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Evaluation of Mathematical Computer Simulation – Modeling in Unexplained Fetal Demise

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Abstract

The goal of this research was to evaluate the possible utility of a mathematical computer simulation modeling approach to the problem of unexplained fetal demise. We reasoned that psychosocial variables might play a role, and that the computer modeling techniques might be most applicable to handling these factors due to the nonlinearity and high degrees of intercorrelation. Thirty-three women were recruited who had experienced unexplained fetal demise within the past 18 months. Data was obtained related to obstetrical course, medical and psychosocial risk factors. Data obtained was from prenatal charts and from careful psychosocial interview with standardized questionnaires asking the women to review their pregnancy and prior lives. The data was entered into a mathematical computer simulation model designed in other research to predict risk for the individual pregnant woman for birth complications, including fetal distress. An iterative methodology was applied in which the women who were incorrectly predicted were compared to healthy controls and to women who were correctly predicted as experiencing fetal demise. From inspection and graphical exploratory data analysis, changes in

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the model were made, until the computer simulation model could correctly predict all 33 cases. This required seven model revisions. One woman was correctly predicted at risk for fetal demise in a separate prospective study taking place concurrently. A model was developed which predicted with 100% accuracy the time of the fetal demise among these 33 cases. The model also continued to accurate predict all cases within a 92 person comparison sample on which the model was initially developed. The model uses a systems dynamics method with feedback loops and non-linear differential equations. It was able to state some relationships among psychosocial and medical variables and use these relationships to make accurate predictions. Comparisons were made with standard statistical methods which yielded little information of interest on this sample and was no help for the individual woman in determining her personal risk status. Computer modeling was judged worthy of further consideration.

Zusammenfassung

Das Ziel dieser Forschungsarbeit war, die Nützlichkeit einer mathematischen Computer-Modellsimulation beim Problem des ungeklärten fötalen Todes zu prüfen. Wir vermuten, daß psychosoziale Variablen dabei eine Rolle spielen könnten und daß Computer-Simulationstechniken geeignet sein könnten, diese Faktoren, bei denen nichtlineare Korrelationen und ausgeprägte Interkorrelationen eine Rolle spielen, zu untersuchen. Es wurden 33 Frauen ausgewählt, bei denen sich ein ungeklärter Tod des Föten im Zeitraum der letzten 18 Monate ereignet hatte. Die Daten umfaßten die Befunde des Schwangerschaftsverlaufes und medizinische und psychosoziale Risikofaktoren. Die Untersuchungsdaten stammten aus den Berichten der Schwangerschaftsuntersuchung und aus einem ausführlichen psychosozialen Interview mit standardisierten Fragen nach dem Verlauf der Schwangerschaft und der Lebensgeschichte. Die erhobenen Daten wurden in ein mathematisches Computer-Simulationsmodell eingegeben, was für ein anderes Forschungsprojekt zur Vorhersage von Schwangerschaftskomplikationen und fötalen Streßzuständen entwickelt worden war. Es wurde eine iterative Methodik angewandt, bei der die Frauen, bei denen die Vorhersage falsch war, mit gesunden Kontrollpersonen verglichen wurden und ebenso mit den Frauen, bei denen das Ereignis des Tod des Fötus korrekt vorhergesagt war. Das Modell wurde den Untersuchungsdaten entsprechend entwickelt und verändert, bis es alle 33 Fälle korrekt vorhersagen konnte. Dies erforderte sieben Revisionen des Modells. Bei einer Frau wurde parallel in einer getrennten prospektiven Studie das Risiko eines fötalen Todes korrekt vorhergesagt. Es wurde weiter ein Modell entwickelt, das den Zeitpunkt des fötalen Todes bei den 33 Fällen hundertprozentig vorhersagt. Das Modell bewies seine Vorhersagekraft bei einer Vergleichspruppe von 92 Personen, für das es ursprünglich entwickelt war. Methodisch verwendet das Modell ein dynamisches System mit feed-back-Schleifen und nichtlinearen Differentialgleichungen. Es war geeignet, Beziehungen zwischen psychosozialen und medizinischen Variablen herzustellen und diese Verbindungen für Vorhersagen zu nutzen. Das Modell wurde mit den üblichen statistischen Methoden verglichen, die wenig relevante Information für die Untersuchungsgruppe ergaben und keine Hilfe bei der Einschätzung des Risikos der einzelnen Frau waren. Die Methode der Computer-Modellsimulation verdient weitere Beachtung.

Introduction

Golańska and Bacz[1] state that:

> Maternity is regarded as a primary value, being the essence of the life of every woman irrespective of the age in which she lives. The child, object of love, allows the mother to satisfy a fundamental (...) need (...).

When pregnancy goes awry and the child dies before birth, the anguish reverberates among family and physician. Obstetrics has concerned itself more and more with the attempted prediction of risk for fetal demise, but has not, to date, been able to accomplish that prediction with great accuracy. Particularly in the medically low risk woman, it has been considered a tragedy when fetal demise occurs. Great lengths are travelled in its prevention, with sometimes questionnable succes.

Most obstetrical texts review the medical risks for fetal demise, but conclude that a good number of cases are unexplained. We wondered of the addition of psychosocial risk factors along with a sophisticated mathematical modeling procedure to consider these factors might explain these previously unexplainable cases. Many researchers have investigated the relationship between psychological factors and pregnancy outcomes. In this research, our goal was an operationalized theoretical model integrating psychosocial factors into the prediction of fetal demise. More than just a theoretical model, the ideas were required to become mathematical equations and to produce a result for pregnant women which would match their actual outcome by history. Then we could be more sure that our theorizing was on the mark. There are several important areas of psychosocial factors that we planned to consider. Stress is one of those areas.

Stress

Stress has been defined as the internal or restricting force that is brought into being in the human organism by interaction with the environment[2]. Selye referred to it as the stereotyped or nonspecific part of the body's response to any demand[3]. Bragonier et al.[4] have defined stress as a generalized adaptation to any stressor agent, in an attempt to maintain homeostasis within the body.

"It increases during nervous tension, physical injury, infection, work or any strenous activity. The stress reaction as initially described by Selye was called the "General Adaptation Syndrome" (GAS) and consisted of: 1) an alarm reaction, the generalized "call to arms" of the body's defense forces; 2) the resistance stage, in which tolerance or adaptation occurs, although frequently at a new setting of the "thermostat of defense"; and 3) the stage of exhaustion, which occurs if the stressor is sufficiently severe and prolonged. Existence of the third stage demonstrates that the capacity to tolerate stress is finite, and although the stage of resistance may appear adaptive, the body can tolerate the higher homeostatic "setting"for only so long before it wears out.

The GAS is mediated by both the coordinating systems that connect all parts of the body with each other: the nervous system and the vascular system .... The intensity of the alarm, the number and route of messenger, and the magnitude of the response depend upon several factors: the non-specific effect of the stressor, specific effects unique to the stressor (the body responds differently to the tubercle bacillus and the gonococcus, for example), and exogenous and endogenous conditioning factors that influence the body's reactivity.

When the alarm reaches the hypothalamus, it is converted into corticotropin releasing factor (CRF), which causes discharge of adrenocorticotropic hormone (ACTH) into the circulation. ACTH in turn stimulates production and release of adrenal glucocorticoids and mineralocorticoids, in amounts appropriate to increase engery available to combat the stressor, facilitate enzyme responses, suppress immune reactions, and enhance connective tissue reactivity ....

While these changes are occuring, the GAS is mediated along another critical pathway, as catecholamines are released by the adrenal medulla. These hormones increase energy availability, elevate pulse and blood pressure, enhance blood flow to striated muscles (at the expense of internal organs), alter coagulation mechanisms, and stimulate the central nervous system .... In pregnancy these hormones decrease uterine blood flow and increase uterine irritability. Measures designed to decrease stress during labor and delivery have been repeatedly demonstrated to decrease the length and ardor of labor and the amount of anesthetic required and to enhance neonatal outcome.

Laboratory research in which uterine activity was measured directly in non-pregnant women demonstrated that unpleasant or frightening stimuli such as sudden noises or the prospect of receiving an injection may lead to increases in the frequency and amplitude of contractions or to desynchronization of uterine activity[5,6]. Presence of a relaxing stimulus, such as having the subject concentrate on a calm, pleasant activity, could quiet the uterus[5].

Selye[7] has found that stress increases oxytocin secretion, a hormone factor associated with uterine contraction and post-partum milk letdown. Uterine sensivity to oxytocin increases as pregnancy progresses[8]. Takahashi and associates[9] performed oxytocin production challenge tests on women, some of whom later developed extreme sensitivity to oxytocin and delivered infants prematurely.

Persons under stress are known to suffer from high muscle tone and a tendency to overreact[10,11]. This tendency has been found in some German studies to characterize women who tend to develop premature labor[12–15]. These studies have shown that a patient's level of neuromuscular reactivity, as measured by the rheobase in her anterior tibial muscle is a good predictor of premature labor. Eipper and Konneck[12] successfully predicted the outcome of tocolytic treatment based upon changes in the desired direction of the rheobase measurements. König and Seidenshur [13] hypothesized that these rheobase measurements pointed to a higher level of autonomic overactivity in those women at risk for premature delivery. Omer [16] has speculated that increased muscle tone and autonomic overactivity may be the common denominator between the anxious individuals and women who deliver prematurely.

Wortis and Freedman [17] provide clinical evidence that, among poor, lower socioeconomic black women, the women's style of reaction to particular life events seems to differentiate women having premature babies from those having full-term deliveries. This finding could help explain Nuckolls et al.'s [18] observation that a life change inventory did not reliably differentiate complication groups. How we react to and perceive life change is probably much more important in activating the adrenalcortical and catecholaminergic responses than what is actually happening. Nuckolls et al. did find that women with high life change had fewer complications when they also had high psychosocial assets.

