MATERNAL AND INFANT IRON STATUS AND FIRST YEAR ILLNESS

BY

SARAH E. DOUGLAS

Submitted to the graduate degree program in Dietetics and Nutrition and the Graduate Faculty of the University of Kansas in partial fulfillment of the requirements for the degree of Master of Science.

_____

Susan E. Carlson, PhD
Chairperson

_____

Peter L. Beyer, MS, RD, LD

_____

Linda Griffith, PhD, RD, CNSC

Date Defended: April 13, 2011

The Thesis Committee for SARAH E. DOUGLAS certifies
that this is the approved version of the following thesis:

MATERNAL AND INFANT IRON STATUS AND FIRST YEAR ILLNESS

_____

Susan E. Carlson, PhD
Chairperson

Date Approved: April 25, 2011

Abstract

The primary research aims were to understand the relationship between maternal postpartum body iron and birth and 4-month infant body iron and to determine if maternal or newborn iron status was a predictor of first year illness. Subjects were 199 pregnant women and their infants. Subjects were a convenience sample from a phase III randomized controlled trial that studied docosahexanoic acid during pregnancy. Medical records and adverse events from parent reports provided incidence of first year illnesses. Blood was obtained for the primary study and analyzed for iron values used in the secondary analysis. Maternal iron status was determined by 28-week hemoglobin, postpartum plasma ferritin, and postpartum plasma transferrin receptor; and infant iron status was determined by plasma transferrin receptor and plasma ferritin from cord blood and 4-month blood. Maternal postpartum body iron was not correlated with neonatal body iron from cord blood or infant blood at 4-months. Maternal postpartum plasma ferritin was inversely correlated with infant body iron at 4-months ($r=-.229$, $p=.029$). Newborn body iron correlated with 4-month body iron ($r=.240$, $p=.047$). We found a small but significant inverse relationship between maternal iron status at delivery and infant iron status at 4-months. We did not find a significant relationship between maternal or infant iron status and incidence of first year illness.

Acknowledgements

I want to thank my research advisor, Dr. Susan Carlson. Dr. Carlson provided direction, knowledge, and countless hours of instruction throughout my thesis. It has been an honor and an inspiration to work with Dr. Carlson.

I would also like to thank Dr. Linda Griffith and Mr. Pete Beyer for serving as thesis committee members. Their encouragement, advice, and wisdom was appreciated.

I offer my sincere thanks to Jocelynn Thodosoff and Elizabeth Kerling for answering my countless questions, being mentors, and providing support throughout this process.

Dr. David Kingsley, Jill Shaddy and Susan Sholtz have offered generous support in the statistical aspect of this thesis. This thesis would not be possible without their help.

Table of Contents

In-Text Tables:

Abbreviations

KUMC: Kansas University Medical Center

SD: Standard deviation

BF: Breastfed

EENT: Eyes, Ears, Nose, and Throat

RESP: Respiratory

GI: Gastrointestinal

Total: Total number

OM: Otitis Media

URI: Upper Respiratory Infection

MBI PP: Maternal body iron postpartum

TfR: Soluble transferrin receptor

Hgb: Hemoglobin

F: Ferritin

Chapter 1
Introduction

Iron is a primary component of the body's immune system (1). The risk of infection increases when iron deficiency anemia is present (2, 3). Pregnant women and children are at the highest risk for iron deficiency anemia and consequently impaired immunity (4). Iron losses from menses can result in low iron stores in women of reproductive age and the iron needs of the growing fetus during pregnancy can increase these deficits (5). The sole source of neonatal iron during pregnancy is maternal iron (6). The placenta carries nutrients to the fetus (7). The role maternal iron plays in the development of neonatal iron stores remains inconclusive in existing literature.

Both high and low maternal iron states have been associated with adverse outcomes for the newborn. Serum ferritin >41ng/mL during the 3rd trimester was associated with a preterm or very preterm delivery (8). Zhou et al. (9) found that hemoglobin >130g/L in the first trimester posed a risk of low infant birth weight and preterm delivery. However, Scalon et al. (10) did not find a relationship between preterm delivery and high hemoglobin in the 1st or 2nd trimester.

In an observational study, to investigate the association between maternal iron deficiency anemia and infant iron status at 9 months of age, Savoie and Rioux (11) found a positive correlation between the mother's hemoglobin ($p=0.02$) and hematocrit ($p=0.04$) during the 3rd trimester and the infant's hemoglobin and hematocrit at 9 months of age. They also found that infants born to women with iron deficiency anemia were more likely to be diagnosed with iron-deficiency anemia ($p=0.055$). Zhou, Gibson, and Makrides (12) studied the relationship of maternal and neonatal iron status with maternal iron supplementation during pregnancy. They found no effect of maternal iron supplementation

on hemoglobin or serum ferritin concentrations in infants, however, maternal hemoglobin at delivery and child hemoglobin at 4 years of age were related ($p \leq .03$) (12). The positive relationship between maternal and neonatal hemoglobin in Zhou, Gibson, and Makrides (12) concurs with results of Savoie and Rioux's (11) observational study.

Studies of the relationship between iron and infant illness could further determine the importance of maternal or newborn iron status. Again, the literature is not consistent on whether iron supplementation in infancy reduces the number of infections in the first year of life. Only two studies have provided iron to newborn infants. Both occurred in populations of infants at risk for illness due to poverty, and only one found supplementation reduced hospitalization for illness. Cantwell studied illness rates in Maori infants, New Zealand natives, treated with injections totaling 250 mg of iron dextran (n=144) or no injection (n=94) in the infants first week of life. In the first two years of life 42.4 of 100 children in the control group were hospitalized for infections compared to 31.9 hospitalizations in the treatment group (13). Damodaran et al. (14) supplemented infants (n=383) from two Indian villages with 100 ug folate and 20 mg elemental iron per day for the first year of life or a placebo. They did not find a significant difference in the frequency or duration of respiratory or enteric infections after 6 or 12 months of supplementation.

Statement of Purpose

The purpose of this secondary analysis is a) to compare maternal postpartum iron stores, plasma transferrin receptor and plasma ferritin, with infant iron status at birth and 4-months of age and b) to compare maternal and newborn iron status at birth to the incidence of infant illness in the first year of life.

Primary Research Questions

1) Are maternal postpartum body iron and infant body iron at birth and 4-months of age related?

2) Is iron status of the mother or newborn related to infant illness in the first year of life?

Chapter 2
Literature Review

Introduction

Iron is a primary constituent for the body's immune system, cell growth, and cell differentiation (1). Neutrophils, a type of white blood cell, determine the ability of phagocytes to kill bacteria (15). Iron deficiency anemia impairs neutrophil activity (16). Neutrophils exhibit an oxidative burst after ingestion of bacteria that is dependent upon an iron-containing b cytochrome (15). Iron is a fundamental element of the enzyme myeloperoxidase, which is responsible for producing oxygen intermediates to kill pathogens (16). Cell-mediated immunity relies on thymus-derived lymphocytes (T-cells) (15) and studies (17, 18) reveal a reduced number of T-cells in iron-deficient pregnant women and children. Ribonucelotide reductase, an iron-containing enzyme, could be potentially responsible for the reduced number of T-cells in the presence of iron deficiency (15). Antigen-mediated immunity is normal in iron-deficient individuals (19, 20).

In this paper, my purpose is to review the role of iron as a predictor of illness rates in infants. There is controversy surrounding iron supplementation during pregnancy. Some clinical studies have investigated the relationship between maternal and neonatal iron status after maternal iron supplementation during pregnancy or by comparing through maternal iron status before or after birth to the incidence of neonatal anemia. Potential factors that can influence iron status such as infant feeding, maternal body mass index, gestational days smoked, gestational age, and maternal ethnicity will be discussed.

Iron is the most common micronutrient deficiency in the world (4). Anemia affects approximately 30% of the population, with the majority of cases being characterized as iron deficiency anemia. Approximately 18% of women in industrialized countries have iron

deficiency anemia (4, 21). Children and pregnant women are at the highest risk for iron deficiency anemia (4). Iron losses from menses can result in low iron stores in women of reproductive age. The needs of the growing fetus during pregnancy can contribute to these deficits (5). Low birth weight, premature birth, exposure to lead, exclusive breastfeeding past 4 months of age without iron supplementation, and inadequate amounts of iron-fortified foods after weaning, particularly to whole cows' milk increase the risk of iron deficiency anemia in children (22). Iron deficiency anemia is a risk factor for poor cognitive and psychomotor development (23-25).

Iron as a Predictor of Illness

Iron deficiency anemia has been associated with impaired immunity and increased susceptibility to infections (2, 3). In a study by Damodaran et al. (14), 383 preschool children in two Indian villages, Anajpur and Masjidpur, were given either a placebo or a supplement of 20 mg elemental iron and 100 ug folate per day during the first year of life. Anemia was diagnosed in 11% of the treatment group compared to 26% of the control group after 12 months of treatment. The difference in anemia between the control and treatment groups was significant ($p<0.02$). The mean hemoglobin was higher in the treatment group than in the control group in the village of Anajpur at both 6 months of age (12.1 versus 11.6; $p<0.05$) and 12 months of age (12.4 versus 11.9; $p<0.05$). The Masjidpur village also showed a significant difference in the mean hemoglobin of treatment and control groups at 6 (11.3 versus 10.5; $p<0.05$) and 12 (12.5 versus 11.4; $p<0.05$) months of age; however, the study found no difference in the frequency or duration of respiratory or enteric infections between infants who were supplemented and infants who were not.

Cantwell (13) studied 238 Maori infants treated with injections totaling 250 mg iron dextran or not in the infants first week of life. According to the World Health Organization's definition of anemia, 75-80% of Maori infants are anemic between 6-11 months of age. Per 100 cases in the control group 42.4 were hospitalized for infections within the first two years of life compared to 31.9 hospitalizations in the treatment group. The number of hospitalizations for infections was 34% higher in the control group. The difference in hospitalizations between the control and treatment groups was statistically significant. In further analysis, the author eliminated wheezy bronchitis from the list of infections due to allergic origin and relationship to family history. He stated there was a difference in the number of hospitalizations; however, he did not provide a p-value for the difference in control and treatment groups. Maori infants were rarely fed iron supplemented formulas during the clinical trial. These two studies [Damodaran et al. (14) and Cantwell (13)] provide different evidence for the effects of post-natal supplementation of iron on infant and child illness, however, they differed in the way supplementation was given and were two different populations.

Iron Supplementation during Pregnancy

Eighty percent of the fetus' iron accumulation occurs during the third trimester (22). Birth hemoglobin serves as an iron source for the first 4-6 months of life in breastfed infants (26). Term infants are typically born with a high hemoglobin concentration.

