Menopausal Hormone Therapy, can we safely use it in women with co-morbidities?

The landscape of menopausal hormone therapy (MHT) has been changing very fast through newer developments across the globe. After a decade of fear and uncertainty, the critical reanalysis of the data of the Women's Health Initiative (WHI) study along with the results of recent studies, have clarified the risks and benefits of systemic MHT. Current data indicates that MHT is beneficial when initiated in younger women closer to the onset of menopause, and in those women who take it for less than 10 years. The recommendations for MHT use have been provided by all the major professional organizations which include the International Menopause Society (IMS), the North American Menopause Society (NAMS), the European Menopause Society (EMAS), the British Menopause Society (BMS), and the Indian Menopause Society (IMS, India). It is important to keep in mind that MHT is a tool that affects the care of menopausal women not only during their transition years, but may extend over a longer period. During this phase, a woman faces many comorbid conditions which require consultation and treatment from multispecialty domains. As gynecologists, we look after the reproductive and sexual health of women during various stages of their lives. But as women develop many other comorbidities or chronic illnesses, we are faced with challenges in their management, especially with the use of MHT.

In order to discuss few of these challenges, a Cross-Specialty Round Table Meeting with representatives from various disciplines related to women's health such as gynecologists, physicians, endocrinologists, rheumatologists, urologists, and oncologists was conducted by the IMS in 2014. Gynecologists presented interesting cases and the multispecialty experts shared their opinions. The case discussion and expert comments are discussed in this Editorial with the intent to share experience-based, practical tips with clinicians, involved in management of midlife women.

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Case 1

Mrs. SK, a 51-year-old woman, presented with polyuria and severe tiredness after stopping desmopress in nasal spray which she had been using since 1996 for Sheehan's syndrome. Mrs. SK had a history of postpartum hemorrhage during her last childbirth followed by amenorrheain 1987. She had osteoarthritis of her knee and type II diabetes for which she was receiving metformin, pioglitazone, and vildagliptin. Her father had coronary heart disease for which he had undergone surgery. On examination; she had a body mass index (BMI) of 24, evidence of osteopenia; and her follicle-stimulating hormone (FSH) levels were normal.

The questions raised were:

- Was the tiredness because of anterior pituitary deficiency or menopause?
- Does she need estrogen therapy?
- Would nonhormonal therapies be better than estrogenin view of her osteoarthritis?

Expert comments

Sheehan's syndrome usually presents with anterior pituitary failure and maybe associated with posterior pituitary deficiency too. Mrs. SK had anterior pituitary and cortisol deficiency, which could be the cause of her tiredness. The amenorrhea is related to Sheehan's syndrome and patients with Sheehan's syndrome should be treated with MHT. If MHT is initiated, it should be continued until the natural age of menopause or up to 10 years after initiation, with proper counseling. Since Mrs. SK is currently 51-years-old, but has completed 25 years since menopause; she would have had the same risks with hormone therapy as a 75-year-old woman; hence, MHT should not be administered to her.

Rheumatologic diseases are more common in women, especially with increasing age. Osteoarthritis is not just an involvement of the cartilage, but affects all articular tissues and finally causes joint failure. Metabolic syndrome, obesity, hypothyroidism, and lack of exercise, contribute to the worsening of knee osteoarthritis. There is no evidence to show that MHT delays the development of osteoarthritis, and hence osteoarthritis should not be the primary indication for starting hormone therapy. Besides, MHT for rheumatologic disease is not indicated in the

absence of other compelling indications. In view of multiple comorbidities, other modalities of treatment may be preferred over hormone therapy. Calcium and vitamin D supplements along with exercise are recommended along with close monitoring of her bone status.

Case 2

A 38-year-old woman, Mrs. TM, had attained premature menopause since 2 years. She had been receiving MHT with conjugated equine estrogen 0.625 mg/day (CEE) along with medroxyprogesterone acetate (MPA) 10 mg/day for the last 12 days of the cycle under annual medical supervision. She did not suffer from hot flushes, had no children, and had a raised serum FSH level.

The question raised was:

- When could she stop taking MHT?

