A STUDY ON THE MENOPAUSAL EXPERIENCE OF KELANTANESE WOMEN

By

HARDIP KAUR DHILLON
SRN., RSCN., SCM., HV Cert.
BN

A Thesis submitted in fulfillment of the requirement for the degree of Master of Science

UNIVERSITI SAINS MALAYSIA

May 2005

ACKNOWLEDGEMENTS

I would like to thank Universiti Sains Malaysia for the funding and the support of Postgraduate and Research Committee, PPSP that made this study possible. My sincere gratitude to Prof. (Dr) Zabidi Azhar Mohd. Hussin, Dean, School of Medical Sciences, Universiti Sains Malaysia, and to Assoc. Prof. Datin Dr. Rashidah Shuib, Coordinator, Women's Health Unit, for their appropriate guidance and encouragement. Special thanks to Assoc. Prof. (Dr) Abdul Manaf, Dept of Community Medicine, who translated the questionnaire from English language to the Malay Language.

I am deeply grateful to my research supervisors, first Dr. Nor Aliza Abdul Ghaffar and later Assoc. Prof. (Dr) Nik Mohd Zaki bin Nik Mahmood, from the Department of Obstetrics and Gynaecology, USM for their support, encouragement and guidance during the course of this research. My special thanks goes to Puan Nik Mahzum Nik Omar, retired Chief Matron, Hospital Universiti Sains Malaysia, who helped towards recruiting Kelantanese women for this study. I would also like to thank my nursing colleagues at the Nurse Education Unit, PPSP and later of PPSK, the Nursing staff at Hospital Universiti Sains Malaysia, and all nursing staff at the menopause clinic HUSM for giving me the support and cooperation that enabled me to complete this study.

My sincere thanks to Dr. Mary Abraham, Director, General Hospital, Kota Bharu, who personally encouraged her nurses to participate in this research. My special gratitude to Sister Jamilah of Ward 11, General Hospital, Kota Bharu and Matron Eshah Ahmad, Community Health Services General Hospital, Kota Bharu who helped organize the participants from as far as Tanah

Merah, Kuala Krai, Pasir Mas and Machang. My special thanks also to Dr. Kamalanathan, Klinik Krai, Kuala Krai, Dr. Devi, Klinik Murni Kota Bharu, The Family Planning Association, Kota Bharu, The Buddhist Association Kota Bharu, and members of the Sikh community, friends and colleagues who all contributed towards getting the participants for this study.

My special thanks goes to Puan Homah bt Hamzah, the community worker at Pringat, Kota Bharu, who took me to many rural areas around Kota Bharu to meet with the women, and to areas that I would never have visited had it not been for her efforts and this study. Through her eyes I was able to appreciate Kota Bharu as seen by the local women. Without her voluntary effort in orgainsing groups of women to meet me at different venues this project would not have been successful. Thank you, Puan Homah. Also a special thanks goes to Ms Ham Siew Ling who patiently helped with the typing, printing, and photocopying of the thesis.

My heartfelt gratitude and thanks to my parents, my late mother Madam Pretam Kaur Hundal, from whom I derive a lot of my inspiration, who unfortunately is no longer here to see me complete this study and my father, Dr. Pretam Singh Dhillon, who believed knowledge is divine and never considered age a hindrance for further study. A big thank you goes to my children, Jasminder Kaur and Sachdev Singh, my husband, Harbindar Jeet Singh, for their understanding and support and cooperation in all ways. Both Jasminder Kaur and Sachdev Singh gave their mother a lot of encouragement and along the way also became aware of menopause. Finally and above all, my appreciation and thanks to the Good Lord, **'SATNAAM WAHEGURU'**, for HIS unending and boundless benevolence that enables us to fulfill our dreams and desires.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABSTRAK

SATU KAJIAN PENGALAMAN PUTUS HAID PADA GOLONGAN WANITA KELANTAN.

Menopaus ataupun putus haid telah dikaitkan dengan pelbagai gejala sementara biasa *(typical)* dan yang bukan biasa (*atypical*). Dipercayai bahawa, berbanding dengan wanita Barat, wanita Asia lebih menanggung atau mengalami kesusahan gejala putus haid atipikal yang berlaku lebih kerapkali daripada gejala tipikal seperti gejala psikologi dan vasomotor. Gejala tipikal juga didapati kurang teruk di kalangan wanita Asia berbanding wanita Barat. Kajian ini melaporkan insiden dan jenis gejala putus haid dari golongan wanita di Kelantan dan jenis-jenis tindakan penjagaan diri yang diambil oleh mereka.

Satu soalan kajiselidik berstruktor separuh (semi-structured) dan boleh dijawab sendiri diberi kepada 326 wanita di negeri Kelantan. Responden berumur 57.01 ± 6.58 (SD) tahun. Mereka yang mengambil bahagian adalah sihat dan sudah mengalami putus haid secara semulajadi. Wanita yang mengalami kencing manis ataupun tekanan darah tinggi yang tidak terkawal, telah dikecualikan daripada kajian ini. Untuk analisa data, statistik deskriptif SPSS telah digunakan.

Keputusan menunjukan umur purata putus haid adalah 49.4 ± 3.4 (SD) tahun, umur mode dan median adalah 50 tahun. Mode bilangan gejala yang diadukan oleh wanita adalah lapan gejala. Insiden gejala atipikal adalah: keletihan (79.1%), perubahan daya tumpuan (77.5%), sakit otot dan tulang (70.6%), sakit belakang / pinggang (67.7%).

Berpeluh di waktu malam (53%), sakit kepala (49.4%), panas muka atau *hot flushes* (44.7%) adalah gejala vasomotor biasa. Perubahan perasaan atau *mood swing* (51%), payah tidur (45.1%), kesunyian (41.1%), merasa cemas (39.8%), rasa sedih / menangis (33.4%) adalah gejala psikologi yang berlaku dengan lazim dalam kajian ini. Gejala urogenital seperti 'stress incontinence', kawalan pundi air kencing yang lemah dan jangkitan trek urinari yang berlaku kadangkala juga dilaporkan.

Peratusan tindakan penjagaan diri bergantung kepada gejala masing masing dan julat adalah antara 47.7% untuk perubahan daya tumpuan ke 100% untuk rasa sedih / menangis dan rasa cemas. Tindakan penjagaan diri termasuk ubatan tradisi, ubatan alternatif, ubatan preskripsi, ambil bahagian aktif dalam kerja komuniti, terima sokongan daripada kawan. Pilihan tindakan penjagaan dipengaruhi oleh kebudayaan, pendidikan dan faktor sosio – ekonomi.

Lebih ramai wanita melaporkan kekurangan amaun sekresi / kebasahan faraj (50.9%) dan kekerapan persetubuhan adalah 2 – 4 kali sebulan (49.7%). Dari segi keseluruhan, 42.3% mendapati kekurangan dalam aktiviti kekerapan persetubuhan selepas putus haid. 69% wanita melapurkan tidak berminat terhadap hubungan seks, dimana 39% kurang minat dan 29.6% tiada minat langsung. Corak yang sama dilaporkan oleh wanita untuk kebangkitan nafsu berahi ("libido"). Pelbagai peringkat ketidak selesaan serta kesakitan semasa persetubuhan dilaporkan oleh 34% wanita.

