The ovary: from conception to death

At the dawn of human life, the ovary was intended to function for the entire lifetime of a woman. Indeed, at that time, life expectancy rarely exceeded 35 years while nowadays it is not unusual for women to live into their 80s. So, is it possible for a natural ovary to go on functioning until death? With potentially several million oocytes residing in each ovary at mid-gestation, could it not be feasible to prolong the function of the ovary until the end of life? Let us return to the conception period and analyze the evolution of the ovarian reserve.

The Ovarian Reserve

The term "true" ovarian reserve is typically used to refer to the population of primordial follicles. A model described by Wallace and Kelsey in *PLOS ONE* (2010) allows the number of primordial follicles present in the ovary to be estimated at any given age. In the field of assisted reproduction, the ovarian reserve denotes the population of small growing follicles (namely small antral follicles that are detected by vaginal ultrasound).

From Conception to Birth and Puberty

Initiation of the resting primordial follicle reserve begins in the fetus, when some 100–2,000 primordial germ cells colonizing the genital ridges enter a massive proliferation process that results in 7×10^6 potential oocytes at mid-gestation. In the human ovary, around 85% of these oocytes are lost before birth. The ovary is the only organ to lose 85% of its potentially functioning cells before it starts working. Some genes involved in inhibiting or inducing apoptosis might act as rheostats to determine the survival or death of germ cells. After birth, the number of non-growing follicles decreases year upon year until puberty, even if no ovarian activity is detectable.

From Puberty to Menopause

The decline in the number of follicles continues throughout reproductive life, during which time approximately 450 monthly ovulatory cycles occur, with the majority of follicles undergoing atresia (degeneration and resorption) during their growth phase. Cyclic folliculogenesis and ovulation, with massive follicular atresia and aging-induced apoptosis, result in ovarian atrophy and reduced fertility.

Numerous mechanisms have been proposed to explain decreased fertility in women >40 years of age, including poor oocyte quality, characterized by abnormalities in the meiotic spindle, chromosome misalignment and shortened telomeres. In some circumstances, depletion of the ovarian reserve at a young age may occur as a consequence of medical therapy. Indeed, around 10% of cancers are diagnosed in women <45 years of age. Advances in cancer therapy over the past two decades have led to remarkable improvements in survival rates, but treatments such as chemotherapy, radiotherapy, and/or surgery can induce premature ovarian failure (POF) in some instances. Pelvic radiation therapy is also known to cause POF, as exposure to 5–10 Gy is toxic to oocytes.

Women with cancer have several options to preserve their fertility and enable them to conceive when they have recovered: embryo cryopreservation; immature or mature oocyte cryopreservation; and ovarian tissue cryopreservation (1). Currently, embryo and mature oocyte cryopreservation following in vitro fertilization (IVF) treatment are the only methods endorsed by the American Society for Reproductive Medicine (ASRM).

Some systemic diseases (like autoimmune and hematological conditions requiring chemotherapy), certain benign diseases (severe and recurrent endometriosis, recurrent ovarian cysts), known risk factors for premature menopause (Turner syndrome, family history), and so-called social reasons (when childbearing is postponed to later in life for social or financial reasons) are also indications for fertility preservation.

If chemotherapy can be delayed or in case of benign diseases or social reasons, oocyte vitrification should be proposed. It should still be stressed that around 20 vitrified oocytes are required to achieve a live birth, success rates in terms of live births are age-dependent (2), and the excellent results obtained in egg donation programs or in the context of social indications cannot be extrapolated to conditions of malignant or even benign diseases (1).

A combination of ovarian tissue cryopreservation followed immediately by controlled ovarian stimulation and oocyte pick-up for vitrification could therefore increase the efficacy of fertility preservation (3). Orthotopic (in the pelvic cavity) reimplantation of cryopreserved ovarian tissue allows restoration of ovarian activity in over 95% of women, with more than 120 live births reported to date. Success rates after ovarian tissue reimplantation are steadily increasing and the live birth rate is estimated to be around 40% in our department.

In our opinion, if the goal is fertility restoration, the pelvic cavity (orthotopic site) provides the optimal environment for follicular development compared with heterotopic sites, as temperature, pressure, paracrine factors and blood supply more closely resemble conditions observed in a physiological situation.

After Menopause

There is no doubt that a better way of life and improved health care have increased life expectancy, going from 48.3 years in 1900 to 80 years in 2000, just one century later. Public health measures are credited with much of this improvement. During the 20th century, despite a brief dip due to the 1918 flu pandemic, the average lifespan in the United States increased by more than 30 years, 25 of which can be attributed to advances in public health efforts.

The consequence of this dramatic upturn in life expectancy is that many women spend 30–40% of their lives in menopause at increased risk of cardiovascular diseases, bone mineral density loss and other symptoms linked to the absence of estrogens. Hormone replacement therapy (HRT)

has beneficial effects on menopausal symptoms, but its use plummeted when the Women's Health Initiative reported an elevated risk of breast cancer in 2002.

It is evident that depletion of sex steroid hormones potentially increases vulnerability to disease in hormone-responsive tissues, including the brain, bone, and the cardiovascular system, leading to chronic conditions, usually after 60 years of age. As stressed by Lobo et al. (4), there is a key opportunity at the onset of menopause to prevent or attenuate these chronic diseases (including obesity and metabolic disorders, cardiovascular disease, osteoporosis, dementia and cognitive decline, as well as cancer), which usually appear around 10 years later.

As stated by Lobo (4), we may have already come full circle regarding HRT use and it should be considered part of a general prevention strategy for women at the onset of menopause. The crucial question now is: Are we able to prolong ovarian activity?

Back in 2003, Amorim et al. (5) reported that cryopreservation of ovarian tissue followed by transplantation could delay natural menopause. A number of years later, in 2015, we demonstrated that long-term endocrine function could persist for more than 7 years after reimplantation of frozen-thawed ovarian tissue (1). These encouraging results led us to speculate that in the future, ovarian cortex cryopreservation at a young age (when the ovarian reserve is still high), followed by reimplantation at menopause, could be an alternative to HRT (1).

As potential treatment for menopause, the graft site could be outside the pelvic cavity (forearm, rectus muscle, etc), as the goal in this case is not fertility restoration. Indeed, if ovarian tissue reimplantation is able to restore ovarian activity after induced menopause, why not propose it to restore sex steroid secretion after natural menopause? Some women who have had their ovarian tissue cryopreserved for fertility preservation purposes, but have not utilized it, might well want to use it to postpone their menopause.

Of course, questions surrounding possible risks and uncertainties will be raised and must be satisfactorily addressed. One important question remains unanswered: Is there an increased risk of cancer after tissue reimplantation? While we are unable to answer this question at present, the debate should at least be opened, taking into account the well balanced benefits of HRT for women potentially spending more than 30 years of their life in menopause.

Ovarian tissue freezing at a young age followed by reimplantation upon reaching menopause– could it be the anti-aging therapy of the future? Surely, if nothing else, we now have enough evidence to conduct a compelling and consequential debate with far-reaching implications for present and future generations.

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