Gorsuch and Key [19] showed that anxiety in the first trimester and life stress in the second and third trimesters, were associated with abnormalities in pregnancy, including prematurity. In 1979 Newton and colleagues [20] modified a Life Events Inventory for use with obstetrical groups. Women who delivered infants prematurely had significantly more major stressful life events during pregnancy, especially during the week before delivery. The more premature the labor, the greater the number of stressful life events to which the women were exposed. In this regard Logan [21] was able to use hypnosis to delay premature contractions.

Other work has demonstrated that potentially any emotional stress in a mother can lead to complications in birth, a lower birth weight of the fetus, and clear psychomotor overexcitability in the infant [22,23].

Anxiety

Levinson and Schnider [24] state:

> "Anxiety may markedly influence pregnancy and the fetus (...) in fact, psychological stress has been cited as the causative factor in habitual abortions. There are several studies in which habitual abortion has been treated with psychotherapy in order to reduce maternal anxiety and stress."

Omer and associates [25] found that pregnant women who later developed premature contractions had higher anxiety scores than those who did not develop them.

Psychological stress and anxiety lead to an abrupt rise on the levels of corticosteriods, catecholamnones, endorphins, and neuromuscular reactivity [10,11,26,27]. Matthews et al. [28] noted that treatments for anxiety, such as relaxation training, decreased catecholamine levels in these patients. Psychological stress and anxiety produced profound increases in secretion of corticoseroids, which in turn, increased the peripheral levels of catecholamines and endorphins. Epinephrine causes a steep increase in the level of F-prostaglandins [29] and of E-prostaglandins [30], both of which are powerful uterine stimulants. Norepinephrine stimulates alpha-adrinergic receptors while epinephrine stimulates both alpha- and beta-adrinergic receptors. Stimulation of alpha-receptors on the uterus increases uterine motility, whereas stimulation of beta-receptors quiets the uterus[31]. Another secondary affect of the corticosteriods is decreased effictiveness of immune system functions, which has also been associated with preterm labor. Omer[16] has hypothesized that the effect of increased secretion of catacholamines in pregnant women, as a result of stress and anxiety, is the predisposition of premature and prolonged labor.

Davids and DeVault[32] prospectively administered a battery of psychological tests to 50 pregnant women and found (after the women gave birth) that the women having abnormal deliveries had markedly higher anxiety levels than the women having normal deliveries.

Personal Characteristics and Birth Outcome

A number of studies have used psychological testing to investigate personality characteristics in relation to birth outcome. Crammond[33] found women who had dysfunctional labor to be inhibited, conventional, emotionally constrained, and have difficulty expressing anxiety. Davids et al.[34] found women who had abnormal pregnancy outcomes to be more egocentric, distrustful, pessimistic, anxious and resentful. Ferreira[35] found feelings of inadequacy or immaturity to be associated with premature birth.

McDonald, Gunther and Christakes[36] used the Minnesota Multophasic Personality Inventory (MMPI) and found more abnormal obstetrical outcomes among women with tested lower ego strengths and higher levels of tension, guilt proneness, intellectualization, and obsessive rumination. McDonald[37] later linked premature rupture of membranes with elevations on the MMPI Social Introversion Scale.

Klein and associates[38] found women who had complications of delivery to have less stable personalities, to be more ambivalent towards pregnancy, and to have more difficult pregnancies. Newton[39] correlated negative attitudes toward motherhood to miscarriages. Negative attitudes toward pregnancy have been related to premature delivery[40–42].

Herms and Gableman[43] showed that women who later delivered prematurely were less well adapted socially and less attached to their families than women who delivered at term.

Interactive Studies

Previous work by Mehl and associates[44–48] found psychosocial variables to interact with medical variables to increase risk of birth complications. Variables associated with higher risks included low social support, social stress, negative beliefs and outlooks, and internal stress. Internal stress was defined as high fear and anxiety, plus low maternal self esteem. Laukaron and Van den Berg[49] and Goshen-Gottstein[50] have indicated that disturbances in maternal attitude toward the child can become the cause of complications in birth or even lead to intrauterine death.

Why Computer Modeling?

There are problems with using general statistics such as t-tests and partial correlation coefficients with prenatal data. T-tests provide a measure of the confidence of a correlation. Passing the t-test, however, does not tell the researcher how important a variable is, or if the variable is causative. It merely states that the range of the variable is fairly tight – that is, that the estimated standard deviation is small relative to the estimated values. In linear regression, the t-statistic is computed as the ratio of the computed coefficient estimate β of the variable to the estimated standard deviation of the coefficient estimate $\partial\beta$. Failure to pass the t-test means only that the data do not permit a significant estimation of the coefficient of relationship between the data. Passing the t-test provides no assurance that a variable is important, only that its coefficient can be estimated with confidence.

The partial correlation coefficient provides the researcher with a measure of the incremental contribution of a single right-hand-side ("explanatory") variable in accounting for variation in a dependent variable. The fit of the estimated equation is computed twice, once with the explanatory variable of interest included and once without its presence. The partial correlation coefficient is determined as a ratio of the coefficient of multiple determination with the variable, R^2 minus that coefficient when the variable has been omitted (R_h^2) divided by 1 minus the coefficient of multiple determination with the variable omitted. Although intuitively appealing as a test of the importance of a variable, Mass and Senge [51] have shown that mathematically the partial correlation coefficient yields no information not already provided by the t-statistic, based upon the relation between the two measures when the partial derivative of the partial correlation coefficient is examined with respect to the t-statistic.

Bell and Bell [52] have noted that the social and medical sciences have tended to rely on an instrumentalist approach of correlating more and more data and/or by finding correlations with a closer statistical fit to the data. This method holds the advantage of encouraging a search for correlations without being constrained to offer explanations for unforeseen relationships. It lessens vulnerability to error, but does not provide a means for validating or disproving the validity of a theoretical model. Bell and Bell argue for the construction of causal models which can be refuted.

Intriligator [53] has described the problems with conventional statistical analysis of data. Computer modeling provides an exit from the five major problems that plague statisticians. The degrees of freedom problem exists in that there is insufficient data for the kind of statistical accuracy that would offer accurate parameter or coefficient estimation, there is a multicollinearity problem in that similar types of data are bunched together and difficult to separate, there is a serial correlation problem in that data from time periods close together tend to similar (because of inherent lags in the system being studied and the fact that some changes occur more slowly over time than others), there are discontinuous and non-linear events in the system being studied which are impossible to calculate with linear, one-equation statistics (the structural change problem), and there are many inaccuracies and biases in measuring medical and psychological variables (the errors of measurement problem).

Data such as these contain multiple covariances and colinearities. These defy estimation with t-test, partial correlation, and linear regression methods. The covariances and colinearities prevent significant relationships from emerging in ones equation statistical tests. Indeed, these statistical methods ignore (and depend upon the non-existence) of feedback loops among the variables under study. Criticism of single-equation testing can be traced as far back as John Maynard Keynes [54], who argued:

> The method [multiple correlation analysis] is a means of giving quantitative precision to what, in qualitative terms, we know already as the result of a complete theoretical analysis .... If the method cannot prove or disprove a theory, and if it cannot give a quantitative guide to the future, is it worthwhile?

Mass and Senge [51] illustrated the weakness of one equation statistical testing in a classic data set from Forrester [55]. Forrester was studying the hypothesis that delays in capital investment influence sharp rises and declines in production capacity and orders booked in industrial plants. He developed a mathematical model of the system which showed that "delivery delay recognized by market" was the driving variable explaining the rises and falls in production capacity and orders booked. Capital investment worked on a much longer 18 year cycle.

Mass and Senge took Forrester's calculated computer data and subjected them to statistical testing. The data were exact because they were calculated by the computer and fit curves precisely. T-test and partial correlation analyses were successful in identifying the important variables. Then 5 to 10% error variations were introduced into the variables. T-test and partial correlation procedures no longer predicted any statistically significant relationships among the variables under study. The model had already been validated by real-world intervention within industrial plants which showed that changed the market's perception of delivery delays smoothed out the production capacity and orders-booked swings.

Psychological and medical data almost always have at least a 10% error variation. 50% error is not that uncommon from day to day [56]. 10% error or variation in a psychological instrument is considered within acceptable ranges. For these reasons, Meadows [57] has recommended analyzing datasets with computer models. She states that computer models are preferable because:

1. they are precise and rigorous,
2. they are explicit and can be examined by critics for inconsistency and error,
3. they can contain much more information than a mental model,
4. they can proceed from assumptions to conclusions in a logical, error-free manner, and
5. they can easily be altered to represent different assumptions or alternate policies.

System dynamics methods of mathematical modeling are best designed to handel data sets with highly inter-correlated variables with multiple colinearites, non-linear discontinuities, time lags in effects, interactive feedback loops, and 10% or greater variations in measurement accuracy.

Systems Dynamics Mathematical Modeling

Systems dynamics was developed at MIT in the 1950's, primarily by Jay W. Forrester. He brought together ideas from three fields that were then relatively new – control engineering (the concepts of feedback and system self-regulation), cybernetics (the nature of information and its role in control systems), and organizational theory (the structure of human organizations and the forms of human decision making). From these basic ideas, Forrester developed a guiding philosophy and a set of representational techniques for simulating complex, nonlinear, multiloop feedback systems. He originally applied these techniques to problems of industrial firms. The first systems dynamics models addressed such general management problems as inventory fluctuations, instability of labor force, and falling market share [58]. The methods developed by Forrester and his group have since been applied to a wide variety of social systems [59,60].

Systems dynamics is a method of dealing with questions about the dynamic tendencies of complex systems, that is, the behavioral patterns they generate over time. The primary assumptions of the systems dynamics paradigm is that the persistent dynamic tendencies of any complex system arise from its causal structure – from physical constraints and social goals, rewards, and pressures that cause people to behave as they do and to generate cumulatively the dynamic behaviors of the total system. Time delays can be crucial determinants of the dynamic behavior of a system. Systems dynamics theory emphasizes the characteristics and consequences of different types of delays, both in information and in physical flows. Nonlinearities are also believed to be important in explaining system behaviors. A non-linear relationship causes the feedback loop of which it is a part to vary in strength depending on the state of the system. The Stella computer program has been developed from its DYNAMO parent to handle mathematically these non-linear, lagged, feedback relationship which are notoriously difficult to mathematically describe and are the statisticians nightmare.

