [12] evaluated the effects of ER:YAG lasers on the symptoms associated with menopause, demonstrating how patients reported subjective benefits, confirmed objectively by the measurements of VHIS (Vaginal Health Index Score), demonstrating above all how it is a practice very well tolerated by patients with a possibility of results achievable quickly and long lasting, up to 24 weeks [12]. According to this study, the ER:YAG treatment is indicated in all those women who present not only the classic symptoms associated with menopause, such as dryness and vaginal atrophy, but also in the treatment of mild-moderate SUI in those women who cannot benefit from hormonal treatments as is the case of patients with history of previous breast cancer [12].

9.5.3 Combination Therapy: Vaginal Topical Medical Therapy and Pelvic Floor Rehabilitation

Significant importance has vaginal topical medical therapy, since oestrogens, which in menopause see a physiological and drastic reduction of their levels, have receptors throughout the genitourinary tract and on the pelvic floor musculature [13]. Oestrogens have an important role in the mechanism of urinary continence since they affect the synthesis of collagen; their topical (vaginal) administration can also act by reducing the frequency and amplitude of the detrusor contractions, thus increasing the sensory threshold of the bladder and promoting relaxation of the detrusor muscle [14]. These oestrogen-dependent mechanisms explain why, with the fall of their values after the menopause, disorders of the urogenital apparatus including the SUI become so frequent. Oestrogenic therapy, in particular estriol, has been extensively demonstrated in literature as being of valid aid in the treatment of urogenital disorders [15]; it also is free of proliferative effect on the endometrium. Intravaginal local therapy with estriol has proven to be effective in the therapy of urogenital atrophy, recurrent infections of the low urinary tract and the SUI in postmenopausal women [16, 17], especially when combined with exercises aimed at the muscular toning of the pelvic floor, a combination that is very well tolerated by the patients [17]. But the effects of combination therapy are only marginal and perhaps not long lasting.

Pelvic floor muscle training should be done for at least 3 months' duration as first-line treatment to women with stress or mixed UI; pelvic floor muscle training programmes should comprise at least eight contractions performed three times per day. Electrical stimulation and/or biofeedback should be considered in women who cannot actively contract pelvic floor muscles in order to aid motivation and adherence to therapy [5].

9.6 Evaluation of Uncomplicated Stress Urinary Incontinence in Women Before Surgical Treatment

Counselling about treatment should begin with conservative options. According to the Committee Opinion of American College of Obstetricians and Gynecologists (ACOG), the evaluation before primary surgery in women with symptoms of SUI includes six steps: (1) history; (2) urinalysis; (3) physical examination; (4) demonstration of incontinence (cough stress test; if stress test is negative, despite patient symptoms of SUI, multichannel urodynamic testing is recommended); (5) assessment of urethral mobility (cotton swab test; patients who lack urethral mobility may be better candidates for urethral bulking agents rather than sling procedures); and (6) measurement of post-void residual urine volume [18]. Table 9.1 shows basic evaluation findings for uncomplicated versus complicated SUI.

9.7 Multichannel Urodynamic Testing

Preoperative multichanel urodynamic testing (MUT) is not necessary before planning primary anti-incontinence surgery in women with uncomplicated SUI, as indicated by observed urinary leakage from the urethra by provocative stress measures, a normal urinalysis result (without urinary tract infection), no POP beyond the hymen and a normal post-void residual urine volume. However, women who have complicated SUI (Table 9.1) may benefit from MUT before initiation of treatment, especially surgery [18].

MUT and voiding cystometry should be performed before surgery, after undertaking a detailed clinical history and examination, in women who have symptoms of OAB leading to a clinical suspicion of detrusor overactivity or symptoms suggestive of voiding dysfunction or anterior compartment prolapse or had previous surgery for stress incontinence [5].

Videourodynamics should be proposed if diagnosis is unclear after conventional urodynamics [5].

9.8 Surgical Therapy

The surgery, by techniques such as the retropubic colposuspension by Burch [19], one of the most widely used until about 15 years ago (with abdominal approach in the past while laparoscopic nowadays), the anterior colporrhaphy by Kelly, or the

Table 9.1 Basic evaluation findings for uncomplicated versus complicated female stress urinary incontinence

	Findings	
Evaluation	Uncomplicated	Complicated
History[a]	UI associated with involuntary loss of urine on effort, physical exertion, sneezing or coughing	Symptoms of urgency, incomplete emptying, incontinence associated with chronic urinary retention, functional impairment or continuous leakage
	Absence of recurrent urinary tract infection No prior extensive pelvic surgery. No prior surgery for SUI	Recurrent urinary tract infection[b] Previous extensive or radical pelvic surgery (e.g. radical hysterectomy) Prior anti-incontinence surgery or complex urethral surgery (e.g. urethral diverticulectomy or urethrovaginal fistula repair)
	Absence of voiding symptoms	Presence of voiding symptoms[c]
	Absence of medical conditions that can affect lower urinary tract function	Presence of neurologic disease, poorly controlled diabetes mellitus or dementia
Physical examination	Absence of vaginal bulge beyond the hymen on examination. Absence of urethral abnormality	Symptoms of vaginal bulge or known pelvic organ prolapse beyond the hymen confirmed by physical examination, presence of genitourinary fistula or urethral diverticulum
Urethral mobility assessment	Presence of urethral mobility	Absence of urethral mobility
Post-void residual urine volume	<150 mL	≥150 mL
Urinalysis/ urine culture	Negative result for urinary tract infection or haematuria	

Table modified from: Committee Opinion. Obstet Gynecol 2014; 123(6): 1403-7 [18]

[a]A complete list of the patient's medications should be obtained to determine whether individual drugs may be influencing the function of the bladder or urethra, which leads to urinary incontinence or voiding difficulties

[b]Recurrent tract urinary infection is defined as three documented infections in 12 months or two documented infections in 6 months

[c]Hesitancy, slow stream, intermittency, straining to void, spraying of urinary stream, feeling of incomplete voiding, need to immediately revoid, postmicturition leakage, position-dependent micturition, and dysuria

suspension with needle, is now mostly replaced by the new minimally invasive surgical techniques of midurethral slings (MUSs) including the tension-free vaginal tape and retropubic (TVT) and the transobturator (TVT-O) tape. Another therapeutic option is the injection of urethral bulking agents (UBAs).

We have not included in this review retropubic colposuspension by Burch or autologous fascial slings because there have been no recent high-quality publications relating to these surgical procedures.

The treatment of the SUI should be carefully selected for each patient by evaluating the type of disorder, the severity of the symptomatology and concomitant factors that may preclude the use of surgery even with the mini-invasive techniques available today. The preoperative counselling should evaluate patient and surgeon satisfaction with treatment by having a discussion during the planning phase of surgery about individual patient's goals and expectations for their treatment and awareness of potential adverse events [20, 21].

9.8.1 Midurethral Slings

The most effective therapy, after the attempt with conservative therapies in case of their failure, is the surgical therapy, which has undergone a breakthrough in the year 1990, thanks to the introduction of the midurethral sling (MUSs), ensuring equal results, in terms of corrective efficacy of the disorder, both compared to the laparotomic Burch colposuspension and the laparoscopic one, but had the undoubted advantage of a lower hospitalization and fewer postoperative complications [22].

NICE 2013 [5] guideline counsels to not offer laparoscopic colposuspension as a routine procedure for the treatment of SUI in women; in fact, only an experienced laparoscopic surgeon working in a multidisciplinary team (MDT) with expertise in the assessment and treatment of UI should perform the procedure [5].

The slings can be made of autologous material, formed by tissue taken from the fascia lata or from the rectus abdominis fascia, or artificial meshes, usually polypropylene monofilament macroporous type 1; in both cases they are introduced by a small vaginal incision and placed "tension-free" in order to guarantee support to the middle urethra. The current trend is aimed at the use of artificial meshes, having been shown the lowest rate of reaction and lowest postoperative complications [23].

The two most used techniques today are the tension-free vaginal tape (TVT), experimented in the year 1990 by Petros and Ulmsten [24, 25], in which the mesh is introduced by the vaginal incision and then directed towards the retropubic space, then coming out from the abdominal wall in the suprapubic area, and the most recent transobturator tension-free vaginal tape (TVT-O), in which the mesh passes through the obturator foramen. Depending on how the needles are inserted during the placement of the sling, we can define the TVT-O (transobturator) technique inside-out (when the needle, bilaterally, goes from the vaginal incision through the obturator membrane and then comes out laterally to the genitocrural fold) and the TOT technique out-inside (when the needles go from an incision a few centimetres from the genitocrural fold and come out in the vaginal incision).

The use of the retropubic midurethral sling (RP-MUS) such as TVT has a higher risk of bladder injury than the TVT-O [26]. Other possible complications of TVT are urinary tract lesions, urinary tract infections and abnormal bladder voiding, which is defined as a post-voiding bladder residual of more than 150 mL. Occasionally, vascular lesions may occur during the placement of the sling due to the passage of the guide trocar in the retropubic space, or intestinal lesions, with risk that increases in case of previous abdominal-pelvic surgery. An indication to the use of retropubic

way is the form of SUI due not to urethral hypermobility but to intrinsic sphincter deficiency (ISD) with fixed urethra: in such cases its use was found to be more effective than that of transobturator way [27].

An evolution of the MUS is represented by the passage of the sling through the obturator foramen, as in the TVT-O, developed precisely to avoid some of the major complications of the retropubic pathway, such as urinary tract and vascular lesions [28]; complications related to non-complete bladder voiding are also reduced. Another advantage of TVT-O compared to the retropubic technique is the reduction of the duration of the operation, only 15 min on average, and a reduction of hospitalization; on the other hand, patients may report pain, more frequently, especially in the inguinal site compared to the TVT [29].

A modified form of the TVT-O procedure is the TVT-Abbrevo® in which a mesh of lesser length, only 12 cm, is used with inside-out technique, from the vaginal incision, coming out laterally to the genitocrural fold. Moreover, in the TVT-Abbrevo®, the obturator membrane [30] is not perforated with the guide scissors. Capobianco et al. [31] studied a sample of 56 patients submitted to SUI correction by TVT-Abbrevo® technique and followed controls in the postoperative period at 12 and 24 months, demonstrating the high level of success of the procedure with 76.6% of patients who showed a regular urodynamic function at 12 months, 17.86% who had a significant improvement in the symptoms and only 1.78% of the patients examined who showed a "de novo" overactive bladder. The benefits obtained were classified both in terms of patient's subjective well-being and objective measured by urodynamic studies, Q-tip test and stress test with cough, with excellent results also in the long term and high safety profile [31].

Both TVT and TVT-O are associated with high long-term success rates [32], with similar results between the two techniques, as demonstrated by a recent Italian meta-analysis on the basis of data concerning 49 examined studies [33].

However, in the UK and across the world, there has been a lot of publicity and legal action relating to a small percentage of women undergoing TVT procedures who have complications such as erosion and pain. However there are differences in complications between TOT and TVT; in fact RP-MUS showed a higher rate of bladder perforations in comparison to TVT-O [26, 33].

9.8.2 Single-Incision Mini Sling

The mini slings represent the third generation of midurethral slings and are differentiated by the use of a single vaginal incision approach as entry and by the less amount of mesh used. It has debated whether or not to submit obese patients to this type of treatment, and a recent study showed that BMI did not affect the outcome (efficacy) of treatment with mini slings [34]. The procedure aims to minimize the risk of major adverse events such as bladder, vaginal, urethral and vascular perforations or erosions and chronic pain that are associated with minimally invasive sling procedures. The SIMSs have shorter tape lengths and different fixation systems to transobturator minimally invasive slings and do not enter the retropubic space

(reducing the risk of major vessel or visceral injury) or the lateral half of the obturator foramen (reducing the risk of groin pain), but they are anchored in the obturator membrane or in the obturator muscles. A special tip anchors the sling in place behind the midurethra. SIMS systems may differ in the length of the sling, the fixation method, the fixation location and the method of tension adjustment or control. The mesh implant is permanent, but, if removal is needed because of infrequent complications, the anchoring system can make the device very difficult or impossible to remove. Furthermore, the evidence on efficacy in the long term is inadequate in quality and quantity [5].

9.8.3 Urethral Bulking Agents

A further alternative to sling surgery (even less invasive) is now represented by the possibility of using injections of "urethral bulking agents" (UBAs), the use of which is recommended in elderly patients, patients with high anaesthesiological risk or patients reluctant to undergo surgery [35, 36]. UBAs act in thickening the urethral walls by injecting them into the submucosa and elevating the urethral mucosa by restoring the natural continence and urethral resistance [36, 37]. The ideal bulking agent should be easily injectable, with good cost-benefit ratio, and biocompatible and should not migrate from the injection site and cause low inflammatory reaction of the affected tissues [38]. It is also indicated in patients who have already undergone surgery without benefit or with recurrence of symptoms. The American Urological Association recommended the use of UBAs in elderly patients, in patients with increased anaesthesiological risk and in patients who refused a more invasive procedure [39]. In addition, the National Institute for Health and Clinical Excellence (NICE) [40] suggests that UBAs are indicated in patients with significant reduction in urethral mobility and in patients who have a history of failure with the conservative therapy of the SUI [39]. Over the years, several materials have been tested, including paraffin, autologous grease, polytetrafluoroethylene, glutaraldehyde combined with bovine collagen, porcine dermis and hyaluronic acid plants. These substances were then abandoned due to health problems, adverse events and marked hypersensitization reactions and because of migration from the injection site [41]. Among the substances used today, as UBAs, the most used are the polydimethylsiloxane (Macroplastique®) and polyacrylamide gel (Bulkamid®). In both cases these are materials that are implanted in the urethral submucosa exerting a mass effect and thus increasing the urethral sphincter pressure and consequently urinary continence. The main advantage of using these agents is the possibility of providing the patient with a less invasive treatment in the care of SUI compared to traditional surgery [42]. For example, polydimethylsiloxane (Macroplastique®) is indicated in the treatment of SUI due to intrinsic sphincter deficiency (ISD). The substance is implanted, during cystoscopy, so as to have direct vision of the area, about 1 cm away from the urethral origin thus going to restore the urethral sphincteric function [43]. There are subjective and objective benefits through urodynamic studies, pad test 24 h and number of incontinence episodes during the day [44]. It is

also possible to repeat the treatment at a distance of time both to consolidate the benefits obtained with the first injection and in case of persistence of the symptoms after the first treatment. Bulking agents are, ultimately, a safe agent in the treatment of SUI, and because of low side effects, they are indicated in case of patients with comorbidities that preclude surgical therapy [45]. Recently, a new silicone-derived elastomer, Urolastic®, was introduced into the medical practice; once injected into the paraurethral tissue in a few minutes, it undergoes a change from the liquid state to solid state thereby supporting the urethra. It has proven to be a material that has a good biocompatibility without risks of migration from the injection site and with an excellent duration in terms of improvement of clinical symptomatology precisely for its physical chemical characteristics, which could make it in the future a new option for the treatment of SUI [46, 47].

Women should be made aware regarding UBAs that repeat injections may be needed to achieve efficacy, efficacy diminishes with time and efficacy is inferior to that of synthetic tapes [5].

9.9 Recurrent Stress Urinary Incontinence

Women whose primary surgical procedures for SUI has failed (including women whose symptoms has returned) should be referred to tertiary care for assessment (such as repeat urodynamic testing including additional tests such as imaging and urethral function studies) and discussion of treatment option by a multidisciplinary team [5].

The prevalence of voiding dysfunction, including urinary retention, following MUS procedures, ranges from 2 to 25% with a surgical intervention required to resolve the problem in 0–5% of patients [48].

The rate of a second surgical treatment for recurrent stress urinary incontinence (RSI) after the initial surgery varies according to the studies [49, 50]. In fact, Jonsson Kunk et al. [49] reported a cumulative recurrence of 14.5% with over 155,000 patients examined 9 years after a primary surgery; the type of repeat surgery performed was sling (70.5%), followed by bulking agents (20.1%), Burch (6.5%), laparoscopic (1.5%), needle (0.8%), total vaginal hysterectomy (0.5%) and Kelly (0.2%) [49]. Fialkow et al. [50] had 8.6% recurrence over 40,000 US women who underwent either a sling or retropubic colposuspension (Burch) for surgical treatment of SUI. In a third recent retrospective study [51], the rate decreased at 6% of women retreated within 5 years following their initial standard anti-incontinence procedures (Burch and sling procedures).

Risk factors for recurrent or persistent urinary incontinence after surgical treatment include ageing; obesity; medical comorbidities, such as diabetes mellitus; previous high-grade incontinence; mixed urinary incontinence; and previous failed surgery [52].

The debate in literature at the moment is still open about which of the operative techniques for female recurrent stress urinary incontinence is the most efficient and safest, but there isn't still a consensus, and there are few data regarding the choice of type of surgery for persistent/recurrent SUI.

The choice of the procedure in case of RSI should be individualized and carefully chosen considering the severity and type of symptoms, medical comorbidities and the

type of previous surgery. A second anti-incontinence procedure is effective in many women with persistent/recurrent SUI, at least in those women candidate to surgery.

MUS surgery appears to be a good choice in case of recurrent SUI. A meta-analysis of 12 prospective studies with a total of 430 women reported good results both in case of previous sling procedure and other procedures such as Burch colposuspension with cure rate of 79% after any previous surgery and 73% after a prior midurethral sling [52, 53]. Results in terms of cure rates seemed to be higher for TVT compared with TOT midurethral sling (80% versus 54% after any prior surgery); however, data about TOT procedures were too few [53].

The previous procedure to which the patient was submitted seemed to play a role in the following choice of treatment demonstrating that a repeated retropubic TVT seems to offer better results than using a TOT following a failed primary TVT [54, 55].

A retrospective study by Cerniauskiene et al. [56] compared 45 women with recurrent SUI after a first surgery procedure of Burch colposuspension, TVT and TOT. As second surgery Burch colposuspension operation, TOT or TVT procedures were performed. According to this study [56], no differences were shown in the outcomes with the different techniques. Nevertheless, minimally invasive techniques undoubtedly had many advantages compared to the Burch colposuspension operation, and nowadays TVT and TOT procedures are the first choice procedures for recurrent stress urinary incontinence treatment. Repeat surgery seemed also to be associated with a higher risk of intraoperative complications and lower success rate than initial surgery [57].

Regarding medical treatments there is no current evidence about the efficacy of conservative management of SUI for women with persistent/recurrent symptoms after surgical therapy. In general, however, conservative measures are not as effective for treatment of SUI as surgery and should be mainly considered in women who decline or are not candidates to surgery.

Urethral injections of UBAs are an option for women with persistent SUI. They are normally reserved to women who wish to avoid or cannot tolerate an invasive procedure. In a retrospective review of 165 women who had recurrent SUI, after undergoing a synthetic midurethral sling procedure, the use of UBAs showed a higher risk of failure in comparison to a repeated sling procedure [58]. In fact, of this group of women, UBAs were used in the treatment of 67 patients, while the other 98 underwent a repeat sling procedure. The group who underwent a urethral bulking procedure had a worst outcome (38.8% of failure) compared with those who underwent a repeated midurethral sling (11.2%) [58]. Injections often need to be repeated to maintain continence.

9.10 Stress Urinary Incontince and Experimental Therapies

There are, nowadays, insufficient clinical data about the use of stem cells (autologous myoblasts, muscle-derived stem cells and autologous fibroblasts) injected in the urethra to treat the intrinsic sphincter deficiency [59].

The artificial urinary sphincter [60] in women has not yet been extensively tested or evaluated with controlled randomized clinical trials. This technique is not recommended as a first-line surgical therapy of SUI [60–62].

9.11 Conclusions

Currently, according to the guidelines 2016 of the European Society of Urology and the Position Statement of 2017 of the European Urogynaecological Association, the synthetic midurethral slings are the gold standard for the surgical treatment of SUI [63, 64]. A recent systematic review and meta-analysis on 28 controlled clinical trials on 15,855 patients showed that midurethral slings are more effective than Burch colposuspension and that the comparison studies between the retropubic and transobturator slings have shown a higher rate of subjective and objective care of the retropubic technique but with greater risk of complications such as intraoperative bladder and vaginal perforation (OR 2.4, $p = 0.0002$), pelvic hematoma (OR 2.61, $p = 0.002$) and urinary tract infections (OR 1.31, $p = 0.04$). There was no statistically significant difference in efficacy between the transobturator inside-out technique and that of outside-in though the risks of vaginal perforation were lower in the inside-out [65]. A recent Cochrane Database Systematic Review of Ford et al. [29] concluded that midurethral slings are as effective as retropubic colposuspension but have a shorter operation time and a lower risk of postoperative complications.

Surgical therapy should be indicated only after conservative (rehabilitative, local oestrogenic) therapies have failed. Lifestyle changes such as weight loss and pelvic floor muscle training should always precede surgery.

The current trend is aimed at the continuous research of new therapeutic strategies in order to achieve an ever better balance between high efficacy and maximum reduction of adverse events.

Table 9.2 shows recommendations on management of female SUI [66].

Current data on new therapies such as laser therapy are still limited in their long-term efficacy while showing results that appear to be good in immediacy and that could have a potential role in the future routine medical therapy of the IUS.

Table 9.2 Recommendation on management of female stress urinary incontinence

	Grade of recommendation
For morbidly and moderately obese women, weight loss helps to reduce UI symptoms	A[6]
Medical therapy and rehabilitation should be the first step of treatment	A[6]
Midurethral slings (MUSs) are the gold standard for surgical treatment	A[6, 29, 63,64]
TVT and TVT-O have high long-term success rates	A[6]
Urethral bulking agents are recommended in elderly patients, in patients with increased anaesthesiological risk and in patients who refuse a more invasive procedure	B[6,39]
The best therapeutic approach for recurrent stress incontinence (RSI) after a sling failure should be individualized. The best choice could be to counsel a repeat MUS (retropubic or transobturator) or bulking agents to women with RSI	C[66]

A: Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomized trial

B: Based on well-conducted clinical studies but without randomized clinical trials

C: Made despite the absence of directly applicable clinical studies of good quality

Practice Points

- SUI is highly prevalent in postmenopausal women.
- Surgical therapy should be indicated only after conservative (rehabilitative, local oestrogenic) therapies have failed.
- The synthetic midurethral slings (TVT and TVT-O) are the gold standard for the surgical treatment of SUI.
- Urethral bulking agents are recommended in elderly patients, in patients with increased anaesthesiological risk and in patients who refuse a more invasive procedure.

Future Research

- Preventive measures of SUI.
- Define new therapeutic strategies of SUI in order to achieve an ever better balance between high efficacy and maximum reduction of adverse events.
- To taste newer and lighter midurethral slings.
- Define stem cell (autologous myoblasts, muscle-derived stem cells and autologous fibroblasts) role whether injected in the urethra to treat the intrinsic sphincter deficiency.

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Screening and Management of Female Sexual Dysfunction During the Second Half of Life

10

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10.1 Introduction

Female sexual dysfunctions (FSDs) are common, affecting 25–43% of women, with lack of desire being the most prevalent. Perimenopausal women report lubrication problems, less sexual participation, orgasm problems, absence of sexual fantasies, less sexual gratification, and decreased sexual interest and activity [1]. FSD increases threefold during climacteric years and is more evident after age 60. Female sexuality is a complex process influenced by many personal and partner factors that may negatively affect quality of life. Although one third to one half of mid-aged women display some degree of sexual problems related to aging and hormonal status, determinant factors may vary according to the studied population, study design, and the used approach [2]. Consequently, clinicians who take care of women should evaluate promptly when they may be vulnerable to sexual dysfunction.

FSD has been linked to the following risk factors: poor physical and mental health, postmenopausal status, stress, genitourinary complaints, sexual abuse, bad relationships, religious beliefs, bad economic conditions, intimate partner violence,

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partner's age, and male sexual dysfunctions (premature ejaculation and/or erectile dysfunction) [3, 4]. Contrarily, protective factors include older age at marriage, partner faithfulness, menopausal hormone therapy, exercise, daily affection, intimate communication, having a positive body image or self-esteem, and the use of hormonal contraception [2, 4–6].

The Fourth International Consultation on Sexual Medicine (ICSM) defined female and male sexual dysfunctions, prevalence, and the risk factors according to the opinion of experts and to current and strong supporting literature [7]. Section 17 of the *International Classification of Diseases (ICD) 11 for Mortality and Morbidity Statistics* defines sexual dysfunctions as syndromes in which adults may have difficulty having satisfying, noncoercive sexual activities [8]. Both organizations used the term FSD.

The fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) classifies female sexual disorders as orgasmic disorder, sexual interest/arousal disorder, and genito-pelvic pain/penetration disorder. The DSM-5 further includes four specific subtypes to categorize the onset of dysfunction: (1) lifelong dysfunction indicating a sexual problem present from the first sexual experience, (2) acquired dysfunction identifying sexual health issues that arise after a time of normal sexual activity, (3) generalized dysfunction referring to sexual issues not limited to a specific situation or partner, and (4) situational dysfunction which occurs with specific partners or situations [9]. Despite this, diagnostic criteria require more precision than before; thus, diagnosis of sexual dysfunction requires the duration of at least 6 months and a frequency of 75–100%. Thus, disorders must cause significant distress, and the "interpersonal difficulty" from the DSM-4 definition has been deleted (American Psychiatric Association, DSM 2013 [9]). The present review will use the old and new nomenclature in order to respect the original articles.

10.2 Screening of Female Sexual Dysfunction

During sexual assessment, questions have to be specific, no assumptions have to be made, and a semi-structured interview is recommended [10]. Common questions that may be included are detailed in Table 10.1. The objectives of the sexual history are identifying the predisposing, precipitating, and maintaining factors of sexual symptoms. Menopausal women have the same sexual concerns as young people,

Table 10.1 Common questions in a semi-structured interview (sexual history)

How often do you feel like having a sexual experience?
Are there any situations that help you feel excited?
Do you remember having any sexual fantasy?
Do you ever have erotic dreams?
Do you feel pleasure with sexual activities? Can you explain what you feel?
What do you think has had an influence in the changes you are experiencing in your sexual function?
How long has it been a problem for you?

and no aspects of sexuality should be avoided [11]. It is recommended to ask about women's current relationship and about partner's possible sexual problems.

Regarding postmenopausal women, Cuerva et al. [12] have suggested to initially omit issues relating to sexuality, unless these are raised by the patient. Then, after 5 min, the gynecologist may offer the possibility of talking about sexuality and ask about possible sexual problems. Using this approach in Spanish women, it was found that 12.1% reported sexual problems during the first 5 min of the interview. However, patients with sexual issues increased to 48.0% when they were asked about sexuality after 5 min. The main factors associated with having a sexual problem were the genitourinary syndrome of menopause (GUSM) and having a stable sexual partner. Therefore, openly asking postmenopausal women about sexuality in gynecological consultations increases the number of diagnoses of sexual problems [12].

Clinicians can also screen women, regardless of age, with the help of a validated sex questionnaire or during a routine review of systems. There are many validated screening tools available. We will briefly mention those which provide a comprehensive assessment of female sexuality and those used to search specific sexual disorders. A high prevalence of different sexual dysfunctions has been reported by using these questionnaires as well as correlations with female sociodemographic and health factors and partner health status and behavior.

10.2.1 Changes in Sexual Functioning Questionnaire

The original Changes in Sexual Functioning Questionnaire (CSFQ) is a test that includes 36 items identifying 5 scales of sexual function [13]. The abridged CSFQ of 14 items (CSFQ-14) provides information about sexual desire, arousal, and orgasm. The tool shows construct validity as a global measure of sexual dysfunction, and the individual scales have internal reliability [14].

In Spanish women aged 40–59 years, higher total CSFQ-14 scores (better sexual function) were correlated with better satisfaction with life and inversely correlated to female age and worse menopausal symptoms. The satisfaction with life score correlated with the total CSFQ-14 score and body mass index (BMI) and inversely correlated with economic problems, female tobacco use, lack of healthiness, menopausal symptoms, not having a partner, and partner's lack of healthiness [15].The prevalence of sexual dysfunction (CSFQ-14 score ≤41) was 46% (premenopausal and postmenopausal). Worse sexual function was associated with severe menopause symptoms, low satisfaction with life, and economic problems [15].

About 64.1% of Spanish postmenopausal women (median age 57 years, 17.1% with hypertension, 66.7% with increased BMI, and 48.7% with depressive mood) displayed CSFQ-14 total scores ≤41, suggesting sexual dysfunction. In addition, CSFQ-14 total scores inversely correlated with quality of life (total, psychological, and urogenital), and arousal sub-scale scored inversely with global quality of life and urogenital symptoms and orgasm with the global quality of life. In this postmenopausal sample, sexual function correlated with female educational level and

partner education and regular exercising. There is also an inverse correlation between CSFQ-14 score and depressed mood [16].

10.2.2 Female Sexual Function Index

The Female Sexual Function Index (FSFI) assesses sexual function of the past 4 weeks. It is composed of 19 questions (FSFI-19) grouped in 6 domains or dimensions: desire (items 1 and 2), arousal (items 3–6), lubrication (items 7–10), orgasm (items 11–13), satisfaction (items 14–16), and pain (items 17–19). Each question can be scored in a Likert fashion from 0 to 5. Higher scores indicate better sexual function [17]. Subsequently, Wiegel et al. [18] determined a cutoff value for the FSFI-19 for the definition of FSD (total FSFI-19 scores of 26.55 or less). Indeed, using this cutoff value, it was found that 70.7% of women with sexual dysfunction and 88.1% of the sexually functional ones were correctly classified. The original FSFI-19 has been validated in several languages. It has been used to assess sexuality of pre- and postmenopausal women and among different ethnical populations and different medical conditions, all displaying good reliability values. Its utility has also been proven in a longitudinal cohort of pre-/postmenopausal British women in whom the main predictors of changes in sexual functioning and satisfaction were desire and arousal [19].

A six-item abridged version (FSFI-6) was developed by Isidori et al. [20] covering desire (original item #2), arousal (original item #4), lubrication (original item #7), orgasm (original item #11), satisfaction (original item #16), and pain (original item #17). Each item is scored as the original FSFI-19. The sensitivity and specificity were 0.93 and 0.94, respectively, at the cutoff of 19 or less. The Spanish language version of the FSFI-6 has been used to study mid-aged Spanish women [1, 2]. Upon multivariate analysis, total FSFI-6 scores positively correlated with both female and partner education and inversely (worse sexual function) with female age, partner alcohol consumption and erectile dysfunction, and total Hospital Anxiety and Depression Scale (HADS) scores and urogenital and somatic symptoms [2].

10.2.3 Decreased Sexual Desire Screener

The Decreased Sexual Desire Screener (DSDS) was specifically developed for use by clinicians not experienced in sexual medicine [21]. It is a five-question self-administered survey that helps identify in a time-efficient manner women with generalized acquired hypoactive sexual desire disorder (HSDD). The DSDS is brief, effective, and self-completed and requires no special training for its application and/or interpretation. The screener includes five simple "yes/no" questions. The first four incorporate the prerequisites for a diagnosis of generalized acquired HSDD: (1) previous satisfaction with her desire/interest in sex; (2) a decrease from prior satisfaction; (3) bothered by the decline in sexual desire; and (4) wish for the improvement of her sexual desire [22]. Responses of no previous satisfaction with

her desire or interest in sex and therefore no decrease from prior satisfaction would be consistent with lifelong low sexual desire or interest. In the fifth item, the patient is asked to identify with "yes or no" responses which, if any, of the seven listed group of factors might apply to her situation, potentially having an adverse effect on her sexual desire/interest [21].

Low sexual desire and the associated distress and behavioral adaptations may impact the partner relationship, or problems in the partner relationship may contribute to low desire. If a woman responds "no" to at least one of the first four questions, then she does not meet the criteria for generalized acquired HSDD but could meet the criteria for either situational or lifelong low sexual desire/interest. If the patient answers "yes" to questions 1 through 4 and "no" to all the factors in question 5, she has generalized acquired HSDD. If any of the factors in question 5 are present, the healthcare provider must evaluate and consider differential diagnoses including biological etiologies of low desire as well as decide whether the responses to question 5 indicate generalized acquired HSDD or situational low sexual desire/interest.

If the DSDS suggests the diagnosis of low sexual interest without distress, distressing lifelong sexual desire, or situational low sexual desire, the healthcare provider should consider strategies that engage education and/or counseling or referral to a specialist. In those with generalized acquired HSDD, the healthcare provider may elicit a sexual history or proceed with the process of care [23].

10.2.4 Screening Tests for Women Who Have Sex with Women

Women who have sex with women may also have sexual dysfunction. Shindel et al. [24] used a modified version of the FSFI-19 to evaluate sexual function in women who have sex with women. This was an Internet-based survey that showed that 24.8% of participants presented FSD, which upon multivariable analysis was independently associated with subjective bothered sexual function, overactive bladder, and having a non-female partner or no partner. In addition, FSFI scores, for all domains (but not desire), were negatively affected by the partner factors and overactive bladder.

10.3 Clinical Assessment of Female Sexual Dysfunction

The clinical assessment of FSD starts by a general approach to women's intimacy-related issues and sexual concerns. When working with special patients like menopausal women, it is convenient also asking about how their specific conditions may affect their sexuality. Specific conditions that may be present in relation to the menopause and can affect sexuality are vasomotor symptoms and the GUSM, pelvic floor disorders, metabolic disorders (overweight or diabetes), adverse mood (depression, anxiety, and perceived stress), or sleep disorders.

The diagnosis of FSD is based on medical and sexual history and self-reports (through questionnaires or diaries) [10]. It should include a comprehensive clinical

interview. The medical history is orientated to identify organic, psychological, and medication issues affecting sexuality. Physical examination is only mandatorily required for sexual pain disorders; however, it may help in every sexual dysfunction at least to confirm normal anatomy and the absence of concurrent gynecological diseases like GUSM or pelvic floor disorders. Laboratory tests are not routinely recommended for the evaluation of FSD. Circulating hormone levels poorly correlate with the assessed sexual function. Androgens, estrogens, and prolactin, among other hormones, are known to be involved in sexuality, but their levels are not independent predictors of women's sexual function. The increase in the prevalence of FSD in the context of menopause shows the important correlation between hormonal status and sexual function, but treatment based only on hormonal therapy does not revert the rise in FSD prevalence. Furthermore, partners of mid-aged women may also have sexual dysfunction and/or work or social issues that may in fact be more negative than hormonal changes as a cause of FSD.

10.4 Female Sexual Function and Comorbidity During the Second Half of Life

Both peri- and postmenopausal women need a detailed gynecologic examination that includes the assessment of (1) pelvic floor disorders such as urinary incontinence, fecal incontinence, prolapse, and high-tone pelvic floor dysfunction and (2) menopausal vasomotor symptoms and emotional changes (depressive symptoms, anxiety, perceived stress, fatigue) because each has been associated with decreased sexual desire [25].

10.4.1 Menopause and Sexuality

Postmenopausal estrogen loss typically leads to vulvovaginal atrophy and dryness, as well as changes in genital function via reduced clitoral blood flow and decreased sensory perception. Genital estrogen application may reduce the negative effect of menopause, if initiated in the early postmenopausal years/time [26, 27]. In the Real Women's Views on Treatment Options for Menopausal Vaginal Changes study, 63% of women with symptomatic vulvovaginal atrophy reported that their symptoms interfered with enjoyment of sexual intercourse, and 47% of partnered women indicated it interfered with their relationship [28]. Twelve percent of women without a partner reported that they were not seeking a sexual partner because of symptoms related to vulvovaginal atrophy [29]. More intense vulvovaginal symptoms were positively related with biological conditions such as surgical menopause, sexual inactivity, economic problems, urinary incontinence, and the use of phytoestrogens [30].

Menopause has long been assumed to result in decreased desire due to the decline in ovarian testosterone production and estrogen loss. It has also been theorized that

fluctuations in testosterone levels lead to decreased libido [31]. Circulating estrone sulfate (E1S) and androsterone glucuronide (ADT-G) are the main metabolites of estrogens and androgens in postmenopausal women. In postmenopausal women, estrogens and androgens are synthesized from circulating dehydroepiandrosterone sulfate (DHEA) and the vagina layers and nerve density [32]. Postmenopausal women who do not have vulvovaginal symptoms in fact have 16% higher levels of the mentioned metabolites as compared to those reporting moderate to severe symptoms. In addition, estrone serum levels are 14.5% higher in asymptomatic women as compared to those without vulvovaginal atrophy [33]. These endocrine aspects are pivotal for low genital tract health and postmenopausal vulvovaginal atrophy; its correction may improve sexuality.

Bilateral salpingo-oophorectomy at any age is associated with lower total and free testosterone levels. Women should be asked about other pelvic operations, trauma, or radiotherapy because these may be associated with pelvic pain and altered ovarian function. Other conditions associated with lower androgen levels are less frequent than oophorectomy, and potentially diminished desires include hyperprolactinemia and hypopituitarism, adrenal insufficiency, primary ovarian insufficiency, and chemical ovarian suppression. Conditions that may increase sex hormone-binding globulin (SHBG) levels, and hence lower free testosterone levels, include hyperthyroidism and human immunodeficiency virus infection [34].

10.4.2 Pelvic Floor Disorders

Disorders of the pelvic floor, including pelvic organ prolapse (POP) and stress urinary incontinence, affect approximately one-third of the female population today. There is conflicting evidence regarding the effect of POP on sexual function. Cross-sectional studies have shown that pelvic floor disorders, including POP, are associated with a large sexual dysfunction burden. Several studies have suggested that pain with sexual activity noted prior to surgery may be attributable to POP. Following surgical repair, most patients experience improvements in their sexual response. However, surgical approaches involving abdominal or transvaginal mesh may result in a decline in sexual function and worsening of dyspareunia [35]. On the other hand, sexual function in women with mild and moderate prolapses may improve with physical rehabilitation.

On the other hand, perineal tears may have a negative impact on female sexual function. Ahmed et al. [36] assessed women who had third- or fourth-degree perineal tears after vaginal delivery (study group), comparing them to women who underwent episiotomy or had minor lacerations (control group). After 12 months, and despite slight improvement, sexual function was significantly lower in those who had tears as compared to the control group. Women in the study group showed significant decreases in FSFI domain scores (desire, arousal, lubrication, orgasm, satisfaction, and pain) 12 months postdelivery [36].

10.4.3 Urinary Incontinence

Urinary incontinence may trigger problems that may contribute to FSD, namely, loss of urine during coitus (coitus incontinence), night losses associated to urgency, and fear of bedwetting [37]. Urinary incontinence related to coitus has been described in two ways: urinary incontinence associated to penetration and associated to orgasm ("squirting") [38]. Fear of malodorous and urinary incontinence during coitus has been associated with alteration of image and self-esteem and, thus, a decrease in sexual activity [39].

Urinary urgency symptoms, especially in the presence of mixed urinary incontinence (MUI), were associated with anxiety disturbances, mood disturbances (depression symptoms), and low quality of life related to stress urinary incontinence that ultimately affect sexual life. Altered sexual domains, as measured with the FSFI, may vary in accordance to the type of urinary incontinence: (1) urgency urinary incontinence may relate to a reduction of lubrication and increase of pain associated to sexual activity; (2) MUI has been related to a reduction of sexual satisfaction; (3) while stress urinary incontinence has no impact on sexual activity [40].

On the other hand, postmenopausal women with urinary incontinence had more severe vulvovaginal symptoms and vice versa [30]. Thus, 77.9% of women presented with at least one vulvovaginal symptom, being the three most prevalent complaints dryness, irritation, and itching. In this population, urinary incontinence of any degree was observed in 54.9%, with 42.6% being slight to moderate and 12.3% severe to very severe. These issues have a negative impact on emotional well-being and body self-image [41]. In addition, vulvar symptoms and diseases may associate with a higher risk for urinary incontinence and other urinary symptoms [42].

10.4.4 Endocrine Disorders

Overt or subclinical hypothyroidism and hyperthyroidism have been associated with reduced sexual desire [43]. Oppo et al. [44] reported that abnormal thyroid function (hypo- and hyperthyroidism) significantly impairs female sexual function, as assessed by the FSFI questionnaire, and that restoration to the euthyroid state is associated with a rapid improvement of most of its domain scores. In addition, biochemical restoration to euthyroidism was associated with normalization of desire, satisfaction, and pain domains, while arousal/lubrication and orgasm remained significantly different as compared to healthy euthyroid controls, in spite of some improvement of the orgasm [44]. Correction of hypothyroidism was associated with a normalization of desire, satisfaction, and pain, while arousal and orgasm remained unchanged. Treatment of hyperthyroid women normalized sexual desire, arousal/lubrication, satisfaction, and pain, while orgasm remained significantly unchanged. It seems that the risk of sexual dysfunction is higher among women with nodular goiter [45].

Polycystic ovary syndrome (PCOS) is often characterized by clinical and/or biochemical signs of hyperandrogenism, with or without oligo-anovulation or anovulation, or polycystic ovaries. Women with PCOS have psychological (feeling less

attractive, less feminine, more depressed) and biological (obesity and infertility) factors that may negatively influence their sexual desire [46]. They have worse sexual function, compromising arousal, lubrication, satisfaction, and more pain during the sexual intercourse, besides also having worse self-perception of their health condition than women with normal gonadal function. Obesity/overweight, clinical manifestation frequently associated to PCOS, negatively correlated to the several aspects of quality of life, significantly worsening physical/psychological relation with the environment and health aspects, but it did not correlate to female sexual function [47]. Infertility and alopecia were the most significant factors that contributed to a low FSFI score in women with PCOS, but other clinical characteristics such as hirsutism, acne, irregular menstruation, and android obesity (waist/hip ratio ≥0.8) were not statistically significantly associated with sexual function [48].

10.4.5 Depressive Symptoms

Depressive symptoms are more prevalent in women than in men, and peculiar hormone changes during reproductive years and menopause may contribute to this gender difference. However, differences in socialization, education, socioeconomic factors, discrimination, and male factors may contribute to the high rate observed during female second half of life. Women with climacteric symptoms, anxiety, perceived stress, and insomnia may also contribute to FSD associated with depressive symptoms [49]. The presence of depressive symptoms confers a 50–70% increased risk of sexual dysfunction, and the occurrence of the latter is associated with a 130–210% increased risk of depression [50]. Adding a layer of complexity, most antidepressants are associated with decreased sexual desire [51]. In the Hypoactive Sexual Desire Disorder Registry for Women study, 34% of a clinical sample of women with acquired, generalized HSDD were found to have concurrent depressive symptoms or were being treated with antidepressant medications. However, 58% of women had not been diagnosed or treated for depression before entering the study [52].

10.4.6 Cancer

The pathogenesis of sexual problems in female cancer patients is multifactorial, relating to medical, psychological, physiological, and sociological factors. Although sexual dysfunctions affecting women with cancer belong to the same categories as FSD seen in the general population, addressing sexual health issues in cancer patients still meets multiple barriers. Cancer or its treatment may bring many emotional and physical changes that induce women to feel less interested in sexual life. Therefore, patients with cancer are prone to neglect sexual life, with a negative impact on the relationships with their partners. Moreover, time constraints, reluctance of physicians in investigating this aspect, and embarrassment of women to ask about these problems may represent further difficulties in approaching sexual problems in cancer survivors.

Cancer by itself, as well as its treatment, may directly produce FSD [53]. Decreased sexual desire is a common issue for women after a diagnosis of breast cancer, ranging from 23 to 80% of women [54]. Sexual problems are independently associated with being postmenopausal (potentially provoked by chemotherapy), having vasomotor symptoms, and taking aromatase inhibitors [55]. Chemotherapy increases the likelihood of sexual complaints compared with surgery and/or radiation [56]. In addition, aromatase inhibitor therapy is associated with vaginal dryness, dyspareunia, and decreased sexual desire.

10.4.7 Medication-Induced Sexual Dysfunction

Chronic use of medication is frequent in postmenopausal women. The most frequently used medications are antidepressants and antihypertensive drugs. This circumstance has to be considered both in the diagnostic and in the therapeutic approach.

10.4.7.1 Antidepressants

Sexual dysfunction is commonly associated with depression. Due to this, it is important to assess possible sexual dysfunctions before and after starting antidepressant therapies [57].

Selective serotonergic reuptake inhibitors (SSRIs) are known to induce sexual side effects, having a negative impact on quality of life [51]. Sexual dysfunctions have also been observed, however, less frequently, with antidepressants that increase noradrenaline or dopamine uptake and the 5-HT2 receptor blockers [58]. It is advised to discuss with the patient these aspects and the possible influence that the use of antidepressants could have on her sexual life, sometimes having to switch from serotonergic reuptake inhibitors to other antidepressants [57].

SSRIs and serotonin-norepinephrine reuptake inhibitors are the most commonly prescribed antidepressants [59]. Possible sexual adverse effects of SSRIs are decreased desire, arousal difficulties, and delayed/absent orgasm. The reported incidence varies among studies and ranges from 30 to 70% [60]. Other medications must be considered as a possible source of sexual dysfunction in menopausal women. A detailed list is shown in Table 10.2.

Antidepressants known to cause sexual dysfunctions in more than 25% of users are fluoxetine, paroxetine, sertraline, venlafaxine, and citalopram [51]. They usually affect sexual desire, arousal, and orgasm. Antidepressants like bupropion, vilazodone, and nefazodone are known to have a low impact on sexual function affecting less than 5% of patients [57].

10.4.7.2 Antihypertensive Drugs

It is still not fully known if antihypertensive drugs are associated with sexual dysfunction in women. Hypertension, per se, is associated with sexual dysfunction. It is difficult to ascertain to what extent will the medication or the disease be responsible of the sexual dysfunction [61]. In men, antihypertensive drugs like beta-blockers and diuretics are known to induce sexual dysfunction [62].

Table 10.2 Medications associated with sexual dysfunction

Antidepressant/mood stabilizers
Selective serotonin reuptake inhibitors
Tricyclic antidepressants
Benzodiazepines
Lithium
Antipsychotics
Cardiovascular medications
Beta-blockers
Digoxin
Lipid lower medications
Other drugs
Oral contraceptives
Gonadotropin-releasing hormone agonist
Antiandrogens
Neuroleptic medications
Steroids
Antiepileptics
Antihistamines
Anticholinergics

Data from the Systolic Blood Pressure Intervention Trial with 690 women and 26.5% sexually active did not find differences in sexual activity among hypertense women using or not using antihypertensive drugs. However, the study found that women taking an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker were more likely to be sexually active than women not using these medications [63]. Data from the National Social Life, Health, and Aging Project found that women using diuretics had a decreased sexual activity [62].

Although further investigation is warranted, considering what is known from men, and the available data related from women, angiotensin-converting enzyme inhibitor or angiotensin receptor blockers may be considered the antihypertensive drugs with less impact on women's sexual function.

10.5 General Management

After the menopause, the most common forms of sexual dysfunction are genitopelvic pain/penetration disorder, sexual interest/arousal disorder, and female orgasmic disorder [64]. Using a stepped care approach is recommended. The PLISSIT model (permission, limited information, specific suggestions, and intensive therapy) is still relevant and recommended to be followed when managing sexual dysfunction [65].

After the sexual interview, the patient's expectations must be assessed. This is useful for checking up on future progress. For many postmenopausal women, sexual intercourse can remain as the main target when seeking for help. Satisfactory sexual intercourse may be one of the goals in many cases. Another good option for checking progress is the use of validated questionnaires.

For the first two steps of the PLISSIT model (permission and limited information), the clinician must work mostly as an education provider [65]. As there is no standard in terms of sexuality, clinicians must avoid giving standard information and provide reassurance [66]. It is important evaluating all possible sexual issues before starting any treatment. Education about sexual anatomy, sexual physiology, and the changes that a woman may suffer after menopause can reduce anxiety and increase acceptance of the normal and pathological changes that may take place [11].

Patients have to be aware of the high prevalence of the GUSM and possible preventive strategies and treatments. It is also important to focus on education aimed at improving the quality of sexual relationship with her partner or partners. It is common that the partners of postmenopausal women may also suffer of chronic medical conditions limiting sexual interaction. If there is a physical limitation, sexual positions or the use of pillows can be taught as part of the specific suggestions [67, 68].

In the third step (specific suggestions), non-pharmacologic options should initially be offered. Non-pharmacologic options include counseling, couple therapy, pelvic physical therapy, psychotherapy, cognitive-behavioral therapy, privacy promotion, body image improvement, and the use of sexual devices. Education on moisturizers, lubricants, and sexual devices and on the possible need of longer foreplay should also be offered. Studies refer that more than 50% of patients describe their treatment as successful after sex therapy [69].

Sensate focus therapy is actually used in most of sexual dysfunctions after menopause. Patients are taught to perform graded series of sensual touching exercises. The objectives of sensate focus therapy are to improve intimacy and reduce sexual-related anxiety while restarting sexual activity gradually. Sensate focus therapy is known to have an important effect on sexual satisfaction and improve symptomatology [70].

When sexual dysfunction has been suffered for a long period, or is complicated with other comorbidities, education may not be enough, and a specialized sex therapy may be indicated, starting the last step (intensive therapy) [71].

10.5.1 Genito-Pelvic Pain/Penetration Disorder

The genito-pelvic pain/penetration disorder is defined when one of the following criteria is presented: pain experienced during attempted or as a result of vaginal penetration; pain, fear, or anxiety in anticipation to intercourse; and tensing of the pelvis in response to attempted penetration [9].

Genito-pelvic pain/penetration disorder is common among postmenopausal women. There are specific conditions in relation to climacteric that can lead to or worsen genito-pelvic pain/penetration disorder. These specific conditions are the GUSM, pelvic floor disorders, and pharmacology-related problems.

10.5.1.1 The Genitourinary Syndrome of Menopause

The GUSM is defined as the combination of signs and symptoms associated with estrogen deficiency that appear in the external genitals, pelvic floor, vagina, urethra, and bladder, which are generally associated to sexual dysfunction [72]. The term was intended to be more inclusive with other symptoms that are not limited to the

vulva and the vagina [73]. It is estimated that the GUSM is present in 50% of postmenopausal women, from 25% in perimenopausal women to 70% in women over 70 years [74]. However, appropriate treatment of different vulvovaginal and urinary complaints requires individual assessment of its components in order to provide a more successful treatment and results [75]. Despite the promotion of some "magic" (panacea) treatments for the syndrome, women still complain because some present a mix of clinical entities that do not respond to a single intervention.

As previously mentioned, low genital tract atrophy is highly prevalent in postmenopausal women, and symptoms' severity is progressive. Vaginal moisturizers and topical estrogen applications have been recommended for decades and still have a place, especially among young postmenopausal women [26]. However, their efficacy is reduced over time since menopause onset increases. A new approach to prevent and treat vulvovaginal atrophy could be based on the vaginal use of DHEA-S or prasterone. Several double-blind, placebo-controlled, randomized trials have shown that daily intravaginal 0.50% prasterone improves moderate to severe dyspareunia and dryness [76]. Oral use of ospemifene is also a good option for women who are not candidates or do not wish to use vaginal treatments [77].

10.5.1.2 Pelvic Floor Disorders

Pelvic organ prolapse or incontinence can be a physical impediment to sexual intercourse. In addition, prolapse and incontinence often lead to a deterioration of the body image and to the capacity of feeling sexually attractive [78]. Urinary and fecal incontinence, per se, can cause sexual dysfunction. These problems usually require surgery as a treatment, being sexual satisfaction after pelvic surgery influenced by the type of performed surgery [79]. Hysterectomy for organ prolapse has been reported as having a positive effect on sexual functioning [80]. Total vaginal meshes are associated with an increase in dyspareunia [81].

General recommendations for managing patients with pelvic floor disorder and sexual dysfunction are:

- Pelvic floor muscle training has demonstrated an improvement in desire, arousal, and orgasm and should be recommended [82].
- Weight control is recommended as an essential part of the specific suggestions. Increased BMI represents a risk factor for both urinary incontinence and sexual dysfunction [83].
- A careful individualized selection of patients and materials prior to any pelvic floor surgery or implantation of vaginal meshes is recommended [79].

10.5.2 Female Sexual Interest/Arousal Disorder

The female sexual interest/arousal disorder is defined by the presence of at least three of the following criteria: reduced/absent interest in sex, few erotic thoughts or fantasies, decreased start and rejection of sex, little pleasure during sex most of the time, decreased interest in sex even when exposed to erotic stimuli, and little genital or non-genital sensations during sex most of the time [9].

As defined in the DSM-4, the HSDD is currently part of the female sexual interest/arousal disorder. The loss of desire is estimated to affect more than 40% of all postmenopausal women, being the most common sexual disorder in this population [12, 84]. The management of the HSDD starts, as stated in the "general management" epigraph, with a stepped care approach. Simultaneously or if the non-pharmacological approach fails, there are specific pharmacological treatments for HSDD.

10.5.2.1 Hormone Therapy

Despite knowing that the level of circulating hormones poorly correlates with observed sexual function, hormone therapy has shown to improve sexual function in specific groups of postmenopausal women [85–87].

Estrogens have been suggested as a possible treatment for HSDD. Obtained evidence from the Women's Health Initiative shows that systemic estrogen did not improve sexual satisfaction or desire [88]. Testosterone has been studied and used for the HSDD. Due to adverse effects, most of the presentations are no longer available, and the use of testosterone is almost restricted to topical formulations. Common side effects related to the use of testosterone include decrease of high-density lipoproteins, hirsutism, acne, and virilizing changes with high dosages [89, 90]. However, the UK NICE Menopause Guideline recommends testosterone supplementation for menopausal women if hormone replacement therapy alone is not effective [91], but no pharmaceutical preparation has been approved in most countries.

Systemic DHEA failed at improving sexual desire in peri- and naturally postmenopausal women but was effective when used in women with adrenal insufficiency [92]. However, a more recent evidence from a meta-analysis suggests that DHEA-S supplementation may improve female sexual function, although with some androgenic side effects [93].

Tibolone has shown to improve sexual function and the satisfactory sexual event rate. In a randomized controlled trial, women using oral tibolone experienced a greater increase in the satisfactory sexual event rate and a reduction in sexuality-related personal distress, compared to the control group using estrogen plus norethisterone [94–96]. The oral use of ospemifene has shown to significantly increase total FSFI scores when compared to placebo, in the domains of sexual pain, arousal, and desire but only among women suffering of GUSM [77].

The use of vaginal DHEA for 12 weeks may improve four domains of sexual function and the desire domain as assessed with the Menopause Specific Quality of Life and Abbreviated Sex Function questionnaires in comparison to placebo. The arousal domain was improved by 68%, arousal/lubrication by 39%, orgasm by 75%, and dryness during rapport [97].

10.5.2.2 Central-Acting Agents

Flibanserin is the only drug in the USA approved by the Food and Drug Administration for female HSDD [98]. Flibanserin is a serotonin receptor 1A agonist/serotonin receptor 2A antagonist that causes a transient central decrease of serotonin and an increase of dopamine and norepinephrine in selected brain areas. Daily oral use of 100 mg of flibanserin at bedtime has shown to increase sexual

desire, improve the number of satisfactory sexual events, and reduce distress associated with low sexual desire in postmenopausal women [99, 100]. Most frequent adverse effects include dizziness, somnolence, nausea, fatigue, and hypotension making 8–13% of women discontinue the drug [101].

Bupropion is a commonly used antidepressant. Bupropion is a norepinephrine and dopamine reuptake inhibitor with no direct serotoninergic effect. In clinical trials bupropion has shown to improve sexual satisfaction, function, and desire in premenopausal women when compared to placebo [102].

Bremelanotide is a melanocortin 3 and 4 receptor agonist. In clinical trials bremelanotide has shown to increase the number of sexually satisfying events in premenopausal women [103]. No randomized controlled trials have been performed in postmenopausal women. Currently a subcutaneous formulation is being studied. It is administered 45 min before anticipated sexual activity.

10.5.2.3 Natural Remedies

Tribulus terrestris is an annual plant that might increase levels of bioavailable testosterone. It has been used in traditional Indian medicine for the improvement of sexual function. A randomized, placebo-controlled trial of 30 premenopausal women in each group showed an improvement in desire, arousal, lubrication, satisfaction, and pain domains of the FSFI [104].

Trigonella foenum-graecum is a traditional herbal drug and spice. In a randomized, placebo-controlled trial of 115 women (*Trigonella* $n = 59$ and placebo $n = 56$) experiencing menopausal symptoms, treatment with *Trigonella foenum-graecum* seed extract significantly improved sexual function [105].

10.5.3 Female Orgasmic Disorder

The female sexual orgasmic disorder is defined by reduced intensity, marked delay, infrequency, or absence of orgasm [9]. The female orgasmic disorder is commonly associated with female sexual interest/arousal disorder; due to this, most of the treatments described for female sexual interest/arousal disorder are useful when treating patients affected with female orgasmic disorder. Specific treatments for the female orgasmic disorder include directed masturbation, coital alignment, sexual enhancement products, and specific pharmacological treatments such as phosphodiesterase type 5 inhibitors and oxytocin.

Masturbation training consists of gradual series of exercises starting with genital auto-exploration, followed by arousal stimuli and ending in masturbation to orgasm (normally in 10–11 sessions) [106]. Various trials have evaluated masturbation training, showing that it increases orgasm consistency, sexual self-acceptance, and sexual pleasure [107].

The coital alignment technique helps improving the frequency of orgasms when having intercourse with a male partner. The coital alignment technique is a variant of the missionary position. The male partner lies above the woman and moves upward until the dorsal side of his penis presses against the clitoris [108].

Improvement in orgasm consistency and sexual pleasure has been observed after using the coital alignment technique [108, 109].

Vibrators and sexually explicit media are often used in masturbation training when enhancing sexual stimulation is needed. Vibrators produce a different orgasmic pattern; they allow more frequent and faster orgasms. It must be taken into consideration that some women may not consider a faster orgasm a better orgasm [110]. Considering that postmenopausal women may not know much about different sizes and types of vibrators and dildos, there is a need for attending physicians to know about the different sizes and materials [111]. Some products may be comfortable for vaginal or anal insertion, but others can cause genital trauma.

Phosphodiesterase type 5 inhibitors have some benefits on arousal and orgasmic function. These drugs work augmenting genital blood flow through the guanosine monophosphate and nitric oxide system. Most studies regarding phosphodiesterase type 5 inhibitor use do not show a clear clinical improvement in women. Phosphodiesterase type 5 inhibitors do not act on central mechanisms associated with subjective sexual experience; this may be the reason why there is no evidence of improvement on women's sexual subjective experience [112].

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Current Treatment Modalities for the Genitourinary Syndrome of Menopause

11

Cemal Tamer Erel

11.1 Introduction

According to the definition of the International Society for the Study of Women's Sexual Health and the North American Menopause Society, genitourinary syndrome of menopause (GSM) describes all symptoms and signs related to external genital, urological, and sexual complaints secondary to hypoestrogenism during menopause [1]. GSM is a more inclusive term than the term previously used as vulvovaginal atrophy, atrophic vaginitis, or urogenital atrophy. GSM is quite commonly seen among premenopausal (15%) and postmenopausal (50%) women [2–4]. GSM usually remains underdiagnosed and remains untreated. Because either the women may be reluctant to mention about their most confidential problems or the clinicians may ignore to ask for the specific symptoms for GSM. It has been remarked that the prevalence of GSM increased by the years after menopause [5].

Although GSM is commonly seen during menopausal period, it may be observed during reproductive period. In the reproductive period, GSM can be related to other physiological or iatrogenic conditions and disorders associated with hypoestrogenism such as women taking oral contraceptives (OCs), those with breast cancer receiving aromatase inhibitors (AIs) and selective estrogen receptor modulators (SERMs), those using gonadotropin-releasing hormone agonist (Gn-RHa) because of different gynecological diseases, and women with hyperprolactinemia or during lactation and hypothalamic amenorrhea.

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11.2 Symptoms and Signs

Symptoms and signs of GSM can be usually evaluated in two categories: genito-sexual and urological. Genito-sexual symptoms are related with the vulvovaginal atrophy. Most common symptoms are vaginal dryness, dyspareunia, loss of libido, lubrication, arousal and dysorgasmia, bleeding or spotting during intercourse, vulvovaginal pain, feeling of pressure, leukorrhea, irritation, burning, tenderness, itching, and vulvovaginal color changes. Since thin vulvovaginal epithelium is inadequately lubricated, intercourse can bring about ulceration and fissures causing dyspareunia and bleeding. Painful intercourse can induce the anxiety toward expected sexual act. Most common signs in the examination of lower genital tract are thinning or pallor of vaginal epithelium, loss of vaginal rugae, increased vaginal friability, intravaginal retraction of urethral meatus, vaginal stenosis and shortening, reduced vaginal-cervical secretion, increased vaginal PH (alkaline), vaginal vault prolapse, cystocele-rectocele-uterine descensus, sagging labia majora due to decreased turgor and elasticity, labial atrophy and shrinkage, fusion of labia minora, shrinkage of clitoris, atrophy of Bartholin glands, introital stenosis, thinning and whitish-reddish color of vulvar skin, and thin gray sparse pubic hair.

On the other hand, most commonly seen urological symptoms and signs result from the uroepithelial atrophy and cystocele. These symptoms are urinary frequency, urgency, dysuria, hematuria, nocturia, postvoid dribbling, stress and/or urge incontinence, and recurrent urinary tract infection. During examination someone can detect the urethral prolapse, polyp, caruncle, retraction of the urethral meatus inside the vagina, cystocele, and stenosis of urethral meatus.

Various epidemiological studies suggested that the vulvovaginal discomfort such as dryness, dyspareunia, itching, burning, and soreness was more prevalent than the urological symptoms (dysuria, urgency, frequency, or incontinence) [5–7]. Most common signs were found as mucosal dryness, loss of vaginal rugae, thinning of the mucosa, fragility, and petechial bleeding.

On the other hand, it has been noticed that GSM was more prevalent and severe in postmenopausal breast cancer survivors who were especially on chemotherapy or hormonotherapy than the normal postmenopausal women [8]. Although both AIs and SERMs are most frequently used drugs as an adjuvant therapy for women with breast cancer, AIs have better outcomes than SERMs [8–10]. These two drugs are recommended to be used at least 5 years in order to reduce the recurrence of risk and death [9]. Although functional mechanisms of these drugs are different, GSM is more severely experienced by AIs users than SERMs.

11.3 Pathophysiology

In the female urogenital area, the vulva is covered by keratinized stratified squamous epithelium, whereas the vestibule, urethra, and vagina are covered by nonkeratinized stratified squamous epithelium. Beneath the uro-vaginal epithelium, there are three distinctive layers: (1) connective tissue layer, (2) muscular tissue layer,

and (3) adventitia. In addition, there is a very rich blood vessel network nourishing these anatomic structures. During the embryologic development of female genitalia, trigone of the bladder, urethra, vestibule, and lower two thirds of the vagina arises from the urogenital sinus. Therefore, all anatomic and histologic structures of female urogenital area express estrogen receptors (both alfa and beta) [2, 8, 11, 12].

Estrogen proliferates the stratified squamous epithelium. Basal cell layers of the vaginal epithelium store glycogen under the influence of estrogen. Predominantly present *Lactobacillus* metabolizes glucose into lactic acid which lowers the vaginal pH to maintain an acidic milieu. Estrogen increases the blood flow in this region [2, 8, 11, 12]. Estrogen induces the collagen-elastin synthesis and production of glycosaminoglycan matrix of the connective tissue [13, 14]. Estrogen also stimulates local production of some substances (cytokines, growth factors) which may play an important role in the regeneration of the genital tissue [13, 14]. Estrogen reduces the inflammatory response of the genital tissue. Estrogen restores the number of sensory nerve ends in the vulvar region [13, 14].

Therefore, estrogen provides the strength of the epithelium, connective and striated muscle tissue in the urogenital region. Expandability and distensibility of vaginal wall increase, rugae formation appears, vulvovaginal secretion increases, and vaginal PH decreases. All conditions which lead to estrogen deficiency cause symptoms of urogenital atrophy as mentioned above.

11.4 Quality of Life (QoL)

The QoL of an individual is usually described as a status of being healthy, comfortable, and able to participate in or enjoy life events. There are generic and disease-specific questionnaires in order to measure the impact of GSM on QoL. However, the measurement of QoL for GSM has many limitations. There is not a unique questionnaire addressing the whole issue of GSM. Since the vaginal discomfort is more frequently encountered in the clinics, the impact of urological symptoms or symptoms due to vulvar discomfort on QoL is usually neglected. According to the new classification of the American Psychiatric Association, genital pain and penetration disorder cause female sexual dysfunction [15]. Genital pain and penetration disorder per se can also trigger the hypoactive sexual desire disorder. Therefore, a doctor should investigate the possible complicated sexual life of a woman with GSM in order to understand the impact of vaginal discomfort on QoL. At this point, either women may be reluctant to open themselves to their doctors about the problems because of personal embarrassment and cultural reasons, or the doctors may not ask the required questions during consultation, since they feel uncomfortable to discuss the sexual issues or have a lack of knowledge about the problems and treatment options [15]. In a recent review article, it has been stated that only 40% of healthcare professionals have asked and talked about their patients' sexual lives [15].

In terms of giving an idea, the Real Women's View of Treatment Options for Menopausal Vaginal Changes (REVIVE) survey claimed that 56% of the participants reported their symptoms regarding the vulvovaginal atrophy with their

health-care professionals [7]. On the other hand, European arm of the REVIVE study reported that health-care professionals asked and talked about symptoms due to vulvovaginal atrophy with 62% of the postmenopausal women participating the survey [16]. Nevertheless, only 10% of the participants initiated the conversation. Recently, the Women's EMPOWER Survey informed that most of the participants were unaware of the symptoms of vulvovaginal atrophy and they did not realize that the condition was a health issue [17]. Instead, these postmenopausal women accepted their symptoms related to vulvovaginal atrophy as a natural part of aging. Moreover, 50% of the women in this study had never used a treatment, and 70% of them had never discussed their symptoms with their health-care professionals.

More or less different studies showed the same results regarding the negative impact of vaginal discomfort and dryness due to vulvovaginal atrophy on sexual life, self-esteem, emotional well-being, and in summary overall QoL [6, 7, 18–20]. The Clarifying Vaginal Atrophy's Impact on Sex and Relationships (CLOSER) survey included 1000 North American menopausal women with their male partners [20]. The majority of male participants of this study reported vaginal dryness as a cause of avoidance of intimacy (78%), loss of libido (52%), and painful sex (59%).

The other issue is the assessment of QoL in sexually inactive women. Therefore, the new questionnaire which would address the sexually inactive women should be developed and validated for the assessment of QoL.

11.5 Examination and Assessment

Careful history taking and examination are the essential parts to identify the impact of GSM on QoL. In the history, previous medical, surgical, gynecological, and obstetric predisposing risk factors to GSM should be identified. Especially other hypoestrogenemic states such as women taking OCs, AIs, SERMs, Gn-RHa, chemotherapy, and radiotherapy and women with hyperprolactinemia or hypothalamic amenorrhea, and women undergone to oophorectomy should be investigated in detail. Habits related with genital hygiene such as the use of soaps, bath gels, powders, lubricants, condoms, pads, tampons, and panty liners or habits to trim or shave the pubic hair should be also asked. Patient's sexual history should include the duration of partner relationship, frequency and quality of sexual activity, and presence of a previous sexually transmitted disease. Lifestyle, diet, exercise, smoking, and alcohol consumption should be taken into consideration.

Most bothersome component of GSM should be determined. The severity and duration should be explored. As mentioned above, since many patients perceive that GSM is an embarrassing issue, they are reluctant to talk about it. Therefore, as the North American Menopause Society (NAMS) suggested, the health-care professionals should be proactive in inquiring the GSM [21].

In the examination, the whole genital area including the vaginal canal and cervix should be carefully evaluated. The vagina may not have normal rugae form and may show thin-pale, shiny epithelium. There may be some erythematous patches or yellowish-green discharge on the vaginal wall. Vaginal canal may have become

narrow and short, and cervical and vaginal secretions may be absent. Therefore, vaginal canal may be stenotic and dry. As a result, during the vaginal speculum insertion, the patient feels pain. Therefore, the small-sized vaginal speculum should be preferred. Someone should also evaluate to determine the pelvic organ prolapse into the vaginal canal.

Inspection of the vestibule and retraction of the urethra toward vaginal canal, urethral caruncle, polyp, prolapse, or stenosis should be looked for. Stenosis of the vaginal introitus should be noted. Digital exam may elicit the tonus of the pelvic floor muscles whether they are tense or relax. Digital exam is also important to assess the factors which lead to sexual dysfunction.

The entire vulva, from the mons pubis to the anus, should be inspected, especially the clitoris, prepicium, labia minus, and labia majora. Dermatological lesion should not be missed out. Labial fusion, shrinkage of the clitoris, and sagging labia majora should be noted. Any change in color, turgor or presence of fissure, erosion, ulceration, finally pubic hair, Bartholin glands, and perianal area should also be checked.

During the examination of the genital area, vaginal smear test and PH measurement should be done for the assessment of vaginal health. Any suspicious lesion in the vulvovaginal area should be stained by Toluidine blue, and biopsy should be taken in order to exclude a malignancy. Biopsy may also be performed to differentiate some dermatological lesions. Q-tip test may help in the diagnosis of stress urinary incontinence. Q-tip can also be used to identify the painful area in women suffering the vulvodynia. Of course, in order to complete the exam, transvaginal ultrasonography is going to give us additional information regarding the uterus, endometrium, and adnexa.

11.6 Treatment Options

GSM is a chronic condition and requires long-term therapy. The essential of the therapy should aim to maintain normal vulvovaginal physiology. The therapy of GSM includes lifestyle modifications and non-hormonal, hormonal, and laser treatments.

