Chapter 1
Female Age and Reproductive Chances

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Introduction

We currently live in an era of family planning and female work-force emancipation, while experiencing an ever-increasing lifespan. With this has come the freedom and ability to delay the age of childbearing and facilitate conception. However, for some women this delay may result in having to undergo assisted reproductive treatment (ART) to achieve pregnancy or even in the inability to conceive at all. While calendar, or 'chronological age' is very much related to biological or 'reproductive age', they can also represent separate entities. This means that while some women will be able to achieve a spontaneous pregnancy at age 35 without any problems, others may then have already missed their window of optimal opportunity. This chapter will cover the basic aspects of the reproductive physiology of the aging woman, as well as the demographics and consequences of postponed reproduction.

Physiology of Reproductive Aging

Oocyte Quantity

During the intra-uterine development of a female she is endowed with a supply of egg cells, or oocytes, which is not able to multiply and will thus decrease throughout her reproductive lifespan. The oocytes are surrounded by a layer of granulosa and theca cells, together constituting a follicle. In its earliest stage of development, while in the resting and non-developing pool, the follicle is considered to be

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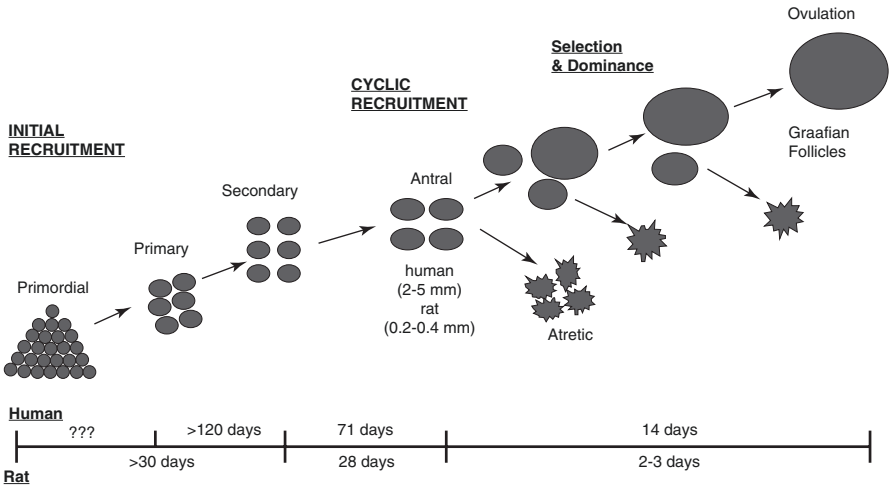

Fig. 1.1 Schematic overview of follicular recruitment and apoptosis

primordial. Starting at birth, follicle numbers in the resting pool decline through apoptosis of the resting follicles. After puberty, primordial follicles are either recruited to undergo development during the menstrual cycle, or go into apoptosis at any stage from resting through development (Fig. 1.1). The vast majority of all ovarian follicles will ultimately be lost through apoptosis [1, 2]. Through these pathways, the follicle pool declines with time, and thus with age.

At around 20 weeks of gestation, the pool of oocytes is fully developed, reaching a number of about seven million [2–4]. At birth, the number of follicles will have already decreased to approximately 1–2 million [4, 5]. With time, the oocyte pool declines further. At menarche, the number of remaining oocytes is thought to be 300,000–400,000 [6], with an estimated 1000 oocytes remaining at the time of menopause [7], marking the end of the female reproductive lifespan. The onset of menopause coincides with the final menstrual period and occurs at an average age of 51 years, with ages between 40 and 60 years considered as the normal variation [4, 8–10].

