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MATERNAL IRON-DEFICIENCY ANEMIA
AT ROCKY MOUNTAIN ALTITUDES

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Cynthia Dickinson Anderson

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MATERNAL IRON-DEFICIENCY ANEMIA AT ROCKY MOUNTAIN ALTITUDES

By

Cynthia Dickinson Anderson

A THESIS

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

MASTER OF SCIENCE IN NURSING

College of Nursing

1999

ABSTRACT

MATERNAL IRON DEFICIENCY ANEMIA AT ROCKY MOUNTAIN ALTITUDES

By

Cynthia Dickinson Anderson

Retrospective survey format was utilized to retrieve existing demographic and longitudinal clinical data from 132 medical records of pregnant women living at 6,000 to 7,000 feet elevation. Normal maternal values for hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration were found for the landmark anemia screening intervals throughout pregnancy. Maternal iron deficiency anemia (MIDA) was operationally defined as an MCV less than 80 fL and either an MCH less than 27 pg or an MCHC less than 32 g/dL. Only 2 cases of MIDA were found due to sampling criteria that selected for normal pregnancies. The 1989 Centers for Disease Control Guidelines were found unreliable in identifying MIDA at 6,000 to 7,000 feet elevation. Recommendations included the abandonment of MIDA screening based solely on measures of hemoglobin and/or hemotocrit, and revision of MIDA screening and diagnostic panels for populations at 6,000 to 7,000 feet elevation.

ACKNOWLEDGMENTS

The author thanks Rachel Schiffman, PhD, thesis chair, for her guidance, persistence and patience for the duration of this project. Her input regarding organization, format, selection of theoretical model, and methods was invaluable. The author is appreciative of her assistance with administrative details and many long distance communications that were "above and beyond the call of duty."

Thesis committee members, Brigid Warren, MSN and Jacqueline Wright, MSN are appreciated for the attention to concepts, implications and specific details throughout the manuscript. Special thanks to Jackie Wright for her many words of encouragement and late night phone calls. The entire committee is thanked for the flexibility and understanding during personal crises the author endured concurrently.

For technical support, the author thanks Brother Brian Dybowski, FSC, PhD, College of Sante Fe, and Jill Ryan, who provided free use of their PC's when the author's old PC "died", and expertise pertaining to SPSS and Excel programs. Thanks also to Gail Bryant, RN, MSN, who reviewed the manuscript several times and provided editorial input. Kaye Arnett at the College of Nursing, Michigan State University is thanked for her expertise and hard work in editing for details of format, and preparation of the final manuscript.

Thanks also go to Elizabeth Gilmore and the Northern New Mexico Midwifery Center at Taos, Drs. Laura Wolfswinkel and Maria Rodriguez at Galisteo OB/GYN in Santa Fe, and David Land, DO, OB/GYN in Las Vegas for agreeing to participate in the study and serving as data collection sites. Special thanks go to Kathy at the Midwifery Center, Susan Dettlebach at Galisteo OB/GYN, and David Land for assisting with arrangements for data collection. Finally, the author wishes to thank the following friends, relatives and colleagues for their support and encouragement: Maggie Anderson, Graydon Anderson, Starr Cross, Paul and Juan Dickinson, Debbie Trimmer, Ric Loyd, Gail Bryant, Judy Oldknow, Lydia Sneesby, Mary Soppe, Jean Glidewell, Connie Martin, Kristi and David Rymph, Elsie Anderson, Linda Wolf, John Ford, Susan Ford Wiltshire, Penny Gonzalez, Jim LaBerge, David Land, Mary Masuk, Barbara Villa Señor, Judith Fleishman, Jan woods, and Lynn Zinser-Kask. Thanks also to Elizabeth Matuk, RN for her inspirational enactment of the advanced practice role and her faith in the profession.

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LIST OF ABBREVIATIONS

APN	=	advaced practice nurse
CBC	=	complete blood count
cc	=	cubic centimeter
CDC	=	Centers for Disease Control
FEP	=	free erythrocyte protoporphyrin
fL	=	femtoliter
g/dL	=	grams per deciliter
IDA	=	iron-deficiency anemia
HCT	=	hematocrit
HGB	=	hemoglobin
HMO	=	health maintenance organization
IDA	=	iron-deficiency anemia
IUGR	=	intrauterine growth retardation
LBW	=	low birthweight
LMP	=	first day of last menstrual period
MIDA	=	maternal iron-deficiency period
MCH	=	mean copuscular hemoglobin
MCHC	=	mean corpuscular hemaglobin concentration
MCV	=	mean corpuscular volume
mg	=	milligram
ml	=	milliliter
μg/dL	=	micrograms per deciliter
μg/L	=	micrograms per liter
NHANES	=	National Health and Nutrition Examination Survey
PCP	=	primary care practitioner

pg = picograms

PIH = pregnancy induced hypertension

RBC = red blood cell

RBC ZP= red blood cell zinc protoporphyrin

RDW = red blood cell volume distributioni width

SGA = small for gestational age

TIBC = total iron binding capacity

TS = transferrin saturation

WHO = World Health Organization

INTRODUCTION

This study describes the appearance of maternal iron-deficiency anemia (MIDA) in a sample of pregnant women living at 6,000 to 7,000 feet above sea level. The purpose of this study was to: a) call attention to the primary care practitioner's dilemma of recognizing MIDA with coexisting compensatory relative polycythemia; b) enhance the recognition of MIDA at Rocky Mountain Altitudes by presenting empiric maternal normal values for red blood cell (RBC) indices collected at the usual landmark screening intervals; c) determine MIDA incidence rates at 6,000 to 7,000 feet elevation; d) test the reliability of the 1989 Centers for Disease Control (CDC) guidelines in identifying MIDA; and e) examine the data for significant relationships between demographic variables and incidence of MIDA.

MIDA is an acquired organic disease occurring during pregnancy, well known as the most common hematologic complication of pregnancy (Bently, 1985 [classic]; Cunningham, MacDonald, Gant, Leveno, & Gilstrap, 1993). Worldwide incidence of MIDA has been estimated at 50 to 60%, ranging to 80% in tropical and developing nations (DeMaeyer & Adiels-Tegman, 1985 [classic]). The Third National Health and Nutrition Examination Survey 1988-1994 (NHANES III) was the first large scale study to include pregnant women and determine MIDA incidence for the general population in the United States. Results for pregnant women are still pending

analysis and publication. Since the introduction of iron fortified foods, baby formulas, and supplemental food programs, there has been a significant decrease in iron-deficiency anemia (IDA) among infants and children. IDA rates in pregnant women and women of child-bearing age remain unchanged (Kim et al., 1992).

