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ADVANCED PARENTAL AGE AND ITS IMPACT ON PROGENY HEALTH: CORRELATING THE UNANI CONCEPTS WITH MODERN SCIENTIFIC EVIDENCE

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ABSTRACT:
Advanced parental age is an important concern in reproductive medicine due to the global trend towards delayed parenthood. Increasing parental age is associated with reduced fertility, adverse reproductive outcomes, and health problems in offspring. Modern research links these effects to changes in gamete quality, chromosomal instability, oxidative stress, mitochondrial dysfunction, impaired DNA repair, and genetic mutations. Unani medicine provides a complementary perspective through the doctrine of *Quwā* (faculties). It includes *Quwwat Muwallida* (generative faculty), *Quwwat Mughayyira* (transformative faculty), *Quwwat Muṣawwira* (formative faculty), and *Quwwat Māsika* (retentive faculty). These faculties regulate the formation of *Manī* (semen), embryogenesis, and foetal development. This review aimed to explore the effects of advanced parental age on reproductive outcomes and offspring health. It correlates age-related changes in *Ruṭūbat-i-Gharīziyya, Ḥarārat-i-Gharīziyya, Mizāj*, and *Quwā* with current evidence from reproductive biology and genetics. A narrative review was conducted using Unani literature and modern biomedical research. Classical concepts were extracted from *Al-Qānūn fi'l-Ṭibb, Kāmil al-Ṣinā'ah al-Ṭibbiyyah, Kitāb al-Kulliyāt, Dhakhīrah Khwārazm Shāhī*, and other standard references. Modern evidence was obtained from peer-reviewed studies on reproductive aging, reproductive genetics, molecular biology, and epidemiology. Unani literature describes a decline in *Ruṭūbat-i-Gharīziyya and Ḥarārat-i-Gharīziyya* with age. This shifts *Mizāj* towards *Bārid Yābis* and weakens reproductive faculties. Modern evidence shows reduced ovarian reserve and poor oocyte quality with advanced maternal age. Advanced paternal age is linked with declining semen quality, DNA damage, de novo mutations, and developmental disorders in offspring. These findings show a close conceptual relationship between Unani principles and modern reproductive biology.

KEYWORDS: Advanced parental age; *Quwā*; Unani medicine; *Mizāj*; Reproductive outcomes.

Abbreviations
A.D., Anno Domini; AMA, advanced maternal age; AMH, anti-Müllerian hormone; APA, advanced paternal age; ATP, adenosine triphosphate; B.C., Before Christ; CDC, Centers for Disease Control and Prevention; DNA, deoxyribonucleic acid; EAMA, extremely advanced maternal age; FSH, follicle-stimulating hormone; OECD, Organisation for Economic Co-operation and Development; VAMA, very advanced maternal age.

INTRODUCTION
The average age at first childbirth has increased in many developed and developing countries because of prolonged education, career advancement, delayed marriage, economic considerations, and wider availability of assisted reproductive technologies.1–3 As a result, the proportion of pregnancies among women aged 35 years or older and fathers aged 40 years or older has increased steadily, making advanced parental age an important public health concern.1,3
Although delayed parenthood may offer social and economic benefits, increasing evidence indicates that advancing parental age influences reproductive efficiency and offspring health.1 Modern biomedical research has shown that advanced maternal and paternal age are associated with a wide range of adverse reproductive outcomes.3 Advanced maternal age is a well-established risk factor for chromosomal abnormalities, obstetric complications, and adverse perinatal outcomes. Advanced paternal age has also gained recognition because of its

association with impaired sperm quality, accumulation of genetic mutations, and an increased risk of neurodevelopmental and certain congenital disorders in offspring. These associations are largely attributed to age-related changes in gametogenesis, oxidative stress, genetic instability, and reduced cellular repair mechanisms.2–4

