Delayed parenthood and its influence on offspring health: what have we learned from the mouse model†

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Abstract

Delayed parenthood is constantly increasing worldwide due to various socio-economic factors. In the last decade, a growing number of epidemiological studies have suggested a link between advanced parental age and an increased risk of diseases in the offspring. Also, poor reproductive outcome has been described in pregnancies conceived by aged parents. Similarly, animal studies showed that aging negatively affects gametes, early embryonic development, pregnancy progression, and the postnatal phenotype of resulting offspring. However, how and to what extent parental age is a risk factor for the health of future generations is still a subject of debate. Notwithstanding the limitation of an animal model, the mouse model represents a useful tool to understand not only the influence of parental age on offspring phenotype but also the biological mechanisms underlying the poor reproductive outcome and the occurrence of diseases in the descendants. The present review aims at i) providing an overview of the current knowledge from mouse model about the risks associated with conception at advanced age (e.g. neurodevelopmental and metabolic disorders), ii) highlighting the candidate biological mechanisms underlying this phenomenon, and iii) discussing on how murine-derived data can be relevant to humans.

Summary sentence This review summarizes the current state of the art on the impact of parental age on reproduction and offspring health in the mouse and discusses on candidate mechanisms behind the increased disease risks for the offspring in the short, medium, and long term.

Keywords: advanced parental age, mouse offspring, aging, gametes’ quality, pregnancy complication, neurological disorders, metabolic disorders, biological mechanisms

Postponement of parenthood—General considerations

Since the 1970s, a shift toward postponement of parenthood has grown significantly in industrialized countries, due to social and economic factors, such as delays in pursuing economic stability, reduced social pressure, and use of anticonception devices [1, 2]. It is currently estimated that at least 30% of women and 45% of men decide to conceive their first child in their late thirties or later, and these numbers are constantly rising [1–3]. Aging is often associated with a decline in fertility in both women and men, resulting in increased time to conception and miscarriage rate as well as high risk of pregnancy complications [4–6]. In addition, epidemiological evidence suggests an association between parental aging (>35 years) and the occurrence of diseases in the offspring [5–7]. The majority of studies described an increased risk of neurodevelopmental disorders (NDD—e.g. autism and schizophrenia) in children conceived by aged parents, while other adult diseases (e.g. metabolic disorders, cancer) have been poorly investigated so far. Currently, the debate on safety and risks of delayed parenthood is still ongoing. However, it is often difficult to compare results from different human studies due to several confounding factors characterizing enrolled populations, including variable social and economic status, genetic heterogeneity, concomitant pathologies, and parental age.

In addition to human studies, a useful tool to investigate safety and risks of delayed parenthood is the use of short-lived animals, such as the mouse model. Notwithstanding the limitation due to biological differences or experimental bias (i.e. end-points, parental age, sample size), the use of the mouse provides several advantages, as discussed in section 6 [8, 9]. In the following sections, we will provide an overview of the impact of aging on reproductive outcomes and offspring health in mice. Specifically, we will describe the current state of the art on pregnancy outcome and postnatal development of offspring conceived by aged parents (at least 8 months old mice, corresponding to at least ≈40 years in human age [10]). Moreover, we will discuss the current knowledge on the biological mechanisms that have been associated with side effects of conception at advanced parental age.

Delayed fatherhood and its influence on pregnancy outcome and offspring health in the mouse model

Early development and reproductive outcome in pregnancies conceived by aged fathers

