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REVIEW ARTICLE

Which side of the coin are you on regarding possible postnatal oogenesis?

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It is well known that oocytes are produced during fetal development and that the total number of primary follicles is determined at birth. In humans, there is a constant loss of follicles after birth until about two years of age. The number of follicles is preserved until the resumption of meiosis at puberty and there is no renewal of the oocytes; this dogma was maintained in the last century because there were no suitable techniques to detect and obtain stem cells. However, following stem cell markers, several scientists have detected them in developing and adult human ovarian tissues, especially in the ovarian surface epithelial cells. Furthermore, many authors using different methodological strategies have indicated this possibility. This evidence has led many scientists to explore this hypothesis; there is no definitive consensus to accept this idea. Interestingly, oocyte retrieval from mature ovaries and other tissue sources of stem cells has contributed to the development of strategies for the retrieval of mature oocytes, useful for assisted reproductive technology. Here, we review the evidence and controversies on oocyte neooogenesis in adult women; in addition, we agree with the idea that this process may occur in adulthood and that its alteration may be related to various pathologies in women, such as polycystic ovary syndrome, premature ovarian insufficiency, diminished ovarian reserve and several infertility and genetic disorders.

Keywords: Ovarian stem cells, Postnatal oogenesis, Female infertility, Ovarian surface epithelium, Diminished ovarian reserve, Premature ovarian insufficiency.

Introduction

In women, optimal fertility is generally reached between the ages of 20 and 30, accelerates after the age of 35, and then declines with age. Women are born with a limited number of oocytes. By the fifth month of gestation, the fetal ovaries contain 500–1300 primordial germ cells (PGCs), which undergo mitosis to generate six to seven million germ cells (GCs) by the 10th week of gestation. Subsequently, between the 11th and 12th week of gestation, the process of mitosis stops, and the germ cells begin meiosis, stopping in prophase I (1).

Waldeyer-Hartz was the first to estimate the number of oocytes contained in the neonatal human ovary (36,000–50,000) (2). Since then the idea has been accepted that at birth the ovary contains all the oocytes for future life, which means that some oocytes could have a lifespan of 45–50 years (3). Afterward, von Hansemann estimated between 40,000 and 80,000 oocytes in a neonatal ovary (4). Hammar and Hellmann counted 194,283 oocytes in an ovary of three-year-and eight-month-old girl who died of

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thyroaplasia (5). Häggström counted 419,911 oocytes in both ovaries of a 22-year-old woman (6). It is currently estimated that a woman's ovaries contain between one and two million oocytes at birth and that this number decreases to about 400,000 at puberty when approximately 300–400 oocytes will undergo a maturation process during ovulation. At menopause, approximately 1000 primary follicles remain to maintain endocrine activity and ovulation (7), as it was described by Zhu et al. (1).

On the other hand, the crucial question of solving infertility problems in assisted reproduction and ovarian pathologies is partly based on the recovery of oocytes from adult women or on the question of whether it would be possible to obtain oocytes from postnatal oogenesis. Moreover, whether it is possible to obtain ovarian or extraovarian stem cells for oocyte production by in vitro methods. However, the existence of postnatal oogenesis in humans has yet to be proven, but we agree with the scientific community that supports the idea that there is a possible smaller number of oocyte renewals during a woman's life. This brief review summarizes the key findings and the state of the art regarding the possible renewal of oocytes and the controversies surrounding it.

Oogenesis during the fetal period of a woman's life

The development of the ovaries involves the origin, growth, and maturation of their gametes to reach a physiological transition appropriate for reproduction, which is achieved through two coordinated processes, oogenesis and folliculogenesis. PGCs and gonads share a common characteristic: they originate without a sexual identity. When PGCs arrive at the genital ridges and interact with the somatic cells and their gonadal environment, the process of differentiation of both PGCs and gonads begins. Once the PGCs are established in the ovaries, a very active period of mitotic proliferation is initiated by the female germ cells, the oogonia, which increase exponentially in number, but soon after, most of these cells undergo atresia. The remaining oogonia, however, enter meiosis during fetal life and have a dictyate arrest at birth.