Over the past 25 years, MIDA has been increasingly associated with serious complications of pregnancy, poor outcomes, and increased maternal and fetal mortality (Garn, Ridella, Petzold & Falkner, 1981; Murphy, Newcombe, O'Riordan, Colles & Pearson, 1986). Concern for maternal and child health has been escalating in Rocky Mountain states as studies reveal increased rates of maternal mortality, late prenatal care, pregnancy-induced hypertension (PIH), premature labor, increased amniotic fluid indices, intrauterine growth retardation (IUGR), low birthweight (LBW) and small for gestational age (SGA) infants (Maternal and Child Health Bureau, Health Services Division, Health and Environment Department & New Mexico Health Systems Agency, 1986; New Mexico Department of Health [NMDH], Public Health Division, Bureau of Vital Records & Health Statistics, 1996; New Mexico Prenatal Care Network & University of New Mexico, School of Medicine, Maternity and Infant Care Project, 1992; Olmas, Figueroa, Rodriguez, Halac, & Irrazabal, 1988; Unger, Weiser, McCullough, Keefer & Moore, 1988; Yancey, Moore, Brady, Milligan & Strampel, 1992; Yancey & Richards, 1994; Yip, 1987; Zamudio et al.,

1993). Over the past 20 years, several studies have noted a direct relationship between increasing altitude and incidence rates for these complications, particularly above 6,000 feet (McCullough, Reeves & Liljegren, 1977; Moore, Hershey, Jahnigen & Bowes, 1982; Unger et al., 1988; Yancey et al., 1992; Yancey & Richards, 1994; Yip, 1987; Zamudio et al., 1993). Most of these complications are known for strong association with MIDA, hypoxia, or errors in blood volume expansion. Premature labor and LBW have been directly linked to MIDA (Cook & Lynch, 1986; Cook, Skikne & Baynes, 1994; Godfrey, Redman, Barker & Osmond, 1991; Scholl, Hediger, Fischer & Shearer, 1992). Direct relationships between MIDA and other complications remain unknown.

At sea level, MIDA is easily recognized, diagnosed and treated with over-the-counter oral iron supplements. At altitudes above 3,000 feet, recognition of MIDA is complicated by the confounding variable of compensatory relative polycythemia. Since there has been so little maternal research at these altitudes, primary care practitioners (PCPs) lack empirically derived altitude-adjusted reference tables for maternal norms of the traditional screening tests, hemoglobin (HGB) and hematocrit (HCT), which are elevated in high altitude dwellers. Considering the high cost of the associated morbidity, there is pressing need for: a) an altitude-appropriate consensus definition for MIDA; b) altitude-adjusted reference tables

of maternal norms for screening and differential diagnostic laboratory tests; and c) the refinement of MIDA screening guidelines for populations at altitudes above 3,000 feet.

Nurses in advanced practice, such as certified nurse midwives, nurse practitioners, and clinical nurse specialists, are strategically positioned in primary care settings to play a significant role in reducing the incidence of MIDA and its associated morbidity. Advanced practice nurses (APNs) are ideally prepared to provide early identification, appropriate intervention, and individualized patient education, which is the most important feature of successful treatment (DeMaeyer, 1989; Food and Nutrition Board [FNB]; Institute of Medicine [IOM], 1993). Until a substantial database can be amassed to support the formulation of altitude-appropriate norms and standards of care, the ability of APNs and other PCPs to recognize MIDA in populations at middle altitudes remains compromised.

The study questions were:

1. What are the mean empiric maternal values for red cell indices (i.e., HGB, HCT, mean corpuscular volume [MCV], mean corpuscular hemoglobin [MCH] and mean corpuscular hemoglobin concentration [MCHC]) measured at the usual screening intervals during the course of pregnancy (i.e., at less than 20 weeks from the first day of the last menstrual period [LMP], 28 weeks LMP, and 36 weeks LMP), at altitudes of 6,040, 6,400 and 7,000 feet?

2. What is the rate of MIDA when MIDA is defined as observed microcytosis (MCV < 80 fL) and hypochromia (MCH < 27 pg or MCHC < 32 g/dL)?
3. What are the mean and range values for HGB and HCT associated with MIDA at each screening interval at altitudes ranging between 6,000 and 7,000 feet elevation?
4. Do the 1989 CDC Guidelines accurately identify MIDA in this population?
5. Is there a significant relationship between demographic variables (i.e., age, race, socioeconomic status, interconceptual time interval, parity, altitude) and MIDA?

Prior MIDA studies rarely utilized longitudinal data. Longitudinal changes revealed by this study may assist in understanding MIDA at altitudes between 6,000 and 7,000 feet. This altitude level marks the onset of significant increases in complications and poor outcomes of pregnancy observed in prior studies (Jackson, Mayhew & Hass, 1988a; Jackson, Mayhew & Hass, 1988b; McCullough, Reeves & Liljegren, 1977; Moore, Hershey, Jahnigen, & Bowes, 1982; Reshetnikova, Burton, Milovanov & Folkin, 1996; Unger et al., 1988; Yancey et al., 1992; Yancey & Richards, 1994; Zamudio et al., 1993).

It is hoped that this study will stimulate support for a large-scale prospective MIDA study encompassing the Rocky Mountain region. A carefully conducted longitudinal study

with multiple data collection sites at altitudes above 3,000 feet would provide an invaluable database. The database would facilitate the development of a consensus definition, standardized tables of norms, and altitude-appropriate standards of care needed worldwide in primary care facilities serving pregnant populations at middle altitudes.

CONCEPTUAL FRAMEWORK

Conceptual Definitions

The concepts under study are maternal iron-deficiency anemia, and Rocky Mountain Altitudes. Each concept is described and defined below.

Maternal Iron-Deficiency Anemia

Maternal iron-deficiency anemia is a treatable disease that appears in many women during pregnancy. MIDA is notoriously asymptomatic and poses serious threats to the health of the pregnant woman and her fetus. To fully understand the concept of MIDA, it is useful to break the term into its parts. One must be familiar with the normal hematology profile for non-pregnant adult women and the normal changes brought about by pregnancy. For this study, one must also be aware of normal hematologic adaptations to altitude in order to distinguish normal from pathologic changes. Discussion of adaptations to altitude is contained in the section entitled "Rocky Mountain Altitudes".

Anemia

Anemia is most simply described as an organic disease characterized by alterations in red blood cell morphology

and diminished oxygen-carrying capacity of red blood cells. These alterations result in decreased tissue oxygenation, impaired metabolism, cell death, impaired function of major organs, and possibly death. Anemias are categorized into three major groups reflecting the size of RBCs (microcytic, normocytic or macrocytic), and then further classified by the density of hemoglobin pigment (hypochromic, normochromic or hyperchromic) contained in the red cells. Structural classifications narrow the range of possible causes for observed anemias (Brown, 1991; Bushnell, 1992).

Iron Deficiency

Iron deficiency is a progressive deterioration in iron status characterized by three distinct stages; first, exhaustion of iron stores, then iron-deficient erythropoiesis, and finally anemia. Exhaustion of iron stores is objectively identified by: a) drops in HGB, HCT, transferrin saturation (TS), and serum ferritin; b) a rise in total iron-binding capacity (TIBC); and c) the absence of stainable iron in bone marrow macrophages. Iron-deficient erythropoiesis is identified by: a) elevated free erythrocyte protoporphyrin (FEP) or red blood cell zinc protoporphyrin (RBC ZP); b) a drop in TS; and c) possibly a drop in MCV. Anemia is marked by all of the indicators above, plus further drops in HGB, HCT, MCV, and MCH or MCHC. Table 1 integrates tables presented in Herbert (1991), Lee (1993b), and Ulmer and Goepel (1988) for reference and cut-off values for each stage, using sea level norms for non-

Table 1.