The National Health and Nutrition Examination Survey (NHANES) in 1988-94 (27) found that 72% of pregnant women used iron supplements and that the mean consumption of these supplements exceeded the tolerable upper limit of 45mg/d by 13mg/d. Fewer than 15% of women of reproductive age taking iron supplements were being treated for anemia.

The use of iron supplements without diagnosis of iron deficiency anemia is controversial and may increase the risk of adverse pregnancy outcomes (28). Iron supplementation in pregnancy can elevate hemoglobin, hematocrit, and serum ferritin (29). During the third trimester, serum ferritin levels >41ng/mL were associated with increased risk of a preterm and very preterm delivery (8). Hemoglobin >130g/L in the first trimester poses risk of preterm delivery and low infant birth weight (9). On the other hand, Scalon et al. (10) did not find that high hemoglobin during the 1st or 2nd trimester was associated with increased risk of preterm delivery. Allen (30) attributes iron deficiency anemia to hypoxia, oxidative stress, and infection after preterm delivery.

Methods to Evaluate Iron Status

Iron deficiency cannot be established by a single laboratory measurement. (22). Hemoglobin lacks sensitivity and can be affected by chronic infections and genetic disorders (31). Thus, serum transferrin receptor, reticulocyte hemoglobin, or serum ferritin in combination with hemoglobin are used to establish iron deficiency (22). Serum ferritin lab values can be altered by inflammation, but C-reactive protein values can confirm or exclude the possibility of inflammation. Serum transferrin receptor and reticulocyte hemoglobin are not affected by inflammation, however, serum transferrin receptor values have not been standardized in infants and children (32).

Cook, Flowers, and Skikne (32) proposed another measure of iron status, body iron. Body iron is the ratio of serum transferrin receptor (TfR) to serum ferritin (F). The total body iron equation is: body iron (mg/kg) = -[log(TfR/F ratio) – 2.8229]/0.1207. A positive body iron concentration signifies iron storage while a negative value characterizes a depletion of iron stores. The body iron calculation may be applied to all blood samples

analyzed for TfR and F, however, studies in infants have not validated the method. In young children and pregnant women repeated laboratory tests indicate the validity of the body iron value. The total body iron equation does have limitations. Serum ferritin lab values can be altered based on inflammation or liver disease and serum transferrin receptor values are not comparable for all commercial enzyme-linked immunosorbent assays.

Relationship Between Maternal and Neonatal Iron Status

The relationship between maternal and neonatal iron status continues to be investigated and remains controversial. Two clinical trials evaluated the relationship between maternal and neonatal iron status after maternal iron supplementation during pregnancy. Zhou, Gibson, and Makrides (12) found no significant effect on hemoglobin or serum ferritin laboratory values in children born to women who took an iron supplement of 20 mg/day during pregnancy. A total of 430 non-anemic pregnant women were randomized to receive the supplement or a placebo from 20 weeks gestation until birth. Hemoglobin values at 6 months and 4 years of age were positively correlated and statistically significant for the children at ($p<0.01$). Maternal hemoglobin at delivery was positively related to child hemoglobin at 4 years of age ($p=0.03$). There were no other statistically significant relationships in the trial. Preziosi et al. (33) did find higher serum ferritin in infants born to iron-supplemented mothers. They randomized 197 pregnant women in Niger, in Western Africa, to receive 100 mg per day of elemental iron or a placebo from enrollment to birth. Maternal blood samples were collected at 6 months gestation, 28 weeks $\pm$ 21 days gestation, at labor, and again at 3 and 6 months postpartum. Neonatal cord blood and infant blood at 3 and 6 months of age were obtained. Iron status was evaluated based on hemoglobin, mean corpuscular volume, serum iron, transferrin

saturation, erythrocyte protoporphyrin, and serum ferritin laboratory values. Differences between cord blood values in the placebo and treatment groups were not statistically significant. Serum ferritin was significantly higher in infants born to iron-supplemented mothers. At 3 months (80±53 versus 99±63; $p<0.05$) and 6 months of age (15±20 versus 26±27; $p<0.05$). The results of Preziosi et al. (33) suggest that infants born to iron supplemented mothers have better iron stores even though this is not apparent in iron measures taken at birth.

The sole source of neonatal iron during pregnancy is maternal iron (6). Several studies have investigated the relationship between maternal and neonatal iron status. Hokama et al. (6) divided a small group of women (n=53) into three groups after delivery: a) those with iron deficiency anemia defined as hemoglobin ≤11.0g/dl and serum ferritin ≤7.1ng/ml, b) those without iron deficiency but with low iron stores defined as hemoglobin >11.0g/dl and serum ferritin ≤7.1ng/dl, and c) those who were not anemic with good iron stores defined as hemoglobin >11.0g/dl and serum ferritin >7.1ng/dl. The researchers did not find significant differences in the mean values of infant‘s cord blood hemoglobin, serum iron, or total iron binding capacity between groups, however, the mean values of serum ferritin differed among the three groups ($p<0.10$). The lowest mean serum ferritin values were observed in infants born to iron deficient mothers.

Savoie and Rioux (11) studied medical records of 75 mothers and their neonates. The mothers were divided into two groups (anemic and non-anemic) based on iron status in the 3rd trimester. Maternal anemia was defined as hemoglobin <110g/L and hematocrit <33%. Infant anemia was defined as hemoglobin <110g/L and infant iron-deficiency anemia was defined as hemoglobin <110g/L and serum ferritin <10ug/L. The researchers

found a positive correlation between the mother's hemoglobin and hematocrit during the 3rd trimester and measures in the infants hemoglobin ($p=0.02$, $r^2=0.10$) and hematocrit ($p=0.04$, $r^2=0.08$). at 9 months of age. They also found that infants born to anemic mothers were more likely to be diagnosed with iron-deficiency anemia ($p=0.055$). At 9 months of age, there was no difference in the mean values of hemoglobin, hematocrit, serum ferritin, or mean corpuscular volume between infants born to non-anemic or anemic mothers at 9 months of age.

The placenta acts as the nutrient transporter between the mother and fetus (7). The placenta transfers iron to the fetus across the syncytiotrophoblast against a concentration gradient. Young et al. (7) investigated the possibility of this mechanism's ability to respond to iron deficiency in the fetus. The researchers compared placental TfR production in ninety-two healthy pregnant adolescents and their neonates. Placental transferrin receptor increases in iron deficiency, and is associated with iron demands (7). Subjects were supplemented with 27 mg of iron for an undisclosed period of time. Placental tissue was analyzed for TfR concentration as were cord blood and maternal blood draw at 21-25 weeks gestation and delivery. Infants with serum ferritin concentration ≤34ug/L had elevated placental TfR compared to infants with serum ferritin concentrations >34ug/L ($p<0.01$). Placental TfR concentration was inversely associated with total body iron at delivery ($p<0.02$).

Predictors of Iron Status

Hay et al. (34) studied 364 mothers and their infants to determine predictors of serum ferritin and serum TfR, a representative of iron storage and needs. Maternal body mass index (BMI) measured in the first-trimester was not correlated with maternal serum

ferritin, however, cord blood serum TfR was positively related to BMI (p=0.20, P=0.001). Gestational age was positively correlated with both cord blood serum ferritin (p=0.13, P=0.016) and cord blood serum TfR (p=0.24,P<0.001).

Pregnant women were categorized as smokers or nonsmokers (34). Occasional smokers were included with nonsmokers for statistical analysis. There was not a significant difference in cord serum TfR based on smoking status, but cord serum ferritin values were lower in infants born to smoking mothers (p=0.025), evidence of lower iron status.

Adebisi and Strayhorn (35) used data from the US 1995-2000 natality files to determine if maternal ethnicity and the occurrence of anemia during pregnancy were related. The natality data was collected by the National Center for Health Statistics under the direction of the Centers for Disease Control and Prevention. The study found that non-Hispanic black mothers were twice as likely (35/1000) as non-Hispanic white mothers (18/1000) to be anemic during pregnancy. Adebisi and Strayhorn did not specify anemia as iron deficiency anemia in their study.

Summary

Iron deficiency is the most prevalent nutritional deficiency in the world. It can hinder productivity, cognitive and psychomotor development and iron deficiency imposes health consequences that are particularly devastating in the developing world where deficiency tends to be very severe (4).

In two clinical trials, neonatal serum ferritin values were influenced by whether the neonate was born to an iron deficient mother or a mother with normal iron stores (6, 33). In each of these studies, mean values of serum ferritin differed significantly among infants born to iron deficient mothers, mothers with low iron stores, and mothers with adequate

iron stores. Serum ferritin values were also found to be significantly higher in infants born to iron-supplemented mothers.

Infants born to anemic mothers appear to have lower iron status and may be more likely to have a diagnosis of iron-deficiency anemia based on a positive correlation between the mother's hemoglobin and hematocrit during the 3rd trimester and the infants at 9 months of age (11).

One study showed post-natal iron supplementation in infants decreased the number of hospitalizations in the first two years of life (13). Another study investigating the effects of post-natal iron supplementation showed there was no difference in the incidence of enteric or respiratory infections in the first year of life (14). The two study populations and the way the supplement was given differed.

No published reports of body iron to assess iron status in neonates exist to my knowledge. As with other age groups, body iron may be a more informative measurement of iron status than serum ferritin alone to assess iron status.

Chapter 3
Methods

Subjects

Subjects were a convenience sample from a phase III randomized control trial of docosahexaenoic acid (DHA) supplementation during pregnancy titled "The Effect of DHA on Pregnancy Outcome". The present proposal was to investigate the relationship between maternal and infant body iron and infant illness.

The primary investigation recruited 350 pregnant women between 8 and 20 weeks gestation. The subjects were recruited from local Kansas City hospitals including Kansas University Medical Center, St. Luke's Hospital, and Truman Medical Center; and by word of mouth, and website advertising (broadcasts to KUMC faculty and staff). The inclusion criteria were: ages 16-35.99 years of age, willing to consume three capsules daily, BMI <40, planned to deliver the infant at the study center hospital, availability by telephone, and absence of illnesses that could adversely influence infant growth and development. For example, women were excluded with some chronic illnesses such as high blood pressure (systolic ≥140mm Hg), diabetes, or morbid obesity. Women were also excluded if they were unable to provide consent in English or had a multiple birth pregnancy.

Infants of all study subjects who had reached one year of age before December 2010 were included in the present analysis if they also had medical records and blood samples. One eligible subject was excluded due to sudden infant death syndrome and another was excluded due to diagnosis of cystic fibrosis. There were 199 mother-baby pairs available for analysis.

The primary study design was a randomized, placebo-controlled phase III clinical trial (36). The intervention was consumption of three capsules of either a corn/soy oil based placebo or an algal oil to provide 600mg/day of docosahexaenoic acid. The study

primary outcomes were gestation duration, visual and cognitive development, and maternal red blood cell fatty acids. This clinical trial is registered at clinicaltrials.gov as NCT00266825.

