

## PROJECT IDENTIFICATION

Project Title: Maternal PKU Resource Mothers Program: A Clinical Trial

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## **MATERNAL PKU RESOURCE MOTHERS PROGRAM: A CLINICAL TRIAL**

### **PURPOSE OF PROJECT AND RELATIONSHIP TO SSA TITLE V MATERNAL AND CHILD HEALTH (MCH PROGRAMS)**

Phenylketonuria (PKU) is a genetic disorder in which there is an absence or inactivity of the liver enzyme, phenylalanine hydroxylase, which is responsible for the conversion of phenylalanine to tyrosine (Hsia, 1970). Since the advent of newborn screening in the 1960's, infants with PKU have been identified and treated with a special formula and low protein diet that protects them from the most severe effects of elevated phenylalanine levels (MacCready, 1974). Maternal PKU refers to the risks to the fetus associated with phenylalanine teratogenicity (Levy and Ghavami, 1996). If the mother has classic PKU, risks to the developing fetus include mental retardation (95%), microcephaly (90%), and congenital heart disease (17%) (Lenke and Levy, 1980). Strict metabolic control prior to and throughout pregnancy greatly reduces these risks (Drogari et al, 1987). The risk of low birth weight, developmental delay, congenital heart disease and other congenital malformations increases with each week that treatment and metabolic control are delayed (Rouse et al, 2000). Women with non-PKU mild hyperphenylalaninemia (MHP), whose natural blood phenylalanine levels are lower than in women with PKU, incur little or no risk for adverse pregnancy outcomes (Levy, Waisbren 1983; Levy et al 1994). This finding underscores the need for metabolic control in maternal PKU. The cost of caring for a single child with maternal PKU syndrome includes cardiac surgery, early intervention, physical therapy, speech therapy, occupational therapy, special education classes, repeated psychological evaluations and psychotherapy for many years. With adequate prevention, these costs are eliminated.

Given the known benefits of dietary therapy, delivery of treatment for maternal PKU should be a straightforward process. However, this is not the case. The diet,

consisting of the special formula (containing the necessary nutrients in protein excluding phenylalanine), measured amounts of fruits and vegetables, and special low protein pastas and breads is extremely restrictive. Meat, fish, beans, nuts, dairy products, soy, and regular grains are not allowed. Preparing the low protein products is laborious and takes practice. There is little variety in the diet and without concerted attention to intake, the young woman may not consume enough calories for her pregnancy needs (Duran et al, 1999). Most reported maternal PKU pregnancies have been late treated (Koch et al, 1994; Hanley et al 1987; Levy, Ghavami, 1996). Metabolic control during pregnancy is strongly dependent upon regulated intake of the full allotment of special formula, which many find to be disagreeable in taste and odor. Compliance is generally poor with consequent adverse outcome (Duran et al, 1999). The majority of young women with PKU terminated the diet during middle childhood, as had once been recommended (Schuett and Brown, 1984). They have difficulties resuming the diet. Many of the women have limited intellectual abilities; the mean IQ is less than 85 (Waisbren et al, 1995). The incidence of emotional disorders is high (Waisbren, Zaff, 1994) and socioeconomic status is low (Waisbren et al, 2000).

The Maternal PKU Collaborative Study (MPKUCS) is a 16-year multi-national prospective study of the effects of dietary treatment during pregnancy in women with PKU (Koch et al, 1993; 1994). The pregnant women received ultrasound examinations, nutrition consultation, and metabolic monitoring as part of the study protocol. Through the MPKUCS, we learned that over 88% of women with PKU continued to attain metabolic control after pregnancy begins. Offspring scores on tests of development correlated with the number of weeks that elapsed until metabolic control was achieved. There was no “safe zone”. Every week counted, in that each week’s delay in maternal metabolic control predicted further declines in scores (Waisbren et al, 2000). Data from the MPKUCS indicated that the majority of women with phenylketonuria (PKU), a genetic disorder affecting metabolism of the amino acid phenylalanine, continue to contact their metabolic clinics after they become pregnant, when damage to the fetus most likely has already occurred (Koch et al, 1994). The MPKUCS also found, however, that a stimulating home environment during the first year of the offspring’s life may attenuate the adverse effects of maternal PKU (Waisbren et al, 1999). Moreover, it is clear from the MPKUCS and other data (Koch et al, 1994; Lenke and Levy, 1980) that planning of pregnancy with metabolic control achieved prior to conception confers the lowest risk to the fetus.

Maternal PKU is becoming a problem of considerable magnitude. The MPKUCS enrolled 554 pregnancies, in which 393 resulted in live births (71%). The number of completed pregnancies increased steadily after 1984 from less than 10 babies in the first year to 64 in 1995. The incidence of PKU in the United States is 1:12,000. Based on US Census Bureau statistics, there are an estimated 5,000 women with PKU of childbearing age and an estimated 300 maternal PKU births per year ([www.census.gov/prod/3/97pubs/p20-499/pdf](http://www.census.gov/prod/3/97pubs/p20-499/pdf)).

The Maternal PKU Resource Mothers Program most directly addressed Priority IX of the MCHB Research Agenda: Development, Evaluation and Validation of MCH Clinical Treatments, Outreach Strategies, Program Interventions, Care Guidelines and Case Management Approaches (8.1.12: randomized controlled studies of the efficacy and cost effectiveness of MCHB-developed and promoted Bright Futures guidelines).

This randomized controlled study directly evaluates the use of a specially designed home visitation program for a well-defined genetic condition. This approach may be applicable to other conditions, such as maternal diabetes, smoking, and alcohol use, in which the mother must significantly modify and monitor her behavior during pregnancy in order to protect the fetus. The intervention model is integrated with the medical home and existing state and local health promotion programs, such as Early Intervention, School Based Health Centers and the Bright Futures Initiative.

