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REVIEW

Effect of advanced parental age on pregnancy outcome and offspring health

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Abstract

Purpose Fertility at advanced age has become increasingly common, but the aging of parents may adversely affect the maturation of gametes and the development of embryos, and therefore the effects of aging are likely to be transmitted to the next generation. This article reviewed the studies in this field in recent years.

Methods We searched the relevant literature in recent years with the keywords of "advanced maternal/paternal age" combined with "adverse pregnancy outcome" or "birth defect" in the PubMed database and classified the effects of parental advanced age on pregnancy outcomes and birth defects. Related studies on the effect of advanced age on birth defects were classified as chromosomal abnormalities, neurological and psychiatric disorders, and other systemic diseases. The effect of assisted reproduction technology (ART) on fertility in advanced age was also discussed.

Results Differences in the definition of the range of advanced age and other confounding factors among studies were excluded, most studies believed that advanced parental age would affect pregnancy outcomes and birth defects in offspring.

Conclusion To some extent, advanced parental age caused adverse pregnancy outcomes and birth defects. The occurrence of these results was related to the molecular genetic changes caused by aging, such as gene mutations, epigenetic variations, etc. Any etiology of adverse pregnancy outcomes and birth defects related to aging might be more than one. The detrimental effect of advanced age can be corrected to some extent by ART.

Keywords Advanced age · Adverse pregnancy outcomes · Birth defect · ART

Introduction

In modern society, due to the demand of the labor market, the progress of contraceptive methods, the extension of life expectancy, and the promotion of assisted reproductive technology, it has become increasingly common for humans to postpone childbearing. However, fertility is often lower at advanced age. According to the data from The National Bureau of Statistics of China (data.stats.gov.cn/), between 2003 and 2015 (except 2010), the fertility rate dropped significantly for pregnant women ≥35 years old (Fig. 1). Simultaneously, people were paying attention to the impact of late motherhood on the health of their children. A retrospective study found that from 2001 to 2010, the proportion of older women receiving prenatal diagnosis increased from 20% to 46% in China [1]. This trend will inevitably lead to a sharp increase in the number of fathers with advanced age.

In most countries, the generally accepted definition of advanced maternal age was ≥ 35 years. Although some studies pointed out that the father's age (≥ 50 years old)

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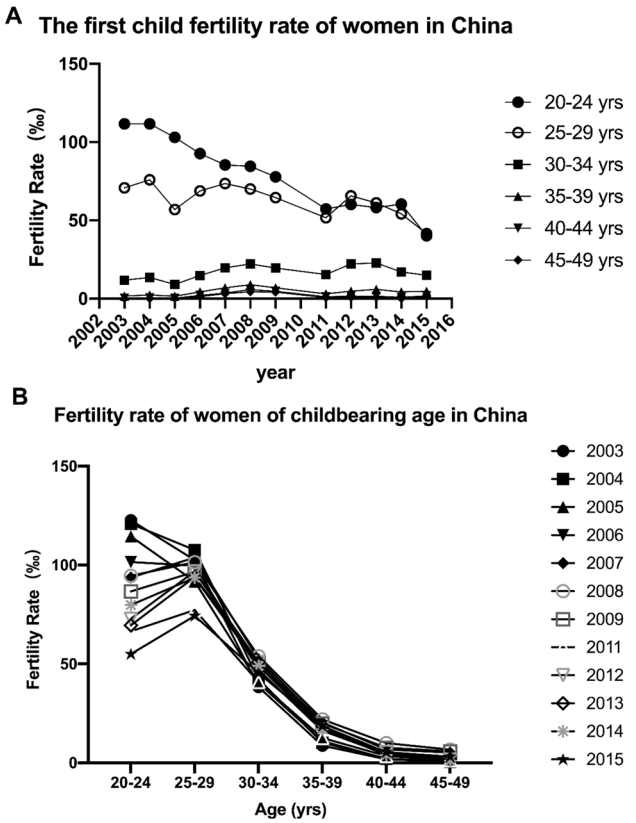

Fig. 1 **a** The fertility rate of women of all ages at the time of birth of their first child from 2003 to 2015. **b** The average fertility rate for women of different ages from 2003 to 2015 (All data comes from data.stats.gov.cn/, except 2010)

might be related to the increased incidence of some specific deformities in offspring, there was no unified standard to define the critical advanced age for men to receive genetic counseling [2, 3].

Many studies have shown the relationship between advanced parental age and many adverse pregnancy outcomes and offspring health [4–6]. However, it was necessary to sort out the effects of advanced age on different types of adverse pregnancy outcomes and offspring health, as well as explore the causes of these risks induced by advanced age in combination with the current mechanistic studies on pregnancy at advanced age. Finally, whether the problems encountered in pregnancy at advanced age can be solved with the help of ART was still not outlined. In this review, we would summarize the key issues above.

The influence of parents' advanced age on pregnancy outcome

Pregnancy outcome was the final result of a fertilization event. The good type of pregnancy outcome was full term live birth, and the adverse pregnancy outcomes were stillbirth, spontaneous abortion, abortion, preterm birth, low birth weight, macrosomia, and other congenital abnormalities.

Male

Although the average age of men who are first time fathers is increasing, there are still few studies on the influence of paternal age on pregnancy outcomes, and the definition of paternal aging is not the same in each study. The research of Zhu JL et al. [2] showed that the age factor might be related to the incidence of preterm delivery after 25 years old. Other studies, however, took 35 [7–9], 40 [10–15], 45 [16–21], and 50 [22–24] years old as the age threshold, respectively. Some studies revealed that male age was the influential factor for spontaneous abortion [7, 8, 10, 11, 17, 22], stillbirth [12, 14], preterm birth [2, 15, 18, 20, 21], low birth weight [9, 20, 21], late fetal death [16], and low Apgar score [19, 20]. While several other studies showed that age may not contribute to preterm delivery [13, 23–26], low birth weight [13, 23, 25, 27], small-for-gestational-age births [13], low Apgar score [13], neonatal or post-neonatal mortality [13], fetal growth restriction [26], and neonatal intensive care unit (NICU) admission [26]. Three studies did not specify a clear definition of advanced paternal age, but they also believed that age did not lead to a high incidence of adverse pregnancy outcomes [25–27]. Slama et al. [7] discovered when the mother's age is less than 30 years, the effect of the father's age on pregnancy outcome was positive. Tough et al. [23] showed that for women with low fertility risk, male age did not have an adverse effect on pregnancy outcome, but male age increased the adverse pregnancy outcome of multiparous women (Table 1). In summary, the definition of advanced paternal age remains unclear at present, and it was also controversial whether advanced paternal age was definitely related to the occurrence of various types of adverse pregnancy outcomes. Therefore, it was necessary to determine the relationship between advanced paternal age and adverse pregnancy outcomes through large-scale epidemiological studies. At the same time, most studies of advanced paternal age failed to pay attention to maternal pregnancy age, which might be a confounding factor on pregnancy outcomes.