Jika dibandingkan dengan sebelum menopaus, ada juga wanita (23.3%) sekarang merasa suaminya kurang berminat seks dengan mereka. Sebahagian besar (66.2%) sudah berkahwin lebih dari 26 tahun. Bagaimanapun ada juga pecahan kecil (7.1%) wanita yang berkata semasa persetubuhan, faraj mereka tidak dapat menyesuaikan dengan ketegangan kemaluan (*penis*) pasangannya. Dan ada juga pecahan kecil (2.1%) wanita mengaku mereka ada masalah seks yang menjejaskan hubungan antara suami – isteri. Ada juga golongan (9.5%) dimana suami mengadu masalah seks yang menjejaskan hubungan suami-isteri. Tentang masalah seksualiti, satu perempat kaum wanita percaya masalah seksualiti ini dapat dipertingkatkan dan lagi satu perempat merasa masalah seksualiti ini tidak dapat diselesaikan. Tindakan yang diambil oleh wanita adalah seperti pengambilan "HRT", Jamu, "Evening Primrose Oil", "Royal Jelly", senaman dan kawalan makanan.

Lebih daripada setengah (55%) wanita tidak mendapat nasihat daripada sesiapa tentang menopaus. Mereka yang ambil nasihat, hanya mengambil daripada golongan kawan sahaja. Hanya 13% responden tidak menyedari bahawa menopaus berlaku kepada mereka. Sumber–sumber pengetahuan responden adalah melalui perbualan dengan kawan, ahli–ahli kesihatan, atau menghadiri bengkel menopaus. Wanita Kelantan kebanyakannya memandang putus haid sebagai proses semulajadi dan menyifatkannya sebagai peristiwa perkembangan khas. Mereka yang melihat putus haid sebagai tanda penuaan, menerimanya sebagai tempoh masa didalam jangkahayat.

Kesimpulan kajian ini, menunjukkan bahawa gejala-gejala menopaus yang dialami oleh wanita di negeri Kelantan adalah bersamaan dengan wanita lain dikebanyakan negara di seluruh dunia. Perbezaan hanya adalah dari segi kekerapan berlakunya gejala–gejala tersebut. Kebanyakan wanita menerima menopaus sebagai satu prosess permulaan meningkat tua. Walaubagaimanapun, mereka akan mengambil pelbagai tindakan penjagaan diri untuk membantu mereka dalam melayari fenomena putus haid atau menopaus.

ABSTRACT

A STUDY ON MENOPAUSAL EXPERIENCES OF KELANTANESE WOMEN

Menopause is associated with numerous transient typical and atypical symptoms. It is believed that Asian women suffer more of the atypical symptoms and fewer, and with lesser severity, the typical psychological and vasomotor symptoms than the western women. This study reports the incidence and nature of menopausal symptoms in Kelantanese women and the self-care actions taken by them.

A semi-structured, self-administered questionnaire was administered to 326 postmenopausal women (aged, 57.01 ± 6.58 (SD) years) residing in the state of Kelantan. The subjects comprised of naturally menopaused, healthy women. Women with uncontrolled diabetes and hypertension were not included. Descriptive statistical analysis was performed on the data using SPSS programme.

Mean age at menopause was 49.4 ± 3.4 (SD) years while both the mode and median were 50 years. The mode for the number of symptoms complained by each woman was 8 (range 0 – 16). The incidences for atypical symptoms was; tiredness (79.1%), reduced concentration (77.5%), musculo-skeletal aches (70.6%) and backache (67.7%). Night sweats (53%), headaches (49.4%) and hot flushes (44.7%) were the typical vasomotor symptoms, whereas mood swings (51%), sleep problems (45.1%), loneliness (41.1%), anxiety (39.8%), and crying spells (33.4%) were the main psychological symptoms.

Majority of the women reported reduced vaginal secretion (50.9%). The commonest coital frequency was approximately 2–4 times per month (49.7%). Overall, 42.3% reported a decrease in the frequency of sexual activity postmenopausally. Over two-thirds (69%) of the women reported either reduced (39%) or absent (29.6%) sexual desire or interest. A similar pattern was also reported for libido. Varying degree of dyspareunia was reported by 34% of the women. Some women (23.3%) had noticed that their spouses' sexual interest in them had reduced compared to before menopause. A small percentage (7.1%) reported that their vagina was not able to accommodate completely an erect penis. A small percentage (2.1%) admitted to having sexual problems, which had an affect on their marital relationship and another group (9.5%) had spouses with sexual problems. A quarter of the women thought their sexuality could be improved while another quarter thought otherwise. More than half (52.6%) did not take any action to improve their sexuality. Those who did, took HRT, "Jamu", Evening Primrose Oil, Royal jelly, did regular exercises and controlled their diet.

The percentage of women taking self-care actions depended upon the symptom, and ranged from 47.7% for reduced concentration to 100% for crying spells and anxiety. Their self-care actions included taking traditional medicine, alternative medicine, prescribed medications, getting actively involved in community work, and having peer support. More than half (55%) did not seek any advice regarding their menopause. Those who did, mainly approached their friends. Some 13% of women were not aware of the menopause when it occurred. The sources of knowledge on menopause, according to the respondents, were friends, health professionals, and attending seminars. Most of the

respondents viewed menopause as a biological event and placed it within the context of their developmental milestones. Those who viewed menopause as a marker of old age accepted it as a time frame within the lifespan

In conclusion, it appears that the menopausal symptoms experienced by women in Kelantan are very similar to those experienced by women elsewhere, albeit, with differing frequencies. Majority of the women accepted menopause as the beginning of the aging process and resorted to numerous self-care actions to help see them through this transition.

LIST OF SYMBOLS, ABBREVIATIONS OR NOMENCLATURE

No.	ABBREVIATIONS	
1.	SPSS	Statistical Package for Social Sciences
2.	LH	Luteinising Hormone
3.	FSH	Follicle Stimulating Hormone
4	HRT	Hormone Replacement Therapy
5.	SWAN	Study of Women's health Across the Nation
6.	KIWI	The Kinsmen Women-health Investigation
7.	MWHS	Massachusetts Women's Health Study
8.	WHO	World Health Organisation

CHAPTER 1

INTRODUCTION

1.1. THE REPRODUCTIVE LIFE OF A WOMAN

A woman's reproductive life begins with menarche, the first menses, or more appropriately after puberty. Puberty in humans is a unique and integrated transition from childhood to young adulthood, which usually occurs between the age of 11 and 16 years in most populations (Sizonenko, 1989). The age of menarche seems to be closely related to extrinsic factors such as living conditions and especially the energy balance of the individual (Thomas *et al.*, 2001). The age at menarche has declined over the last hundred years in most developing and developed societies. This, in part, may be due to the improved nutrition and health care available to growing children in these societies.

The earliest changes marking the beginning of puberty evidently occur in the hypothalamo-pituitary-gonadal-axis where there occurs an increased Gonadotrophin Realising Hormone (GnRH) surges during sleep (Styne, 1994). What initiates this is unclear although recent evidence suggests a role for neuron-astroglia communication, via neuregulin-oestrogen receptor beta B4/2 (NRG-erbB4/2) signaling, in the timely unfolding of the sexual maturation process (Prevot *et al.*, 2003). In addition, some other neuro-endocrine factors probably control the onset of puberty namely; cerebral adrenergic and/or dopamine neurotransmitters, endogenous opiods and melatonin from the pineal gland (Mann & Plant, 2002). This leads to an increased secretion of pituitary gonadotropins, Luteinising Hormone (LH) and Follicle Stimulating Hormone (FSH), which in turn stimulate the gonadal function i.e. estradiol secretion and maturation of the

ovarian follicle. Many believe gonadal maturation (gonadarche) is preceded by an adrenal maturation known as adrenarche, which begins about 2 years before gonadarche (Guyton & Hall, 2000). However, the earliest recordable events at puberty are the increasing secretions of LH and FSH.

