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Key Ethical Issues in Pediatric Research: Islamic Perspective, Iranian Experience

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Abstract

Objective: The importance of pediatric research especially in the ethically proven trials resulted in considerable legislative attempts in association with compiling ethical guidelines. Because of children's vulnerability conducting pediatric research raises different ethical issues; the two most important of which are informed consent and risk-benefit assessment. Differences in religious and socio-cultural context limit implication of ethical standards.

Methods: At the aim of finding a solution we critically reviewed guidelines, and literatures as well as Islamic points in addition to comparing different viewpoints in application of ethical standards in pediatric research.

Findings: The literature review showed that pediatric research guidelines and authors' viewpoints have the same basic ethical core, but there are some variations; depend on cultural, religious, and social differences. Furthermore, these standards have some limitations in defining informed consent according to child's age and capacity upon application

Conclusion: In this regard Islamic approach and definition about growth development and puberty sheds light and clarifies a clearer and more rational address to the issue.

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Key Words: Children; Pediatric Research; Ethics; Islamic Law

Introduction

Pediatric research needs enrolment of children in clinical investigations which empowers us in diagnosis, prevention or treatment of children's diseases[1,2]. Although children will benefit from clinical research, their participation in research accompany important ethical challenges; the most important of which are informed consent and risk-benefit assessment issues. Generally children are considered as vulnerable subjects, so their informed consent is not valid and they need to be protected from harms of the research[2-4]. History of medical research in vulnerable subjects, for example mentally ill children in Willowbrook Hospital, shows children exploitation. Consequently, in order to protect them in clinical researches some standards and guidelines have been compiled which state some recommendations for this purpose[5]. According to these codes children only are enrolled in the researches which were previously performed in animals, older children or adults[6]. The Declaration of Helsinki and Council for International

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Organization of Medical Sciences (CIOMS) are the most important, which emphasize that the researchers should prefer participants' well-being and interests instead of science or society interests[2]. Also, these guidelines suggest that risk-benefit assessment should be performed in pediatric research and research ethics committees should achieve this assessment; they explain the importance of children's assent and researchers' obligation to respect children's unwillingness or their dissent[5]. These recommendations accompany some difficulties which limit their application in different societies and communities. For example, because of the lower level of standards in developing countries, risk assessment in pediatric research is much more critical than in developed countries. In addition, in developing countries the lower level of education of parents and lack of proper perception of the research procedure and its risks, provides proper condition for child abuse in research. Accordingly, many countries have codified the pediatric research guidelines and regulations which are similar in essential ethical principles, nonetheless they have differences in some other issues which depend on their social, cultural and religious differences.

In Iran pediatric medicine has a long history and Razes is known as the father of pediatric medicine whose work shows his involvement in pediatric research[7]. The same as in other countries, pediatric research in Iran is evaluated by institutional ethics committees according to the Iranian guideline in pediatric research codified by Islamic law and jurists' opinion.

Reducing the risk of pediatric research to the least needs critical consideration of the concept of vulnerability, informed consent and assent in children which helps providing higher level of standards in investigations. In this study we aimed to review the limitations of the current standards for protecting pediatric participants in medical research, to identify challenges in applying ethical standards in pediatric research according to their age, mental development, and capacity, and to indicate Islamic approach. In this review we will present new insights into special concepts of ethical issues such as vulnerability, informed consent and assent in order to increase accuracy and fairness in pediatric research.

Literature review

Literature review was conducted to identify studies which pointed key ethical issues in pediatric research. PubMed, Web of Sciences and Scopus were searched from 2000 to 2010 using the keywords including Islam, Islamic view, children, informed consent, assent, risk-benefit assessment, and vulnerability. We limited our search to the English articles. Our literature review resulted in some special definitions such as vulnerability, informed consent, etc from different points of view which will be discussed in the following.

Vulnerability

Vulnerability is defined by international ethical guidelines for biomedical research involving human subjects (CIOMS 2002) as: "Vulnerable persons are those who are relatively (or absolutely) incapable of protecting their own interests, they may have insufficient power, intelligence, education, resources, strength or other needed attributes to protect their own interests"[8].

Obviously, vulnerability depends on time, place, position and many circumstances which a person lives with[9], but some authors describe vulnerability according to competency.

