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WHAT'S NEW IN MANAGEMENT OF MENOPAUSE

MENOPAUSE

- Menopause is the permanent cessation of menstruation due to loss of ovarian follicular function. It is diagnosed retrospectively after 12 months of amenorrhea.
- Average age at menopause is 50 years.
- FSH level remains consistently high and estradiol low.

PERIMENOPAUSE

- It is the time period preceding menopause when fertility wanes and menstrual cycle irregularity increases, until the first year after cessation of menses.
- Perimenopause precedes menopause by 2 to 8 years, with an average of 4 years.

PERIMENOPAUSE

- The pituitary and selected ovarian hormone response is irregularly irregular during perimenopause.
- Propensity of anovulatory cycle produce a hyper-oestrogenic and hypo-progestagenic environment.

SYMPTOMS

- It is difficult to determine whether the symptoms that develop in the midlife of an women are due to ovarian senescence or to other age related changes.
- There is strong evidence that menopause can cause Hot flash, night sweat, irregular bleeding & vaginal dryness.

SYMPTOMS

- There is moderate evidence that it can cause sleep disturbance in some women.
- There is inconclusive evidence that ovarian aging is the major cause of mood swing, depression, impaired memory, somatic symptoms, urinary incontinence & sexual dysfunction

TREATMENT

- Hormone therapy (HT)remains the main effective treatment for menopause. (Therapies including estrogen, progestogen and combined regimens).
- Observational studies suggest that HT prevent cardiovascular & other chronic diseases, but randomized trials have not confirmed the benefits.

TREATMENT

- Indeed the largest HT trail to date, the Women's Health Initiative (WHI), examined more than 27,000 postmenopausal women age 50 to 79 (mean 63), for an average 5 – 7 years, was stopped early because of an overall unfavorable benefit-risk ratio in both estrogen-progestin and estrogen alone arm.

DEFINITE BENEFIT: VASOMOTOR SYMPTOMS

- The mechanism underlying vasomotor symptoms are still not well understood
- Compelling evidences indicate that estrogen therapy is highly effective for vasomotor symptoms.

NONHORMONAL THERAPY FOR VMS

- Selective serotonin reuptake inhibitor (SSRI), Serotonin-norepinephrine reuptake inhibitor, some Antiepileptic drug and other centrally acting drug.
- Venlafaxine, desvenlafexine, paroxetine, citalopram and escitalopram are effective in reducing hot flashes

NONHORMONAL THERAPY FOR VMS

- Gabapentine may be specially useful in patients with night time flash, night sweat and repeated wakening.
- Clonidine a alpha 2 adrenergic agonist is slightly more effective than placebo but are of limited use for significant side effects.

DEFINITE BENEFIT: OSTEOPOROSIS

- Osteoporosis is characterized by diminished bone strength with risk of fragility fracture. Diagnosis is based on assessment of BMD by DXA scan.
  (T-score <-2.5 Osteoporosis &
  <-1 to <-2.5osteopenia)
- Hormone therapy decreases incidence of all fractures, including vertebral & peripheral.

OSTEOPOROSIS

- Although HT prevent osteoporosis in all age after menopause, age at the initiation of HT is important.
- In age group 50 to 60 years or within 10 years of menopause, the benefit over weights the risk of HT, in age group 60-70 requires individual risk benefit calculation & HT should not be started after the age of 70.

OSTEOPOROSIS

- Lifestyle change should be a part of treatment.
- Postmenopausal women need a dietary reference intake of 1000-1500mg of elemental calcium.
- Vit-D supplementation has been shown independently to lower the risk of fracture,
- Tibolone also prevent vertebral & non-vertebral fractures.

OSTEOPOROSIS

- Bisphosphonates are potent inhibitor of bone resorption with proven efficacy in fracture prevention.
- A drug free period should be considered after 3 years of IV zoledronic acid or 5 years of oral alendronate to avoid unwanted side effects.

OSTEOPOROSIS

- Selective estrogen receptor modulator (SERM) raloxifene & bazedoxifene reduce vertebral fracture.
- Parathyroid hormone (PTH) significantly reduce risk of vertebral fracture.
- Denosumab a human monoclonal antibody at a dose of 60mg sc six monthly significantly reduce fracture risk.

DEFINITE RISK: *ENDOMETRIAL CANCER*.

- The association of endometrial hyperplasia & neoplasia with unopposed estrogen therapy is well known. The risk depends on dose & duration of treatment.
- A combined analysis of 30 observational studies found tripling of endometrial cancer risk among short term users (1-5 years) and tenfold increased risk among long term users(>10years).

ENDOMETRIAL CANCER.

- Cyclic progestogen given for more than 10days monthly reduce this rate to that seen with placebo,
- whereas continuous combined estrogen-progestogen therapy is rarely associated with endometrial hyperplasia.
- Levonorgestrel releasing intrauterine system has been reported to be more effective than sequential progestogen therapy.

ENDOMETRIAL CANCER.

- Tibolone is also extensively used as a from of HT.
- A large epidemiological study showed almost three fold increase in endometrial cancer over a mean follow up of nine years.
- However other studies have found that tibolone does not induce endometrial hyperplasia or cancer.

