Miranda A. Farage · Kenneth W. Miller
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Editors

Skin, Mucosa and Menopause

Management of Clinical Issues

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Foreword

Skin, Mucosa, and Menopause: Management of Clinical Issues is a unique volume that brings together experts from around the world to focus on two very important parts of the body – skin and mucosa.

Skin aging begins at birth, and with life expectancy increasing in most countries, skin demands our attention. Most people would like a healthy and inoffensive exterior enveloping their bodies. Aging affects the skin of both men and women, but women experience a major shift in hormones at midlife that adds to the complexity of skin, mucosa and physiological changes associated with aging.

The respected contributors selected by the editors bring their global expertise and perspective to a wide variety of topics from physiologic changes of menopause and aging to genital symptoms associated with low estrogen, hair and nail changes, autoimmune effects on skin, the effects of appearance and function on quality of life and self-esteem, as well as health policy implications. There is an effective blend of clinical issues and research findings that will appeal to both the clinician and the researcher.

The latest research on oxidative stress and cytokines and their role in skin damage and healing are presented. The effects of genetics, the immune system, the environment, and the decline in many sex steroids are explored.

From a clinical perspective, symptoms are of utmost importance, and for postmenopausal women, vaginal dryness is an almost universal symptom. The changes in vaginal mucosa related to low estrogen levels can be severe enough to adversely affect quality of life.

Many options for women are discussed, including the roles of hormone therapy, cosmeceuticals and cosmetic surgery. Healthy aging and quality of life go hand in hand. Understanding skin, mucosa and physiology as they relate to menopause will improve both.

This comprehensive volume should broaden the perspectives of researchers and clinicians and motivate ongoing interest in skin and mucosa to the benefit of midlife women.

Mayfield Heights, OH, USA — Margery L.S. Gass, MD

Preface

The global population is aging. One in eight people worldwide will be over the age of 65 by year 2030. For the first time in history, the elderly will outnumber younger generations.

What was previously thought of as "old" (i.e., age 40) is no longer considered old. Indeed, people aged 70 often do not consider themselves old. This population remains intellectually vibrant and will contribute broad experience, a wiser perspective, and more mature judgment to society. We should embrace this change.

Our societal institutions must address the implications of this demographic shift. The medical and public health communities can make a positive contribution in this regard. Of the many challenges ahead, three significant areas come to mind. The first is our outlook and attitudes. We can shift the paradigm from being considered "old" toward respecting the value of maturity. Second, we must help society recognize and better accommodate age-related changes in physiology, sensory perception, mobility, reflexes and cognitive abilities, and assist our social institutions to adapt to the physical, emotional and social needs of older adults. Third, notwithstanding considerable popular and commercial interest given to the health issues of aging men, the fact is that women generally live longer and will comprise a more substantial portion of the older population. The experience of the older woman will gain prominence and must be addressed in a thoughtful and comprehensive way.

This volume focuses on the older woman and specifically on the major life transition of menopause. This transition is accompanied by changes in urogenital morphology, physiology, tissue atrophy, sexuality, susceptibility to infection, and urinary continence and function. Because menopause is defined by the cessation of menstruation, with attendant connotations of decline, it is traditionally seen as a loss. Moreover, because of its association with sexuality, the challenges of menopause also remain somewhat taboo. We must redefine the experience of menopause from being a "loss" to being a life transition in which the health and helping professions can offer support. This volume compiles a breadth of fundamental understanding about postmenopausal health and well being. It is our hope that the information provided herein will contribute to better health outcomes and a thriving quality of life for the older woman. Armed with this knowledge and a positive perspective, let us affirm menopause as the transition through which our mothers, partners, sisters, and friends come of age as wise and wonderful elders of society.

Researchers and clinicians who have contributed to this volume hope to promote a better understanding to women's menopausal state. We hope that this compilation will be valuable to its intended audience. Your editors welcome comments and suggestions.

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Many thanks go to the significant efforts of all the contributors of this book and the valuable time they dedicated to preparing their chapters. This book represents the fruits of a jointly conceived and executed venture and has benefited from global and diverse partners.

We would also like to single out Diane Lamsback (Developmental Editor, Springer) for a special recognition. Her great efforts, time, discipline and dedication helped moved this book forward in a timely and organized manner. In addition, we would like to thank both Sverre Klemp and Ellen Blasig (Springer) for their help in moving this book forward.

