

# Combined first-trimester versus second-trimester serum screening for Down syndrome: A cost analysis

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**OBJECTIVE:** The purpose of this study was to compare the cost-effectiveness of combined first-trimester screening for fetal Down syndrome with second-trimester maternal serum triple screening.

**STUDY DESIGN:** A first-trimester screening approach that used nuchal translucency measurement and maternal serum screening was evaluated against second-trimester maternal serum triple screening in a hypothetical population. Screening sensitivities and screen-positive rates were 91% and 5% for the first-trimester approach and 70% and 7.5% for the second-trimester approach, respectively. The costs of fetal Down syndrome, live-born Down syndrome cost, and total costs (screening plus live-born costs) were calculated for each screening program.

**RESULTS:** First-trimester screening was associated with lower screening and live-born Down syndrome costs versus second-trimester serum screening. Total Down syndrome screening costs were 29.1% lower with first-trimester screening.

**CONCLUSION:** In this hypothetical model, combined first-trimester screening for fetal Down syndrome was more cost-effective than universal second-trimester triple serum screening. (Am J Obstet Gynecol 2003;188:745-51.)

**Key words:** Cost-effectiveness, fetal Down syndrome, prenatal screening, nuchal translucency, serum screening

Many advances in fetal Down syndrome screening have occurred since the National Institutes of Health advised maternal age-based screening in 1979.<sup>1</sup> The pace has quickened over the past 10 years, with the introduction of second-trimester maternal serum and ultrasound-based screening methods for fetal Down syndrome and, more recently, with the development of first-trimester screening programs. In the United States, second-trimester maternal serum screening for fetal Down syndrome is the standard, whereas in the United Kingdom and other parts of Europe, a first-trimester screening approach that incorporates ultrasound and biochemical screening has been advocated. Although all would agree that both methods are an improvement over age-based screening alone, controversy persists regarding which method is most efficacious and cost-effective. Several authors have reported on the economic evaluations of alternative prenatal Down syndrome screening programs.<sup>2-4</sup> In the only

study to compare second- and first-trimester screening directly, Vintzileos et al<sup>5</sup> found that first-trimester screening with nuchal translucency alone was more expensive than second-trimester serum screening. A similar comparison of second-trimester serum screening with combined first-trimester screening (nuchal translucency and biochemistry) for fetal Down syndrome is lacking. This study sought to compare the cost-effectiveness of combined first-trimester screening with second-trimester maternal serum screening for fetal Down syndrome.

## Material and methods

This cost-effectiveness analysis was from a health care perspective. A hypothetical population of 10,000 patients that was modeled with the 1997 nationwide maternal age distribution in which 9.6% of births were to women  $\geq 35$  years of age served as the screening group.<sup>6</sup> Screening was provided to women of all ages; women  $>35$  years of age were not excluded from the analysis. The patient's a priori risk for fetal Down syndrome was based on both maternal age<sup>7</sup> and gestational age, with the use of the formula of Snijders et al.<sup>8</sup> In all 10,000 patients, a singleton, viable intrauterine pregnancy was assumed at the time of screening. The number of Down syndrome pregnancies was estimated by multiplication of the number of fetuses at each maternal age by the a priori risk for Down syndrome. First- and second-trimester fetal Down syndrome

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**Table I.** Screening cost estimates

<i>Procedure</i>	<i>First trimester (\$)</i>	<i>Second trimester (\$)</i>
First-trimester ultrasound cost	150	150
First-trimester serum screen cost	60	
Second-trimester triple screen cost		80
Second-trimester ultrasound cost		200
Consult, amniocentesis/chorionic villi sampling, chromosomes cost	1000	1000

