An Economic Evaluation of Prenatal Strategies for Detection of Trisomy 18

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An economic evaluation of prenatal strategies for detection of trisomy 18

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OBJECTIVE: The objective of this study was to perform an economic evaluation of prenatal diagnostic strategies for women who are at increased risk for fetal trisomy 18 caused by either fetal choroid plexus cysts discovered in a conventional sonogram or an abnormal triple screen.

STUDY DESIGN: The prevalence of trisomy 18 in the presence of second-trimester fetal choroid plexus cysts and also in the presence of abnormal triple screen were made on the basis of previously reported studies. A cost/benefit analysis and cost-effectiveness determination of 3 strategies were performed: (1) no prenatal diagnostic workup of at-risk patients, (2) universal genetic amniocentesis of all at-risk patients, and (3) universal second-trimester targeted genetic ultrasonography of all at-risk patients with amniocentesis (for fetal karyotyping) reserved only for those with abnormal ultrasonography results.

RESULTS: The strategy of no prenatal diagnostic workup was the least expensive approach, costing $1,650,000 annually in the United States. The more costly approach was the strategy of universal amniocentesis for detecting fetal trisomy 18 in the presence of either second-trimester choroid plexus cysts or abnormal maternal serum screening, generating an annual cost of approximately $12 million and 40 fetal losses as a result of amniocenteses. The strategy of targeted genetic ultrasonography generated an annual cost of only $5 million and 8 fetal losses as a result of amniocenteses.

CONCLUSIONS: Routine second-trimester amniocentesis in patients at increased risk for fetal trisomy 18 caused by either the presence of fetal choroid plexus cysts or abnormal triple screening is not justified from the cost/benefit point of view. (Am J Obstet Gynecol 1998;179:1220-4.)

Key words: Trisomy 18, economic evaluation, screening

At present 2 screening methods are used for the prenatal identification of pregnant patients at increased risk of carrying fetuses with trisomy 18, the ultrasonographic and the maternal serum screening methods. The presence of fetal choroid plexus cysts can be easily identified by second-trimester conventional ultrasonography. Although choroid plexus cysts may be seen in approximately 1% of normal second-trimester fetuses, they can be found in approximately 50% of fetuses with trisomy 18.[1] The other screening technique for trisomy 18 could be maternal serum screening, with low levels of -fetoprotein (AFP), unconjugated estriol, and human chorionic gonadotropin indicating an increased risk for trisomy 18.[2] In the presence of an increased risk for trisomy 18 caused by either fetal choroid plexus cysts or abnormal maternal triple screening, either second-trimester genetic amniocentesis or genetic-targeted ultrasonography has been recommended as a means of follow-up. However, the economic impact of these strategies has not been fully evaluated.

The purpose of this study was to perform a cost/benefit analysis and cost-effectiveness determination of 3 different strategies in the presence of increased risk for fetal trisomy 18: (1) no further diagnostic workup, (2) universal genetic amniocentesis, and (3) universal genetic ultrasonography with amniocentesis reserved only for those with abnormal ultrasonography results.

Methods

This economic analysis was conducted from the health care payer's point of view.

Risk for trisomy 18 caused by the presence of fetal choroid plexus cysts. The prevalence of choroid plexus cysts in normal second-trimester fetuses is approximately

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1%.[1, 3] In a review of 12 population-based studies with more than 60,000 pregnancies the overall prevalence of aneuploidy in second-trimester fetuses with choroid plexus cysts was found to be 6.5%; 74% of the chromosome abnormalities were trisomy 18.[3] This extensive literature review involving 21 articles established that the prevalence of trisomy 18 in cases with fetal choroid plexus cysts is 4.8%.[3] In 87% of the cases the choroid plexus cysts are isolated findings, whereas in 13% of the cases the choroid plexus cysts are associated with other fetal abnormalities.[3] However, the prevalence of trisomy 18 in the presence of isolated choroid plexus cysts is only 1.3%.[3] By use of the presence of second-trimester fetal choroid plexus cysts as an ultrasonographic screening tool, there will be a false-positive rate of 1%[1, 3] and a sensitivity of 42%[4] in detecting fetal trisomy 18. The overall risk for trisomy 18 in the presence of choroid plexus cysts in a conventional sonogram is 4.8% or approximately 1:20.[3] It was assumed that the identification of fetal choroid plexus cysts in a conventional sonogram may be followed up by either a policy of straight genetic amniocentesis or targeted genetic ultrasonography (with amniocentesis reserved only for those with abnormal ultrasonography results).