The Unani system of medicine, also known as *Ṭibb-i-Unānī*, is a comprehensive, classical healing tradition rooted in the teachings of *Buqrāṭ* (Hippocrates) 460-370 BC, *Jālīnūs* (Galen), and later enriched by eminent Islamic scholars. In Unani medicine, *Umūr Ṭabīʻiyya* (Factors of existence) constitute the foundational framework governing human health, disease progression, and therapeutic intervention.5 Among the seven *Umūr Ṭabīʻiyya*, namely *Arkān* (Elements), *Mizāj* (Temperament), *Akhlāṭ* (Humours), *Aʻḍā'* (Organs), *Arwāḥ* (pneuma), *Quwā* (Faculties), and *Afʻāl* (Functions), *Mizāj* occupies a fundamental role. It reflects the unique physiological, psychological, and reproductive constitution of an individual, thereby influencing overall health and reproductive function.6,7 *Mizāj* not only influences disease susceptibility but also guides diagnostic and treatment protocols in the Unani system. 8 The theory of *Mizāj* is closely linked with the concept of *Ruṭūbat-i-Gharīziyya* (Innate Humour) and *Ḥarārat-i-Gharīziyya* (Innate Heat), both of which change throughout the human lifespan.6 9 In the context of life-stage transitions and constitutional health, *Ibn Sīnā* provides a detailed explanation of *Amrāḍ-i-Shakal* (morphological disorders). He states that such disorders often originate during intrauterine life. According to him, these conditions arise from the weakening of *Quwwat-i-Muṣawwira* (formative faculty) and *Quwwat-i-Mughayyira* (transformative faculty) present in the *Manī*. When these faculties fail to perform their functions effectively, normal formation and differentiation of the fetus are compromised.10

Considering the growing trend of delayed parenthood and the increasing recognition of its implications for offspring's health, it becomes important to explore these phenomena through both traditional and contemporary perspectives. Correlating classical Unani concepts with current biomedical findings may provide a broader conceptual framework for understanding how advanced parental age influences progeny health.

Therefore, the present review aims to examine the impact of advanced parental age on progeny health and to correlate these findings with the Unani concept of reproductive faculties and related principles described in classical texts.

2. MATERIALS AND METHODS

This narrative review was developed using information obtained from classical Unani literature and contemporary biomedical literature. Primary Unani sources were examined to explore the *Asnān Arbaʻa*, age-related physiological changes, and alterations in *Ruṭūbat Gharīziyya, Ḥarārat Gharīziyya, Mizāj*, and *Quwā* with particular emphasis on their possible implications for reproductive health. Major classical sources consulted include *Al-Qānūn fi'l-Ṭibb, Kāmil al-Ṣināʻah al-Ṭibbiyyah, Kitāb al-Kulliyāt, Dhakhīrah Khwārazm Shāhī*, along with other relevant Unani literature.

Modern scientific evidence related to ageing biology, reproductive ageing, molecular biology, hallmarks of ageing, cellular and molecular mechanisms of senescence, age-related alterations in reproductive function, and the effects of advanced parental age on pregnancy and offspring health was retrieved from scientific literature indexed in PubMed, Scopus, Web of Science, and Springer-indexed journals. Relevant literature addressing the biological mechanisms underlying reproductive ageing and age-associated changes in fertility and progeny health was considered for the review.

The information obtained from both traditional and modern sources was critically examined and thematically analysed. The concepts of ageing and age-associated alterations in *Ḥarārat Gharīziyya and Ruṭūbat Gharīziyya* described in Unani literature were interpreted in relation to contemporary concepts of biological ageing, reproductive ageing, cellular senescence, molecular alterations, and reproductive physiology. Particular attention was given to areas where the two knowledge systems provide comparable conceptual explanations, while maintaining the distinction between traditional theoretical constructs and experimentally established biomedical mechanisms.

The findings were subsequently synthesized to develop a conceptual correlation between the Unani understanding of ageing and contemporary evidence on reproductive ageing, its underlying biological and molecular processes, and the potential consequences of advanced parental age for offspring health.

3. *Asnān Arbaʻa* (four stages of life):

Unani scholars have categorized human life into four distinct stages, referred to as *Asnān Arbaʻa* (four stages of life), each governed by a specific type of *Mizāj* and characterized by variations in the quantity and quality of *Ruṭūbat-i-Gharīziyya*.6 7 9 10 The first stage, *Sinn-i-Numū* (Childhood), spans from birth to approximately 30 years and is dominated by a *Ḥārr Raṭb Mizāj* (hot and moist temperament), where *Ruṭūbat-i-Gharīziyya* is in excess, surpassing the requirements for sustaining *Ḥarārat-i-Gharīziyya*.6 7 10 The second stage, *Sinn-i-Shabāb* (Adulthood), occurs between the ages of 30 and 40 years and is governed by a *Ḥārr Yābis Mizāj* (hot and dry temperament). During this phase, *Ruṭūbat-i-Gharīziyya* is sufficiently balanced to preserve *Ḥarārat-i-Gharīziyya* optimally, thereby supporting peak physical strength and metabolic efficiency.6 9 10 The third stage, *Sinn-i-Kuḥūlat* (Middle Age), extends from 40 to 60 years and is marked by a gradual shift towards a *Bārid Yābis Mizāj* (cold and dry temperament).7 The final stage, *Sinn-i-Shaykhūkhāt* (Senility), begins at the age of 60 and lasts until death. It is dominated by a progressively weakening *Bārid Yābis Mizāj*, accompanied by a significant depletion