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Above all, our everlasting gratitude, thanks and love go to our parents, who inspired us, and to our families and children, who supported, helped and encouraged us all the way with their incredible patience. Your continuous care, unconditional love and sacrifice made all this possible, and easier to achieve.

Miranda A. Farage, MSc, PhD
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Abbreviations

3′ UTR	3 prime Untranslated region
5-meC	5-Methylcytosine
AA	Alopecia areata
AAB	Autoantibody
AFC	Antral follicle counts
AGA	Androgenetic alopecia
AGE	Advanced glycosylation end-products
AID	Autoimmune disease
AIH	Autoimmune hepatitis
ANA	Anti-nuclear antibody
APC	Antigen presenting cell
Ar	Androgen receptor
AS	Ankylosing spondylitis
AVF	Altered vaginal flora
BMI	Body mass index
BP	Base pair
CAD	Coronary artery disease
CBT	Cognitive behavioral therapy
CI	Confidence interval
CLA	Cutaneous lymphocyte antigen
CML	N^{ε}-[Carboxymethyl-]lysine
CNS	Central nervous system
CPA	Cyproterone acetate
CS	Cervantes Scale
CVD	Cardiovascular disease
CVE	Cardiovascular events
DC	Dendritic cell
DEJ	Dermal epidermal junction
DHEA	Dehydroepiandrosterone
DHT	Dihydrotestosterone
DIV	Desquamative inflammatory vaginitis
DS	Down syndrome
dsDNA	Double-strand deoxyribonucleic acid
E1	Estrone
E2	Estradiol
E3	Estriol
EAE	Experimental autoimmune encephalomyelitis

ECG	Electrocardiogram
EPT	Estrogen and Progesterone therapy
ER	Estrogen receptor
ERE	Estrogen responsive element
FFA	Frontal fibrosing alopecia
FL	Fructosalysine
FMP	Final menstrual period
FPHL	Female pattern hair loss
FR	Free radicals
FSH	Follicle-stimulating hormone
GM-CSF	Granulocyte macrophage colony stimulating factors
GPx	Glutathione peroxidase
HapMap	Halotype map
HAT	Histone-acetylation enzyme histonacetyl transferase
HERS	Heart and Estrogen/Progestin Replacement Study
HRT	Hormone-replacement therapy
HT	Hormone therapy
ICC	Intraclass correlation coefficient
IFNGR	Interferon gamma receptor
IFN-γ	Interferon-gamma
Ig	Immunoglobulin
IGF	Insulin-like growth factor
IL	Interleukin
IKβ	Inhibitory Kβ
JAK	Janus kinase
LH	Luteinizing hormone
LP	Lichen planus
LPP	Lichen planopilaris
LPPAI	Lichen Planopilaris Activity Index
LPS	Lipopolysaccharide
LPV	Localized provoked vestibulodynia
LS	Lichen sclerosus
LSC	Lichen simplex chronicus
LUMINA	Lupus in Minorities: Nature vs. Nature
meC	Methylcytosine
MENQOL	The Menopause-Specific Quality of Life Questionnaire
MHC	Major histocompatibility complex
MIF	Macrophage inhibitory factor
miRNA	Micro ribonucleic acid
MMP	Matrix metalloproteinase
MPA	Medroxyprogesterone acetate
MQOL	The Menopause Quality of Life Scale
mRNA	Messenger ribonucleic acid
MRS	Menopause Rating Scale
MS	Multiple sclerosis
mtDNA	Mitochondrial DNA
ΔΨm	Mitochondrial membrane potential
MZ	Monozygotic