The time at which puberty begins is evidently linked to the attainment of a predetermined weight to height ratio. The precise trigger for puberty is still not clearly understood but there are indications that it may be related to the attainment of a critical level of energy stores in the form of subcutaneous fat (Mann & Plant, 2002; Thomas *et al.*, 2001). When once a sufficient energy store has been attained a signal is then transmitted to an area of the brain associated with the commencement of menarche. The nature of the signal is unknown but recent studies implicate leptin, an adipocyte hormone, as the possible signal, albeit a rather permissive one (Mann & Plant, 2002). Serum levels of leptin correlate positively with percentage body fat and are known to increase linearly with increasing age in children (Rogol, 2002; Saenger, 1994).

From puberty till menopause, i.e. forty years or so, a woman experiences regular menstruation every 28 – 35 days. Although the age of menarche has decreased over the last century, the age of menopause however has remained relatively unchanged over the same period of time (Santoro & Tortoriella, 1999). The relationship between the age of menarche and the age at menopause is unclear. An earlier study of population trends had suggested that an early menarche might be associated with a later age of menopause in the population as a whole (Frisch, 1987). A later study however failed to show an association between the age of menarche and age of menopause (van Noord *et al.*, 1997).

Interestingly, the age of menopause in daughters appears to correlate to the age of maternal menopause or the age at menopause in siblings (Cramer *et al.*, 1995), suggesting a genetic basis for menopausal age. Although to date no specific genes controlling or delaying menopause have been identified, but reports of the presence of deletional abnormalities in the long arm of the X chromosome in families of women with premature ovarian failure (Krauss *et al.*, 1987; Ahmed-Ebbiary *et al.*, 1994; Massart *et al.*, 2001) seem to suggest a link. The close relationship between genes that regulate reproductive fitness in women and genes that regulate the rate of ageing and susceptibility to diseases associated with ageing remains intriguing. Clearly, further studies are necessary to determine whether genes on the X chromosome or on other chromosomes influence the timing of natural menopause. The nature of the event nevertheless does suggest a genetic regulation or influence.

Numerous other factors have also been suggested to influence the age of menopause. Chemical exposure may lower the age of menopause by depleting the ovary of oocytes and women may be exposed to these chemicals in their workplace, at home, and through exposure to contaminated drinking water near hazardous waste sites as well as direct or indirect smoking (Silbergeld & Flaws, 1999). Although these possibilities have been suggested but direct or even convincing, corroborative evidence is still lacking to confirm the role of external factors on the age of menopause. Thomas *et al.* (2001) suggest that the age of menopause is sensitive to an intrinsic parameter such as the reproductive history of the individual.

1.2 MENOPAUSE

Menopause is defined as a permanent cessation of menstruation marking the end of the reproductive capability of a woman. Natural menopause is recognised to have occurred following 12 consecutive months of amenorrhoea for which there is no other obvious pathological or physiological cause (WHO Technical Report series 866, 1996). At present, there is no biological marker available to confirm the event immediately. It is a normal concomitant of aging in all women, which occurs universally in women during midlife (George, 1985).

Despite having appropriate terminology recommended in 1980 by a WHO Scientific Group (WHO Technical Report series 670, 1981) on Research on the Menopause, the word "menopause" has often been used loosely to describe the various stages surrounding the phenomenon. It is now widely recognised that menopause is preceded by a number of tell–tale signs that indicate the beginning of the eventual cessation of menses. These may occur from between a few months to a few years before menopause. The phase when a woman begins to experience various signs and symptoms before the actual cessation of menses is called *Perimenopause*. During this *menopausal transitional* phase various endocrinological, biological and clinical features of approaching menopause commence, and continue into the first few years after menopause. *Premenopause* refers either to the one or two years immediately before menopause or to the whole of the reproductive period prior to menopause. *Postmenopause* is defined as the phase, dating from the final menstrual period (FMP), regardless of whether the menopause was induced or spontaneous.

Although menopause, defined as the eventual and final cessation of menstruation, is an event that is experienced by all women and therefore considered a natural event, a debate nevertheless continues as to its exact status.

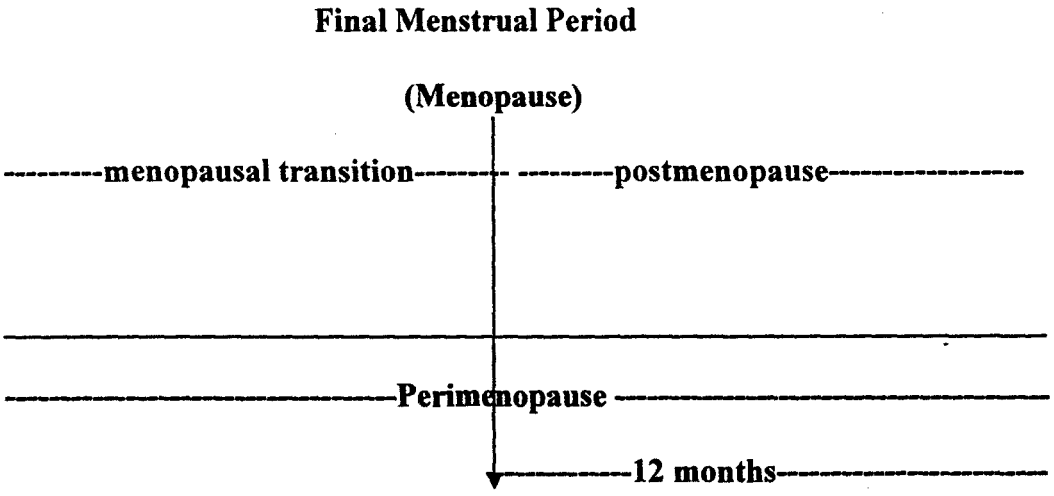

FIGURE 1.1 RELATIONSHIP BETWEEN DIFFERENT TIME PERIODS SURROUNDING MENOPAUSE (adapted from WHO Technical Report series, 866, 1996)

There are two schools of thought on how menopause is actually viewed (Bungay *et al.*, 1980; Andrist & MacPherson, 2001). The first, a predominantly biomedical model, perpetuates the idea that menopause is a condition resulting from estrogen deficiency, associated with ill-health for the majority of women and manifested in symptoms that are largely similar in all cultures as they arise principally from oestrogen withdrawal or deficiency.

The second view, however, emphasises the social meaning of menopause. Their argument is that most women go through this transition uneventfully and that the health changes and symptoms associated with it are more a function of aging rather than of

hormonal changes (Andrist & MacPherson, 2001; Obermeyer, 2000). Within the social context, menopause is considered a natural end of the reproductive phase of a woman's life. Sociological critiques argue that to define menopause solely in terms of health and illness gives it a medical perception and changes the meaning of menopause. On the other hand, to treat it solely as a natural phenomenon requiring no medical intervention may also be considered inappropriate. Although the extent to which reproductive aging interacts with somatic aging is poorly understood, there is no doubt that the aging process itself may be influencing some of the complaints of women during menopause. Indeed, reproductive aging is often a confounding variable in studies of somatic aging, or *vice-versa* in women (Santoro & Tortoriello, 1999).

There is however no doubt that menopause by itself is responsible for some of the complaints of women going through this transition. Menopause and other age-related changes occurring in a woman's body are partly a natural process programmed into their genes from the moment of conception. Most of the ageing occurs gradually, but the decline and eventual cessation of reproductive functioning in women is somewhat more abrupt and therefore somewhat problematic at times. There is therefore now emerging an intermediate view amongst many a gynaecologist and sociologist that while menopause is a natural and an inevitable phenomenon, there may be a need for some intervention particularly for women who may suffer considerable distress during this transition.

