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Original Article

A cost-effectiveness analysis comparing two different strategies in advanced maternal age: Combined first-trimester screening and maternal blood cell-free DNA testing

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ABSTRACT

Objective: To estimate cost efficacy of first-trimester screening strategies based on nuchal translucency (NT) and maternal blood cell-free DNA (cfDNA) testing in women with advanced maternal age (AMA).
Materials and methods: This was a retrospective population-based analysis of all pregnant women with AMA booked for combined first-trimester screening (cFTS) in China over a 3-year period. The assumed screening strategies were the following: cFTS (Strategy 1), cfDNA testing as a first-tier investigation replacing biomarkers after NT measurement (Strategy 2), and cfDNA testing combined with dating ultrasound for all women (Strategy 3). The direct costs were compared between strategies.
Results: Strategy 1 was completed in 6443 women with AMA. The respective detection rates were 94.5% and 90.9% for trisomies 21 and 18, with a total screen-positive rate of 13.5%. Such a policy resulted in 871 invasive tests and a total cost of $747,870 or a cost of $116 per person tested. Strategy 2 would result in a total cost of $1,812,570, or a cost of $281 per person tested, with increased detection rates for trisomies 21 and 18, and a decreased number of invasive tests compared with strategy 1. The total cost of Strategy 3 would be $1,675,430, or a cost of $260 per person tested with the least number of invasive tests.
Conclusion: The cfDNA modalities have the advantages of higher detection rate for common trisomies and lower screening-positive rate. However, the cost of cfDNA testing needs to decrease significantly if it is to replace the current cFTS practice in a population of AMA on a purely cost effectiveness basis.

Introduction

Advanced maternal age (AMA) refers to women giving birth at an older age. Although there are various definitions of specific age in different countries, AMA is associated with adverse reproductive effects including increased risk of conceiving fetuses with trisomy 21. In China, AMA is defined as age 35 or older for women at the time of estimated date of confinement (EDC). Currently, invasive diagnostic testing (IDT) only based on maternal age is seldom offered in China. More often IDT is recommended only for pregnancies with a positive prenatal screening result based on either biochemical blood analyses, ultrasound scans, or both. The combined first-trimester screening (cFTS) using nuchal translucence (NT) thickness and serum biomarkers to assess aneuploidy risk at 11–14 weeks gestation has been publicly funded in Guangzhou city, the capital of Guangdong province in southern China since 2013. Using a risk cut-off of one in 270, we previously reported a detection rate (DR) of >90% for trisomy 21 at a false positive rate (FPR) of >10% in women of AMA [1]. While cFTS can detect most of affected pregnancies, more than 10% of women of AMA still have to sustain IDT.

Maternal blood cell-free DNA (cfDNA) testing is an advanced aneuploidy screening tool because it allows a simple maternal blood test to obtain a very high level of accuracy in detection of fetal common trisomies, especially trisomy 21 (at least 99.5% of DR with a FPR of 0.2%) [2–4]. Despite its superior performance, it is not anticipated that cfDNA testing will be used as a publicly funded, population-wide first-tier screening test at its present price. Nowadays cfDNA testing is most often reserved as a second-tier screen for women identified as high risk by cFTS, or as a first-tier screen for selected population such as AMA women [5–7]. In this study we describe the economic performances of early screening

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strategies in the era of cfDNA testing for women with AMA in China. The purpose was to explore the possibility of replacing cFTS by cfDNA testing in the future with a considerable reduction in the costs of cfDNA testing.

Materials and methods

This was a retrospective study, which involved all patients ≥35 years of age who had participated in the cFTS program at 11^{+0} to 13^{+6} weeks of gestation, at Guangzhou Women and Children Medical Center, Guangdong, China, in the period from January 2013 to June 2016. We compared three screening policies in the same population with AMA as following (Fig. 1):

(a) Strategy 1 (cFTS): current practice. All women received a NT scan, followed by IDT in those with NT ≥ 3.0 mm, and by cFTS for those with NT < 3.0 mm. Women with a cFTS risk ≥1/270 were offered IDT. Only patient-specific risks for trisomies 21 and 18 were estimated from a combination of maternal age, NT, serum free β-hCG and PAPP-A (risk of trisomy 13 was not provided in our first-trimester risk calculation algorithms using the PerkinElmer Life Cycle software).
(b) Strategy 2 (NT/cfDNA): all women had a NT scan, and those with NT ≥ 3.0 mm had IDT. The remaining women with NT < 3.0 mm:
   i) who ≥35 years had cfDNA testing;
   ii) who ≥36 years had cfDNA testing, and those <36 years had cFTS;
   iii) who ≥37 years had cfDNA testing, and those <37 years had cFTS;
   iv) who ≥38 years had cfDNA testing, and those <38 years had cFTS;
   v) who ≥39 years had cfDNA testing, and those <39 years had cFTS;
   vi) who ≥40 years had cfDNA testing, and those <40 years had cFTS.
(c) Strategy 3 (universal cfDNA): all women had cfDNA testing following a dating ultrasound.