Stages of Iron Deficiency with Cut-Off Values for Common Laboratory Indicators

INDICATOR	REFERENCE RANGE	DEPLETED IRON STORES	IRON-DEFICIENT ERYTHROPOIESIS	ANEMIA
HGB (g/dL) [a, b]	12.0-16.0	> 1% drop	8.0-14.0	≤ 8.0
HCT (%) [a, b]	37-47	2-4% drop		> 4% drop
Transferrin saturation (%)[b]	35 ± 10	30	< 16	< 16
Transferrin receptor (mg/L)	2.8-8.5	6.4		> 8.5
Serum ferritin (μg/L)[b]	100 ± 60	20	10-12	< 12
TIBC (μg/L)[b]	330 ± 30	360	390	410
FEP (μg/dL RBC)[b,c]	15-80	30	100	100-1000
RBC ZP (μg/dL)[b,c]	≤14		> 60	> 60

Table 1 (cont.)

INDICATOR	REFERENCE RANGE	DEPLETED IRON STORES	IRON-DEFICIENT ERYTHROPOIESIS	ANEMIA
MCV (μ^3)	80-95	no change	maybe < 80	< 80
MCH (pg)	27-31	no change	no change	< 27
MCHC (g/dL)	32-36	no change	no change	< 32
Serum iron (μg/dL)	120 ± 30	115	< 60	< 40

Note. Values for non-pregnant women at sea level, integrating tables from: a) "Diagnosis and treatment of iron disorders: Introduction and medicolegal considerations," by V. Herbert, 1991, Hospital Practice, 26(Suppl. 3, April), p.4-6. Copyright 1991 by McGraw-Hill Technological Group; b) "Microcytosis and the anemias associated with impaired hemoglobin synthesis," by G.R. Lee, 1993, in Wintrobe's Clinical Hematology (9th ed.) by G.R. Lee, T.C. Bothwell, J. Foerster, J.W. Athens and J.N. Lukens (Eds.), 1993, pp.791-807. Copyright 1993 by Lea & Febiger [publishers]; c) "Anemia, ferritin and pre-term labor," by H. Ulmer & E. Goepel, 1988, Journal of Perinatal Medicine, 16(5-6), pp. 459-465. Copyright 1988 by the World Association of Perinatal Medicine, Walter DeGruyter, Inc. [publisher]. [a]Values vary with altitude, stage of pregnancy, age, gender, race and cigarette smoking. [b]Values vary when inflammatory disease is present. [c]Values vary with lead poisoning.

deficiency often co-exists with other nutritional deficiencies (i.e., folic acid, vitamin B_{12}, and protein) which alter the expected values for some laboratory indicators.

Iron-Deficiency Anemia

Dorland's Illustrated Medical Dictionary defines iron-deficiency anemia (IDA) as an "anemia characterized by low or absent iron stores, low serum iron concentration, elevated free erythrocyte porphyrin, low transferrin saturation, elevated transferrin, low serum ferritin, low hemoglobin concentration or hematocrit, and hypochromic microcytic red blood cells" (Dorland's Illustrated Medical Dictionary, 1994, p. 73). IDA is the most common nutritional deficiency worldwide, affecting 1.2 billion people (Viteri, 1994). The NHANES III data suggests that 3.3 million women of child-bearing age in the U.S. have IDA (Looker, Dallman, Carroll, Gunter & Johnson, 1997).

In the past, many studies used World Health Organization (WHO) cut-off values for HGB as the only determinant to define IDA. Hemoglobin by itself is a poor indicator of iron status because it does not isolate iron-deficiency from acute inflammatory processes, chronic disease, thalassemias, or hemoglobinopathies. Normal ranges for HGB vary by gender, age (Yip, Johnson & Dallman, 1984), race (Isaacs, Altman & Yalman, 1986; Lazebnik, Kuhnert & Kuhnert, 1989; Meyers, Habicht, Johnson & Brownie, 1983; Perry, Byers, Yip & Margen, 1992), cigarette smoking,

duration of pregnancy (Scott & Pritchard, 1967) and altitude (Buys de Jorge et al., 1988; Dainiak, Spielvogel, Sorba & Cudkowicz, 1989; Hurtado, Merino & Delgado, 1945 [classic]; Piedras, Loria & Galvan, 1995). Recent nutritional surveys and IDA studies have used various combinations of laboratory indicators to define "true IDA". As laboratory technology advances, definitional criteria vary considerably, and it becomes difficult to compare studies.

In the United States, the majority of IDA is due to acute blood loss, or dietary patterns of: a) inadequate intake of bio-available heme-iron containing foods; b) excessive intake of substances that block iron absorption in the duodenum and gastrointestinal tract; c) inadequate intake of substances that enhance iron absorption; or d) the combined effects of all three patterns (Dimperio, 1988; Farley & Foland, 1990; Finch & Cook, 1984). Other common causes of IDA include chronic blood loss, or malabsorption syndromes as encountered in chronic disease, sprue, substance abuse, eating disorders (i.e., anorexia, bulimia, and pica), or following surgical excision of portions of the stomach, duodenum, or small intestine. Less common causes of microcytic hypochromic anemias include: a) accelerated hemolysis; and b) genetic or chemically induced errors of metabolism that affect the synthesis of either the heme or globin portion of the HGB molecule (i.e., thalassemias, hemoglobinopathies, sideroblastic anemias, gallium treatment, lead or aluminum toxicity).

High rates of IDA are consistently reported for infants, children, adolescents, women who are menstruating, pregnant or lactating, and hemodialysis patients. Populations commonly identified as high risk include the poor, minorities, and the geographically isolated. Although 11 to 25% of American women of child bearing age have no iron stores, only three to five percent have frank anemia (Cook, Skikne, Lynch & Reuser, 1986; Dallman, Yip & Johnson, 1984; IBNMRR, 1993; Looker, Dallman, Carroll, Gunter & Johnson, 1997; Pilch & Senti, 1984). In U.S. studies prior to 1990, rates of IDA in Hispanic Americans were just slightly above those for non-Hispanic Whites, and rates in Native Americans were higher than those for Hispanics but less than rates in Blacks (Fanelli-Kuczmarski & Woteki, 1990; Looker, Johnson, McDowell & Yetley, 1989; National Center for Health Statistics & Department of Health and Human Services, 1985). The NHANES III data reveals a significant increase in IDA for Hispanics which is now higher than rates reported for Blacks (Looker, Dallman, Carroll, Gunter & Johnson, 1997). One out of four American prenatal clients has impaired iron status prior to conception. At highest risk are pregnant adolescents with pre-existing high iron demand to accommodate maternal growth, and impoverished, multiparous women with closely spaced pregnancies who fail to recover iron stores prior to conception (Dimperio, 1988; Lanzkowsky, 1985; Leshan, Gottlieb & Mark, 1995).

