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EMAS position statement: Late parenthood

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ABSTRACT

Introduction: During the last decades, couples in Europe have been delaying parenthood, mainly due to socio-demographic factors that include increased rates of university education and employment in women and poorer financial status.
Aims: The aim of this position statement is to provide and critically appraise evidence on the impact of late parenthood, focusing on the pathophysiology and management of male and female infertility, pregnancy complications and long-term offspring health.
Materials and methods: Literature review and consensus of expert opinion.
Results and conclusions: Advanced parental age is associated with infertility and pregnancy complications and may have an impact on long-term offspring health. All adults of reproductive age should receive counseling on the risks of advanced parental age, so they can make informed decisions about the timing of childbearing. All parents-to-be of advanced age should receive advice on the potential pregnancy, neonatal and long-term offspring health-related issues. These tasks require an interdisciplinary approach that could lead to patient-centered, informed decision-making strategies.

1. Introduction

During the last decades, couples in Europe have been delaying parenthood, with the mean maternal age at first delivery showing an average increase by one year with each decade since the 1970s [1]. A similar increase has been reported with paternal age. There is no universal definition of advanced reproductive age in women, as its effects occur rather as a continuous spectrum than a clear threshold. Advanced age of childbearing has been related to socio-demographic factors, such as increased rates of university education and employment in women and poorer financial status. Additional factors include couple infertility and the development and wide application of contraceptive methods [1]. It has been established that fertility potential declines with advancing age, especially after the mid-30s, alongside with an increased risk of pregnancy complications.

Recently, the Stages of Reproductive Aging Workshop + 10 (STRAW + 10) has been updated, in an effort to describe the reproductive function of the aging woman, improve comparability of studies and facilitate clinical decision-making [2]. Similarly, clinical tools to assess the aging man have been described [3]. Recent developments in the field of assisted reproduction technology (ART)

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provide clinically significant options for the management of infertility in both men and women [4].

The aim of this position statement is to provide and critically appraise evidence on the impact of late parenthood, focusing on the pathophysiology and management of male and female infertility, pregnancy complications and long-term offspring health.

2. Pathophysiology of infertility due to advanced age

2.1. Males

Paternal age has not been recognized as a major concern for fertility, though the first reference on the topic dates from the 1930s [5]. Increasing paternal age is associated with decreasing androgen concentrations, a deterioration of semen quality and an increase in pregnancy complications and adverse outcomes for offspring [6–9].

Late-onset hypogonadism (LOH) has been defined as a series of symptoms in older adults related to testosterone deficiency [10]. It has been estimated that a decline in testosterone concentrations is initiated at approximately 40 or even 30 years of age [11,12].

Similar to women, older men are more likely to have acquired infections affecting fertility or have medical and surgical conditions, such as erectile dysfunction and malignancies. Deterioration in lifestyle, such as lack of physical exercise that leads to obesity, and altered behavior, such as reduced frequency of sexual intercourse, also affect male fertility.

Increasing age in males has been associated with an increasing rate of sperm DNA fragmentation, possibly due to oxidative stress [13]. Loss of apoptosis and a higher frequency of point mutations have also been described. The latter may be due to the fact that the germ cells of the aging male have undergone a large number of mitotic replications, that increases the possibility of errors [8].

2.2. Females

In contrast to men, age has long been recognized as the most significant risk factor for infertility in women. The ovarian reserve diminishes, the hormonal environment is altered and oocyte quality (specifically, chromosomal, morphologic and functional abnormalities) worsens with age. Women of advanced age are more likely to have acquired infections (such as Chlamydia) affecting tubal patency and function or suffer from endometriosis, uterine fibroids and endometrial polyps. Deterioration in lifestyle, such as lack of physical exercise that leads to obesity, smoking, increased alcohol consumption and altered sexual behavior, such as reduced frequency of sexual intercourse, also affect female fertility.

According to data coming from ART studies, oocyte quality seems to be the most significant factor affecting age-related female infertility. Specifically, oocyte mitochondrial function is impaired [14] leading to dysfunction of the meiotic spindle [15]. Mitochondrial dysfunction and oxygen radicals play a key role in reproductive senescence [16]. In contrast, when ART is performed with donor oocytes, recipient age does not significantly affect pregnancy success [17].

Animal experimental models have found that adult ovaries may contain a small number of mitotically active germ cells [18,19], questioning the traditional concept that oocytes are only formed during fetal life and the capacity for germ-cell renewal is lost after birth.

3. Management of infertility due to increasing age

3.1. Males

Infertility in the aging male should be carefully assessed and specific causes should be always sought. Clinical tools have been developed for late-onset hypogonadism (LOH) screening, such as the Saint Louis University Androgen Deficiency in the Aging Male (ADAM) and the Aging Male Symptom (AMS) rating, with a sensitivity of 96% and a specificity of 30% [3]. Due to the low specificity, their use has not been established [20].

Testosterone replacement therapy (TRT) could be considered in men with LOH, as it improves body composition, bone density and fracture rate, sexual function and components of metabolic syndrome [20]. TRT is absolutely contraindicated in men with prostate or breast cancer and untreated obstructive sleep apnea, polycythemia and severe congestive heart failure. Age per se is not a contraindication to TRT [20]. Management of aging men with LOH should include individual assessment of co-morbidities and careful risk versus benefit estimation [12].

ART has been used in cases of subnormal sperm parameters. Intrauterine insemination (IUI) is preferred, especially in milder cases. It has been suggested that IUI should be an option when the total motile sperm count is more than 5 million [21]. In vitro fertilization (IVF) and intra-cystoplasmic sperm injection (ICSI) are the other two options. As ICSI involves the direct injection of a single sperm into the cytoplasm of an oocyte, there is no lower threshold of sperm count. In cases of azoospermia, testicular sperm extraction (TESE) with or without micro-surgical techniques (micro-TESE) could be used in combination with ICSI. An alternative to the use of partner's sperm is artificial insemination with donor sperm (AID).

3.2. Females

Since age is a well-recognized risk factor for infertility, fertility preservation has been suggested to women who wish to postpone childbearing. Appropriate methods include embryo cryopreservation or oocyte cryopreservation, using either slow freezing or vitrification [22,23]. Embryo cryopreservation is the most established technique. Nevertheless, it requires the use of sperm that limits its application to women who have a male partner. If a male partner is not available, oocyte cryopreservation can be used for fertility preservation. Nevertheless, more evidence is needed for oocyte cryopreservation to be first-line option in everyday clinical practice [24], especially for women over 38 years of age [25]. In any case, informed decisions should be based on realistic estimations of the probability of a live birth and legal and social implications should be taken into consideration [25].

Management of infertility should start early. Thus, it has been suggested that a woman should seek medical investigation as soon as six months after regular unprotected intercourse without conception, when 35–40 years of age, and immediately, when over 40 years [26]. Other guidelines suggest an even lower age threshold [27]. Although it was believed that women with polycystic ovary syndrome (PCOS) may have an extended fertile window, recent data do not support this hypothesis [28].

In Europe, there is neither legally defined nor universally accepted upper limit of age for an IVF procedure (Table 1). When cycles are financed by public funds, different limits apply [29]. As an example, in UK there is no legally defined upper limit of age; nevertheless, (partial) financial reimbursement is available only for women undergoing IVF who are under 40 years of age [29]. On clinical grounds, patient characteristics (i.e. duration of infertility), antral follicle count (AFC) as measured by transvaginal