Prenatal Diagnosis: A Directive Approach to Genetic Counseling Using Decision Analysis

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The decision which prospective parents face concerning mid-trimester amniocentesis for prenatal diagnosis was examined by decision analysis. The prospective parents' decision depends on the likelihood of the birth of a child affected by a genetic disorder, the risk of amniocentesis, and the probability that the diagnoses provided by the amniocentesis will be correct. The couple's decision must also depend on their attitudes toward each possible outcome. The likelihoods of the outcomes can be obtained from appropriate medical consultation, while the relative costs or burdens of the outcomes should be obtained from the prospective parents. A truly informed decision for this couple can then be formulated from these probabilities and values, thus allowing genetic counseling to be more directive. The technique is illustrated for the prenatal diagnosis of Down's syndrome, meningomyelocele, and Duchenne muscular dystrophy.

Amniocentesis has become increasingly available as a tool for prenatal diagnosis of a variety of genetic disorders [1-3], and several authors have suggested that prenatal diagnosis be made available to large segments of the population [4,5]. Unfortunately, the decision to employ amniocentesis is difficult [6]; prenatal diagnosis raises ethical issues which certainly do not rest solely with the physician for their resolution.

The medical issues relating to amniocentesis are not simple: the procedure can be followed by complications [1,2,4,7,8], most commonly spontaneous abortion, and can provide erroneous information [7-13]. Since amniocentesis and therapeutic abortion often bewilder prospective parents, the physician cannot assume that merely describing the procedure (and even its associated false positive and false negative rates) provides a couple with a basis for making a truly informed decision.

This problem can be approached by decision analysis, a general technique for making choices under the conditions of uncertainty [14-18]. Such analyses are being applied to an increasing number of problems in medicine [19-24]. The technique replaces a complex decision with a series of simpler decisions. In so doing, it separates the probabilities of the various outcomes from the relative values of these outcomes; therefore, it has been proposed as a means of obtaining more patient participation in the clinical decision-making process [22,25]. Prior medical applications of decision analysis have dealt with situations in which the optimal choice was determined largely by the medical issues. In contrast, decisions about prenatal diagnosis are highly dependent upon the parents' attitudes toward the various outcomes.

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Consider a set of prospective parents concerned about the possibility of giving birth to a child affected by a disease detectable by amniocentesis. Assume that they would have a therapeutic abortion if the fetus were known to be affected. If they would not consider a therapeutic abortion, then the procedure would have been performed largely for purposes of reassurance; although amniocentesis in that circumstance may be appropriate, it is not included in this analysis.

The Decision Tree

This decision can be represented by the tree shown in Fig. 1. The square node on the left denotes the choice between having an amniocentesis and carrying a pregnancy to term with no further information about the fetus. Each circular node denotes a chance event which neither the physician nor the parents can control.

The first tier of chance nodes denotes the possibility of spontaneous abortion subsequent to the first trimester. The probability of a spontaneous abortion without amniocentesis is denoted by \( s \); the probability after amniocentesis is \( s + a \). The second tier of chance nodes describes the actual state of the fetus. The probability of an affected fetus is \( d \); the probability of an unaffected fetus is therefore \( 1 - d \). This actual diagnosis, however, is unknown during the pregnancy. The final tier of chance nodes denotes the result of the amniocentesis. The chance of an abnormal amniocentesis although the fetus is actually unaffected (a false positive result) is \( p \). Thus, the chance of a normal result given an unaffected fetus is \( 1 - p \). The chance of a normal amniocentesis although the fetus is affected (a false negative result) is \( n \); thus the chance of detecting an affected fetus is \( 1 - n \).

Utility of the Outcomes. The possible outcomes are each assigned a value, or utility, which represents their relative desirability to the prospective parents. The first and fourth branches of the tree represent the occurrence of a spontaneous abortion after the first trimester; the utility of that outcome is denoted by \( U_s \). The second and fifth branches represent the birth of an unaffected child; the utility of that outcome is \( U_u \). The third and eighth branches represent the birth of an affected child; the utility of that outcome is \( U_A \). Finally, the sixth and seventh branches represent an abnormal result of the amniocentesis followed by a therapeutic abortion. In the sixth branch the result was falsely positive—an unaffected fetus was aborted. The utility of that outcome is \( U_{TU} \). In the seventh branch, the amniocentesis result was correct—an affected fetus was aborted. The utility of that outcome is \( U_{TA} \). These definitions are summarized in Table 1.