1.3 PHYSIOLOGY OF MENOPAUSE

The locus of reproductive aging is the ovary. Menopause is not a sudden event but is the cumulative result of events, some already beginning in fetal life where the attrition of oocytes begins and continues during the lifespan of the female. Although the ovarian size increases at puberty and until early adult life, with fluctuations caused by follicle and corpora luteal growth and pregnancy, by the age of 40, however, there occurs a slow but steady decrease in the ovarian size until menopause. The rate of decrease in ovarian size is greater in the perimenopausal period (Jorgensen *et al.*, 1987) and during 5 to 10 years postmenopause, after which the rate of decrease in size slows down (Goswamy *et al.*, 1988). The decreased ovarian size after menopause often reflects changes in the supporting tissue and stromal cells while the decrease in ovarian size in perimenopausal women is mainly due to loss of oocytes and follicles. Oppermann *et al.* (2003) evaluated the relationship between ovarian volume and age, hormonal levels, obesity and phases of menstrual cycle in pre-and perimenopausal women. No statistical difference was reported in ovarian volume related to the phases of the menstrual cycles. However, ovarian volume was significantly smaller in all age groups over 40 years compared with the 35-to-39 year's age group. No association was observed between ovarian volume and body mass index. From the age of 40 years onwards the size of the ovary decreases initially due to increased loss of oocytes and after menopause due to loss of stromal cells.

1.3.1 FOLLICLE OR OOCYTE ATTRITION

Attrition of oocytes or primordial follicles is considered the main factor that contributes to ovarian failure (Klein & Soules, 1998). Two primary factors are thought to dictate the timing of ovarian senescence, which serves as a driving force behind the menopause in

omen. The first is the size of the initial stockpile of primordial follicles endowed shortly ter birth and the second is the rate at which the population of these primordial follicles lost from the ovaries during postnatal years (Tilly, 2003).

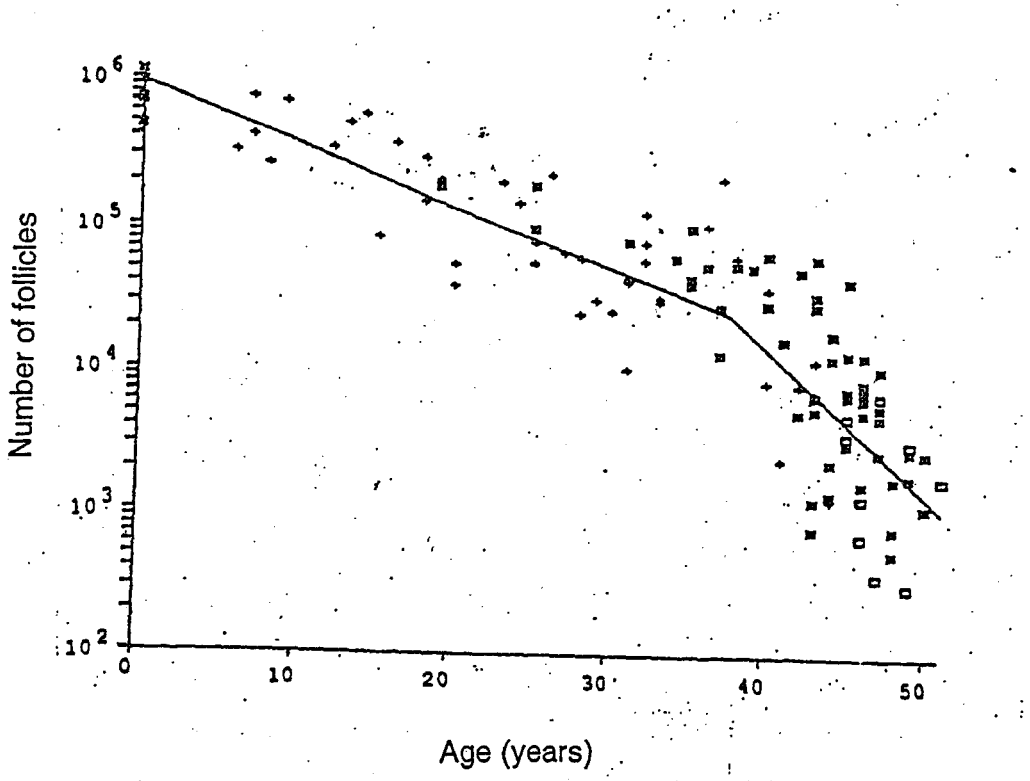

FIGURE 1.2 AGE RELATED DECREASE IN THE TOTAL NUMBER OF PRIMORDIAL FOLLICLES (PF) WITHIN BOTH HUMAN OVARIES FROM BIRTH TO MENOPAUSE (Adapted from Faddy *et al.*, 1992).

The maximum number of follicles is found during fetal development. From the start of oogenesis *in utero*, a process of oocyte or follicle attrition occurs simultaneously so that by birth, only 2 million primary oocytes exist and by the onset of puberty, only 400,000 remain. This constitutes the entire supply of potential ova for the woman's reproductive life because no new oogonia can be formed (Berne & Levy, 2000; Faddy & Gosden, 1996; Gosden & Faddy, 1994). The loss of follicles is primarily due to atresia rather than

ovulation because over 40 years of reproductive life, with monthly spontaneous ovulation, only about 480 follicles actually ovulate (Longscope, 1999), the rest just become atretic (Figure 1.2). Just before menopause there is an increase in the rate, at which follicles become atretic and disappear (Guyton & Hall, 2000; Rutishauser, 1994; Godsen & Faddy, 1994; Utian, 1980). It is uncertain if the ovary is without any follicles at the time of menopause. Richardson & Nelson (1990) did find a few ovaries without follicles at menopause, but others have reported that the ovaries still contain primordial follicles, even in women who are 10 years post menopausal (Gosden, 1987; Costoff & Mahesh, 1995). However, with continuing attrition, very few oocytes are left when menopause begins and these are unable to sustain the reproductive capacity (Silbergeld & Flaws, 1999).

The precise mechanism that is responsible for the follicular attrition is unclear, and it is uncertain what decides on which follicle goes on to develop into a matured follicle and which one undergoes atresia. Programmed cell death or apoptosis has been suggested to be responsible for the loss of up to 99.9 per cent of the mammalian female germ cells, which eventually drives to irreversible infertility and ovarian failure – the menopause in human (Houmard & Seifer, 1999; Berne & Levy, 2000; Tilly, 1996). Programmed cell death or apoptosis is characterised by condensation and fragmentation of DNA by endonucleases followed by phagocytosis.

If ways could be developed to delay or slow the rate of attrition of the primordial follicles, it may become possible to delay the onset of menopause.

1.3.2 THE OVARY AFTER MENOPAUSE

Following menopause, the ovary becomes smaller, slightly fibrotic, and the surface is pitted. The older ovary has reduced primordial follicles with an increase in fibroblasts and connective tissue, and the stromal cells apparently becoming more abundant. The ovaries of the postmenopausal women are smaller than those of premenopausal women and consist primarily of stromal cells. The morphologic changes include an atrophy of the ovarian cortex, which once housed most of the primordial follicles, and an apparent hyperplasia of the medulla where most of the interstitial or stromal cells are found (Utian, 1980; Taylor *et al.,* 1951). As both the theca interna and granulosa cells, the usual sources of estrogen and progesterone, are gradually lost, the stroma (interstitial) becomes more abundant and active. It becomes the main source of steroids. Stromal tissue from the ovaries of women up to 30 years after menopause has been shown to secrete androstenedione and estradiol *in vitro* (Dennerfors *et al.,* 1980). The aging ovaries of most menopausal women do secrete testosterone but little androstenedione and little or no estradiol (Longcope, 1999; Cutler & Garia, 1984).

