ur website **www.jaypeebrothers.com,** for detailed information on medicine books, visit our website **www.jaypeebrothers.com**

Association of Physicians of India
Indian College of Physicians

Monogram

Hormone Replacement Therapy in Menopause and Andropause



Editor
VN Mishra

JAYPEE

Contents

Section I Postmenopausal Hormone Replacement Therapy

1. **Physiology of Female Hormones in Menopause and Perimenopausal Transition** **3**
   Tripti Nagaria

   Demographic Changes in the Population of World and India *3*
   Nomenclature of the Stages of Reproductive Aging *4*
   Changes in the Hormone Level during the Menopause Transition *7*
   Endocrinological Changes of Menopause *11*

2. **Nuances of Postmenopausal Hormone Replacement Therapy** **17**
   Alka Kriplani, Seema Singhal

   Review of Evidence *17*
   Postmenopausal Hormone Replacement Therapy: Clinical Implications *18*
   Practical Guidance on Hormone Replacement Therapy Prescription *21*
   Management of Adverse Effects *23*
   Follow-up *24*

3. **Hormone Replacement Therapy Formulations and Route of Administration** **27**
   Suryaprakash Dhaneria

   Hormonal Replacement Therapy *27*
   Administration of Hormone Replacement Therapy by Oral Route *28*
   Administration of Hormone Replacement Therapy by Non-oral Route *29*
   Hormone Replacement Therapy in Surgical Menopause *30*
   Adverse Effects and Contraindications of Hormone Replacement Therapy *31*
   Alternatives to Hormone Replacement Therapy *31*

4. **Journey of Hormone Replacement Therapy** **34**
   Nalini Mishra, Mamta Katarey

   Important Milestones *35*

5. **Managing Vasomotor Symptoms in Menopause** **45**
   Abha Singh

   The Vasomotor Symptoms *45*
   Risk Factors for Vasomotor Symptoms *46*
   How do Vasomotor Symptoms affect the Quality of Life? *46*
   Management of Vasomotor Symptoms *47*

6. Role of Hormone Replacement Therapy in Prevention and Treatment of Osteoporosis in Menopause **53**
Alok Chandra Agarawal, Manju Agrawal
Effects of Menopause on Bone *53*
Osteoporosis *53*
Changes in Bone Mass with Age *54*
Pathophysiology of Osteoporosis *55*
Signs and Symptoms of Osteoporosis *56*
Diagnosis *56*
Biochemical Markers of Bone Turnover *58*
Management *58*
Hormone Replacement Therapy *59*
Role of Raloxifene *60*
Role of Tibolone *60*
New Drugs in Developmental Phase *60*
Other Modalities of Treatment *61*
Treatment with Bisphosphonates *62*
Treatment with Denosumab *62*

7. Changing Concepts of Hormone Replacement Therapy in Coronary Artery Disease **69**
VN Mishra, Sameer Vyas
Evidence from Observational Studies *69*
Women's Health Initiative Study *70*
The Heart and Estrogen Progestin Replacement Study *70*
Other Secondary Prevention Trials *71*
The "Timing Hypothesis" *72*
Effects of Treatment Duration *73*
Recent Ongoing Trials *74*

8. Role of Hormone Replacement Therapy in Genitourinary Syndromes of Menopause **79**
Vatsla Dadhwal
Urogenital Changes Secondary to Estrogen Loss *79*
Genitourinary Symptoms *80*
Diagnosis *80*
Treatment *81*
Follow-up *83*

9. Cognition, Dementia and Estrogen: Present Understanding **86**
Sanjay Sharma, Parag Rameshrao Aradhey, Pranita Sharma
Observational Studies *86*

10. Postmenopausal Hormone Replacement Therapy and Risk of Cancers **91**
Soumitra Ghosh
Forms of Hormone Replacement Therapy *91*
Cancer Risks with Postmenopausal Hormone Replacement Therapy *92*