## GOALS AND OBJECTIVES

The goal of this project was to assess the value of a home visitation program to help women with PKU attain metabolic control prior to and throughout pregnancy in order to prevent the adverse effects of maternal PKU. In addition, this project sought to provide outreach before pregnancy to all adolescent girls and young women tracked by the metabolic centers and to all families after a baby was born. Only those randomized to the treatment group received the support of Resource Mothers during pregnancy. The research question was whether the Resource Mothers program yielded benefits beyond what was provided by basic metabolic services, as well as outreach before and after pregnancy.

## METHODOLOGY

The study was a *randomized controlled clinical trial* (Spilker, 1991). There are three key features to this type of design (Knapp, Miller, 1992): random assignment, a control group, and an intervention.

Subjects were randomly assigned to the group receiving the services of a Resource Mother or to a control group receiving the same treatment plan without a Resource Mother, stratified by clinic and whether or not the woman initiated treatment prior to pregnancy.

The participating clinics were: Children's Hospital (Harvey Levy, MD) in Boston, St. Christopher's Hospital (Warren Grover, MD) in Philadelphia, Children's Memorial Hospital (Barbara Burton, MD) and the University of Illinois Medical Center (George Hoganson, MD) in Chicago, Emory University School of Medicine (Louis Elsas, MD) in Atlanta, Waisman Center, University of Wisconsin (Jon Wolff, MD) in Madison, and Johns Hopkins Hospital (Michael Geraghty, MD) in Baltimore. All have experience treating maternal PKU. The *control group* received the same treatment as the *experimental group* except for the services of a Resource Mother according to a Maternal PKU Treatment Plan that included indices for determining blood phenylalanine levels and nutritional intake. In addition, it included "decision trees" to direct the health care providers to institute additional services (such as MCH case management) or alternate strategies (such as changes in formula composition) if the woman failed to gain weight or attain metabolic control. The treatment plan specified the number of visits to the maternal PKU clinic, the timing of ultrasound evaluations, and the frequency of blood testing for metabolic levels.

Outreach and follow-up were provided to adolescent females with PKU. Copies of a brochure describing PKU and maternal PKU were distributed to the women and to their schools and medical homes. The Department of Public Health in Massachusetts listed Maternal PKU as a risk factor on the confidential section of the Birth Certificates. This triggers follow-up from the Department of Public Health and automatically qualifies the child for Early Intervention. Care providers were encouraged to refer all offspring from late or inadequately treated pregnancies to Early Intervention.

The Resource Mothers Intervention was developed to provide pregnant women with PKU information, emotional support and practical assistance. The Resource Mothers focus on increasing the woman's supports and decreasing her stress. Preliminary data suggest that it is important for them to individualize their activities to meet the specific needs of the pregnant woman and at the same time, maintain a nonjudgmental, supportive relationship. In accordance with the Study Protocol, the Resource Mother met 20 times with the young woman with PKU. The timing of the visits depended on the needs of the woman. Some women required weekly visits during the time of treatment initiation. Later in pregnancy, most of the women had grown accustomed to the dietary regimen and required visits less frequently. Two visits took place after the baby was born to help the mother adjust to parenthood. The activities of the Resource Mothers included cooking

meals and snacks, teaching new recipes, purchasing necessary supplies for formula preparation and measuring food, and accompanying the woman to regular prenatal or metabolic clinic appointments. The Resource Mothers sometimes helped with completing applications for WIC or other forms of assistance. They explained maternal PKU to extended family members and friends. They listened to concerns, encourage communication with the metabolic center, and facilitate referrals. Resource Mothers were paid \$800 for their work for each completed pregnancy and \$250 for pregnancies that were not completed. They also were reimbursed for travel and phone calls.

#### Primary Hypotheses:

Women with PKU followed by an intervention that includes Resource Mothers compared to women with PKU followed by an identical intervention without Resource Mothers will:

1. attain metabolic control sooner.
2. have babies with better outcome at birth.
3. have babies with better outcome at one year of age.

These predictions are justified by previous experiences with Resource Mothers and preliminary results of the Maternal PKU Collaborative Study (Koch et al, 1994).

#### Secondary Hypotheses:

Women who have Resource Mothers will:

4. have greater adherence to the Maternal PKU Treatment Plan.
5. have better weight gain during pregnancy.
6. consume a greater percentage of recommended formula, protein, calories, fat, phenylalanine and tyrosine.
7. provide a more stimulating and stable environment for their children.

The secondary hypotheses address factors that may be closely related to the variables evaluated in the primary hypotheses. For example, metabolic control is related to adherence to treatment (the regularity with which the women keep prenatal and metabolic clinic appointments and send in blood samples for phenylalanine level determinations), greater intake of the special formula and low protein foods, and increased weight gain. These outcomes are predicted based on our experiences with the Resource Mothers Program.

#### Additional Hypotheses and Analyses:

It is hypothesized that women in the Resource Mothers group will have greater social support, more knowledge of maternal PKU, higher self-esteem, more positive attitudes about treatment, better home organization and fewer life stresses. It is also hypothesized that the women in the Resource Mother's group will be hospitalized less often during pregnancy. Hospitalization may have an independent influence on outcome and hence is added as a mediating variable. There are no hypotheses regarding the use of community services or locus of control (degree to which the women perceive life's events as under their control). Having a Resource Mother may lead to more extensive utilization of community resources or, conversely, to less of a need for such services. Similarly, having a Resource Mother may increase a woman's sense of responsibility for the pregnancy or increase her dependence on an outside support. The cost of the Resource Mother's Program will be calculated and reported. However, analyses concerning cost-benefit of such programs are beyond the scope of this study.