The stromal cells accumulate lipids and form the lipid band which becomes noticeable after the age of about 35 years (Fienbergh & Cohen, 1965). Histochemical studies have revealed that the lipid band is positive to cholesterol and related to steroids, but devoid of the oxidative enzyme activity *(glucose-6-phosphate* and *3B-ol dehydrogenases)* found in the stromal theca as well as theca interna cells. These missing enzymes are required for steroid hormone synthesis (Fienbergh & Cohen, 1965). Luteinising hormone (LH) receptors are present on the stromal cells in abundance but FSH receptors are not seen (Vihko, 1996). Because some stromal cells contain the aromatase complex (Inkster &

Bodie, 1991), the reduced number of FSH receptors may explain in part the lack of estrogen secretion from the ovary in most postmenopausal women (Longcope *et al.*, 1980).

1.3.3 HORMONAL CHANGES IN MENOPAUSE

As a woman with regular cycles comes closer to the end of the reproductive years, many changes usually manifest within her body. Some of these include 1) the selection and development of a dominant follicle occurs earlier, 2) there is earlier ovulation, 3) there is a short follicular phase and total cycle length may shorten. Fertility becomes significantly compromised long before overt clinical signs, such as cycle irregularity, occur. Eventually, towards the end of the reproductive years and with the disappearance of almost all follicles, ovarian secretion of estradiol virtually ceases (Figure 1.3), and estrone produced from theca cells then becomes the predominant estrogen (Berne & Levy, 2000). At about the same time inhibin levels too start to decrease in menstruating women (Batista *et al.*, 1995). Reduced inhibin concentration may be related to the gradual decline in the number or quality of oocytes in the ageing ovary. Inhibin rather than the oestrogen concentration declines first in the premenopausal group suggesting inhibin as a possible marker for ovarian function towards the end of the reproductive life (Batista *et al.*, 1995).

In addition, as the follicles become fewer, menstrual cycle irregularity becomes apparent (Upton, 1982) and the frequency of ovulatory cycles decreases. The orderly pattern of estradiol increase and decrease is lost. With anovulatory cycles, the production of progestrone remains low (<1.0 g/ml). By now, both the estradiol and progesterone

concentrations are lesser then those in younger women (Metcalf, 1988). With menopause, there is a decline in estradiol concentration, which is relatively sharp for the first 12 months and then declines gradually over the ensuing years. Similar to estradiol, the concentration of estrone, a weaker estrogen also declines.

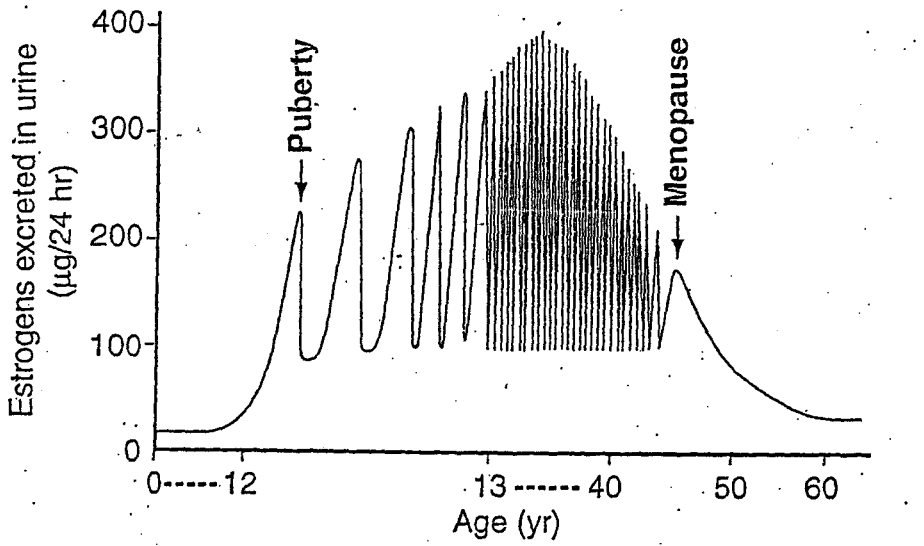

FIGURE 1.3 SECRETION OF OESTROGEN THROUGHOUT THE SEXUAL LIFE OF A HUMAN FEMALE (Adapted from Guyton & Hall, 2000. p 940)

As menopause approaches, there also occurs an increase in gonadotrophin levels. These levels continue to increase during the early phase of postmenopause and then decline thereafter (Figure 1.4) (Lenton *et al.*, 1988). The pattern of pituitary-ovarian hormones throughout the menstrual cycle is also altered as menopause approaches (Robertson & Burger, 2002). Before and during menopause (Burger *et al.*, 1995; Metcalf et al., 1981), the most dramatic change happens in the secretion of FSH by the pituitary and many women have an increase in the level of FSH even when menstrual cycle persists although the cycles are irregular. However, those women with regular cycles, the FSH may

ıcrease intermittently (Burger, 1996). With the cessation of menses, FSH levels rise and hen plateau within the first couple of years (shown in the Figure 1.4).

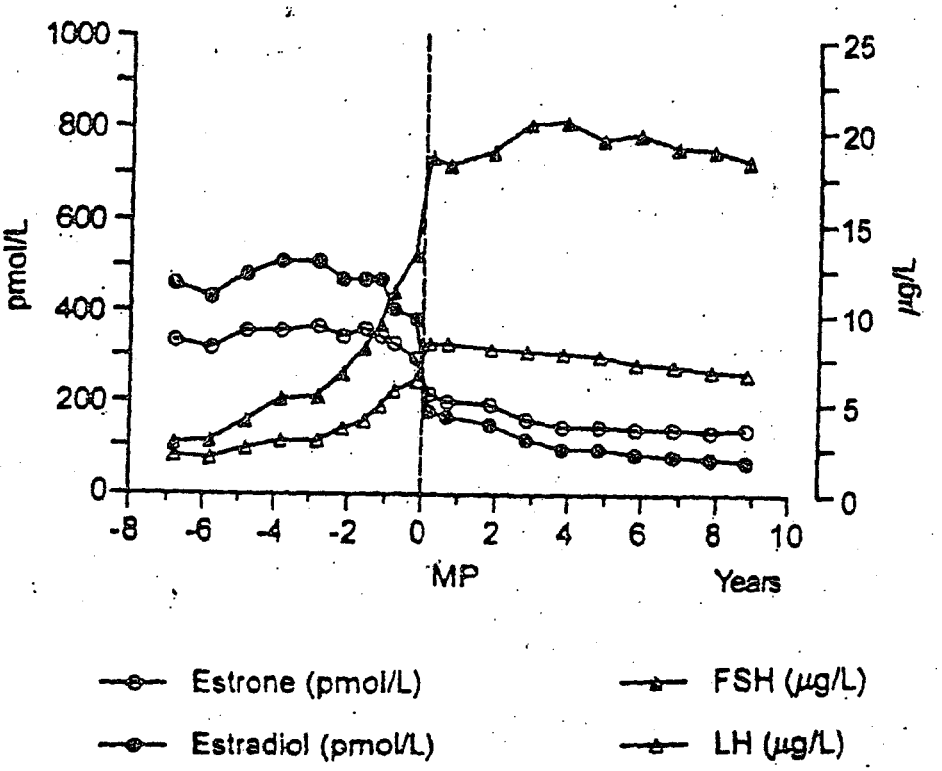

FIGURE 1.4 MEAN SERUM LEVELS OF FOLLICLE-STIMULATING HORMONE, LUTEINISING HORMONE, ESTRADIOL AND ESTRONE, SHOWING THE PERIMENOPAUSAL TRANSITION (Adapted from Rannevik *et al.*, 1995)

The precise reason for this is unclear, but much of this rise is due to a decline in ovarian estrogen (Reyes *et al.*, 1977) and inhibin B which normally inhibit FSH secretion, as the ovary is the major source of inhibin (Kwekkeboom *et al.*, 1990). Serum inhibin B is believed to reflect the age-related decrease in ovarian follicle reserve, which is the primary source of serum inhibin B. With the decline in the follicle number, the level of circulating inhibin (Burger, 1996) also decreases. However, the levels of follistatin have been reported to remain relatively constant at menopause (Kettle *et al.*, 1996).