In this study period, we had 6649 women with AMA who had received cFTS, but only 6443 women with definite follow-up data were enrolled, in whom prenatal karyotyping or pregnancy outcome was obtained. Approval for the study was obtained from the ethics committee of the hospital (No. 2016111808).

To estimate the economic effect of cfDNA testing in screening strategies, we made the following assumptions: 1) all the patients would receive the same cfDNA-based methodology; 2) the DR and FPR for trisomies 21 and 18 are 99.0% and 0.2%, respectively; and, 3) the failure rate of cfDNA testing is 1%, and these cases are offered IDT. We estimated the costs of screening for trisomies based on the real first-trimester screening charges at our center (US dollar currency exchange rate, 2016): NT ultrasound of $30 (free of charge), biomarkers of $30 (free of charge), IDT (including charges of invasive procedure, rapid molecular karyotyping and cell culture karyotyping) of $420 (free of charge), cfDNA testing of $240 (out-of-pocket expense) and dating ultrasound of $10 (out-of-pocket expense).

Results

The study population consisted of 6443 women with AMA who received the first-trimester screening program (Strategy 1). For contingent risk cut-offs of NT ≥ 3.0 mm and 1: 270, the detection rates were 94.5% (52/55) and 90.9% (20/22) for trisomies 21 and 18, respectively, with a total screen-positive rate of 13.5% (871/6443) (Table 1). Such a policy resulted in 871 invasive tests. The costs were 6443 × $30 for NT scan, 6292 × $30 for biomarkers analysis, plus 871 × $420 for IDT, resulting in a total cost of $747,870 or a cost of $116 per person tested.

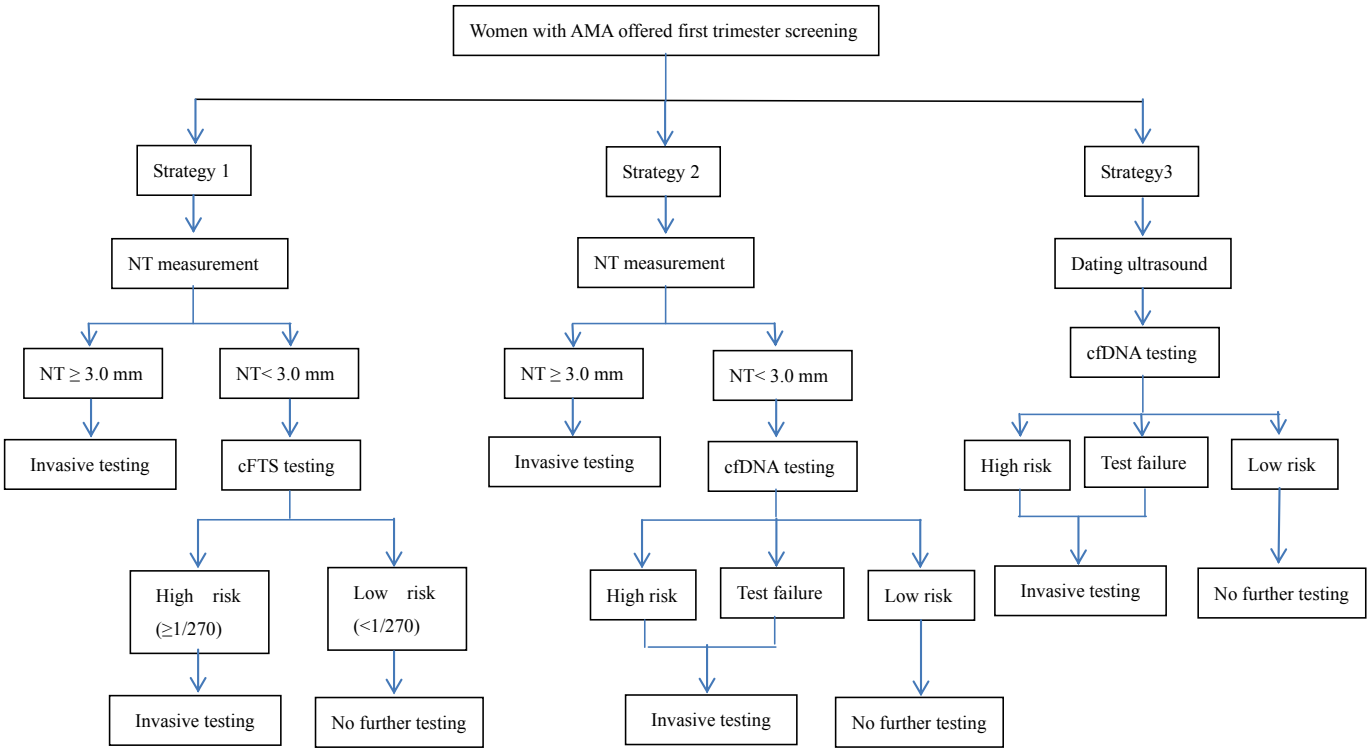

Fig. 1. The flowchart of first trimester screening in women of advanced maternal age using different strategies.