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The Iranian Newborn Multiples Registry (IRNMR): a registry protocol

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ABSTRACT

Purpose: Over the last decades, several twin/multiples registries have been developed worldwide, mostly concentrated in Europe and high-income countries (HICs). In Iran, we lack accurate nationwide epidemiological and biobank data on twins. We established the Iranian Newborn Multiples Registry (IRNMR) to evaluate the role of genetics and environmental factors in the variation of phenotypes among newborn monozygotic (MZ) and dizygotic (DZ) twin pairs. IRNMR is a multicenter hospital-based registry. **Materials and methods:** In the pilot phase, we collected epidemiological data from multiples born in Imam Khomeini Hospital complex and Aban Hospital located in Tehran, the capital of Iran, with a population exceeding 8 million, Allameh Bohlool Gonabadi Hospital, Gonabad, Razavi Khorasan, and Shahid Sadoughi Hospital, Yazd, Iran. **Results:** The IRNMR has recruited 457 sets of newborn twins and multiples so far. We hold follow-up sessions by mother and child health professionals to monitor multiples' growth, development, diseases, and mortality. **Conclusions:** We successfully developed a newborn multiples registry in Iran. This registry will create an invaluable database to study the relative influence of genes and environmental factors on various chronic diseases, growth, development, and behavioral disorders. We intend to collaborate with other centers to develop a large multicenter nationwide multiple birth registry and biobank in Iran.

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Introduction

Studies on monozygotic (MZ) twins (who have identical genetic content) compared with dizygotic (DZ) twins (who are genetically as similar as other siblings but share a common environment) are of great importance in assessing the attributable risk of genetic and environmental factors in growth and development, etiology of chronic diseases (such as cancer, obesity, diabetes, Alzheimer's, cardiovascular pathologies, psychological disorders), and other health outcomes [1]. Thus, twins' information has been collected and registered for decades in many developed countries throughout the world, including Denmark [2], Sweden [3], Australia [4], Netherlands [5], Finland [6], the United Kingdom [7], Italy [8], the United States [9,10], South Korea [11], Sri Lanka [12], Hungary [13], China [14,15], etc. Although these studies have led to the

publication of more than 5,000 research papers in various fields of medical sciences [16], most of the twin registers are concentrated in Europe and high-income countries (HICs) [17]. There are limited longitudinal twin cohort studies in low- and middle-income countries (LMICs). Thus, it seems necessary to embark on a twin registry in these areas to achieve credible results and carefully evaluate the impact of genetics and environmental factors on chronic diseases and behavioral disorders [17,18]. Accurate nationwide epidemiological and biobank data on twins also lack in Iran [19]. This issue triggered us to develop a multicenter registry, the Iranian Neonatal Multiples Registry (IRNMR). We aim to collect epidemiological data from newborn twins/multiples and their parents from the whole country. In the next phase of the registry, we will collect biological samples of the twins/multiples

and their parents to establish a biobank. The data will create an invaluable platform for researchers to study the effects of genetics and environment on growth and development, etiology of the diseases, physical and mental disorders, and other health outcomes of interest. This report presents the protocol and results of the pilot phase of the IRNMR, established in 2017, to shed more light on the strengths and limitations of the project.

Methods

Registry database

The Iranian Newborn Multiples Registry (IRNMR) is a multicenter hospital-based cohort, a national registry in Tehran, the capital of I.R. Iran, with a population exceeding 8 million. We established the IRNMR to recruit Iranian newborn twins/multiples up to 28 days. Currently, we compile birth records of the infant multiples born in Imam Khomeini Hospital Complex (a tertiary referral hospital in Tehran), Aban Hospital (an infertility referral center in Tehran), Allameh Bohlool Gonabadi Hospital, Gonabad, Razavi Khorasan, and Shahid Sadoughi hospital, Yazd, Iran. Data of the multiples and their parents are collected *via* a structured interview. Multiple pregnant women are contacted for consent to be recruited in the registry as well. The questionnaire takes approximately 10 min to fill out. It collects data on the parents' names, age at delivery, education and occupation, height and weight, marital status, cigarette, and water-pipe smoking, ethnicity, consanguinity among the parents, a history of infertility, current address and contact information, national code, twins' sex, birth date, birth weight, preterm birth, the APGAR score, type of pregnancy, type of delivery, past medical history and family history of any diseases. The zygosity (monozygosity/dizygosity) is also ascertained based on the placental histology reports or reports of the first-trimester ultrasonography if the placental histology report is unavailable. The follow-up sessions are held to record their diseases and mortality and to monitor their growth and development. The IRNMR is a volunteer registry. Parents not interested in continuing the study will be excluded.