The impact of Advanced Paternal Age (APA) on early-life development is still not clearly described. Epidemiological studies on aged men reported reduced fertility, increased risk
of spontaneous miscarriages, and a negative impact of APA on the efficiency of assisted reproductive technologies [6]. Differently, studies on rodents have shown conflicting results [11–15]. The observed discrepancies might be related to the variations in the genetic background and the age of old mice used in different studies. Some authors reported no influence of APA on pregnancy rate, litter size, body weight at birth and weaning, pre-weaning mortality, and sex ratio [11]. Differently, Katz-Jaffe et al. [12] described poor reproductive outcomes, such as reduced in vivo fertilization, poor in vitro development to blastocyst stage, reduced implantation/live birth, and increased miscarriage rate associated with outbred CF1 males at age ≥12 months. Other studies reported that natural conception at APA (12–15 months) resulted in low fetal and placental weight and in increased fetal: placental weight ratio [12, 13]. Furthermore, epigenetic and transcriptomic abnormalities in mouse APA placenta and fetal tissues have been described. For example, Denomme et al. [13] reported the perturbation of the epigenetic profile of the Kcnq1ot1 imprinting control region in mouse placenta conceived at APA. This perturbation was associated with impaired expression of five imprinted gene clusters (Mest, Airn/Igf2, H19, Dlk1/Dio3, and Kcnq1ot1), known to be involved in growth, development, and metabolism. Altered gene expression in APA placenta and corresponding fetal brain was also described by Stankiewicz et al. [14] using microarray analysis. The impaired development and perturbation of epigenetic and transcriptomic profiles in APA placenta and fetuses are indicative of perturbation of developmental programming, which can lead to increased predisposition to postnatal diseases (e.g. NDD, metabolic syndrome) [15]. Collectively, these studies indicate a detrimental influence of paternal age on male gametes leading to a perturbation of developmental programming during in utero life.

**Postnatal development, behavior, and health of mouse offspring conceived by aged fathers**

In the last decade, studies on rodents identified APA as a risk factor for the occurrence of neurodevelopmental/neurological conditions as well as cardio-metabolic and immune disorders in offspring [11, 16–23].

Regarding the neurological health, behavioral abnormalities in APA offspring, such as impaired cognitive functions, reduced sociability, increased repetitive behavior, and/or anxiety-like behaviors, have been observed (see Table 1 for details). In addition to behavioral observations, Foldi et al. [17] reported an altered pattern of cerebral growth in APA male offspring, but not in females. Results indicated that the cerebral cortex was thinner and underdeveloped in APA neonates, while it had an increased volume (mainly in the rostral area) in adult APA offspring, when compared to offspring conceived by young fathers [17]. The observed phenotypes resemble the main traits of some NDD (e.g. autism and schizophrenia) and neurological diseases in humans, thus being in line with epidemiological studies showing a higher incidence of these conditions in offspring conceived by aged fathers.

More recently, other authors focused their attention on various health abnormalities that may be caused by APA. Xie et al. [19] described reduced longevity and increased incidence of aging-associated pathologies (i.e. myocardial fibrosis, muscle atrophy) in mouse APA offspring. Also, increased levels of circulating T cells were described in adult mouse APA offspring [19], suggesting an impairment of the immune system. Furthermore, adult APA offspring displayed alterations in lipid and glucose metabolism [16, 19], such as increased levels of triglycerides and cholesterol, impaired glucose tolerance and insulin action, well-known risk factors for cardio-metabolic disorders (i.e. diabetes, hypertension). Moreover, transgenerational effects of APA were reported for both behavioral and metabolic abnormalities in mouse offspring [16, 21]. Thus, current literature confirms APA as risk factor for neurologica/neuropsychiatric diseases, as shown also by human studies, and suggests an association with cardio-metabolic and immune disorders in adult mouse offspring, and further generations.

**Candidate biological and molecular mechanisms**

In the last few years, scientists have been investigating the changes occurring in the sperm of aged individuals which may influence embryo development and contribute to the increased incidence of postnatal diseases [19, 20, 24–27]. Thus far, the accumulation of de novo mutations and/or epigenetic changes in male gametes has been suggested as the main cause of risk associated with delayed fatherhood [24].