The study setting was the University of Kansas Maternal and Child Nutrition Development Laboratory in Kansas City, Kansas (36).

The Human Subject Committee, Institutional Review Board, at the University of Kansas Medical Center, St. Luke's Hospital of Kansas City, Missouri, and the University of Missouri, Kansas City approved the primary study (36). The Kansas University Medical Center Human Subjects Committee (HSC) approval number is 10186. The privacy board at Truman Medical Center and St. Luke's hospital approved the primary study. The secondary analysis for the present proposal utilized data collected under an approved amendment by the KUMC HSC and served as the informed consent (see **Appendix A**).

Adverse Events

The incidence of illness was recorded based on medical records and parent report of events at routine (6 weeks, 4, 6, 9, 10, and 12 months) infant clinic visits. Adverse events were recorded and coded into a Microsoft Access database (Microsoft Windows 2007, Seattle, Washington, USA) modified from one used in a previous study (36) (also **see Appendix B, C**). Medical records were requested immediately after each child's first birthday (see **Appendix D**). All accounts of infant illness were retrieved from the database for subjects until one year of age. Only subjects who reached one year of age by December 2010, were included to allow time to receive and code the medical records prior to data analysis (see **Appendix E**).

Body Iron Assessment

Hematologic values were obtained from medical records to be used in data analysis and calculations of iron status, as described below.

The calculation of body iron in maternal and neonatal blood was used to assess the relationship between the two at delivery. The total body iron equation is: body iron (mg/kg) = -[log(TfR/F ratio) – 2.8229]/0.1207. The TfR/F ratio is the ratio of serum transferrin receptor to serum ferritin (32). Body iron was determined on maternal postpartum blood and neonatal cord blood. Analyses for serum ferritin and serum TfR values were completed by Elizabeth Kerling, MS, RD. Body iron (mg/kg) has the advantage that only two specific measures of iron status are needed to determine iron status, however, as noted earlier, body iron has not been validated for use with infants. The present study will make such an evaluation.

Statistical Analysis

Maternal body iron and infant body iron were compared by Pearson's correlation coefficient. Correlations between maternal plasma ferritin, 28-week hemoglobin, maternal plasma TfR, cord blood and 4 month plasma ferritin and plasma TfR, gestational days smoked, ethnicity, iron supplement use during pregnancy, infant feeding (human milk vs. formula), and maternal body mass index were analyzed to determine other possible relationships.

Linear regressions between the dependent variable, maternal postpartum body iron, and predictor variables, neonatal body iron from cord blood and 4-month neonatal body iron were completed.

Odds-ratios were used to determine the relative difference in incidence of infant illness among mothers and infants divided into four quartiles based on their iron values. Maternal body iron values for the four quartiles were: Quartile 1 (-6.8-2.3 mg/kg), Quartile 2 (2.4-5.0 mg/kg), Quartile 3 (5.1-7.44 mg/kg), Quartile 4 (7.442-14.9 mg/kg). Maternal hemoglobin from 28-week gestation values were: Quartile 1 (8.4-11g/L), Quartile 2 (11-11.5g/L), Quartile 3 (11.6-12.1-g/L), Quartile 4 (12.1-14g/L).

Statistical analysis was performed using Predictive Analysis Software 18.0 (SPSS Inc, Chicago, IL, USA). Statistical significance was defined at $p \leq 0.05$.

Chapter 4
Results

Sample Characteristics

My analysis included 199 pregnant women and their infants. The study population was 63.3% Caucasian, 30.2% African American, 5% Hispanic and 1.5% other. Twenty-one percent of the samples' mothers took iron supplements, in addition to their prenatal vitamins, which contained a lower concentration of iron during pregnancy and 78.5% did not. The mean gestational age at delivery was 39.41 ± 1.46 weeks. The mean measured body mass index was 27.13 ± 5.24 kg/m^2. Twenty percent of the sample breastfed for less than 6 days, 14.5% breastfed for 7-42 days, 10% breastfed for 43-120 days, and 37% breastfed for greater than or equal to 121 days. Sample characteristics are shown in **Table 1**.

Table 1. Sample Characteristics

Maternal Ethnicity n=199	Caucasian: 63.3% African American: 30.2% Hispanic: 5% Other: 1.5%
Iron Supplement Use during Pregnancy n=199	No: 78.5% Yes: 21%
Gestational Age n=199	Mean ± SD: 39.41 ± 1.46 weeks
Body Mass Index n=165	Mean ± SD: 27.13 ± 5.24 kg/m^2
Infant Feeding n=163	0-6 days BF: 20% 7-42 days BF: 14.5% 43-120 days BF: 10% ≥121 days BF: 37%

Iron status indicators are shown in **Table 2**.

Table 2. Iron Status Indicators

	Mean Body Iron (mg/kg)	TfR (mg/dL)	Ferritin (ug/L)	Hgb (g/dL)
Neonates Cord Blood	8.41 ± 2.74 (0-15) n=130	8.852 ± 2.93 (.85-19.73) n=132	154.49 ± 99.05 (22-650) n=132	
Infant Blood at 4-months of age	6.30 ± 2.72 (-4-12) n=96	6.603 ± 1.54 (3.19-12.83) n=98	67.9 ± 47.7 (6.78-257.7) n=96	
Mother at Delivery	4.55 ± 3.95 (-7-15) n=194	5.11 ± 2.7 (1.22-19.52) n=194	32.98 ± 27.34 (4-208) n=194	
Mother at 28 weeks Gestation				11.53 ± 933 (8-14) n=187

Relationship between Maternal and Infant Body Iron

The relationship between maternal postpartum body iron and birth and 4-month infant body iron is shown in **Table 3**. Maternal postpartum plasma ferritin was negatively correlated with 4-month neonatal body iron ($r=-.229$, $p=.029$). The correlation suggests birth iron may not be the best indicator of iron status, and suggests the fetus' iron may get redirected some conditions. No other significant correlations were observed between variables.

Table 3. Correlation between Maternal Postpartum Body Iron and Infant Body Iron

	Maternal Body Iron	Maternal Transferrin Receptor	Maternal Plasma Ferritin
Neonatal Body Iron	r=.056 p=.528 n=130	r=-.070 p=.428 n=130	r=-.068 p=.440 n=130
Body Iron at 4 months of age	r=-.137 p=.196 n=91	r=-.065 p=.541 n=91	r=-.229 p=.029* n=91
Neonatal Plasma Ferritin	r=.102 p=.245 n=132	r=-.019 p=.825 n=132	r=.048 p=.582 n=132
Neonatal Transferrin Receptor	r=.005 p=.950 n=132	r=.097 p=.270 n=132	r=.086 p=.327 n=132
Plasma Ferritin at 4 months of age	r=-.123 p=.246 n=91	r=-.073 p=.490 n=91	r=-.195 p=.064 n=91

Transferrin Receptor at 4 months of age	r=.076 p=.458 n=97	r=.027 p=.794 n=97	r=-.010 p=.922 n=97

*p<0.05 (two-tailed)

Linear regression did not show a significant association between maternal postpartum body iron and birth and 4-month infant body iron. Maternal postpartum body iron accounted for only 0.3% of the variance in neonatal body iron from cord blood (R^2=.003). Maternal postpartum body iron accounted for only 2% of the variance in 4-month infant body iron, was (R^2=.019). Neither suggests any relationship. However, maternal ferritin was related to 4-month infant body iron.

Iron and Incidence of Infant Illness

The relationship between iron status of the mother and infant illness in the first year of life is shown in **Table 4**.

Table 4. Correlation between Maternal Iron Status and Incidence of Infant Illness

	EENT	RESP	GI	TOTAL	OM	URI
Maternal Body Iron n=194	r= .110 p= .126	r=-.018 p=.798	r=-.005 p=.942	r=.040 p=.583	r=.109 p=.129	r=-.089 p=.215
Maternal Transferrin Receptor n=194	r=-.138 p=.054	r=-.051 p=.483	r=.050 p=.488	r=-.074 p=.304	r=-.115 p=.112	r=.016 p=.820
Maternal Plasma Ferritin n=194	r=.083 p=.249	r=-.013 p=.860	r=.091 p=.208	r=.057 p=.428	r=.034 p=.638	r=-.102 p=.159
Maternal Hgb at 28 weeks Gestation n=187	r=.096 p=.191	r=.017 p=.815	r=-.118 p=.107	r=.019 p=.796	r=.123 p=.093	r=.029 p=.694

*p<0.05 (two-tailed)

Maternal transferrin receptor and occurrence of eyes, ears, nose, and throat illnesses were inversely correlated at (r=-.138, p=.054) (see **Table 4**).

The relationship between iron status of the infant and infant illness in the first year of life is shown in **Table 5**. No significant correlation was found between infant illness in the first year of life and infant iron status. Non significant trends between neonatal plasma

ferritin (r=-.144, p=.099), neonatal plasma transferrin receptor (r=-.158, p=.070) and occurrence of eyes, ears, nose, and throat illness were inversely correlated. The non significant trends suggest an inverse relationship between EENT illness and poorer iron status.

Table 5. Correlation between Neonatal Iron Status and Incidence of Infant Illness

	EENT	RESP	GI	TOTAL	OM	URI
Neonatal Body Iron n=130	r= .015 p=.870	r=.066 p=.455	r=-.132 p=.135	r=-.002 p=.986	r=.095 p=.281	r=-.008 p=.929
Body Iron at 4-months of age n=96	r=.084 p=.414	r=.102 p=.321	r=.060 p=.560	r=.109 p=.289	r=.005 p=.965	r=.031 p=.767
Neonatal Plasma Ferritin n=132	r=-.144 p=.099**	r=-.032 p=.717	r=-.123 p=.161	r=-.116 p=.186	r=-.047 p=.595	r=-.092 p=.296
Neonatal Transferrin Receptor n=132	r=-.158 p=.070**	r=-.103 p=.240	r=.022 p=.802	r=-.113 p=.197	r=-.146 p=.095**	r=.018 p=.834
Plasma Ferritin At 4 months n=96	r=-.011 p=.916	r=.033 p=.748	r=-.064 p=.536	r=-.010 p=.926	r=-.032 p=.755	r=-.036 p=.727
TfR at 4 months	r=-.048 p=.636	r=-.051 p=.621	r=-.080 p=.431	r=-.072 p=.482	r=-.160 p=.117	r=-.064 p=.532

n=98						

*p<0.05 (two-tailed)

**p<0.10 (two-tailed)

Potential iron effectors including: formula feeding, maternal ethnicity, gestational days smoked, and iron supplementation during pregnancy were correlated with iron laboratory values. Days formula fed was significantly correlated with 4-month body iron (r=.313, p=.008). Maternal ethnicity (r=.229, p=.002) was correlated with hemoglobin at 28 weeks gestation and iron supplementation during pregnancy (r=-.322, p=.000) was inversely correlated with hemoglobin at 28 weeks gestation. Gestational days smoked correlated inversely with plasma ferritin from cord blood (r=-.203, p=.019).