11.6.1 Lifestyle Modifications

Recently as suggested by the European Menopause and Andropause Society (EMAS), optimizing the lifestyle modifications for maintaining postreproductive health should be the principal purpose [22]. Since smoking is a risk factor leading to hypoestrogenism, it may worsen the GSM [2, 4, 23]. Being overweight is associated with two- to fourfold increased risk of GSM compared to normal women [11]. Exercise, especially strengthening the pelvic floor muscles, may reduce the GSM [24]. Sedentary lifestyle may increase the GSM [5]. Continuation of sexual activity may prevent the GSM [2, 4, 5]. Overall, sexual activity may have a positive impact on maintaining the normal vulvovaginal physiology in climacteric women.

11.6.2 Moisturizers and Lubricants

The North American Menopause Society [NAMS] recommends the vaginal lubricants and moisturizers as first-line therapy for GSM [21].

Moisturizers contain plant-based or synthetic (mostly polycarbophil-based) polymers for adhering the epithelial cells on the vaginal wall. These substances save and release water into the epithelium to hydrate till the balance of the water content inside the epithelium is equalized. Hence, moisturizers optimize the water content of the epithelium. Moisturizers lower the vaginal PH as well. They help the tissue regeneration and maintain the tissue integrity. Therefore, moisturizers should be continuously used for a long term [2, 4, 12, 25]. The Endocrine Society has recently suggested the vaginal moisturizers to be used at least twice weekly in women with GSM [26].

On the other hand, lubricants are applied to the vulvovaginal area and only used during sexual intercourse. They prevent the dryness and friction which may cause vaginal irritation, burning, bleeding, or discomfort. Lubricants may be used concomitantly with moisturizers. Lubricants are different types of products which may be water-, oil-, silicone-, or hyaluronic acid based. In the market, different lubricants have varying different features in terms of pH and osmolality. Higher osmolality may cause irritation and damage the epithelium of the vaginal wall. Glycol content of the lubricants determines osmolality of the lubricants, whereas paraben content in the lubricants which is stated as an endocrine-disrupting chemical due to the weak estrogenic activity may have a role in carcinogenesis [27, 28]. The PH of the lubricants should be the same as in the vagina of a reproductive woman [2, 4, 12, 25]. While the petroleum content in some lubricants may increase the risk of bacterial vaginosis, oil content may increase the *Candida* species [29].

In conclusion, the right moisturizers and lubricants provide similar moisture, PH, osmolality, and microbiata of the normal vaginal epithelium to an atrophic, dry vaginal epithelium. Vaginal secretion resembles those of normal vaginal epithelium during the reproductive period. Hence, they facilitate sexual intercourse by preventing the vaginal dryness, pain, and discomfort. In addition, ideal moisturizers and lubricants should not cause adverse reactions. Since the hormonal use is contraindicated in women with breast cancer (BC), both moisturizers and lubricants can effectively be a choice of treatment [30].

11.6.3 Hormonal Treatments

Hormonal treatments can be applied as local or systemic route. Estrogens, androgens, SERMs, and selective tissue estrogenic activity regulator (STEAR) are used for the treatment of GSM.

11.6.3.1 Local or Systemic Estrogen Therapy

Estrogen therapy is an effective treatment for women with GSM. Estrogen restores the normal vaginal secretion, microbiota, PH, epithelial color, and appearance. It

increases epithelial proliferation up to the superficial layer, hence, the vaginal maturation index. Estrogen stimulates the glycogen storage in the superficial squamous cells. Lactobacilli are dominant in the vaginal milieu in the presence of estrogen. Therefore, in the dominance of *Lactobacilli*, production of lactic acid from the glycogen lowers the vaginal PH. Estrogen also induces the collagen synthesis in the connective tissue layer surrounding the vagina which maintains the elasticity, coaptability, and integrity of the vagina. Estrogen does not only display those effects on the vagina but also on all other tissues having the estrogen receptors in the urogenital area.

Currently in the market, a wide variety of local vaginal estrogen products are available for the treatment of GSM. These are estradiol-containing tablets and rings; estriol pessaries, creams, and ovules; and conjugated estrogens. According to the guidelines of many international societies concerned with menopause, all doses and types of local estrogen preparations, currently available, are effective in the treatment of GSM [21, 22, 26, 31–34]. Those are especially effective in the improvement of vaginal dryness, discomfort, dyspareunia, dysuria, urgency, frequency, recurrent urinary tract infections, and incontinence. Indeed, the Cochrane 2016 review pointed out that there was no evidence of a difference in efficacy in the treatment of vaginal atrophy between the various intravaginal estrogenic preparations [35]. It also signified no evidence of a difference in adverse events (such as vaginal irritation, itching, or discharge) in various estrogenic preparations. However, the most appropriate dose, regimen, duration of use, and route of administration should be carried out for effectiveness and safety issues in the treatment of GSM when the estrogen application is considered [34]. Therefore, lower dose and limited duration of use (less than a year) of these vaginal preparations usually do not need the use of progesterone to encounter the unopposed estrogen for the protection of endometrial hyperplasia [21, 31–36]. Recently, it has been reported that vaginal softgel capsule containing solubilized estradiol might provide an alternative choice to current local treatment for postmenopausal women with GSM [37, 38]. This softgel has an advantage of applying without the need of an applicator and being adhesive to the vaginal epithelium. The treatment of the GSM with the lower dose of vaginal estrogens does not have any impact on exceeding the levels of serum estrogen concentration above the postmenopausal levels [12]. At the beginning of the therapy, the vaginal estrogen absorption due to the atrophy may be excessive, but later, the absorption rate decreases.

On the other hand, the main indication for systemic hormone therapy (HT) administering either oral or non-oral route is the vasomotor symptoms. Beyond the vasomotor symptoms, GSM is another indication for the use of systemic HT. HT is given as estrogen plus gestagen to a woman with intact uterus but given as only estrogen to a woman without a uterus. The chronic use of systemic unopposed estrogen therapy can cause a stimulation on the endometrium leading to proliferation, hyperplasia, and finally carcinoma. There are also unusual side effects of systemic HT such as breast tenderness, vaginal bleeding or spotting, nausea, and weight gain. Systemic HT may have an increased risk of stroke, venous thromboembolism, coronary heart diseases, and breast cancer depending upon some variables (such as

age, the time between the last menstrual period and the initiation time for the HT, estrogen-only or estrogen plus progestin therapy, type and administration route of estrogens and progestins) [26, 32, 34]. Oral systemic HT may not relieve hundred percent of the GSM (75% relief) as even the vasomotor symptoms (85% relief) [39]. Oral estrogen administration may increase the hepatic production of sex hormone-binding globulin, then may cause a decrease in the free form of estradiol in the circulation. Therefore, non-oral route such as patches and gels may be preferred in women with GSM who do not give a sufficient response to orally administered HT.

Systemic HT is contraindicated for breast cancer survivors suffering from GSM while they are using adjuvant hormone therapy [9, 10]. Non-hormonal management should be the first choice in the treatment of breast cancer survivors with GSM [3, 15]. Although there is not a solid evidence regarding the safety issue of using the vaginal lower dose of estrogens in these women, ultralow dose of local estriol or very low-dose (4 μg) softgel capsule of estradiol may be offered for the shortest time [38, 40]. Since AIs especially reduce the blood estradiol level, low-dose vaginal estrogens should not have any increased impact on BC. Management should be based on consulting the situation with the oncology team and having information about the patient's preference, need, and perception regarding the benefits and risks. Informed consent should absolutely be provided.

There is no scientific evident data that local vaginal estrogens increase the risk of breast and endometrial cancer and thromboembolism in women with GSM. Local vaginal estrogens do not treat the vasomotor symptoms nor prevent the osteoporosis.

11.6.3.2 Tibolone

Tibolone is structurally related to 19-nortestosterone derivatives and exhibits weak estrogenic, progestogenic, and androgenic activities [41]. Tibolone is primarily metabolized into δ4, 3β-hydroxy, and 3α-hydroxy isomers. These isomers have different binding affinities for estrogen, progesterone, and androgen receptors. Tibolone has estrogenic effects on vaginal tissue, whereas it shows androgenic effects in the brain. Therefore, tibolone improves vaginal dryness, reduces dyspareunia, and increases libido. Unfortunately, tibolone should not be used in breast cancer survivors with GSM because of a significant increase in cancer recurrence rate [42]. In summary, tibolone may be a good alternative choice for postmenopausal women with GSM, especially suffering from sexual dysfunction not only due to genital pain and penetration disorders but also due to hyposexual desire disorders.

11.6.3.3 Selective Estrogen Receptor Modulators (SERMs)

SERMs exhibit tissue-specific estrogen receptor agonistic or antagonistic activity. Different SERM compounds show different effects in the different tissue having different molecular and functional complexity of the estrogen receptors, mainly different expression patterns of estrogen receptor alpha and beta [43]. SERMs interact with different coactivator and corepressor molecules, and then they cause a conformational change in the complex of estrogen receptor dimer and in the gene expression [44]. Most of SERMs show estrogen receptor agonistic activity on bone,

whereas most of them have an antagonistic effect on the breast. Moreover, excluding bazedoxifene, all other SERMs display the agonistic activity on estrogen receptors in the endometrium [44].

Ospemifene from the SERM family is recently used for the treatment of symptoms due to vulvovaginal atrophy in women who do not want to use estrogen-based therapy or have a contraindication to use the estrogen. Ospemifene has agonistic effects on vaginal tissue [45]. Recommended dose (60 mg/daily) of ospemifene ameliorates dyspareunia and vaginal dryness and improves the maturation index and vaginal PH [45–47]. A very recent publication of six, phase II and III randomized, double-blind, multicenter placebo-controlled studies, evaluating the effects of ospemifene 60 mg on the breast, cardiovascular system, and bone in postmenopausal women, has reported that the most commonly reported treatment-emergent adverse events (TEAEs) with ospemifene were hot flush (8.5%) and urinary tract infection (6.5%) [48]. Discontinuation of ospemifene due to TEAEs was found to be low (7.6%). When the long-term use (up to 52 weeks) of ospemifene for the treatment of GSM was evaluated in terms of adverse effect on breast cancer, cardiovascular disease, deep vein thrombosis, and endometrial stimulation, it seemed to be safe. But, there does not exist solid evidence regarding the safety issue of ospemifene use in the breast cancer survivors as well as the evidence regarding the efficacy issue on urologic components of the GSM [9, 10, 49].

11.6.3.4 Tissue-Selective Estrogen Complex (TSEC)

The TSEC is a compound which comes from merging a SERM (bazedoxifene, BZA) and an estrogen (conjugated equine estrogen, CEE). Therefore, an ideal TSEC would combine the estrogenic agonistic activities (on vasomotor symptoms, vulvovaginal atrophy, and bone) with the estrogen-antagonistic activities (on the endometrium and breast).

Indeed, a review of the randomized controlled studies regarding the efficacy of a certain type of TSEC compound (BZA plus CEE) has clearly shown the improvement in the maturation of the vaginal epithelium and PH [26, 49, 50]. An increase in the percentage of superficial cells while a decrease in the parabasal cells was observed. It has been reported that there was a reduction of the severity in GSM including dyspareunia, vaginal dryness, itching, and burning, in both two different doses of BZA plus CEE (20 mg BZA plus 0.425 mg CEE and 20 mg BZA plus 0.625 mg CEE). Moreover, BZA plus CEE-specific TSEC reduces the hot flushes and sleep quality and subsequently improves the quality of life. It has a positive impact on the bone, whereas it exerts estrogen-antagonistic activity on the breast and endometrial tissue. But there is no solid evidence regarding the safety issue of BZA plus CEE use in the breast cancer survivors as well as the evidence regarding the efficacy issue on urologic components of the GSM [9, 10, 26, 49]. Venous thromboembolism risk of BZA plus CEE should not be ignored.

11.6.3.5 Local Androgens

Although the prescription of testosterone is very common for the treatment of hypoactive sexual desire disorder in women, the FDA has not approved testosterone as a

therapy option because of the lack of evidence regarding the long-term safety issue [51]. On the other hand, androgen receptors present throughout the urogenital tract. After menopause not only a decrease in estradiol levels in the circulation is seen, but also a decrease in circulating levels of testosterone is detected. In accordance with this decrease in testosterone levels in the circulation, there is an extinction of androgen receptors in the tissue of the urogenital tract likewise all other different types of tissues expressing the androgen receptors. However, androgen supplementation induces the replenishment of androgen receptors in the tissue of the urogenital tract [52]. In addition, the vaginal epithelium expresses the aromatase activity which converts the androgens to estrogens [53].

Recently, the use of intravaginal testosterone for treatment of vulvovaginal atrophy in women has been reviewed for efficacy and safety issues in six clinical trials of which three included the women taking AIs [54]. The publication suggests that intravaginal testosterone decreases vaginal pH, provides the vaginal dominance of Lactobacilli, and improves the vaginal maturation index [53]. GSM, including dryness and dyspareunia, is improved significantly by the application of intravaginal testosterone. However, there are some weak points of the studies such as the duration of the use of intravaginal testosterone, the number of patients, the lack of placebo group, and finally the uncertainty of the effect on sexual function. These prevent us to reach a firm conclusion regarding the safety and efficacy of intravaginal use of testosterone.

Another weak androgen is dehydroepiandrosterone (DHEA) which is mainly produced in surrenal gland and has been recently used for the treatment of GSM [55, 56]. DHEA starts to decrease at around the age of 30. For insufficient production of estrogens and androgens after menopause, DHEA becomes the exclusive source for these sex steroids in peripheral tissues. Indeed, each peripheral tissue having the ability of expression of some specific steroid-forming enzymes transforms DHEA into the appropriate small amounts of estrogens and androgens for the absolutely intracellular and local action [57]. On the other hand, there are intracellular steroid-inactivating enzymes in humans which inactivate the estrogens and androgens at the site where they are synthesized inside the cell.

Local use of vaginal DHEA successfully treats women with GSM. The clinical data regarding the small dose of intravaginal DHEA shows an improvement in the vaginal maturation index and PH without significant changes in serum estradiol and testosterone levels [57]. Intravaginal DHEA provides improvement in sexual desire/interest, arousal and orgasm and lessens pain during sexual activity. It relieves dyspareunia, vaginal dryness, irritation, or itching without systemic effect. It also ameliorates vaginal epithelial thickness, integrity, and color and increases the vaginal secretion [55]. It can be concluded that the daily intravaginal administration of 0.50% (6.5 mg) DHEA is effective in the treatment of GSM without systemic effect. Moreover, daily use of 6.5 mg (0.50%) DHEA has been found to be comparable efficacious with 0.3 mg CEE or 10 μg E2 in the treatment of GSM [56]. There is no clinical evidence regarding the intravaginal use of DHEA on specifically urological symptoms. Although there is not any evidence regarding the intravaginal use of DHEA in breast cancer survivor, the recommendation has been thought to be acceptable by some authors [10, 11].

11.6.4 Laser Treatment

Light amplification by stimulated emission of radiation (LASER) is currently suggested to be used for the treatment of GSM [2, 8, 58–62]. Before looking into the available clinical evidence regarding the results of laser treatment in women with GSM, it would be better to mention briefly the laser basics and its tissue effects. Three important characteristics of laser light are collimation, monochromy, and coherence. Wavelength of laser light can be in the different electromagnetic spectrum ranging from the ultraviolet (157–400 nm), visible (400–800 nm), near-infrared (800–3000 nm), mid-infrared (3000–30,000 nm) to far infrared (more than 30,000 nm). Laser light may be absorbed, transmitted, reflected, and scattered by the tissue. Absorption of laser light by the target tissue which is the most important effect may cause photothermal (most desirable effect), photochemical, and photomechanical reactions. Besides the energy power applied, the different wavelength and tissue chromophore (such as melanin and hemoglobin) and water content determine the photothermal effects of laser light in the tissue. Melanin and hemoglobin absorb the light in the spectrum of visible and near-infrared, while the water in the mid-infrared. On the other hand, the same applied energy may cause a different effect in the tissue (such as superficial carbonization, coagulation, and cell activation due to thermal conduction) by changing the parameters of power and exposure time of the laser light [58].

Nowadays, two forms of laser are mainly used for the treatment of GSM in the market: carbon dioxide (CO_2) and erbium:yttrium-aluminum-garnet (Erb:YAG). Emitted wavelength of CO_2 laser light is 10,600 nm, while it is 2940 nm for Erb:YAG laser. When compared to the Erb:YAG laser to CO_2 laser in terms of their technical features and tissue effects, Erb:YAG laser has nearly 16 times more absorption rate in water, less penetration depth, and thermal diffusion without ablation. Hence, Erb:YAG laser usually has less discomfort, erythema, edema, and faster recovery rate [58, 60].

There are two types of laser beam delivery techniques: fractional ablative and non-ablative techniques. Fractional laser beams create microscopic tissue injury columns alongside the non-traumatized tissue columns which stimulate the recovery. In the non-ablative technique, Erb:YAG laser is used in the smooth mode pulse by altering the pulse duration without causing ablation in the tissue [58]. There are two types of laser effects in the target tissue in terms of timing: early or immediate effect and late effect [58, 59]. The first and early effect is the thermomechanical effect. Thermomechanical effect which usually occurs when the epithelial tissue heats above the 60–65 °C is the tissue ablation and then the tissue tightening by the immediate shrinkage of the collagen. Moreover, the heat conduction is transmitted to the deeper layer of the epithelium by decreasing temperature down to 40–45 °C. This range of tissue temperature is ideal for the breakdown of the collagen fibrils and also cell activation. This is the second or late effect of laser light in the target tissue. This effect takes time. Because at this point, 40–45 °C temperature increases the heat shock response (HSR); in turn heat shock protein production by the tissue increases [58]. HSP70 especially plays an important role in the expression of some growth factors (such as transforming growth factor-β, basic

fibroblast growth factor, epidermal growth factor, vascular endothelial growth factor, platelet-derived growth factor), cytokines (such as tumor necrosis factor-α), and interleukin-1β in the target tissue [58]. These local factors are responsible from the inflammatory response, fibrogenic process, and the new production of collagen and extracellular matrix. In addition, these substances improve the microvascularization and enhance the oxygenation of the tissue.

Indeed, histopathologic studies verify collagen remodeling, new collagen synthesis (neocollagenogenesis), the increase in elastin content (elastogenesis), and new formation of blood capillaries (neoangiogenesis) after an immediate tissue shrinkage following laser treatment [58, 59, 63–65]. There is an increase in tissue collagen and elastin content. The vaginal epithelium gets thicker. Rugae formation reappears. The vagina becomes tight and elastic. Superficial epithelial cells of the vagina contain glycogen; thus, vaginal microbiata changes to normal flora and the vaginal PH decreases [58–62, 66, 67].

Laser treatment for GSM can be applied by a specifically designed vaginal or urethral cannula or external beam shot directed to the vulva. Although both laser types (CO_2 and Erb:YAG) can be applied to vulvovaginal area, intraurethral cannula is recently present only for the application of the Erb:YAG laser [68]. Even the intraurethral cannula can safely be inserted along the urethra under the ultrasonographic guidance [69]. Although most of the studies are lacking solid evidence, they reach a consensus on that both types of laser treatments improve the atrophic vaginal epithelium [58–67, 70–76]. The studies usually have the limited number of patients, short duration of follow-up, no consistency regarding the evaluation and treatment protocols, and finally lack of control groups and proper randomization. However, available data has shown that the intravaginal laser application improved the Vaginal Health Index Score (VHIS) which includes vaginal elasticity, pH, discharge, mucosal integrity, and moisture [60–62, 70–76]. Another consisting result is the fact that Visual Analog Scale (VAS) for the vaginal dryness, dyspareunia, itching, burning, and dysuria has shown an improvement after the vaginal laser treatment of GSM [60–62, 70–76]. Usually, three laser sessions have been recommended for the treatment of symptoms due to the vaginal atrophy, but an extra fourth or fifth sessions might further increase the GSM symptom-free rate [60, 62, 70–72, 74]. Recently, it has reported that the improvement in the atrophic vaginal epithelium provided by the laser treatment was found to be comparable with the estrogen treatment [60, 70]. Even the laser treatment is better, since its maintenance of vaginal health continues longer duration after the cessation of therapy [60]. Its effect on the vaginal health can last ranging from 12 to 24 months [71, 72, 76]. Intravaginal laser treatment also provides an increase in sexual gratification [63, 73, 74, 76–78]. This improvement in sexual function is not only due to vaginal health, but it also ameliorates the vaginal relaxation in some degree [60, 63]. Moreover, intravaginal laser application was defined as an acceptable procedure by most of the patients [66]. Breast cancer survivors with vulvovaginal atrophy may be treated safely and effectively by intravaginal laser application [71, 75]. In addition to vaginal atrophy symptoms, other symptoms (such as pain, itching, burning) due to lichen sclerosus et atrophicus, lichen planus, and other atrophic changes in the vulva may be improved by the application of laser light [58].

Intravaginal laser application may treat the urological components of the GSM such as dysuria, frequency, urgency, and urinary incontinence [58–60, 74, 76–82]. After the laser application, most of the studies report an improvement in urological symptoms which are usually determined by the International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form (ICIQ-UI SF). Although there is not a randomized controlled trial, intravaginal laser treatment may relieve the symptoms of stress urinary incontinence (SUI) [77–82]. Erb:YAG laser has been used to treat the SUI in most of the studies. It has been suggested that younger age and normal BMI women with moderate to severe SUI showed better improvement [79]. The patients who had more severe UI had the greatest benefit from the laser therapy [78, 81]. On the other hand, patients with SUI had a higher rate of improvement than those with mixed urinary incontinence [81]. In addition to the success of laser therapy for SUI, a study reported a decrease in pad weights before and after the operation, while no differences were found in urodynamic values [77]. Three years after the initial treatment, the laser therapy might be repeated in some patients with mild incontinence [81]. Optimal results can be achieved after three sessions with 3–4-week interval. Specific group of patient having SUI with poor intrinsic sphincter function who is defined as intrinsic sphincter deficiency (ISD) may be treated by the application of an intraurethral cannula with non-ablative Erb:YAG laser tip [68]. During this treatment, ultrasound guidance of the intraurethral laser cannula allows us to treat the patients with ISD, safely [69].

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Laser Treatment for Vulvovaginal Atrophy

12

Marco Gambacciani

12.1 Introduction

The genitourinary syndrome of menopause (GSM) is a chronic and progressive condition that includes a constellation of symptoms related to the decline of circulating ovarian hormones, as vulvovaginal atrophy (VVA), vaginal dryness, dyspareunia, recurrent urinary tract infections, and urinary incontinence [1–5]. GSM can affect up to 70% of women [1–5]. GSM is defined as a collection of signs and symptoms involving changes to the vulva, vagina, urethra, and bladder, including, but not limited to, dryness, burning and irritation, poor lubrication, discomfort or pain, impaired sexual function, and urinary symptoms of urgency, dysuria, and recurrent urinary tract infections [1–5].

The diagnosis of GSM is clinical, based upon characteristic symptoms, associated with typical signs on physical examination. Classic vaginal findings include a pale, dry vaginal epithelium that is smooth and shiny, with loss of most rugation. Women may present with some or all of the signs and symptoms, which must be bothersome jeopardizing sexual activity and the quality of life [1–5].

Several therapeutic options are available to alleviate GSM symptoms, including hormonal and non-hormonal products. The non-hormonal moisturizers and lubricants may provide only a temporary relief. Local vaginal estrogen administration is nowadays considered the treatment of choice [1–5]. However, some women may not wish to take hormone preparation for long term or have absolute contraindications to estrogen therapy [1–5]. In addition, different studies report that the compliance to local therapies is very low, and the rate of discontinuation in the first few months is high.

Recently a selective estrogen receptor modulator (SERM), ospemifene, has been introduced as oral agent for dyspareunia treatment. It provides an alternative to oral and local estrogen therapies [6–8]. New management strategies for GSM can

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increase our armamentarium in order to offer a wide range of options to enable women to choose, considering the benefits and risks associated with each strategy. Today the laser therapy may offer new options in order to stimulate tissue repair and to restore normal vaginal functions.

12.2 Principles of Laser

Current medical lasers emit wavelengths from the ultraviolet to the mid-infrared portions of the spectrum [9]. Laser treatment has been safely and effectively used in many areas including gynecology. The different wavelengths are specifically absorbed by a tissue component, a specific chromophore, including hemoglobin, melanin, and water [9].

The concept behind laser procedures to treat vulvovaginal conditions is to use a wavelength having high water absorption, such as the carbon dioxide (CO_2) laser and the Erbium (Er:YAG) [9, 10]. Laser treatment induces tissue remodeling, with histological evidence of the restoration of vaginal mucosa, a thickening of the epithelium, with the maturation of epithelial cells, a new formation of papillae indenting the epithelium with newly formed and extended small vessels. In addition, in the connective tissue underlying the epithelium, the formation of new thin fibrils and morphological features of fibroblasts supporting a renewal of the extracellular matrix with functional restoration [9, 10] are generated.

12.3 Types and Mechanisms of Action of Laser Used in Vaginal Atrophy

Fractional CO_2 laser was the first used to treat vaginal atrophy. According to the concept of fractional photothermolysis, these lasers ablate a fraction of the vaginal mucosa in the treatment area. An array of microscopic thermal wounds is created that ablates the vagina within very tiny zones; adjacent to these areas, the mucosa is spared and leads to natural healing process that builds new healthy tissue. In 2011, Gaspar et al. [11] first demonstrated that vaginal fractional CO_2 laser treatment induced a significant improvement of clinical and histological signs of vaginal atrophy. Successively, Salvatore et al. [12] reported in a short-term study that after CO_2 laser treatment, vaginal symptoms and dyspareunia improved in postmenopausal women.

The microablative fractional CO_2 laser effects on vaginal atrophy lead to an improvement of both sexual function and quality of life [13]. These papers opened a new era for non-hormonal treatment of GSM. All the above data were obtained with the same microablative fractional CO_2 laser technology [11–13]. Other CO_2 laser systems are marketed for the treatment of GSM, using different devices and different technologies, claiming the effects obtained using the abovementioned apparatus [11–13]. However, at the moment no solid efficacy figures and convincing safety data are available for GSM treatment with different CO_2 lasers.

At variance of CO_2 laser, the second-generation vaginal erbium laser (VEL®) stimulates photothermal effects by a non-ablative thermal diffusion to the vaginal walls [9, 14]. The studies of the thermal effects of a non-ablative 2940 nm

erbium are conducted using precisely controlled, sequentially packaged bursts of pulses (SMOOTH® mode) [9, 14]. The "smooth mode pulse," with a duration of 250 ms, consisted of a fast sequence of individual micropulses (300 μs) with intrapulse intervals of 50 ms. In this mode, vaginal mucosa temperatures increased to 60–65 °C, without inducing superficial ablation, with an increased vascularization and a deep collagen remodeling and new collagen synthesis [9, 14]. Thus, the specifically designed sequence of SMOOTH Er:YAG laser pulses can be delivered to the vaginal tissue in order to achieve controlled heating of the collagen in the deeper mucosa layers, without ablation or overheating of the mucosa surface, resulting in the generation of new collagen and an overall improvement of treated tissue tightness and elasticity. VEL usually is associated with a very low incidence of discomfort, erythema, edema, and fast recovery rate [14–29].

Specific vaginal probes have been designed to enable a uniform and well-controlled VEL distribution on the whole length and circumference of the vaginal canal. As for the first-generation microablative CO_2 laser, also for the erbium laser, we have to underline that the core of the published data was obtained using the specific SMOOTH erbium in yttrium aluminum-garnet crystal (Er:YAG) technology. The SMOOTH® mode allowing the use of full beam and patterned handpieces to deliver Er:YAG laser energy with different fluences to the vaginal tissue is a patented and registered technology which differs from other Er:YAG lasers on the market. Therefore, the term vaginal erbium laser (VEL) refers to SMOOTH® mode technology.

12.4 Vaginal Erbium Laser

Recent publications suggest that VEL may provide a new noninvasive treatment with non-ablative, second-generation photothermal vaginal therapy [14–29]. Vaginal laser stimulates profound effects on the vaginal epithelium and lamina propria [14–16]. Gaspar et al. [15] presented seminal data on the effects of VEL in comparison to estrogen vaginal administration. Other groups reported the improvement of GSM as well as stress urinary incontinence and initial grades of vaginal prolapse in VEL-treated patients [14–29].

In a prospective study, the effects of VEL in women with GSM were compared with another group of women treated with vaginal estriol administration, a standard treatment of GSM [19]. Signs and symptoms were evaluated subjectively by the visual analog scale (VAS) and objectively by the vaginal health index (VHIS) [19]. Three applications of VEL every 30 days induced a significant improvement in both subjective symptoms of vaginal dryness and dyspareunia and objective evaluation of VHIS. These changes were matching those induced by 3 months of vaginal estriol administration [19]. In both groups the VAS scores for vaginal dryness and dyspareunia showed a significant improvement with VEL treatments or 12 weeks of estriol. However, in the estriol group a reduction of efficacy was seen 12 weeks after the end of treatment. Conversely, in the VEL group, the same positive results were maintained throughout all the study period up to the 6 months of follow-up. In that study [19] the VEL treatment was performed in PMW suffering from GSM without any previous or concomitant treatment with estrogens or even non-hormonal vaginal creams. Therefore, the effects of VEL seems to be independent from any

pretreatment, suggesting that VEL can be proposed in PMW that cannot be treated with hormones, as in breast cancer survivors. In fact, in a parallel study [26], it has been demonstrated that VEL is effective and safe for the treatment of GSM in postmenopausal breast cancer survivors [26]. In these particular set of patients, VEL improved both dryness and dyspareunia, inducing a rapid and long-lasting positive effect on the appearance of vaginal mucosa, up to the 12 months after the VEL treatment [26].

These observations are of relevance, since one of the frequently asked questions is how long the laser effects can last. This issue was evaluated in a large prospective, longitudinal study conducted in more than 200 women [28]. The results of this study indicate that the VEL effects are rapid and long-lasting in PMW suffering from GSM. Patients were treated with three VEL applications, and follow-up evaluations were performed up to 24 months from the last laser application. Vaginal dryness and dyspareunia showed a significant decrease after the first VEL treatment, and in the follow-up period, the dryness and dyspareunia values were significantly different from baseline values during the follow-up period up to the 12 months of observation. Conversely, the values measured after 18 and 24 months from the last VEL application were not significantly different anymore from basal values [28]. It is noteworthy that 73.6% of them ($n = 151$) reported that the VEL treatment was effective for 12–18 months [28]. Only 8 patients (3.9%) affirmed that the treatment was not effective in reducing GSM symptoms, while total of 174 (84.9%) patients decided to repeat the VEL procedure [28].

Thus, this large longitudinal study [28] can be of help in setting the timing of when a repeated laser procedure(s) can be offered. The positive action on VEL thermotherapy may last at least 1 year, and it can be suggested that 12 months could be a therapeutic window for the vast majority of women. Therefore, a new VEL procedure could be indicated every 12 months. In this view, the use of a non-ablative laser such as VEL with the smooth mode is particularly appropriate in younger women suffering from GSM in which we can imagine many laser procedure during their lifetime. Thus, VEL is appropriate for women that cannot or do not want to be treated with hormones, such as breast cancer survivors, often young and sometimes premenopausal before cancer treatment. In addition VEL can be of help in women who do not accept long-term use of moisturizing and lubricants for the interferences with sexuality.

This study [28] demonstrates that the large majority of patients were satisfied, as demonstrated by the high percentage (85%) that chooses to repeat the treatment. The possible difference in the outcomes of VEL treatment with or without estrogen or other non-hormonal pretreatment or the current use of other therapies is a matter of future randomized studies.

12.5 Conclusions

In conclusion, although data from large randomized trials are not available, the results from a large number of observational studies are encouraging (Table 12.1). The effect of laser treatment is comparable to that exerted by local hormone

Table 12.1 Vaginal erbium laser (VEL) treatment for the genitourinary syndrome (GSM) of menopause: key points

• VEL is a noninvasive, ambulatory procedure
• VEL is effective in the treatment of GSM
• The results are rapid and long-lasting
• The clinical effects are comparable to local estrogen treatment
• VEL is intrinsically safe and can be repeated every year

treatment in postmenopausal women suffering from GSM. Cohort prospective long-term studies show that the second-generation VEL-Smooth® procedure is effective and intrinsically safe, if applied with the appropriate parameters, and no serious adverse effects were ever reported. Thus, VEL-Smooth® for vaginal functional restoration can be seen as an effective, noninvasive ambulatory procedure for the treatment of GSM. VEL-Smooth® can increase our armamentarium in order to offer a new, long-term therapeutic option, to improve the quality of life, allowing women to choose, considering the limits and the balance between benefits and risks associated with each therapeutic approach.

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Laser Treatments in Female Urinary Incontinence

13

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Abbreviations

BMI	Body mass index
CRC	Collagen Remodeling Capacity
Er:YAG	Erbium:yttrium-aluminum-garnet
FSFI	Female sexual function index
GSM	Genitourinary syndrome of menopause
ICIQ-UI SF	International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form
ISD	Intrinsic sphincter deficiency
ISI	Incontinence Severity Index
LUTS	Lower urinary tract symptoms
MUS	Mid-urethral sling
OAB	Overactive bladder
OABSS	Overactive Bladder Symptoms Score Questionnaire
PISQ12	Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire
POP	Pelvic organ prolapse
QoL	Quality of life
RTD	Residual thermal damage
SUI	Stress urinary incontinence
UCP	Urethral closure pressure
UI	Urinary incontinence
VEL	Vaginal erbium laser

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13.1 Introduction

A wide spectrum of treatments for stress urinary incontinence (SUI) include non-invasive (pelvic floor muscle training, weight reduction, laser interventions), minimally invasive (bulking methods), less invasive (sling and mesh), and invasive surgical procedures. Less invasive operative techniques are relatively effective but are still related to >15% complications (bleeding, erosions, urethral injury, infection, chronic pain, and urine retention) [1], while conventional surgery relates to anesthesia risks and high recurrence rates (25%) [2].

The association between pelvic organ prolapse (POP) and SUI with collagen is well established. The expression levels of Type I and Type III collagen are significantly lower in patients with POP and SUI when compared to the controls ($p < 0.01$) [3], and pubocervical fasciae of incontinent women have a lower collagen content [4]. Postmenopausal hormonal deficiency with increased degradation of collagen reserve is a possible explanation for the failure of many surgical procedures aimed at correcting prolapse/incontinence with a frequent recurrence of symptoms [5].

Contemporary scientific and technological breakthroughs have led to better clinical outcomes with less invasive procedures with shorter recovery times and lower implicated costs. In this sense, recent evidence supports laser treatment as an alternative and effective intervention for SUI [6].

13.2 Mode of Laser Action and Protocol for Its Use for Stress Urinary Incontinence

Pulsed laser photothermal energy can improve collagen structure and initiate neocollagenesis in the skin [7] and pelvic floor with nearby tissue as well [8]. An increase in temperature breaks up intermolecular cross-links and stabilizes the collagen triple-helix structure, thus resulting in the shortening of collagen fibers with consequent neocollagenesis, elastogenesis, neoangiogenesis, and increased fibroblast pool. In addition, morphometry showed an increase of the volume density of blood capillaries and the thickness of the epithelial layer [9].

The Er:YAG laser SMOOTH® mode beam (Fotona, Slovenia) is strongly absorbed in water which is the major constituent of human soft tissue. Precisely controlled sequences of non-ablative Er:YAG laser pulses are delivered to the intravaginal mucous tissue in order to achieve controlled heating of the collagen in the deeper mucosa layers (lamina propria), without ablation and overheating of the mucosa surface, so avoiding the risk of perforation with accidental lesions of the urethra, bladder, or rectum. Recommended parameters are laser spot size of 7 mm, frequency of 1.6 Hz, and fluence (laser energy emitted per unit area) of 6.0 J/cm^2. Mechanical pull of the deeper tissue layers following shrinkage of the upper, photothermally processed tissue layers further contributes to the tightening effect [10]. No general anesthesia is needed. The lower vaginal third and introitus can be covered with a thin layer of anesthetic cream. Treatment regimen consists of three sessions 3–4 weeks apart. When the process of neocollagenesis is well on its way, and assuming the

patient Collagen Remodeling Capacity (CRC) was not fully reached during the first session, with the second and third session, some previously not affected collagen fibers are additionally captured. Minor side effects include sensation of warmth, increased vaginal discharge, and rarely transient urge urinary incontinence [11].

CO_2 laser system MonaLisa Touch® (DEKA, Florence, Italy) intravaginal therapy is delivered once a month for 3 consecutive months. Recommended settings [12, 13] of the microablative fractional CO_2 laser ($MFCO_2$-Laser) are as follows: D-pulse mode, dot power 40 W, dwell time 1000 μs, and dot spacing 1000 μm for the treatment of the vaginal canal and the dot power 24 W, dwell time, 400 μs, and dot spacing 1000 μm for the treatment of the vaginal introitus. The procedure is performed in the outpatient setting and does not require any specific preparation or anesthesia. Patients are recommended to avoid coital sexual activity for at least 3 days after each laser application as mild inflammatory reaction may last up to 48 h.

13.3 Stress Urinary Incontinence (SUI)

The first pilot study regarding Er:YAG laser for the treatment of female SUI started on September 20, 2009 [14]. The degree of incontinence and its impact on quality of life were assessed with the International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form (ICIQ-UI SF) [15] tool, where a maximum score of 21 represents permanent incontinence.

The inclusion criteria for entering the study were a history of vaginal delivery, SUI, normal cell cytology, negative urine culture, and a vaginal canal, introitus, and vestibule free of injuries and bleeding. The exclusion criteria were severe prolapse and damage of the rectovaginal fascia, urge incontinence, severe neurological conditions associated with incontinence (multiple sclerosis, spinal cord injury, stroke, Parkinson's disease), neurogenic bladder, insulin-dependent diabetes mellitus, current urinary tract infection, hematuria, age <18 and >70 years, pregnancy, less than 24 weeks after vaginal delivery, body mass index (BMI) >30 kg/m^2, intake of photosensitive drugs, injury and/or active infection in the area to be treated, and undiagnosed vaginal bleeding.

At the first follow-up measurement (1 month after the intervention), the number of those with an ICIQ-UI score = 0 increased from zero to 17/52 (42.3% continent). At the second follow-up measurement, 2–6 months after the intervention, 18/47 (38.3% continent) had an ICIQ-UI score = 0 (Fig. 13.1). From the baseline to the second follow-up, a total of 34/47 (72.3%) of participants experienced improvement, whereas 11/47 (23.4%) experienced no change in the ICIQ-UI score, and two (4.3%) experienced worsening of symptoms. No major adverse events throughout the course of laser treatment and the follow-up period were noticed or reported. The rare mild reported symptoms such as slight edema, vaginal discharge, and transient urgency vanished spontaneously after 8 days.

Ogrinc et al. published a study of 175 women with newly diagnosed SUI (66%) and mixed urinary incontinence (MUI, 34%) [16]. Patients were treated according

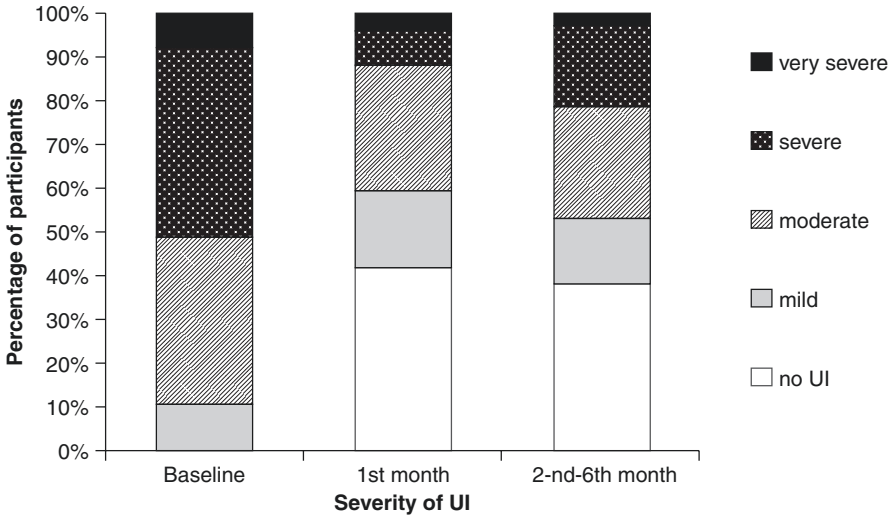

Fig. 13.1 Kloving's categories of ICIQ-UI SF score severity at the baseline and follow-up visits. *ICIQ-UI* International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form, *UI* urinary incontinence. Reproduced with permission from Fistonic et al. [14]

to the uniform Er:YAG laser protocol. Follow-ups were performed at 2, 6, and 12 months after procedure. Results were based on the Incontinence Severity Index (ISI) and the reduction in ICIQ-UI SF scores. One year after laser treatment, 77% of the SUI patients and only 34% of mixed UI remained continent. No difference in efficacy was noted between pre- and postmenopausal patients.

In another study [17], using the same Er:YAG protocol for SUI, urodynamic studies, pad testing, lower urinary tract symptoms (LUTS), and sexual function were assessed before and after treatment. The authors concluded that the procedure for mild SUI was effective at 6-month follow-up, but was not for the patients with an initial pad weight >10 g. Moreover, it improved LUTS, quality of life (QoL), and sexual function. Urodynamic values did not differ across the timeline. The authors speculate that this paradox originates from tighter and more elastic collagen that acts as a "hammock," preventing urine leakage and reducing pad weights. Although procedure follow-up was only up to the sixth month, authors summarize that IncontiLase™ should not replace mid-urethral sling (MUS) surgery as the standard therapy for SUI patients who fail to improve following first-line therapy. In addition, authors stress that the injection of bulking agents has been reported to have a cure rate of 53–73.2%, which is better than the cure rate of 39.3% they achieved at a 6-month follow-up with IncontiLase™. In conclusion authors admit that, based on its minimally invasive nature and the lack of significant adverse effects, the IncontiLase™ procedure may be used as an alternative therapy for mild SUI cases.

In a long-term, 24-month follow-up study [18] of 114 postmenopausal women suffering from SUI, the vaginal erbium laser (VEL) treatment induced a

significant decrease of baseline ICIQ-SF scores of 12.2 ± 2.5. The ICIQ-UI SF scores remained significantly ($p < 0.01$) lower than basal values 1 (4.8 ± 1.8), 3 (6.2 ± 1.9), 6 (7.0 ± 2.3), and 12 (8.0 ± 1.8) months after the last VEL application. Scores after 18 (9.3 ± 2.7) and 24 (9.9 ± 2.8) months from the last VEL application were, however, not significantly different from the baseline values. This study shows for the first time that VEL treatment significantly improves the genitourinary syndrome of menopause (GSM) at 12 months after the last laser application, while the effects decrease afterward. The study confirms that VEL is effective in the treatment of GSM, with clinical effects similar to those exerted by established local therapies.

Several other observational studies in which Er:YAG was used for mild to moderate SUI also showed improvement of SUI symptoms [19–21]. Up to date, there is only one patient-blinded randomized controlled trial for SUI [22] consisting of 114 women patients receiving a single-session of non-ablative thermal-only Er:YAG laser treatment. This study reported improvement of SUI symptoms, QoL (ICIQ-UI SF), and sexual function (PISQ12 and FSFI) in premenopausal parous women. A 21.4% (12/56) of the laser group patients were continent 3 months after treatment according to ICIQ-UI SF (score = 0) in comparison to only 3.6% (2/56) continence in the sham control group. Covariates age, BMI, and parity had no significant effect on the outcome. All pelvic floor muscle variables, derived from perineometry studies (duration and maximum pressure), showed a significant improvement in the laser group but not in the sham control group.

Carbon (CO_2) laser has been used for the treament of GSM, particularly focusing on the vulvovaginal atrophy segment [8]. To date, very few studies regarding CO_2 laser treatment of SUI have been published.

Isaza et al. [23] used the SmartXide2 V2LR fractional microablative CO_2 laser system (MonaLisa Touch™; Deka, Florence, Italy) in a prospective study of 161 postmenopausal women suffering from mild SUI. Patients received four sessions 30–45 days apart. SUI was evaluated using the 1-h pad test and the ICIQ-UI SF at the baseline and at 12, 24, and 36 months of follow-up. Basal ICIQ-UI SF score (14.34 ± 2.65) significantly decreased 12 (7.09 ± 1.1, $p < 0.001$), 24 (7.49 ± 0.94, $p < 0.001$), and 36 months (6.76 ± 0.82, $p < 0.001$) of follow up. The 1-h pad test reduced from 9.89 ± 0.57 g at the baseline to 3.52 ± 1.89 g, 3.55 ± 1.88 g, and 3.72 ± 2.05 g at 12, 24, and 36 months, respectively (all $p < 0.001$). Histology analyzed pretreatment and 6 weeks after the first treatment showed essentially thicker epithelium with a higher population of intermediate and superficial cell shedding. Nevertheless, such multiple ablative vaginal treatments raise concerns regarding the possibility of vaginal scarring and infection, which can be reduced with the use of a non-ablative treatment [22].

The prospective observational study regarding the efficacy of fractional CO_2 laser in postmenopausal women with moderate to severe clinical signs of GSM [24] showed significant improvement of dyspareunia, dryness, burning, itching, dysuria, urgency, and SUI scores assessed by standard questionnaires. Participants received intravaginal therapy, once a month for 3 consecutive months, with a CO_2 laser system

(MonaLisa Touch®, DEKA, Florence, Italy). As a secondary outcome, authors noted that urinary symptoms improved, as scores of the urinary and QoL questionnaires significantly decreased. ICIQ-UI SF at the baseline was 8.1 ± 5.6 vs. 3.4 ± 4.3 at the 3rd month of follow-up. All participants showed a >5-point improvement in the King's Health Questionnaire (KHQ) score, which includes psychometric aspects of urinary incontinence. Despite this, authors concluded that factors predictive of ideal CO_2 laser therapy candidates were not identified. Considering predictive, preventive, and personalized medicine (PPPM) current goal is not only to predict the risk of an adverse clinical event but also benefits [25]. A recent study [26] identified predictors for the segment of patients achieving optimal short term Er:YAG laser treatment outcomes. The best results after Er:YAG laser treatment of SUI should be expected in younger women (<47.5 years) with a body mass index of <23.3, average newborn birth weight of >3.6 kg, ICIQ-UI at a baseline of <10, and a perineometer squeeze duration at a baseline of >3.51 s.

However, despite the rigorous selection of patients, in a certain group, laser treatment will not succeed. Namely, SUI is not only induced by urethral hypermobility, as a result of weakening or disruption of the pelvic floor musculature and/or pubourethral ligament, but also due to the weakening of the urethral sphincter, resulting in more severe intrinsic sphincter deficiency (ISD) [27]. The urethral sphincter function depends on the muscular component; the rhabdosphincter, extending along 60–70% of the urethra length; and the mucosal or intrinsic component, extending across the urethra and contributing to urethral closure [28]. Gaspar et al. [29, 30] hypothesized that by targeting the mucosal component of the urethral sphincter, urethral coaptation ability would be able to increase. Authors used the novel Er:YAG intraurethral cannula (IntraLase™, Fotona, Slovenia). As assessed by a questionnaire addressing QoL (ICIQ-UI SF) and the 1-h pad test, therapeutic efficacy was measured at 3 and 6 months after the procedure. ICIQ-SF scores improved by an average of 64% at 3 months and by 40% at 6 months. The 1-h pad test showed a reduction of the quantity of leaked urine by 59% at 3 months and by 42% at 6 months.

Patel [31] enrolled women whose urodynamic studies showed a maximal urethral closure pressure (UCP) of less than 40 cm H_2O. Subjects received three fractional CO_2 laser treatments 4 weeks apart. Three months posttreatment, urodynamic reevaluation showed an increase in maximal UCP from 19 to 33 cm H_2O at pretreatment to 45–73 cm H_2O posttreatment.

13.4 Overactive Bladder

Perino et al. [32] analyzed the effect of CO_2 laser treatment in postmenopausal women with overactive bladder (OAB) symptoms (≥8 times micturition/24 h) and ≥1 symptoms of GSM (itching, burning, reduced lubrication, superficial and/or severe dyspareunia) in the previous 3 months. OAB symptoms were assessed using the validated Overactive Bladder Questionnaire Short Form (OAB-Q SF). Results at 1-month follow-up after the third laser session indicated

a significant reduction of the number of micturitions and number of urge episodes ($p < 0.0001$). Since atrophy of muscles and reduction of collagen content may be important factors in the increased prevalence of urinary incontinence, authors stress that fractional CO_2 laser system can irradiate deeper layers of the vaginal wall, ultimately enhancing tissue trophysm and reactivating the extracellular matrix and collagen synthesis, with beneficial effects in the three layers of the vaginal wall, in contrast to estrogens or other local therapies that only treat the epithelium.

Besides improvement of SUI episodes using the Er:YAG protocol, Tien and coauthors [17] also found a positive effect over OAB, as evidenced by the improvements in the Urgency Severity Scale Questionnaire (USS), the Overactive Bladder Symptoms Score Questionnaire (OABSS), nicturia episodes, and daytime frequency episodes. Since the majority of women with stress predominant MUI experience significant improvement in OAB symptoms following incontinence surgery [33], authors speculate that their findings may be at least partly related to SUI improvements following laser treatment.

In patients with SUI, urine leakage into the proximal urethra may stimulate urethral afferents and facilitate the voiding reflex [34]. Lin et al. [35] hypothesized that laser therapy may slightly increase the entire urethral pressure, including proximal urethral pressure, and in turn alleviate OAB symptoms due to a reduction of the bladder reflex response observed in SUI patients. Their treatment consisted of two sessions, 4 weeks apart using the Er:YAG laser (XS Dynamis, Fotona, Slovenia). OABSS scores were significantly improved at 3-month follow-up ($p < 0.027$), especially in terms of urinary frequency ($p < 0.001$). However, symptom scores were not sustained at the 12-month follow-up. By most patients' report, the optimal therapeutic effect was maintained for the duration of 3–6 months, similar to results observed by Fistonic et al. [14] (2–6 months). Neocollagenesis induced by Er:YAG SMOOTH® mode can change the composition of the pelvic floor structures and thus increase pressure over the entire length of the urethra. In SUI patients, the increased proximal urethral pressure may alleviate OAB symptoms by reducing the bladder reflex response.

13.5 Vaginal Microbiota

An effect of laser on vaginal microbiota has been reported by Athanasiou et al. They assessed the effect of microablative fractional CO_2 laser ($MFCO_2$-laser) therapy on the vaginal microenvironment of postmenopausal women [13]. Findings suggest that in their sample of 53 postmenopausal women with moderate to severe GSM symptoms, the completion of three laser therapies (at monthly intervals) significantly increased *Lactobacillus* ($p < 0.001$) and normal flora ($p < 0.001$), which decreased vaginal pH from a mean of 5.5 ± 0.8 (baseline) to 4.7 ± 0.5 (third month, $p < 0.001$). The prevalence of *Lactobacillus* changed from a baseline value of 30–79% at 3 months. Clinical signs and symptoms of bacterial vaginosis, aerobic vaginitis, or candidiasis did not appear in any participant. Although significant

decreases were observed only for *E. coli* and *Mobiluncus*, there was a trend of lower growth of all *Lactobacillus* antagonists.

Authors suggest that the observed increase of the normal vaginal epithelial cells confirms the results of the histological study of Zerbinati et al. [36] where it was demonstrated that one of the effects of the $MFCO_2$-Laser therapy on the vaginal mucosa was the high degree of epithelial exfoliation, with superficial cells filled with glycogen shedding at the epithelial surface. In conclusion, authors believe that $MFCO_2$-Laser therapy is a promising treatment for the improvement of postmenopausal vaginal health, aiding the repopulation of the vagina with normally existing *Lactobacillus* species and reconstituting the normal flora as that observed in the premenopausal status.

13.6 Histology

Histological changes in the epithelium and lamina propria, following fractional CO_2 laser treatments (CO_2 RE Intima, Syneron Candela, Wayland, MA), correlated with clinical findings of vaginal hydration and pH in SUI patients [37]. At the 3-month follow-up, biopsies showed increased collagen and elastin staining, as well as a thicker epithelium with an increased number of cell layers and a better degree of surface maturation (increase in the ratio of parabasal, intermediate, and superficial cells showing an estrogenic effect). At the 6-month follow-up, histology showed increased submucosal vascularity with increased collagen and elastin deposits (Fig. 13.2).

Histological study of vaginal wall biopsies showed signs of neocollagenesis, elastogenesis, neoangiogenesis, reduction of epithelial degeneration and atrophy, and an increase of the fibroblast population after non-ablative Er:YAG laser SUI treatment (IncontiLase™, Fotona, Slovenia) [38].

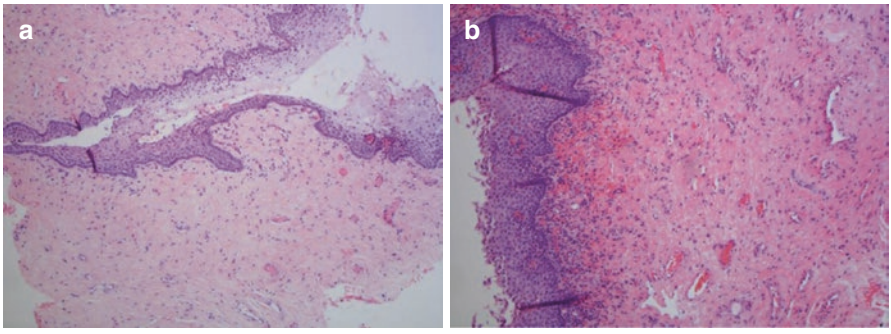

Fig. 13.2 (**a**) Pretreatment histology of a 59-year-old woman. (**b**) At 8 months post-baseline, histological findings showed increased submucosal vascularity, as well as increased collagen deposits and elastic fibers. Reproduced with permission from Samuels and Garcia [37]

13.7 Non-ablative Photothermal Er:YAG Laser and Microablative Fractional CO_2 Laser in SUI Treatment: Differences

Lasers used in SUI treatment emit thermal energy at the different wave lengths (Er:YAG 2940 nm; CO_2 10,600 nm), but they both induce similar changes related to increased tissue trophysm such as retraction of collagen, neocollagenesis, elastogenesis, enhanced density of connective particles, and neovascularization. CO_2 laser thermal action spreads to the depth of 50–125 μm in the vaginal tissue, causing superficial vaporization. Under the same conditions, Er:YAG laser reaches only 5–20 μm in depth with no ablation at all [8].

Er:YAG laser has 10–15 times the affinity for water absorption compared with carbon dioxide laser. Mucous membranes have a very high percentage of water, which is a good target for the Er:YAG laser beam. Because of the extremely high absorption in water, the incident photon energy is almost totally attenuated in the first few micrometers of the tissue, producing at appropriate parameters a very controlled column of ablation with an extremely narrow band of secondary coagulation. This process has been known as residual thermal damage (RTD) [39]. This translates into shorter down time with quicker healing and has been the cornerstone for the use of the Er:YAG in full-face ablative laser resurfacing when compared to the CO_2 laser, which has a much larger RTD zone [40]. That was a rationale for Lee to use Er:YAG in the treatment of the vaginal relaxation syndrome [41]. The authors emphasize that the depth control associated with the Er:YAG wavelength offers major benefits as ablative damage depth is minimized. Multiple micro-pulses create a shallow, few μm-thick epidermal windows in the vaginal epithelium with minimal RTD, and subsequent micro-pulses create a pulse-stacking effect without further ablation but with thermal buildup down into the lamina propria, increasing the RTD zone. Only Er:YAG laser is characterized by the critical temperature above ablation temperature, making this laser the safest medical laser for dual-tissue regeneration mechanism (DRM) non-ablative resurfacing (Fig. 13.3) [42].

Athanasiou et al. [13] stress out, based on Hutchinson-Colas et al. [43] and Helbig et al. [44], that erbium YAG laser only has a thermal effect, while the $MFCO_2$-Laser has both ablative and thermal effects, thus stimulating heat shock proteins and other factors (e.g., TGF-β), promoting neocollagenesis and neoangiogenesis, and consequently resulting in tissue rejuvenation.

13.8 Review Papers

Most review articles discuss different methodological aspects of the published studies regarding the use of laser for the treatment of the GSM, vaginal relaxation syndrome, and urinary incontinence [11, 45–50]. Conte et al. [51] reviewed the use of laser for the treatment of female SUI in seven prospective, single-centered, and non-comparative studies without control groups. All studies used Er:YAG or a CO_2 laser. Primary outcomes were ICIQ-UI SF scores in six studies and the pad test in

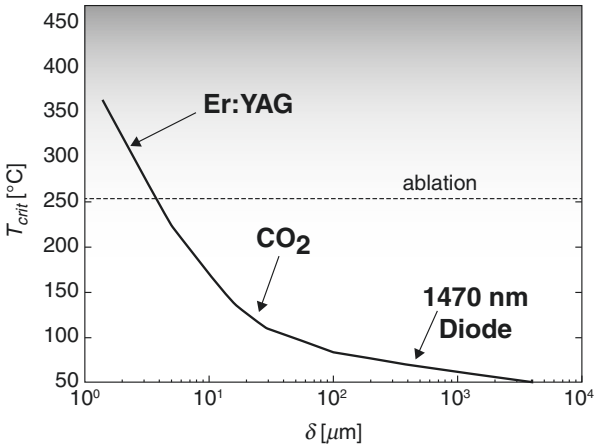

Fig. 13.3 Critical temperature depends on penetration depth. Only Er:YAG laser is characterized by the critical temperature above ablation temperature. Reproduced with permission from Lukac et al. [42]

one. Follow-up ranged from 5 to 36 months. Improvement rates ranged from 62 to 78%. No major adverse events were noted. Minor side effects included sensation of warmth, increased vaginal discharge, and transient urge urinary incontinence. Authors stand for more rigorous and adequately powered trials to assess the benefits and adverse event profile of laser treatment of SUI, as compared with other minimally invasive procedures.

An updated technical bulletin on laser for GSM and SUI was prepared by the urogynecology committee and approved by the Board of the Society of Obstetricians and Gynaecologists of Canada [52]. Analyzing contemporary reviews on the SUI topic, conclusion is that short-term observational studies of small patient number with the use of intravaginal laser have demonstrated improvements in symptoms of SUI. Evidence is insufficient to offer intravaginal laser therapy as an effective modality for the treatment of SUI compared to alternate managements such as pelvic floor physiotherapy, incontinence pessaries, or surgery.

The Canadian group [53] summarized Er:YAG laser therapy as a minimally invasive, alternative treatment option for female SUI and that laser therapy has yielded reasonable initial outcomes with an acceptable low cost and safety profile. At the same time, authors emphasized that it was not clear which group of patients will respond better to this therapy, as the mechanism of action was still somewhat vague. In this sense, a recently published predictive model [26] detects patients' baseline characteristics that may aid at achieving the best results after Er:YAG laser treatment for SUI. A clinically relevant decrease in the ICIQ-UI (minimum important difference, MID) of >30% can be predicted based on age, body mass index, average newborn birth weight, perineometer squeeze duration, and pre-intervention ICIQ-UI score. In addition, the first single-blinded sham study regarding Er:YAG laser treatment for SUI [22] moderately reduced frequent criticism on the lack of

randomized controlled trials in this field. Results showed a significant improvement in 114 women at the 3rd month follow-up, with a single-session treatment with non-ablative thermal-only Er:YAG laser.

A systematic critical review published in July 2018 analyzed 17 eligible studies including 652 (12 studies) and more than 240 patients (5 studies) treated with Er:YAG-laser and CO_2 laser, respectively. Authors concluded that the use of laser for women with urinary incontinence seems a promising minimally invasive alternative to the current standard therapies. On the other hand, there is still lack of evidence showing long-term safety and effectiveness. Additionally, all reviewed studies included only patients with primary urinary incontinence, so there is no information about these treatments on patients previously treated with surgery [54].

Upon the review of the literature derived from the PubMed database up to July 2018, using the key words "laser" and "urinary incontinence", 326 articles were found. After exclusion for incontinence in male, laser use in surgery, and non-laser techniques, 34 articles met criteria regarding laser use in women with urinary incontinence. Twelve of them were review articles and 22 were original papers. Laser effect in SUI patients was analyzed in 19 and OAB patients in three articles. Authors used Er:YAG laser in 16 studies, while CO_2 laser was used in six studies. A total of 1310 patients were enrolled at the 1–36 months of follow up (average 7.9 months).

Although laser is an attractive [45] novel, non-hormonal but expensive [47] new technology for the treatment of the GSM, additional studies are needed to explore the long-term safety and efficacy of various laser therapies for genitourinary symptoms as most of published evidence rely on short-term follow-up (1–6 months). Three studies extended to 12–24 months (Er:YAG) [16, 18, 35] and 1–36 months (CO_2) [23]. To date, only one patient-blinded randomized controlled laser sham trial for SUI, using Er:YAG laser, has been published [22]. Also, future studies need to be designed taking mentioned considerations into account, including the histological assessment performed immediately after treatment, which will help compare morphology at baseline with changes in the vaginal architecture following laser procedure [41]. Next studies should focus on the individual patient level in order to predict personal risk or benefit based on the decision of undergoing a given proposed procedure [26, 55]. Simultaneously, predictive systems may impact public health policies in terms of prevention [56].

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Metabolic Syndrome and Excessive Body Weight in Peri- and Postmenopausal Women

14

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14.1 Introduction

The metabolic syndrome (MetS), previously known as the insulin resistance syndrome or syndrome X, was first described by Reaven in 1988, and it is a complex of interrelated risk factors for cardiovascular risk and diabetes. In women, the loss of sex hormones during aging contributes to changes in body mass, musculoskeletal integrity, sexual dysfunction, and long-term risks of health and disease. The MetS increases in prevalence after menopause and consists of insulin resistance, abdominal obesity, dyslipidemia, elevated blood pressure, and pro-inflammatory and prothrombotic states. This syndrome usually precedes the development of diabetes mellitus and carries a twofold increased risk for cardiovascular events.

Similar, the prevalence of obesity (body mass index [BMI] $\geq$ 30 kg/m^2) is higher in postmenopausal women than in premenopausal women. This is a consequence of a multifactorial process that involves reduced energy expenditure due to physical inactivity, which is sometimes compounded by depression, as well as to muscle atrophy and a lower basal metabolic rate. Although the menopause, *per se,* is not associated with weight gain, it leads to an increase of total body fat and a redistribution of body fat from the periphery to the trunk, which results in visceral adiposity. Increased BMI and upper body fat distribution (indicated by waist-to-hip ratio) and menopausal estrogen decline are associated with adverse metabolic changes such as insulin resistance

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and a propensity to develop type 2 diabetes mellitus and dyslipidemia characterized by high triglyceride levels (TG), low high-density lipoprotein (HDL-C) cholesterol levels, and an increased frequency of small, dense low-density lipoprotein (LDL-C) particles. Altered adipokine secretion, which leads to chronic inflammation, is a possible mechanism that links abdominal obesity to its metabolic consequences.

Insulin resistance and diabetes have been associated with greater cardiovascular risk among women in different clinical trials. Moreover, data from a meta-analysis suggest that the risk for fatal coronary artery disease associated with diabetes is 50% higher in women, whereas diabetes and hypertension represent the two most important cardiovascular risk factors in women, especially when they occur in association [1–4].

Cross-sectional and longitudinal studies using waist circumference or the waist-to-hip ratio show no effect of menopause on body fat distribution. By contrast, studies using dual-energy X-ray absorptiometry (DXA) showed increased trunk fat in postmenopausal women. Moreover, studies using computed tomography and magnetic resonance imaging (MRI) show that postmenopausal women have greater amounts of intra-abdominal fat compared to premenopausal women.

Collectively, these studies confirm that the menopause transition is associated with an accumulation of central fat and, in particular, intra-abdominal fat. Postmenopausal women had 36% more trunk fat, 49% greater intra-abdominal fat area, and 22% greater subcutaneous abdominal fat area than premenopausal women. The menopause-related difference in intra-abdominal fat persisted after statistical adjustment for age and fat mass, whereas no differences were noted in trunk or abdominal subcutaneous fat [5, 6]. In vivo and in vitro studies indicate that estrogen receptors (ER) are mechanistically implicated in endocrine-related diseases. Recent studies with ER knockout mice have helped to unravel the role of ER in brain degeneration, osteoporosis, cardiovascular diseases (CDV), and obesity [7]. In humans, hormones help integrate metabolic interactions among major organs that are essential for metabolically intensive activities like reproduction and metabolic function. Sex steroids are involved in the metabolism of adipocytes and also influence the sex-specific remodeling of particular adipose depots. The concentrations of sex hormones partially control fat distribution: men have less total body fat but more central/intra-abdominal adipose tissue, whereas women tend to have more total fat in gluteal/femoral and subcutaneous depots. Weight and abdominal fat distribution differ among women of reproductive age and menopausal women. Estrogen function is mediated by nuclear receptors that are transcription factors that belong to the superfamily of nuclear receptors. Two types of nuclear ERs have been identified, the alpha (ERα) and beta (ERβ) receptors. Human subcutaneous and visceral adipose tissues express both ERα and ERβ, whereas only ERα mRNA has been identified in brown adipose tissue. ERα plays a major role in the activity of adipocytes and sexual dimorphism of fat distribution. Polymorphism of ERα in humans has been associated with risk factors for CVD. Lipolysis in humans is controlled primarily by the action of β-adrenergic receptors (lipolytic) and α2A-adrenergic receptors (antilipolytic) [8]. Genazzani's group in 2006 evaluated the effects of climacteric modifications on body weight and fat distribution [9]: they selected 2175 untreated normal healthy women attending a menopause clinic. Women were divided into

three groups, premenopausal, perimenopausal, and postmenopausal, and compared them with 354 postmenopausal women receiving different forms of HRT. The total body fat tissue mass and distribution were analyzed using DXA. Body weight and BMI were significantly higher in perimenopausal and postmenopausal than in premenopausal women. Fat tissue and regional fat tissue as a percentage of total fat tissue were higher in the trunk and arms in perimenopausal and postmenopausal than in premenopausal women. Instead, in age-matched HRT-treated postmenopausal women, the fat tissue was similar to that in the premenopausal group. Perimenopausal and postmenopausal women show a shift to a central, android fat distribution that can be counteracted by HRT.

14.2 The Menopausal Transition and Cardiovascular Risk

Early after the menopause women begin to gain weight, and their body fat is redistributed from a gynecoid to an android pattern. The increase in BMI and the proportion of visceral fat are strongly correlated with the development of hypertension, insulin resistance, and a number of metabolic risk factors for CVD. It is otherwise known that the menopause is associated with an increase of TG, LDL-C, and lipoprotein-a (Lp(a)). Levels of HDL-C gradually fall after the menopause, although concentrations always remain significantly higher in women as compared to men. This finding could be considered a protective factor for female subjects.

CVD is the number one cause of death globally, both for men and women. It is well documented that morbidity and mortality rates from CVD are higher in men than in women; however, this gender gap narrows after the menopause suggesting a role of female sex hormones and aging. In fact, the incidence of CVD in women increases substantially with aging, probably because the menopause diminishes the gender protection hence contributing to an adverse impact over cardiovascular risk variables. Nevertheless, whether this higher cardiovascular risk is a function of aging or a consequence of the loss of endogenous estrogen due to the menopause or both has been debated in the literature for many years [10].

Several studies in recent years have analyzed the differences of hormonal modifications observed during the menopausal transition between obese and normal-weight women. For instance, the results of the study of Women's Health Across the Nation (SWAN) are worth mentioning; SWAN is a multicenter, multiethnic longitudinal study designed to characterize the physiological and psychosocial changes that occur during the menopausal transition and to observe their effects on subsequent health and risk factors for age-related diseases. A total of 3302 women were enrolled at seven clinical sites between 1996 and 1997. At the time of enrollment, women were premenopausal, non hormone users, and aged from 42 to 52. The participants were self-identified as African-American (28%), Caucasian (47%), Chinese (8%), Hispanic (8%), or Japanese (9%). SWAN has a multidisciplinary focus and thus has repeated measures of bone health, cardiovascular risk factors, psychosocial factors, and ovarian hormones [11]. In this set, Matthews et al. evaluated the change in coronary heart disease (CHD) risk factors in relation to a very particular and critical

period of women's life that is the final menstrual period (FMP). Women who experienced a natural menopause (1054 out of the total) were analyzed independent of age and other confounders. The results showed significant increases in total cholesterol, LDL-C, and apolipoprotein B (Apo B) within a year of the FMP; importantly, the rate of change relative to FMP did not vary by ethnicity, suggesting that menopause had a uniform influence on lipids. The other risk factors changed in a linear pattern consistent with chronologic aging: TG, Lp(a), insulin, factor VIIc, and systolic blood pressure increased; diastolic blood pressure, tissue plasminogen activator antigen, fibrinogen, and high-sensitivity C-reactive protein did not change [10].

Similar to the SWAN study, in the Penn Ovarian Aging Study (POAS), obese women had lower estradiol (E2) and follicular stimulating hormone (FSH) levels than nonobese women. However, more rigorous analysis of hormonal changes between obese and nonobese women before and after the FMP found that the patterns of change in FSH and estradiol (E2) in relation to the FMP were not statistically different. The E2 change was less pronounced in obese women when compared with nonobese women. The rate of E2-blunted decline observed among obese women is physiologically corroborated by a similarly blunted FSH rise surrounding the FMP in obese versus nonobese women. Ultrasound data have shown no difference in antral follicle count between obese and nonobese women in their late reproductive years (40–52 years). This lack of difference does not support low ovarian reserve as the mechanism underlying lower E2 levels in obese women premenopausally, mechanism which is currently unclear.