A competent person is able to make a decision autonomously to achieve particular healthcare or research assignment; so competency is an ability that depends on time and the type of assignment. A person may be competent in one time or for one assignment and not in another one[10]. Consequently, a person may be sometimes competent for some functions. Substantially, the abilities of thinking, understanding and decision making autonomously are the most important characteristics of a competent person[10]. If the research subject is not able to decide autonomously for participating in research, he / she is vulnerable[11]. Furthermore, some authors believe that children are at greater risk of abuse and children vulnerability is more vicious because they and even their parents may feel obliged to agree participation in medical research; therefore, they are vulnerable and need specific protection[2,4]. However some investigators showed that children with severe illnesses were

able to understand their condition and treatment planning and they could compete in their medical health care, even they could undertake the responsibility of their treatment[12,13]. Therefore, many authors believe that we should consider capacity and competency of children according to their maturity related to age, because they are not vulnerable and incapacitate in all aspects of their activities[14].

It seems that, vulnerability is not a well-defined standard for children's protection in research and all researchers or ethicists do not agree on all aspects of vulnerability.

Informed consent

The expression of informed consent was firstly applied in 1957[11]. Research participants are involved in medical decisions since the end of the 20th century. Therefore, taking informed consent has become a key process in conveying information between researcher and subject[15].

Although informed consent is playing fundamental role in recruiting subjects especially vulnerable individuals in medical research[9], it is substantially less creditable in children because the third party such as parents, guardians, etc supports children in medical decision making and decides for them[14]. Sometimes parents' concerns about children raise difficulties in their perception and decision making[3]. In addition the fear of not receiving suitable treatment and care results in parents' agreement with their children's participation in research[3]. Furthermore, in stressful or emergency circumstances, information transfer is not done properly[16]. Parents' education may affect their perception and decision as was shown in a study in Australia in 1990, which indicated that better educated parents allow less to participate their children in research[17]. Likewise, parents always do not decide on the basis of the children's best interests; however their consent should not be against the child's interest[1,3]. So it seems that obtaining a true informed consent in pediatric research is not easily possible because it should be taken from actual subject[4]. According to this, children's competency, capacity, and perception in taking children's informed consent are major challenging issues[16].

Taken together, informed consent is a process that many factors, such as child's health, parents' perception, culture, religion and education, and the research environment may affect it.

Children's assent

Children involved in research, can give assent or dissent from participation. The researchers should ask child's willingness for participating in research and the child can withdraw[6]. Children's assent is defined as "a child's affirmative agreement to participate in research"[11]. A simple preference for participation in research is child's assent. This definition may imply to identify risks and benefits or to understand the results of the research by child[18].

Children's perception of research information depends on their age and development, but their development is not similar at the same age; some children understand some aspects of research earlier than the others[19]. Although guidelines of countries such as South Africa, Uganda, India and Kenya state the importance of assent and dissent of pediatric participants[20-23]; they do not mention the fine age of children for giving an assent or consent; nevertheless, Iranian guideline propounds age of 7[24,25].

In this regard and for further clarifications in finding the best age, several studies were performed. Some studies show that children older than 11 understand information better than younger children as it was confirmed at age 9 in one study[26] whereas the other ones consider age 7 for understanding[27]. Furthermore, in a study conducted on healthy children who were referred for vaccination, it was found that two-thirds of participants understand blood sampling, but they don't understand its reason[28]. Some are referring to "The Rule of Seven". This rule divides children into three age groups: under age 7, between 7-14 years old and over 14 years old. According to this rule, the third group of children is able to decide in some occasions such as research participation, but the ability of the second group in decision making must be evaluated[19].

In spite of the principle role of the special policy or guidance in defining the age of decision making, the definition of local law about the age of maturity is another major concern[27].

Risk-benefit assessment in pediatric research

Children are vulnerable because they are less competent than adults and cannot understand all information in research; consequently, researchers should protect them and pay enough attention to risk-benefit assessment in pediatric research[29]. Of course, this protection should not motivate withdrawing some pediatric researches because they are deprived from benefit. Also we cannot assure the benefit of some experiments in children trials, because the results of these trials are well specified later[4]. In addition different types of risks are suggested in pediatric research such as physical, psychological or social risks which may occur during or after performing a research project[30].