The monotropic FSH rise is an early endocrine event that first indicates a woman is approaching the end of her reproductive potential. Soules *et al.* (1998) hypothesised that when the number of preantral follicles in both ovaries drop below a threshold, then there is a subtle decrease in inhibin B which leads to the monotropic FSH rising which in turn accelerates follicular depletion and the attainment of the menopause. In addition to FSH, LH too increases, albeit to a lesser extent then FSH.

These hormones therefore tend to increase at least for a while during the perimenopausal period and the initial phase after menopause. Plasma gonadotrophins increase to levels four to ten times those characteristic of the follicular phase, and FSH levels even exceed LH levels. Although the cycle of gonadotrophin secretion is lost, pulsatility continues to persist (Berne & Levy, 2000). Hormonal patterns during the luteal phase of the menstrual cycle also show changes with age but these changes are poorly understood (Robertson & Burger, 2002). The later rise in serum LH during menopausal transition is due to cessation of ovarian follicle development.

Although LH may be increased before menopause in some women (Metcalf & Livesey, 1985), its level, however, remains in the normal range in most women. At menopause, LH levels rise and plateau after about 12 months of amenorrhoea (Longcope *et al.*, 1986). Like in the case of FSH, much of this rise is caused by the decline in ovarian estrogen secretion and the resultant loss of the negative feedback. LH levels decline in later years (Metcalf & Livesey, 1985). The increasing circulating levels of FSH and LH result from increased pituitary secretion of gonadotrophins without a change in their metabolism. 'The pulses of LH and FSH are increased in amplitude but not in frequency. To what

degree the changes in the hypothalamic-pituitary-ovarian axis are caused by the ovary alone is not certain (Wise *et al.*, 1996).

In most postmenopausal women the major source of circulating oestradiol is from peripheral aromatisation of androgen (Ganong, 1999). Menopause is also associated with a decrease in ovarian androgen. With a fall in secretion of androstenedione, a major source of testosterone, results in a decline in circulating testosterone in most postmenopausal women. The levels of androstenedione are also lower in postmenopausal women (Burger et al., 1995).

1.3.3 (a) Adrenal Gland

During early development, the increases in size in both the ovary and the adrenal gland are parallel but after 35 years of age, the adrenal gland continues to maintain its size whereas the ovary tends to decrease in size sharply due to follicular atresia (Figure 1.5). In addition to a decline in oestrogen, there is also a very slow decline in androgen status (i.e. androstenedione and testosterone), which may not be adequately detected at the time of perimenopause. However, in comparing 24-hour levels of premenopausal and perimenopausal women, testosterone was found to decline significantly (Figure 1.6). Premenopausally, the ovary secretes approximately 25% of circulating testosterone, 50% androstenedione, and 20% dehydroepiandrosterone (DHEA) with the adrenal gland contributing the remainder. But postmenopausally, the levels of these hormones drop by about 15% to 50% because of declining ovarian function and decreased adrenal function. The latter is age related rather than menopause (Carlstom *et al.*, 1988). The ovary however does continue to secrete androgen following menopause and is responsible for

approximately 50% of the total circulating testosterone. The circulating levels of cortisol and aldosterone are also not affected by menopause (Parker *et al.*, 1981).

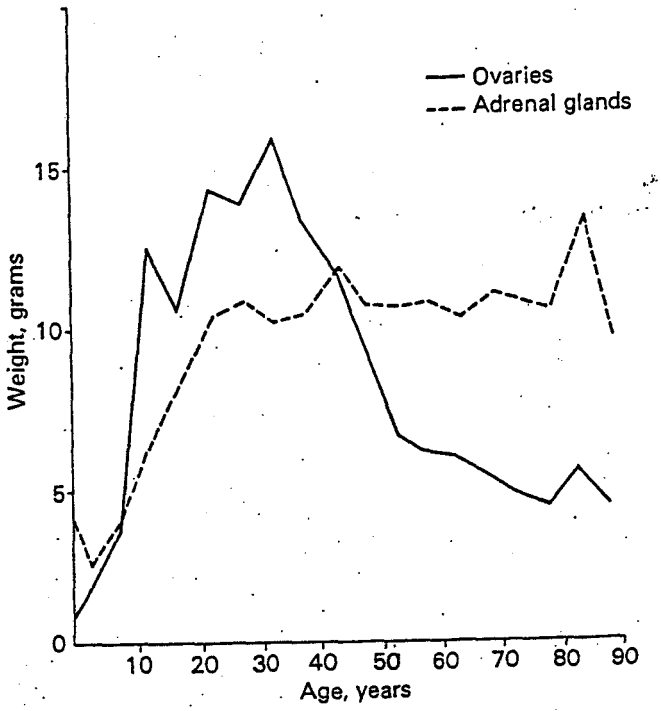

FIGURE 1.5 AGE RELATED CHANGES IN OVARIAN AND ADRENAL SIZE (Adapted from Cutler & Garcia, 1984 p3.)

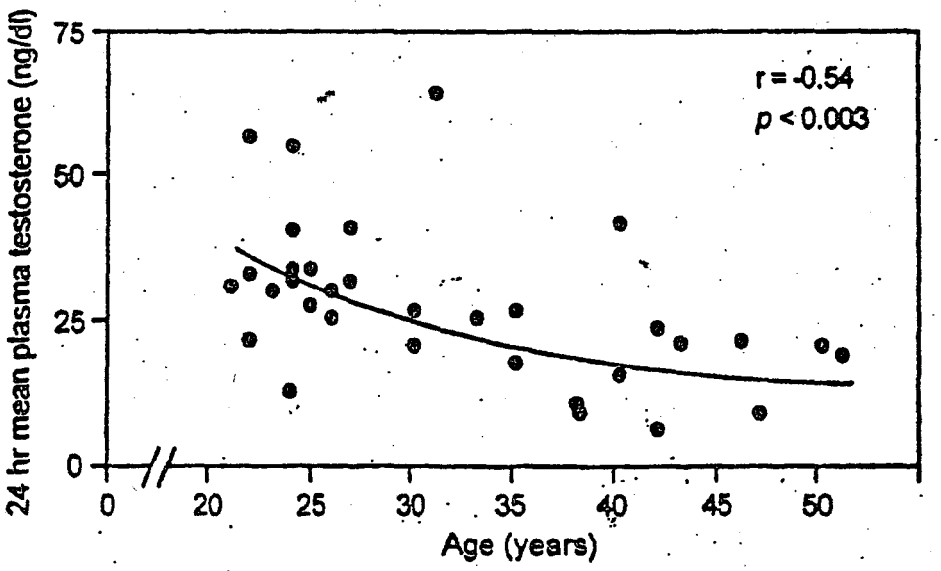

FIGURE 1.6 24-hour MEAN PLASMA TOTAL TESTOSTERONE (T) LEVEL COMPARED WITH AGE IN NORMAL WOMEN (Adapted from Zumoff *et al.*, 1995)

1.3.3(b) Hormone Metabolism

Although there are marked changes in the secretion of ovarian and pituitary hormones, however, there are no real changes in the metabolism of these hormones. The overall metabolism of FSH, LH, androgens and oestrogen is not altered by the sudden changes in their secretion and production that occur during menopause (Longcope, 1999). However, there is a shift in one pathway of androgen metabolism: aromatization in peripheral tissues such as adipose tissue, muscle, and probably skin. This change in the aromatization pathway is important to estrogen production.