Although IDA is often asymptomatic, some clients present with complaints of paresthesias, reduced endurance for activity, chronic fatigue, difficulty in concentration, burning or soreness of the tongue, ulcers or fissures at the corners of the mouth, or chronic gastritis. IDA has been associated with a long list of impairments including: reduced attention span, learning disabilities, impaired cognitive, psychomotor and physical development in children and adolescents, impaired cell-mediated immunity, reduced numbers of circulating T cells, reduced killing capacity of polymorphonuclear leukocytes, reduced physical work capacity, impaired oxidative metabolism, and impaired athletic performance (as cited in Cook & Lynch, 1986, and in Cook & Skikne, 1989). Chronic IDA may manifest as koilonychia ("spoon nails"), glossitis, stomatitis, esophageal webs, chronic or atrophic gastritis, and malabsorption (as cited in Cook & Lynch, 1986).

Normal Hematologic Changes During Pregnancy

Over the past forty years, research has yielded significant insight into the physiologic coping mechanisms of human pregnancy. Scott and Pritchard's classic 1967 study revealed significant differences in HGB concentration between pregnant and non-pregnant women, and fluctuations in maternal HGB throughout the course of pregnancy. In this study of healthy young women with proven iron stores and normal folate levels, Scott and Pritchard (1967) found mean hemoglobins of 11.5 g/dL in women 16 to 22 weeks LMP, and

12.3 g/dL in pregnant women at term, compared to a mean HGB of 13.7 g/dL in the non-pregnant control group. During pregnancy, the white blood cell count normally rises to between 10,000 and 14,000 cells per ml of whole blood. Total blood volume gradually increases until the twentieth week LMP, and rapidly expands between 20 and 32 weeks LMP. At 32 weeks LMP, blood volume expansion stabilizes at a level ranging between 20 and 150% above baseline (an increase of at least 1000 cc) until delivery. Plasma volume rises minimally in the first 12 weeks, more dramatically between 12 and 32 weeks LMP, and remains at a level about 50% above baseline between 32 weeks LMP and delivery. The maternal red cell mass increases by 35 to 45% (250-500 cc) throughout pregnancy, with the greatest rise occurring between 28 and 36 weeks LMP. Throughout pregnancy, maternal stroke volume and cardiac output increase, reaching a maximum at term of about 30% above baseline (Bently, 1985; Hytten, 1985; Scott & Pritchard, 1967; Viteri, 1994).

Normal Changes in Iron Demand During Pregnancy

In the first trimester, iron demand increases only slightly, and iron stores, if present, supply the additional iron required. In the second trimester, there is a normal period of hemodilution, commonly referred to as the "physiologic anemia of pregnancy", as plasma volume increases faster than RBCs can be synthesized. The uterus, placenta and fetus are undergoing rapid growth. In an attempt to keep pace with the demand for red cells, the

spleen releases immature red cells, remaining maternal storage iron is "dumped" into the maternal circulation, and increased erythropoietin is released from the glomeruli of the kidneys. At 26 to 28 weeks LMP, significant drops in HGB can be detected. A drop of 2.2 g/dL below baseline is considered normal (Scott & Pritchard, 1967). Peak iron demand occurs at about 32 weeks LMP. At 36 weeks LMP, iron demand drops until delivery, and a HGB value 1.4 g/dL below baseline is normal (Scott & Pritchard, 1967). At delivery, average maternal blood loss is about 400-500 cc. The maternal red cell mass contracts to pre-pregnancy levels in the initial post-partum period. Total "iron cost" of a normal singleton pregnancy ranges between 500 and 700 mg iron (Bently, 1985; Dimperio, 1988; Lamparelli et al., 1988b; Lee, 1993b). Breast-feeding women continue to have slightly increased iron demand for the synthesis of breast milk, even when they are not menstruating.

There is general agreement that it is nearly impossible for pregnant women to meet their increased needs for iron in the latter half of pregnancy through dietary sources alone (Bently, 1985; DeCherney & Pernoll, 1994; DeMaeyer, 1989; FNB & IOM, 1993; Kitay, 1994; Letsky, 1991; Viteri, 1994; Williams & Wheby, 1992). Universal iron supplementation during the latter half of pregnancy, a common practice in developed countries, is still debated in the literature following reports of excessive perinatal mortality, fetal growth retardation, LBW, PIH, and pre-term delivery

associated with maternal iron toxicity and above-average maternal HGB concentrations (Garn, Ridella, Petzold & Faulkner, 1981; Goodlin, Holdt & Woods, 1982; Koller, 1982; Koller, Sagan, Ulstein & Vaula, 1979; Koller, Sandevei & Sagen, 1980; Murphy, Newcombe, O'Riordan, Coles & Pearson, 1986). For this reason, it is important to identify those who truly require additional iron prior to initiating iron therapy.

Evaluation of Iron Status During Pregnancy

There is a long tradition of reliance on HGB and HCT as inexpensive screening tests for MIDA. For the past 15 years, serum ferritin (the new "gold standard"), TS, FEP, and serum transferrin receptor have been promoted as more sensitive indicators of maternal iron status (Guyatt et al., 1992; Ho, Yuan & Yeh, 1987; Lazebnik, Kuhnert & Kuhnert, 1989; Lee, 1993b; Lewis & Rowe, 1986; Marsh, Nelson & Koenig, 1983; Schifman, Thomasson & Evers, 1987; Skikne, Flowers & Cook, 1990; Ulmer & Goepel, 1988; Yepez et al., 1994). None of the newer indicators are mentioned in the American College of Obstetricians and Gynecologists (ACOG) "Standards for Obstetric-Gynecologic Services" (ACOG, 1989), nor in the "Guidelines for Perinatal Care" co-authored with the American Academy of Pediatrics (AAP)(AAP & ACOG, 1992). Serum iron measures are of questionable merit for differential diagnosis of MIDA since a) levels often fall during pregnancy even when iron stores are present, b) there is wide diurnal variation in individuals, and c) there is

significant variation from laboratory to laboratory (Lee, 1993b).

In 1985, Bull and Hay (1985) concluded that norms for MCV, MCH and MCHC are universal and reliable as laboratory quality assurance standards. Although red cell distribution width (RDW) is 90-100% sensitive for iron deficiency, it is only 50-70% specific (Lee, 1993a). Ulmer and Goepel (1988) make a strong case for eliminating HGB and MCH determinations altogether, since serum ferritin levels less than 20 µg/L are diagnostic of IDA (depleted stores) at any time during pregnancy, and highly predictive of pre-term labor ($p < 0.001$). They observed pre-term (before 37 weeks LMP) labor rates of 52% when third trimester ferritin was less than 10 µg/L, 43% with values between 10 and 20 µg/L, and nine percent when ferritin was above 20 µg/L. They also found that HGB and MCH were poorly correlated with both serum ferritin and pre-term labor.

