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# Ethical issues associated with advanced paternal age and genetic disorders in their offspring

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**ABSTRACT**

Nowadays, couples postpone parenthood into their fourth or fifth decade of life due to different reasons such as economic situation and industrialization. Several studies have shown disadvantages of advanced maternal age and its effects on offspring health. However, there are few studies concerning effects of advanced paternal age (APA) on offspring health. Hence, appropriate progress has not been made in genetic counseling of this issue. Some scientists believe that advanced age doesn't have detrimental effects on semen parameters, but majority of scientists are of the opinion that semen parameters such as volume, count, morphology and motility will decrease with increasing age. Moreover, it has been revealed that APA is in close relationship with incidence of some diseases such as Achondroplasia, congenital malformations, Autism, Schizophrenia and some cancers in infants. Based on the quadruplet ethical principles, the right of aged parents is conserved for childbearing, but genetic counseling along with conservation of parents' autonomy would be useful to healthy childbearing.

**Keywords**: Advanced paternal age, Offspring genetic disorders, Medical ethics, Genetic counseling.

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## Introduction

Presence of fathers at age of forties or fifties and even more is not unusual anymore in our community. Nowadays, birth frequency in third and fourth decades of mother's life has increased significantly in comparison with recent decades (figure 1). Mean paternal age has increased dramatically at the time of first birth (1). In recent years, due to industrialization, changing patterns of education, socioeconomic status, growing demand for human forces and employment and also paradigms shift about woman positions in society, parents usually have mental and occupational concerns, hence, couples postpone parenthood into their fourth or fifth decade of life (2, 3). Different studies have been accomplished on disadvantages of advanced maternal age and its effects on offspring health and it is obvious that the high incidence of bearing unhealthy child in aged women (1). In menstrual cycle of women, just one oocyte releases every month, thus

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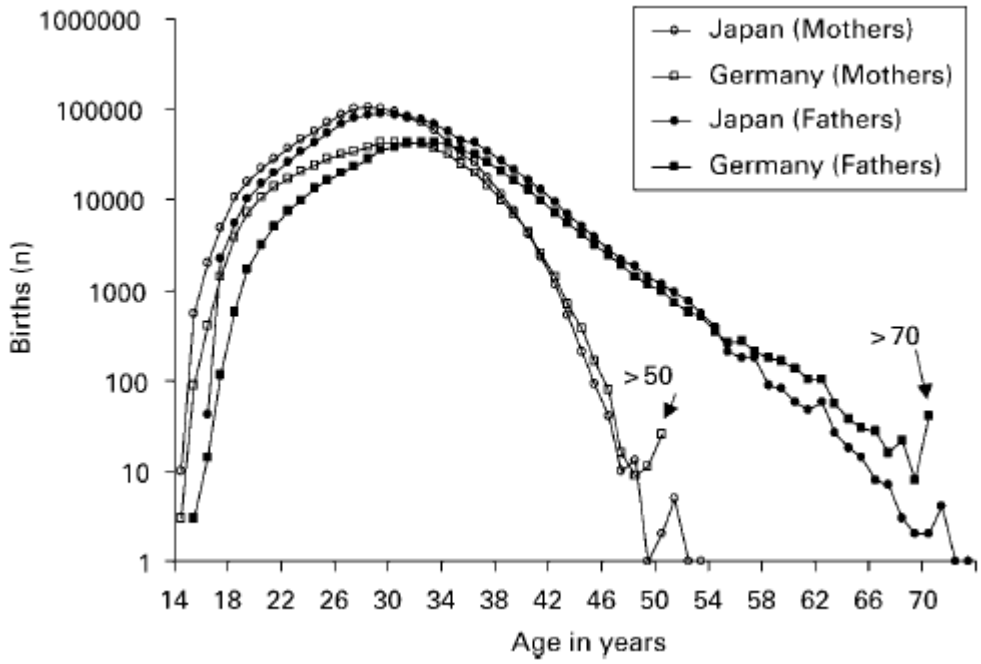


**Figure 1.** Parental age at the time of birth of offspring in Germany and in Japan. Birth data of German mothers aged 50 years and German fathers 70 years are represented as one dot respectively (Rolf and Nieschlag, 2000).

mutation occurrence especially trisomies increase in direct association with advanced maternal age.