The reason for these adverse pregnancy outcomes might be related to reduced semen quality [28]. The main reasons why advanced age affects sperm quality are as follows. First,

Table 1 The effect of advanced paternal age on pregnancy outcome

Correlation	Type of pregnancy outcome	Male age (yrs)	Year	Author
Positive	Spontaneous abortion	≥40	2002	de La Rochebrochard , et al. [10]
		≥35	2003	Slama R, et al. [7][a]
		≥35	2005	Slama R, et al. [7]
		≥40	2006	Kleinhaus K, et al. [11]
		>45	2007	Maconochie N, et al. [17]
		>50	2019	Nguyen BT, et al. [22]
	Still birth	≥40	2004	Astolfi P, et al. [18][b]
		>40	2017	Urhoj SK, et al. [12]
	Preterm birth	>25	2005	Zhu JL, et al. [2]
		≥40	2005	Astolfi P, et al. [14]
		>45	2006	Astolfi P, et al. [14]
	Low birth weight	≥35	2006	Reichman NE and Teitler JO [9]
	Late fetal death	>45	2004	Nybo Andersen AM, et al. [6]
	Low Apgar score	>45	2006	Sun Y, et al. [19]
	Preterm birth, low birth weight, low Apgar score	≥45	2018	Khandwala YS, et al. [20]
	Preterm birth, low birth weight, very preterm birth	>45	2012	Alio AP, et al. [21]
Negative	Preterm birth, low birth weight, small-for-gestational-age births, low Apgar score, neonatal or post-neonatal mortality	≥40	2008	Chen XK et al. [13]
	Preterm birth, low birth weight		2002	Abel EL, et al. [25]
		>50	2003	Tough SC, et al.[c] [23]
	Preterm birth	≥50	2006	Basso O and Wilcox AJ [24]
	Low birth weight		2003	Nahum GG and Stanislaw H [27]
	preterm birth, fetal growth restriction, NICU admission		2017	Hurley EG, et al. [26]

[a]Women age<30 yrs

[b]Women age ≥30 yrs, when women age are 30~34 yrs, the adverse can be modified

[c]Negative for low risk women / Positive for women with multiple births

the sperm development microenvironment would change with aging. For example, Leydig and Sertoli cells, which have important functions for spermatogenesis, would be affected by environmental alterations and reduced in number. Second, advanced age influences the male hormone levels dramatically, such as an increase in the serum follicle-stimulating hormone (FSH) levels [29] and a decrease in the concentration of androgen and sex hormone binding globulin (SHBG) [30], which also led to the problems of sperm quality. Third, abdominal obesity, erectile dysfunction [31], as well as gonad infection [32] also increase in men with advanced age, all these factors might lead to the occurrence of poor sperm quality. As is well known, the genetic and epigenetic messages in gametes are transmitted into offspring after fertilization [33, 34]. Sperm quality problems continue in embryos and eventually cause many adverse pregnancy outcomes such as spontaneous abortion, premature delivery, and stillbirth due to abnormal embryo quality during pregnancy.

Female

The female reproductive system not only produces gametes but also host fertilization, implantation, and development of the fetus in fallopian tubes and uterus during pregnancy. In the past decade, most of the studies about older women and pregnancy outcomes revealed that maternal age was often associated with miscarriage [35–38], preterm birth [36, 39–64], stillbirth [45, 51, 52, 55, 56, 60, 65–70], low birth weight [42, 43, 47, 49–53, 56, 60, 71–73], neonatal death [40, 51, 52, 60, 65, 68], perinatal neonatal death [40, 52], low Apgar score [43, 60, 65, 74], small for gestational age [35, 37, 40, 42, 57, 67, 75], large for gestational age [55, 75], macrosomia [43, 51, 55, 76], intrauterine growth restriction [43, 73, 76], NICU admission [43, 52, 61, 65], and post-term birth [50]. It was generally recognized that advanced maternal age referred to women over the age of 35, but the age threshold can be raised to 40, 45, or even 50 years to consider age as a risk factor for pregnancy, and that the incidence of adverse pregnancy outcomes were positively related with age [46]. However, other studies have also shown that a maternal age ≥30 was closely related to

adverse pregnancy outcomes [40, 43, 51, 68]. In the meantime, the researchers also noted that maternal age was not an independent risk factor for poor pregnancy outcomes, other factors, such as education level, singleton or twin, number of pregnancies, paternal age, and previous health status should be excluded from the analysis [41, 47, 50, 68, 73]. After excluding these confounding factors, Ankarcrona et al. [77] concluded that the women with advanced age were not associated with the occurrence of low Apgar score. Kanmaz et al. [78] showed that advanced age did not increase the risk of adverse pregnancy outcome, but instead increased the probability of having pregnancy complication. Some studies suggested that advanced age was not necessarily associated with all adverse pregnancy outcomes. As Zhu et al. [46] stated in a retrospective study on twin births, women ≥ 35 years were associated with preterm birth, but not with neonatal adverse outcomes and stillbirth. Frederiksen et al. [36] suggested that advanced age was associated with miscarriage and preterm birth, but not increased risk of stillbirth. Khalil et al. [37] showed that women ≥40 years were associated with miscarriage, low gestational age, but not with stillbirth, spontaneous preterm birth, and large gestational age neonates. In addition, the risk of adverse pregnancy outcomes was also different at different age stages. Hsieh et al. [60] considered women ≥35 years to be related with early preterm delivery (before 34 weeks of gestation), a birth weight <1500 g, low Apgar scores, fetal demise, and neonatal death. When women are ≥40 years, preterm delivery (before 37 weeks of gestation) becomes a new risk factor (Table 2). In summary, there were more studies on the correlation between advanced age and pregnancy outcomes in women than that in men. Although different studies had different results in some types of adverse pregnancy outcomes, the relationship between advanced maternal age and adverse pregnancy outcomes was more definite overall.

