ISSN: 2576-2842

Review Article

Journal of Gynecology & Reproductive Medicine

Potentiality of Postponing Menopause through Ovarian Auto-graft Transplantation

Abdelmonem Awad Hegazy

[1]*Consultant of Obstetrics and Gynecology; Professor of Human Anatomy and Embryology, Faculty of Medicine, Zagazig University, Egypt*

[2]*College of Biotechnology, Misr University for Science and Technology, Egypt*

***Corresponding author**
Abdelmonem Awad Hegazy, Consultant of Obstetrics and Gynecology; Professor of Human Anatomy and Embryology, Faculty of Medicine, Zagazig University, Egypt & College of Biotechnology, Misr University for Science and Technology, Egypt

Submitted: 10 Feb 2020; **Accepted:** 22 Feb 2020; **Published:** 11 Mar 2020

Abstract

Menopause is a critical stage in the life of women in which the menses stop with loss of fertility. Deprivation of female hormones especially estrogen might be accompanied with some physical and psychological disorders. Therefore, this mini-review aimed to highlight the anatomy of the ovary at different age stages and to discuss the possibility of using technology of cryopreservation in postponing the menopause to alleviate its associated disorders and ensure healthy life for women. Ovarian tissue cryopreservation has been successfully used for rescuing the harvested ovary from destruction that could be caused by chem- or radiotherapy used in cases of cancer management. Then, slices of such tissues re-implanted into the patients give good results restoring the fertility and hormonal production. Therefore, it is suggested that trials to re-transplant ovarian auto-graft might be performed to postpone the menopause in volunteers in order to preserve endocrine function of ovary.

Keywords: Menopause Postponing; Ovary; Cryopreservation; Auto Graft Transplantation

Introduction

Menopause is a critical age stage in the female life where the menstrual cycles stop; and hence consequent loss of fertility. It might be associated with many psychological and organic changes, including moodiness, nervousness, and atrophic changes affecting female genitalia and breasts [1], sexual dysfunction, bone weakness and metabolic disorders predisposing to diabetes and cardiovascular diseases [2].

It occurs naturally around the age of 50 years, through consumption of ovarian follicles that begin during fetal life of females. There are many factors could hasten its occurrence such as surgical removal of ovaries and exposure to radiations or taking some drugs and chemotherapies [3]. More effective therapies are in need to alleviate menopausal symptoms and afford healthy physical and sexual life for women [2]. Trials to postpone the menopause could be beneficial in this respect [3].

The aim of this review was to explore the ovary' structure at different age stages and to discuss the reliability of clinical employment of cryopreservation and transplantation in restoring the ovarian function after menopause.

Anatomy

Ovaries are the primary gonads in females. They are a pair of organs, one each side. Ovary is an almond in shape measuring about 2 and 4 cm in dimensions. It is situated on the side wall of pelvis in ovarian fossa bounded by uterine (fallopian) tube and broad ligament (anteriorly), ureter and the internal iliac vessels (posteriorly) and external iliac vessels (superiorly). However, in multiparous women, the site is variable, hanging down in Douglas (rectouterine) pouch. The ovary is connected to the posterior layer of the broad ligament by a fold of peritoneum called mesovarium. The fold transmits the blood vessels, nerves and lymphatics of the ovary [4].

The ovary is covered by a thin single layer of cells, called germinal epithelium. This gonad is formed of two main regions; outer functional layer, called cortex and inner fibrous and vascular region, called medulla. The cortex of ovary contains ovarian follicles (Figure 1). At birth, they are primary follicles including primary oocytes. Then with onset of sexual maturity at each menstrual cycle, some primary follicles begin to mature. Only one in most cases reaches maturity forming mature Graafian follicle (MGF) and the others degenerate. MGF ruptures at the ovarian surface releasing its contained cell "secondary oocyte", a process known as ovulation. The released oocyte degenerates within 24 hours in absence of fertilization; however, if ferritization occurs, it divides to give rise ovum of which nucleus mixes with that of sperm to form zygote. This ovarian cycle is then responsible for production of egg for reproduction as well as secretion of two female hormones; feminine hormone called estrogen mainly at the first half of cycle and the other hormone essential for gestation (or pregnancy) called progesterone at the second half [1].

At menopause, the ovary shrinks in size with loss of the oocytes. The cortex decreases in size with blurring the line between it and the medulla. There is fragmentation of the corpora albicans. The medulla shows scarring and fibrosis. The surface of ovary looks with pits due to scars. The blood vessels become narrower with hyalinization of their walls and constriction of lumen [4,5].