11. Phytoestrogens and Menopause **99**
VN Mishra, Ishan Mishra
Phytoestrogens and Menopause *99*

12. Hormone Replacement Therapy and Cerebrovascular Accidents **107**
Apoorva Pauranik, Ashish Patel

Early Studies: Rise of Hormone Replacement Therapy *107*
Recent Randomized Controlled Trials: Fall of HRT *109*
Recommendations *114*
Future Directions and Unanswered Questions *114*

13. Selective Tissue Therapy: Options in Menopause **121**
Nalini Mishra, Devanshi Vyas

Tibolone *121*
Estrogen Receptor Modulators *128*
Benefits of Raloxifene *129*
Risks of Raloxifene *131*

Section II Andropause and Testosterone Replacement Therapy

14. Andropause: A Myth or Reality **137**
VN Mishra, Hemant Katarey

Physiology of Testosterone *138*
Age-related Changes in Testosterone *138*
Clinical Manifestations *140*
Diagnosis *141*

15. Testosterone Replacement Therapy in Andropause: Current Scenario **146**
Susheel Jindal

16. Changing Clinical Profile with Testosterone Replacement Therapy **151**
Prabhat Panday

Synthesis and Mechanism of Action *151*
Diagnosis of Testosterone Deficiency *154*
Measuring Testosterone Levels *154*
Benefits of Testosterone Replacement Therapy *155*
Contraindications to Testosterone Replacement Therapy *158*
Safety Issues with Testosterone Replacement Therapy *158*

17. Cardiovascular Diseases and Testosterone Replacement Therapy **165**
KK Saxena, Arif Wahab

Biological Effects of Testosterone on the Cardiovascular System *165*
Epidemiological Association between Testosterone and Cardiovascular Diseases *167*

18. Testosterone: Aging and Longevity **174**
VN Mishra, Nalini Mishra

Testosterone Aging and Longivity *175*

Index *179*

2 CHAPTER

Nuances of Postmenopausal Hormone Replacement Therapy

Alka Kriplani, Seema Singhal

JAYPEE BROTHERS

INTRODUCTION

The management of menopause is one area where gynecologists also become physicians, dealing not only with consequences of withdrawal of ovarian hormones but also of advancing age. Postmenopausal hormone therapy (PMHT) is the most effective treatment for symptoms of estrogen deficiency. The controversies surrounding hormone replacement therapy (HRT) have left many women and healthcare providers confused. In the past few years lot of new analysis on the subject has been done and previous assumptions have been challenged, however, majority of clinicians do not have enough guidance on how to imply these findings in their clinical practice.[1] The risk benefit ratio of HRT is debatable. A drastic reduction in HRT prescriptions has been noted following report of women's health initiative trial (USA) and Million Women Study (UK)[2,3] newer evidence has suggested that the negative attitude to the use of HRT in symptomatic women cannot be justified.[4] The use of HRT is an individual decision, provided woman receives correct scientific information and appropriate advice. The 2013 British menopausal society and women's health concerns recommend that all women should be able to access advice on how they can optimize their menopause transition and beyond, with particular reference to lifestyle and diet and an opportunity to discuss the pros and cons of complementary therapies and HRT.[5]

REVIEW OF EVIDENCE

- *The heart and estrogen/progestin replacement study (HERS) I and II*: In 1970s HRT was promoted because of protective effect of estrogens on cardiovascular system, however evidence was not of good quality and therefore first randomized controlled trial (RCT) was conducted named as heart and estrogen/progestin replacement study[6] to identify if HRT could prevent recurrence of coronary heart disease in women with established coronary heart disease (CHD). It was noted that the women who received HRT did not benefit, rather were at increased risk of venous thromboembolism (VTE) and gall bladder disease. The effects were more pronounced in first year and the women who continued HRT beyond one year experienced more reduction in recurrence of cardiovascular disease (CVD) events. Same cohort was followed in HERS II trial and it was concluded that this benefit did not persist and therefore it was concluded that HRT should not be used for secondary prevention of CVD.[7]