Potential risks in pediatric research can be categorized into three levels of minimal, low and high[1], but appointment and definition of minimal risk is difficult and depends on the type of research procedure, therapeutic or non-therapeutic research, benefit from research, individual differences between children, age and developmental level of the child[3]. According to the different stages of growth development, we can divide children into different age groups; consequently, research on them imposes different limitations and problems.

In many guidelines, risk in pediatric research is divided in a different way which considers different levels of risk as minimal, more than minimal and high, but this hierarchy is not accurate because definition of these levels is not well clarified[31]. Some guidelines consider the risk of daily life as a scale and define the minimal risk not greater than experienced risks in the daily life of children. Obviously the risks in daily life of children are not the same. For example, some children live in some regions of the world that natural disasters occur regularly or some children are compelled to work. Therefore these children face greater risks in their daily life and risk assessment in these groups of children is difficult and inexact. Generally minimal risk procedures are noninvasive such as answering the question, height and weight measurement, and urine or blood sampling. Low risk procedures are invasive, but they have slight pain, tenderness or scare. But high risk procedures cause great burdens or major side effects, and they are not acceptable for research project. High risk procedures should be done on children if they are accompanied by treatment planning, and have direct benefit for participant. If children participate in a research which imposes more than minimal risk and without benefit such as blood sampling for non-therapeutic research, researchers and ethics committees should consider that. Of course, pediatric assent is very important too[1].

Taken together the risk-benefit analysis in pediatric research should be performed more precisely and ethics committees must assess the risk-benefit of the projects.

Islamic perspective on children

Depending on the four principles of bioethics which was proposed by Beauchamp and Childress respect for autonomy highlights the necessity of informed consent and accordingly Islam points at respect for patients[32,33]. Islamic viewpoint considers intrinsic rights for individuals even for children. Regarding the Islamic teachings, children have the right to be treated kindly, to be given medical care in case of illness, and not to be given demanding tasks.

In Islam parents' role is highly regarded. Parents are the child's legal guardians who are responsible for protecting child[34]. Parents who neglect their child lose the custody of the child.

The parents' guardianship is temporary in Islam. As in secular laws, any sexual or physical abuse will result in losing the guardianship temporarily or permanently. Accordingly, the holy prophet has stated: "The parents are equally responsible for their duties towards children and should be responsible for any negligence"[35]. The important issue which has to be taken into account is that Islamic viewpoint about children depends on their age. There is no defined set of behaviors in Islam during these ages. There might be local customs in each country.

During the first six years, parents need to be lenient with their children and let them ask their questions. Children at these ages are more competent to be nurtured rather than trained. In this respect, the holy prophet has stated: "In the first seven years, children should be treated leniently (for example no formal training or

disciplined method should be planned out for them) and any children who ask questions should be provided with answers as adults"[35].

Islamic view pays enough attention to the comprehension and lack of comprehension means no responsibility. Islam considers three stages of decisional capacity related to the age; the first 7 years of life in which there is no comprehension, no responsibility but civil responsibility is applicable; age of 7 until puberty in which there is weak comprehension; after puberty in which the decisional capacity is complete[35]. According to this the most critical childcare period is between ages 7 to puberty or between 7 to 14[35,36]. During these years, children are exposed to religious and academic training. The holy prophet has stated: "In the next seven years (i.e. 7-14) teach them"[35]. Hence the age of 7 until puberty is considered as the age of assent and the age of consent is after puberty [36].

Children should be encouraged to start doing small chores and taking responsibilities appropriate to their level of abilities and education but they shall not be given demanding tasks.