### **MODEL OF SET OF RELATIONSHIPS BETWEEN VARIABLES**

EXOGENOUS OR INDEPENDENT

VARIABLES

MEDIATING VARIABLES

DEPENDENT OR OUTCOME VARIABLES

GROUP: RESOURCE MOTHER or NO RESOURCE MOTHER

(Check for comparability on Intervening Variables:

Demographic factors and

Medical History)

ADHERENCE TO TREATMENT PLAN

HOSPITALIZATION DURING PREGNANCY

MATERNAL METABOLIC CONTROL

BIRTH OUTCOME

DEVELOPMENT AT ONE YEAR

HOME ENVIRONMENT

#### **IV. EVALUATION**

An internet data collection system was used to compile data obtained from the following evaluative instruments:

1. Registration and Background Form: This questionnaire, administered by the Study Coordinator, provided information related to stratification and random assignment. The woman was asked questions regarding the timing of diet initiation in relation to pregnancy, which formed the basis for group assignment (treatment prior to or after pregnancy). Background information was also obtained. Maternal IQ was obtained from the Wechsler Adult Intelligence Scale-Revised (Wechsler, 1981).
2. Maternal PKU Treatment Pregnancy Progress Forms provided data on weekly maternal blood phenylalanine levels, monthly diet records, weight, and pregnancy complications.
3. Offspring outcome at birth Form: The Study Coordinator obtained data from the newborn nursery on gestational age, gender, birth weight, birth length and birth head circumference and information about any anomalies.

4. The degree to which the experimental and control treatments are delivered according to the intervention plan was evaluated through a Data Collection completed by the Study Coordinator. This form listed each intervention (such as visits to metabolic center and blood testing) and had columns to record the date each was completed. This form also listed other community support services to be checked off if used. 5. Offspring outcome at one year was evaluated by complete medical examination and a battery of psychological tests, including the Bayley Scales of Infant Development, Second Edition (Bayley, 1993); the test of Receptive Expressive Emergent Language-2<sup>nd</sup> Edition (REEL-2) (Bzoch, League, 1991). The Home Observation for Measure of the Environment (HOME Scale) (Caldwell, Bradley, 1984).

6. Psychosocial Pre- and Post-Tests were administered to all subjects. These included the following

a. Social Support Questionnaire, adapted from Fishbein and Ajzen (1975). The degree to which others in the social network support "keeping strictly to the diet" was one of the best predictors of adherence to medical recommendations in a previous study (Waisbren et al, 1991; Waisbren et al, 1995).

b. Knowledge of Maternal PKU (Shiloh et al, 1990) This ten-item test has become a standard measure of knowledge of basic genetic and treatment facts. This test was validated on a population of women with a mean IQ of  $85 \pm 14$  (range 60 - 119) and has a validity coefficient of .63.

c. Self-Esteem Questionnaire (Coopersmith, 1967) A standard measure of self-esteem, this 25 item questionnaire is still frequently used with adults, partly because of its simple language and easy scoring. This scale was predictive of adjustment in newly diagnosed diabetic adolescents (Jacobson et al, 1987) and was found to correlate .95 with longer measures of self-esteem (Coopersmith, 1967).

d. Locus of Control (Nowicki, Duke, 1974) Another standard instrument, this test is used to rate the degree to which people attribute events in their lives to their own actions or to forces outside of their control. It has excellent reported reliability and validity and can be administered to those with a fifth grade reading level.

e. Home Organization Scale, developed for the Resource Mothers Program, is a checklist of supplies and activities related to the diet. Although not validated, In pilot studies, this measure was found to be associated with SES but not with IQ.

f. The List of Threatening Experiences, a life stress questionnaire (Brugha, Cragg, 1990) This is a list of 12 possible experiences that are deemed stressful, such as loss of a loved one, divorce, homelessness and loss of work. Reliability coefficients ranged from .7 to .9. In terms of concurrent validity, the sensitivity of the questionnaire was .89 and specificity was .88.

g. Attitudes about Treatment Questionnaire is a revised version of an instrument used in an evaluative study of the maternal PKU camp (Waisbren et al, 1997). It includes statements to be rated on a 5 point scale assessing the woman's attitudes about the formula, low protein diet, the pregnancy, her ability to cope and her rating of her relationship with her Resource Mother, if applicable. It has not been validated, but taps a variable that was highly predictive in the psychosocial study (Waisbren et al, 1991;1995). Results on this scale were not related to IQ.

Some of the subjects may have limited intellectual abilities. The Resource Mothers and Study Coordinators assist women who may not understand the questionnaires and interview questions. The instruments used in this study have all been used previously with this population and no differences in scores were related to IQ. This suggests that the tests are equally valid for individuals with average and below average intellectual abilities. Some subjects may experience agoraphobia when not on a phenylalanine-restricted diet. However, when diet is resumed, these symptoms dramatically dissipate (Waisbren and Levy, 1991), making it unlikely that agoraphobia

will decrease the sample size.

Data analysis proceeded according to our primary model, which postulates that the independent variable (Resource Mother support) affects maternal metabolic control, the home environment and offspring outcome by way of altering the mediating factor of adherence to treatment protocol. The first step will be to test for potential biases between the randomly selected study groups in terms of the "intervening variables". Due to the random selection process, it is hoped that the groups will be comparable. If not, separate analyses may have to be performed for the subgroups. Although we expect the Resource Mothers treatment group to attain metabolic control sooner and hence have better outcomes, we will conservatively use two-tailed tests and confidence intervals in order to be able to comment on results that may occur in the opposite direction to our hypotheses.

Analyses to test the specific hypotheses are as follows:

Hypothesis 1: The Resource Mothers treatment group will attain metabolic control sooner. The nonparametric Wilcoxon Mann Whitney test will be performed on the number of weeks from treatment initiation to metabolic control, since all women who achieve metabolic control prior to pregnancy receive a score of 0 weeks.

Hypothesis 2: The Resource Mothers treatment group will have babies with better outcome at birth. A T-test based on z-scores of birth head circumference, birth weight and birth length will be used. The relative occurrence of congenital heart disease and other anomalies will be analyzed by the Fisher's Exact Test.