The occurrence of de novo mutations in aging mouse sperm has been poorly investigated while epidemiological and computational studies reported significant increase of mutation rate in human germline, which may be associated with the risk of various diseases [25]. The increased de novo mutation rate in aged sperm may be caused by the so-called “selfish spermatogonial selection”, a mechanism that favors the propagation of spermatogonial cells carrying advantageous mutations and led to the enrichment of the mutant subpopulation over time [26]. Several studies have described the occurrence of epigenetic changes (rather than de novo mutation) in aging mice and their gametes. Milekic et al. [20] reported the loss of methylation at the regions flanking transcription start sites in sperm from aged males and that these changes were i) maintained in the brain of the resulting offspring and ii) associated with an impaired expression of genes involved in the onset of neurological and developmental disorders. Xie et al. [29] identified 484 differentially methylated promoter regions (299 hypermethylated, 185 hypomethylated) when comparing sperm from young and aged mice by reduced representative bisulfite analysis. Pathways analysis for the differentially methylated regions showed significant enrichment of pathways related to senescence, aging, and longevity (such as mTOR signaling, PTEN signaling, IGF1 signaling, p53 signaling, and immunoregulatory processes). Moreover, the epigenetic abnormalities in aged sperm were associated with the differential expression of 459 micro RNAs involved in various pathways including mTOR, insulin, and growth factor signaling. More recently, Yoshizaki et al. [27] described DNA hypomethylation in aged sperm and identified a key role of REST/NRSF binding motifs for the onset of adult disease in APA offspring. Similarly, Zhao et al. [26] reported methylation changes in APA sperm associated with alterations in several autism-associated and glucose metabolism pathways. Furthermore, the epigenetic defects observed in the sperm of aged males can persist in the offspring sperm [20], thus mediating a transgenerational inheritance of APA-induced phenotypes. Other studies suggested that APA side
Table 1. Influence of advanced paternal age on behavioral phenotype of mouse offspring

| Study                     | Strain                  | Father Age  | Behaviors examined                                      | Outcome | Ref. |
|---------------------------|-------------------------|-------------|---------------------------------------------------------|---------|------|
| Yoshizaki et al. (2021)   | C57BL6/J                | >12 months  | Vocal communication                                      | −       | [27] |
| Zhao et al. (2020)        | C57BL/6                 | 12–18 months| Locomotion                                              | −       | [16] |
|                           |                         |             | Sociability                                             | −       |      |
|                           |                         |             | Repetitive                                              | +       |      |
|                           |                         |             | Anxiety                                                 | +       |      |
| Foldi et al. (2019)       | C57BL/6                 | 15 months a | Anxiety                                                 | = a     | [4]  |
|                           |                         | 24 months b | Exploration                                             | = b     | [17] |
|                           |                         |             | Locomotion                                              | −       | [18] |
|                           |                         |             | Learned helplessness                                    | =       |      |
|                           |                         |             | Sensorimotor gating                                     | =       |      |
|                           |                         |             | Repetitive (grooming)                                   | =       |      |
|                           |                         |             | Cognitive function                                      | −       |      |
| Xie et al. (2018)         | C57BL6 J Rj             | > 21 months | Vocal communication                                      | = c,d   | [19] |
| Yoshizaki et al. (2016)*  | WT (C57BL6/JCrj) /      | Sperm from 12 months old | Locomotion                                          | = c     |      |
|                           | Sey/+ mutant           |             |                                                    | + d     | [55] |
|                           |                         |             | Depression                                              | = c,d   |      |
|                           |                         |             | Sociability                                             | = c,d   |      |
|                           |                         |             | Anxiety                                                 | = c,r   |      |
|                           |                         |             | Exploration                                             | =       | [22] |
|                           |                         |             | Locomotion                                              | =       |      |
|                           |                         |             | Learned helplessness                                    | =       |      |
| Janecka et al. (2015)     | C57BL/6                 | 9–12 months | Anxiety                                                 | =       |      |
|                           |                         |             | Exploration                                             | =       |      |
|                           |                         |             | Locomotion                                              | =       |      |
|                           |                         |             | Sensorimotor gating                                     | =       |      |
|                           |                         |             | Sociability                                             | =       |      |
|                           |                         |             | Learning and memory                                     | =       |      |
|                           |                         |             | Vocal communication                                      | +       |      |
|                           |                         |             | Locomotion                                              | =       |      |
|                           |                         |             | Exploration                                             | −       | [21] |
|                           |                         |             | Sociability                                             | −       |      |
|                           |                         |             | Social novelty                                           | −       |      |
|                           |                         |             | Anxiety                                                 | +       |      |
|                           |                         |             | Repetitive behavior                                     | +       |      |
|                           |                         |             | Anxiety                                                 | +       |      |
|                           |                         |             | Locomotion                                              | =       | [17] |
|                           |                         |             | Exploration                                             | +       |      |
|                           |                         |             | Sociability                                             | −       |      |
|                           |                         |             | Learned helplessness                                    | =       |      |
|                           |                         |             | Sensorimotor gating                                     | =       |      |
|                           |                         |             | Exploration                                             | −       | [23] |
|                           |                         |             | Locomotion                                              | =       |      |
|                           |                         |             | Sociability                                             | −       |      |
|                           |                         |             | Avoidance learning                                      | −       | [11] |

