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Review

Periconceptual care and offspring health at birth and long term, from the perspective of Avicenna**Mohammad Ansaripour¹, Mohsen Naseri², Mohammad Mahdi Esfahani³, Iraj Nabipour⁴, Fatemeh Rakhshani⁵, Arman Zargaran⁶, Roya Kelishadi⁷**

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ABSTRACT

Periconceptual care such as lifestyle plays an important impact role in offspring health. The aim of the present study was to clarify the perspective of Avicenna on periconceptual care. Avicenna (980–1037 A.D.) was one of the outstanding Persian physicians, who made great contributions to the field of medical sciences, in particular, obstetrics. In advance, Avicenna's book, *Canon of Medicine*, was considered to find his perspectives on periconceptual care. Then, his ideas and theories were compared to the current findings by searching the keywords

in main indexing systems including PubMed/MEDLINE, Scopus and Institute for Scientific Information Web of Science as well as the search engine of Google Scholar. Current investigations show that gamete quality, pregnancy outcome, and offspring health at birth and long term depend on both parents' lifestyle in pre- and periconceptual period, as well as the intrauterine environment. Avicenna believed that seminal fluid, sperm, ovum, and developing conditions *in utero* were influenced by the stages of food digestion and the function of some organs. On the other hand, food digestion and function of the organs also depend on each parent's lifestyle and environmental factors. He mentioned 6 principles of healthy lifestyle: exercise, nutrition, sleep and awareness, excretion of body wastes and retention of necessary materials, psychic features, as well as air and climate. Thus, a multicomponent healthy lifestyle should be considered by parents of child-bearing age in an appropriate period before and in early pregnancy as well as elimination of any disorders in parents, to give birth to more healthy offspring.

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1. Introduction

The periconceptual period is associated with future noncommunicable diseases in adulthood [1,2]. In humans, this period consists of about 14 weeks before and 10 weeks after conception, and the essential reproduction processes including gamete production and early embryogenesis occur in this period [3]. Gamete quality, pregnancy outcome, and fetus health depend on both parents' lifestyle in pre- and periconceptual period, as well as the intrauterine environment [1,3–5]. Adulthood diseases including coronary heart disease, hypertension, stroke, type 2 diabetes, and osteoporosis are attributed not only to

environmental and genetic factors but also *in utero* conditions [1,6]. It is believed that traditional medicine systems can help to promote various health issues in communities; thus, the World Health Organization intends to integrate traditional medicine into official health systems worldwide [7].

Persian medicine (PM) is one of such traditional medicine systems that focus on lifestyle to maintain health and treat numerous diseases [8–10]. PM has a long history dating back to at least 8000 years ago. Later, in the early medieval period (9th–12th century A.D.), PM became the main medical system in the Islamic civilization with an extension from the border of China to Western Europe, famous scientists and verbal sources in different languages [10,11].

Avicenna (980–1037 A.D.) was one of the outstanding Persian physicians in that era who made great contributions to the field of medical sciences, in particular obstetrics [10]. His great medical encyclopedia, the *Canon of Medicine* [10], was considered as the main medical textbooks in medical universities in the East and West until the 17th century A.D. It was also used in some Western countries like Belgium until the early 20th century A.D. [12]. Although in the current view, the healthy lifestyle basically focuses on nutrition and exercise [13–15], Avicenna mentioned 6 principles for health (called as *Setteh Zarorieh*) as essential topics in lifestyle issues in this book [10,12].

The present study aimed to review the Avicenna's points of view on periconceptual care based on *Canon of Medicine*. Moreover, his ideas were compared to the current findings to evaluate his knowledge on the subject.