In the next phase of the registry, we intend to collect the biological samples containing the mother's blood, the umbilical cord blood sample, and the umbilical cord tissue after the twins' birth in the delivery room to establish a biobank. For this purpose, after delivery and obtaining informed consent from the parents, 6 ml of the parents' blood will be

collected in an EDTA-containing tube and frozen along with the umbilical cord blood sample umbilical cord tissue. For each newborn, two 6-cc tubes containing EDTA and a 3-cc clotted tube will be collected from the umbilical cord vein. After the blood sample is taken, 2.5 cm of umbilical cord tissue will be washed using an irrigator and a saline buffer phosphate (PBS) and placed in a 2 ml cryotube. Finally, the mother's blood sample, the umbilical cord, and the umbilical tissue will be placed in a cold box and transferred to the freezer within 30 min. The mother's blood sample and a blood sample of the separated umbilical cord are centrifuged at 2500 g for 10 min. The isolated plasma will then be transferred to the -20°C freezer, and the remaining umbilical cord blood will be transferred to a 4°C refrigerator to extract DNA. The whole process will be completed within 1 h. Eventually, a 6-cc EDTA-containing tube of umbilical cord blood, along with a cryotube containing umbilical cord tissue sample, will be transferred to the -20°C freezer immediately after delivery.

Data management and analysis

We computerize the data *via* the District Health Information Software 2 (DHIS2) system (<http://twinregistry.ir>). DHIS2 is the most extensive open-source, web-based, and Java-based health management information system (HMIS) platform used by 67 LMICs to collect, validate, and present patient-based data of disease registries. This modular platform is capable of adequately presenting and registering mother-twin and mother-father relationships. We will use STATA 14.1. (StataCorp LP, College Station, Texas, USA) for the statistical analyses. The biobank data will be analyzed by the Biobanking software (Modul-Bio, France).

Ethical considerations

All procedures in the IRNMR comply with the Declaration of Helsinki's principles of treating human subjects and has been approved by the Deputy of Research and Ethics Committee of Tehran University of Medical Sciences (code: IR.TUMS.VCR.REC.1398.449). The purpose of the registry is explained to the parents of the twins/multiples and the contributors. All of the parents were recruited voluntarily, and written informed consent (appended to the protocol paper) is obtained from all participants. Twin/multiple families are reassured that no risk will derive from the participation in the registry and that the information they provide will remain confidential. As an advantage, all

the participants will get some consultations by a mother and child health specialist for free. Besides, we visit twins without making an appointment in our centers. In case of detection of a curable or incurable disease, measures will be taken to refer the participants to specialized medical centers.

Registry status

The IRNMR has recruited and followed 457 sets of newborn twins/multiples so far, including 258 identical and 183 fraternal twin pairs, and 16 triples. We are collaborating with other centers to expand the registry to the whole country in the near future. We will report complete results in our subsequent reports.

Discussion

We established the Iranian Newborn Multiples Registry, named IRNMR, in 2017 to register the Iranian neonate twins/multiples. We also intend to develop newborn twin/multiples biobank for genetic and epigenetic studies. To date, we have compiled 457 neonate twins and multiples from three hospitals located in two cities of Iran.

Over the last decades, several twin registries have been developed worldwide. The Swedish Twin Registry (STR) of the Karolinska Institute, the largest registry with 216,258 twins, was built up in the late 1950s to study the effect of smoking and alcohol consumption on cancer, cardiovascular diseases (CVD), and nonspecific chronic lung disease while controlling for genetic predisposition to the disease [3]. There are approximately 30 ongoing studies based on this database, covering various public health problems [20]. Xu et al. [21] conducted a case-control study using 8,534 twins from the STR to examine the association of midlife overweight and obesity with dementia, Alzheimer's disease (AD), and vascular dementia (VaD) in late life. They found that midlife overweight and obesity independently increase the risk of dementia, AD, and VaD. Using the Danish Twin Registry (DTR) database, the oldest and among the largest registries with 86,000 twin pairs, Hilker et al. [22] estimated the heritability of schizophrenia to be 79%. In 2007, a multivariate genetic analysis was conducted on nine endophenotypes related to the metabolic syndrome from 625 adult twin pairs from the DTR [23]. According to their findings, the endophenotypes associated with metabolic syndrome do not share common genetic or familial environmental factors. Among low- and middle-income countries, Sri Lanka Twin Registry has

been recently established to study the etiology of mental illness and the impact of challenges to early brain development on future mental health [18].

A unique strength of this multicenter registry is that the IRNMR will be the first newborn twin biobank in Iran to the best of our knowledge. Analysis of bio-samples, including the parents' and the umbilical cord blood samples and the umbilical cord tissue, will provide an invaluable platform for providing physical and psychological support for them and their families. However, this registry faces some limitations. Firstly, the refusal of parents to participate or not being interested in continuing the study is inevitable. We try to restrict this limitation by providing physical and psychological support for twin/multiples families, such as free education, consultations, and visiting twins/multiples without making an appointment. Next, there are challenges in blood sampling accuracy, biosample transfer and storage, and DNA extraction. We hope to overcome this by allocating funds to efficient human resources and purchasing the most up-to-date equipment.

We successfully implemented a newborn multiples registry in Iran. Fortunately, the pilot phase indicates that the study is conceivable. Final results of the epidemiological and biobank research on the IRNMR can provide an invaluable database for studying the role of genetics and environment on desired health outcomes. It will also be a precious platform for investigating particular growth and developmental diseases in multiples. We intend to develop a large multicenter nationwide multiple birth registry and biobank in Iran.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

Authors' contributions

KZ, HA, and RB conceived the registry and designed the experiments. KZ, RB, MSH, and SR are carrying out the research. SR prepared the first draft of the protocol. RB and KZ contributed to the preparation of the final version. All

authors were involved in the revision of the draft manuscript and have agreed to the current version.

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