Once a Muslim reaches the age of puberty, religious duties such as prayer or fasting become obligatory. Puberty is defined in two ways: having spiritual awareness (maturity) and logical thinking (reasoning). The former is often evident at a certain age, 9 for girls and 15 for boys when, as it was cited above, religious responsibilities begin. The latter is identified according to the person's ability to live and function independently which does not start at a certain age. A mentally mature person is considered as an adult in making legal and medical decisions. In Islamic countries the issue of maturity is defined based upon specific cases. Nonetheless, some Islamic countries move toward determining a person's maturity based on the relatively fixed age of 15 (for both boys and girls) for making legal decisions such as voting, marriage, and certain ownerships. Such a dichotomy in the issue of children and adults appears to be in conflict with secular laws. According to secular laws, a Muslim patient can decide on his/her medical problems at the age of 18. In Islam adulthood is considered the stage of learning and parents' supervision. At this stage they need parents' advice. Parents should encourage their children to think independently and rationally. The holy prophet has stated: "from 14 to 21 years of age, children are reminded to follow their parents' advice and have their company"[35,37]. As the children's guardians, parents respect their children and evaluate their ideas about various issues. The prophet has had the youth to assume more important responsibilities and has encouraged them to participate in social and charity activities such as educating and feeding the poor[38].

Eastern cultures, by stressing on respecting elders and preferring the views of the family over their own, are authoritarian and patriarchal by nature. Muslim family is father-oriented rather than patriarchal and the father acts as a counselor[39]. Independence is not as important as western secular societies.

Islamic concepts and secular viewpoints are similar in the issues of health, treatment, and children rights. Notable exceptions include greater emphasis on the value of life, puberty, and youth issues concerning marriage and family planning.

The following is a theoretical discussion based on Islamic theology on the concepts of health, disease, and care for children.

Children rights prove to be one of the most important human rights, since if children are not afforded special protection and care, they won't be in physical and mental health and won't be able to efficiently contribute to the society. Islam has therefore imposed duties on parents and the government from the very beginning of childhood to deliver a healthy and useful human to the society. On the contrary, it was not until the twentieth century that children's rights law was officially formulated[40].

1942 witnessed the first international effort and the Declaration of the Rights of the Child was issued in November 1952. This convention consists of a preamble and 54 articles in three parts. PART I, Article 1 to Article 42, has addressed the following issues: definition of a child, enjoyment of equal rights, set forth in the convention, by all children, supporting children deprived of their families, adoption, and disabled children[41].

According to the Convention on the Rights of the Child, every human being below the age of eighteen years is considered to be a child. This definition has identified the end of the childhood

but has not mentioned the beginning of childhood[40]. According to Shi'a jurisprudence (Islamic jurisprudence) and in contrast to Convention on the Rights of the Child, the childhood begins when the sperm is combined with female egg and puberty is the end of childhood. Every human being from the very instant of combination of sperm with egg enjoys a set of specific rights which can by no means be overlooked. Here are three rights of an unborn child:

a) Right to live: accordingly to which, abortion is prohibited in Shi'a jurisprudence and a legal punishment is considered.

b) Diyya (Blood money): if, as the result of killing a pregnant woman, the embryo dies or is aborted, Diyya of the embryo in every stage of development is added to the mother's Diyya.

c) Postponement of punishing pregnant women: if a pregnant woman commits a crime and if imposing the penalty results in hurting her child, the penalty is postponed. Article 91 of the Islamic Penal Code indicates: "An adulterous shall not be punished while pregnant or in menstruation or when, following birth and in the absence of a guardian, the newborn's life is in danger. If, however, the newborn becomes the ward of a guardian, the punishment shall be carried out".

d) The right of ownership and inheritance: Like others, the embryo inherits a sum of money, and if he/she is born alive, receives the sum of inheritance.

The end of childhood is, however, associated with the emergence of signs and physiological changes in the structure of the body and the age in which these signs emerge is identified as the age of puberty. According to the most of Jurisprudents (Faqih, plural Fuqahā, an expert in Fiqh), the age of puberty is often 15 for boys and 9 for girls.

Reaching puberty does not denote losing parental support in all cases and in cases in which the child is likely to be hurt, in addition to puberty, the child's growth also needs to be substantiated. If, for example, the child owns some properties, his/her parent is in charge of those properties. Reaching puberty, the child can take the position of his/her properties only if his/her growth is substantiated. The child's growth is validated through the following ways:

1. Through the child's parents: Some time before reaching puberty, the child is assigned with a couple of financial affairs by his/her parents and his/her ability in working out financial affairs is evaluated. If the child's ability in preserving and using his/her properties rationally is attested, the parents shall return his/her properties.
2. Through people other than the child's parents (e.g. people aware of the child, testify the child's growth).
3. Through corresponding to the conventions: without the need for validation through evaluating the child or the need for people to testify his/her growth.