The quartiles maternal body iron, and maternal 28-week hemoglobin, was unrelated to the incidence of EENT, RESP, or GI infant illness (see **Table 6, 7, 8**). The percentage of infants diagnosed with an EENT, RESP, or GI illness did not trend up across quartiles with poorer iron status. Quartile 1 contains infant illness data for infants whose mothers had a maternal body iron value between (-6.8-2.3 mg/kg) and 28-week hemoglobin between (8.4-11g/L). Quartile 2 maternal body iron values were between (2.4-5.0 mg/kg) and 28-week hemoglobin (11-11.5g/L). Quartile 3 maternal body iron values were between (5.1-7.44 mg/kg) and 28-week hemoglobin (11.6-12.1-g/L). Quartile 4 maternal body iron values were between (7.442-14.9 mg/kg) and 28-week hemoglobin (12.1-14g/L).

Table 6. Maternal Iron Status related to Incidence of EENT Infant Illness

	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Maternal Body Iron n=194	27/48* 56%** n=48	39/48 81% n=48	37/49 76% n=49	31/49 63% n=49
Maternal Hgb at 28 weeks Gestation n=187	24/47 51% n=47	32/47 68% n=47	36/47 77% n=47	27/46 59% n=46

*Numerator is the number of study subjects infants diagnosed with an EENT illness.
Denominator is the number of study subjects infants in each quartile (n).
**Percentage of infants with an EENT illness from that quartile.

Table 7. Maternal Iron Status related to Incidence of RESP Infant Illness

	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Maternal Body Iron n=194	33/48* 69%** n=48	37/48 77% n=48	29/49 59% n=49	30/49 61% n=49
Maternal Hgb at 28 weeks Gestation n=187	34/47 72% n=47	35/47 74% n=47	30/47 64% n=47	26/46 57% n=46

*Numerator is the number of study subjects infants diagnosed with a RESP illness.
Denominator is the number of study subjects infants in each quartile (n).
**Percentage of infants with a RESP illness from that quartile.

Table 8. Maternal Iron Status related to Incidence of GI Infant Illness

	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Maternal Body Iron (Postpartum) n=187	19/48* 40%** n=48	22/48 46% n=48	18/49 37% n=49	17/49 35% n=49
Maternal Hgb at 28 weeks Gestation n=187	25/47 53% n=47	15/47 32% n=47	19/47 40% n=47	15/46 33% n=46

*Numerator is the number of study subjects infants diagnosed with a GI illness.
Denominator is the number of study subjects infants in each quartile (n).
**Percentage of infants with a GI illness from that quartile.

Chapter 5
Discussion

My analysis did not find a significant relationship between maternal and neonatal iron status determined by the body iron equation on the incidence of first year illness. The study further showed no significant association between maternal postpartum body iron and birth and 4-month infant body iron. Damodaran et al. (14) found no difference in the frequency or duration of respiratory or enteric infections in two Indian villages of iron supplemented preschool children (n=383). These study results are similar with my analysis, however, it is important to note the study population in Damodaran et al. had a much higher risk of infection and most likely malnutrition. Although, non significant trends between neonatal serum ferritin (r=-.144, p=.099), neonatal serum transferrin receptor (r=-.158, p=.070) and occurrence of eyes, ears, nose, and throat illness were found and inversely correlated. The non significant trends suggest an inverse relationship between EENT illness and poorer iron status. Although, there was no significant association between maternal and infant body iron at birth it is important to note maternal postpartum serum ferritin was negatively correlated with 4-month neonatal body iron (r=-.229, p=.029) suggesting a possible redirection in iron transfer to the fetus which could occur under some circumstances (5). Neonatal body iron from cord blood and 4-month neonatal body iron were positively correlated and statistically significant (r=.240, p=.047). The finding is small, but a significant relationship between maternal iron status at delivery and infant iron status at 4-months of age. Additionally, the finding is similar to results of Zhou, Gibson, and Makrides (12) regarding hemoglobin. Neonatal serum ferritin from cord blood and 4-month serum ferritin were correlated (r=.390, p=.001). These correlations demonstrate that iron status of infants at birth predicts iron status in early infancy. The correlations

suggest maternal body iron at birth and infant cord blood is not a good indicator of maternal or infant iron status but that body iron may be a good indicator.

Limitations

The total body iron equation does have limitations. Serum ferritin lab values can be altered based on inflammation or liver disease. Serum TfR values may not be comparable between or among studies because there are a variety of enzyme-linked immunosorbent assays. A limitation is the absence of C-reactive protein values, an indicator of inflammation (16). Individuals diagnosed with liver disease did not meet inclusion criteria. In young children and pregnant women repeated laboratory tests indicate the authenticity of the body iron value (16).

There was potential for human error in recording and coding medical records. One individual recorded and coded medical records and then a study coordinator checked recording and coding to reduce potential error. Medical records confirmed report of adverse events. In the event the subject was not seen at a hospital or clinic, parent report was the only source of adverse events.

The subject's parent or guardian reported clinics and hospitals visited for adverse events. If a parent or guardian does not provide a location the subject previously visited to the study team, medical records are not received from this institution. This limitation can cause misrepresentation of incidence of illness.

Subjects used for my analysis were a convenience sample from a phase III randomized control trial of docosahexaenoic acid (DHA) supplementation during pregnancy. Half of the pregnant mothers were supplemented with 600mg/d of docosahexaenoic acid or a corn/soy oil placebo. Researchers (37) have found infants

supplemented with DHA have a reduced incidence of upper respiratory infections, wheezing, asthma, and allergic diseases. The reduced number of illnesses has been shown in children up to three years of age (37). DHA in supplemented mothers may have affected the incidence of illness in their infant's first year of life.

Neonatal hemoglobin values were unavailable for study infants. Hemoglobin provides adequate iron for the first 4-6 months of life in breastfed infants (26) and could have provided an additional iron status measure. Hemoglobin could potentially better predict illness rates in the first year of life.

Subjects were not divided into groups based on ethnicity for the purpose of statistical analysis.

Future Studies

Future studies should be conducted to further examine birth iron status as a predictor of infant iron status. Future studies should focus on the potential influence of maternal serum ferritin on neonatal iron status. As previously stated, a single measurement cannot characterize iron status. Researchers may consider expanding the number of iron markers to include mean corpuscular volume, serum ferritin, serum transferrin receptor, transferrin saturation, and reticulocyte hemoglobin.

Conclusion

Although not a primary research question outcome, this secondary analysis provides evidence that iron status at birth continues to influence iron status at 4-months of age as evidenced by serum ferritin and body iron concentrations. The evidence that body iron declines through a period of infancy has been discovered in past research regarding

hemoglobin (22). Future studies expanding the length of study and the number of iron markers analyzed is essential.

Chapter 6
Summary

The purpose of this secondary analysis was to compare maternal postpartum iron stores, serum transferrin receptor and serum ferritin, to birth and 4 month infant iron status and to compare maternal and newborn iron status at birth to the incidence of infant illness in the first year of life. Maternal postpartum serum ferritin, postpartum serum transferrin receptor, 28-week hemoglobin, and neonatal serum transferrin receptor, and serum ferritin at birth and 4-months were collected in the primary study and used to establish iron status in the secondary analysis. Subjects were a convenience sample from a phase III randomized controlled trial studying docosahexanoic acid in pregnancy. Medical records and parent reported adverse events at routine clinic visits determined incidence of infant illness in the first year of life. The secondary analysis results showed no statistical significance between maternal and neonatal body iron and no significance between maternal or neonatal body iron and first year illness. However, maternal postpartum serum ferritin was significantly correlated with 4-month neonatal body iron. Neonatal body iron from cord blood and 4-month infant body iron were also positively correlated at statistical significance.

Prior research by Damodaran (14) supports the secondary analysis results stating there is no relationship between newborn or maternal iron status and the incidence of first year illness.

These results suggest iron status at birth may predict iron status in 4-month infants and maternal postpartum serum ferritin could predict iron status at 4-months of age. To conclude iron status at birth may predict long-term iron status in pediatric populations will need future research.

References

1. Beard JL. Iron biology in immune function, muscle metabolism and neuronal functioning. J Nutr 2001;131:568S-580S.

2. Chandra RK. Reduced bactericidal capacity of polymorphs in iron deficiency. Arch Dis Child 1973;48:864-866.

3. Bhaskaram C, Reddy V. Cell mediated immunity in iron- and vitamin- deficient children. Br Med J 1975;3:522-522.

4. World Health Organization. Micronutrient deficiencies. Version current. 2010. Internet: http://www.who.int/nutrition/topics/ida/en/index.html (accessed 2 October 2010).

5. Yip R. Iron. In: Bowman B, Russel RM, eds. Present knowledge in nutrition. 8th ed. Washington, DC: ILSI Press, 2001;311-18.

6. Hokama T, Takenaka S, Hirayams K, et al. Iron status of newborns born to iron deficient anemic mothers. J Trop Pediatr 1996;42(2):75-77.

7. Young, M.F., Pressman E, Foehr M.L., et al. Impact of maternal and neonatal iron status on placental transferring receptor expression in pregnant adolescents, Placenta (2010), doi:10.1016/j.placenta.2010.08.009.

8. Scholl TO. High third-trimester ferritin concentration: associations with very preterm delivery, infection, and maternal nutritional status. Obstet Gynecol 1998;92:161-166.

9. Zhou LM, Yang WW, Hua JZ, Deng CQ, Tao X, Stolzfus RJ. Relation of hemoglobin measured at different times in pregnancy to preterm birth and low birth weight in Shanghai, China. Am J Epidemiol 1998;148:998-1006.

10. Scalon KC, Yip, Schieve LA, Cogswell ME. High and low hemoglobin levels during pregnancy: differential risks for preterm birth and small for gestational age. Obstet Gynecol 2000;96:741-748.

11. Savoie N, Rioux F. Impact of maternal anemia on the infant's iron status at 9 months of age. Can J Public Health 2002;93:203-207.

12. Zhou S, Gibson R, Makrides M. Routine iron supplementation in pregnancy has no effect on iron status of children at six months and four years of age. J Pediatr 2007;151:438-40.

13. Cantwell RJ. Iron deficiency anaemia of infancy. Clin Pediatr 1972;11:443-9.

14. Damodaran M, Naidu AN, Sarma KV. Anaemia and morbidity in rural preschool children. Indian J Med Res 1979;69:448-456.