On the one hand, advanced maternal age led to oocytes quality problems. There were many causes of decreased oocyte quality in advanced age. For example, problematic meiotic spindles occurred more frequently in aged oocytes, resulting in embryos with abnormal chromosome segregation. As a result, the embryo could not be implanted or it will be aborted naturally [79, 80]. On the other hand, the adverse pregnancy outcomes of older women such as miscarriage and stillbirth, might be related to placental dysfunction. Vascular dysfunction in older women led to insufficient perfusion of uterus and placenta [81]. In addition, other metabolic dysfunctions that were caused by abnormal pancreas islet function at an advanced maternal age could induce chronic diseases such as gestational diabetes, eclampsia, and aggravate placental problems during pregnancy [62, 82]. Even if the fetus could continue to grow in the uterus, there might be intrauterine growth restriction, adverse neonatal or perinatal neonatal outcome [83]. In addition to the uterine hemodynamics, the aging of the myometrium in older women also led to impaired myometrium contractile, prolonging the process of labor. Abnormal uterine action not only increased the incidence of cesarean delivery (CS), but also led to adverse neonatal outcomes such as low Apgar score, NICU admission, and even neonatal or perinatal death [84].

Parents' advanced age leads to birth defects of their offspring

The concept of birth defects was usually difficult to define, as it included a variety of different diseases, such as neonatal chromosome ploidy abnormalities, monogenic genetic diseases, some congenital diseases, behavioral characteristics, and mental disorders. The correlation between advanced age and the risk of birth defects remains controversial, but the incidence of many well-defined syndromes did increase with age [85].

Chromosome aneuploidy in offspring

Aneuploidy was mainly caused by non-disjunction of chromosomes of the gametes during meiosis, and it was often fatal. Trisomy was the most common type of chromosome aneuploidy.

Male

The effect of paternal age on chromosome aneuploidy was still controversial [86, 87]. A study had shown that there was no significant correlation between paternal age and multiple aneuploid forms (haploid, triploid, partial deletion/duplication) in donor oocyte cycle [88]. Another study showed that when the female partner was older than 35 years old, the paternal age would have significant effects on the incidence of Down syndrome [89]. With regard to Klinefelter syndrome (47, XXY chromosome karyotype of offspring), studies have shown that 50% of the causes were attributed to a male factor [90], but whether it was related to the age of the male partner was unknown [91–93]. Another study of Klinefelter syndrome found that older men were more likely to produce XY sperm [94]. The chromosome abnormality in men with advanced age might be related to the mitotic activity of spermatogonia. Unlike the oocyte, the formation of spermatozoa in men would not be interrupted and lasts a lifetime. In adults, the process of spermatogenesis had 23 mitoses per year, spermatogonia in a 35-year-old man might have undergone 540 mitoses, and the number of mitoses at high frequencies led to an increased risk of transcriptional errors in DNA with age [95, 96]. DNA replication occurred before each cell division, and mutations were usually caused

Table 2 Influence of advanced maternal age on pregnancy outcome in recent 10 years

Type of pregnancy outcome	Female age (yrs)	Year	Author
Lower birthweight	39±3.22	2020	Yin O, et al. [71]
Still birth, neonatal death (up to 28 days), Apgar score at 5 minutes <7, NICU admittance for at least 24 hours	≥40	2020	Kortekaas JC, et al. [65]
Repeated abortion	>35	2019	Casteleiro A, et al. [38]
Preterm birth	>40	2019	Londero AP, et al. [39]
Iatrogenic prematurity	≥45	2019	Claramonte Nieto M, et al. [63]
Preterm birth, small for gestational age, neonatal mortality and postneonatal mortality	≥30	2019	Schummers L, et al. [40]
Preterm birth	≥35	2019	Schildberger B, et al. [41][a]
Small for gestational age, low birth weight, preterm birth	≥35	2019	Koshida S, et al. [42]
5-minute Apgar score <7	>40	2019	Ankarcrona V, et al. [77][b]
Birth weight less than 2500 g	>40	2019	Marozio L, et al. [72]
5-minute Apgar score <7, perinatal mortality, post-term pregnancy	>35	2019	Kanmaz AG, et al. [78][b]
Preterm birth	>40	2018	Fuchs F, et al. [62]
Small for gestational age infants, spontaneous late preterm delivery	≥35	2018	Kahveci B, et al. [35]
Preterm birth, Low birthweight, Macrosomia, Intrauterine growth restriction, Apgar score < 7 at 5 minute, NICU admission	≥30	2018	Shan D, et al. [43]
Small for gestational age, stillbirth, and intrauterine fetal death	>45	2018	Arya S, et al. [67][c]
Intrauterine fetal death, preterm birth	>50	2018	Khatibi A, et al. [45]
Preterm birth	≥35	2018	Zhu C, et al. [46][d]
Miscarriage, and birth before 34 weeks of gestation	≥35	2018	Frederiksen LE, et al. [36][e]
Low birth weight, preterm birth	≥35	2017	Goisis A, et al. [47][a]
Still birth	≥35	2017	Lean SC, et al. [66]
Preterm birth	≥45	2017	Ogawa K, et al. [48]
Iatrogenic and spontaneous preterm delivery	≥48	2017	Fitzpatrick KE, et al. [44]
Fetal death and infant death	≥30	2017	McLennan AS, et al. [68][a]
Apgar score < 7 at 5 minute	40-49	2017	Cakmak Celik F, et al. [74]
Intrauterine growth retardation, fetal macrosomia	≥40	2016	Zapata-Masias Y, et al. [76]
Prematurity, low birth weight	≥45	2016	Haslinger C, et al. [49]
Antepartum stillbirth	≥35	2016	Walker KF, et al. [69]
Preterm births, post-term births, low birth weight	≥41	2015	Almeida NK, et al. [50][a]
Small or large for gestation age infants	>35	2015	Schimmel MS, et al. [75][f]
Preterm birth	≥35	2015	Fall CH, et al. [64]
Macrosomia, stillbirth, preterm birth, neonatal death, and low birth weight	>30	2014	Weng YH, et al. [51]
Preterm birth, stillbirths, early neonatal mortality, perinatal mortality, low birth weight, and NICU admission	≥35	2014	Laopaiboon M, et al. [52]
Preterm birth, and both low and very low birth weight infants	≥40	2014	Barton JR, et al. [53]
Preterm birth	>45	2014	Mehta S, et al. [54]
Miscarriage, small-for-gestational age neonate	≥40	2013	Khalil A, et al. [37][g]
Stillbirth, preterm birth, very preterm birth, Macrosomia, extremely large for gestational age	≥40	2013	Kenny LC, et al. [55]
Stillbirth, preterm birth and low birth weight	≥45	2013	Carolan M, et al. [56]
Small for gestational age infants, preterm birth	>35	2012	Ludford I, et al. [57]
Preterm birth	≥45	2012	Laskov I, et al. [58]
Intrauterine fetal death	≥40	2011	Ohana O, et al. [70]
Spontaneous preterm labor	≥40	2011	Kathiresan AS, et al. [59]
Intra uterine growth restriction, low birth weight	≥35	2011	Salem Yaniv S, et al. [73][a]
Early preterm delivery (before 34 weeks of gestation), a birth weight <1500 g, low Apgar scores, fetal demise, and neonatal death	≥35	2010	Hsieh TT, et al. [60][h].
Preterm birth, NICU admission	≥50	2010	Yogev Y, et al. [61]