Avicenna's birthplace was *Afshaneh*, a village near Bukhara (the capital of Samanid dynasty) in northeast Persia. He was a master of medicine, chemistry, logic, astronomy, and philosophy in the 10th century [16]. At the age of 17, he served as a physician in the court of the king of Bukhara [16]. The *Canon of Medicine*, his great medical book, has 5 volumes. Volume 3 has 3 chapters on urology, obstetrics, and gynecology. He discussed pregnancy, prenatal, and postpartum care in this book [17]. Current investigations show that he has explained correctly contraception recipe [18], prenatal and perinatal care [16], the heart as the first functional organ of fetus [19], as well as definition and treatment of abnormal uterine bleeding with medicinal plants [20] and extraction of placenta after delivery [21], and perineal injury and its surgical treatment [22]. He knew some medicinal plants like *Berberis vulgaris* as an abortive agent [17].

We considered Avicenna's *Canon of Medicine* to find his perspectives on the reproductive system in both male and female, healthy gamete, and healthy lifestyle.

Then, his ideas and theories were compared to the current findings by searching the keywords (exercise, nutrition, sleep, mental health, season, and offspring health with periconceptual period, semen quality, healthy lifestyle, Avicenna, Persian medicine, and traditional medicine) in the main indexing systems including PubMed/MEDLINE, Scopus and Institute for Scientific Information Web of Science as well as the search engine of Google Scholar.

2. Gamete disorders

2.1. The general understandings

Avicenna believed that the origin of the genesis of human's body is the male's semen and female's ovum. He mentioned that the health of offspring depends on the health of semen and ovum [23]. Also, in PM, it was believed that the sperm, semen, and ovum could be disordered as a result of inappropriate lifestyle and nutrition [24]. Current findings support Avicenna's beliefs. It is known that the cytological and molecular changes in the process of ovulation, fertilization, and fetal development during the periconceptual period affected by environmental factors, cause potential metabolic abnormalities in developing embryo, and also affects the long-term health of the child [1,25]. These changes, which lead to epigenetic inheritances, are the biologic processes that cause meiotic and mitotic changes in gene description without changing the sequence of deoxyribonucleic acid.

The changes include ubiquitination, and phosphorylation, all of which happen in relation to the environment and are called epimutation. The inheritable components or the potentiality for familial diseases based on nongenetic factors and environmental effects are transferred at the early stage of forming the risks of diseases. This nongenetic alteration in phenotype is a response to environmental factors [6].

The increased risk of developing type 2 diabetes, brain stroke, and osteoporosis in adulthood is considered as a result of mother's malnutrition or impediment in placenta, and rapid environmental changes resulting from improvement of social and economic factors. These changes can be seen in more than one generation. The role of epigenetic processes is identified in the early stages of some forms of cancers [6,26,27].

2.2. The relationship between gamete production and organs function

Avicenna described four stages and levels affecting the food in the body, which was called "Hazm"; it means digestion and it is similar to the concept of metabolism. These stages were gastric, hepatic, vascular, and organic stages. It was believed that the first stage is gastric digestion. Also, humors (yellow and black bile, phlegm, and blood) are produced during the

second stage. Then, humors are consumed by the organs of the body. All these four stages have a longitudinal relationship with each other and emerge one by one [23]. Avicenna believed semen (*mani*) is one of the products in the fourth stage (organic) [17]. He noticed to pay attention to the gastric stage, in order to have healthy semen alongside good nutrition. If there is a poor function of the gastrointestinal tract, the stages of digestion will be impaired, even with suitable nutrition. Avicenna believed that correct function of all organs of the body depends on the healthy lifestyle [23].

3. Components of a healthy lifestyle

In PM, health maintenance is dependent on the 6 essential factors as described in Table 1 [9,10,23]. Of these 6 factors, exercising, nutrition, and sleep are of utmost importance [23]. Avicenna believed that all of the reactions in the body, especially the changing stages of food, are under the influence of these factors. Consequently, the functions and quality of the end products of organs like seminal fluid, sperm, and ovum are affected by these 6 essential factors [23].

Table 1. Healthy lifestyle components in Persian medicine.