Maternal Iron-Deficiency Anemia

Maternal IDA is a pathologic deterioration in maternal iron status, beyond the lower limits of normal changes attributable to pregnancy alone. MIDA is objectively identified by: a) the presence of microcytic [MCV < 80 fL], hypochromic [MCH < 27 pg or MCHC < 32 g/dL] RBCs, b) drops in HGB greater than 2.2 g/100 ml from baseline, c) drops in HCT greater than 4% from baseline, d) TS less than 16%, e) serum ferritin less than 10 µg/L, f) serum transferrin receptor greater than 8.5 mg/L, g) TIBC greater than 410

μg/L, h) FEP greater than 100 μg/dL RBC, or RBC ZP greater than 60 μg/dL, i) serum iron less than 40 μg/dL, and j) the absence of stainable iron in bone marrow macrophages. Further confirmation of MIDA is achieved with a two week trial of oral iron supplements, resulting in a rise in HGB of 2 g/dL or more.

Approximately 95% of maternal anemias in the U.S. are due to iron-deficiency (Bently, 1985; Cook, Skikne, Lynch & Reuser, 1986; Dallman, Yip & Johnson, 1984). Pilot samples from NHANES II 1976-1980 revealed U.S. MIDA rates of 10.7 to 25.5% (Expert Scientific Working Group, 1985). Prior U.S. studies of low-income women reported a third trimester MIDA incidence of 18 to 24% in Whites, and 38 to 45% in Blacks (CDC, 1990; Kim et al., 1992). Incidence of MIDA in low-income women varied significantly by race: non-Hispanic Whites were lowest (9.5% in the second trimester, 24% in third trimester), followed by Hispanics (11% and 32% respectively), then Asians and Pacific Islanders (12% and 27%), then Native Americans (13% and 33%), and highest rates were in non-Hispanic Blacks (22% and 45%). Among all races, rates of MIDA in the third trimester were at least double the rates observed in the second trimester (CDC, 1990; and as cited in IBNMRR, 1993, p. 17).

Maternal risks of MIDA. The increased risk of maternal death during pregnancy is 4.6% with mild MIDA and 11.25% with severe MIDA (as cited in Viteri, 1994). MIDA has been associated with the following maternal complications and

poor outcomes of pregnancy: pre-eclampsia, PIH, feto-maternal hemorrhage (Frikiche, Cusumano, Senterre & Lambotte, 1990), post-partum hemorrhage, cardiac failure during labor, and poor tolerance of minimal blood loss during delivery. Suppression of the immune system in anemic pregnant women increases their vulnerability to urinary, vaginal and cervical infections, pyelonephritis, tuberculosis and malaria (as cited in Viteri, 1994).

Fetal risks with MIDA. Infants of women who had mild MIDA during pregnancy are at low risk for hematologic deficits at birth. However, infants of women who had severe MIDA are often premature, LBW, and at high risk for IDA, low iron stores, and smaller circulating hemoglobin mass, which manifests at two months of age (as cited in Viteri, 1994). Poor fetal outcomes associated with MIDA include: dysmaturity, SGA, LBW (Unger et al., 1988; Fleming et al., 1989), pre-term birth (Klebanoff, Shiono, Selby, Trachtenberg & Graubard, 1991), abortion, stillbirth, and fetal hypoxia during labor (Bhargava et al., 1989; Colmer, 1990).

Definitions of MIDA. In 1989, the CDC published guidelines and definitional criteria for IDA in infants, children, pregnant women (see Table 2), and women of child bearing age for use in the public health sector (CDC, 1989). The criteria listed cut-off values for HGB and HCT only. Reference tables were based on data from NHANES II and four European iron supplement studies conducted between 1975 and

Table 2.

CDC Criteria - Cut-off Values for IDA in Adult Women at Middle Altitudes

			PREGNANT					
	NON-PREGNANT		≤20 wks LMP		28 wks LMP		36 wks LMP	
ALTITUDE[a]	HGB[b]	HCT[c]	HGB	HCT	HGB	HCT	HGB	HCT
sea level	12.0	36.0	10.6	32.0	10.7	32.0	11.4	34.0
5000-5999	12.5	37.5	11.1	33.5	11.2	33.5	11.9	35.5
6000-6999	12.7	38.0	11.3	34.0	11.4	34.0	12.1	36.0
7000-7999	13.0	39.0	11.6	35.0	11.7	35.0	12.4	37.0
8000-8999	13.3	40.0	11.9	36.0	12.0	36.0	12.7	38.0
9000-9999	13.6	41.0	12.2	37.0	12.3	37.0	13.4	40.0
10,000+	14.0	42.0	12.6	38.0	12.7	38.0	13.4	40.0

Note. Suggested cut-off values for IDA in women aged 18 to 45 years as calculated from tables in "CDC Criteria for Anemia in Children and Childbearing-Aged Women", Mortality and Morbidity Weekly Report, 38(22), 400-404 (June 9, 1989).
[a]Elevation in feet. [b]HGB g/dL. [c]HCT %.

1982. Additional calculations were suggested for smoking and altitude adjustments. Altitude adjustments were based on data from children in mountain states, and a classic Peruvian study on men (Hurtado, Merino & Delgado, 1945).

Examples of operational definitions used in prior MIDA studies are:

1. HGB < 11.0 g/dL at anytime during pregnancy (WHO, 1972),
2. HGB < 11.0 g% and serum ferritin < 12 ng/ml in pregnant women at term (Ho, Yuan & Yeh, 1987),
3. HGB < 11.0 g/dL, TS < 16.0% and serum ferritin < 12 µg/L in Black pregnant women at term [at 5,000 feet elevation] (Lamparelli et al., 1988a),
4. "Low HGB" and 2 abnormal values out of 3 for serum ferritin (< 12 µg/L), FEP (> 28 µg/dL), or TS (< 16.0%) in post-partum Nigerian women (Daouda et al., 1991),
5. "a hemoglobin concentration (or hematocrit) that is below the 95% confidence interval (i.e., below the 2.5th percentile) for healthy, well-nourished individuals of the same age, sex, and stage of pregnancy", with cut-off values for first, second and third trimester HGB and HCT as follows: HGB < 11.0, 10.5, and 11.5 g/dL respectively, and HCT < 33, 32, and 34% respectively (Life Sciences Research Office, 1984, as cited in FNB & IOM, 1993),
6. serum ferritin < 12.0 µg/dL [at 5,200 feet elevation] (Lamparelli et al., 1988b), and

7. HGB < 10.0 or 11.0 g/dL [at 5,400 feet elevation] (Watson & Murray, 1969).

Conceptual definition of MIDA. MIDA is a treatable, frequently asymptomatic disease acquired during pregnancy, due to a failure to meet the increased physiologic requirements for iron. This failure of adaptation may be rooted in physiologic, psychologic, social, economic, political or environmental circumstances. These circumstances may include, but are not limited to: a) pre-conceptual nutritional status, b) dietary patterns, c) eating disorders, d) substance abuse, e) religious practices, f) cultural practices related to pregnancy, g) socioeconomic status, h) closely spaced pregnancies, i) extremes of age at conception, j) geographic isolation, k) political environment, or l) possible genetic factors related to race. MIDA is a serious threat to maternal and infant health. It is known to cause premature labor and LBW infants, and is associated with numerous complications of pregnancy and poor pregnancy outcomes.

