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Review Article

Maternal Age and Infertility

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Introduction

The incidence of female infertility is growing worldwide, reaching rates from 10 to 20%. It has been reported diverse risk factors associated with this medical complication [1]. The nature of these factors can be environmental-dependent, consequence of a specific genotype or caused by the aging. This review pretends to clarify the connection between age and fertility. It is well-known that among the most complex aspects of the Biology are the changes that age produces in the organism. The aging of all organs and tissues also affects fertility: a woman's ability to have offspring is strictly dependent on her age [1,2] mainly due to its negative effect on the oocyte quality and the drop of the ovarian reserve. As a consequence, women undergo irregular cycles, infertility, miscarriages and birth defects.

The most fertile period in women is reached in the first half of the woman's 20s and begins declining in the third decade of life, producing a drastic fall after the 35 years of age [3]. Menopause, known as the cessation of a woman's natural ability to reproduce, usually occurs between the late 40s and early 50s. In fact, the statistical probability of having offspring naturally at age 50 is 0%. Due to all the scientific evidences, in this biological field, women over the age of 35 are usually defined as women of advanced maternal age. This decrease in fertility is clearly visible at 38 according to data published by the HFEA (Figure 1) [3].

However, the women´s age not only affects the ovarian reserve, but also the quality of the oocytes. Our clinical results using oocytes from a donor reflect that the gestation rate among women older than 50 remains equal to that of younger patients (<35 years old) [4]. Further evidence of the decline of the oocyte quality is clearly seen in the rate of aneuploidies when blastocyst biopsy is performed. In our clinic, the data obtained last year showed that the percentage of abnormal embryos is 53.3% in patients of 35 years old, increasing to 95.6% when patients have 44 years old (data from IVI Valencia). This shows that, at least partially, the worsening of oocyte quality is due to meiotic errors [5].

Different studies attempt to explain the relationship between the woman's age and the worsening of oocyte quality. The most highlighted physiological effects are described below:

Chromosomal Abnormalities

A higher incidence of oocyte aneuploidies with increasing female age has been well documented [1,6], mainly due to a nondisjunction [7,8]. In fact, maternal age is the main factor associated with numerical chromosomal aberrations, trisomies in the embryo, lower development potential in pre and postimplantation embryos, and obstetric complications [7,8].

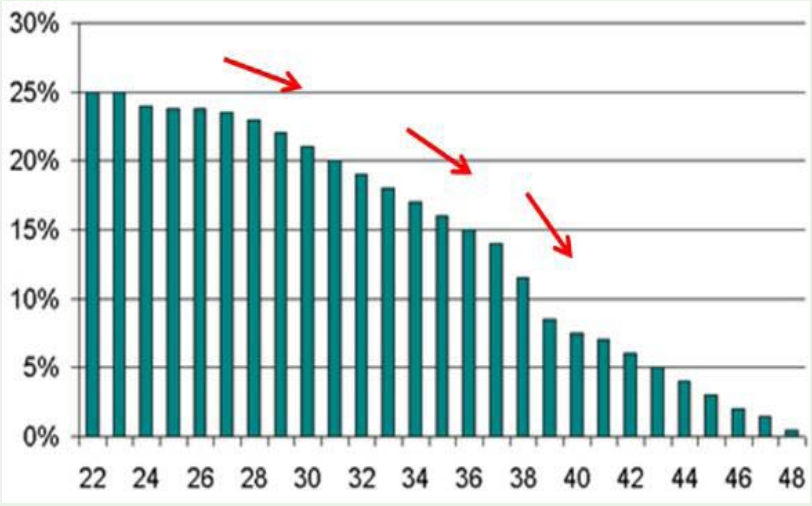

Figure 1: Age (years) versus the probability of getting pregnant (conception probability per month).

In the murine model, oocyte aging (both *in vitro* and *in vivo*) is associated with a higher percentage of oocytes with abnormalities in chromosomal distribution and DNA decondensation [9-12].