Hypothesis 3: The Resource Mothers treatment group will have babies with better outcome at one year of age. A T-test will be used to compare the DQ, motor development, and language quotients of offspring in each group.

Hypotheses 4, 5, 6, 7: The Resource Mothers treatment group will have greater adherence to the Maternal PKU Treatment Plan, a higher percentage of recommended weight gain, a higher percentage of recommended nutrient intakes and provide a more stimulating environment for their child at one year. These hypotheses will be tested using the Wilcoxon Mann Whitney test. We selected this statistical test over parametric tests because of concerns about distribution, especially in the measurement of the home environment. Our experience has been that a bimodal distribution often occurs. For similar reasons, nonparametric correlations will be used to determine if percent of recommended nutrition intake is related to birth outcome and development at one year.

#### Additional Analyses:

To test our model of the set of relationships between variables, hierarchical regression analyses will be used according to procedures that are described below. To begin, we will predict each outcome (i.e., weeks to metabolic control, birth measurements and DQ) from the most proximal variable, for example, the predictive value of *adherence to treatment* to the outcome: *weeks to metabolic control*. Next, we will predict the outcome variable from the independent variable, *Resource Mothers Group*. Both these analyses are hypothesized to be significant. Finally, we will conduct the hierarchical regression, entering adherence to treatment plan first. Now it is hypothesized that the independent variable (Resource Mothers Group) no longer has predictive value. This would indicate that the Resource Mothers program is successful because it has an impact on adherence to treatment plan and not because of other factors. These procedures will be repeated for each outcome variable.

Other descriptive analyses will be conducted. The number of community services used and the cost of the Resource Mothers program will be presented through descriptive statistics. Paired T-tests will be used to compare the pre- and post scores on the psychosocial tests in each study group. These analyses permit the "full story" to be told. A new treatment may be associated with positive outcomes. However, some negative

results may also occur. For example, compared to controls, the Resource Mothers group may attain metabolic control sooner, but also experience a lowering in self-confidence or locus of control. Moreover, if the Resource Mothers Program does not lead to better outcomes, we will want to know about the attitudes, sense of social support, degree of stress and other psychosocial factors that might have interfered with the program's objectives.

## RESULTS/OUTCOMES

In the first three years of the study 50 cases were enrolled and provided data on metabolic control. Fifty-six percent of these cases came to medical attention prior to pregnancy including two women who had never discontinued the diet. Forty-four pregnancies occurred in 35 women, resulting in 28 live births and 6 spontaneous abortions (14%). Ten women are currently pregnant, 3 women are still on diet and planning to become pregnant, and 3 never became pregnant but have discontinued the diet. Table 1 shows the background characteristics of women in the treatment and control groups. There is no significant difference in the age, IQ, or mean off diet blood phenylalanine between the two groups. In addition, the groups did not differ with respect to the number of previous children or previous pregnancy losses. The Resource Mothers group had more women in the lowest two socioeconomic classifications (70%) versus the control group (43%). Three additional women were recruited but declined participation.

As seen in Table 2, there were 15 births in the Resource Mothers group and 13 in the control group. Fifty-three percent (8) of women in the Resource Mothers group were in metabolic control (blood phenylalanine consistently below  $360 \mu\text{mol/L}$ ) by 10 weeks gestation, as compared to 39 percent (5) in the control group. It took a median of 9 weeks for women to attain blood phenylalanine levels compared to 14 weeks in the control group. This difference was not statistically significant. Table 2 shows no difference in the median birth measurement Z scores of offspring in the Resource Mothers and control groups.

Table 3 provides a more detailed breakdown of when women with PKU who completed pregnancies attained metabolic control, taking into account when diet was initiated. Differences were small in the groups treated prior to pregnancy. However, some patterns emerged in the groups that began treatment after pregnancy occurred, although these differences did not reach statistical significance. Women who began diet after conception and had a Resource Mother attained blood phenylalanine levels  $<360 \mu\text{mol/L}$  a median of 14 weeks earlier than the control group. They were in metabolic control by 10 weeks gestation 44 percent of the time compared to 17 percent of the time in women who started diet after conception but did not have a Resource Mother. However, even those with a Resource mother tended not to be in optimal metabolic control on average until the second trimester.

Nutritional analyses of monthly food records showed no significant differences in intakes of energy, protein, fat, phenylalanine or tyrosine between the groups. Daily protein intake averaged 77 grams in the control group and 74 grams in the Resource Mothers group. All groups had low energy and fat intakes, with a mean energy intake of 2285 calories and a fat intake of 26 percent of energy. The average weight gain was 11.6 kg during pregnancy; 53 % of women were either over or underweight at the time of enrollment and several obese women lost weight during pregnancy. Despite recommendations to continue diet after giving birth, only four women have done so.

The psychosocial questionnaires administered at 6 and 32 weeks gestation showed that women with PKU in all groups have good knowledge about the risks and treatment of maternal PKU. The mean score on the Knowledge of Maternal PKU Test in both the Resource Mothers and control groups was 9 (+/- 1) out of a possible score of 10. Both groups of women also rated themselves as having the highest degree of social support,

with a mean score of  $>6$  (range 4-7) on a Likert Scale of 1-7. Likewise, women scored themselves highly on their ability to cope with pregnancy (mean score for all groups was 6 (+/-1) (range 1-7) of a possible 7. No significant differences were found in measures of self-esteem, locus of control, or life stress. For the sample as a whole, coping scores were related to timing of metabolic control with those under control earlier reporting an easier time coping with the diet. Stress also tended to relate to the timing of metabolic control with those in control earlier reporting fewer stressful circumstances during the pregnancy. Attitudes toward the formula tended to decline more in the control group than in the Resource Mothers group. The Resource Mothers group reported a higher need for a Resource Mother while the control group did not report such a need.