15. Dallman P. Iron deficiency and the immune response. Am J Clin Nutr 1987;46:329-334.

16. Spear AT, Sherman AR. Iron deficiency alters DMBA-induced tumor burden and natural killer cell cytotoxicity in rats. J Nutr 1992;122:46-55.

17. Grosch-Worner I, Grosse-Wilde H, Bender-Gotze Ch, Schafer KH. Lymphozytenfunktionen bei Kindern mit Eisenmangel. Klin Wochenschr 1984;62:1091-1093.

18. Srikantia SG, Bhaskaram C, Prasad JS, Krishnamachari KAVR. Anaemia and immune response. Lancet 1976;(1(7973);1307-1309.

19. Chandra RK, Saraya AK. Impaired immunocompetence associated with iron deficiency. J Pediatr 1975;86;899-902.

20. Bagchi K, Mohanram M, Reddy V. Humoral immune response in children with iron-deficiency anaemia. Br Med J 1980;280:1249-1251.

21. Allen L. Pregnancy and iron deficiency: unresolved issues. Nutr Rev 1997;55(4):91-101.

22. Baker RD, Greer FR, and the Committee on Nutrition American Academy of Pediatrics. Diagnosis and prevention of iron deficiency and iron-deficiency anemia in infants and young children (0-3 years of age). Pediatrics 2010;126(5):1040-1050.

23. Lozoff B, Jimenez E, Wolf AW. Long-term developmental outcome of infants with iron deficiency. N Engl J Med 1991;325:687-694.

24. Walter T, De Andraca I, Chadud P, Perales CG. Iron deficiency anemia: Adverse effects on infant psychomotor development. Pediatrics 1989;84:7-17.

25. De Andraca I, Castillo M, Walter T. Psychomotor development and behavior in iron deficient anemic infants. Nutr Rev 1997;55:125-132.

26. Dallman PR. Nutritional anemias in childhood: iron, folate, and vitamin B12. In: Suskind RM, Lewinter-Suskind L, eds. Textbook of Pediatric Nutrition. 2nd ed. New York, NY: Raven Press 1993:91-105.

27. Cogswell ME, Kettle-Khan L, Ramakrishnan U. Iron supplement use among women in the United States: science, policy, and practice. J Nutr 2003;133(suppl):1974S-1977S.

28. Rush D. Nutrition and maternal mortality in the developing world. Am J Clin Nutr 2000;72(suppl):212S-240S.

29. Scholl T. Iron status during pregnancy: setting the stage for mother and infant. Am J Clin Nutr 2005;81:1218S-1222S.

30. Allen LH. Biological mechanisms that might underlie iron's effects on fetal growth and preterm birth. J Nutr 2001;131:581S-589S.

31. Garby L, Irnell L, Wener I. Iron deficiency women of fertile age in a Swedish community: II. Efficiency of several laboratory tests to predict the response to iron supplementation. Acta Med Scand 1969;185(1-2):107-111.

32. Cook JS, Flowers CH, Skikne BS. The quantitative assessment of body iron. Blood 2003;101(9);3359-3364.

33. Preziosi P, Prual A, Galan P, Daouda H, Boureima H, Hercberg S. Effect of iron supplementation on the iron status of pregnant women: consequences for newborns. Am J Clin Nutr 1997;66:1178-1182.

34. Hay G, Refsum H, Whitelaw A, Melbye E, Haug E, Borch-Johnsen B. Predictors of serum ferritin and serum soluble transferring receptor in newborns and their associations with iron status during the first 2 years of life. Am J Clin Nutr 2007;86:64-73.

35. Adebisi O, Strayhorn G. Anemia in Pregnancy and Race in the United States: Blacks at Risk. Fam Med 2005;37(9):655-662.

36. Minns L, Kerling E, et al. Toddler formula supplemented with docosahexaenoic acid (DHA) improves DHA status and respiratory health in a randomized, double-blind, controlled trial of US children less than 3 years of age. Prostaglandins Leukot Essent Fatty Acids 2010;82(4-6):287-93.

37. Birch EE, Khoury JC, Berseth CL, et al. The impact of early nutrition on incidence of allergic manifestations and common respiratory illnesses in children. J Pediatr 2010;156:902-6, 6 e1.

APPENDIX A

Consent Form

CONSENT FORM

The Effects of DHA on Pregnancy and Infant Outcome

(Kansas University DHA Outcomes Study or KUDOS)

Sponsor: NIH (1R01 HD047315)

INTRODUCTION

As a pregnant woman who is between 8 and 20 weeks of gestation, you are being invited to enroll in a research study of a nutrient (DHA) that is a component of normal brain and important for brain development. The centers involved in the study are the University of Kansas Medical Center in Kansas City, Kansas, St. Luke's Hospital in Kansas City Missouri, and Truman Medical Center in Kansas City, Missouri. If you decide to enroll in this study, your baby will participate in research procedures at the University of Kansas Medical Center. Dr. Susan Carlson is the main investigator for this study. A total of 350 pregnant women will be enrolled in this study between October 2005 and January 2010.

You do not have to participate in this research study. It is important that before you make a decision to participate, you read the rest of this form. You should ask as many questions as you need to understand what will happen if you participate in the study.

BACKGROUND

Docosahexaenoic acid (DHA) is a fat that is found in very large amounts in the brain. DHA is important for how my baby sees and learns. Breast milk and, since 2002, US formulas contain DHA. Many studies have shown that DHA in the diet helps the baby's vision, attention, and ability to learn. In this way, DHA is considered an important nutrient for babies after they are born.

DHA may also be important before babies are born. Four studies found that women's DHA during pregnancy was related to higher infant/child function. These studies are called observational studies, meaning that the women's normal DHA status was studied in relation to development of the baby/child. There is only one study that gave women DHA during pregnancy and measured development of their babies/children. That study showed higher IQ at 4 years of age in children whose mothers took fish oil capsules during the last 6 months of pregnancy. (Fish oil contains a lot of DHA). However, because women in the study also consumed DHA while they were breastfeeding they provided more DHA to their babies after they were born. Therefore, the study does not prove that giving DHA before babies are born will help their development. There are no studies that have varied DHA intake only during pregnancy. You and your child are being asked to participate in such an experimental study.

PURPOSE

The purpose of this study is to determine if a dietary supplement of DHA during pregnancy will help babies be born at the right time and help their development. If you decide to be in the study, you will have a 50-50 chance of receiving capsules with the supplement of DHA or ordinary food oil, which does not contain any DHA.

HSC Submission Date:08/25/2009
HSC Approval Date:12/28/08
HSC Approval (Payment)Date: 2/11/08
HSC Approval (HSC Address) Date: 11/3/05
HSC Approval (Rev CF COI) Date:

HSC #: 10186
Approval Date: 5/28/10 to 5/27/11
Assurance #: FWA00003411

PROCEDURES

If you choose to enroll yourself and your infant in this study, the investigators will record some information from your medical record about your pregnancy and medical history. They will also ask you a few questions about foods that you usually eat. You will have a blood sample collected from a vein in your arm. One-half teaspoon of blood will be drawn. The blood will be used to measure DHA in your blood as well as other nutrients. You will be asked to provide a current address and phone number where you can be contacted. .

During pregnancy: You will be randomly assigned (like flipping a coin) to capsules witl DHA-oil or ordinary food oil (which does not contain any DHA). The DHA-oil is the same o that is used in US infant formulas and has been fed safely to millions of infants.

You will be given enough capsules each month to take 3 capsules each day and you agre to try to consume all 3 capsules. If you consume all 3 capsules, you will consume 600 mg o DHA. The capsules are relatively small and you should find them easier to swallow tha many nutrient supplements. They are orange-flavored, so if you burp (common in pregnanc and in the first week of taking any nutrient supplement), the taste should not be unpleasant You do not need to take the capsules at any specific time as they are a nutrient and not a drug. However, you should decide upon a regular time to take them so that taking the capsules will become a habit and you won't forget. For example, you might wish to take them just before you go to bed or when you have your first beverage of the day.

Neither you nor the investigators will know which capsules you have been assigned to. On the day you enroll for the study, we will send you home with your first bottle of capsules. About 30 days later (early enough so that you do not run out of capsule), you will receive another bottle of capsules in the mail. AT THAT TIME, YOU AGREE TO PLACE THE FIRST BOTTLE WITH ANY REMAINING CAPSULES IN THE ENVELOPE AND DROP IT INTO THE MAIL.

This process will be repeated each month until your baby is born and you will continue to take 3 capsules per day until your baby is born. Each time you receive a new bottle, you will mail back the bottle that you have been using and that day will open and begin using the new bottle.

The investigators will contact you by phone at least once per month. They will ask about capsule intake and they will ask how you are doing. Maintaining contact with our study personnel on a monthly basis is very important.

IF YOUR PHONE NUMBER OR ADDRESS CHANGES AT ANY TIME DURING THE STUDY, YOU WILL LET THE INVESTIGATORS KNOW BY CALLING 913-588-3781 AND LEAVING A MESSAGE.

Delivery: After you are admitted to the hospital to deliver, you should telephone study personnel or ask the person at admitting to telephone them. You will be given a cell phone number today to call. Once you deliver your baby, the investigators will visit you in the hospital to collect data about your delivery and your baby's health. A sample of your baby's cord blood will be collected after delivery by nurses at the hospital and given to the

HSC #: 10186
Approval Date: 5/28/10 to 5/27/11
Assurance #: FWA00003411

investigators. A nurse will also draw a small blood sample (one-half teaspoon) from you while you are in the hospital. The blood samples will be used to measure DHA and other nutrients. The investigators will visit you, and give you an appointment for your baby's first follow-up visit at KUMC.

Visit 1 (6 weeks of age): The investigators will measure how your baby sees using a test that involves placing 3 electrodes directly on your baby's head. The process involves cleaning the area then placing a small amount of paste similar to toothpaste on the head. The electrodes are placed on top of the paste. The electrodes will be used to record your baby's brain waves while he/she is looking at pictures. Your child's weight, height and head circumference will be measured again and you will be asked questions about what your baby eats. If you are breastfeeding your baby, you will be asked to provide a teaspoon of breast milk to the investigator. The sample will be frozen and analyzed for fats that are found in the capsules. The visit should last about 40 minutes. You should arrive on time and allow that amount of time for the visit.

Visit 2 (4 months of age): The investigators will measure how your baby sees using the same test as before and another vision test. Your baby will wear a pair of plastic glasses during the second test. In another test, your child will be given an object to look at several times. The investigator will measure how long he/she looks at the object and how quickly he/she stops looking at the object. Your child will be video recorded during the test. Your baby's heart rate will be measured during the test. Your baby's height, weight and head circumference will be measured and you will be asked about what food your baby eats. Your baby will have a blood sample collected by either heel stick or drawn from a vein. If it is necessary to use a heel stick, the investigator may use a cream or spray that will numb the area before obtaining the sample. One-half teaspoon of blood will be drawn. The blood will be used to measure DHA and other nutrients. You should let the investigator know if your baby has been sick or not acting well since his/her last visit. The visit will take 60-90 minutes.