**Table II.** First- versus second-trimester screening efficacy

	<i>Second trimester</i>		
	<i>First trimester</i>	<i>Best case</i>	<i>Worst case</i>
Sensitivity (%)	91	78	70
Screen-positive rate (%)	5	5	7.5
Down syndrome, estimated (No.)	21	21	19
Patients with positive screen results (No.)	500	500	750
Amniocenteses/chorionic villi sampling performed:	400	400	600
80% uptake (No.)			
Down syndrome, detected (No.)	15.3 (72.9%)	13.1 (62.4%)	10.6 (55.8%)
Yield (n/N)	1/26	1/31	1/57
Down syndrome, missed (No.)	5.7	7.9	8.4
Down syndrome, live born (No.)	4	5.5	6.6

loss rate before term was estimated at 30% and 21%, respectively.<sup>8</sup>

For the purposes of this study, a first-trimester screening approach that used maternal biochemistry for pregnancy-associated plasma protein A and free  $\beta$ -human chorionic gonadotropin combined with fetal nuchal translucency, as previously described, was chosen. For each marker, the multiple of the median was determined, and a likelihood ratio was calculated as described by Krantz et al.<sup>9</sup> First-trimester ultrasound screening performed at 11 to 14 weeks of gestation included the measurement of the nuchal translucency and a detailed anatomic survey. The fetal Down syndrome risk was determined by the multiplication of the patient's a priori risk by the likelihood ratio for each marker. Patients with an adjusted risk for women greater than or equal to 35 years of age (1/270 women) were considered screen positive (screen positive rate = patients who screened positive/patients who were screened). Two prospective trials that evaluated screening results for fetal Down syndrome with the use of the first-trimester approach have been performed in the United States, with estimated screening sensitivities of 78%<sup>10</sup> (worst case scenario) and 91%<sup>9</sup> (best case scenario) at a screen positive rate of 5%. A third prospective English trial reported an intermediate sensitivity of 86% with a screen-positive rate of 6.7%.<sup>11</sup> For purposes of this study, sensitivity analysis was performed with the use of worst and best case scenarios at a 5% screen-positive rate.

Regarding patients in the second-trimester screening protocol, it was assumed that all the patients underwent routine first-trimester ultrasound screening to confirm

fetal number, fetal viability, and gestational age. Although it is possible that some aneuploid fetuses would be detected with routine first-trimester ultrasound (eg, increased nuchal translucency), it was assumed for the purposes of this study that this number was negligible. Maternal serum triple screen for  $\alpha$ -fetoprotein (AFP), human chorionic gonadotropin, and unconjugated estriol was the second-trimester screening method that was chosen for comparison. Second-trimester ultrasound evaluation for the presence of fetal markers of Down syndrome was not performed. Patients with an adjusted risk of women who are  $\geq 35$  years old were considered screen positive. Little prospective data exist on the efficacy of second-trimester serum screening for fetal Down syndrome. In a group of women who were  $< 35$  years old, Haddow et al<sup>12</sup> reported a 60% sensitivity for fetal Down syndrome, with a screen-positive rate of 9.4% at a fetal Down syndrome risk screen cutoff value of 1 of 270 women. Adjustments in this screening efficacy are required when consideration is given to screening the older women and when ultrasound dating is used. In older women, with a higher incidence of fetal Down syndrome, the screen-positive rate and sensitivity will increase.<sup>13</sup> When ultrasound dating is used for the calculation of the second-trimester serum screen fetal Down syndrome risk, the screening sensitivity is increased, and the screen-positive rate was reduced.<sup>12,14</sup> After an adjustment for the maternal age distribution in our population and the universal use of first-trimester ultrasound dating, a sensitivity of 70% and a screen-positive rate of 7.5% were assumed.

Our primary model assumed that all patients who undergo second-trimester screening would have undergone

**Table III.** First versus second trimester cost comparison

	First trimester	Second trimester	
		Best case	Worst case
First-trimester ultrasound (\$)	1,500,000	1,500,000	1,500,000
Serum screen (\$)	600,000	600,000	800,000
Second-trimester ultrasound (\$)	0	0	150,000
Amniocentesis/chorionic villi sampling (\$)	400,000	400,000	600,000
Screening cost (\$)	2,500,000	2,500,000	3,050,000
Live-born Down syndrome cost (\$)	2,000,000	2,750,000	3,300,000
Total cost (\$)	4,500,000	5,250,000	6,350,000
Amniocentesis-related losses (No.)	2	2	3