Risk for trisomy 18 caused by abnormal triple screen. When a maternal serum screening protocol is followed with fixed low multiples of the median cutoffs, the combination of maternal serum AFP 0.75, unconjugated estriol 0.60, and human chorionic gonadotropin 0.55 has been associated with an 85% sensitivity in detecting trisomy 18 with a false-positive rate of only 0.5%.[2] One fetus with trisomy 18 is expected to be detected among 14 cases with abnormal maternal serum screening results.[2] This risk (1:14) is very similar to the risk for trisomy 18 in the presence of fetal choroid plexus cysts in conventional ultrasonography, which was found to be 4.8% or approximately 1:20.[3]

To estimate the cost generated by a strategy of not pursuing any prenatal diagnostic workup, it was assumed that the average lifetime cost of neonates born with trisomy 18 is approximately $7500. To derive this estimate we took into consideration the fact that 50% of infants with trisomy 18 born alive die within 1 week of birth, 90% die within 5 months, and only 5% survive the first year.[5, 6] Because the median life expectancy for trisomy 18 is 5 to 6 days[5, 6] and for Down syndrome is more than 50 years,[7-10] this estimate of $7500 was considered reasonable, given the lifetime medical care cost of approximately $60,000 (1998 dollars) for an infant born alive with Down syndrome.[11, 12] In addition, this average lifetime cost of $7500, which applies only to those fetuses with trisomy 18 born alive approximates the cost incurred in infants born alive with trisomy 18 at our institution (St. Peter's Medical Center). The number of infants born alive with trisomy 18, however, is only 33% of the total number of second-trimester fetuses with trisomy 18.[13]

To estimate the cost associated with universal genetic amniocentesis of at-risk patients the following assumptions were made: (1) The prenatal diagnosis of trisomy 18 will lead to pregnancy termination in all cases; (2) the genetic amniocentesis "package" (ultrasonographic guidance for the procedure plus the cost of the amniocentesis procedure plus the laboratory cost for karyotyping) is approximately $1200.

To estimate the cost associated with a strategy of universal genetic-targeted ultrasonography, with amniocentesis reserved only for those with abnormal ultrasonographic results, the following assumptions were made: (1) Genetic-targeted (nonconventional) ultrasonography has a sensitivity (detection rate) for trisomy 18 of at least 80%, which is a very conservative estimate (range of reported sensitivities 83% to 100%[14-17]), and a false-positive rate no more than 15% (range of false-positive rates 7% to 14%[15, 17-21]); (2) the prenatal diagnosis of trisomy 18 will lead to pregnancy termination in all cases; (3) only 33% of second-trimester fetuses with trisomy 18, missed by genetic ultrasonography, are born alive; (4) the cost of genetic-targeted ultrasonography is approximately $300. The costs of the ultrasonography 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, Georgia. Medirisk's medical reimbursement cost estimates are made on the basis of 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.

Results

On the basis of the annual number of births in the United States it is reasonable to expect that there are approximately 4 million second-trimester pregnancies annually.[22] Approximately 63% of these pregnancies (ie, 2.5 million) are screened by multiple serum analytes[23]; 0.5% of these (or 12,500) will be at increased risk for trisomy 18 with a prevalence for trisomy 18 of 1 in 14.[2] It is assumed that 80% (or 10,000) will agree to invasive testing. The same approximate number of pregnancies (ie, 10,000) would also be candidates for prenatal diagnosis of trisomy 18 if the ultrasonographic identification of fetal choroid plexus cysts is used as the screening criterion. This number of 10,000 was derived on the basis of the following assumptions: (1) Approximately two thirds of all pregnancies (ie, 2,640,000) will have an indication for a conventional ultrasonography examination[24]; (2) if 45% of these conventional ultrasonographic examinations are done in the second trimester, approximately 1.2