NADPH	Nicotine adenine dinucleotide phosphate
NF-Kβ	Nuclear factor kappa-light-chain enhancer
NGFs	Non-growing follicles
NK	Natural killer
$NO^{\bullet}$	Nitric oxide radical
NOS	Nitric oxide synthase
NVA	National Vulvodynia Association
$O_2^{\bullet-}$	Superoxide anion
OC	Oral contraceptives
$^{\bullet}OH$	Hydroxyl radical
$ONOO^-$	Peroxynitrite radical
OS	Oxidative stress
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PMA	Post-menopausal aging
PMNs	Polymorphonuclear leukocytes
POF	Premature ovarian failure
PPAR	Peroxisome-proliferator activated receptor
PR	Progesterone receptor
PTPN	Protein tyrosine phosphatase
PUFA	Polyunsaturated fatty acids
PUPPP	Pruritic urticarial papules and plaques of pregnancy
QoL	Quality of life
QST	Quantitative sensory testing
QWB	Quality of well-being
RA	Rheumatoid arthritis
RC	Respiratory control
RCS	Reactive chlorine species
RNP	Ribonucleoprotein
RNS	Reactive nitrogen species
$ROO^{\bullet-}$	Peroxyl radical
ROS	Reactive oxygen species
RR	Relative risk
RSS	Reactive sulfur species
RVVC	Recurrent vulvovaginal candidiasis
SASP	Senescence-associated phenotype
SCC	Squamous cell carcinoma
SERMs	Selective estrogen receptor modulators
SHBG	Sex hormone-binding globulin
SLE	Systemic lupus erythematosus
SLEDAI	SLE Disease Activity Index
SM	Sphingomyelin
SNP	Single nucleotide polymorphisms
SNRIs	Selective norepinephrine reuptake inhibitor
SOD	Superoxide dismutase
SS	Sjögren's syndrome
SSRIs	Selective serotonin reuptake inhibitor
STAT4	Signal transducer and activator of transcription 4

STS	Skin tensile strength
SWAN	Study of Woman's Health Across the Nation
T1DM	Type 1 diabetes mellitus
TA	Traction alopecia
TBG	Thyroid binding globulin
TDA	Transdermal administration
TET	Transdermal estrogen therapy
TEWL	Trans-epidermal water loss
Tfh cell	Follicular helper T cell
Th	T helper cell
TIMP	Tissue inhibitors of metalloproteinases
TLR	Toll-like receptors
TMD	Temporomandibular joint and muscle disorder
TNF-α	Tumor necrosis factor-alpha
TNF-β	Tumor necrosis factor-beta
TPO	Thyroid peroxidase autoantibody
Treg	Regulatory T cells
TSECs	Tissue selective estrogen complexes
UC	Ulcerative colitis
UDCA	Ursodeoxycholic acid
UQOL	Utian Quality of Life
UTR	Untranslated region
UV	Ultraviolet
VMI	Vaginal Maturation Index
VMS	Vasomotor symptoms
VTE	Venous thromboembolism
VVA	Vulvovaginal atrophy
VVC	Vulvovaginal candidiasis
VVS	Vulvar vestibular syndrome
WCA	Women climacteric aging
WHI	Women's Health Initiative
WHO	World Health Organization
WHOQOL	World Health Organization Quality of Life
WHQ	Women's Health Questionnaire

Contents

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Part I

Skin, Physiological Changes, and Menopause

What Is Menopause? An Overview of Physiological Changes

1

Aikaterini E. Deliveliotou

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1.1 Introduction

The extension of life and population aging are world-changing events that will have profound impacts on generations to come. In 1990 there were an estimated 467 million women aged 50 years and over in the world. This number is expected to increase to 1,200 million by the year 2030 [1]. More than 30 % of the female population of the United States is currently postmenopausal, and this percentage is predicted to increase in the next decades [2]. These demographic trends will exacerbate the economic and social challenges as well as the medical and psychological implications posed by a growing female, elderly population [3]. But if the extension of life achieved in the coming decades can be converted into healthy productive years, then these challenges could be counterbalanced by an equal measure of opportunity and the emergence of a dynamic and equitable aging society.

Because the loss of ovarian function has profound impact on the hormonal milieu in women and on the subsequent risk for the development of disease via the loss of estrogen production, improving our understanding of reproductive aging is critical to care for all women.

1.2 Definitions: Terminology

Reproductive aging is a continuum beginning in utero and ending with menopause. The stages along this continuum have been difficult to define.

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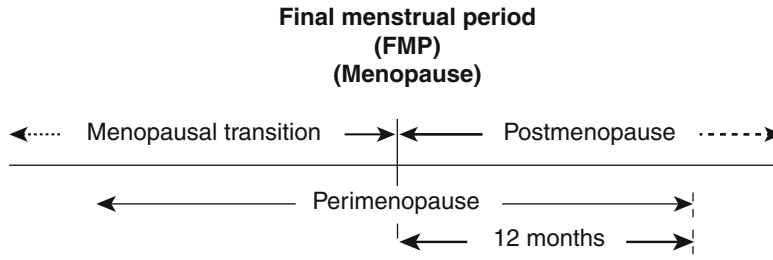

Fig. 1.1 Relationship between different time periods surrounding the menopause. (Reproduced, with permission of the publisher, from World Health Organization Scientific Group. Research on the menopause in the 1990s [5])

Numerous terms have been used clinically, including perimenopause, menopausal transition, climacteric, menopause, and postmenopause, to describe the various nodal points surrounding the menopause. In 1980, a WHO Scientific Group on Research on the Menopause proposed some definitions, in order to be used in studies and reports on the menopause and to extract comparable findings, and there are shown in Fig. 1.1 [4].