In specifying any set of utilities, the absolute values used can be arbitrary; the only requirement is that the utilities be represented on a single consistent scale. For most parents the birth of an unaffected child would be the best outcome and the birth of an affected child would be the worst outcome; the occurrence of a spontaneous abortion and the performance of a therapeutic abortion would have intermediate utility.

Probability of the Outcomes. The likelihood of any of the eight possible outcomes is equal to the product of the probabilities along the path leading to that outcome. For example, the probability of an unaffected child after amniocentesis (branch 5) is \( (1 - [s + d]) \times (1 - d) \times (1 - p) \). The probability of each of the eight outcomes is summarized in Table 1.

Assumptions of the Analysis

Several assumptions were made in structuring this problem. Any decision about amniocentesis must involve similar assumptions, although they are often implicit and
FIG. 1. The Decision Tree. The square node at the left denotes the decision; each circular node denotes a chance event not under the control of either the physician or the parents. The symbol on the interior of each branch of the chance nodes denotes the probability of that event occurring, given that all prior events on that path have already occurred.

TABLE 1
Utility and Probability of Each Outcome*

| Outcome                                      | Utility | Probability |
|----------------------------------------------|---------|-------------|
| No Amniocentesis                             |         |             |
| Spontaneous abortion                         | $U_S$   | $s$         |
| Unaffected child                             | $U_U$   | $(1 - s)(1 - d)$ |
| Affected child                               | $U_A$   | $(1 - s)$    |
| Amniocentesis                                |         |             |
| Spontaneous abortion                         | $U_S$   | $(s + a)$   |
| Unaffected child                             | $U_U$   | $(1 - [s + a])(1 - d)(1 - p)$ |
| Therapeutic abortion of unaffected fetus (false positive test) | $U_{TU}$ | $(1 - [s + a])(1 - d)p$ |
| Therapeutic abortion of affected fetus (true positive test) | $U_{TA}$ | $(1 - [s + a])d(1 - n)$ |
| Affected child                               | $U_A$   | $(1 - [s + a])dn$ |

*d = probability of fetus being affected by given disease
$s = \text{spontaneous abortion rate without amniocentesis}
\ a = \text{additional chance of spontaneous abortion after amniocentesis}
\ n = \text{false negative rate}
\ p = \text{false positive rate}
not available for examination and discussion. The technique of decision analysis requires these assumptions to be explicit.

This analysis does not consider the issues of adoption and subsequent pregnancies; it assumes that the effect of these factors can be incorporated into the utilities assigned to the five outcomes. The only "cost" of amniocentesis considered here is spontaneous abortion; maternal complications, pain, non-fatal fetal complications, and dollar cost are ignored. This analysis considers only a single test for an affected fetus; if several separate tests are to be done, then the probability of an affected fetus, the utility of an affected child, and the false positive and negative rates must be adjusted appropriately.

Occasionally, an amniocentesis will not be successful; either no fluid will be obtained or the fetal fibroblasts centrifuged from the amniotic fluid will fail to grow in cell culture. Although this occurs in approximately ten percent of amniocenteses, if a second sample is obtained this "no data" rate falls to under one percent. Although a portion of these residual "no data provided" amniocenteses will result in an affected child and should be included among the false negatives, this effect is small and can be ignored.

ANALYSIS OF THE TREE

When the decision about prenatal diagnosis is made, the parents cannot know whether the fetus is affected; they must make their decision despite this uncertainty. Decision theory [14–24] states that they should choose the option which has the higher expected value, calculated by summing the product of the probability and the utility of each of the possible outcomes of that option. For example, the expected value of "No Amniocentesis," $EV_{\text{NoAmnio}}$, is (referring to Table 1):

$$sU_S + [(1 - s)(1 - d)]U_U + [(1 - s)d]U_A.$$

In a similar manner, one can calculate the expected value of "Amniocentesis," $EV_{\text{Amnio}}$.