In humans and other mammalian species, the onset of meiosis is approximately at week 11–12. Later, oocytes are arrested at the diplotene stage of prophase I in the germinal vesicle (GV) stage and may remain in this arrested stage for months, years, or decades (8–10). Oocytes are enclosed by a single layer of squamous follicular cells that form the primordial follicles (11). Oocytes must undergo cytoplasmic and nuclear maturation, also known as oocyte developmental competence, to have the potential to be fertilized, and to transport the essential maternal transcripts that will control embryonic development up to the morula stage (12–15).

Oocyte cytoplasmic maturation involves the accumulation of mRNA, proteins, substrates, and nutrients that are required for embryonic development (16–18); whereas oocyte nuclear maturation is conditioned by organelle maturation (mitochondria, ribosomes, endoplasmic reticulum, cortical granules, and the Golgi apparatus), and epigenetic maturation (de novo methylation, histone post-traductional modifications, and chromatin remodeling) (15,19).

Oocytes initiate a growth phase when the chromatin in the GV is decondensed and transcriptionally active, and follicular cells simultaneously become cuboidal and proliferate, giving rise to primary and secondary follicles (11,20–24).

After puberty, oocytes resume meiosis during each menstrual cycle when a surge of luteinizing hormone (LH) triggers the final maturation of a dominant follicle. Nuclear maturation of oocytes is necessary to restart meiosis. GV rupture then occurs, and oocytes pass to metaphase I until reaching metaphase II (13,14,25). At metaphase II (MII) the oocyte is arrested for the second time until fertilization occurs. Fertilization reactivates meiosis II and completes maturation to start embryonic development (26).

Meiotic competent oocytes assemble microtubule organizing centers (MTOCs), which will be essential for the assembly of a spindle (27–30), that will be required to direct the first meiotic divisions and the second meiosis after fertilization.

The study of the ovary, and in particular of oogenesis in adult mammals, has generated interest over the years, and advances in both scientific and technological knowledge have made it possible to address this interesting line of research with new questions to be solved using new analytical tools. Initially, histological techniques were used to study the ovaries of cats, rats, dogs, guinea pigs, monkeys, and humans (31–35). Subsequently, experimental methods focused on the analysis of the germinal epithelium of the rat ovary where colchicine was used to arrest mitosis (36), India ink was used to mark the germinal epithelium *in vivo* (37), and for vital staining (38), and tannic acid and carbolic acid were used to perform unilateral castration and destroy the germinal epithelium (39). In addition, the effect of high doses of follicle-stimulating hormone (FSH) on the ovaries of immature monkeys, was evaluated (40).

The ovarian surface epithelium (OSE) has been proposed as a source of ovarian stem cells in humans (2,41–44), and mice (45). It is a natural source of germ cells in the fetal period of life (33,46), and this cell layer can be considered as a "germinal epithelium" (2,31,47). OSE scanning and transmission electron microscopy have revealed numerous germ cells of 10 μm in diameter within the OSE of the human fetus, at 7–24 weeks of intrauterine life (48), supporting the idea that this cell layer may contain a stem cell niche. Recent evidence on the purification and *in vitro* propagation of premeiotic germ cells from neonatal and young adult mouse OSE cells has shown that these cells can generate a developmentally competent oocyte in a transplanted host female, providing

further support for this idea (49). These results suggest that both neonatal and adult mouse ovaries contain stem cells capable of producing functional oocytes (49,50). It has been widely reported that ovarian function declines with age due to a reduction in the number of ovarian follicles. In general, fertility begins to decline after the age of 30 leading to sterility at menopause (51,52). In humans, rats, and mice, the ovary is a unique organ that exhibits impaired function with advancing age (53,54).

However, several diseases including genomic alterations and environmental and iatrogenic processes such as radiotherapy, and chemotherapy, alter oogenesis. Furthermore, the oogenesis process in adult women may be controversial, but in rodents, it is highly accepted. In this brief review, we have described the main dogma and data regarding the oogenesis controversy in adult humans and other mammals.

