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An economic evaluation of second-trimester genetic ultrasonography for prenatal detection of Down syndrome

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OBJECTIVE: The objective of this study was to perform an economic evaluation of second-trimester genetic ultrasonography for prenatal detection of Down syndrome. More specifically, we sought to determine the following: (1) the diagnostic accuracy requirements (from the cost-benefit point of view) of genetic ultrasonography versus genetic amniocentesis for women at increased risk for fetal Down syndrome and (2) the possible economic impact of second-trimester genetic ultrasonography for the US population on the basis of the ultrasonographic accuracies reported in previously published studies.

STUDY DESIGN: A cost-benefit equation was developed from the hypothesis that the cost of universal genetic amniocentesis of patients at increased risk for carrying a fetus with Down syndrome should be at least equal to the cost of universal genetic ultrasonography with amniocentesis used only for those with abnormal ultrasonographic results. The main components of the equation included the diagnostic accuracy of genetic ultrasonography (sensitivity and specificity for detecting Down syndrome), the costs of the amniocentesis package and genetic ultrasonography, and the lifetime cost of Down syndrome cases not detected by the genetic ultrasonography. After appropriate manipulation of the equation a graph was constructed, representing the balance between sensitivity and false-positive rate of genetic ultrasonography; this was used to examine the accuracy of previously published studies from the cost-benefit point of view. Sensitivity analyses included individual risks for Down syndrome ranging from 1:261 (risk of a 35-year-old at 18 weeks' gestation) to 1:44 (risk of a 44-year-old at 18 weeks' gestation). This economic evaluation was conducted from the societal perspective.

RESULTS: Genetic ultrasonography was found to be economically beneficial only if the overall sensitivity for detecting Down syndrome was >74%. Even then, the cost-benefit ratio depended on the corresponding false-positive rate. Of the 7 published studies that used multiple ultrasonographic markers for genetic ultrasonography, 6 had accuracies compatible with benefits. The required ultrasonographic accuracy (sensitivity and false-positive rate) varied according to the prevalence of Down syndrome in the population tested.

CONCLUSIONS: The cost-benefit ratio of second-trimester genetic ultrasonography depends on its diagnostic accuracy, and it is beneficial only when its overall sensitivity for Down syndrome is >74%. (Am J Obstet Gynecol 1998;179:1214-9.)

Key words: Genetic ultrasonography, economic evaluation, second-trimester ultrasonography

Several studies have been published regarding the usefulness of second-trimester ultrasonography in the prenatal detection of fetuses with Down syndrome. Second-trimester ultrasonographic markers that appear to be useful in the prenatal detection of Down syndrome include the presence of 1 structural anomaly such as short femur, short humerus, pyelectasis, increased nuchal fold thickening, echogenic bowel, choroid plexus cysts, hypoplastic middle phalanx of the fifth digit, and wide space between the first and second toes.[1-9] By combining multiple second-trimester ultrasonographic markers, some studies have reported sensitivities for detecting fetuses with Down syndrome that range between 50% and 93%.[1-9] Because of these high detection rates, some investigators have advocated the use of a comprehensive ultrasonographic assessment by evaluating multiple ultrasonographic markers as an adjunct to maternal age and maternal serum biochemistry to adjust the risk and modify clinical management for patients at increased risk for carrying a fetus with Down syndrome.[5, 6, 8, 9]

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Table I. Assumptions for cost-benefit model

1. Prevalence of Down syndrome among women at risk is 1:100.
2. The prenatal diagnosis of Down syndrome will lead to pregnancy termination in all cases.
3. Among second-trimester fetuses with Down syndrome, 70% are born alive.[10, 11]
4. Costs:
   C_{amnio} = $1200
   $C_{U/S}$ = $300
   C_{DS} = $500,000[12, 13]

C_{amnio}, Sum of costs for (1) ultrasonography before and during amniocentesis, (2) procedure fee, and (3) karyotype; *$C_{U/S}$*, cost of genetic ultrasonography; *C_{DS}*, lifetime cost of neonates with Down syndrome.

However, there are no data regarding the economic appraisal of this approach.

The objective of this study was to perform an economic evaluation of second-trimester genetic ultrasonography. More specifically, we sought to determine the diagnostic accuracy requirements (from the cost-benefit point of view) of second-trimester ultrasonography (with amniocentesis reserved for only those with abnormal ultrasonographic results) with respect to the current practice of offering genetic amniocentesis to women who are at increased risk for carrying a fetus with Down syndrome (because of either advanced maternal age or abnormal maternal serum screening results). An additional objective was to determine the possible impact of second-trimester genetic ultrasonography for the US population on the basis of the accuracies in previously published ultrasonographic studies.