[a]Maternal age should not be assessed as an independent risk factor, other factors must be taken into consideration

[b]Advanced maternal age has no relationship with adverse pregnancy outcome

[c]The result is compared to advanced maternal age (35-39 and 40-44 years)

[d]In twin pregnancies, there are no relationship between adverse neonatal outcomes, stillbirth and maternal age

[e]Advanced maternal age don't increase the risk of still birth

[f]Primiparous women with advanced maternal risk did not have increased incidence of large for gestational age infants, but instead has significantly increased incidence of small for gestation age infants

[g]Advanced maternal age is not a risk factor for stillbirth, spontaneous preterm delivery, large-for-gestational age neonate

[h]Preterm delivery (before 37 weeks of gestation) was related to women ≥40 yrs

by uncorrected errors in DNA replication. The frequency of these mutations continually accumulated in the offspring, that is, as the paternal age of next generation increases, so did the frequency of XY mutations [97]. Due to a large number of cell divisions during spermatogenesis, it could be speculated that advanced paternal age could increase the frequency of ab initio mutation [98].

Female

Advanced maternal age was an important risk factor for fetal chromosome abnormalities [99]. Among the common types of chromosome abnormalities, the incidence of trisomy 18, trisomy 21, and XXY were closely related to advanced maternal age at the time of pregnancy [100–102]. By synthesizing several meta-analyses and large population data studies on the relationship between gestational age and the incidence of trisomy 21, a review concluded that with increasing age, the incidence of Down syndrome doubled at age 30 and again at age 35 [103]. Another large-scale epidemiological survey of 46,258 pregnant women over 35 years old in China found that the proportion of fetal 21 trisomy syndrome increased significantly in women over 39 years [1]. Additionally, advanced paternal age might increase the incidence risk of trisomy 21 in older women [104]. The main cause of chromosome abnormality in offspring of older women was related to oocyte quality. With advanced maternal age, there was an increase in frequency of chromosome abnormality in oocytes. This was primarily due to reduced centromere cohesion, weakened homologous recombination, failed spindle assembly checkpoint, chromatin epigenetic changes, and oocyte extracellular factors also played a role in chromosome errors [105] (Table 3). The imbalance of multiple regulatory mechanisms against normal chromosome ploidy within oocyte as a result of age might ultimately lead to chromosomal abnormalities in old oocytes and this abnormality is inherited by the offspring.

Neurological and psychiatric disorders of offspring

Male

By referring to previous studies, we found that there was an important correlation between parental age and the nervous system development of offspring. Kazaura et al. retrospectively analyzed 1,869,388 newborns from Norway and found that the risk assessment of nervous system malformations of paternal age 45–49 was 2.5 and 1.3 times higher than that of paternal age 25–29, respectively [106]. Advanced paternal age might also affect the neuropsychiatric system of the offspring after birth. Autism spectrum disorder (ASD) was a kind of widespread developmental disorder that often occurs in children. It was mainly manifested by abnormal language ability, communication disability, narrow interest, and stubborn behavior pattern. Older fathers increased the risk of ASD in offspring compared with younger fathers [107], and the father's age was an independent risk factor for ASD in offspring [108, 109]. Kong et al. confirmed that there was a correlation between the paternal age and ab initio mutation by sequencing the whole genome of parents and their offspring from 78 Icelandic families, and this relationship was more pronounced in genes with ASD [98]. Another study compared the level of gene expression in lymphocytes between children diagnosed with ASD and healthy children. It was found that the decreased distribution of genes related to transcriptional regulation in lymphocytes was associated with ASD and the increased age of fathers. This suggested that the different ASD gene expression profile might attribute to advanced paternal age [110]. Excluding sociology and other factors, a study showed that advanced paternal age was also associated with schizophrenia [111–113]. A meta-analysis showed that the offspring of older fathers were 1.66 times more likely to develop schizophrenia than the offspring of younger fathers [114]. Schizophrenia patients related to advanced paternal age showed differences in language and behavior ability with other schizophrenia patients, and female offspring had early onset [115]. An increase in ab initio mutations in the germ cells of older fathers [116], allele length variations, and an increased risk of chromosome breakage [117], might eventually lead to an increased risk of schizophrenia in offspring. Other studies have shown that male offspring from paternal age>55 were 1.37 times more likely to be diagnosed with bipolar disorder than those of men aged from 20 to 24 [118]. However, a prospective cohort study based on part of the Israeli population showed that, when the age of the father at the time of the birth of first offspring was controlled, older fathers did not mean an increased risk of schizophrenia or bipolar disorder. The association between the offspring of older fathers and these two diseases was more likely to come from psychosocial factors [119]. Another study using twins as a model also showed that as paternal age increased, the influence of genetic factors on the incidence of mental disorders decreased while that of environmental factors increased [120]. Moreover, the father's age might also be related to the neurocognitive index score of the offspring. When the neurocognitive index was evaluated at different age stages of the offspring, it could be found that older fathers' age was related to lower score [121]. Another study pointed out that there was a U-shaped relationship between the father's age and the IQ score of the offspring [122]. In a cohort study of 96,654 children, the researchers found that offspring of fathers aged 35 or older were more likely to be diagnosed with epilepsy [123]. In an animal study, researchers also verified the influence of older fathers on ASD and abnormal behavior of the offspring [124–127]. At the same time, it should be noted that different