of *Ruṭūbat-i-Gharīziyya*, which becomes insufficient to sustain *Ḥarārat-i-Gharīziyya,* ultimately resulting in diminished vitality and increased vulnerability to illness. 9

Table 1. Age-Related Variations in Mizāj, Ruṭūbat-i-Gharīziyya, And Ḥarārat-i-Gharīziyya 6,7,9–11

Stage of Life	**Approximate Age Range (Years)**	**Dominant Mizāj (Temperament)**	**Status of *Ruṭūbat-i-Gharīziyya* (Innate moisture)**	**State of *Ḥarārat-i-Gharīziyya (Innate* heat)**	**Key Physiological Characteristics**
Sinn-i-Numū (Childhood)	Birth~ 25	*Ḥārr Raṭb* (hot and moist)	Excessive; exceeds the requirement for sustaining *Ḥarārat-i-Gharīziyya*	Well supported due to abundance of innate moisture	Active growth and development, high regenerative capacity
Sinn-i-Shabāb (Adulthood)	25-35	*Ḥārr Yābis* (hot and dry)	Balanced; sufficient to maintain *Ḥarārat-i-Gharīziyya* optimally	Preserved at an optimal level	Peak physical strength, metabolic efficiency, and vitality
Sinn-i-Kuhūlat (Middle Age)	35-60	Shift towards *Bārid Yābis* (cold and dry)	Gradually declining	Slowly weakened due to reduced *Ruṭūbat-i-Gharīziyya*	Gradual decline in strength and physiological functions
Sinn-i-Shaykhūkhāt (Senility)	≥60	*Bārid Yābis* (cold and dry)	Markedly depleted; insufficient to sustain *Ḥarārat-i-Gharīziyya*	Significantly diminished	Reduced vitality, increased susceptibility to illness

4. *Quwā* (Faculties):

In Unani medicine, *Quwā* are one of the seven *Umūr Ṭabī'iyya*, ranked sixth in the hierarchy.5,6,7,9,10. They are intrinsic powers that enable the organs to perform various physiological functions, essential for maintaining life and ensuring the continuity of the species. No bodily function occurs without a corresponding *Quwwat,* making them the causative agents of all *Af'āl*. Unani scholars classify *Quwā* into three main types: *Quwwat Ṭabī'iyya* (Natural Faculty), *Quwwat Ḥaywāniyya* (Vital Faculty), *Quwwat Nafsāniyya* (Psychic Faculty). 6,10,11

