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SPECIAL ARTICLE

Non-invasive prenatal diagnosis from the perspective of a low-resource country ☆

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ABSTRACT

Current clinical practice in obstetrics has shifted the paradigm from a conventional prenatal approach based on invasive procedures, risking both fetus and mother, to non-invasive prenatal testing for some fetal conditions via the analysis of cell-free fetal DNA in maternal blood. In the past 15 years, much research has been devoted to refining the methodology for measuring cell-free fetal DNA in maternal circulation and to exploring clinical applications of this technology as a potential tool for prenatal diagnosis. Since the rapid spread around the world of prenatal diagnosis based on cell-free fetal DNA, it is time to start thinking how this cutting-edge technology might influence current practice of obstetrics in low-resource countries.

1. Introduction

One of the current challenges in obstetrics is to reduce the high rate of maternal mortality that largely affects low-income countries, and in turn accounts for 99% of all maternal deaths worldwide [1]. Peru has one of the highest maternal and perinatal mortality rates in Latin American, despite the fast and steady growth in its economy in the past 10 years. The situation is further aggravated because the number of mothers dying as a consequence of pregnancy and birth varies greatly across the country. Thus, rural populations such as Puno and Huancavelica, located far away from the cosmopolitan capital, show maternal mortality rates as much as 7-fold higher than that in the capital [2]. The large difference in the rate of maternal mortality among women from the same country is mainly due to a deficient political system that is unable to deliver a proper healthcare system throughout the country. Access to appropriate health services for many women in Peru, as in most low-income countries, remains an elusive dream.

While we are still struggling with these public health problems, non-invasive diagnosis (NIPD) of fetal conditions via the analysis of cell-free fetal DNA (cffDNA) has been translated from research into clinical practice, and is currently being offered to pregnant women in some high-income countries for a few fetal conditions. Furthermore, several clinical applications are being explored and it is almost certain that this technology will be part of routine prenatal care in the future.

Despite the great potential of this new technology to change clinical care of the mother and fetus, it is clear that women living in rural and remote areas, such as Huancavelica, Puno, and many such regions around the world, are still far from benefiting from NIPD. Herein, we raise questions on the introduction and possible role of cffDNA in low-resource countries.

2. Overview of non-invasive prenatal diagnosis

Since the discovery of cffDNA floating in maternal circulation in 1997 [3], and shortly thereafter of cell-free fetal RNA [4], intensive efforts have been made to challenge the technical difficulties in measuring these 2 molecules in order to translate this approach into clinical practice. At present, prenatal diagnosis using cffDNA is being offered to pregnant women in some high-income countries with the following clinical applications.

(1) Fetal blood group genotyping of rhesus D in maternal plasma for all immunized pregnant women. This is implemented as national health policy in countries such as the United Kingdom [5], The Netherlands [6], France [7], and Sweden [8]. It is thought that the determination of fetal blood group genotype via a cffDNA approach may prevent about 40% of women receiving prenatal anti-D prophylaxis unnecessarily [9].
(2) Early diagnosis of fetal sex for the management of X-linked genetic diseases such as Duchenne muscular dystrophy, where male-bearing pregnancies are primarily at risk, and congenital adrenal hyperplasia, where female fetuses can start receiving early steroid treatment until definitive diagnosis [10].
(3) Diagnosis of various single-gene disorders such as Huntington's disease, myotonic dystrophy [11], achondroplasia, and thanatophoric dysplasia [12], among others. Recently, prenatal diagnosis of sickle cell anemia has been achieved in up to 82% of

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cases [13], and indeed a growing number of genetic conditions are being tested by means of cffDNA.

(4) Effective screening for fetal aneuploidy. Traditionally, diagnosis of fetal aneuploidy relies on the karyotyping of trophoblast cells obtained by chorionic villi sampling or by amniocentesis, which is universally performed in both high- and low-income countries. Owing to the overwhelming evidence for the high accuracy and extremely low false-positive rate of cffDNA for the screening of trisomy 21 and other aneuploidies such as 13, 18, and monosomy X in high-risk populations [14,15], the American College of Obstetrics and Gynecology and the Society for Maternal-Fetal Medicine have very recently issued a joint committee opinion stating that cffDNA can be offered to women at high risk of aneuploidy if the women receive strict pretest counseling [16]. At the same time, they state that it is not yet time to introduce cffDNA as part of routine prenatal laboratory assessment. More recently, a study carried out among pregnant women in their first trimester undergoing routine screening has confirmed a detection rate of more than 99% for trisomy 21 and 18 with a false-positive rate of less than 1% [17], which in turn opens up new possibilities for routine clinical obstetric care. Screening for aneuploidy based on cffDNA is currently being offered to high-risk women through a few private companies in the United States and China.

