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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

Table 1
Age as a legal eligibility criterion for IVF in Europe.

Country	Age limit (years)
Austria	No limit
Belgium	<45
Denmark	<45
Finland	No limit
France	Child-bearing age
Germany	No limit
Greece	<50
Italy	Child-bearing age
The Netherlands	<45
Portugal	No limit
Spain	No limit
Sweden	Child-bearing age
UK	No limit

Source: [29].

ultrasound and serum concentrations of Anti-müllerian hormone (AMH) and basal FSH can be used to predict ovarian reserve and assist in the decision to pursue or not ovarian stimulation for IVF [30–32].

Active management of age-related infertility is based on ART, including intrauterine insemination (IUI) combined with ovarian stimulation, IVF and intra-cytoplasmic sperm injection (ICSI), with or without oocyte donation. In infertile women over 40 years of age, IVF should be considered as a first-line option [33]. However, older poor responders in IVF have a lower range of pregnancy rates compared with their younger counterparts (1.5–12.7 versus 13–35%, respectively) [34]. IVF success rates decrease with age, being approximately 4–6% for women 42 year-old or older [35]. According to a recent meta-analysis [36], the addition of recombinant luteinizing hormone (LH) to ART cycles may improve implantation and clinical pregnancy rates in women of advanced age in comparison with recombinant FSH-only protocols. Natural (unstimulated) IVF cycles, with frozen-thawed embryo transfer (FET) constitute an alternative option. They have been defined as ART cycles in which the woman does not receive drugs to stimulate her ovaries to produce an excessive amount of follicles; instead, one follicle develops naturally. Natural cycles can be offered in women of advanced age with diminished ovarian reserve and/or poor ovum quality, for whom stimulated IVF cycles are not a realistic option [37].

Optimizing the hormonal environment is of vital importance in all women seeking fertility assistance. However, according to current guidelines [38], universal thyroid function and thyroid autoimmunity screening is not included in the initial evaluation. Nevertheless, it should be considered in women who undergo ART procedures, as ovarian hyperstimulation could significantly affect thyroid function [39,40] and thyroid autoimmunity may lead to miscarriage [41,42]. Metabolic assessment, especially glucose tolerance evaluation by means of fasting plasma glucose or oral glucose tolerance test (OGTT), have to be considered in women of advanced age undergoing ART.

It has been suggested that supplementing the diet of older women with mitochondrial nutrients, such as CoQ10 and r-alpha lipoic acid, may be beneficial, as it could improve oocyte and embryo quality [16]. However, there is insufficient evidence to recommend this.

The use of ovarian stem cells is attracting attention. Studies in mice have shown that these cells can be cultured to a mature oocyte stage in vitro, and when injected into a germ-cell depleted ovary can form follicles and result in the birth of healthy offspring [43,44]. Similar protocols of oocyte maturation by mitotically active germ cells, isolated from ovaries of reproductive-age women have been described, but to date no successful pregnancies have been documented [45,46].

4. Pregnancy complications due to increasing age

4.1. Males

Advanced paternal age has been associated with both miscarriage and fetal chromosomal anomalies [9]. The associated conditions are those caused by single base substitution mutations in the FGFR2, FGFR3 and RET genes, and include Pfeiffer, Crouzon and Apert syndromes, achondroplasia, thanatophoric dysplasia and multiple endocrine neoplasia syndromes (MEN2A and MEN2B) [47]. It has also been suggested that advanced paternal age may have an effect on Down and Klinefelter syndromes [47]. Other associated medical conditions include cardiac defects, developmental disorders, behavioral disorders, neurological disease and cancer [8].

Recently, a genome-wide association study (GWAS) assessed 78 parent-offspring trios and provided evidence that the diversity in single-nucleotide polymorphism (SNP) rate is dominated by paternal age at conception, adding on average two additional mutations per year [7]. On the contrary, a large study on copy number variations (CNV) failed to provide evidence for an association between increased rate of genomic deletions and duplications in the proband and increased paternal age [48].

A second trimester fetal ultrasound, performed between 18 and 20 gestational week, is unlikely to detect medical conditions associated with advanced paternal age. Nevertheless, individualized genetic counseling to address specific concerns should be available to all couples [47].