In the POAS, the anti-Müllerian hormone (AMH) was found to be lower in obese women compared to nonobese ones in the late reproductive years, demonstrating the complex relationship between obesity and reproductive hormones in women approaching the menopause. Follicular dysfunction and alterations in the central nervous system regulation of hormonal levels among obese women may be factors, but additional research in this area is required. The blunted magnitude of change in reproductive hormones in obese women during menopausal transition may be related to the modification in the primary source of circulating E2 as the menopausal transition progresses; the primary source of circulating E2 in premenopausal period is the ovary, whereas in postmenopause, the primary source of circulating E2 is the aromatization of androgens within the adipose tissue. This change in E2 source provides postmenopausal obese women with a non-ovarian reservoir of estrogen that normal-weight women do not have, which may blunt gonadotropin rises and mitigate ovarian estrogen loss related with the menopause. These hormonal alterations may also blunt menopause-associated adverse health effects [12, 13]. Data from the Women's Healthy Lifestyle Project provide clear evidence that weight gain and increased waist circumference, along with elevations in lipid levels and other CVD risk factors, are preventable through lifestyle intervention in healthy menopausal-aged women. In fact, although these changes are inevitable with age and menopause, physical activity may attenuate the impact of both events. Thus, weight gain prevention should be recognized as an important health goal for women before they approach the menopause and women should make regular physical activity [14].

14.3 Other Menopausal Changes Related to Excessive Body Weight

Genitourinary syndrome (GSM) is a relatively new terminology describing vulvovaginal changes at menopause, as well as urinary symptoms of frequency, urgency, nocturia, dysuria, and recurrent urinary tract infections. Vaginal dryness is common after the menopause and unlike vasomotor symptoms (VMS) it usually persists and may worsen with time. Urogenital symptoms are effectively treated with either local (vaginal) or systemic estrogen therapy. Pelvic floor dysfunction is more common in the overweight and obese women. Risk factors for developing pelvic organ prolapse (POP) can be divided into obstetric, lifestyle, comorbidity, aging, social, pelvic floor, and surgical factors. The most important lifestyle factor is a higher BMI. Obesity may impair pelvic floor function increasing intra-abdominal pressure that damages pelvic musculature and nerve; this is linked to conduction abnormalities and obesity-related comorbidities including diabetic neuropathy and intervertebral disc herniation [15, 16].

14.4 Management of Women with the MetS and Obesity Across the Menopause

All women at midlife should be encouraged to maintain or achieve a normal body weight, be physically active, adopt a healthy diet, limit alcohol consumption, and quit smoking. Some women find that avoidance of spicy food, hot drinks, and alcohol lessens their VMS. Obesity is associated with a greater likelihood of VMS, although women who are overweight (BMI from 25 to <30 kg/m^2), as opposed to obese (BMI $\geq$ 30 kg/m^2), are more likely to have severe symptoms. For obese women, weight loss may lessen VMS, as well as reduce the risks of CVD; diabetes; urinary incontinence; breast, pancreatic, and endometrial cancer; and dementia.

Estrogens seem to influence glucose homeostasis through increased glucose transport into cells, whereas the lack of estrogens has been associated with a progressive decrease in glucose-stimulated insulin secretion and insulin sensitivity as well as with insulin resistance. These may explain why HRT administration to postmenopausal women is associated with a significant decrease in the incidence of type II diabetes. Estrogen deficiency is the principal pathophysiological mechanism that underlies menopausal symptoms, and various estrogen formulations are prescribed as menopausal hormone therapy, which remains the most effective available therapeutic option. The addition of progesterone aims at protecting against the consequences of systemic therapy with estrogen only in women with intact uteri [17], namely, endometrial pathologies, including hyperplasia and cancer. The risk-benefit ratios of all treatment options must be considered, taking into acount the nature and severity of symptoms and individual treatment-related risks.

In the systemic circulation, E2 and estrone, as well as testosterone, are partly bound to sex hormone-binding globulin (SHBG), as well as to albumin. Increasing or decreasing SHBG levels will affect the amount of unbound circulating estrogen and testosterone [18].

Obesity is a biologically plausible risk factor for venous thromboembolism (VTE), but the mechanisms underlying the relation of obesity with VTE are not totally understood. A strong positive correlation between plasminogen activator inhibitor-1 (PAI-1) levels and BMI has been reported. PAI-1 is the main fibrinolytic inhibitor, and reduced plasma fibrinolytic potential may be a risk factor for venous thrombosis. Decreased fibrinolysis due to a high level of PAI-1 could explain in part the association of VTE with overweight and obesity. Moreover, other studies suggested that an increased BMI was associated with higher levels of prothrombotic factors such as fibrinogen and factor VII (F-VII). Thus, both oral estrogen and obesity may have synergistic effects on the unbalance between procoagulant factors and antithrombotic mechanisms. By contrast, transdermal estrogen appears to have little or no effect on hemostasis. Alternatively, increased C-reactive protein levels have been reported in obese individuals with a history of VTE, and low-grade inflammation could explain in part these findings. In addition to the effects on hemostasis and inflammation, obesity may also have direct mechanical effects on the venous system. An increased BMI may result in a higher VTE risk through an increased intra-abdominal pressure and a decreased venous return. These effects may result in venous hypertension, varicose veins, and venous stasis which promote the development of VTE [19].

For those who require pharmacological therapies, average dose HRT is the most effective treatment for VMS [20] with reductions in both frequency and severity in the order of 75%, and the improvement of quality of life in symptomatic women [21]. HRT should be avoided in those with unexplained vaginal bleeding, active liver disease, previous breast cancer, coronary heart disease, stroke, personal history of thromboembolic disease, or a known high inherited risk. CVD risk factors do not automatically preclude HRT but should be taken into account. Upregulation of the hepatic synthesis of procoagulants is another known effect of oral estrogens. Transdermal estradiol does not seem to increase the risk of venous thromboembolic events. Evidence shows that transdermal estrogen ($\leq$50 μg) is associated with a lower risk of deep vein thrombosis, stroke, and myocardial infarction compared to oral therapy and may be the preferred mode of treatment in women with an increased thrombosis risk, such as obese women and smokers. In addition, unlike oral estrogen, transdermal estradiol does not increase the risk of gallbladder disease [22, 23].

Estrogen therapy restores the normal vaginal flora, lowers the pH, and thickens and revascularizes the vaginal lining. The number of superficial epithelial cells is increased and symptoms of atrophy are alleviated. Importantly, low-dose vaginal estrogen improves vaginal atrophy without causing proliferation of the endometrium. Given the documented efficacy and proven safety, vaginal estrogen is the first-line approach to treat symptoms of vaginal atrophy in the majority of women: vaginal estrogen is effective, and while systemic absorption does occur, it does not induce endometrial hyperplasia. Concerns regarding systemic absorption has lead to the tendency that vaginal estrogens be avoided in breast cancer patients

taking aromatase inhibitors. The relationship between HRT and urinary incontinence depends on the delivery route. Systemic HRT worsens urinary incontinence, but vaginal treatment may improve urge incontinence and prevent recurrent urinary tract infections. Using very low doses for the first few weeks is helpful if irritation occurs, and indeed lower doses of vaginal estrogens, with less frequent administration, often yields satisfactory results [16, 24].

In conclusion, initiation of hormone therapy is usually contraindicated in women with a personal history of breast cancer or VTE or those with a high risk for breast cancer, thrombosis, or stroke. Transdermal estrogen therapy may be considered and preferred when highly symptomatic women with type 2 diabetes mellitus or obesity, or those at high risk of CVD, do not respond to non-hormonal therapies. In general, initiation of of HRT is not recommended for women who are aged >60 [25].

In order to avoid undue chronic stimulatory effects on the endometrium, control menstrual bleeding, avoid abnormal bleeding, and avoid cancer development, the combination of the estrogen with a progestogen is needed. Endometrial cancer is the most common gynecologic cancer: it is estimated that risk of endometrial cancer increases about 59% for every 5 units of increase in BMI (kg/m^2) and overweight and obesity are responsible for 57% of all cases of endometrial cancer in the USA. Obesity increases exposure to estrogen unopposed by progesterone in pre- and postmenopausal women. The inclusion of progesterone appears to increase breast cancer risk, but progestogens are still indicated to prevent endometrial hyperplasia and cancer risk [26].

Progesterone is naturally produced in women in the ovaries (particularly the corpus luteum), in the placenta, and to a certain extent in the adrenal glands. There are a variety of synthetic progestogens. One of these progestogens, dydrogesterone, is a retro-progesterone, and another, drospirenone (DRSP), is spironolactone derivative. The "newer" progestogens belong to different classes based on their structure. For each of them, progestogenic, as well as antiestrogenic action, is common. The antiandrogenic effect is relevant for dienogest (DNG) and DRSP and lesser for nomegestrol acetate (NOMAC). None of them have a glucocorticoid effect. DRSP is different due to its strong antimineralocorticoid action and has a favorable effect on blood pressure. In addition, these progestogens do not interfere with the positive effect of estrogens on lipid and carbohydrate metabolism, they do not augment hemostasis processes as monotherapy, and they avoid the induction of abnormal proliferation of the endometrium in doses clinically tested. Therefore, all three progestogens appear to be suitable for the treatment of menopausal women [27].

Nonetheless, considering that HRT could create important health risks, it is highly desirable the discovery of new alternatives for the management of menopause-related symptoms, with minor side effects. Over the past 15 years, hormone preparations of dehydroepiandrosterone (DHEA) have been available over the counter and have been sold as the "fountain of youth." DHEA serves as a precursor for estrogens and androgens from fetal life to the postmenopause, and many people believe that DHEA is merely an inactive precursor pool for the formation of bioactive steroid hormones. DHEAs represent the most abundant sex steroid in plasma in humans (more than 1000 times higher than estradiol and testosterone levels), but its serum concentration goes down to 10–20% of its maximum level by around the

age of 70. The large difference between low and high serum DHEA levels has a major clinical impact. Among postmenopausal women with coronary risk factors, lower DHEA levels were linked to higher CVD and all-cause mortality [25]. Several studies had previously demonstrated that 1-year treatment, using administration of 10 mg DHEA daily in symptomatic postmenopausal women with lower (fifth percentile) baseline DHEA sulphate levels, improved climacteric and sexual symptoms and directly reversed some age-related changes in adrenal enzymatic pathways, including adrenal DHEA and progesterone synthesis [28–30].

14.5 Non-hormonal Treatments

In the past 2 years, two new pharmaceutical preparations were approved in the USA and Europe for the treatment of menopausal symptoms: an oral selective estrogen receptor modulator (SERM), ospemifene, for the treatment of moderate to severe pain during intercourse associated with vulvovaginal atrophy [31] and a tissue-selective estrogen complex (TSEC), a combination of oral conjugated equine estrogen (CEE) and bazedoxifene (BZA, a SERM), for the management of moderate to severe VMS in women with an intact uterus. Tissue selectivity is achieved through the concurrent use of estrogen and a SERM, which replaces a progestogen and selectively blocks the undesirable actions of estrogen. In the case of CEE-BZA the proliferative effects of estrogen are blocked in the uterus and possibly also the breast, whereas the bone-sparing actions of estrogen are preserved. The role of testosterone for the treatment of postmenopausal desire or arousal disorders and the long-term implications of such a therapy in postmenopausal women are unclear. The motivation for combining CEE-BZA is to retain the beneficial effects of estrogens over VMS, vulvovaginal atrophy, and bone while incorporating the antiestrogenic effects of the SERM on the breast and endometrium to improve the overall safety profile [32]. The combination of 20 mg BZA and 0.45 mg CEE is the only approved drug to date for the management of moderate to severe VMS in the USA and Europe [33].

Tibolone is a synthetic steroid that is rapidly converted into two metabolites with estrogenic activity and to a third metabolite characterized by a mixed progestogenic/androgenic activity. Tibolone controls hot flushes, sweating, and mood symptoms and is effective at improving libido, due to its androgenic component. Randomized, controlled studies show that tibolone increases bone mineral density and reduces fracture risk. These beneficial effects are seen over long-term treatments [34] (over 10 years) and in both early and late postmenopausal women, as well as in women with established osteoporosis. The combined analysis of randomized clinical studies of tibolone indicates no increase in risk of breast cancer development compared with the placebo group. Tibolone treatment is associated with a reduction of proliferation and a stimulation of apoptosis in normal breast cells that is possibly attributable to the impact of this compound on the activity of estrogen-metabolizing breast enzymes [35]. The metabolization of tibolone is tissue selective, and the conversion to the progestogenic metabolite is particularly active in the endometrium. Investigation of endometrial histology in women treated with

tibolone shows no hyperplasia and a high level of atrophic endometrium, indicating no proliferative effect of this molecule.

Some non-hormonal therapies are effective against menopausal VMS and should be considered for women who do not wish to take estrogens or those with contraindications. For VMS, many drugs have demonstrated efficacy in several studies: paroxetine, fluoxetine, and citalopram (which are selective serotonin reuptake inhibitors); venlafaxine and desvenlafaxine (selective noradrenaline reuptake inhibitors); clonidine (α_2-adrenergic receptor agonist); and anticonvulsants (gabapentin and pregabalin). Paroxetine and fluoxetine are potent cytochrome P450 2D6 (CYP2D6) inhibitors, and as they decrease the metabolism of tamoxifen (a SERM used in the treatment of breast cancer)—which may reduce its anticancer effects—these drugs should be avoided among tamoxifen users. However, consistency of treatment response and efficacy of the various alternative options remain questionable [33, 36–38].

14.6 Conclusions

MetS refers to a clustering within the same individual of hyperinsulinemia, mild to severe glucose intolerance, dyslipidemia, hypertension, an increased risk for CVD and diabetes. Parallel to this, adipose tissue could be an "insulator" and interfere with normal thermoregulatory mechanisms of heat dissipation. Women with higher abdominal adiposity, particularly subcutaneous adiposity, report an increase of VMS during the menopausal transition and in the early postmenopause. Healthy weight among mid-aged women who are early in the menopausal transition may help prevent VMS. Overweight women may suffer psychosocial consequences, with a significant impact on self-esteem and general well-being: obese postmenopausal women have lower health-related quality of life, physical functioning, energy, and vitality compared with normal-weight women. Obesity is also a major risk factor for pelvic floor dysfunction, some cancers (endometrial, breast and colon) and musculoskeletal disorders, especially osteoarthritis (a highly disabling degenerative disease of the joints). It could be necessary to encourage lifestyle measures in addition to therapeutic interventions throughout the menopausal transition in order to control menopausal obesity and to manage menopause-related symptoms, with mild side effects (Tables 14.1 and 14.2).

Table 14.1 Mechanisms by which estrogen may exert beneficial cardiovascular effects

Direct effects	Indirect effects
Nitric oxide production and release ↑	Total cholesterol ↓, LDL ↓, HDL ↑
Prostacyclin production and release ↑	Antioxidant effects: oxidation of LDL ↓
Endothelin-1 production and release ↓	Blood pressure ↓
Cytokine release ↓	Insulin sensitivity ↑
Inflammation ↓	Homocysteine ↓
Smooth-muscle cell growth ↓	Ischemia/reperfusion injury ↓, cardiac hypertrophy ↓
Atherosclerotic plaque progression ↓	

Table 14.2 Criteria for the diagnosis of metabolic syndrome

	WHO (1999)	ATP-III (2001)	IDF (2005)
Fasting glucose	Diabetes mellitus, impaired glucose tolerance	>110 mg/dL	>100 mg/dL or previously type-II diabetes
Blood pressure	≥140/90 mmHg or use of medication	>130/85 mmHg or use of medication	>130/85 mmHg or use of medication
Dyslipidemia (TG)	≥150 mg/dL	≥150 mg/dL	≥150 mg/dL
Dyslipidemia (HDL-CH)	<35 mg/dL for males	<40 mg/dL for males	<40 mg/dL for males
	<39 mg/dL for females	<50 mg/dL for females	<50 mg/dL for females
Central obesity	WHR >0.9 in males	Waist circumference	Waist circumference
	>0.85 for females and/or BMI >30	≥102 cm for males	>94 cm for males
		≥88 cm for females	>80 cm for females for Caucasian race
Microalbuminuria	Urinary albumin excretion ratio ≥20 μg/min or albumin:creatinine ratio ≥30 mg/g		
Diagnostic criteria	MD type II or IGT and two criteria	Three or more criteria	Central obesity and two criteria

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Metabolic Syndrome and Atherosclerosis in Nondiabetic Postmenopausal Women

15

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15.1 Introduction

Metabolic syndrome (MetS) is one of the most prevalent conditions predisposing to cardiovascular disease (CVD). Although various criteria have been proposed for the definition and diagnosis of the syndrome, the most commonly used is the Joint Interim Societies (JIS) MetS definition. According to these criteria, the diagnosis of MetS is established in the concomitant presence of any three of the following: (1) increased waist circumference depending on ethnicity (e.g. >94 cm for men and >80 cm for women from a Mediterranean population), (2) hypertension (systolic blood pressure > 130 mmHg and/or diastolic blood pressure > 85 mmHg or known hypertension on drug treatment), (3) decreased concentrations of high-density lipoprotein cholesterol (HDL-c) (<50 mg/dL), (4) increased concentrations of triglycerides (TG) (>150 mg/dL or known hypertriglyceridemia on drug treatment) and (5) hyperglycaemia (fasting glucose >100 mg/dL or known glycaemic disorder on drug treatment) [1]. Insulin resistance is considered as the pathophysiological hallmark

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of all parameters of MetS and is mostly met in centrally obese individuals [2]. Many researchers have doubted the importance of the syndrome and the need for such a diagnosis. However, the cardiometabolic factors that MetS includes increase independently and additively the risk for the development of type 2 diabetes mellitus (T2DM), atherosclerosis and CVD [3]. Therefore, their recognition and treatment are of great value.

Menopause represents the end of reproductive life of women, as the result of depletion of the follicle pool in ovaries. Transition to menopause is associated with a substantial decrease in oestrogen concentrations and a less intense one in androgen concentrations, resulting in a state of relative androgen excess. This imbalance is further amplified by the decrease in sex hormone-binding globulin (SHBG) concentrations [4]. These hormonal changes are accompanied by other phenotypical, metabolic and biochemical changes. Postmenopausal women have significantly higher rates of obesity compared with women of reproductive age [5], and they present a more atherogenic lipid profile, derangement of glucose homoeostasis and body fat redistribution into an "android" pattern with increased visceral adiposity [6, 7]. These changes increase the likelihood to develop MetS and, possibly, atherosclerosis and CVD [8]. Indeed, the prevalence of MetS in postmenopausal women is higher compared with women of reproductive age [9–12]. Whether these phenomena are independent of the chronological ageing itself has been a matter of scientific discussion.

The aim of this chapter is to analyse and qualitatively synthesise current information regarding MetS and atherosclerosis in postmenopausal women without preexisting diabetes. The following topics are discussed: (1) the effect of menopause on the risk of MetS as a whole, (2) the effect of menopause on individual components of MetS and (3) the risk of atherosclerosis and CVD in women after menopause.

15.2 Menopause and the Metabolic Syndrome

The prevalence of MetS in women older than 20 years old in the USA is 23.4% [2]. The prevalence of MetS in postmenopausal women ranges between 31 and 55% in different studies [9, 10], depending on the diagnostic criteria and ethnicity, as well as on dietary, cultural and environmental factors. In any case, postmenopausal women present a significantly higher prevalence of MetS compared with premenopausal women [9–12].

Small studies have indicated that MetS is not associated with the menopausal status after adjustment for age [13, 14]. However, larger studies support that menopause affects the prevalence of MetS after adjustment for age and/or body mass index (BMI) [15–17]. Subgroup analysis of a cross-sectional study in women with premature menopause revealed that these women had significantly higher risk of MetS compared with age-matched premenopausal women (40% vs. 24%, respectively) [16]. Interestingly, decrease in SHBG concentrations and increase in serum testosterone concentrations were significantly correlated with the development of MetS in postmenopausal women, while the decrease in oestradiol concentrations was not [18]. It has been demonstrated that the increase in androgen-to-oestrogen

ratio over the menopausal transition is associated with increased incidence of MetS, independently of ethnical background or other possible confounders [19]. Similarly, in a study in 362 postmenopausal women, those in the highest quartile of free androgen index (FAI) had a fivefold higher likelihood to present MetS when compared with women in the lowest quartile of FAI after adjustment for age and ethnicity [20], indicating an essential association between free androgen concentrations and the presence of the syndrome.

The years after menopause also seem to affect the prevalence of MetS. It has been reported that the risk for MetS increases during the first 14 years after menopause. The peak incidence was shown in the group of women between 10 and 14 years after the last menstrual cycle [odds ratio (OR) 4.0, 95% confidence interval (CI) 1.6–9.8], while after this time the incidence decreased [15]. In accordance, Park et al. reported that the peak prevalence of MetS is reached in around mid-60 years of age in women [9]. Of note, surgical menopause is associated with a 1.5-fold higher risk of MetS in comparison with natural menopause. This was demonstrated by a recent meta-analysis, which included 428 surgically menopausal women and 1259 naturally menopausal women from three observational studies with low heterogeneity (OR 1.5, 95% CI 1.2–1.9, $p < 0.001$) [21]. The exact mechanism is not clear; however, the sudden decrease in oestrogen concentrations after surgical menopause may play an essential role.

15.3 Menopause and the Individual Components of the Metabolic Syndrome

15.3.1 Central Obesity

One of the most notable phenotypical changes in women after menopause is weight gain, associated with an increase in total body fat mass and central abdominal fat accumulation, as well as loss of muscle mass and strength [22]. Various studies have shown that the transition from pre- to post-reproductive life is associated with an increase in waist circumference and waist-to-hip ratio (WHR) [20, 23, 24]. Even after adjustment for BMI and other possible confounding factors, postmenopausal women present about fivefold risk of central obesity compared with premenopausal women [25]. A recent meta-analysis, including 12,277 premenopausal and postmenopausal women, revealed that the mean waist circumference was by 4.1 cm increased in postmenopausal women (95% CI 3.1–5.1). Regarding BMI, results from a study including 14,445 subjects showed that it was significantly higher too in postmenopausal women (0.94 kg/m^2, 95% CI 0.7–1.2) [21].

The use of accurate body composition assessment techniques, such as dual-energy X-ray absorptiometry (DXA) or computed tomography (CT), has provided evidence that the main parameter affected during the menopausal transition is that of intra-abdominal fat [26–28]. When perimenopausal women were studied for 4 years, only women who reached menopause showed an increase in visceral fat. In addition, these women presented significant reduction in energy expenditure from fat oxidation, which favoured an increase in total body and visceral fat, without

important changes in energy intake [29]. Another study suggested that the increase in abdominal obesity (OR 3.0, 95% CI 1.1–8.3) associated with menopause is time-dependent and occurs primarily in the early postmenopausal period, mainly within the first 5 years after the last menses [15]. Interestingly, the peak prevalence of MetS in postmenopausal women is seen later in life, during the mid-1960s [9].

15.3.2 Insulin Resistance

Insulin resistance is the pathophysiological hallmark of MetS and originally was included within the diagnostic criteria [30]. It is highly associated with central obesity. Abdominal fat deposition after menopause leads to systemic low-grade inflammation through the action of cytokines and adipokines which results in insulin resistance in the peripheral tissues. Decreased lean muscle mass due to sarcopenia further contributes to this phenomenon. However, few studies investigated the possible direct effect of menopause, independently of changes in body composition. With the use of intravenous glucose tolerance test (IVGTT), insulin sensitivity was found to be decreased in postmenopausal women in early studies [31, 32]. Such differences were not detected with the use of euglycaemic, hyperinsulinaemic clamp, which constitutes the gold standard, but it cannot always detect clinically important alterations [33, 34].

Bidirectional pathophysiological associations between MetS, insulin resistance and androgens have been proposed, indicating that the higher the concentrations of androgens, the higher the degree of insulin resistance [35]. This association may be mediated by ovarian androgens, as adrenal hyperandrogenism does not further deteriorate the metabolic profile of women with polycystic ovary syndrome (PCOS) [36]. Even after menopause, there is evidence indicating a positive independent association between insulin resistance, increased FAI and decreased concentrations of SHBG [4, 37].

15.3.3 Dyslipidaemia

Women after menopause present multiple disturbances in their lipid profile, with increase in total cholesterol (TC), increase in low-density lipoprotein cholesterol (LDL-c) and increase in TG, as well as decrease in HDL-c concentrations [6, 7, 38]. Close monitoring of lipid profile in perimenopausal women from the SWAN (Study of Women's Health Across the Nation) study revealed that changes in TC and LDL-c concentrations are associated with menopause per se rather than with chronological ageing [39]. This is not the same for HDL-c concentrations, as they seem to be affected by both chronological and ovarian ageing [39, 40]. TG concentrations increase steadily during the menopausal transition [38, 41], but this change is strongly affected by the presence of central obesity [38]. Regarding sex hormone concentrations during menopause and lipids, a significant negative correlation of

TC and LDL-c with SHBG and a positive correlation with FAI was reported, but not with testosterone or oestradiol concentrations. Multiple regression analysis indicated that this association was affected by waist circumference [13].

Furthermore, concentrations of apolipoproteins may also change after menopause. Postmenopausal women demonstrate higher apolipoprotein B (apoB), as well as A-I (apoA-I) and A-II (apoA-II) concentrations compared with premenopausal women, which result in significant changes in the cholesterol content of LDL and HDL particles [7, 42]. Lipoprotein (a) may slightly increase during the menopausal transition; the evidence, however, is inconclusive [43].

15.3.4 Hypertension

Age represents a strong risk factor for hypertension in both genders. The prevalence of hypertension in the USA increases from 11.6% between 20 and 39 years to 37.3% between 40 and 59 years to 67.2% for ≥60 years of age. Interestingly, after the age of 65 years, the prevalence of hypertension in women is higher compared with that in men [44–48]. Hypertension is more prevalent in postmenopausal women compared with that in premenopausal women of the same age. The incidence of hypertension increases steeply during the first years after the last menstrual cycle [45, 49]. Central obesity and insulin resistance essentially affect the risk of hypertension. The follow-up of 3848 postmenopausal Hispanic women for 3 years showed that 27.3% of normotensive at baseline women progressed to prehypertension and 9% to hypertension and the likelihood of this progression was much higher for those who had a BMI ≥25 kg/m^2 [50]. Similarly, a study from India, including 415 postmenopausal women 40–85 years of age, demonstrated that the development of hypertension was affected primarily by central obesity and waist circumference [51]. Another study from Tunisia revealed a higher prevalence of hypertension in postmenopausal women compared with premenopausal women of similar age (72.8% vs. 26.0%, $p < 0.001$). Waist circumference and insulin resistance were the strongest predictors for hypertension too [52].

There are also cross-sectional studies which suggest that menopause increases the risk of hypertension, independently of age and BMI [38, 53]. On the other hand, there are various, epidemiological mainly studies, which did not find any differences in blood pressure between premenopausal and postmenopausal women after adjustment for age and BMI [54–56]. A recent meta-analysis, pooling data from 12 studies and 1211 women, concluded that both systolic [mean difference (MD) 6.1, 95% CI 3.8–8.4] and diastolic blood pressure (MD 3.5, 95% CI 2.1–4.9) were significantly increased in postmenopausal women but without any adjustment [21]. The relative androgen excess associated with menopause may also play a role in the development of hypertension. In a study of 180 postmenopausal women followed up for 29 months, 13% of women in the highest FAI quartile developed new-onset hypertension as compared to only 4% in the lower quartiles [57]. The same group investigated 411 consecutive apparently healthy postmenopausal women and showed that FAI was an independent determinant of systolic blood pressure [58]. In general,

hypertension is more common in postmenopausal women and is strongly associated with central obesity and insulin resistance and cardinal metabolic consequences of menopause.

15.3.5 Impairment of Glucose Homeostasis

Hyperglycaemia, even in the milder type of impaired fasting glucose (IFG, fasting glucose ≥100 mg/dL), represents one of the criteria for MetS. In a study evaluating women at midlife, fasting glucose concentrations in postmenopausal women were higher compared with those in premenopausal women (93.9 ± 7.6 vs. 96.8 ± 7.0 mg/dL, $p = 0.001$). Multivariable analysis including various potential confounders, such as age, BMI, TG, TC, LDL-c, HDL-c, systolic and diastolic blood pressure as well as menopausal status, showed that menopause remained an independent risk factor for increased fasting glucose, along with BMI and TG concentrations [59]. A meta-analysis pooled data from 15 trials and 12,466 participants for this parameter and, even though with high heterogeneity (I^2 95%), resulted that fasting glucose concentrations were significantly increased in postmenopausal women compared with premenopausal ones (MD 4.6, 95% CI 3.9–5.3). The same difference was found for fasting insulin concentrations (MD 20.9, 95% CI 2.1–39.7) [21].

Regarding T2DM development after menopause, the initial findings of the Study of Women's Health Across the Nation (SWAN) proposed that it is related with age and was not associated with the hormonal changes due to the decline of ovarian function [39, 60]. However, later analysis of the same data resulted that lower oestradiol concentrations contributed 47% higher risk for the clinical presentation of T2DM [61]. Further studies followed and confirmed these results. The European Prospective Investigation into Cancer (EPIC)-InterAct study, which followed women for 11 years, provided evidence that menopause before the age of 40 years contributed 32% greater risk for T2DM [62]. A study in 16,299 women from China showed that menopause before 45 years of age was associated with 20% greater risk for T2DM compared with the normal age at menopause [63]. Studies with surgically menopausal women reported increased risk up to 57% for T2DM [64]. A recent analysis of data from 124,379 postmenopausal women from the Women's Health Initiative (WHI) study, after adjustment for chronological age, is of great interest. This analysis provided evidence that women with less than 30 years between menarche and menopause presented 37% greater risk for T2DM compared with women having 26–40 years of reproductive lifetime [65]. Therefore, it seems that menopause and its consequences can predispose to the development of T2DM, independently of and additively to ageing.

15.4 Menopause, Metabolic Syndrome and Atherosclerosis

The adverse cardiometabolic profile which occurs after menopause can ultimately predispose to increased CVD risk. Indeed, endothelial dysfunction is evident early during the menopausal transition [66]. The Framingham Heart Study is one

of the first major studies which demonstrated a higher incidence of CVD events in postmenopausal women compared with age-matched premenopausal women [67]. The evidence is more robust regarding premature ovarian insufficiency (POI) (menopause before 40 years of age) and early menopause (menopause between 40 and 45 years of age). A recent meta-analysis of prospective cohorts showed that women with POI present an increased risk for ischaemic heart disease mortality [relative risk (RR) 1.48, 95% CI 1.02–2.16] and all-cause mortality (RR 1.39, 95% CI 1.10–1.77) [68]. Another meta-analysis also provided evidence that POI is associated with increased risk of ischaemic heart disease [hazard ratio (HR) 1.69, 95% CI 1.29–2.21] and total CVD mortality (1.61, 95% CI 1.22–2.12) [69]. Early menopause is also associated with a higher CVD risk, but to a lower extent than POI. One meta-analysis concluded in slightly increased risk for death from ischaemic heart disease in women with early menopause compared with those after normal menopause (RR 1.09, 95% CI 1.00–1.18) [68], while another one showed that early menopause increases the risk for coronary heart disease (RR 1.50, 95% CI 1.28–1.76), total CVD mortality (RR 1.19, 95% CI 1.08–1.31) and all-cause mortality (RR 1.12, 95% CI 1.03–1.21) [70]. Of note, surgical menopause is soundly associated with increased risk for CVD. The risk for coronary heart disease was more than twofold increased in women with bilateral oophorectomy (RR 2.2, 95% CI 1.2–4.2) [71]. It has been established that surgical menopause under the age of 45 years is not only firmly linked with increased CVD risk [71, 72] but also with a higher all-cause mortality [73].

In large population studies, the increase in the risk of CVD in postmenopausal women was largely attributed to coexisting metabolic risk factors [74]. MetS is a major contributor to atherosclerosis and CVD in postmenopausal women. When 473 postmenopausal women without T2DM were studied, MetS was found in 17.3% of them. Pulse wave velocity increased linearly with the accumulation of features of the syndrome, while carotid artery intima-media thickness was independently affected by MetS [75]. In the same cohort, the triglyceride-glucose index (TyG index) was shown to be strongly associated with carotid atherosclerosis and arterial stiffness mainly in lean postmenopausal women, while MetS was proved to be a better predictor of subclinical atherosclerosis in overweight and obese women [76]. A comparative analysis of data from young postmenopausal women ($n = 101$) with men ($n = 85$) without T2DM, matched for other risk factors, resulted that the prevalence and severity of carotid atherosclerosis was similar between the two populations [77]. In accordance, an Iranian prospective cohort study that followed women for 12 years reported that women who had MetS were those who developed CVD more often (24.2% vs. 15%) [78]. Data from the Rotterdam Study with a median follow-up of 7.2 years also indicated that the presence of MetS was associated with a slightly increased risk of coronary artery disease (HR 1.08–1.32) [79].

In another study with 120 healthy postmenopausal women with low-to-medium calculated cardiovascular risk, subclinical atherosclerosis was found to be highly prevalent, especially in those with higher age, more years since menopause and increased insulin resistance and blood pressure [80]. The relative androgen excess associated with menopause may has been implicated in atherosclerosis development

too. In the same population of healthy postmenopausal women [80], it was shown that total testosterone and FAI were the most important predictors of common carotid artery intima-media thickness [81]. Similarly, FAI was the only significant independent predictor of pulse wave velocity after adjustment for age, smoking, BMI, insulin resistance and lipid concentrations. On the contrary, dehydroepiandrosterone sulphate (DHEA-S) concentrations were shown to exhibit a negative association with arterial stiffness [81].

15.5 Conclusions

Transition to menopause is associated with changes in fat tissue distribution, which predispose to central obesity and increased risk for the development of MetS. The substantial decrease in oestrogen concentrations, the state of relative androgen excess and the decrease in SHBG concentrations may mediate these phenotypical and metabolic consequences. Regarding individual components of MetS, some of them seem to be affected by menopause per se, such as glucose metabolism, while some others seem to be the result of increased central obesity and insulin resistance, such as hypertension. The lipid profile worsens after the menopause, but whether this phenomenon is irrespective of age, BMI and central obesity is inconclusive. The presence of MetS appears to increase the CVD risk after menopause. Surgical menopause is strongly associated with a higher prevalence of MetS and increased risk for CVD. Bearing in mind that most women will spend more than one-third of their lifespan in the postmenopausal status, public health strategies should encourage women to maintain normal body weight during the transition to post-reproductive life, in an attempt to counteract the inevitable consequences of both chronological and ovarian ageing.

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Polycystic Ovary Syndrome-Related Risks in Postmenopausal Women

16

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16.1 Introduction

Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder of reproductive life, with an estimated prevalence of 6–20%, depending on the criteria used [1]. Three different definitions have been used so far: (a) National Institutes of Health (NIH) (1990), which requires the presence of both hyperandrogenism and oligo- or anovulation; (b) Rotterdam criteria (2003), which requires two out of the following three, oligo- or anovulation, hyperandrogenism (either clinical or biochemical), and polycystic ovarian morphology (PCOM); and (c) Androgen Excess PCOS Society (AEPCOS), which requires the coexistence of hyperandrogenism (either clinical or biochemical), as a sine qua non for PCOS diagnosis, and either PCOM on ultrasound or clinical anovulation [1]. According to NIH criteria, the prevalence of PCOS is estimated at 8.7%, rising to 17.8% with the Rotterdam criteria and approaching 12% with the AEPCOS definition [2]. These criteria can be applied only in premenopausal women, after excluding other causes of androgen

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excess [1]. In postmenopausal women, there is no uniform definition of PCOS. A potential, but precarious, diagnosis can be indirectly set in cases of menstrual irregularity (oligo- or amenorrhea) during the reproductive ages and current clinical and/or biochemical hyperandrogenism [3, 4].

PCOS has been associated with metabolic disorders, with insulin resistance (IR) being the central pathogenetic component. These disorders include impaired glucose metabolism [predisposing to type 2 diabetes mellitus (T2DM)], dyslipidaemia, hypertension and central adiposity [1, 3]. Whether these PCOS-related cardiometabolic risk factors are also translated into an increased cardiovascular disease (CVD) risk in postmenopausal life remains to be established.

The purpose of this chapter is to present current data on the association between PCOS and the risk of co-morbidities, such as T2DM, hypertension, CVD and cancer, in postmenopausal women.

16.2 Diabetes Mellitus in Postmenopausal Women with PCOS

In general, PCOS is associated with increased IR and concomitant higher risk of impaired glucose tolerance (IGT) or T2DM. The prevalence of IR in lean and obese PCOS women is estimated at 30% and 70%, respectively [5]. Only obese women with PCOS are prone to exacerbating IR and developing T2DM during the ageing process. Thus, not all women with PCOS should be considered as "high risk" of T2DM, since weight loss may ameliorate T2DM risk [6]. Except for body mass index (BMI), the risk of developing IGT or T2DM is dependent on the ethnicity (higher in Hispanic than non-Hispanic PCOS women), the PCOS phenotype (type 1, including all three Rotterdam criteria, presents the highest IR and type 4, with PCO morphology and hyperandrogenism, the lowest), testosterone (positive relation with IR) and sex hormone-binding globulin (SHBG) concentrations (negative relation with IR) [1].

A meta-analysis of 35 studies, published in 2010, showed that women with PCOS are at a 2.5-fold risk of IGT [OR 2.48, 95% confidence interval (CI) 1.63–3.77] and more than fourfold risk of T2DM (OR 4.43, 95% CI 4.06–4.82). These OR remained significant after adjustment for BMI (OR 2.54, 95% CI 1.44–4.47 for IGT and 4.00, 95% CI 1.97–8.10) for T2DM [7]. However, in this meta-analysis only two studies were conducted in premenopausal women [8, 9]. The first [8] included 28 perimenopausal women with PCOS (mean age 51.9 years) and showed a higher risk of T2DM compared with 752 non-PCOS controls (32% versus 8%, $p < 0.001$), as defined by increased fasting plasma glucose (FPG) concentrations ($\geq$7 mmol/L). Except for the small sample size, another limitation was the low proportion of postmenopausal women (35.7%) [8]. The second study [9] was conducted exclusively in postmenopausal women with PCOS and showed a higher risk of T2DM; nevertheless, it was withdrawn due to inability of the authors to replicate the original results.

In general, few studies have assessed T2DM risk in postmenopausal women. One retrospective study included 2301 women with PCOS, defined by the NIH and Rotterdam criteria. For the age groups 45–54, 55–64 and >65 years, the ORs for T2DM were 3.75 (95% CI 2.59–5.43), 2.89 (95% CI 1.57–5.34) and 7.09 (2.15–23.35), respectively, compared with the general female population. The overall OR was 2.02 (95% CI 1.71–2.38). This increased T2DM risk was affected by a history of hypertension, older age, obesity and South Asian ethnicity [10]. However, a prospective cohort study in 295 postmenopausal women with PCOS (defined as premenopausal menstrual irregularity and postmenopausal biochemical hyperandrogenism) failed to show an independent effect of the history of PCOS on the development of T2DM in later life, after a median follow-up of 9.3 years [11]. In a cross-sectional study, the prevalence of T2DM in postmenopausal women with PCOS ($n = 106$, defined by a history of both cycle irregularities and biochemical hyperandrogenism) was higher than in women without PCOS ($n = 171$, 20% versus 7%, $p < 0.01$) [12].

The effect of menopause per se on the deregulation of glucose metabolism during the menopausal transition should be considered when assessing the impact of PCOS history on T2DM risk. This is mainly attributed to the increased abdominal obesity and concomitant insulin resistance as well as to a defect in insulin secretion, as a result of oestrogen depletion [13]. It is not clear if these pathogenetic mechanisms are entirely independent of the ageing process [13]. Another confounding factor could be the past use of oral contraceptives (OC), anti-androgens or insulin sensitizers that may affect evolution to T2DM following menopause in women with PCOS. Of note, a recent meta-analysis showed that OC use does not affect FPG (irrespective of the regimen) or IR indices, such as the homeostasis model assessment of insulin resistance (HOMA-IR) [14]. Concomitant use of anti-androgens, such as cyproterone acetate, may increase HOMA-IR and abolish possible beneficial or neutral effects of OC [15].

16.3 Arterial Hypertension in Postmenopausal Women with PCOS

Most studies show a higher prevalence of (mainly systolic) hypertension in women with PCOS, at least in their later post-reproductive life, compared with the general population [1]. The exact pathogenetic mechanisms are not fully elucidated, since both BMI and IR may play a role. Independent factors have been suggested, such as activation of the renin-angiotensin system by testosterone; testosterone seems to increase plasma renin concentrations and angiotensin-converting enzyme activity [16], although this hypothesis has not been confirmed [17].

In general, data regarding the effect of PCOS on the risk of developing hypertension in postmenopausal women are inconclusive, mainly due to the different study design, the small number of patients and the various definitions used. A prospective study (including 35 women with PCOS and 68 age-matched controls, mean

age 70.4 and 70.7 years, respectively, with 21 years of follow-up) showed a higher prevalence of hypertension in PCOS (histologically verified Stein-Leventhal syndrome at wedge resection) compared with controls (69% versus 41%, $p = 0.008$) [18]. However, another prospective cohort study in 295 postmenopausal women failed to show an independent effect of PCOS on the development of hypertension in later life, after a median follow-up of 9.3 years [11].

A cross-sectional study included 286 asymptomatic postmenopausal women (43 with PCOS) and showed that PCOS was characterised by higher systolic and diastolic blood pressure (BP) compared with controls. However, BP did not reach hypertensive levels in either group [systolic BP, 127.0 ± 20.5 versus 118.3 ± 15.3 mmHg, ($p = 0.001$); diastolic BP, 78.7 ± 11.8 versus 74.4 ± 10.2 mmHg ($p = 0.014$)] [19]. However, a cross-sectional study did not find any difference in either systolic or diastolic BP between perimenopausal women with ($n = 35$) or without PCOS ($n = 752$). Of note, only ten PCOS women were postmenopausal [8].

Some confounding factors should be taken into consideration when evaluating the risk of hypertension in postmenopausal women with a diagnosis of PCOS. Transition to menopause per se may increase the risk of arterial hypertension, irrespective of BMI [20, 21]. The decline in oestrogen concentrations during menopause and the decline in oestrogen/androgen ratio increase the production of vasoconstrictive factors, such as endothelin and angiotensinogen, as well as the sympathetic activity [22]. The effect of OC use during the reproductive years on the development of hypertension in later life is not known, although current data do not indicate such a detrimental effect [14].

16.4 Dyslipidaemia in Postmenopausal Women with PCOS

PCOS has been associated with an atherogenic lipid profile in 70% of the cases, including increased low-density lipoprotein cholesterol (LDL-c), very-low-density lipoprotein cholesterol (VLDL-c), triglyceride (TG) and free fatty acid concentrations, as well as decreased high-density lipoprotein cholesterol (HDL-c) concentrations, mainly HDL2-c, due to reduced apolipoprotein A-I (apoA-I). The quality of LDL particles is also affected in PCOS, since it is characterised by the predominance of small and dense LDL particles and higher concentrations of oxidised LDL-c. These disorders of lipid metabolism are independent of BMI but may be aggravated by obesity and IR [1]. On the other hand, menopause per se is also associated with these alterations [23, 24], as well as a potential increase in lipoprotein (a) [Lp(a)] concentrations [25], further augmenting CVD risk.

It can be concluded that the effect of PCOS on lipid profile in postmenopausal women cannot be precisely estimated, taking into account the heterogeneity in PCOS definition and study design, as well as the use of hypolipidaemic drugs and OC in the past [26]. Prospective cohort and cross-sectional studies have shown either a null effect of PCOS history on lipid profile [8, 11] or an increase in TG and a decrease in HDL-c concentrations during postmenopausal years [12, 18, 19]. No difference has been identified in any lipid parameters in the retrospective studies [27].

16.5 Cardiovascular Risk in Postmenopausal Women with PCOS

Data from premenopausal women indicate that PCOS confers a potentially higher CVD risk in these patients, considering the higher prevalence of traditional CVD risk factors and CVD surrogate markers, such as arterial stiffness and carotid intima-media thickness (cIMT), compared with their age-matched controls. However, whether postmenopausal women with PCOS are indeed at a higher risk of CVD events compared with postmenopausal women without a history of PCOS has not been yet established. Many factors compromise the exact estimation of this risk. First, most data derive from retrospective cohort and case-control studies. Second, the definition of PCOS in postmenopausal women is quite obscure, based mostly on the history of irregular menses during the reproductive age and the presence of biochemical or clinical hyperandrogenism. Third, the ultrasound criterion of PCOM cannot be implicated in postmenopausal women. Fourth, some of these women have been treated with agents that may have affected the metabolic profile with unknown consequences on their CVD risk, such as OC and/or anti-androgens. Fifth, some clinical features in postmenopausal women, such as menstrual irregularities, may be attributed to other surgical or anatomical causes than PCOS. This limitation is further expanded considering that the pattern of menstruation due to PCOS during the reproductive ages usually improves during the last years before the menopausal transition. Sixth, the most crucial parameter compromising an independent effect of PCOS on CVD risk is the age- and menopause-associated deterioration of the metabolic profile (including body fat redistribution leading to increased central adiposity [28], dyslipidaemia [23, 24], deregulation of glucose metabolism [29, 30], arterial hypertension [30]), which confers a well-established CVD risk.

Three meta-analyses have been conducted on the concept of assessing CVD risk in women with PCOS. Despite the heterogeneity in study design and quality, as well as PCOS definition, these meta-analyses showed a higher CVD risk in PCOS than in women without PCOS. However, this risk was found to be lower than the one predicted by the accumulation of CVD risk factors during the premenopausal ages. The first one [31], which included three retrospective and two prospective studies, showed a twofold increased risk for the composite outcome of coronary heart disease (CHD) events and stroke [pooled relative risk (RR): 2.02, 95% CI 1.47–2.76]. After using BMI-adjusted risk data, the RR remained significant (1.55, 95% CI 1.27–1.89) [31].

The second meta-analysis [32] assessed the risk for nonfatal CHD events and stroke between women with and without PCOS and showed no significant results (OR: 1.61, 95% CI 0.82–3.15 and 1.63, 95% CI 0.96–2.78, respectively). When the analysis was confined to women older than 45 years, the risk for nonfatal stroke was increased in women with PCOS (OR: 1.94, 95% CI 1.19–3.17), whereas this was not true for CHD (OR: 1.70, 95% CI 0.92–3.11). This difference was not shown, when the analysis was restricted to studies ($n = 3$) with similar BMI values between women with and without PCOS.

The third meta-analysis included data from five case-control and five cohort studies. It also showed an increased risk of CVD in women with PCOS compared with controls (OR: 1.30, 95% CI 1.09–1.56), especially for CHD (OR: 1.44, 95% CI 1.13–1.84). In a subgroup analysis, the risk remained increased only for case-control and prospective cohort studies (OR: 1.79, 95% CI 1.16–2.77 and 1.20, 95% CI 1.06–1.37, respectively), but not for retrospective studies [33].

The effect of PCOS on CVD risk cannot be safely extrapolated to postmenopausal women, mainly for two reasons. First, the proportion of postmenopausal women in the study samples was relatively small or not reported [8, 27, 34]. Second, the diagnosis of PCOS was not based on NIH or Rotterdam criteria in most studies, but on menstrual irregularity [35, 36]. In some studies, the number of women with PCOS was very small to draw safe conclusions for CVD risk [8, 18, 37]. A study that overcame most of these methodological restraints [10] included 2301 women with PCOS, using the NIH or Rotterdam criteria. For age groups of 45–54, 55–64 and >65 years, the OR for myocardial infarction (MI) were 10.63 (95% CI 4.93–22.90), 9.27 (95% CI 3.73–23.03) and 12.88 (95% CI 3.41–48.00), respectively. The OR for the composite outcome of MI, angina, heart failure, cerebrovascular death and CVD death was increased for these age groups (2.95, 95% 1.81–4.83; 3.09, 95% CI 1.64–5.84; and 6.31, 95% CI 1.84–21.56, respectively), providing evidence for an association of PCOS with CHD risk in postmenopausal life. In a logistic regression analysis, this risk was affected by age, history of hypertension and smoking, but not by BMI and T2DM [10].

A cross-sectional study conducted in 390 postmenopausal women with clinical features of PCOS showed a higher prevalence of angiographic coronary artery disease (CAD) compared with women without PCOS. Furthermore, the cumulative 5-year CVD event-free survival was lower (78.9% versus 88.7%) [9]. However, this study was withdrawn because of the inability of the authors to replicate their results [11]. Eight years later, the same group published the results from their prospective cohort (n = 295), after a median follow-up time of 9.3 years. PCOS was defined as premenopausal menstrual irregularities in combination with postmenopausal biochemical hyperandrogenism. The study failed to show an effect of the history of PCOS on the development of CAD, CVD and all-cause mortality [11].

The risk for CVD in women with PCOS seems to be elevated even from the premenopausal ages. A Danish register-based study (n = 18,112, median age 29 years, range 23–35 years, follow-up time 11.1 years) showed that women with PCOS were at an increased risk of CVD [hazard ratio (HR): 1.7, 95% CI 1.7–1.8] compared with their age-matched controls. The total CVD event rate was 22.6/1000 patient-years and a median age at CVD diagnosis of 35 (range 28–42) years. This risk was affected by obesity, T2DM, history of infertility and/or previous OC use [38]. Hyperandrogenism did not seem to affect CVD risk in postmenopausal women with PCOS [12, 39].

Premenopausal women with PCOS have a higher prevalence of subclinical atherosclerosis compared to controls as it is evident by surrogate markers for CVD, such as arterial stiffness [assessed by means of pulse wave velocity (PWV)], arterial structure (evaluated by means of cIMT) and coronary artery atherosclerosis (CAC)

[1, 40]. This association is confirmed by two meta-analyses [41, 42]. In postmenopausal women, very few studies exist. In one representative study of asymptomatic postmenopausal women (n = 286), PCOS diagnosis was independently associated with increased arterial stiffness, as assessed by PWV. No difference in cIMT was observed between postmenopausal women with and without PCOS [19].

The Coronary Artery Risk Development in Young Adults (CARDIA) study assessed a mixed population of pre- and postmenopausal women for CAC (n = 982) and cIMT (n = 988). Fifty-five of those (mean age 45.4 years, 12.7% postmenopausal) were defined as PCOS, when both menstrual irregularities and hyperandrogenism existed. The prevalence of CAC was higher in PCOS compared with healthy controls or those women with isolated irregular menses or isolated hyperandrogenism, yielding an OR of 2.69 (95% CI 1.37–5.25), independently of CVD risk factors, such as obesity, menopausal status, hypertension, smoking, HOMA-IR and TG. Similar OR were observed for PCOS with regard to internal cIMT (OR: 2.00, 95% CI 1.07–3.75) [43]. However, others found no association between PCOS phenotype and indices of subclinical or clinical CVD in postmenopausal women [12].

16.6 Cancer Risk in Postmenopausal Women with PCOS

PCOS is characterised by chronic hyperoestrogenaemia, unopposed by progesterone, due to anovulation, a state associated with increased risk of some types of cancer, such as breast, endometrial and ovarian cancer. In a meta-analysis (11 studies, 919 women with and 72,054 without PCOS), no increased risk was found for breast cancer (OR: 0.95, 95% CI 0.64–1.39), a finding that remained non-significant after excluding studies conducted in women older than 54 years (OR: 0.78, 95% CI 0.46–1.32) [44]. Other systematic reviews and meta-analyses were confirmatory [45, 46]. However, PCOS has been associated with a high risk of endometrial cancer (OR: 2.79, 95% CI 1.31–5.95), which was further increased when studies including women >54 years were excluded (OR: 4.05, 95% CI 2.42–6.76) [44]. However, these findings were not adjusted for BMI. Studies that reported effect estimates adjusted for BMI provided inconsistent results with either increased or attenuated ORs or lack of significance [45].

The association between PCOS and ovarian cancer has been attributed to the chronic androgen exposure and the presence of androgen receptors in normal ovarian cells [45]. The aforementioned meta-analysis [44] did not show any association between PCOS and ovarian cancer risk (OR: 1.41, 95% CI 0.93–2.15), which reached significance after excluding studies in women aged >54 years (OR: 2.52, 95% CI 1.08–5.89). Perhaps, there is an association of PCOS with an increased risk of only the serous borderline subtype of ovarian cancer [45]. This finding was not supported by a recent study for any ovarian cancer both for women with self-reported PCOS and those with a history of menstrual cycle length >35 days [47].

The potential effect of obesity and long-term use of OC [48] should be taken into consideration when evaluating the link between PCOS and cancer. In a nationwide study, the OR for cancer ranged from 1.09 (95% CI, 0.96–1.23) with <1 year of OC use to 1.38 (95% CI, 1.26–1.51) with >10 years of use [49].

16.7 Conclusions: Future Perspectives

PCOS is associated with an increased prevalence of CVD risk factors, such as deregulation of glucose metabolism, dyslipidaemia and arterial hypertension, predisposing to the development of subclinical atherosclerosis and CVD. Despite the clustering of these risk factors, an association between PCOS and CVD has not been established in the post-reproductive life, at least to the extent that would be expected. Many reasons contribute to this phenomenon, such as the heterogeneity of both PCOS and CVD definitions in postmenopausal women, study design, small sample size, amelioration of menstrual pattern with ageing and insufficient follow-up. Well-designed, high-quality prospective studies are needed to establish whether the history of PCOS confers an independent CVD risk in postmenopausal women, irrespective of obesity, ageing and menopause per se. Finally, there is no evidence of an association between PCOS and breast or ovarian cancer, as a consequence of prolonged unopposed oestrogen and androgen stimulation. However, this is not the case for endometrial cancer, although an independent effect of obesity should be considered.

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Sleep and Sleep Disturbances in Climacteric Women

17

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17.1 The Importance of Sleep

Good and sufficient sleep is necessary for good quality of life [1, 2] and health. Chronic sleep disturbances are associated with both physical and mental negative health consequences, like with cardiovascular diseases [3–6], diabetes [7, 8], depression [9], and cognitive impairment [10, 11]. In addition, sleep disturbances are related to increased work absenteeism [12–15], poor work performance [16, 17], accidents, and increased healthcare costs [18, 19]. Sleep disturbances increase in prevalence during climacteric [20, 21], thus influencing in health-related quality of life, work productivity, and healthcare utilization [22].

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17.2 The Sleep Regulation and Measuring the Sleep Quality

The sleep-wake cycle is regulated by two biological processes, which interact and balance each other, the circadian process C and homeostatic process S [23]. Circadian rhythm (circa *dia*) is an approximately 24-h regulation cycle of the body's internal processes and alertness levels [24]. Sleep-wake homeostasis, process S, is an internal mechanism that produces a pressure to sleep and regulates sleep intensity; i.e., the longer awake, the stronger the need to sleep, and vice versa. Several brain areas are involved in regulation of sleep, most importantly the medulla oblongata, pons, formation reticularis, midbrain, thalamus, hypothalamus, preoptic area, basal forebrain, hippocampus, and cerebral cortex. Of neurotransmitters, adenosine and nitric oxide [25] and gamma-aminobutyric acid (GABA), hypocretin, and histamine [26] are critical for sleep regulation. Also various hormones, such as growth hormone, cortisol, melatonin, prolactin, and ovarian hormones, are involved [27–34].

Sleep quality is divided to subjectively reported sleep quality (*subjective sleep quality*) and objectively measured sleep quality (*sleep architecture*). Subjective sleep quality and daytime consequences (fatigue, tiredness, reduced attention, cognition or memory impairment, mood disturbance, or irritability) are evaluated with structured questionnaires or sleep diaries. Subjective sleep quality is most commonly worsened by insomnia symptoms (e.g., difficulty initiating or maintaining sleep, or too early morning awakening) but sometimes by sleep disordered breathing (SDB) or restless legs syndrome (RLS) as well. One or more insomnia symptoms which occur at least three times per week during at least 1 month with daytime symptoms are required for the definition of insomnia disorder [35]. Generally, older age, female sex, and lower socioeconomic status, as well as previously diagnosed insomnia, positive family history of insomnia, and poor perceived mental and general health are risk factors for insomnia [36–39]. Also several systemic diseases and the use of medicaments may induce sleep disturbances [40, 41].

Sleep can be objectively measured with polysomnography (PSG), which consists of an electroencephalogram (EEG), electrooculogram (EOG), and electromyogram (EMG). Sleep is divided into wake, non-rapid eye movement (NREM) sleep, and REM sleep. NREM is further divided into stages N1–N3 (former S1–S4). N3 (former S3 and S4) is also called as slow-wave sleep (SWS) [42–44] (Fig. 17.1). In addition to the percentages of sleep stages and total sleep time, sleep latency, sleep efficiency, slow-wave activity (SWA), and the number of arousals and awakenings are typically determined from PSG-measured sleep. The optimal average sleep duration in order to maintain good health ranges from 7 to 8 h [45]. Shorter and longer sleep durations have been associated with increased morbidity and mortality in general populations [46–49]. The basic challenge for evaluating sleep quality and sleep disorders is that the correspondence between subjectively and objectively measured sleep is not unambiguous [50–53]. However, the individual's perceptions of sleep disturbance and daytime consequences are more likely to direct diagnosis and treatment.

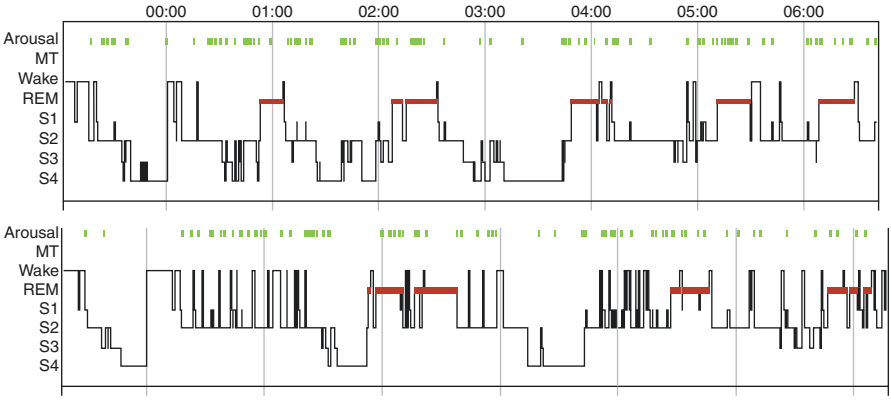

Fig. 17.1 Hypnograms derived from the polysomnograms of the same woman. Premenopausal situation (upper hypnogram) and perimenopausal situation 6 years later (lower hypnogram). Note especially the sleep fragmentation. *MT* movement time, *S1* stage 1 non-REM sleep, *S2* stage 2 NREM sleep, *S3* stage 3 NREM sleep, *S4* stage 4 NREM sleep. *Data from Lampio* et al., *2017*

17.3 Subjective Sleep Quality and Insomnia Symptoms in Climacteric

Sleep disturbances, especially insomnia symptoms, are one of the most bothersome symptoms in climacteric, being reported by 40–60% of climacteric women [54]. Both cross-sectional [55–59] and longitudinal [60–63] studies confirm that the prevalence of perceived sleep disturbances increases in the menopausal transition, even after controlling for age. A meta-analysis of 24 cross-sectional studies reported higher odds of experiencing sleep disturbance relative to premenopause in perimenopausal (1.60), postmenopausal (1.67), and surgically menopausal (2.17) women [64]. The most common sleep-related complaint is nighttime awakenings [55, 58, 61, 63], although also difficulty falling asleep increases across the menopausal transition [55, 58, 61, 63]. The increase in early morning awakening is shown to level off from late perimenopause to postmenopause [55, 58, 61, 63]. Although the insomnia symptoms inevitably increase in climacteric, the research about insomnia disorder in climacteric is limited. The phone interview of nearly 1000 women showed that 26% of perimenopausal women qualified for a DSM-IV diagnosis of insomnia, with difficulty maintaining sleep the most common symptom [65]. As for increasing follicle-stimulating hormone (FSH), the association with greater odds of waking up several times was found, whereas decreasing estradiol (E_2) was associated with higher odds of difficulty falling and staying asleep [61]. Despite this clear increase in poor sleep quality as women enter climacteric, the severity and persistence of poor sleep, as well as the extent of impairment in daytime function, vary between women.

17.4 Sleep Architecture in Climacteric

Even though the evidence for declining subjective sleep quality in climacteric is strong, polysomnographic (PSG) studies have generally not found a corresponding negative change in sleep architecture. The observed mismatch between subjective and objective sleep quality [66] has been explained by a possible influence of psychological state on sleep quality judgments by affecting the sleep appraisal process rather than sleep itself [67]. Also, most PSG studies have been cross-sectional with small sample sizes and differences in definitions of menopausal stages, age ranges, presence of systemic diseases and sleep disorders, and sleep-recording techniques. Some studies have found no differences in sleep architecture between pre- and postmenopausal women [68–72], while a few studies have reported more slow-wave sleep (SWS) in peri- and postmenopausal women than premenopausal women [59, 73–76]. More SWS could be interpreted as reflecting a better sleep pattern, on the one hand, but alternatively could reflect a recovery response to sleep deprivation. A single study has found more time spent awake and lower sleep efficiency in peri- and postmenopausal women compared to premenopausal women, but all studied women were insomnia patients [77].

Few studies have investigated the association between serum concentration of FSH and PSG measures. A cross-sectional study of women mostly in the early menopausal transition without sleep complaints found that higher FSH concentrations were associated with more wakefulness after sleep onset, awakenings, and arousals, after adjusting for age and BMI [78]. However, in women with insomnia symptoms, PSG measures did not correlate with FSH, whereas they were associated with anxiety and symptoms of depression [78]. In a small study with a group of pre- and postmenopausal women with diagnoses of depression, FSH concentration was positively associated with wakefulness after sleep onset and negatively associated with SWS [79]. Further, in another cross-sectional study, a more rapid rate of FSH change over the previous few years was associated with higher amount of SWS and longer total sleep time during a subsequent sleep study [80]. In the only longitudinal, 6-year follow-up study addressing changes in PSG measures across the menopausal transition, at follow-up, women had a shorter total sleep time, lower sleep efficiency, more wakefulness after sleep onset, and more awakenings after adjusting for vasomotor symptoms, BMI, and mood (Fig. 17.1). These changes in sleep were linked with advancing age rather than increased FSH levels. Increasing FSH was associated with a greater proportion of SWS, presumably reflecting an adaptive change to counteract the age-related sleep fragmentation [73] (Table 17.1).

Only limited work about PSG measures in climacteric women with insomnia disorder exists. One study showed substantial objective sleep disruption, with a poorer sleep efficiency, more wakefulness after sleep onset, and shorter total sleep time, matching the subjective poor sleep quality in this group compared to women without insomnia [81]. Further, women with insomnia were more likely to have objectively measured hot flashes, and the presence of hot flashes predicted the number

Table 17.1 Polysomnography sleep studies in menopausal transition

Authors	Study design	Sample characteristics	Findings	Comments
Shaver et al. 1988 [72]	Cross-sectional	Pre-, peri-, and postmenopausal women aged 40–59 y (n = 76)	No differences in sleep parameters between the groups	Peri- and postmenopausal women experiencing hot flashes had longer REM latency and tended to have lower SE compared to women without hot flashes
Young et al. 2003 [59]	Observational epidemiologic study	Pre-, peri-, and postmenopausal women, mean age 46.3 y, SD 8.1 (n = 589)	Peri- and postmenopausal women had more SWS, and postmenopausal women had less S2, and higher SE compared to premenopausal women	Peri- and postmenopausal women were more dissatisfied with their sleep quality compared to premenopausal women. No adaptation night
Sharkey et al. 2003 [76]	Cross-sectional	Pre- and postmenopausal women aged 45–56 y (n = 25)	Postmenopausal women had more SWS and less S1	No difference in subjective sleep quality. Two consecutive laboratory nights
Freedman et al. 2004 [71]	Cross-sectional	Pre- and postmenopausal women with and without hot flashes, aged 46–51 y (n = 31)	No differences in sleep parameters	Most awakenings preceded a hot flash, but not vice versa in the three consecutive laboratory nights
Kalleinen et al. 2008 [70]	Cross-sectional	Young (aged 20–26 y), premenopausal (aged 45–51 y) and postmenopausal (aged 59–71 y) (n = 61)	No differences between pre- and postmenopausal women. Young women had longer TST, higher SE and SWA, more SWS, and less WASO compared to pre- and postmenopausal women	Postmenopausal women were less satisfied with their sleep quality compared to premenopausal women. Two consecutive laboratory nights

(continued)

Table 17.1 (continued)

Authors	Study design	Sample characteristics	Findings	Comments
Sowers et al. 2008 [80]	Sleep was studied cross-sectionally and FSH annually 7 y prior the sleep study	At the time of the sleep study, women were premenopausal, early or late perimenopausal, and postmenopausal, median age 52 y (n = 365)	More rapid rate of FSH change was associated with more SWS and longer TST	More rapid rate of FSH change was associated with poorer subjective sleep quality. Two nights of in-home PSG
Hachul et al. 2009 [69]	Cross-sectional	Early and late postmenopausal women aged 50–65 y (n = 30)	No differences in sleep parameters	Two consecutive laboratory nights
Hachul et al. 2010 [75]	Cross-sectional	Reproductive (mean age 38.8 y [SD 10.4]) and postmenopausal (55.9 y [SD 7.9]) women (n = 931)	More SWS, less S2 and REM in postmenopausal women compared to reproductive women; after adjustment of age and BMI, only greater chance of having AHI >5 for postmenopausal	No adaptation night
Campbell et al. 2011 [68]	Cross-sectional	Pre-, early peri-, late peri-, and postmenopausal women aged 48–59 y (n = 321)	No differences in PSG measures. Beta EEG power, indicating arousal, ↑ in late peri- and postmenopausal women, but no difference in delta EEG power	Beta EEG power was related to hot flash frequency. Three consecutive in-home PSG-measurement nights. Results adjusted with age and other covariates
Xu et al. 2011 [77]	Cross-sectional	Pre-, peri-, and postmenopausal women aged 40–59 y (n = 74)	Longer total wake time and lower SE in peri- and postmenopausal women compared to premenopausal women	All subjects were insomnia patients. No differences in subjective sleep quality. Three consecutive laboratory nights

(continued)

Table 17.1 (continued)

Authors	Study design	Sample characteristics	Findings	Comments
de Zambotti et al. 2015 [78]	Cross-sectional	Young (aged 18–27 y) and perimenopausal women with and without insomnia (aged 43–52 y) (n = 44)	FSH ↑ was associated with WASO, awakenings and arousals ↑ in perimenopausal non-insomniacs, but not in insomnia patients in young women FSH ↑ was related to WASO and N1 ↑	In perimenopausal insomniacs TST correlated with anxiety and depression. No adaptation night
Hachul et al. 2015 [74]	Cross-sectional	Reproductive (mean age 34.6 y, (SD 8.4)), early (5.22 y (5.3)), and late (63.3 y (8.6)) postmenopausal women (n = 535)	More N3, higher AHI, and lower SaO_2 in postmenopausal women compared to premenopausal, no difference between early and late postmenopausal women	Wide age range (20–80 y), results were adjusted with age, BMI, blood pressure. No adaptation night
Lampio et al. 2017 [73]	6-year follow-up	At baseline all women (mean age 46 y, SD 0.9) were premenopausal and at the follow-up in different stages of menopausal transition (n = 60)	Increase in FSH associated with SWS ↑, after controlling for BMI, vasomotor and depressive symptoms	Aging was associated with shorter TST, lower SE, increased transitions from SWS to wake, increased WASO and amount of awakenings after controlling for confounding factors

n number, *y* year, *REM* rapid-eye movement sleep, *SD* standard deviation, *SWS* slow-wave sleep, *S2* stage 2 non-rapid eye movement (NREM) sleep, *SE* sleep efficiency, *S1* stage 1 NREM sleep, *FSH* follicle-stimulating hormone, *TST* total sleep time, *PSG* polysomnography, *WASO* wake after sleep onset, *N1* stage 1 NREM sleep, *N3* stage 3 NREM sleep, *SD* standard deviation, *EEG* electroencephalogram, *AHI* apnea-hypopnea index

of PSG awakenings per hour of sleep [81]. According to another study, where subjective sleep quality and PSG measures were compared between premenopausal and peri-/postmenopausal women with insomnia disorder, subjective sleep quality and depression were similar between the two groups, whereas peri-/postmenopausal women had a longer PSG-defined total wake time and lower sleep efficiency, suggesting that PSG measures of sleep quality are impacted to a greater extent in peri-/postmenopausal than in premenopausal women with insomnia disorder [77].

17.5 Primary Sleep Disorders in Climacteric

Sleep disturbances may arise in climacteric in association with primary sleep disorders, such as sleep disordered breathing (SDB), restless legs syndrome (RLS), and periodic limb movement disorder (PLMD) [21, 82]. SDB is characterized by snoring, upper airway obstruction, inspiratory flow limitation, and excessive daytime sleepiness [83]. An apnea-hypopnea index (AHI) of five or more per hour of sleep indicates SDB [83]. The prevalence of SDB is higher in men than in women before menopause [84]; however, the prevalence increases in women following menopausal transition [85–89]. The postmenopausal women have shown to be 2.6 times more likely to have an AHI $\geq$ 5 per hour and 3.5 times more likely to have an AHI $\geq$ 15 per hour, compared with premenopausal women, after adjusting for confounding factors (age, BMI, and smoking) [88]. In the recent longitudinal analyses of the same data, AHI increased from premenopause to peri- and postmenopause, independent of age and changes in body habitus, although these factors were also associated with AHI [85]. Furthermore, in a large follow-up study, the hazard ratio for OSA in women with surgical menopause was 1.27 compared in women with natural menopause independently of age at menopause. The increased OSA risk due to surgical menopause persisted for over 15 years into the postmenopausal period and was more pronounced in leaner women, as well as among women who never used menopausal hormone therapy (MHT). OSA risk associated with surgical menopause was attenuated among physically more active women [90]. The greater prevalence of SDB after menopause might, in part, be due to the loss of the protective effects of female reproductive steroid hormones, especially progesterone, which have shown to have respiratory stimulative effects [88, 89], as well as changes in fat distribution after menopause [86]. The clinical picture of SDB in women usually differs from that of men, and therefore women are probably more likely to be undiagnosed. Women are more symptomatic with lower AHI compared to men, and they have more prolonged partial upper airway obstruction and report insomnia as a symptom of SDB more frequently [91, 92]. Of importance, patients with SDB and insomnia-like symptoms have higher burden of cardiovascular, pulmonary, and psychiatric comorbidity and lower adherence to continuous positive airway pressure treatment compared to patients with traditional sleepy phenotype despite less severe SDB in terms of AHI [92].