Table 3 The correlation between advanced parental age and various kinds of birth defects in offspring

Kinds of birth defect	Aging type	Year	Author
Chromosome aneuploidy			
Down's syndrome	Both aging (30-39)	2016	Sotonica M, et al
	Maternal	2012	Agopian AJ, et al. [104][a]
	Paternal	2009	Oliver TR, et al[b]
	Paternal or maternal	2003	Fisch H, et al. [89]
	Paternal or maternal	2001	Jyothy A, et al
	Paternal	2001	Carothers AD, et al[b]
	Maternal	2000	Muller F, et al
	Maternal	1996	Yoon PW, et al
	Paternal	1995	McIntosh GC, et al
	Paternal (>41)	1981	Stene J, et al
	Paternal	1981	Erickson JD, et al
	Paternal	1978	Matsunaga E, et al
	Paternal (>55)	1977	Stene J, et al
Down's syndrome and other chromosomal anomalies	Paternal (≥40)	2007	Yang Q, et al. [85]
Klinefelter's syndrome	Paternal or maternal	1988	Carothers AD, et al
Trisomy 18	Maternal	1999	Naguib KK, et al
Trisomy 21, 18 and 13	Paternal	2015	Steiner B, et al
	Paternal	2018	García-Ferreyra J, et al
Other chromosomal abnormality diseases			
Pfeiffer syndrome	Paternal	2013	Chokdeemboon C, et al
Prader-Willi syndrome	Maternal	2013	Cho SY, et al
	Maternal	2018	Butler MG, et al
Crouzon syndrome and Pfeiffer syndrome	Paternal	2000	Glaser RL, et al
Potocki-Lupski syndrome	Paternal or maternal	2012	Popowski T, et al[b]
Noonan syndrome	Paternal	2004	Tartaglia M, et al
Huntington's disease	Paternal	1993	Goldberg YP, et al
Neurological and psychiatric disorders			
ASD	Paternal or maternal	2016	Sandin S, et al
	Paternal	2015	Khaiman C, et al
	Both aging	2015	Durkin MS, et al
	Paternal or maternal	2014	Idring S, et al
	Maternal (>35)	2014	Maramara LA, et al. [141]
	Paternal (35-49) or maternal (≥35 or ≥40)	2013	Lampi KM, et al. [142]
	Paternal	2012	Puleo CM, et al
	Paternal	2012	van Balkom ID, et al
	Paternal or maternal	2012	Guinchat V, et al
	Paternal	2008	Tsuchiya KJ, et al
	Maternal or paternal	2007	Croen LA, et al[c]
	Paternal	2006	Reichenberg A, et al. [107]

Table 3 (continued)

Schizophrenia	Paternal	2020	Lan KC, et al.
	Paternal	2019	Wang SH, et al. [113]
	Paternal (≥35)	2017	Fond G, et al
	Paternal	2016	Liebenberg R, et al[b]
	Paternal	2015	Ek M, et al[b]
	Paternal	2015	Wang SH, et al[b]
	Paternal	2014	Sørensen HJ, et al[b]
	Paternal	2014	Sørensen HJ, et al
	Paternal (>30)	2012	Wu Y, et al. [112]
	Paternal (>55)	2011	Frans EM, et al
	Paternal (>32)	2011	Naserbakht M, et al
	Paternal	2005	Tsuchiya KJ, et al
	Paternal or maternal	2005	Malaspina D, et al. [112]
	Paternal	2004	Sipos A, et al. [111]
	Paternal	2002	Brown AS, et al
	Paternal	2002	Dalman C, et al
	Paternal	2002	Malaspina D, et al[b]
	Paternal	2001	Malaspina D, et al
Sporadic schizophrenia	Paternal or maternal	2019	Kollias C, et al. [137]
Catatonic schizophrenia	Maternal (>35)	2012	Kleinhaus K, et al. [138]
Familial aggregation of schizophrenia	Paternal	2012	Svensson AC, et al[b]
ASD and schizophrenia	Paternal	2017	Janecka M, et al. [204]
	Paternal or maternal	2008	Weiser M, et al
ASD, psychosis, and bipolar disorders	Paternal	2014	D'Onofrio BM, et al
Schizophrenia and bipolar disorder	Paternal	2020	Weiser M, et al. [119]
Schizophrenia and other mental disorders	Paternal (>25) or Maternal (>22)	2018	Fountoulakis KN, et al. [144]
Neurodevelopmental disorders such as ASD, bipolar disorder and schizophrenia	Paternal	2009	Saha S, et al. [121]
Pervasive developmental disorders/ASD	Paternal	2017	Merikangas AK, et al. [147]
Cerebral Palsy	Maternal (>35)	2018	Schneider RE, et al
Epilepsy	Maternal	2018	Dreier JW, et al. [139]
	Paternal	2005	Vestergaard M, et al. [123]
Eating disorder	Paternal (>40)	2014	Racine SE, et al. [120]
Anorexia nervosa and all eating disorders	Paternal (>45)	2017	Javaras KN, et al
Nonaffective psychosis	Maternal	2011	Miller B, et al. [114][a]
Psychotic disorders	Maternal	2010	Lopez-Castroman J, et al. [145]
Psychotic-like symptoms	Paternal	2015	Foutz J, et al

Table 3 (continued)