Number	Healthy lifestyle factors	Current interpretation
1	Sufficient movement and rest	Physical activity
2	Fit to man use of food and drinks	Nutrition/diet
3	Suitable sleep and wakefulness	Sleep
4	Good ambient air	Weather/climate
5	Excretion of body wastes and retention of necessary materials	Stability of the internal environment
6	Control of psychological reactions	Mental health

3.1. Exercise/physical activity

There seems to be no need to explain the importance of exercise and diet in the current scientific era, but it is worth mentioning that in PM, enough exercise was defined as starting to sweat, and tachypnea without feeling exhausted. In terms of intensity and duration, moderate exercise stimulates heat in the body [23]. It seems that elevating heat improves food digestion process and other stages of food metabolism in the body.

Avicenna mentioned that moderate exercise could prevent some diseases by excreting of body wastes and facilitating food digestion. It makes the body agile. Good digestion leads to a lower accumulation of waste matters in the body [23,28]. The best time for exercise is after evacuating urine and feces and before eating [23].

Excretion of body wastes and proper gastric digestion also make a hepatic and cellular function or metabolism to operate much better [29], and in turn improve the quality of the

end products of the fourth stage of food metabolisms like hormones, enzymes, seminal fluid, sperm, and ovum.

In recent studies, the potential benefits of regular exercising on health include blood pressure reduction, a decreased risk of cardiovascular diseases, body weight management, improved insulin sensitivity and glucose metabolism, reduced oxidative stress, decreased concentrations of pro-inflammatory cytokines and C-reactive protein in peripheral circulation, and improved plasma lipid and lipoprotein profiles [30,31]. These advantages and their positive effects on parents' health may impact fetal development [30]. For example, short-term and long-term effects of physical activity on offspring's health would be the reduction of risk of neural tube defects (NTDs) and improvement of youth academic performance, respectively [30,32].

3.2. Nutrition and dietary habits

From the perspective of Avicenna, two types of foods are considered. Type one has a nature like human temper of which the consumption is unlimited and the other has a hot, cold, dry and moist nature with a limited consumption due to changing temperament of the body. Examples of food of cold and moist nature are yoghurt and lettuce. Additives like pepper and thyme, and vegetables like mint have a hot and dry nature [23]. Current findings demonstrate that foodstuffs with hot or cold nature have biochemical and physiological effects. These effects include a change in thermogenesis, autonomic nervous system, immune systems, endocrine system, digestive enzymes [33,34,35], central temperature and energy expenditure [36]. Thus, Avicenna believed that foodstuffs should be selected more from the type one. The most important foods of type one are the meat of young lamb, good-quality bread (prepared from fully fermented flour of whole organic wheat), compatible sweets and also fig and grape as fruits [23].

Red meat especially lean lamb, as a protein with high biological value, provides all essential amino acids, vitamins, and minerals. A balanced diet with moderate amounts of red meat meets the needs for health [37,38].

Bread, specially made from the whole wheat flour, consists of complex carbohydrates, proteins, lipids, fiber, vitamins, minerals, and enzymes as well as antioxidant agents. Bread prepared from fully fermented flour and bran is more nutritious than nonfermented food product and makes the minerals more available to the body due to the reduction of phytic acid levels. Consumption of bread in balanced quantity can provide a significant amount of nutrients for the body. The complex carbohydrates help balance blood glucose levels [39,40].

Fig (*Ficus carica* L.) as an important source of minerals and vitamins has several biological activities including antibacterial, antiviral, antifungal, antihelminthic, antioxidant, and anticarcinogenic. It can treat constipation [41].

Another fruit that Avicenna has introduced is grape (*Vitis vinifera*) which has a variety of biological properties including anti-inflammatory, antioxidant, anticancer, antimicrobial, antiviral, hepatoprotective, cardioprotective, and neuroprotective activities. Polyphenols in grapes have beneficial effects on obesity, metabolic syndrome, and type 2 diabetes. Also, utilization of grape products may lead to cognitive improvements [42,43].