But in men, because of production of millions of sperms every day and difficult evaluation of mutation occurrence in these released sperms, few studies have been done on APA and its effect on child health. Meanwhile, appropriate progress have not accomplished in genetic counseling of such population, therefore, genetic counselors can't offer fundamental and useful helps to aged couples wishing to have child. Previous studies have showed that maximum fertility rate is in women with 22-26 years old, but, it gradually declines after age of 35 and after age of 39 a dramatic decline takes place. Finally, due to depletion of ovary from follicles in menopausal period, the fertility rate ceases completely (4). Increasing maternal age is associated with high incidence of trisomies, Spontaneous abortion, congenital disorders and birth mortality. Decrease ovarian reserve and increased oocyte chromosomal abnormalities in aged women, are the most important reasons behind these kinds of disorders (5).

Regarding increased life expectancy among people, they suppose that have sufficient energy in advanced age for childbearing. Also due to recent developments in the field of assisted reproductive technology (ART) and invent modern therapeutic methods such as in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), parents' concerns about their ability to bring baby in advanced ages have declined. At present, 3-6% of births in developed countries are the results of ART methods (6).

Scientists have different ideas about APA and its effects on ART results. Some believe that APA decreases pregnancy rate, but Spandorfer et al. believes that there is not any significant relationship between APA and pregnancy rate (7).

The Function of Male reproductive system is adverse to women and doesn't cease abruptly and can maintain the fertility to the end of life. But, some factors will change in parallel with increasing paternal age. For example, infertility rate in 35 and 40 year old men will reduce from 18% to 28%, respectively (8).

Sartorius et al. has shown the effects of APA on semen parameters (9). Semen Volume declines along with APA, but, there are different opinions about other semen parameters such as motility, concentration and morphology (10). Some researchers believe that APA hasn't any effects on semen parameters, but majority of them believe that along with increasing paternal age, semen parameters such as volume, count, morphology and motility will decline (11, 12). They claim that increase in paternal age to more than 50 years old cause 3-22% decrease in semen volume, 3-37% decrease in sperm motility and 4-18% increase in morphological sperm abnormality. Morphological changes in testis due to low concentration of testosterone in advanced ages (13) could induce quantitative and qualitative decrease in spermatogenesis (12, 14).

There is not any significant relationship between APA and success rate of fertilization, implantation, pregnancy, abortion and live birth. Nevertheless, APA hasn't direct association with cleavage-embryo (2 and 3 days) quality, but APA is in close relationship with blastocyst formation rate and could induce blastocyst formation decrease. This decrease is due to paternal genome activation prior to blastocyst formation stage (10).

However, evaluation of the effects of APA on offspring is an important issue that has caused growing attention paid by medical staff. Many studies on aged fathers' children have shown the high occurrence of some diseases such as Autism, Achondroplasia, hemophilia, Hutchinson Gilford progeria syndrome, congenital anomalies, Schizophrenia and some cancers in infants (15-19). Different studies have shown the indirect relationship between advance maternal age and Child's intelligence, but Sukanta Saha et al. in 2009 reports that increasing paternal age hasn't such effects on child's intelligence (20).

In addition to high incidence of physical disorders in children of fathers more than 40 years old age, mental and psychic disorders are another subject that due to induction of fewer communication and reciprocal misapprehension between children and fathers could interfere with their life.

There are a lot of instances in all parts of Iran that young girls, because of financial and welfare problems, have decided to marry aged men to improve their own and family life, even in some cases they childbeared. There are also some instances that media has some telecasts about marriage of a young girl and an aged man that lead to parturition without any pointer about their side effects of such marriages. These instances are some incorrect culture that media are injecting propaganda into society.

Here, there are questions that will arise whether these aged men should know about the risk of having baby with these high risks of different disorders. What is the role of media and organizations in this approach? And what is opinion of Islam about this issue?

**APA and offspring disorders**

Birth of healthy baby is more important than childbearing. In humans like other mammals, mainly this is the male gender that introduces de novo mutation into genetic pool. Before puberty, spermatogonia stem cells undergo 30 mitotic divisions and after this period, these cells are divided every 16 days, or 23 per year. At ages 20

and 40, the number of sperm divisions reach to 150 to 610, respectively and finally to 840 divisions every year. In contrast, the number of divisions in oogonia stem cells is almost 22 divisions that all of them occur in fetal life. Thus, mutation occurrence in male germ cells maturation process is much more possible than in female (21).

De novo mutations occurrence in advanced aged are considered as main cause of several important sporadic autosomal dominant diseases such as Hutchinson-Gilford progeria, Achondroplasia (22), Schizophrenia (17, 19, 23) and thanatophoric dysplasia (24). Recent studies have shown that the risk for complex disorders such as prostatic cancer (25), nerve system cancers (26) and congenital birth defects (27) such as cleft lip and cleft palate (28) as well as spontaneous abortion, preterm labor, prenatal mortality, low birth weight may increase along with increasing paternal age.