- *The Women's Health Initiative study*: This RCT was planned to evaluate the effect of HRT on healthy post menopausal women between 50–79 years with a particular interest in cardiovascular outcome. The trial had a combined arm where women with intact uterus were given conjugated equine estrogen (CEE) and medroxy progesterone acetate (MPA) or placebo. Another arm with hysterectomized women received only CEE or placebo. In 2003 the combined CEE+MPA arm was closed consequent to increased reporting of adverse events as breast cancer, cardiovascular disease and stroke, however reduction was noted in fractures, colorectal cancer and diabetes.[2] In 2007 the data was reanalyzed and it was noted that giving HRT to women within 10 years of menopause was associated with fewer risks and reduction in cardiovascular events. Giving HRT to women many years (>20 years) after menopause was associated with harm.[8]
- *The Million Women Study*: This was an observational study that evaluated the risk of cancer (breast, endometrial and ovarian) with respect to differences in HRT regimen and routes of administration in women aged 50–64 years. Women attending the NHS breast screening program were invited and subsequently were followed by completion of a questionnaire. A significant risk was seen in women on combined HRT than estrogen only and Tibolone arms[9] several publications have questioned its design, analysis and conclusion. It was concluded that this study probably overestimated the risk of breast cancer.[10]
- *2012 Cochrane collaboration systemic review:* This review assessed the clinical effects of using HRT for one year or more. The review concluded that there was no indication to use HRT for primary or secondary prevention of CVD or dementia or protection of cognitive function. There was a significant reduction in the risk of bone fractures after five years of use. The study had insufficient data to assess the risk of long term HRT use in perimenopausal women or post-menopausal women younger than 50 year of age.[11]

POSTMENOPAUSAL HORMONE REPLACEMENT THERAPY: CLINICAL IMPLICATIONS

Benefits of HRT

Vasomotor symptoms: Estrogen therapy is the most effective treatment for moderate to very severe hot flushes improvement is noted within four weeks.[12] (discussed in details in a separate chapter).

Urogenital symptoms: Women who have dyspareunia, recurrent urinary infections due to atrophic vaginitis are benefitted by vaginal administration of estrogens and an added oral progestin is not required. Treatment needs to be continued for longer durations.[13] Topical estrogens may help to prevent recurrent UTIs and may impart some relief in urge incontinence as well[14] (discussed in details in a separate chapter).

Osteoporosis: HRT reduces the risk of spine, hip fractures and other osteoporotic fractures. Many studies have suggested that lifelong HRT is required for fracture prevention, as protection wears off rapidly after cessation of therapy. There is now some evidence that a few years of treatment with HRT around time of menopause may have a long-term effect on fracture reduction. Estrogen still

JAYPEE BROTHERS

remain the best option especially in younger (<60 years) and/symptomatic women. In elderly women other alternatives such as bisphosphonates should be considered. Considering the risk of breast cancer with longer treatment PMHT is not recommended solely for treating women with osteoporosis, and if given for this reason should be given only for short period of time before other treatment are initiated.[15] Tibolone conserves bone mass and reduces the risk of vertebral and non-vertebral fractures[16] (discussed in details in a separate chapter).

Colorectal cancer: HRT reduces the risk of colorectal cancer as evident by Women's Health Initiative (WHI) and Nurses Heath study (34% reduction), however, current data do not allow prevention as a recommendation and there is no data for impact of non-oral HRT on colorectal cancer.[17]

Other benefits: HRT has been implicated as neuroprotective, preserving cognitive function and reducing the risk of Azheimer's disease. Some protection against Parkinson's disease has also been seen. The young healthy post menopausal woman has the greater benefit. There may be window of opportunity for preserving cognitive functions if HRT is used early in the menopause[17,18] (discussed in details in a separate chapter).