Oocyte Quality

In addition to a decrease in absolute follicle numbers with time, the aging ovary is also affected by a deterioration of oocyte quality. In the development from a primordial follicle to fertilization, it is necessary for the oocyte to undergo two stages of meiosis in order to reach a haploid state. With advancing female age, the ability of the oocyte to undergo successful and high quality meiosis decreases, as reviewed by Handyside et al. [11]. Experimental mice studies demonstrated increased aneuploidy rates resulting from impaired meiotic divisions of oocytes in long-living

females, also known as meiotic non-disjunction, with various causative mechanisms related to errors in the cohesion and division of chromatids [12–15]. In humans, embryonic and fetal aneuploidies due to failures in both the meiosis I and II stages more often stem from aneuploidies in oocytes than spermatozoa [11, 16–18]. In assisted reproduction embryos, the number of aneuploidies exponentially increased with increasing maternal age [19, 20]. The significantly lower aneuploidy rate in older women with donor oocyte pregnancies confirms the aging oocyte to be the most important contributor to aneuploidic pregnancies [21].

Another consequence of female aging for the ovary is the effect on mitochondrial DNA, which is maternally inherited. Mitochondrial DNA functions as a reactive oxygen species (ROS) scavenger and is involved in cell metabolism by generating ATP for several functions [22]. As a woman ages, mitochondrial DNA sustains more damage and an increase in the number of mutations. After meiosis, the oocytes of aging women therefore increasingly contain damaged mitochondrial DNA, with a concomitant decline of total mitochondrial DNA content [22–24].

Besides the intrinsic aspects of aging described above, oocyte quality is also suggested to be influenced by extrinsic factors related to aging such as lifestyle (e.g. smoking [25]), disease and environmental factors and oxidative stress exposure [11, 26]. These factors may cause damage to the oocyte directly, but are also known to influence the epigenetic cell milieu. In animal studies, aging was associated with changes in DNA methylation and histone modification in oocytes, which resulted in an increased aneuploidy rate [27]. Epigenetic modifications are thought to lead to disturbances in the RNA expression necessary for follicular development, changes in the expression of DNA governing the meiosis process, and post-ovulatory DNA modifications [27], which in turn can cause aneuploidy.

The Reproductive Consequences of Biological Aging

Oocyte Quantity Decline

During the development of follicles recruited from the primordial follicle pool, a constant interplay consists between hormones produced by the follicular granulosa cells and those secreted from the hypothalamus and pituitary. This enables the regular cyclic pattern of ovulation and menstruation. When the primordial follicle pool, and thus the number of developing follicles selected from this pool, decrease to a certain threshold, the endocrine balance is altered [28]. Briefly, the relative lack of released gonadal hormones, such as estradiol and inhibin B initiates a mitigated negative feedback signal to the hypothalamus and pituitary, leading to an increase in gonadotrophin-releasing hormone (GnRH). The ensuing higher levels of FSH in combination with the decrease of FSH-sensitive follicles [4] cause dysregulation of follicle development and release. Initially, the increase of FSH-levels gives the development of antral, and selection of dominant, follicles an impulse. This results in an uninhibited dominant follicle selection during the menstrual cycle, which

therefore remains regular. With increasing FSH levels, the chance of early, or 'advanced' dominant follicle growth increases [29]. This leads to the shortening of the menstrual cycle, which is the first noticeable sign of decreasing ovarian reserve. Eventually, the relative lack of available antral follicles inhibits the regular selection of a dominant follicle and ovulation, thus leading to an irregular length of the menstrual cycle, marking the beginning of the perimenopausal transition [28, 30]. The irregularity of menstrual cycles becomes more pronounced in the late stage of the perimenopausal transition, which continues until the final menstrual period, heralding the onset of menopause [30]. The time between the onset of irregular cycles and the onset of menopause is thought to be similar for all women, irrespective of their age at menopause (albeit studied in a population of women in which age at menopause ranged between 44 and 55 years) [31].

