Enhanced First Trimester Screening for Trisomy 21 with Contingent Cell-Free Fetal DNA: A Comparative Performance and Cost Analysis

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Abstract

Objective: Prenatal screening for trisomy 21 is a standard of care. Emerging cell-free fetal DNA (cffDNA) technologies can improve screening performance, but they are expensive. This study was conducted to propose a contingent screening model that would incorporate cffDNA technology, would remain affordable, and could be applied equitably in a publically funded system.

Methods: Using performance and cost parameters from published literature, four prenatal screening strategies were compared. Scenario 1 modelled integrated prenatal screening (first trimester nuchal translucency and biochemical markers from both the first and second trimesters) with no cffDNA. Scenarios 2 and 3 modelled first trimester combined screening (FTS) and "enhanced FTS" (adding serum placental growth factor and alpha fetoprotein to FTS), respectively, with contingent cffDNA following a positive result. Scenario 4 modelled cffDNA as the primary screening test.

Results: Scenario 1 provides a known detection rate (DR) of 88%, with a false positive rate (FPR) of 3.3%. Scenarios 2 and 3 result in a DR of 94% and overall FPR of 0.59% and 0.33%, respectively, comparable to the DR of 96% and FPR of 0.1% with primary cffDNA (assuming the published test failure rate of 3%). The total cost, cost per woman screened, and cost per case of trisomy 21 detected were lower with scenario 3 (enhanced FTS with contingent cffDNA) compared with primary cffDNA or scenario 2 (FTS with contingent cffDNA).

Conclusion: Enhanced FTS with contingent cffDNA following a positive result provides a similar performance to that of primary cffDNA at a substantially lower cost.

Key Words: Prenatal screening, trisomy 21, first trimester combined screening, enhanced first trimester screening, cell-free fetal DNA test

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Résumé

Objectif : Le dépistage prénatal de la trisomie 21 fait partie des pratiques de soins normales. Les technologies émergentes utilisant l'ADN acellulaire (ADNac) fœtal peuvent en améliorer l'efficacité, mais coûtent cher. Notre étude visait à proposer un modèle de dépistage selon les besoins qui utiliserait ce type de technologie, qui demeurerait abordable et qui pourrait être appliqué de façon équitable dans le système public de santé.

Méthodologie : À l'aide de différents paramètres d'efficacité et de coût trouvés dans la littérature, nous avons comparé quatre méthodes de dépistage prénatal. La méthode 1 consistait en un dépistage prénatal intégré (clarté nucale au premier trimestre et mesure de marqueurs biochimiques aux premier et deuxième trimestres) et ne mesurait pas l'ADNac fœtal. Les méthodes 2 et 3 étaient un dépistage combiné au premier trimestre, respectivement régulier et approfondi (dépistage régulier avec détermination des taux sériques du facteur de croissance placentaire et de l'alphafœtoprotéine), suivi de la réalisation d'un test mesurant l'ADNac fœtal selon les besoins, soit en cas de résultat positif. Quant à la méthode 4, elle utilisait la mesure de l'ADNac fœtal comme test de dépistage primaire.

Résultats : La méthode 1 a un taux de détection (TD) connu de 88 %, et un taux de faux positifs (TFP) de 3,3 %. Les méthodes 2 et 3 sont associées à un TD de 94 %, et ont respectivement un TFP global de 0,59 % et de 0,33 %, comparativement à un TD de 96 % et à un TFP de 0,1 % pour la méthode 4, soit le dépistage primaire au moyen de l'ADNac (si le taux d'échec correspond à celui de la littérature, qui est de 3 %). Le coût total, le coût par patiente et le coût par cas de trisomie 21 détecté étaient inférieurs pour la méthode 3 par rapport à la méthode 4 et à la méthode 2.

Conclusion : La méthode consistant à réaliser un dépistage combiné approfondi au premier trimestre puis un test mesurant l'ADNac fœtal en cas de résultat positif a une efficacité comparable à celle de la mesure de l'ADNac fœtal comme test de dépistage primaire, mais elle est considérablement moins coûteuse.

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INTRODUCTION

Prenatal screening for trisomy 21 is a standard of care internationally. Prenatal screening is mostly offered by primary care providers because pregnant women attend their primary provider (a family doctor, unless they self-refer to midwifery) for their first visit and remain there or are referred to an obstetrician or maternal fetal medicine subspecialist. Systematic prenatal screening for trisomy 21 and trisomy 18 was introduced in Ontario in the early 1990s. Currently the uptake rate is approximately 68%.[1] Integrated prenatal screening has been the dominant test because of its high detection rate and low false positive rate compared with first trimester combined screening. However, IPS requires two separate blood samples, with no result until the second trimester.[2]

The cell-free fetal DNA test has significantly improved the accuracy of prenatal screening for trisomy 21, 18, and 13, although it is much more expensive than conventional screening tests. Internationally, it has been challenging to offer equitable access to cffDNA and maintain the overall cost of prenatal screening within publically funded health care systems. Several studies have suggested that a more cost-effective approach is to offer cffDNA to women who have a positive primary screening result, allowing for an overall FPR comparable to that of primary cffDNA but at a substantially lower cost.[3–7] With this approach, the final DR is limited by that of the primary screening test. Therefore, it is desirable to have a primary test with both an improved DR and with results available in the first trimester. Such a test will reduce the numbers of cffDNA tests required, while not compromising accuracy or timeliness of results. Previous studies including one from our group showed that FTS could be improved by adding two additional serum markers: first trimester alpha fetoprotein and placental growth factor.[8–11] Enhanced FTS has a similar performance to IPS for detection of trisomy 21.[8] In addition, pregnancy-associated plasma protein A and PlGF used in the EFTS are markers that can potentially be incorporated into an algorithm to screen for placental insufficiency syndromes.[12] A contingent approach of cffDNA, with EFTS as the primary screening test, could then provide a screening option for placental disorders along with aneuploidy.[13]

Using information from published studies, the current study compared the cost and performance of several screening strategies with the aim of identifying a screening option for trisomy 21 that maximizes performance and minimizes costs and could thus be considered for incorporation into a provincial prenatal care package.

ABBREVIATIONS

AFP	alpha fetoprotein
cffDNA	cell-free fetal DNA
CVS	chorionic villus sampling
DR	detection rate
EFTS	enhanced first trimester combined screening
FPR	false positive rate
FTS	first trimester combined screening
hCG	human chorionic gonadotrophin
IPS	integrated prenatal screening
NT	nuchal translucency
PlGF	placental growth factor
PAPP-A	pregnancy-associated plasma protein A

METHODS

We modelled four separate screening strategies, or "scenarios," to compare cost and performance for the specific "target" of trisomy 21. Modelling for the study was based on a cohort of pregnant women in Ontario from April 2011 to March 2012.[1]

Table 1 shows the baseline assumptions set to model the performance and cost for each scenario.

Screening scenario 1 modelled IPS as the only screening test. cffDNA was not included in this scenario. IPS includes maternal age, nuchal translucency, and PAPP-A measured between 11 and 13+6 weeks' gestation, intact human chorionic gonadotrophin, AFP, and unconjugated estriol measured between 15 and 18 weeks' gestation. The result of the IPS is reported after the second blood test is completed. Women who receive a positive IPS result are offered amniocentesis. IPS has been the most common approach used in Ontario prior to the introduction of cffDNA (thus our "baseline" scenario) because of its superior performance compared with FTS, albeit with a delay