Methods

This economic evaluation was conducted from the societal perspective. The basic hypothesis of our cost-benefit equation is that the cost generated by universal genetic ultrasonographic evaluation of patients at risk for Down syndrome should be no greater than the cost generated by universal amniocentesis of these patients at high risk. The cost generated by universal genetic ultrasonography (second half of the equation) should include the following: (1) the cost for all normal results of genetic ultrasonography (specificity and false-negative rate), (2) the cost of the amniocentesis "package" for all those with abnormal genetic ultrasonographic results (sensitivity and false-positive rate), and (3) the lifetime cost of all live-born infants with Down syndrome, after taking into consideration that 70% of second-trimester fetuses with Down syndrome will be born alive.[10, 11]

Thus, on the basis of the assumptions of Table I and assuming a sample of 100 patients, the cost-benefit formula is summarized as follows: (C_{amnio} 100) = $C_{U/S}$ [(specificity 99) + (1 – sensitivity)] + C_{amnio}[sensitivity + (1 – specificity) 99] + C_{DS}[(1 – sensitivity) 0.70] where

Table II. Accuracy of second-trimester genetic ultrasonography with multiple ultrasonographic markers for detection of Down syndrome: Summary of published studies

	Sensitivity		*False-positive rate*	
Reference	*No.*	*%*	*No.*	*%*
Benacerraf et al,[1] 1992*	29/32	91	77/588	13
Nadel et al,[2] 1995	59/71	83	88/694	13
DeVore and Alfi,[4] 1995	13/15	87	107/1000	11
Nyberg et al,[3] 1995	9/18	50	27/374	7
Vintzileos et al,[6] 1996	13/14	93	54/406	13
Bahado-Singh et al,[8] 1996	10/11	90	132/962	14
Bromley et al,[9] 1997	44/53	83	31/177	17
TOTAL	148/182	81	439/13,613	12

Abnormal test result is 1 abnormal ultrasonographic markers.
*Not included in calculation of total.

Table III. Required minimum sensitivities for given false-positive rates to achieve benefit according to maternal age–related prevalence of Down syndrome

Maternal age (y)	*Risk for Down syndrome at 18 wk*[11]*	*Sensitivity (%)*		
		False positive rate 5%	*False-positive rate 10%*	*False-positive rate 15%*
35	1:261	36	39	43
36	1:205	50	52	55
37	1:159	61	63	65
38	1:122	70	72	73
39	1:93	77	78	80
40	1:71	82	83	84
41	1:53	87	88	88
42	1:40	90	91	91
43	1:30	92	93	93
44	1:22	95	95	95

C_{amnio} represents the cost for the amniocentesis package (ultrasonography before and during amniocentesis, the amniocentesis procedure, and karyotype cost), *$C_{U/S}$* represents the cost of genetic ultrasonography, *C_{DS}* represents the lifetime cost of neonates born with Down syndrome, *1 – sensitivity* is the false-negative rate, and *1 – specificity* is the false-positive rate.

It was assumed that the cost of the amniocentesis package (ultrasonography before and during the procedure plus the cost of the amniocentesis procedure plus the laboratory cost for karyotyping) was $1200 and the cost of genetic ultrasonography is approximately $300 (ratio 4:1, or difference in costs of $900). These costs of the ultrasonographic and amniocentesis package are compatible with average regional clinical practice data and were obtained from the Medirisk tables. Medirisk is a nationwide medical cost-profiling company located in Atlanta.

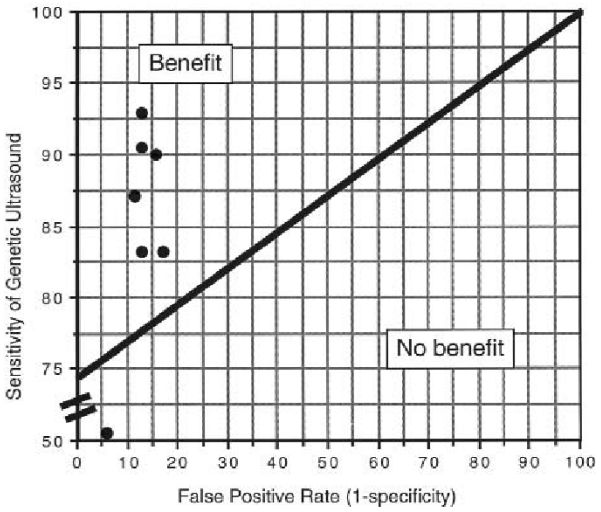

Fig 1. Graph showing *line* (balance) between sensitivity and false-positive rate of genetic ultrasonography that determines benefit for various combinations of sensitivities and false-positive rates (1:100 prevalence of Down syndrome). Graph also shows plotting of diagnostic accuracy (sensitivity vs false-positive rate) of previously published studies with multiple ultrasonographic markers for prenatal detection of Down syndrome.