Rocky Mountain Altitudes

The term "Rocky Mountain Altitudes" was selected to connote the environment within which this study was conducted, and to highlight the impact of environment upon the definitional criteria for MIDA. In conceptualizing "environment" as a variable one must consider both the physical and social circumstances affecting a population. The interaction between physical and social environment

variables may be so intertwined that it is impossible to isolate the variables to observe effects due strictly to one variable. Environmental, socioeconomic and demographic factors exert substantial physiologic influences on the sample population for this study. The effects of these variables are described following a brief discussion of terms encountered in the literature.

It is helpful to be reminded of the mathematical conversion factor of 3.281 (1,000 meters=3,281 feet) when reviewing and comparing altitude literature, as both measures frequently appear. When reviewing physiologic studies conducted at high elevations, the following terms are common. In discussions of observed variations, the term "at altitude" is often used as a convenient contraction for "at altitudes above 3,000 feet or 1,000 meters". Although no formal criteria were encountered, the term "high altitude" generally referred to elevations above 3,000 meters or 10,000 feet (i.e., Pamir, Tien Shan and Rocky Mountains), and "very high" or "extremely high altitude" referred to elevations above 5,000 meters or 15,000 feet (i.e., Andes and Himalayas). In Colorado studies, Denver (elevation 5,000 feet) was considered "at middle altitude", whereas Leadville (elevation 10,000 feet) was "at high altitude".

Physical Environment

The Rocky Mountain region hosts a population of about 12.5 million, and includes the states of Arizona, Colorado,

Idaho, Montana, New Mexico, Utah and Wyoming. Each state contains mountains higher than 12,500 feet, with the highest peak at 14,400 feet. Altitudes of populated areas range from plateaus at 3,000 feet to mountain villages at 10,000 feet or more.

The sites included in this study, Taos, Las Vegas, and Santa Fe, New Mexico, are located at altitudes of 6,040, 6,400 and 7,000 feet respectively. The town sites are located on the measured plateaus, but their outskirts merge with foothills of the Sangre de Cristo and Santa Fe mountains, whose nearby peaks range between 11,000 and 13,000 feet. The Sangre de Cristo range is considered the southeastern fork of the Rocky Mountains. The climate is arid high desert with diurnal air temperature variations of 20 to 40 degrees Fahrenheit and significant winter snowfall at elevations above 5,000 feet. Although New Mexico's population density is 13.94 people per square mile, one third of the population lives within 30 miles of Albuquerque city limits. Only three out of 33 counties have populations above 100,000. The remainder of the state is quite rural and there are large land areas of wilderness scattered throughout the state. For the cities included in this study, city limits range from about five to twelve miles in diameter. In all three cases, rural environments begin within 2 miles of city limits. All three cities lie between 60 and 140 miles northeast of Albuquerque.

Normal hematologic adaptations to altitude. As an adaptation to the physiologic stress of lower atmospheric pressure and lower oxygen tension, acclimated populations at altitudes above 3,000 feet demonstrate compensatory relative polycythemia due to chronic hyperactive erythropoiesis (Athens & Lee, 1993; Buys de Jorge et al., 1988 [classic]; Reynafarje, Lozano & Valdivieso, 1958 [classic]; Ross, 1988; Winslow et al., 1989). The resulting larger red cell mass is revealed as elevated RBC count, HGB and HCT, potentially masking signs of anemia. Total blood volume is increased, but total plasma volume is decreased, resulting in increased blood viscosity (Athens & Lee, 1993; Dainiak, Spielvogel, Sorba & Cudkowicz, 1989; Sanchez, Merino & Figallo, 1970).

Red cell indices at altitude. Table 3 summarizes reference values for RBC indices in adult non-pregnant women at sea level, and presents empiric values obtained in studies of non-pregnant women at sea level and at altitudes above 3,000 feet. Note the altitude-dependent variations in RBC count, HGB and HCT, whereas other indices remain stable within sea level normal limits.

There are minor discrepancies in the literature regarding changes in MCV at altitude. Most investigators report a slight increase (upper limits of normal range) or no change from sea level norms. In Mexico, Ruiz-Arguelles et al. (1980) observed a significant drop of more than five percent in mean MCV between sea level and 6,000 feet,

Table 3.

RBC Indices at Sea Level and at Altitudes Above 3,000 Feet

	SEA LEVEL[a]	SEA LEVEL[b]	3280 FEET[c]	6100 FEET[c]	7280 FEET[c]	7457 FEET[d]	8760 FEET[c]
HGB (g/dL)		13.5	13.8	14.5	14.6	15.2	15.3
range	12-16	11.7-15.5				12.8-17.7	
HCT (%)		40.0	42.4	45.0	44.6	45.4	46.9
range	37-47	35-45				41.5-50.0	
RBC (million/mm^3)		4.42	4.69	4.92	4.99	5.01	4.95
range	4.2-5.4	3.8-5.1				4.27-6.01	
MCV (fL)		90.0	90.9	91.2	89.7	91.2	94.7
range	80-95	81-100				71-105.5	
MCH (pg)		30.6				30.33	
range	27-31	27-34				25-35	
MCHC (%)		33.9	32.3	32.4	32.7	33.37	32.6
range	32-36	32-36				29.3-37	
n=		1999	91	110	71	100	91

Note. All values are for non-pregnant women.
[a]Pagana & Pagana (1992) [textbook]. [b]Yip, Johnson & Dallman (1994) [data from NHANES II, races pooled]. [c]Ruiz-Arguelles et al. (1980) [required transferrin saturation > 15%]. [d]Robles-Gil & Gonzáles-Terán (1948) [includes ages 14-25]. Complete source references are presented on the Reference List.

indicating larger numbers of small red cells. Between 6,000 and 7,000 feet, MCV was stable but below lower limits of sea level norms. At 8,700 feet, mean MCV returned to sea level norms. The bulk of data supports the concept of universal normal limits of human RBC size, independent of race, gender, age or altitude. MCV may increase by 3 million/mm^3 in smokers at any altitude, due to increased levels of carboxyhemaglobin.

In Equador, Yepez et al. (1994) conducted a one month trial of iron and folic acid supplementation, comparing responses at sea level and at 9,200 feet elevation. They utilized an altitude correction factor suggested by Hurtado et al. (i.e., 4% for every 1000 meters above sea level). They found WHO cut-off values for HGB to have high specificity, but low sensitivity (58%) at sea level, and no sensitivity at 9,200 feet elevation. They concluded that HGB alone was a poor criteria for anemia at both sea level and 9,200 feet.