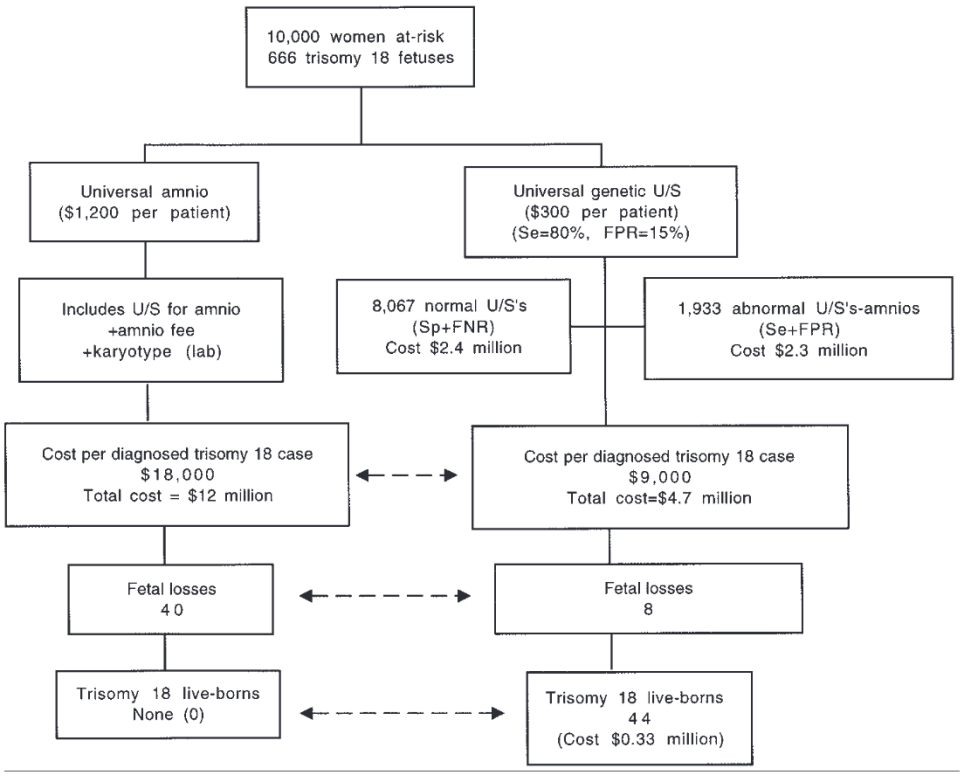

Fig 1. Comparison of cost-effectiveness between amniocentesis and genetic ultrasonography for prenatal detection of trisomy 18 in US population (costs were rounded to nearest million). *U/S,* Ultrasonography; *Se,* sensitivity; *FPR,* false-positive rate; *Sp,* specificity; *FNR,* false-negative rate; *amnio,* amniocentesis.

million second-trimester sonograms are expected annually; (3) because the prevalence of fetal choroid plexus cysts in second-trimester sonograms is 1% and 80% of the mothers will accept invasive testing, approximately 10,000 pregnancies will be candidates for prenatal detection of trisomy 18 as a result of the identification of fetal choroid plexus cysts on a conventional sonogram. The prevalence of trisomy 18 in this fetal choroid plexus cyst population is 4.8%,[3] or approximately 1:20. This risk is similar to the 1:14[2] seen after abnormal maternal serum screening.

