

BIOL30001 – Reproductive Physiology

Lecture 3.1: Menopause

Menopause: What and When?

- The menopause is the final menstrual period
- Average age of menopause is around 51-52 years; the age range is ~48-55 years – data predominantly driven by western society
- Defined retrospectively *after 12 months of absent periods*
- Perimenopause, Menopause Transition, Climacteric
 - The period when ovarian function starts to decline, cycles are irregular (follicular phase generally is shorter) and the menopausal symptoms appear
 - Begins mid to late 40s and ends one year after menopause
 - 'The Menopause' refers to the last menstrual period
- Post-Menopause
 - The whole lifetime after menopause
 - No periods, no ovulations, steroid hormones low, cannot conceive
- Early Menopause
 - 40-45 years, affects 5-8% of women
- Premature Ovarian Insufficiency (POI), premature menopause
 - Menopause prior to 40 years old, affects 2% of women
 - May have intermittent ovarian activity – may be linked to a low ovarian reserve

Changes in Age of Menopause

- Increased life expectancy from ~42 to ~85 in 100 years with 95% women now reaching menopause and then the post-menopausal period
- Factors regulating the age at natural menopause are poorly understood/ controversial
 - Absolute Regulators of Menopause
 - Genetic factors are important
 - Cigarette smoking results in slightly earlier menopause (1-2 years) – this is due to the toxicity of chemicals in cigarettes causing destruction of primordial follicles. There are also cardiovascular changes that occur, which impact blood flow to the ovaries
 - Surgical history – more specifically a hysterectomy (removal of the uterus – not the ovaries or cervix) may reduce the age at menopause by around 3-4 years due to disruption of the systems and its blood flow. Paracrine factors released from the endometrium may impact the lifestyle – potential impact from the invasiveness of the surgery
 - Probable Factor Affecting Menopause
 - Ethnicity – Hispanic and African American women tend to undergo menopause earlier than Caucasian women, while Asians tend to experience it later.
 - Controversial Factors Affecting Menopause
 - High BMI: apparently supposed to have an impact on fertility
 - Age at menarche (<12 years): controversial, 31% of women undergo menopause earlier if they have their first period earlier (before 12). Possibly due to changes in puberty and fertility
 - Nulliparity: it was found that women that had no children were 5x more likely to go through menopause early
 - The effect of contraceptive pills is also very controversial

Age Related Decline in Ovarian Follicle Numbers

- A female foetus at 20 weeks of gestation has ~4-5 million follicles
- When the child is born, she has ~1-2 million follicles
- By the time they hit puberty, there is ~300,000-400,000 follicles left
- At around age 37, there is ~100,000 followed by a steep decline in fertility (significant age) – there will also be a decline in quality (specifically with chromosome segregation)
- Those who have early menopause are thought to have a low ovarian reserve than the standard female

Perimenopause Aetiology

- Ovarian primordial follicles decrease with age at accelerated rate of loss from 37 years
- Follicles become progressively more resistant to stimulation from FSH and LH
- Follicles that do develop may not secrete sufficient estradiol and progesterone (from ovulated corpus luteum) to produce regular menstruation – can be erratic/ short cycles, may also have a couple months off in between
- Decrease in estrogen (and progesterone), because there are follicles that act like a brake (through AMH), as the number of follicles to create this brake reduces, follicular negative feedback also reduces – potentially leading to multiple ovulations – also because females may believe they are no longer ovulating and neglect to use contraception – risk of down syndrome, genetic diseases and twins
- Irregular anovulatory cycles lead to prolonged unopposed oestrogen
 - This may lead to endometrial hyperplasia and an increased cancer risk

Peri-Menopause Endocrine Changes

- Decreased ovarian inhibin B, and decreased AMH from the ovarian granulosa cells – this leads to a less effect 'brake' system
- Gradual rise in FSH as the follicles are less responsive to gonadotrophins
- Fluctuations in oestradiol and progesterone
- No substantial changes in androgen levels during this timeframe
- Sex steroid levels fluctuate markedly on daily basis

- Measuring sex steroids is not useful when a woman of normal menopausal age develops symptoms

Menopause Aetiology

- Decline in oocyte quantity and quality in the years preceding
- Loss of ovarian follicular activity at menopause
- Very low estrogen (and progesterone) - present at low concentrations, being produced in fat cells
- Increased FSH/LH levels - fired from the brain
- Cessation of menstruation
- Cessation/reduction of sexual drive