A systems dynamics model is considered useful with a high degree of confidence when:

1. Every element and relationship in the model has identifiable real-world meaning and is consistent with whatever measurements or observations are available.
2. When the model is used to simulate historical periods, every variable exhibits the qualitative, and roughly quantitative, behavior that was observed in the real system.
3. When the model is operated under extreme conditions, the model system's operation is reasonable.

The concept of validity is addressed in systems dynamics models by requiring performance characteristics of models that are qualitative and demanding.

General Methodology

Subjects

Subjects were recruited through obstetrical practitioners who cared for women who had experienced medically unexplained fetal demise. The 33 women were generally from middle or higher socioeconomic status, and had been considered low-risk during their pregnancy. The study is retrospective and non-random. This was necessary, since medically unexplained fetal demise is a rare event. We were seeking to validate a theory that psychosocial factors play a role in fetal demise. We hypothesized that the fetal demise was medically unexplained because of a failure to consider psychosocial factors and because of a failure to appreciate the synergistic effect of the important variables. Because we are pre-specifying the theory, and not using the data to empirically derive theory, the effects of selecton biases are diminished. Additionally, the effects of recall biases would be expected to be similar for all women and across types of variables. If we could predict each woman's fetal demise with a pre-specified mathematical model, we reasoned this would offer some validation of the theory that psychosocial factors may play a role in fetal demise.

Subject Characteristics

The subjects chosen were entirely medically low risk. The mean age was 29 with a range from 18 to 36. Twenty-seven of the women were primigravidae. One woman was secundigravida. One woman was having her third child and two their fourth child. All women were Caucasian. All women were well-insured, began prenatal care by the end of the first trimester (at the latest), and had all recommended procedures and tests. No other significant medical diseases were present. The women came from San Francisco, Minneapolis and Vermont. No differences were observed in characteristics of the women from any of these locations.

Variables Studied and Measured

After obtaining informed consent, a time-oriented history was taken on these women in which they had been interviewed regarding their perception of relationship support, family support, support from friends and community, level of worrying (anxiety), levels of depression, levels of self-esteem, levels of work stress and personal stress, level of general physical health, activity levels, levels of exercise, alcohol and drug usage, and perception of proximity of current diet to a perfect diet. The subjects rated these variables on an easy to understand "0" to "10" scale, participating in the creation of graphs to display the ups and downs of these variables. Consistent with systems dynamics thinking, we believed that the shapes of the curves and relative magnitudes were more important than exact measurements of such hard to measure constructs. The interview booklet is available from the author by request ("Timeline Health History") and is sufficiently easy to use that many patients are now doing their own timeline without interviewer assistance.

Anxiety was also measured with the Taylor Manifest Anxiety Scale. Depression was assessed with the Beck Depression Inventory. Life Stress was also quantified with both the Perception of Life Events and the Life Events Scale for Obstetric Groups. The Perceived Social Support Questionnaire was used and was subdivided into a score for support from the relationship and support from family and friends. Interviewing was conducted with skin conductance and EMG physiological monitoring in place. A "Magnitude of Autonomic Responsiveness" to questions was constructed which consisted of a rating of the overall variability of skin conductance to questions and the subject's awareness of that variability. The level of autonomic responsiveness was determinded by comparing highest and lowest levels of skin conductance and EMG during the interview session. Levels of body tension were assessed via the resting and average reading on the EMG which was always applied to the forehead.

The interviewer was asked to assess during the interview several other factors (again on a zero to ten scale). These were faith in the natural process, quality of relationship of the woman to her physician or midwife, how safe the woman felt to labor in the hospital, and the quality of her labor support. Two interviewers were utilized and there ratings were found to agree above 0.9 consistently from watching videotapes of the principal investigator interviewing clients before they began the assessment process. While the factors were subjective, they were reported as easy for the interviewers to assess. (At the time of writing this paper, this portion of the interview has been operationalized through development of an expert system knowledge base which will analyze women's responses to questions and determine these variables.)

The level of prenatal bonding to the infant was assessed via a scale constructed from the Pregnancy Research Inventory and from the first seven questions on the Attitudes toward Pregnancy Inventory.

Questions were asked to determine level of rest and recreation, and the physician or midwife provided data on estimated fetal weight and pelvic size, as well as all other medical and obstetrical variables. All variables were assessed over a two year period and all the data used for that two year period. Questions were asked regarding previous obstetrical history, drug and alcohol and cigarette utilization, and number of previous normal deliveries. No woman was more than 18 months since the fetal demise. Eighty percent were within one year of fetal demise.

The computer model for prediction of delivery outcome was developed on a separate sample of individual. The process of development of this simulation model is described at lenght elsewhere[62]. Each component of the model with its various equations has also been described and explored with comparative sensitivity analyses. (Series of manuscripts under editorial review, 1991, request from the autor all model equation manuscripts.)

Because of the computerized nature of this research, all variables have been operationally defined. The variables used in the computer model are summarized below. It has been our policy to use only those variables necessary to make an accurate prediction, even if important variables from the literature are missing from the model.

Another factor that may be noted is large number of psychosocial variables. As noted elsewhere (Mehl et al., manuscript under editorial review, 1991, available upon request from the author), *in constructing the computer model to explain delivery outcome to low risk patients, the addition of psychosocial risk-factors was essential to gain accuracy in prediction.*

Variables currently in use by our preliminary computer model include the following (items followed by a **U** are updated each trimester for the past three month period.) We have variables covering each risk category mentioned as important by the Institute of Medicine in their study on preventing low birthweight. In the following the letters **DM** represent the Demographic Risk Category, the letters **MP** represent the Medical Risk Predating Pregnancy category, the letters **MC** represent the Medical Risk in Current Pregnancy Category, the letters **BE** represent the Behavorial Risk category, the letters **HC** represent the Health Care risk category, and the letters **EC** represent the Evolving Concepts of Risk category.

1. Quality of diet (assessed on a 1 to 10 pt. scale from 24 hour recall using the Food Processor software program and subjectively rated over the past 10 years by the patient as defined on the Diet section of the Timeline Health History. **U, BE**
2. State-trait anxiety as defined by the Spielberger State-Trait Anxiety Inventory. **U, EC**
3. Time of previous conceptions and deliveries. **MP**
4. Exercise (hours per week and intensity) over the past 10 years, rated by the patient according to guidelines given in the Exercies section of the Timeline Health History. **U, MP**
5. Perceived anxiety (patient self-rating scale for the past 10 years), defined in the "Level of Worrying" section of the Timeline Health History. **U, EC**
6. Caffeine use over the past 10 years defined by patient estimation of number of cups per day. **U, BE**
7. Variations in smoking over the past 10 years by patient rating of the number of packs or cigarettes smoked per day. **U, BE**
8. Kobasa Hardiness Index. **U, EC**
9. HIV status (patient reporting). **U, MC**
10. Marijuana and other drugs use over the past 10 years, measured on a patient self-reporting form from the Timeline Health History. **U, BE**
11. Patient's perceptions of family support over the past 10 years, measured on a patient self-reporting form from the Timeline Health History. **U, EC**
12. Patient's Perceptions of support from friends over the past 10 years, measured on a patients self-reporting form from the Timeline Health History. **U, EC**
13. Patient's perceptions of work stress over the past 10 years, measured on a patient self-reporting form from the Timeline Health History. **U, EC**
14. NIMH Pregnancy Research Inventory (P.R.I.) scale of Negative hormonal effects. **U, MC, DM, EC**
15. P.R.I. scale of respiratory symptoms. **U, MC**

16. Patients ratings of levels of alcohol use over time (separated by beer, wine, and hard liquor) and rated as drinks per day or week, over the past 10 years, measured on a patient self-reporting form from the Timeline Health History. **U, BE**
17. Patient's perceived personal stress over the past 10 years, measured on a patient self-reporting form from the Timeline Health History. **U, EC**
18. Number of sexual contacts over the past 10 years. **U, BE**
19. P.R.I. rating, "tired of being pregnant". **U, EC, MC**
20. Patient's perception of relationship quality over the past 10 years, measured on a patient self-reporting form from the Timeline Health History. **U, EC**
21. P.R.I. tiredness rating. **U, MC**
22. Vitamin usage over time. **U, HC**
23. P.R.I. gastrotestinal symptom rating. **U, MC**
24. P.R.I. allergy rating. **U, MC**
25. P.R.I. circulatory symptoms. **U, MC**
26. Galvanic Skin Response (GSR) & Electromyography (EMG) data (when available)
    - Reactivity, EMG & GSR
    - Initial & final GSR
    - Initial & final EMG
    - Maximum change GSR & EMG
    - Average reading GSR & EMG. **U, MC, EC**
27. P.R.I. Anxiety rating. **U, EC**
28. P.R.I. Number of physical symptom scores. **U, MC**
29. Age. **DM**
30. Specific life events from the Life Events for Obstetric Groups and the Perceived Life Events Inventory. **U, EC**
31. Cholesterol and triglyceride levels. **MC**
32. Cortauld emotional Control Scale (CEC). **EC**
33. Systolic and diastolic blood pressures over the past 10 years. **U, MC, MP**
34. Body tension ratings. **U, MC, EC**
35. Estimated infant size obtained from prenatal records and/or linearly estimated as a combination of the patient's own birth weight and ordinal position relative to the birth weights of her siblings. **U, MC**
36. Parity. **DM**
37. Pelvic dimensions obtained from clinical estimates from the prenatal record. **MC**
38. Height. **MC**
39. Weight variations over the past 10 years, obtained from patient self-report. **U, MC, MP**
40. Prenatal attachment rating obtained from the Expert System which analyzes patient response to the Pregnancy Thematic Apperception Test (10 pictures to which patients respond with stories about what the people in the picture are thinking and feeling, what is happening, and how the situation will resolve.) **EC**