The prevalence of RLS and PLMD increases with age, and RLS is more common in women [93]. Freedman et al. found periodic limb movements and apneas to be the best predictors for poorer sleep efficiency in peri- and postmenopausal women reporting sleep disturbances [94]. However, in a group of asymptomatic postmenopausal women, the incidence of periodic limb movements was unrelated to E_2 or FSH levels [95], suggesting that the increase in prevalence of RLS and PLMD after menopause may be related more to aging than to hormonal changes.

In addition to primary sleep disorders, other medical disorders, as well as use of medications, become more common with advancing age and may affect sleep in midlife women [41, 96, 97]. In one of the few prospective studies assessing predictors for menopausal sleep disturbances, medical diseases and use of prescribed

medication predicted future sleep disturbances [98]. In another prospective study, depressive symptoms, personal crises, use of medications affecting the CNS, and perceived impaired general health already 5 years before menopause predicted various sleep disturbances in menopausal transition [99].

17.6 Contributing Factors for Sleep Disturbances in Climacteric

17.6.1 Vasomotor Symptoms (Hot Flashes and Sweating)

Several factors contribute for sleep disturbances in climacteric (Fig. 17.2). Nocturnal hot flashes and sweating are an important component of sleep disturbance during midlife: self-reported vasomotor symptoms are consistently associated with poorer self-reported sleep quality and chronic insomnia [57, 61, 65, 100]. Women with

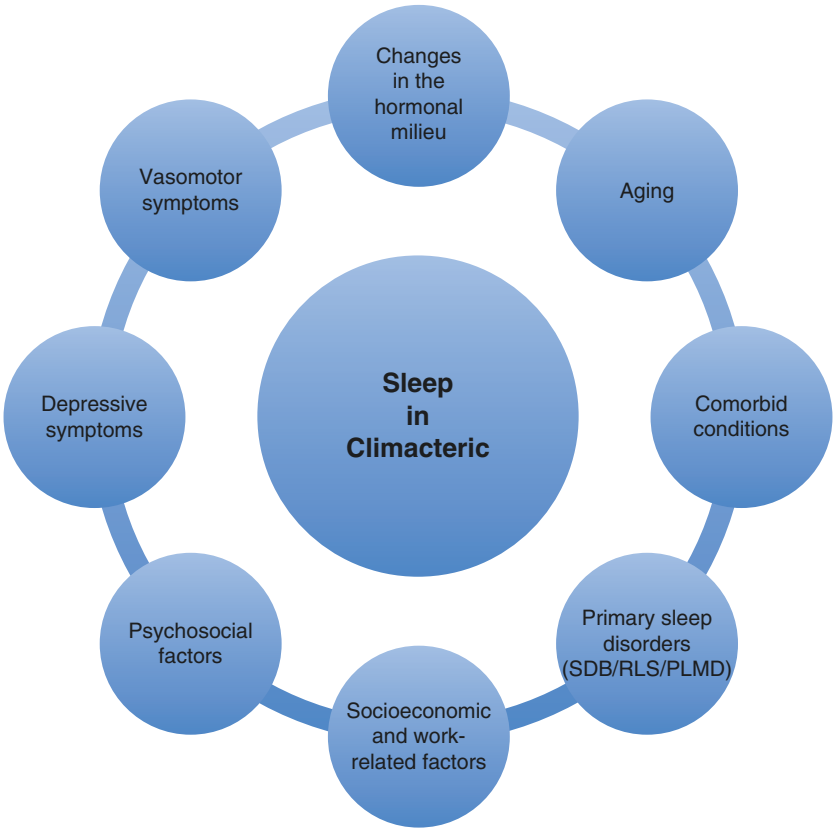

Fig. 17.2 Factors contributing for sleep quality and sleep disorders in climacteric. *SDB* sleep-disordered breathing, *PLMD* periodic limb movement disorder, *RLS* restless legs syndrome

moderate-severe hot flashes are almost three times more likely to report frequent nocturnal awakenings compared to women without hot flashes [101]. However, studies that investigated relationships between reported vasomotor symptoms and objectively measured sleep (with actigraphy or PSG) have produced conflicting results, with no relationship [59, 71] or with association between hot flashes and disrupted sleep [102–104].

Objectively measured vasomotor symptoms have been linked to sleep disruption in some [102, 103, 105, 106], but not all [71, 94, 104] studies. Differences between studies might relate to the classification of hot flashes in association with awakenings [102], as well as between-women variability in the impact of hot flashes on sleep. In an experimental model of new-onset hot flashes in young premenopausal women treated with a gonadotropin-releasing hormone agonist, hot flashes were linked with more PSG awakenings, more wakefulness after sleep onset, and more stage 1 sleep [107], providing a link between hot flashes and disturbed sleep. In an analysis of the overall impact of hot flashes on sleep architecture, wake time attributed to hot flashes was responsible for, on average, 27% of objective wakefulness after sleep onset, although there was wide variability in hot flash impact between women [102]. Additionally, an awakening occurred simultaneously with the majority (69%) of hot flashes. The strong overlap in timing between hot flash onset and awakenings suggests that these events may be driven by a common mechanism within the central nervous system in response to fluctuating estrogen levels, although sweating triggered by a hot flash may still contribute to or extend the interval of waking [102].

17.6.2 Depressive Symptoms

Risk for depression increases in climacteric, independently of other factors [108–111]. Women have been reported to be two to four times more likely to develop major depressive disorder in the menopausal transition and early postmenopause compared to premenopause, after adjusting for confounding factors [109].

Mood and sleep disturbances act in a bidirectional relationship [112, 113]. This relationship has also been documented in climacteric women [114–116]. In a longitudinal study, depressive symptoms were unrelated to menopausal status or annual change in E_2 but were associated with hot flashes and sleep disturbance [117]. Further, in another longitudinal study, the presence of subjective sleep problems at baseline was an important predictor of persistent/recurrent major depressive disorder at follow-up [118]. Studies about the association between sleep architecture and depressive symptoms have produced, however, conflicting results. In one study, more depressive symptoms were associated with lower sleep efficiency and shorter total sleep time in perimenopausal women and with a higher percentage of REM sleep in postmenopausal women [116]. In contrast, in another study, mood symptoms were not independently related to sleep architecture, but anxiety symptoms were related to longer sleep onset latency and lower sleep efficiency; however, this was found only in women who

also reported vasomotor symptoms [119]. Moreover, hot flashes and depressive symptoms have shown to be associated with different sleep disturbance patterns, with hot flashes being exclusively associated with frequent awakenings whereas depression was uniquely associated with difficulty falling asleep and too early morning awakening [120]. In addition, an intervention study in depressive perimenopausal women found that improvement in depression was predicted by improved sleep and increasing E_2, but not by alleviation of vasomotor symptoms [121].

17.6.3 Psychosocial and Sociodemographic Factors

In midlife, women face several challenges and personal life stressors, including changing family roles, loss of significant others, health concerns and worries about getting old, as well as alterations and increasing demands at work or retirement [122]. Life stressors and experiencing stress may contribute to sleep disturbances [122–124]. Indeed, perceived stress and poor perceived health have been associated with subjective sleep disturbances in midlife women [63, 97]. Furthermore, midlife women with higher chronic stress exposure over a 9-year follow-up period were more likely to have insomnia and more wake in objectively measured sleep than participants with moderate stress exposure [125]. Concerning work stress with sleep disturbances, a recent prospective study with over 24,000 participants (82% women, mean age 44 years) showed that the disappearance of job strain was associated with lower odds of insomnia symptoms [126]. In a study of 131 Egyptian teachers in the menopausal transition (aged 46–59 years), the most important menopausal symptoms that affected their work capacity and performance were tiredness (83%) and sleep disturbances (64%) [127]. A larger study of 961 midlife women found that insomnia symptoms were the most problematic menopausal symptoms to affect daily life and working performance [128]. As for work stress and sleep disorders in climacteric, postmenopausal women had worse sleep than premenopausal women during working days, but few differences during leisure days, showing an existing coping mechanism of work stress after menopause and the requirement of enough rest [129].

Some socioeconomic factors are protective against the development of sleep disturbances in climacteric; higher educational level [100], lower financial strain [130], and satisfactory marriage [131, 132] are all related to fewer sleep disturbances. Further, the prevalence of menopausal sleep disturbances is influenced by race and ethnicity: Caucasian women have higher rates, while Hispanic women have lower rates of sleep disturbances [61]. A study assessing the burden of menopausal sleep disturbances on societal costs concluded that menopausal chronic insomnia, characterized by nighttime awakenings, was linked with increased healthcare utilization and associated costs, decreased work productivity, and decreased health-related quality of life after adjustment for demographics and comorbidity [22].

17.7 Management of Sleep Disturbances in Climacteric

As the reasons for sleep disturbances in climacteric are potentially multiple, and sometimes overlapping, before prescription of the treatment, the causes behind should be accurately evaluated. For note is that for some women, sleep disturbances may be transient and thus not requiring any active treatment, whereas for other women, sleep disturbances may be severe, with a significant impact on daytime functioning and quality of life and thus necessity for treatment. In addition, occasionally combined treatments may be required, such as for women who have depression in addition to severe vasomotor symptoms and sleep problems. The cornerstone of management of sleep disorders is good sleep hygiene: appropriate sleeping environment, regular sleep-wake rhythm, sufficient exercise, and avoidance of stimulants, i.e., coffee, especially too late in the evening. Treatment options include MHT, non-hormonal pharmacological medications, and non-pharmacological and self-management strategies (Table 17.2).

17.7.1 Menopausal Hormone Therapy

Several studies have evaluated the effect of MHT on sleep; however, findings are mixed and difficult to compare, given the heterogeneity in study populations and tools to evaluate sleep and various MHT preparations (formulation, dose, and type of administration). According to a recent meta-analysis, MHT modestly improves subjectively evaluated sleep disturbance [133]. In most studies, improved sleep quality has co-occurred with improvement of vasomotor symptom [133–137]. However, there are also some data of enhanced sleep quality with MHT without the report of vasomotor symptoms [135]. PSG studies examining the effect of MHT

Table 17.2 Treatment of climacteric sleep disturbances

Non-pharmacological treatment
Sleep hygiene
Appropriate sleeping environment (calm, dark, appropriate temperature; comfortable bed)
Regular sleep-wake rhythm
Reducement of daytime stimulants
Regular daytime exercise
Relaxation techniques
Behavioral techniques, i.e., stimulus control or sleep restriction
Cognitive-behavioral treatment of insomnia (CBT-I)
Menopausal hormone therapy
Antidepressants (i.e., low-dose selective serotonin/serotonin noradrenaline reuptake inhibitors, mirtazapin)
Gabapentin
Melatonin
H1-antihistamin
Sleep medication (i.e., intermediate-acting benzodiazepines, “Z-drugs”)

on sleep architecture in menopausal women share the same problems with study design as the studies evaluating subjective sleep quality and MHT. In addition, those studies are rare, and the results are conflicting. Some studies have observed positive changes in sleep architecture with MHT [138–141], mainly decreasing wake after sleep onset, although other studies found no improvement [142–144].

17.7.2 Non-hormonal Pharmacological Medications

Of other treatment options, low-dose selective serotonin/serotonin norepinephrine reuptake inhibitors have shown to reduce hot flashes to some extent and modestly reduce insomnia symptoms in women with hot flashes [145–147], although the adverse-effect profiles of these medications need to be carefully considered. Evidence from a single trial shows that gabapentin improves sleep quality in perimenopausal women with hot flashes and insomnia [148]. As for sleep medication, melatonin, antihistamine, intermediate-acting benzodiazepines, and so-called Z-drugs can be used, although especially the two latter with short-term only.

17.7.3 Cognitive-Behavioral Treatment and Other Non-pharmacological Treatments

Cognitive-behavioral treatment of insomnia (CBT-I) is considered the primary intervention for patients with chronic insomnia [149], and it is superior to sleep medication alone in the long term [150]. Recently, a study using CBT-I during the menopausal transition in a randomized clinical trial of peri- and postmenopausal women with insomnia symptoms and daily hot flashes showed that 8 weeks of CBT-I led to a greater reduction in insomnia symptoms, with improvements maintained at 6 months posttreatment [151]. An open trial of CBT-I in women with menopausal sleep problems also found a reduction in insomnia (and depression) symptoms posttreatment [152].

Other non-pharmacological approaches for treating menopausal insomnia, like acupuncture, yoga, massage, exercise, and nutritional supplements containing soy isoflavones, have been used, with mixed effects [153].

17.8 Conclusion

Sleep quality decreases and sleep disturbances increase in climacteric. Sleep problems may be severe and thus deteriorate daytime functioning and quality of life in part of the women, having often also long-term consequences for mental and physical health. Climacteric symptoms, especially vasomotor symptoms, typically interfere with sleep and are strongly associated with reports of sleep disturbances as well as PSG-measured wakefulness. However, also other factors directly related to climacteric (e.g., hormonal changes), as well as a variety of health and/or life

circumstances (e.g., SDB or movement disorders, mood disturbances, presence of medical conditions, or life stressors), have an impact and thus should be evaluated. Given the presence of distinctive sleep-disruptive factors (e.g., hot flashes) and the multifactorial nature of sleep disturbances in climacteric women, treatment needs to be tailored.

Disclosure Statement The authors have nothing to disclose.

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Impact of Menopause on Brain Functions

18

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18.1 Introduction

Menopause, defined as cessation of menses after 1 year, represents an important transition in reproductive states in women. It occurs at a median age of 51, preceded by 4–6 years of cycle alterations, and it's associated with fluctuating hormone levels and emergence of symptoms like sleep disturbances, mood and memory changes, cognitive impairment, hot flushes, and vaginal dryness. Those symptoms occur with different grades of severity, frequency, and duration and can invalidate women's life. In this scenario, specific brain areas are involved: olfactory bulb, thalamus, hypothalamus, amygdala, mammillary bodies, nucleus accumbens, septum, hippocampal formation, parahippocampal gyrus, insula, orbitofrontal cortex, medial prefrontal cortex, and cingulate gyrus. Increasing evidences suggest that cognitive complaints after menopause may represent an important marker for early neural dysfunction and dementia connected with the physiological postmenopausal loss of estradiol. In fact, even if subjective cognitive decline can be associated with nonmenopause-related conditions (i.e., normal aging; psychiatric, neurologic, and medical disorders; substance use; and drug effects), several studies demonstrate organic neurological changes caused by sex hormone deprivation [1]. This opens new frontiers to an additional understanding of peripheral hormones affecting cognitive and, in general, neurological functions.

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18.2 From Reproductive Age to Menopausal Transition

The estrogen and progesterone synthesis from enzymatic modifications of cholesterol takes place primarily in the ovaries but also in the adrenal gland and adipose tissue. The two main active estrogens in nonpregnant women are estrone and estradiol, while pregnant women also produce significant quantities of estriol. Gonadotropins, luteinizing hormone (LH), and follicle-stimulating hormone (FSH), released from the pituitary gland under hypothalamus control, modulate both production and secretion. During the entire life, physiological hormonal fluctuations may determine organic and cognitive changes (Fig. 18.1). During childhood, estrogen and progesterone

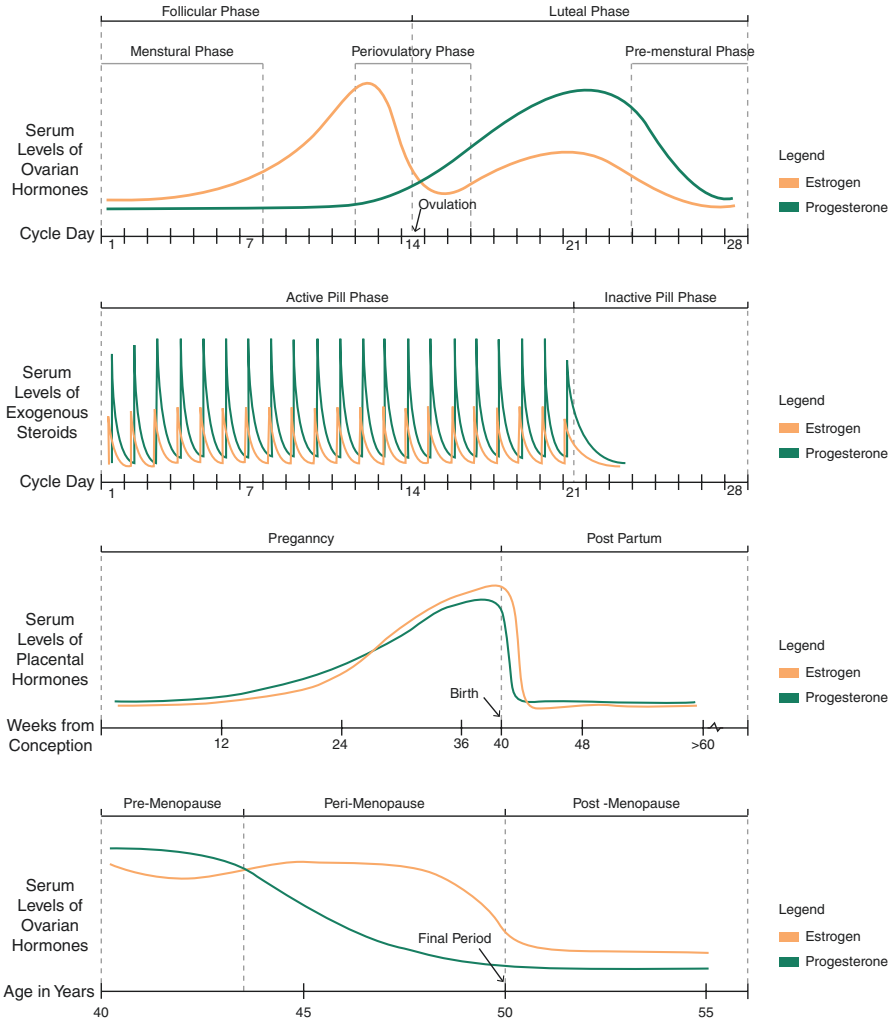

Fig. 18.1 Fluctuations and modifications of sexual steroids in different physiological and paraphysiological scenarios throughout women's life

levels are low but increase at the onset of puberty under the influence of LH and FSH leading to regular menstrual cycling. In this last scenario, it's possible to identify two phases: follicular phase when serum estrogen levels are high and progesterone low and luteal phase when progesterone level is high compared to the estrogen level. It's interesting to notice that luteal phase can be associated with several premenstrual symptoms such as abdominal bloating, cramping, weight changes, headaches, decreased concentration, depression, irritability, and anxiety. Specific hormonal changes happen during pregnancy: both estrogen and progesterone increase across the three trimesters and then return to baseline after parturition. During postpartum phase on the one hand, the high prolactin level suppresses the synthesis of sex hormones (GnRH mediated) so that ovulation can't occur; on the other hand, the relatively low estrogen level detected can cause in some women postpartum depression. Interestingly, another hormonal modification starts during perimenopause when progesterone levels decline more quickly than estrogen. Instead, levels of progesterone and estrogen become permanently low after menopause transition. Specifically, the decline of sex steroid and inhibins leads to a loss of hypothalamic feedback inhibition that stimulates GnRH and gonadotropin production. Moreover, the decrease inhibin production results in a decreased activin receptor inhibition and, together with the increase in bioavailable activin, leads to a further increase in the secretion of GnRH and gonadotropins. As a consequence, without a negative feedback, the elevated secretion of GnRH, LH, and FSH causes ovarian senescence and impairment.

18.3 Estrogen Receptor Alpha and Beta

Estrogen receptors are members of the nuclear receptor superfamily and DNA-binding transcription factors localized in synaptic terminals, dendritic spines and shafts, axons, mitochondria, and glial cell. It's possible to identify two different isoforms, ER α and ER β, differing in expression and actions [2]. Both are able to heterodimerize, suggesting that different responses are modulated by their coexistence [3]. During aging, changes in the ratio ER α/ER β regulate estrogen-mediated gene transcription and control memory, cognition, attention, sensory integration, mood, emotion, and motivation [4]. In this scenario estrogens act both via traditional and nontraditional mechanisms, on the one hand binding ER α or ER β in the nucleus and on the other hand cooperating in association with lipid rafts and receptors like G protein-coupled estrogen receptor (GPER) [5]. In the classical mechanism, after the dimerization between receptors, a binding to a DNA estrogen receptor (ERE) occurs; thus transcription of estrogen-sensitive genes and proteins can initiate. It's interesting to notice that there is a higher affinity between ER α and ERE than the one with ER β that may reflect in a more successful transcription. In nonclassical mechanism, estrogens bind to membrane-bound receptors, including GPER, which activates second messenger systems, causing the resulting response. Evidence suggests a combination of both membrane-initiated and genomic actions to affect transcription.

Evidences have demonstrated that ERs may be integrated into the plasma membrane: it's reasonable that they may be localized in lipid rafts microstructures and they would take part in cell survival with other molecules which may modulate

their physiological activities. The list includes GPI-anchored receptors, G protein-coupled receptors (adrenergic receptors, adenosine receptors, and cannabinoid receptors), glutamate receptors (AMPA, NMDA, mGluR), neurotrophin receptors (tyrosine kinase receptors, TrkA, TrkB, ephrin receptor, Eph, c-Ret, ErbB), Src family receptors (c-Src, Lyn, Fyn), cell adhesion molecules (NCAMs, TAG-1, Thy-1), and proteins associated with myelin glycosynapse (LINGO1, p75, NgR1, myelin-associated glycoprotein). What is certain is that numerous studies demonstrate the lipid raft involvement in nervous system functioning like modulating synapsis, neuronal plasticity, cell-cell communication, myelin organization and stability, autophagy, neuronal survival, and neurodegeneration and protection from oxygen deprivation, stroke, and Aβ- and glutamate-induced toxicities [6].

18.4 ER α

It's primarily expressed as a nuclear receptor in prefrontal cortex, in hippocampus, and especially in amygdala and hypothalamus**,** regions that mediate memory and emotional process; however, an extranuclear form is found in both cytoplasmic and membrane locations including within dendritic spines and at the synapse (Fig. 18.2). Gonzalez et al. [7] demonstrated that expression of ER α in the nuclei of pyramidal

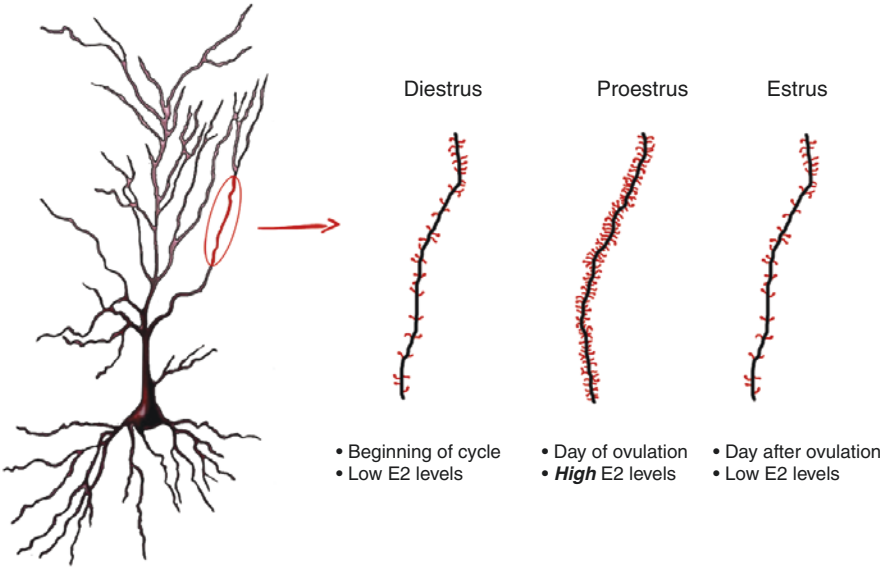

Fig. 18.2 Estradiol regulates spine synapses on hippocampal pyramidal neurons through ER α. In the diestrus phase, when estradiol levels are low, spine densities are also low. During proestrus, when ovulation occurs, both estrogen levels and spine densities increase in parallel. In the estrus phase, the day after proestrus, the system prepares for the next cycle, and spine densities return to baseline

cell of the hippocampus could occur from 15 gestational week to adulthood where it was maintained with the association of the cytoplasmatic isoform. Moreover, during the transition period to menopause, we assist to an increased expression of ERα-splice variant (MB1) as an indicator of its potential role during aging.

Supporting the importance of ER α in neuronal process, the study by Wang AC et al. "Synaptic estrogen receptor-alpha levels in prefrontal cortex in female rhesus monkeys and their correlation with cognitive performance" asserts that in ovariectomized female monkeys, estradiol treatment with the presence of postsynaptic ER α improves cognitive performance.

Moreover ER α nonneuronal expression may contribute to estrogen actions, including injury-sensitive expression of ER α in glial cells.

18.5 ER β

This receptor is transcribed from a different gene than ER α, and for this reason, despite similar properties, it has both ligand-dependent and ligand-independent actions. It's expressed as a nuclear receptor in the hippocampus, neocortex, claustrum, and thalamus, participating to preservation of neuronal integrity. ER β is also found in the mitochondria, protecting from the oxidative and metabolic stress implicated in Alzheimer and Parkinson disease. Its first detection appears at 15 gestational weeks in proliferative zones, and then, at 25 gestational weeks, ER β is detected in cortical neurons, both in the nuclei and in the cytoplasm. This condition changes during life; in fact in adulthood much of the nuclear isoform is lost, while cytoplasmatic ER β receptors become predominant; however, the total percentage of synapse connected to ER β decreases.

18.6 Neuroendocrine Changes Across the Menopausal Transition

Hypothalamic-pituitary-adrenal axis activity regulates several physiological and neurological functions by monoamine neurotransmitter and glucocorticoids. Given the early change of GNRH and FHS in middle-aged women before ovarian decline, the hypothesis outlined is that HPA undergoes independent functional modifications during its physiological aging. The dysregulation of this axis causes loss of coordination with ovarian hormonal secretion. In particular the loss of estrogenic sensitivity at the hypothalamic level determines an increased production of gonadotropins that, with a concomitant lower ovarian response to FSH and LH, leads to anovulatory cycles.

Furthermore, the general evidence is that in areas such as the prefrontal cortex, limbic system, and hypothalamus, high levels of ERs are expressed so that, thanks to its interactions with ER alpha and beta estradiol, these can modulate the synthesis, release, and metabolism of peptides like dopamine, serotonin, acetylcholine, β-endorphin, and neurosteroids, such as allopregnanolone and dehydroepiandrosterone (DHEA) (Fig. 18.3) [8]. In fact, during climacterium and menopause, the

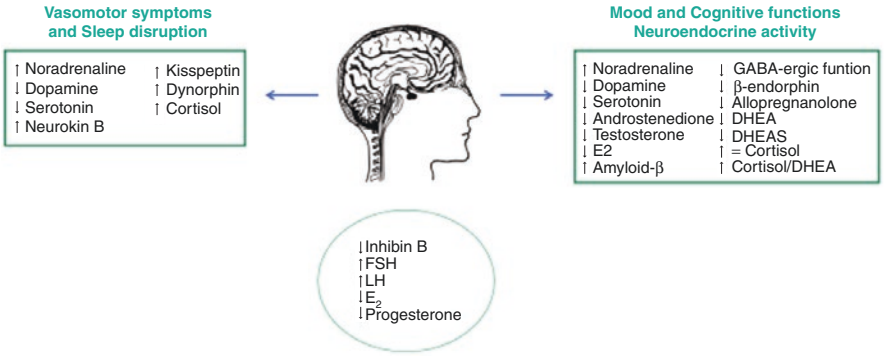

Fig. 18.3 Hormonal and neurosteroid modifications related to the neuroendocrine changes across the menopausal transition

fluctuation of steroid hormones induces a dysregulation of neurotransmitter pathways that concomitant with the persistently high levels of FSH and LH leads to neurologic, mood, memory, sleep, and thermoregulation disturbances. Moreover, the decreases in both DHEA/cortisol ratio and androgens may have implication in the lack of energy, sexual arousal and satisfaction, and learning and memory processes [9]. Finally, a study by Farrag et al. [10] suggested that surgical menopause obtained with oophorectomy before the natural onset of menopause may result in a more negative symptom manifestation when compared to oophorectomy after the menopause transition is completed.

18.7 Symptoms and Consequence

18.7.1 Mood Disorders and Depression

Mood disorders are the second leading cause of disability in developed countries, affecting over 350 million people worldwide without distinction of sex, age, and social status.

Epidemiologic data suggest two different incidence and prevalence peaks of depressive symptoms in women: the first at 40s and the second between 55 and 64 years, following the trend of menopause transition. During this period, the risk of developing mood disorders is greater the more the woman is exposed to sex hormone fluctuations rather than to their decline. Since perimenopause can last for several years, the risk of developing depression increases over time as the transition is longer [11]. Furthermore the Mayo Clinic Cohort Study of Oophorectomy and Aging by Rocca et al. asserts that mono- or bilateral oophorectomy before the onset of menopause can cause a major risk of anxiety symptoms, standing for a risk factor for depression.

Underlying all these modifications are some emerging hypotheses such as the reduction of neurosteroids and the expression of high serum MKP-1 levels.

Low circulating allopregnanolone levels (caused by ovarian failure) could be responsible for depressive symptoms in vulnerable women since they determine a consequent reduced synthesis of GABA-A receptor in specific brain areas deputed to mood and emotional control [12].

Ling-yun et al. [13] find a correlation between high serum MKP-1 (a protein that inactivate mitogen-activated protein kinase MAKP-1), low serum levels of brain neurotrophic derived factor (BDNF), and depression. However more studies need to be elaborated.

Moreover vasomotor symptoms represent an index of increased prevalence of mood disorders that can be studied in the late reproductive years. Indeed, Boulant et al. [14] confirm this association describing an increased number of hot flushes episodes in women with severe depressive symptoms rather than in those without mood alterations. In addition, general data support the fact that high levels of anxiety correlate with more severe and frequent vasomotor symptoms.

Finally as glucose is fundamental for brain metabolism, a decrease in its blood concentration and consumption in the hippocampus, parahippocampal gyrus, and temporal lobe, shown by 18F-FDG_PET images, may have a plausible role in mood disorders [15].

18.8 Alzheimer Disease

Alzheimer disease, one of the major neurodegenerative causes of dementia, mostly affects women (16.7% versus 9.1% for men). This is confirmed by several evidences which show the influence of sex hormone fluctuation on brain changes during women aging. The transition from pre-menopause to menopause may represent the crucial time frame in which the metabolically active and healthy status of the female brain switches to a hypometabolic and oxidative state.

Short et al. [16], studying gonadotrophin levels in Alzheimer postmenopausal women, prove the relation between increased production of amyloid-β and high levels of FSH and LH. Indeed, the use of leuprolide acetate reduces the plaque formation blocking FSH and LH release.

Long et al. [17], testing neuronal mitochondria, suggest that the reduction of ER β expression in the mitochondria associated with a consequent increase in oxidative stress may play an important role in Alzheimer disease in women.

Many other studies on apolipoprotein E (APOE), a protein responsible for the transport of lipids in the blood, show that its expression is stimulated in specific brain areas dedicated to learning and memory including the hippocampus and cortex by interactions between 17β-estradiol and ERs. In particular, increasing evidence indicates that the link between APOE4 and Alzheimer disease is far more prominent in women, suggesting that female sex hormones play a role in modulating the effect of this protein in the development of this neurodegenerative disorder.

Finally, data like the one by Brinton et al. [18] demonstrate a significantly reduced risk for the development of Alzheimer in women who start estrogen therapy immediately after menopause, while this benefit disappears and turns into adverse effect if therapy is taken years later after menopause.

18.9 Sleep Disruption

Sleep disturbances are one of the major complaints of women during climacterium because of their impact on the quality of life, mood, productivity, and general physical health. Specifically, as for brain functions, multiple studies show the correlation between sleep deprivation and reduced hippocampus and parietal gray matter volume, causing decreased memory, cognitive impairment, and increased risk of β-amyloid accumulation [19]. The biological mechanism underlying sleep difficulties is still unclear; however, the suprachiasmatic nucleus may have a relevant role, thanks to its ER β expressions which follows a diurnal rhythm [20]. Furthermore lower levels of inhibin B, which represent a marker for early menopausal transition, can be used to predict poor sleep quality. Instead, the same marker role in late menopausal transition and in postmenopause is described by high urinary FSH levels. As confirmed, the FSH increase is associated with longer sleep duration, indicative of less restful and non-REM sleep [21]. Moreover, the Penn Ovarian Aging Study 8 asserts that the decrease in sex hormone levels is associated with worse sleep quality and more severe sleep problems such as obstructive sleep apnea (considering the respiratory-stimulating properties of progesterone).

18.10 Thermoregulation

Hot flushes are one of the characteristic symptoms of perimenopause, affecting about 80% of women, with an average duration of about 7 years. They are described as sudden increases in body temperature associated with profuse sweating and redness mainly of the upper body, followed by dissipation within seconds to minutes. The frequency and severity of such episodes can affect the woman's lifestyle, leading in some cases to stress, anxiety, and drowsiness [22]. Behind this there is the thermoregulatory center, located in the hypothalamus and more specifically in the anterior nucleus and the adjacent preoptic area regions. As the temperature varies from the baseline, endocrine production initiates control mechanisms to increase or decrease energy production/dissipation as needed to return to the initial temperature. Thermoregulatory dysfunctions can be associated with alteration of the noradrenergic and serotoninergic pathways that occur during estrogen level fluctuations. As a matter of fact, the progressive reduction of vasomotor system during menopausal transition indicates a readjustment of the brain to the different sex hormone concentrations. Despite the certain role of the hypothalamus, new theories have been proposed. A hypothesis deriving from RMN studies of brain functions suggests a control of thermoregulation also at subcortical level, showing an activation of the insula and anterior cingulate cortex during hot flushes [23]. Another finding is the association between thermoregulatory dysfunction and low brain glucose metabolism highlighted by 18F-FDG PET. As confirmed, in the SWAN study, the rising of hot flushes frequency is related to a simultaneous increase in fasting blood glucose and HOMA index. Finally other factors play a role in this scenario:

low levels of adiponectin, high levels of leptin, and cytokine monocyte chemotactic protein 1 indicating a strong association with impaired glucose homeostasis in perimenopausal women [14].

18.11 Migraine

Headache is one of the relatively common symptoms that occurs during menopause, increasing in peri- and decreasing in postmenopausal period. It tends to be more frequent for menopausal women who experienced premenstrual migraine during fertile years; however, its prevalence is stable at between 10 and 29% [24]. Migraine in women is usually caused by the abrupt decline in estrogen levels that occurs both before menses and during menopausal transition. In fact, several findings confirm the importance of areas such as hippocampus and prefrontal cortex rich in ERs, in influencing electrical excitability and neurotransmission, thanks to the release of neurotransmitters and neuropeptides. Emerging data suggest that the typical pulsing pain reported could be exacerbated by changes in estradiol levels in the brain that induce an inflammatory neurogenic state and determine vasodilatation and plasma extravasation [25].

In this scenario, the age at the onset of menopause represents a critic parameter that impacts differently cognitive outcomes, influencing hormone therapy efficacy, and for this reason it has to be examined in depth in future researches.

18.12 Imaging of the Menopause

Increasing evidence for hormone-dependent modification of function and behavior during the menstrual cycle leads to research of the corresponding data from neuroimaging. The study conducted by Hagemann et al. [26], using MRI to investigate brain volume changes connected to estrogens in fertile women, asserts that there is an increase in gray matter volume and a decrease in cerebrospinal fluid between the luteal and periovulatory phases, while no changes are detected in white matter volume. The hippocampus, parahippocampal gyrus, fusiform gyrus, cingulate cortex, insula, middle frontal gyrus, thalamus, and cerebellum are areas found to have a hormone structural plasticity. In these regions, estrogen seems to have trophic effects.

Goto et al. [27], using the same technique and comparing neurological volume changes in premenopausal vs. postmenopausal women, show a significant decline in hippocampal volume in the second group of studies rather than the first.

Thanks to MRI and PET, Kantarci et al. [28] studied the effects of oral conjugated equine estrogen (oCEE, Premarin 0.45 mg/dL), transdermal 17β-estradiol (tE2, Climara 50 μg/day), and placebo therapy within 3–36 months after the onset of menopause. This study leads to a major finding: no difference is detected in global brain volumes and cognitive function between mHT group (tE2 or oCEE)

and placebo group 3 years after the exposure to mHT. However, during those first 3 years, white matter hyperintensity volume increases in the oCEE group more than in placebo and dorsolateral prefrontal cortex volumes are preserved (and correlated with lower global cortical β-amyloid deposition) in the tE2 group more than in the placebo. Furthermore, PET images show a correlation between the lower PiB uptake (i.e., β-amyloid deposition) and the preservation of the dorsolateral prefrontal cortex volume in the tE2 group (but not in the oCEE group). The subsequent normalization of changes in brain structure after the cessation of mHT confirms the transient mHT effects and the difference in all formulations.

18.13 Hormonal Treatment and the Brain

Studies on the effects of postmenopausal hormone treatment on cognitive functions are still not conclusive; however, new evidences suggest that cognitive effects are influenced by specific hormone formulations [29]. The KEEPS Cog study analyzing the efficacy of oral conjugated equine estrogen and transdermal estradiol suggests the second formulation to have a more effective action on cognitive function in peri- and early menopausal women. In general, more positive cognitive effects have been identified with the single estrogen therapy rather than the one combined with progestin. For example, the combination of equine estrogen with medroxyprogesterone acetate (MPA) may not have the same positive effects of estrogen alone because of the MPA neutralizing activity. In addition, the new common trend leads to think that progestins and progesterone have no the same influence on neurobiological mechanisms of cognitive function and that progesterone is probably more beneficial and less dangerous than its synthetic counterparts. As confirmed, verbal ability appears to be negatively influenced by progestins, while those formulations with less antiestrogenic effects seem to have neutral or positive impact on benefits conferred by estradiol treatment. Moreover neurotrophic and neuroprotective progesterone actions are well known in animal models (i.e., modifying hippocampus response, reducing cell inflammation, protecting from traumatic brain injury and cerebral ischemia) so that it gives the input to examine in depth its potential effects on women postmenopausal cognition.

A study conducted by Berent-Spillson et al. [30] demonstrates the association between both estrogen or progesterone treatments and activation of verbal processing and encoding. In particular these treatments are found to be in association with an increase in number of words remembered, while only progesterone is related to visual memory task. These results are aligned with the general evidence that menopausal estrogen treatment increases prefrontal activation and cognitive processes, thanks to mechanisms like modulation of interactions with neurotransmitter systems, growth factors, and dendritic spine density. Although much more data needs to be collected, the general evidence is that estrogen treatment has positive effect on neurological activity exclusively in the initial period after the cessation of the menstrual cycle or immediately following surgical menopause, while it has deleterious effects in older women.

18.14 Prospective

Having laid the foundations of neurobiological and hormonal changes and their correlation with menopause encourages us to elucidate molecular mechanisms, cognitive pathways, and homeostasis as aging occurs. This will yield insight into how and when the brain responds to endogenous hormone changes as well as to exogenous hormone treatment. Moreover, it will permit to develop new opportunities for menopausal women that not only solve undesirable symptoms but also potentially prevent, attenuate, or postpone cognitive and affective changes. One interesting target would be focusing on receptor dynamics and synaptic regulation rather than on circulating estrogen and progesterone levels, in the way to develop more successful treatments.

Another finding that needs to be more investigated is the differential effect of natural versus surgical menopause. In fact several studies suggest that the abrupt loss of estrogens induced by oophorectomy/ovariectomy in humans produces a more severe consequence in cognitive and synaptic health than what happens with the gradual loss of estrogens in natural menopause. These differences may suggest distinct treatment regimens more efficacious for each condition.

In conclusion, more detailed investigations are required to develop more specific and effective interventions tailoring the treatments to each woman's need.

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Vasomotor Symptoms: Clinical Management

19

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Vasomotor symptoms (VMS) or "hot flashes" are the most common complaint during the menopausal transition, occurring in up to 80% of women, with approximately 33% experiencing more than ten episodes per day [1, 2]. Despite the high prevalence, only a minor seek medical attention for treatment.

The pathophysiology of the hot flash is not fully understood and is likely related to multiple factors. Changes in reproductive hormones and in thermoregulatory mechanisms are involved. The thermoregulatory zone is narrowed and becomes more sensitive to subtle changes in core body temperature. Small increases in temperature trigger thermoregulatory mechanisms causing the sensation of a hot flash (vasodilatation, sweating, and decreased skin resistance) [1, 3]. They affect quality of life (QoL) and appear to be associated with adverse health outcomes including cardiovascular, bone, and brain health [4]. VMS may also interfere with sleep and cause chronic sleep disruption [1, 5].

Symptoms are progressive during the menopausal transition until early postmenopausal stage and can last 7.4 years. Women who experience early VMS have the longer total duration: 11.8 years being that 9.4 years is after the final menstrual period (FMP) [6].

Frequency, duration, and severity of symptoms appear to vary by culture and ethnicity. African American women reported the most vasomotor symptoms, and Asian women reported the fewest symptoms compared with other groups in a study that assessed menopause symptoms in a large sample of women with diverse ethnic backgrounds [6].

The management of VMS is based on the symptoms' intensity and frequency and the women's medical history and personal choice. Usually, the

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pharmacological treatments are used for women with moderate to severe hot flashes (symptoms that interfere with usual activities or usual activities cannot be performed).

19.1 Non-pharmacological Treatments

19.1.1 Behavioral Measures

Besides the lack of data from well-structured clinical trials, these behavioral measures are recommended. These measures help the core body temperature not to increase and not to initiate mechanisms to dissipate heat [7].

Higher temperatures are triggers for vasomotor symptoms, and identifying that is recommended [8, 9]. Also it is recommended avoiding spicy foods and stressful situations, alcohol intake, hot foods, or liquids [8].

Although other lifestyle changes, like performing aerobic physical exercises, yoga practice, or weight loss, have beneficial effects on several aspects of the physical and psychological health of the individual, they are not yet supported by high-quality evidence for improving VMS [8, 10, 11].

19.1.2 Other Techniques

Other potential options may include cognitive behavioral therapy (CBT), mindfulness-based stress reduction (MBSR), relaxation, paced respiration, hypnosis, and vitamin E.

CBT effectively reduced the impact of VMS by an average of 50% after 8 h of group CBT or self-help CBT with benefits maintained at 6 months. Improvements in QoL are more expressive in individuals who experienced group CBT. The frequency of night sweats reduced subjectively and objectively in healthy women who underwent CBT [12, 13]. This technique is recommended for management of hot flashes [8].

Current evidence does not support the efficacy of MBSR for VMS [9, 14]. There is insufficient evidence to recommend relaxation techniques [14, 15]. Paced breathing was previously recommended but has been found to be ineffective [9].

Hypnosis is recommended for treatment supported by randomized controlled trials [8, 16]. The mean reduction in hot flash score was 18.83 (80.32%) for the clinical hypnosis intervention compared with 3.53 (15.38%) for controls ($P < 0.001$; 95% CI 12.60–17.54) [8, 16].

The improvement superior to placebo for VMS in some pilot studies using vitamin E has been suggested. It was tested in a study with women treated for breast cancer, with a marginal reduction when compared with placebo (mean of 1 less

episode/day). At the dose of 800 international units (IU)/day, it is well tolerated and not associated with toxicity [17].

Some preliminary data suggest that stellate ganglion blockade (SGB), by local injection of anesthetic into the sympathetic nerve fibers of the neck, may reduce vasomotor symptoms in women with contraindications to HT. This is an invasive and costly procedure, and more evidence is needed [7, 8].

Initial evidence suggests that transcranial direct current stimulation (tDCS) showed a trend in VMS improvement. Complementary data are needed [18].

19.1.3 Alternative Techniques

19.1.3.1 Acupuncture

Several studies have been conducted to assess the effectiveness of acupuncture for the management of VMS with contradictory results [8, 19–23]. A systematic review published in 2017 concluded that acupuncture was more effective than no treatment [21]. Comparison with hormonal therapy with estrogen (HT) found that acupuncture was less effective than HT for hot flash frequency [8, 20].

19.1.3.2 Phytoestrogens

Phytoestrogens are found naturally in foods. Its chemical structure is compared with intrinsic estradiol, acting as an estrogen agonist or antagonist. This occurs with respect to the type of estrogen receptor present in various tissues [24].

Isoflavone components genistein and daidzein are found in soy products that bind to estrogen receptors and have both estrogen agonist and antagonist properties. Soy supplementation with soy foods or soy extracts, including derivatives and metabolites, has been extensively studied, and there's no conclusive evidence to be more effective than placebo for VMS treatment [25–27]. Their safety are not established. Some limitations are the uncontrolled manufacturing process with resulting variability in composition and poor quality studies [8].

Black cohosh (*Actaea racemosa* L.—previously *Cimicifuga racemosa*) active compounds are unknown, as well as the mechanisms of action. After 23 weeks of black cohosh or placebo use, there was no significant difference in VMS treatment in perimenopausal or postmenopausal women [28]. There is insufficient evidence to support its use—and safety—for menopausal symptoms [8].

Other herbal treatments that have been studied for VMS include ginseng, St. John's wort, *Ginkgo biloba*, *Trifolium pratense* (red clover), maca, and dong quai (*Angelica polymorpha*). However, the overall quality of evidence for these therapies is poor. Despite the "natural" appeal, there is no data that phytoestrogens are proven to be superior to placebo in most well-designed studies, and, little is known about their safety, particularly in women with contraindication to hormone therapy (HT). Current evidence from randomized controlled trials does not support specific diet regimens such as plant-based diets or supplementations for the management of VMS [7–9, 24].

19.2 Pharmacological Treatments

19.2.1 Hormonal Treatment

19.2.1.1 Hormone Therapy

Systemic HT, with estrogen alone or in combination with progestogen, is the most effective therapy for vasomotor symptoms related to menopause [4, 29]. HT was found to reduce VMS frequency in 75% (IC: 64%–82%) and symptom severity in 87% (RR: 0.13; IC95%: 0.27) [30].

The candidates for HT are symptomatic women, younger than 60 years or who are within 10 years of FMP. The therapy should be individualized, taking into account the potential benefits and risks. The lowest dose that offers relief should be used, since it may have lower risks and may reduce the adverse events such as breast tenderness and vaginal bleeding [4, 29].

The association of estrogen and progestogen is required for the endometrial protection in women with a uterus [4, 29].

19.2.1.2 Combination of Selective Estrogen-Receptor Modulator (SERM)/Estrogen: TSEC

Bazedoxifene is a SERM that in combination with an estrogen results in a tissue-selective estrogen complex (TSEC). This class of drug is available for the treatment of VMS and osteoporosis prevention [4]. The association of bazedoxifene and conjugated equine estrogen (CEE) has estrogen agonist effects on bone, antagonist effects on the endometrium, and apparently neutral effects on breast. It promotes a decrease in the incidence of hot flashes with no increased risk of endometrial hyperplasia, without the need for a progestogen. It has also been associated with a lower incidence of breast pain and tenderness than other therapies. In addition, breast density does not increase [31, 32].

The combination of bazedoxifene with CEE is indicated for women with moderate to severe VMS who have breast tenderness with estrogen-progestin therapy or for women who cannot tolerate oral progestin therapy [4].

19.2.1.3 Tibolone

Tibolone is a synthetic steroid with tissue-specific estrogenic and progestogenic effects and appears to have a beneficial effect on bone density, vasomotor symptoms, and vaginal symptoms without estrogenic effects on the uterus [33, 34].

Tibolone is not FDA-approved and is not available in the United States.

19.2.1.4 Compounded Bioidentical Hormones

Bioidentical hormones are substances that are chemically similar or structurally identical to those produced by the body. Most compounded preparations have not undergone any rigorous clinical testing for either safety or efficacy, so the purity, potency, and quality of compounded preparations are a concern. There are no controlled trials which support claims for better efficacy and safety concerns.

Data do not support the use of progestin-only medications, testosterone, or compounded bioidentical hormones for the treatment of vasomotor symptoms [4, 7, 24, 29].

19.2.2 Nonhormonal Treatments

There are some options for women with moderate to severe VMS who are not candidates or don't want to use hormone therapy. It also can be tried in women who experience recurrent hot flashes after stopping HT.

The choice will depend whether the patient is taking tamoxifen, the pattern of hot flashes, and the presence of a mood disorder or sleep problem.

19.2.2.1 Selective Serotonin Reuptake Inhibitors (SSRIs)/ Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

Although paroxetine 7.5 mg/day is the only nonhormonal medication approved by the FDA for treatment of moderate to severe VMS of menopause, other SSRIs, SNRIs, and others show evidence of efficacy. SSRIs and SNRIs are the most effective nonhormonal pharmacologic alternatives, demonstrated in placebo-controlled trials and meta-analysis [8, 9, 35, 36].

Some drugs have been tested and have shown some degree of efficacy in symptomatic women. Although no head-to-head trials have been performed, indirect comparisons suggest that paroxetine [35, 37, 38], venlafaxine [39–41], desvenlafaxine [42–45], citalopram [46], and escitalopram [47, 48] have a similar benefit for hot flashes. These drugs appear to be equally effective [36].

These medications increases the levels of serotonin and norepinephrine, both implicated in the origin of hot flashes. The clinical response is rapidly observed, usually in 2 weeks, and is associated with mild to moderate improvements in symptomatic postmenopausal women. Reduction in hot flash frequency varies from 25 to 69% and severity from 27 to 61%. There's no difference between the responses in women with surgical or natural menopause [8]. Suggested dose of SSRI and SNRI for hot flash treatment is expressed in Table 19.1.

There's no consistent evidence to use fluoxetine and sertraline to hot flash treatment [35, 49–53].

Besides that, the use of paroxetine or fluoxetine is not recommended to treat hot flashes in women who use tamoxifen. These drugs may interfere with the

Table 19.1 Suggested dosing of SSRI and SNRI for hot flash therapy

Drug	Suggested dose (mg/day)
Paroxetine salt	7.5
Paroxetine	10–25
Escitalopram	10–20
Citalopram	10–20
Desvenlafaxine	100–150
Venlafaxine	37.5–150

Modified from the North American Menopause Society [8]

Table 19.2 Suggested gabapentin and pregabalin doses for hot flash therapy

Drug	Suggested dose (mg/day)
Gabapentin	900–2400
Pregabalin	150–300

Modified from the North American Menopause Society [8]

metabolism of tamoxifen by inhibiting cytochrome CYP 3A and CYP 2D6 reducing the effect of treatment of breast cancer [54].

19.2.2.2 Gabapentin and Pregabalin

Gabapentin is an antiepileptic drug whose action seems to involve a direct effect on the hypothalamus. Although it's used for neuropathy and neuralgia, some evidences have shown improvement in frequency and severity of hot flashes at 900 mg/day [8, 9, 35, 36, 55–57].

Gabapentin, SSRIs, and SNRIs have similar effects to reduce the VMS [58]. Gabapentin may be an option in some women whose hot flashes are primarily at night, interrupting sleep (because drowsiness can be an adverse event). Other adverse events include dizziness and unsteadiness, mainly at first week. Higher doses seem to be as effective as estrogen, but adverse events limit the use [8]. Suggested dose of gabapentin and pregabalin for hot flash treatment is expressed in Table 19.2.

Also there's evidence that pregabalin is effective for treatment of hot flashes [59].

19.2.2.3 Clonidine

Clonidine is an alfa-adrenergic agonist, with antihypertensive action. The decrease of VMS occurs by the reduction of central and peripheral vascular reactivity but is less effective than SSRIs, SNRIs, gabapentin, and pregabalin [9, 35].

The use is limited by security and adverse events of hypotension, dry mouth, sedation, dizziness, and constipation.

19.2.2.4 Sulpiride

Sulpiride is an atypical neuroleptic that can act on serotonin receptors in low doses. Originally, it is known that this drug has clinical positive effects on schizophrenia and for mood spectrum disorder treatment.

One pilot clinical trial comparing sulpiride 50 mg/day versus placebo results in improvement of frequency of hot flashes after 4–8 weeks, with minimal adverse events [60].

19.3 Conclusions

VMS are the most common complaint during the menopausal transition and postmenopausal women.

The management of hot flashes is individualized and based on symptom's intensity and frequency and women's medical history and personal choice. The aim is to promote QoL offering evidence-based information and safety and effective treatments, when needed.

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Vasomotor Symptoms, Metabolic Syndrome, and Cardiovascular Risks

20

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20.1 Vasomotor Symptoms and Metabolic Syndrome

Although the majority of menopausal women suffer from vasomotor symptoms (VMS; hot flushes and night sweats), the underlying etiopathology behind them is not fully identified. However, the decrease in endogenous estrogens and an elevated central sympathetic tone, mediated through alpha-2 adrenergic receptors, have been associated with a narrowed thermoneutral zone in the thermoregulatory center in the brain possibly causing VMS [1]. Menopausal symptoms and their impact on the quality of life are described. Abundant data link metabolic disturbances to the activation of the sympathetic nervous system [2]. This is, in turn, associated with changes in blood pressure (BP) [3], dyslipidemia [4], and the development of insulin resistance [2], which all are components of the MetS. Although both VMS and MetS are linked to sympathetic overactivity, it is unclear whether VMS are an independent risk factor for MetS.

20.1.1 VMS and BP

Cross-sectional data on BP and VMS are mixed. For instance, one study found that in lean and healthy postmenopausal women, the more frequent the VMS, the lower the systolic BP [5]. Data on no association between VMS and BP [6] also exist. In

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another study both systolic and diastolic BPs were significantly higher in menopausal women with VMS, when compared with asymptomatic women [7]. Of note, women with VMS and increased BP [7] were overweight with a mean BMI between 26 and 29 kg/m^2. On the contrary, in studies [6, 7] showing lack of association, the women were lean (mean BMI ≤25 kg/m^2).

The Study of Women's Health across the Nation (SWAN) is a large and ethnically diverse longitudinal study of the menopausal transition with long follow-up and 3302 women enrolled [8]. One of the reports from the SWAN study focuses on the association between VMS and BP [9]. In this study (n = 2839), data on VMS and BP was collected at each annual study visit, and mean follow-up was 8.2 years. Women with ≥6 days with VMS during the preceding 2 weeks had greater increases in diastolic BP over time than did asymptomatic women or those with less symptoms. Symptomatic women were also at an increased risk of developing prehypertension or hypertension during follow-up (hazard ratio of 1.39, 95% CI 1.09–1.79).

20.1.2 VMS and Lipids

As regards lipids, in the SWAN study [10], the presence and frequency of VMS after 8 years was associated with higher lipid and lipoprotein levels. Overall, good quality data on VMS and lipids seems scarce. In a recent pooled analysis [11], data on VMS and lipids consisted of only two studies. A larger number of studies were analyzed for night sweats, and the meta-analysis showed that night sweats were associated with significantly increased levels of total cholesterol (0.17 mmol/L, 95% CI 0.03–0.31) and LDL-cholesterol (mean difference: 0.07 mmol/L, 95% CI 0.01–0.13).

A Korean cross-sectional study on 1906 postmenopausal women with no current HT use addressed specifically the relation between VMS and MetS [12]. The study showed that women with VMS had a higher risk for MetS and that the relationship was stronger for women with a BMI over 25 (OR 2.1, 95% CI 1.3–3.5).

According to a recent systematic review on VMS and metabolic health [13], many studies suffer from high heterogenicity and do not possess the quality to make definite conclusions. However, the majority of data point toward an unbeneficial association between VMS and BP and lipids, to name a few [11], and obesity may well be a factor that modulates these relations [14].

20.1.3 VMS, Obesity, and Insulin Resistance

The prevalence of obesity is increasing steadily in the Western world, and this is in line with the growing incidence of MetS [15]. According to the World Health Organization statistics, the worldwide prevalence of obesity nearly doubled between 1980 and 2008. Excessive body weight and the related MetS are mutually related. Briefly, the hormonal changes in menopause are associated with an increase in total

and abdominal adipose tissue [16–18], and these changes, together with estrogen deficiency, are well-known risk factors for insulin resistance and type 2 diabetes mellitus, elevated BP, dyslipidemia, and MetS.

Both epidemiologic and longitudinal studies have linked obesity with postmenopausal VMS [19–22]. The mechanisms are by far not clear, but there is support for the idea that adipose tissue-derived adipokines may be one link between increased adiposity, metabolic disturbances, and VMS. Abdominal obesity is characterized with chronic low-grade inflammation of adipose tissue, which results in impaired adipokine secretion and metabolic dysregulation [23]. Adipokines have been shown to influence the central nervous system, the body temperature [24, 25], as well as sympathetic nerve activity [26]. In the SWAN study, higher odds of VMS in pre- and early perimenopause was related to an adverse adipokine profile [22].

Altered adipokine profile and an increased sympathetic nerve activity have been linked to impaired glucose metabolism as well [26]. However, there are conflicting data on the association between VMS and insulin resistance [14]. In some, but not all studies, elevated BMI explained the positive association between VMS and insulin resistance [27–30]. However, there is a growing number of data that links increased adiposity, adipokines, metabolic disturbances, and VMS in postmenopausal women.

20.2 Vasomotor Symptoms and Cardiovascular Disease

20.2.1 VMS and Subclinical CVD

Vascular aging, seen as endothelial dysfunction and development of subclinical atherosclerosis, increases the risk of later CVD. Studies on VMS, endothelial dysfunction, and subclinical atherosclerosis, some of them reviewed here, have yielded somewhat conflicting results.

Findings from the SWAN study point toward endothelial dysfunction and subclinical CVD in women with VMS. In a cross-sectional setting of the SWAN study (n = 432–492), women with VMS had poorer endothelial function assessed as brachial flow-mediated dilatation (FMD) [31]. Symptomatic women also had greater aortic calcification and greater carotid intima-media thickness (CIMT) than asymptomatic women [32]. This effect was independent of traditional cardiovascular risk factors, hormone therapy (HT) use, or estradiol levels. Relation between VMS and CIMT was most pronounced in overweight and obese women and in women with persistent VMS. However, no association between symptom status and CIMT progression during a 2-year follow-up was found. A follow-up of the SWAN study [33] shows that long-lasting VMS that begin already in the early menopausal years are associated with a higher CIMT at approximately 59 years of age, when compared with women who traverse through menopause with a low frequency of VMS. Perhaps the longevity of symptoms may be of more significance than just the presence of them?

On the contrary, two studies on recently postmenopausal women with a low CVD risk profile found no adverse effect of VMS on vascular function [34], coronary artery calcification (CAC), or CIMT [35]. Both studies included only lean women; thus, obesity may indeed be a factor that modifies the risk profile associated with vasomotor symptoms. Also, the estrogen-only arm of the WHI trial shows contrasting results as regards CAC [36]. Women with a history of VMS had significantly *reduced* odds for CAC (OR 0.66, 95% CI 0.45–0.98) compared with women with no VMS. Moreover, estrogen therapy in women with VMS, initiated within 2 years from menopause, resulted in an even lower risk of CAC (OR 0.48, 0.26–0.89), indicating perhaps a more beneficial effect of estrogen therapy in women with VMS. This finding is supported by data from a randomized, placebo-controlled trial, which shows that in women with tolerable VMS or no VMS at all, oral estradiol led to unbeneficial vascular reactivity as assessed by pulse wave analysis and rises in BP. Women with intolerable VMS showed no unbeneficial effects of HT on vascular function, and BP actually decreased during the 6-month intervention [37].

20.2.2 VMS and CVD Outcomes

The exact mechanism by which VMS may affect risk factors for CVD is not known. In addition to risk factors, such as MetS and its components or endothelial dysfunction, researchers have also investigated whether presence of VMS influences clinical outcomes.

An Italian observational study [38] examined whether a history of VMS could affect the outcome of acute coronary syndrome (ACS). A total of 373 consecutive women undergoing coronary angiography due to ACS were followed for 1 year, and data on VMS history was gathered through questionnaires. Women with VMS at menopause were younger at the time of the ACS than asymptomatic women. However, the extent of calcifications at angiography or incidence of cardiovascular events, such as stroke or recurrent ACS at 1 year, did not differ between the groups. Of note, information on VMS was recalled, and the researchers were not able to adjust for possible confounding factors, so these results need to be interpreted cautiously.

A large (n = 11,725) Australian longitudinal population-based study [39] with a 14-year follow-up sought to elucidate whether there could be a difference between hot flushes or night sweats on the risk of incident CHD. The participants were surveyed for VMS and CHD events with repeated self-completed questionnaires at approximately 3-year intervals. Cause of death was confirmed from a national register. Menopause status, type (hot flushes or night sweats), and frequency of VMS and HT use were queried at every survey point. Adjusting for age, menopause status, and lifestyle and chronic disease factors revealed a similarly increased risk for developing CHD for women with frequent hot flushes (OR 1.70, 95% CI 1.16–2.51) or night sweats (OR 1.84, 95% CI 1.24–2.73). Of note, long duration of VMS did not further increase the risk of CHD in this population.

The data on VMS and CVD risk are not unanimous. As regards hard outcomes, an observational study found a decrease in all-cause mortality associated with VMS. The Rancho Bernardo study [40] included white middle- to upper-middle class women, and the researchers distinguished between hot flushes and night sweats instead of overall VMS. During the average 11.5-year follow-up, hot flushes alone were not associated with all-cause mortality, but in women with both hot flushes and night sweats, the risk of all-cause mortality was 28% lower compared with women without VMS. This finding was independent of body mass index, past or current use of estrogen or progestin, physical exercise, and smoking habit. The study included a very selected group of women, and of course, the findings cannot be directly extrapolated to women of other ethnic origins or other social classes.

The longevity of VMS and the cardiovascular effects of estrogen are of interest also when considering the discontinuation of HT. The mean duration of vasomotor symptoms is longer than previously thought, even up to 7–10 years [41]. On the other hand, many current guidelines recommend that HT should be used for the shortest possible time. Both epidemiological [42, 43] and clinical studies have shown an increased risk for overall mortality [44] and CVD outcomes [42, 45] after HT discontinuation. In a Finnish nationwide study, the risk increases were evident during the first post-HT year and significantly higher in women who were younger than 60 years of age at HT discontinuation [42, 43]. Although the mechanisms behind this finding are not known, one interesting possibility is the reoccurrence of VMS in women under 60 years of age at HT discontinuation, and an increased sympathetic activity, which could predispose some women to fatal arrhythmias [46]. Also, withdrawal of the vasodilatory effect of estrogen could lead to vasoconstriction and result in ischemia.

20.2.3 Timing of VMS and CVD Risk

Another piece in the puzzle is the possible impact of the timing of VMS on cardiovascular health. The HERS trial studied women with established CHD. For women with VMS (mean age at baseline 63 years), the risk of CHD events during the first year of HT was ninefold compared to those with no VMS (mean age at baseline 67 years) [47]. The observational arm of the WHI study (WHI-OS) [48], in turn, showed that VMS during menopausal transition did not associate with CVD, whereas women with VMS starting in their sixties or later were at increased risk for CHD, stroke, total CVD, and all-cause mortality, compared with women without a history of VMS. Of note, 44–55% of women in the WHI-OS were current HT users.

Also the Women's Ischemia Syndrome Evaluation (WISE) addressed the timing of VMS on CVD mortality and nonfatal events [49], and the findings are contradictory to those of HERS and WHI. The WISE study was a four-center prospective cohort study on women (n = 254, mean age 67 years) undergoing coronary angiography due to a suspicion of myocardial ischemia. Nonfatal events were unaffected by the VMS status, but women with early-onset VMS (before age 42) had three times higher CVD mortality risk than women with later-onset VMS (after age 42).

Interpretation of the findings is complicated by the fact that also women without VMS had an increased mortality risk when compared with women with later-onset VMS. Women with early-onset VMS had also a lower FMD than women with no or later-onset VMS. Of note, some of the women with early-onset VMS could perhaps suffer from premature ovarian insufficiency, which is an independent CVD risk. Moreover, women with early-onset VMS were obese, whereas women with later-onset VMS were only overweight ($p < 0.05$). Once again, obesity could play a role here.

20.3 Importance of VMS Measurement

Increasing attention has been given to how VMS are measured, and concerns have been raised that self-reported and recalled VMS may be subject to several biases [50–52]. Recent studies have utilized both objective and subjective methods to assess VMS [53, 54]. In two studies that assessed VMS and markers for subclinical CVD, the women (aged 40–60 years) recorded their VMS for 3 days in an electronic hot flush diary and a wrist actigraph and wore a physiologic hot flush monitor for 24 h. The median numbers of physiologically detected and self-reported hot flushes were 12 and 5, respectively, indicating that women do underreport their symptoms. The VMS data were compared to brachial artery FMD ($n = 272$) and CIMT ($n = 295$) measurements and controlled for common CVD risk factors. Age bore an impact on the association between physiologically monitored hot flush frequency and brachial FMD. Greater VMS frequency was associated with poorer FMD among women aged 40–53 years, when compared with older women. For this youngest tertile of women, VMS also accounted for the most variance in FMD. In this setting age did not affect CIMT, but women with ≥4 self-reported VMS or with ≥10 physiologically measured VMS had higher CIMT and more carotid plaque than non-flushers. The presence of carotid plaques was positively related to physiologically measured VMS only in women aged 54 or more.

Taken together, women may underreport their symptoms, which may enhance the importance of physiological measurements. Furthermore, different markers for CVD may show different temporal relations to VMS. Whether this in later life translates to clinical CVD, especially with early-onset, long-lasting VMS, needs to be determined.

20.4 Summary

Menopausal VMS are a form of neurovascular dysregulation, and they show a complex interplay with different risk factors for CVD. Current data point toward an increased risk of MetS and CVD in women with VMS. Thus, clinicians should consider screening their patients with VMS for MetS and CVD risk factors.

Majority of the studies are cross-sectional, and the presence and frequency of VMS is often recalled rather than observed. Furthermore, VMS may not have been

included in the original study protocol, and the power to detect differences may be low. Thus, we need studies specifically designed to investigate VMS, and future research needs focus on using also objective methods to assess what type of VMS is the most relevant as regards cardiovascular health.

As VMS may negatively affect the quality of life, the use of HT is often needed. Future research should also try to elucidate whether HT possibly reverses any unbeneficial effects of VMS. Some of the questions that still remain open are as follows: (1) if VMS indeed are a risk factor for CVD, should also mild symptoms be treated, and (2) due to the longevity of symptoms, and a possible adverse effect of the discontinuation of HT use in women under 60 years of age, should longer treatments be encouraged?

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Menopause and Age-Related General Health Risk: A Woman's Heart Needs Her Hormones

21

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21.1 Introduction

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality, and about two out of three individuals will suffer from some form of the CVD [1]. Although the lifetime risk of CVD is equal in males and females, it is well established that in women CVD occurs later, and the incidence increases significantly after the menopause. Three major CVD are coronary heart disease (CHD), cerebrovascular disease (stroke), and venous thromboembolism (VTE). Epidemiological data shows the lifetime risk of CHD is higher in males than in females at a younger age (at age 40 approximately 50% for men and 32% for females) [2]. VTE also tends to be more prevalent in males; the risk of the first episode is twice as high in males as in females [3, 4]. Referring to the stroke risk, data are unfavorable for women; at the age of 55 years old, the risk of the first incident of cerebrovascular disease is higher than in men [1].

Gender differences in cardiovascular pathophysiology are believed to be an effect of multiple mechanisms, including the contribution of sex hormones, sex chromosomes, and epigenetic mechanisms [5]. In this chapter, we will focus on links between the risk of CHD and hormonal changes related to menopausal transition and the role of endogenous and exogenous estrogens in modifying the CHD risk.

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21.2 Estrogens Effects on the Cardiovascular System

At the cellular level, estrogens exert their effects through two kinds of estrogen receptors (ERs) α and β which may act in different compartments of the cell: cytoplasm/nucleus and mitochondria. Nuclear receptors act as transcription factors; estrogens cause dissociation of ER from heat shock proteins which lead to dimerization of ER subunits and direct up- or downregulation of gene transcription. In general, nuclear ERα is responsible for cell proliferation and anti-apoptotic effects, whereas ERβ causes differentiation and apoptosis [6]. Since these receptors modulate transcription processes, their effects are considered as long-acting. The rapid action of estrogens is mainly dependent on the activation of the membrane ER. The primary membrane receptor has been identified as a G protein-coupled receptor (GPR30), which is expressed in veins and arteries [7].

In the CVS, these receptors are probably responsible for mediating vasodilatation after exposure to estrogens. Kinases act in this phenomenon as a second messenger and activate endothelial nitric oxide synthase (NOS) [8]. In mitochondria, ERβ is the more abundant form. Activation of mitochondrial ER is believed to induce cell protective mechanisms, by inhibition of apoptosis [9]. ERα and β are expressed in the heart, but some gender-specific differences are present, i.e., ERβ expression is higher in males than females [10].