**Table IV.** Influence of first-trimester ultrasound screening use on second-trimester screening efficacy

	0% Ultrasound screening	50% Ultrasound screening	100% Ultrasound screening
Down syndrome, estimated (No.)	19	19	19
Sensitivity (%)	57	63.5	70
Screen-positive rate, initial (%)	9.9 (14)	8.7 (10.8)	7.5
Patients with positive screen, initial (No.)	1400	1075	750
Patients with positive screen, final (No.)	990	870	750
Amniocenteses/chorionic villi sampling performed: 80% uptake (No.)	792	696	600
Down syndrome, detected (No.)	8.7 (45.8%)	9.7 (51.1%)	10.6 (55.8%)
Yield (No.)	1/91	1/72	1/57
Down syndrome, missed (No.)	10.3	9.3	8.4
Down syndrome, live born (No.)	8.1	7.3	6.6

a limited first-trimester ultrasound screening previously. The percentage of patients who have undergone ultrasound screening before the second-trimester serum screening is unreported typically. Available data suggest that approximately 50% of patients who underwent second-trimester serum screening had undergone a previous ultrasound examination.<sup>12,14</sup> Benn et al<sup>14</sup> found that, when ultrasound dating was used for purposes of second-trimester fetal Down syndrome risk calculation, sensitivity increased 23%, and the initial and revised screen-positive rates were reduced by 46% and 24%, respectively. From these estimates, we calculated that the second-trimester screening sensitivity would be reduced from 70% to 57% in patients without ultrasound dating. Likewise, the initial and final (after correction for dates and fetal number) screen-positive rates would increase from 7.5% to 14% and 9.9%, respectively, without the benefit of ultrasound dating. These revised screening parameters were used for those patients who underwent second-trimester screening without previous ultrasound screening in our sensitivity analysis of ultrasound usage rates of 0% and 50%.

Table I lists the regional cost estimates that are based on insurance reimbursement for the year 2000. Acceptance of invasive testing after a positive prenatal screen for Down syndrome is not universal. Spencer et al<sup>11</sup> reported that 83% of patients accepted invasive testing after an abnormal first-trimester screen for Down syndrome. Cunningham and Thompkinson<sup>15</sup> found that 71% of the patients in the California triple-marker program ac-

cepted amniocentesis after an abnormal second-trimester serum screen. For purposes of this model, an acceptance rate of 80% for invasive testing was assumed for patients with positive screening results in the first and second trimester. We assumed that all cases of fetal Down syndrome that were identified would be terminated. The number of patients who were screened positive who were offered and who underwent invasive testing was calculated for each screening program. In addition, the fetal Down syndrome detection rate (percentage of fetuses with Down syndrome that were diagnosed by amniocentesis), yield (Down syndrome fetuses that were diagnosed/amniocentesis that were performed), and Down syndrome live born (undiagnosed cases of fetal Down syndrome who survived until delivery) were determined. A procedural loss rate of 1 in 200 pregnancies was used to estimate the number of fetuses who were lost as the result of diagnostic testing (amniocentesis or chorionic villi sampling) for each screening program. The screening cost for each program was the summation of all costs that were involved with screening. The live-born Down syndrome cost was derived by the multiplication of the number of live-born cases of Down syndrome by the lifetime medical and nonmedical cost estimate of \$500,000.<sup>16</sup> The total cost for each program was the sum of the screening and live-born Down syndrome costs. For purposes of this study, only costs that were directly or indirectly related to fetal Down syndrome screening were considered. Secondary costs that were related to amniocentesis-related loss of fetal life, pregnancy termination procedures, and

**Table V.** Influence of first-trimester ultrasound use on second-trimester screening cost

	0% Ultrasound screening	50% Ultrasound screening	100% Ultrasound screening
First-trimester ultrasound (\$)	0	750,000	1,500,000
Serum screen (\$)	800,000	800,000	800,000
Second-trimester ultrasound (\$)	280,000	215,000	150,000
Amniocentesis (\$)	792,000	696,000	600,000
Screening cost (\$)	1,872,000	2,461,000	3,050,000
Live-born Down syndrome cost (\$)	4,050,000	3,650,000	3,300,000
Total cost (\$)	5,922,000	6,111,000	6,350,000
Amniocentesis-related losses (No.)	4	3.5	3

screening for other fetal chromosomal and/or structural anomalies were not included in this analysis.