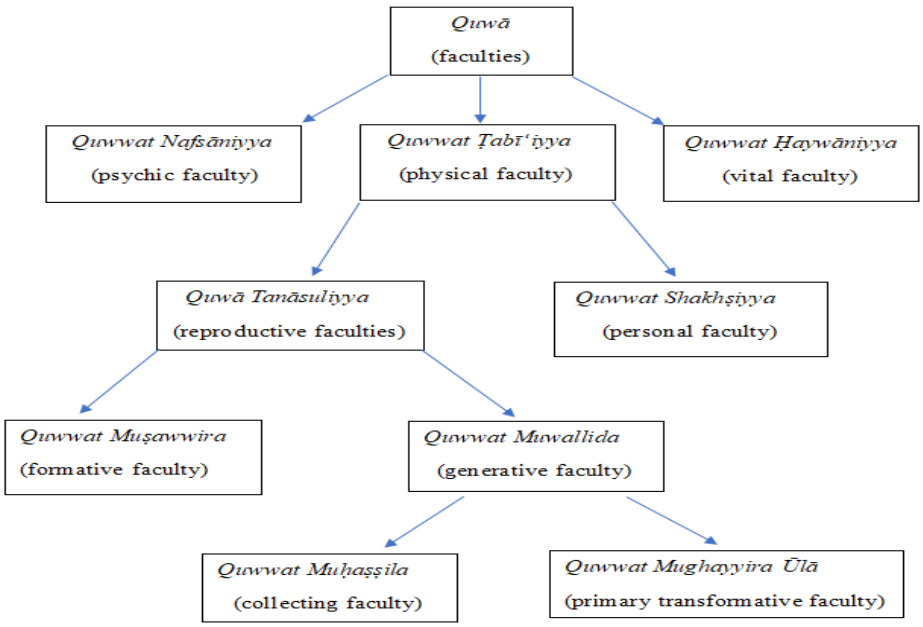

Fig. Classification of *Quwā*

Quwwat-i-Tanāsuliyya (Reproductive Faculty): This faculty is responsible for reproductive functions, including the generation of offspring, preservation of the species, and regulation of reproductive organs and secretions.6

5. Concept of *Manī:*

According to early Unani authorities, the concept of *Manī* has been explained in different ways. *Rabban Ṭabarī* (810–895 A.D.) described *Manī* as a substance that originates from the concoction of blood. *Ḥakīm Kabīruddīn* further elaborates tha*t Manī* is a specific white fluid formed in the *Khuṣyatayn* (gonads) of both males and females. It possesses a distinct odour, resembling that of *Khurmā* (dates).5

From the perspective of Hippocrates (460–370 B.C.), *Manī* appears to be a *Mutashābih al-Ajzā'* (homogeneous substance), but in reality, it is not so. Rather, it is composed of diverse constituents with distinct *Mādda* (matter) and *khawāṣṣ* (peculiar properties). For this reason, philosophers referred to it as *Mushābiha al-Imtizāj*, meaning that although *Manī* appears uniform, it is actually a composite of multiple elements with different characteristics.6

In the framework of Unani medicine, *Manī* is considered a form of *Fuḍla* (waste product). However, unlike morbid waste products such as *Barāz* (faeces), *Bawl* (urine), and *'Araq* (sweat), which are harmful if retained, *Manī* belongs to the second category of waste matter. This type is generated from the refinement of essential *Ghidhā*' (nutriment) and, although it is surplus for the individual, it is indispensable for the preservation of the species. A classical analogy is drawn from *Laban* (mother's milk): it is waste matter for the mother, yet it is essential nourishment for the infant. Similarly, *Manī* is a superfluous product for the adult body but plays a vital role in the continuity of human life.5,6,12

5.1 Mechanism of formation of *Manī*:

The formation of semen in Unani physiology is attributed to the harmonious action of *Quwā* governed by *Ṭabī'*at (Physis).

1.Role of *Quwwat-i-Muwallida* (Generative faculty)

oThe *Quwwat-i-Muwallida* is the principal faculty responsible for procreation. It acts through its sub-faculty, *Quwwat Muḥaṣṣila* (collecting faculty), which draws the raw material of *Manī* from the *Amshāj-i-Badan* (basic body compounds containing hereditary characteristics).6

2.Retention by *Quwwat-i-Māsika* (Retentive Faculty)

oBlood, circulating throughout the body, requires a specific duration of retention for transformation. The convoluted vascular structures of the *Khuṣyatayn* allow *Quwwat-i-Māsik*a to retain the blood, providing the necessary time for change.6,12

3.Transformation by *Quwwat-i-Mughayyira* (Transformative Faculty)

oQuwwat-i-Mughayyira of gonads acts upon the retained material under the influence of *Harārat-i-Gharīziyah*. This heat is an indispensable tool of *Ṭabī'at*, affecting the conversion of blood into semen.6 12

Thus, the gonads function as the site where nutritive matter is refined, retained, and finally transformed into *Manī*.5,6,12

6. *Takwīn-i-Janīn*:

In Unani medicine, the initiation of *Takwīn-i-Janīn* (Formation of fetus) is described as a systematic process governed by both material and functional principles. According to the classical physicians, the process begins when *Manī* is discharged into the vaginal tract and advances towards the fallopian tube.5,7,13 Owing to its *Mizāj-i-Ḥārr* (hot temperament), the male *Manī* is endowed with inherent motility, enabling it to actively move towards the site of the female *Manī*, where the initial stage of fusion occurs.11 Unani scholars emphasize that the male *Manī* functions as the active formative principle due to its heat and mobility, while the female *Manī,* together with *Dam-i-Ḥayḍ* (menstrual blood), provides the receptive and nutritive substratum necessary for embryonic nourishment.5,7

