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Comparing outcomes and costs between contingent and combined first-trimester screening strategies for Down's syndrome

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ABSTRACT

Objective: To compare a contingent strategy with a combined strategy for prenatal detection of Down's syndrome (DS) in terms of cost, outcomes and safety.
Study design: The contingent strategy was based on a simulation, removing measurement of the free beta subunit of human chorionic gonadotropin (free βhCG) and calculating the DS risk retrospectively in 32,371 pregnant women who had been screened with the combined strategy in the first trimester. In the contingent strategy, a risk between 1:31 and 1:1000 in the first trimester indicated further testing in the second trimester (alpha-fetoprotein, inhibin A, unconjugated oestriol and free βhCG). The cut-off risk values for the contingent and combined strategies in the first trimester were 1:30 and 1:250, respectively, and the cut-off risk value for integrated screening in the second trimester was 1:250. Costs were compared in terms of avoided DS births, and the ratio of loss of healthy fetuses following invasive procedures per avoided DS birth was calculated.
Results: The combined strategy had sensitivity of 40/44 (90.9%) and a false-positive rate of 2.8%. Corresponding values for the contingent strategy were 39/44 (88.6%) and 1.3%, respectively. Only 11% of pregnant women required tests in the second trimester, and the approximate cost reduction for each avoided DS birth was 5000€. The ratio of lost healthy fetuses following invasive procedures per avoided DS birth improved by up to 0.65.
Conclusion: The contingent strategy has similar effectiveness to the combined strategy, but has lower costs and fewer invasive procedures.

Introduction

Down's syndrome (DS), or trisomy 21, is the most common aneuploidy, affecting one in every 800 live births, and is the most prevalent known cause of mental retardation.

When prenatal screening based on maternal age was introduced in the 1970s, cytogenic analysis was performed on amniotic fluid obtained from amniocentesis in pregnant women aged ≥35 years. Biochemical markers in maternal blood were incorporated in the mid-1970s, followed by fetal ultrasound markers. The aforementioned markers, along with maternal age, have given rise to a series of biochemical–ultrasonographic screening strategies.

Over the last 15 years, great improvements in the prenatal screening of aneuploidies have been introduced. The most common indication of invasive prenatal procedures is the detection of aneuploidy, and such procedures have been associated with the risk of abortion. Therefore, they should only be performed when there is a high risk of carrying an affected fetus. A recent meta-analysis by Akolekar et al. concluded that the procedure-related risks of miscarriage following amniocentesis and chorionic villus sampling (CVS) are much lower than previously thought [1]. The estimated procedure-related risks of miscarriage prior to 24 weeks in women undergoing amniocentesis and CVS are 0.11% and 0.22%, respectively. In most developed countries, it is practically routine to provide an individual risk for every pregnant woman, combining maternal age with ultrasonographic and

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biochemical markers; if this risk exceeds a pre-decided cut-off, a definitive diagnosis is offered by means of an invasive test. Findings by Lo et al. about the presence of DNA fragments, both maternal and fetal, in maternal blood established the biological 'base' and enabled the development of a new-generation sequencing strategy for the detection of fetal aneuploidies [2]. Although prenatal diagnosis based on free fetal nucleic acids in maternal blood is already technically feasible [3,4], its high cost makes it inapplicable to public health models.

Various screening strategies have been described, including combined, integrated, triple, quadruple, sequential and contingent strategies. All strategies have advantages and disadvantages, and they have been evaluated in various populations [5–7]. Cost-effectiveness studies have also been published for contingent, sequential and integrated strategies, but with limited and contradictory results [5,7].

In times of economic difficulties and expenditure restriction, investigation of the cost-effectiveness of diagnostic tests for DS has particular significance [8].

A study performed by the Spanish Ministry of Health on prenatal diagnosis of DS in Spain reported that a contingent screening strategy represents the most cost-effective approach, and is preferred by Spanish pregnant women as it results in fewer invasive procedures [9].

Optimization of this strategy involves the measurement of markers when they have the greatest discriminatory power. This involves measurement of nuchal translucency (NT) and pregnancy-associated plasma protein A (PAPP-A) in the first trimester, and measurement of the free beta subunit of human chorionic gonadotropin (free βhCG), alpha-fetoprotein (AFP), unconjugated oestriol (uE_3) and inhibin A in the second trimester (quadruple screening), based on evidence that free βhCG shows low discriminatory power in the first trimester [10].