Expert comments

Women with premature menopause usually do not suffer hot flushes. However, after receiving hormone therapy for 10 years, till her natural age of menopause, the chances of hot flushes could increase, especially if therapy is abruptly discontinued. Hence, MHT may be continued beyond 10 years after counseling her about the risks and benefits involved. On the other hand it could be discontinued gradually with tapering doses over a period of 6 months to a year followed by alternative options if needed. Mrs. TM could be offered safer options of progesterone such as micronized progesterone or the use of levonorgestrel (LNG) intrauterine device.

Case 3

Mrs. AS, a 60-year-old, postmenopausal woman since 10 years presented with urge in continence and recurrent urinary tract infections (UTIs). She was evaluated for repeated infections and treated with antibiotics. Despite various courses of antibiotics, her symptoms were persistent. On examination she had an atrophied vagina, with a cystocoele, a first degree uterine prolapse, and the urine culture showed no colonization. There was no demonstrable stress urinary incontinence.

The question raised was:

- How should we treat her for her incontinence?

Expert comments

Ms AS should undergo examination and investigations for the identification of a potential cause of recurrent infections such as residual urine, local vaginal infection, genital prolapse, and presence of diabetes; which could be the causes of repeated infection. Hence, a close coordination between the gynecologist and an urologist is essential in such cases.

Urethral stenosis and cystocele may cause incomplete emptying of the bladder. Uroflometry is useful to determine urethral stenosis or the presence of a cystocele. More than 50 ml of post-void residual urine in the urinary bladder is a simpler test easily accessed by ultrasound, which could be the cause of urge incontinence. Other causes like pressure symptoms due to uterine or ovarian tumors should also be ruled out. Cystoscopy is usually not required except in cases of interstitial cystitis. Apart from biopsy, cystoscopy does not add much value to the diagnosis or treatment of urge incontinence, but the dilatation of the urethra during cystoscopy may temporarily help the symptoms if they are due to incomplete emptying of the bladder.

If the urethral meatus is narrow, then dilatation of the urinary meatus may be useful. Local estrogen therapy may help in relieving urethral stenosis and anatrophied vagina. It is difficult to regain the normal texture of vaginal tissue after the onset of atrophy, hence as a preventive measure, early local treatment is recommended. Vaginal estrogen therapy should be continued as long as distressful symptoms remain. After the control of acute symptoms, the dose should be tapered. Very low dose (once a week or once in 2 weeks) should be used as maintenance treatment. If required, treatment can be continued indefinitely, although safety data beyond 1 year are not available. There is insufficient evidence to suggest annual endometrial surveillance in asymptomatic women using vaginal estrogen therapy.

Medications are available for treatment of recurrent infections, prevention of recurrent infections, and treatment of pure urge incontinence. Imipramine, tolterodine, solifenacin darifenacin, and selective antimuscarinics like trospium chloride can be used for urge incontinence. Unfortunately, these drugs only work for a short period.

For the treatment of acute UTI, agents preventing adhesion of *Escherichia coli* to the urinary epithelium such as cranberry and D-mannose could be useful. In recurrent infection, a probiotic can be given for a prolonged period.

Case 4

A 52-year-old woman, Mrs. ST, a chronic smoker, presented with the chief complaints of hot flushes, 10-15 episodes during the day and four to five episodes during the night, night sweats, and palpitations. She was menopausal since 3 years and had decreased libido, dyspareunia, and excessive vaginal dryness with itching. Since the last 4 years she had irregular cycles with a scantymenstrual flow. Her quality of life was impaired due to her symptoms. Mrs. ST was a known case of type II diabetes mellitus since 5 years along with hypothyroidism for many years, for which she was receiving treatment.

Mrs. ST had three full-term normal deliveries with all her babies being overweight. Both her parents were diabetic and her mother had died due to myocardial infarction. She had a BMI of 27 and her blood pressure was 120/76 mmHg, with no other abnormal findings except for vaginal candidiasis. Her diabetes was not well-controlled with an HbA1c of 7.5%. She also had dyslipidemia and established osteoporosis in her spine.