ENDOMETRIAL CANCER.

- Tamoxifene the first true SERM had small but definite association with endometrial hyperplasia. Raloxifene & bazedoxifen in low to moderate dose has similar effect.
- But in bazedoxifene in high dose reduce endometrial thickness.
- More recently a regimen combining SERM bezedoxifene with estrogen has been introduced as a progestogen free alternative for women with uterus.

DEFINITE RISK: *VENOUS THROMBOEMBOLISM*

- Meta-analysis of observational studies found that oral estrogen was associated with 2.5 fold increased risk of venous thromboembolism.
- Results from WHI indicate nearly 2 fold increase risk in estrogen progestin arm and 50% increased risk in estrogen alone.
- Transdermal estrogen appears to be safer alternative.

DEFINITE RISK: *BREAST CANCER*

- The risk of breast cancer in women over 50 years associated HT is a complex issue.
- The increase risk is primarily associated with addition of a progestogen to estrogen therapy and related to the duration of use.
- The risk may be lower with micronized progesteron and dydrogesterone.

BREAST CANCER

- The risk of breast cancer with HT is small and decrease after treatment is stopped.
- Some observational data suggest that length of interval between menopause onset and initiation of HT, may influence the association.
- A gap time of 3-5 years have higher HT associated breast cancer risk.
- However this association remains inconclusive.

DEFINITE RISK: *GALLBLADDER DISEASE*

- Large observational studies report 2-3 fold increased risk of gallstones among postmenopausal women taking oral estrogen.
- WHI found 55% more chance of gallbladder disease in both estrogen only and estrogen progestin arm.

PROBABLE OR UNCERTAIN RISK OR BENEFIT

Coronary heart disease (CHD):

- HT has potential for improving cardiovascular risk profile through its beneficial effect on vascular function, lipid level and glucose metabolism.
- Ht has also been shown to reduce the incidence of new onset diabetes mellitus.

CORONARY HEART DISEASE (CHD):

- There is strong and consistent evidence that estrogen therapy is cardio-protective if started around the time of menopause and
- **May be harmful** if started 10 years after menopause.

STROKE:

- Stroke incidence may be increased if HT is started in women of >60 years of age but not associated with hemorrhagic stroke.
- Initiation of HT at <60 years of age or with in 10 years of menopause has no effect.

COGNITIVE FUNCTION & DEMENTIA

- A meta analysis of 10 case control & cohort studies suggested 34% decreased risk of dementia in postmenopausal women with HT.
- Subsequent randomized trials including WHI have failed to demonstrate any benefit.

COLORECTAL CANCER

- Observational studies have suggested that HT reduces the risk of colon & rectal cancer.
- In WHI estrogen-progestin was associated with significant 38% reduction of colorectal cancer over 5.6 years period, but no benefit was found with 7 years of estrogen only.
- WHI also found that estrogen-progestin was associated wit increased rates of lung cancer mortality.

PROBABLE OR UNCERTAIN RISK OR BENEFIT

- On the basis of limited observational data it was hypothesized that HT increases risk of ovarian cancer .
- Result from WHI support the hypothesis.
- WHI also found that HT was associated with increase risk of urinary incontinence.

TREATMENT

- One of the most complex health care decision is whether to use postmenopausal Hormone therapy (HT).
- Rational use of postmenopausal HT requires balancing the potential benefits and risks.
- Authorities word wide, like International Menopause Society (IMS)has produced new recommendations.

TREATMENT

- Determine the indication of HT:
  *Moderate to severe menopausal symptoms.
  *To prevent osteoporosis in women with high risk of fracture who can not tolerate other therapies.
- Vaginal estrogen can be used to treat urogenital symptoms.

TREATMENT

- Benefit and risk of such therapy should be reviewed with the patient.
- Potential side effects especially vaginal bleeding that may result from estrogen-progestin therapy should be noted.
- Contraindication of such therapy should ruled out.

CONTRAINDICATIONS OF HT

- Unexplained vaginal bleeding
- Active liver disease
- Venous thromboembolism
- History of endometrial and breast cancer.
- History of CHD
- History of TIA or stroke.
- Diabetes mellitus.

TREATMENT

- Hyper-triglycerideamia & Active gallbladder disease are relative contraindication.
- Non-hormonal therapies should be considered when necessary.
- Short term & early use (<5years for estrogen-progestin and <7 years for estrogen alone) is appropriate for most cases .

TREATMENT

- Androgen level decline with age in women.
- There is strong evidence that androgens influence female sexual function & androgen therapy may be useful for women who have loss of sexual desire and arousal.

LONG TERM USE

- Reasonable candidates are those who have
  *Persistent severe vasomotor symptoms along with increased risk of osteoporosis.
  *Who have no personal or family history of breast cancer in 1st degree relative.
  *Who have strong personal preference for the therapy.

TREATMENT

- Alternative therapies like isoflvone preparations, traditional chines medicines, black cohosh etc have limited evidence of efficacy and safty.
- Meditation, relaxation, controlled breathing, behavioral therapy may be useful.

Thanks