Medirisk's medical reimbursement costs estimates are based on data from health insurance companies, health maintenance organizations, and other managed care organizations. The company has a 10-year experience with medical payment research data analysis. The lifetime cost of neonates born with Down syndrome was fixed at approximately $500,000. This is the incremental cost (costs beyond those generally incurred for the average neonate). This cost includes both direct costs (medical, developmental, and special education) and indirect costs (lost productivity, including wages, from early death or disability). This amount was derived from previous work on estimates of the economic costs of birth defects[12, 13] and adjusted for inflation to reflect 1998 dollars.

After fixing of the cost of the amniocentesis package, the cost of genetic ultrasonography, and the lifetime cost of Down syndrome, the cost-benefit equation was mathematically manipulated to determine the levels of sensitivity with the corresponding specificity values (and therefore false-positive rates) compatible with net benefits. A graph representing the balance between sensitivity and false-positive rate was constructed to determine cost-benefit ratios. We then examined the diagnostic ultrasonographic accuracies of previously published studies from the cost-benefit point of view. We included only studies in which the sensitivity and false-positive rates were stated or could be calculated from the raw numbers. The last step was to determine the possible economic impact of genetic ultrasonography for the United States on the basis of the average ultrasonographic accuracy for the published studies. The current practice is to offer amniocentesis to women older than 35 years and to younger women with abnormal serum screening results, and it was assumed that the overall prevalence of fetal Down syndrome is 1:100 in this at-risk population.[14] The next step of our study was to perform sensitivity analyses and calculate the minimum sensitivities of genetic ultrasonography required to achieve net benefits according to individual maternal age-specific prevalences of Down syndrome (range of risks 1:261-1:44).[11] This subject-specific analysis was accomplished by manipulating our formula with various levels of prevalence of Down syndrome and false-positive rates of 5%, 10%, and 15%.

Results

Fig 1 is a graph of the balance (straight line) between sensitivity and false-positive rate of second-trimester genetic ultrasonography that determines overall benefit, along with a plot of the diagnostic accuracies of the published studies.[1-4, 6, 8, 9] This graph was used to determine benefit depending on the accuracy (sensitivity and false-positive rate) of genetic ultrasonography and also to compare cost-benefit ratios between studies. The greater the distance above the straight line, the greater the benefit of the ultrasonographic performance in the study. As seen in Fig 1, 6 of the 7 studies had diagnostic accuracies compatible with net benefits.[1, 2, 4, 6, 8, 9] As stated in the Methods section, the graph was constructed around a difference in cost between the amniocentesis package and genetic ultrasonography of $900. If this difference were <$900, the line would move up, indicating that higher sensitivities are required to achieve net benefits. On the other hand, if the difference were >$900, the line would move down, indicating that lower sensitivities are needed to achieve benefit. Table II summarizes in detail the diagnostic accuracies of the second-trimester genetic ultrasonographic studies that used multiple ultrasonographic markers for the prenatal detection of Down syndrome. With an abnormal result defined as the presence of 1 ultrasonographic marker, the sensitivities ranged between 50% and 93% and the false-positive rates ranged between 7% and 17%. In analysis of pooled data from all studies, the overall sensitivity was 81% and the overall false-positive rate was 12%. In calculating the overall sensitivity and false-positive rate, the study by Benacerraf et al[1] was excluded because the same patients were also reported on in the study by Nadel et al.[2] The overall sensitivity of 81% and the overall false-positive rate of 12% correspond to net benefits.