Our retrospective experience shows that patients of advanced maternal age (≥40 years old), have a high incidence of aneuploid embryos (85.3%). The rate of aneuploidies in embryos increases with the maternal age, increasing from 79.0% in women aged 40 and over 90% in women over 44 years of age [5,13]. These patients substantially improve their clinical results when undergo a PGD cycle, avoiding the transference of aneuploid embryos that either do not result in gestation or cause an abortion [14].

Alterations in the Redox Potential and Mitochondrial Activity

Alterations related to mitochondrial malfunction that may contribute to anomalous formation of the meiotic apparatus in women of advanced reproductive age have been widely described [15], as well as affecting calcium metabolism or initiating a series of events that end with the atresia of the oocyte. It is believed that this mechanism is especially useful in oocyte atresia during follicular growth. It is known that cytochrome C leakage from nonfunctional or damaged mitochondria is a key factor in the initiation of apoptosis pathways by the activation of caspases. The outer membrane of the mitochondria, as well as the endoplasmic reticulum and the nuclear envelope express Bcl-2 proteins on its surface. It appears that this Bcl-2 protein inhibits the release of cytochrome C, whereas cell death promoting proteins, such as Bax, stimulate the opening of channels causing massive water entry into the mitochondria, causing their death and allowing different factors of the mitochondria to escape (such as cytochrome C). It has been speculated that cellular homeostasis is regulated by a Bcl-2-Bax heterodimer as it would involve the activation of caspase pathways that activate endonucleases that fragment DNA [8]. Conversely, the Bcl-2 protein also helps maintain mitochondrial membrane potential. The mismatch in this potential is accompanied by a release of ROS that is normally controlled by antioxidant systems. Nevertheless, this ability in oocytes from women of advanced reproductive age [1,16] may be impaired.

On the other hand, oocytes from advanced maternal age show the generation of oxidative stress, mainly due to an excess of ROS produced during oocyte metabolism. This oxidative stress has been postulated as one of the major causes of aging of the oocyte and the embryo. This situation triggers changes in other conditions or cell molecules, such as:

1. A lower ability to counteract reactive oxygen species [16], for example by decreasing the intracellular concentrations of the antioxidant system GSH.
2. Lipid peroxidation [17].
3. Opening of ion channels, altering calcium homeostasis causing an increase in cytosolic calcium and producing mitochondrial dysfunction [18,19]. The excess of ROS causes the release of calcium from the endoplasmic reticulum, resulting in a greater mitochondrial permeability. As a consequence, the mitochondrial membrane potential becomes unstable, causing mitochondrial dysfunction and decreasing ATP production. In addition, this increase in calcium often alters different activation or signalling pathways [20].
4. DNA oxidation, mitochondrial DNA damage and lower ability to repair damaged DNA. The levels of 8-oxo deoxyguanosine (8-OHdG), an oxidized derivative of deoxyguanosine, are much higher in oocytes of older women [17].
5. Inadequate cell cycle control. In mice, age has been found to be associated with a higher rate of cell fragmentation and premature release of cortical granules {{225 [10]; 62 [11]; 68 [12]}}, events that have been linked to an inadequate cell cycle control.
6. Gene expression altered depending on maternal age. Changes in gene expression have been found when comparing women of advanced maternal age and young women [21]. Suppressed pathways related to obtaining energy, DNA repair mechanisms, stress response and transcription control were found. In contrast, the expression of different apoptotic markers was found to be increased in older women. Very similar results were obtained by analyzing the gene expression in granulosa cells from women of different age groups [22].

Conclusion

All these evidences show that age implies a decrease in ovarian reserve and oocyte quality and help to explain lower rates of fertilization, lower embryo development, higher aneuploidy rates, higher abortion rates and obstetric complications in reproductively older women, which ultimately translates into lower probabilities of gestation and to have a healthy newborn at home [23].

For this reason, fertility preservation is an increasingly important strategy. It is understood as such to safeguard the gametes due to risking the loss of reproductive capacity, providing an opportunity to conceive and having offspring at a future date [24]. Currently, the preservation of fertility by social causes is increasingly recurrent, as more and more women decide to postpone maternity [25,26]. This is an indication for non-medical reasons per se. The social impact and the ethical connotations of this alternative are worthy of an in-depth debate and analysis.

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