These foodstuffs introduced by Avicenna have beneficial effects on homeostasis which help develop the good conditions *in utero* during the periconceptual period.

Drinking extremely cold water in the wrong time may harm the liver, seminal fluid, and sperm by contracting the canals and vessels, as well as lowering the nourishment of fetus.

Before breakfast, and immediately after exercising, bathing, and sexual intercourse are among the wrong times for drinking cold water [17,23]. Parents must consume suitable foods all of the time, especially during the periconceptual period. Suitable foods mean different kinds of food and moderate in amount and nature. Food should be eaten in moderate amount when you feel hungry and should be chewed completely [23].

New findings show that an excess in demand for energy and nutrients occurs during pregnancy because of an increased cellular metabolism, developing concepts, and extending tissues associated with pregnancy and maternal adipose tissue storage. Protein translation, enzymatic reactions, and gene expression regulation need to adjust maternal macronutrient and micronutrient supply, which affect the short-term and long-term health of the child [1,44].

Table 2 shows the nutrient requirements during pregnancy. The baseline estimates of protein vary according to the country but the protein recommended daily allowance of 0.8 g/kg current body weight per day is recommended during the periconceptual period [45].

Table 2. Nutrient requirements during pregnancy.

Nutrient	United States, Canada	World Health Organization
Calories (added to baseline, kcal)	340–452	85–475
Protein	Base + 0.3 g/kg current body weight per day	Base + (0.7–31.2) g/d
Fat	–	Polyunsaturated fatty acid 6%–11% kcal
Linoleic acid	13 g	Omega-6 2.5%–9% kcal
α -Linolenic acid	1.4 g	Omega-3 0.5%–2% kcal
Carbohydrate	175 g	55% kcal

Folate (μg)

600

600

Parental malnourishment in the periconceptional period may result in developing obesity, inflammation, glucoregulatory pathways disruption, hypertension, and metabolic syndrome conditions in offspring during aging. Maternal malnourishment can increase the risk of preterm birth, low birth weight, intrauterine growth restriction, iodine deficiency disorders, and NTDs [4,46,47]. Animal studies demonstrate maternal nutrition state can influence blood and reproductive tract metabolite concentrations and fetal development [44]. Maternal obesity can lead to developing gestational diabetes, giving birth to a large infant and preterm delivery [48,49]. Both higher and lower intakes of carbohydrates are problematic. Lower dietary intakes of total carbohydrate, fructose, and linoleic acid are associated with the increased risks of d-transposition of great arteries (dTGA) and higher intakes of the high-glycemic index foods in obese women are associated with the increased risk of NTDs [50,51]. The association between balanced protein energy supplementation during the periconceptional period and the reduction of the incidence of stillbirth and intrauterine growth restriction has been shown. This supplementation has also a positive association with placental and birth weights [5,52]. Animal studies have demonstrated that a low-protein diet during the periconceptional period leads to the adult onset of noncommunicable diseases like hypertension and cardiovascular diseases [5,53].

The Mediterranean dietary pattern (high intakes of vegetables, fruits, rice, olive oil, nuts and fish and low intakes of processed meat) has positive impacts on the fetal growth, quality of embryo, and birth outcomes but the Western dietary pattern (processed meat and high-dairy diet) can increase the risk of being small for gestational age [54]. Lower dietary intake of micronutrients in early pregnancy is associated with an increased risk of adverse birth outcomes. Lower intakes of vitamins A, B12 and E, as well as folate, riboflavin and niacin lead to dTGA, and similarly, lower intakes of zinc, vitamin C and methionine are associated with risks of NTDs [50,51]. Iron deficiency hinders early fetal growth [1] and folate deficiency increases the risk of NTDs [44]. Thiamine, niacin and pyridoxine intake in the periconceptional period may help the prevention of orofacial clefts [55]. During early stages of embryogenesis, both undernutrition and an excess amount of a micronutrient may have a teratogenic effect [1]. Maternal alcohol intake during the early pregnancy has a negative impact on placental weight and can cause developing intrauterine growth restriction in animal models [56].