In The Civil Code of the Islamic Republic of Iran, the age of growth has not been specified but since validating growth in different cases is so demanding, determining a conventional age of growth appears to be necessary. According to jurisprudence, the age of growth seems to be under 18.

However, in Shi'a jurisprudence the age of growth is not cited for only financial considerations, but identifying the age of puberty is necessary for contributing to society and for penalty purposes.

Iranian Experience

The special group guideline in Iran not only gives a good attitude to our researchers about children subjects but also is an appropriate guidance for key ethical issues in pediatric research. This guideline was compiled by the Medical Ethics and History of Medicine Research Center (MEHMRC), the Deputy Minister of Research and Technology of MOHME, and the Endocrinology and Metabolism Research Centre (EMRC) of the Tehran University of Medical Sciences (TUMS) in 2005[42]. Our guideline is emphasized on 20 key ethical points in pediatric research, the two most important of which are age groups of children and responsibility of ethics committees[24]. The definition of age group of children in Iranian guideline is according to Islamic law. In Islamic law literature, the age of puberty and the age of growth are different. When a boy is 15 years old, or a girl is 9 years old, he or she is considered as an adult because their body, mental and natural growth is complete[43]. According to Iran Civil Law, all people have worthiness for right owner from

birth to death, but they can perform their rights provided that they become adult (*Balegh*), mature (*Rashid*) and rational (*Aghel*). Iran Civil Law emphasizes that 18 years is the age of growth (*Rushd*); thus, an 18 year old boy or girl is a mature person. Sometimes seat of judgment can prove maturity. A mature person is mentally capacitated and is able to understand information. Therefore, if it is proven that a 15 year old child is mature; he or she can implement his/her rights. Furthermore, there is the possibility that a rational person, who has a proper perception and is able to comprehend, is not considered mature. In fact, Islamic law states that a mature and rational adult, is competent; therefore, he or she is able to conceive information and to make a decision (Fig. 1). On the other hand, a minor person, who is not adult and is able to comprehend information, is named "discerning minor" (*Momayez*). Consequently, discerning minor may make a decision. Indeed, pediatric research guideline in Iran divides children into two age groups: under 7 years old and 7-15 years old. If a research is designed on under 7 year old children, the researchers should obtain parents' (father and mother or legally authorized representatives) consent and children's assent. Research on 7-15 year old children needs getting consent from parents and the child.

In addition, Iran pediatric research guideline explains the role and responsibilities of ethics committees in pediatric research by 5 statements. Institutional ethics committees in Iran should assess risk and benefit of pediatric research. Also, in emergency situation in which taking consent is not possible, ethics committees can approve the research. If the researchers doubt child abuse, ethics committees should judge. Moreover, Iran guideline states that if parent's decision is different from child's interests, ethics committees can consider it. On the other hand, if parents' decision deprives their children from research benefit that cannot be received by another way, the ethics committees can interfere. Taken

