

## Preservation of Ovarian Function Beyond Menopause

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Estrogen production is essential for the well-being of women of all ages to sustain general and bone health, skin quality, and brain function. Although there are numerous sources of estrogen in the body (e.g., fat cells), ovaries remain the main organ of their synthesis. Menopause usually occurs between 42 to 60 years of age and is often accompanied by many worrisome symptoms, including but not limited to hot flashes, osteoporosis, decreased libido, depression, and weight gain. In cases of premature menopause (natural or iatrogenic), these symptoms may be more pronounced and appear at a much earlier age.

Before 2002, standard practice had been to recommend estrogen replacement therapy (ERT) to most if not all women in menopause. More than 90% of those patients used it to treat hot flashes, prevent osteoporosis and other disorders related to age-related hormonal deficiency. ERT became a controversial issue over the last decade. Many have rejected ERT since a large, federally funded study found that ERT could increase a woman's risks for heart disease, strokes, as well as breast and endometrial cancer [1].

Women's Health Initiative (WHI) trial first looked at the benefits of taking two hormones-estrogen and progestin, and then examined the risks and benefits of taking estrogen alone. The first part of the study was abandoned in 2002 when early results suggested that ERT increased the risk of heart disease, stroke, breast cancer, and possibly dementia. As a result, researchers observed a sharp decline in overall hormonal use afterward as women heeded their doctor's warnings. In 2005 and 2012, the U.S. Preventive Services Task Force recommended against using the combined therapy or estrogen alone to prevent chronic conditions in postmenopausal women. As a result of these developments, new options appeared on the horizon to be discussed below [2]:

### Alternative Medicine and Bioidentical Hormones

Some menopausal symptoms may possibly be relieved by diet and lifestyle changes. The estrogens were found in tofu, soybeans, and wild yams, dong quai, chaparral, damiana, licorice, black cohosh, motherwort, and fennel, among others. Hot flashes may be partially alleviated by sleeping in a cold room, relaxation, and breathing exercises. A water-soluble lubricating cream (with or without estrogen) can decrease vaginal dryness to some extent. However, scientific discussion of these remedies cannot be conducted due to

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the lack of prospective randomized studies published in reputable peer-reviewed journals [3].

### Compound Bioidentical Menopause Hormonal Therapy

In 2012, ACOG put together a Committee Opinion on the topic [4]. The potential advantages of compounded hormonal therapy compared with FDA approved conventional medications include greater dosage flexibility and potential cost. Compounded preparations are not regulated by the FDA. ACOG's statement on bioidentical hormones reads as follows:

“Because of a lack of FDA oversight, most compounded preparations have not undergone any rigorous clinical testing for either safety or efficacy, the purity, potency, and quality of compounded preparations are a concern. Patients should be counseled that menopausal hormonal therapies that are proved to be safe and effective by the FDA are more appropriate for their use than individual pharmacy-compounded preparations. Physicians should exercise caution in prescribing compounded hormones when FDA approved alternatives exist.”

### Ovarian Tissue Auto Transplantation

Fresh ovarian tissue and whole ovary transplantation was first reported by Silber, who described the procedure in monozygotic twin pairs discordant to minimize rejection for premature ovarian failure [5]. Ten twin pairs underwent ovarian transplantation and nine have undergone transplantation with cryopreservation of spare tissue. Eight had a fresh cortical tissue transplant, one of whom received a second frozen-thawed transplant after the first ceased functioning 3 years later. All recipients reinitiated ovulatory menstrual cycles.

The main goal of ovarian transplantation have been the restoration of ovarian function and fertility in cases of pelvic/abdominal radiation in cases of malignancy or premature menopause [6,7].

The lessons from this experience are obvious – ovarian transplantation and auto transplantation allows to restore hormonal profile in most cases and achieve pregnancy if desired in some [8-11]. With the firm knowledge that ovarian transplantation yields positive results, we extended the indicators to include symptomatic menopause. In 2000 we created the first Ovarian Tissue Banking. The research protocol was as follows [12]:

**Step 1:** After obtaining approval from the Institutional Review Board, patients age 40 and under were included in this study. Normal ovarian function was established prior to ovarian tissue harvesting using hormonal assay, pelvic ultrasonography, and endometrial sampling if indicated.

**Step 2:** Ovarian cortical tissue retrieved with the patient's consent during indicated obstetrical or gynecological procedures (cesarean section in 15, minilaparotomies and tubal ligation in 12, gynecological surgeries for benign conditions in 22) was frozen.

**Step 3:** Thawing and transportation. At a later time (15 plus years later) or when medically indicated, strips of cortical tissue were thawed, prepared by washing in a 1% human albumin mixed with a normal saline sterile solution to be inserted into a subcutaneous pocket of a postmenopausal symptomatic patient. Fifteen-year-old specimens were reassessed and in 85% of cases were found to be suitable for auto transplantation [13].

Recently, Silber found that follicle-stimulating hormone (FSH) levels sharply decreased to normal between 69 days and 133 days after the procedure [14]. Anti-Mullerian hormone (AMH) levels rose to higher levels between 133 days and 227 days post-procedure before dropping to very low levels. AMH remained at low levels despite the fact that [transplant] would last 8-10 years. Compared with egg freezing, there is a benefit to performing ovarian tissue freezing. The cost of ovarian tissue freezing is also roughly 1/10th that of egg freezing, and the procedure is less burdensome than multiple cycles with the potential for ovarian hyperstimulation, "because the greater primordial follicle recruitment decreases as the ovarian reserve decreases, you can put a piece of ovary tissue back every 8 years.

### Doctors and Patient Education

Confusion in the field of academic menopause research resulted in controversy in doctors and patient education. The American Society for Reproductive Medicine used to have a "menopause day," but the society no longer offers a track for menopause. Christianson, et al., reported that most residents did not feel comfortable managing menopause patients with 75.8% reporting feeling "barely comfortable" and 8.4% feeling "not comfortable at all [15]." These authors developed a menopause medicine-teaching curriculum for OB/GYN residents. Core topics included menopause physiology, hormone therapy, breast health, bone health, cardiovascular disease, and autoimmune disease.

In conclusion, it appears that "menopause" medicine traditionally shared between gynecologists, internists, and endocrinologists does not have a clear path. The pendulum has been swinging too often from universal acceptance of ERT for the lifetime or its rejection due to complications. Therefore, it is important to continue research in clarifying indications for ERT and developing new approaches to an old problem.

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