The parents would be expected to be indifferent toward amniocentesis if the expected values of the two options were equal. Thus, the probability ($d$) of a child's being affected at which $EV_{\text{Amnio}}$ equals $EV_{\text{NoAmnio}}$ is a threshold probability [23]: for probabilities above the threshold, amniocentesis should be performed; for probabilities below the threshold, amniocentesis should not be performed. One can determine the threshold by setting $EV_{\text{Amnio}} = EV_{\text{NoAmnio}}$ and solving for $d$. The resulting expression for the threshold can be simplified by several substitutions.

Definition of the Costs of the Outcomes. As used in this paper, a "cost" is a measure of the relative burden [27] of an outcome to the prospective parents. The differences between the utility of an unaffected child ($U_U$) and the utility of each of the four other outcomes is a measure of the relative burden of those latter outcomes. Fig. 2 summarizes these costs. The cost of an affected child ($C_A$) is the difference between the utility of an unaffected child and the utility of an affected child. The cost of a spontaneous abortion ($C_S$) is the difference between the utility of an unaffected child and the utility of a spontaneous abortion. Similarly, the cost of the therapeutic abortion of an affected fetus ($C_{TA}$) is the difference between the utility of an unaffected child and the utility of such an abortion; the cost of the therapeutic abortion of an unaffected fetus ($C_{TU}$) is the difference between the utility of an unaffected child and the utility of such an abortion.

Although the risk of spontaneous abortion might be expected to increase with repeated amniocenteses, this does not occur until the number of attempts exceeds three [26].
**Definition of the Risk of Amniocentesis.** The ratio, \( a/(1-s) \), of the "additional chance of spontaneous abortion after amniocentesis" to the "probability of continued pregnancy" is a measure of the risk of amniocentesis and will be denoted by \( r \). This risk must, by definition, fall between zero and one. In this paper we assume that \( s \) is 5% and \( a \) is 0.5%; thus, \( r \) is 0.005. One recent study [4,26] demonstrated that the risk might be even lower, i.e., \( s \) was 3.2%, \( a \) was 0.3%, and thus \( r \) was 0.003.

**The Threshold Probability**

We shall denote the threshold probability by \( T \). Making the above substitutions, we find that

\[
T = \frac{(1-r)pC_{TU} + rC_S}{(1-r)[pC_{TU} - (1-n)C_{TA} - nC_A] + C_A}
\]

In this equation, \( r \) is the risk of the amniocentesis, \( n \) is the false negative rate, \( p \) is the false positive rate, \( C_S \) is the cost of spontaneous abortion, \( C_A \) is the cost of an affected child, \( C_{TA} \) is the cost of the therapeutic abortion of an affected fetus and \( C_{TU} \) is the cost of the therapeutic abortion of an unaffected fetus. The error and risk rates (\( n, p, \) and \( r \)) are measured on a scale of zero to one. The costs may be measured on any consistent scale, but a scale of zero to 100 is most convenient, with the highest cost (usually \( C_A \), the cost of an affected child), being defined as 100. Although the equation appears complex, the advent of small, hand-held calculators makes its use feasible.

The most important factors governing the decision about amniocentesis are the relative cost or burden of therapeutic abortion\(^3\) (\( C_{TA} \)) and the probability of a child's being affected (\( d \)). The equation for the threshold probability can be used to create a graphical representation of this relation, as shown in Fig. 3. If, for a particular set of

\(^3\)In our experience with this technique, most parents consider \( C_{TA} \) and \( C_{TU} \) to be of similar magnitude; in such cases we use \( C_{TA} \) to represent both costs.
FIG. 3. The Relation Between the Probability of a Child's Being Affected and the Cost of Therapeutic Abortion. The curve establishes two areas of recommendation, "Amniocentesis" and "No Amniocentesis." If a point corresponding to the CTA and d (e.g., 25 and 0.5) for a given couple is plotted in the figure, then the area within which that point lies specifies the optimal choice for that couple. For this illustrative curve, we assumed that Cₐ, CTA and CTU were all equal, that p was 0.43, and that n was 0.005 (see Case 3). In order to make the diagram clearer, we arbitrarily assigned r a value of 0.1. Since the actual risk of amniocentesis is much lower (0.005), the true curve would be shifted far to the left and the shaded area would be much larger.

