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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.

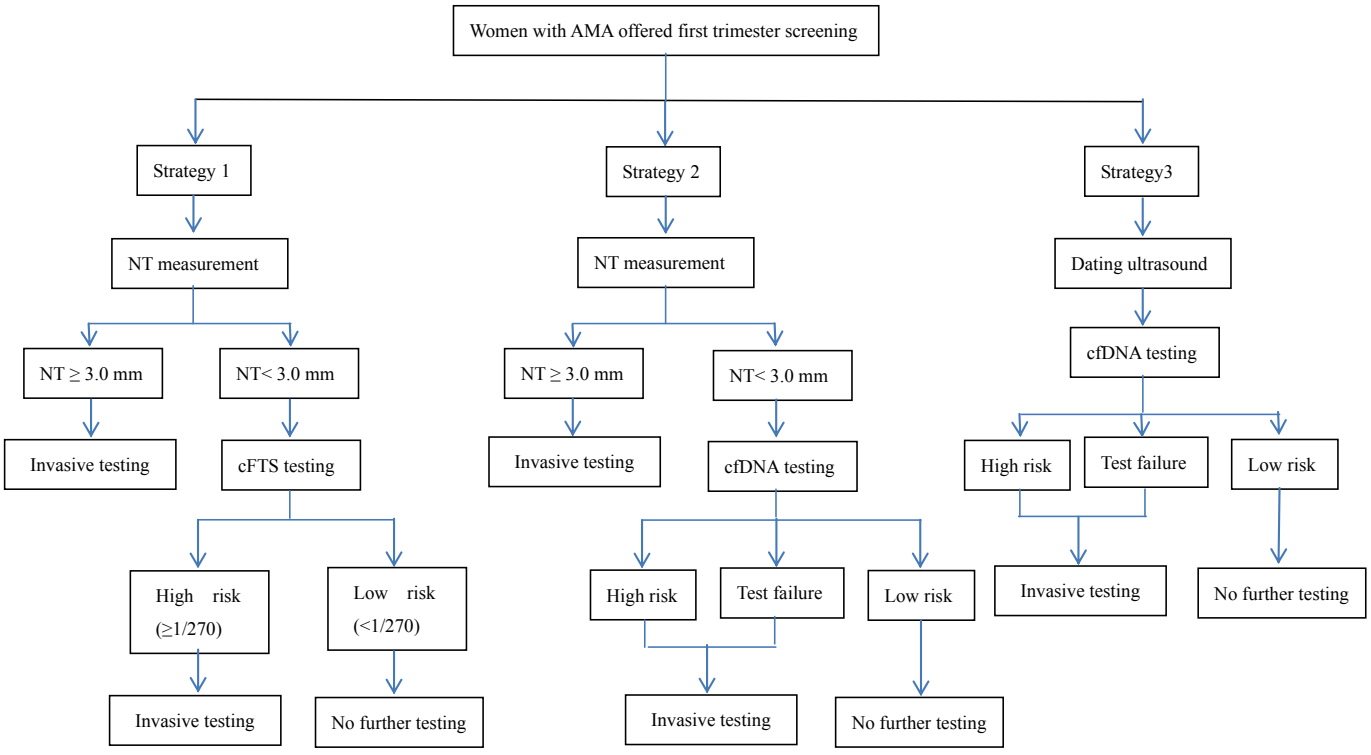

Fig. 1. The flowchart of first trimester screening in women of advanced maternal age using different strategies.

Table 1
Effectiveness of screening pregnant women with advanced maternal age for trisomies 21 and 18 according to Strategy 1.

Age(y)	N	Aneuploises		NT ≥ 3.0 mm			N	cFTS-positive (NT < 3.0 mm)		
		Tri 21	Tri 18	n (%)	T-21	T-18	(cFTS)	n (%)	Tri 21	Tri 18
35	1840	7	2	25 (1.4)	4	1	1815	97 (5.3)	3	1
36	1479	7	2	26 (1.8)	4	1	1453	93 (6.4)	3	1
37	1105	8	3	28 (2.5)	4	2	1077	123 (11.4)	3	0
38	689	6	3	17 (2.5)	3	2	672	89 (13.2)	3	1
39	499	7	3	21 (4.2)	4	2	478	79 (16.5)	2	0
≥40	831	20	9	34 (4.1)	11	6	797	239 (30.0)	8	3
Total	6443	55	22	151 (2.3)	30	14	6292	720 (11.4)	22	6

cFTS, combined first-trimester screening.

In Strategy 2, there were 6292 AMA women with a NT < 3.0 mm. If these women received universal cfDNA testing, the total number of IDT would be 109 (33 cases of trisomies 21 and 18, 13 false-positive cases, plus 63 cases with test failure). Such a policy based on NT and cfDNA testing would result in a total cost of $1,812,570, or a cost of $281 per person tested (Table 2). If the price for cfDNA testing is halved to $120, the cost per person tested would be $164. The costs of the contingent cfDNA testing stratified according to maternal age are showed in Table 2.