Further elaboration is provided by *'Ali ibn al-'Abbās al-Majūsī* (Haly Abbas, 10th century). He explained that following fertilization, the *Quwwat-i-Māsika* of the *Raḥim* (uterus) becomes operative, securing the fused entity within the uterine environment. This retention is regarded as indispensable, since it ensures stability, protection, and continuity of growth for the developing conceptus. In the absence of this faculty, the fertilized entity would fail to implant, and pregnancy could not be sustained.11

6.1 Gestational stages of embryo development:

1. *Zubdah* (Froth Stage)

As described by *Ibn Hubal Baghdādī* (12th century) and *Jurjānī* (11th century), the first week of embryonic development is known as *Zubdah*, meaning froth. When male and female *Manī* combine to form the zygote, it exhibits a frothy or foamy appearance due to its innate heat.7,11,13 This stage may correspond with the process of cleavage in modern embryology, during which the zygote undergoes rapid mitotic cell divisions, giving it a bubble-like appearance.

2. *'Alaqah* (Leech-like Stage)

The second week of development is termed '*Alaqah*, derived from the Arabic word for leech. During this period, a trophoblastic layer forms around the zygote, enabling it to attach firmly to the uterine wall. The analogy of a leech reflects both its appearance and its function, as the developing embryo adheres to the uterine lining and derives sustenance by absorbing maternal nutrients, much like a leech.7

3. *Muḍghah* (Chewed Flesh Stage)

By the end of the fourth week, the embryo enters the *Muḍghah* stage, literally described as resembling a piece of flesh. At this phase, the *A'ḍā' Ra'īsa* (vital organs) begin to differentiate and separate from one another. The

comparison to chewed flesh highlights the irregular surface impressions formed as tissues and organ primordia emerge, a description that aligns with modern observations of early organogenesis.7,13

4. *Janīn* (Embryo/Foetus Stage)

By the second month of gestation, the embryo is fully formed and is referred to as the *Janīn.* At this stage, the organs are distinguishable, and structural development becomes more pronounced. With the emergence of sensation and movement, the *Janīn* is elevated to the stage of *Ḥaywān* (living being/animal), signifying the transition from mere structural existence to a dynamic entity exhibiting life functions.7,9,11,13

6.2 Organ Formation:

According to Unani philosophers and physicians, the faculties *Quwwat Mughayyira Ūlā* (primary transformative faculty) and *Quwwat Muṣawwira* (formative faculty) play a central role in the formation and differentiation of foetal organs.5,6 These *Quwā* are inherent in *Manī* and *Nuṭfa*, and initiate their action soon after conception. Once the *Mizāj* of the embryo is established, the *Quwwat Mughayyira Ūlā* refines individual parts, imparting them with organ-specific temperament, consistency, and function.6 *Ibn Hubal Baghdadi* describes the function of this formative faculty as not only producing cavities such as pericardial, pleural, and abdominopelvic spaces, but also determining the surface texture of organs according to their characteristic needs.7

It is emphasized in Unani literature that the action of *Quwwat Mughayyira Ūlā* ceases once each part of the embryo becomes sufficiently prepared for organogenesis, while the role of *Quwwat Muṣawwira* also concludes once the structural design is achieved. Thereafter, the processes of growth and functional adaptation are carried forward by *Quwwat-i-Nāmiya* (faculty of growth) and *Quwwat Ṭabī'iyya*.6,10,11 Moreover, the maternal contribution of *Quwwat Ḥaywāniyya* is crucial during the early embryonic stages, until the fetal heart develops and begins to sustain its own functions. At this juncture, the embryo becomes capable of receiving the influences of both *Quwwat Ṭabī'iyya* and *Quwwat Nafsāniyya*.