1.2.1 Menopause

Menopause is the most identifiable event of the perimenopausal period and should be characterized as an event rather than a period of time. The most widely used definition for natural menopause is as defined by the World Health Organization as at least 12 consecutive months of amenorrhea not because of surgery or other obvious causes [5]. When referring to menopausal age or onset of menopause in this chapter, we mean natural menopause as defined above. This cessation of menses resulting from the loss of ovarian function is a natural event, a part of the normal process of aging, and is physiologically correlated with the decline in estrogen production resulting from the loss of ovarian follicular function and therefore represents the end of a woman's reproductive life.

1.2.2 Perimenopause

The perimenopausal period includes the time before, during, and after menopause, when the endocrinological, biological, and clinical features of approaching menopause commence. The years immediately preceeding and the decades afterward, however, are of far greater clinical significance. The length of this period varies, but it is usually considered to last approximately 7 years, beginning with the decline in ovarian function in a woman's 40s and continuing until she has not had a menstrual period for 1 year [6]. Perimenopause usually begins in the mid- to late 40s; it is often uneventful but may be abrupt and symptomatic. The term "climacteric" should be abandoned to avoid confusion. Symptoms that begin with the menopausal transition usually continue into the postmenopausal period.

1.2.3 Menopausal Transition

The period of hormonal transition that precedes menopause is sometimes known as the menopausal transition period and is characterized by a varying degree of somatic changes that reflect alterations in the normal functioning of the ovary. Early recognition of the symptoms and the use of appropriate screening tests can minimize the impact of this potentially disruptive period [6]. In many cases, however, it is difficult to differentiate stress-related symptoms from those associated with decreasing levels of estrogen. For this reason, both stress and relative estrogen deficiency should be considered when managing problems associated with the menopausal transition.

In some women, menstrual irregularity is the most significant symptom of the menopausal transition [7]. Because abnormal bleeding is one of the most common symptoms of uterine

problems, menstrual irregularity during the perimenopause should be evaluated carefully. Often uterine bleeding associated with this transition period is secondary to normal physiologic estrogen fluctuations rather than underlying pathology and may be treated medically [8].

1.2.4 Postmenopausal Period

The postmenopausal period is one of relative ovarian quiescence following menopause [4, 6]. Given the current lifespan of women in the United States, this period can comprise more than one-third of the average woman's life. During this prolonged period, women are susceptible to health problems associated with estrogen deficiency that tend to be chronic rather than acute. First of all osteoporosis is not clinically apparent until decades after menopause, when unfortunately it becomes harder to treat. Additionally, the impact of estrogen deficiency on cardiovascular disease is often confused with age-related changes, while, because of the peripheral conversion of both ovarian and adrenal androgens to estrogen, the loss of ovarian function does not result in an acute estrogen deficiency in all women.

1.2.5 Time of Natural Menopause

Natural menopause occurs at a median age of 51.4 years and is more or less normally distributed with a range roughly between 42 and 58 years [7, 9, 10]. However, there is no way to predict when an individual woman will have menopause or begin having symptoms suggestive of menopause. The average age of menopause has remained invariable during the last decades.

Environmental factors explain only a small part of the age variance at which menopause commences [11]. The variation in natural menopause is a trait predominantly determined by interaction of multiple genes, whose identity and causative genetic variation remains to be determined. Based on the fact that there is a strong association between age at menopause between mothers and daughters, it is suggested that there might be a largely genetically determined trait [12]. Furthermore, the onset of menopause does not appear to be related significantly to race, parity, height, weight, socioeconomic status, nutritional status, or age at menarche [13]. On the other hand the interaction among environmental factors such as smoking (known to accelerate the age of menopause by 1.5–2 years), body mass index (BMI), alcohol use, and socioeconomic status and genetic risk may be important [14]. As a result, it has been noticed that menopause occurs earlier in nulliparous women, in tobacco smokers, and in some women who have had hysterectomies [11, 15].