RESULTS

parents, a point corresponding both to the cost or burden that therapeutic abortion would be for those parents and to the probability of a child's being affected is plotted on that graph, e.g., CTA of 25 and d of 0.5, then the position of that point will correspond to the optimal choice for those parents. If the point lies in the shaded area below the curve, then amniocentesis would be appropriate.

INTERPRETATION OF THE SOLUTION

The threshold probability is affected by the relative burden of the outcomes, the risk of amniocentesis, and the quality of information provided by the test, i.e., the false positive and false negative rates. Table 2 summarizes the effects of changes in various parameters upon the threshold, while Fig. 4 illustrates the effects of variation in the risk and information content of amniocentesis for a broad range of values which should encompass most situations likely to be encountered clinically. In that figure, each curve is analogous to the curve in Fig. 3. The area beneath each curve specifies those situations in which amniocentesis should be recommended.

The Risk of Amniocentesis. The left-hand portion of Fig. 4 shows the effect of changes in the risk of amniocentesis (r). Each curve describes the relation between the cost of abortion and the probability of an affected fetus for a single value of r. For prospective parents to continue to elect amniocentesis as the risk of the procedure increases, either their perception of the burden of therapeutic abortion must decrease or the probability of their having an affected child must increase.

The Quality of Information. The right-hand portion of Fig. 4 illustrates the effect
TABLE 2

Effects on the Threshold

| Increase in Parameter | Interpretation                                      | Effect on Threshold |
|-----------------------|-----------------------------------------------------|---------------------|
| $C_A$                 | Increased burden of an affected child               | Decrease            |
| $C_S$                 | Increased burden of spontaneous abortion            | Increase            |
| $C_{TA}$              | Increased burden of therapeutic abortion of an affected fetus | Increase |
| $C_{TU}$              | Increased burden of therapeutic abortion of an unaffected fetus | Increase |
| $a,s,r^*$             | Increased risk of amniocentesis                     | Increase            |
| $n$                   | Increased chance of false negative                  | Increase            |
| $p$                   | Increased chance of false positive                  | Increase            |

*Increases in either $a$ or $s$ will increase $r$.

FIG. 4. The Effects of Risk and Errors on the Thresholds. Each diagram contains a set of curves analogous to the curve in Fig. 3. The left-hand diagram illustrates the effect of changes in the risk of amniocentesis. Risks ($r$) of .001, .01, .10 and .30 are plotted for false positive ($p$) and false negative ($n$) rates of zero. The right-hand diagram illustrates the effects of errors. False positive and false negative rates of 0.0, .05, .10 and .20 are plotted, for a risk of .005. It was assumed that $C_S$, $C_{TA}$ and $C_{TU}$ were all equal.

of the information content of the amniocentesis on the threshold. As the error rates increase, the threshold increases. Thus, as the information provided becomes less reliable, parents should be less likely to choose amniocentesis.

The Effect of Changes in the Model

The decisions suggested by this analysis will be optimal only to the extent that our model of the outcomes of pregnancy is correct. We shall now modify the original model and consider the effect on the decision of two additional outcomes—a child damaged by the amniocentesis and a child affected by another disorder, not subject to prenatal detection.

The effect of non-fatal fetal complications of amniocentesis would be to increase the threshold probability. Specifically, both the numerator and the denominator of
the threshold equation should be increased by \((1 - r)(1 - p)P_{\text{dam}} C_{\text{dam}}\), where \(P_{\text{dam}}\) is the probability of such complications and \(C_{\text{dam}}\) is the cost of that outcome. The birth of a child presumably damaged by amniocentesis is, however, extremely rare and should exert little effect on the decision.