Resource Mothers spent an average of 12 hours of home visitation time (ranging up to 33.5 hours) with pregnant women and an additional 2.5 hours in telephone calls. One woman in the Resource Mothers group who agreed to participation never responded to numerous attempts to be visited by her Resource Mother.

Preliminary findings showed small differences in the course and outcome of pregnancy between women with PKU who received the services of a Resource Mother and those who did not. There were no significant differences in terms of when metabolic control was attained or in birth measurements. However, one woman in the Resource Mothers group was never visited by her Resource Mother and she failed to achieve metabolic control throughout pregnancy, and one other woman permitted only a single visit, but attained metabolic control by 9 weeks gestation. Resource Mothers appeared to offer the most benefit to women who came to medical attention already pregnant. Women with late treated pregnancies attained strict metabolic control a median of 14 weeks sooner when they had a Resource Mother.

Women who came to medical attention during pregnancy, did so relatively early, by an average of 5.7 weeks gestation, indicating that women with PKU understand the need for diet during pregnancy. The high scores by all groups on the Knowledge Test of Maternal PKU also indicate that women are well educated about the risks of maternal PKU.

More women with PKU are now coming to medical attention before conceiving and controlling blood phenylalanine more strictly than during the years of enrollment in the MPKUCS (1983-1996) (2). In the MPKUCS, 40 percent of women came to attention prior to conception whereas in this study, 56 percent of women were on diet before conception. In addition, 25 percent of women in the MPKUCS were in control by 10 weeks gestation, whereas 46 percent were in this study. There are several possible reasons for the changing trend. First, the MPKUCS definitively showed the importance of the timing of blood phenylalanine control on pregnancy outcome, so that now the message given to women with PKU about risks and benefit of diet is consistent and research-based. The knowledge gained by the MPKUCS has been clinically helpful in counseling women who come to attention after pregnancy about their chance of a good developmental outcome if they are able to achieve metabolic control by 10 weeks gestation. In addition, there is a consensus about the importance of diet for life, and more women with PKU are returning to diet for their own benefit, not just for the purpose of protecting the fetus during pregnancy. Lastly, there are many more medical foods and specialty low protein foods available than in the past, making the diet more palatable and convenient and therefore easier to follow. Nevertheless, very few women are able to achieve strict metabolic control before and during pregnancy.

There was no difference in women's nutritional intake during pregnancy between the group who had the services of a Resource Mother and those who did not. Protein and tyrosine intake appeared adequate and energy and fat intake was below recommended requirements in both groups. Since protein and tyrosine are primarily supplied by the metabolic formula, it appears that women in the study adhered to formula consumption. This may be partially explained by the variety of metabolic formulas currently available that help to satisfy different taste needs. However, many of the newer metabolic

formulas do not contain fat, and fat and energy intakes may have suffered as a result. In the MPKUCS fat intakes correlated with better birth outcomes (Koch et al, 1993). The average weight gain during pregnancy of 11.6 kg is within recommendations (Matalon et al, 1998 ) but weight gain varied widely and did not appear to be related to group assignment.

One troubling finding was how few women with PKU were able to maintain the phenylalanine-restricted diet after their infant was born. Women with PKU on average felt more negative about the formula and the diet at the end of pregnancy than the beginning, and at both times the scores were low. Therefore, it may not be surprising that few women have remained on diet, despite strong encouragement to do so. The MPKUCS showed that the deleterious effects of high maternal blood phenylalanine on the fetus during pregnancy could be somewhat mediated by a stimulating post-natal environment (Waisbren et al 2000). Adults with PKU who are off diet have increased depression, anxiety and diminished executive functioning ability (Pietz et al, 1997), therefore women who remain on diet after pregnancy are likely to have fewer mental health issues and be better able to deal with the stress of parenting. Resource Mothers make one post-partum visit at present, but more support for women with PKU may be needed during this time.

Research has shown that three factors are needed to successfully return to the PKU diet: social support, positive attitudes and a perception of treatment as manageable (Finkelson et al 2001). The Resource Mothers are especially helpful in providing emotional support and giving assistance to make the diet more manageable. It is more difficult to intervene in changing attitudes; some women with PKU have negative feelings about the diet and a long history of family stress and disordered eating which may require more intensive psychological intervention to change (Antshel et al 2002).

The study indicates that Resource Mothers are well accepted by women with PKU, in that only 3 women declined participation on the grounds that they did not need intervention. The majority of women who received the services of a Resource Mother felt that they needed these services, although none had the maximum of 20 visits called for in the protocol, one did not allow any visits and one allowed only a single visit. Home visits were made more in the first half of pregnancy when women were more likely to have problems with diet adjustment and nausea. Careful training and supervision is required to ensure that the Resource Mother is able to provide support in a non-judgmental way, yet enable the pregnant woman to maintain diet adherence. While time management studies were not part of the current research, clinicians who worked with Resource Mothers felt that the Resource Mother relieved the time spent on managing maternal PKU patients, even when including the time spent on training and supervision.

In summary, preliminary findings in this study of the contribution of Resource Mothers to diet adherence during maternal PKU pregnancies showed no significant differences in metabolic control and pregnancy outcome between the Resource Mothers and control groups. However women who began diet after pregnancy did achieve strict blood phenylalanine control sooner if they had the services of a Resource Mother. Nevertheless, more cases are needed to be conclusive about these results. Since women with PKU who began diet before conception compared to later treated women are almost twice as likely (61 vs. 33%) to attain metabolic control prior to 10 weeks gestation, it is of great public health importance to identify programs and methods that improve the number of women who are on diet before pregnancy. Finally, since a stimulating home environment is critical to the ultimate development of offspring from maternal PKU pregnancies and since high blood phenylalanine levels are associated with depression and other mental health problems, more effort needs to be directed at strategies for keeping women on diet after delivery. In the future, the Resource Mothers may best be used for outreach efforts aimed at maintaining diet for life and strict metabolic control before pregnancy, for home visiting women who are having difficulty with the diet during pregnancy, and for helping women stay on diet after pregnancy.