Risks of HRT

Breast cancer: Risk of breast cancer with HRT is comparable with that of late natural menopause (2.3% vs 2.8% per year). The increased risk of breast cancer with combined HRT than estrogen alone has to be balanced against reduction in risk of endometrial cancer provided by addition of progesterones.[19] The risk of breast cancer decrease after stopping HRT and after 5 years the risk of breast cancer is no greater than that in women who have never been exposed to HRT.[15] It is observed that increased risk of breast cancer was observed in women with long term use of PMHT.[20] Risk was lesser in women with estrogen only therapy and less androgenic progestin (dydrogesterone or micronized progesterone) supplements. Association is lesser with sequential therapy than with continuous combined regimens. Increased risk was observed when treatment was started soon after onset of menopause or woman had lean body mass and higher mammographic breast density.[15,16,19] Combination of Bazodoxifene (SERM) with estrogens prevents estrogen induced hyperplasia and thus precludes the requirement of adding progestogen and therefore does not increase the risk of breast cancer.[21] Tibolone is also known to reduce the risk of invasive breast cancer.[16,17]

Endometrial cancer: Risk of endometrial cancer is increased with unopposed systemic estrogen replacement therapy.[15,16] Long-term use of sequential combined HRT especially when continued for more than 5 years may be associated with a higher risk of endometrial cancer than continuous combined regimens.[22] Oral treatment and not topical with low potency formulations is also associated with increased relative risk of endometrial neoplasia.[23]

Thromboembolism: The risk of thrombosis is usually seen after initiation of HRT and falls over the next one year.[24] Women who are smokers, sedentary, obese, have thrombophilia (factor V laiden mutation) have a higher baseline risk of VTE and therefore careful evaluation is essential before starting the therapy.[17]

JAYPEE BROTHERS

The background risk of VTE in woman aged 50–59 years is 5/1000, this increases to 7/1000 after 5 years of estrogen only and 12/1000 for 5 years of estrogen and progestogen.[18] Dydrogesterone and micronized progesterone have better risk profile than medroxy progesterone acetate in terms of VTE.[24] Transdermal route should be preferred in those who have risk factors for VTE.[25]

Uncertainties

CHD prevention: Outcome with respect to CHD prevention is mainly affected by timing, duration of HRT as well as preexisting cardiovascular disease. Coronary plaque accumulation is reduced by more than half among young women treated with estrogen, but not among elderly women.[15] Thus, estrogen might have beneficial effects on the development of atherosclerosis when it is given to young, healthy woman soon after onset of menopause and is avoided in older women (>60) years who are more likely to have established cardiovascular disease.[8] Recent evidence has suggested that MHT might have a protective effect on CHD in symptomatic women but not in asymptomatic women. Adding progesterone especially medroxy progesterone acetate and not dydrogesterone or natural micronized progesterone might have an unfavorable effect on CHD. It is uncertain whether transdermal delivery is better than oral therapy in terms of CHD risk. Role of estrogen in the primary or secondary prevention of coronary heart disease (CHD) has not been confirmed in randomized controlled trials with both oral and transdermal therapy.[15] Tibolone does not have a deleterious effect on CHD or VTE.[16]

Stroke: WHI trial suggested that both estrogens only and combined HRT are associated with increased risk of stroke; however such an increased risk was not observed in HERS study. HRT cannot be recommended for the primary or secondary prevention of stroke. Caution should be exercised when prescribing HRT in women over the age of 60 particularly when they have a risk factor for stroke or thromboembolism. Transdermal route may be advantageous.[5,15,16] Tibolone is also associated with increased risk of stroke.[16]

Dementia and cognition: Estrogen replacement may be associated with some reduction in the risk of Alzheimer's disease but it does not improve already established disease. Use of hormonal therapy only in midlife was related to a 26% decreased risk of dementia but those taking hormones only in later life had an increased risk. There is some evidence to suggest preventive effect of estrogens when started in early post menopause. Neither unopposed estrogen nor combined estrogen-progestin therapy should be given to women over age 65 years for preservation of cognitive function and prevention of dementia.[15,17]