41. Feeling safe in the hospital, obtained from patients ratings on a 1 to 10 scale of how safe they feel in the hospital or other situation in which they will be delivering. **U, EC**
42. Rating of body awareness when available, or, when not, estimated from the patient's ability to decrease highest GSR or EMG readings obtained in a session. **U, EC**
43. Number of normal deliveries. **MP, DM**
44. Number of previous Cesareans. **MP**
45. Single motherhood. **U, DM**
46. Quality of labor support rating, obtained from research staff rating of the labor support team with which the patient will be delivering. This rating is on a 1 to 10 scale and has already been made through discussions with practitioners in the local area and patients who have delivered with these practitioners. This is a subjective measure, but only needs to be accurate within a range of low, medium, or high. **HC**
47. Effectiveness of psychotherapy rating, obtained from patient rating on a 1 to 5 scale from a form used in Level II. **U, HC**
48. Hours of daily activity and effort within that activity over the past 10 years, measured on a patient self-reporting form from the Timeline Health History. **U, BE**
49. Patient's perceived self-esteem over the past 10 years, measured on a patient self-reporting form from the Timeline Health History. **U, EC**
50. Patient's perceived depression over the past 10 years, measured on a patient self-reporting form from the Timeline Health History. **U, EC**
51. Beck depression inventory score. **U, EC**
52. UCLA loneliness score. **U, EC**
53. Occurence of vacations during the past 10 years. **BE**
54. Rating of faith/belief in the natural process of childbirth obtained from the Expert System which analyses patient response to the Prenatal TAT. **EC**

Explanation for the Large Number of Variables

Given the relatively large number of data which we have collected, it is important to stress that this research represents a different methodology than standard, statistically based, correlational studies using multivariate regression techniques for data analysis. Mumford et al.[63] note, "Because individuality is manifest in a wide variety of ways, any attempt to formulate a general classification of persons is likely to be forced to employ a fairly large number of significant indicators if an adequate definition of the similarities and differences among individuals is to be obtained .... It can usually be expected that the accuracy of the classification will improve as more information concerning the individual becomes available .... Diversity in the nature of the indicators ... is likely to enhance the accuracy ... by incorporating more unique information concerning similarity in the behavior and experiences of individuals .... An attempt should be made to obtain a large and diverse set of reasonably accurate indicators." Mumford et al.'s comments are directly applicable to computer modeling research which is technically similar to the problem of correctly classifying individuals. We will be searching for clues as to cluster of individuals who behave in various predictable manners. These different clusters represent non-linearities and discontinuities in the data, with the task becoming one of correctly determining the requirements for transition from one cluster to another. In a standard statistically based study, having a large number of variables would be viewed with suspicion since some would be statistically significant based entirely on chance. Statistical significance as a concept is not so important in our type of research, however. What matters is that we can grasp the differences between states of normalcy and states of abnormality, determine the thresholds for transitions between these states of abnormality, determine the thresholds for transitions between these states, and correctly classify individuals in a dynamic manner which allows their classifications to change over time. The larger number and diversity of measures allow us to do this more effectively.

The computer simulation calculated three variables: fetal condition at birth, likelihood for uterine dysfunction and likelihood for Cesarean delivery. Fetal demise was considered likely when fetal condition reached critically abnormal levels more than two weeks before the estimated date of confinement.

Comparison Group

For comparison purposes patients were pulled from our database who had given birth with fetal distress or normally (without fetal demise). These patients' outcomes had already been correctly predicted by the computer model. They were used during the iterative evaluation process to be sure than the model could still correctly predict their outcomes while being modified to predict all cases of fetal demise. This group consisted of 92 women, also from San Francisco, Tucson, Portland, Oregon, and the Burlington, Vermont area. These women had a wider range of socioeconomic characteristics from lower to upper class, all had prenatal cared (required for us to obtain data), varied in their insurance status from none to some, and were 62% primigravidae. Their mean age was 27 with a range from 16 to 42. In this research, these women's outcomes had already been correctly predicted. The requirement was that the model continue to successfully predict these women's outcomes *after any modifications made to correctly predict the cases of fetal demise. Thus, the model must continually remain predictive of all past cases as well as new cases.* The results of predictions for this group of women are described in another publication (Mehl et al., 1991, manuscript under editorial review, available from the author.)

Systems Dynamics Method

In this type of mathematical modeling, first we seek to determine whether or not a particular variable X is an important determinant of observed oscillations in a variable Y. A model must be constructed which contains enough endogenous structure to portray how changes in one variable, say X, affect the present and future values of both X and Y. High levels of anxiety, for example, may predict higher levels of pregnancy risk in the future, for example. The model should generate a pattern of oscillatory behavior in *Y* similar to that observed in real life.

Working industrial models often contain between 1000 and 2000 variables. The goal is the simplest possible model that correctly describes the historical behavior of the dependent variables. The model should initially include all those factors about which the researchers are interested, and all those variables which may confound and affect those factors.

The second step of model testing involves simulating the model both with and without the direct influence of *X* upon *Y*. We ask, how does the behavior of variable *Y* change as a result of deleting the direct link between *X* and *Y*? For example can we predict pregnancy risk without any reference to psychological data. If so, perhaps that data is unnecessary and therefore unimportant. If medical factors alone will not describe the historical changes in health status and pregnancy outcome (that has been the findings to date) then what are the crucial psychological and social variables that must be included to obtain accurate prediction.

The third step in model testing involves analyzing the causes of the behavior observed in the second step. If the behavior of *Y* is relatively unaltered, what other variables appear to dominate the behavior? If *Y*'s behavior is altered significantly, what direct and indirect links between *X* and *Y* account for the change in behavior?

A fourth step in model analysis is the formulation of further research to test model predictions or relationships or the development of plans for interventions which would be predicted by the model to make large changes in the dependent variables. Such computer model guided research allows for elegant and simple studies which demonstrate the validity of the model's predictions.

In this study the original computer model predicted initially 19 of the cases of fetal demise. The remaining cases were studied carefully using visual inspection and graphical exploratory data analysis methods, and hypotheses were developed for changes in model structure which would correctly predict the incorrect cases. Modifications were made in the computer model. Seven revisions were required to predict all cases in this study. After each revision, all previous cases were rerun through the model to determine if the model still correctly predicted these cases. A random assortment of previously correctly predicted normal cases and cases with fetal distress but without fetal demise were also subjected to reanalysis to be sure that the revised model continued to correctly predict these cases as well.

Prospective Validation of the Computer Model

A prospective validation of the computer model is currently underway. At the time of the writing of this paper, 40 cases have been run through the model and 36 of the predictions have been entirely accurate. The cases being run are randomly obtained from practitioners and (by our request) may be completely low risk or high risk, or neither. Another prospective validation study is currently in progress with Dr. Robert Sokol of Wayne State University School of Medicine, in which we are predicting birthweights and lengths of gestations for a dataset collected by his research group. These results will be available from the author after presentation at the Research Society on Alcohol, June, 1991.

Statistical Analysis

Statistical treatment was also applied to the data using cluster analysis, regression analysis, general scatterplotting with and without smoothing, and discriminant analysis.

Results

After seven revisions, the model accurately predicted the time of fetal demise for all 33 women in the sample, while continuing to correctly predicted lack of fetal distress/fetal demise for 71 of the 92 women in the comparison group whose babies did delivery in good condition. The model continued to correctly predict 20 cases of fetal distress/poor fetal condition from the database from patients known to have had this condition. When the "potential for fetal distress" line (which is directly affected by predicted fetal oxygenation) exceeded the threshold for fetal distress, then fetal distress was considered 100% likely. When the threshold was crossed two weeks in advance of labor, the outcome was predicted as fetal demise. There was one prospective prediction of fetal demise made during the time of this study which in fact occured.

The model consists of three major feedback loops with interactions among these loops. Figure 1 diagrams variables affecting the "potential for uterine dysfunction." The inverse of this would reflect the potential for normal birth. On some diagrams, the potential for uterine dysfunction is also listed as the potential for complicated births. (These were early simulations before we discovered that we were actually predicting uterine dysfunction.) Figure 2 showes variables affecting the "potential for Cesarian birth". Figure 3 illustrates variables affecting the "potential for fetal distress" or fetal oxygenation/fetal condition. The model "rides on top" of a psychosocial kernel which handles social support, life stress, alcohol and substance use, quality of relationships, etc. The psychosocial kernel passes important variables into the birth model which serves as one if its subroutines.

Figures 4 to 7 are from the woman for whom we made a prospective prediction of fetal demise (unfortunately discounted by her obstetrician.) This woman had an average estimated size for dates fetus, had high body tension and low body awareness, felt moderately safe in the hospital, perceived herself as having high family support, and had average rating on prenatal bonding. Figure 4 shows the actual predictions which were made. The predicted variables for fetal distress and major complications cross the threshold for danger after 6 months of pregnancy. The actual fetal demise occurred at 34 weeks. Figure 5 shows that average life stress remained constantly high, body awareness (reflecting ability to relax) and offset sympathetic arousal was constantly average, and body tension was constantly high. A precipitous drop in self-esteem occured 6–9 months