"The central dogma of reproductive biology" and the concept of neooogenesis in adult mammals, including women

Historically, Waldeyer-Hartz, (2), was the first to hypothesize that in adult mammalian species and birds, no additional oocytes can be produced in the ovary after the postnatal period and that oocytes originate from the OSE during a limited period in early life. This was the beginning of the greatest controversy in the field of biology that continues to this day. Various research groups provided evidence to support or refute this idea, but years later, we would come to know it as the central dogma of reproductive biology regarding the concept of postnatal oogenesis or neooogenesis.

Between 1901 and 1956, evidence was presented to support the idea of neooogenesis in some adult mammalian ovaries, as well as oogenesis during sexual maturity, oogenesis in the adult human ovary, and the estimation that new oocytes are formed from the germinal epithelium in the human ovary between the ages of 20 and 40 (31,32,35–37,55–62). However, despite these works, the idea proposed by Waldeyer-Hartz still prevailed (2), as seen in the works by Kingery and Pearl and Schoppe (47,63). Kingery proposed that all oocytes that degenerate during fetal life are restored by oocytes that develop in the adult ovary (47). This idea was further reinforced by the work of Allen and Allen and Creadick (31,36), who argued that new oocytes arise from the germinal epithelium by mitotic division. Similarly, Pearl and Schoppe (63), asserted that there can be no increase in the number of primary oocytes after the formation of the ovary, a concept that years later Zuckerman would mention as the correct description of the "basic biological doctrine" (64). Subsequent studies focused on explaining the regenerative capacity of the rabbit and rat ovary (65,66), as well as postnatal oogenesis by analyzing the number of normal and atretic oocytes in the rhesus monkey, considering two possible mechanisms of oocyte depletion, atresia alone or the combination of atresia with a decreased neooogenesis (3).

Based on the postulates of Waldeyer-Hartz, Kingery, Pearl and Schoppe, and Zuckerman (2,47,63,64) confirmed that in rats, mice, rhesus monkeys, rabbits, dogs, guinea pigs, and humans, the number of oocytes in the ovaries decreases with age. From this point on, Zuckerman's work would become what we know as "the central dogma of reproductive biology", which postulates that most mammalian females have the potential to generate a limited reserve of oocytes during fetal development (64). These oocytes, surrounded by granulosa cells, are described as ovarian follicles incapable of dividing (64,67). A few years later, Peters H, et al. (68), demonstrated that the period of oocyte formation in the mouse occurs only during the premeiotic S phase. The formed oocytes remain during the adult stage. Similarly, Crone M, et al. and Morita Y, et al. (69,70), identified large oval cells in the OSE of young and adult mouse ovaries that resemble germ cells in fetal ovaries. The central dogma was that female mammals are born with a limited, non-renewable supply of germ cells, all of which are arrested in meiosis I and form functional units described as follicles (64,71–74). Since then, several research groups have conducted studies in several mammalian species that support neooogenesis.

Research conducted in adult prosimians has contributed to the identification of oogonia during interphase and at different stages of mitosis, as well as oocytes during the meiotic prophase (75,76). It has been suggested that the mitotic activity of germ cells forms clusters within the ovarian cortex that can incorporate tritiated thymidine, indicating mitosis and DNA synthesis during the estrus and anestrus stages (77,78).

Johnson and his collaborators demonstrated that in young and adult mice, ovarian mitotically active germ stem cells (GSCs) express the germ-cell marker Mvh, and the meiotic entry marker synaptonemal complex protein 3 (SYCP3) (79). Further work by Johnson and colleagues (80) found that bone marrow transplantation (BMT) could restore oocyte production in chemotherapy-sterilized wild-type mice, as well as in ataxia telangiectasia-mutated gene-deficient mice, after oocytes were observed in peripheral blood transplants, concluding that bone marrow is a potential source of oocyte-producing germ cells in adulthood. Furthermore, Lee and coworkers proposed that BMT could rescue long-term fertility in CTx-treated female mice, provided that germ stem cells (GSCs) can replenish oocytes and eliminate the effects of busulfan and cyclophosphamide as well as the action of *CABLES1*, like an associated key gene that restricts the rate of oocyte renewal in adult mouse ovaries (81,82). In addition, further evidence supported the hypothesis of postnatal follicular renewal from immature putative germ cells in postnatal and adult C57BL/6 mouse ovaries (83). It has been