Visit 3 (6 months of age): The investigators will measure how your baby sees using the test that requires him/her to wear a pair of plastic glasses. In another test, he/she will be given an object to look at several times (just like at 4 months of age). The investigator will measure how long he/she looks at the object and how quickly he/she stops looking at the object. Your child will be video recorded during the test. Your baby's heart rate will be measured during the test. Your baby's height, weight and head circumference will be measured. You will be asked questions about what your baby eats. You should let the investigator know if your baby has been sick or not acting well since his/her last visit. The visit should take 40 -60 minutes.

Visit 4 (9 months of age): Your baby will have both tests that measure how he/she sees. In another test, your child will be given an object to look at several times (just like at 4 and 6 months of age). The investigator will measure how long he/she looks at the object and how quickly he/she stops looking at the object and your baby's heart rate will be measured during the test. Your child will be video recorded during the test. Your baby's height, weight and head circumference will be measured. You will be asked questions about what your baby eats. You should let the investigator know if your baby has been sick or not acting well since his/her last visit. The visit should take about 40-60 minutes.

HSC #: 10186
Approval Date: 5/28/10 to 5/27/11
Assurance #: FWA00003411

Visit 5 (10 months of age): During this visit your baby will be placed on your lap in front of a small table. A test will be completed with a small toy, foam block and 2 cloths that will be placed in front of your child. You will also take a short language test. The small toy will be given to your child to keep. In another test, your baby will be asked to take turns with the researcher building fun toys. After your baby has played for a moment with the pieces, the researcher will show him or her how to build the toy. Then, your baby will be given a turn to put the toy together. Your baby's turn will happen either immediately or after 10-minutes of play with other things. We will show your child objects in groups of 2 and 3 to see how long they look at the objects. Your child will be video recorded during the tests. You should let the investigator know if your baby has been sick or not acting well since his/her last visit. You will be asked questions about what your baby eats. The entire 10-month visit should last 70 minutes.

Visit 6 (12 months of age): The investigators will measure how your baby sees using both vision tests. Your child will be video recorded while playing with an interesting toy and the investigator will use the recording to measure some aspects of attention. We will show your child objects in groups of 2 and 3 to see how long they look at the objects. Your child's height, weight and head circumference will be measured. You will be asked questions about what your baby eats. You should let the investigator know if your child has been sick or not acting well since his/her last visit. We will request your child's medical record from his/her doctor. The visit should take about 2 hours. It is important that your child be rested before the testing at this visit. If for some reason your baby cannot finish the tests that day – this may happen if he/she is unusually fussy or tired – you will be asked to return to finish the remaining tests within 7 days.

Visit 7 (18 months of age): The investigators will measure how your child sees using the test that he/she had while wearing plastic glasses. Your child will be video recorded while playing with an interesting toy and the investigator will use the recording to measure some aspects of attention. Your child will also be given a standardized test to measure mental and physical development. Your child's height, weight and head circumference will be measured. You will be asked questions about what your baby eats. You will be asked questions about the words your child uses and understands. You should let the investigator know if your child has been sick or not acting well since his/her last visit. The visit should take about 2 hours. It is important that your child be rested before the testing at this visit. If for some reason your child cannot finish the tests that day – this may happen if he/she is unusually fussy or tired – you will be asked to return to finish the remaining tests within 7 days.

RISKS

Some redness, soreness, or bruising may occur at the site of blood sampling. There is also a very slight risk of infection.

You may experience burping from the capsules and find this unpleasant

There are no known risks of consuming the amount of DHA you will be provided if you receive the DHA. Even if you forget to take your capsules for one or two days, there is no known risk of deciding to "catch up" on the third day. The amount is smaller than pregnant

HSC #: 10186
Approval Date: 5/28/10 to 5/27/11
Assurance #: FWA00003411

women in many countries eat every day. Nevertheless, you could develop a problem that has not been observed before.

NEW FINDINGS STATEMENT

You will be informed if any significant new findings develop during the course of the study that may affect your willingness to participate or to allow your child to participate in this study.

BENEFITS

You and your child may or may not benefit from participating in this study. If you receive the supplement, it may help your baby to be born at the right time and your baby's/child's development. If you will not get the supplement, your baby and you will not be getting any of those benefits. It is also possible that all infants/children will get some benefit from being followed closely with developmental testing. It is hoped that additional information gained in this research study may be useful in understanding if DHA can help your baby be born at the right time and help your baby's vision, attention, and learning as he or she grows. You will receive a video recording of your infant doing the 4, 6, and 9 month looking test when the 12 month visit is complete.

ALTERNATIVES

You do not have to participate in this study to be able to take DHA supplements while you are pregnant. You may purchase capsules containing DHA at local stores without a prescription (for example, Osco, Costco, Wal-Mart). There are also several brands of prenatal supplements with DHA available by prescription or over the counter. The prenatal capsules typically contain 200 mg of DHA each and are marketed to take one capsule/day as a DHA supplement.

COSTS

Capsules containing either DHA or food oil will be provided to you at no cost while you are participating in this study. You will not incur any costs because of your or your child's participation

PAYMENT TO SUBJECTS

If study investigators are able to communicate with you each month you will be given 2 bonus gift cards to either Wal-Mart or Target of $25 each. The first gift card will be given to you half way through your treatment phase if communication is maintained at least one time each month during the first half of your treatment. The second gift card will be given at delivery if communication maintained at least one time each month during the second half of your treatment.

Additionally, if the study investigators are called after you are admitted for delivery you will be given your choice of a bonus gift card worth $50 from either Wal-Mart or Target. You may make the call yourself or have someone else call for you. Study personnel will give you the gift card when they come to the hospital after your baby is born.

Once your baby is born,you will receive a check for $50 after your baby completes each of the following visits: 6 weeks, 4 months, 6 months, 9 months, and 10 months. You will receive a check for $100 after your child completes each of the following visits: 12 and 18 months.

The reimbursements are to cover the costs of transportation and to partially compensate you for your time required to participate in the study.

Your name, address, social security number, and the title of this study will be given to the KUMC Research Institute. This is done so that the Research Institute can write a check for study payments. Payments are taxable income.

IN THE EVENT OF INJURY

In the event you experience any serious health problem (hospitalization, life-threatening illness, or death) for any reason during your pregnancy, you should immediately seek treatment or help in the way you normally would as if you were not in a study. You should let Susan Carlson, Ph.D. know about any of these problems as soon as possible by calling her office (913-588-5359) or the study office (913-588-3781). A message may be left at both numbers. Dr. Carlson may also be reached at home (816-960-1805).

INSTITUTIONAL DISCLAIMER STATEMENT

If you believe you have been injured as a result of participating in research at Kansas University Medical Center (KUMC), you should contact the Director, Human Research Protection Program, Mail Stop #1032, University of Kansas Medical Center, 3901 Rainbow Blvd., Kansas City, KS 66160. Compensation to persons who are injured as a result of participating in research at KUMC may be available, under certain conditions, as determined by state law or the Kansas Tort Claims Act.

Truman Medical Center (TMC) will provide medical attention to you if you suffer any injury or harm as a direct result of participating in this research project. TMC, your study doctor, and the sponsor of this study will decide, at their discretion, who should pay for the medical care. TMC will provide treatment to you in the event of any medical emergency while present at TMC, whatever the cause. Moreover, you will have the benefit of the coverage of any existing healthy insurance you own. Participation in this research study does not take the place of routine physical examinations or clinic visits to your person physician. If you believe you have been injured as a result of participating in this study you are encouraged to contact the study investigator, Dr. Susan Carlson, at her work number, 913-588-5359.

The University of Missouri-Kansas City appreciates the participation of people who help it carry out its function of developing knowledge through research. Although it is not the University's policy to compensate or provide medical treatment for persons who participate in studies, if you think you have been injured as a result of participating in this study, please call the investigator, Dr. Susan Carlson at 913-588-5359 (work) or Sheila Anderman, IRB administrator of UMKC's Adult Health Sciences Institutional Review Board at 816-235-6150

CONFIDENTIALITY AND PRIVACY AUTHORIZATION

Names of subjects or information identifying subjects will not be released without written permission unless required by law. Videotapes of your baby when he/she is looking at pictures and playing with toys will be used only by the investigators and their students and to make a videotape copy for you. The videotapes will be secured under lock and key like all other information that could be linked directly to your child. The videotape of your child will not be shown without specific permission from you and even then would not identify your

HSC #: 10186
Approval Date: 5/28/10 to 5/27/11
Assurance #: FWA00003411

child by name. Efforts will be made to keep you and your child's personal information confidential. Researchers cannot guarantee absolute confidentiality. If the results of this study are published or presented in public, information that identifies you and/or your baby will be removed.

The privacy of you and your child's health information is protected by a federal law known as the Health Insurance Portability and Accountability Act (HIPAA). If you choose to participate in this study, you will be asked to give permission for researchers to use and disclose your and your baby's health information that is relevant to the study.

To perform this study, researchers will collect health information about me and my child from his/her and my medical records and from the study activities that are listed in the Procedures section of this consent form. My and my baby's study-related health information will be used at KU Medical Center by Dr. Carlson, members of the research team, Truman Medical Center, St. Luke's Hospital and the KU Hospital Medical Record Department, the KUMC Research Institute and officials at KUMC and at Truman Medical Center that oversee research, including the KUMC Human Subjects Committee, the IRB that governs St. Luke's Medical Center and Truman Medical Center and other committees and offices that review and monitor research studies.

Dr. Carlson and her team may share information about me and my baby with representatives of Martek Biosciences, the monitoring company who verifies study data, the laboratory that processes study lab samples, other business partners who help with the study, the U.S. Food and Drug Administration (FDA), and U.S. agencies that govern human research (if and when regulatory compliance issues arise). Martek Biosciences (Columbia, MD) donated the capsules for this study that is otherwise supported by the National Institute of Child Health and Human Development.

Some of the persons or groups that receive my and my baby's study information may not be required to comply with HIPAA privacy laws. My and my child's information may lose its federal protection if those persons or groups disclose it.

Permission granted on this date to use and disclose my health information remains in effect indefinitely. By signing this form I give permission for the use and disclosure of my and my child's information for purposes of the study at any time in the future.

If I enroll in the study, the investigators cannot tell me what capsule I was assigned to until the study ends. This may be after I have stopped taking the capsules.

QUESTIONS

I have read the information in this form. Dr. Carlson or her associates have answered my question(s) to my satisfaction. I know if I have any more questions after signing this I may contact Dr. Carlson or one of her associates at (913) 588-5359. If I have any questions about my or my child's rights as a research subject, I may call (913) 588-1240 or write the Human Subjects Committee, University of Kansas Medical Center, 3901 Rainbow Blvd. MSN 1032, Kansas City, KS 66160.