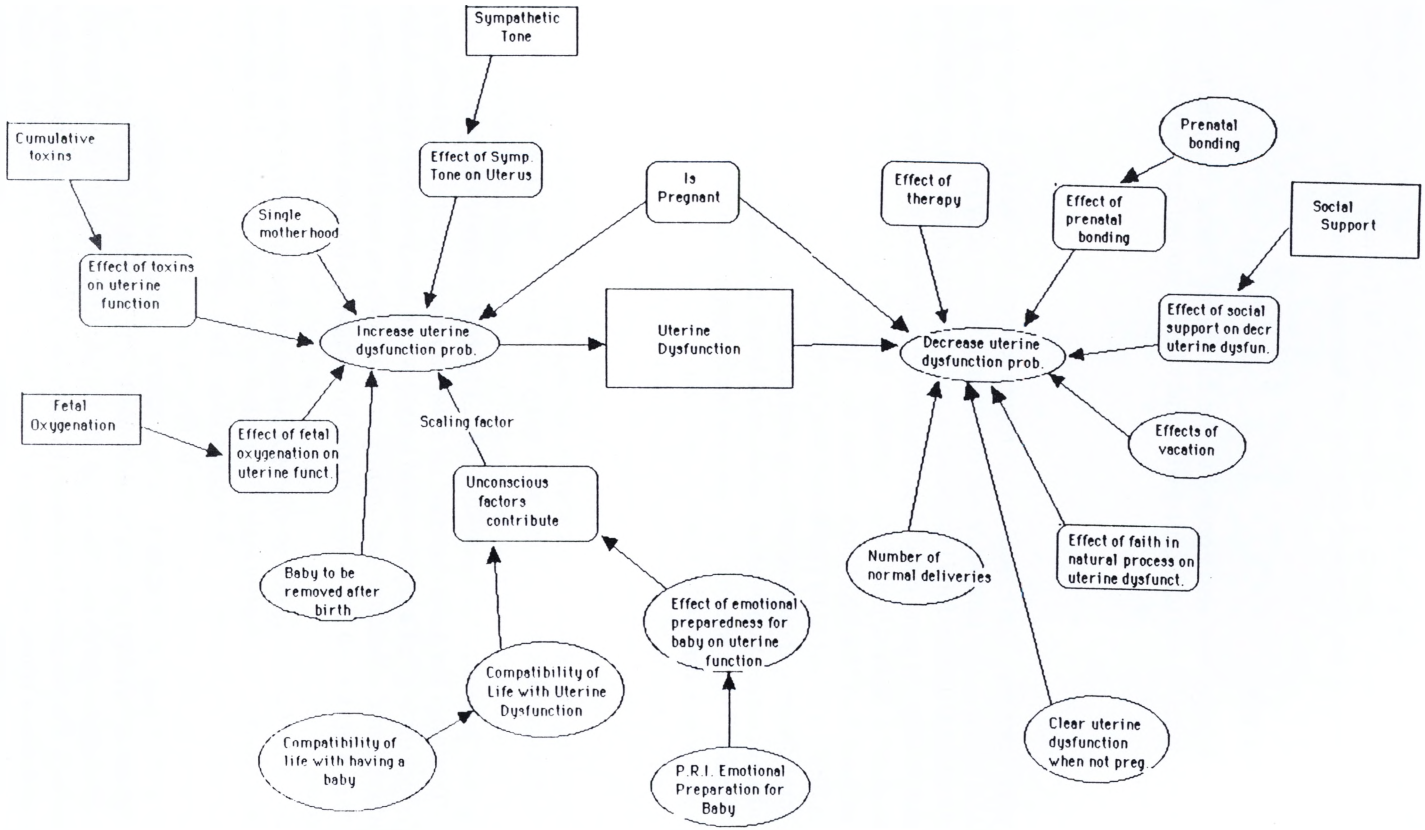

Fig. 1. The component of the model which simulates uterine dysfunction.

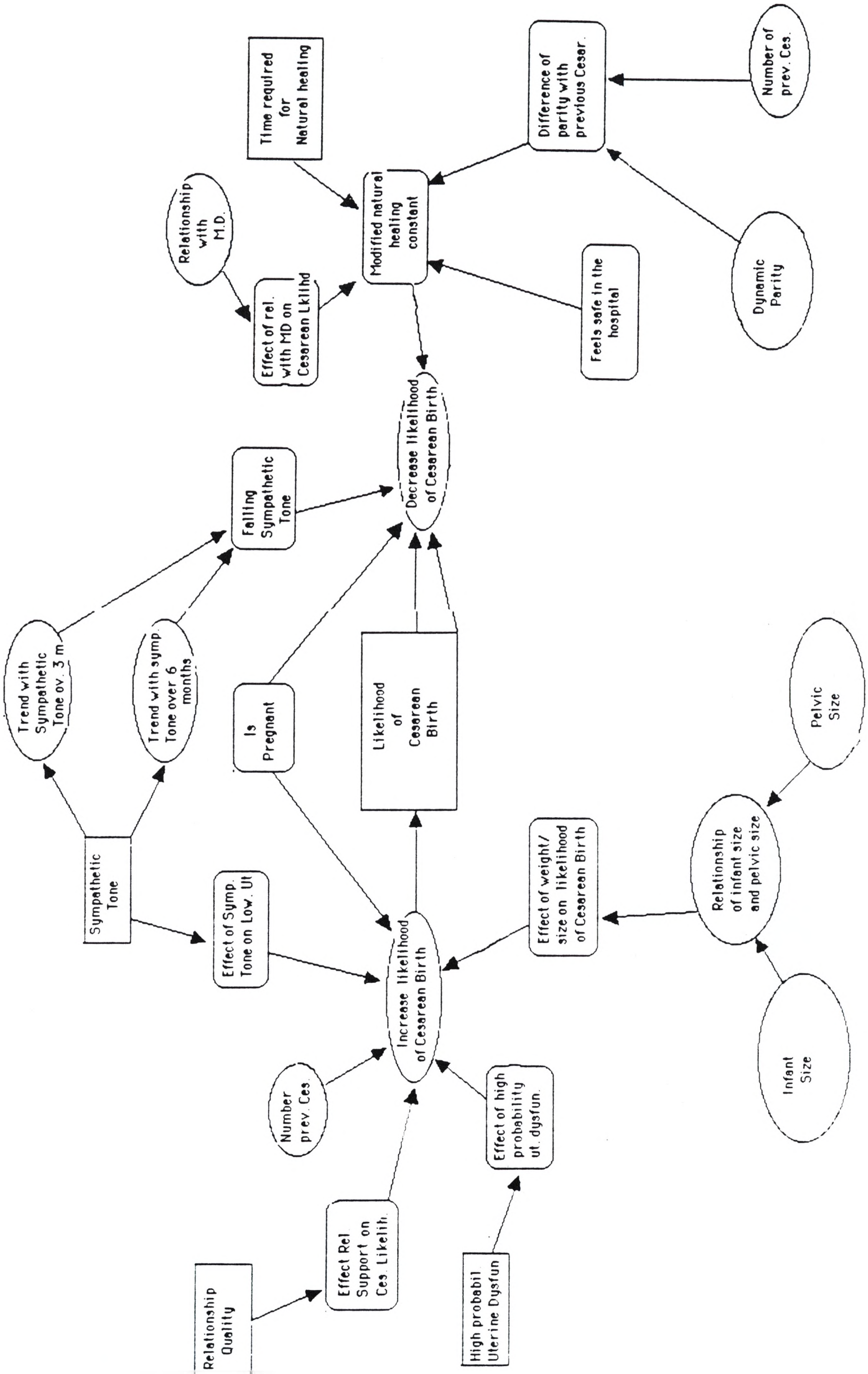

Fig. 2. The component of the model which simulates likelihood of Cesarean Birth.

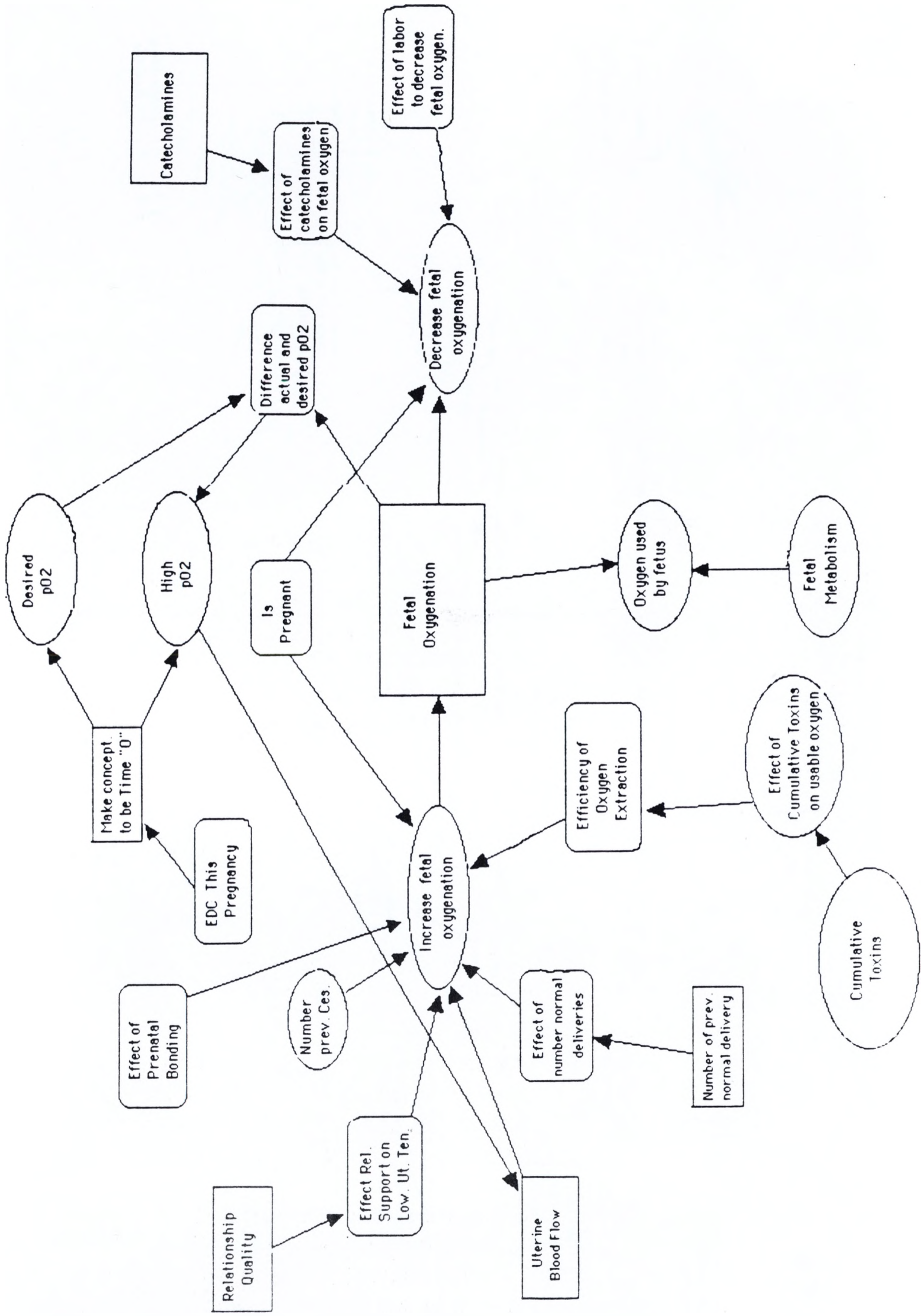

Fig. 3. The component of the model which simulates fetal condition/oxygenation.