The next step was to manipulate the formula according to various maternal age–specific prevalences of Down syndrome to determine the required ultrasonographic accuracies to achieve net benefits in various populations (sensitivity analyses). Table III demonstrates the required

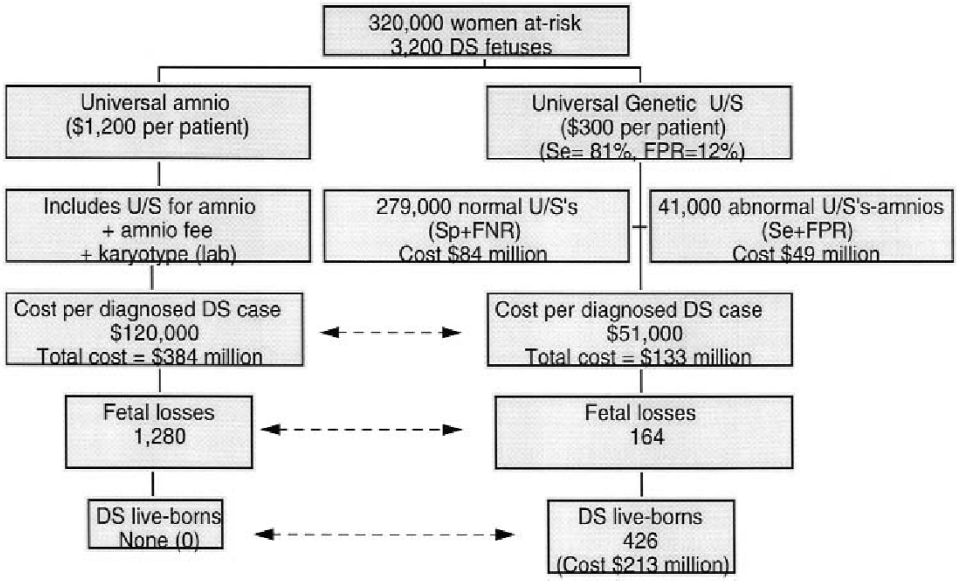

Fig 2. Comparison of cost-effectiveness of second-trimester genetic ultrasonography versus amniocentesis among women at increased risk for carrying a fetus with Down syndrome (prevalence of Down syndrome 1:100); dollar amounts have been approximated and rounded up to nearest million. *DS,* Down syndrome; *amnio,* amniocentesis; *U/S,* ultrasonography; *Se,* sensitivity; *FPR,* false-positive rate; *Sp,* specificity; *FNR,* false-negative rate.

minimum sensitivities for given false-positive rates (5%, 10%, and 15%) according to maternal age–specific prevalences of Down syndrome. Required individual sensitivities ranged between 36% and 95%, depending on the prevalence of Down syndrome.

Fig 2 compares the cost-effectiveness of a policy of offering second-trimester genetic ultrasonography with that of a policy of offering routine amniocentesis to women at increased risk for carrying a fetus with Down syndrome. The assumptions used with this model were as follows: (1) On the basis of the annual number of births in the United States, it is reasonable to expect approximately 4 million second-trimester pregnancies annually. (2) Approximately 10% of the women with these second-trimester pregnancies (400,000) are at increased risk for carrying a fetus with Down syndrome because of advanced maternal age (35 years),[15] but we assumed that only 8% (320,000 pregnancies) are available and willing to undergo prenatal diagnosis, including those with abnormal serum screening results. (3) The procedure-related fetal loss rate from amniocentesis is approximately 1:250.[16] With an overall sensitivity of genetic ultrasonography of 81% and a false-positive rate of 12% (the averages of the published studies), the savings would be approximately $38 million and 1116 fetal lives each year. The cost for prenatal diagnosis generated by genetic ultrasonography, including the normal ultrasonographic results and the cost of amniocentesis because of abnormal ultrasonographic results, would be approximately $133 million. By using genetic ultrasonography, the cost per diagnosed case of Down syndrome would be brought down to $51,000, compared with $120,000 per diagnosed case of Down syndrome when universal genetic amniocentesis is used. Because the expected number of live-born infants with Down syndrome missed by second-trimester ultrasonography will be 426, there would be an additional cost of $213 million generated by these live-born infants. By adding $213 million to the prenatal diagnosis cost of $133 million, the total cost of using genetic ultrasonography would become $346 million annually. This is $38 million less than the total cost associated with genetic amniocentesis, which is $384 million. In addition, 1116 fetal losses would be prevented by universal genetic ultrasonography. At this point it should be explained that a strategy of using no prenatal diagnosis is the most costly, because it would result in 2240 live-born infants with Down syndrome and therefore generate a cost of >$1 billion annually.