21.2.1 The Action of Estrogens on Cardiac Function

Many animal studies have been conducted to elucidate the relationship between estrogens and the heart [11, 12]. Experimental data on ovariectomized mice, which mimic the postmenopausal hormonal milieu, bring some insights. In pathological models of pressure overload, augmented hypertrophy of myocardium was revealed in ovariectomized mice in comparison to mice supplemented with estrogens. Moreover, models of volume overload (i.e., aortocaval fistula) showed more severe left ventricular eccentric hypertrophy and pulmonary edema in ovariectomized females vs. intact individuals [13]. Experimental models also showed a cardioprotective potential of estrogens, which is mediated by both types of ERs [11, 14, 15]. Estrogens have a potential to attenuate the heart injury after ischemia. Female animals suffer from milder injury after ischemia in comparison to male counterparts; in one study the mean infarct in females was 37% vs. 48% in males [16]. This protective action is believed to be dependent on a number of mechanisms including an increase in nitric oxide signaling, increasing transcription of cardioprotective genes like heat shock proteins and nitric oxide synthase via ER nuclear receptor. On the other hand, estrogens also influence the expression of genes involved in metabolism like prostaglandin D2 synthase, lipoprotein lipase, and peroxisome proliferator-activated receptor gamma coactivator 1 alpha, to name a few [11].

Estrogens exert a protective action on myocardial contractility by altering the expression of several regulators of contractility: ventricular β1-adrenoreceptor, intracellular calcium homeostasis related to the L-type Ca2+ channel, cardiac sarcoplasmic reticulum Ca2+ uptake, and Ca2+ sensitivity of cardiac myofilaments

[5]. Animal experiments demonstrated that estradiol has a negative inotropic effect on ventricular myocytes mediated by reducing systolic Ca2+ influx [10].

21.2.2 The Action of Sex Steroids on the Vasculature

The presence of ERs has been confirmed in the wall of peripheral vessels: ERα is predominant in myocytes and ERβ in endothelial cells.

The genomic effects of estrogen action in the peripheral circulation are related to the regulation of gene expression involved in vascular tone and remodeling, e.g., nitric oxide synthase, cyclooxygenase, prostacyclin synthase, collagen, elastin, metalloproteinases, and enzymes involved in reactive oxygen species (ROS) elimination [17, 18]. Estrogens stimulate the proliferation of endothelial cells and, in contrast to androgens, inhibit proliferation of vascular smooth muscle cells in the blood vessel wall. They also inhibit endothelin-1 expression [19]. Moreover, ER stimulation decreases the angiotensin receptor (AT1) in smooth muscles [20]. Altogether, these mechanisms contribute to the anti-atherogenic action of estrogens in the blood vessel wall. On the other hand, ERβ stimulation may increase the pro-inflammatory and atherogenic processes, including destabilization of the atheromatous plaque once it is formed [21]. Estrogens also inhibit calcium channels and activates BKCa channels, both of which are vasodilatory [22].

Non-genomic, rapid action of estrogens on the peripheral circulation is predominantly linked to vasodilation. This action is mediated mainly through stimulation of NO synthesis. Also increased production of PGI2 and endothelium-derived hyperpolarizing factor has been reported. Interestingly activation of GPR30 is responsible for the proapoptotic action, as opposed to the classical nuclear ER-mediated pathway [22] (Table 21.1).

Table 21.1 Summary of crucial actions of estrogens on the heart and blood vessels, according to [22]

Heart			
Genomic changes	*Ischemia*	*Remodeling*	
↓ Adhesion molecules	↓ Ischemia/ROS	↓ Fibrosis	
↓ Inflammatory cytokines	↓ Necrosis	↓ Pathologic hypertrophy	
↓ Metalloproteinase expression	↓ Apoptosis		
Blood vessels			
Endothelium-dependent	*Smooth muscles*	*Inflammation*	*Atherosclerosis*
↑NOS	↓ Proliferation	↓ROS	↓LDL
↑NO	↓ AT1R	↓ Inflammatory cytokines	↑ HDL
↑Relaxation	↓ Ca channels		↓ Adhesion molecules
↑ Flow-induced dilation			↓ Monocyte adhesion

21.3 Hormonal Alterations of Menopausal Transition and Their Influence on CVS

21.3.1 Hormonal Changes During Menopause

The menopause is defined as the last spontaneous menstrual period, reflecting the cessation of ovarian function in women. The age of menopause in Western countries is typically between 51 and 52 years old and is determined genetically [23]. The menopause is related to significant changes in the hormonal milieu of women, which in turn has a substantial impact on CVS function. The decrease in estrogen concentration is marked, on average the estradiol concentration is 55 pmol/L, ranging from 35 to 90 pmol/L [24]. A surgical menopause is related to even more profound hypoestrogenism, below 35 pmol/L. Also, estrone concentration drops, but to a smaller extent than estradiol (30 pg/mL). The estrone concentration may be higher in overweight/obese females, due to aromatization of peripheral androgens. Interestingly, ovaries continue to produce androgens (testosterone, androstenedione). Adrenal synthesis of androgens in postmenopausal women decreases, approximately 2% per year [25]. The sex hormone-binding globulin (SHBG) concentration also decreases, which result in a higher proportion of free active androgens.

21.3.2 The Influence of Decreased Endogenous Levels on CVS Function

The lack of steroidal activity of the ovary has profound consequences on CVS function. In general, there are two main types of effects. One is related to direct vascular and cardiac action of estrogens, as described above. The other is related to indirect actions: modification of metabolic parameters, coagulation balance, and inflammation. It is difficult to assess if direct or indirect effects are more important, but generally these mechanisms are viewed as equal.

The most marked metabolic alterations following menopause are rises in total and LDL cholesterol, which in turn are strong risk factors for CHD. Also, changes in body fat distribution, blood pressure, and glucose and insulin metabolism are observed. Other changes in lipid metabolism develop after menopause, such as increases in triglycerides, very-low-density lipoproteins, and lipoprotein(a). Also, oxidation of LDL-C is increased, while high-density lipoprotein cholesterol (HDL-C) concentrations decrease [26, 27].

Some changes in coagulation balance have also been observed, but an increase of some factors (fibrinogen, factor VII) is balanced by endogenous anticoagulants (e.g., antithrombin, proteins C and S) [1, 26]. The rise in inflammatory markers (e.g., C-reactive protein) is a phenomenon related to increasing CHD risk.

Direct effects relate to actions of estrogens on the CVS. Reduced activity of nitric oxide synthase and prostacyclin synthesis is observed after menopause. Moreover, endothelin concentrations increase, and blood flow through the blood vessels generally decreases [28–30].

21.4 Exogenous Estrogens and CHD Risk Factors

21.4.1 Metabolic Effects

Estrogens are known to decrease total and LDL-C and increase HDL-C. These effects are more significant with oral than with transdermal estrogen. The impact on triglycerides is dependent on the route of administration. Triglycerides are increased with oral estrogen but decreased with transdermal estrogen administration [31]. Lipoprotein (a) is reduced by HRT, and this contributes to the overall beneficial impact of exogenous estrogens on the lipid profile [32, 33].

Another risk factor for CHD is insulin resistance. Oral estradiol appears to reduce insulin resistance more effectively than transdermal estradiol [34]. For conjugated equine estrogens (CEE), the effect is dose-dependent, and high doses may worsen glucose tolerance. Some of these metabolic effects of estrogen can be negated or reversed by the addition of androgenic progestogens.

Interestingly, HRT is able to decrease the central deposition of body fat, which is another risk factor for CHD [35].

21.4.2 Exogenous Estrogens Impact on CHD Surrogates: Timing Hypothesis

To date, a large body of evidence has been collected regarding the issue of possible effects of exogenous estrogens on CHD risk factors. The first experimental and observational studies brought very optimistic conclusions about the beneficial effects on the CVS and risk factors for CHD. A wave of enthusiasm for estrogens for the primary prevention of CHD was countered by the preliminary results of the Women's Health Initiative (WHI) study [36, 37]. WHI was a large randomized clinical trial (RCT) which showed an increase in cardiovascular morbidity in women treated with combined oral HRT. These first results from WHI dramatically changed doctors and patients perception of HRT and resulted in a withdrawal of therapy in the majority of patients. Subsequent analysis of the WHI [37] and other RCTs changed our understanding of the relationship between exogenous hormones and circulatory system. Currently, our knowledge about the complex and multifactorial relationship between "hormones and women's hearts" brings us better understanding. Recent meta-analyses of existing RCTs and some more recent RCTs have highlighted the "timing hypothesis." This hypothesis proposes that giving exogenous hormones to

relatively young (soon after menopause) otherwise healthy women brings benefits for CHD. However, older women may be affected by early, asymptomatic CHD, and initiation of HRT in this group may be less beneficial. This hypothesis was supported by a number of experimental and clinical studies.

A study of cynomolgus macaques placed on an atherogenic diet following surgical menopause showed that CEE administration reduced the amount of atheromatous plaque by 70% compared with placebo [38]. In a similar study, animals were put on an atherogenic diet before undergoing oophorectomy. The degree of the protective effect of CEE on atheromatous plaque formation was smaller (50%) in this study [39], suggesting less benefit in those with already established arterial disease. The timing hypothesis originated in a third macaque experiment. This time the randomization to CEE/placebo occurred with a delay of the equivalent of six human years after surgical menopause. This study found no difference in atheromatous plaque extent in both CEE and placebo groups [40]. This series of studies shows that the introduction of hormonal therapy soon after cessation of ovarian function can improve CHD risk.

A similar conclusion comes from a human RCTs. The Early versus Late Intervention Trial with Estradiol (ELITE, n = 643) compared two groups of women, early postmenopausal (<6 years) and late postmenopausal (at least 10 years), treated with oral estradiol plus sequential vaginal progesterone versus placebo. Oral estradiol 1 mg daily reduced carotid artery atheroma progression if initiated within 6 years of the onset of menopause, while no such effect was seen in those initiated treatment beyond 10 years postmenopause [41]. The trial failed to reveal any effect of HRT on coronary artery calcium scores.

The Kronos Early Estrogen Prevention Study (KEEPS n = 868) also measured surrogates of CHD in women within 3 years of menopause onset, randomized to either CEE 0.45 mg daily, transdermal estradiol 50 μg, or placebo for 4 years. In this study, there was no difference between the groups regarding carotid artery intima-media thickness changes or coronary artery calcification scores. Furthermore, endothelial function, measured as a reactive hyperemia index using digital volume tonometry, was not altered by HRT [37]. A subset of women enrolled in KEEPS (n = 76) were followed up for an additional 3 years. At 7 years, carotid artery intima-media thickness (CIMT) increase in the treatment group compared with the placebo group was not different. The authors concluded that the CIMT increase was mainly dependent on chronological age and timing of menopause [37].

21.4.3 HRT Effects on CVD Clinical Endpoints

Recently, data from several RCTs have been published assessing clinical endpoints in patients taking HRT for primary or secondary prevention of CHD (see Table 21.2 for a summary).

The Women's Health Initiative (WHI, n = 27,347) studies remain the largest primary prevention studies. After 5.6 years of treatment with CEE 0.625 mg plus MPA 2.5 mg daily or 7.2 years of treatment with CEE 0.625 mg alone, HRT was

Table 21.2 Table with a summary of trials reporting cardiovascular disease (based on [42])

Study, year	Participants, design	Main result
PEPI, 1995 [43]	175 E vs. 348 EP vs. E vs. 178 EmP vs. placebo – 3 years	CHD 1 (E: 0.6%) vs. 1 (EP: 0.3%) vs. 3 (EmP: 1.7%) vs. 0 (placebo); **NS**
ERA, 2000 [44]	100 E vs. 104 EP vs. 105 placebo—3.2 years	CVE 29 (29.0%) vs. 28 (26.9%) vs. 34 (32.4%); **NS**
STOP-IT, 2001 [45]	121 E/EP vs. 121 E/EP + calcitriol vs. 123 calcitriol vs. 123 placebo	CVE 8 (E/EP: 3.3%) vs. 7 (calcitriol only or placebo: 2.8%) **NS**
EPAT, 2001 [46]	111 E vs. placebo—2 years	CVE 3 (2.7%) vs. 4 (3.6%); **NS**
WAVE, 2002 [47]	**Women with a confirmed coronary stenosis** 124E vs. 86 EP vs. 213 placebo	MI or CD 26 vs. 15 (**HR, 1.9**; 95% CI, 0.97–3.6)
WHI EP, 2002 [36]–2013 [37]	8506 EP vs. 8102 placebo—5.6 years	CHD 196 (0.41%) vs. 159 (0.35%); **HR, 1.18** (95% CI, 0.95–1.45)
WHI E, 2004 [48]–2013 [37]	5310 E vs. 5429 placebo – 7.2 years	CHD 204 (0.55%) vs. 222 (0.58%); **NS**
Greenspan, 2005 [49]	66 E vs. 121 EP vs. 186 placebo – 3 years	CHD 66 (16.3%) vs. 62 (16.6%); **HR 1.03** (95% CI, 0.73–1.46)
EPHT, 2006 [50]	404 EP vs. 373 placebo – 3.4 years	CVE 11 (15.7%) vs. 8 (11.1%); **NS**
EMS, 2009 [51]	70 EP vs. placebo – 2 years	CVE 2 (0.2%) vs. 7 (0.3%) vs. 0 (0.0%); ***p* = 0.016**
WISDOM, 2007 [52]	826 E vs. 2196 EP vs. 2189 placebo – 1 year (closed because of WHI results)	

CHD coronary heart disease, *CI* confidence interval, *CVD* cardiovascular disease, *CVE* cardiovascular event, *DOPS* Danish Osteoporosis Prevention Study, *E* estrogen only, *EP* estrogen plus progestin, *EMS* Estrogen Memory Study, *EPAT* Estrogen in the Prevention of Atherosclerosis Trial, *EPHT* Estonian Postmenopausal Hormone Therapy Trial, *ERA* estrogen replacement and atherosclerosis, *HR* hazard ratio, *MI* myocardial infarction, *NS* nonsignificant, *PEPI* Postmenopausal Estrogen/Progestin Interventions Trial, *RR* relative risk, *STOP-IT* Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection, *WHI* Women's Health Initiative, *WISDOM* Women's International Study of Long Duration Oestrogen After Menopause

not significantly superior to placebo in terms of myocardial infarction or coronary death. The hazard ratio (HR) for coronary heart disease in women within 10 years of menopause on combined HRT was 0.90 (95% CI, 0.56–1.45), while in women more than 20 years postmenopause, the HR was 1.52 (95% CI, 1.07–2.17) ($p = 0.08$). On the other hand, the number of coronary interventions and coronary atheroma formation indices was smaller in women initiating estrogen treatment below age 60 years compared with placebo [37]. The hazard ratio (HR) for coronary heart disease in women within 10 years of menopause on estrogen-alone HRT was 0.50 (95% CI, 0.22–1.18), while in women more than 20 years postmenopause, the HR

was 1.08 (95% CI, 0.83–1.40) (p = 0.16). Furthermore, with long-term follow-up post-intervention in those women initiating estrogen-alone treatment below age 60 years, there was a significant reduction in CHD events compared with placebo, HR **0.65** (95% CI, 0.44–0.96) [37]. Reduction in CHD was also observed in the Danish Osteoporosis Prevention Study (DOPS, n = 1006), a randomized trial of women in the early postmenopause. HRT for 10 years (oral estradiol with or without norethisterone acetate addition) reduced by approximately half the risk of death, admission to hospital for heart failure, and myocardial infarction, in comparison to no treatment. In the same study, no increased risk for any cancer, including breast cancer, VTE, or stroke, was observed [53]. However, this study was criticized for being underpowered to draw these conclusions [54].

Recently, the US Preventive Services Task Force (USPSTF) published a review, regarding hormonal therapy as primary prevention for chronic conditions. The group reviewed the available data regarding combined hormonal therapy and risk of coronary heart disease. Data from six clinical trials were included, but only three were eligible for meta-analysis. They provided data on more than 18,000 individuals and treatment duration of 2–5 years. Overall, unselected data showed the numerically higher but nonsignificant risk of coronary events in women treated with HRT versus placebo (2.1% vs. 1.7%; RR, 1.23 [95% CI, 0.996–1.520]) [42]. In the same statement, authors found evidence that timing of HRT initiation in relation to the menopause onset is of importance, and early initiation of HRT is not related to increased risk of coronary disease. This review has been heavily criticized [55]. The National Institute for Health and Care Excellence (NICE) guideline on the diagnosis and management of menopause concluded that HRT does not increase the risk of death related to CHD and estrogen-only HRT may be linked to decreased risk of CHD [56].

A recent Cochrane database meta-analysis of 19 RCT of HRT versus placebo or no treatment included over 49,000 women. The authors conclude that there is strong evidence that HRT in postmenopausal women for either primary or secondary prevention of CVD has little if any benefit [57]. This strong conclusion was criticized later in the literature [58]. According to the same Cochrane review, initiating HRT within 10 years of menopause had a significant 50% reduction in the endpoint of myocardial infarction or death, while there was no significant change in those initiating HRT beyond 10 years postmenopause [57]. The optimal duration of HRT use for CHD prevention remains to be determined, but need not necessarily be lifelong.

21.5 Summary and Future Perspectives

A woman's heart needs her hormones. This is the truth from the cellular to the clinical level and also for endogenous and exogenous hormones. Even though the preliminary results from the WHI appeared unfavorable and some ongoing RCTs were then closed, further analysis of WHI results supported the "critical window" hypothesis and showed an eventual benefit for CHD prevention. Contemporary studies revealed surrogate and clinical results confirming the protective action of

estrogens on the CVS. Many questions still require answers and need further studies. Firstly, what is the upper limit of age for the safe introduction of HRT, and what are the safe starting doses at different ages? Similarly, what about comorbidities which increase CHD risk? Tailoring therapy to individuals with certain conditions may remain an unsolved problem for many years, due to difficulties in conducting appropriate clinical trials. More attention is needed for the characterization of benefit/risk ratios for different estrogens, progestogens, and routes of administration. Non-oral estrogen administration has less adverse effects on coagulation activation compared with oral administration, although this could in part also be related to dosage. Regarding progestogens, non-androgenic preparations potentially may be safer, because they do not exert the adverse metabolic and vascular effects seen with androgenic progestogens. There are still many unanswered questions, but it is time to change the WHI paradigm of a harmful influence of estrogens on CHD. The totality of current evidence shows that HRT can be beneficial for the primary prevention of CHD when given appropriately.

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Menopausal Hormone Therapy to Prevent Chronic Conditions

22

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Abbreviations

AD	Alzheimer's disease
BC	Breast cancer
BMD	Bone mineral density
CE/BZA	Combination of conjugated estrogens and bazedoxifene
CHD	Coronary heart disease
CVD	Cardiovascular disease
E2	Estradiol
E4	Estetrol
E-MHT	Unopposed estrogen therapy
EP-MHT	Combined therapy of estrogen and progestogen
ER	Estrogen receptor
FSFI	Female Sexual Function Index
HR	Hazard ratio
HSDD	Hypoactive sexual desire disorder
KEEPS	Kronos Early Estrogen Prevention Study
LMP	Last menstrual period
LNG-IUS	Levonorgestrel-releasing intrauterine system
MHT	Menopausal hormone therapy
P4	Natural progesterone
POP	Pelvic organ prolapse
QoL	Quality of life
RCT	Randomized controlled trial
ROS	Reactive oxygen species

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SERM	Selective estrogen receptor modulator
TSEC	Tissue-selective estrogen complex
VMS	Vasomotor symptoms
VTE	Venous thromboembolism

22.1 Introduction

Menopause is a biological process that occurs as a part of aging in women. The symptoms of the menopause go beyond vasomotor effects (hot flashes and night sweats). Other symptoms associated with the onset of the menopause include potential alterations in sexual response, musculoskeletal complaints, mood swings, irritability, and sleep disorders, all of which affect quality of life and for which menopausal hormone therapy (MHT)—previously known as hormone replacement therapy—has proven beneficial.

Because chronic disease rates generally increase with age, absolute risks tend to be greater in older women, even if the relative risks remain similar. Guidelines [1] and systematic reviews [2] have expressed that MHT is not indicated for the prevention of chronic conditions. Given recent findings, specifically regarding the effect of the timing of MHT initiation on woman's health risk, it seems appropriate to reassess the clinician's approach to menopause based on recent data. In an era of personalized medicine, a more holistic approach needs to be made inclusive of menopausal symptoms. Health advice should be tailored across the life course and encompass a healthy diet, physical activity, as well as pharmacological interventions such as MHT [3].

22.2 Menopausal Hormone Therapy

The concept of menopausal hormone therapy (MHT) after menopause is based on clinical observations that elderly women with very low serum estrogen levels have a higher incidence of osteoporotic fractures; coronary heart disease (CHD); onset of VSM, such as hot flashes and night sweats; and, most importantly, loss of quality of life (QoL).

By convention, MHT includes any estrogenic or estrogen-like therapy, such as estrogen therapy, alone or in combination with progestogens, tibolone and the combination of conjugated estrogens and bazedoxifene (CE/BZA), and even testosterone. We will name the unopposed estrogen therapy as E-MHT, the combined therapy of estrogen and progestogen as EP-MHT, and hormone therapy for menopause as MHT.

22.3 How to Prescribe MHT

Women with an intact uterus require an estrogen antagonist (usually a progestogen) in addition to estrogen to prevent endometrial hyperplasia. For women whose last menstrual period (LMP) was less than 12 months ago, the progestogen should be

cyclical. Use of continuous combined estrogen and progestogen too soon after the LMP can result in unpredictable breakthrough bleeding. For women whose LMP was more than 12 months ago, continuous combined estrogen plus progestogen therapy can be used. Approved pharmaceutical preparations with combinations of estrogen and progestogen have been shown in clinical trials to provide symptom relief and endometrial protection [4].

22.3.1 Contraindications

Before MHT is prescribed to symptomatic women, personal and familial risk factors should be taken into consideration, as should age and time since onset of the menopause. MHT may not be suitable for some women with a greater risk of cardiovascular disease (CVD) or transient ischemic attack; a greater risk of thromboembolic disease (e.g., those with obesity or a history of venous thrombosis), stroke, active liver disease, and unexplained vaginal bleeding; or a greater risk of some types of cancer, such as breast cancer [5]. Age and duration of estrogen deficiency at initiation of MHT should be taken into account.

22.3.2 Dose

Dose and time of administration seem to be the main indicators of safety in MHT. The importance of the type of estrogen and the route of administration remains open to debate. Even if women whose menopause is of recent onset have similar and substantial reductions in hot flashes and night sweats with doses of oral or transdermal estrogens that are lower than the standard doses, it is important to transmit the message that the dose necessary to obtain the desired effect must be used. We suggest starting at the lowest dose possible for the formulation and adjusting according to response.

22.3.3 Route

All routes of administration of estrogens seem to be equally efficient for relief of symptoms, although their metabolic effects differ. Transdermal formulations should be taken into consideration because of their less severe adverse effects: as they avoid the first-pass effect in the liver, there may be no accumulation of metabolites with estrogenic activity. Oral estrogens should be avoided in women with hypertriglyceridemia, active gallbladder disease, or known thrombophilias such as factor V Leiden (without a personal history of venous thromboembolism [VTE]). Transdermal estrogen is also preferred for women with migraine headaches with auras.

In addition to oral and transdermal estrogen preparations, estrogen is available as a vaginal ring and as a topical spray, cream, or gel. Percutaneous E_2 gel is another parenteral preparation and passes through the skin and then forms a reservoir in the

epidermal layer for continuous release of E_2 [6]. Compared with patches, gel has lower adverse skin effects and could provide higher E_2 serum values with less day-to-day variation [7].

22.3.4 Adding a Progestogen

All women with an intact uterus need a progestogen in addition to estrogen to prevent endometrial hyperplasia, which can occur after as little as 6 months of unopposed ET [8]. When use of progestogens, natural progesterone (P4), or its synthetic alternative dehydrogesterone, is necessary—administered at appropriate doses via the route chosen (oral or vaginal)—this is considered the safest approach [9]. Additionally, risk of venous thromboembolism and breast cancer does not appear to increase with use of P4 plus estrogens as shown with synthetic progestins plus estrogens in large observations studies, and no detrimental effects of P4 in HT have been found on outcomes related to cardiovascular disease or cognition [10].

In women using a levonorgestrel-releasing intrauterine system (LNG-IUS) that is active at onset of symptoms, addition of other progestogens is not necessary [11]. This alternative may be valid—albeit off-label—for women who do not tolerate oral progestogens. Another option can be found in the combination of bazedoxifene with conjugate estrogens. In this combination, bazedoxifene prevents the endometrial hyperplasia induced by estrogens; therefore, it is not necessary to administer a progestogen.

22.3.5 Duration of Use

In the absence of other factors, age is not a limitation for the duration of MHT. Decisions on a longer or shorter duration of MHT should be taken on an individual basis and according to the risk for various diseases (venous thrombosis, stroke, and some types of cancer). MHT can be interrupted if symptoms disappear. The duration of treatment-free periods should be as short as possible and will depend on the reappearance of symptoms.

22.3.6 Monitoring

The use of MHT during the menopause does not imply the need to carry out tests other than those corresponding to basic health tests in this age group. As with any medical intervention, treatment should be on an individual basis using the best available evidence to maximize benefits and minimize risks, with regular re-evaluation of the risks and benefits of continuing or suspending menopause MHT.

22.3.7 Discontinuation

Options for discontinuation are either to stop treatment immediately or to gradually wean off by decreasing the dose or number of days per week. Given that strong evidence does not exist to indicate differential outcomes for tapering or abruptly stopping, both methods can be used, and this decision should be based on the woman's preference. Recent data suggesting that discontinuation of MHT may lead to increased cardiovascular morbidity and mortality do not yet indicate whether the risks can be mitigated through tapering the dosage [12]. This clearly warrants further investigation.

22.3.8 Custom-Compounded Bioidentical Hormone Therapy

Although most often used to describe custom-made MHT formulations compounded according to a clinician's prescription, the term *bioidentical hormone* refers to hormones identical to those made by the ovaries. We do not recommend the use of alternative MHT (also incorrectly known as "bioidentity") [13]. There is no scientific evidence in favor of greater efficacy or safety with these products. Very often, the content or release of the components is inconsistent; consequently, lower or higher quantities of the biologically active hormone are administered [14]. No controlled clinical trials support efficacy or rule out concern over safety.

22.3.9 Early Menopause

In women with early-onset menopause (primary ovarian insufficiency) and those who undergo bilateral salpingo-oophorectomy before age 50 years, MHT is recommended at least until they reach the age for spontaneous menopause in the general population. Systemic MHT is an effective approach to treat the symptoms of hypoestrogenism and mitigate long-term health risks if there are no contraindications to treatment. Hormone therapy is indicated to reduce the risk of osteoporosis, cardiovascular disease, and urogenital atrophy and to improve the quality of life of women with primary ovarian insufficiency [15].

22.4 MHT and Vasomotor Symptoms

Vasomotor symptoms (VMS) continue to be the main indication for MHT. The most efficient approach for relief of the VMS of the menopause at any age comprises MHT based on estrogens alone or in combination with progestogens, tibolone, and the combination of conjugated estrogens and bazedoxifene (CE/BZA). Findings from randomized clinical trials (RCTs), as well as preclinical, clinical,

and epidemiologic studies, clarify the favorable benefit-risk profile for MHT use by recently menopausal women with bothersome vasomotor and related menopausal symptoms.

- A Cochrane review of double-blind, randomized, placebo-controlled trials of oral MHT concluded that estrogen therapy, alone or in combination with progestogens, is highly effective in alleviating hot flushes and night sweats. Hot flush frequency was reduced 75%, and severity decreased as well [16]. The dropout rate due to side effects was only marginally increased in the MHT groups.

22.4.1 Tibolone

Tibolone is a drug with complex tissue-specific action that exhibits a combination of estrogenic, progestogenic, and slight androgenic activity. Its variable profile explains its clinical effects, depending on the target tissue where it is metabolized, its metabolites' affinity for and potency in hormone receptors, and probable enzymatic activity modulation. Tibolone, used at the daily dose of 2.5 mg, may be less effective than combined MHT in alleviating menopausal symptoms although it reduced the incidence of vaginal bleeding [17]. There are the same concerns about their long-term safety as with estroprogestins [18].

22.4.2 Conjugated Estrogen-Bazedoxifene

The combination of conjugated estrogen with a selective estrogen receptor modulator (SERM), bazedoxifene, also called tissue-selective estrogen complex (TSEC), is projected as a progestogen-free option for the treatment of estrogen deficiency symptoms in postmenopausal, non-hysterectomized women. A combination conjugated estrogen 0.45 and 20 mg bazedoxifene tablet is effective in reducing VMS frequency and severity, as well as sleep parameters when compared to placebo [19]. In addition, TSEC has shown improvements in quality of life and vaginal atrophy. In respect to MHT using progestogens, the benefits of TSEC are found mainly in the bleeding pattern, amenorrhea rate, and reduction in mammary repercussion (i.e., breast tenderness and radiological density) [20]. It can be an alternative to conventional combined estrogen-progestin therapy. Its efficacy and safety have been evaluated in randomized controlled trials (RCT) compared with placebo or menopausal hormone therapy (MHT) [21], but long-term data are lacking.

22.5 MHT and Other Menopause-Related Symptoms

Other menopause-related symptoms including mood swings, sleep disturbance, sexual dysfunction, and myalgia may improve with MHT [22].

22.5.1 Sleep Disturbance

Poor sleep quality is common in recently menopausal women. Sleep quality improved with MHT formulations. The relationship of VMS with domains of sleep suggests that assessing severity of symptoms and domains of sleep may help direct therapy to improve sleep for postmenopausal women [23].

22.5.2 Mood Lability/Depression

During the menopausal transition, there is an increased risk of depressive symptoms and depressive disorders. Although there are few trials, it seems that treatment with estrogens, alone [24] or combined with progesterone [25, 26], which could minimize estradiol (E2) fluctuation and/or withdrawal, is an effective treatment for perimenopausal depression. MHT, alone or in combination with an antidepressant as a selective serotonin reuptake inhibitor (SSRI), is effective for women who experience lability or depression of mood during the perimenopause [27].

22.5.3 Joint Aches and Pains

It is unclear whether the pain is related to estrogen deficiency or a rheumatologic disorder, but MHT has been shown to have some benefit in alleviating arthralgia associated with menopausal transition and can be considered in women who report distressing vasomotor symptoms [28, 29]. SERMs and estrogen may represent therapeutic options to treat joint diseases in the future [30]. A new group of estrogen-related drugs, TSECs, may have the potential to protect other joint tissues [31].

22.5.4 Sexual Function

The perimenopausal and postmenopausal periods are associated with many symptoms, including sexual complaints. MHT treatment with estrogens alone or in combination with progestogens was associated with a small to moderate improvement in sexual function, particularly in pain, when used in women with menopausal symptoms or in early postmenopause (within 5 years of amenorrhoea), but not in unselected postmenopausal women. Since oral estrogen increases the liver's production of sex hormone-binding globulin, resulting in lower free (bioavailable) testosterone, sexuality concerns may represent a reason to prefer the use of transdermal as opposed to oral estrogen [32].

Evidence regarding other MHTs (synthetic steroids and SERMs) is of low quality, and we are uncertain of their effect on sexual function. The current evidence

does not suggest an important effect of tibolone or of SERMs alone or combined with estrogens on sexual function [33]. Available data are not adequate to provide counseling by the physicians in menopausal women regarding the efficacy of vaginal therapies as an alternative to estrogens, on all parameters of sexual function [34].

22.6 Urogenital Atrophy

The female genital and lower urinary tracts share a common embryological origin, arising from the urogenital sinus, and both are sensitive to the effects of the female sex steroid hormones, which may be the reason for frequent symptoms related to the lower urinary tract in menopause [35]. Recently, a panel of experts incorporated this increased frequency of urinary tract symptoms into a unifying concept called "genitourinary syndrome of menopause" (GSM) [36]. While the creation of a new medical entity has been widely debated and criticized, it highlights how menopause does not affect solely vaginal tissues.

The beneficial effects of estrogen therapy include both the improvement of symptoms associated with vaginal atrophy and the restoration of the vaginal anatomy [37]. Both systemic estrogen and vaginal estrogen are effective for the symptoms of genitourinary atrophy, although in women who only have GSM with no other menopausal symptoms (e.g., flashes), vaginal estrogens are more efficient. Vaginal estrogens can be used at any age, and progestogens typically are not prescribed to women using any of these products [38].

- A Cochrane review of 30 randomized, controlled trials involving 6235 women reported that the efficacy of any estrogenic formulation in relieving symptoms of VVA was similar [39].

22.6.1 Promestriene

Promestriene is an analogue of estradiol which is minimally absorbed, and it has been shown to be effective in reversing atrophic changes caused by estrogen deficiency in women undergoing natural or surgically induced menopause. Given the absence of systemic activity, promestriene may be a good choice in women requiring purely locally estrogen and those who have survived or who are at risk of breast cancer and who have severe vulvovaginal symptoms [35]. There are little data available in the literature, mostly consisting of small, open-label, short duration studies and few RCTs. After a long-term market experience (almost 40 years), the side effects were very rarely reported in pharmacovigilance data, whereas the effectiveness to relieve atrophy was good [40].

22.6.2 Ospemifene

Ospemifene is a systemic selective estrogen receptor modulator (SERM) that acts as an estrogen agonist in the vagina and appears to have no clinically significant estrogenic effect on the endometrium or breast. A 1-year clinical trial did not identify endometrial safety concerns [41]. However, hot flushes were reported by 7.2% of participants randomized to ospemifene 60 mg vs. 2.0% of those randomized to placebo. Although there may be the possibility of its use in breast cancer survivors who are disease-free and who have completed their anticancer treatment, as with systemic MHT and low-dose vaginal ET, package labelling for ospemifene cautions against using this medication in women with a personal history of breast cancer or thromboembolic disease.

The International Society for the Study of Women's Sexual Health (ISSWSH) stressed the importance of androgens for women with GSM as they support genitourinary tissue structure and function. In the vagina, androgens and estrogens regulate vaginal mucin production in epithelial cells, and sex steroid hormones may regulate androgen and estrogen expression in genitourinary tissues. Although positive immunostaining for estrogen and androgen has been demonstrated in human vulvar tissue, estrogen was less prevalent, and androgen was more prevalent when compared with vaginal tissue. Clitoral hypertrophy is considered one of the most sensitive markers for excess androgen production in women through menopause [42].

22.6.3 Transdermal Testosterone

Transdermal testosterone has shown efficacy for the treatment of hypoactive sexual desire disorder (HSDD) in both naturally and surgically postmenopausal women, either alone or in combination with estrogen [43]. In RCTs at 24 weeks in women with natural or surgical menopause and referring HSDD, a 300 μg/day testosterone patch significantly improved the measures of primary efficacy of sexual desire and the frequency of satisfying sexual events (measured by patented instruments) versus placebo [44, 45]. Levels of sexually related distress also decreased significantly compared to placebo. However, given the concern about the long-term safety of the use of testosterone in postmenopausal women [46], their use has been declining.

Treatments for GSM should combine both androgenic and estrogenic actions, such as seen with esterified estrogens with methyltestosterone and tibolone, which exerts estrogenic, progestogenic, and androgenic effects.

22.6.4 Vaginal Prasterone

Vaginal prasterone, another name for dehydroepiandrosterone (DHEA), an androgen derivative, has shown effectiveness in treating GSM [47]. In placebo-controlled

clinical trials, daily insertion of dehydroepiandrosterone vaginal ovules decreased vaginal pH, improved the vaginal epithelial maturation index and vaginal epithelial thickness and integrity, and increased vaginal secretions resulting in improvement in dyspareunia.

Clinical trial data addressing the use of vaginal testosterone are limited; longer as well as larger studies are needed to assess efficacy and safety. Information related to systemic testosterone therapy and low testosterone therapy for GSM is insufficient; more trials are needed in a postmenopausal population to determine whether testosterone therapies are beneficial.

Several RCTs have demonstrated that low-dose vaginal estrogen, intravaginal prasterone, and oral ospemifene effectively treat GSM and related dyspareunia. Although libido can improve with adequate treatment of dyspareunia, these biological improvements alone do not guarantee a good sexual response. However, DHEA has showed that all the six domains of the Female Sexual Function Index (FSFI) are improved over placebo (from $P = 0.047$ to 0.0005), by an action exerted exclusively at the level of the vagina, in the absence of biologically significant changes of serum steroids levels [48]. A study evaluated the long-term (52 weeks) effect of treatment with daily intravaginal 0.50% (6.5 mg) DHEA on the various domains of female sexual function using a questionnaire at baseline, week 26 and week 52 [49]. Postmenopausal women with at least one mild to severe symptom of VVA and who had completed the questionnaire at baseline and at least one post-baseline time point were included in the analysis ($n = 154$). All domains of sexual function analyzed increased as well as the total score [49]. Also, a randomized trial found that ospemifene (60 mg/day, 12 weeks) resulted in improvements in sexual pain, arousal, and desire domains of the FSFI, a validated measure of function sexual activity [50].

On the other hand, vaginal estrogens reduce irritative urinary symptoms, such as frequency and urgency, and have been demonstrated to reduce the likelihood of recurrent urinary tract infections in postmenopausal women [51]. Although incontinence is a significant problem for aging women, the effect of estrogen deficiency remains unclear [52].

- In a Cochrane review, 34 trials were identified which included approximately 19,676 incontinent women of whom 9599 received estrogen therapy (1464 involved in trials of local vaginal estrogen administration). Urinary incontinence may be improved with the use of local estrogen treatment. However, there was little evidence from the trials on the period after estrogen treatment had finished and no information about the long-term effects of this therapy was given. Conversely, systemic MHT using conjugated equine estrogen may worsen incontinence [53]. There were too few data to reliably address other aspects of estrogen therapy, such as estrogen type and dose, and no direct evidence comparing routes of administration.

Menopause is reckoned to be a key event associated with the emergence or a worsening of pelvic organ prolapse (POP). Symptoms and severity increase significantly across the menopausal transition [54]. Despite this, it is difficult to

differentiate the specific contribution of estrogen withdrawal from that of the aging process per se. Pelvic organs, and their muscular and connective tissue supports, are estrogen-responsive. The use of postmenopausal systemic hormone therapy also stimulates steroid hormone receptors in the pelvic floor [55]. Based on the Cochrane analysis, the impact of postmenopausal hormone therapy on the pelvic floor support is, however, still unclear [56]. Controversy remains as to whether the use of local estrogens before and/or after vaginal surgery is beneficial. The use of local estrogens improves the rate of vaginal maturation at the time of surgery and increases the thickness of the vaginal epithelium, but this does not translate into increased vaginal subepithelial/muscularis thickness [57], and, therefore, possible surgical advantages still need to be demonstrated.

22.7 Cardiovascular Effects

The effect of MHT on cardiovascular health remains unclear and controversial. The many of the apparent benefits of MHT observed in epidemiologic studies were not found in the randomized trials. Rather than a reduction in risk of CHD events, an increase was seen [58, 59]. Possible methodologic explanations for the striking difference in CHD data include "healthy user" bias, older age of the study population, and timing of initiation of therapy.

The impact of age and years since menopause on the relationship between MHT initiation and health outcomes, also known as the *timing hypothesis*, has been identified as one of the important factors explaining the complex, and sometimes discrepant, findings. Specifically, it has been found that women who were less than 10 years from menopause or aged between 50 and 59 years at baseline when MHT was started had lower *hazard ratios* (HR) for CHD than women initiating MHT at an older age [60], which in turn would be related to the health of the underlying vascular tissue or other factors, such as the reduction in or downregulation of estrogen receptors (ER) [61].

In fact, available scientific evidence supports the hypothesis that MHT halts progression of atherosclerosis in women whose menopause is of recent onset but that it would have a neutral or adverse effect in older women or if it is started more than 10 years after onset of the menopause. In addition, when initiated late in the atherosclerotic process, MHT could have adverse effects, potentially destabilizing existing plaques and triggering a coronary event [62, 63]. There is greater support for the possibility that the metabolic effects of estrogens can vary with age and time since onset of the menopause, and there is evidence that ER may be more functional and sensitive at the initiation of the menopause than afterward. As a result, any preventive treatment for CHD, including MHT, is more effective in younger women with less established atherosclerosis.

However, although there is biological plausibility, the "timing" hypothesis has not been tested in an RCT as hard endpoints of myocardial infarction or CVD mortality are not possible in a young healthy population. Use of "intermediate" endpoints with a high correlation to CHD has been proposed and has been incorporated into the design of ongoing RCTs, namely, KEEPS and ELITE.

- The *Early* versus *Late Intervention Trial with Estradiol* (ELITE) attempted to demonstrate the *timing hypothesis* for atherosclerosis progression [64]. The main finding was that women who started MHT within 6 years of menopause had a significantly lower atheroma progression than those who initiated it beyond 10 years past of menopause. These findings support a benefit of MHT in the primary prevention of CHD, particularly when it begins near the onset of menopause.
- *Kronos Early Estrogen Prevention Study* (KEEPS) is a multicenter, randomized, double-blinded, placebo-controlled trial, designed to test the hypothesis that low-dose MHT, either oral or transdermal, along with oral micronized progesterone, initiated in recently postmenopausal women will reduce the progression of subclinical atherosclerosis, defined by carotid artery intima-media thickness and coronary artery calcification.

  After 4 years of early use of MHT, the progression of atherosclerosis was not affected despite improving some markers of cardiovascular disease risk [65]. At first glance, the first KEEPS results were frustrating, since many expected to see clear cardioprotective outcomes in hormone users, which apparently was not the case. However, these KEEPS results are not surprising, since they reflect the almost nil expected progression of atherosclerosis during 4 years of follow-up in recently menopausal healthy women who had no atherosclerotic burden at the beginning of the study [66].

In addition, there is evidence that factors related to the type, the dose, and the route of delivery of MHT affect the risk of cardiovascular disease. Not only that, but there is strong suggestion that low-dose MHT via the transdermal route does not increase the risk of VTE, and biological data support this difference between oral and transdermal estrogens [64, 67]. However, KEEPS did not find any meaningful differences between transdermal and oral MHT with regard to effects on thromboembolic and cardiovascular markers (VTE and CVD events were not assessed) [65].

The use of a progestogen and its type most probably has an impact on cardiovascular risk: norpregnane derivatives are associated with higher risk of VTE, whereas micronized progesterone appears safe [68, 69]. In conclusion, transdermal estrogens alone or combined with micronized progesterone may represent the safest alternative for women who require MHT [67].

So far, there is no firm support for the use of MHT solely for the prevention of CHD, but evidence of the use of MHT in the primary prevention of CHD in postmenopausal women continues to accumulate.

22.8 Cognition, Mood, and Psychosocial Functioning

Although a relationship between the development of cognitive impairment and lifestyle-related risk factors, such as obesity, tobacco, and alcohol use, has been reported, age is still the strongest risk factor for dementia and other neurodegenerative

disorders [70]. Estrogen has an array of action mechanisms underlying cognitive benefits [71]. Recently, some studies reported a significant effect of estrogen on DNA repair enzymes in the brain [72]. However, research on this issue and the related mechanisms are still scarce.

Many observational studies and meta-analyses agree that the use of estrogens in mid-life reduces a woman's risk of subsequent dementia, whereas MHT initiation in late life could have deleterious effects [73]. Regarding the impact of estrogen on cognition, the effects of timing, route of administration, and dosage remain to be clarified. The timing hypothesis for dementia has been recently challenged by RCT [74] assessing the impact of oral estrogen on cognition.

Three large randomized trials found that MHT initiated early in menopause and continued for less than 7 years had no impact on cognitive function [26, 74, 75]. The Cache County (Utah) long-term prospective cohort study, however, found that MHT started early in menopause and continued for 10 years or longer was associated with a significant reduction in risk of Alzheimer's disease (AD) or other dementia [76].

Of note are results from the 2017 report of 18-year cumulative mortality among WHI participants [77]. In that study, mortality from AD and other dementia was lower among participants who were randomly assigned to treatment with estrogen alone versus placebo (HR, 0.74; 95% confidence interval [CI], 0.59–0.94). With estrogen-progestin therapy, the HR was 0.93 (95% CI, 0.77–1.11), and the *pooled* HR for the 2 trials was 0.85 (95% CI, 0.74–0.98) [77].

Cognitive impacts of progestogen differ widely by preparation. Analogous to estrogen, natural progesterone (P4) could be neuroprotective, stimulate synaptic plasticity, and enhance hippocampal neurogenesis [78]. Moreover, P4 might improve cholinergic neurotransmission. In animal and in vitro experiments, synergistic effects of E_2 and P4 have been reported [79]. Small, short-term clinical trials of progesterone show no meaningful effect on cognition. The quality of evidence is low, but overall findings do not reveal consistent, clinically important effects of progesterone on cognitive function in women [80].

Although MHT should not be considered in the prevention of dementia, these new studies reinforce the "critical window" hypothesis [81], leaving open the possibility that initiating systemic MHT soon after the onset of menopause (especially in surgical menopause) and continuing it in the long term may have positive cognitive benefits and may decrease the risk of AD. It is necessary to evaluate the individual characteristics of the patients, the possible benefits and risks, and ongoing assessment over time.

Based on findings from observational studies, the timing hypothesis posits that estrogen may preserve neurologic function and decrease the risk of dementia when administered early in menopause; however, the effects may be neutral or even harmful if estrogen is initiated later in life [75, 76].

22.9 Cancer

Sex steroids are not known to damage DNA directly. They can stimulate or inhibit cell proliferation and thus can modulate tumor developmental progression. However, it is important to consider that not all estrogens and progestins are used with the same dosage and route of administration (for oral, transdermal, and estradiol intranasal) and, mostly, different estrogens do not show the same bioavailability and tissue effects. The available data do not allow to discriminate for all these variables, and therefore it is inappropriate to consider jointly all forms of hormonal therapy.

During the 18 years of follow-up Women's Health Initiative (WHI) studies, cancer mortality rates were almost identical between hormone users and nonusers (8.2% vs. 8.0%; HR, 1.03 [95% CI, 0.95–1.12]) [77].

22.9.1 Breast Cancer

The relationship between estrogens to postmenopausal development of breast cancer (BC) is controversial, and the results of studies with respect to causality are mixed. Both in the original WHI study and in the long-term follow-up of this population, the incidence of BC increased with combined EP-MHT. The use of estrogen only was paradoxically associated with a decrease in BC incidence [82, 83].

The slightly increased relative risk of BC could have been related to the duration of hormone use or the sequential administration of progestin therapy or even the progestogen formulation itself. In contrast, MHT users had more localized tumors and better survival rates. Individual risks were very small. Several other studies have reported differences in risk related to the type of MHT regimen.

- The safer risk profile of natural progesterone and dydrogesterone respects to other synthetic progestins, as showed in the E3N study, a French observational study of teachers, on menopausal MHT [84]. The increase in risk of breast cancer observed with the use of synthetic progestogens seems to apply preferentially to ER+ carcinomas, especially those ER+/PR−, and to affect both ductal and lobular carcinomas [85].
- Similarly, a Finnish observational study reported that sequential progestin use resulted in a smaller increased risk of BC than did continuous progestin use, but one should note that in this study most patients used NETA [86].

Regarding BC, the time hypothesis is also supported by several studies. Contrary to what happens in the cardiovascular and cognitive systems, starting therapy later than 5 years after the onset of menopause is associated with a significant reduction in BC risk, because the estrogen deprivation associated with menopause determines a sensitization of breast cancer cells to the proapoptotic effects of estrogen, whereas immediate initiation has no advantageous effects [87]. Furthermore, hormone receptor-positive breast cancers in postmenopausal women respond to treatment with high-dose estrogen therapy, while similar tumors in premenopausal women

do not. This paradoxical response to addition or deprivation of estrogen can explain both decrease in BC after initiation of MHT and the decrease following cessation of treatment [88].

22.9.2 Another Cancer

We do not consider ovarian cancer to be a major consideration when deciding to take MHT for symptomatic relief, because the absolute risk of ovarian cancer with MHT is very low. On the other hand, we did not consider in the assessment of the use of MTH the positive effect on the risk of colorectal cancer seen with combined conjugated equine estrogen-medroxyprogesterone acetate use [89].

22.10 Osteoporotic Fracture

Numerous studies have shown the effectiveness of MHT in preventing bone loss in postmenopausal women with and without osteoporosis. From a regulatory perspective, it may be rational to separate the indication of MHT for prevention from treatment of osteoporosis. But both prevention and treatment of osteoporosis share a common clinical goal, which is prevention of fractures. The efficacy of MHT on fracture reduction in postmenopausal osteoporotic women has been demonstrated in some small RCTs [90, 91]; however, there are no large long-term RCTs (i.e., more than 2–3 years as required by the Regulatory Agencies for bone mineral density data).

Given that bone mineral density (BMD) is considered a surrogate marker for osteoporotic fracture and that there are other approved osteoporosis drugs, high-quality antifracture evidence of MTH in women with postmenopausal osteoporosis may be forever unavailable.

Although the effect of BMD preservation dissipates rapidly after discontinuation of MHT [92], it seems that there is no accelerated bone loss [93] or rebound fracture risk after stopping MHT [94]. Limited evidence suggests that the long-term residual bone preservative benefit may extend for years after the interruption of MHT [94]. Evidence from both human and animal studies suggests that estrogen can enhance muscle mass and strength [95] and increase collagen content and preserve the health of collagen-rich tissues, including the intervertebral discs [96]. Women reporting continuous or remote past MHT use had significantly less pronounced kyphosis than never users by their mid-80s [97]. Maintenance of lean paraspinal muscle mass and intervertebral disc heights is essential to prevent kyphosis and vertebral fracture.

Along with a “timing hypothesis” supported by a critical mass of data and emerging evidence of residual skeletal benefit after HT discontinuation, MHT as a bone-sparing agent has a distinct value in treating postmenopausal women with or without established osteoporosis. It may be considered first-line therapy for some patients with appropriate indications mentioned above.

22.11 Mortality

A new analysis from the Women's Health Initiative (WHI) randomized trials examined all-cause and cause-specific mortality during the intervention and post-intervention follow-up periods (total cumulative follow-up of 18 years) [77]. The primary outcome measure was all-cause mortality in the two pooled trials and in each trial individually. There was no link between MHT and all-cause mortality in the overall study population (ages 50–79) in either trial. However, there was a trend toward lower all-cause mortality among the younger women in both trials. In women aged 50–59, there was a statistically significant 31% lower risk of mortality in the pooled trials among women taking active MHT compared with those taking placebo, but no reduction in mortality with MHT among older women (*P* for trend by age = 0.01) [77].

22.12 Conclusions

Hormone therapy continues to have an important clinical role in the management of menopausal symptoms. Currently available evidence does not support the use of MHT for chronic disease prevention. However, the absolute risks of adverse events in younger women are much lower than in older women, and the quality-of-life benefits are likely to outweigh the risks for many women who seek treatment for symptoms in early menopause. Given the lack of validated primary prevention strategies other than lifestyle changes for younger women (<60 years), MHT is considered a good strategy—taking into account current knowledge thereof—for reducing the risk of osteoporosis fractures in menopausal women and for reducing the frequency of CHD and general mortality of women in their sixth decade (or in the 10 years since onset of the menopause), unless there are specific contraindications.

In conclusion, our understanding of the benefits and risks of MHT has advanced substantially. The guidance for physicians and women should reflect this evolution and emphasize the individualization and shared decision-making that facilitates appropriate decisions regarding the use of MHT.

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Selective Estrogen Receptor Modulators (SERMs): State of the Art

23

Santiago Palacios

23.1 Introduction

During and after menopause, women may experience various symptoms, such as vasomotor symptoms and genitourinary syndrome associated with menopause, attributable to the decrease in estrogen levels, with the consequent physiological changes [1]. In addition, there has been shown to be a strong link between decreased estrogen levels and loss of bone mass with the consequent risk of osteoporosis and fracture [2].

Hot flushes affect 50–82% of women undergoing menopause [3], and 40–50% have vaginal atrophy [4]. In addition, more than 40% of women have low bone mass between the ages of 50 and 60 [5].

Estrogen therapy at menopause is considered the number one treatment for both hot flushes and vulvovaginal atrophy, and most scientific societies consider estrogen therapy to be a very effective treatment for the prevention and/or treatment of osteoporosis [2, 6–8].

But estrogen therapy, even local, has its contraindications. After any gynecological or hormone-dependent cancer, it is preferable to start with non-hormonal therapies [8]. On the other hand, in general, concerns about the possible stimulating effects of systemic estrogen on the breast and endometrium as well as other negative effects of long-term estrogen treatment may be a barrier to its use [9]. Another important point is that adherence to drugs prescribed for long-term conditions is often poor [10, 11].

Therefore, the search for an alternative to estrogen therapy, both systemic and local, has proved necessary. Selective estrogen receptor modulators have been used for more than 30 years and have made it possible to avoid many of the side effects of estrogens. The possibility of them being used for the therapeutic purpose of treating

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osteoporosis and vulvovaginal atrophy has been investigated. The result of this is the emergence of various selective estrogen receptor modulators (SERMs) with different applications, ranging from the prevention and treatment of breast cancer to the prevention and treatment of osteoporosis or even dyspareunia and vulvovaginal atrophy.

The aim of this paper is to briefly compare the pharmacology of different SERMs and provide a detailed review of the available clinical data on their effects. The relevant English-language articles, published between 1985 and 2018, were first identified through a PubMed database search with the search string "selective estrogen receptor modulator or SERM." Furthermore, a specific review has been made of each individual SERM.

23.2 Selective Estrogen Receptor Modulators

SERMs are compounds with a molecular structure different from that of steroids. They share their selective binding to estrogen receptors (ER) with steroids and produce an estrogen agonist or antagonist effect depending on the target cell and hormonal environment. They have been developed with the aim of producing specific positive estrogenic effects on some target tissues, but with negative or neutral estrogenic effects on other tissues [12].

They were first known as antiestrogens and developed for the treatment of breast cancer. The four best known SERMs are tamoxifen, raloxifene, bazedoxifene, and ospemifene, wherein tamoxifen is currently being used for the prevention and treatment of breast cancer, both raloxifene and bazedoxifene for the treatment of osteoporosis, and ospemifene for dyspareunia or vulvovaginal atrophy. Therefore, the main aim of the pharmacological development of SERMs is to increase the benefit/risk ratio compared to estrogen therapy in the prevention and treatment of several highly prevalent, chronic, postmenopausal diseases that are associated with this state of estrogen deficiency.

Tamoxifen, a drug that was introduced more than 40 years ago for the treatment of hormone-dependent breast cancer, has been considered an antiestrogen for decades because of its blocking action on the binding of endogenous estrogens to the estrogen receptor (ER) of neoplastic breast cells. However, several studies suggest that tamoxifen may have a protective action on bone tissue (estrogen agonist) [13]. Raloxifene is the first SERM approved for preventing and treating osteoporosis [14]. In addition, raloxifene is as effective as tamoxifen in reducing the risk of breast cancer in postmenopausal women [15] and does not significantly affect the risk of cardiovascular disease [16]. Bazedoxifene has been shown to be effective in reducing vertebral and, in a high-risk group, non-vertebral fractures [17]. Finally, the first SERM, ospemifene, has recently been approved in the USA and Europe for the treatment of dyspareunia in the USA and for patients with vulvovaginal atrophy who are not eligible for estrogen treatment in Europe [18].

This class of drugs has enormous potential in the primary and secondary prevention of various types of estrogen-dependent tumors, postmenopausal osteoporosis, and vulvovaginal atrophy.

23.3 SERM Classification

There is an extensive list of compounds that can be considered SERMs for which results are available in either in vitro or in vivo animal cell models and in human experiments. There are more than 60 molecules already described with a SERM pharmacological profile [19]. Table 23.1 provides a summary of the main SERM groups classified according to chemical structure [20]. But they could also be divided by generations (Table 23.2) [21]. Certain phytoestrogens, such as genistein and daidzein, also appear to have a SERM-type pharmacological profile. There are currently three main chemical classes of SERM approved for clinical use: triphenylethylene derivatives, such as tamoxifen and ospemifene, used to treat and prevent breast cancer and vulvovaginal atrophy, respectively, and clomiphene to induce

Table 23.1 Classification of SERMs

Class	Examples
Triphenylethylenes	Tamoxifen
	Clomiphene
	Droloxifene
	Fispemifene
	GW-5638
	Idoxifene
	MDL-103,323
	Miproxifene
	Ospemifene
	Toremifene
Benzothiophenes	Raloxifene
	Arzoxifene
	LY-117018
Indoles	Bazedoxifene
	Pipendoxifene
Naphthalenes	Lasofoxifene
	Trioxifene
Benzopyrans	EM-800
	Acolbifene
	Levormeloxifene
	Ormeloxifene
	NNC 45-0781 and derivatives
	SP-500263

Table 23.2 Classification of SERMs

Generation	Product	Class
1°	Clomifene Tamoxifen	Triphenylethylene Triphenylethylene
2°	Raloxifene	Benzothiophene
3°	Bazedoxifene Lasofoxifene Ospemifene	Indole Naphthalene Triphenylethylene
TSEC	Bazedoxifene + conjugated estrogens	Indole + estrogen

ovulation; benzothiophene derivatives, such as raloxifene, used for the treatment and prevention of osteoporosis; and indoles such as bazedoxifene used for the treatment of women at risk of osteoporotic fracture.

23.4 Mechanism of Action

To understand the mechanism of action of SERMs, we must remember how estrogen works. After the binding of the hormone to the receptor, a hormone-receptor complex is formed, which in turn binds to another complex of the same characteristics to form homodimers, which acquire a unique spatial configuration and bind to DNA with high affinity and to different cofactors and stimulate or inhibit gene transcription by means of the AF-1 and AF-222 regions. The DNA region to which the activation domains or activation factors of the AF-1 and AF-2 transcription are attached is called the estrogen response element (ERE), which is a specific area and which, thanks to the spatial structure created by the hormone-receptor complex and its attachment to this area of DNA, causes a series of specific cofactors to bind together and activate or repress a series of genes [22].

To explain why the response induced by SERMs, after their binding to the receptor, may be similar or different from that induced by estrogens themselves, the spatial configuration of the SERM-receptor complex must be understood. Thus, after its binding to the receptor, the SERM creates an anomalous configuration of the hormone-receptor complex that causes it to be located in a different area of the DNA from the ERE and to bind to another type of cofactor, which entails another type of message and genetic expression. This makes each SERM unique [23, 24] (Fig. 23.1).

23.5 Main SERMs

23.5.1 Triphenylethylenes

23.5.1.1 Tamoxifen

Tamoxifen, a triphenylethylene derivative, has been used for more than 45 years. The accumulated clinical experience of more than ten million women/year is

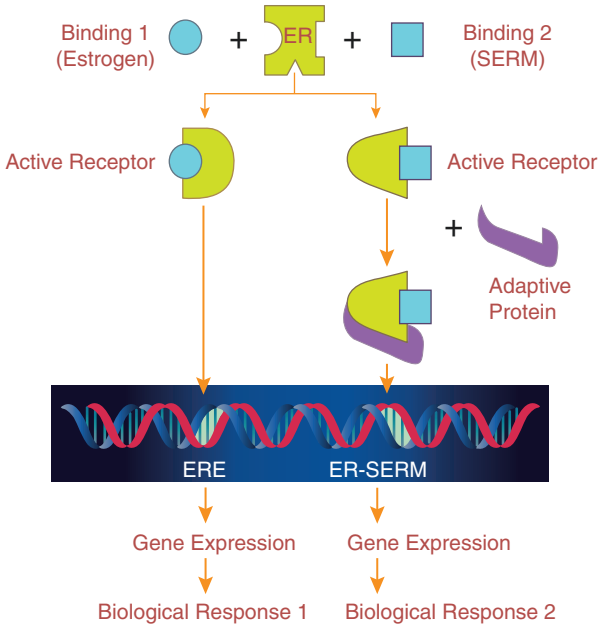

Fig. 23.1 Mechanism of action of SERMs

evidence of its beneficial effect in the treatment of breast cancer and in the primary prevention of women at high risk of developing this disease [25–27]. It is important to note that treatment with a first-generation SERM such as tamoxifen is effective in all subgroups of breast cancer except ER-negative tumors in premenopausal women, which is not surprising given its mechanism of action.

Tamoxifen has been widely used in the adjuvant treatment of invasive breast cancer involving surgery and chemotherapy. It has been shown to be effective in preventing new contralateral tumors and local or peripheral recurrences [28, 29]. After 1, 2, and 5 years of adjuvant treatment, relapses were reduced by 21, 19, and 47% and mortality by 12, 17, and 26%, respectively.

The most relevant study for primary prevention is the Breast Cancer Prevention Trial (BCPT, NSABP-P1) [25]. The women were randomly assigned to receive either tamoxifen (6681) or placebo (6707) for 5 years. However, the trial was stopped early because the findings provided strong evidence of a reduction in breast cancer with tamoxifen therapy. The administration of tamoxifen was effective in reducing the annual rate of ER+ tumors, both invasive and in situ, by 69%, but was not effective in reducing the recurrence of ER− tumors.

Tamoxifen has a partial estrogenic agonist effect in the uterus, and this effect has caused concern as it increases the incidence of endometrial pathology and endometrial cancer. The likelihood of a woman developing endometrial cancer in the general population is low, ranging from 12 cases per 100,000 women aged 40 to 84 cases per 100,000 women aged 60 [30]. Tamoxifen increases the risk of endometrial cancer according to most studies. Relative risks (RR) appear to vary between 1.3 [31] and 6.4 [25] for 20 and 40 mg/day doses.

In the Breast Cancer Prevention Trial, the reduction in breast cancer risk with tamoxifen was accompanied by an increase in the incidence of invasive endometrial cancer (mean RR = 2.53). The increased risk was observed primarily among women aged ≥50 years with a RR = 4.01, whereas among those aged 49 years or less, the RR was 1.21 [25]. However, it appears that adding metformin to tamoxifen may reduce this increased risk of endometrial cancer [32].

A meta-analysis of 55 trials in 37,000 women showed that the risk of breast cancer recurrence was significantly reduced by 18%, 25%, and 42% after 1, 2, or 5 years, respectively, of adjuvant tamoxifen therapy compared to no treatment [33].

Ding and Field [34] examined the effect of tamoxifen on bone health in postmenopausal women with early breast cancer and found that bone mineral density (BMD) is retained in the spine and hip, but not the wrist [34]. While there is no evidence that tamoxifen reduces the risk of fracture, the incidence of fractures is lower in users of tamoxifen than in users of aromatase inhibitors [35]. Recently a large cohort study found that the risk of fracture in premenopausal women with breast cancer and tamoxifen was twice that of the control group, with the risk being similar in postmenopausal women [36]. Tamoxifen is not suitable for the prevention or treatment of postmenopausal osteoporosis.

In tamoxifen users, the risk of deep vein thrombosis and pulmonary embolism is twice as high as in the general population. This increase, however, does not imply increased mortality in the pool of randomized trials of tamoxifen as an adjuvant treatment for early breast cancer [33].

23.5.1.2 Clomiphene

Clomiphene, which may be considered the first SERM for clinical use, is also a derivative of triphenylethylene but has been used since 1967 exclusively for ovulation induction [37], and no research exists for its clinical use in postmenopausal women. However, there are data in rats that show it to have the same positive effect on bones as estrogen [38]. A recent review indicates a possible increased risk of thyroid cancer and malignant melanoma, especially if clomiphene is used in more than six cycles [39]. This fact must be confirmed with further trials.

23.5.1.3 Ospemifene

Ospemifene belongs to the family of triphenylethylenes. It is a biologically active metabolite of toremifene (desamino-hydroxy-toremifene) that demonstrated prevention of bone loss and reduced cholesterol levels in castrated rats without weight gain in the uterus [40]. In addition, in in vitro studies, it acts as a potent estrogen antagonist in ER-positive breast cancer cell lines [41]. Ospemifene greatly reduces the incidence of breast carcinomas in comparison to control mice and was similar to tamoxifen in dimethylbenzanthracene (DMBA)-induced breast tumors [42].

Ospemifene proved more estrogenic than raloxifene, as shown by changes in serum levels of follicle-stimulating hormone and sex hormone-binding globulin. Neither ospemifene nor raloxifene stimulated the endometrium, but in contrast to raloxifene, ospemifene had a clear estrogenic effect on the vagina [43]. For this reason, a comprehensive clinical program was conducted on its effect on vulvovaginal atrophy.

Ospemifene has been assessed for the treatment of postmenopausal women with vulvovaginal atrophy in two 12-week phase III trials, two long-term safety extension trials, and one 52-week safety and efficacy trial [44–47]. The first trial with ospemifene (60 mg) was randomized, double-blind, and placebo-controlled. It included 919 women with moderate to severe vulvovaginal atrophy (ospemifene, $n = 463$; placebo, $n = 456$) and lasted 12 weeks [46, 47]. The women were subdivided into two strata according to whether subjective perception was more important for dyspareunia or vaginal dryness. Both strata, dyspareunia and vaginal dryness, had their own randomization programs and were analyzed as independent trials. The trial with dyspareunia patients included 605 participants. At 12 weeks, 60 mg ospemifene produced a statistically significant improvement compared to placebo at all the points analyzed: percentages of decrease in parabasal cells ($p < 0.0001$) and increase in superficial cells ($p < 0.0001$) in the rate of vaginal maturation, reduction in vaginal pH ($p < 0.0001$), and improvement in symptoms related to vulvovaginal atrophy ($p = 0.0001$) [46].

Another 12-week, randomized, double-blind, placebo-controlled, phase III trial assessed the efficacy and safety of ospemifene (30 or 60 mg/day) in 826 postmenopausal women with moderate to severe vulvovaginal atrophy (ospemifene 30 mg/day, $n = 282$; ospemifene 60 mg/day, $n = 276$; placebo, $n = 268$) [44]. Compared to placebo, ospemifene (30 and 60 mg) significantly increased the percentage of surface cells and decreased the percentage of parabasal cells (improved maturation rate) at weeks 4 and 12 ($p < 0.001$ for all comparisons for both doses and placebo); a significantly greater reduction in vaginal pH was also observed in the ospemifene group compared to the placebo group at weeks 4 and 12 ($p < 0.001$) for both doses of ospemifene. After 12 weeks of treatment, ospemifene (30 and 60 mg) significantly decreased the vaginal dryness symptom rating compared to placebo ($p = 0.04$ and 0.021 for the 30 and 60 mg ospemifene groups, respectively). Also, 60 mg ospemifene significantly reduced the symptom rating of the women who reported dyspareunia as the major symptom in comparison to placebo ($p = 0.023$).

In this trial, an endometrial biopsy was performed at the beginning to rule out endometrial hyperplasia and adenocarcinoma. At the end of the 12-week efficacy study, patients were invited to enroll in a further 40-week, double-blind, safety extension study for a total of 52 weeks of treatment: ospemifene 30 mg/day, $n = 62$; ospemifene 60 mg/day, $n = 69$; and placebo, $n = 49$ [45]. Endometrial safety was assessed by transvaginal ultrasound and biopsy. At week 52, an increase in mean endometrial thickness of 0.68 and 1.14 mm was observed with ospemifene 30 and 60 mg/day, respectively. The vast majority of endometrial biopsy samples were atrophic or inactive.

In a post hoc analysis of a pool of six phase II and three double-blind, randomized clinical trials, hot flushes (8.5% vs. 3.3% placebo) and urinary tract infections (86.5% vs. 4.8%) were found to be the most frequent side effects [47].

We can conclude that it is the first non-hormonal oral alternative for vulvovaginal atrophy. It is a selective estrogen receptor modulator (SERM) that selectively exerts agonistic effects on vaginal tissue. Sixty milligrams of ospemifene has been shown to reduce symptoms of dyspareunia and vaginal dryness significantly compared to placebo and to be safe at 52 weeks.

23.5.1.4 Toremifene

Toremifene has been in clinical use for more than 20 years for the treatment of advanced hormone-sensitive breast cancer and the adjuvant treatment of early breast cancer, and there is experience of use in more than 500,000 women/year [48]. The incidence of secondary endometrial cancer was lower with toremifene than with tamoxifen and similar to raloxifene. The risk of stroke, pulmonary embolism, and cataracts may be lower with toremifene than with tamoxifen, and the risk of pulmonary embolism and deep vein thrombosis may be lower than with raloxifene [49, 50].

After 5 years of follow-up, toremifene 60 mg/day has no substantial negative effect on bone mineral density in pre- or postmenopausal women and may have a positive influence on lipids [51].

23.5.2 Benzothiophenes

23.5.2.1 Raloxifene

Raloxifene was originally designed as a drug to treat breast cancer, but its clinical development later focused on the prevention and treatment of postmenopausal osteoporosis, becoming the first SERM approved to prevent and treat this metabolic bone disease [52]. Raloxifene has also been investigated for the primary and secondary prevention of cardiovascular disease in postmenopausal women [16] and for the prevention of breast cancer in high-risk women [53]. After tamoxifen, raloxifene is the SERM with the most information available on its pharmacological effects in postmenopausal women, due to the size of its clinical program (more than 40,000 women included in phase III trials) and the fact that, since its commercialization in 1998, it is estimated that more than one million patients/year have been treated with the drug. Initial research in experimental osteoporosis models in castrated rats showed that raloxifene induces a bone anti-resorptive effect similar to estrogens, but without inducing endometrial proliferation [54]. In the same animal model, it was shown to have a very estrogen-like effect on lipid metabolism [54, 55]. In in vivo and in vitro studies on ER-positive breast cancer, raloxifene has also been shown to inhibit tumor growth and spread [56].

The MORE trial in postmenopausal women with osteoporosis has shown that raloxifene reduces bone turnover markers by 25–35% after 1 year of treatment and reduces the relative risk of new vertebral fractures by 30–50% after 3 years of treatment [14]. According to a meta-analysis including seven clinical trials, raloxifene at doses of 60 mg or 120/150 mg a day reduces the risk of vertebral fracture by 40% (RR, 0.60; 95% CI, 0.49–0.74) and 49% (RR, 0.51; 95% CI, 0.41–0.64), respectively [57].

The rate of invasive ER-positive breast cancer, a secondary objective in the MORE trial, showed an 84% reduction after 4 years of follow-up [58]. Moreover, during the next 4 years of follow-up, invasive ER-positive breast cancer was reduced by 66% [59]. These results have not been associated with any harmful effects on the endometrium [60] or the pelvic floor [61].