In this framework, *Raḥim* is not only considered a nurturing environment that provides diet, protection, and requisite heat for the growth and development of the fetus, but also as the exclusive site where the *Quwwat Mughayyira Ūlā* and *Quwwat Muṣawwira* operate. These faculties are limited to the embryonic stage and are not active in postnatal life. Thus, the sequential and coordinated action of these *Quwā* ensures the transformation of *Nuṭfa* into a fully formed foetus with organ-specific temperament, structure, and function.6,11

7. Unani Basis of Reproductive Ageing:

Sinn-i-Kuḥūlat corresponds to middle age, spanning from approximately 35-40 years to 60 years. In this phase of life, the *Mizāj* begins to shift gradually towards *Bārid Yābis.* This transformation is primarily due to the progressive decline of *Ruṭūbat-i-Gharīziyya*, which plays a pivotal role in maintaining and safeguarding *Ḥarārat-i-Gharīziyya.* As *Ruṭūbat-i-Gharīziyya* diminishes, it becomes inadequate to support *Ḥarārat-i-Gharīziyya,* resulting in a corresponding decrease in vital heat. Since *Ruṭūbat-i-Gharīziyya* serves as the protective medium for innate heat and is continuously consumed throughout life, its depletion is a natural and irreversible process. Consequently, during this phase, the gradual decline of the *Quwā* begins, leading to reduced physiological efficiency and the early signs of functional deterioration.6,7,9–11

In advanced age, the process of formation of *Manī* is compromised due to the decline of *Quwwat-i-Muwallida,* which is responsible for extracting and refining the raw material of *Manī.* Consequently, the *Manī* produced in this stage of life becomes defective and deficient in vitality. If such a defective *Manī* participates in conception, the inherent *Quwwat Muṣawwira* and *Quwwat Mughayyira Ūlā* present in the *Nuṭfa* fail to perform their functions adequately. This functional impairment predisposes the offspring to genetic anomalies and structural malformations.

Furthermore, in advanced maternal age, the *Raḥim* itself is affected by the shift towards a cold and dry temperament. As a result, it is unable to provide the requisite *Ḥarārat* necessary for the nourishment, growth, and proper structural development of the foetus. This dual pathology, defective gametogenesis in parents and an inhospitable uterine environment in mothers, collectively increases the likelihood of genetic disorders, developmental defects, and poor viability in offspring.

8. Advanced Parental Age: Definition and Epidemiology

8.1 Advanced Maternal Age:

Advanced maternal age (AMA) is conventionally defined as pregnancy at 35 years or older at the expected date of delivery. This age threshold was introduced because the risk of fetal chromosomal abnormalities and pregnancy-related complications increases after 35 years. Women aged 40 years or above are commonly classified as having very advanced maternal age (VAMA), whereas pregnancies at 45 years or older are considered extremely advanced maternal age (EAMA).14 Although these categories are widely accepted in obstetric practice, maternal age acts as a continuous risk factor and adverse reproductive outcomes increase progressively with advancing age rather than at a single cut-off.14–16

8.2 Advanced Paternal Age:

Unlike maternal age, there is no universally accepted definition of advanced paternal age (APA).17,18 Most clinical studies define APA as 40 years or older, whereas others use a threshold of 45 years depending on the study population and outcome of interest. This variation reflects the gradual decline in male reproductive function with age and the absence of a clear biological transition comparable to menopause in women. Nevertheless, advancing paternal age has gained increasing attention because of its association with impaired fertility, genetic alterations, and adverse health outcomes in offspring.1,17,18

8.3 Epidemiology

Delayed parenthood has become increasingly common worldwide. The proportion of pregnancies among older mothers and fathers has increased steadily over the past few decades, making advanced parental age an important public health concern.1

Maternal age at first childbirth has increased across many high-income countries and is also rising in several middle-income nations. According to the Organization for Economic Co-operation and Development (OECD), the average age at first birth has increased steadily during the past three decades in most member countries. Similar demographic changes have been reported across Europe, North America, Australia, Japan, and South Korea.19

In the United States, the Centers for Disease Control and Prevention (CDC) has documented a continuous rise in births among women aged 35 years and older over the past three decades. Birth rates among women aged 40–44 years have also increased steadily, reflecting the growing contribution of older mothers to overall births.14

A similar demographic shift has been observed among fathers. The average age of fatherhood has increased in many countries because of changing social and economic patterns. Population-based studies from Europe and North America have reported a steady rise in the proportion of fathers aged 40 years and above. Although men remain fertile throughout life, delayed fatherhood has become increasingly relevant because of its association with adverse reproductive and offspring outcomes.17,20

9. Biological Basis of Reproductive Aging (Modern Medicine)

9.1 Female

9.1.1 Decline in Ovarian Reserve

Female reproductive aging is associated with a gradual decline in ovarian reserve. The number of primordial follicles decreases continuously throughout life because of follicular atresia and ovulation.21,22 This decline accelerates after the mid-thirties and results in reduced fertility and lower chances of natural conception. Serum *anti-Müllerian* hormone (AMH) and inhibin B levels decrease, whereas follicle-stimulating hormone (FSH) levels increase, reflecting diminished ovarian function.21,22