In Strategy 3, if all of the 6443 AMA women received universal screening based on dating ultrasound and cfDNA testing, the total cost would be $1,675,430, or a cost of $260 per person tested (Table 3). If the price for cfDNA testing is halved to $120, the cost per person tested would be $140.

Table 4 illustrates the performances and costs for the cfDNA strategies compared with current practice. Based on trisomies detection and procedure-related loss avoidance, the new screening strategies are superior to Strategy 1. However, Strategy 1 is more value for money unless the price of cfDNA testing would decreased substantially.

Comment

A first trimester ultrasound scan that included NT measurement was implemented routinely in our prenatal screening program. We used NT of 3.0 mm as a cut-off because there are several studies in which NT ≥ 3.0 mm was used for pregnancy outcome evaluation, and reported adverse outcomes varying from 43 to 75% [8–11]. In a previous survey, we found that the prevalence of increased fetal NT (≥3 mm) was 0.9% (143/15,947) in our first-trimester population [12]. Considering this distribution of NT being under the commonly accepted FPR of 5%, patients with NT 3.0 mm and above were targeted for IDT in our clinical practice.

Since 2013, the Strategy 1 was free at our center. All the costs involved in the NT measurement, serum biochemical analyses and IDT were paid by the local government. In this study, we made an economical possibility assessment of replacing cFTS with cfDNA modalities. The results from our cohort demonstrate that using the Strategy 2, the cfDNA testing in all AMA women with a normal NT would decreased substantially the number of IDT by 70.1%. However, the substitution of cfDNA testing for cFTS is significantly more expensive, increasing the cost per person tested from $116 to $281. Even the price for cfDNA testing is halved from $240 to $120, the cost per person tested for contingent cfDNA testing would be $164, still higher than that needed for current practice. For cfDNA testing to be cost-comparable with cFTS under this contingent universal strategy, the price would have to decrease to $71. Nevertheless, if using the Strategy 2 with women aged over 39 years being considered high risk and offered cfDNA testing at its current price, the cost would be comparable to that of Strategy 1. Whilst the screening costs would be equivalent, there are the benefits of decreasing IDT by 30.3%.

The >90% DR in Strategy 1 requires specifically trained ultrasound performers and a continuous quality control program for the ultrasound unit. These prerequisites for establishing a strong screening policy may hamper the NT screening in region lack of specifically trained ultrasound operators and high-resolution sonographic equipment. Therefore we appraised the economic performance of Strategy 3. A dating scan assessing CRL is relative simple as opposed to a NT screening program. The cost of a dating scan ($10) is only one third of NT examination ($30) at our center. However, we found that even if the charge for cfDNA testing would be halved, the total cost of Strategy 3 is still higher than that of Strategy 1. The price would have to decrease to $96 in order to achieve to be cost-comparable with current program.

Owing to its high cost, cfDNA testing is currently positioned as a triage test in pregnancies referred for IDT, and is not recommended to be implemented as a first-tie method of screening for the whole population. This is also the case at our center [13]. There are also other economic assessment studies which conclude that cfDNA testing is cost effective only if it is embedded into a contingent screening policy. Cuckle et al. [14] reported that a contingent policy whereby 10%–20% women were selected for cfDNA testing by conventional screening was considerably more cost-efficient, and universal cfDNA testing will only become affordable by public health purchasers if costs fall substantially. Morris et al. [15]

Table 2
The costs of screening pregnant women with Strategy 2.

Age	Cost	Cost of IDT	Biomarker (NT < 3.0 mm)			cfDNA (NT < 3.0 mm)			Cost	Cost	Cost[a]
(y)	(of NT)	(NT ≥ 3.0 mm)	n	IDT	Cost	n	IDT	Cost	(total)	(per person)	(per person)
35	193,290	63,420	0	0	0	6292	109	1,555,860	1,812,570	281	164
36	193,290	63,420	1815	97	95,190	4477	83	1,109,340	1,461,240	227	156
37	193,290	63,420	3268	190	177,840	3024	61	751,380	1,185,930	184	128
38	193,290	63,420	4345	313	261,810	1947	43	485,340	1,003,860	156	120
39	193,290	63,420	5017	402	319,350	1275	32	319,440	895,500	139	115
≥40	193,290	63,420	5495	481	366,870	797	22	200,520	824,100	128	113

IDT, invasive diagnostic testing.
[a] Cost calculated by assuming halved price of cfDNA testing.

Table 3
The costs of screening pregnant women with Strategy 3.

