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Review of Prenatal Aneuploidy Screening Uptake Rate and Trends in Iran, and Developed Countries

Ali Najafi [1] and Seyed Mohammad Akrami [1, *]

[1] Department of Medical Genetics, Tehran University of Medical Sciences, Tehran, Iran

[*] *Corresponding author*: Department of Medical Genetics, Tehran University of Medical Sciences, 1417613151, Tehran, Iran. Email: akramism@tums.ac.ir

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Abstract

Prenatal screening of different anomalies including chromosomal aneuploidies have become a part of routine pregnancy care in most countries around the world. These tests can help pregnant mothers to have informed decisions. In this study we gathered relevant scientific and governmental/official data about uptake rate of these screenings in different developed countries and Iran. We have tried to use the latest articles and reports, and also consider to the global trend of screening and abortion policies in developed countries. Also, some pitfalls when comparing prenatal screening of different countries will be explained. These data can help to have a better insight about Iran's prenatal screening status when compared with developed countries to improve public health policies.

Keywords: Prenatal Diagnosis, Down Syndrome, Aneuploidy

1. Context

In recent years, discussions related to the reduction of Iran's population growth rate and the possibility of population decline in the coming decades have become a hot topic, and the causes and solutions have been discussed. In the meantime, perhaps the most controversial issue within these discussions is about fetal health screening and related policy changes, which have even affected the "population youth and family support" bill of the Joint Commission of the Islamic Parliament of Iran. The current debates are mainly on trisomies 21, 18, and 13, and in this paper, we will review the screening uptake rates of these aneuploidies alongside worldwide policy trends in this area. In letter to editor entitled "Debates on Down Syndrome Screening in Iran" in the current journal, we have discussed the etiology and debates on prenatal screening in this country. Therefore, here we will first have an overview of fetal screening and the screening-related legal abortion. Then look at screening uptake rate and relevant issues in more details. Also, will discuss some pitfalls when comparing prenatal screening rate between different countries.

2. Data Acquisition

In this review for gathering prenatal screening data from around the world specially developed countries, we used Google with 7 different languages to find governmental/official reports and used Google Scholar and PubMed for relevant Papers. The search combined terms including, but not limited to, "prenatal screening", "uptake rate", "participation", "coverage", "policies" and "utilization". After primary search, we had to more specifically search for data from missing important countries. Also, different pitfalls when comparing prenatal screening and abortion, between different countries were extracted from the papers.

3. Prenatal Screening

Screening is a process of identifying apparently healthy people who may be at increased risk of a disease or condition. They can then be offered information, further tests and appropriate treatment to reduce their risk and/or any complications arising from the disease or condition (1). It is estimated that about 2.5 - 3% of all infants are born with major congenital anomalies, half of which with genetic etiology. Due to the high mortality and morbidity rate, financial and emotional burden, and other difficulties caused by the birth of these fetuses, various approaches, especially different types of prenatal screenings, have been used for early diagnose of them.

Trisomy 21, 13 and 18 are the most common autosomal trisomies. Trisomy 21 well known as Down syndrome has

a prevalence of about 1.5 to 1.6 per 1000 live births (2). The prevalence of the other two trisomies, also known as Patau syndrome and Edwards syndrome, is about 1 in 12,000 and 1 in 6,000 live births, respectively (3). The 5-year survival rate of trisomy 13 is about 9.7% and this rate for trisomy 18 is about 12.3%. Rare cases of these patients have lived up to the second decade of life. Affected infants have major congenital malformations such as congenital heart defects, emphysema, renal abnormalities, and central nervous system involvement (3, 4).

As studies have shown that the risk for having a child with trisomies 21, 18 and 13 increases with maternal age, in some countries it was recommended that amniocentesis or chorionic villus sampling be performed in women older than 35, 38, or 40 years. They could be karyotyped subsequently for trisomy or other chromosomal abnormalities. Drawbacks of this procedure included the need for a high number of invasive samplings, i.e., chorionic villus sampling (CVS) or amniocentesis, and the fact that most of these children are born from mothers under these age cutoffs. In fact, much more deliveries from women under the ages of 40 and 35, makes the overall number of trisomic babies born from these mothers to be more. So fetal screening methods were gradually developed. The purpose of these tests was to identify pregnancies which are at higher risk for having an affected fetus so invasive tests could be offered to them. Since the 1980s, attentions to prenatal screening of Down syndrome (trisomy 21) increased, leading to identification of trisomy 13 and 18, as well as some rare and fatal cases such as triploidy besides it (5). The screening tests in developed countries have become part of routine pregnancy care since the 1990s (6). In Denmark, for example, where screening tests were offered to all pregnant women from 2004-2005, the number of invasive samplings, which was about 70,000 per year between 2000 and 2003, declined to about 35,000 in 2006 (7). Despite halving the number of invasive diagnostic tests, there was a 25% increase in the detection rate of fetuses with trisomy 21 (7). These benefits were despite the fact that the screening coverage in 2005 - 2006 was still around 73.5%, which has now reached more than 92% (8).