Comment

Although many studies have been published regarding the diagnostic efficacy of second-trimester genetic ultrasonography for the prenatal detection of Down syndrome, there is virtually no information on the cost-benefit of this approach. During the past 4 years we have offered second-trimester genetic ultrasonography as well as straight amniocentesis without genetic ultrasonography to women at increased risk for carrying a fetus with Down syndrome, and we have used the ultrasonographic results to guide management.[6] The patients are counseled, and amniocentesis is frequently performed if the genetic ultrasonographic result is abnormal. This prac-

tice has resulted in a continuously increasing proportion of women who prefer to have a genetic ultrasonogram rather than amniocentesis as a first option. During the year 1996, the proportion of women choosing genetic ultrasonography as a first option in our unit was 55.2%.[17] We therefore felt obliged to perform an economic evaluation of second-trimester genetic ultrasonography.

It is likely that managed care and capitation will fix the fees for amniocentesis and ultrasonography in the near future. The lifetime cost of a baby born with Down syndrome is also relatively fixed. Formulas for determining the benefits of specific tests should therefore rely on diagnostic accuracy and prevalence of the disease. The diagnostic accuracy of a test may vary from operator to operator and from unit to unit. It is important to underscore the fact that a diagnostic test may be beneficial in some hands but not in others. Also, the same diagnostic accuracy (sensitivity and false-positive rate) may or may not be beneficial depending on the prevalence of the disease. In a review of the literature on genetic ultrasonography with multiple markers for the prenatal detection of Down syndrome, 6 of the 7 published studies were found to have accuracies compatible with benefits,[1, 2, 4, 6, 8, 9] but 1 was found not to have a benefit.[3] The critical question therefore may not be whether second-trimester genetic ultrasonography is economically beneficial in general but whether specific operators or institutions have accuracies that are cost-effective after the prevalence of Down syndrome in the tested population is taken into consideration.

In this article we present a formula that is based on ultrasonographic diagnostic accuracy and can be used in cost-benefit analysis. With this approach, performance from the cost-benefit point of view can be compared between studies by plotting their sensitivities and corresponding false-positive rates (Fig 1). The greater the distance above the straight line (balance), the greater the benefit. The individual maternal age–specific risks for Down syndrome (prevalence of the disease) should also dictate whether a specific ultrasonographic accuracy is compatible with cost-benefit. For instance, a sensitivity of 80% combined with a false-positive rate of 15% is beneficial for women as old as 39 years but is not beneficial for women at least 40 years old (Table III). Similarly, the formula could be applied to Down syndrome prevalences as established by biochemical serum screening.

Although some of the assumptions around which the formula was constructed could be challenged, one may construct a similar cost-benefit equation, and therefore levels of diagnostic accuracy, by using one's own local charges for amniocentesis and ultrasonography as well one's own local statistics for any of the assumptions made. Our formula did not take into consideration costs generated by other aspects or consequences of prenatal diagnosis (genetic counseling or abortions) because these services would occur in both strategies. The cost of abortions, although directly generated by the prenatal diagnosis strategies, does not really represent an additional cost beyond that justified by the pregnancy itself. Certainly continuation of these pregnancies would have resulted in costs related to the birthing process anyway. Finally, inclusion of the costs of induced abortions or lost productivity (indirect costs) from the abortions (or fetal losses) did not significantly change the conclusions (results are not shown).

According to our analysis, routine second-trimester genetic ultrasonography in the United States has the potential to avoid 1116 amniocentesis-related fetal losses per year. This has to be balanced against the birth of 426 live-born infants with Down syndrome per year, which may be unacceptable for some families. However, no monetary value was attached in this study either to the emotional burden of raising a child with Down syndrome or to the emotional burden of guilt from a fetal loss caused by amniocentesis. An argument against genetic ultrasonography may be related to the possibility that chromosomal abnormalities other than Down syndrome may be missed by this strategy. However, ultrasonography has been shown to be extremely reliable in detecting trisomies 18 and 13, with detection rates of 83%[18] and 91%,[19] respectively. In addition, these and other autosomal trisomies are not usually compatible with life[10] and therefore are not associated with any significant costs. In our opinion, the detection of chromosomal abnormalities other than autosomal trisomies is only a by-product of genetic amniocentesis. From the cost-benefit point of view, amniocentesis to detect these other chromosomal anomalies is not justified because they are extremely rare or the consequences of these abnormalities (eg, sex aneuploidy) for health and costs are limited.

Unfortunately, today many managed care organizations and other health care providers are concerned about costs rather than cost-benefit analyses when evaluating medical tests or strategies. It is our view that the time has come to develop and apply objective measures of cost-benefit and cost-effectiveness analyses, rather than simple measures of costs. We have already adopted this approach by presenting this economic analysis of second-trimester genetic ultrasonography.

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