### Results

Our model estimated that 21 cases of fetal Down syndrome would be present at the time of the first-trimester screen. Because of the spontaneous loss of some of these fetuses with advancing gestation, we estimated that 19 fetuses would be present at the time of the second-trimester screen. Table II compares the efficacy of the first- and second-trimester screening programs. The higher sensitivity of the combined first-trimester screen translated into a higher fetal Down syndrome detection rate and, consequently, fewer live-born cases of Down syndrome. The lower screen-positive rate that was associated with the combined first-trimester screen resulted in 50% fewer screen-positive pregnancies and amniocenteses. With second-trimester maternal serum triple screening, 57 amniocenteses would be performed to diagnose a single case of fetal Down syndrome. In the best case scenario, one case of Down syndrome was detected for every 26 amniocenteses that were performed (1/31 amniocenteses in the worst case scenario) after an abnormal first-trimester screen.

In addition to its improved screening efficacy, combined first-trimester screening for fetal Down syndrome is associated with lower screening and total costs compared with second-trimester triple screening (Table III). The lower screening cost with the first- versus the second-trimester method was primarily a consequence of fewer amniocenteses that were performed. The estimated lifetime costs for live-born Down syndrome cases was also less in patients who underwent first-trimester screening, which is a reflection of the higher sensitivity of the test. In summation, the total cost that is associated with the first-trimester screening program was 17.3% lower under the worst and 29.1% lower under the best scenario compared with universal second-trimester maternal serum triple screening. At a national level, significant cost savings could be realized with the adoption of first-trimester fetal Down syndrome screening. With 4 million births annually in the United States, the total Down syndrome screening costs of second-trimester screening under our model would be 2.54 billion dollars. This is in contrast to an an-

nual total screening cost of 2.1 billion dollars and 1.86 billion dollars for first-trimester screening under the worst and best scenario, respectively.

With less usage of first-trimester ultrasound scans, the screening and total costs of second-trimester screening are reduced as shown in Tables IV and V. However, these cost savings are offset by an increase in liveborn Down syndrome costs. Second-trimester serum screening is less efficacious when gestational age based on menstrual dates is used; the sensitivity decreases, and the screen-positive rate increases.<sup>14</sup> Despite more women with screen-positive results and an increased number of invasive procedures with decreased first-trimester ultrasound use, fewer cases of fetal Down syndrome are identified (8.7 vs 10.6 cases with 0% and 100% ultrasound screening, respectively). Consequently, increased costs are incurred as the result of a greater number of liveborn Down syndrome infants. The overall screening cost savings that are realized from foregoing routine first-trimester ultrasound dating in all patients before second-trimester serum screening is slight (\$428,000, 6.7%). Despite this marginal cost savings, the total screening costs that are associated with 0% and 50% ultrasound use before second-trimester screening were greater than those that were associated with first-trimester screening (Table VI).

### Comment

In this cost analysis, first-trimester combined screening for fetal Down syndrome was associated with lower screening costs, fewer live-born Down syndrome births, and less total cost compared with second-trimester serum triple screening. The cost advantage can be attributed to the higher sensitivity and lower screen-positive rate of the first-trimester screen. This improved screening efficacy allowed for the allocation of medical resources to patients at greatest risk for fetal Down syndrome, which is a point that is reflected in an improved yield. Despite 50% fewer amniocenteses, a larger percentage of Down syndrome fetuses were detected under both first-trimester screening scenarios (best and worst case). First-trimester screening resulted in fewer Down syndrome infants; consequently, the live-born Down syndrome costs were also lower in both first-trimester scenarios compared with sec-

**Table VI.** Cost summary for first- and second-trimester screening

	<i>Screening cost (\$)</i>	<i>Live-born cost (\$)</i>	<i>Total cost (\$)</i>
First-trimester screening			
Best case scenario	2,500,000	2,000,000	4,500,000
Worst case scenario	2,500,000	2,750,000	5,250,000
Second-trimester screening: ultrasound scan use			
0%	1,872,000	4,050,000	5,922,000
50%	2,461,000	3,650,000	6,110,000
100%	3,050,000	3,300,000	6,350,000

ond-trimester screening. The results of our analysis are consistent with those of Gilbert et al<sup>3</sup> who found combined first-trimester screening to be more cost-effective than second-trimester triple screening.