The effect of additional causes of birth defects would be to decrease the threshold probability. Specifically, \((r(1 - p) + p)P_{\text{other}} C_{\text{other}}\) should be subtracted from both the numerator and the denominator of the threshold equation, where \(P_{\text{other}}\) is the chance of a child’s being affected by any such non-diagnosable disorder and \(C_{\text{other}}\) is the cost or burden of such a disorder. Thus, the existence of non-diagnosable birth defects should make parents more amenable to amniocentesis. Although such disorders are not uncommon, i.e., approximately 2–4% of pregnancies may result in a major congenital malformation, the calculated thresholds would be changed only to a minor extent since both \(r\) and \(p\) are small.

**Genetic Counseling**

Although the literature suggests that genetic counseling should be non-directive [1,2], that goal is rarely accomplished [28]. The physician imparts his own biases either subtly or at the explicit request of the parents. Furthermore, even if such non-directive counseling could be accomplished, the parents would still face the difficult task of remembering all the relevant data provided and incorporating them into a rational decision. Since the optimal decision for a particular couple can be determined from the equation for the threshold probability, it might be more reasonable to direct the counseling toward that “best” decision.

It is, of course, not necessary for the parents to understand, or even to be aware of, the mathematical details of this analysis. Rather, they should be counseled about the consequences of pregnancy with and without amniocentesis. The genetic counselor should be aware of the information content (\(n\) and \(p\)) and the risk (\(r\)) of the procedure in the hands of his obstetrical and genetic colleagues. If he could obtain measures of the parents’ attitudes toward the various outcomes, then he could provide more explicit guidance.

**OBTAINING THE PARENTS’ ATTITUDES**

To use this analysis, the physician must have some means of assessing, in a quantitative manner, the parents’ attitudes both toward abortion and toward having an affected child. The costs of abortion are determined largely by the parents’ perception of the “cost” of an affected child. If they view an affected child as a grave calamity, the relative cost of abortion will be low; if they view an affected child as a minimal inconvenience, then the relative cost of abortion will be high. The use of illustrations like Fig. 1 can make such counseling easier, and the actual determination of costs may help the parents understand the problem.

A convenient method is available for obtaining such costs in the course of the counseling that precedes the decision about amniocentesis. The physician first presents the five possible outcomes and asks which would be the best and which would be the worst for the prospective parents. Assume that the best and worst outcomes chosen by the couple are “unaffected child” and “affected child,” respectively. Assign a cost of 100 to the worst outcome (\(C_A = 100\)). What remains is to assign consistent costs to the remaining three outcomes: spontaneous abortion (\(C_s\)), the therapeutic abortion of an affected fetus (\(C_{TA}\)), and the therapeutic abortion of an unaffected fetus (\(C_{TU}\)).
The burden of therapeutic abortion is considered first. Explain to the parents that they will be asked to make some difficult choices in several hypothetical situations. Ask them to assume that some woman is pregnant and that they have a fifty-fifty chance of having an affected child. If no further diagnostic information about that pregnancy were available, would they elect to have a therapeutic abortion? If they answer “yes,” ask them whether they would still elect a therapeutic abortion if the chance of an affected child were twenty-five percent, or ten percent. By answering a series of such questions, the couple can specify that point at which they would be indifferent between therapeutic abortion and carrying the pregnancy to term. This point of indifference determines the cost of therapeutic abortion. Thus, prospective parents who would be indifferent if their chance of having an affected child were 25% effectively assign a cost of 25 to therapeutic abortion.

The burden of spontaneous abortion is considered next. Although some parents assign nearly equal costs to therapeutic and spontaneous abortion, many assign a somewhat lower cost to spontaneous abortion. To obtain $C_S$, ask the parents to consider a hypothetical pregnancy with no further diagnostic information available. For various probabilities of having an affected child, ask them to express preference between carrying the pregnancy to term and spontaneously aborting. Again the cost of spontaneous abortion ($C_S$) is equal to the likelihood at which they would be indifferent.