Ovarian cancer: There is only a slight increase in the risk of ovarian cancer with Estrogen only and combined HRT, only when used for a long duration. However the risk returns to normal on discontinuation of HRT. Post operative HRT does not affect the survival of epithelial ovarian cancer patients.[25,26]

Others: The impact of HRT on glycemic control and cardiovascular outcomes in diabetic women is not well studied.[15,16] HRT also increase the risk of gallbladder disease, however transdermal therapy confers lower risk than oral.

JAYPEE BROTHERS

PRACTICAL GUIDANCE ON HORMONE REPLACEMENT THERAPY PRESCRIPTION

Balancing Risks

A detailed history will reveal any existing medical problem or family history of cardiovascular disease or cancer. There are certain factors such as lifestyle and age that increase the risk of disease as such more than taking any HRT. There are certain non-modifiable factors such as age, family history, early menarche, late menopause, and there are factors like obesity and alcohol that can be modified. Therefore, it is prudent to take a holistic approach and explore lifestyle and family history before prescribing any medications. Baseline BMI, BP should be measured. Pretreatment mammogram, endometrial thickness measurement, cervical smear are not mandatory. However, specific symptoms should be explored by appropriate investigations before any treatment.[27] Administering HRT for symptom relief during the early phase of menopausal transition is now described as the "window of opportunity", however, there is lack of any robust evidence to support the benefits of HRT given in this period before aging has advanced and collagen has been lost.[18] A study was carried out to assess the correct timing and long-term effects of HRT on cardiovascular disease in recently postmenopausal women. The study was discontinued of the intervention at 11 years but follow up was continued for a total of 16 years. After 10 years women on HRT were found to have had a reduction in mortality and cardiovascular events, and no increased risk of VTE, stroke or cancer. The health benefits were seen for up to 6 years after stopping. The UK Medicines and Healthcare Products Regulatory Agency (MHRA) (UK Public assessment report HRT: Safety update) recommended that optimum regimen, duration and dose of HRT has to be individualized according to woman's circumstances. The lowest effective dose should be used for the shortest possible time and at least yearly evaluation of pros and cons should be done.[27,28] When counseling, women should be reassured that the absolute risk of complications for symptomatic otherwise healthy, young postmenopausal women taking menopausal hormone therapy (MHT) for five years is very low **(Tables 2.1 and 2.2)**. Starting HRT in women over 60 years is usually not recommended.[29] For women with premature (<40 years) or early

Table 2.1 Current major indications and contraindications for MHT

Indications	*Contraindications*	*Not indicated*	*Not contraindicated*
• Moderate to severe climacteric symptoms • Osteoporosis • **Urogenital symptoms**: – Vaginal atrophy – Overactive bladder – Recurrent urinary tract infections	• Survivors of breast cancer and endometrial cancer • Stroke • Thrombo-embolism	• Genuine stress incontinence • Prevention of coronary heart disease • Colorectal cancer • Prevention of dementia	• Past history of benign breast disease • Previous abnormal smear • Depression • Diabetes • Controlled blood pressure • Hyperlipidemia • Obesity • Smoking • Thyroid disease