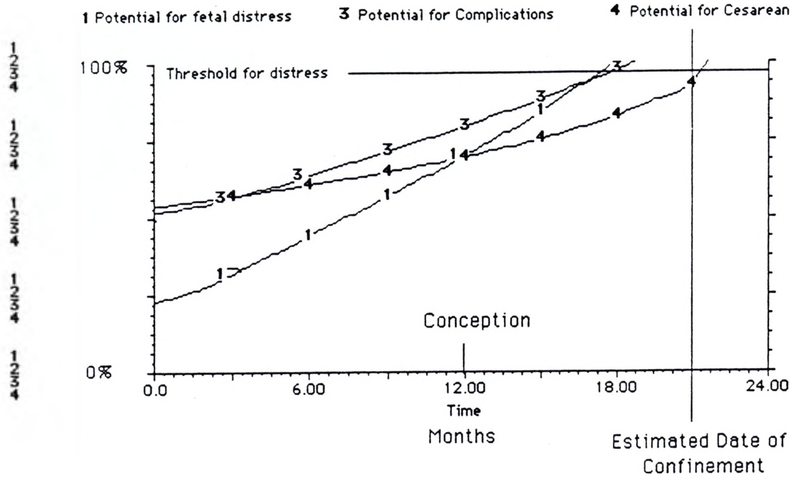

Fig. 4. Client for whom prospective predictions of 100% probability for fetal demise was made. The potential for fetal distress reaches 100% at 6 months of pregnancy (18 months from the beginning of the data collection). Line 3, the potential for complications, also reaches 100% (crossing the threshold for which something will happen) at 6 months of pregnancy. Actual outcome was a fetal demise at 8 months of pregnancy. (Medically unexplainable).

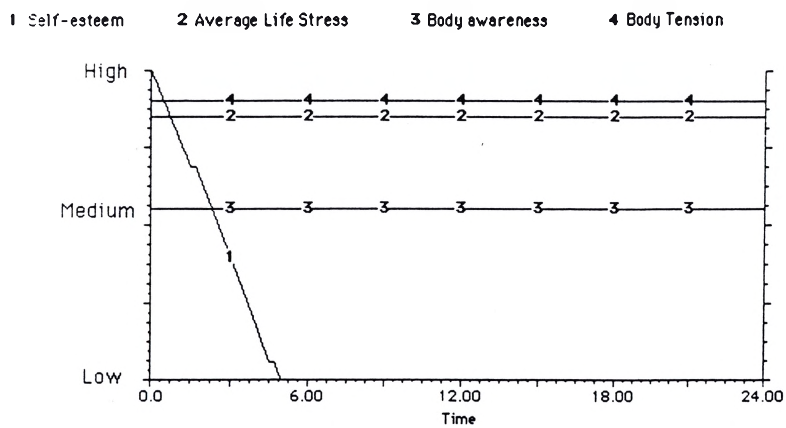

Fig. 5. Patient characteristics for patient with sudden drop in low self-esteem, who has high life stress and body tension, and low levels of body awareness (and ability to change body tension).

before she conceived. Figure 6 shows that stress and anxiety were consistently very high, activity was consistently above average.

To show the kinds of predictions made by the model, we illustrate a group of relatively similar women, comparing what happens to them and the predictions made.

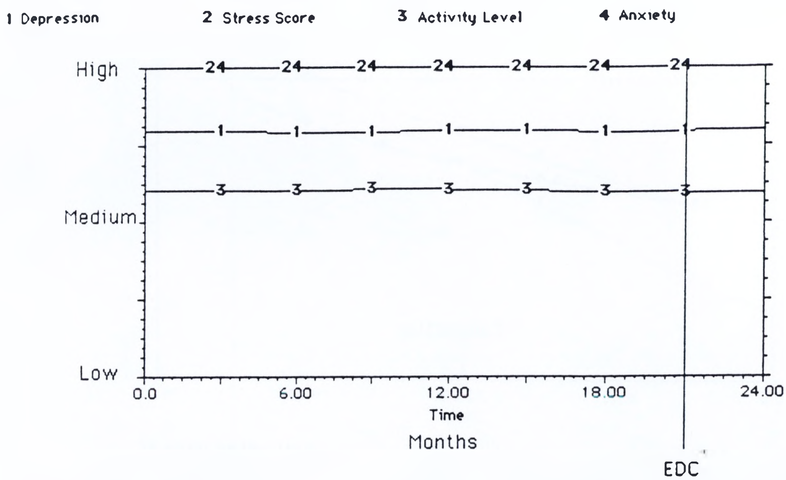

Fig. 6. More patient characteristics for patient with predicted fetal demise. Stress and anxiety are high, depression is at high-medium levels, and activity levels are above average. These remain stable and adverse through the pre-conception and pregnancy periods.

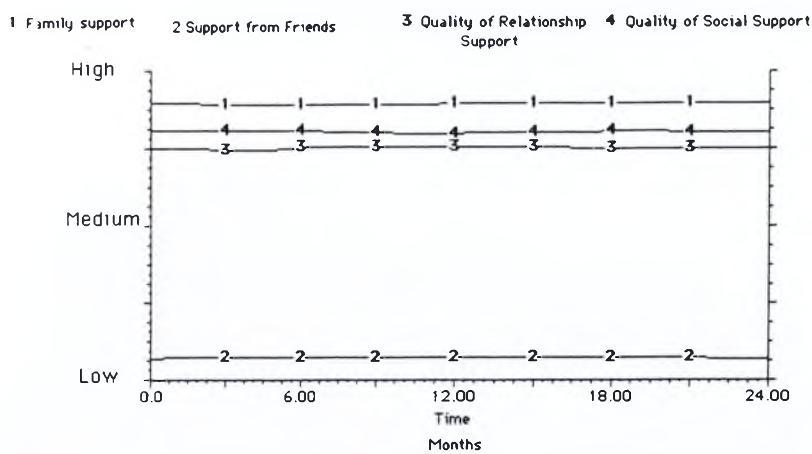

Fig. 7. Further patient characteristics for the patient with predicted fetal demise. Support from friends is low, quality of relationship support is above average, and family support is high along with social support.

Figure 8 shows prediction for a woman who had all of the above characteristics except that her self-esteem was high. This woman also smoked occasionally (under 1 pack per day). In this case fetal distress during labor was predicted and occured. This woman was from the comparison sample.

Figure 9 shows the results for a woman similar to the woman of Fig. 8 except that she had higher workstress, more pessimistic expections (beliefs) about

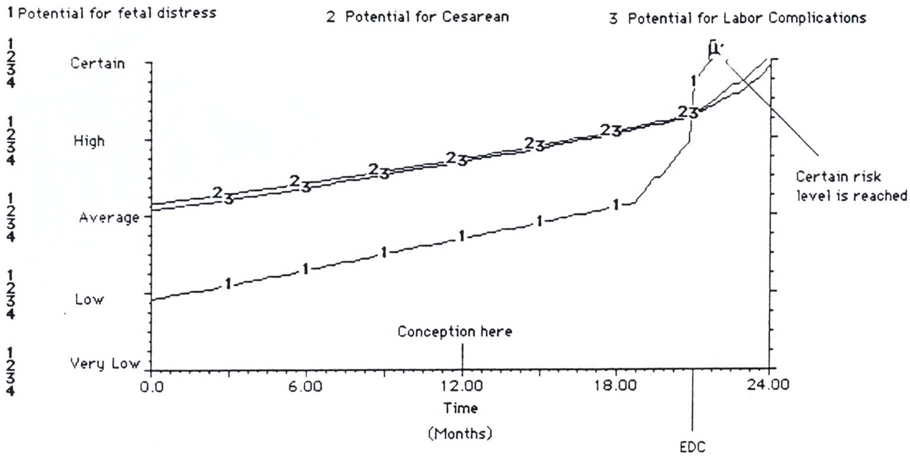

Fig. 8. The women depicted here is similar to the woman of Fig. 4, but has much higher self-esteem. This of course affects several other variables in small ways. In this case fetal distress occurs during labor. This woman also smoked less than 1 pack per day.

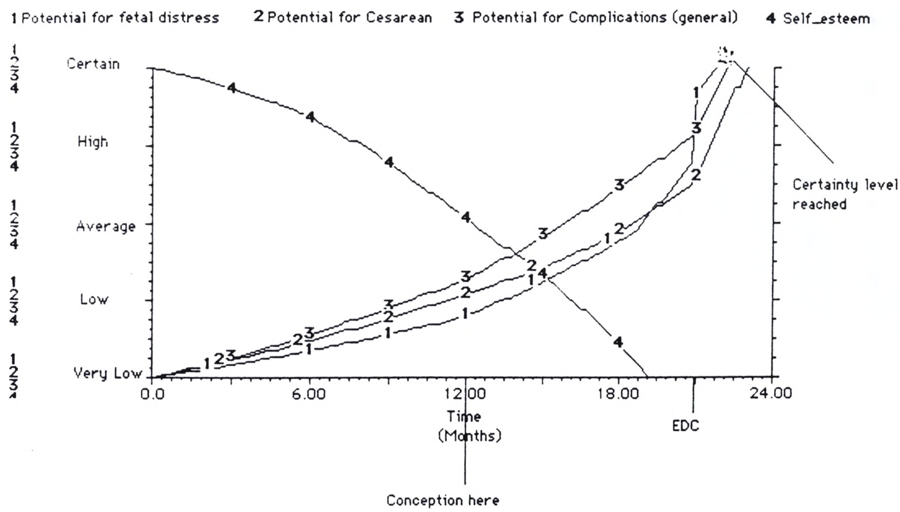

Fig. 9. This woman is very similar to the woman of Fig. 8 (including smoking) except that she has higher workstress, has more pessimistic beliefs about the birth process (health beliefs), has lower family support, and has average self-esteem. The fetal demise occurred just before she entered labor.

the birth process, lower family support and only average self-esteem. The fetal demise occured just before she entered labor.