Table 1: Summary of behavioral abnormalities in mouse offspring conceived at advanced paternal age. = normal behavior, − reduced behavior, + increased behavior, c,r. – contrasting results, * offspring produced by IVF.

effects may be mediated by i) the impaired expression of Ace-1, Prmt1 and 2, Smcp, genes involved in spermatogenesis and fertility [12], and ii) DNA damages induced by oxidative stress [28].

In addition, the influence of paternal aging on offspring development and health may be mediated by the seminal plasma [29]. The seminal plasma is a complex medium, containing several molecules (e.g. nutrients, proteins, signaling molecules, cell-free genetic material), that participate in the transport of sperm along the female reproductive tract. It has been shown that these molecules regulate various processes in the female reproductive tract (e.g. the recruitment of dendritic cells and neutrophils into the uterine tissues, the priming of regulatory T cells, remodeling of the uterine vasculature, regulation of maternal immunological responses to paternal antigens), which are crucial in early development, pregnancy progression, and postnatal health and well-being of the offspring [29, 30]. So far, it is known that seminal plasma quality can be affected—for example—by lifestyle and diet [29, 30], while further studies are necessary to verify how and whether age can influence seminal plasma composition and its potential effects on APA embryos/offspring in the short, medium, and/or long term.
Delayed fatherhood, reproduction, and offspring health: Take-home message

The previous paragraphs summarize the outcome of the studies investigating the influence of aging in male mice on reproduction and the health of offspring. When looking at spermatozoa, there are minor discrepancies on the influence of age on qualitative and quantitative sperm parameters (e.g., morphology, concentration, motility) among studies. These may be due to the experimental designs, i.e., differences in the mouse strain used, age cutoff, methodology, environmental conditions, and/or health status of individual animals. However, several studies indicate that aging is correlated with a decline of sperm quality that may interfere with male reproductive potential and early embryonic development [11–15]. The cited studies on post-implantation and postnatal development collectively support the idea that conception at APA is associated with i) low reproductive potential and high risk of pregnancy loss [11–15] and ii) predisposition to adult diseases, in particular NDD [16–23]. The correlation between APA and increased predisposition to other diseases (e.g., cardiometabolic disorders) has been suggested. Indeed, more studies are needed to support (or deny) these findings. Among the mechanisms behind the side effect of APA, available data can be interpreted to suggest that accumulation of de novo mutation and epigenetic abnormalities in sperm is the main mechanism behind the effects of APA on reproduction and offspring health [19, 20, 24–26]. On the other hand, the extent to which APA may affect seminal plasma quality and impact reproductive performance should also be investigated. Current literature suggests that seminal plasma has an important reproductive function [24–29]; however it is not clear yet whether age has an influence on the seminal plasma features, resulting in perturbation of offspring pre- and postnatal development [24–29].