JAYPEE BROTHERS

Table 2.2 Menopausal hormone replacement therapy regimens

Estrogen only therapy	
Indications	Women who had hysterectomy Vaginal therapy
Preparations and dose	CEE (0.3–0.625 mg/day), estradiol (1–2 mg/day), estradiol valerate (2 mg/day), estriol, transdermal estradiol (0.025–0.050 mg/day)
Estrogen and progesterone therapy	
Indications	Women with intact uterus
Types	**Sequential therapy:** Estrogen for 20–28 days followed by progesterone for 10–14 days Prescribed in late perimenopause or early postmenopause **Continuous therapy:** Prescribed in late menopause
Preparations and dose	**Strong androgenic compounds:** Medroxy progesterone acetate, (10 mg/day for 10–14 days or 2.5 mg/day for continuous use). Norethisterone acetate (continuous combined regimen—1 mg/day), levonorgestrel (IUS) **Low androgenic compounds:** Dydrogesterone (10 mg/day), Micronized progesterone (200 mg/day), **Antiandrogenic compounds:** Cyproterone acetate Antimineralocorticoid: Drospirenone
Tibolone	Synthetic steroid with estrogenic, progestogenic and androgenic characteristics. Dose: 2.5 mg daily

(<45 years) menopause current guidelines recommend HRT up to 50 years for treatment of vasomotor symptoms and bone health.[15,17,18]

Starting HRT

Hot flushes, mood changes, tiredness, arthralgia and vaginal dryness may start several months or years before periods stop. There is no need to measure FSH levels to confirm ovarian failure in women over the age of 45 years presenting with such symptoms. Amenorrhea need not be waited before HRT starts. The dose used should be tailored to control menopausal symptoms. When starting HRT some women may experience breast tenderness, especially if they have been estrogen deficient for some time. This usually resolves by 3 months of treatment.[18]

Adjusting Regimens

Women who have had a hysterectomy: If both ovaries are also removed then women should be given unopposed estrogens and there is no need to give progestogens. However, in a woman with one or both ovaries intact one should look for menopausal symptoms, if present unopposed estrogens should be given. If there are nosymptoms then FSH should be checked.[18]

Women with an intact uterus: Progesterone is added to estrogens to reduce the increased risk of endometrial hyperplasia and carcinoma which occurs with

JAYPEE BROTHERS

unopposed estrogens.[18] Women with <1 year amenorrhea can be given either no bleed HRT or Monthly bleed HRT. In no bleed HRT woman is given progesterone either every day or every 13 week for 14 days. In monthly bleed HRT progestogens can be given sequentially every 4 weeks for 10–14 days. Treatment can be adjusted according to side effects and bleeding patterns. In case of unscheduled bleeding alternate regimen can be used.[18]

For perimenopausal women: Sequential or cyclic therapy should be given to those women who have inherent ovarian activity. Alternatively intrauterine levonorgestrel can be given and this is especially useful in women with heavy menstrual bleeding or needing contraception. Continuous combined regimens should not be used in perimenopausal women because of high risk of irregular bleeding. The options available are monthly cyclic or 3 monthly cyclic regimens.[17,18,28]

For postmenopausal women: Continuous combined regimens should be used because of lack of induced bleeding. Continuous combined treatment may have a reduced risk of endometrial cancer compared with sequential regimens as continuous combined regimen is associated with endometrial atrophy.[27]

Duration of Treatment

Duration of treatment depends on the indication and period for which therapy is seeked. The lowest dose should be used for the shortest amount of time. Estrogen and progeterone therapy should be given maximum for duration of 5 years.[29] Thereafter women should be evaluated for recurrence of symptoms if any. For prevention and treatment of osteoporosis treatment needs to be continued for life, as BMD falls on discontinuation. Most epidemiologic studies have shown those 5–10 years of HRT soon after menopause does not give any significant reduction in the risk of hip fracture 30 years later. This is the woman's discretion if she continues with lifelong HRT after knowing small increase in the risk of breast cancer, VTE, stroke associated with long-term use of combined HRT or changes to other agents such as raloxifene, bisphosphonate or strontium ranelate.[30]

Stopping HRT

There is paucity of data to advice clinical practice. Whatever evidence is available, it does not show clear benefit of stopping abruptly or gradually. The main issue is recurrence of symptoms like hot flushes and some women may continue to flush even upto 80 years of age. Doses can be gradually lowered as older women need lesser estrogens to control their symptoms. If urogenital symptoms predominate, topical estrogens should be advised.[5,17,31]