In addition to APA, consanguineous marriage is another factor that could increase genetic diseases. Risk of birth of unhealthy infant is 2-3 folds higher than non-consanguineous marriage (29, 30). Table 1 shows some disorders in offspring that may increase due to APA (31).

**APA and genetic counseling**

Term APA is often used in genetic counseling and it is referred to men that are more than 40 years old experiencing having child for the first time. Especial attention paid to precise genetic counseling prior to marriage, can decline the frequency of genetic disorders (29, 32).

Despite advanced maternal age, at present, genetic counseling clinics are not referral centers for aged men who want to have baby. Genetic counselors are usually unable to offer necessary and useful helps to aged parents. Nowadays, there are no special screening and diagnostic tests detecting all fetus disorders related to APA. In such cases, if pregnancy comes to existence, they can, like others, be subjected to same diagnostic instructions regarded necessary. Nevertheless, high risk of Down syndrome due to increasing maternal aged can be discussed. Due to high risk of Down syndrome and some forms of autosomal dominant diseases such as thanatophoric dysplasia, it is highly recommended to perform ultrasound in 18-20 weeks' gestation in order to evaluate embryo growth and development. However, probability of prenatal genetic diagnosis in most of the above-mentioned diseases, prior to ensoulment and proposing therapeutic abortion is impossible.

**APA and medical ethics**

Ethical issues related to APA and offspring disorders can be discussed based on quadruplet ethical principles: 1) Respect for autonomy 2) Duty of beneficence 3) non- maleficence 4) Respect for justice.

Based on autonomy principle, human has complete authority and liberty for marriage and childbearing. Thus, not only genetic counseling prior to gestation hasn't any confliction with autonomy but also it provides more human munificence protection via knowing more information. Also about some issues such as seeking of informed consent forms from patients prior to sampling and secrecy that are related to patient's autonomy, have to be observed in genetic counseling clinics. Whereas, patients confer to these clinics arbitrarily, thus, not only no harm is inflicted but, Duty of beneficence principle is respected due to sufficient knowledge collection.

In non-maleficence principle that are in overlap with Duty of beneficence principle, we

**Table 1.** Advanced paternal age and risk of genetic disorders in baby (summarized from Toriello and Meck).

| Type | Type Specific condition | Age | Relative risk | Population risk | Adjusted risk |
|---|---|---|---|---|---|
| Autosomal dominant | Achondroplasia | 50> | 7.8 | 1/15,000 | 1/1923 |
| | | 30–34 | 3.5 | | 1/4285 |
| | | 35–39 | 4 | | 1/3750 |
| | | 40–44 | 8 | | 1/1875 |
| | | 45–49 | 9 | | 1/1666 |
| | | 50–54 | 12 | | 1/1250 |
| | Apert | 50> | 9.5 | 1/50,000 | 1/5263 |
| | Pfeiffer | 50> | 6 | 1/100,000 | 1/16,666 |
| | Crouzon | 50> | 8 | 1/50,000 | 1/6250 |
| | Thanatophoric dysplasia | 35> | 3.18 (1.48–6.89) | 1/20,000–1/50,000 | 1/6290–1/15,723 |
| Chromosomal | Down syndrome | 40–44 (20–29) | 1.37 (0.48–3.86) | 1/1200 (mat. age 20–29) | 1/876 |
| | | 45–49 (20–29) | | | 1/448 |
| | | >49 (20–29) | 2.68 (0.76–9.51) | | 1/267 |
| | | 40–44 (25–29) | | | |
| | | 45–49 (25–29) | 4.5 (1.0–20.3) | Use maternal age as baseline for counseling purposes | |
| | None given | >49 (25–29) | 1.45 (1.26–1.68) | | |
| | None given | “May be increased” | | | |
| | | “Paternal age effect in association with maternal age (>35) effect” | 1.28 (1.04–1.57) | | |
| | | | 1.39 (1.04–1.83) | | |
| | Klinefelter syndrome | 50 (20’s) | 1.6c (0.69–3.0) | 1/500 men | 1/312 men |
| Congenital anomalies | VSD | >40 (<40) | 1.69 | 1/200 | 1/118 |
| | ASD | >35 | 1.95 | 1/400 | 1/205 |
| Other complex disorders | Epilepsy | 35–39 | 1.18 (1.02–1.26) | 1/100 | 1/85 |
| | | 40–45 | | | 1/770 |
| | Schizophrenia | >50 (20–24) | 1.3 (1.08–1.55) | 1/100 | 1/22 |
| | | 35–44 (15–24) | 4.62 (2.28–9.36) | | 1/62.5 |
| | | 45–54 (15–24) | | | 1/62.5 |
| | | >54 (15–24) | 1.6 (1.0–2.6) | | 1/26 |
| | | >49 (<25) | 1.6 (0.8–3.1) | | 1/33 |
| | | >32 (<28) | 3.8 (1.3–11.8) | | 1/33 |
| | Autism | >40 (<30) | 3 | 1/1000 | 1/174 |
| | Breast cancer | >40 (<30) | 3 (1.49–6.04) | 1/8.5 | 1/5.3 |
| | Prostate cancer | >38 (<27) | 5.75 (2.65–12.46) | 1/5.9 | 1/3.5 |
| | Multiple sclerosis | 51–55 (21–25) | 1.6 (1.04–2.32) | | |
| | | | 1.7 (1.0–2.8) | | |
| | | | 2.0 (1.35–2.96) | | |
| Other | Spontaneous Miscarriages | >35 (<35) | 1.26 (1.0–1.6) | 1/7 | 1/5.3 |
| | Preeclampsia | 35–44 (25–34) | 1.24 (1.05–1.46) | 1/62 | 1/50 |
| | | >44 (25–34) | | 1/62 | 1/34 |
| | Relative infertility | >39 (<39) | 1.8 (1.04–1.51) | 1/14 couples | 1/6.2 |
| | Low birth weight | | 2.3 (1.67–3.17) | | |
| | | >34 (20–34) | | 1/40 | 1/23 |
| | | | 1.7 (1.3–2.2) | | |