demonstrated that oocytes can be spontaneously generated from embryonic stem cells (ESCs), which can have morphological and physiological characteristics of ovarian follicles (84). Zhang et al. observed the presence of cell aggregates, corresponding to cell populations unrelated to ovarian follicles, that expressed germline and stem cell surface markers in adult mouse ovaries (85). Szotek et al. identified a population of label-retaining cells (LRCs) in the OSE of adult H2B–GFP mouse ovary as candidate somatic stem/progenitor cells (86). Zou et al. purified by immunomagnetic isolation and maintained in culture for 6–15 months a GSC line in neonatal and adult mice, with normal karyotype, high telomerase activity, and the expression of pluripotency and germline genes (87). Niikura et al. identified premeiotic germ cells in the OSE of aged mouse ovaries with high expression of the *Stra8* and *Dazl* genes. They also observed a positive correlation between *Stra8* expression and follicle regeneration after doxorubicin treatment in young adult female mice (54). Pacchiarotti J, et al. identified two populations of GFP-Oct4 positive cells in both neonatal and adult mouse ovaries, based on their size and distribution (88). The first group consisted of small cells found in the OSE that corresponded to GSCs that maintained telomerase activity, expressed germ cell and stem cell markers, had normal karyotypes, and formed embryoid bodies (EBs). The second group consisted of larger cells corresponding to oocyte-like cells (OLCs) that were surrounded by follicular structures. Gong et al. established two lines of ESCs-like cells in mice, from adult ovarian stromal cultures with a fibroblast monolayer that expressed pluripotent markers and formed EBs and teratomas (89). White YAR, et al. purified mitotically active cells in both adult mice and humans that can be expanded *in vitro* and spontaneously generate oocytes. Injection of GFP-transfected human oogonial stem cells into human ovarian cortical biopsies results in the formation of follicles containing GFP-positive oocytes after xenotransplantation, into immunodeficient female mice (90). Esmaeilian Y, et al. provided evidence for differential expression of *Oct4, Nanog*, and *Sox2* in prepubertal and adult mouse ovaries and suggested that mouse ovaries have cells with stem cell characteristics (91). Hu et al. confirmed the existence of female germline stem cells (FGSCs) in postnatal and adult mouse ovaries; they showed the expression of germ cell markers Mvh, Dazl, Figla, Zps, and stem cell markers Oct4, Klf4, c-myc, Nanog, CD49f, Sox2, CD133, SSEA1, and SSEA4 (92). Bhartiya et al. demonstrated that pregnant mare serum gonadotropin (PMSG) treatment resulted in induced very small pluripotent embryonic-like stem cell (VSEL) activity in the OSE, leading to the proliferation and differentiation of GSCs into oocytes and primordial follicle assembly, besides increased FSH receptors (FSHR), in adult mouse ovaries (93). Park ES, et al. suggested that exposure of oogonial stem cells (OSCs) to BMP4 in the adult mouse ovary, resulted in rapid phosphorylation of BMPR-regulated Smad1/5/8 proteins, followed by the increased expression of the meiosis genes *Stra8, Msx1*, and *Msx2* (94). Sriraman et al. provided evidence that OSE cells, cultured from chemoablated ovaries formed clusters of proliferative cells and oocyte-like structures, and were positive for MVH and GDF9 (95). Moreover, they showed that the direct stimulatory action of FSH induced OSE proliferation and differentiation into premeiotic germ cell clusters. Guo et al. postulated the presence of active GSCs in adult mouse ovaries and their function in replenishing the primordial follicle pool under physiological conditions (96).