The peripheral aromatisation of androstenedione and testosterone is significantly greater in postmenopausal women then younger women. Therefore, with the decline in ovarian secretion, peripheral aromatisation becomes the major source of oestrogens in postmenopausal women (Longcope, 1999). Because adipose tissue is an important site for aromatisation, the slightly higher levels of circulating oestrogens in obese postmenopausal women is probably a reflection of the increased aromatisation.

1.4 CLIMACTERIC

The word climacteric comes from a Greek word, which literally means, "rung of a ladder" (Stoppard, 1999). The word "climacteric" accurately describes the ongoing changes and symptoms, which occur within the transitional phase. It has no time limit, and may last from between 5 to 15 years. The relationship between menopause transition and symptom reporting appeared to be transitory, with reported rates showing an increase

in the perimenopause and a compensatory decrease in the postmenopause (McKinlay *et al.*, 1992).

As a woman is going through the transitional phase, she begins to adapt from a productive to a non-productive phase (Figure 1.7). Menopause or the final cessation of menses is one of the events, which may occur abruptly or gradually in the climacteric phase. However, after menopause, it is important to note that the production of oestrogen does not completely stop. When the ovary ceases to produce estrogen, the adrenal gland takes over by converting androstenedione into oestrone. Since the level varies from person to person, in some women it may be sufficient to minimize or prevent altogether some of the troublesome menopausal symptoms, while others may have insufficient levels to cause moderate to severe symptoms. In other words, during climacteric, some women may have none or mild complaints while others may develop moderate to severe complaints, which may require medical treatment. Climacteric symptoms are also known to vary between women from developed and developing countries. The major menopausal symptoms, amongst the Ghanaian women were tiredness, sleeplessness, palpitations, weight gain, hot flushes, irritability, anxiety and headache (Kwawukume *et al.*, 1993). Headache was the most common climacteric symptom while the hot flush was the least prevalent amongst the Filipino women. On the other hand, in the Turkish women the most common symptoms were muscle and or joint and or bone pain (Neslihan *et al.*, 1998). Only 18% (n=427) of factory workers in China experienced hot flushes and the climacteric symptoms were more pronounced at the perimenopausal period (Tang, 1994). The author suggested that these women's different climacteric pattern could be related to their introspective abilities to cope adequately or in an impersonal manner.

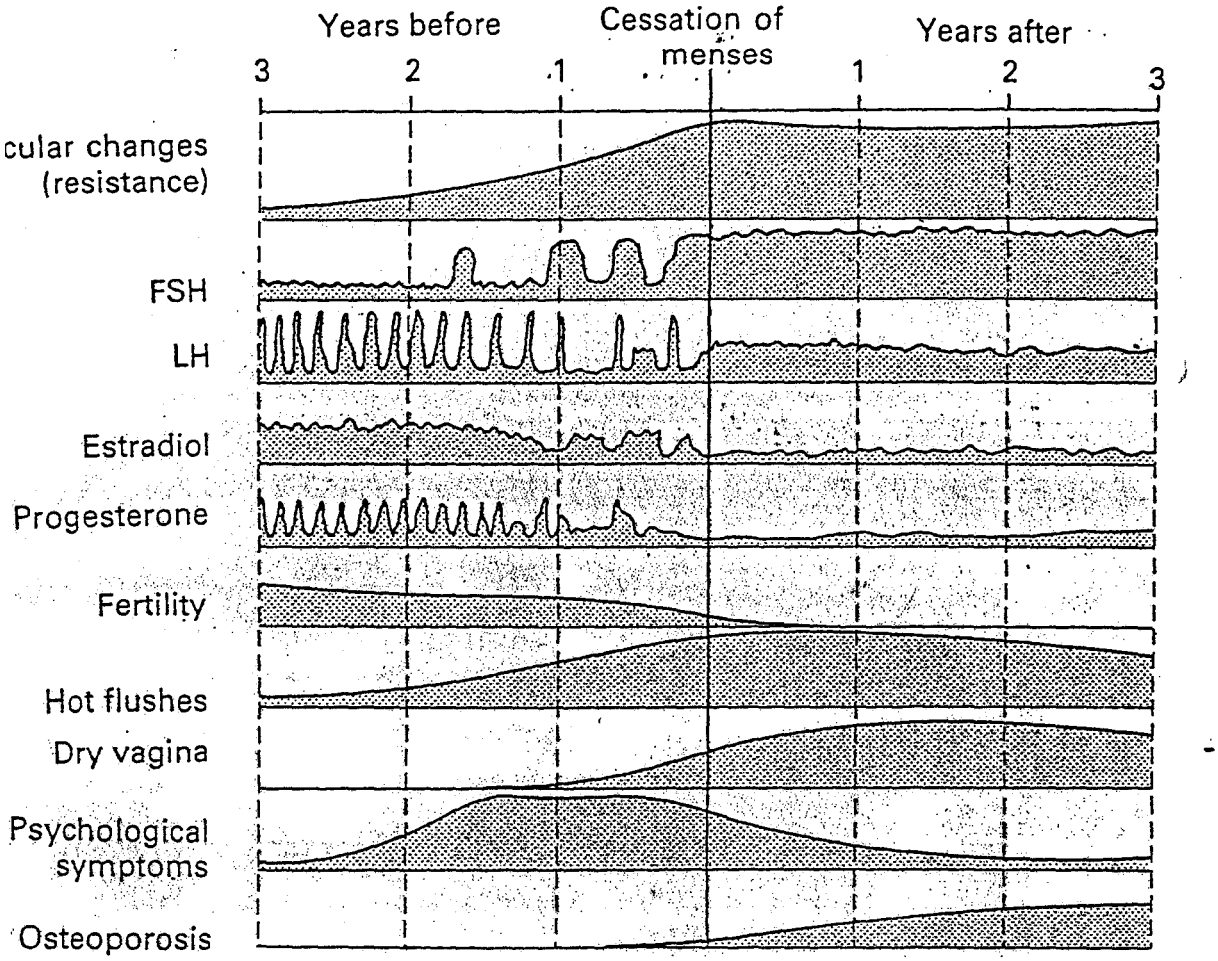

FIGURE 1.7 TIME COURSE AND HORMONAL CHANGES AND SYMPTOMS ASSOCIATED WITH MENOPAUSE (Adapted from Rutishauser, 1994. p. 622)

A Swedish study revealed that the Swedish women only associated vasomotor symptoms and joint pain with postmenopausal status where the other symptoms such as negative moods, decreased sexual desire, memory problem, sleep-related symptoms, vaginal dryness, urogenital problems, and vitality were significantly related to psychosocial factors, life-style and attitude to menopause (Olofsson & Collins, 2000). The Study of Women's Health across the Nation (SWAN), a cross-sectional study conducted between

1995 and 1997 in USA (Gold, *et al.*, 2000), investigated the factors related to menopausal and other symptoms in a multiracial/ethnic sample of 16,065 women aged 40 – 55 years. The results of the study showed that low socioeconomic status, particularly low educational level and poverty were associated with significantly increased reporting of almost all symptoms. Moreover, women who had healthy lifestyles were associated with lower prevalence of virtually all symptoms (Gold *et al.*, 2000).