The burden of the therapeutic abortion of an unaffected fetus must be determined for those parents who do not consider all therapeutic abortions to be of equal cost. For such parents $C_{TA}$ and $C_{TU}$ must be assessed separately. To assess the cost of the therapeutic abortion of an affected fetus, ask the couple to consider the hypothetical pregnancy described above (with no further diagnostic information available). Ask them to specify, for various chances of having an affected child, a preference between that pregnancy and the therapeutic abortion of a different hypothetical pregnancy in which the aborted fetus is found to be affected. The point of indifference determines $C_{TA}$. The parents can assess $C_{TU}$ in a similar manner, but now they must consider the choice between the “no further information available” pregnancy and the therapeutic abortion of a different pregnancy in which the fetus is found to be unaffected.

ILLUSTRATIVE CASES

This section will present three typical situations in which amniocentesis might be employed and where the techniques presented above can help the prospective parents make their decision.

Case 1: Down's Syndrome

A twenty-five year old woman seeks genetic counseling three years after the birth of a child with Down’s syndrome. She and her husband wish to have another child but are frightened of the prospect of another affected child and reluctant to consider therapeutic abortion. The mother is found to have a balanced D-G translocation; thus, the chance of a recurrence is roughly 10% [29].

Analysis. Assume that karyotyping for detection of translocation trisomy 21 has reported false positive and false negative rates of 0.5% in your laboratory [7-13,26]. The parents felt that the burden of therapeutic abortion of either an affected or an unaffected fetus would be high. They were indifferent between therapeutic abortion and carrying a pregnancy to term when their chance of having a child with Down’s syndrome reached 85% ($C_{TA} = 85$ and $C_{TU} = 85$); they were indifferent between
carrying the pregnancy to term and spontaneous abortion when their chance of having an affected child reached 60% (thus, $C_S = 60$).

Using the equation with $r = 0.005$, $n = 0.005$, $p = 0.005$, $C_A = 100$, $C_S = 60$, $C_{TA} = 85$ and $C_{TU} = 85$, one finds that if the probability of having an affected fetus is above 0.05 then amniocentesis is the better choice. Despite this couple’s initial reluctance to consider therapeutic abortion, they should be encouraged to have an amniocentesis because their 10% recurrence risk is above the 5% threshold calculated from their own values.

**Case 2: Meningomyelocele**

A couple seeks genetic counseling after the death of their first child with meningomyelocele. Careful examination of that child revealed no evidence of a syndrome or chromosomal abnormality [30]. They would like to have additional children but would prefer therapeutic abortion to the prospect of having another affected child.

*Analysis.* This couple has a 2% recurrence risk for this multifactorial disorder [30]. Discussion with these parents reveals that for them $C_S = 5$, $C_{TA} = 20$ and $C_{TU} = 60$. However, the laboratory in your area has reported a false positive rate of 1% for the detection of neural tube defects by amniotic fluid alpha-fetoprotein concentration. Since 10% of these defects are closed and therefore not detectable by this technique, the false negative rate is roughly 10% [31–34]. Using the above values, one finds the threshold probability to be 0.009, well below the recurrence risk. Thus, these parents should be encouraged to have amniocentesis. Note, however, that if the false positive rate of alpha-fetoprotein determination by your laboratory were 5%, the threshold would then be 4%, somewhat higher than the 2% recurrence risk for this couple. In that situation, the better choice would be to decline amniocentesis.

**Case 3: Duchenne Muscular Dystrophy**

A couple with a positive family history for Duchenne muscular dystrophy seeks information about prenatal diagnosis. The woman’s brother and maternal uncle died of this disorder. Exercise CPK determinations were performed on the woman for carrier detection [35], but the results were equivocal. The couple wish to consider the possibility of prenatal sex determination with the prospect of aborting a male fetus.

*Analysis.* Since the woman’s chance of being a carrier for this X-linked recessive disorder is 50%, the chance of a male child’s being affected is 25%. Since only 25% of males and no females will be affected, the chance of this couple’s having an affected child is 12.5%. All of the female fetuses (50%) and 75% of the male fetuses (50% × 75%, or 37.5%) will be unaffected (total 87.5% of all fetuses), but 37.5%/87.5%, or 43% of these will be males and therefore subject to therapeutic abortion. Thus, the false positive rate ($p$) for detection of affected fetuses by prenatal sex determination is 0.43. The false negative rate ($n$) for detecting affected fetuses will be determined by the error rate of prenatal sex determination, roughly 0.005 [7–13,26].