The findings of our study are dependent largely on the sensitivity and screen positive rates that were used in the model. Our estimates for the screen-positive rate and sensitivity for both first- and second-trimester screening are derived from published prospective trials. Although many second-trimester screening programs have incorporated inhibin A (quad screen) into the triple screen, the lack of prospective trials that evaluate screening efficacy prohibited comparison. It must be acknowledged that the screening sensitivities and false-positive rates that were used in this analysis are theoretic and probably represent best estimates. In clinical practice, it is much harder to estimate these screening characteristics. It is commonplace for multiple laboratories, with different and sometimes unknown sensitivity and false-positive rates to be performing screening in a single-patient population. First-trimester screening, through the use of ongoing quality assurance (required to maintain certification in nuchal translucency measurement) and reference laboratory standardization may be in the best position to offer reliable, consistent screening results.

Our model assumed that all Down syndrome fetuses that were identified would be terminated. If fewer Down syndrome fetuses were terminated, higher live-born and overall costs because of the birth of more Down syndrome infants would result. Under the current model, if only 70% of identified fetal Down syndrome pregnancies were terminated, under the best first-trimester screening scenario, 3.2 additional cases of live-born Down syndrome would result. In comparison, 2.5 additional cases would occur with second-trimester screening. The cost advantage of first-trimester screening remains, despite the additional \$350,000 cost differential (0.7 case of live-born Down syndrome × \$500,000 lifetime cost/case) compared with second-trimester screening.

There are other potential benefits that are associated with first- and second-trimester fetal Down syndrome screening programs. Although both approaches will detect fetuses with aneuploidy other than Down syndrome, first-trimester combined screening appears superior. In

the study by Krantz et al,<sup>9</sup> all cases of fetal trisomy 18, triploidy, monosomy X, and two of three cases of trisomy 13 were detected with the use of combined first-trimester screening. Although second-trimester serum screening may allow for the detection of 60% to 70% of fetuses with trisomy 18,<sup>17</sup> the detection rate for trisomy 13, monosomy X, and triploidy is unknown. Kim et al<sup>18</sup> reported that only 20% of women (1/5 women) of advanced maternal age who carry fetuses with trisomy 18 or 13 or monosomy X were triple-screen positive. An additional cost benefit could be expected with the avoidance of some of these live births.

Through the use of AFP, maternal serum triple-screen testing will also detect pregnancies at increased risk for neural tube, abdominal wall, and other congenital anomalies. Making this serum screen available to women who undergo first-trimester screening would require additional expenditures. Assuming the cost of a second-trimester maternal serum AFP screen to be \$40, a cost increase of \$400,000 (\$40 × 10,000) would be incurred to provide this screen to all patients receiving first-trimester screening. Despite this marginal cost increase, the cost advantage of first-versus second-trimester screening remains. Any cost that is related to the evaluation of patients with an elevated maternal serum AFP would be shared equally between the first- and second-trimester screening group. Similarly, the costs that are associated with second-trimester ultrasound screening for fetal anomalies in patients with screen-negative results would fall equally on patients who receive first- and second-trimester screening. For the purposes of this study, we did not include these costs in our analysis because it was our intention to limit our focus to costs that were related to fetal Down syndrome screening. However, targeted fetal evaluation at 11 to 14 weeks of gestation can detect many fetal anomalies, which include open neural tube defects and abdominal wall defects that are diagnosed traditionally in the second trimester.<sup>11,19</sup> These diagnoses can be made earlier, without additional screening costs. Furthermore, chromosomally normal fetuses with a thickened nuchal fold in the first trimester are at increased risk for other structural and genetic abnormalities.<sup>20</sup> Detection of these affected fetuses may facilitate the prenatal detection of anomalies that might otherwise go undetected.