Delayed motherhood and its influence on pregnancy outcome and offspring health in mouse model

Early development and reproductive outcome in pregnancies at advanced maternal age

Decline of female reproductive functions over time is characterized by a decrease in oocyte reservoir, low oocyte quality, and high risk of pregnancy loss or complications, as widely described in several mammalian species [31–40]. Mouse models showed that aged females (>10 months old) are able to produce progeny, however pregnancies are characterized by smaller litter size and increased rate of complications/pregnancy lost when compared to pregnancy outcome in young females [32–34].

Regarding early embryonic development, Velazquez et al. [32] described i) decreased fertilization rate in oocytes from aged females but no differences in the ovulation rate and ii) reduced total number of cells (mainly trophoderm) in the blastocysts from aged females. Other studies reported that oocytes from aged females displayed deterioration of mitochondrial function and energy production as well as reduction of telomere lengths, which have a negative impact on oocytes’ quality and, subsequently, on early embryo development [35–37]. These studies confirm the decline of female gamete quality with aging leading to detrimental effects on embryonic development.

Regarding post implantation development, an association between AMA and increased risk of pregnancy complications (such as pregnancy loss and fetal malformations, impaired placental development, difficulties in spontaneous parturition, and low birth weight) has been widely described [33, 34, 38–40]. For example, Woods et al. [40] showed that at least two-thirds of fetuses conceived by aged mothers were characterized by fetal growth retardation, cardiac edema, brain and neural tube defects, as well as vascular defects (e.g., dilated dorsal aorta and/or major brain artery). When looking at placental development, reduced number of trophoblastic giant cells in the junctional area of 18.5-day post coitum placentae from aged females suggests an impaired ability to establish a functional feto-maternal interface [39]. In another study, impaired fetal development in AMA pregnancy was associated with placental defects (such as reduced size of the fetal trophoblast-derived portion and abnormalities in placental labyrinth) and perturbation of placental transcriptome [40]. Also, impaired proinflammatory T-cells response has been described at the maternal-fetal interface in aged females [37, 39], which can contribute to difficulties during parturition in AMA pregnancies. Altogether these studies demonstrate a reduced fertility of aged females and the high risk of pregnancy abnormalities/complications that may compromise developmental programming and in utero life and, later, affect the health of adult offspring (see section 3.2).

Postnatal development, behavior, and health of mouse offspring conceived by aged mothers

As described above, AMA is associated with increased delivery complications and perinatal mortality as well as with reduced body weight at birth [33, 38], which per se are known risk factors for adult diseases [15]. Available data on postnatal development indicate an increased risk of cardio-metabolic and neurological disorders in AMA offspring [32, 33, 38, 39, 41, 42]. Some authors reported that AMA offspring displayed high blood pressure, indicative of predisposition to cardiovascular diseases [32]. Also, altered T-cell phenotypes, which may suggest abnormalities in the immune system, have been reported in AMA offspring [38]. Velazquez et al. [32] observed increased body weight and impaired glucose metabolism in adult female AMA offspring [32]. These findings are indicative of an increased risk of cardio-metabolic disorders in offspring conceived by aged mothers, mainly in female offspring. Other studies showed impaired cognitive function, locomotion, and anxiety in AMA offspring (see Table 2), which may suggest an increased risk of neuropsychiatric diseases in adulthood [33, 39, 41, 42]. In addition, Sampino et al. [33] described altered patterns of gene expression in the hippocampus of adult male AMA offspring. Thus, the data published so far suggest a negative impact of conception at AMA on the health status of mouse offspring. However, further studies are necessary to confirm those findings and to better characterize how and to what extent AMA influences the health status of mouse offspring, thus contributing to the onset of various diseases in adult mice.