Figure 10 displays the results for another woman in the sample who was similar to the woman of Fig. 9 except for more personal stress and her relationship support falling to zero 4 months into the pregnancy when her husband left her for another woman. Fetal demise occurs eight months into the pregnancy.

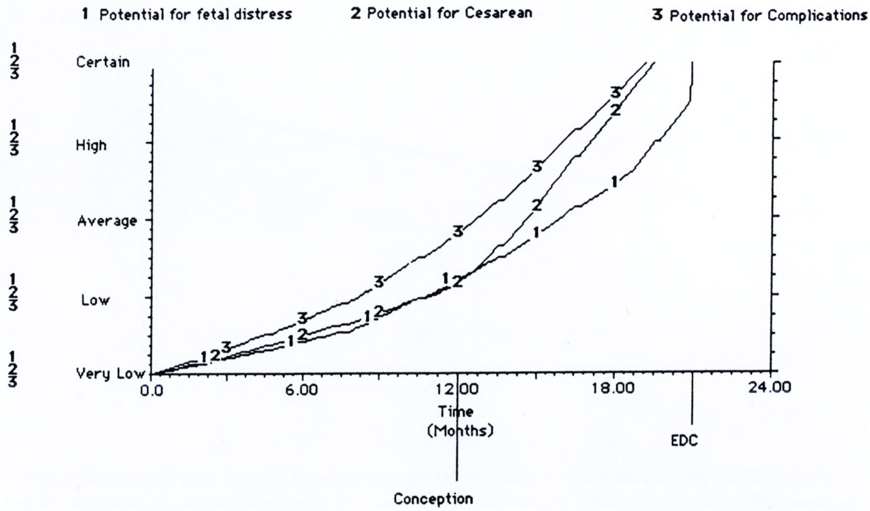

Fig. 10. The woman depicted here was similar to the woman of Fig. 9 except for more personal stress, and relationship support suddenly falling to zero at 16 months (4 months into the pregnancy). The fetal demise occured at 20 months (8 months into the pregnancy).

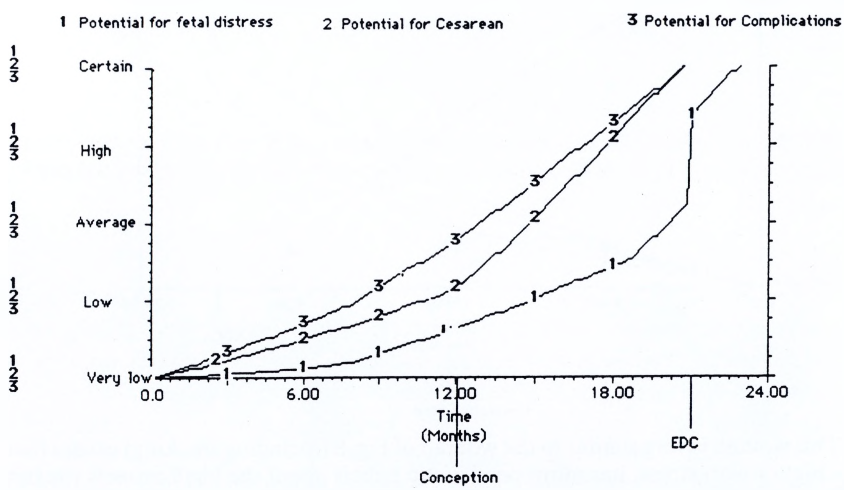

Fig. 11. Provides an interesting variation on the conditions set forth in Fig. 10. This woman had a very similar situation, but did not smoke. Her social support rose at the same time that her relationship support disappeared, and she had an excellent relationship with her obstetrician in which she felt very supported and nurtured. There is fetal distress in labor but no fetal demise.

Figure 11 shows a woman similar to the ones who have been presented (especially the woman of Fig. 10) except that this woman did not smoke. Her husband also left her during pregnancy, but she had social support which rose to offset the gap and also an excellent relationship with her obstetrician. Fetal distress occured during labor but there was not fetal demise. This woman was from the comparison sample.

Figure 12 shows a woman who was similar to the woman of Fig. 11 (this woman perceived her husband as absent and completely unsupportive even though he did not physically leave) who had lower self-esteem, high autonomic arousal, and higher life stress. This situation resulted in a fetal demise during early labor.

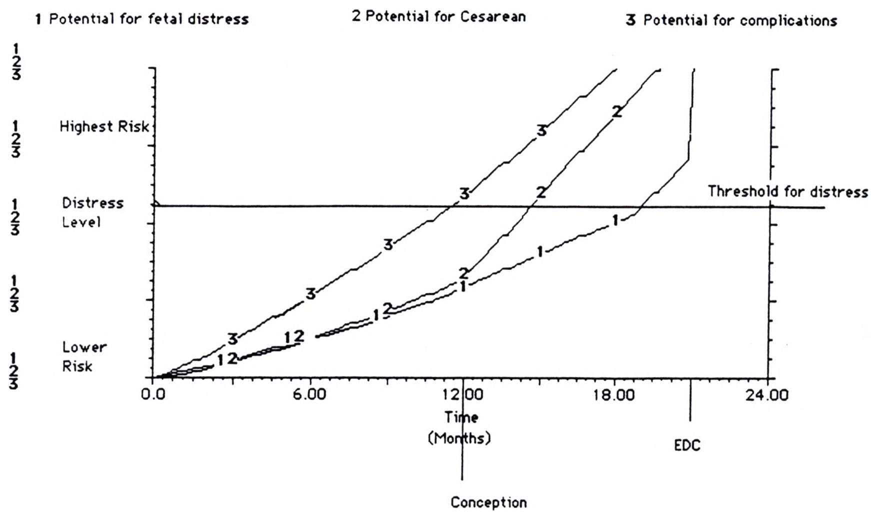

Fig. 12. Depicts a woman similar to the woman of Fig. 11 except for lower self-esteem, high autonomic arousal, and higher life stress. This case was a fetal demise during early labor.

Figure 13 shows another woman with very poor relationship support from her husband, otherwise similar to the woman of Fig. 12 except that her skin conductance responses showed wider ranges and more variability, with an ability to decrease arousal. Her baby was also smaller at delivery. She had less life stress. She experienced fetal distress during labor but not in advance of the process. This woman was from the comparison sample.

Figure 14 shows a woman who had a normal delivery (from the comparison sample.) She had high relationship support, high family support, was estimated to have a large pelvis, had high ratings on prenatal bonding, excellent labor support, and had received psychotherapy and hypnotherapy during her pregnancy. Otherwise her characteristics were the same as the woman of Fig. 13.

Figure 15 presents data from a woman who was similar to the woman of Figs. 14 and 13 in characteristics except that she did not have psychotherapy and hypnotherapy during pregnancy and had less adequate relationship support. She had a fetal demise days before labor (which began 2-1/2 weeks late). A non-stress test was not done.

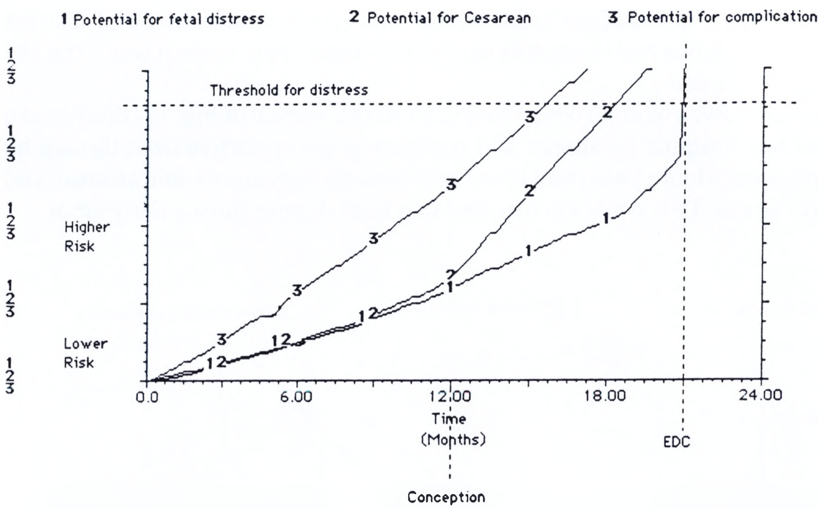

Fig. 13. Presents data from a woman who was very similar to the woman of Fig. 12. except that her skin conductance response was much stronger and more robust and her baby was smaller (approx. 6 pounds compared to 7 1/2). She had lower external life stress. She experienced distress in labor, not in advance of labor.