3. How is prenatal diagnosis currently being offered in high-income countries?

Most countries in Latin America, the Middle East, Sub-Saharan Africa, and South Asia lack a national policy of screening for fetal aneuploidy and abnormalities [18]. Prenatal diagnosis is based primarily on ultrasound examination of the fetus in the second or third trimester of the pregnancy. Although all hospitals and a great number of private doctors offer ultrasound, the examination is performed with no systematization and most frequently for fetal biometry, and there are few referral centers for advanced assessment [19].

In addition, invasive procedures are mainly limited to amniocentesis, but access to this procedure is often restricted because of high cost, limited resources for the technical process of cellular culture, and ignorance among both mothers and healthcare workers that the service is available [18]. Furthermore, many women seek professional advice when they are in the second half of the pregnancy or when there is a clinical complication.

4. Why should NIPD be introduced into low-resource countries?

From the viewpoint of justice in healthcare, we argue that people from low-resource countries also require access to prenatal diagnosis. There is indeed a need for implementing prenatal diagnosis—both invasive and non-invasive—on a systematic and equitable basis in low-income countries, wherein congenital disorders have largely been neglected as a health problem.

First, it is a fact that many of these countries are undergoing an epidemiologic transition, and hence congenital disorders are now contributing significantly to perinatal morbidity and mortality [20].

Second, even when abortion is not an option for women from many low-income countries, prenatal diagnosis is invaluable because most women will be reassured when the results are favorable. Conversely, when an abnormality is found, they will have more time to prepare themselves for the adverse situation. Moreover, diagnosis of a fetal condition might help healthcare workers to plan the birth and to refer the pregnant woman to a proper tertiary center.

Third, in low-income countries many women do not want to risk the fetus, and hence they flatly reject any invasive test even after a positive result from a screening. In a survey carried out in Chile, for example, 94% of the population desired screening for aneuploidy using ultrasound (i.e. nuchal translucency), but only 38% stated that they would undergo invasive diagnosis if the results were positive [21].

Last, but not least, we believe that there is no reason to offer an invasive test with subsequent risk of miscarriage when there is the option of a non-invasive diagnosis with no risk. Withholding this current option from pregnant women during counseling is unethical even for low-income families. A choice of currently available options should be offered to pregnant women regardless of the social, cultural, or economic conditions, and regardless of whether or not the test is performed in their town or country. There is always an option of traveling abroad to seek further assessment or management.

5. What are the main difficulties in introducing NIPD into low-resource countries?

First, one of the main difficulties in introducing NIPD into low-resource countries is that people have to pay in order to gain access to some of the health services. In Latin America, 20%–40% of people do not have access to any kind of health insurance and they are literally excluded from the health system [22]. Thus, even when the option of cffDNA testing might be commercially available, only a minority of them would have access to the test.

Second, most low-income countries lack clinical and diagnostic facilities for genetic medicine, including trained personnel for prenatal genetic counseling [18]. There is, however, experience in implementing a genetic service for the prenatal screening of some inherited traits in some low-resource countries.

Third, the introduction of such new technologies may be limited by cultural beliefs among patients and healthcare providers [18]. Last, about 16% of pregnancies occur among adolescents [23], which may hinder the process of counseling and choice-based decision.

6. Overcoming the difficulties in introducing NIPD into low-resource countries

We believe that the potential difficulties, as listed above, in introducing NIPD into low-resource countries can be overcome.

First, we require a firm commitment from health policy-makers to confront the issues of implementing prenatal diagnostic services in different major hospitals, which in turn would permit the development of regional and international networks. We might take the example of countries such as India and Cameroon, which have succeeded in establishing prenatal screening services [24,25]. Moreover, the implementation of such services has to progress alongside the establishment of clear screening policies for congenital defects. There is no longer a reason to believe that low-income countries are not capable of obtaining and appropriately applying molecular genetics technologies [18].

Second, we have to define clearly what can be diagnosed and what cannot be diagnosed with cffDNA at the time of counseling. This will facilitate the process of transmitting the information from the healthcare provider to the pregnant woman. Third, education of women and training of healthcare providers are crucial processes before the introduction of this technology.

7. The perpetual problem of abortion

There is still controversy in offering prenatal diagnosis in countries where abortion is not permitted [26]. In most low-resource countries, induced abortion is legal only when the pregnancy threatens the health or life of the mother. Unfortunately, 40% of women live in countries where abortion is legally prohibited; as a result, many women seek clandestine abortions under unsafe circumstances, risking their health and life. It is believed that 97% of these unsafe abortions are carried out in low-income countries [27]. A survey in Peru showed that the prevalence of self-reported induced abortion was 13.6%