Candidate biological and molecular mechanisms

The poor reproductive outcome and the risk of postnatal diseases in offspring due to AMA, described in the paragraphs above [31–42], have been associated with poor quality of
aging oocytes (i.e. increased chromosome aberrations, mutation, epigenetic defects), as well as with suboptimal uterine support to fetal development [34–45].

Available data suggest that aging-related abnormalities in the hypothalamic–pituitary–ovarian axis may negatively affect both the female gametes and the uterine environment [34, 40, 43, 44]. Other studies described that aged-females’ oocytes are characterized by karyotypic imbalances, high aneuploidy rate, as well as epigenetic, transcriptomic, and proteomic abnormalities [34, 43, 44], which might explain the low gamete quality and competence as well as the reduced developmental potential of resulting embryos. Microarray-based gene expression analysis showed that 5% of MII oocyte transcripts were affected by female age and that several differentially expressed transcripts were associated with epigenetic modifications, such as DNA-methyltransferases and DNMT-associated protein-1 [43, 44]. Other authors reported abnormalities in the proteomic profile of aged oocytes [45]. In particular, aged oocytes were characterized by reduced abundance of proteins linked with the nucleus and oxidative stress/damage, which may contribute to the increased rate of aneuploidy previously reported by others [44]. More recently, Woods et al. [40] described that the age-related reproductive decline was mainly due to impaired decidualization and placentation defects. In this study, authors described that pregnancy in old females was characterized by defective fetal-placental development. However, following transfer of embryos from old females into young recipients, the development of both embryo and placenta was largely restored.

These studies showed that the low reproductive potential of aged female mice is associated with the combination of low gametes quality and abnormal uterine environment, which may interfere with developmental programming of the early embryo/fetus and negatively affect the health of the new individual in the short, medium, and long term.

**Delayed motherhood, reproduction, and offspring health: Take-home message**

The previous paragraphs summarize the current state of the art on the effects of AMA on maternal reproduction and the health of offspring conceived by old females. The general finding is that conception at AMA is associated with i) low reproductive potential and high risk of pregnancy complication due to low gametes’ quality and sub-optimal uterine environment [32–40, 43–45] and ii) a potential predisposition of the offspring to adult diseases [31, 32, 38, 39, 41, 42]. While the long-term effects of AMA have been widely confirmed in mice, further research is needed to explain underlying etiologies and causality. As female aging perturbs both gamete and uterus, future studies should better focus on discerning the effects of genetic/epigenetic perturbation carried by the oocyte from those abnormalities occurring in the uterine environment.

### Transgenerational effects of advanced parental age

In recent years, the dogma of genetic inheritance and our understanding of disease susceptibility have been revolutionized by the extensive evidence supporting the key role of parental environment in the transmission of information across subsequent generations [46]. Several studies described that various factors (e.g. diet, exposure to toxicants, early life stress) have an impact in shaping the descendants’ phenotype beyond the direct progeny [47–49]. Similarly, the multisystem pathology associated with aging may represent a triggering factor causing transgenerational adaptation and the appearance of altered phenotypes in subsequent generations. Recent epidemiological studies in humans reported that the grandfather’s age is associated with an increased risk of autism and schizophrenia, independently from paternal or maternal age [50, 51]. Concurrently, a previous study has corroborated this observation in mice, as both the offspring and the grand-offspring of old males were characterized by autism-like behaviors [21]. Moreover, Zhao et al. [16] confirmed the presence of autism-like disorders and observed aberrant glucose metabolism in the first and second generations conceived by old male mice. On the other hand, the effects of grand-maternal age on the descendants’ phenotype have received less attention in mice, while studies in insects and other taxa have provided consistent evidence of transgenerational influences of maternal aging on lifespan, reproductive fitness, and other phenotypic traits [52–54]. Aging negatively affects both male and female gametes [20, 26, 44, 45], thus directly modifying the genetic or epigenetic information inherited by the descendants. Moreover, when a mother is exposed to an environmental insult, such as aging, her offspring’s germline (which will give rise to the F2 generation) may be directly reprogrammed thus causing intergenerational effects [46, 52–54]. Those effects may also extend to the F3 generation and beyond, giving rise to a true transgenerational inheritance, which occurs when the F2 germline is not directly exposed to the aged maternal body.
In summary, the current state of the art from murine studies corroborate the concept of the transgenerational inheritance of diseases [55–57] for the conception at APA, while further investigations are needed for AMA. Future studies would be useful to understand whether the effects of parental aging may affect further generation that the F2.