This study is being continued for another year with support from the National Institutes of Child Health and Development (NICHD).

Class, Race and Ethnicity: PKU is virtually unknown among Black, Ashkenazi Jewish, and Asian populations. Due to learning disabilities, reduced intellectual abilities, and emotional difficulties many women with PKU have limited education and jobs requiring little skill. They marry men like themselves and hence are most often of lower or low middle SES. Of the 50 cases enrolled, the ethnic and class breakdown was as follows:

SES American Indian/ Alaskan Native Asian/Pacific Islander Black Hispanic White Total Low 00011314  
Low Mid. 00001515

Middle 00001616

Upper Mid. 000055

High 000000

TOTAL 00014950

## VI. PUBLICATIONS/PRODUCTS

- Rohr F, Munier A, Sullivan D, Bailey I, Gennaccaro M, Levy H, Brereton H, Gleason S, Goss B, Lesperance E, Moseley K, Singh R, Tonyes L, Vespa H, Waisbren S. The Resource Mothers Study of Maternal PKU: Preliminary Findings. Submitted to J. Inherit Metab Dis. 6/200, revised 11/2003.
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PKU Primer This is a colorful, easy-to-read brochure for community health care providers treating adolescents and adults with PKU. This is now in its second "printing", with over 500 copies distributed to clinics, health centers, schools, camps, and families. There is a section on maternal PKU that has been useful for distribution to obstetricians, as well.

Resource Mothers Training Manual: This is a notebook containing 9 "packets" or sections related to maternal PKU, the Resource Mothers Program, and the Randomized Clinical Trial. There are reprints, exercises for training, and sample forms. The Treatment Protocol is also included. This Training Manual is also included in the Resource Mothers Website.

Website: The Resource Mothers Website is part of the website developed for the New England Consortium of Metabolic Programs. It can be accessed at

## VII. DISSEMINATION/UTILIZATION OF RESULTS

Presentations: The Resource Mothers Program has been presented at numerous conferences for professionals and parents. These include the following:

Dr. Waisbren

2000Invited Address: Psychosocial factors and Dietary AdherencePhenylketonuria: Screening and Management. NIH Consensus Development Conference

2001Invited Address: What do we offer our teenagers and Adults: The Importance of SAM (Social Support, Attitudes and Manageability)

Australian Society for Inborn Errors of Metabolism, Cairns, Australia2001Invited

Address: Prospective Study of Expanded Newborn Screening for Metabolic DisordersHuman Genetics Society of Australasia, Cairns, Australia

2001Grand Rounds: Psychosocial aspects of the management of PKU in children, adolescents and adults -- a model for chronic disease of paediatric originThe Children's Hospital at Westmead, Sydney, Australia

2002Invited Address: Maternal PKU Resource Mothers ProgramInternational Maternal PKU Collaborative Study: Bethesda, Maryland

2002Invited Address: Cognitive and behavioral development in maternal PKU OffspringInternational Maternal PKU Collaborative Study: Bethesda, Maryland

2002Presenter: Scientific Review, Department of Psychiatry, Children's

HospitalScientific Review Committee of the Children's Hospital2003Maternal PKU:

Progress and ChallengesNew England Connection for PKU and Allied DisordersFran Rohr, MS RD -Presentations

2001Resource Mothers Study of Maternal PKUNew England Consortium of Metabolic Disorders Annual Mtg

Worcester, MA2002Adults on Diet: Strategies for SuccessMid Atlantic Regional PKU

Meeting, Myerstown, PA2003How Can I Return to Diet?International Adult PKU

Conference Warwick, RI2003Lessons Learned from Adults with PKUSHS International Conference,

Boston, MA

Dianne Sullivan made several trips to teach low protein cookery to Resource Mothers, parents and professionals working with PKU, as well as to describe the Resource Mothers program to other parents and clinicians:

2001

Mar. New England Connection Conference, MA

May Maine Family Weekend  
May New Jersey Mid Atlantic Group Walk A Thon  
June Parent Day, Cherry Hill NJ  
Aug. Maryland Family Weekend  
2002

Feb Childrens Hospital Los Angeles Resource Mothers Training  
Mar.Parent Day, Trenton NJ  
Mar New England Connection Conference, MA  
May Maine Family Weekend  
Oct. National Coalition for PKU & Allied Disorders  
Nov. New England Connection Family Cooking Demonstration  
Nov NE Consortium- Presentation on Resource Mothers  
2003

Jan. Tampa FL Parents Day  
Feb. Atlanta, GA Parent Cooking Demonstration  
Mar. New England Connection Conference, MA  
May Maine Family Weekend  
Iowa Family Education Day  
June Rhode Island Family Gathering  
July Adult Conference for PKU: Cooking Demo , Workshop on Resource Mothers  
Sept Connecticut, Parents Weekend  
Oct Illinois, Parent Weekend

#### C. New England Consortium:

In 1998, the New England Consortium of Metabolic Programs was formed with support from the New England Regional Genetics Group (NERGG). In New England, most patients with metabolic disorders are followed in varying degrees by clinics or pediatric specialists that are associated with this Consortium. The Consortium brings together healthcare professionals at all levels involved in identifying and treating individuals with genetic biochemical disorders.

The goals of the Consortium are to disseminate information, collaborate in the development of social support programs and educational materials for families, provide training for students in medicine and related fields, jointly develop research projects, and establish uniform treatment protocols for children with metabolic disorders.

The Consortium consists of an informal collaboration of metabolic centers throughout New England that work together to provide a forum for communication and the possibility for joint projects to carry out our goals. At our annual meeting, a select group of invited members of the Consortium gather in Worcester, MA to discuss the latest developments in inborn errors of metabolism. Representatives from each New England state are invited to share the events occurring within their centers and breakout sessions are also included during the meeting to promote the exchange of ideas and knowledge across the region.