Athens and Lee (1993) suggested that there may be adaptive mechanisms which result in specific local hematologic variations. They listed geographic, geologic, occupational, cultural, dietary pattern, lifestyle and racial factors which may explain the red cell indicator differences observed by Winslow et al. (1989), who compared Himalayan Sherpas to Andean Quechas living at the same altitude level.

Other indicators of iron status at altitude. Serum ferritin, TS and TIBC appear to be unaffected by altitude, and are useful as diagnostic determinants of anemia (Hofvander, 1968; Ross, 1972). Although serum iron is unaffected by altitude, it is a poor measure of iron status during pregnancy (Lee, 1993b).

Socioeconomic Environment

Population figures from the 1994 census for Taos, Las Vegas, and Santa Fe were as follows: town site populations were 4,400, 15,600, and 62,500 respectively, and county populations were 25,000, 27,350, and 112,200 respectively. The major racial groups populating the state were non-Hispanic Whites (50%), Hispanics of both Spanish and Mexican descent (40%), and Native Americans (9%) including Pueblo, Apache, Kiowa and Navajo groups. In 1994, New Mexico was ranked the eighth fastest growing state in the nation and the Rocky Mountain region hosted five of the ten fastest growing states (NMDH, 1996).

The following statistics reflect 1994 New Mexico data unless otherwise noted. Per capita personal income statewide was $17,106, ranking New Mexico 47th in income, with 20% of the population living below federal poverty level. Per capita personal income in Taos county was $13,569, in San Miguel county $12,294 and in Santa Fe $22,538. The 1994 national rate for families living below poverty level was 10%. In Taos, San Miguel and Santa Fe counties, rates were 23.8, 26.3 and 10.4% respectively. The

Medicaid eligible population statistics for March 1997 were as follows: for the entire state, 14.53% (245,802 out of 1,691,645), for Taos, San Miguel (Las Vegas) and Santa Fe counties, 8.6%, 23.32% and 7.12% respectively (personal communication, Anthony Garcia, New Mexico Medical Assistance Office, May 1997 [see Appendix A]). The median age was 32.4 years, reflecting the unusually high fertility rate and large population of children. There were on average 33 marriages, 27 divorces, 76 births and 33 deaths per day statewide (NMDH, 1996; NMDH, 1997).

In 1994, the New Mexico birthrate, which has been significantly higher than the national birthrate for the past 20 years, was at an all time low of 16.7 live births per 1,000 population compared to the national rate of 15.2. Birthrates in Taos, San Miguel and Santa Fe counties were 14.6, 14.4 and 13.3 respectively. In 1993, the statewide birthrate among mothers aged 15 to 19 years was 37% higher than national averages. Forty percent of births and 80% of legal induced abortions were to unmarried women. Ninety-eight percent of births occurred in hospitals. Eighty percent of births were physician assisted and about 17.5% were certified nurse midwife assisted.

In 1994, there were five maternal deaths in New Mexico, yielding a maternal death rate of 18 per 100,000 live births compared to 7.0 nationally. In 1995, the New Mexico maternal death rate was 11.1 compared to 6.3 nationally. The statistic for maternal death rate varies widely each

year, and is skewed due to the small population. The New Mexico maternal death rate is generally above national rates. Causes of maternal deaths between 1992 and 1995 were PIH, pregnancy-related infection, pulmonary embolism and hemorrhage due to placenta previa. Fetal and infant mortality rates are consistently lower than national rates (NMDH, 1996; NMDH, 1997).

The 1994 statewide incidence of LBW was one out of every 14 births, 7.3%, or 73 per 1,000 live births. LBW was above national averages in mothers aged 25 to 39 years. Five New Mexico counties reported LBW rates between 20 and 43% in mothers under 15 years old. Four counties reported LBW rates between 25 and 40% in mothers over 40 years old. The three year aggregate incidence of LBW for 1993 to 1995 in Taos, San Miguel and Santa Fe counties was 10.1%, 10.5% and 6.7% respectively, compared to the national rate of 7.3% (NMDH, 1996; NMDH, 1997).

In summary, Taos and San Miguel counties had high rates of poverty and LBW whereas Santa Fe had rates closer to national rates. Birthrates in all three counties were 1-2% lower than the national rate. Fetal and infant death rates were lower than national rates. Maternal deaths were not analyzed by county, so no conclusion can be drawn. Two of the four causes of maternal death listed were complications associated with MIDA in the literature.

Conceptual Definition of Rocky Mountain Altitudes

In conceptualizing the term "Rocky Mountain Altitudes", one concludes that a) Rocky Mountain inhabitants live at altitudes ranging from 3,000 to 10,000 feet elevation, b) these elevations are considered "middle altitude" by informal standards, and c) middle altitude is an environmental factor that exerts a physiologic stress, resulting in hematologic adaptations. Hematologic adaptations to altitude are expressed objectively as elevations in some RBC indices (RBC count, HGB and HCT), increased blood volume and viscosity, and decreased plasma volume, all of which vary directly with increasing altitude. There is insufficient published data to determine altitude specific corrected norms for these adaptations, or whether the hyperactive erythropoietic adaptation to middle altitude is sufficient to withstand the additional stress of pregnancy.

The literature suggests that socioeconomic status and certain demographic variables are strongly associated with IDA. Also, there may be unidentified local or genetic factors influencing hematologic adaptation to altitude. These factors may be impossible to isolate individually from the effects of altitude alone. Of particular concern in this study are the factors of race, socioeconomic status, high fertility and possible frequent travel to altitudes more than 1,000 feet lower or higher than the domicile.

For this study, Rocky Mountain Altitudes is conceptually defined as: a) an arid, mountainous physical environment of such high vertical elevation above sea level that atmospheric pressure and oxygen tension are reduced, forcing human inhabitants to physiologically adapt in the form of hyperactive erythropoiesis, elevated RBC count, and elevated HGB and HCT values; and b) a socioeconomic environment of low population density, high fertility, high divorce rate, low per capita income, and an unusual racial mix.

Theoretical Framework

This study could have been applied to several theoretical frameworks including: a) Roy's Adaptation Model - the physiologic mode; b) a physiologic version of Bertalanffy's Systems Theory; and c) a modified, physiologic version of Stress Theory, integrating concepts from Selye, Hill, and McCubbin. However, the Starfield model of "The Health Services System" (Starfield, 1996), popularly known as "The Starfield Model of Primary Care", was selected as the most appropriate framework. Although all of these models can be used to explain the physiologic phenomenon under study, Starfield's model also clarifies a constellation of issues encountered in the primary care context.

Starfield's Model

Starfield's model first appeared in the literature in 1973 (Starfield, 1973). In 1992, Starfield elaborated upon

the concepts in the model, demonstrated the application of the model to primary care, and described potential applications to evaluation of services and policy development (Starfield, 1992). In 1996, Starfield discussed the use of the model for guiding primary care research (Starfield, 1996). Starfield's model presents an effective framework for a) identifying particular features of the health care system, and b) understanding how these features impact the function of the system, and the health status of the population. A creative integration of systems and interactionist theories, the model a) classifies health-services variables into categories of structure, process and outcome, b) illustrates the relationship between the categories, and c) identifies intervening factors in the primary care context. Ultimately, the model reveals the relationship between the primary care system and the health status of the population it serves as the result of an interactive process between the providers of care and the receivers of care. By simply shifting focal points, the same model can be utilized by several disciplines for multiple purposes (i.e., developing standards for clinical practice, focusing and directing research, evaluating health service delivery). The model utilizes familiar, straightforward concepts that readily address a) the practitioner's dilemma of problem recognition [MIDA], b) the influence of the peculiar environment [Rocky Mountain

Altitudes], and c) the relationship between problem recognition and health outcome.