HSC #: 10186
Approval Date: 5/28/10 to 5/27/11
Assurance #: FWA00003411

SUBJECT RIGHTS AND WITHDRAWAL FROM THE STUDY

My and my child's participation in this study is voluntary and the choice to not participate or to quit at any time can be made without penalty or loss of benefits. Not participating or quitting will have no effect upon the medical care of treatment my child receives now or in the future at the University of Kansas Medical center. The entire study may be discontinued for any reason without my consent by the investigator conducting the study, by the sponsor of the study, or the FDA. My child's participation can be discontinued by the investigator or by the sponsor if it is felt to be in my child's best interest or if I do not follow the study requirements. If I choose to withdraw before my child is 18 months of age, I may be asked to answer questions about the study on the telephone.

If I want to cancel permission to use my or my child's health information, I should send a written request to Dr. Carlson. The mailing address is Susan Carlson, Ph.D., Dept. of Dietetics and Nutrition, MS 4013, 4019 Delp, University of Kansas Medical Center, 3901 Rainbow Boulevard, Kansas City, KS 66160. If I cancel permission to use my child's health information, the research team will stop collecting any additional information about me and my child.

Should the study be terminated prior to the completion of my pregnancy, neither the investigator nor the University of Kansas Medical Center will be under any obligation to provide me with DHA capsules used in the study.

HSC #: 10186
Approval Date: 5/28/10 to 5/27/11
Assurance #: FWA00003411

CONSENT

Dr. Carlson or her associates have given me information about this research study. They have explained what will be done and how long it will take. They explained the inconvenience, discomfort and risks that may be experienced during this study.

By signing this form, I give my permission for my and my child's health information to be used and disclosed for the purposes of this research study. If I choose not to sign this form, my child and I will not be able to participate in the study.

I voluntarily consent to my and my child's participation in this research study. I have read the information in this form and have had an opportunity to ask questions and have them answered. ***I will be given a copy of the signed form to keep for my records.***

_____
Type/Print Subject's Name

_____ _____ _____
Signature of Subject Time Date

_____
Type/Print Name of Person Obtaining Consent

_____ _____
Signature of Person Obtaining Consent Date

_____
Type/Print Name of Principal Investigator

_____ _____
Signature of Principle Investigator Date

HSC #: 10186
Approval Date: 5/28/10 to 5/27/11
Assurance #: FWA00003411

May the investigators contact you after the study is over to ask if you interested in continuin your child's participation? If you agree to be contacted, the investigators would explain an new study to you later and you would have the chance to decide if you wanted to participat at that time (please circle your response).

Yes

No

You may choose not to be contacted in the future and still be able to participate in the mai study.

_____
Type/Print Subject's Name

_____ _____ _____
Signature of Subject Time Date

_____
Type/Print Name of Person Obtaining Consent

_____ _____
Signature of Person Obtaining Consent Date

_____
Type/Print Name of Principal Investigator

_____ _____
Signature of Principle Investigator Date

HSC #: 10186
Approval Date: 5/28/10 to 5/27/11
Assurance #: FWA00003411

APPENDIX B

Adverse Event Electronic Code List

Body System	Code	Event
BODY AS A WHOLE	BODY024	ABNORMAL UMBILICUS
	BODY028	ACCIDENT
	BODY014	ALLERGY
	BODY036	ANAPHYLACTIC SHOCK
	BODY025	ANAPHYLAXIS
	BODY010	ANEMIA
	BODY007	APPARENT LIFE-THREATENING EVENT (ALTE)
	BODY017	ASPHYXIA
	BODY029	ASYMETRICAL FAT FOLD
	BODY015	BENIGN MASS
	BODY030	BREAST ENLARGEMENT
	BODY032	CARRIER BIOTIN DEFICIENCY
	BODY002	DEHYDRATION
	BODY016	DEVELOPMENTAL DELAY
	BODY021	DIAGNOSTIC PROCEDURE
	BODY034	DRUG ALLERGY
	BODY004	EXCESSIVE CRYING
	BODY003	FAILURE TO THRIVE
	BODY022	FEVER
	BODY038	FEVER OF UNKNOWN ORIGIN
	BODY033	FOOD ALLERGY
	BODY012	FUSSINESS
	BODY005	INFECTION
	BODY035	INSECT STING ALLERGY
	BODY001	IRRITABILITY
	BODY023	MICROCEPHALY
	BODY018	PAIN
	BODY027	PECTUS EXCAVATION
	BODY026	PLAGIOCEPHALY
	BODY019	REACTION TO VACCINE
	BODY008	RULE OUT SEPSIS
	BODY009	SEPSIS
	BODY020	SHORT STATURE
	BODY039	SPHEROCYTOSIS
	BODY006	SUDDEN INFANT DEATH SYNDROME (SIDS)
	BODY013	SURGERY
	BODY037	SYSTEMIC FUNGAL INFECTION
	BODY031	TEETHING
	BODY011	WEAKNESS

Body System	Code	Event
CARDIOVASCULAR	CARD007	ARRHYTHMIA
	CARD001	BRADYCARDIA
	CARD010	CARDIAC DEFECT
	CARD006	CARDIOMYOPATHY
	CARD002	CONGENITAL HEART DISEASE
	CARD003	COR PULMONALE
	CARD004	HEART MURMUR
	CARD005	HYPERTENSION
	CARD008	PERICARDIAL EFFUSION
	CARD009	TACHYCARDIA

Body System	Code	Event
EYES, EARS, NOSE AND THROAT	EENT020	ABNORMAL REFRACTION
	EENT039	ALLERGIC CONJUNCTIVITIS
	EENT037	ALLERGIC RHINITIS
	EENT038	ALLERGIC RHINO-CONJUNCTIVITIS
	EENT041	ALLERGIC SINUSITIS
	EENT031	BACTERIAL EYE INFECTION
	EENT026	BLIND
	EENT022	CATARACTS
	EENT036	CHOANAL STENOSIS
	EENT006	CONJUNCTIVITIS
	EENT008	CORNEAL ABRASION
	EENT029	EAR DRAINAGE
	EENT024	EAR WAX EXCESSIVE
	EENT018	EYE MOVEMENT DISORDER
	EENT023	EYELID INFECTION
	EENT013	HEARING DEFICIT
	EENT032	HEMANGIOMA
	EENT040	INFECTIOUS CONJUNCTIVITIS
	EENT043	INFECTIOUS RHINITIS
	EENT015	INFECTIOUS RHINITIS/SINUSITIS
	EENT042	INFECTIOUS SINUSITIS
	EENT012	LARYNGEAL EDEMA
	EENT034	LARYNGOMALACIA
	EENT025	LASER SURGERY/CRYOTHERAPY
	EENT021	MYRINGOTOMY/TM TUBES
	EENT002	NASAL CONGESTION
	EENT003	NASAL/TEAR DUCT OBSTRUCTIONS
	EENT030	OTITIS EXTERNA
	EENT001	OTITIS MEDIA
	EENT004	PURULENT RHINITIS
	EENT027	RETINAL DETACHMENT/HEMORRHAGE
	EENT014	RETINOPATHY OF PREMATURITY
	EENT011	RHINORRHEA
	EENT028	SEPTAL DEVIATION
	EENT010	SNEEZING/ITCHING
	EENT007	STAPH INFECTION IN EYE
	EENT019	SWALLOWING DISORDER
	EENT009	THRUSH
	EENT017	TONSILLECTOMY/ADENOIDECTOMY
	EENT016	TRAUMA

Body System	Code	Event
EYES, EARS, NOSE AND THROAT	EENT033	TUGGING AT EAR
	EENT035	VARIX
	EENT005	WATERY EYE

Body System	Code	Event
ENDOCRINE	END003	ABNORMAL LABORATORY RESULT
	END004	ADRENAL HYPERPLASIA
	END001	ADRENAL INSUFFICIENCY
	END002	HYPOTHYROIDISM

Body System	Code	Event
GASTROINTESTINAL	GI018	ABDOMINAL CRAMPING
	GI036	ABDOMINAL DISTENTION
	GI008	ACUTE GASTROENTERITIS
	GI043	ALLERGIC COLITIS
	GI045	ALLERGIC ENTEROCOLITIS
	GI046	ALLERGIC ESOPHAGITIS
	GI044	ALLERGIC GASTROENTERITIS
	GI010	ANAL FISSURE
	GI039	ANAL IRRITATION
	GI048	ANAL SWELLING
	GI023	BLOATING
	GI009	BLOODY STOOL
	GI025	BURPING
	GI007	COLIC
	GI014	COLITIS
	GI006	CONSTIPATION
	GI020	COW'S MILK INTOLERANCE
	GI040	DEFECATION PROBLEM
	GI005	DIARRHEA
	GI022	DYSPEPSIA (INDIGESTION/HEARTBURN)
	GI001	EMESIS
	GI002	EXCESSIVE SPITTING
	GI030	FEEDING PROBLEMS
	GI037	FEEDINGS WITHHELD DUE TO INTOLERANCE
	GI024	FLATULENCE
	GI017	FREQUENT STOOLS
	GI003	G.E. REFLUX
	GI004	GAS
	GI035	GASTRIC RESIDUALS
	GI031	GASTRIC TUBE PLACEMENT
	GI015	GI INFECTION
	GI038	HARD STOOLS
	GI051	HEMORRHOID
	GI032	HEPATIC CALCIFICATION
	GI041	HUNGER
	GI021	ILEUS
	GI047	INFECTIOUS GASTROENTERITIS
	GI049	LOOSE STOOLS
	GI050	MUCOUS IN STOOL
	GI027	NAUSEA

Body System	Code	Event
GASTROINTESTINAL	GI028	NECROTIZING ENTEROCOLITIS
	GI033	PERIANAL FISTULA
	GI011	PERIRECTAL ABSCESS
	GI042	PERSISTENCE OF UMBILICAL CORD
	GI016	PYLORIC STENOSIS
	GI034	RECTAL STENOSIS
	GI012	SALMONELLA IN STOOL
	GI013	SPITTING UP
	GI029	STOMATITIS
	GI026	STRAINING
	GI019	UMBILICAL HERNIA

Body System	Code	Event
METABOLIC AND NUTRITION	MAN009	ABNORMAL LABORATORY RESULT
	MAN005	ELECTROLYTE INBALANCE
	MAN008	FAILURE TO THRIVE
	MAN003	FETAL MALNUTRITION
	MAN011	FORMULA REJECTION
	MAN010	GLUTARIC ACIDEMIA TYPE 1
	MAN002	LACK OF APPETITE
	MAN006	MALNUTRITION
	MAN004	OSTEOPENIA/RICKETS
	MAN007	POOR WEIGHT GAIN
	MAN001	WEIGHT LOSS