Community outreach is another important goal of the New England Consortium; Resource Mothers Program, the Teen Challenge Program, adult weekends, camps, and other activities have all been met with great success. Through the New England Consortium website we have developed a center for information where individuals can learn about metabolic disorders, support groups, the latest recipes, current events happening in New England, and more as the Consortium continues to develop and expand.

## VIII. FUTURE PLANS/FOLLOW-UP

The study has one more year of support from NICHD. Thereafter, it is hoped that Parent Organizations will provide funds to continue the program. We have also submitted several grant proposals to continue research in adherence to maternal PKU recommendations. These studies will focus on the Genetic and Biologic Risk Perceptions of women with PKU. Hopefully, by gaining a better understanding of the experiences, perceptions and behavior of women with PKU who are of childbearing age, we will be able to supplement the Resource Mothers Program with other interventions that might reduce the number of unplanned and inadequately treated pregnancies.

Another outgrowth of this project has been the development of an Adult PKU Guide This is a collaborative effort on the part of the Resource Mothers, the Children's Hospital, and Applied Nutrition, a medical food manufacturer. The guide contains all the information needed to return to diet, including explanation of the disorder, insurance letters, social support and other resources.

## TYPE/AMOUNT OF SUPPORT AND RESOURCES NEEDED TO REPLICATE

The costs of training Resource Mothers includes funds for travel by the trainers. Materials are now available on the web at no cost. Operating costs, to provide stipends and travel funds for Resource Mothers, are about \$1,000 per pregnancy. Supervision would need to be provided by the clinical nutritionist or physician following the patient.

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Table 1. Background variables of all women enrolled in the Resource Mothers Study of Maternal PKU (n=50)

Randomization Group	Resource Mothers	Control	Number
			27
	23% On diet before pregnancy (n)		52
			(13)65
			(15)
Age (mean +/-SD)			
(range)			
			29.7 (5.8)
			21 - 37
			29.1 (5.4)
	18 - 38	Socio-economic status	
(% in lowest 2 of 5 SES classifications)			
			70
			43
IQ (mean +/-SD)			
(range)			
			91.1 (10.6)
			74 - 113
			(n=18)
			95.2 (13.1)
			75 - 114
	(n=17)	Off diet blood phenylalanine (mg/dl)	
mean (+/-SD)			
(range)			
			21.0 (5.1)
			11.6 - 28.4
			(n=21)
			21.9 (7.6)
			(9.2 - 34.0)
			(n=20)

Table 2. Blood phenylalanine (PHE) control of women with PKU in the Resource Mothers and control groups and birth measurement Z scores in their offspring

Randomization	Resource Mother	Control	Births
	15	13	Weeks gestation after which blood PHE <360 µmol/L*
			9
			(0-never)14
	(0-never)	% Under metabolic control by 10 weeks gestation (n)	
			53
			(8/15)
			39
			(5/13)

Birth Weight Z score*	0.1 (-3.4 – 1.3)
	-0.5 (-1.6 – 2.2)
Birth Length Z score *	-0.3 (-3.9 – 3.1)
	0.7 (-1.4 – 2.5)
Birth Head Circumference Z score *	-1.1 (-5.8 – 2.5)
	-0.7 (-3.6 – 1.2)*Median (range)

Table 3. Blood phenylalanine control in women with PKU in the Resource Mothers and control groups according to when diet began (n=44)

Started Diet	Prior to pregnancy	Post pregnancy
Randomization		
(n)Resource Mother		(11)Control
		(11)Resource Mother
		(14)Control
		(8)Births
		679
when diet began*	prior	6 Weeks gestation
	prior	5.6
		(4.0-6.6)6.0
	(4.4-7.1)% of women under metabolic control by 10 weeks gestation	
		67
		(4/6)
		57
		(4/7)
		44
		(4/9)
		17
<360 µmol/L*	(1/6)Weeks gestation after which blood PHE	
		9
		(0-never)
		8
		(0-28)
		26
		(5-never)
		40
	(6-never)Blood PHE (µmol/L) during pregnancy (mean +/- SD) (range)	
		5.2 (2.2)
		(2.4 - 9.9)
		4.7 (1.6)
		(2.9 - 8.3)

8.1 (5.7)  
(2.5 - 18.9)  
6.5 (2.0)  
(3.8 - 9.1)\*median (range)

Table 4. Maternal PKU Treatment Plan — Schedule of Assessments Summary

**When Diet is Initiated:**

**Metabolic Clinic Visit**

Assessment of Nutrient Intake

Laboratory Assessments including

Amino Acids

Pre-albumin

Serum Cholesterol

Ferritin

Vitamin B12

CBC

RBC folate

Evaluation of Support Systems (questionnaires)

Intelligence Testing if none on record

**Weekly throughout pregnancy:**

Blood phenylalanine (and in some clinics, tyrosine)

Feedback from metabolic clinic

**20 times during pregnancy:**

Home visitation by a Resource Mother - a mother who has a child with PKU herself, is familiar with the diet and has been trained to provide assistance to women on the diet.

**Monthly throughout pregnancy:**

Nutrient analysis of dietary intake

Each Trimester:\*

(\*this is the minimum number of clinic visits; many clinic protocols include more frequent visits)

Metabolic Clinic Visit

Assessment of Nutrient Intake

Laboratory Assessments (same as when diet is initiated)

Obstetrician visits:

The number of visits is determined by the obstetrician- usually once per month until the last month of pregnancy, and then once per week.

Ultrasounds:

Two ultrasounds are recommended - one at about 6 weeks to determine how far along the pregnancy is, and the second between 18-20 weeks when the heart and other organs can be visualized.

**Other services:**

Referrals to community health and nursing programs will be made as needed.