Mental disorders, cerebral diseases	Maternal (>35)	2017	Hviid MM, et al
Bipolar disorder	Paternal (≥50)	2014	Chudal R, et al
	Paternal or maternal	2013	Brown A, et al[b]
	Paternal	2008	Frans EM, et al. [118]
Neurocognitive dysfunction	Paternal	2009	Saha S, et al. [121]
Cognitive impairment	Maternal (40-44)	2013	Myrskylä M, et al[c]
Neural tube defects	Paternal	1995	McIntosh GC, et al
Abnormal child behaviour, including internalising and externalising behaviours	Paternal	2015	Tearne JE, et al[b]
Attention-deficit/hyperactivity disorder	Paternal or maternal	2015	Chudal R, et al. [136][b]
Obsessive compulsive disorder	Maternal	2017	Chudal R, et al
Neurodevelopmental disorders with epilepsy, intellectual disability	Paternal	2019	Taylor JL, et al
Cardiovascular system diseases			
Congenital heart defects	Paternal	2019	Taylor JL, et al
	Paternal	1994	Olshan AF, et al
	Maternal or paternal	2009	Materna-Kiryluk A, et al
Eye-, heart-, circulatory-, rheumatic-, neonatal diseases, and congenital malformations	Maternal (>35)	2017	Hviid MM, et al
Heart defects, tracheo-oesophageal fistulaoesophageal atresia, other musculoskeletal/integumental anomalies	Paternal (≥40)	2007	Yang Q, et al. [87]
Heart defects, tricuspid atresia, right outflow tract defects, hypospadias 2nd degree or higher, male genital defects excluding hypospadias, and craniosynostosis	Maternal (35-40)	2004	Reefhuis J, et al
A less favorable lipid profile(cardiovascular risk factors)	Paternal	2019	Ahn HY, et al
Patent ductus arteriosus	Paternal	2015	Su XJ, et al[a]
Abnormal carotid intima	Maternal	2020	Nyasordzi J, et al. [181][c]
Immune system disease			
Asthma	Paternal or Maternal	2018	Thomsen AML, et al[b]
Allergic rhinitis	Maternal (≥40)	2020	Lu HY, et al. [182]
Multiple sclerosis	Maternal or paternal	2010	Ramagopalan SV, et al[b]
Birth defects and congenital malformations			
Oral clefts	Both aging	2015	Berg E, et al
	Paternal	2017	Ly S, et al[b]
	Maternal	2015	Figueiredo JC, et al
Birth defects	Paternal	2012	Grewal J, et al
	Maternal	2005	Thong MK, et al
	Maternal	2003	Chia SE, et al
Congenital cataracts, reduction defects of the upper limb	Paternal	1995	McIntosh GC, et al
Hypospadias	Maternal (>40)	2005	Porter MP, et al. [185]
	Maternal (>30)	2001	Fisch H, et al. [184]
Hypospadias and cryptorchidism	Maternal	2019	Estors Sastre B, et al
Preauricular cyst, nasal aplasia, cleft palate, hydrocephalus, pulmonic stenosis, urethral stenosis, and hemangioma	Paternal	1991	Savitz DA, et al
Musculoskeletal Congenital Anomalies	Paternal (>40)	2015	Urhoj SK, et al. [162]
Congenital malformations	Paternal (>45)	2008	Zhu JL, et al

Table 3 (continued)

Tumor or other malignant disease			
Breast cancer (before 40 yrs)	Paternal	2007	Weiss-Salz I, et al
Leukemia	Maternal (≥35)	2018	Imterat M, et al
Acute lymphoblastic leukemia	Both aging	2018	Petridou ET, et al. [170]
Childhood cancers (acute lymphoblastic leukemia)	Paternal	2017	Urhoj SK, et al. [12]
Childhood acute lymphoblastic leukemia and acute myeloid leukemia	Paternal	2012	Larfors G, et al
Early onset cancer	Paternal	2020	Greenberg DR, et al
Pediatric cancer	Maternal or paternal	2017	Wang R, et al
Testicular cancer and cryptorchidism	Maternal	1996	Møller H, et al
Testicular germ cell tumors	Paternal	2017	Levine H, et al[b]
Retinoblastoma	Maternal	2014	Saremi L, et al. [183]
Dying before the age of 5 years	Paternal (≥40)	2014	Urhoj SK, et al. [174]
Neurofibromatosis type 1	Paternal	1993	North K
Other diseases of offspring			
Obesity	Maternal (≥35)	2012	Myrskylä M, et al
Reduced bone mass	Maternal	2012	Rudäng R, et al
Early age of menarche	Paternal or maternal	2010	Shrestha A, et al[d]
Male infertile	Maternal	2001	Tarín JJ, et al. [186]
Decline fertility (female)	Maternal	2018	Basso O, et al. [187]

[a]The correlation was established dependent on maternal age.

[b]The correlation was negative.

[c]The correlation was related to the sex of offspring.

studies employed different definitions of what "advanced paternal age" should be, so studies investigating the impact of fathers in the mental health of their children should properly defined the age threshold. One study analyzed the patient population by dividing them into three different age groups: 35, 45, and 55, and they found that only age 55 yielded a statistically significant different [128]. However, the specific determination of the age threshold needed to be supported by further research. Nevertheless, the epidemiological association between the father's age and adverse neuropsychiatric outcomes of offspring was still very reliable. Using neuroimaging, Gale-Grant et al. found that the increase in age-related germline mutations might affect the development of white matter in offspring [129].

As previously described, male germ cells underwent hundreds of cell divisions before fertilization, and DNA repair mechanisms maintained the fidelity of DNA replication. However, overall number of point mutations in male spermatogonia accumulated over time. A study found that genetic mutations in older fathers mainly affect the function of the mitochondrial respiratory chain, and the occurrence of mental illnesses such as schizophrenia and ASD was usually associated with mitochondrial dysfunction, which can partially explain the association between mental illness and older fathers [130]. Moreover, animal studies have also found extensive changes in the transcriptome of medial posterior frontal cortex in offspring of older men, and most of these differentially expressed genes were associated with the etiology of ASD [131], and these ASD risks might last for generations [132]. In recent years, the theory that epigenetic changes caused abnormalities in the nervous system of offspring with older fathers had been paid more attention. Epigenetics refers to the changes in gene expression levels based on non-gene sequence changes, including DNA methylation, histone modification, chromosome remodeling, and noncoding RNA regulation, which mainly affect the genomic function and characteristics through the regulation of gene transcription or translation processes. Among these types of epigenetics, aberrant DNA methylation damage during spermatogenesis could be transmitted to offspring [133, 134]. In addition, it was supported that the epigenetic changes caused by the aging of fathers were associated with the susceptibility to schizophrenia in offspring [135]. In summary, the mechanism by which old fathers led to neurological and psychiatric disorders in offspring might be associated with accumulated DNA site mutations and aberrant epigenetic changes in the spermatogenic cells.