Body System	Code	Event
MUSCULOSKELETAL	MS002	CRANIOSYNOSTOSIS
	MS004	DEFORMITY
	MS001	FRACTURE
	MS006	HIP CLICK
	MS007	HIP TIGHTNESS
	MS008	KNEE CLICK
	MS005	TORTICOLLIS
	MS003	TRAUMA

Body System	Code	Event
NERVOUS	NER007	ABNORMAL EEG
	NER010	ABNORMAL TONE
	NER021	BEHAVORIAL ISSUE
	NER012	CEREBRAL PALSY
	NER013	CONCUSSION
	NER011	CYST
	NER003	DIZZINESS
	NER015	ENCEPHALOPATHY
	NER004	FAINTING
	NER006	HEADACHE
	NER005	IMPAIRED CONGNITION
	NER009	INTRACRANIAL HEMORRHAGE
	NER014	MACROCEPHALY
	NER002	MENINGITIS
	NER020	MICROCEPHALY
	NER016	PARESIS
	NER017	PERIVENTRICULAR LEUKOMALACIA
	NER001	SEIZURE
	NER018	SHUNT REVISION
	NER019	TETHERED SPINAL CORD
	NER008	VENTRICULOMEGALY/HYDROCEPHALUS

Body System	Code	Event
RESPIRATORY	RESP025	ABNORMAL X-RAY FINDING
	RESP013	APNEA
	RESP008	ASTHMA
	RESP009	BRONCHIOLITIS
	RESP005	BRONCHITIS
	RESP017	BRONCHOPULMONARY DYSPLASIA
	RESP002	COUGH
	RESP004	CROUP
	RESP022	CYANOSIS
	RESP018	LARYNGITIS
	RESP012	PHARYNGITIS
	RESP007	PNEUMONIA
	RESP014	POSITIVE PRESSURE VENTILATION
	RESP020	PULMONARY EDEMA
	RESP021	PULMONARY HYPERTENSION
	RESP019	PULMONARY INSUFFICIENCY
	RESP016	REACTIVE AIRWAY DISEASE
	RESP015	REINTUBATION
	RESP010	RESPIRATORY DISTRESS SYNDROME
	RESP011	RESPIRATORY SYNCYTIAL VIRUS (RSV)
	RESP003	STREP THROAT
	RESP023	TACHYPNEA
	RESP024	TONSILLITIS
	RESP001	UPPER RESPIRATORY INFECTION (URI)
	RESP006	WHEEZING

Body System	Code	Event
SKIN	SK014	ANGIOEDEMA
	SK021	ATOPIC DERMATITIS
	SK027	BACTERIAL SKIN INFECTION
	SK012	CHICKEN POX
	SK030	CONTACT DERMATITIS
	SK001	DIAPER RASH
	SK003	DRY SKIN
	SK004	ECZEMA
	SK015	ECZEMA/SEBORRHEA
	SK018	EDEMA
	SK023	ERYTHEMA
	SK028	FUNGAL SKIN INFECTION
	SK017	HEMANGIOMA
	SK006	IMPETIGO
	SK024	INCLUSION CYST
	SK022	INFECTION
	SK031	INSECT BITE
	SK026	INTERTRIGO
	SK019	IV INFILTRATE
	SK008	JAUNDICE
	SK011	NEONATAL ACNE
	SK025	NEVUS
	SK010	OTHER RASH
	SK013	PRURITIS
	SK005	SEBORRHEA
	SK007	STAPH INFECTION
	SK016	TRAUMA
	SK009	URTICARIA
	SK029	VIRAL SKIN INFECTION
	SK020	WART
	SK002	YEAST INFECTION

Body System	Code	Event
UROGENITAL	UG012	ABNORMAL GENITALIA
	UG016	ABNORMAL URINE
	UG014	CIRCUMCISION
	UG003	FETAL MALNUTRITION
	UG007	HYPOSPADIAS
	UG005	INGUINAL HERNIA
	UG009	LABIAL ADHESIONS
	UG002	LACK OF APPETITE
	UG013	PENILE ADHESION
	UG010	PENILE LESION
	UG011	RENAL CALCULUS
	UG008	UNDESCENDED TESTES
	UG004	URINARY TRACT INFECTION
	UG001	VAGINAL DISCHARGE
	UG006	VESICO-URETERAL REFLUX
	UG015	VULVITIS/VAGINITIS

APPENDIX C

Adverse Event List

Diagnosis	Adverse Events Included
Eyes, Ears, Nose, Throat (EENT) Diagnosis	• Abnormal Refraction • Allergic Conjunctivitis • Allergic Rhinitis • Allergic Rhino-conjunctivitis • Allergic Sinusitis • Bacterial eye infection • Blind • Cataracts • Choanal Stenosis • Conjunctivitis • Corneal Abrasion • Ear Drainage • Ear Wax Excessive • Eye Movement Disorder • Eyelid Infection • Hearing Deficit • Hemangioma • Infectious Conjunctivitis • Infectious Rhinitis • Infectious Sinusitis • Laryngeal edema • Laryngomalacia • Laser Surgery/Cryotherapy • Myringotomy/TM Tubes • Nasal Congestion • Nasal/Tear Duct Obstruction • Otitis Externa • Otitis Media • Purulent Rhinitis • Retinal Detachment/Hemorrhage • Retinopathy of prematurity • Rhinorrhea • Septal Deviation • Sneezing/itching • Staph infection in the eye • Swallowing disorder • Thrush • Tonsillectomy/adenoidectomy • Trauma • Tugging at Ear • Varix • Watery Eye

Gastrointestinal (GI) Diagnosis	• Abdominal Cramping • Abdominal Distention • Acute Gastroenteritis • Allergic Colitis • Allergic Enterocolitis • Allergic Esophagitis • Allergic Gastroenteritis • Anal Fissure • Anal Irritation • Anal Swelling • Bloating • Bloody Stool • Burping • Colic • Colitis • Constipation • Cow's Milk Intolerance • Defecation Problem • Diarrhea • Dyspepsia • Emesis • Excessive Spitting • Feeding Problems • Feedings withheld due to Intolerance • Flatulence • Frequent Stools • G.E. Reflux • Gas • Gastric Residuals • Gastric Tube Placement • GI Infection • Hard Stools • Hemorrhoid • Hepatic Calcification • Hunger • Necrotizing Enterocolitis • Perianal Fistula • Perirectal abscess • Persistence of Umbilical Cord • Pyloric Stenosis • Rectal Stenosis

Gastrointestinal (GI) Diagnosis	• Salmonella in Stool • Spitting Up • Stomatitis • Straining • Umbilical Hernia • Rotavirus • Stomatitis • Umbilical Hernia
Respiratory (RESP) Diagnosis	• Abnormal X-ray Finding • Apnea • Asthma • Bronchiolitis • Bronchitis • Bronchopulmonary Dysplasia • Cough • Croup • Cyanosis • Laryngitis • Pharyngitis • Pneumonia • Positive Pressure Ventilation • Pulmonary Edema • Pulmonary Hypertension • Pulmonary Insufficiency • Reactive Airway Disease • Reintubation • Respiratory Distress Syndrome • Respiratory Syncytial Virus • Strep Throat • Tachypnea • Tonsillitis • URI • Wheezing
Upper Respiratory Infections (URI)	• URI alone
Otitis Media (OM)	• OM alone

APPENDIX D

Consent for the Release of Information

THE UNIVERSITY OF KANSAS HOSPITAL
CONSENT FOR THE RELEASE OF CONFIDENTIAL INFORMATION

I, _____ born on _____, hereby

authorize _____ to disclose to:

The University of Kansas Medical Center

3901 Rainbow Boulevard MS 4013

Kansas City, Kansas 66160-7200

Attention: Infant/Toddler Nutrition Research Clinic Phone: (913) 588-5743; **Fax: (913) 945-6621**

the following information:_____

_____

_____

_____

_____

I understand that my medical records (including any alcohol or drug abuse information) may be protected by Federal Regulations. I also understand that I may revoke this consent at any time except to the extent that action has been taken in reliance on it (e.g., probation, parole, etc.) and that in any event this consent expires automatically as described below.

SPECIFICATION OF THE DATE, EVENT, OR CONDITION UPON WHICH THIS CONSENT EXPIRES (if left blank this consent expires in one year)

_____

EXECUTED THIS _____ DAY OF _____, 20_____

_____ (Witness)

_____ (Signature of Patient)

_____ (Signature of patient, guardian, or authorized representative)

_____ (Nature of relationship)

PROHIBITION ON REDISCLOSURE: THIS INFORMATION HAS BEEN DISCLOSED TO YOU FROM RECORDS WHOSE CONFIDENTIALITY IS PROTECTED BY FEDERAL LAW. FEDERAL REGULATIONS (420 FR PART 2) PROHIBIT YOU FROM MAKING ANY FURTHER DISCLOSURE OF THIS INFORMATION EXCEPT WITH THE SPECIFIC WRITTEN CONSENT OF THE PERSON TO WHOM IT PERTAINS. A GENERAL AUTHORIZATION FOR THE RELEASE OF MEDICAL OR OTHER INFORMATION IF HELD BY ANOTHER PARTY IS NOT SUFFICIENT FOR THIS PURPOSE. FEDERAL REGULATIONS STATE THAT ANY PERSON WHO VIOLATES ANY PROVISION OF THIS LAW SHALL BE FINED NOT MORE THAN $500, IN THE CASE OF A FIRST OFFENSE, AND NOT MORE THAN $5,000, IN THE CASE OF EACH SUBSEQUENT OFFENSE.

Drug Abuse Office and Treatment Act of 1972 (21 USC 1175) Comprehensive Alcohol Abuse and Alcoholism Prevention, Treatment, and Rehabilitation Act of 1970 (42 USC 4582)

APPENDIX E

Adverse Event Log Sheet

Adverse Event Log Sheet

Subject ID _____ Subject DOB _____/_____/_____

AGE AT EVENT: _____ months

Adverse Event _____ Start Date: _____/_____/_____

Code _____ Stop Date: _____/_____/_____

Ongoing: _____/_____/_____

Serious: Yes No

Action taken (circle none or list as applicable):

None

Medications

Other, specify_____

Hospital/Clinic seen at _____

Reported at visit _____

Coded ☐ Entered ☐ Checked ☐

AGE AT EVENT: _____ months

Adverse Event _____ Start Date: _____/_____/_____

Code _____ Stop Date: _____/_____/_____

Ongoing: _____/_____/_____

Serious: Yes No

Actions taken (circle none or list as applicable):

None

Medications

Other, specify_____

Hospital/Clinic seen at _____

Reported at visit _____

Coded ☐ Entered ☐ Checked ☐