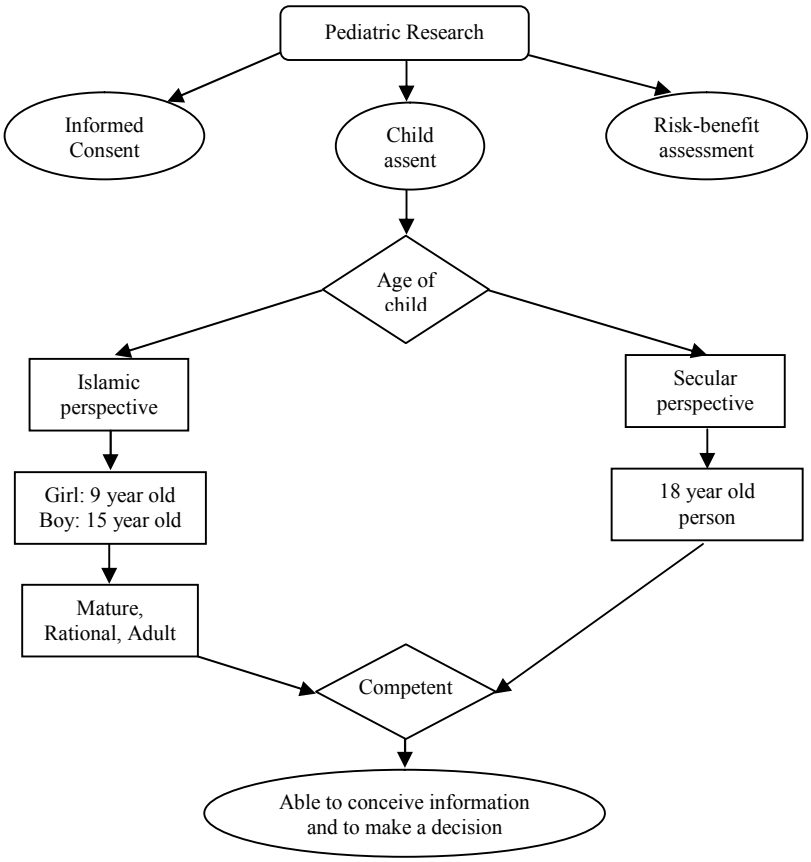

Fig. 1: Children competency for decision making

together, pediatric research guideline in Iran clarifies two important sides of pediatric research including child age and ethics committees' responsibilities. It recommends that ethics committees should adhere a clear policy by which they are empowered to consider age group of children, to determine child vulnerability and to do risk–benefit assessment correctly.

Ethical Guideline for Research with Children in Iran

1. The purpose of the research should be obtaining more information about children's hygiene, health, and health care.
2. Conducting research with children is only allowed if it is not possible with adults.
3. Researches which do not directly lead to profit the children participants are not essentially immoral. But once these researches create benefits for future generations of children, they are considered to be ethical. The research should not, however, risk hurting the child.
4. Risk assessment should be carried out by all the persons involved in the research: parents, legal guardians, researchers, involved experts, research ethics board and even the children (if possible).
5. Children, in terms of legitimacy in giving consent, are divided into two groups: children under 7 years of age and children between 7 to 15 years old.

a) In the case of children under 7, a written consent should be gained from the child's legal guardian and utmost effort should be put into obtaining the assent of the child.

b) In the case of children aged 7-15 years, the consent of both the child and his/her legal guardian needs to be sought. Where the two groups' decisions do not match, the issue is referred to ethics board.

6. Children should be involved in making decisions on their hygiene, health, and improvement as much as possible. The child has the right to be given the necessary information, to express his/her opinions and to decide. Methods used in providing information and gaining consent, should be appropriate to the child's age and understanding.
7. Where the guardian's dissatisfaction deprives the child of the research and its benefits which cannot be gained in any way other than the research, the issue is referred to ethics board.
8. In cases where the researcher doubts the parents' decision for the child, the judgment is handed over to ethics board or the court. In the case of child abuse, for example, the parents may decide against the child's benefits.
9. If the parents are under 16, they could give their consent on behalf of their child only if it is figured out that they can decide rationally.
10. Children with the sufficient capacity should be encouraged to have their parents involved in the research results. However, the child's opinion should anyhow be respected.
11. In the case of children lacking the capacity, if the disclosure of the information seems necessary, the parents should be informed.
12. The child's legal guardian can withdraw his responsibility for making decision on the child's behalf. Another person who is legally considered the child's guardian should be, therefore, replaced by the previous guardian.
13. No monetary incentive should be provided to children or their legal guardians. They should, however, be paid for the costs they have incurred for participating in the research.
14. The parents should be encouraged to consult relatives, health care providers, and independent counselors for participating in the research.
15. Parents should accompany their child in the course of conducting the research.
16. Questions, worries, and discomforts of the parents should be responded.
17. Where it is not required for the research to be conducted with a specific age group, older children should be preferred over younger ones for participating in the research.
18. In emergency situations, conducting research with children without gaining prior consent, if confirmed by ethics board, is allowed and ethical.
19. Immediately after conducting the research with children in emergency situations, the consent of the child and his/her parents should be sought for this research and the following participations as well.
20. Conducting research with disabled children should be confined to cases in which the results

are not obtained through doing research with adults and normal children.

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