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Economic analysis of prenatal screening strategies for Down syndrome in singleton pregnancies in Turkey



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ABSTRACT

Objectives: To examine the costs and outcomes of different screening strategies for Down Syndrome (DS) in singleton pregnancies.

Study design: A decision-analytic model was developed to compare the costs and the outcomes of different prenatal screening strategies. Five strategies were compared for women under 35-year of age: 1A) triple test (TT), 2A); combined test (CT), 3A) Non-invasive Prenatal Screening Test by using cell free fetal DNA (NIPT), 4A) and 5A) NIPT as a second-step screening for high-risk patients detected by either TT, or CT respectively. For women ≥ 35 -year of age, 1B) implementing invasive test (amniocentesis –AC) and 2B) NIPT for all women were compared. Data was analyzed to obtain the outcomes, total costs, the cost per woman and the incremental cost-effectiveness ratios (ICERs) for screening strategies.

Results: Among the current strategies for women under 35 years old, CT is clearly dominated to TT, as it is more effective and less costly. Although, the current routine practice (2A) is the least-costly strategy, implementing NIPT as a second step screening to high-risk women identified by CT (5A) would be more effective than 2A; leading to a 10.2% increase in the number of detected DS cases and a 96.3% reduction in procedural related losses (PRL). However, its cost to the Social Security Institution that is a public entity would be 17 times higher and increase screening costs by 1.5 times. Strategy 5A would result in an incremental cost effectiveness of 6,873,082 (PPP) US\$ when compared to the current one (2A). Strategy 1B-for offering AC to all women ≥ 35 -year of age is dominated over NIPT (2B), as it would detect more DS cases and would be less costly. On the other hand, there would be 206 PRL associated with AC, but NIPT provides clear clinical benefits as there would be no PRL with NIPT.

Conclusions: NIPT leads to very high costs despite its high effectiveness in terms of detecting DS cases and avoiding PRL. The cost of NIPT should be decreased, otherwise, only individuals who can afford to pay from out-of-pocket could benefit. We believe that reliable cost-effective prenatal screening policies are essential in countries with low and middle income and high birth rates as well.

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Introduction

Down syndrome (DS) is the most frequent aneuploidy worldwide; and it is recommended that all women be offered screening for “trisomy 21” [1,2]. Various maternal serum biomarkers with or without ultrasonographic “nuchal translucency” (NT) measurement are commonly used for DS screening: These tests

can be performed during first trimester (double test, combined test) and/or second trimester (triple test and quadruple test) [3–6].

Maternal blood is a source for circulating cell free fetal DNA and advanced technology now enables to isolate and analyze these fragments by different methods [7–9]. “Noninvasive prenatal testing by fetal cell free DNA” (NIPTfc = NIPT) is an alternative screening strategy with its high positive detection rate at around 99% with a false positive rate of 0.1–1% [10].

Using a decision analytical model, the implementation of NIPT was compared with current screening strategies (i.e. conventional tests followed by an invasive diagnostic testing for women at screen-positive and those of advanced maternal age). The models

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included NIPT (i) was replaced with conventional tests [11], (ii) was used as a secondary test following a positive screening result [12–14], or (iii) was considered in as universal and contingent [15–18]. Some studies have shown that NIPT with high detection rate increases the costs, while contingent NIPT may result in lower costs via decreasing unnecessary invasive procedures and related losses which should be implemented as an optional secondary screening test [12–14,16,17,19]. In addition, NIPT is more cost-effective than conventional maternal serum screening when the lifetime costs of DS live-births are considered [16,18].

It should be noted that these studies have been undertaken in various countries with different health systems, where costs and practices differ. In Turkey, the Social Security Institution (SSI), being the sole purchaser of health services as a government entity, ensures the health insurance coverage to the whole population. The social health insurance is also compulsory. Therefore, there is a limited role for the private health insurance. People can use both public and private settings in which the SSI makes contracts. The contracted private providers are allowed to charge patients extra up to a certain limit for covered services based on fees chargeable to the SSI. In case of using private hospitals, people have to make these additional payments [20]. NIPT has not been listed among screening tests and is not paid by neither the public nor the private health insurance schemes. In addition, countries also differ in demographic characteristics. For example, in Turkey the percentage of women who gave birth and who are above 35 years of age was around 14% in 2015, which affects the prevalence of fetal DS and therefore the positive predictive value of NIPT [21]. We believe that reliable cost-effective prenatal screening policies are essential in countries with low and middle-income and high-birth rates as well. To this respect, the aim of this study is to compare the costs and outcomes of different prenatal screening strategies in Turkey.