Fig 1 compares the cost-effectiveness of universal amniocentesis versus universal genetic ultrasonography (with amniocentesis reserved for those with abnormal ultrasonographic results) for evaluating these 10,000 pregnancies that could be at risk from either fetal choroid plexus cysts or abnormal triple screening. With an overall sensitivity of genetic ultrasonography for trisomy 18 of 80% and a false-positive rate of 15%, the savings from a strategy of genetic ultrasonography would be approximately $7.3 million and 32 fetal lives per year. If the prevalence of trisomy 18 in this population of 10,000 women is approximately 1 in 15 (range 1:14 to 1:20), then a total of 666 second-trimester fetuses with trisomy 18 is expected to be present in this second-trimester fetal population. The cost for prenatal diagnosis generated by genetic ultrasonography, including the normal sonograms and the costs of the amniocentesis "packages" as a result of abnormal sonogram results, would be approximately $4.7 million. By use of genetic ultrasonography, the cost per diagnosed case of trisomy 18 is $9000 as compared with $18,000 per diagnosed case of trisomy 18 when universal genetic amniocentesis is used. Because genetic ultrasonography is expected to miss 44 infants born alive with trisomy 18, an additional cost of $300,000 will be generated by these trisomy 18 neonates. By adding $330,000 to the prenatal diagnosis cost of $4.7 million, the total cost of genetic-targeted ultrasonography becomes $5 million annually. This is $7 million less than the total cost associated with universal genetic amniocentesis, which is $12 million. In addition, 32 fetal losses will be prevented by universal genetic-targeted ultrasonography, assuming a fetal loss rate associated with amniocentesis of 1 in 250. A strategy of using no prenatal diagnostic workup in these 10,000 pregnancies would result in approximately 220 infants born alive with trisomy 18, generating a total cost of $1.65 million and no associated invasive procedure-related fetal losses.

Comment

Although many studies have been published regarding the clinical significance of second-trimester fetal choroid plexus cysts, it has been controversial whether genetic amniocentesis should be offered routinely in these patients. Most investigators agree that the risk for trisomy 18 is extremely high in the presence of associated anomalies and genetic amniocentesis should be offered in this setting. Even with isolated fetal choroid plexus cysts some investigators advocate offering cytogenetic studies when a choroid plexus cyst is identified prenatally; however, according to others chromosome analysis should be performed only if additional fetal abnormalities are present or the cysts are large or bilateral or persist beyond 23 weeks' gestation. At present, despite the controversy over the practice of offering routine amniocentesis for detecting trisomy 18 in the presence of isolated fetal choroid plexus cysts, most investigators would offer amniocentesis in the presence of additional associated abnormalities or other risk factors.[1, 13, 14] On the other hand, some investigators advocate genetic amniocentesis in the presence of abnormal maternal serum screening for trisomy 18 because of the high prevalence (ie, 1 in 14) of trisomy 18 in this setting.[4] Although amniocentesis has been proposed as a cost-effective follow-up of abnormal maternal serum screening for trisomy 18,[4] our results show that the most costly approach is a strategy of universal amniocentesis regardless of the type of original risk (ie, presence of fetal choroid plexus cysts or abnormal maternal serum screening). As has been pointed out by some investigators,[1] the maternal age also has to be taken into account before assessing the risk of aneuploidy and, therefore, the risk for trisomy 18 in all fetuses with choroid plexus cysts. However, according to our analysis universal amniocentesis was not cost-effective even in the setting of the most extreme risk for trisomy 18 (ie, 1:3 as seen in a 44-year-old woman with fetal choroid plexus cysts[1] found in a conventional sonogram).

In comparing universal amniocentesis versus genetic-targeted ultrasonography we did not consider costs generated by other aspects or consequences of prenatal diagnosis (ie, genetic counseling or abortions, spontaneous or induced) because these would occur in both strategies. In addition, the cost of abortions, although directly generated by the prenatal diagnostic strategies, does not really represent an additional cost greater than that justified by the pregnancy itself. Certainly continuation of these pregnancies would have resulted in costs related to the birthing process anyway. Inclusion of abortions in our calculations did not change the conclusions significantly (results not shown).

Our results are not surprising because trisomy 18 is a chromosomal abnormality associated with a high percentage of fetal and newborn wastage (ie, only 33% of second-trimester fetuses with trisomy 18 will be born alive; of those born alive approximately 50% will die within a week and 90% will die by the age of 5 months).[5, 6] Only 5% survive their first year.[5, 6] This excessive mortality rate is the main reason why the approach of no prenatal diagnostic workup is the least costly. If some costs are justified for the prenatal detection of trisomy 18 because of maternal autonomy, psychologic, or patient anxiety reasons, we believe that genetic-targeted ultrasonography should be the strategy of choice. From the cost-effectiveness point of view, routine offering of amniocentesis for prenatal detection of trisomy 18 is not justified in the presence of either fetal choroid plexus cysts or abnormal triple screening.

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