As mentioned above, beside of adequate micronutrient and macronutrient intake, attention must be paid to proper diet and nutritional habits by parents.

3.3. Sleep and awareness

Sleeping during the day is not recommended unless summertime. The sleeping time begins in the evening or early at night and lasts till before sunrise. This way of sleeping improves the digestion of food and *nozj* of body wastes [23]. *Nozj* means the preparation of body wastes for excretion by changing them to a moderate density or viscosity. Excretion of body wastes enhances the heat in the body, which causes higher and better metabolism.

In PM, sleeping reinforces vital force, removes fatigue, and calms individuals psychologically [23]. In recent years, epidemiological evidence suggested that sleep impairment is a known cause of metabolic health, poor glucose control, hyperglycemia, elevated insulin, and diabetes [57].

A six-year follow-up cohort study demonstrated a relationship of trouble sleeping and sleep apnea to diabetes risk, independent of multiple diabetes risk factors, and mental characteristics [58].

Also, a large population-based case control study showed poor sleep during the periconceptual period may significantly increase the risk of NTDs, especially the risk of spina bifida independent of some risk factors of NTDs such as severe stressful life events, flu or fever and sedative use [57].

3.4. Excretion of body wastes and retention of necessary materials

The excretion of body wastes, and healing constipation, are also two important factors that should be taken into account, since they are very crucial in preventing the diseases, as well as improving the process of producing gametes, and the pregnancy outcome [23]. Blood is a vital substance, which must be maintained in the body. Hypermenorrhea in women reduces vital force and in turn leads to loss of energy, impairment of gastric digestion, and loss of appetite [17]. On the other hand, pregnancy is associated with increased energy demand and nutrients requirement because it increases cellular metabolism and the rate of growth and development [1]. Since anemia can affect neurochemistry and neurobiology in early life [59], it is necessary to eliminate anemia during the preconceptional period.

3.5. Psychological features

Anger, happiness, pleasure, and fear are examples of psychological states that a lack of moderation in each of them may deteriorate the temperament of the body and lead to disorders and diseases [23]. Stress is associated with decreased testosterone secretion and impaired semen quality [60]. The results of human-based studies demonstrated that

psychological stress affects the length of the menstrual cycle, duration, and amount of menstrual bleeding, causes anovulation due to hypothalamic-pituitary-adrenal axis dysfunction, and increases the levels of corticotropin-releasing hormone and glucocorticoids [61].

3.6. Air and climate

Air strengthens vital force, modifies and purifies the human body during inhalation and exhalation. To this effect, the air should be clean and nonpolluted. Climate, as an environmental factor, plays an important role in human body temperament, both positive and negative. Hence, individuals should be protected against extremely hot, cold, dry, and moist weather conditions.

Since gastric digestion is weaker in summer (warm season) compared to winter, the fast-burning foods with cold temperament should be consumed and the amount of food should be reduced [23].

Several studies demonstrated a seasonal pattern of birth weight. Both high and low temperature is associated with low birth weight but it seems cold exposure is more effective. However, it is not clear how temperature affects fetal growth [62]. One study showed that maternal exposure to hot tubs, saunas, or electric blankets in the early gestational period was associated with NTDs but the associations between NTDs and activities in hot place or in the sun were not significant [63]. Another study demonstrated the birth weight of infants born in the winter was higher than that of infants born during late spring and summer. The investigators suggested that it is the result of exposure to a low temperature of winter during midgestation [64].

According to PM evidence, the present research indicated that the seasonal pattern of fetal growth is dependent on the quality of sperm and ovum. The infants born in the winter are the results of fertilization of gametes in the spring that have been produced in the last winter with a more suitable gastric digestion. It is reversed for the infants born in the summer.