**Formula and Low Protein Food:**

Each state and clinic has its own method for coverage of formula and low protein food. Emergency funds are available, if all other means of coverage have been exhausted.

**Birth and After:**

Newborn Pediatric Exam  
Referral to Early Intervention  
Home Visit by Resource Mother  
Developmental Testing at age 1 year

KEY WORDS

Maternal PKU, phenylketonuria, home visitation,  
PROJECT IDENTIFICATION

Project Title: Maternal PKU Resource Mothers Program: A Clinical Trial

Project Number: IR40MC00162

Project Director: Susan Waisbren, PhD

Grantee Organization: Children's Hospital Boston

Address: Children's Hospital, IC Smith Building, 300 Longwood Avenue, Boston, MA  
02115

Phone Number: 617-355-4686 or 617-355-7346

Email address:

Home Page:

Project Period: 8/1/1999 - 8/31/2003

**Total Amount of Grant Awarded: \$263,318**ABSTRACT OF FINAL REPORT

PURPOSE:

Women with phenylketonuria (PKU) are at risk for bearing children with congenital heart defects, microcephaly, mental retardation and low birth weight which are due to the teratogenic effects of elevated maternal blood phenylalanine on the developing fetus. The risk to offspring in maternal PKU is related to the mother's degree of metabolic control before and during pregnancy. Currently women with PKU are advised to maintain a phenylalanine-restricted diet throughout life. However, many women with PKU of childbearing age fail to achieve the recommended degree of blood phenylalanine control (2-6 mg/dL; 120 - 360  $\mu$ mol/L). Those who discontinued the diet in childhood are at the highest risk. Only five percent of women with PKU in a large maternal PKU collaborative study had blood levels within this recommended range from conception

throughout pregnancy.

The Resource Mothers Program was initiated to provide social support and enhance positive attitudes in women with PKU who were pregnant or planning pregnancy. Resource Mothers have children with PKU and are familiar with the stresses and challenges of the diet. A Resource Mother is trained to visit the homes of the women with PKU to offer support and technical assistance in adhering to medical recommendations.

#### GOALS AND OBJECTIVES

The primary goal of this project was to assess the value of the Resource Mothers Program in helping women with PKU attain metabolic control prior to and throughout pregnancy. In addition, this project sought to provide outreach before pregnancy to all adolescent girls and young women tracked by the metabolic centers and to all families after a baby was born.

#### METHODOLOGY

The study was a randomized controlled clinical trial. Subjects were randomly assigned to the group receiving the services of a Resource Mother or to a control group receiving the same treatment plan without a Resource Mother, stratified by clinic and whether or not the woman initiated treatment prior to pregnancy.

Children's Hospital Boston coordinated this study which included eight contributing clinics throughout the United States. During the course of the study 30 Resource Mothers and 8 coordinators received training about PKU, maternal PKU, nutrition, pregnancy, psychosocial issues, and home visitation. Coordinators also received training in supervision of Resource Mothers and data collection methods.

Women with PKU who were planning a pregnancy or came to clinical attention already pregnant were enrolled. The *control group* received the same treatment as the *experimental group* except for the services of a Resource Mother according to a Maternal PKU Treatment Plan

Outreach and follow-up were provided to adolescent females with PKU. Copies of a brochure describing PKU and maternal PKU were distributed to the women and to their schools and medical homes. The Department of Public Health in Massachusetts listed Maternal PKU as a risk factor on the confidential section of the Birth Certificates. This triggers follow-up from the Department of Public Health and automatically qualifies the child for Early Intervention. Care providers were encouraged to refer all offspring from late or inadequately treated pregnancies to Early Intervention.

Data collected included information on pregnancy and adherence to the maternal PKU protocol. Psychosocial questionnaires measured knowledge of maternal PKU, self-esteem, locus of control, and stress at 6 and 32 weeks gestation. Offspring outcome was measured at birth and at one year of age.

## RESULTS

Fifty women were enrolled in the study, and accounted for 44 pregnancies which resulted in 28 live births, and 6 spontaneous abortions. Ten women are currently pregnant and another 6 have not become pregnant. Fifty-six percent of enrolled women began the diet prior to becoming pregnant. Fifty three percent of women in the Resource Mother group were in metabolic control by 10 weeks gestation as compared to 39% in the control group. In addition, women who began diet after pregnancy and had a Resource Mother attained metabolic control earlier (median gestational age of 26 weeks in the RM group vs. never in the control group). There was no difference in birth measurement Z scores of offspring born to women in the Resource Mothers group compared to controls. Women in the Resource Mothers group had a more positive attitude toward the diet at the end of pregnancy, but few women in either group remained on diet after delivery.

## PUBLICATIONS/PRODUCTS

A guide for community health care providers, PKU Primer, was developed as part of this project. A website, including the Resource Mother's Training Guide, an

interactive Maternal PKU Knowledge Test, and a description of the Resource Mothers Program was also designed and implemented. It is in the Patients/Parents section of the website for the New England Consortium of Metabolic Programs:

[www.childrenshospital.org/newenglandconsortium](http://www.childrenshospital.org/newenglandconsortium)

#### DISSEMINATION/UTILIZATION OF RESULTS

Resource Mothers programs are being developed in other parts of the country. Experienced Resource Mothers travel to assist with the training. Numerous presentations are planned and a manuscript has been submitted for publication.

#### FUTURE PLANS/FOLLOW-UP

The study has one more year of support from NICHD. Thereafter, it is hoped that Parent Organizations will provide funds to continue the program.

#### TYPE/AMOUNT OF SUPPORT AND RESOURCES NEEDED TO REPLICATE

The costs of training Resource Mothers includes funds for travel by the trainers. Materials are now available on the web at no cost. Operating costs, to provide stipends and travel funds for Resource Mothers, are about \$1,000 per pregnancy. Supervision would need to be provided by the clinical nutritionist or physician following the patient.