9.1.2 Oocyte Aging

Human oocytes remain arrested in prophase I of meiosis from fetal life until ovulation. Prolonged meiotic arrest leads to spindle abnormalities, impaired chromosome segregation, reduced DNA repair, and loss of chromosomal cohesion. These changes reduce oocyte quality and increase the risk of meiotic errors.23,24

9.1.3 Mitochondrial Dysfunction and Chromosomal Nondisjunction

Advancing maternal age impairs mitochondrial function and increases oxidative stress, resulting in reduced ATP production and compromised oocyte competence.25,26 Defective spindle assembly and weakened chromosomal cohesion further increase the risk of chromosomal nondisjunction.27 Consequently, fetal aneuploidy increases progressively with advancing maternal age. Large population-based cohort studies have consistently demonstrated that the incidence of chromosomal abnormalities rises markedly after 35 years of age, with trisomy 21, trisomy 18, and trisomy 13 showing the strongest age-related increase.28,29

9.2 Male

9.2.1 Decline in Semen Quality

Male reproductive aging is associated with gradual deterioration in semen quality. Semen volume, sperm motility, morphology, and vitality decline with age because of reduced Sertoli and Leydig cell function and impaired spermatogenesis. Testosterone levels also decrease progressively, contributing to reduced reproductive potential.30

9.2.2 DNA Damage, Oxidative Stress, and Epigenetic Alterations

Aging sperm exhibit increased DNA fragmentation, oxidative stress, and epigenetic alterations. The continuous division of spermatogonial stem cells also leads to the accumulation of de novo genetic mutations with advancing age. Together, these changes impair sperm function, reduce fertilization potential, and increase the risk of adverse reproductive outcomes and genetic disorders in offspring.30,31

9.2.3 Adverse Reproductive Outcomes and Offspring Health

Advanced parental age is associated with adverse reproductive outcomes and long-term health effects in offspring. Advanced maternal age is linked to reduced fertility, spontaneous miscarriage, fetal aneuploidy, and chromosomal disorders, including Down syndrome (trisomy 21), Edwards syndrome (trisomy 18), Patau syndrome (trisomy 13), Turner syndrome (45, X), and Klinefelter syndrome (47, XXY). 16,23–25Advanced paternal age has been associated with impaired fertility and an increased risk of adverse offspring outcomes, particularly neurodevelopmental disorders such as autism spectrum disorder, schizophrenia, and bipolar disorder.30 It has also been linked to congenital skeletal dysplasia, including achondroplasia, and certain childhood malignancies, such as acute lymphoblastic leukemia and retinoblastoma.31,32 Collectively, these findings emphasize that both maternal and paternal aging influence reproductive success and contribute to the genetic and developmental health of future generations.

The combined effects of maternal and paternal aging compromise gamete quality and reproductive capacity. These biological changes provide the mechanistic basis for the increased risk of adverse reproductive and offspring outcomes associated with advanced parental age. Current biomedical evidence thus highlights the importance of recognizing parental age as a critical determinant of reproductive and perinatal outcomes, warranting careful clinical counselling and risk stratification in reproductive medicine.

10. DISCUSSION

Advanced parental age is increasingly recognized as an important factor influencing reproductive outcomes and offspring health. Contemporary evidence shows that increasing maternal and paternal age is associated with reduced fertility, adverse pregnancy outcomes, and a higher risk of genetic and developmental disorders.1–4 These effects arise from age-related changes in gamete quality rather than chronological age alone. In women, reproductive aging is associated with reduced ovarian reserve, deterioration of oocyte quality, mitochondrial dysfunction, oxidative stress, impaired DNA repair, and chromosomal nondisjunction.21,23,26,28 In men, reproductive aging is characterized by declining semen quality, increased DNA fragmentation, oxidative stress, epigenetic alterations, and accumulation of de novo mutations due to continuous spermatogonial cell divisions. Together, these changes compromise reproductive capacity and increase the likelihood of adverse reproductive and offspring outcomes.16,30,31