Evidence of stem cells in the human ovary

A growing body of evidence suggested the possibility of the existence of neooogenesis in adult human ovaries, opening a new avenue for intensive research in this field (41,43,44,50,79,80,97–115). Many of these works were based primarily on studies performed first in rodents and later on oogenesis from human OSE cells and possible extra-ovarian sources, which will be briefly described in the following paragraphs.

Oogenesis in adult humans and mammals: realities and controversies

There is vast evidence that oocyte renewal can occur in adult human ovaries; however, the debate in the scientific community is still controversial. A very elegant, convincing, and detailed review by Tilly's group (113) and others, described the scientific evidence for oogenesis in adult mammals, including humans (79,80,110,116). OSCs from mice differentiated into oocytes *in vitro* are suitable to be fertilized and implanted into sterilized animals resulting in embryonic development. Thus, the purpose of our comments, in addition to previous works, is related to our observations of the possible involvement of the OSE in the induction of cell transition, and their ability to induce new cell-differentiated populations, such as granulosa cells and possible oogonia cells. If granulosa cells can renew stem cells, they are likely to be recruited by oogonial cells in differentiation. Indeed, in patients with diminished ovarian reserve (DOR), we demonstrated that epithelial cells in the OSE of these patients expressed stem cell markers such as SOX2, NANOG, and OCT4, and these cells exhibited migration and invasion into the stroma (53), similar to what was previously reported by Bukovsky A, et al. (43). Interestingly, other reports by Vital-Reyes et al. indicate that the ovaries of these patients did not present an increase in apoptosis, nor a reduction in primary follicles, suggesting a decreased or suppressed stem cell population (117). Our research group agrees with the idea that the ovary, like many other human tissues, contains a reserve of the stem cell population capable of renewing functional tissue cells.

If there is evidence of granulosa cell renewal in the ovary, it has probably been recruited by renewed oocytes, but possibly with a very limited population (53). Our studies were inconclusive due to the limitations of human biopsies and the ethical aspects of obtaining ovarian human tissue. Therefore, further studies are needed.

Restoration of Oogenesis in Adults Using Stem Cells from Different Sources, Including Preserved Ovaries and Restoration of Ovarian Reproductive Function

The recovery of ovarian and reproductive function is emerging as a promising strategy to preserve fertility, as well as to reduce the impact of chronic diseases on reproductive health and those related to reproductive age and to extend reproductive capacity in the future (1,118). Infertility is a global problem affecting 48 million couples, with women accounting for 37 % of infertility cases. This number continues to increase leading couples to turn to strategies that can solve the problem, such as assisted reproduction technologies (ART) (119,120), *in vitro* fertilization (IVF) (121–123), and intracytoplasmic sperm injection (ICSI) (124), among others. However, none of these techniques have been able to completely solve the problem, since infertility has a complex origin, which can be caused by genetic, epigenetic, or chromosomal abnormalities, including copy number variations (CNVs), or even by autologous germline mitochondrial energy transfer (AUGMENT) factors (113,125–127), in aging oocytes, all of which can positively impact folliculogenesis and oogenesis. Due to this diversity of reproductive alterations, the search for new or improved assisted reproductive technologies is an ongoing research effort.

Recently in patients with premature ovarian insufficiency (POI), advances in stem cell technology have been proposed that increase the likelihood of *in vitro* gametogenesis derived from human induced pluripotent stem cells (hiPSCs) which could provide new therapeutic strategies for infertile couples successfully overcoming significant problems related to immunological rejection, and ethical issues related to the human embryo. We refer to the generation of patient-specific stem cells that can be reprogrammed (118). Here, neooogenesis may provide a new strategy to preserve fertility, delay menopause, and treat infertility.

Although not widely used in most cancer fertility preservation centers, the biobank of cryopreserved ovarian tissue provides a substantial source of biological material to study the OSC population of women (128). Several studies have reported the existence and origin of OSCs derived from various sources such as bone marrow (110), ovarian cortex (129), OSE (101,108), skin-derived stem cells (130), and pancreatic stem cells (131). OSCs can proliferate and differentiate into different developmental stages of oogenesis. OSCs or ovarian stem cell-like cells have been identified using several methods including fluorescence-activated cell sorting (FACS), and magnetic-activated cell sorting (MACS) (90,108,110,129,132,133) (Fig. 1).

