International Journal of Research Studies in Medical and Health Sciences
Volume 4, Issue 9, 2019, PP 19-21
ISSN : 2456-6373

Can Menopausal Symptoms be Treated with Ovarian Auto Transplantation?

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INTRODUCTION

Menopause is an expected stage of every women's life, but symptomatic menopause is not. A hundred years ago, the average life expectancy in women corresponded to the age of menopause. Today, most women live beyond 80 years and spend 30-40% of their lives being postmenopausal. In the 1980s and 90s, estrogen replacement therapy (ERT) was administered to millions of women to relieve menopausal symptoms.[1] However, it all changed with the publication of the results from the Women's Health Initiative (WHI) randomized clinical trials in 2002, suggesting that ERT is associated with an increased risk of breast and endometrial cancer.[1,2] The risks and benefits of ERT are dose-dependent.[3] The pharmaceutical industry attempted to partially resolve the issue of individualization of ERT by manufacturing at least six different types of Minivelle patches (0.024mg, 0.0375mg, 0.05mg, 0.075mg, and 0.1mg). The choices offered by the pharmaceuticals are useful but fail to caliber dose based on the needs of the individual patient. When making this decision, it is important to consider three factors that affect the risk-benefits of ERT: age at initiation, dose of hormone, and route of administration.[3] Estrogen deficiency may result in significant bone loss, vaginal and bladder atrophy, among other symptoms.[3,4] Therefore, the earlier after menopause ERT is initiated, the better the long-term outcome.[3]

RESULTS

We recently reported a computer program for an individual approach to ERT. The computer program was designed to develop the minimal effective dose of HRT to address the needs of individual patients. Progestins were added if indicated. The majority of patients were using estrogen skin patches. Transdermal estrogen has an additional safety benefit in that it avoids the hepatic "first pass" effect, and thus, associated changes in clotting factors and other hepatic proteins. The patient's symptoms and prerogatives were assigned different scores depending on the severity of their symptoms.[5] Assume that the total surface of the patch corresponds to the score of 10. Calculate the score for a patient (for example, 17). It follows that the patient needs 1.7 patches. The computer program is available online.[5] Although the individualized computer assisted administration of ERT is an advancement compared to routine ERT use, it still requires pharmaceutical preparations to treat symptomatic menopause.

In 2000 we created a first ever Ovarian Tissue Banking. Research protocol was as follows:[6]*

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 ultra-sonography 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.

*No Pause trademark pending

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 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. Our research team used the technique of transplantation of ovarian cortical strips to the forearm.[6]

DISCUSSION

This manuscript describes our experience with using frozen ovarian tissue obtained during

opportunistic ovarian resection to address possible symptomatic menopause. The obvious negative side of such an approach is that women will harvest and conserve ovarian tissue they may never need transplantation for the following reasons: A) menopause may be either asymptomatic or very mild requiring no therapy. B) patient may succumb prior to menopause for other reasons, such as diseases, accidents etc. C) Long-term conservation may not provide a viable ovarian tissue for all women. D) Transplant may not take. Therefore, ovarian tissue harvesting and expenses on freezing and conservation may not be useful. Anderson et al.[8,9] established that cryopreservation of ovarian tissue maintains viable follicles that support fertility and menstrual cycles upon reimplantation. Silver[10] reported a patient experienced restoration of ovarian function for almost 7 years after having had a transplantation. Another patient in their series had regular menstrual cycles for 10.5 years after having 62% of one ovary transplanted. Others also report on a prolonged period of hormone function from transplantation ovarian tissue.[11] Anderson et al.[12] proposed to use ovarian transplant to postpone menopause and delay osteoporosis. They stated that many women will not want to continue having menstrual cycles beyond the natural menopause. Alternatively, some women may wish to undergo endometrial ablation or even hysterectomy to avoid menstruation.[12] Ovarian tissue may be grafted subcutaneously using local anesthesia.[7,12] Millions of women worldwide have already had ovarian tissue frozen for fertility preservation. For various reasons, a large number of these women have not used their tissue by the time they reach menopause and will have tissue available for continued ovarian function. Another promising development in the field has to do with activation of dormant follicles as a new approach to ovarian failure.[13,14] Primordial follicles are dormant in ovaries.

Kawamura, et al.[15]named a number of intraovarian factors including vascular endothelial growth factor morphogenetic protein 4, BMP7, basic fibroblast growth factor, and keratinocyte growth factor, which have been shown to be important for primordial follicle activation from the dormant state. These authors attempted to activate dormant primordial follicles pharmacologically through manipulating the functions of intracellular signaling pathways. Although the results are promising they are still limited to animal species and are not currently used in humans.

In summary, currently ovarian tissue banking and auto-transplantation remains to be the only non-pharmaceutical option to deal with option to deal with symptomatic menopause.

Post Scriptum: Our original research caused some skepticism in the scientific community until a recent T.V. show conducted by CBS news cited doctors at Profam(Birmingham, U.K.) who recently performed similar procedures on 10 women[16].

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Citation: *BM Petrikovsky, "Can Menopausal Symptoms be Treated with Ovarian Auto Transplantation?", International Journal of Research Studies in Medical and Health Sciences. 2019; 4(9): 19-21.*