These parents are concerned about the prospect of aborting an unaffected fetus. Lengthy discussion reveals that for them $C_{TU} = 90$, $C_{TA} = 20$ and $C_S = 10$. Using these values, we find that the threshold probability is 0.33. The risk of a child’s being affected (0.125) is well below this threshold; hence this couple should be encouraged to decline amniocentesis. The high threshold relates largely to the high false positive rate in using prenatal sex determination to detect fetuses affected with muscular dystrophy.
DISCUSSION

The decision of whether or not to utilize prenatal diagnosis must rest with the prospective parents who seek genetic counseling. Unfortunately the choice is not simple [6]. It involves balancing the risk of amniocentesis against the information which the procedure can provide. The medical literature does not deal with the problem in a clear, logical fashion. Although amniocentesis may be indicated when the chance of complications from the procedure is less than the chance of an affected child [3], the decision must reflect the attitudes of the prospective parents. The decision is sufficiently complex, however, that many couples find it bewildering. Decision analysis provides a systematic means of both communicating the issues to the parents and obtaining measures of the relative costs or burdens of the outcomes from them.

The physician must advise the prospective parents of the likelihood of each possible outcome: the birth of an unaffected child, the birth of an affected child, a spontaneous abortion, and a therapeutic abortion. The prospective parents can provide measures of the relative burden of each of these outcomes by answering two questions:

Given no further diagnostic information, at what chance of a pregnancy's resulting in an affected child would you choose to have a therapeutic abortion?

Given no further diagnostic information, at what chance of a pregnancy's resulting in an affected child would you prefer that the pregnancy end by spontaneous abortion?

If the birth of an affected child is the worst outcome and the birth of an unaffected child is the best, answers to these questions provide the relative costs or burdens of therapeutic abortion, spontaneous abortion, and the birth of an affected child.

The Threshold and Sensitivity Analysis

A specific set of attitudes concerning the possible outcomes determine a threshold probability [23] of having an affected child. If the chance of an affected child exceeds that threshold, amniocentesis should be recommended; if the chance is below that threshold, amniocentesis should be discouraged. Another threshold exists for situations in which the likelihood of a child's being affected and the risk of amniocentesis are both high: if that threshold is exceeded then therapeutic abortion might be undertaken without prenatal diagnosis. Those situations were not considered in this analysis.

This threshold forms the basis for one kind of sensitivity analysis. Although the probability of a couple's having an affected child may not be precisely known, reasonable estimates of the range can often be made. If the entire range lies on one side of the threshold, then the decision would be constant for any value within that range. In such circumstances, the decision is said to be "insensitive" to changes in that parameter. If the range extends on both sides of the threshold, then the decision may be "sensitive" to changes and some care must be taken to narrow the range.

Another type of sensitivity analysis can be performed upon the thresholds themselves by calculating several alternative thresholds, based on different estimates of the relative costs of the outcomes, the risk of amniocentesis, and the quality of information provided. The effect of false positives and false negatives is greatest when the cost of the procedure is low. Indeed, since the risk of the procedure is relatively low,
variations in the false negative and false positive rates have major effects upon the
decision; physicians must not only themselves consider these error rates but must also
discuss them with prospective parents.

*Trisomy 21 and Maternal Age*

Case 1 dealt with the issue of amniocentesis for detection of *translocation* Down's
syndrome. Since the incidence of *non-disjunction* Down's syndrome increases with
advancing maternal age [29], parents are often offered amniocentesis when maternal
age is over thirty-five. The threshold for amniocentesis should reflect that dependency
on maternal age, but the age at which the procedure is indicated should vary with
parental attitudes. Fig. 5 demonstrates a typical relation between the cost of abortion
and maternal age. The curve is quite flat below age thirty since the incidence of
Down's syndrome is less affected by maternal age in that range. Even at that age some
couples might elect prenatal diagnosis if they consider either the burden of a Down's
child to be high or the burden of an abortion to be low.