In order to compare the relative effects and safety of raloxifene and tamoxifen and the risk of developing invasive breast cancer and other outcomes of the disease, the Study of Tamoxifen and Raloxifene (STAR) was conducted. It is a prospective randomized double-blind trial conducted in 19,747 postmenopausal women with a mean age of 58.5 years and an increased risk of breast cancer in 5 years (mean risk 4.03%). The results of the STAR trial show that raloxifene and tamoxifen are equally effective in reducing the risk of breast cancer in postmenopausal women. This means that tamoxifen and raloxifene can reduce the risk of breast cancer by half in 5 years. There were 36 cases of uterine cancer with tamoxifen and 23 with raloxifene (RR, 0.62). No differences were found in other types of cancer or in episodes of ischemic heart disease or stroke. Thromboembolism events occurred less frequently in the raloxifene group (RR, 0.70). The number of osteoporotic fractures in the different groups was similar. There were fewer cataracts (RR, 0.79) in women taking raloxifene. There was no difference in the total number of deaths or cause of death [15].

The effect of raloxifene on coronary heart disease (CAD) has been studied in the Raloxifene Use for the Heart (RUTH) trial. Ten thousand one hundred and one postmenopausal women with coronary heart disease or multiple risk factors for coronary heart disease were assigned 60 mg raloxifene or placebo. Compared to placebo, raloxifene had no significant effect on the risk of primary coronary events (RR, 0.95) and reduced the risk of invasive breast cancer (RR, 0.56). Raloxifene was associated with an increased risk of fatal stroke (RR, 1.49) and venous thromboembolism (RR, 1.44). Raloxifene reduced the risk of clinical vertebral fractures (RR, 0.65). Raloxifene did not significantly affect the risk of heart disease.

Therefore, raloxifene is suitable for the treatment and prevention of osteoporosis in postmenopausal women in the USA and Europe [52]. In the USA, it is also recommended for reducing the risk of invasive breast cancer in postmenopausal women with osteoporosis and in women at high risk of invasive breast cancer [52].

In recent years, various randomized trials have shown that raloxifene administration appears to be effective and safe in improving psychotic symptoms in postmenopausal women with schizophrenia [62].

23.5.2.2 Arzoxifene

Arzoxifene, a potent raloxifene-like benzothiophene, has demonstrated an antagonist potency ten times greater than raloxifene in MCF-7 breast cancer cells and endometrial cancer cell lines [63]. In both ovariectomized rats and rats with ovaries, arzoxifene does not increase uterine weight [64].

Arzoxifene has shown skeletal effects similar to raloxifene in experimental osteoporosis models [65, 66]. In phase II with different doses of arzoxifene in women with estrogen receptor-positive but tamoxifen-resistant breast cancer and with advanced or metastatic breast cancer, positive results were shown in reducing disease progression time [67] and response rates [68].

However, the data from the pivotal studies, although they showed a decrease in vertebral fractures and breast cancer in this population [69, 70], did not show it to

have more potency than raloxifene but did show it to have more gynecological side effects than in the placebo group [71]. These data made the company decide not to submit it for registration.

23.5.3 Indoles

23.5.3.1 Bazedoxifene

Bazedoxifene is one of the newest SERMs recommended for the prevention and treatment of postmenopausal osteoporosis.

In preclinical models, bazedoxifene increases bone mineral density and bone strength in rats. Bazedoxifene did not stimulate the proliferation of MCF-7 cells but inhibited the proliferation induced by 17β-estradiol. In an immature rat uterus model, bazedoxifene was associated with less uterine weight gain than ethinyl estradiol or raloxifene [72–74].

In phases I and II, the data reveal that bazedoxifene is safe, very well tolerated, and effective. After therapy of just 3 months in 494 postmenopausal women, bazedoxifene (at doses as low as 5 mg/day) showed effects on bone turnover and LDL-cholesterol markers comparable to those seen with raloxifene. There were no increases in hot flushes or endometrial thickness [75].

Bazedoxifene was assessed in two phase III studies. In a 2-year prevention trial involving 1583 healthy postmenopausal women with low or normal bone mineral density (BMD), patients received daily doses of 10, 20, or 40 mg of bazedoxifene or 60 mg raloxifene or placebo, and all took 600 mg of elemental calcium daily [76]. All three doses of bazedoxifene and the raloxifene were equally effective in maintaining bone mineral density (BMD) in the hip, lumbar spine, femoral trochanter, and femoral neck. Within 6 months, all three doses of bazedoxifene had already demonstrated a significant reduction in BMD loss compared to placebo. The differences in the mean percentage of BMD in the lumbar spine relative to baseline at 24 months with 10, 20, and 40 mg bazedoxifene, compared to placebo, were 1.08 ± 0.28%, 1.41 ± 0.28%, and 1.49 ± 0.28%, respectively (with a statistical significance of $p < 0.001$ for all of them).

A pivotal phase III trial was conducted to assess the efficacy and safety of bazedoxifene in preventing fractures in postmenopausal women with osteoporosis (55–85 years of age) [77]. Participants received daily treatment with 20 mg ($n = 1886$) or 40 mg ($n = 1872$) of bazedoxifene, 60 mg of raloxifene ($n = 1849$), or placebo ($n = 1885$), as well as a daily supplement of 1200 mg of calcium and 400–800 IU of vitamin D. Among 6847 subjects in the intention-to-treat population, the incidence of new vertebral fractures was significantly lower ($p < 0.05$) with 20 mg bazedoxifene (2.3%), 40 mg bazedoxifene (2.5%), and 60 mg raloxifene (2.3%) compared to placebo (4.1%), with relative risk reductions of 42%, 37%, and 42%, respectively. The effect of treatment was similar among subjects with or without prevailing vertebral fracture ($p = 0.89$). The incidence of non-vertebral fractures with bazedoxifene or raloxifene was not significantly different from placebo. In an analysis of a subgroup of women at higher risk of fracture (femoral neck T-score ≤ 0.0 and/or one

moderate or severe vertebral fracture or multiple mild vertebral fractures; $n = 1772$), 20 mg bazedoxifene showed a 50% and 44% reduction in the risk of non-vertebral fracture relative to placebo ($p = 0.02$) and 60 mg raloxifene ($p = 0.05$), respectively.

The 3-year study was given a 2-year extension, involving a total of 4216 women and providing 5-year data [78]. The raloxifene arm was discontinued after 3 years; subjects receiving 40 mg bazedoxifene were switched to 20 mg bazedoxifene after 4 years. At 5 years, the incidence of new vertebral fractures in the intention-to-treat population was significantly lower with 20 mg (4.5%) and 40/20 mg (3.9%) bazedoxifene compared with placebo (6.8%, $p < 0.05$), with relative risk reductions of 35% and 40%, respectively. The incidence of non-vertebral fractures was similar between the groups. In a subgroup of women at high risk of fracture ($n = 1324$; femoral neck T-score ≤ -3.0 and/or ≥ 1 moderate or severe or ≥ 2 mild vertebral fracture), 20 mg bazedoxifene showed a reduced risk of non-vertebral fracture compared with placebo (37%, $p = 0.06$).

A further 2-year extension was conducted. At 7 years the cumulative incidence of new vertebral fractures remained significantly lower in the 20 mg bazedoxifene group, 30.4% less than in the placebo group ($p < 0.001$) [79].

In terms of bazedoxifene safety data, the number of reported heart disorders and cerebrovascular events was equally low among all treatment groups treated for up to 7 years [77, 78]. Although pulmonary embolism and venous thrombosis of the retina increased in the treatment groups compared to placebo, this was not statistically significant [80–82]. However, the risk of deep vein thrombosis increased significantly after 3 years (RR 8 (95% CI 1.01–64.25)) [80–82]. After 3, 5, and 7 years, there was no difference in the incidence of breast cancer between the different groups [80–82]. Bazedoxifene has shown a good safety profile in the incidence of vaginal bleeding, uterine cancer, and ovarian cysts among the groups treated for up to 7 years [80–82].

The only adverse effects found with bazedoxifene and which increased compared to the placebo group were hot flushes ($p < 0.001$) and leg cramps ($p < 0.01$). Most of the adverse reactions that occurred during the clinical trials were mild to moderate and did not result in discontinuation of treatment [80–82].

Thus, in a meta-analysis of four randomized and placebo-controlled trials, it is concluded that the use of bazedoxifene reduces the incidence of vertebral fractures and increases bone mineral density at 3 and 7 years. Furthermore, serious adverse events such as myocardial infarction, stroke, venous thromboembolic events, and breast cancer do not increase during this period of use [17].

A new approach to hormone therapy is to combine an estrogen with a SERM in order to achieve all the positive effects of estrogens and even increase them and avoid their negative effects by using a SERM, and this combination is called the tissue-selective estrogen complex (TSEC). The purpose is to decrease hot flushes, prevent and treat vulvovaginal atrophy, and prevent bone loss, without stimulating the breast or endometrium. Bazedoxifene in combination with conjugated estrogens in doses of 0.45 or 0.625 mg significantly reduces vasomotor symptoms [83], improves vaginal symptoms [83], and increases bone mineral density in the lumbar spine and hip [83]. It is clear that this is a promising treatment for both vasomotor symptoms and the prevention of osteoporosis [84].

23.5.4 Naphthalenes

23.5.4.1 Lasofoxifene

The main representative of this SERM group is lasofoxifene. This compound selectively binds to both estrogen receptors (alpha and beta) with a high affinity and a mean inhibitory concentration that is similar to that observed with estradiol and higher than those reported for other SERMs (raloxifene and tamoxifen) [85]. Lasofoxifene has a significantly higher bioavailability than other SERMs due to increased resistance to glucuronidation of the intestinal wall.

In preclinical models of postmenopausal osteoporosis, lasofoxifene inhibited bone turnover and reduced bone loss [86]. In animals, lasofoxifene did not alter endometrial thickness, the glandular area of the endometrium, or the basal area of the luminal epithelium, compared to control animals [86, 87].

Two phase III clinical trials have been conducted: Osteoporosis Prevention and Lipid Lowering (OPAL) and Postmenopausal Evaluation and Risk Reduction with Lasofoxifene (PEARL). The OPAL trial involved 1907 non-osteoporotic postmenopausal women aged 40–75 years, who were randomly assigned to 0.0025, 0.25, or 0.5 mg/day of lasofoxifene or placebo for 2 years. At 2 years, lumbar BMD increased by 1.5, 2.3, and 2.3% with 0.025, 0.25, and 0.5 mg lasofoxifene, respectively, compared to a decrease of 0.7% in placebo users. Vaginal atrophy (assessed by vaginal pH or by an increase in the percentages of intermediate and superficial vaginal cells) improved after 1 and 2 years of treatment, at all doses of lasofoxifene compared to placebo [88, 89].

The PEARL trial is a randomized pivotal trial involving 8556 women aged 59–80 years, with a BMD *T*-score of −2.5 or less in the femoral neck or spine. It was randomized for the women to receive a daily dose of lasofoxifene (0.25 or 0.5 mg) or placebo for 5 years. Compared to placebo, lasofoxifene at a dose of 0.5 mg per day was associated with a lower risk of vertebral fracture (13.1 vs. 22.4 cases per 1000 person-years; RR, 0.58; 95% confidence interval (CI), 0.47–0.70), non-vertebral fracture (18.7 vs. 24.5 cases per 1000 person-years; RR, 0.76; 95% CI, 0.64–0.91), ER-positive breast cancer (0.3 vs. 1.7 cases per 1000 person-years; RR, 0.19; 95% CI, 0.07–0.56), coronary heart disease events (5.1 vs. 7.5 cases per 1000 person-years; RR, 0.68; 95% CI, 0.50–0.93), and strokes (2.5 vs. 3.9 cases per 1000 person-years; risk ratio, 0.64; 95% CI, 0.41–0.99). At a dose of 0.25 mg per day, compared with placebo, lasofoxifene was associated with a lower risk of vertebral fracture (16.0 vs. 22.4 cases per 1000 person-years; RR, 0.69; 95% CI, 0.57–0.83) and stroke (2.4 vs. 3.9 cases per 1000 person-years; risk ratio, 0.61; 95% CI, 0.39–0.96) [90, 91].

However, both the lower and higher doses of lasofoxifene, compared to placebo, were associated with an increase in venous thromboembolic events (3.8 and 2.9 cases vs. 1.4 cases per 1000 person-years; RR, 2.67 (95% CI, 1.55–4.58) and 2.06 (95% CI, 1.17–3.60), respectively). Endometrial cancer occurred in three women in the placebo group, two women in the low-dose lasofoxifene group, and two women in the high-dose lasofoxifene group. The death rates per 1000 person-years were 5.1 in the placebo group, 7.0 in the low-dose lasofoxifene group, and 5.7 in

the high-dose lasofoxifene group [91]. Lasofoxifene increased hot flushes and leg cramps at both doses (0.25 and 0.5 mg) ($p < 0.001$ and <0.001) [90]. Although it was submitted and accepted for the treatment of osteoporosis by the European health authorities, this product was never launched on the market because the company decided not to do so because the FDA requested further trials before its acceptance. Recently lasofoxifene has been acquired by another company to investigate its use for the treatment of breast and ovarian cancers.

23.6 Conclusions

There is an estrogenic agonist effect that may be beneficial either on the bone or on the vagina and which appears to be an effect dependent on the greater or lesser potency of the SERM (in postmenopausal women). The SERMs assessed appear to have antiestrogenic or neutral effects on the breast; tamoxifen, raloxifene, and lasofoxifene have shown antiestrogenic effects in clinical trials; and bazedoxifene and ospemifene have shown antiestrogenic effects in preclinical trials but appear to be neutral in clinical trials to date. Most SERMs have been associated with a slightly increased risk of venous thromboembolism (VTE). The cardiovascular and cardiometabolic effects of SERMs in clinical trials appear to be positive or neutral. The adverse effects of tamoxifen, relative to other SERMs, on the endometrium are well documented.

We currently have extensive experience concerning the risks and benefits of SERMs (Table 23.3). Therefore, we know the benefits that are ideally required of a SERM, such as those that help in the prevention and treatment of osteoporosis, those that help in the primary and secondary prevention of breast cancer, and those that may represent added cardiovascular benefits. Now, thanks to ospemifene, we can add treatment of dyspareunia and vulvovaginal atrophy. We also know the possible side effects to be avoided: the risk of endometrial cancer with tamoxifen, and venous thrombosis, and the possible increase in hot flushes with all SERMs. Therefore, the search for what we require of a SERM is clear.

In the short term, it does not seem realistic to expect a SERM to be able to meet all requirements. But each SERM that appears provides more information on efficacy and safety.

Table 23.3 Intensity of clinical effects in clinical trials with SERMs

	E effect in bone	E effect in vagina	E effect in endometrium	Anti-E effect in breast
Tamoxifen	+/–	=	++	+++
Raloxifene	+++	=	=/+	+++
Bazedoxifene	+++	=	Anti E	=
Ospemifene	+	+++	=/+	=

E estrogenic, *anti-E* antiestrogenic, + mild, ++ moderate, +++ intense, = neutral, +/– controversial

Another interesting concept would be TSEC, a combination of bazedoxifene with conjugated estrogens as a possible alternative to classical hormonal treatment and which opens up the possibility of different combinations.

Meanwhile, the rapid developments in the molecular biology of the ER activation cascade, together with advances in genomics and chemistry and proteomics, make us optimistic about the future of different estrogen modulators in the medium term.

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Management of Osteoporosis in Postmenopausal Women

24

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24.1 Introduction

Osteoporosis is a systemic disease of the skeleton consisting of a reduction of bone mass and deterioration of bone microarchitecture. Loss of bone strength and increased risk for fragility fracture are the consequences. Osteoporosis translates in the bone, as for other systems in the body, the impact of aging, which imposes a progressive deterioration of the biological regulators. There is a gradual, unfavorable disequilibrium between bone formation and bone resorption, which leads to the mentioned net loss of bone mass and disintegration of bone architecture.

The development of osteoporosis in concomitance with aging is universal, but as for other noncommunicable chronic diseases (NCD), the progression is asymmetrical. The variables responsible of the individual differences are several, among

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them, genetic susceptibility, lifestyle, hormonal problems, etc. Also important, the propensity to fall, a strong variable with an impact in the risk of fracture, varies between individuals.

Because aging is a global phenomenon, osteoporosis occupies a privileged position among the causes of morbidity and mortality. According to the International Osteoporosis Foundation (IOF), it is estimated that the disease affects 200 million people worldwide [1]. Common sites for osteoporotic fracture are the spine and the hip but also the distal forearm, pelvis, proximal humerus, ribs, and distal femur. Given the population trends, the impact of the disease is expected to increase. So the 1.66 million hip fractures diagnosed worldwide in 1990 are estimated to reach 6.26 million in 2050 [1].

Osteoporotic fractures are followed by increased mortality and loss of healthy life years (HLY). Hip fracture, for example, requires hospitalization in most cases and is associated with risk of death. Data from Sweden forecast that around 1% of all deaths are due to hip fracture, something that is only slightly lower to deaths due to breast cancer [2].

Osteoporosis particularly affects women. Studies from different sources estimate that one in three women over age 50 will suffer osteoporotic fractures, the corresponding figures in men being one in five [3–5]. The reasons are that women (1) have more fragile bone architecture, (2) have a longer life expectancy, and (3) suffer menopause. The impact of menopause resides in the high sensitivity of bone metabolism to estrogens. The size of the effect is huge, and postmenopausal osteoporosis (PMO) is the most prevalent form of the disease as opposed to involutional osteoporosis, which is that due to aging.

24.2 Biological Background

24.2.1 The Tissue Structure of Bone

Against its static appearance, the structure of bone is subjected to a continuous process of change, which is known as bone turnover or bone remodelling. There is of course inert material, composed of hydroxyapatite, a calcium salt, which gives consistency, and that contributes to the stable shape. There is also organic components, including cells and a thick network of collagen that, once mineralized with hydroxyapatite, provides a strong structure, which warrants both resistance and flexibility to absorb impact energy without breaking.

All those material components organize according to two different basic structures, cortical and trabecular bone.

Cortical bone, the main component of long bones, is comprised of successive apposition of osteons, basic organizations composed of concentric layers of compact bone (lamellae) encircling a central canal (Haversian canal). The strength provided by such a structure is optimal.

Trabecular bone, which is found in the vertebral bodies or the distal portions of long bones, has a spongelike structure. A network of interconnected trabecular plates provides a structure in which the energy is transmitted efficiently while maintaining a light texture. The intertrabecular spaces are filled with bone marrow.

24.2.2 The Cells in Bone

The three basic cell types in bone are osteoclasts, osteoblasts, and osteocytes. All the three work in a harmonious and continuous process that governs bone turnover and regularly provides renovated bone.

Osteoclasts and osteoblasts derive from progenitor cells in the near bone marrow and articulate a process within the so-called bone multicellular unit (BMU) (Fig. 24.1).

Bone remodelling results from a program in which resorption, a responsibility of osteoclasts, is the initial step. Osteoclasts firstly differentiate to become multinuclear cells capable of digesting damaged bone areas [6]. As a result of a coupled and well-concatenated process, osteoblasts differentiate subsequently and start synthesizing protein in the form of a matrix called osteoid, which fills up the cavities created by osteoclasts. This is the phase of bone formation. Osteoid undergoes a slow process of mineralization along several months in order to consolidate new bone. One crucial condition during this process is that the balance between resorption and formation is finally neutral, i.e., the volume of renovated bone equals that digested, so that there is not a net loss of material.

Osteocytes are key cells that derive from the osteoblasts that leave buried under the osteoid. Although apparently isolated within a mineralized mass, osteocytes are interconnected through a network of cytoplasmic dendritic processes extending through a thick net of canaliculi. This sophisticated system acts as a sensitive sensor capable of detecting areas of bone fatigue (microcracks, etc.) in which remodelling is desirable [7].

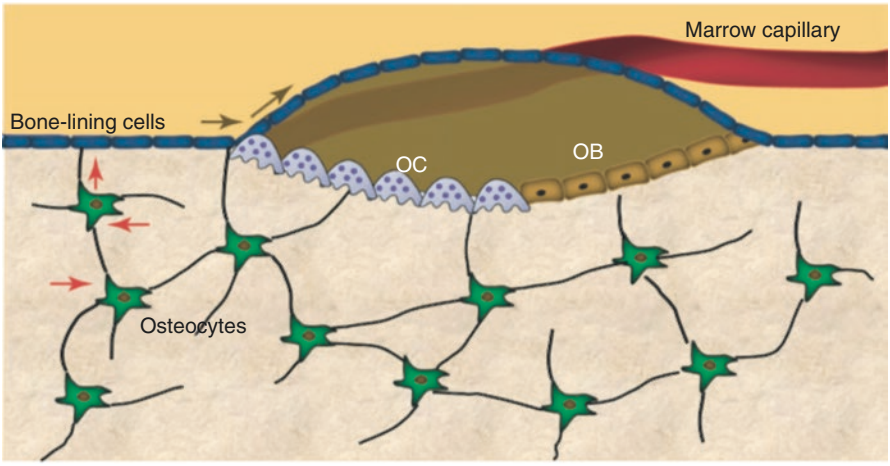

Fig. 24.1 The basic multicellular unit (BMU) includes the coupled collaboration between osteoclasts, osteoblasts, and osteocytes. The canopy of the bone lining cells and one associated marrow capillary are also included in the figure. There is a net of canaliculi that serves to interconnect osteocyte dendritic processes. (With permission of Elsevier from Khosla S, et al. Trends Endocrinol Metab. 2012; 23:576–81. Permission conveyed through Copyright Clearance Center, Inc.)

There is a very detailed knowledge of the molecular mechanisms subserving the elaborated process of bone renovation (for review see [8, 9]). Osteocytes are the main regulatory cells involved in the control of bone resorption and formation, modulating the function of osteoclasts and osteoblasts at a molecular level. One key step is the contribution of osteocytes to the secretion of a crucial cytokine, the receptor activator of nuclear factor κB ligand (RANKL), which plays a necessary role in the differentiation of osteoclasts from progenitor cells [6]. Interleukin-1 (IL-1), interleukin-11 (IL-11), interleukin-17 (IL-17), tumor necrosis factor-α (TNF-α), and prostaglandin E2 contribute to increased RANKL secretion, while 17beta-estradiol downregulates its production [10]. Osteocytes modulate bone turnover by secretion of not only RANKL but also other specific factors, like sclerostin (SOST) and Dickkopf-1 (DKK1), inhibitors of osteoblast activity, as well as macrophage colony-stimulating factor (M-CSF) and osteoprotegerin (OPG), substances regulating osteoclast functions. Results from previously conducted studies indicate that RANKL, acting on its receptor located on precursor cells, cooperates with M-CSF in osteoclastogenesis upregulation. On the other hand, osteocytes produce also OPG, a soluble factor inactivating RANKL, nitric oxide, and transforming growth factor β (TGFβ), and thus contribute to decrease in osteoclast formation [11].

Noteworthy, recent studies indicate that interleukin-20 (IL-20) is considered a relevant factor in regulation of osteoclasts activity. IL-20 has the ability to upregulate the expression of RANK and other markers of osteoclast differentiation (like nuclear factor of activated T-cells c1 [NFATc1], c-Fos, cathepsin K, and tartrate-resistant acid phosphatase [TRAP]). Additionally IL-20 stimulates production of cathepsin G by osteoclasts, which subsequently contributes to the increase of soluble RANKL (sRANKL) secretion from osteoblasts, thus osteoclastogenesis promotion [12].

24.2.3 The Key Role of Estrogens

Clinical investigators in the middle of the previous century already detected the association between ovarian function and bone metabolism. More recent basic work detected the presence of estrogen receptor (ER) mRNA expression in cell cultures and in both animal and human tissues [13–15]. Soon afterward, both the ERα and the ERβ were found in histological sections of the growth plate and in mineralized bone as well as in cell cultures of the three bone cellular types.

The experimental work has run in parallel with a series of clinical findings. Observations in individuals with genetic deficiencies confirmed that estrogens were the key regulator of bone metabolism not only in women but also in men [16, 17], and clinical studies in ovariectomized women proved that treatment with estrogens prevented bone loss [18]. The evidences have accumulated throughout the years to generate a solid body of knowledge confirming the crucial role of estrogens as regulators of bone metabolism [19].

One important point to understand the role of estrogens relates with the pathophysiological basis of PMO. The neutral balance in the process of bone remodelling, mentioned above as a condition to maintain the integrity of bone mass, starts being unbalanced as a result of aging. Resorption progressively separates from formation, which stays behind. In fact, involutional osteoporosis is the result of the prolongation of that slow disequilibrium during years.

Menopause in women imposes an acceleration of that process, and this has been proved to be the responsibility of estrogens that, therefore, act as the closing gate preventing the rapid loss of bone. Estrogens are, therefore, bone anti-resorptives. Clinical observation is consistent with that premise, and, for example, there is already an initial increase of bone loss during the perimenopausal years, when there are only slight reductions in the ovarian output of estrogens [20]. Also studies with bone biochemical markers across the menopausal transition are eloquent since there is an increase of markers of bone resorption in parallel with the decline in circulating estrogens. As a result of the coupling process between osteoclasts and osteoblasts, there is also an increase in markers of bone formation but of lower magnitude [21].

The identification of ER in osteocytes and osteoblasts raises questions about a potential effect of estrogens on both cell types. The action on osteocytes has been indirectly evaluated through histological assessments in bone biopsies during the use of analogues of gonadotropin-releasing hormone (aGnRH) [22]. There is an increase in cell apoptosis, which seems to be probably followed by an osteoclastogenic response emanating from signals released from the dying osteocytes [23]. The mechanism for the apoptosis of osteocyte associated with estrogen loss is unknown, although animal experiments suggest that might be related with increase of oxidative stress [24].

The action of estrogens on osteoblasts is less apparent. As for osteocytes, estrogens reduce apoptosis of osteoblasts, although the mechanisms for such an effect are still elusive (for review, see [19]).

24.3 Diagnosis of Postmenopausal Osteoporosis

There are three main tools, clinical history, radiological imaging, and biochemical markers. All the three have to be used under the framework of a basic principle: the assessment of PMO and the interventions to reduce risk or treat the established disease need to be organized bearing in mind that the objective should always be the reduction of fragility fracture.

24.3.1 Clinical Assessment

Clinical history should be always the first and necessary step in every evaluation of PMO. Two important measures at this step are to identify major risk factors for fragility fracture and to discard secondary osteoporosis.

Table 24.1 Major risk factors for fragility fracture

Age
Fracture history after age 54
Parental hip fracture
Densitometry showing hip osteoporosis

Table 24.2 Main causes of secondary osteoporosis

Endocrine-metabolic	History or actual hypogonadism (anorexia nervosa, early menopause, post-chemotherapy, etc.)
	Cushing syndrome
	Hyperthyroidism
	Hyperparathyroidism
	Diabetes mellitus
Nutritional	Malabsorptive disease/malnutrition
	Chronic liver disease
	Chronic alcoholism
Drugs	Glucocorticoids
Collagen diseases	Osteogenesis imperfecta
	Ehlers-Danlos syndrome
	Marfan syndrome
Others	Rheumatoid arthritis
	Multiple myeloma
	Prolonged immobility
	Mastocytosis

The major risk factors have been traditionally considered to be four (Table 24.1), although the recent introduction of tools to calculate absolute risk has reduced the value of this analysis, since every relevant factor, and not only those in Table 24.1, is introduced and given the relative weight in the risk calculation. Age is a central risk factor, something of particular importance in the clinical management of women with PMO. Also important in anamnesis, potential causes of secondary osteoporosis should be detected (Table 24.2). Some of those are not too prevalent, and therefore there is insufficient information about the size of the relative risk. Therefore, they have not been included in the risk calculator algorithms.

In practical terms, it has been useful to separate risk factors in two groups, attending to whether they are modifiable or not. There is little point in paying attention to those that are unmodifiable, such as age, ethnicity (e.g., lower risk in blacks as compared with Caucasians), female gender, significant loss of height (4 cm at least) [25], etc., but preventive measures may be taken against the modifiable factors, such as sedentariness, smoking, very low body mass index, or very low calcium intake (<500 mg/day, see below).

24.3.1.1 Predictive Potential Based on Risk Factors (Risk Calculators)

The increased power of modern epidemiological databases together with the sophistication of advanced computational statistics has allowed for the design of tools

with potential to predict the absolute risk of fracture. The Fracture Risk Assessment algorithm (FRAX) from the World Health Organization (WHO) predicts the 10-year risk of hip fracture or major osteoporotic fracture. FRAX is supported by potent scientific societies, like the IOF or the National Osteoporosis Foundation (NOF).

Despite being customized to different countries or regions in the world, there is a debate about the utility of FRAX. Retrospective and some prospective studies have suggested that the predictive potential in practice is limited, specifically in some countries [26, 27]. Part, but not all, of the debate moves around the threshold for intervention. Even so, the low sensitivity to predict fracture of the imaging techniques (e.g., densitometry; see below) makes FRAX a very helpful instrument [28]. Moreover, one key factor of FRAX has been the rehabilitation of clinical risk factors, age mainly, in the decision-making.

24.3.2 Radiological Imaging

Several radiological techniques have been developed to provide information useful in the assessment of the strength of the skeleton.

The most popular technique at present is dual X-ray absorptiometry (DXA), which measures bone mineral density (BMD) at both the spine and the hip (Fig. 24.2), and that has been taken by the WHO as the gold standard to diagnose osteoporosis (hip *T*-score ≤ -2.5). Moreover, DXA may be used to monitor the response to treatment, although with some limitations because accuracy is poor with variations of as much as 7% in repeated measures.

The basis of DXA utility resides in that the absorption of X-ray is very sensitive to the content of calcium in the tissue. Modern densitometry machines may measure both areal and volumetric densitometries, but areal densitometry is preferred because it accounts for some two thirds of bone strength. In this way the technique offers a quantitative parameter that directly relates with the risk of fracture. Moreover, recent technical developments have improved imaging so that deformities of the vertebral bodies may be identified and conventional X-ray assessments are no longer necessary.

24.3.2.1 DXA in Practice

The simplicity of DXA use and the low radiation of the technique invite to perform universal screening in women as soon as they enter menopause. However, and for general population, that should never be done before the age in which a minimum fracture risk already exists, and this occurs at 65 years. This is a general *dictum* of most scientific societies, such as the US Preventive Services Task Force (USPSTF) (level B recommendation) [29]. This is not the case, however, in women with any risk factor, as those mentioned in Tables 24.1 and 24.2.

Another important point concerning DXA refers to the potential for monitoring, which may apply to women with or without treatment. The limited accuracy of the technique has been already mentioned, and substantial changes need to have occurred to get a reliable report. Of course, this also depends on the speed of loss,

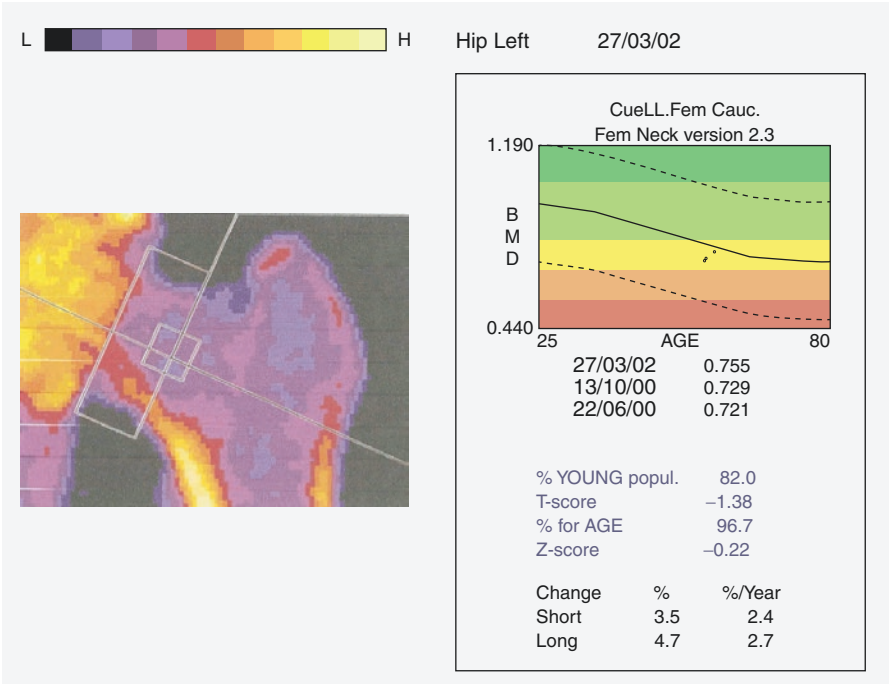

Fig. 24.2 Standard report of a densitometry scan of the hip. The *X*–*Y* diagram shows BMD in the *Y*-axis (g/cm^2) and age (years) in the *X*-axis. The middle line represents the mean population value as a function of age. Scans at different dates may allow for follow-up studies

but it seems wise to wait for at least 1 year before performing a second DXA, and, ideally, the interval should extend to 2 years. This will help to prevent diagnostic errors and to reduce unnecessary anxiety in women.

24.3.2.2 Imaging Alternatives to DXA

The poor accuracy of DXA in monitoring BMD evolution and the issue of bone quality motivated a National Institutes of Health consensus conference, which urged to search for imaging alternatives [30].

High-resolution peripheral quantitative computed tomography (HR-pCT) provides purely trabecular BMD, which may be more sensitive to therapy. Also, there is already experience, although most in the research setting, which separately measures trabecular and cortical bone architecture with HR-pCT (Fig. 24.3). Translating this information into assessment of bone quality remains as a challenging issue at present.

There is experience with other techniques. Quantitative ultrasound has been extensively investigated due to the low cost and the easiness to use in the office. Much of the work has been performed on the calcaneus, with the speed and attenuation of sound as principal variables. Quantitative ultrasound has demonstrated

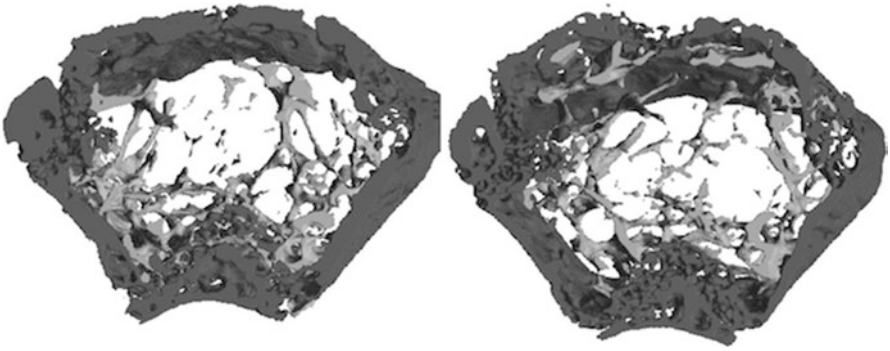

Fig. 24.3 A micro-CT figure of mice bones shows that the technique offers clear separation between cortical and trabecular bones. Information may be obtained about a list of parameters concerning the trabecular network, such as number of trabeculae, trabecular thickness, etc.

predictive potential of fragility fractures that, together with the poor correlation with BMD, has been taken to claim that the technique is measuring parameters related with bone quality. However, several insufficiencies, like a monitoring performance even worse than that of DXA and the variety of techniques and parameters, moved the International Society of Clinical Densitometry to prioritize DXA as the reference technique [31].

Magnetic resonance is attractive because of the lack of radiation. The 3T technology has been shown to offer enhanced trabecular bone architecture imaging but mainly restricted to peripheral bones. Efforts to get quality information from the proximal femur are still challenging. There is much hope in the potential of this technology, although the actual state is far from becoming competitive with the easy-to-perform DXA [32].

Trabecular bone score (TBS) is a new technological procedure that aims at giving information about bone texture and microarchitecture. The method consists of software that works on the spine imaging provided by some specific densitometers. The understanding is that the standard DXA offers a global assessment of bone density in the area of interest, while TBS would be capable of distinguishing the irregularities of the density map, something that would be close to the bone microarchitecture. It seems that TBS might improve the fracture risk prediction of conventional DXA in specific cases, like, for example, diabetes [33, 34] or women with osteoarthritis [35], but the experience is still short [36].

24.3.3 Biochemical Markers

The metabolic activity of osteoclasts and osteoblasts releases different molecular products that should be accessible for measurement in blood or urine. Since both types of cells are coupled at the BMU, markers of either cell should work as reliable indicators of the resorption activity. Ideally, bone markers should form the most

appropriate approach to assess resorption, with the added advantage of being real time. However, important conditions are specificity of cell type to prevent contamination from other sources and an appropriate correspondence between resorption and the cellular output of the marker in question.

Much has been advanced in this field in the latter years. Although there is a list of candidates, scientific societies like the IOF or the Federation of Clinical Chemistry and Laboratory Medicine have selected the degradation products of type I collagen, both the carboxy (CTX-1) and the amino-terminals (NTX-1) like the most consolidated option for assessing resorption. Formation markers have been less popular, but again, the procollagen type I propeptide, an osteoblast-derived protein, is preferred, and more specifically the N-terminal fraction, PINP, has been selected in most studies.

24.4 Prevention and Treatment

Osteoporosis shares with other NCD a long subclinical period. There is, therefore, room for risk reduction strategies before the incidence of a clinical event, in this case the fragility fracture. Since age is a decisive risk factor and the peak prevalence of fractures occurs in older subjects (80 years for hip fracture), PMO offers a splendid opportunity for risk reduction. Lifestyle plays a crucial role at all ages, and, when risk is sufficiently high, the pharmacological option should be at hand.

24.4.1 Lifestyle

Osteoporosis is not different to other NCD, and omission of toxics (essentially smoking and excessive alcohol), balanced nutrition, and physical activity (PA) are the three pivotal measures.

Smoking has a detrimental dose-response effect on bone metabolism. The third National Health and Nutrition Examination Survey, 1988–1994 (NHANES-III), already proved an inverse association between cotinine, a metabolite of nicotine, and BMD in 14,060 subjects, men and women [37]. There are also data about fractures. The analysis of data from the Women's Health Initiative study concluded that tobacco use was an independent risk factor for fragility fracture [38].

24.4.1.1 Nutrition

Protein

This field has advanced dramatically in recent years. From calcium, which has been a common variable in clinical guides, attention has been shifted to protein intake. European investigators have found how decisive is the diet with adequate protein intake to accomplish a good bone capital during childhood and adolescence [39]. This mechanism reproduces at more advanced age, since increase in diet protein is followed by a lower bone loss and a reduction of fragility fractures [40–42].

Calcium

A sufficient intake of calcium has been claimed in the vast majority of clinical guides. There is evidence showing that the consumption of calcium is followed by an increase in the blood circulating levels, which induces a reduction in the levels of parathyroid hormone (PTH). PTH is one main regulator of serum calcium, a crucial second messenger, so that when the circulating level of calcium decreases, PTH mobilizes calcium from the skeleton, the main reservoir. Vitamin D modulates the efficiency of intestinal calcium absorption. The daily recommended amount of calcium, which oscillates between 1000 and 1500 mg depending on the individual profile, has been fine-tuned in more recent publications [43]. Because data from populations with very low calcium intake show good bone health, and because increases in calcium intake may perhaps entail some risk, scientific societies of the UK like the National Osteoporosis Society recommend a daily amount slightly lower (700 mg) [44]. This agrees with experimental studies showing that the balance between intake and losses of calcium in the body moves around 700–750 mg [45].

The caution with excessive calcium ingestion is reinforced by data showing that the risk of urolithiasis [46], cardiovascular disease [47, 48], or even fractures [49] might increase. This evidence comes from observational studies in most cases, but because calcium supplementation, even when administered with vitamin D, has no [50] or a very limited protective effect, and only with older, institutionalized adults [51], discretion in recommending calcium intake is mandatory.

24.4.1.2 Physical Activity

There are two potential strengths in favor of the preventive role of PA, the reduction in the propensity to fall and the improvement of the density and quality of bone. Data in the latter years have supported those two assumptions.

The regular practice of PA is supposed to increase the neuromuscular coordination that should improve equilibrium. The expected reduction in falls has been reported [52].

The other strength of PA resides in the expected increase of bone resistance as a result of the response to the mechanical overload brought with exercise. The experiences of microgravity environments, as that of astronauts in space travels, have been eloquent. Increased bone resorption, in the presence of unchanged rates of bone formation, rapidly leads to net loss of bone mass [53]. Moreover, an association exists between body mass index and bone mass, and it is brown fat, which is promoted as a result of PA, the variant more clearly related with BMD [54].

Clinical studies support the above data. Both BMD data with DXA, ultrasound attenuation in the heel, and bone quality as measured by HR-pCT have found improvement of different sizes with PA during childhood and adolescence [55] or in young women [56, 57]. Protective effect has been found also in the case of postmenopausal women [58] although some discrepancies exist in what concerns the type of exercise, namely, resistance exercise vs. resistance training combined with high-impact or weight-bearing exercise [59].

The prospects in what refers the risk of fracture, given the overall benefit in bone resistance plus the expected reduction in falls, should be encouraging. This has been

indeed the conclusion of 1 meta-analysis including 22 cohort studies, which found an inverse association between PA and total fracture risk, especially hip and wrist fractures [60]. However this position is not unanimous [61], so further research is still required.

24.4.2 Hormone Therapy

The decline in the production of estrogens is the key factor in PMO. Moreover, this hormonal loss produces symptoms and quality of life deterioration in many women. Consequently, the administration of estrogens seems the most appropriate intervention to revert the lost benefits.

In the specific area of PMO, there is a wealth of studies showing how estrogens (or hormone therapy, HT, in a more general denomination that includes the option of combination with progestogens when women have a uterus) stop the process of menopausal bone loss and even recover the accumulated losses. But even more, HT reduces the risk of fragility fracture, as shown in the WHI study [62]. These data are important because HT demonstrated anti-fracture efficacy even in general, nonselected population.

Hormones do not seem to have a significant residual effect after treatment withdrawal, with most of the BMD gain being lost in 1–2 years [63].

Despite so, the present indication of HT is only the treatment of symptoms associated with menopause. The unfavorable balance resulting from the increase in breast cancer risk or cardiovascular disease was the trigger of this limitation. Even so, the European Medicines Agency accepts the use of HT for the "prevention of osteoporosis in postmenopausal women at high risk of future fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of osteoporosis" [64].

It cannot be discarded that a better knowledge of the actions of HT at either the breast or the vasculature might change that restricted position in the future.

24.4.3 Pharmacological Management

One key point that needs to be insistently stressed is that the purpose of treating osteoporosis is the reduction of the risk of fracture. The target should be fracture, and not BMD, although it is well known that both are related. That means that in women with low BMD who have a low risk of fracture, pharmacological treatment should not be used. Most women living the postmenopausal period only require lifestyle habits to reduce the risk of osteoporosis. Some of them will already have densitometric osteoporosis, but as far as age is not advanced, the risk is probably low and lifestyle should keep being the best recommendation. Of course, drugs will have to be used in some women because the fracture risk is high enough. There are several treatment options.

24.4.3.1 Selective Estrogen Receptor Modulators (SERMs)

SERMs define a few families of compounds with affinity for the ER. However, the molecular differences with estrogens determine that binding to the receptor is followed by an array of actions moving between the extremes of pure agonism and absolute antagonism. These properties depend on the binding molecule but also of the target tissue [65]. That property converts SERMs in very attractive molecules, with the potential to achieve estrogenic or antiestrogenic effects a la carte.

Raloxifene and bazedoxifene are the two SERMs approved for treating osteoporosis. The pivotal studies have shown that both raloxifene and bazedoxifene achieve increases in BMD and reduce the risk for vertebral but not hip fractures [66, 67]. There was a protective effect against nonvertebral fractures in corresponding post hoc analyses [67, 68].

Raloxifene has demonstrated reduction in the risk for breast cancer [69], although as for estrogens and also for bazedoxifene, an increase in deep vein thrombosis was apparent in the pivotal studies.

Bazedoxifene has demonstrated a more antagonistic effect than raloxifene in endometrium, and this interesting property has been taken as the basis for development of new formulations in which bazedoxifene is mixed with estrogens (conjugated equine estrogens, 0.45 mg/day) to counterbalance the oncogenic potential of estrogens on the endometrium. The potential advantage of bazedoxifene against progestogens is that it probably deactivates their oncogenic potential in the breast. There is still insufficient information about endometrial safety of the estrogen-bazedoxifene combination.

Health economy analyses have shown acceptable cost-effectiveness of SERMs [70, 71]. SERMs are a good option for starting treatment in PMO, because they are effective in vertebral fracture, which is the most prevalent in not such older women. Moreover, a reduction of breast cancer risk needs to be considered as an additional benefit. So, selection of a SERM and, at an age in which hip fracture may be a real threat, the option of an alternative may be adequate [72].

24.4.3.2 Other Anti-resorptives

Bisphosphonates

Bisphosphonates are a family of molecules that share a high affinity by the calcium salts in the bone (hydroxyapatite), where they remain for years. Once the area is digested by osteoclasts as a result of the remodelling process, bisphosphonates enter into the cytoplasm and create a series of dysfunctions leading to osteoclast apoptosis. Nitrogen-containing bisphosphonates (alendronate, risedronate, ibandronate, pamidronate, and zoledronate) are particularly potent in that regard [73]. As a consequence, there is a decrease in bone remodelling that stabilizes in a few months.

Some bisphosphonates are administered intravenously when a rapid action is needed because their gastrointestinal absorption is poor. The oral administration

may be daily, weekly, or monthly. According to meta-analyses of the pivotal studies, the anti-fracture efficacy moves around relative risk 0.4–0.6 for vertebral fracture and 0.6–0.8 for nonvertebral fracture [74]. Ibandronate has not provided data about hip fracture.

Safety is an important issue. Osteonecrosis of the jaw (ONJ) and atypical femoral fracture have been reported, usually in oncological individuals using high dosages but also in long-term users. A systematic review of the International Task Force on Osteonecrosis of the Jaw concluded that the incidence oscillates between 0.001 and 0.01%, which is ten times more than that in untreated general population [75]. The association with atypical femoral fractures comes from observational studies, although official agencies as EMA have recognized them as an adverse effect [76]. The absolute figures of these fractures are very low when compared with the typical ones, suffered by the untreated population. This should not be, therefore, an argument to refrain from treating when indicated [77].

There is a difficulty with adherence of bisphosphonates, and this impacts effectiveness. It is estimated that there is a global increased risk of 28% in hip fracture and of 43% in vertebral fracture as a consequence of the poor adherence to bisphosphonates [78].

Denosumab

The first biological option for treating osteoporosis is denosumab, a totally human antibody against RANKL. The Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) is the pivotal study that demonstrated a 68% reduction in vertebral fractures, a 20% in nonvertebral fractures, and a 40% in hip fractures with denosumab [79]. The anti-resorptive power of denosumab is higher than of bisphosphonates, as shown in comparative studies with alendronate [80, 81].

Adverse effects are not different to bisphosphonates in what refers to the drastic reduction in bone remodelling, so ONJ [82] and atypical femoral fractures have been described as well, although in less number, possibly because of the more recent appearance of denosumab in the market [83]. Denosumab, in turn, bears a specific group of adverse events, which relate with the role of RANKL as an immunological agent. A higher susceptibility to infections, such as those of the urinary tract, cellulitis, etc., is observed [84].

Adherence seems to be better for denosumab than for bisphosphonates [85] something subsequently suggested by a retrospective 2-year assessment [86]. The optimal use of denosumab has been presented in a position statement of the European Menopause and Andropause Society (EMAS) [87]. Essentially, denosumab is most appropriate for women with PMO and high risk of fracture so that it should be used as a first-line option with women of advanced age or with risk of hip fracture.

24.5 Conclusion

Osteoporosis should be addressed from the infancy, but menopause is a crucial moment for women. It is important to take care of the skeleton along the whole life by adhering to a healthy lifestyle, which is particularly so at menopause and the years that follow. This is appropriate and sufficient for most women. Whether HT is prescribed because of menopausal symptoms, additional benefit is expected for the bones. When fracture, and not just low BMD, is a risk of enough size, osteoporotic medications should be considered. SERMs may be a good option during the years in which vertebral fracture is a threat. Moreover, SERMs protect breast and have no risk of ONJ or atypical femoral fractures. Then, when age adds sufficient risk, bisphosphonates may be of help, and also denosumab should enter as an option in cases of higher risk or when bisphosphonates are not eligible.

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Anabolic Agents for the Treatment of Postmenopausal Osteoporosis

25

Salvatore Minisola

25.1 Osteoporosis Definition and Its Burden

Osteoporosis is characterized by low bone mass (easily quantified by bone mineral density (BMD) measurement) and qualitative structural decay of bone tissue (not easily evaluated by current techniques); therefore, both quantitative and qualitative skeletal alterations lead to increased bone fragility which results in fractures [1]. Mistakenly often considered an inevitable consequence of aging, osteoporosis with its ominous consequences of fractures represents a substantial and ever-growing burden on healthcare systems in many countries around the world [2].

It has been estimated that ten million Americans over the age of 50 have osteoporosis, so that about 1.5 million fragility fractures occur each year [3]; another 34 million Americans are considered at risk of disease. Concerning the economic burden, the cost has been estimated to be around $17.9 billion per year. In European Union (EU), a report estimated that in 2010, 6.6% of men and 22.1% of women aged 50 years had osteoporosis, while the number of fragility fractures was estimated to be 3.5 million. The annual direct costs attributable to fracture treatment in the EU are approximately € 24 billion. However, if we consider indirect costs such as long-term care and fracture prevention therapies, this figure rises to € 37 billion per year [4, 5].

Another important factor not commonly taken into consideration is represented by the deterioration of quality of life of those incurring in a fracture event [6, 7].

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25.2 Standard Therapies for Osteoporosis

The mainstays of treatment (and prevention) of osteoporosis are represented by fall avoidance [8], weight-bearing exercise [9], and adequate calcium and vitamin D intake [10–12]. These general measures can be effective [13] especially in elderly subjects confined to nursing home and vitamin D deficient; however, medical therapy is needed when a previous fracture has already occurred.

Pharmacological therapy is aimed at decreasing the risk of fracture, mainly correcting the imbalance between bone resorption and formation at the level of bone remodeling units [14]. Indeed, there are a number of available drugs that have been shown to reduce the risk of future fractures based on both experimental and clinical data. Therefore, osteoporosis should be no more viewed as an inevitable consequence of aging. These pharmacological agents can be broadly divided into two subgroups: those decreasing bone resorption (acting on osteoclasts) and those increasing skeletal formation (acting on osteoblasts).

Antiresorptive agents [such as estrogens, bisphosphonates, selective estrogen receptor modulator, and the monoclonal antibody to receptor activator of nuclear factor kappa-B ligand (denosumab)] reduce the rate of bone resorption followed by a decrease in the rate of bone formation due to the coupling between these two processes; after about 6 months, a new equilibrium between the two phases of bone remodeling is reached although at a lower rate. These changes are associated with increases of bone mineral density and maintenance of some improvement of structural and material properties of bone leading to reduction of bone fragility. Long-term increases in bone mass are largely secondary to an increase in mineralization density that is a consequence of reduced bone turnover [15].

25.3 Anabolic Therapies

Anabolic drugs hold the ability to increase bone mass to a greater extent than traditional antiresorptive agents.

25.3.1 Teriparatide

The first available drug licensed as an anabolic treatment for osteoporosis was represented by parathyroid hormone (PTH) 1-34 (teriparatide). It stimulates bone formation, particularly in those skeletal segments rich in trabecular bone such as vertebrae, thus reducing both vertebral and non-vertebral fractures [16]. PTH improves bone quality and strength by inducing more favorable changes in microarchitectural features such as connectivity, density, and geometric properties compared to antiresorptive agents [17, 18].

In addition, owing to its ability to primarily stimulate bone formation, PTH 1-34 should be considered a first-line therapy in glucocorticoid-induced osteoporosis, which is associated with reduced bone formation [19, 20]. Studies comparing

antiresorptive drugs vs. PTH 1-34 have indeed demonstrated the superiority of teriparatide both in terms of improvements in bone strength [21] and reduction in vertebral fractures [22].

A recent trial (VERO study) evaluated for the first time the anti-fracture efficacy of teriparatide compared to risedronate in 1680 postmenopausal women with at least two moderate or one severe vertebral fracture and a bone mineral density *T*-score of less than or equal to −1.0. At 24 months, new vertebral fractures occurred in 28 (5.4%) of 680 patients in the teriparatide group and 64 (12.0%) of 680 patients in the risedronate group (risk ratio 0.44, 95% CI 0.29–0.68; $p < 0.0001$). Clinical fractures occurred in 30 (4.8%) of 680 patients in the teriparatide group compared with 61 (9.8%) of 680 in the risedronate group (hazard ratio 0.48, 95% CI 0.32–0.74; $p = 0.0009$). Non-vertebral fragility fractures occurred in 25 (4.0%) patients in the teriparatide group and 38 (6.1%) in the risedronate group (hazard ratio 0.66; 95% CI 0.39–1.10; $p = 0.10$). This was the first head-to-head study between an antiresorptive agent (risedronate) and an anabolic agent (teriparatide) that shows that the risk of new vertebral and clinical fractures is significantly lower in patient receiving teriparatide than in those receiving an antiresorptive agent [23]. Most importantly the anti-fracture efficacy of teriparatide was consistent in a wide range of patients setting, including treatment-naïve and previously treated risedronate patients [24].

It is important to keep in mind that, when we use teriparatide (which primarily stimulates bone formation), an increase in osteoclastic activity can be observed after a certain period; this foretells the closure of the so-called anabolic window, thus limiting further accrual of bone mass [25]. When treatment with teriparatide is stopped, there is a rapid decline in bone mineral density. Therefore, it is desirable to administer an antiresorptive agent following the completion of the treatment with teriparatide, so that gains obtained are maintained [26].

25.3.2 Abaloparatide

This is a 34-amino acid peptide which incorporates critical N-terminal residues, shared by PTH and PTH-related protein (PTHrP) followed by sequences unique to PTHrP. Preclinical studies have clearly demonstrated that both peptides activate the same receptor; however, their kinetics are different determining dissimilar responses. It has been hypothesized that the two molecules favor different receptor conformations with abaloparatide binding with high affinity but only for a short period of time, thus limiting the duration of signaling compared with teriparatide.

Miller and coworkers [27] reported the efficacy and safety of abaloparatide administered in a daily dose of 80 μg subcutaneously for 18 months. A total of 2463 patients were initially randomized and 1901 completed the investigation. Women were subdivided into three groups receiving subcutaneous injection of placebo, abaloparatide 80 μg, or open-label teriparatide 20 μg, respectively. In the modified intention-to-treat population analysis (defined as the intention-to-treat analysis in participants who had both pretreatment and post-baseline X-rays), new vertebral fractures occurred less frequently compared with placebo (0.58% vs. 4.22%; RR

0.14, 95% CI 0.05–0.39, $p < 0.001$). In the teriparatide group, new morphometric vertebral fractures were detected in six women (RR 0.20, CI 0.08–0.47, $p < 0.001$ vs. placebo). Somehow similar results were obtained considering non-vertebral fractures; the Kaplan-Meier estimated event rate for non-vertebral fracture was lower with abaloparatide in respect to placebo group [2.7% in patients treated with abaloparatide vs. 4.7% in placebo-treated patients; hazard ratio, 0.57 (95 CI 0.32–1.00) $p < 0.049$]. There were not significant differences in respect to teriparatide group (HR 0.79, CI 0.43–1.45, $p = 0.44$), even though the Kaplan-Meier estimated event rates in this last group were not significantly different from placebo-treated patients (HR 0.72, CI 0.42–1.22, $p = 0.22$).

Considering bone mineral density, it is important to note that mean improvements with abaloparatide were significantly greater than those with teriparatide at the total hip and femoral neck at 6, 12, and 18 months ($p < 0.001$). Regarding lumbar spine there was a statistical significant difference ($p < 0.001$) at 6 and 12 months.

It is also important to underline the changes in bone turnover markers in patients treated with abaloparatide or teriparatide. Indeed, there was a similar increase of serum procollagen type I N-terminal propeptide (P1NP) and a less increase in serum carboxy-terminal cross-linking telopeptide of type I collagen (β-CTX) in abaloparatide-treated patients compared to those treated with teriparatide. This finding might be ascribed to the differential binding to PTH type 1 receptor, thus determining a more transient stimulation and lower expression of osteoblast-derived RANK-ligand. This very initial uncoupling of bone formation and resorption may justify the very rapid increase of bone mass with consequent rapid protection against future fracture. This could be particularly important in the immediate period after a fracture occurs; indeed a number of studies have documented that the risk is higher soon after the initial event and then declines with time [28].

Finally, concerning safety, there were more withdrawals from the study in abaloparatide-treated group (9.9% vs. 6.8% in the teriparatide and 6.1% in the placebo groups, respectively) because of adverse events mainly represented by nausea, dizziness, headache, and palpitations. This negative aspect, if conformed in future studies, implies a stringent medical surveillance.

Data from this original investigation have been subsequently reanalyzed, demonstrating that abaloparatide maintains its effect in postmenopausal women with osteoporosis, regardless of age, previous fracture, or basal BMD value [29].

The US Food and Drug Administration (FDA) approved abaloparatide for the treatment of osteoporosis in 2017. Approval by the European Medicine Agency (EMEA) is pending.

25.3.3 Romosozumab

An important component of the Wnt signaling pathway, a well-known metabolic route to drive osteoblast proliferation and commitment, is represented by sclerostin. This is a glycoprotein mainly secreted by osteocytes (and to a lesser extent by cementocytes and mineralized hypertrophic chondrocytes) which is a potent

inhibitor of osteoblastogenesis. Sclerostin secreted from osteocytes reaches the bone surface through the canaliculi where it binds to co-receptors LRP5 and LRP6. It prevents co-receptor localization with frizzled protein and Wnt, thereby decreasing osteoblastogenesis and bone formation [15, 30].

The link between sclerostin and bone formation is very well illustrated by two rare genetic decreases. Both sclerosteosis (due to a less of function mutation) and Van Buchem disease (caused by a deletion downstream of sclerostin gene, which includes sclerostin protein) are characterized by high bone mass. In this context, some scientists suggested that the effect of parathyroid hormone therapy in humans is mediated, at least in part, by a decrease in serum sclerostin levels [31, 32]. In addition, genetic studies have shown that polymorphism in sclerostin gene is associated with low bone mineral density in older men and women, further emphasizing a causal link between modified sclerostin expression and bone mineral density.

These observations led to explore the pharmacological inhibition of sclerostin by a monoclonal antibody in various animal models of bone disease. Data obtained in experimental animals showed a consistent effect of sclerostin antibody (from now on called romosozumab) to increase bone formation, bone mass, and strength at various skeletal sites [33].

Romosozumab has been evaluated in a double-blind study at a monthly dose of 210 mg versus placebo in more than 7,000 postmenopausal osteoporotic patients [34]. At 12 months of treatment, romosozumab was associated with a risk of new vertebral fracture that was 73% lower than the risk observed in the placebo group (16 of 3321 patients in the romosozumab group vs. 59 of 3322 in the placebo group; risk ratio 0.25, confidence interval 0.16–0.47, $p < 0.0001$). Non-vertebral fractures had occurred in 56 patients of the romosozumab group compared with 75 in the placebo group ($p = 0.10$).

After 12 months of romosozumab therapy, the positive percent changes of BMD therapy were 13.3, 6.9, and 5.9 at lumbar spine, total hip, and femoral neck, respectively.

Concerning markers of bone turnover, the serum levels of procollagen type I N-terminal propeptide peaked at day 14, while the levels of β-CTX decreased reaching the maximum decline at day 14 and then remained below the level of placebo group during the whole treatment period.

Regarding safety profile, all adverse events were balanced between active treatment and placebo.

Romosozumab has been also investigated in another trial in which 4093 postmenopausal women with osteoporosis and a fragility fracture were randomly assigned to receive monthly subcutaneous romosozumab or weekly oral alendronate for 12 months, followed by alendronate for 12 months in both groups. After 24 months, new vertebral fractures occurred 6.2% in the romosozumab-to-alendronate group compared with 11.9% in the alendronate to-alendronate group (48% lower risk of new vertebral fractures in the romosozumab-to-alendronate group). There was a 27% lower risk of clinical fractures and 38% lower risk of hip fractures [35].

During the first year of treatment, serious cardiovascular adverse events were observed more often with romosozumab than with alendronate, a finding not observed in the previous trial utilizing this humanized monoclonal antibody [34]. This could be theoretically ascribed to the reported involvement of sclerostin in aortic vascular smooth muscle remodeling or calcification. Some have also suggested that the comparison drug (alendronate) may be cardioprotective, so that the rate of cardiovascular events in the romosozumab group could be relatively higher than expected. Owing to these concerns, approval for romosozumab remains pending by both FDA and EMEA.

25.4 Practical Considerations for Anabolic Drugs on the Market

Before starting the administration of an anabolic agent, we must exclude possible causes of secondary osteoporosis, because in this case, the treatment is not curative (the same applies to antiresorptive agents). Both teriparatide and abaloparatide should not be administered in hypercalcemic patients and those at possible increased risk of osteosarcoma (i.e., patients with Paget's disease, undergoing radiation therapy, or with bone metastases) or in those with increased alkaline phosphatase values of unknown origin. It is also important to exclude at the beginning of therapy raised values of endogenous parathyroid hormone, because this represents a contradiction, on theoretical grounds, to the exogenous administration of the hormone. Since many cases of secondary hyperparathyroidism are linked to hypovitaminosis D, it is important to test and replenish the patient in this particular situation [36, 37]. As both teriparatide and abaloparatide might exacerbate hypercalciuria, it is important to evaluate, in basal conditions, the 24-h urinary calcium excretion. Once the therapy has been started, there are no official guidelines on how to biochemically monitor the patient for serum calcium and uric acid or for 24-h urinary calcium excretion. In any case serum calcium should be obtained 24 h after the last drug injection. If hypercalcemia is found, the first step is a reduction in the amount of calcium and vitamin D administered. If hypercalcemia persists, drug therapy should be adjusted to every other day [38]. If after this change hypercalcemia persists, it is prudent to discontinue treatment.

25.5 Conclusions

New anabolic drugs will increase the portfolio of compounds available to treat bone fragility; they also represent an opportunity to change our way of prescribing drugs in the most common and threatening metabolic bone disease. Indeed, unlike the majority of chronic diseases, which are generally treated by a combination of drugs, current practice in the field of osteoporosis is the administration of only one drug at a fixed dose. However, the chronic nature of osteoporosis will force doctors to find alternative solutions by adding and switching therapies with the goal of

both prolonging the period of treatment and more importantly avoiding side effects consequent to long-term use of drugs. Therefore, osteoporosis should be no more viewed as an inevitable consequence of aging and estrogen deficiency but as a disease for which we have a wide selection of effective drug treatment with anabolic drugs having a prominent place.

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The Links Between Osteoporosis and Sarcopenia in Women

26

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Highlights

1. Global aging will cause an increase in chronic diseases such as osteoporosis and sarcopenia.
2. The frequent coexistence of both diseases suggests cross talking between bone and muscle.
3. Different studies have shown that bone and muscle produce cytokines that affect the other.
4. The cellular senescence, with its production of cytokines, would be caused by musculoskeletal aging.
5. Improving lifestyles and decreasing senescent cells should be the therapeutic objective.

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26.1 Introduction

26.1.1 Epidemiology

A substantial and increased proportion of morbidity and mortality due to chronic disease occurs in people aged 60 years and older. Within the leading contributors to disease burden in older people are the diseases of the musculoskeletal system, being responsible for 7.5% of the total global burden [1]. There is an emphasis on maintaining an active lifestyle to reduce the risks of obesity, cardiovascular diseases, cancer, osteoporosis, and diabetes in older people. However, musculoskeletal conditions profoundly limit the ability of people to make these lifestyle changes.

In this group of diseases, osteoporosis and sarcopenia are two disorders that seriously impair the health of older women. Currently it is estimated that over 200 million people worldwide suffer from osteoporosis. Approximately 30% of all postmenopausal women have osteoporosis in the United States and in Europe. In the different Latin American countries, between 8 and 22% of women over 50 have osteoporosis at the level of the femoral neck [2]. At least 40% of these women will sustain one or more fragility fractures in their remaining lifetime. With modest assumptions concerning secular trends, the number of hip fractures could range between 7.3 and 21.3 million by 2050. The major demographic changes will occur in Asia [3]. The socioeconomic impact of hip fractures will increase markedly throughout the world, and there is an urgent need to develop preventive strategies, particularly in the developing countries.

Loss of muscle mass and strength, which in turn affects balance, gait, and overall ability to perform tasks of daily living, is hallmark sign of sarcopenia. Prevalence increased from 13–24% in persons under 70 years of age to >50% in persons over 80 years of age and was slightly greater in Hispanics than in non-Hispanic whites. Globally, with a conservative estimate of prevalence, sarcopenia affects >50 million people today and will affect >200 million in the next 40 years. Sarcopenia represents an impaired state of health with a high personal toll consisting in mobility disorders, increased risk of falls and fractures, impaired ability to perform daily activities, disabilities, loss of independence, and increased risk of death [4, 5].

26.1.2 Osteoporosis and Sarcopenia: Are They Two Different Diseases?

A growing evidence shows that osteoporosis and sarcopenia share many common pathways including the sensitivity to reduced anabolic hormone secretion, increased inflammatory cytokine activity, and anabolic or catabolic molecules released by the skeletal muscle or by the bone cells which affect the other tissue (i.e., myokines and osteokines). Studies using animal models in the setting of hind limb unloading or botulinum toxin (Botox) injection also reveal that muscle loss can induce bone loss. Moreover, muscle-derived factors such as irisin and leptin can inhibit bone loss induced by unloading [6]. Therefore, it is not surprising that, although osteoporosis

and sarcopenia are different nosological entities, the coexistence of both diseases in the same individual is not uncommon. The association of these two diseases has led to the development of the term "osteosarcopenia" to diagnose those patients suffering from both diseases. Actually, osteosarcopenia has been defined as the presence of sarcopenia and osteopenia or osteoporosis. Endocrine disorders, mainly diabetes, abnormal thyroid function and low levels of vitamin D, sex steroids, growth hormone (GH) and insulin-like growth factor-1 (IGF-1), malnutrition, obesity, and the use of corticosteroids are also associated with osteosarcopenia [7].

The prevalence of osteosarcopenia varies with age, sex, and country. A study of community-dwelling Chinese elders older than age 65 found prevalence of osteoporosis-sarcopenia in 10.4% of men and 15.1% of women [8]. Studies in Australian persons with previous history of falls reported that 40% of this high-risk population had osteopenia-sarcopenia. Being a female; having a history of osteoarthritis, oophorectomy, or cancer; and impaired mobility were risk factors for osteosarcopenia in this Australian cohort [9]. Data presented by Campodónico in the Congress of the Argentine Association of Menopause in 2016 shows that osteosarcopenia is found in 9.7% of Chilean women between 35 and 69 years. Although the prevalence of osteosarcopenia may be different in each study group, its diagnosis has significant clinical implications. Patients with osteosarcopenia are more susceptible to occurrence of fragility fracture, poor quality of life, and higher mortality [10].

26.2 Pathophysiology

26.2.1 Role of Cytokines

The biological explanation of the association of low bone mass with sarcopenia is not based solely on the anatomical proximity of the muscle to the bone, but could be based on the cross talk between both organs. Muscle produces cytokines, called myokines, such as myostatin, transforming growth factor beta β, activin, interleukin-6, and monocyte chemoattractant protein-1 (MCP-1) which have a negative influence on bone metabolism. On the other hand, bone produces other cytokines such as sclerostin that decreases muscle mass. Osteosarcopenia would be produced by the interaction of these cytokines with aging, genetic factors, lifestyles, and chronic diseases (Fig. 26.1) [11].

26.2.2 A New Actor: Cellular Senescence

The paradigm of the pathophysiology of osteosarcopenia shown in Fig. 26.1 could be complemented with the concepts of cellular senescence described more than 40 years ago. Fibroblasts in cultures initially undergo rapid division; but afterwards, they lose their capacity for duplication. However, they remain viable in a senescent state for many weeks. Later, cellular senescence was understood as an irreversible arrest of the growth that occurs when the cells undergo aggressions that may be

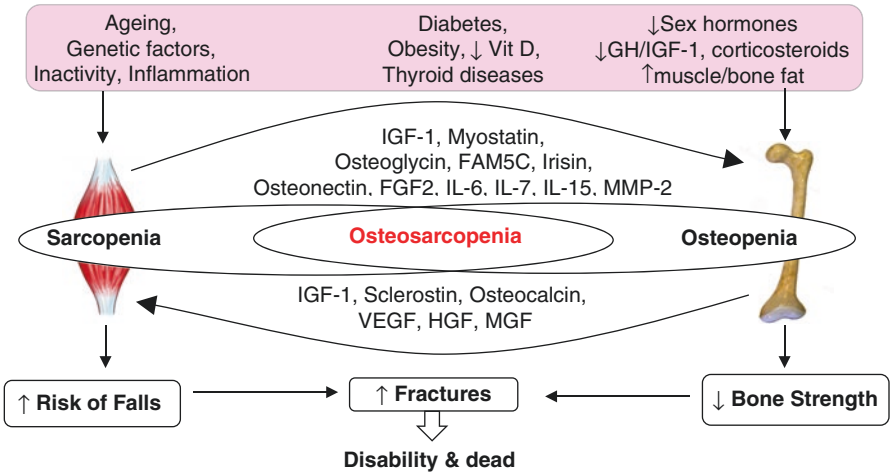

Fig. 26.1 Pathophysiology of osteosarcopenia. *FAM5C* family with sequence similarity 5, member C, *FGF2* fibroblast growth factor 2, *GH* growth hormone, *HGF* hepatocyte growth factor, *IGF-1* insulin-like growth factor 1, *IL* interleukin, *MGF* mechano-growth factor, *MMP-2* matrix metallopeptidase 2, *VEGF* vascular endothelial growth factor, *Vit D* vitamin D. (Modified with permission from: Hirschfeld HP, Kinsella R, Duque G. Osteoporos Int 2017; 28:2781–90)

oncogenic. Therefore, cellular senescence is an important mechanism to prevent the proliferation of potential cancer cells [12].