1.2.6 Induced Menopause

There are some medical and surgical conditions that can influence the timing of menopause. The term induced menopause is defined as the cessation of menstruation which follows either surgical removal of both ovaries or iatrogenic ablation of ovarian function by chemotherapy or radiation.

1.2.6.1 Surgical Menopause

It is called the surgical removal of the ovaries (oophorectomy) throughout reproductive period and results in an immediate cessation of estrogen production. In more than 40 % of women who have hysterectomies, both ovaries are removed, and this is usually performed at a significantly younger age than the age of natural menopause. In this case, there is no perimenopause, and after surgery, hot flashes and other acute symptoms associated with the perimenopausal period often become especially intense [15]. In addition, long-term surgical menopause has been associated with significantly higher risk for osteoporosis than has natural menopause [16]. On the other hand, recent data suggest that surgical menopause is not a key determinant of cardiovascular disease (CVD) risk factor status either before or after elective surgery in midlife [17]. These results should provide reassurance to women and their clinicians that hysterectomy in midlife is

unlikely to accelerate the CVD risk of women, in contrast to older reports that women with a hysterectomy had a worse risk profile and higher prevalence and incidence of CVD [18]. If a hysterectomy is not accompanied by the removal of both ovaries in a woman who has not yet reached menopause, the remaining ovary or ovaries are still capable of normal hormone production. In this case, a woman cannot menstruate but hormonal production from the ovaries can continue up until the normal time when menopause would naturally occur. At that time women could report the other symptoms of menopause such as mood swings and hot flashes, which are not therefore associated with the cessation of menstruation.

1.2.6.2 Cancer Chemotherapy and Radiation Therapy

Chemotherapy and/or radiation therapy in a woman of reproductive age can result in menopause. The effect of such a treatment on ovarian function is directly depended on the type and location of the cancer as well as the toxicity of the medications used [19]. In this case, the symptoms of menopause may begin during the cancer treatment or may develop in the months following the treatment, independently of the woman's age.

1.2.7 Premature Menopause

Premature menopause or premature ovarian failure (POF) is defined as the spontaneous occurrence of menopause before the age of 40, occurring in 0.1 % of women under 30 years of age and 1 % of women by age 40 [20, 21]. This definition is rather arbitrary, because it is based on age only. POF is a collective term for which proposed causes include autoimmune disease, syndromes such as fragile X, or inherited (genetic) factors [22]. Genetic factors are thought to have a strong association with POF. Among patients with idiopathic POF, a higher incidence of family history of early menopause and infertility has been noted so that a familial transmission is observed in 30–40 % [23]. Although inheritance appears to be either X-linked or autosomal dominant sex limited, paternal transmission cannot be excluded. Furthermore, women with POF have a genetic pattern similar to whose with idiopathic early menopause (between the ages of 40 and 45), suggesting the existence of common underlying causal factors in both entities. Women with premature menopause are at risk of premature death, neurological diseases, psychosexual dysfunction, mood disorders, osteoporosis, ischemic heart disease, and infertility. Public enlightenment and education is important tool to save those at risk [24].

1.3 Physiology of the Normal Menopause

The ovary is unique in that the age associated with decline in function (to complete failure) appears to have remained relatively constant despite the increase in longevity experienced by women over the last century [25]. The primary determinant of reproductive age in women is the number of ovarian nongrowing (primordial, intermediate and primary) follicles (NGFs). The leading theory regarding the onset of menopause relates to a critical threshold in oocyte number and particularly the number of ovarian follicles present in the ovary. Therefore, the number of ovarian granulosa cells available for hormone secretion appears to be the most critical determinant of age at menopause, steroid hormone secretion, and gonadotrophin levels [26].

Human follicles begin their development during the fourth gestational month. Approximately 1,000–2,000 germ cells migrate to the gonadal ridge and multiply, reaching a total of five to seven million around the fifth month of intrauterine life [27, 28]. In female fetus, between the 12th and 18th week, the germ cells will enter meiosis and differentiate so that all germ stem cells have differentiated prior to birth. At this point, replication stops and follicle loss begins so that the population of NGFs is estimated to be approximately 500,000–1 million at birth, which represents the initial NGF endowment in women. At menarche 500,000–600,000 follicles exist, while in the adult woman through a combination

of recruitment toward dominant follicle development and ovulation or atresia, the stock of NGFs is depleted [29, 30]. The pioneering work of these investigators led to the understanding that ovarian follicle number decreases with increasing age and that ultimately few, if any, follicles remain following menopause [31, 32].