3.1. Prenatal Screening and Medical Abortion in Iran

In Iran, with the help of verse 14 of Surah Momenun and related hadiths and three years after the religious decree of the Supreme Leader in response to a question about abortion in 2002, the legislation on medical abortion was passed by the Islamic Parliament of Iran and its compliance with Sharia and the Constitution was approved by the Guardian Council (9). All the necessary precautions in law enforcement have been done focusing on the nuances considered by the Forensic Medicine Organization of the country in the last 16 years. Prenatal aneuploidy screening had started in Iran even before this legislation, but in 2013, the Down Syndrome Screening Guideline was issued by the Ministry of Health to make the screenings more uniform throughout the country. The latest version of this guideline was released in 2020 (10). Based on this guideline, like most of the developed countries, prenatal screening is offered to all Iranian pregnant women.

3.2. Prenatal Screening Uptake Rates and Its Worldwide Trends

Screening programs to identify high-risk fetuses and then perform diagnostic tests for chromosomal aneuploidies, especially Down syndrome, involve a variety of protocols. These procedures in the first trimester of pregnancy mainly include ultrasonography and nuchal translucency (NT) measurement, examination of biochemical markers of maternal blood and combination of the results with maternal age-related risk, and also in the second trimester include testing of 3 or 4 biochemical markers in maternal blood and anomaly scan usually at 18 - 20 weeks of gestation. Different combinations of the above methods are performed under different names such as combined test, integrated test, and etc. In addition, the non-invasive prenatal testing or NIPT (with an accuracy of about 99% for identifying the 3 autosomal trisomies) is rapidly becoming more widespread in recent years.

Our survey on fetal health screening in Europe and other developed countries has shown that screening is offered to all pregnant women in Belgium, Denmark, Finland, France, Switzerland, South Korea, etc., and the expenses are reimbursed (11, 12). Table 1 shows the uptake rate of prenatal screening in 18 countries.

In the EUROCAT's 2010 report (11) it was stated that these screenings are restricted in Ireland, Northern Ireland and Malta. At the time abortion was illegal in these countries. Meanwhile, according to 2018 laws in Ireland and 2019 laws in Northern Ireland this abortion ban was lifted. Apart from this, we found no other examples of national restrictions imposed on fetal health screening in European or other developed countries, and the differences between countries were mainly in screening protocols and the amount of insurance coverage for these tests.

An important point to consider is whether the global trend in the use of fetal health screening in different countries is decreasing or increasing? In this regard, one good example is the United States. In 1988, only about 22% of pregnancies were screened for Down syndrome. This figure rose to about 50% in 1992, and continued to rise to 72% in 2012 (28). In the case of Australia (Victoria, with a quarter of the country's population), prenatal serum screening increased from 1.6% in 1996 to 83% in 2013 (13). During the same period, due to the use of screening tests

Table 1. Prenatal Aneuploidy Screening Uptake Rate of Some Developed Countries

Countries	Prenatal Screening Uptake Rate (%)	References
Australia	83	(13)
Belgium	78.7	(14)
Canada	69.9	(15)
Denmark	92.4	(8)
England	84	(16)
France	88.2	(17)
Germany	Up to 85	(18)
Iceland	79	(19)
Italy	94	(20)
Netherlands	48.3	(21)
Russia	77	(22)
Scotland	76	(23)
Spain	78.4	(24)
South Korea	More than 95	(12)
Sweden	About 50	(25)
Switzerland	More than 80	(26)
Turkey	66.2	(27)
United States	72	(28)

to identify high-risk individuals, the number of invasive tests performed had halved (13). In the case of the Netherlands, where overall prenatal screening uptake rates are lower than in other developed countries, it was just from 2007 that prenatal screening was offered to all pregnant women. The utilization rate of these tests has increased from about 5% at the beginning of the 21st century to around 35% in 2010 and to above 48% in 2019 (21, 29). Also in the Netherlands, the participation rate in the 20-week fetal anomaly scan is 90% (30), which is about twice the participation rate in the first trimester screening, and this is probably due to the fact that pregnant women must pay out of pocket for the first trimester screening or NIPT but the second trimester anomaly scan is fully reimbursed in this country (31).