MANAGEMENT OF ADVERSE EFFECTS

A woman should always be warned of expected adverse effects at the time of starting HRT, this will help to reduce her anxiety and improve compliance.[5] The most common estrogen related adverse effects include fluid retention, bloating, breast tenderness, nausea, headaches, leg cramps and dyspepsia. Progesterone related effects are fluid retention, breast tenderness, headaches, migraine, mood

JAYPEE BROTHERS

swings, depression, acne, lower abdominal pain and backache. Weight gain is not an adverse effect of HRT.[32] Adverse effects are usually transient and resolve without any change in treatment. Women should be encouraged to persist for about 12 weeks for resolution. However if symptoms persist beyond this, the options are either to reduce the dose or change estrogen/progestogen type or route.

Heavy withdrawal bleeds during sequential therapy can be managed by either increasing the dose or changing the type of progestogen or administering intra uterine progestogen releasing device. However if problem still persist, pelvic pathology should be ruled out. Persistent bleeding should be investigated after 6 months with an ultrasound scan and/endometrial biopsy. Breakthrough bleeding with continuous combined regimen is common in first 3–6 months of therapy. If it continues thereafter it should be investigated as for post-menopausal bleeding.[17,18,28,29]

FOLLOW-UP

Once established on HRT an annual follow up is a must.[5] HRT poses no effect on blood pressure and thus frequent monitoring of BP is not required.[30] Counseling regarding requirement of additional contraception in perimenopausal women who are on sequential therapy is necessary. Women on sequential HRT for more than 5 years may be switched to continuous combined therapy to avoid endometrial hyperplasia.

SUMMARY

Postmenopausal hormone therapy (PMHT) is indicated in patients aged < 60 years for relief of climacteric symptoms. HRT should be prescribed for shortest possible duration and lowest dosage. Hormonal therapy should neither be used for the prevention of cardiovascular disease nor for improving cognitive function or reducing the risk of dementia.

REFERENCES

1. Rymer J, Wilson R, Ballard K. Making decisions about hormone replacement therapy. BMJ. 2003;326:322-6.
2. Chlebowski, RT Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. JAMA. 2003;289(24):3243-53.
3. American College of Obstetricians and Gynecologists, and Committee on Gynecologic Practice. ACOG committee opinion. Risk of breast cancer with estrogen-progestin replacement therapy. International journal of Gynecology and obstetrics: the official organ of the International Federation of Gynecology and Obstetrics. 2002;76(3):333.
4. Shapiro S., Farmer RD, Mueck AO, et al. "Does hormone replacement therapy cause breast cancer? An application of causal principles to three studies Part 1. The Collaborative Reanalysis." Journal of Family Planning and Reproductive Health Care. 2011;37(2):103-9.
5. Panay, Nick, et al. The 2013 British menopause society and women's health concern recommendations on hormone replacement therapy. Menopause international 2013.