Using the combined data from these studies, it has been suggested that the decline in ovarian follicles associated with aging was best described by a biphasic-exponential model, which was better fitted to the data than either a linear or single exponential model, as shown in Fig. 1.2 [33]. In this model, the total follicular endowment at birth is estimated to be 952,000, with an initial rate of decay of −0.097. At the age of 38 years and a follicle count of 25,000, a sudden increase in decay occurs to over twofold the initial rate (−0.237). At this point, the rate of follicular atresia accelerates. In the absence of this acceleration, the model suggests menopause would be delayed until age 71. The unexpectedly faster rate of ovarian aging afterwards lowers the follicle population to 1,000 at approximately 51 years and is adopted as the menopausal threshold as it corresponds to the median age of menopause. The cause of this accelerated depletion is not well defined. It is also clear that if the factor influencing the rate of decline is follicle number and not age, other factors which might account for a diminished follicle number (genetic risk and possible toxic exposure) would lead to an earlier rate of accelerated decline and an earlier age of menopause.

Realizing the biological implausibility of a sudden acceleration in follicular depletion, a

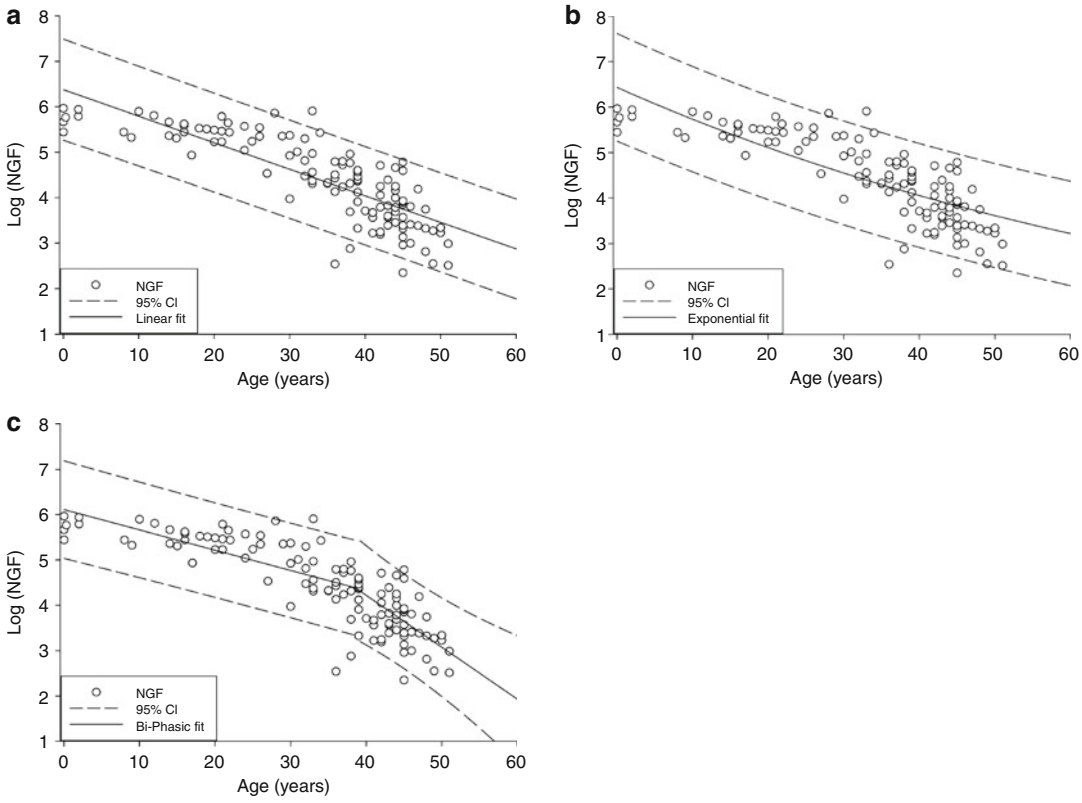

Fig. 1.2 Models of ovarian NGF decay. The log of the ovarian NGF number is plotted versus age (years). (**a**) Linear model, (**b**) exponential model, and (**c**) biphasic-exponential model. *Solid lines* indicate the fitted model with *dashed lines* representing the 95 % confidence interval ($n = 122$) (Reprinted from Hansen et al. [26], by permission of Oxford University Press)