Unani medicine offers a complementary explanation through the concept of *Asnān Arba'a* and age-related changes in *Ruṭūbat-i-Gharīziyya, Ḥarārat-i-Gharīziyya, Mizāj,* and *Quwā. Sinn-i-Kuḥūlat* and *Sinn-i-Shaykhūkhāt* are characterized by a gradual shift towards a *Bārid Yābis* temperament, accompanied by depletion of innate moisture and weakening of innate heat.6,7,9–11 These changes weaken *Quwwat-i-Muwallida, Quwwat-i-Mughayyira, Quwwat-i-Muṣawwira*, and *Quwwat-i-Māsika*, resulting in defective *Manī,* impaired embryogenesis, and reduced reproductive capacity. Unani literature also considers the *Raḥim* an essential determinant of successful pregnancy. Age-related changes in uterine temperament are believed to reduce its ability to provide adequate nourishment, retention, and support for the developing embryo.

The present review demonstrates several conceptual similarities between classical Unani principles and contemporary biomedical evidence. Modern medicine explains reproductive aging through molecular, genetic, hormonal, and cellular changes; however, Unani medicine attributes it to the gradual decline of *Ruṭūbat-i-Gharīziyya* and *Ḥarārat-i-Gharīziyya,* leading to weakening of *Quwā* and alteration of *Mizāj*.1,3,6,9–11,23,25 Although the explanatory models differ, both systems recognize that advancing age reduces reproductive capacity and increases the risk of adverse reproductive outcomes.

A close conceptual relationship is also evident in gamete formation. Modern evidence attributes impaired gamete quality to mitochondrial dysfunction, oxidative stress, chromosomal abnormalities, and accumulation of de novo mutations. Unani medicine explains defective *Manī* through impairment of *Quwwat-i-Muwallida*, *Quwwat-i-Mughayyira,* and *Quwwat-i-Māsika*. Likewise, both systems consider the embryonic stage critical for normal fetal development. Modern embryology links disturbances during early embryogenesis with congenital anomalies and pregnancy loss, whereas classical Unani literature attributes these abnormalities to defective formative and transformative faculties. Both perspectives also emphasize the importance of the intrauterine environment. Modern studies associate reproductive aging with reduced endometrial receptivity and impaired placental function, while Unani medicine describes age-related changes in the *Raḥim* that reduce its ability to support implantation and fetal growth.

Despite these similarities, important differences should be acknowledged. Modern medicine explains reproductive aging through experimentally validated molecular and cellular mechanisms. In contrast, Unani medicine interprets these changes through the concepts of *Ruṭūbat-i-Gharīziyya*, *Ḥarārat-i-Gharīziyya, Mizāj, and Quwā*. Therefore, the correlations presented in this review should be understood as conceptual rather than direct biological equivalence.

A major strength of this review is the integration of classical Unani concepts with current evidence from reproductive biology and genetics. This approach provides a broader understanding of reproductive aging while preserving the theoretical framework of both systems.

The review has certain limitations. The Unani concepts discussed are derived from classical literature, and their correlation with modern reproductive biology remains interpretative. Direct experimental evidence linking *Mizāj, Quwā,* or *Ruṭūbat-i-Gharīziyya* with specific molecular or genetic markers is limited. In addition, variation in the definition of advanced paternal age across studies may influence comparison of reported outcomes.

Future research should focus on evaluating classical Unani concepts using contemporary scientific methods. Studies exploring the relationship between *Mizāj*, reproductive biomarkers, gamete quality, and reproductive outcomes may provide stronger evidence for these conceptual correlations. Collaborative research involving reproductive medicine, genetics, and Unani scholars may further improve the understanding of reproductive aging and support the development of integrative approaches to preconception counselling and reproductive healthcare.

Overall, this review demonstrates that classical Unani medicine and modern biomedical science, despite their different theoretical foundations, arrive at similar observations regarding the effects of advancing parental age on reproduction. Integrating these perspectives provides a broader understanding of reproductive aging and may guide future interdisciplinary research in reproductive medicine.

11. CONCLUSION

Advanced parental age is associated with reduced reproductive potential and an increased risk of adverse reproductive and offspring outcomes. Although Unani medicine and modern biomedical science explain these changes through different theoretical frameworks, both recognize that aging adversely affects gamete quality, embryonic development, and reproductive success. The conceptual correlation presented in this review provides

an integrative perspective on reproductive aging and highlights the need for further interdisciplinary research to strengthen the evidence base for integrative reproductive medicine.

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