Materials and methods

A decision-analytical modeling is used for comparing different strategies of prenatal testing to detect DS cases within the framework of “antenatal care programmes” in Turkey. The main concerns of this study are the number of DS cases detected, the number of procedural related losses (PRL), and combined costs of screening and diagnostic tests as well as the cost per cases detected/PRL avoided, and incremental cost-effectiveness.

Clinicians usually offer one of the antenatal DS screening tests to all pregnant women under 35 years of age. “Combined test” (CT) and “triple test” (TT) are the most popular applications in Turkey. CT enrolls maternal age, gestational week, NT measurement by ultrasonography plus maternal blood beta human chorionic gonadotropin (β -hCG) and serum pregnancy-associated plasma protein-A (PAPP-A); and TT measures maternal age, gestational age, maternal α -fetoprotein –AFP, unconjugated estriol (uE3), and (β -hCG). The alternative screening tests and protocols such as double test, quadruple test, and integrated test are not that much common in Turkey [4,6,22]. NIPT is based on the analysis of cell free fetal DNA fragments circulating in maternal blood by using different technologies and is applied after the 10th gestational week [10]. NIPT with better prediction has started to be popular in recent years, but is not reimbursed by the national health insurance and mostly applied in private settings in Turkey.

If a woman under 35-years of age is found to be at high-risk ($\geq 1/250$) by prenatal screening (mostly by CT or TT), she is offered one of the invasive tests, including chorionic villus sampling, amniocentesis (AC) or cordocentesis for the prenatal diagnosis of DS and other chromosomal aneuploidies. NIPT protocol is not well established but this test is used in a similar manner as other

prenatal screening tests (patient is referred to a tertiary hospital for invasive prenatal testing if the test result is positive).

AC is considered to be an easy and safe method in Turkey, and usually applied to pregnant women between 14–22th gestational weeks. In Turkey, if there is an anomaly, it is legally possible to conduct termination until the 24th week. Therefore, TT can be conducted in Turkey as late as the 22nd week [22]. AC can be performed by obstetricians while CVS and cordocentesis generally performed by perinatologists and have some limitations. Offering an invasive test for women over 35-years of age is mandatory because of administrative regulations and legal consequences [22]. Considering to this background we have conducted two different analyses: for women a) <35 years-of-age (5 strategies) and b) ≥ 35 years-of-age (2 strategies).

Strategies for prenatal testing for women “< 35 years-of-age”

Strategy 1A) Triple Test (TT) is offered between 14–22th gestational weeks. Women who are detected as high-risk group ($\geq 1/250$) by TT will undergo AC.

Strategy 2A) Combined Test (CT) is offered between 11–14th gestational weeks. Women who are detected as high-risk group ($\geq 1/250$) by CT will undergo AC.

Strategy 3A) Cell free fetal DNA testing–NIPT replaces all other noninvasive tests; Women who are detected as high-risk will undergo AC.

Strategy 4A) TT and NIPT for high-risk pregnancies: All women are offered TT. High-risk pregnancies are considered for further screening by NIPT. Only women identified as NIPT-positive will have AC.

Strategy 5A) CT and NIPT for high-risk pregnancies: All women are offered CT. High-risk pregnancies are considered for further screening by NIPT. Only women identified as NIPT-positive will have AC.

Strategies for prenatal testing for women “ ≥ 35 years-of-age”

Strategy 1B) AC – current practice: All women-are offered AC.

Strategy 2B) NIPT: NIPT replaces AC; Women who are detected as high-risk will undergo AC.

The number of women who gave birth in 2015 was 1,312,880 (actual number); 1,125,904 of them were <35years of age and 186,976 women were ≥ 35 [23]. The analysis is done for these two groups and the results are reported accordingly. The model inputs and the characteristics of each screening test, DS-detection rates, DS-screening sensitivity and specificity were taken from published literature (Table 1). The estimated prevalence of DS according to women’s age was obtained from Turkish data [23].

In calculating the costs and consequences of each strategy, the entire sample was assumed to consent for prenatal testing. We also assumed that AC is the only invasive procedure since there is no data in Turkish registries related to invasive test preferences, and that all women who were detected as high-risk or NIPT-positive would have AC with additional visit to the obstetrician. The low-risk or NIPT-negative women would not have further tests.

The analysis was done from the payer perspective with a high and low-cost scenarios. The reimbursement fee schedule of the SSI as the sole public health insurance is used in low-cost estimates [28]. As public insurance coverage is universal and compulsory, there is no co-payment in screening procedures. Therefore, we do not take into account individual’s out-of-pocket payments in low-cost estimates. These fees represent the lowest possible costs for screening programmes. The high-cost estimates are based on both SSI fees and the private healthcare prices that involve additional charges to the SSI fees. The additional amount is paid by women who may prefer to use private settings and the rest is paid by the

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