Although we know that OSCs can generate new oocytes, the methodological issues of obtaining ovarian OSCs, ESCs, and induced pluripotent stem cells (iPSCs) used to generate new oocytes *in vitro*, should not be overlooked (134–136). There is great potential for OSCs to generate oocytes that can counteract the alterations observed in infertile cancer survivors and patients with POI, in addition to the problems associated with menopause, which could help preserve fertility in older women who have not yet been able to become mothers (Fig. 1).

OSCs express specific markers, including the fluorescent-labeled dead box polypeptide 4 (DDX4), which is the most commonly reported marker when OSCs are isolated by FACS and MACS methods, as well as other germ cell markers such as PRDM1, PRDM14, and DPPA3, SSEA-4 and FRAGILIS. However, some reports mention that they are not ovarian specific, but we have stem cell markers such as OCT4, SOX2, SSEA-4, SALL4, CDH1, and LEFTY1, and oocyte-specific markers such as ZP3, SYCP3, and c-KIT (108).

It has been reported that OSE cells can differentiate into oocytes and granulosa cells (101), while VSELS and OLCs obtained from OSE scrapings can proliferate and differentiate into OLCs (137). Furthermore, in humans, FGSCs have opened new opportunities for understanding human oogenesis. However, it should be noted that the scarcity of available adult human ovarian tissue for ethical reasons, impedes future research and its potential clinical applications.

The human adult ovary is a source of oocyte recovery for reproductive purposes

In vitro maturation (IVM) of oocytes has been proposed as a tool that could support ART and obtain better results in patients who present infertility, and in women with polycystic ovary syndrome. Lee (138) used adult pluripotent stem cells (ASCs) derived from human adipocytes, along with a conditioned ASCs-CM medium applied to the porcine oocyte, and IVM to evaluate the efficiency of ASCs in oocyte development and subsequent embryonic development. This was presented as a proposal to improve oocyte cultures and thus obtain better results that would favor the maturation and optimal development of the oocytes, thus increasing the chances of a successful outcome when performing assisted reproduction.

From this work, we can consider ASCs as ideal candidates in regenerative medicine due to their stable differentiation ability, easy expansion, and isolation to obtain adequate quantities (139). For these reasons, ASCs are reliable for application in medicine.

Accumulating evidence over the years has shown that, in mammals, mice, and humans, the presence of FGSCs