However, it has become evident that senescence involves more than a simple cessation of cell growth. These senescent cells stop their growth, thus contributing to the depletion of stem cell proliferation and cell aging. In addition to their capacity to suppress tumorigenesis, cell senescence could also promote chronic inflammation associated with aging. Several common molecular pathways have been identified that are associated with both aging and low-grade inflammation. Senescent cells have an altered secretion pattern SASP that comprises a complex mix of factors including cytokines, growth factors, chemokines, matrix metalloproteinases, telomere shortening, and decondensation of pericentromeric satellite DNA (Fig. 26.2). SASP has been related with inflammation that leads to cellular transformation and chronical diseases [13].

In bone, cellular senescence has been studied in animals and human beings. For example, in mice p16Ink4a expression, a senescence marker was significantly higher with aging in osteoblasts, osteocytes B cells, T cells, and myeloid cells. Furthermore, in vivo quantification of senescence-associated distension of satellites (SADS), i.e., large-scale unraveling of pericentromeric satellite DNA, revealed significantly more senescent osteocytes in old compared with young bone cortices [14]. The same study analyzed a panel of 36 established SASP factors (p16INK4a, p16 cyclin-dependent kinase inhibitor 4A, multiple tumor suppressor 1, p21, p51, etc.) in bone biopsies from women, which found that 12 SASP factors were significantly higher in the bone from old subjects compared with young ones.

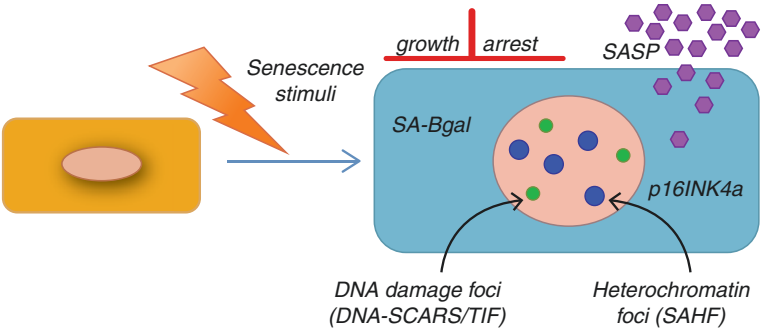

Fig. 26.2 Hallmarks of cellular senescence. *DNA-SCARS* DNA segments with chromatin alterations reinforcing senescence, *p16INK4a* tumor suppressor protein, *SA-Bgal* senescence-associated beta-galactosidase, *SAHF* senescence-associated heterochromatin foci, *SASP* senescence-associated secretory phenotype. (Copy with permission from Rodier F, Campisi J. Four faces of cellular senescence. J Cell Bio 2011; 192:547–56)

In the muscle, stem cell (satellite cells) function is essential for organismal homeostasis, providing a renewable source of cells to repair damaged tissues. Regeneration of skeletal muscle relies on a population of stem cells, which are impaired in very old individuals undergoing sarcopenia. Aged satellite cells lose the repression of locus, which switches stem cell reversible quiescence into a pre-senescent state; upon regenerative or proliferative pressure, these cells undergo accelerated senescence [15].

Therefore, as in the bone, in the muscle there are markers of cellular senescence in the elderly. We could conclude by pointing out that pathologically the central process that joins osteoporosis with sarcopenia is aging, which in the light of current knowledge would be determined by cellular senescence. It could even be suggested that the processes that have been described separately for both diseases, which involve a series of cellular mechanisms mediated by biochemical mediators of cellular metabolism, would be mere intermediaries of a central process that is cellular senescence. In the next few years, we expect to have the answers to these questions.

26.3 Diagnosis of Osteoporosis and/or Sarcopenia

The study of bone mass should be performed with double-photon bone densitometry. The World Health Organization has defined a number of threshold values (measurements) for osteoporosis. The reference measurement is derived from bone density measurements in a population of healthy young adults (*T*-score). Osteoporosis is diagnosed when a person's bone mineral density is equal to or more than 2.5 standard deviations below this reference measurement. Osteopenia is diagnosed when the measurement is between 1 and 2.5 standard deviations below the young adult reference measurement.

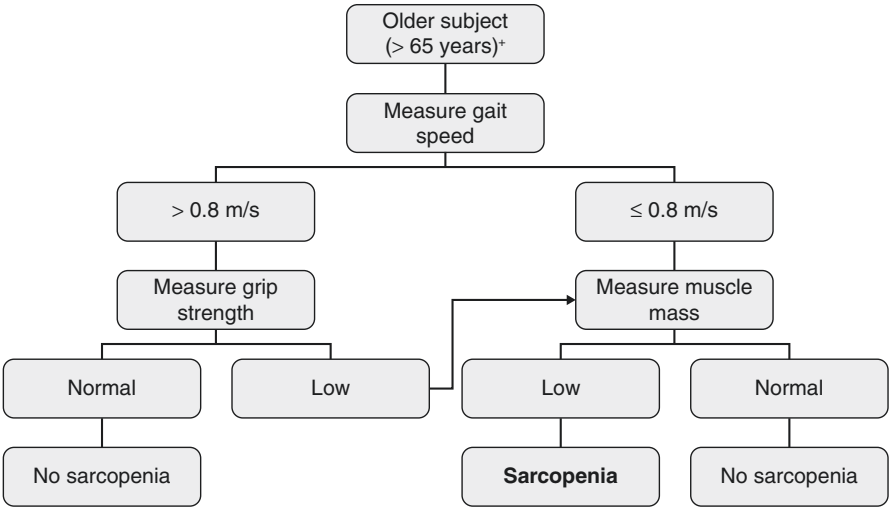

Fig. 26.3 EWGSOP-suggested algorithm for sarcopenia case finding in older individuals. From: Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis. Age and Ageing 2010; 39, 412–23

Sarcopenia is the loss of muscle mass, strength, and function related to aging. The European Working Group on Sarcopenia in Older People (EWGSOP) developed a practical clinical definition and consensus diagnostic criteria for age-related sarcopenia (Fig. 26.3) [16].

The diagnosis of osteosarcopenia includes the presence of osteopenia/osteoporosis and sarcopenia in the same patient.

26.4 Treatment of Osteoporosis and/or Sarcopenia

26.4.1 Treatment Today

At present, the available therapeutic options to treat osteoporosis are mostly limited either to decreasing bone resorption or to increasing bone formation, and both approaches could be associated with serious side effects. Although estrogen replacement therapy is now rarely used for the prevention or treatment of osteoporosis, it continues to be a valid alternative, especially in women with climacteric symptoms. Additional pharmacological options have been developed, including a selective estrogen receptor modulator (raloxifene), bisphosphonates (alendronate, risedronate, ibandronate, and zoledronic acid), a human monoclonal antibody to receptor activator of nuclear factor κ-B ligand (RANKL, denosumab), and the parathyroid hormone. The new preparation of conjugated estrogens/bazedoxifene has been approved by the US Food and Drug Administration to prevent postmenopausal osteoporosis. However, the suspension of these treatments may cause loss of bone

gain obtained with the treatment. This has led to the search for new therapeutic options, without having achieved to date a therapy that satisfies the expectations of physicians and patients. In addition to the mentioned pharmacological options, a diet with an adequate supply of proteins, calcium, and fruits is necessary. Physical activity and the maintenance of adequate levels of vitamin D are essential measures [17].

In relation to sarcopenia, the main causes for the development of this disease are hormonal changes (reduced release of testosterone, estrogen, and growth hormone), nutritional deficiencies, chronic inflammation, and particularly a decrease in physical activity due to a sedentary lifestyle with advancing age. Therefore, treatment must first be focused on reversing these causes. A combination of exercise and high protein intake (≥1.2 g/kg/day), with a relatively high content of animal protein and fractioned throughout the day, has the highest potential in improving different parameters of sarcopenia. In patients with sarcopenic obesity, we must add as an objective the achievement of moderate weight loss [18]. Potential medical treatments of sarcopenia are not evidence based and can be used in selected cases but not in all sarcopenic patients. They include androgenic hormones, estrogens, GH, and angiotensin-converting enzyme inhibitors. A meta-analysis of the estrogen-based treatments indicated that this therapy benefits strength [19]. This could explain why those women taking at least 80% of their hormonal prescriptions in the WHI study showed fewer falls compared with placebo [20]. There is evidence that both exercise training and vitamin D supplementation may benefit musculoskeletal health in older adults, and it is plausible that in combination their effects may be additive [21].

If we think that patients who have a musculoskeletal disease also have a high frequency of other comorbidities, it is not surprising that the elderly use many medications. If we add to this the fact that the elderly population is steadily increasing, we can understand why the use of polypharmacy in this age group has increased markedly in recent years. This is reflected in a study conducted in Scotland showing that between 1995 and 2010, the proportion of adults dispensed ≥5 drugs doubled to 20.8% [22]. Fundamentally, this is because current treatment strategies for all chronic age-related morbidities are disease-specific, with each drug targeting a single disease or condition, e.g., a statin for cardiovascular risk reduction, an antihyperglycemic agent for diabetes, a bisphosphonate for osteoporosis, etc. This inevitably leads to polypharmacy and the resultant problems related to adverse drug interactions and compliance.

26.4.2 Treatment in the Future

The paradigm of cellular senescence allows us to see chronic diseases as a single disease originated in the increase in the population of senescent cells and, therefore, think of a unique therapy for chronic diseases. Theoretically, the decrease in senescent cells or their biochemical mediators could stop the progression of chronic diseases such as osteoporosis and sarcopenia.

An option to decrease cellular senescence is to reduce senescent cells by activating a suicide gene with a drug. Baker using transgenic mice with accelerated aging, which permits inducible elimination of senescent cells (expressing p16Ink4a) upon administration of a synthetic drug (AP20187), showed that reduction of the senescent cell burden ameliorated multiple aging phenotypes in adipose tissue, skeletal muscle, and eyes. P16Ink4a found in these tissues contributes to the acquisition of age-related pathologies [23]. While initial studies used genetic approaches for the killing of senescent cells, recent approaches showed similar effects with both senolytic products (quercetin and dasatinib) and drugs that inhibit the production of the pro-inflammatory secretome of senescent cells (SASP) using a Janus kinase (JAK) inhibitor. The JAK pathway is activated in adipose tissue with aging and plays an important role in regulating inflammatory cytokines produced by senescent cells [24].

Farr et al. treated old mice with bone loss for 2–4 months, with three antiaging interventions, (activation of suicide gene, use of senolytic drugs, and use of SASP blocking drugs), similarly improving bone mass and microarchitecture in both trabecular and cortical bone [25]. On the other hand, the positive effect of estrogens on bone could be due to the decrease in cellular senescence and the increase in osteogenic differentiation. Oophorectomized rats express less special AT-rich sequence-binding protein 2 (SATB2), a protein that regulates cell differentiation in stem cells, which is associated with greater senescence and less osteogenic differentiation. The administration of E2 causes greater expression of SATB2, which is inhibited by blocking the estrogen receptor (ER-β). These results indicate that estrogen prevents osteoporosis by promoting cell differentiation and by inhibiting the senescence of stem cells through a RE-β/SATB2 pathway [26].

Muscle repair and regeneration depends on a population of quiescent stem cells, called satellite cells, and is impaired in very old individuals with sarcopenia. Stem cell function is essential for organismal homeostasis, providing a renewable source of cells to repair damaged tissues. Old age causes an induction of p16INK4a in satellite cells, which translates into a senescent state, a condition in which there is a disorder in the regeneration of muscle fibers and tissue loss. Thus, cell senescence is causally implicated in the intrinsic defective regeneration of sarcopenic muscle. Interestingly, p16INK4a silencing induces rejuvenation of satellite cells, restoring regeneration in geriatric muscles. This suggests that genetic rejuvenation of satellite cells by preventing p16INK4a expression may be an effective way to prevent poor regeneration phenotypes in humans undergoing sarcopenia [14]. As previously mentioned, estrogen decreases cellular senescence, which would explain the results of the Women's Health Initiative Study that indicate that women who adequately complied with hormone therapy had fewer falls, which could reveal better muscle function [17]. The elimination of senescent cells or the inhibition of the production of their SASP (cytokines, metalloproteinase, etc.) in mice and even in humans has shown positive results not only in muscle and bone diseases but also in osteoarthritis, insulin resistance, atherosclerosis, cardiac function, and frailty. All this opens a wide range of possibilities for an eventual use in humans in the coming years [27].

26.5 Conclusion

There is an emphasis on maintaining an active lifestyle to reduce the impacts on obesity, cardiovascular conditions, cancer, osteoporosis, and diabetes in older people. However, musculoskeletal conditions profoundly limit the ability of people to make these lifestyle changes. Therefore, physicians must give special importance to musculoskeletal diseases and understand that they are framed within the problems of aging. Therefore, the presence of osteoporosis or osteopenia forces us to look for other comorbidities that occur with increasing age. Today we have specific therapies for each of them, but it is likely that in the next few years, all these diseases will be confined within the same paradigm, cellular senescence, and we will probably have therapies capable of changing the quality of life of the aging human being.

Conflicts of Interest The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this document.

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Female Sarcopenic Obesity

27

Fidel Hita-Contreras

During the twentieth century, the overall life expectancy of the human population is rapidly increasing worldwide. The global share of older people (aged 60 years or over) increased from 9.2% in 1990 to 11.7% in 2013, and it is predicted that by 2050, it will reach 21.1% of the world population, with 392 million persons aged 80 years or over, more than three times the present [1]. Aging is associated with a progressive loss of tissue and organ function over time [2]. With aging, there is an increased risk of unfavorable changes in body composition, including a decrease in muscle and an increase in fat mass [3].

27.1 Obesity

Overweight and obesity represent worldwide phenomena, which are associated with a risk to develop several chronic diseases such as type 2 diabetes and metabolic syndrome, cancer, rheumatoid arthritis and osteoarthritis, cognitive impairment and dementia, gallbladder disease, and those affecting the cardiovascular system [4, 5]. Besides, both obesity and aging impose various functional limitations on the human body, resulting in a severe burden on quality of life [6], and it is estimated that a 2.3% of global disability-adjusted life years are caused by overweight or obesity [7].

With increasing longevity, the proportion of postmenopausal women is also on the rise. Obesity and central adiposity are major health problems during the postmenopausal years. Estrogen deficiency linked to the menopausal transition has been shown to be associated with the increase in visceral fat mass and waist to hip ratio changing from a gynoid to an android body fat distribution pattern, where fat accumulates on the upper portion of the abdomen instead of the hips [8, 9]. However other authors have reported that chronological aging but not menopause

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was associated with the increase in weight and waist circumference during the fifth and sixth decades of life, while menopausal status was not associated with these changes [10]. As well as hormonal changes and aging, weight gain at midlife has been also attributed to the reduction in energy expenditure of women who have undergone menopause compared with premenopausal women, mainly as a result of the reduction in physical activity [11].

Body mass index (BMI) is the most commonly employed instrument to assess overweight and obesity in global population-based adult research and is assessed by dividing an individual's weight (kg) by her height (m^2). A BMI < 25 kg/m^2 indicates normal weight, 25 ≤ BMI < 30 kg/m^2 overweight, and BMI ≥ 30 kg/m^2 obesity [12]. However, several issues regarding BMI as a tool for obesity assessment have been reported. Its validity to assess obesity status in older adults has been recently questioned [13, 14], especially in older women due to those menopause-related changes in body composition and height decrease associated with kyphosis, shortening of the spinal vertebrae, or thinning of weight-bearing cartilage [15], which may result in BMI overestimation, causing weight category misclassifications. Moreover, BMI has little correlation with adipose mass, which in the second half of life tends to become troncular. To this respect waist circumference has been used to assess abdominal obesity. Overweight status and obesity have been reliably linked to coronary artery disease, congestive heart failure, and gallbladder disease using waist circumference to determine overweight and obese status [16]. Waist circumference of 102 cm and over for men and of 88 cm and over for women has been described to assess abdominal obesity [17].

BMI also fails to differentiate between lean and fat tissue. Imaging techniques such as magnetic resonance imaging (MRI) or computed tomography (CT) are the gold standard for evaluating the distribution of body fat, but the high cost and low availability make it difficult to use in large population studies. In clinical practice, dual-energy X-ray absorptiometry (DEXA) and bioelectrical impedance analysis (BIA) are the most frequently used methods to assess body composition and calculate body fat percentage. When DEXA was employed for body composition assessment, a body fat percentage of more than 28% and 40% of body fat percent for elderly men and women, respectively, have been used to define obesity [18]. A cutoff point of 27% and 38% of body fat percentage for elderly men and women, respectively, has been described to determine obesity with BIA [19].

27.2 Sarcopenia

One of the dramatic changes associated with human aging is the progressive decline of skeletal muscle mass. As the human body ages, the skeletal muscle mass declines annually approximately by 0.1–0.5% starting from age 30, and this gradual decrease, which has been suggested to be approximately 6% per decade after midlife, is accompanied by a simultaneous reduction of strength [20, 21]. There are significant differences among individuals in peak muscle mass, the age at which muscle loss begins, and the amount of muscle that is lost over time [22]. In women there a sharp decline in muscle mass after menopause has been described [23].

The term "sarcopenia" was first proposed by Rosenberg in 1989 to describe the decline of muscle mass associated with aging [24]. Since then, sarcopenia has been defined as the loss of skeletal muscle mass and strength that occurs with advancing age [25].

In the last 20 years, several different definitions of sarcopenia have been proposed, but no consensus has been reached. For instance, Baumgartner et al. [26] used a measure of relative muscle mass, since absolute muscle mass is correlated strongly with height and thus calculated an index of relative skeletal muscle mass as appendicular skeletal muscle mass (kg)/height^2 (m^2). They defined sarcopenia as the index of relative skeletal muscle mass being less than two standard deviations below the mean of a young reference group. On the other hand, Janssen et al. [27] converted absolute skeletal muscle mass (kg) to percentage skeletal muscle mass (muscle mass/body mass × 100) and termed the skeletal muscle index. They defined class I and II sarcopenia when values were within 1–2 and <2 standard deviations of young adult values.

Since then, muscle strength and physical performance have incorporated to muscle mass in the criteria for sarcopenia diagnosis. In 2010, the European Working Group on Sarcopenia in Older People (EWGSOP) defined sarcopenia as "a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life and death" [28]. Therefore, diagnostic criteria included low muscle mass (presarcopenia) together with low muscle strength or physical function (sarcopenia). The presence of the three diagnostic criteria refers to severe sarcopenia. Several groups such as the Foundation for the National Institutes of Health (FNIH) Sarcopenia Project [29]; International Working Group (IWG) [30]; Society of Sarcopenia, Cachexia, and Wasting Disorders (SCWD) [31]; and the European Society for Clinical Nutrition and Metabolism Special Interest Group on cachexia-anorexia in chronic wasting diseases (ESPEN) [32] have published operational criteria to define sarcopenia, using different assessment tools or cutoff points. For instance, while the EWGSOP employed appendicular skeletal muscle mass/height^2 as skeletal muscle mass index, the FNIH Sarcopenia Project used appendicular lean mass divided by body size (ALM_{BMI}). SCWD and ESPEN criteria are similar to those described by the EWGSOP, while IWG took a different cutoff point for gait speed when assessing physical performance.

As for muscle mass assessment, CT and MRI are also considered as the gold standard for estimating muscle mass given that they allow distinguishing fat from other soft tissues [33]. DEXA has been shown to be the preferred alternative method to CT and MRI for research and clinical use since it may discriminate between fat, bone mineral, and lean tissues and estimate appendicular skeletal muscle mass [28]. Bioelectrical impedance analysis estimates lean and fat body mass at the molecular level with good correlation with MRI [34] and DEXA [35]. Although positive correlations have been described between calf circumference and appendicular skeletal muscle mass and skeletal muscle index, and thus it could be used as a surrogate marker of muscle mass for diagnosing sarcopenia [36], anthropometric measurements such as this one or calf circumference are not recommended for diagnosing sarcopenia given that they are prone to error [28].

Regarding muscle strength, handgrip strength is commonly used in research and clinical practice [37], since it has been reported to be highly correlated with lower extremity muscle strength [38], which is important in gait, posture, and physical function. Knee flexion and extension techniques may be suitable for research studies, but their use in clinical practice is limited by equipment and training special requirements [28].

There are a number of methods to evaluate physical performance. The Short Physical Performance Battery test, which combines gait speed, chair-rise time, and balance assessment, is one of the most commonly used tools in the research of sarcopenia [39]. Among other tests, usual gait speed, which is a part of the Short Physical Performance Battery test, but can also be obtained from the timed up-and-go test, can be used as a single parameter to provide a predictive value for disability [40].

27.3 Sarcopenic Obesity

Aging-related decrease in muscle and fat mass increase may be masked by a stable body weight, resulting in a phenotype called sarcopenic obesity which is id defined as the coexistence of both sarcopenia and obesity [41]. Although it has gained significant attention from the scientific community in recent years, there is no universally accepted definition. Therefore, true prevalence estimations are unclear due to several factors such as the lack of consensus regarding diagnostic criteria or definitions (i.e., muscle mass alone or together with muscle strength and/or physical performance for sarcopenia) or differences associated with ethnicity in study populations [42]. For instance, Kemmler et al. [43] reported a SO prevalence that ranged from 4.1% (EWGSOP criteria + body fat >25%) to 2.1% (IWGS criteria + body fat >30%) in community-dwelling ≥ 70 years men. There is also divergence in terms of the chosen outcome to define sarcopenia (i.e., appendicular skeletal muscle mass, skeletal muscle mass, or fat-free mass) and obesity (i.e., body mass index, waist circumference, or body fat percentage). To this respect, fat accumulation and redistribution associated with muscle loss do not necessarily lead to BMI increase, and Han et al. [44] suggested that waist circumference gives a better indication of adiposity and sarcopenic obesity than BMI.

The prevalence of sarcopenic obesity also varies with regard to the cutoff points and methods used for its diagnosis (Table 27.1). For instance, with DEXA, Baumgartner et al. [41] reported that the prevalence of SO was 2% in 60–69 years old people from New Mexico and 10% for those ≥80 years. When using a Relative Skeletal Muscle Index, 8.9% of men and 7.1% of women (70–79 years old, USA) sarcopenic obese (appendicular lean mass/height^2) [45], but prevalence was higher (60 years and older, USA) when using appendicular lean mass/BMI, ranging from 16 to 40% [46].

27.3.1 Etiopathogenesis

The etiopathogenesis of sarcopenic obesity is a complex process where several common pathophysiological mechanisms interplay (Fig. 27.1). These factors involve

Table 27.1 Prevalence of sarcopenic obesity in female population using various definitions and criteria

	Study group	Body composition assessment	Sarcopenia definition	Obesity definition	Sarcopenic obesity prevalence (females) (%)
Batsis et al. [46]	Adults >60 years (USA)	DEXA	ALM/BMI	PBF	27.3
			ALM	PBF	12.6
			ALM	BMI	0.2
Bouchard et al. [47]	Adults 68–82 years (Canada)	DEXA	ASM/height^2	PBF	10.82
Oh et al. [48]	Adults >60 years (Korea)	DEXA	ASM/weight	BMI	31.10
Öztürk et al. [49]	Adults ≥65 years (Turkey)	BIA	ASM/height^2 Handgrip strength Gait speed	BMI	12.5
Moreira et al. [50]	Women 40–65 years	BIA	ASM/height^2	WC	7.1

ALM appendicular lean mass, *ASM* appendicular skeletal muscle mass, *BIA* bioelectrical impedance analysis, *BMI* body mass index, *DEXA* dual-energy X-ray absorptiometry, *PBF* percent body fat, *SMM* skeletal muscle mass, *WC* waist circumference

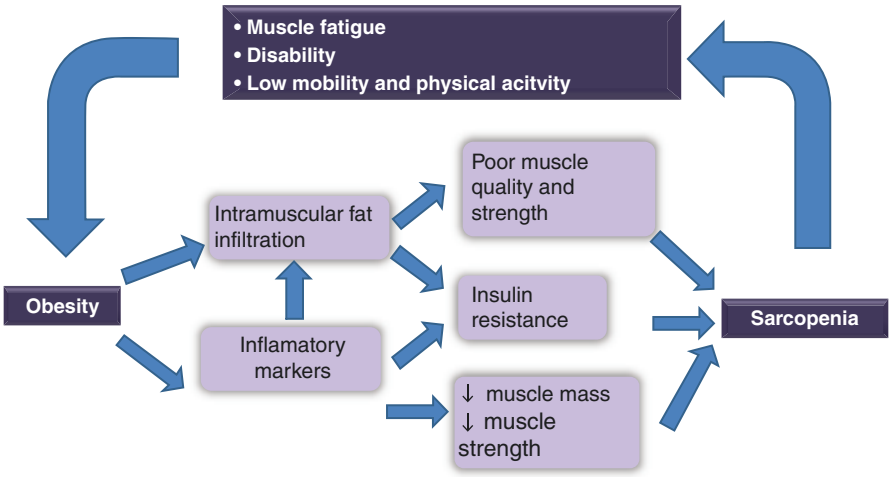

Fig. 27.1 Association of sarcopenia and obesity

lifestyle factors such as diet, low physical activity and sedentary behavior, smoking, hormone changes (insulin, growth factors, vitamin D), oxidative stress, neuromuscular changes, or immunological (proinflammatory cytokines) factors [51].

Aging-related changes in body composition seem to be strongly interconnected. With age, and together with muscle mass decrease, there is an alteration in body fat

distribution where visceral fat and waist circumference increase, whereas subcutaneous fat decreases. Besides, there is an important increase in muscle fat infiltration [52].

The aging process is characterized by a state of chronic inflammation, known as "inflammaging." It is an important link among obesity, insulin resistance, aging, and age-associated diseases [4]. Inflammation leads to local and systemic increment of proinflammatory makers, such as tumor necrosis factor-α, interleukin-1β or 6, interferon-γ, inflammatory adipokines, chemokines, and free fatty acids [53].

Obesity and sarcopenia are interconnected. Abdominal fat deposit has been described to be more proinflammatory than general obesity. Increased intramuscular and intrahepatic fat contribute to insulin resistance [54] which may affect protein degradation, protein synthesis, and muscle growth through locally released adipokines and free fatty acids. Adipokines secreted from fat tissue could lead to muscle wasting and fatty infiltration [55] which may cause an inflammatory state within the muscle. With this proinflammatory environment, obese people preferentially mobilize muscle, not fat, leading to fat increase and muscle loss and thus sarcopenic obesity.

27.3.2 Consequences

Obesity-related consequences are widely studied and debated modern epidemics and are related to a substantial and rising percentage of healthcare costs [56]. Among others, obesity is associated with an increased risk of type 2 diabetes, hypertension, dyslipidemia, and cardiovascular disease [57]. Sarcopenia is also known to be linked with adverse glucose metabolism and metabolic syndrome, in middle-aged and older nonobese people [58].

Sarcopenia also represents a significant influence on healthcare charges, mainly attributed to its strong effect on disability, and the increased healthcare expenditures in disabled persons [59]. Compared with sarcopenia or obesity alone, individuals with sarcopenic obesity have been reported to have poorer physical function and 2.5 times higher risk of reporting disability regarding instrumental daily living activities [18]. Obesity has been also associated with disability, and BMI and waist circumference have been described as important predictors of the onset or worsening of mobility disability in the older adult [60].

In sarcopenic obese people, both sarcopenia and obesity might synergistically increase their health-related deleterious effects [42], with, among others, worse cardiovascular risk profiles [61]. However, there are conflicting results, and several studies have reported that, compared with sarcopenic obesity, obesity has more cardiovascular risk factors in older women [62]. Sarcopenic obesity also presents a negative effect on lower functional capacity, a higher risk of falls [35], and a loss of independence [63].

Regarding mortality rates, Janssen et al. [64] reported that higher BMI values may be related to a lower risk, but if obesity is combined with low muscle strength, the risk of mortality may overcome the protective effect. Elderly people with sarcopenia have decreased survival rates following acute illness and with a doubled risk of nosocomial infection [65]. As for sarcopenic obesity, it has been associated with

significantly higher risk of all-cause mortality compared to nonsarcopenic, non-obese subjects [66]. Nevertheless, in the study published by Batsis et al. [19] with data extracted from NHANES III study, older women with sarcopenia had a higher risk of all-cause mortality, independent of obesity.

27.3.3 Management

Differences regarding sarcopenic obesity definition and diagnose lead to difficulties in comparing the effectiveness of the strategies that target this entity [67]. Taking into account the complexity of sarcopenic obesity etiopathogenesis, its management requires a multifactorial approach [68].

Obesity management has traditionally centered on decreasing weight rather than increasing muscle. It mainly aims to reduce intra-abdominal fat through caloric restriction. As mentioned above, obesity is associated with several chronic illnesses, and in this way, intentional weight loss in obese patients can have important clinical benefits or prevent many of the obesity-related risk factors for cardiovascular diseases as well as improvements in osteoarthritis or type 2 diabetes mellitus [69]. It has been also described that a moderate weight loss determines a significant improvement in insulin resistance, in fat distribution, and, more importantly, in muscle lipid infiltration [70]. Besides, excess caloric intake that results in obesity may lead to abnormal surges in serum-free fatty acids and glucose levels, which are linked high levels of oxidative stress, accelerating sarcopenia [71].

Therefore, a correct diet approach is of great importance in obesity management. A recent study analyzed several diet patterns in postmenopausal women and showed that with independence of age, menopausal age, total daily caloric intake and daily physical activity, and high consumption of unrefined cereals and legumes together with low intake of refined cereals were associated with lower BMI, waist circumference, and waist to height ratio. Nevertheless, greater consumption of red meat and potatoes, and low consumption of nuts, coffee, and tea, was associated with an increase in these three obesity parameters.

In postmenopausal women, physical exercise benefits in age-related diseases such as disability and falls, metabolic syndrome, cardiovascular diseases, or dementia, and cognitive function impairment has been widely described [72]. Nevertheless, the addition of exercise to energy restriction does not appear to have an additive effect on the amount of weight lost [42]. Moreover, weight loss induced by energy restriction alone may be costly in terms of losses in fat-free mass, and thus, muscle mass may decrease together with total body weight.

Several strategies have been described in the recent years regarding the treatment and management of sarcopenia, mainly aimed to improve muscle mass and function [73]. The most important approaches include nutritional and physical exercise interventions, either alone or combined, which have been shown as effective strategies not only for sarcopenia treatment but also to prevent the onset and the development of risk factors for sarcopenia, such as obesity, diabetes, chronic low-grade inflammatory state, cardiovascular accidents, and hormonal deficit. In a recent review,

Sgro et al. [74] concluded that that even in the case of overt hormonal deficiency, replacement therapy may be recommended not only because of the direct effects on muscle mass and performance but also because a good hormone milieu represents a requisite for adaptive process of supercompensation to training-induced stimulus. At this respect, recent studies in rats have shown that hormone replacement therapy with growth and/or parathyroid hormone may be an effective strategy in sarcopenia prevention and treatment [75, 76].

27.3.3.1 Physical Exercise

The benefits of distinct forms of programmed physical exercise programs on muscle mass and function have been demonstrated in different age groups. For instance, Crane et al. [77] studied muscle strength in three different age groups (20–39, 40–64, and 64–86 years), concluding that muscle strength significantly decreased with age, and people who practiced long-term aerobic exercise had significantly higher muscle strength assessed by several methods such as grip strength, relative maximal isometric knee extension torque, and absolute and relative 1-RM knee extension. In addition, it has been shown that, in well-trained older adults, skeletal muscle structure analyzed by muscle biopsies is more similar to the active young men than to that of the age-matched sedentary men [78].

It has been widely described that prolonged resistance exercise, which has been shown to be effective and safe even in very old and frail subjects, leads to specific type II muscle fiber hypertrophy in healthy young and older men [79]. Aerobic exercise training has also important benefits, and it is more suitable to maintain and/or increase aerobic and cardiovascular fitness and conserves muscle mass by improving muscle blood flow and decreasing oxidative stress [80].

Resistance exercise is currently described as the most effective exercise strategy to improve muscle mass, strength, and function in older people, but most of these studies have been performed among older, nonsarcopenic obese adults [81, 82]. When analyzing the effects of programmed physical exercise on people with sarcopenic obesity, only a few randomized controlled trials have been published. At this respect, Gadelha et al. [83] found improvements in both fat-free mass and sarcopenic obesity index that considered appendicular FFM based on height and fat mass, after 24 weeks of progressive resistance training.

The benefits of both aerobic and resistance exercises combined in sarcopenic obesity people have been studied, and thus Park et al. [84] found improvements in waist circumference, physical performance, fat mass, and muscle strength in postmenopausal women aged 65 years and over. Chen et al. [85], in a study performed in men and women aged 65–75 years, found an increase in muscle mass and a decrease in total fat mass and visceral fat area after resistance and aerobic exercises alone or combined (concurrent exercise), compared with participants who did not train. Muscle strength performance and serum IGF-1 level were also superior in the trained groups, especially after resistance exercises. Nevertheless, despite these improvements in sarcopenic obesity parameters, a clear conclusion cannot be drawn due to the disparity of the results obtained and the heterogeneity in the assessment of the sarcopenic obesity-related outcomes and criteria [86].

Between the recent training modalities, whole-body electromyostimulation (WB-EMS) has been proven to be effective in increasing muscle thickness, muscle fiber cross-sectional area, and knee extension strength in healthy human skeletal muscles [87]. More specifically, WB-EMS has shown benefits in muscle strength in different target populations such as elite soccer players [88] or postmenopausal women [89]. In 2016, Kemmler et al. [90] reported that, in middle-aged men, WB-EMS effects on general strength and body composition are similar to those obtained by high-intensity resistance training exercise. Nevertheless, WB-EMS studies carried out in sarcopenic obese people usually employee a combination of this exercises and dietary supplementation and will be described below.

27.3.3.2 Nutrition

Nutrition is a key factor in the development of both sarcopenia and obesity, although while sarcopenia is associated with an inadequate nutritional intake, obesity may be a result of an excess in the energy intake consumption (together with low energy expenditure) [91]. Consequently, nutritional strategies focused on sarcopenic obese people should target an optimal nutrient intake to increase skeletal muscle mass or prevent muscle mass loss, as well as to decrease excess fat mass.

Hypocaloric diets are very effective for losing weight in obese older adults. However, this strategy is highly undesirable in sarcopenic obese people, since it is estimated that about 25% of this weight loss is skeletal muscle mass, and can also have harmful effects for the micronutrient status and bone mineral density. Thus, in sarcopenic obesity, a weight loss diet should always focus on the preservation of muscle mass and could be combined with a high-protein diet and/or micronutrient supplementation [67].

Dietary amino acids have been demonstrated to have a positive regulatory effect on the muscle protein synthesis [92]. Protein intake may also be a significant factor for sarcopenia prevention and management. In older adults (>65 years), a dietary protein intake of 1.0–1.2 g/kg is recommended to maintain and regain the muscle mass and function in the long term, while it should be higher (1.2–1.5 g/kg) in individuals that suffer from chronic diseases [93]. This can reduce the risk of chronic diseases and improve outcomes [94]. Nevertheless it has been reported that an excessive intake of protein could be very harmful for the 65 and younger population [95].

The type of protein and the amino acid composition are also relevant for muscle mass preservation or gain during weight loss. Whey protein, the soluble protein fractions extracted from diary milk [96], can stimulate whole-body and muscle protein synthesis [97] and could represent an effective countermeasure to prevent muscle atrophy associated with physical inactivity and muscle unloading during aging [42]. Nevertheless, it has been reported that whey protein ingestion has a greater anabolic effect in the elderly than the essential amino acids that it contains [98]. An intake of leucine (2.0–2.5 g/day), mainly derived from animal sources, has been reported to improve the postprandial muscle protein synthesis in elderly men [99]. Beta-hydroxy-beta-methylbutyrate, a metabolite of leucine, can improve this muscle loss, but to date only a small number of studies have shown increases in lean

(muscle) mass and some muscle function and physical performance parameters in older people with or without resistance exercise and in muscle mass preservation during bed rest [100]. Other essential amino acids such as L-arginine [101] or L-cysteine [102] have been shown to have beneficial effects regarding insulin resistance in type 2 diabetic patients.

Protein source (plant or animal) and intake timing are also of importance. Overall, animal-derived dietary protein seems most effective in eliciting muscle protein synthesis [103]. Regarding the timing of protein intake, a more evenly distribution of dietary protein intake (every 3–4 h), instead of protein consumption during the three main meals, has been associated with higher muscle strength, physical performance, and skeletal muscle mass in older adults [104, 105].

As for older people with sarcopenic obesity, hypocaloric diets should be supplied with adequate protein, which may help to prevent muscle loss [106] and improve adherence to low energy intake [107]. Ensuring adequate dietary protein intake using high-quality proteins should be of importance in adults with sarcopenic obesity, with the quality of the protein being more important than the quantity [42]. It has been described that whey protein and essential amino acid meal replacement during weight loss induced by caloric restriction diet promote a reduction of adipose tissue and a modest loss of lean tissue in the elderly population people [108]. However, although the combination of a hypocaloric high-protein diet seems to be effective in the prevention of sarcopenic obesity, this strategy does not seem to be effective for its treatment [67].

Another strategy is to combine different anabolic nutrients. It has been recently reported that the combination of vitamin D with whey protein, which has been enriched with leucine, could increase protein synthesis and finally promote muscle mass gain in older adults [109]. The risk of developing micronutrient deficiencies such as 25-hydroxyvitamin D; vitamin B6, C, and E; selenium; magnesium; or zinc is relatively high in obese adults, who, in addition, are especially at risk for micronutrient deficiencies when following a weight loss diet [110]. On the other hand, some of these minerals as well as low 25-hydroxy-vitamin D status are associated with the development of sarcopenia [111, 112], and vitamin D supplementation has been demonstrated to improve several sarcopenic parameters in older adults [113].

27.3.3.3 Exercise + Nutrition

As mentioned above, a combination of different approaches seems to be more appropriate than one single strategy, whether it is nutrition or exercise, in sarcopenic obesity management.

The addition of exercise to a hypocaloric diet in obese older adults attenuates the loss of skeletal muscle mass [114], and it also improves muscle strength and performance [67]. In frail obese adults, a hypocaloric diet together with the combination of aerobic and resistance exercise is more effective for improving the functional status than the combination of low energy diet with either aerobic or resistance exercises alone [115].

As for the combination of exercise and nutrition, Liao et al. [116] reported that, in overweight and obese elderly people, higher increases in lean mass, muscular

volume, and leg strength are observed after resistance exercise combined with protein supplementation, in comparison with resistance exercise alone. However, they found that obese participants did not show greater change in muscle volume and grip strength compared with nonobese. Diet supplementation (particularly high protein intake or protein supplementation) combined with exercise is the most common strategy to counteract sarcopenic obesity. A recently published meta-analysis [117] focused on sarcopenic obese people has concluded that exercise alone and together with dietary supplementation improve muscle-related outcomes and reduce fat-related outcomes. However, the authors state that there is a need for better-designed randomized controlled trials with systematic evaluation of the different types of exercise and dietary supplements. More specifically, Kim et al. [118] analyzed the effects of progressive sequence of resistance and aerobic training and amino acid supplementation with tea catechin alone and combined. They observed that, although exercise and nutrition have beneficial effects on individual variables of body composition and physical function, improvements in muscle mass and variable combinations such as skeletal muscle mass index and fat percentage or physical performance and fat percentage were not found. When analyzing randomized controlled trials with combined nutritional supplements and exercise on sarcopenic obese population, WB-EMS is the most commonly used form of exercise. In a project performed in sarcopenic obesity community-dwelling women aged over 70 years, WB-EMS increased muscle mass and functional capacity, but the effect on body fat was minor, and the addition of protein-enriched supplements did not increase the effects of WB-EMS alone [43]. In the same project, when studying the effects on the metabolic syndrome [119], isolated WB-EMS did not induce significant improvements, but combined with low-dose protein supplementation, more favorable results were observed. In a similar project carried out in men (>70 years), improvements in fat and muscle mass, muscle strength, and gait velocity were observed in both WB-EMS alone and combined with protein supplements [120, 121].

27.4 Conclusions

Aging-related decrease in muscle and fat mass increase may be masked by a stable body weight, called sarcopenic obesity. Estimation of the prevalence is difficult due to the lack of consensus regarding sarcopenia definition and the heterogeneity in the assessment of the sarcopenic obesity-related outcomes. Different common pathophysiological mechanisms, such as lifestyle, immunological, endocrine, or vascular factors, are involved in its pathogenesis. A proinflammatory environment seems to play an important role in the association between sarcopenia and obesity. Postmenopause is associated with an increase in visceral adipose tissue, an important source of inflammatory markers. Sarcopenic obesity management requires a multifactorial approach, and several strategies, such as physical exercise or diet, either alone or combined have been studied in literature, but the limited number of studies focused on sarcopenic obesity people and the variability regarding the outcome measures and study designs preclude firm conclusions. An adequate

combination of hypocaloric diet focused on losing weight in obese older adults and an appropriate protein intake have been described to be important factors for sarcopenic obesity prevention and treatment. Among the different forms of exercise, resistance and aerobic exercise programs, as well as more recent modalities such as whole-body electromyostimulation, seem to be effective in sarcopenic obesity management.

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Cognitive Decline in Women: The ZARADEMP Study

28

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28.1 Introduction

The aging of the world's population is well documented. According to the United Nations (UN) [1], the number of people aged 60 or over worldwide is expected to more than double from 962 million in 2017 to 2.1 billion in 2050. Moreover, given the higher life expectancy worldwide, the number of people aged 80 or over is expected to triple by 2050, from 137 million in 2017 to 425 million in 2050. In Europe, 25% of the population is already aged 60 years or over, and this figure is expected to reach 35% by 2050 [1].

The risk of cognitive impairment and dementia increases with age [2], given that advanced age is the strongest risk factor for dementia in all regions [3]. In addition, subjects with cognitive impairment have a higher risk of progression to dementia [2].

Dementia is traditionally defined as a syndrome of global deterioration of intellectual function occurring in clear consciousness and caused by brain disease; to qualify for the diagnosis, the deterioration must be severe enough to adversely affect activities of daily living (ADL) [4]. Alzheimer's disease (AD) is the most common type of dementia, accounting for an estimated 60–80% of cases [5]. Vascular dementia (VaD), defined as dementia resulting from ischemic or hemorrhagic brain lesions, is also relatively prevalent in population studies [6], being the sole cause of dementia in about 10% of dementia cases [5].

The construct "mild cognitive impairment" (MCI) has been widely used worldwide to define the gray area between intact cognitive functioning and clinical dementia [7]. MCI represents a heterogeneous entity and it is a concept in evolution

Table 28.1 Diagnostic criteria for mild cognitive impairment (MCI)

Petersen mild cognitive impairment criteria (MCI-P)	DSM-5 mild neurocognitive disorder criteria (MCI-DSM-5)
Subjective memory complaint, usually corroborated by an informant	Concern of the individual, a knowledgeable informant, or the clinician that there has been a decline in one (or more) cognitive domain
Isolated memory impairment on neuropsychological testing compared to healthy subjects matched by age and education level	A modest impairment in cognitive performance, documented by standardized cognitive assessment
Preserved general cognitive function	Cognitive decline involves memory and/or other cognitive functions (attention, language, executive function, perceptual-motor, social cognition)
Intact activities of daily living	Cognitive deficits do not affect independence in activities of daily living, but greater effort or compensatory strategies might be required
No dementia	Cognitive deficits do not occur exclusively in the context of delirium
	Cognitive deficits are not better explained by another mental disorder (such as psychosis or depression)

[7]. The first definition (by Petersen, MCI-P) [8] focused on memory problems (Table 28.1), but, thereafter, diagnostic criteria were broadened to include impairment in other areas of cognitive functioning. MCI can be classified into two subtypes: amnestic MCI (aMCI), if performance on episodic memory tests is poor, and non-amnestic MCI (naMCI), in the case of poor performance on tests covering cognitive domains other than memory, such as executive functions, language, or visuospatial abilities. The latest version of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) [4] recognizes mild neurocognitive disorder as a predementia stage of cognitive impairment that shares many of the features of MCI (MCI-DSM-5) (Table 28.1).

In 2015, the number of people living with dementia worldwide was 46.8 million, and this figure is predicted to increase to 131.5 million by 2050 [3]. Apart from the personal and family burden of the disease, the global cost of dementia is estimated to be US $818 billion, including medical costs, social care workforce costs, and the significant contribution from informal caregivers [3].

In 2014, 62% of people over 80 were women [9]. This survival bias and, eventually, other sex and gender differences between women and men might explain the higher prevalence of dementia reported among women [9], specifically AD [10]. However, less than half of the up-to-date scientific literature on dementia focuses specifically on women or, more generally, gender issues [9], even though a need to prioritize dementia as a global women's health issue has been recognized [9].

In this chapter, we first describe the profile of cognitive aging in women and summarize epidemiological data on cognitive impairment and dementia, specifically in women. We will then discuss biological, societal, and cultural potential risk factors for cognitive impairment and dementia in women.

28.2 Cognitive Performance in Healthy Older Women

Differences in cognitive performance between men and women are consistently discussed in the literature, despite the controversial influence of biological and sociocultural factors. Adult women show an advantage over men in tasks related to memory, verbal fluency, and fine motor skills. Conversely, they perform worse in visuospatial tasks——such as rotation of an object or space navigation——and motor tasks, ——such as throwing an object to hit a target [11].

Even in healthy subjects older than 65, there is a clear, age-related decline in performance on executive functioning (mainly inhibition), verbal fluency, verbal memory, and cognitive speed tasks [12]. Some studies suggest that the pattern of sex differences in cognition observed in young adults declines in old age [11] and that there is a decline in the cognitive functions in which women outperform men, clearly significant in verbal fluency [13]. However, other studies [14] report that such differences persist throughout the life span: older women have higher scores than men on psychomotor speed, verbal learning, and memory tests, whereas they underperform on visuo-construction and visual perception tasks [14].

28.3 Epidemiology of Cognitive Impairment and Dementia in Older Women

To document prevalence and incidence of cognitive impairment and dementia in women, we will mainly summarize findings of collaborative studies across Europe——the European Studies of Dementia (EURODEM) project——[6, 15] and worldwide, ——the Cohort Studies of Memory in an International Consortium (COSMIC) project [16]. Both include longitudinal population-based studies of cognitive aging with large samples of subjects aged 60 or over who were not identified as having dementia, such as the Zaragoza Dementia and Depression (ZARADEMP) project [17, 18], a five-wave epidemiological enquiry in which a sample of 4803 subjects living in a large Spanish city was interviewed at baseline.

28.3.1 Mild Cognitive Impairment in Women

28.3.1.1 Prevalence and Incidence of MCI

Heterogeneity in the concept and diagnostic criteria of MCI may partly explain the wide differences in its prevalence reported to date [19, 20].

When MCI was diagnosed according to the scores in the Mini-Mental State Examination (MMSE) (MCI-MMSE), defined by a score range from 24 to 27 (with a maximum of 30) [21], the collaborative COSMIC study found an overall prevalence of 12% (95% CI 11.5–12.4) and no sex differences [21]. Prevalence of MCI-MMSE increased with age, but the pattern across age groups was different for men and women: for women, the increase in prevalence was from ages 70–79 to 80–89 and for men, from ages 60–69 to 70–79 [21].

When MCI was diagnosed by a neuropsychological test representing each of the four cognitive domains (memory, language, processing speed, and executive functioning), the COSMIC study found that the strongest association with sex was for memory, with women performing better than men across the COSMIC cohorts. However, this result comes from developed nations, where women have been afforded the same educational opportunities as men [22]. Women tended to perform worse than men on all other cognitive measures but not statistically significantly so for any measure. Processing speed exhibited the strongest decline with age in both sexes. Decline in other cognitive domains showed an interaction of sex with age, with a trend toward a faster decline in women [22].

Regarding MCI subtypes, the COSMIC study [21] found an overall prevalence of 2.0% (95% CI 1.7–2.2) for aMCI and 3.9% (95% CI 3.6–4.2) for naMCI. Prevalence of aMCI did not differ significantly across age groups or by sex; however, prevalence of naMCI across age groups showed a different pattern for women and men, similar to that defined for MCI-MMSE. A meta-analysis published in 2016 [23] that examined sex differences on incidence and prevalence of MCI subtypes found only differences in the prevalence of naMCI, with a higher prevalence among women, apparently mediated by neurological conditions (since studies that specifically

Table 28.2 Epidemiological data of cognitive impairment in the overall population and, specifically, in women, found in the ZARADEMP study

	Overall	Women
Prevalence of MCI	**% (95% CI)**	**% (95% CI)**
MCI-P	6.9 (6.5–7.3)	8.3 (7.8–8.8)
MCI-DSM-5	2.5 (2.1–2.9)	3.3 (2.8–3.8)
Prevalence ratio of MCI (over men)		**OR (95% CI)**
MCI-P		0.88 (0.7–1.2)
MCI-DSM-5		1.4 (0.9–2.1)
Prevalence of global dementia	**% (95% CI)**	**% (95% CI)**
1988–1989	5.5 (2.9–9.8)	4.8
1994–1996	3.9 (3.3–4.5)	5.0
Prevalence ratio of dementia (over men)		**OR (95% CI)**
1994–1996		2.1 (1.5–3.1)
Incidence of dementia	**IR (95% CI)**	**IR (95% CI)**
Global dementia	8.6 (7.2–10.2)	9.6 (7.7–11.8)
AD	5.4 (4.3–6.7)	6.8 (5.2–8.7)
Incidence rates of dementia (over men)		**IRR (95% CI)**
Global dementia		1.3 (0.9–1.9)
AD		1.8 (1.1–3.0)

MCI mild cognitive impairment, *MCI-P* MCI according Petersen criteria, *MCI-DSM-5* MCI according DSM-5 criteria ("mild neurocognitive disorder"), *AD* Alzheimer's disease, *OR* odds ratio, *IR* incidence rate (per 1000 person-years), *IRR* incidence rate ratio, *CI* confidence interval

excluded participants with known neurological conditions did not report significant sex differences).

In the ZARADEMP study, prevalence of MCI in women varies, depending on the diagnostic criteria applied (Table 28.1), between 3.3% (MCI-DSM-5) and 8.3% (MCI-P), which is higher than the prevalence in the overall population (Table 28.2) [20]. However, in multivariate models——after controlling by age, educational level, anxiety, and depression——differences in the prevalence of MCI in women over men were not statistically significant (Table 28.2).

28.3.1.2 Outcomes of MCI in Women

MCI is consistently associated with a higher risk of progression to dementia. According to the data of a meta-analysis including seven community studies from Japan, China, Sweden, France, and Austria [24], the annual conversion rate (ACR) from MCI to AD ranged from 5.4 to 11.5% (median: 7.1%). In the ZARADEMP study [25], ACR for dementia was 1.9% for MCI-P and 3.4% for MCI-DSM-5, being 1.2 and 2.2% for AD, respectively. Subjects diagnosed with MCI had a higher risk of progression to dementia than non-cases at 4.5-year follow-up (HR = 2.9 (CI 95% 1.8–4.5) for MCI-P and HR = 5.3 (CI 95% 3.3–8.6) for MCI-DSM-5), independently of age, sex, educational level, and comorbidity with anxiety or depression [25]. In a similar follow-up period, a French community study [26] found a higher conversion rate from MCI to dementia for men (8%) than for women (6%). Moreover, they found gender-specific risk profiles. The factors significantly

associated with progression to dementia on MCI females were disability on instrumental ADL (IADL) (OR = 3.5 (95% CI 2.1–5.9)), lower education (OR = 2.2 (95% CI 1.3–3.6)), ApoE4 allele (OR = 2.1 (95% CI 1.4–4.0)), subclinical depression (OR = 2.0 (95% CI 1.1–3.6)), anticholinergic medications (OR = 1.8 (95% CI 1.0–3.0)), and age (OR = 1.1 (95% CI 1.1–1.2)) [26]. The factors significantly associated with progression to dementia on MCI males were ApoE4 allele (OR = 3.2 (95% CI 1.7–5.7)), stroke (OR = 2.8 (95% CI 1.2–6.9)), lower educational level (OR = 2.3 (95% CI 1.3–4.1)), disability on IADL (OR = 2.2 (95% CI 1.1–1.2)), and age (OR=1.2 (95% CI 1.1–1.2)) [26].

In line with previous studies [27, 28], the ZARADEMP study found an increased mortality rate for subjects diagnosed with MCI [29]. MCI-DSM-5 was associated with a significant increased risk of mortality even after controlling by age, sex, education, medical risk factors, and psychiatric conditions (OR = 1.24 (CI 95% 1.01–1.53)) [29]. Some studies stratifying their results by sex found neither significant differences by sex strata [27] nor an increased risk of mortality in MCI males compared to women [30].

28.3.2 Dementia in Women

28.3.2.1 Prevalence and Incidence of Dementia in Women

The EURODEM collaborative study, including 11 European cohorts from the community and a total of 2346 cases of dementia [15], found an age-standardized prevalence of dementia of 6.4% (4.4% for AD and 1.6% for VaD). In the United States (USA), a higher prevalence of AD (10%) is reported [5]. Prevalence of dementia increases steeply with age, with rates doubling approximately every 5 years [31]. Consistent with international literature [5, 31, 32], the EURODEMP study found that the prevalence of AD increased continuously with age and was higher in women than in men (Fig. 28.1) [15]. For VaD, an age-dependent difference in the prevalence between men and women was reported: under 85 years old, prevalence was higher in men; from that age onward, prevalence was higher in women (Fig. 28.1) [15]. Table 28.2 shows the prevalence of dementia in the ZARADEMP study [17].

Regarding the incidence of dementia, results of the EURODEMP and ZARADEMP studies are also consistent with other international reports that found an increased risk of dementia by age and in women, specifically for AD [5, 31, 32]. The EURODEMP study, recruiting 8 community cohorts, with pooled data including 836 cases of dementia and a 42,996 person-years follow-up [6, 33], found that women had a 30% higher risk of dementia. In all studies, there was an exponential increase in dementia incidence with age, even in the very old. The rates continued to increase with age in women, whereas they plateaued in men at age 85. For AD, the pooled data showed that incidence rates among women were higher and increased more steeply by age than in men, whose rates plateaued at age 85. For VaD, the incidence rates increased with age, without any substantial difference by sex. Incidence rates of dementia and AD in the ZARADEMP study are shown in Table 28.2 [18].

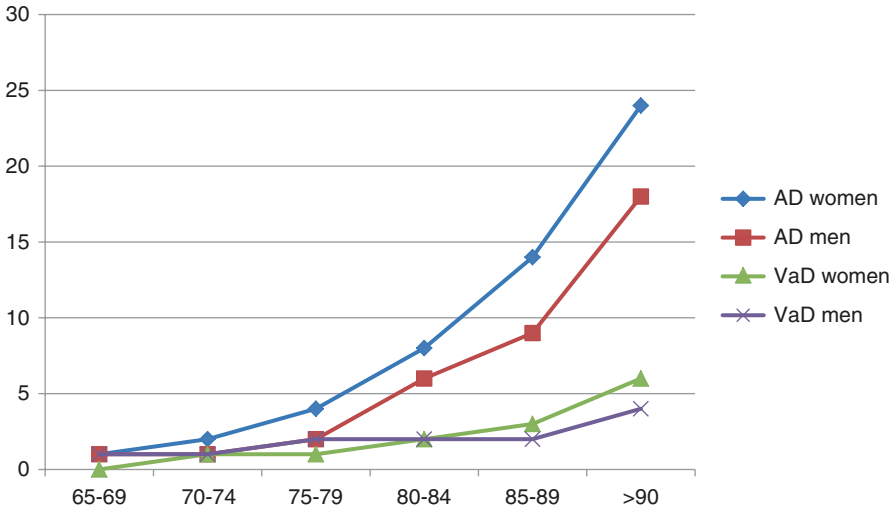

Fig. 28.1 Prevalence of Alzheimer's disease (AD) and vascular dementia (VaD) by age and sex (EURODEMP project). *Adapted, with permission from the publisher, from Lobo et al. 2000 [15]. The pooled prevalences for the groups aged 65–69, 70–74, 80–84, 85–90, and 90 and older were for AD, 0.7%, 2.3%, 4.3%, 8.4%, 14.2%, and 23.6% in women and 0.6%, 1.5%, 1.8%, 6.3%, 8.8%, and 17.6% in men, and for VaD, 0.1%, 0.6%, 0.9%, 2.3%, 3.5%, and 5.8% in women and 0.5%, 0.8%, 1.9%, 2.4%, and 3.6% in men

Public health planners use incidence rates of dementia to estimate the projected disease burden in a population. While incidence rates reflect the actual experience of a cohort, risk estimates are required to predict how much disease a population may expect. Lifetime risk (LTR), calculated at several ages, has been defined as the probability that a person of a specific age has of suffering the condition at that time in his or her life. Consistent with the results from the Framingham study in the United States [34], LTR in the ZARADEMP study [18] was reported to be higher in women than in men, both for overall dementia and AD. Lifetime probability of suffering dementia for women aged 65 was 19.7% (vs. 14.1% in men) and aged 85, 20.4% (vs. 16.8% in men). The corresponding figures for AD in women were 16.7% and 17.6% (vs. 8.4% and 10.9% in men). Differences regarding sex were independent of the educational level, although they tended to decrease in subjects older than 85 [18].

A recent review of international data investigating the changes in prevalence and incidence of dementia over time suggests a current decline in both [35]. The ZARADEMP study [17], which compares data from 1994 and 1987 (Table 28.2), and a Swedish study [36], which compares data from 2001 and 1995, did not find a significant reduction in the prevalence of dementia in the total population, but they found decreases in prevalence higher than 50% in men. Studies that investigated trends in the incidence of dementia found notable differences in subpopulations, particularly between sexes [35]. A British study, which compares data from 2008 to 1991 [37], found that a decrease in the incidence of dementia was confined to men.

The Framingham study (USA), which compares data from 2005 to 1985 [38], found that in women, the decrease occurred earlier than in men and continued over time. A French study, comparing data from 1999 to 1988 [39], found that the decrease in the incidence of dementia was driven by an effect in women. The authors [35] concluded that diagnosis of dementia, as of any disorder, is contextual and can change across time and geographies. They also reported that societal changes and improvements in living conditions, education and healthcare, as we will discuss later, might have been responsible for these observed trends.

28.3.2.2 Outcomes of Dementia in Women

Women with AD seem to deteriorate faster in the earlier stages of the disease and show poorer cognitive profiles at the same stage of dementia than men [40].

Women have a broader spectrum of dementia-related behavioral symptoms with a tendency for depression [32, 41], anxiety, and delusions [42], while aggression is more frequent in men [32].

AD is a leading cause of disability and poor health and is officially listed as the fifth leading cause of death for people aged 65 and over, despite it being frequently unrecognized as cause of death by official sources [5]. The ZARADEMP study found an increased risk of mortality in moderate and severe cases of dementia [43], and that risk increased in parallel with the degree of cognitive impairment (measured by the MMSE), with HR = 2.08 (95% CI 1.42–3.04) in the most severe stage (MMSE score <10) [44]. In this sample, severe cognitively impaired people were more likely to be women, illiterate, and widowed. However, the increased risk of mortality for cognitive impairment was independent of these and other variables related to health status, the population attributable fraction (PAF) of cognitive impairment being 3.49% (95% CI 1.38–6.40) [44]. However, a European study [45] found a higher risk of death in men with dementia than in women. Survival in subjects older than 85 at 2 years was 81% in women without dementia (vs. 76% in men without dementia) and 60% in women with dementia (vs. 52% in men with dementia). Survival at 5 years was 52% in women without dementia (vs. 44% in men without dementia) and 27% in women with dementia (vs. 16% in men with dementia) [45].

The aforementioned European study [45] found that the probability of being in institutional care increased with age and was significantly higher for cases of dementia in both sexes; however, women were more likely to be in an institution than men. This could be due to societal and cultural factors, because women take on a role as caregivers more frequently than men do [9]. Care for patients with dementia takes place 80% of the time by families and is provided by women 78% of the time [32].

28.4 Risk Factors for Cognitive Impairment in Women

In addition to several biological explanations for the sex differences observed in the prevalence and incidence of MCI and dementia, the effects of sociocultural aspects, i.e., gender differences, should also be studied [33] (Table 28.3).

Table 28.3 Potential modifiable risk factors for cognitive impairment and/or dementia in women

Risk factors for cognitive impairment in women
Estrogen depletion in early menopause (?)
Depression
Diabetes
Mid-life hypertension
Mid-life obesity
Dyslipidemia
Smoking
Alcohol (?)
Diet high in saturated fats
Low educational level
Jobs with low intellectual demand
Lack of physical exercise

(?) Factors with controversial effects

28.4.1 Biological Risk Factors

Differences on brain reserve: Women have a smaller cerebral brain volume than men [11, 46], so they have less ability to cope with pathological insults compared to men and more probability of showing clinical symptoms of AD at the same level of brain pathology [46].

Genetics: The E4 allele of the apolipoprotein E (ApoE4) is the strongest known genetic risk factor for late-onset AD; its effects have been reported to be more pronounced in women than in men [46].

Hormones: Estrogen receptors have been found in several areas related to cognition in the brain, which could explain (at least partially) differences in cognition found between women and men in adult life and the decline in some cognitive functions in women after menopause [13]. Moreover, estradiol exerts neuroprotective actions——enhancing neuronal growth and formation of synapses——and increases the synthesis of acetylcholine, which is a key neurotransmitter in the regulation of attention and memory. Therefore, depletion of estradiol could increase the risk of cognitive impairment and AD in women [13].

There is evidence in the literature of an association between a prolonged exposure to female hormones——i.e., women with later menopause and longer reproductive period——and better cognitive performance and delayed cognitive decline, despite no evidence of association between prolonged exposure to female hormones and a lower risk of dementia [47].

Hormonal therapy (HT) could have positive effects on cognition during a critical period in early postmenopause, for example, in women after a hysterectomy; however, HT positive or negative effects affect physical health for periods longer than 10 years [13].

Estrogens are also involved in the regulation of behavioral mood through interaction with the serotoninergic systems, so periods of hormonal fluctuations (such as perimenopause) are related to increased vulnerability to mood disorders such as depression [13], which is also associated with cognitive impairment and dementia in different ways.

Depression: Epidemiological studies based on community samples consistently find a higher prevalence of depression in women than in men [41]. Moreover, women are also more frequent on psychopharmacological drugs [48].

Depression has been significantly associated with MCI and dementia. In the ZARADEMP study, more than 50% of cases of depression and/or anxiety were also diagnosed with MCI-P, and more than 50% of MCI cases had comorbidity with depression or anxiety [20]. A French community study [26] also found that both women and men with MCI were more likely to have depressive symptoms and to take anticholinergic medications than cognitively healthy subjects. In said study, women with MCI were more likely to suffer from insomnia and to have poor subjective health, disability, and social isolation. The ZARADEMP study, consistently with the literature [49], found not only a frequent comorbidity between depression and dementia [41] but also a longitudinal increased risk for dementia, specifically AD, in cognitively healthy subjects with more severe depression (HR = 4.30 (95% CI 1.39–13.33)) [50].

Cardiovascular risk factors. Many factors that increase the risk of cardiovascular disease are also associated with a higher risk of dementia:

- *Diabetes:* Type 2 diabetes is a risk factor for cognitive impairment and dementia (VaD and AD) [51]. Diabetes is a relatively frequent diagnosis in the community (8.7%) [52]. Globally, more men than women are diagnosed with diabetes, but there are large sex ratio differences in the prevalence of diabetes across countries that parallel those of obesity, the most prominent risk factor for diabetes in both sexes [53]. Moreover, women have a greater relative risk of cardiovascular complications and mortality in the presence of diabetes [53].
- *Mid-life obesity* has been reported as an independent risk factor for cognitive impairment and dementia [54], specifically in women [55].
- *In some studies*, *hyperlipidemia and mid-life hypertension* have been associated with cognitive decline and dementia [54]. Hypertension, generally asymptomatic, was the most prevalent medical condition in the ZARADEMP sample (61.7%), and it was significantly more prevalent in women (65.1% (95% CI = 63.3–66.9)) [52]. Estrogens improve the lipid profile and promote vasodilatation and antioxidant activities; therefore, menopause leads to an overturn of all these effects on vascular health [13].

Survival bias: The higher overall lifetime risk of dementia in women might be influenced by the combined effect of the longer life expectancy among them and a selective survival to age 65 of men with the lowest risk of developing dementia. Mortality from cardiovascular causes starts in mid-life, so men who die earlier from cardiovascular diseases might have had, if they had survived, the highest risk of dementia [34].

28.4.2 Social and Cultural Factors

Education: Previous studies consistently found that subjects with a low educational level, specifically women, have a higher risk of AD [10, 56]. A higher level of

education has been related to an increase in cognitive reserve; therefore, subjects with a higher level of education may take longer to reach the threshold of dementia detection at a same degree of pathological insult to the brain.

Occupation: Some studies [57, 58] have reported an increased risk of cognitive impairment and/or dementia in subjects who have a predominantly manual occupation in life compared to subjects with occupations that involve higher intellectual requirement.

There are gender-specific societal changes in intellectual lifestyle across different generations and countries, in the context of specific economic, political, social, and cultural background [35]. For example, an epidemiological study recruiting a large sample of older subjects from several developed countries worldwide (SCOPE) found significant differences in the level of education by sex, more notable at university level, with a considerably greater percentage of men who had attended university (11.1%) compared to women (3.1%) [48]. In Spain, the ZARADEMP study found a significant higher proportion of illiterate women (10.1%) than men (4.2%) [59]. In the last decades, women living in developed countries are afforded the same educational and occupational opportunities as men; thus, a different sex-specific trend on incidence and prevalence of dementia might be expected in future epidemiological studies.

Lifestyle: Lifestyle behaviors may influence cardiovascular health and, also, the risk of dementia.

- **Diet:** Emerging evidence suggests that a diet low in saturated fats may be associated with reduced Alzheimer's and dementia risk [5].
- **Exercise/physical activity:** Aerobic and multimodal combined training have been reported to improve global cognition and some cognitive domains in both men and women; however, evidence in the literature suggests that physical exercise could have more positive effects on executive function in women than in men [60] and that the protective effect of physical activity on the risk of dementia could be specific to women [55].
- **Smoking**: Some studies found that smoking was associated with an increased risk of AD, specifically in men [10]. However, others reported that both men and women were affected by smoking-related neurological disturbances to a similar extent [61]. According to these studies [61], smoking is associated with dementia and deficiencies in general intellectual abilities and several cognitive domains: executive functions, cognitive flexibility, learning and memory processing speed, and working memory.
- **Alcohol:** Some studies have reported that moderate alcohol consumption may decrease the risk of dementia [55, 62–64]. However, the evidence is not strong enough, and other studies, such as the ZARADEMP study [65], did not find such a protective effect; moreover, a trend toward greater odds of dementia has been associated with heavier alcohol consumption among men and participants with an apoE4 allele [63].

In current older generations, drinking and smoking patterns have been very different between men and women, with a much higher proportion of drinkers [59, 65] and smokers [48, 59] among men. Globally, the prevalence of smoking is higher for

men than for women (40% vs. 9% in 2006); however, in the United States and Europe, the prevalence of female smoking nowadays is high (around 17% and 22%, respectively) [66] and might result in a higher risk of cardiovascular diseases and dementia in women compared to previous generations.

28.5 Conclusion

The higher prevalence of dementia among women has resulted in a growing recognition of the role of gender in dementia, with emerging evidence suggesting the need to acknowledge and prioritize dementia as a global health issue for women [9].

However, less than half of the published research focusing on dementia refers specifically to women or to gender issues [9]. In this chapter, we have discussed some differences on distribution of risk factors for cognitive impairment and/or dementia between men and women and an eventual differential vulnerability between them to such risk factors. Future research on cognitive impairment and dementia should stratify the analysis by sex for a better understanding of this issue. The understanding of sex and gender differences will help to define individualized treatment and preventive interventions for cognitive impairment.

Conflict of Interest P. Gracia-García has received honorarium and support for attendance to scientific meetings from Servier and Pfizer; C. de la Cámara has received funding to attend scientific meetings from Janssen, Lundbeck, and Otsuka. None of these companies have influenced the content of this work. The other authors declare that they have no conflict of interest.

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Managing Menopause and Post-reproductive Health: Beyond Hormones and Medicines

29

Skye Marshall and Margaret Rees

29.1 Introduction

Women and health professionals have been exploring nonhormonal- and nonmedication-based approaches to managing menopausal symptoms and optimising post-reproductive health for many years. In 2002 and 2003, the first publications of the Women's Health Initiative and Million Women studies on menopausal hormone therapy (MHT) raised safety concerns with regard to cancer and cardiovascular risks [1, 2]. Although long-term follow-up has shown no association between MHT and all-cause, cancer-related or cardiovascular-related mortality and guidelines have supported its use, there are still concerns about continuation beyond the age of 60 [3–5]. Furthermore, the US Preventive Task Force does not recommend the use of MHT for the primary prevention of chronic diseases after the menopause [6]. As women are living longer, there are increasing concerns about chronic disease such as cardiovascular disease, osteoporosis, dementia and cognitive decline which can adversely affect quality of life and independent living. The focus of a holistic approach is to have a high quality of life and maintain independence—specifically by maintaining bone and muscle mass, function and strength and cognition. Both physical activity and an adequate diet are required for that.