*Consistency*

The techniques presented in this paper allow the physician to suggest a rational
decision to individual couples by replacing the complex decision by a series of simpler
ones. If the prospective parents do not follow the suggestions of this analysis, they are
not wrong; rather, their decision is inconsistent either with the choices they made
when assessing the costs of the possible outcomes or with the structure of the model
itself. Either those simpler decisions were incorrect, the model was inappropriate, or
the ultimate decision about prenatal diagnosis was illogical.

As was explained above (c.f., *Assumptions of the Analysis*), maternal pain and
complications, non-fatal fetal complications, and dollar costs were ignored. In
circumstances where these or other factors not explicitly considered in the model are
important, the model would have to be extended. For example, if facilities for
processing amniotic fluid continue to be expensive and of limited availability, then
resource constraints will limit the total number of amniocenteses which can be
performed. In such circumstances it would not be appropriate to allow the parents' attitudes to be the only utilities considered; overall societal good should also be
considered explicitly.

*Evaluation*

This decision analytic model should allow prospective parents to make better
decisions concerning prenatal diagnosis, but, of course, this hypothesis must be tested
in a clinical trial. A major obstacle in conducting such a trial lies in the establishment
of criteria for the evaluation of decisions. Since different parents will assign quite
different costs to the possible outcomes, it will be difficult to make comparisons: a
decision that might be optimal for one set of parents might be inappropriate for
another set in similar circumstances.

A first step in the evaluation of this technique might be to examine the acceptance
of this technique by prospective parents and to document their retention about the
possible outcomes of a pregnancy. Prior studies [27,28,36] have established the range
of results that can be expected through classical "non-directive" counseling and might
form a basis for comparison. In our experience with the clinical application of this
technique, most prospective parents easily understood the questions by which we
assessed their utilities toward the potential outcomes of their pregnancy and seemed
pleased with the explicit manner in which their attitudes were incorporated into the
decision-making process.
FIG. 5. The Effect of Maternal Age in Down's Syndrome. The threshold cost of abortion is plotted against maternal age. Thresholds were calculated from age-specific occurrence rates [29]. The curve is analogous to the curve in Fig. 3, with the assumptions that $r = 0.005$, $n = 0$, $p = 0$, $C_{TU} = C_{TA}$, and $C_{S} = 0.5 \times C_{TA}$. In other words we assumed that the error rates were very small and that the burden of spontaneous abortion was one half the burden of therapeutic abortion. Although the curves shown in Figs. 3 and 4 (threshold cost as a function of the probability of a child's being affected) are convex upwards, the curve in this figure is concave upwards because the abscissa in this figure is maternal age, not probability. The relation between maternal age and the probability of a child's being affected by Down's syndrome rises quite sharply as age increases, and this sharp rise governs, in large part, the shape of the curve in this figure.

**Decision Analysis and Informed Consent**

Social pressures and recent court decisions [37] have underscored the need that patients understand all the issues involved in selecting diagnostic and therapeutic procedures. This necessity is nowhere more important than in circumstances such as prenatal diagnosis in which medical guidelines are not clearly established and decisions are governed by subjective, ethical issues. Unfortunately, simply providing the medical facts may not be sufficient to form a basis for informed consent [38]. Several studies have shown a low rate of information retention after genetic counseling [27,36]. Hence, the physician must insure that the parents understand the issues involved. Avoiding the problem by not discussing amniocentesis would do an injustice to the prospective parents and might make the physician legally liable if a child affected by a "preventable" malformation were born [37].

The techniques presented in this paper can be used to help achieve informed consent. The use of explicit diagrams (e.g., Fig. 1) can increase the parents' appreciation of their options. By obtaining the parents' assessment of the relative cost of the various outcomes and by incorporating these values into the decision-making process, the physician can make the parents equal partners in the decision. Such a partnership is, however, not without additional difficulties for both the parents and the physician. The parents must provide answers to several difficult, soul-searching questions; the physician must both communicate the issues to the parents and incorporate their attitudes into the decision-making process. These difficulties constitute part of the burden of informed consent.
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