In the Netherlands and Belgium, NIPT is offered to all pregnant women. Twenty five to fifty percent of the Dutch, Italians, Austrians, Spaniards, and people in many US states and Australia use the test (32). Even in Belgium, where NIPT is free for all citizens, its uptake rate is more than 75% (32). So, we have to take these values into account in our calculations when assessing prenatal screening uptake rates and for example if we want to consider only first trimester combined test as Down syndrome prenatal screening test we may say the rate for Netherlands is 1.7% while after adding rate of NIPT to it we have the rate of 48.3% (21).

In Sweden, as another country with the lowest prenatal screening rates in Europe, participation rate for pregnant women in prenatal screening was shown to be about 33% in a study (33). At the time of the study (2011 to 2013), a number of counties in the country had not yet adopted a policy of offering screening to mothers (33). However, in the three years that this study was conducted, it was observed that the participation of pregnant women in the combined test increased from 29 to 36%. Of course, it should be noted that the rate of use of ultrasound in the same study was close to 98% (33). In a later study this rate was mentioned to be about 50% (25). Also, in communication with one of Sweden's genetic counselors (Dr. Charlotta Ingvoldstad Malmgren) who is active in the field of fetal health screening, she stated that there is still a huge difference in the screening policy between different counties in this country and therefore the administration of Sweden's municipalities and regions (Sveriges kommuner och regioner) wants to prepare a report on how to standardize the fetal health screening protocol across this country by the end of 2021.

In the case of England, fetal health screening is offered to all pregnant women, and the fetal anomaly scan from week 18 to week 20 is performed for 99.1% of pregnancies (16). Also in most of the other developed countries this fetal anomaly scan is performed for near all women.

Among the developed countries, Norway seems to be the only country where to have a legal restriction on the possibility of prenatal screening (32). But recently, the Stortinget, or the Norwegian parliament, has passed amendments asking the government to make sure that the first-trimester screening is offered to all pregnant women and they are free to access an NIPT (34).

There isn't a clear view of Iranian women's participation rate in prenatal screening. A recent controversial thesis in Iran based on a sample size of 720 women has estimated that the Down syndrome screening rate in 2017 was 94.6% but the Ministry of Health data shows that this rate for 2018 was 48.1% and for 2019 it was 50.1% which is much lower than the values of the study (35). While the data of the Ministry of Health from a health information registry system called SIB seems to be more realistic, but any value in between 50 and 94.6% is within the range of developed countries.

4. Some Pitfalls When Comparing Prenatal Screening and Abortion Rates of Different Countries

Different limits defined in the guidelines of different countries does not mean that in fact they have exactly the same or lower amount of error. As an example in the latest NHS report, despite the definition of 2.5% for the maxi-

mum false positive rate in Down syndrome screening, the average false positive rate in the laboratories of this country was 2.6% (16).

Different countries may use different prenatal screening methods and if someone compares first trimester combined test between the countries, he/she can't say that has compared their prenatal screening uptake rates. Also, while the global trend of the coverage of prenatal screening is changing, you can't compare current state of one country with the state of another country in a decade ago.

Considering the rate of performed secondary or supplementary tests as the false positive rate of first-tier screening tests is not correct as many people can request these tests while having a negative first trimester screening result or even without any prior test. Also, prevent using very small or low-quality studies for drawing the screening state of a country.

It should also be noted that these screenings are not just for Down syndrome and these fetuses are only a part of fetuses with disabilities that are identified in the procedure of the tests and as a result, the cumulative costs of their birth are much higher than the figures associated with the Down syndrome alone. High rate of consanguineous marriages in Iran makes prenatal screening and diagnosis more important (36-38). Fetal health screening programs help to increase the quality of population and reduce the negative psychological, economic and social consequences of the birth of trisomy fetuses.

5. Conclusion

In summary, it can be stated that the rate of prenatal screening in developed countries is more than 70% and the worldwide trend of this rate is increasing. It should be noted than NIPT is increasingly playing a major role in prenatal aneuploidy screening worldwide. Traditional serum screening seems to be replaced in near future in many countries by NIPT, which in turn, can further increase the prenatal screening uptake rates.

Suggestions that can be made to reduce the cost of screening and the need for invasive testing include efforts to reduce the cost of the NIPT test. In this regard, Belgium, by maximizing the automation of this process and the use of alternative materials, instead of the official ones, for the next generation sequencing machines (NGS), was able to reduce the cost of this test significantly and implement it as the first-tier test in national prenatal screening (14). Of course, the new proposed Down Syndrome Screening Guideline developed by the Genetics Office of the Ministry of Health is also designed to further reduce invasive testing, improve the quality and performance of laboratories and sampling, and also to respect the right of pregnant women to whether participate in the screenings or not. Any screening program may have defects and it is important to assess and revise them in reasonable time intervals based on firm scientific evidences with the help of related scientific communities.

Footnotes

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