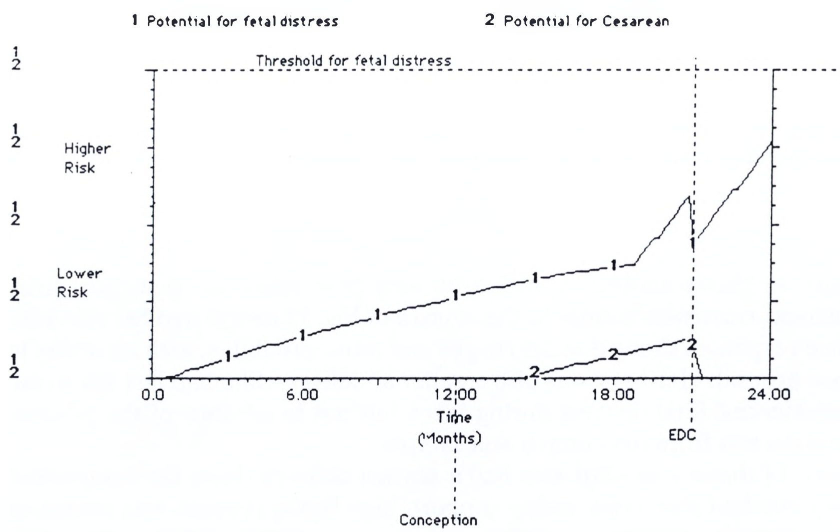

Fig. 14. Presents data from a woman who was very similar to the woman of Fig. 11. except that she had high perceived relationship and family support. Her mother had experienced a normal, natural delivery. She was estimated to have a large pelvis. She had high ratings on prenatal bonding. She had quality labor support; and received a combination of psychotherapy and hypnotherapy during pregnancy.

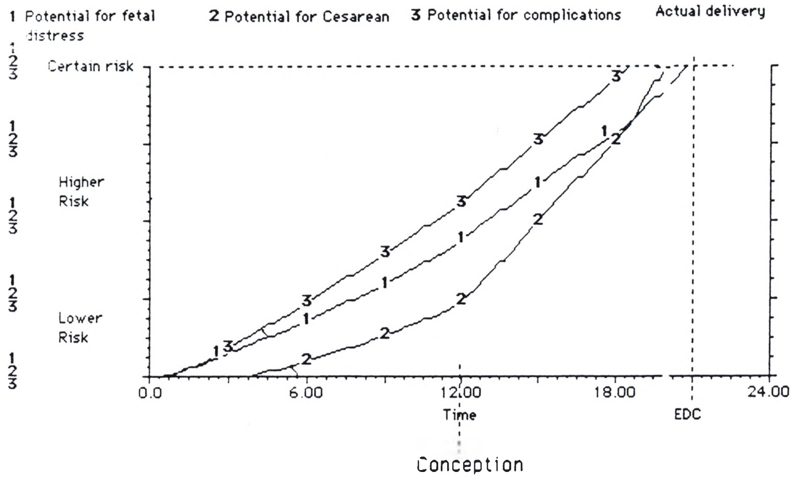

Fig. 15. Presents data from a woman who was very similar to the woman of Fig. 14 except that she did not have psychotherapy and hypnotherapy during pregnancy. The result is a fetal demise before labor (days).

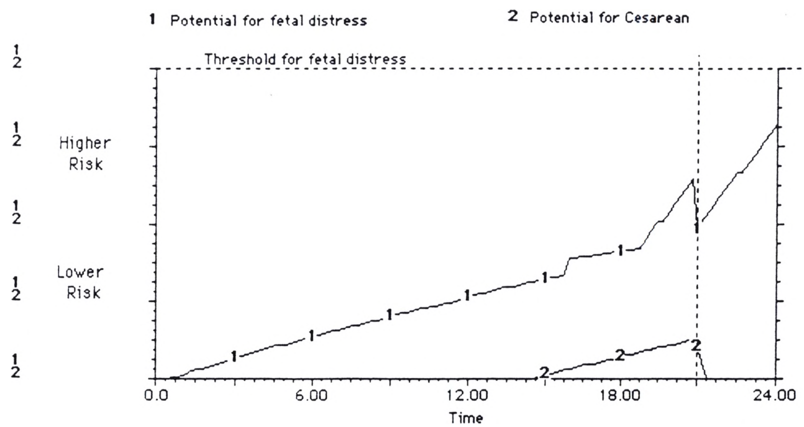

Fig. 16. Presents data for a woman very similar to the woman of Fig. 14 with high relationship stress occuring after time 16 months. There is no distress predicted or occuring.

Figure 16 shows a woman (from the comparison sample) similar to Fig. 14 except that relationship stress begins to build after 16 months (four months into the pregnancy.) No distress is predicted or occurs.

Results of Statistical Analyses

Standard statistics were not helpful in this sample size at making any discrimination. For these reasons there were no figures or tables to present regarding statistical findings. Examination of the means of presentation from Figs. 4 to 16 shed some light on this finding. The results show high degrees of synergy and nonlinearity. While the outcomes are mathematically predictable using non-linear differential equations, they are not statistically predictable using linear regression equations. The prediction requires many equations with iterative solutions and cannot be accomplished with one-equation models.

Sensitivity Analysis

Figure 17 displays the results of sensitivity analysis varying simultaneously all factors which change fetal condition. The *y*-axis is a relative scale; the units have no meaning. What is important is to see that a hundred-fold difference in fetal condition can be generated by the model when we vary conditions from every factor being at its worst to every factor being at its best.

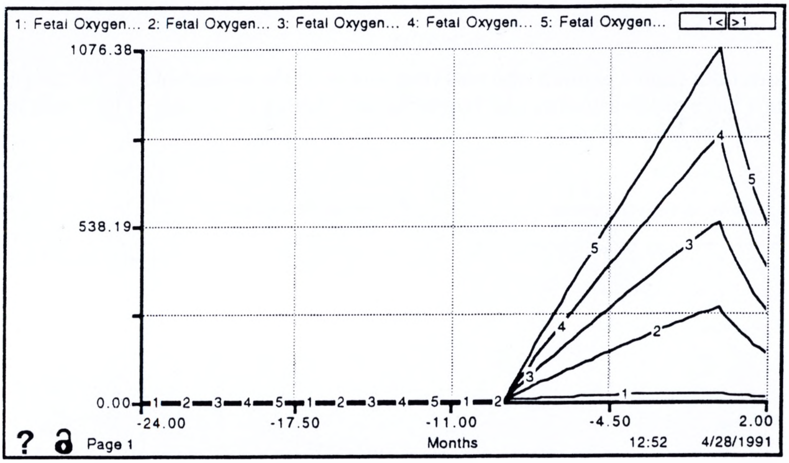

Fig. 17. Shows a comparative sensitivity analysis of the effects of varying all factors which impinge upon fetal condition/oxygenation from all being at their worst levels to all being at their best levels. A 100-fold difference is possible in fetal condition. The *y*-axis is a comparative scale. The numbers themselves are not in meaningful units. The *x*-axis represents time. There is an 18 month equilibration period before the pregnancy begins.

In Figure 18, we see the effects of just varying the rate of uterine blood flow during pregnancy. We can see that his factor alone will produce a four-fold difference in fetal oxygenation from its worst level to its best.

Conclusions

This was not a random sample. These women were recruited from around the United States from colleagues of the author. This was necessary because fetal demise is not a common event. The author specifically requested medical unexplained cases to simply his job at prediction. A computer model was developed which integrated psychosocial data with medical data to accurately predict risk

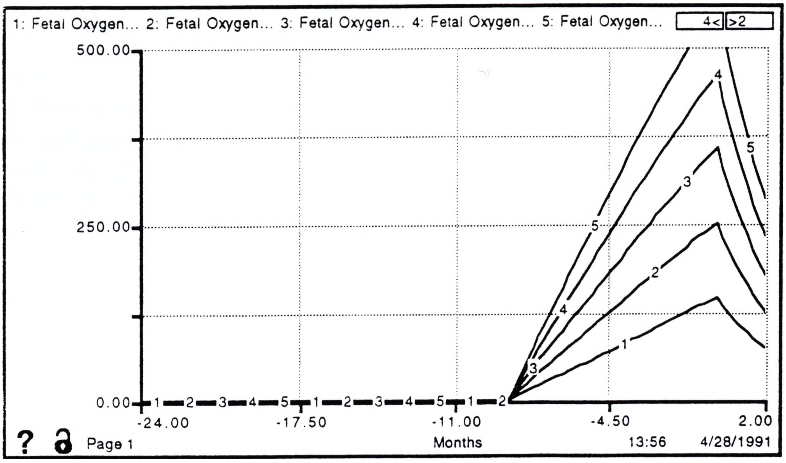

Fig. 18. Shows a comparative sensitivity analysis of the effects of varying uterine blood flow rates upon fetal condition/oxygenation from the lowest possible to the maximal rate. A 4-fold difference is possible in fetal condition. The *y*-axis is a comparative scale. The numbers themselves are not in meaningful units. The *x*-axis represents time. There is an 18 months equilibration period before the pregnancy begins.

for fetal distress and fetal demise. While the author could not try every combination of variables, it appeared that the psychosocial variables were necessary in order to predict risk for fetal distress/ fetal demise. The model's existence and success confirms that psychosocial variables interact with medical ones in obstetrical risk, that a general systems approach in which the interaction of variables with each other is appreciated and built upon is useful and gives hope to the vision that birth complications can be prevented through prenatal intervention with those variables that are amenable to change.

Of importance is the failure of standard statistical techniques (cluster analysis, regression analysis, discriminant analysis) to make accurate predictions. These type of statistical methods require linear data. The success of the systems dynamics method with this data set using highly non-linear assumptions shows that obstetrical risk factors do not lend themselves readily to a linear treatment. The author suggests that it will be impossible to arrive at a comprehensive and generally all-encompassing model of pregnancy complications using statistical models. The data is highly intercorrelated and the non-linear effects prevent the usual assumptions of general statistics from being valid.

In a non-linear computer modeling approach it is not possible to specify the contribution of any given variable to the whole picture as it is with multiple regression, for example. What we can do is sensitivity analysis, which shows how important a given variable is in the final result. Nevertheless, this measure can change if other parameters are simultaneously changing. Within this type approach, self-esteem changes its contribution in different circumstances with different combinations of variables. What we can offer is a model which is predictive and does describe relationships among variables. The model can be explored with references to itself or a patient to better understand the underlying reality which the model mirrors.

Understanding psychosocial risk factors did make it possible for a computer system to explain 33 cases of previously unexplained fetal demise. These findings have implications for consideration of psychosocial factors during pregnancy and for thinking about how research should be conducted when the body is considered as a complex system. Engineering tools such as these reported here may be more relevant to understanding the dynamic physiological phenomena of birth than one equation, linear statistical models.

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