Oocyte Quality Decline

Although changes in the menstrual cycle pattern are indicative of having reached the later stages of reproductive aging, they will already have been preceded by a decline in fertility. Figure 1.2 summarizes the putative stages of fertility decline with age, from optimal fertility to menopause. At a mean age of 30–31 years, the per-cycle chance of achieving an ongoing pregnancy starts to decrease, due to either impaired fertilization or implantation [32, 33]. Data from a contained, religious community not applying any form of reproductive constriction, in the Québec

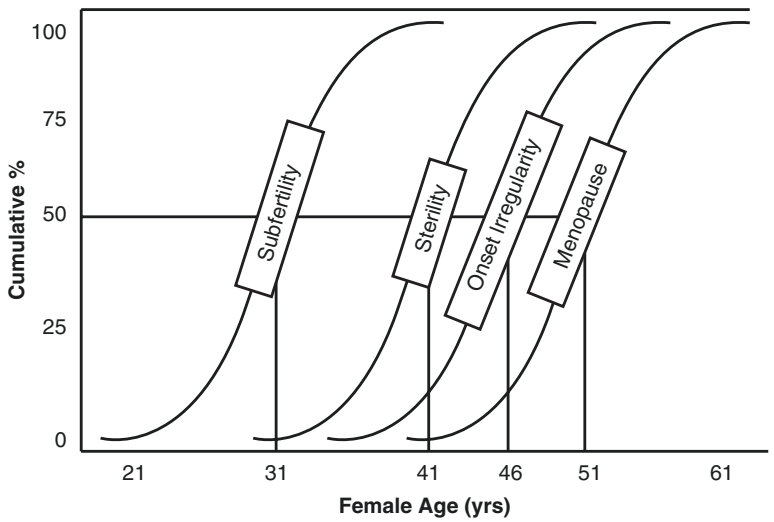

Fig. 1.2 Stages of fertility decline and menstrual cycle changes with increasing female age. Re-used from [6]

region in the early nineteenth century suggest that natural sterility subsequently occurs at an average age of 41 years, with a putative fixed interval of 10 years before the onset of menopause [34]. The occurrence of natural sterility a whole decade before the follicle pool is depleted can be problematic for women delaying their age of conception. It was recently estimated that women who wish to have respectively two or three children through natural conception should start as early as age 27 or 23 in order to have a 90% chance of realizing this objective [35].

The impact of deteriorating oocyte quality on fertility extends further than just fertilization. Miscarriage rates start increasing in women trying to conceive after 30 years of age, and exponentially so after age 35 [36]. The observed miscarriage rates are likely only the tip of the iceberg, as a large number of pregnancies may have miscarried before they could become clinically apparent [6]. Chromosomal abnormalities lie at the heart of at least 50% of all known miscarriages in the general population [37], but even in the event of an ongoing pregnancy, chromosomal abnormalities can still occur. The incidence of trisomy 13, 18 and in particular 21 sharply increases with advancing maternal age [14, 38, 39]. Between the age of 15 and 45, the incidence of a fetus with Down syndrome (trisomy 21) increases from 0.6/1000 to 4.1/1000 [40, 41]. In a large epidemiological study from the United Kingdom, at least 95% of all Down syndrome cases were associated with meiotic non-disjunction [42].

The importance of oocyte quality in addition to quantity is exemplified by a group of women with the same extent of diminished ovarian reserve, wherein younger women had significantly better pregnancy rates [43]. Furthermore, oocyte quantity decline cannot independently predict implantation and pregnancy rates [44]. Male and uterine factors are also an important aspect of fertilization and implantation, but the high pregnancy rates in older women with donated oocytes suggest that the aging oocyte plays a primary role [45].

Measuring Reproductive Aging

Chronological aging does not necessarily follow the same pace as reproductive aging. It can thus be the case that two women of the same chronological age have a very different ‘reproductive age’ and, as a result, different reproductive chances. A method of quantifying ovarian age was searched for in the field of ART, in order to individualize ovulation induction dosages and estimate the feasibility of fertility treatment.