Female

In a population-based cohort research, the effect of maternal aging on the neurocognitive and emotional development of offspring remained controversial [136]. However, some epidemiological studies have shown that the advanced age of women was related to schizophrenia [137, 138], epilepsy [139], ASD [140–142], and the cognitive ability of offspring [143]. In a case-control study, in addition to the association between advanced paternal age and schizophrenia, maternal age was also an independent risk factor for this mental disorder [144]. Lopez-Castroman et al. reviewed follow-up data from 30,965 patients from 1980 to 2007 and showed that the risk of mental illness increased linearly with the mother's age [145]. More often, mother's age had the same effect as father's age, which was independently associated with high risk of ASD in the offspring [146, 147].

As for the reasons why the mother's age affected the cognition and mental condition of their offspring, a study found that advanced maternal age can lead to dysregulation of DNA methylation patterns in homologous ectodermal cells of offspring with ASD, and its regulated expressed protein had an interaction relationship with known ASD-related causative genes, and epigenetic dysregulation in ASD patients of offspring from mothers with advanced maternal age may in turn be related to parental gamete aging and environmental effects during embryogenesis [148]. Aoulad Fares et al. showed that genomic instability caused by telomere shortening potentially increased the risk of neural tube defects [149]. In addition to previously mentioned genetic mechanisms, a study pointed out that the brain cortical volume of offspring increased with parents' age and the influence of father and mother on the brain cortex of offspring was different. Older fathers had more influence on the cortex surface area of the offspring, while older mothers had more influence on the cortex thickness. The effects of maternal age on cortical thickness might lead to differential neurocognition among offspring [150]. Subtle behavioral changes and cortical morphological changes in offspring have also been demonstrated in a mouse model [151]. The change of internal and external environment might had influenced the brain development before the offspring born to parents of advanced age [152]. There was a mutually regulated signal pathway between the fetal brain and the maternal skeletal system, and osteocalcin secreted by osteoblasts could combine with fetal neurons across the placental barrier to participate in the regulation of anxiety, depression, learning, and memory function. Older pregnant women might affect the cognitive function of their offspring through osteocalcin and thus contributed to the maternal influence on fetal brain development [153]. Pregnancy was a special immune process, and the inflammatory pathway that caused bad neurobehavior of offspring was intrauterine inflammation [154]. For example, intrauterine IL-6 levels during pregnancy affect the ASD phenotype [155], white matter, cognitive ability [156, 157], and the development of amygdala in offspring [155, 158]. The abnormal inflammatory state in the uterus of an older woman could also lead to brain damage

in the newborns [159]. Prenatal mental state of pregnant women (tension, anxiety, and depression) also affected fetal brain development [160]. How advanced maternal age might bring changes in the immune environment of the uterus to affect fetal nervous system still needed further investigation. Similarly, gestational complications caused by advanced age, such as gestational diabetes, increased the risk of different schizophrenia phenotypes in offspring [161]. Sunwoo et al. also showed that maternal immune activation changed the expression profile of miRNA in the midbrain of mouse offspring, which was associated with an increased risk of ASD in offspring [154] (Table 3). In summary, the effect of advanced maternal age on neuropsychiatric disorders in offspring was not only affected by gene-level factors in gametes, but also because mothers are involved in the gestation process of embryos, and the effects of internal and external environmental factors throughout pregnancy might have an impact on the occurrence of neuropsychiatric disorders in offspring, which requires our attention in future studies.

The influence of the parents' advanced age on other diseases of their offspring

Male

Many epidemiological studies have demonstrated the effects of advanced age on other systems of offspring. As the father ages, the risk of congenital musculoskeletal abnormalities in offspring increases [162]. Aging might lead to an increase in the frequency of mutations at specific gene loci that affected cartilage development in offspring, resulting in an increase in the incidence of chondrodysplasia [163]. Advanced paternal age was also related to some autosomal dominant diseases, such as Crouzon syndrome, Apert syndrome, Pfeiffer syndrome, myositis ossificans, and Marfan syndrome [164]. The effect of paternal age on the high incidence of these diseases was attributed to accumulated spermatogonia replication errors, *FGFR3* and *FGFR2* gene mutations in the sperm of older fathers, for example, were associated with some bone dysplasia diseases [165–167]. A retrospective study analysis showed that the risk of multiple sclerosis increased steadily with paternal age, regardless of the maternal age, and the risk was twice as high at the age of 55 as that of the father at the age of 25 [168]. The advanced paternal age might also be associated with the occurrence of malignant diseases in offspring, such as an increased risk of leukemia [169], acute lymphoblastic leukemia [170], nervous system cancer [171], and premenopausal breast cancer in offspring [172]. In addition, endocrine tumors, type I neurofibroma and retinoblastoma were also significantly related to paternal age, but the results were not consistent across different studies [173]. The offspring of older fathers aged over 40 years might have an increased risk of death before the age of 5 due to congenital malformations, malignant tumors, and external factors caused by age-specific point mutations [174]. Advanced paternal age was also associated with offspring reproductive health. An epidemiological survey from the United States found that older fathers led to a decreased mating rate in the offspring [175]. In mouse experiments, it was also found that advanced paternal age affected sperm concentration, sperm motility, and anogenital distance of offspring, indicating the effect of paternal age on the reproductive health of the next generation [176].

In summary, advanced paternal age was associated with not only the risk of neuropsychiatric diseases in offspring, but also musculoskeletal diseases, malignant diseases, and reproductive health in offspring, and the causes of these diseases were also associated with genetic changes due to increasing age.