The question raised was:

- Can MHT be offered to a woman with diabetes having severe menopausal symptoms?

Expert comments

Mrs. ST should be treated for her vaginal candidiasis with antifungal treatment and her osteoporosis should be dealt with administration of calcium, vitamin D, and bisphosphonates. Her vasomotor symptoms should not be treated with MHT till her medical problems were controlled; hence she would need to be treated with alternative therapy. Desvenlafaxine is an effective nonhormonal treatment option for vasomotor symptoms in postmenopausal women. As Mrs. ST has uncontrolled diabetes, dyslipidemia, and a family history of cardiac problems; she is predisposed to coronary atherosclerosis. Statins may be added and lifestyle modifications with weight reduction and exercise should be recommended. Aspirin for primary prophylaxis of cardiac disease is not indicated.

Case 5

A 42-year-old woman, Mrs. PA, presented with complaints of severe bone and joint pains and severe hot flushes since 6 months. She underwent hysterectomy due to multiple fibroids at 34 years of age, following which she underwent bilateral salpingo-oophorectomyfor a large cystadenoma of her left ovary at 41 years of age. Mrs. PA was a known case of diabetes since 7 years and was on oral antidiabetic drugs. There was no history of hormone intake, malignancy or major illness in the past. Mrs. PA had a BMI of 28 and on clinical examination, nothing abnormal was detected.

The question raised was

- "As Mrs. PA has attained premature iatrogenic menopause, should at a young age of 41 years, should she be offered MHT to prevent long-term effects such as osteoporosis?

Expert comments

MHT should be offered as therapy to Mrs. PA, especially as the ovarian cystadenoma was benign and should be continued till the natural age of menopause, that is, 50 years. A baseline mammography, pelvic ultrasound, and Papsmear should be done prior to starting MHT. In case of a positive family history of breast cancer, mammography should be initiated at least 5 years before the age of the youngest affected family member. Mammography after the age of 50 years is useful, while between 40 and 50 years of age, its role is still controversial. If normal mammography can be repeated every 2-3 years, digital mammography is better than old analog mammographs and tomosynthesis is more sensitive than digital mammography. Mammography may not be able to detect 30-50% of lesions in young patients, especially with dense breast tissue. Hence, along with mammography, ultrasound should also be done. However, ultrasound also has its limitations. Ultrasound does not pick up clusters of microcalcification, which is an early sign of breast cancer. It can pick up nonpalpable lesions and helps to take a biopsy of even a very small lesion. A baseline magnetic resonance imaging (MRI) of breast may also be suggested for women with a strong positive family history of breast cancer.

Case 6

Mrs. SS, a 54-year-old woman, had severe vasomotor symptoms. Her mother had suffered from postmenopausal breast cancer and she was BRCA 1 positive.

Question raised was:

- "How do we manage her menopausal symptoms as she is at a high risk of breast cancer?"

Expert comments

Oophorectomy, mastectomy, chemoprevention, and surveillance are the four management options for BRCA-positive patients. The patient should be adequately counseled prior to testing for BRCA, because if the result is positive and the patient is unwilling to accept any of the management options, then she would have to live all her life with the stress of the possibility of developing of breast cancer in future.

If the option of oophorectomy is selected, fallopian tubes should also be removed during surgery. Patient should be counseled for bilateral mastectomy as well as bilateral salpingo-oophorectomy. With bilateral prophylactic mastectomy, 97% of the breast cancers can be prevented. Similarly, even after oophorectomy, cancer can originate from the peritoneum of the fallopian tubes. Index mutations can be used for the prediction of breast cancer. However, there is no Indian data about such index mutations.

With the available options available today, there are still many unanswered questions:

- Is there an increased radiation related cancer risk with surveillance and repeated radiation?
- Does prophylactic surgery increase health concerns like myocardial infection?
- Does chemoprophylaxis stimulate cancer in other organs?

In light of these questions, a balance ddecision should be taken.

We thank all the experts at the Round Table Discussion for the time and contribution.

The participants of this round table discussion were

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SUGGESTED READING

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