Oocyte Quantity Markers

The past decade saw the emergence of several markers that represent the size of the remaining primordial follicle pool. Here, we briefly present two such markers frequently used in clinical practice, also known as ovarian reserve tests (ORT): antral

follicle count (AFC) and anti-Müllerian hormone (AMH). From the non-growing pool, follicles are continuously selected to develop under the influence of FSH. Although the primordial follicle pool cannot be directly measured, the number of antral follicles, which can be determined by ultrasound, is directly correlated to the number of primordial follicles [46, 47]. Another proxy of the size of the primordial follicle pool is AMH [48], which is produced by the granulosa cells of small developing follicles [49, 50] and can be measured in the peripheral circulation. Both AFC and AMH give an indication of the expected response to ovarian stimulation [51–53], but are also used as markers of the reproductive lifespan. Antral follicle count and AMH concentrations can better predict age at menopause than chronological aging or family history alone, in which respect AMH appears superior to AFC [54]. Predicting the age at which a woman will reach menopause could potentially guide women and clinicians in decisions regarding family planning (when to start having children) and fertility treatment. However, despite initially hopeful results of age at menopause prediction with AMH, it is still not possible to pinpoint an exact age at menopause for an individual woman [54].

Oocyte Quality Markers

In order to provide an estimation of the reproductive chances of women with advanced age, it would be desirable to have a marker of oocyte quality in addition to oocyte quantity. In theory, if the aging processes that influence both oocyte quantity and quality run in parallel, the decline in oocyte quantity could also be a measure of deteriorating oocyte quality. There is some dispute as to whether markers of oocyte quantity are indeed representative oocyte quality. This can be divided into two categories: fecundability, or the per-cycle chance of achieving a pregnancy, and fetal or embryonic aneuploidy. Levels of AMH below 0.7 ng/mL were associated with a 62% reduced chance of achieving pregnancy in an ovulatory cycle [55], but others found no association between ovarian reserve markers and pregnancy rate [56–58] or time to pregnancy [59]. With regard to fetal aneuploidy, there is evidence suggesting that trisomy occurrence is related to reduced AMH levels [60], or decreased ovarian reserve due to congenital ovarian absence or unilateral surgery [61, 62], whereas no association between oocyte quantity and fetal aneuploidy is reported elsewhere [63, 64]. The latter is supported by a study in which embryonic aneuploidy rates were strongly related to maternal age, but not to the number of available embryos per stimulated cycle [19]. In other words, oocyte quantity does not appear to be unequivocally related to oocyte quality. The use of oocyte quantity markers for fertility work-up and counseling may therefore be limited. To date, there are still no known markers that are solely indicative of oocyte quality.

Strategies for Reproduction at Advanced Age

In practice, the majority of women will be able to successfully achieve an ongoing pregnancy. Those who do not and have clear reasons for their sub- or infertility, such as tubal factor, azoospermia, or anovulation may benefit from targeted treatment strategies to their problem. However, when a reduced oocyte quantity or quality lies at the heart of involuntary childlessness, the solution is less simple. To date, there are no known ways to increase oocyte quantity or improve oocyte quality. Treatment for ovarian aging therefore currently has a more preventative nature: women are advised not to postpone a pregnancy for too long and should consider lifestyle habits such as smoking to be a constant threat factor for their (future) fertility. At a late stage of ovarian aging, oocyte donation, using eggs form young or at least previously fertile women, may be the only remaining treatment option for a viable euploidic pregnancy.

Key Message

1. Female aging is associated with a decline in quantity and quality of oocytes.
2. The decline in oocyte quantity ultimately results in the onset of menopause, while the decline in oocyte quality leads to an increased proportion of chromosomal abnormalities.
3. Reproductive aging is associated with a loss in fertility and increase in miscarriage rates.
4. Oocyte quantity can be measured through proxy markers, but there are currently no available markers of oocyte quality.
5. Besides prevention, there are currently no treatment options for the consequences of female reproductive aging.

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