have to mention that application of genetic counseling before gestation has many advantages for aged parents and regarding disadvantages in this respect, we should point to time spent, financial expenditure as well as possible anxiety.

In Respect for justice principle, the concerns are results of insufficient services to poor people. By through incorporation of genetic counseling into primary health care system (PHC), poor people can benefit from these facilities.

Because of insufficient screening or diagnostic tests regarding detection of APA associated diseases in fetus and inability of genetic counselors in offering adequate guidance, parents have to pay more attention prior to decision of gestation.

Although, media are free to show interesting and exceptional documentary programs in order to attract more audiences, this is highly recommended that they express detailed side effects and disadvantages of childbearing in advanced ages along with precautions in this respect before or after such programs.

About importance of subject, we searched in PubMed and sid.ir with Persian and English keywords of ethics, genetic counseling and advanced paternal age but we were able to find few related papers which shows how novel the current subject is. Moreover it shows that people and counselors don't tend to pay attention to possible disease occurrence in Children of aged parents. The important point is that, in modern societies, culture of getting help from genetic counselor's experiences, especially in the cases of APA, is not as important as it should be. Hence it is on part of media and governmental organs such as ministry of health and welfare organizations to institutionalize this trend. The importance of subject is persuasion of more childbearing in society that requires more cares and attention.

**APA and Islamic sources**

Regarding the subject, we were unable to find direct verse or narration in related websites and software database to encourage APA. However in some sources, two points have been mentioned that are as follows;

In the Noble Qur'an, Maryam sura, versus 1-9, has been said that Zechariah would always remain steadfast in prayer to God. As he reached his old age, Zechariah began to worry over who would continue the legacy of preaching the message of God after his death and who would carry on the daily services of the temple after him (33). Zechariah started to pray to God for a son, As the Qur'an recounts "And (Zechariah) said: O my LORD, my bones decay, my head is white and hoary, yet in calling You, O LORD, I have never been deprived. But I fear my relatives after me; and my wife is barren. So grant me a successor of your own who will be heir to me, and heir to the house of Jacob; and make him obedient to You, O LORD" (34). As a gift from God, Zechariah was given a son by the name of John (Yahya).

Narration; Saad Ibn Tarif said that a woman has been brought to Omar. This woman had married with aged man and this oldster had died on his wife's chest. After months, she childbeared but his sons claimed that this newborn is not own our father and they introduced some witnesses. But Imam Ali when saw this boy who couldn't stand up correctly due to his father's senility, Imam Ali found out that this boy is son of this father. Therefore, Imam Ali gathered father's sons and told them this boy is your brother and heir of your father (35).

## Conclusion

Based on the quadruplet ethical principles, the right of aged parents is conserved for

childbearing, but genetic counseling along with conservation of parents' autonomy would be useful to healthy childbearing.

## Conflict of Interest

The authors declared there is no conflict of interest.

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