Menopause Ovarian and Endocrine Change

- Important to use contraception during this time - this is because ovulation may intermittently occur, even though it is less frequent
- Ovarian primordial follicle stores are exhausted by atresia and ovulation but this is retrospective
- Oestradiol declines following menopause - as there is a lack of negative feedback
 - FSH >40uL
 - LH > 30-40uL
- Androstenedione is still produced by the ovary and adrenal gland and is converted in peripheral tissues to oestrone (E1) = low levels
- Androgens gradually decline during reproductive life but no dramatic change after menopause

Hormonal Summary

Image can be retrieved from
lecture slides - not included due
to copyright

Aetiology of Premature Menopause/Premature ovarian Insufficiency (>40 years)

- Idiopathic (>70% of cases) - spontaneous POI
- Rare Causes: galactosaemia (lack of galactose breakdown enzyme)
- Autoimmune: Addison's disease (problems with steroid production), thyroid abnormality
- Genetic: Turner's syndrome (XO), fragile X syndrome (occurs in both girls and boys, linked to low IQ, and poor mental capabilities for males and low ovarian reserve in females)
 - Deletions in the X chromosome between positions 13 and 26 can affect ovarian function
- Iatrogenic: surgery/chemo/radiotherapy (8-19% of women under 40)

Premature Menopause / Premature Ovarian Insufficiency

- Diagnosis of POI:
 - No periods for 4 months before age 40
 - FSH levels greater than 40mL/umL on 2 occasions at least 1 month apart (never rely on one); day 2-6 of cycling
 - Exclusion of all other causes of absent periods, such as stress, accompanied by a chromosome test
- Management of POI:
 - NO CURE
 - Actually still need contraception, lifetime chance of ever conceiving 5-10%
 - Often prescribed with hormone replacement therapy (HRT) to maintain the health of other organs during menopause because during this time there is also a decline in the cardiorespiratory tracts and bone density. This may lead to an increase mortality
 - For young women/girls - monitoring key is susceptible
 - If chemo/surgical - move ovaries away in the potential case of ovarian cancer (however, this method is still in its experimental stages)
 - Ovarian cryopreservation
 - Superovulation - egg freezing or IVF
 - Egg donation

Oestrogen Related Consequences of Menopause

- Incidence of Symptoms
 - 20-40% of women have menopausal symptoms requiring treatment
- Short Term
 - Vasomotor symptoms - hot flushes, night sweats, formication - skin thin, dry and itchy

- Urogenital symptoms - vaginal dryness, atrophic vaginitis, dyspareunia (pain during sex), dysuria (pain during urination), frequency
- Sleep disturbance
- Reduced libido
- Depression, anxiety, liable mood
- Memory loss, fatigue (may be due to not sleeping)
- Medium to Long-Term
 - Bone loss and osteoporosis - this is generally set in mid 20s
 - Weight gain - change in body form (pear to apple shape), decreased sensitivity of tissues to insulin (hyperglycemia)
 - Cardiovascular disease: increase blood cholesterol, renin (Angiotensin II), linked to hypertension

Hot Flashes

- Most common symptom - occurs in 80% of women
- Mechanisms are not known - hypothalamus thermoregulation
- Lasts ~4 minutes on average (1 to >10 times a day)
- Up to 30-50% resolve after 3 to 12 months
- Up to 40% may continue to have significant symptoms up to 10 years after menopause
- Increased with smoking, alcohol, surgical menopause, caffeine, weight
- Main reason why women request treatment - affects quality of life
- Oestrogen: most effective treatment, 80% reduction
- Meditation usually a useful technique used commonly to provide relaxation to reduce anxiety

Urogenital Symptoms

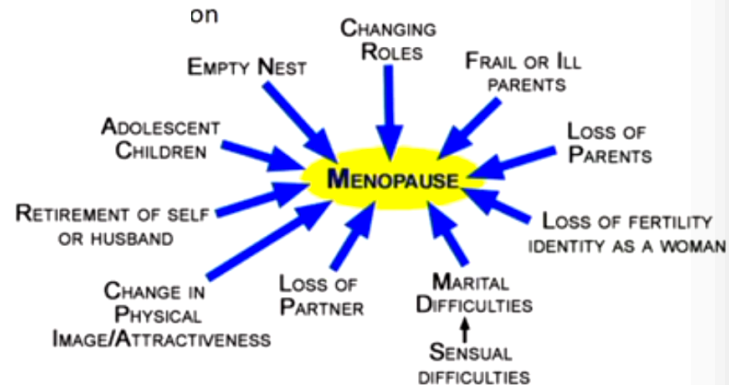
- Start at late peri-menopause
- Affect ~40% of post menopausal women
- Persist or worsen over time - atrophy of E2 sensitive tissues
- Vaginal dryness, discomfort, pruritis, dyspareunia, UTI (changes to alkaline pH) and urgency - epithelium thinning
- Pallor dryness, redness, decreased rugosity
- Endometrial atrophy - thin, exposed vessels, can cause bleeding
- First line is intra-vaginal oestrogen (not systemic HRT)
- For most patients