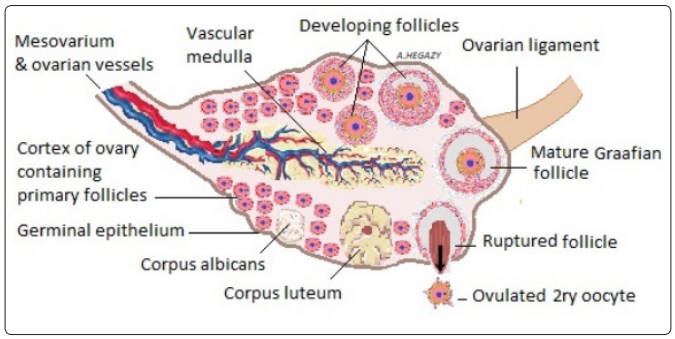

Figure 1: Structure of ovary

Unilateral Ovariectomy and Fertility

Despite the occurrence of ovulation only in one ovary, the ovaries on both sides are in a continuous follicular depletion. Such ovarian consumption continues even in periods where the gonad is non-function such as that during pregnancy after formation of placenta or at use of contraceptive pills [3,6]. Unilateral ovariectomy has nearly no effect on ability of fertility and its stage that extends for about 30-40 years of female life, extending from age menarche to menopause. There are many studies confirming that unilateral ovariectomy is accompanied with compensatory changes in the remaining ovary regarding endocrine function and ovulation [7-10]. Similarly, other authors added that unilateral ovariectomy has no effect on the follicular reserve of intact ovary [11,12]. Moreover, Bjelland et al performed a survey to compare the age onset of menopause in women with unilateral ovariectomy with others having intact ovary on both sides [13]. They found a slight difference with earlier menopausal occurrence in case of removal of ovary on one side than in women having the two ovaries with a mean difference of only about one year (mean: 49.6 years viz. 50.7 years, respectively). The consumption of ovarian follicles is a continuous and steady process occurring in each ovary irrespective of ovulation that takes place in one of them [14]. Moreover, use of contraceptive pills that even block of ovulation doesn't affect the process of follicular degenerations in the ovaries [15]. Therefore, removal of one ovary doesn't influence the other in regard to hastening or depressing ovarian follicles loss in the other intact one [16]. Not only affect the onset age of menopause, but also unilateral ovariectomy has no significant effect on the female fertility outcome in comparison with other pelvic or abdominal surgeries such as appendectomy or cholecystectomy [17].

Cryopreservation Technology

Cryopreservation is a promising technology developed to meet the currently increased demands for preserving fertility for women whose reproduction is in a danger caused by a disease or chemo- or radiotherapy [14]. Harvesting the ovarian tissue for such purpose should be achieved before or up to the female age of 35 years. This is because there is age-related follicular loss after the previously mentioned age [18]. Nowadays, the only approved methods by American Society of Reproductive Medicine are mature oocyte and embryo cryopreservation done for IVF (in vitro fertilization) procedures [19]. However, authors don't adopt the programs of oocyte cryopreservation especially for restoring fertility following anti-cancer therapies. They use alternative techniques through preserving tissue instead of oocytes. This is because of retrieval of oocytes might require several stimulated ovarian cycles to obtain the enough numbers due to very low success per each egg that reaches only 5% pregnancy rate. Furthermore, the re-implanted tissue does not only restore the lost fertility but also keeps the ovarian endocrine function [20-22]. Many studies confirmed the applicability of ovarian tissue preservation technique for restoring fertility; and called to stop considering it still an investigational approach [23-25]. Such technique has been used in order to protect the harvested gonads from cytotoxic effect and degeneration following therapy used for management of cases of cancer, and then return the preserved tissue after thawing to her owner after the end of management [19,26]. On contrary to mature oocyte and embryo, cryopreservation of ovarian tissue carries less ethical and moral ethics especially in case of human auto-transplantation. Also, it doesn't depend on age of fertility period or phase of menstrual cycle [27].

Ovarian auto-grafting

Ovarian tissue could be obtained through laparoscopic harvesting total ovary on one side (unilateral ovariectomy), partial ovariectomy or fragments of ovarian cortex. The ovarian tissue is then preserved in small pieces (1 cm/0.5 cm each). There is an accumulating evidence of utility success of ovarian auto graft to prevent or postpone the premature ovarian failure [28]. The implanted ovarian tissue called artificial ovary could restore the endocrine function and the ability to get successful pregnancy [29].

The natural plasticity of the ovarian tissue makes its grafting easily to revascularize and restore its functions. Moreover, it could be transplanted in various sites; either orthotopically into pelvis or heterotopically to subcutaneous tissues or others [30,31]. Whether the site is selected, it should be ensured that there is a good communication between the ovarian graft and host tissues of female recipient to avoid its possible ischemia and follicular atresia [27].

Therefore, if we could obtain one ovary and slice it into small pieces for cryopreservation; and re-implant even part of it before or around the age of menopause, this might postpone the menopause, maintain the ovarian endocrine function and lengthen the fertility life of women. The remaining parts of harvested ovary might be used as a backup for replacing the primary graft if needed. The procedure of re-implanting ovarian tissue might be done into the cortex of intact ovary through Douglas pouch approach under guidance of ultrasonography such as performed for retrieving oocytes used in in-vitro fertilization (IVF) [32].

Conclusions

Menopause is a critical age stage in the females' life. It affects their entire health including physical, sexual and psychological aspects. Previous studies mentioned that surgical removal of one ovary doesn't affect the other one; and consequently, not affect the age incidence of cessation of menses. At the same time, there is a continuous consumption of the ovarian reserve of follicles and oocytes.

Meanwhile, ovarian tissue cryopreservation has been successfully used for rescuing the harvested ovary from destruction that could be caused by chem- or radiotherapy used in cases of cancer management.

Then, slices of such tissues re-implanted into the patients give good results restoring the fertility and hormonal production. Therefore, it is suggested that trials to re-transplant ovarian auto-graft might be performed to postpone the menopause in volunteers in order to preserve endocrine function of ovary.

Acknowledgements

The author thanks all staff members of Faculty of Medicine, Zagazig University & College of Biotechnology, Misr University for Science and Technology (MUST), Egypt. The diagram in the paper is made by the author.

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