In Catalonia [11] and the Balearic Islands, the combined screening strategy in the first trimester relies on the measurement of NT, PAPP-A and free βhCG. Quadruple screening is reserved for women who are too late for first-trimester screening.

To the authors' knowledge, no studies on the contingent strategy have been published to date, investigating measurement of PAPP-A and NT in the first trimester, and AFP, uE_3 and inhibin A in the second trimester. The usefulness of PAPP-A and free βhCG measurements in trisomy 21 screening is dependent on gestational age. As PAPP-A is a better test at earlier gestations and free βhCG is a better test at later gestations [10], the aim of this study was to perform a retrospective multicenter analysis of the cost-efficacy and safety of a contingent strategy for DS screening, calculated in a simulated way, without measurement of free βhCG in the first trimester. The contingent strategy was compared with combined screening in the first trimester in pregnant women screened between 2009 and 2010 at four public centers in Catalonia and the Balearic Islands.

Materials and methods

This study included 32,371 women with a single fetus who had undergone combined screening in their first trimester between 2009 and 2010 at three public centers in Catalonia (13,684 at Hospital Clínic; 2051 at Hospital Vall d'Hebron and 11,247 at Catlab) and one public centre in the Balearic Islands (5389 at Hospital Son Espases). At the time of screening, all women were between 8 and 13 weeks of gestation. Risk of DS was calculated based on maternal age, NT, PAPP-A and free βhCG.

The main characteristics of these pregnant women are shown in Table 1, and the distribution of gestational age at the time of ultrasonography for the measurement of NT and blood analysis is shown in Table 2. It should be noted that 26,982 (83.3%) women were screened in two steps (blood extraction at gestational weeks 8–10 and ultrasound at 12 weeks), and 5389 (16.6%) women underwent both steps on the same day.

Table 1
Main characteristics of pregnant women participating in the study.

Variable	Values	
Age (years) mean (SD)	31.1 (5.0)	
Weight (kg) mean (SD)	64.6 (12.3)	
Smoking	Smokers: 4695	14.5%
	Non-smokers: 27,676	85.5%
Ethnicity	Caucasian: 27,839	86.0%
	Arabic: 2104	6.5%
	Afro-Caribbean: 1004	3.1%
	Oriental: 680	3.1%
	Other: 744	2.3%

SD, standard deviation.

The main biochemical markers were measured using time-resolved fluoroimmunoassay in an autoanalyser DELFIA Xpress 6000 (PerkinElmer Life Sciences/Wallac Oy, Turku, Finland). All the laboratories where samples were processed were accredited in accordance with the protocols of the National Institute for Health and Clinical Excellence, and participated in an external quality control (UK-NEQAS). The results of the markers were corrected for weight, ethnicity, smoking habit and insulin-independent diabetes, and expressed in multiples of the median for pregnant women of the same gestational age. Population values were obtained from local women who had been screened previously. The medians of the markers were monitored frequently to ensure stability. NT was measured according to the criteria of the Fetal Medicine Foundation. Measurement quality was controlled according to criteria described by Cuckle [10]. Individual risks were calculated using Lifecycle Version 3.1 (PerkinElmer Life Sciences/Wallac Oy, Turku, Finland). The population parameters used in this software came from studies by Cuckle et al. [12].

The same software for risk calculation was used for the contingent strategy: after removing the measurement of free βhCG, the risk of DS was calculated retrospectively for the 32,371 pregnant women using maternal age, NT and PAPP-A. Positive and intermediate cut-off values were based on receiver operating characteristic curves (data not shown). Only women with DS risk between 1:31 and 1:1000 were screened in the second trimester using free βhCG, AFP, uE_3 and inhibin A. Using these cut-off risk values, sensitivity was the same as for other cut-off values described in other strategies, but the number of iatrogenic fetal losses was reduced. Sensitivity of 92% and a false-positive rate of 5%, as described in the SURUSS study [6] for integrated screening, were used to determine the number of positive results and the total number of cases with DS that would be detected.

The cut-off risk values for the contingent and combined strategies in the first trimester were 1:30 and 1:250, respectively, and the cut-off risk value for integrated screening in the second

Table 2
Distribution of gestational age based on ultrasound and blood analyses.

Gestational weeks	Ultrasound	Blood analyses
<9	–	1031 (3.2%)
9	–	5532 (17.1%)
10	–	13,613 (42.1%)
11	7834 (24.5%)	6661 (20.6%)
12	18,413 (56.9%)	5534 (17.1%)
13	6024 (18.6%)	–
Total	32,371 (100%)	32,371 (100%)