JAYPEE BROTHERS

6. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA. 1998; 280(7):605-13.
7. Grady D, Herrington D, Bittner V, et al. Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/progestin Replacement Study follow-up (HERS II). JAMA. 2002;288:49-57.
8. Rossouw JE, Prentice RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. JAMA. 2007; 297:1465-77.
9. Million Women Study Collaborators. Breast Cancer and HRT in the Million Women Study. Lancet. 2003;362:419-27.
10. Panay N. Commentary regarding recent Million Women Study critique and subsequent publicity. Menopause Int. 2012;18:33-5.
11. Majoribanks J, Farquhar C, Roberts H, et al. Long-term hormone therapy for perimenopausal and post-menopausal women. Cochrane Database Syst Rev. 2012.
12. Simon JA Snabes MC. Menopausal hormone therapy for vasomotor symptoms: balancing the risks and benefits with ultra low doses of estrogen. Expert Opinion on Investigational Drugs. 2007;16:2005-20.
13. Lynch C. Vaginal estrogen therapy for the treatment of atrophic vaginitis. J Women's Health. 2009;18:1595-606.
14. Perrotta C, Aznar M, Mejia R, et al. Estrogens for preventing recurrent urinary tract infections in post-menopausal women. Cochrane database of systematic reviews 2:CD005131.
15. Rozenberg S, Vandromme J, Antoine C. Postmenopausal hormone therapy: risks and benfits. Nat Rev Endocrinol. 2013;9:216-27.
16. Cummings SR, Ettinger B, Delmas PD, et al. The effects of tibolone in older post menopausal women. New England Journal of Medicine. 2008;359:697-708.
17. Margaret Rees. Menopause In: Shaw RW, Luesley D, Monga A, editors. Gynaecology. 4th ed. Churchill Livingstone: Elsevier, 2011.
18. Bakour SH, Williamson J. Latest evidence on using hormone replacement therapy in the menopause. The Obstetrician and Gynecologist. 2015;17(1):20-8.
19. Narod SA. Hormone replacement therapy and the risk of breast cancer. Nature Reviews Clinical Oncology. 2011;8(11):669-76.
20. Fournier A, Mesrine S, Boutron Rault MC, et al. Estrogen progestogen menopausal hormone therapy and breast cancer: does delay from menopause onset to treatment initiation influence risks? J Clin Oncol. 2009;27:5138-43.
21. Practice Bulletin No. 141: Management of Menopausal Symptoms. Obstetrics and Gynecology. 2014;123(1):202-16.
22. Nelson HD, Walker M, Zakher B, et al. Menopausal hormone therapy for the primary prevention of chronic conditions: A systematic review to update the U.S. Preventive Services Task Force recommendations. Ann. Intern. Med. 2012;157:104-13.
23. Johnson SR, Ettinger B, Macer JL, et al. Uterine and vaginal effects of unopposed ultralow-dose transdermal estradiol. Obstet Gynecol. 2005;105:779-87.
24. Canonico M, Bureau PG, Lowe GD, et al. Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and metaanalysis. BMJ. 2008;336:1227-31.
25. Olie V, Canonico M, Scarabin PY. Risk of venous thrombosis with oral vs transdermal estrogen therapy among postmenopausal women. Curr Opin Hematol. 2010;17: 457-63.
26. Bull D, Green J, Reeves G. Ovarian cancer and hormone replacement therapy in the Million Women Study. The Lancet. 2007;369:1703-10.
27. North American Menopause Society. The 2012 hormone therapy position statement of The North American Menopause Society. Menopause. 2012;19:257-71.

JAYPEE BROTHERS

28. Barber B, Daley S, O'Brien J. Dementia. In: Keith L, Rees M, Mander T (Eds) Menopause, Postmenopause and Ageing. RSM Press, London; 2005 .pp. 20-34.
29. Stuenkel C, et al. A decade after the women's health initiative – the experts do agree. J Clin Endocrinol Metabol. 2012;97:2617-8.
30. Writing group on Osteoporosis for the British Menopause society council. Prevention and treatment of osteoporosis in women. Menopause International. 2007;13:178-81.
31. Liu B, Berel V, Balkwill A. Gall bladder disease and use of transdermal vs oral hormone replacement therapy in postmenopausal women: prospective cohort study. BMJ (Clinical Research edition) 337:a386.
32. Kongnyuy EJ, Norman RJ, Flight IHK, et al. Ostrogen and Progestogen hormone replacement therapy for perimenopausal and post menopausal women: weight and bodyfat distribution. Cochrane database Syst Rev, 2000.

JAYPEE BROTHERS

for detailed information on medicine books, visit our website **www.jaypeebrothers.com,** for detailed information on medicine b

Available at all medical bookstores
or buy online at www.jaypeebrothers.com



JAYPEE BROTHERS
Medical Publishers (P) Ltd.
www.jaypeebrothers.com
Join us on facebook.com/JaypeeMedicalPublishers