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The World Health Organization has raised concerns about physical inactivity and provided general guidance regarding physical activity in people aged over 65 [7, 8]. Thus:

1. Older adults should do at least 150 min of moderate-intensity aerobic physical activity throughout the week or do at least 75 min of vigorous-intensity aerobic physical activity throughout the week or an equivalent combination of moderate- and vigorous-intensity activity.
2. Aerobic activity should be performed in bouts of at least 10 min duration.
3. For additional health benefits, older adults should increase their moderate-intensity aerobic physical activity to 300 min per week or engage in 150 min of vigorous-intensity aerobic physical activity per week or an equivalent combination of moderate-and vigorous-intensity activity.
4. Older adults, with poor mobility, should perform physical activity to enhance balance and prevent falls on 3 or more days per week.
5. Muscle-strengthening activities, involving major muscle groups, should be done on 2 or more days a week.
6. When older adults cannot do the recommended amounts of physical activity due to health conditions, they should be as physically active as their abilities and conditions allow [8].

In addition to meeting age- and gender-related nutrient targets, there has been increasing focus on the additional health benefits of specific dietary patterns, such as the Mediterranean diet, the DASH (Dietary Approaches to Stop Hypertension) diet, the MIND (Mediterranean-DASH Intervention for Neurodegenerative Delay) diet and the Okinawa diet [9]. However, whether benefits are attained when implementing these dietary strategies in later years as opposed to long-term adherence requires examination [9]. Maintaining lean body mass is important, as protein-energy malnutrition in older people, which can occur at any weight, can cause decreased quality of life and independence and increased morbidity and mortality [10–12].

This chapter will explore the recent evidence (published within the past 10 years) for diet and exercise lifestyle options for post-reproductive health in women, specifically examining interventions for menopausal vasomotor symptoms, cardiovascular disease, osteoporosis, dementia and cognitive decline.

29.2 Menopausal Vasomotor Symptoms

Menopausal vasomotor symptoms (VMS), including hot flushes and night sweats, are experienced by up to 80% of women during menopause, making them the most common menopausal symptoms with a significant negative impact on quality of life [13]. Hot flushes are most frequent in the 12 months following the final menstrual period; and total duration of symptoms is heavily dependent upon the timing of symptom onset, where onset during premenopause can increase duration to over

10 years and onset after menopause may limit duration to less than 4 years [14–18]. Other factors associated with increased duration of symptoms have been identified as younger age, stress, depression, symptom sensitivity, African American ethnicity, higher BMI and increased abdominal adiposity [15, 16, 19]. Non-medical management options recommended by the National Institute for Health and Care Excellence (NICE) include regular exercise, achieving a healthy body weight, avoiding possible triggers (such as spicy foods, caffeine, smoking, alcohol), reducing stress and environmental changes such as wearing lighter clothing and sleeping in a cooler room [20].

29.2.1 Dietary Interventions for the Improvement of Menopausal Vasomotor Symptoms

There is observational and interventional evidence to suggest that adherence to dietary guidelines, and a high consumption of plant-based foods in particular, is associated with decreased longevity and severity of VMS independent of weight loss.

The Australian Longitudinal Study on Women's Health ($n = 6040$ women with a natural menopause) found that consumption of either a fruit-based dietary pattern or a Mediterranean-style diet decreased the odds of reporting vasomotor symptoms by approximately 20% (OR, 0.81 [95%CI, 0.71–0.93] $P < 0.001$ and OR, 0.80 [95%CI, 0.69–0.92] $P < 0.001$, respectively) [21]. Conversely, dietary patterns with a high intake of fat and sugar increased the risk of vasomotor symptoms [21]. Similarly, Beezhold et al. found that perimenopausal vegans and women with the highest intakes of vegetables or berries reported the least bothersome vasomotor symptoms [22]. However, these observational findings reflect long-term usual dietary habits and provide no evidence as to whether the same benefits are realised if changes are made once symptoms commence.

The Women's Health Initiative ($n = 6104$ postmenopausal women with VMS) randomised controlled trial (RCT) delivered intensive education and counselling to achieve a dietary pattern which aimed for a low total dietary fat intake (<20% of total energy), high fruit and vegetable intake (≥5 serves/day) and high whole-grain intake (6 serves/day) [23]. The dietary intervention, which is focussed on increasing plant-based foods and reflects most dietary guidelines [24], resulted in 14% increased likelihood of VMS elimination at 1-year follow-up (multivariate OR, 1.14 [95%CI, 1.01–1.28] $P = 0.04$); however, there was no significant improvement in those who had moderate to severe symptoms at baseline (multivariate OR, 1.10 [95%CI, 0.81–1.48] $P = 0.54$) [23]. The improvement in symptoms was driven by both the changes in dietary patterns and changes in adiposity, where those in the intervention were 330% more likely to lose ≥5 lbs (OR, 3.3 [95%CI, 3.1–3.5]) and those in the control group were 230% more likely to gain ≥5 lbs (OR, 2.3 [95%CI, 2.1–2.25]) [23]. However, the change in dietary pattern still produced beneficial effects even in the context of weight gain, where women in the intervention group who gained ≥10 lbs were still 52% more likely to eliminate symptoms than women

who maintained weight in the control group (uncontrolled OR, 1.52 [95%CI, 1.02–2.27]) [23]. Thus the effect of the plant-based dietary intervention on VMS was over and above the effect of weight change, suggesting that plant-based dietary patterns are important and give a substantial benefit whether or not the individual is able to achieve a healthy body composition [25].

Supporting this, studies which examined the effect of non-plant-based diet, exercise and/or surgery-induced weight loss have found minimal or no effect on VMS improvement once change in weight is controlled for. A randomised trial (n = 338 women with high BMIs) [26], which aimed to induce weight loss via a low-calorie diet (1200–1500 kcal/day) and increased physical activity over 6 months, found that women with hot flushes at baseline were 223% likely to report a slight improvement in VMS (unadjusted OR, 2.23 [95%CI, 1.19–4.15] P = 0.01). However, when adjusted for the weight loss and other confounding variables, the low-energy but non-plant-based diet and physical activity had no effect on VMS (adjusted OR, 1.92 [95%CI, 0.95–3.89] $P > 0.05$) [26]. Weight loss induced by bariatric surgery (n = 69 women with VMS) resulted in a decrease in the severity of hot flushes at 6 months post-surgery; however, there was no significant change in the prevalence of vasomotor symptoms or vaginal dryness [27].

Therefore, to reduce the duration and severity of VMS, available evidence suggests that before and/or at the onset of menopausal symptoms, women should be supported to consume a plant-based dietary pattern which suits their preferences and resources and to achieve a healthy body composition through decreased adiposity if possible.

29.2.2 Nutraceutical and Herbal Interventions for the Improvement of Menopausal Vasomotor Symptoms

In line with the finding of dietary patterns, evidence for the use of supplements to improve VMS shows support for plant-based therapies and phytoestrogens (plant-derived xenoestrogens) in particular. A meta-analysis of 18 studies (n = 4 studies using dietary soy isoflavones; n = 14 studies using phytoestrogen supplements) showed that phytoestrogen consumption decreased hot flush incidence by 1.12 (95%CI, –1.12 to −0.95) per day [28]. Two pooled studies of phytoestrogens found night sweat incidence decreased by 1.44 (95%CI, –1.77 to −1.11) per day [28]. The meta-analysis also found some evidence for some herbal supplements, where black cohosh decreased hot flush incidence by 1.12 (95%CI, –1.46 to −0.77; n = 4 studies) per day and red clover (a source of phytoestrogens) reduced hot flush incidence by 0.69 (95%CI, –1.12 to −0.27; n = 7 studies) per day [28]. However, confidence in these estimated effect sizes is low due to large variance between studies, where many studies reported no effect of phytoestrogen or herbal supplementation. The same group has also found that phytoestrogen supplementation is associated with an increase in body weight which per se may affect VMS [29]. Regarding other supplements commonly used for VMS, the small amount of evidence for Chinese

medicinal herbs and non-Chinese medicinal herbs shows no likelihood of benefit [28]. A more recent well-designed RCT found evidence supporting the combined supplementation of red clover isoflavone extract and lactic acid probiotics, where 12 months of supplementation resulted in decreased hot flush incidence of 4.3 (95%CI, −6.8 to −2.3) per day; the severity of the flushes also substantially decreased [30].

Currently, evidence is not yet convincing enough to support recommendation of plant and/or herbal supplements for the relief of VMS. This is particularly important in the context of safety concerns, where there is evidence of serious adverse events. Of the supplements used for VMS, black cohosh caused most serious adverse events and has resulted in cases of liver failure (requiring liver transplants in some cases), nerve and heart damage and death [31, 32]. Soybean supplementation has been found to have drug interactions (with levothyroxine, seaweed and estradiol) and, when used with melatonin in relieving menopausal symptoms, leads to a case of heart complications, drowsiness and headache [31]. Red clover appears to have the least reported adverse events, with only one documented case [31].

29.2.3 Avoidance of Dietary Triggers for the Management of Menopausal Vasomotor Symptoms

The avoidance of caffeine, spices and alcohol as possible triggers of hot flushes are frequently recommended and are even included on the NICE guidelines [20]; however, there has been a paucity of research examining association of these dietary components and VMS. Studies with measurement of Scoville heat units or capsaicin content of spicy foods are lacking. A large cross-sectional observational study of Spanish-speaking women found some association between very frequent consumption of spicy foods and hot flushes, but no association with occasional consumption [33]. The study also found no association of VMS with alcohol consumption [33]. A small cross-sectional study found an association between caffeine intake and greater VMS [34]. It should be acknowledged that cross-sectional research gives no evidence of causality; and clinical trials are needed prior to suggesting menopausal women change their preferred dietary behaviours, especially if such changes may decrease quality of life or social engagement or limit adherence to a plant-based diet (in the context of limiting spicy foods).

29.2.4 Exercise

While exercise is promoted for its general health benefits, studies examining its effect on VMS are conflicting. In 2014 a Cochrane systematic review ($n = 5$ RCTs, $n = 733$ women), comparing exercise with no active treatment, exercise with yoga and exercise with MHT, was found insufficient to show whether exercise is an effective treatment for VMS [35]. A three-arm RCT [36] ($n = 261$ women) compared two 6-month exercise interventions and a control group, where participants in both

exercise interventions groups were offered two face-to-face consultations with a physical activity facilitator to support engagement in regular exercise [36]. In addition, one exercise group received a menopause-specific information DVD and written materials to encourage regular exercise, and the other exercise group was offered the opportunity to attend exercise social support groups in their communities. At 6 months neither of the exercise intervention groups reported significantly less frequent hot flushes/night sweats per week than controls. The cross-sectional Spanish Flamenco project (n = 191 perimenopausal women) found no association between physical fitness and VMSs [37]; however, the Blatt-Kupperman menopausal index was used, whose validity has been questioned [38].

Conversely, some studies have reported beneficial outcomes following exercise interventions. An RCT involving 154 women that were provided with aerobic training for 6 months reported reduced prevalence of VMS for up to 4 years [39, 40]. The evidence with regard to other exercise modalities such yoga, Tai Chi and Pilates is limited, although two systematic reviews have found that yoga may be useful for bothersome vasomotor symptoms [41, 42].

Therefore, although the evidence is not strong for exercise producing additional benefits for VMS symptoms, it should continue to be encouraged for the menopausal and postmenopausal women due to its benefit on overall health and wellbeing.

29.3 Cardiovascular Disease

Cardiovascular disease (CVD) in women is the number one cause of death worldwide [43]. An estimated 17.7 million people died from CVDs in 2015, representing 31% of all global deaths. Of these deaths, an estimated 7.4 million was due to coronary heart disease, and 6.7 million was due to stroke. In Europe, CVD is responsible for over 3.9 million deaths a year or 45% of all deaths. In men, CVD accounts for 40% of all deaths, while in women, it is responsible for 49% of all deaths. By comparison, cancer accounts for just under 24% in men and just under 20% in women [44]. Modifiable risk factors for CVD include smoking, physical inactivity, central adiposity, excessive alcohol consumption and saturated and trans fats [45, 46].

As with lifestyle approaches to managing VMS, plant-based dietary patterns and physical activity are important for decreasing the risk of CVD. To help prevent heart attacks and strokes, the WHO recommend daily physical activity for at least 30 min, consuming at ≥5 serves of fruit and vegetables and limiting salt to 1 teaspoon [47].

29.3.1 Dietary Interventions to Decrease Risk of Cardiovascular Disease

Over the past several decades, there has been much debate and research focussed around the causative and/or preventative effects of single nutrients or foods on cardiovascular health [48]. These ongoing debates around the best or worst type of

fatty acid, low-carbohydrate versus low-fat diets or modifying dairy or types of meat have distracted from the fact that humans do not eat foods or nutrients in isolation, leading to no consistent evidence about which approach is superior or how it should fit into the overall diet [49, 50]. Reflecting the importance of the overall balance of foods and synergistic effects between nutrients in a meal, both researchers and clinicians are instead shifting focus to examine the overall dietary pattern and its influence on health [49]. Although the American Heart Association still recommends changes to single nutrients, such as shifting from saturated to unsaturated fats, they recommend that this should occur simultaneously in an overall healthful dietary pattern such as the Dietary Approaches to Stop Hypertension (DASH) or Mediterranean diet [51].

The traditional Mediterranean dietary pattern is well known for its association with improved long-term health outcomes, especially in relation to cardiovascular disease. The dietary pattern is characterised by consisting of predominantly plant-based (fruit, vegetable and wholegrain) meals which frequently incorporate olive oil, fish and red wine; but the Mediterranean diet also includes other lifestyle factors such as physical activity and eating socially [52]. Therefore, shifting from saturated fats to unsaturated fats as well as limiting sodium through decreased consumption of highly processed foods would occur naturally when changing to a Mediterranean dietary pattern, without an unhelpful focus on single nutrients. Adherence to the Mediterranean dietary pattern is often quantitatively measured through a diet quality index (DQI), such as the Trichopoulou score [53], MEDAS [54] or MEDI-LITE [55], which can be used in the clinic as well as research.

The most recent meta-analysis reporting on CVD outcomes found that women with the highest Mediterranean DQI scores had 30% decreased risk of coronary heart disease or acute myocardial infarction (RR, 0.70 [95%CI, 0.64–0.78]; $n = 6$ studies; 0% heterogeneity), 17% decreased risk of stroke (RR, 0.83 [95%CI, 0.71–0.97]; $n = 3$ studies; 0% heterogeneity) and 15% decreased risk of CVD (RR, 0.85 [95%CI, 0.72–0.99]; $n = 3$ studies; 86% heterogeneity) compared to women with the lowest scores (i.e. lowest adherence to the Mediterranean dietary pattern) [56]. However, this high-impact evidence is based on observational studies which reflect on lifelong adherence to the Mediterranean dietary pattern. The few intervention studies which have implemented the Mediterranean diet in older women have shown that implementation in later life stages still has beneficial outcomes. Specifically, RCTs have demonstrated improved CVD risk factors such as HbA1c, adiposity, blood pressure, lipid profiles, inflammation and carotid atherosclerosis [57, 58], 30% decreased risk of CVD events (HR 0.70 [95%CI, 0.53–0.91]) [55] and 19% decreased risk of all-cause mortality in women with a history of myocardial infarction (OR, 0.81 [95%CI, 0.74–0.87]) [59].

The DASH dietary pattern was specially designed 20 years ago to improve cardiovascular health. DASH has a focus on both food and nutrients, recommending increased fruit, vegetables, wholegrains and low-fat dairy but also aiming to limit sodium, saturated and total fat. Evidence of benefit for cardiovascular health is convincing overall [60]; however, little evidence exists for benefit in older women. Two meta-analyses of observational studies, where the majority of the 260,011

participants were middle- and older-aged women, found that those with diets which imitated the DASH diet had 20% decreased risk of CVD (RR, 0.80 [95%CI, 0.74–0.86]; $n = 6$ studies, 14% heterogeneity) [61] and CVD-death (RR, 0.80 [95%CI, 0.76–0.85]; $n = 11$ studies, 30% heterogeneity) [62]. Only one intervention study has been conducted in older women ($n = 95$ postmenopausal women), where a variation of the DASH diet which included lean red meat was used. The diet implemented for 14 weeks improved some CVD risk factors including blood pressure and body weight even in women taking antihypertensive medication but did not improve lipid profiles [63].

Although the DASH diet is highly researched internationally, less than 30% adhere to the diet when it has been recommended by a health professional, and less than 1% of Western populations follow the diet overall [60]. Poor adherence may be due to the dietary pattern being "synthetically designed" as opposed to "naturally occurring", where it does not reflect the food environment or lifestyle of populations as the Mediterranean diet does.

In addition to the specific DASH and Mediterranean dietary patterns, increased adherence to the Dietary Guidelines for Americans, as measured by various DQIs, is also associated with improved cardiovascular outcomes in observational studies of older women. Compared to those who had the worst adherence to the guidelines, older women with the highest DQI scores had 23–28% decreased risk of CVD events and 21–28% decreased risk of CVD death [62]. Furthermore, a Cochrane review has shown that omega-3 supplements are ineffective for cardiovascular health, and the authors recommend increasing fish intake [64].

Maintaining a good metabolism and normal weight are key factors in reducing the risk of cardiovascular disease, as shown by the 30-year follow-up data from the Nurses' Health Study involving 90, 257 women [65]. The study found that cardiovascular disease risk of women with metabolically healthy obesity was increased compared with women with metabolically healthy normal weight, but risk was considerably higher in women with metabolically unhealthy normal weight, overweight and obesity, highlighting that metabolism is a greater risk factor than adiposity. The metabolic health benefits of intensive weight management were illustrated in a randomised control which resulted in remission of type 2 diabetes [66]. This 12-month randomised controlled trial recruited 306 individuals in the primary care in the UK. Participants were aged 20–65 years who had been diagnosed with type 2 diabetes within the past 6 years, had a body mass index of 27–45 kg/m^2 and were not receiving insulin. The intervention comprised withdrawal of antidiabetic and antihypertensive drugs, total diet replacement (825–853 kcal/day formula diet for 3–5 months), stepped food reintroduction (2–8 weeks) and structured support for long-term weight loss maintenance. Diabetes remission was achieved in 68 (46%) participants in the intervention group and six (4%) participants in the control group [66]. Remission varied with weight loss in the whole study population, with achievement in none of 76 participants who gained weight, six (7%) of 89 participants who maintained 0–5 kg weight loss, 19 (34%) of 56 participants with 5–10 kg loss, 16 (57%) of 28 participants with 10–15 kg loss and 31 (86%) of 36 participants who lost 15 kg or more [66]. However sustained weight loss is difficult to achieve after

the menopause, and then there is the issue of weight regain. It is therefore essential not to stigmatise overweight and obese women but encourage health at every size through a healthy dietary pattern and physical activity.

Overall, evidence for improving cardiovascular health in postmenopausal women aligns with evidence to improve VMS, where women should be supported to consume a plant-based dietary pattern. Choice of dietary pattern should be patient- and family-centred, aligning with their preferences, resources and lifestyle so as to increase adherence. Self-monitoring through online DQIs such as the Healthy Eating Quiz (http://healthyeatingquiz.com.au/) [67] can support implementation with quantitative and personalised feedback, but without the burden of single-nutrient measurement.

29.3.2 Nutraceutical Interventions to Decrease Risk of Cardiovascular Disease

Most of the focus on improving CVD outcomes has been on modifying dietary intakes as opposed to nutraceutical interventions; however, there has been some interest in antioxidants, polyphenols and omega-3 supplements, all prevalent components in the Mediterranean diet. There has also been concern about calcium and vitamin D supplementation in postmenopausal women, where use has been hypothesised to increase risk of CVD [68].

Oxidative stress is thought to be directly involved in aetiology of atherosclerosis leading to the examination of antioxidants for preventing CVD. Observational studies of diets high in antioxidants have found beneficial effects [69]. However, supplementation of antioxidants has produced conflicting findings with some evidence of benefit, no effect and in some cases harm as the supplements become pro-oxidative in vivo [69, 70]. Currently, supplementation of antioxidants for CVD is not recommended, and instead a high consumption through a plant-based diet should be supported.

A meta-analysis comparing usual or refined olive oil with high polyphenol olive oil showed improvements in CVD risk factors including malondialdehyde (MD, −0.07 μmol/L [95%CI, –0.12 to −0.02 μmol/L), oxidised LDL (SMD, –0.44 [95%CI, –0.78, −0.10 μmol/L]), total cholesterol (MD, 4.5 mg/dL [95%CI, –6.54, −2.39 mg/dL) and HDL cholesterol (MD, 2.37 mg/dL [95%CI, 0.41, 5.04 mg/dL]) [71]. However, most of the samples included in the meta-analysis were in younger males and females, with only one study conducted in postmenopausal women (n = 10 from Italy) who were given 50 g/day of high polyphenol olive oil. Although sample was small and presumably had baseline adherence to the Mediterranean diet, an additive effect of the high polyphenol olive oil was demonstrated in this group in regard to decreased oxidative DNA damage [71].

Due to the anti-inflammatory properties of omega-3, fish is often hypothesised as one of the main contributors to improved CVD outcomes associated with the Mediterranean diet [66]. However, two recent meta-analyses found that when omega-3 is consumed in supplemental form, it has found no evidence of effect for CVD outcomes [64, 72] and is not recommended for older adults [73].

While calcium and vitamin D supplements have been widely adopted to preventing or managing osteoporosis in postmenopausal women, there has been concern that they increase CVD risk and should be avoided. However, a meta-analysis in postmenopausal women (n = 18 studies, n = 63,653) found no evidence to indicate increased risk of CVD or all-cause mortality with calcium supplementation, with or without vitamin D [68].

Overall, there are no nutraceuticals currently recommended for use in postmenopausal women to improve CVD outcomes, and calcium and vitamin D may be recommended when indicated with no concern for increasing CVD risk. Although there may be benefit from high polyphenol olive oil, consumption of 50 mL of unheated oil is likely to be impractical for most women, and obtaining high polyphenol olive oil outside of the Mediterranean region may also be difficult. Instead, evidence continues to support a plant-based dietary pattern which includes olive oil and fish, such as the Mediterranean dietary pattern.

29.3.3 Exercise

Considerable evidence has established the value of high levels of physical activity for the prevention and treatment of CVD [74]. With the realistic proviso that physical activity is *anything* that makes you move your body and burn calories, and that *something* is always better than nothing, the American Heart Association recommends the following for overall cardiovascular health [75]:

- At least 30 min of moderate-intensity aerobic activity at least 5 days per week for a total of 150
- At least 25 min of vigorous aerobic activity at least 3 days per week for a total of 75 min or a combination of moderate- and vigorous-intensity aerobic activity
- Moderate- to high-intensity muscle-strengthening activity at least 2 days per week for additional health benefits
- For lowering blood pressure and cholesterol:
- An average of 40 min of moderate- to vigorous-intensity aerobic activity three or four times per week

An increase in the use of "passive" modes of transport has been associated with declining physical activity levels. A UK Biobank study of 263,450 participants (n = 106,674; 52% women; mean age 52.6) found that cycle commuting was associated with a lower risk of cardiovascular disease, cancer and all-cause mortality, while walking commuting was associated with a lower risk of cardiovascular disease only [76]. In addition the prospective Women's Health Study (n = 27,536 recruited in 1992–1995; followed to 2013) found that the level of global cardiovascular risk did not modify the inverse association between leisure time activity and incident CVD [77]. There is therefore a need to provide safe and affordable facilities and environments for women to exercise in [78, 79].

29.4 Osteoporosis

Osteoporosis causes more than 8.9 million fractures annually worldwide but is mainly a disease of older women where it affects 1 in 3 women compared to 1 in 5 men, and the majority of fractures occur in those ≥80 years [80, 81]. The total number of people with osteoporosis in Europe has been predicted to rise by 23%, from 27.5 million in 2010 to 33.9 million in 2025, due to the increasing proportion of elderly people in the population. Modifiable factors for the nonsymptomatic disease in women include smoking, excessive alcohol intake, adiposity, limited weight-bearing exercise, calcium intake, serum vitamin D, blood pressure and cholesterol levels [82]. Osteoporosis does not only limit physical function through fractures; a systematic review found that hip fracture increases risk of death by 8.4–36%, where death was highest in the days and weeks following the index fracture, but the risk remained elevated for months to years [83]. The UK 2016 NICE recommendations for the prevention of fragility fractures regarding advice on diet and exercise include [84]:

- Eat a balanced diet as this may improve bone health.
- Drink alcohol within recommended limits, as alcohol is a dose-dependent risk factor for fragility fracture.
- Take regular exercise (tailored to the person) to improve muscle strength. Encourage:
- Walking, especially outdoors, as this will increase exposure to sunlight, increasing vitamin D production.
- Strength training (such as weight training) of different muscle groups (e.g. hip, wrist and spine).
- A combination of exercise types, for example, balance, flexibility, stretching, endurance and progressive strengthening exercises.
- Calcium and vitamin D supplementation.

29.4.1 Dietary Interventions to Decrease Risk of Osteoporosis

The key dietary interventions for musculoskeletal health are maintaining an adequate intake of calcium and vitamin D as well as ensuring adequate protein intake [85–87]. During the ageing process, the absorption of calcium decreases, and therefore the daily dietary requirement goes up [88]. As this often occurs simultaneously with decreasing appetite, many older women do not meet their dietary calcium requirements. Recommendations on daily calcium intake vary worldwide. For example, in women over 50 years, the USA recommends 1200 mg [89], Australia recommends 1300 mg [88], but the UK National Osteoporosis Society (NOS) recommends only 700 mg [90]. Beyond calcium, other nutrients play a key role in maintaining bone mineral density, including vitamin D, vitamin K, fluoride, potassium, boron and magnesium [88].

Dietary patterns during childhood and young adulthood have a large impact on bone mineral density in older age; however, they are not modifiable risk factors to manage osteoporosis in postmenopausal women [91]. However, dietary changes in older women can have beneficial effects where the goal is to maintain and prevent loss of bone mineral density. A randomised trial which provided postmenopausal women with intensive dietary and physical activity counselling plus three daily serves of calcium and vitamin D fortified dairy (milk and yoghurt) for 30 months prevented loss of arm, total spine and total body bone mineral density, whereas the control group continued to lose bone mineral density [92]. Because foods which are rich in calcium are also sources of other nutrients beneficial for bone health, such as protein, magnesium and vitamin D (usually fortified), women with inadequate intakes should be supported to meet requirements via foods and beverages whenever possible [91].

In addition to consuming the required nutrients, the diet must also avoid excess phosphate, alcohol and caffeine [91]. There is research to show that restrictive weight loss diets such as a low-fat diet enhance bone mineral density loss [93]. This highlights the detrimental effect that restrictive diets may have on the risk of osteoporosis in older women and supports the use of liberalised plant-based diets which are rich in vitamins and minerals as well as dairy and fish for calcium and protein.

29.4.2 Nutraceutical Interventions to Decrease Risk of Osteoporosis

The first study to examine calcium and vitamin D was undertaken over 20 years ago (n = 3270 women, mean age 84 ± 6 years) and found that vitamin D3 and calcium supplements reduced the risk of hip fracture and other nonvertebral fractures [94]. Since then there have been many studies and analyses of calcium and vitamin D supplements alone or in combination on fracture. The results are contradictory and may depend on the study population, compliance with therapy and background dietary intake [95]. However, calcium and vitamin D play a key role in bone metabolism and are therefore has advised as an integral part of osteoporosis management in guidelines worldwide [96, 97].

However, there is no consistent evidence that calcium supplementation at, or above, recommended levels reduces risk of osteoporosis. Clinical trials have produced inconsistent results regarding the role of calcium supplements regarding fracture risk [98–101]. An expert consensus meeting of the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) and the International Foundation for Osteoporosis (IOF) concluded that supplementation with calcium alone for fracture reduction is not supported by the literature [102]. Caution has also been expressed in recommending calcium supplements in women whose diet is replete, because of an increased risk of renal stones and cardiovascular disease such as found in the Women's Health Initiative trials [103–106].

The main source of vitamin D is cutaneous synthesis and in northern latitudes occurs only in the summer, resulting in deficiency for about half of the year [107].

Dark skin pigmentation, excessive sun protection (shade, extensive clothing cover, sunscreen use, limited mobility) and air pollution also reduce vitamin D skin synthesis. Other risk factors for vitamin D deficiency include poor diet or food quality, adiposity, malabsorption syndromes, medication use (e.g. anticonvulsants, antiretrovirals) and skin ageing. Emerging evidence is associating vitamin D deficiency with not only osteoporosis but also cardiovascular disease, diabetes, cancer, infections and neurodegenerative disease [108]. Fortified foods do not necessarily provide sufficient amounts of vitamin D, and regular sunlight exposure (without sunscreens) for 15 min, 3–4 times a week, in the middle of the day in summer generate healthy levels in adults but may still be inadequate in older adults due to the thinning of the skin [91, 108].

Vitamin D supplementation can be undertaken with either vitamin D2 (ergocalciferol) or vitamin D3 (cholecalciferol). In the UK, national guidelines aim to increase supplement use to prevent vitamin D deficiency among at-risk groups including people aged over 65, but prescribing policy depends on local clinical commissioning groups [109, 110]. The UK Scientific Advisory Committee on Nutrition (SACN) recommended a reference nutrient intake (RNI) of 400 IU daily for adults of all ages in 2016 [111]. However, in postmenopausal women at increased risk of fracture, the available evidence supports the use of higher doses. In two 2009 meta-analyses, a protective effect of vitamin D on falls was only seen at daily doses ≥700 IU ((RR, 0.81 [95%CI, 0.71–0.92; n = 7 studies; n = 1921 participants) [112] and improvement in fracture risk only seen at >400 IU (RR, 0.80 [95% CI, 0.72–0.89); n = 9 studies; n = 33,265 participants) [113]. Since then, two subsequent meta-analyses found that vitamin D alone did not improve bone mineral density (n = 23 studies, n = 4082, 92% older women) [114] or prevent fractures; however, dosing was not considered in the analyses [115]. Reflecting the best available evidence, the UK National Osteoporosis Guideline Group (NOGG) recommends that in postmenopausal women who are at increased risk of fracture, a daily dose of 800 IU of cholecalciferol should be advised [97].

Although evidence is unclear for calcium and vitamin D supplemented alone, both vitamin D and calcium for bone mineralisation, and evidence supports combined supplementation for the prevention of fractures [115]. A 2016 meta-analysis (n = 8 studies, n = 30,970 participants) of combined calcium and vitamin D supplements decreased the risk of total fracture by 15% (SRRE, 0.85; 95% confidence interval [CI], 0.73–0.98) and hip fracture by 30% (SRRE, 0.70; 95% CI, 0.56–0.87) [116]. Although the Women's Health Initiative clinical trial results published in 2017, which supplemented 1000 mg of calcium and 400 IU of vitamin D, did not prevent height loss in healthy postmenopausal women, the vitamin D dose was likely inadequate, height is a less sensitive marker of bone mineral density, and the height loss in both intervention and control groups was well below the 2 cm criterion for fracture risk [117, 118]. In 2017 an expert consensus paper of the European Society for Clinical and Economic Aspects of Osteoporosis, the Osteoarthritis and Musculoskeletal Diseases (ESCEO) and the International Foundation for Osteoporosis (IOF) concluded that calcium and vitamin D supplementation leads to a modest reduction in fracture risk, although population-level intervention has not been shown to be an effective public health strategy [102].

Soy isoflavone, a type of phytoestrogen, acts as oestrogen agonists and antioxidants in bone cells, leading to interest in isoflavone supplementation for the preservation of bone mineral density in postmenopausal women. A meta-analysis identified that benefits have only been achieved with doses ≥80 mg/day supplemented for >12 months, where bone mineral density of the lumbar spine improved by 6.0 mg/cm^2/year ([95%CI, –0.7–2.7] $P = 0.08$; $n = 8$ studies; $n = 654$ women). There was no difference in effect between isoflavones supplemented as an extract or consumed as part of soy products such as isolated soy protein [119]. There has not been a review of other forms of phytoestrogens on osteoporosis risk. Individual RCTs have suggested other phytoestrogens may be beneficial [120–122]; however, a meta-analysis of RCTs is needed prior to making clinical applications.

Thus, aligning with recommendations for other post-reproductive health, dietary patterns and lifestyle factors are the most important strategy for preventing bone mineral density loss and fractures. Adequate calcium, vitamin D and other vitamin and mineral intakes should be achieved through dietary modification where possible, as the synergistic effects of food and nutrients in vivo achieve the greatest outcomes. In order to evaluate the overall dietary pattern for optimal bone mineral density, individualised dietary assessment and intervention by a dietitian should be considered. If nutrient requirements cannot be met by diet alone, supplementation and/or fortification of combined calcium and vitamin D (at doses of ≥700 IU/day) may then become appropriate [96]. If calcium intake is adequate but peak serum vitamin D levels cannot be achieved through diet and sun exposure, single vitamin D supplementation at ≥700 IU/day should be considered. There may be additional benefits of consuming high doses of soy isoflavones, which may be achieved through dietary consumption of soy products or supplementation.

29.4.3 Exercise

With regard to osteoporosis, a Cochrane review found that exercise had a relatively small, but possibly important, effect on bone density (1%) compared with control groups ($P < 0.05$) [123]. Physical exercise, furthermore, reduces the risk of falls in the elderly, indirectly influencing fracture rates [124, 125]. In 2018 the US Preventive Services Task Force (USPSTF) found adequate evidence that exercise interventions have a moderate benefit in preventing falls in older adults [126]. Gait velocity declines with age with the greatest fall in the women over 70 [127]. Identifying the age of gait velocity decline of healthy women could allow timely interventions to slow the general decline associated with lower gait velocities, such as falls and fracture. Various types of exercise can be undertaken (weight bearing, back extension, Tai Chi, Pilates, vibration), but it is unclear what types, intensity and duration are the most benefit [128, 129].

29.5 Dementia and Cognitive Decline

Dementia has become a public health priority with substantial impact on not only individuals and their families but also health-care, economic and welfare systems of whole societies. In the 1980s, the governments of developed countries started to express concern about rapid population ageing with dementia and cognitive decline being important causes of disability in later life. However, recent evidence suggests stable or decreased prevalence over the last decades [130, 131].

Dementia is a progressive, irreversible decline in cognition that, by definition, impacts on a patient's pre-existing level of functioning. The clinical syndrome of dementia has several aetiologies with overlapping pathological and clinical features. Alzheimer's disease (AD) is the most common, thought to be present in 50–75% of cases [132]. Other processes include vascular, Lewy body and frontotemporal pathologies. Dementia and cardiovascular disease have many common risk factors, including hypertension, hypercholesterolaemia, obesity and diabetes. Cardiovascular disease is an important risk factor for cognitive decline in postmenopausal women. In the Women's Health Initiative Memory Study, women with CVD tended to be at increased risk for cognitive decline compared with those free of CVD (hazard ratio [HR], 1.29; 95% CI, 1.00–1.67) [133].

29.5.1 Dietary Interventions to Decrease Risk of Dementia and Cognitive Decline

As with cardiovascular health, there has been some focus on single nutrients and their effect on brain ageing [134]. However, as nutrients are consumed as part of dietary patterns and not alone, such research is not helpful when needing to make recommendations to individuals. Observational studies have shown that pant-based dietary patterns, and the Mediterranean diet in particular, have been associated with improved cognitive function in ageing [135]. High Mediterranean DQI scores (i.e. greater adherence to the Mediterranean diet), as well as more frequent legume and fish consumption [two Mediterranean diet core foods], have been associated with greater cortical thickness in a cross-sectional sample [134]. In a prospective cohort study, low Mediterranean DQI scores in an older Scottish cohort were predictive of total brain atrophy over a 3-year interval [136]. Fish and meat consumption did not drive this change, suggesting that other components of the Mediterranean diet or, possibly, all of its components in combination are responsible for the association with improved brain ageing [136].

A meta-analysis of observational studies showed that older adults who had the highest Mediterranean DQI were 21% less likely to develop cognitive disorders (RR, 0.79 [95%CI, 0.7–0.90]; $n = 8$ studies) [137]; however, no effect was found when examining outcomes in older women only [137]. This finding is supported by Psaltopoulou et al. [138], where meta-regression found that the Mediterranean diet

was more protective against stroke for males than for females. However, males and females benefited equally from the Mediterranean diet in regard to depression and cognitive impairment. Another significant finding from both meta-analyses is that benefits for cognitive outcomes were only found in those with the highest adherence to the Mediterranean diet; and moderate adherence provided no benefit [137, 138]. Intervention studies have demonstrated that commencing a Mediterranean diet, supplemented with high polyphenol olive oil, in later age may still have some benefits for cognitive function [139].

For those who are unable to follow the Mediterranean diet, other dietary patterns, such as adherence to national dietary guidelines in, have also been associated with lower psychological distress; however, the effect sizes were lower than that of the Mediterranean diet [140]. Furthermore, observational studies have also shown older adults who had a very high consumption of fish (≥4 vs. <1 fish serving/week) had a slow rate of memory decline, equal to being 4 years younger [141].

29.5.2 Nutraceutical Interventions for Improved Cognitive Function

Reflecting the great interest in the preservation of brain function in ageing, nutraceuticals thought to prevent cognitive decline are widely available and consumed. There has been interest in omega-3, vitamin D, resveratrol, saffron and polyphenols.

Some RCTs have found that high doses of omega-3 polyunsaturated fatty acids (2.2–2.4 g/day supplemented for 6 months) given to older adults with no or mild cognitive decline showed mild improvements in memory [142]. However, RCTs using lower doses have found no effect on cognitive function with interventions of up to 5 years [142, 143]. Furthermore, no studies have identified any benefit of omega-3, supplemented alone or in combination with vitamins and minerals, for the prevention and treatment of dementia [73, 144].

Higher serum vitamin status has been associated with improved memory in a large observational study of French older adults (33% women) [145]. Epidemiological evidence also supports associations between low serum 25(OH)D concentrations and poorer cognitive performance in community-dwelling older populations, although an optimal 25(OH)D level for cognitive health could not be determined. The RCT part of the Women's Health Initiative which supplemented 1000 mg of calcium and 400 IU of vitamin D3 to 2034 older women found no significant protective effect against dementia or cognitive impairment. However, serum vitamin D status was not measured, and 400 IU may be an inadequate dose for effect. Therefore, the effect of raising 25(OH)D concentrations on cognitive function remains unclear, as there is a paucity of interventional evidence [146]. Further research is required before vitamin D can be recommended as a preventative supplement for cognitive decline; however, adequate serum vitamin D status should be achieved for overall health.

Resveratrol is a polyphenol found in red grapes, berries and red wine. A meta-analysis of resveratrol supplementation found doses of 150–500 mg improved delayed recognition (SMD, 0.39 [moderate effect size] [95%CI, 0.08–0.7]; $n = 3$ studies; $n = 166$ participants] and negative mood (SMD, –0.18 [small effect size] [95%CI, –0.31 to −0.05]; $n = 3$ studies; $n = 163$ participants], where most participants were older adults and > 50% were women [147]. Although there were no side effects, no improvement in many other measures of cognitive function was found, and resveratrol supplements may have a high financial cost. Although no meta-analysis has been done considering all forms of polyphenols on cognitive function, qualitative synthesis in a systematic review identified many clinical trials of berry juice, cocoa and isoflavone supplementation which reported beneficial outcomes. However, evidence is not yet strong or clear enough for clinical recommendations [148].

Although there is good emerging evidence supporting saffron supplementation for the treatment of depression and anxiety, no studies have yet been conducted in older adult samples [149]. Therefore, further research is required before it can be recommended for postmenopausal women.

Overall, high doses of omega-3 polyunsaturated fatty acids and resveratrol may have some benefit on cognitive performance in older women; however, effect sizes are modest, there is no evidence of improvement in dementia risk, and the impact of cost and convenience should be considered. If supplements are used, women should also be supported to have a high polyphenol intake from the diet, such as following a plant-based dietary pattern, with a focus on polyphenol-rich foods such as tea, coffee, soy, cocoa, fruits and vegetables. Postmenopausal women should be regularly evaluated for serum vitamin D status, which should be corrected via food or supplemental strategies; however, there is not yet evidence to support vitamin D supplementation for the protection against cognitive decline.

29.5.3 Exercise

While there is extensive literature about the exercise programmes for people with dementia, there is increasing evidence that physical activity (PA) reduces the risk of cognitive decline and dementia [150]. Furthermore there is a growing body of literature that recognises the positive effects of exercise on mood, anxiety, stress and depression [151]. Data from 11,391 men and women (aged ≥50) were obtained from the English Longitudinal Study of Ageing cohort. Assessments were carried out at baseline (2002–2003) and at biannual follow-ups (2004–2013) [150]. Older adults who carried out moderate to vigorous activity at least once per week had a 34–50% lower risk for cognitive decline and dementia over an 8–10-year follow-up period. From pre- to post-dementia diagnosis, those who decreased PA levels had a larger decrease in immediate recall scores, compared to those who maintained or increased PA levels. Other forms of activity may be of benefit. Thus, data from the Scottish Health Survey 2012–2013 of 9709 adults found that gardening was

positively associated with mental health [152]. Gardening has the advantage of being potentially cost-effective and a culturally acceptable enjoyable community-based health initiative [153].

29.6 Conclusion

A new holistic approach to menopause and post-reproductive health beyond medicines is required. Overwhelmingly, evidence supports the early adoption of an active lifestyle and a plant-based dietary pattern which also contains regular consumption of fish and vitamin D fortified dairy. The Mediterranean diet appears to provide the best outcomes for postmenopausal women; however, any plant-based dietary pattern which aligns with the lifestyle and values of the individual should be supported. Although early adoption of these lifestyle and dietary changes may provide the best outcomes, changes to the diet and activity levels made later in life still provide benefits. There is some evidence supporting specific nutraceuticals for post-reproductive health outcomes; however, food-first strategies should be recommended prior to supplementation. Restrictive, low-energy diets focussed on weight loss are not likely to provide any benefit to be sustainable in older women, and may reduce bone mass, and should therefore be avoided. Instead, promotion of an active lifestyle and a plant-based dietary pattern are likely to naturally decrease adiposity and increase muscle mass, leading to additional benefits; however, even if no change in body composition is achieved, outcomes are still likely to improve. For women at high risk of chronic disease, individualised dietary assessment and intervention by a dietitian is recommended to help make sustainable changes. Implementation also requires teaching of other health and allied health professionals at an early stage. Of primary importance, interventions need to be affordable, feasible, acceptable and enjoyable with a focus on improving quality of life.

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Effects of Exercise on Menopausal Prevalent Conditions

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30.1 Introduction

Physical activity is the antidote to sedentary lifestyle and its consequences, and includes all forms of muscle movement. Physical activity may range from ordinary activities such as walking or household tasks up to other hard tasks, such as sports or several active leisure pursuits. Exercise refers to physical activity specifically intended to improve health and/or fitness. There are three main types of exercise: stretch, strength, and aerobic exercises. Stretch exercising allows avoiding injury and ameliorates performance; strength exercise helps control weight and also avoid injury while stimulating bone formation; and aerobic exercise protects cardiovascular health, that consumes fat mass and contributes at maintaining a healthy weight and fitness.

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Physical activity induces cardiocirculatory, endocrine, and metabolic benefits. Scientific research during the last three decades has demonstrated that exercise is a countermeasure against obesity, cancer, cardiovascular disease, and even mortality. It seems that exercise stimulates the immune system [1], mobilizes and delivers oxygen and substrate to maintain energy turnover [2] and modifies genetic susceptibility to obesity [3]. In addition, myokine and myometabolites may interfere against degenerative diseases and the ageing of systems [4]. The term exercise corresponds to physical activity aimed at improving health and fitness. Programmed exercise has been used to study different health outcomes. Programmed exercise is frequently recommended for peri-, postmenopausal and older women. Although programmed exercise may have benefits, some recommendations have been based on the results from observational studies, and thus clinical effects are less than expected.

The menopausal transition is associated with endocrine adjustments and changes in social environment. During this stage, several symptoms and co-morbid complications are frequent and may vary in intensity and duration. Although vasomotor symptoms are perhaps the most frequent during those years, others may prevail for longer periods and can be more prevalent than vasomotor symptoms, such as changes in body composition and metabolic outcomes, depressive symptoms, musculoskeletal pain, insomnia or sleep disturbances, and both muscle mass and performance [5–10]. Despite several studies, it has been difficult to establish the true relationship between the benefits of exercise on these symptoms or conditions during the second half of female life. The purpose of this chapter is to review current data from selected observational studies, randomized controlled trials (RCTs), and meta-analyses regarding the effects of programmed exercise on body composition, insulin sensitivity and metabolic endpoints, vasomotor symptoms, sleep quality, and emotional prevalent conditions (depressive symptoms, anxiety, and perceived stress) in women during the second half of life.

30.2 Changes in Body Composition and Physical Activity in Mid-Aged and Older Women

Ageing and menopause have impact on body composition, physical fitness, and exercise. Changes in body composition is also a marker of the risk of chronic diseases. Around the menopause, there are changes in body composition, although weight may stay stable. Total fat mass progressively increases, with a selective accumulation in the intra-abdominal compartment, whereas subcutaneous fat may stay stable [11]. During early postmenopausal years, the level of physical activity is responsible for the variations of fat distribution that occured during the menopausal transition, while the menopause onset, *per se*, has a secondary role [12].

Longitudinal studies in perimenopausal women have shown that there is some reduction in energy balance which contributes to total and abdominal fat accumulation. In general, body fat and weight increased significantly over time only in those women who became postmenopausal. Using dual-energy X-ray absorptiometry

(DEXA) one study reported [13] that 2 years before the onset of the menopause, physical activity decreased and remained low. Follow-up studies using magnetic resonance imaging (MRI) indicate that during the menopausal transition, total abdominal fat increases despite no changes in body weight, waist circumference, and physical activity, and this evolution was not related to the menopause [14]. In non-obese premenopausal women (mean age 49 years at baseline), a longitudinal study showed that there is an increase in fat mass, fat mass percentage, trunk fat mass, visceral fat, plasma glucose, and high-density lipoprotein cholesterol (HDL-C). However, women did not have metabolic deterioration during the 5-year follow-up [15].

Using MRI, Withaker et al. [16] reported that body mass index (BMI), visceral adipose tissue (VAT), and subcutaneous adipose tissue (SAT) accrual in adult men and women increased over a 7-year period. Changes in BMI were smaller than those observed for VAT, SAT, and VAT/SAT ratio. In addition, VAT, SAT, and VAT/SAT gain decreased linearly, and this deceleration was greater in men than in women.

The main objective of physical activity and programmed exercise is to maintain a healthy body composition and functional/physical independence. Physical activity can improve body composition, although it can be masked if only body weight or BMI is measured, and the benefits of exercise are more pronounced in postmenopausal women than in premenopausal ones. In addition, estrogen hormone therapy can also provide benefits to body composition [17]. Walking interventions produce beneficial changes in body composition in peri- and postmenopausal women. A meta-analysis of RCTs reported that walking for at least 4 weeks produced a significant reduction in BMI, body weight, and body fat percentage [18].

In young people, strength training improves body composition. In middle-aged women, body fat is reduced 1.3% and fat-free mass increased 656 g for each day per week of training. Therefore, this type of exercise has a better impact on body composition while age, energy, and protein consumption have small effects. Despite this, when results are adjusted for differences in physical activity and menopausal status the correlations weakened significantly [19].

A RCT regarding a 12-month exercise program, including aerobic and muscle strength training in sedentary postmenopausal women (50–69 years), was not associated to changes in weight, BMI, and hip circumference although total body fat and percentage of body fat were reduced when compared to the control group [20]. Therefore, exercise induced changes in body composition and had a positive effect on fat distribution. A meta-analysis of RCTs of menopausal women reported a moderate effect of short-term exercise on body fat mass, waist circumference, triglyceride levels, and bone mineral density as compared to women who did not perform exercise [21].

A high adherence to a healthy dietary pattern (Mediterranean diet) is inversely associated with overweight/obesity in peri- and postmenopausal women. The occurrence of low to severe problems during female midlife is positively associated with overweight/obesity. It seems that a high adherence to the Mediterranean diet pattern and a body mass index of 25 kg/m^2 or lower may improve quality of life in peri- and postmenopausal women [22]. Dietary and exercise intervention may reduce body weight and improve body composition in obese peri- and postmenopausal women.

A meta-analysis of RCTs showed that a combination of diet and exercise was associated with greater weight loss than dietary intervention alone. In addition, diet combined with exercise produced greater fat and lean mass loss than diet alone. It seems that exercise may enhance the changes produced by diet over body weight and composition [23].

In healthy older women (aged 61–81), combined aerobic and low- to moderate-intensity exercise for 10 weeks increased muscle strength and gait speed, independent of the order of the exercise combination. In addition, there was improvement in dynamic balance with moderate-intensity combined training [24].

There is a great discussion regarding the importance of lifestyle and exercise in older subjects with sarcopenic obesity in terms of improving muscle mass and performance, and therefore indirectly preventing falls (and thus fractures). A recent meta-analysis of RCTs reported that exercise alone or combined with dietary supplementation for at least 6 weeks in elder individuals increased grip strength (upper extremity performance), gait speed (lower extremity performance), and appendicular skeletal muscle mass. In addition, both interventions were associated with a reduction of waist circumference, total and trunk fat mass. Therefore, exercise may improve both body composition and muscle performance even in that particular population [10].

30.3 Effect of Exercise on Insulin Sensitivity, Anthropometry, and Metabolic Outcomes in Postmenopausal Women

Physical activity and regular exercise may improve different endocrine endpoints, including insulin sensitivity, glucose homeostasis, and lipid metabolism. Physical activity and exercise (all types of muscular activity) are key factors at maintaining glycemic control and insulin sensitivity. Physical activity may also contribute at avoiding excessive body weight and co-morbidities such as hypertension, dyslipidemia, the metabolic syndrome, and some cancers related to insulin resistance.

Data regarding the effects of exercise on insulin sensitivity in postmenopausal women is controversial. We recently performed a systematic review and meta-analysis of seven RCTs regarding the effects of programmed exercise for at least 12 weeks of duration on insulin and related outcomes, anthropometric endpoints, and metabolic blood variables [25]. Displayed in Table 30.1 are the effects of programmed exercise on circulating levels of insulin, insulin growth factor 1 (IGF-1), IGF-binding protein 3 (IGFBP-3), and values of the homeostatic model assessment-insulin resistance (HOMA-IR). The duration of programmed exercise was classified as “mid-term exercise intervention” (MTEI) for 3–4 months; and “long-term exercise intervention” (LTEI), corresponding to 6 to 12 months of duration. Among the most important findings were that exercise for 3–4 months was associated with significant lower circulating insulin levels and a reduction of the HOMA-IR values when compared to controls; while there were no significant effects of exercise intervention of 6–12 months in comparison to controls. In addition, there were no significant differences for circulating levels of IGF-1, glucose, and triglycerides with

Table 30.1 Meta-analysis of randomized controlled trials: mean differences (and 95% confidence intervals) between baseline and post-intervention regarding primary and secondary hormone and metabolic outcomes

Outcome	Exercise interventions (*n*)	Exercise (*n* = women)	Control (*n* = women)	Mean difference (95% CI)	I^2 (%)	*P*
Insulin (pmol/L)						
– Mid-term EXE intervention	3	110	109	−6.50 (−11.19; −1.82)	0	0.006
– Long-term EXE intervention	4	269	222	−6.73 (−16.91; 3.44)	0	0.19
HOMA-IR						
– Mid-term EXE intervention	3	110	109	−0.18 (−0.34; −0.03)	0	0.02
– Long-term EXE intervention	3	229	199	−0.13 (−0.76; 0.50)	39	0.68
IGF-1 (ng/mL)						
– Mid-term EXE intervention	2	109	107	30.98 (−41.68; 103.64)	87	0.40
– Long-term EXE intervention	2	204	173	0.66 (−12.09; 13.41)	0	0.92
IGFBP-3 (ng/mL)						
– Long-term EXE intervention	2	204	173	−307.15 (−848.62; 234.33)	64	0.27
BMI (kg/m^2)						
– Mid-term EXE intervention	3	45	44	−1.48 (−2.48; −0.48)	0	0.004
– Long-term EXE intervention	3	182	136	−0.72 (−1.92; 0.48)	0	0.24
Waist circumference (cm)						
– Mid-term EXE intervention	3	45	44	−1.87 (−3.02; −0.72)	0	0.001
– Long-term EXE intervention	3	182	136	−3.74 (−6.68; −0.79)	0	0.01
Weight (kg)						
– Long-term EXE intervention	3	182	136	−1.67 (−5.40; 2.06)	0	0.38

(continued)

Table 30.1 (continued)

Outcome	Exercise interventions (*n*)	Exercise (*n* = women)	Control (*n* = women)	Mean difference (95% CI)	I^2 (%)	*P*
Body fat (%)						
– Mid-term EXE intervention	3	45	44	−2.99 (−4.85; −1.14)	0	0.002
Glucose (mmol/L)						
– Mid-term EXE intervention	3	110	109	−0.38 (−0.88; 0.11)	66	0.13
Long-term EXE intervention	4	269	222	0.00 (−0.13; 0.14)	12	0.97
Triglycerides (mmol/L)						
– Mid-term EXE intervention	3	110	109	−0.13 (−0.30; 0.03)	0	0.12
– Long-term EXE intervention	3	152	135	−0.07 (−0.26, 0.12)	0	0.47

Heterogeneity of studies as measured by I^2. Data from Bueno-Notivol et al. [25]
BMI body mass index, *CI* confidence interval, *EXE* exercise, *HOMA-IR* homeostasis model assessment of insulin resistance, *IGF-1* insulin growth factor 1, *IGFBP-3* insulin growth factor binding protein

both MTEI and LTEI. On the other hand, there was a significant reduction in BMI and body fat percentage after MTEI, and in waist circumference after both MTEI and LTEI [25].

Postmenopausal women have lower body fat oxidation and lower energy expenditure during exercise, and some four kg less of lean body mass (LBM) than premenopausal women [26]. In non-obese late premenopausal and early postmenopausal women, performing high-intensity aerobic exercise for 3 months reduced body weight, waist circumference, and fat mass while increasing lean body mass. This programmed exercise reduced diastolic blood pressure, total cholesterol, low-density lipoprotein-cholesterol (LDL-C), and improved insulin response during the oral glucose tolerance test [27]. Training increased insulin sensitivity by several mechanisms, including augmented expression of hexokinase and glycogen synthase, and the dephosphorylation of glycogen synthase [28].

Metabolic and endocrine effects may vary depending on the type of exercise. For instance, a 60 min session of Nordic walking intervention, three times/week, for 12 weeks produced beneficial changes on BMI, fat mass, insulin levels, blood pressure, and probably on endothelial function in healthy postmenopausal women [29].

Di Blasio et al. [30] reported that supervised walking training for 13 weeks in postmenopausal women produced a significant reduction of the plasmatic ratio of cortisol/dehydroepiandrosterone-sulfate (DHEA-S), which is related to the volume of exercise. A minimum training is needed to obtain the significant endocrine benefit. This kind of programmed exercise also influenced inflammatory markers [31].

30.4 Vasomotor Symptoms

Vasomotor symptoms, especially hot flashes and night sweats, sometimes associated with difficulty or disrupted sleep and depressive symptoms, are very common in peri- and postmenopausal women [32]. Duration and severity of hot flashes and night sweats are quite variable and more intense in obese women [33]. In general, these symptoms are related to estrogen changes and respond to hormone therapy. As adiposity increases during the menopause transition so do hot flashes, night sweats, and sleep disturbances. While adiposity increases insulin resistance, weight gain after menopause increases the prevalence of sleep apnea that may contribute to poorer sleep and a higher perception of nocturnal hot flashes and sweats [34].

In African American and Latin American women, vasomotor symptoms may persist for a median of 7 years during the menopausal transition, and may last for a longer time if there are negative affective factors, perceived stress, and a history of psychiatric consultation [35, 36]. Some women may complain of vasomotor symptoms even after their sixties. In Australian community-dwelling older women, vasomotor symptoms were associated with depressive symptoms [32].

The effect of physical activity and exercise over vasomotor symptoms is erratic or nil. Luotto et al. [37] reported that aerobic training may reduce hot flushes. The meta-analysis of the few available RCTs suggests that exercise versus no physical activity may have not benefit over the frequency or intensity of vasomotor symptoms. In addition, there were no differences between groups regarding the frequency or intensity of vasomotor symptoms when exercise was compared with yoga [38]. The Active Women Trial reported that a 6-month exercise intervention, with a further 6-month follow-up, reduced the weekly frequency of vasomotor symptoms; although the reduction was not statistically significant [39]. However, there were improvements in secondary outcomes such as depressive symptoms and anxiety, sleep quality, and sexual behavior, despite the fact that these improvements were not significantly different as compared to the control group. Therefore, the evidence suggests that exercise may have no benefits and thus no increase of physical activity should be advised [38, 39].

Yoga has been recommended for the management of vasomotor symptoms. Despite this, a RCT reported that Yoga among healthy women for a 12-week period did not improve vasomotor symptoms as compared to usual activity; although it may reduce insomnia as measured by the Insomnia Severity Index (ISI) [40]. Therefore, exercise, yoga, and other relaxation techniques are not recommended for the management of vasomotor symptoms [41]. In women with excessive body weight, exercise may initiate hot flashes in order to compensate the increase of body temperature. The final consequence is that exercise may be disappointing, and full belly breath and hydration are recommended to reduce exercise heat-induced hot flashes.

30.5 Sleep Quality and Insomnia

Insomnia and sleep disorders are very common in peri- and postmenopausal women, reaching in some populations up to 30–40% [5–7, 9]. Sleep disturbances may affect 45% of women aged more than 65 years, being associated with higher BMI and waist circumference. The presence of insomnia was inversely associated with physical fitness, and women without sleep disturbances showed better quality of life [42].

Insomnia is associated with sleepiness, fatigue, inability to concentrate in daily tasks, higher chances of accidents, tendency to gain weight, damage of personal or professional relationships, irritability and anxiety during the daytime [6]. Some sleep alterations may be related to hormone imbalances and menopause-related symptoms (mostly vasomotor symptoms and nocturia). However, women with mood disorders, particularly those with depressive symptoms and anxiety may have difficulty to fall asleep and/or early awakenings. In addition, chronic insomnia in mid-aged women may also be associated to different co-morbid conditions, including obstructive sleep apnea and the restless legs syndrome which require an appropriate assessment and treatment [43]. The consequences of poor nocturnal sleep are fatigue, sleepiness, irritability, and poor work efficacy. In postmenopausal women, the long-term consequences of poor quality of sleep and insomnia include increased morbidity and mortality [44, 45].

Menopause hormone therapy may improve both vasomotor symptoms and sleep disorders. However, the current use of hormones has decreased during the last decade or so. Hence, currently, the management of sleep disorders and insomnia can be approached by changes in lifestyle, specific pharmacologic medications, and alternative therapies [46].

There is a correlation between regular exercise and the reduction of insomnia mediated by a decrease of tension and body temperature, hence contributing to sleep and staying asleep. This is a reasonable alternative to the use of pharmacologic drugs. Full benefits may be obtained for instance by jogging up to five miles/week or by spending some time in the gym, and sometimes the best time for exercise is not later in the day. However, exercise in the evening may be associated with the benefits related to dietary habit modification [47].

Rubio-Arias et al. [48] reported a meta-analysis of RCTs assessing the effect in mid-aged women of programmed exercise for at least 8 weeks on sleep quality, sleep disturbance, and/or insomnia, using respectively the Pittsburgh Sleep Quality Index (PSQI) and the Insomnia Severity Index (ISI) (Table 30.2). Low-moderate levels of programmed exercise decreased the PSQI score as compared with controls. In a subgroup analysis, moderate aerobic exercise had a positive effect on sleep quality while programmed yoga did not have a significant effect on sleep quality. In three studies (two studies of yoga and one of aerobic exercise), there was a non-significant reduction in the severity of insomnia when compared to controls as measured with the total ISI score (Table 30.2).

A RCT reported that yoga and aerobic exercise interventions had no significant effects on sleep actigraphic sleep parameters in menopausal women with hot flashes and poor self-reported sleep quality [49]. Another RCT reported that progressive

Table 30.2 Meta-analysis of randomized controlled trials: mean differences (and 95% confidence intervals]) in sleep quality as assessed with the Pittsburgh Sleep Quality Index (overall effect and subgroup by type of physical activity), and insomnia with the Insomnia Severity Index

Outcome	Exercise interventions (*n*)	Exercise (*n* = women)	Control (*n* = women)	Mean difference (95% CI)	I^2 (%)	*P*
Pittsburgh Sleep Quality Index						
– Overall effect	5	354	396	−1.34 (−2.67; 0.00)	68	0.05
– Aerobic activity	3	198	226	−1.85 (−3.62; −0.07)	73	0.04
– Yoga	2	156	170	−0.46 (−1.79; 0.88)	0	0.50
Insomnia Severity Index	3	194	275	−1.44 (−3.28; 0.40)	0	0.13

Heterogeneity of studies as measured by I^2. Data from Rubio-Arias et al. [48]
CI confidence interval

relaxation exercises (once a week, for 8 weeks) and sleep hygiene training may improve insomnia in postmenopausal women as measured with the Women's Health Initiative Insomnia Rating Scale [50].

30.6 Effect of Exercise on Depressive Symptoms, Anxiety, and Perceived Stress

Reports indicate that exercise has benefits on the mental health, by creating a subjective sensation of well-being, but also through brain mechanisms improving the production of some neurotransmitters and neurotrophic factors that favor neuronal function and their connections. In addition, exercise may also contribute by regulating emotions and the respiratory function which may be positive for the anxious status [50]. However, clinical results cannot be generalized to different ages or conditions. We reviewed the most recent evidence from RCTs and meta-analyses related to women during their second half of life (Table 30.3).

30.6.1 Depressive Symptoms and Exercise

Depending on the diagnostic procedure, the prevalence of depressive symptoms may increase two-fold in women during their second half of life as compared to men [8, 53, 54]. It is important to consider that a large proportion of women with depressive disorders may have autoimmune thyroiditis [55]. In addition, depressive symptoms are more common among women who take antidepressants, are obese or tobacco consumers, live in insecure economic situations, have lower educational or economical level, have menopause-related symptoms (vaginal atrophy or vasomotor symptoms) or pelvic floor symptoms, and lack regular physical exercising. Contrary to this, having a partner and a paid job exerted a protective role [8, 32, 56].

Table 30.3 Meta-analysis of randomized controlled trials: standardized mean differences (and 95% confidence intervals) between baseline and post-intervention regarding depressive and anxiety symptoms

Outcome	Exercise interventions (*n*)	Exercise (*n* = women)	Control (*n* = women)	Mean difference (95% CI)	I^2 (%)	*P*
Depressive symptoms						
– Mid-term EXE intervention	7	368	441	−0.44 (−0.69; −0.18)	64	0.0008
– Long-term EXE intervention	6	602	573	−0.29 (−0.49; −0.09)	57	0.005
Anxiety symptoms						
– Mid-term EXE intervention	8	437	502	−0.42 (−0.81; −0.02)	87	0.04
– Long-term EXE intervention	7	536	477	−0.03 (−0.18; 0.13)	29	0.74

Heterogeneity of studies as measured by I^2. Data from Pérez-Lopez et al. [51] and Martínez-Domínguez et al. [52], respectively
CI confidence interval

Depressive mood affected 36% of mid-aged South American women (peri- and postmenopausal), with a higher rate observed among minorities (Afro-Colombian or Quechua women) due to ethnicity or other social discriminatory factors, hot flush severity, hormone therapy use, sedentary lifestyle, perceived unhealthy status, and lower educational level. Contrary to this, higher coital frequency and having a healthy partner without premature ejaculation were associated to less depressed mood [57].

The meta-analysis of few small RCTs reported that exercise may be mildly effective at reducing symptoms of depression, and compared to psychological or pharmacological treatments exercise seems to be less effective in adults aged 18 and over [58]. Exercise may be beneficial for people with mild and moderate depression and mood swings, if they are healthy enough to perform physical activity [59, 60]. A recent meta-analysis of RCTs suggests that exercise may be recommended in women during the second half of life with mild to moderate depressive symptoms, and the benefits may be obtained with exercise of low to moderate intensity (Table 30.3). The benefit of exercise was similar to physical activity of low and moderate intensity. Therefore, women with co-morbid conditions would benefit even with low-intensity physical activity [51].

It is likely that exercise be an opportunity for recreation and social meeting in women with depressive symptoms in their second half of life. In addition exercise improves motor and cognitive functions, and may be as effective as antidepressants [61]. Endorphins, cytokines, and other inflammatory markers have not been studied in peri- and postmenopausal women before, during, or after physical activity.

Exercise may also improve serotonin secretion since physical exercise modulates neurogenesis which is associated with mood improvement and changes in serotonin levels, tryptophan metabolism, and insulin sensitivity [25, 62, 63]. It is also possible that some muscle biochemical signals may improve central nervous system functions and reduce depressed mood [64].

30.6.2 Anxiety Symptoms and Exercise

Anxiety symptoms (ASs) are very prevalent among mid-aged and older women although there is no clear relationship with the menopausal transition. Available studies were characterized as having poor measurement of both menopausal status and anxiety symptoms; in addition, confounding factors such as severity of vasomotor symptoms or sleep disorders were not clearly assessed [65]. It has been postulated that the severity of the majority of menopausal symptoms, including anxiety symptoms, are related to the way recent life conditions and events are perceived during the midlife and later years [66]. It has been repeatedly reported that anxiety symptoms can be reduced by regular exercise, especially if having time to focus on breathing [67].

Several meta-analyses have studied the effect of exercise or physical activity on mild to moderate anxiety symptoms in the general population [68, 69]. However, a recent meta-analysis of RCTs including mid-aged and older women reported that mid-term (12 weeks to 4 months) programmed exercise of low to moderate intensity was associated with a mild and significant reduction of anxiety symptoms as compared to controls (Table 30.3). However, long-term exercise interventions for 6–14 months were not associated with a reduction of anxiety symptoms [52]. It seems that the benefits of exercise on anxiety symptoms are limited in time, becoming less effective over time. It remains to be demonstrated if more intense exercise can prolong or maintain the reduction of anxiety in long-term programmed exercise.

The aforementioned meta-analysis had some limitations, including the heterogeneity of analyzed RCTs, the use of small samples of subjects, limited information regarding secondary outcomes and confounding factors, and the lack of more objective endpoints including inflammatory markers.

30.6.3 Perceived Stress and Exercise

Perceived stress is a reaction to environmental conditions associated with the activation of the nervous system, negative sensations and, if sustained, with adverse health consequences. In addition, perceived stress is influenced by family and social factors, general health, smoking and other drug use, insomnia and anxiety, education, and financial difficulties. Different approaches have recommended including physical activity and exercise, psychological technique, relaxation, behavioral therapies, and programmed exercise.

Perceived stress is more prevalent in women than in men, with high rates among women during the second half of life [70]. Factors related with higher perceived

stress include female age, lower education, lower psychological and urogenital quality of life, and financial difficulties [7]. Stress in premenopausal women is associated with a reduction in cognitive parameters such as attention, fluency, and language ability without affecting memory; while in postmenopausal women the majority of cognitive functions are reduced [71]. Longitudinal studies also showed that perceived stress is associated to increased C-reactive protein levels in women, but not in men [72].

According to observational studies, physical activity and exercise are recommended to reduce perceived stress [73, 74]; although there are controversial results in women during their second period of life (midlife and older women) [75–77]. We performed a meta-analysis of five RCTs regarding the effect of exercise on perceived stress, as measured with the Cohen Perceived Stress Scale, in middle-aged and older women [78]. Programmed exercise did not have any significant effect on measured perceived stress in mid-term and long-term interventions as compared to controls.

30.7 Effect of Exercise on Bone Mineral Density

There are several meta-analyses reporting the effect of exercise on bone mineral density (BMD) indicating a significant increase on femoral neck and lumbar spine BMD [79–81]. Contrary to this, another meta-analysis reported that in premenopausal women high-intensity progressive resistance training increased BMD at the lumbar spine but not at the femoral neck [82]. Future studies should provide better information on the effect of exercise at different ages and with different intensity and duration of physical activity.

30.8 Limitations of Current Evidence and Future Directions

The World Health Organization recommends that adults should engage in at least 150 min of moderate-intensity aerobic physical activity throughout the week or engage in at least 75 min of vigorous-intensity aerobic physical activity throughout the week or an equivalent combination of moderate- and vigorous-intensity activity [83]. However, sedentary women can incorporate walking into their everyday life and progressively move to more intense exercise for major muscle groups. Daily activities, such as walking and climbing, have also shown health benefits and are consistent when people exercise over longer periods of time [84]. Despite this, there are also biased information from observational studies favoring exercise as the panacea for many aspects [85] which are not confirmed by RCTs.

The available evidence included a variety of types of exercise by intensity and frequency which are not comparable and do not allow a systematic assessment in order to define risks and benefits. The American College of Sport Medicine has Guidelines for Physical Activity in Adults with general recommendations for physical activity, aerobic activity, and strength activity [86]. Clinicians should counsel postmenopausal and older women on how much physical activity and programmed

exercise is needed to maintain a healthy status, to promote weight loss and to maintain weight and obtain realistic expectations on the different outcomes reviewed in this manuscript.

Although the minimum recommended aerobic physical activity (150 min of moderate or 75 min of vigorous exercise per week) can improve cardiovascular health [87], the levels of programmed exercise should be tailored according to the outcomes to be corrected (insulin sensitivity, blood metabolic endpoints, emotional complaints), and according to the individual health status, age, and clinical goals. New alternatives to conventional programmed exercise, such as whole body electromyostimulation, or complements, such as adequate dietary supplementation, need to be assessed in postmenopausal women [10, 88].

Futures studies should incorporate more sophisticated and well-defined clinical and metabolic outcomes in order to improve the current limitations of available studies and define the effect of exercise on different prevalent conditions during the second half of life.

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