4.2. Females

Advanced maternal age, traditionally defined as over 35 years of age, is a well-recognized risk factor for pregnancy complications, such as miscarriage, ectopic pregnancy, multiple gestation, and intrauterine growth retardation (IUGR). Cesarean delivery and dysfunctional labor are more common. Fetal and neonatal morbidity and mortality are higher as well [27,49,50]. Since the rate of chromosomal and gene abnormalities as well as congenital malformations is high in offspring of women of advanced age, prenatal diagnostic procedures should be encouraged. Amniocentesis, chorionic villus sampling (CVS) and fetal blood sampling are available options [51]. Non-invasive screening tools for prenatal diagnosis of single gene and chromosomal disorders have also been developed, such as cell-free fetal DNA from maternal plasma. However, for the time being, their use cannot be considered as standard practice [51].

The older pregnant woman is more likely to present with medical conditions that may affect both her own and fetal health, such as pre-existing and pregnancy-related hypertension, and pregestational and gestational diabetes. However, older women may be more resilient and report lower symptoms of depression and anxiety during pregnancy [52]. This is not true for women conceiving through ART, who show high levels of anxiety and more intense emotional attachment to the fetus [52].

5. Offspring long-term health

Both maternal and paternal advanced age has been associated with various conditions and diseases in the offspring. A recent, large, population study demonstrated that offspring born to mothers younger than 25 or older than 35 years of age have worse outcomes, in terms of mortality, self-rated health, height, obesity and number of diagnosed conditions, compared with those born to mothers aged 25–35 years [53].

Except for genetic syndromes, congenital defects and perinatal complications that may affect long-term health, there is recent evidence that advanced parental age is independently associated with offspring health during childhood and later in life, by affecting immune, neuro-developmental, psychological and cognitive parameters [49,54–58]. Specifically, advanced maternal age has been associated with diseases during childhood, such as asthma, leukemia, central nervous system tumors, autism [57], neurocognitive disorders [49] and type 1 diabetes [54]. The risk of diabetes increases by 5% with each 5-year increase in maternal age [54]. Similarly, advanced paternal age has been associated with schizophrenia [58], autism [56], bipolar disorders [55] and cancer [8]. Advanced paternal, but not maternal, age has been strongly associated with increased leukocyte telomere length of the offspring [6], the latter considered to be an adaptive signal of reproductive lifespan.

6. Conclusions

Advanced age in both men and women is associated with infertility and pregnancy complications and may have an impact on offspring long-term health. Increased paternal age may lead to infertility by affecting hormonal and semen parameters, whereas infertility associated to increased maternal age is mainly the result of a combination of low ovarian reserve and poor oocyte quality. In case of pregnancy, both paternal and maternal advanced age are associated to pregnancy complications during early and late pregnancy, as well as to long-term offspring health, by affecting immune, neuro-developmental, psychological and cognitive parameters. Thus, 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. Hormonal assessment and management can provide significant assistance in the management of male and female infertility of advanced age. ART is not an efficient treatment in women of advance reproductive age, who use their own oocytes. All older parents-to-be should receive advice on the potential pregnancy, neonatal and long-term offspring health-related issues. As the latter requires an interdisciplinary approach, patient-centered, informed, decision-making strategies have to be implemented.

7. Recommendations

Males

- Infertility in the aging male should be carefully assessed and the specific causes should be always sought.
- 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.
- Techniques for subnormal sperm parameters include IUI, ICSI, IVF, TESE and AID.

Females

- Women need to be informed that their gametes are finite and their quality deteriorates with time, making pregnancy achievement a task of increasing difficulty as maternal age advances.
- When pregnancy is to be postponed for various reasons, fertility preservation by either oocyte or embryo cryopreservation should be considered.
- IVF, using the woman's own oocytes, is not an efficient treatment modality above 40 years of age, since it is associated with poor pregnancy rates.

Couples

- All older parents-to-be should receive advice on the potential pregnancy, neonatal and long-term offspring health-related issues.
- As late parenthood requires an interdisciplinary approach, patient-centered, informed, decision-making strategies have to be implemented.

Contributors

GM, IL, EMK and DG prepared the initial draft, which was circulated to EMAS board members for comment and approval, production was coordinated by MR and DG.

Provenance and peer review

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Competing interests

None declared.

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