At this point, one has also to take the menopausal status of the women into consideration during the climacteric phase. The symptoms and their intensity may depend upon the stage the women is in during climacteric i.e. whether perimenopause or postmenopause. Women in the early stages of menopause or perimenopausal are more likely to report of tiredness, stiff joints, difficulty in sleeping and hot flushes compared with premenopausal women (Brown *et al.*, 2002). Interestingly, a Dutch study revealed that the prevalence and intensity of climacteric symptoms appear to increase during the menopausal transition and stay high during the postmenopause (Barentsen *et al.*, 2001). Dennerstein *et al.* (2000) cited that by postmenopause almost all women in her study were reporting at least one symptom and most were reporting five or more symptoms. In this longitudinal study the average number of symptoms increased by 17% within late perimenopause and postmenopause. This reflects not only the broad spectrum of time span in the climacteric phase but also the varying symptoms and intensity of the symptoms within that transition. Hence, some women will have no symptoms and others will vary from mild to severe symptoms.

Menopausal symptoms have been divided into four groups (Greene, 1976; Holte & Mikkelsen, 1991). The first group comprises of symptoms associated with vasomotor instability (e.g. hot flushes, night sweats, excessive sweating and sleep disturbance). The second group comprises of psychological symptoms (anxiety, forgetfulness, impatience and feeling of wanting to be alone). The third group consists of somatic symptoms (e.g. headaches, lower backache, skin dryness and skin patches). The fourth group consists of uro-genital complaints (e.g. frequency of micturition, avoiding intimacy, changes in sexual desire and vaginal dryness).

1.4.1. Vasomotor Instability

Hot flushes are evident in about three-fourths of postmenopausal women and believed to be due to vasomotor instability associated with declining oestrogen. Insufficient studies have been performed to examine the risk factors for hot flushes. Few studies that are available, suggest that there may be present in some women, risk factors that may make them more susceptible to hot flushes. For example, smoking, low body weight, little or no exercise, and early menopause, are all associated with increased risk of hot flushes (Stearns *et al.*, 2002; Whiteman *et al.*, 2003). These risk factors may determine whether a woman has hot flushes or not and hence not all women experience them.

The average hot flush lasts about 4 minutes but it can last a few seconds or as long as 10 minutes. The hot flushes vary widely in both frequency and intensity, occurring only a few times during the day and sometimes several times in an hour. The reason for this wide variation in intensity and frequency is uncertain. When hot flushes occur at night, it

creates bigger problems. The symptom will wake the sufferer up and the action not only causes sleep disturbances to the woman but also to the spouse.

During a hot flush, the woman will have a feeling of heat, which occurs quite suddenly and may involve the chest, neck and face. It may or may not be accompanied by reddening of the skin. Following a hot flush, perspiration occurs which is often described as night sweat. The precise mechanism for the hot flush is still not clearly understood. In normal circumstances, when the body starts to overheat, the temperature-regulating centre in the hypothalamus initiates a response that causes the blood vessels near the skin to dilate and permit heat to dissipate from the body surface. Perspiration or sweating then cools the body as water in the sweat evaporates from the skin. In the hot flush of menopause, there however is no overheating of the body *per se,* rather there is the mistaken perception by the body that there is increased heat in the body. The reason for this is unclear. It may be due to a dysfunction or alteration in the functioning of the central thermoregulatory centers in the hypothalamus caused by changes in falling estrogen levels at the time of menopause. It is believed that during menopause low estrogen levels reduce the number of receptors that control norepinephrine release, which in turn, causes the temperature-regulating cells to fire abnormally and release norepinephrine at inappropriate times. The norepinephrine creates the illusion that the body is overheated and triggers normal heat-loss mechanisms in an attempt to end the imaginary spell of overheating (Freedman, 2001). A more recent hypothesis, however, proposes that oestrogen withdrawal causes a decline in circulating serotonin, thus increasing the sensitivity of the hypothalamic serotonin ($5HT_{2\alpha}$) receptors. After an internal or an external stimulus, serotonin concentration rises and the serotonin ($5HT_{2\alpha}$)

receptor is stimulated. As a result there is a change in the thermoregulatory set point and a hot flush sensation is felt (Berendsen, 2000). Both hot flushes and night sweats are self-limiting, and with the gradual increase in the production of estrone, the symptom tends to disappear (Rutishauser, 1994). Clearly the precise mechanism of the symptom is still not yet understood and it is also unknown as to why the hot flushes are felt more on the face and neck region and very little at the extremities.

Hot flushes and night sweats were reportedly more common among Australian postmenopausal women particularly night sweats, which increased in intensity and remained high for quite sometime postmenopausally (Brown *et al.*, 2002). The 39% incidence of troubling hot flushes experienced by Melbourne menopausal women was similar to Sydney menopausal women (Ballinger, 1985). Symptom patterns experienced by Australian women in Melbourne were also similar to those reported in North America (Dennerstein *et al*, 1993; McKinlay *et al.*, 1987) and European women (Holte & Mikkelsen, 1991). Some studies on Asian women however, tended to show a lower incidence of vasomotor symptoms. For example, only 16.4% Taiwanese women had hot flushes and 11.8% had night sweats (Fuh *et al.*, 2001). Similarly, in Singapore 17.6% of women had hot flushes, 8.9% night sweat, 23.4% had difficulty in sleeping and 11.1% sweated more then usual (Chim *et al.*, 2002). Amongst the Thai women, however the incidence was somewhat higher, where 33% had hot flushes, 32% night sweat, 52% insomnia (Punyahotra & Dennerstein, 1997). Damodaran *et al.* (2000) in Kuala Lumpur found that 56% of the urban menopausal Malaysian women complained of hot flushes. The reason for the difference in the incidence between the Australian, European and

Asian studies is uncertain. Clearly more studies are needed to understand this phenomenon and in particular the factors affecting it.

Palpitation and dizziness may occur with hot flushes or on their own. The feeling of faintness or dizziness may be accompanied by the unpleasant awareness of the heart beating rapidly or even irregularly (Anderson, 1983). In a Thai study, 41% of postmenopausal women had palpitations, which they described as "rapid heart", while 68% had episodes of dizziness (Punyahotra & Dennerstein, 1997). A Taiwanese study revealed 43.6% postmenopausal women complained of dizzy spells (Fuh *et al.*, 2001), while only 9% postmenopausal Australian women from Melbourne complained of dizzy spells and 9.9% had rapid heartbeat. The reason for the differences in the incidence is not immediately apparent. Clearly, there seems to be a difference in the incidence and, may be, the intensity of postmenopausal symptoms in the different populations. Although the prevalence of palpitation and dizziness is small compared to other symptoms, it is nevertheless important to note that these symptoms are associated with the transitional phase.

1.4.2 Psychological symptoms – emotion and behaviour

Dennerstein, *et al.* (1993) noted that 13.9% of women in the Melbourne study experienced dysphoria, which is a state of unease and mental discomfort. Others suffered from nervous tension (40%), feeling sad (28.7%), having difficulty concentrating (18.3%), lack of energy (38.0%), and troubled sleep (41.4%). These symptoms were not to be confused with major psychiatric disorders. This finding indicated that there was a prevalence of minor psychological symptoms among Caucasian women aged 45 – 55