This secondary screening benefit has been best studied in regard to congenital heart defects. In a study group of 398 fetuses with a thickened nuchal translucency (>3.5 mm), 28 of 29 cases of major heart defects were diagnosed antenatally.<sup>21</sup> Additional cost benefits could be realized with the antenatal identification and avoidance of these affected live births. A program of second-trimester serum screening would not be expected to identify many of these fetuses because most patients with serum screen-negative results would not receive ultrasound evaluation.

Models for universal first-trimester screening exist in the United Kingdom and elsewhere, where they have been accepted largely on the basis of the improved screening efficacy. With a limited number of sonographers who are trained in nuchal translucency measurement, routine first-trimester screening remains unavailable to most sonographers in the United States. In the short term, it is likely that first-trimester screening will be available in large ultrasound referral practices. Ultrasound resources are available widely across the country, and in fact, in many private obstetric offices. Currently, many pregnant women undergo ultrasound screening in the first trimester for a variety of reasons. If screening is to be provided to all pregnant women, then training, certification, and surveillance of many of these sonographers will be required. Efforts are underway currently in the United States to facilitate the training and surveillance of sonographers in the performance of first-trimester nuchal translucency screening. With increased patient demand and physician acceptance of first-trimester screening, wider availability of trained sonographers can be expected.

Rowley<sup>22</sup> noted that the aim of genetic screening should be to maximize the options that are available rather than to reduce the prevalence of genetic diseases. To this end, first-trimester combined screening offers the pregnant patient an alternative method to evaluate her fetal Down syndrome risk. When given the option of screening earlier in pregnancy, women prefer first-trimester screening.<sup>23,24</sup> When testing for the fetal Down syndrome risk earlier in pregnancy is provided, women are afforded prenatal diagnostic options that are unavailable to those women in the second trimester. Chorionic villus sampling and early amniocentesis can be provided to patients with abnormal results who are in need of early fetal karyotyping. For others who are considering fetal karyotyping, a reassuring first-trimester screening result may be sufficient to allow the women to pursue the lower risk option of routine amniocentesis and to forego chorionic villi sampling<sup>23</sup> or early amniocentesis. Patients who pursue the pregnancy termination of an abnormal fetus who was identified in the first trimester may be afforded pregnancy termination options that are unavailable in the second trimester. Furthermore, these couples can be provided privacy with their decision because the information is obtained before the point when most women ap-

pear pregnant. The improved yield that is associated with first-trimester screening translates to fewer amniocenteses and thus to fewer procedural-related losses of unaffected fetuses. In the current model, first-trimester screening was associated with the procedural loss of two fetuses versus the loss of three fetuses in the second-trimester screening. Although the benefits for limiting the number of procedural-related losses is obvious, the economic and emotional costs that are incurred with the loss of a normal fetus after invasive testing is much harder to quantify. At the individual patient level, these important secondary benefits cannot be overstated.

In the United States, we remain bound to a strategy for fetal Down syndrome screening that is based in part on maternal age, despite the poor efficacy of this approach.<sup>17</sup> Universal maternal serum triple screening in the second trimester offers some distinct advantages leading some investigators to question the wisdom of maternal age-based Down syndrome screening.<sup>2,3</sup> Universal first-trimester combined screening has been shown to have equal, if not better, efficacy<sup>9-11</sup> compared with second-trimester screening and, in this analysis, was associated with lower screening and live-born Down syndrome costs. This cost advantage, combined with the other potential prenatal screening and maternal benefits, supports the consideration of universal first-trimester fetal Down syndrome screening.

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### Correction

In the article by Svedas et al (Svedas E, Nisell H, VanWijk MJ, Nikas Y, Kublickiene KR. Endothelial dysfunction in uterine circulation in preeclampsia: Can estrogens improve it? *Am J Obstet Gynecol* 2002;187:1608-16), the expression "blood flow-mediated dilatation" should be "flow-mediated dilatation" because in this in vitro study blood was not used for measurements of flow-mediated dilatation.