Female

The impacts on offspring of advanced maternal age were more negatively affected because of high complication rate during pregnancy. It was convinced that advanced maternal age can have a negative impact on the blood pressure of offspring [177, 178], and an increased incidence of congenital heart disease was also observed in the offspring of older mothers [179]. Women's cardiovascular system was no longer adapted to pregnancy in the process of aging, and damage to the structure and function of uterus and placenta would increase the risk of adverse pregnancy outcome [5]. Gestational complications such as gestational diabetes mellitus could also lead to a high incidence of cardiovascular disease in the early stages of fetal development [180]. In addition, a population follow-up study from Germany showed that advanced age affected the carotid intima-media thickness of female offspring in adulthood [181]. Maternal age at delivery was also associated with allergic diseases such as asthma, food allergy, and allergic rhinitis in offspring [182]. In a case-controlled study from Iran, Saremi et al found that older women increased the risk of retinoblastoma in their offspring [183]. Women who delayed childbearing age might also increase the risk of hypospadias in their offspring [184, 185]. Finally, aging in women might negatively affect the fertility of offspring [186, 187].

The molecular mechanism of various subsequent health risks faced by the offspring of older mothers remains elusive. Therefore, relevant conclusions on such subject and common definition of advanced maternal age still need to be supported by further large sample studies with multicenter data. Kaytor et al. have shown that intergenerational CAG nucleotide instability increased with aging in pregnant women, and nucleotide repeat instability was associated with cancers and nervous system diseases [188]. Moore et al. used high-throughput sequencing technology to analyze the blood

DNA methylation of 2740 adult women and their mothers. It was found that the mother's age affected the epigenetic changes of disease-related gene loci in the female offspring [189] (Table 3). In addition to the above factors of abnormal inheritance of gamete abnormalities caused by advanced age to offspring, it should be noted that advanced age easily affected the pregnancy environment of the mother, which can also adversely affect offspring health.

The intervention of ART and fertility in the older

The emergence of ART brought hope to older couples who wanted to have healthy offspring. ART could effectively help solve the aforementioned problems of decreased gamete quality caused by advanced age, select high-quality gametes by morphological or biological criteria, and detect the quality of early embryos after fertilization by the same ways, such as time lapse imaging [190] and preimplantation genetic screening (PGS) [191], which had a great degree of guarantee for the safety of advanced-aged parental embryos before implantation.

For men, some studies found that ART could rescue the adverse effects of advanced paternal age on offspring. In a multicenter retrospective study from 2016 to 2018, after analyzing the association between paternal age and embryonic aneuploidy in 1202 IVF/ICSI cycles, the study found that paternal age was not significantly associated with multiple aneuploidy forms (haploid, trisomy, partial deletion/repetition) [88]. Although the decline of sperm concentration and motility in older men might affect the fertilization rate and blastocyst formation rate, it did not affect the quality of blastocyst or the pregnancy rate of ICSI cycle [192]. Other studies found that old father and young father showed no significant difference of aneuploidy rate, fertilization rate, implantation rate, pregnancy rate, abortion rate and live birth rate after accepting IVF treatment [88, 192–194]. However, some studies still confirmed that the advanced paternal age had a negative effect on treatment outcome. Sperm from older men showed lower fertilization potential and blastocyst formation rate after receiving IUI or IVF treatment [195]. It also increased the relative risk of neurocognitive impairment, some cancers and aneuploidy-related syndrome in the offspring [194]. Another increased risk was the sperm DNA fragments (SDF). Studies have shown that the proportion of SDF was positively correlated with age. Among men between the ages of 60 and 80, the percentage of SDF was 88% [165]. In laboratory studies, more than 30% of DNA fragments were considered to be abnormal and are associated with poor ART outcomes [196]. It was therefore necessary to screen out high-quality sperm by effective laboratory methods.

Considering the relationship between older men and semen quality, ART could also help prevent damage to sperm by advanced age by freezing sperm at a young age. However, there were no studies to compare the efficacy and safety of using young frozen sperm and older fresh sperm for IVF, and it should be noted that the process of freezing sperm was not risk-free [197].

The fertility requirements of older women were reflected in the increasing number of women receiving ART every year. First, whether ART improved pregnancy rates in women of advanced age was uncertain. For example, according to the data in the past decade, for women over 40 years, ART had almost no significant improvement on the pregnancy rate [198]. When young women were treated with assisted fertility therapy such as controlled induced ovulation and IUI, the probability of conception would increase, women with advanced maternal age, however, had a decreased rate of pregnancy after medical intervention. Even if normal-looking blastocysts were obtained, trophoblast biopsies often found a high proportion of aneuploidy [199, 200]. Second, ART did not reduce the risk of pregnancy outcomes in women with advanced age [201]. A multicenter retrospective cohort study from Northern Europe showed that while older women who received ART were still at great risk of adverse maternal and neonatal outcomes, the effect was greater in women with natural conception [202].

For preventive measures, through publicity and education, more women could recognize the risk of giving birth at an advanced age and complete giving birth at the best reproductive age as much as possible. Fertility preservation could also be performed by vitrifying oocytes or blastocysts at a young age. With the help of PGT, it could effectively screen aneuploid blastocysts resulting from meiotic errors and improve the cumulative pregnancy rate in older women. In addition, older women faced more problems after receiving ART treatment than older men, which might be due to that in addition to gametes, endometrial factors, placental factors, pregnancy complications, hormone levels, and inflammatory status would also affect the growth and development process after implantation. Therefore, ART for older women should be accompanied by adjustment of their physical status through drugs or other treatment modalities.

Considering that ART might also interfere with the health of offspring, necessary evaluation was needed to explain the role of ART in older patients. Therefore, when considering the use of ART for older couples, doctors should consider the intervention effect at ART in addition to the uncertainty of gamete quality caused by advanced age, so as to provide more reliable genetic counseling for the patients [203].

Conclusion

For a long time, large-scale epidemiological investigations have shown that advanced age in fathers or mothers posed a great risk for adverse pregnancy outcomes and offspring health. However until now, the exact risks that were brought by advanced parental age had not yet reached the unified standard. This review summarized the effects of older fathers and mothers on pregnancy outcomes, birth defects of offspring, possible mechanisms, and ART on older parents. Giving birth at an advanced age would still be the trend of social development now and in the future. On the basis of the existing investigation and research data based on human beings, we need more non-human primate experiments (the basic experiments of advanced age were mainly carried out in rodents, but the effects of some environmental factors could not be modeled in rodents [204]) to thoroughly explore the mechanism behind the declined reproductive function in human. With the help of ART, we could apply more research findings to clinical practice to cope with the reproductive challenges.

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