4. Discussion

Health improvement, longevity, and high quality of life are all in relation with being healthy both physically and psychologically. These conditions can be met by reaching a healthy lifestyle or controlling environmental factors [65]. However, it is necessary to have a healthy body from birth to reduce healthcare spending and burdens [1]. In fact, from the viewpoint of Avicenna and new medical sciences, the modification of the parents' lifestyle and the

elimination of their diseases are important strategies for reproducing a potent generation. Epigenetic diseases occur due to slight changes in the sperm, ovum or fetus genome and they can be prevented before fertilization [6,25]. There is an increased risk of prematurity and low birth weight, admission to a neonatal unit, perinatal mortality, spontaneous abortion, congenital abnormalities and childhood illness in assisted reproduction specially, with intracytoplasmic sperm injection compared with naturally conceived offspring. Also, the risk of such defects was higher in the infertile couples [66–70]. It shows that abnormality in the ovum and in total count and motility of sperms, as well as chemical and physical conditions of seminal fluid, may lead to offspring morbidity. The frequency of ejaculation, hydration and nutritional state may influence the seminal fluid [17].

Since environmental toxicants such as metals, pesticides, teratogenic, carcinogenic and endocrine disrupting agents excrete to seminal and ovarian follicular fluid [1], parents should avoid these agents in the periconceptual period. In PM, moderate exercise, suitable diet, and sleep were recommended to excrete body wastes and toxic agents from human body [23]. Furthermore, according to PM, attention should be paid to the condition of other organs like the liver, brain, heart, stomach, as well as male and female genitals [71]. In other words, any disorder in sperm and semen is the sign of malfunctioning in one or more organs of the body [17]. New epidemiological studies show a link between semen quality and somatic diseases. Low semen volume, low sperm concentration, impaired sperm motility, low total sperm count, and low total motile sperm count were all associated with higher mortality compared with normal parameters, but abnormal sperm morphology was not associated with higher risk of death. Moreover, as the number of abnormal semen parameters increases, the risk of death rises as well [72]. The etiology of this association is not clear but genetic, hormonal, lifestyle (smoking, alcohol consumption and psychological stress) or *in utero* factors show a link between fertility and somatic health [73,74]. Follicle-stimulating hormone, luteinizing hormone, inhibin B, testosterone, and free thyroxine levels are associated with semen quality. Lower circulating testosterone levels were reported in infertile men compared with fertile ones and also it was introduced as a risk factor for cardiovascular and respiratory diseases and mortality [75,76]. It shows that diseases and disorders in parents must be eliminated before fertilization as well as reforming their lifestyle. Avicenna believed that severe indigestion reduces the feeding of the fetus [17].

Although, in new medical sciences, guidelines on lifestyle management are predominantly based on nutrition and physical activity to prevent disease [13–15,77], in PM there are four other essential factors that have to be considered.

Another point worth mentioning is that although 14 weeks before and 10 weeks after fertilization is considered as an important period and disorders of different organs of the body should be eliminated to have a healthy periconceptional period, you might need more time before pregnancy. The concepts of PM are derived from the different paradigm of medicine; therefore, we simply clarified them for a better understanding. We stated new issues of health maintenance for parents and in turn new ways to enhance the health level of the new generation.

5. Conclusion

In order to have good short-term and long-term effects on the health of children and to achieve a maximum level of health, parents of childbearing age must have a planned pregnancy and pay attention to multicomponent healthy lifestyle during the periconceptional period, including good ambient air, sufficient movement (physical activity) and rest, suitable sleep and wakefulness, fit to man use of food and drinks, right excretion of body wastes and retention of necessary materials, and control of psychological reactions. Elimination of diseases or disorders emerging in body organs of parents should be considered, which may prolong more than 14 weeks before fertilization.

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Competing interests

We declare that we have no conflict of interest.

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