Other Symptoms

- Musculoskeletal aches and pains
- Skin thinning, dryness and itchiness (formication)
- Hair thinning and loss, male pattern baldness in some women - this is due to androgens (E2 ratio)
- Facial hair growth
- CNS, decrease memory - especially after surgical induced menopause, slow thinking and cognitive function, potential links to Alzheimers

Menopause and Emotional Health

- Psychological symptoms affect 25-50% of women
- No direct evidence for increased depression
- Decreased serotonin levels
- Adolescent children
- Empty Nest
- Changing roles
- Frail or ill parents/ loss of parents
- Loss of fertility (and identity as a woman)
- Marital difficulties
- Loss of partner
- Change in physical attractiveness / personal image
- Retirement of self/ husband leading to potential loss of income and confidence



Oestrogen-Related Consequences of Menopause: Long Term

- Oestrogen deficiency increases bone reabsorption - osteoclast activity
- Directly impairs gut calcium absorption
- Directly increases renal calcium excretion
- Sharp acceleration of bone loss during the initial 5 years following menopause (3-5%/year)
- Rate of loss then falls back to the age related loss of 1%/year - ethnicity a factor
- Low bone mass increases fracture risk - increased mortality

Early Prevention of Long Term Bone-Related Consequences

Early prevention is very important; the following things are recommended:

- High calcium intake (diet -1200mg/day), Vitamin D (800-1000U/day)

- Weight bearing exercise
- Good nutrition - avoid toxins, alcohol, caffeine, smoking
- Hormone replacement therapy - only helpful before 60 years old - this prevents fractures

Body Weight, Shape and Lipid Metabolism

- As age increases, there is a natural tendency for one to gain weight. There is also a decrease in lean mass and increase body and trunk fat
- There is also an absence of oestrogen at menopause:
 - Increased lipoprotein lipase enzyme
 - Increased cholesterol and LDL and decreased HDL
- Plus, power lipolysis in gluteal and abdominal regions:
 - Slower fat metabolism
 - Body shape changes from female pear shape to male apple shape

Cardiovascular Risk

- Major killer of women - contributes to ~50% of deaths
- Lack of E2 - increases risk of coronary heart disease (CHD), similar to men
- After menopause, increasing central adiposity, decreased resting energy expenditure, worsening CVS, lipid and metabolic profiles
- Hypertension (HT) - lack of oestrogen affects on the renin angiotensin system
- Potentially mediated by low oestrogen and loss of inhibition of metabolic neuropeptides
- Together with insulin-resistance (diabetic women) further increases the CHD risk post menopausal
- HRT does not prevent cardiovascular disease (CVD), may exacerbate in some women

Hormone Replacement Therapy

- Safe and effective if used in peri-menopausal or early postmenopausal women (<5 years of menopause) with vasomotor symptoms
- If given using these guidelines - no contradictions (breast/endometrial cancer/cardiovascular issues), if so case by case
- HRT contains oestrogen to treat symptoms and progestin (if needed) to protect the endometrium

Risk of HRT

- Women's health initiative JAMA 2002, 2004
- Combined oestrogen and progestin, given to post menopausal women 50-79 years
 - Increased risk of stroke
 - Increased risk of clots
 - Increased risk of breast cancer
 - Increased incidence of coronary heart disease

Menopause

Clinical Practice Guidelines

- Maybe a time of significant physiological, emotional and physical change during mid-life
- Lifestyle advice remains the main focus for the mid-life woman. Important to understand these changes so we may best address the needs of women
- Limited efficacy/safety data on complementary medicines
- HRT indicated only for moderated to severe menopausal symptoms - flushes, urogenital, women should consider the risks and benefits
- Use HRT at the lowest dose and for the shortest duration possible, in peri-menopausal or early post menopausal women not >60 years
- Healthy women with no contraindications
- Do not use HRT for prevention of CVD or dementia. HRT is not a first line treatment for osteoporosis