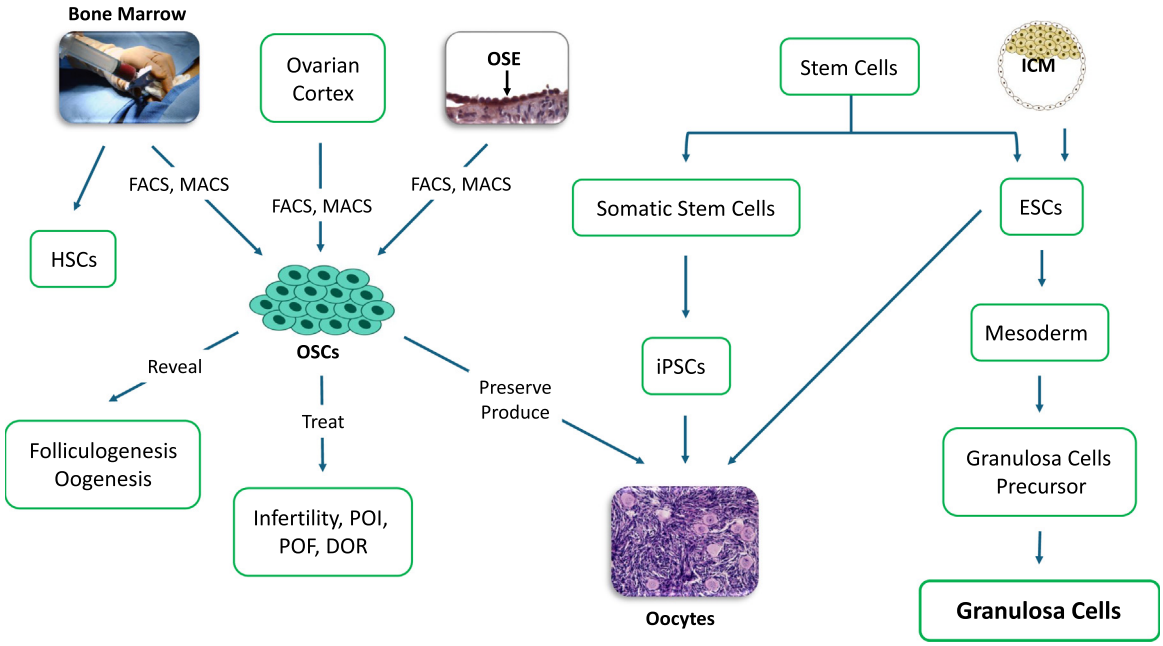

Fig. 1. Schematic summary of ovarian cell types and putative cell sources, the process of differentiation into mature oocytes and granulosa cells, identification methods, and their use in the treatment of infertility. Oogonial stem cells (OSCs) are derived from a variety of sources, including bone marrow, ovarian cortex, skin-derived stem cells, and pancreatic stem cells. OSCs can proliferate and differentiate into different developmental stages of oogenesis. OSCs can be identified by various methods, including fluorescence-activated cell sorting (FACS) and magnetically-activated cell sorting (MACS). OSCs are a potential treatment for women with infertility diagnosed with premature ovarian insufficiency (POI), premature ovarian failure (POF), and diminished ovarian reserve (DOR).
Modified from Gong SP, et al., and Truman AM, et al.

is responsible for carrying out neooogenesis in postnatal ovaries (79,87,140,141). However, in humans, abnormalities in germline development have been reported to lead to serious diseases, including infertility and cancer.

Currently, diseases associated with ovarian dysfunction have become prevalent in women whose menstrual cycle frequency and duration are often altered (142), and in some cases, POI or polycystic ovary syndrome may or may not occur.

Spermatogonial stem cells (SSCs) can differentiate into other cell types including oocytes, and it has been reported that these ovarian organoids can produce offspring (143), which is why this cell type has been able to maintain fertility and provide support in other genetic diseases, such as Klinefelter's syndrome (144).

Recently, a study based on single-cell RNA sequence analysis (scRNA-seq) of adult human ovarian cortical tissue, claimed that OSCs do not exist (97,145), and the groups claiming neooogenesis have worked with perivascular cells (PVCs), instead of OSCs, after isolation by MACS or FACS. However, the methodology of these studies has also been refuted by technical problems in isolating different types of ovarian cells (113).

Intervention strategies to delay ovarian aging have now been proposed in murine models and women. These preclinical trials may show potential for improving female fertility. Significant progress has been made in the field of sino-therapy to prolong the reproductive life of mammalian females (146,147). Antioxidants such as resveratrol, nicotinamide mononucleotide, NAC, melatonin, and coenzyme Q10 may prevent oxidative damage and delay ovarian aging (1).

Finally, clinical trials have been conducted using cytoplasmic transfer to improve oocyte quality and employ mitochondrial enrichment, where some or all of the healthy cytoplasm is transplanted into oocytes from infertility patients to perform oocyte rescue (1,148,149).

Conclusions

Although there is much evidence in favor of oogenesis in mammals including humans, there is still controversy in the scientific community between those who support the idea of postnatal oogenesis and those who deny its existence, which emphasizes the need for further research, by using or generating new methodologies in animal models for use in human clinical trials. This is of great importance not only for the treatment of infertility but also for POI and other obstetrical and gynecological diseases.

Ethical statement

An ethical statement is not applicable as this study is based exclusively on published literature.

Conflict of Interest

The authors have no competing interests to declare.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.arcmed.2024.103071.

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