	Ultrasound		Biomarker	cfDNA	IDT	Cost	Cost
	NT ($30)	Dating ($10)	($30)	($240)	($420)	(total)	(per person)
cFTS	6443	0	6292	0	871	747,870	116
cfDNA	0	6443	0	6443	154[b]	1,675,430	260 (140[a])

[a] Cost calculated by assuming halved price of cfDNA testing. cFTS, combined first-trimester screening; IDT, invasive diagnostic testing.
[b] 154 = 77+(6443−77) × 0.2% + 6443 × 1% = 77 + 13+64 = 154 (assuming 0.2% of FPR and 1% of failure rate).

Table 4
The performance and costs of different screening strategies.

	No. of trisomies detected (%)[a]	No. of IDT	No. of PRL	Cost (per person)
Strategy 1	72 (93.5)	871	8	116
Strategy 2[b]	77 (100)	260	2	281
Strategy 3	77 (100)	154	1	260

IDT, invasive diagnostic testing; PRL, procedure-related loss.
[a] Only trisomies 21 and 18 calculated.
[b] cfDNA testing was done in women ≥35 years after NT scan.

investigated the costs and outcomes of cfDNA testing as contingent testing and as first-tier testing compared with the current screening program in the UK National Health Service (NHS). They reported that if the NHS cost was at the lower end of the range of cfDNA price (£400-£900) in the private sector then at a selected population (cut-off of ≥1/150) cfDNA testing as contingent testing would be cost neutral or cost saving compared with current screening. Other Australian population cohort studies found that contingent cfDNA testing or cfDNA testing for selected high-risk patients (>40 years) was the most cost-effective strategy [16,17]. Our study demonstrated that even if the price would be halved, cfDNA testing is still more expensive than current cFTS in universal screening for women with AMA. For cfDNA testing to replace cFTS in high-risk population in China, the cost would have to decrease significantly.

On the other hand, cfDNA testing as a second-tier tool used in screen-positive groups has not taken advantage of its superior performance in improving the overall efficacy of population screening. Furthermore, the provision of the cFTS for all women and cfDNA testing for a selected women after cFTS may lead to double screening with an unnecessary increase in the cost. Therefore application of first-tier cfDNA screening replacing cFTS may be worthwhile in select population based on aneuploidy risk. The women with AMA are the most suitable group for first-tier cfDNA screening. We can expect a sharp decrease in cost of cfDNA testing in the coming years. This decrease would be driven by the competition among different commercial companies and also by future advances in technology. For example, the price has decreased from $600 in 2013 to $300 in 2014, and to $240 in 2015 in China [18].

There are several limitations to our study. First, this was not a real prospective study, but a model-based analysis of costs and outcomes of cfDNA testing. We only focused on the different performances of different screening policies on a purely cost-effectiveness basis regarding charges of the screening and diagnostic components. The indirect costs associated with a screening program has not been addressed in this study. For example, the economic costs and social as well as psychological implications of non-detected cases and false-positive test results are also important characteristics for each testing strategy. The costs of procedure-related loss, the savings of diagnosing and termination of pregnancies affected with an aneuploidy fetus, or cost of the lifetime care for a subject with trisomy 21 are not attempted to assess. The inclusion of these downstream outcomes may support the cfDNA screening. Walker et al. [19] determined the cost effectiveness of cfDNA testing as a replacement for current screening practice using a societal cost perspective. They reported that cfDNA testing is more effective and less costly than current screening modality even at its present price when the lifetime costs of trisomy 21 live births are considered. Second, our study assumed 100% uptake to demonstrate the potential costs and outcomes of screening, and may overestimate the actual costs and benefits. Women's educational level, values and personalised counseling are the determinants of women's choice of cfDNA testing or invasive prenatal testing [20–22]. Third, although cfDNA testing has an impressively increased DR of common aneuploidies and decreased number of IDT, it unfortunately also results in a lower diagnostic yield of other chromosomal aberrations. This disadvantage is not surprising as approximately 30% of aberrations found in patients with positive cFTS results are not the common trisomies [23].

In summary, our data demonstrate that adoption of cfDNA screening into the Chinese screening program is hindered by cost. Application of first-tier cfDNA screening at its current price is not worthwhile even in women with AMA. For cfDNA testing to replace cFTS in women with AMA, the cost has to decrease to less than $100. Currently, cFTS will still be the primary screening tool for this high-risk population, and cfDNA testing is used in screen-positive group. For women of very AMA (e.g. ≥39 years old), universal cfDNA screening is cost-efficient. This algorithm may be most effective in reducing the rate of IDT, with a potential consequent reduction in rates of miscarriage related to the procedures. Indeed, a more comprehensive and longer-term economic estimation incorporating direct and indirect costs is undertaken in China with a regional government funded project of universal cfDNA screening for women with AMA. This will guide decision-making around the provision of prenatal screening.

Conflict of interest

None.

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