The mouse as a model organism for human

The mouse has been considered as an excellent animal model for human diseases for many decades. More recently the validity of the murine model and how it can be relevant to humans has been a subject of debate. Biological research is generally based on the “biological unit” concept, suggesting that what is true in mouse must also be true in human or other species. However, we have learnt that even if genetic regulatory mechanisms and other basic biological processes have a common evolutionary origin, they might have undergone specie-specific adaptions during evolution and thus not being anymore fully conserved among species. For example, even if human and murine genomes are similar, they do not completely overlap. Indeed, there are several DNA variations linked to diseases that are not comparable between humans and mice [reviewed in 58, 59]. Also, there are differences in physiology and metabolism between mouse and human [reviewed in 60]. These aspects must always be considered when designing preclinical studies, as well as while drawing conclusion and translating results to human.

Notwithstanding the limitation of an animal model, the mouse still provides several advantages:

- a defined genetic background;
- the possibility to work under well-defined and controlled experimental conditions, thus reducing confounding factors (e.g. genetic, lifestyle, concomitant pathology, subfertility);
- the wide availability of validated and reliable behavioral, anatomical and functional phenotyping methods, which have high translational validity. For example, although the lack of higher mental functions, typical of the human species, the mouse shows quantitative phenotypes called intermediate traits or endophenotypes comparable to human ones. These traits can be present in prodromal and active stages of the disease and can be more frequent than the full disorder [61–65];
- short inter-generational intervals.

Thus, data from murine model can provide useful information to understand the etiology of diseases and to establish tools and biological markers to be applied in human research and clinic.

Concluding remarks

The present review provides an overview of i) the impact of parental age (maternal and paternal) on reproduction and offspring health in the murine models, and ii) the candidate mechanisms behind the increased disease risks for offspring health in the short, medium, and long term (Figure 1). To the extent that the current trend toward parenthood postponement is unlikely to be reversed, it is necessary to understand risks associated with it. Further research and large-population studies are needed to improve our understanding of the consequences of delayed parenthood and the underlying mechanisms. Current literature strongly supports the causative link between parental age and NDD, while the potential risk of
other diseases (e.g., immune or cardiometabolic disorders) due to parental age has not been fully exploited. Thus, focused and well-designed studies need to be implemented to i) verify the causal link between the occurrence of immune disorders, cardiometabolic disorders, cancer in the offspring conceived by age parents, and ii) to understand the etiological mechanisms leading to the increase incidence of a specific diseases. Through focused studies, it will be possible to provide exhaustive answers and, consequently, contribute to advance our knowledge in this research area, to offer the best counselling plan to couples planning to conceive a child and establish preventive strategies to improve health and quality of life in the offspring from aged parents.

Authors’ contribution

FZ worked on conception of the work, writing—drafting the article; SS did the writing—drafting and critical revision of the article; AC did the writing—critical revision of the article; MZ worked on writing—critical revision of the article, and TS did the writing—drafting the article; SS did the writing—critical revision of the article, and FZ worked on conception of the work, writing—drafting the article; All authors approved the final version to be published.

Conflict of interest

Authors declare no conflict of interest.

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