The goal of any health services system is to promote the well being of the population it serves. The population ("persons") defines "well being" and identifies specific health care needs within the context of its cultural beliefs and values, religious beliefs, prevailing political structure, socioeconomic structure, and physical environment. The function of the primary care system is to serve as the individual's first point of contact with the health services system. The primary care system (out-patient services) must effectively address a wide variety of health concerns, whether of an acute, chronic or maintenance nature. Where it is available, secondary care (out-patient specialist services) is activated when individuals present health problems requiring more sophisticated assessment, monitoring or intervention related to a particular body system. Tertiary care (hospitalization) is activated when intense specialized care is required to preserve and restore the health of the individual.

Structure

Using Figure 1 as a reference point, it is clear that structural features must effectively interface with the social and physical environment, in order to be relevant to the population ("persons") served. The structure must include personnel that are educated to address issues identified by "persons" as health care needs. The range of

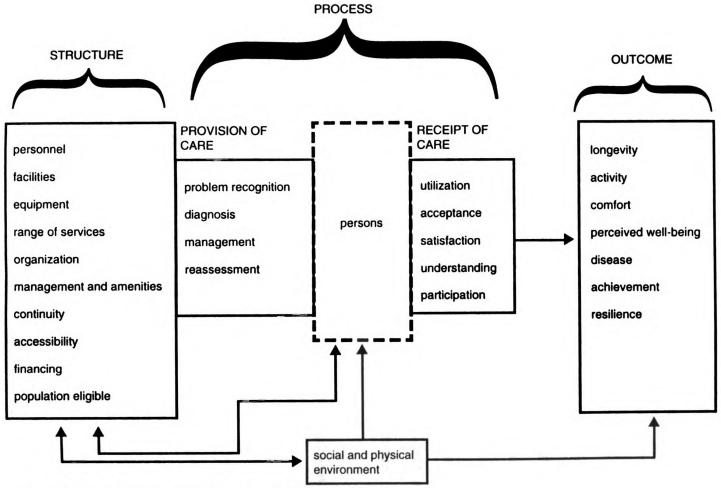

Figure 1. The Starfield Model of The Health Services System.
Note. adapted from **Primary Care: Concept, Evaluation and Policy** by B. Starfield, 1992 New York: Oxford University Press, p.13. Copyright 1973 by Barbara Starfield, MD. Figure is rotated from vertical to horizontal format.

services must address a variety of health concerns. The system must be accessible (physically and financially) and culturally acceptable to a significant portion of the population, and provide some assurance of continuity. The means of financing the system must be appropriate, adequate and acceptable within the context of the socio-cultural, political and physical environment to permit continuation of the system. Facilities and equipment must be adequate to allow provision of care, and appropriate for the social and physical environment. Management and amenities within the system must promote the function and continuation of the system. All structural features must be in place and functional to permit the process of care to occur (Starfield, 1992).

The bi-directional arrow connecting structure and environment implies that environmental features (i.e., physical environment, socioeconomic factors, cultural beliefs related to health, social structure) exert strong influence over structural features (i.e., location, size and type of facilities, transport, type and use of supplies and equipment, range of services, types of personnel, financing, eligible population). It also implies that structure affects both the social and physical environment. Examples of structure affecting the social environment include: a) the employment of members of the population; b) the provision of services to the target population; c) the potential introduction of different beliefs or values; and

d) the attraction of visitors (staff or clients) from other locations. Examples of structure affecting the physical environment include: a) changes related to transportation of people, supplies and equipment; b) building or alteration of physical structures related to the provision of services (i.e., roads, facilities, support services, housing, food services, waste management); and c) increased utilization of natural resources and utilities.

The bi-directional arrow connecting persons and structure implies that "persons" exert strong influence on structure and vice versa. "Persons" identify specific health concerns. Unless structure addresses these concerns, "persons" will not utilize the system. Structure must define the limits on the range of services and the population eligible in order to a) establish realistic expectations and maintain credibility with "persons", and b) promote the effective function and continuation of the system (Starfield, 1996).

Process

The process of care is dependent upon structure, but features both the individual and interactive activities of the providers of care and the recipients of care. The provider must be able to recognize health problems, diagnose problems accurately, manage problems with the use of appropriate and acceptable interventions, and reassess the effectiveness of the management plan. The provider must be educated and skilled, communicate effectively, be aware of

the social and physical environmental factors affecting "persons", provide health education related to specific diagnoses, and perform these functions in a manner acceptable to "persons". The receiver must access the system (utilization) and participate in the process of care by: a) presenting health concerns; b) participating in the assessment phase; c) understanding the health problem; d) providing input in the selection of a management plan that is acceptable to both parties; and e) participating in the plan of care. The effectiveness of the interactive process determines outcome.

Outcome

According to Starfield's model, the health outcome for the receiver, and ultimately, the health status of the population are the result of the interactive process of care, as indicated by the uni-directional arrow linking process and outcome. If there has been good interaction, outcomes will be favorable (i.e., prevention or management of disease, increased comfort, longevity, activity and well being of persons utilizing the system). If there has been poor interaction, outcomes will be unfavorable (i.e., no change, spread or increase in disease, or worsening of health status). Unfavorable outcomes can be traced back to ineffective process or structure.

Outcome is also partially dependent on social and physical environment, as indicated by the uni-directional arrow linking these portions of the model. For instance,

geographic isolation or catastrophic environmental events such as drought, flood, or earthquake certainly impact the health status of a population, but these events are not necessarily a poor reflection on the primary care system. Likewise, the social environment may preclude favorable outcomes. An example might be the mother who obtains high quality baby formula intended for her malnourished infant but defeats the purpose by diluting it to low nutrient value to feed all four of her children.

MIDA at Rocky Mountain Altitudes Applied to Starfield's Model

In applying this study to Starfield's model (Figure 2), the areas of direct fit include "physical environment" and "problem recognition". Figure 2 includes additional structure, process and outcome features of primary care for prenatal clients to complete the picture. The "physical environment" (Rocky Mountain Altitudes) alters the hematologic norms of "persons" (pregnant women), obscuring "problem recognition" (MIDA) using conventional standards of care (screening practices). Failure to recognize the problem leads to delayed or mis-diagnosis and inadequate management, potentially resulting in maternal or fetal complications and poor pregnancy outcome.

In addition to the relationships between variables noted by Starfield, Figure 2 notes the additional relationship between environment and the provider features of problem recognition and diagnosis with a unidirectional

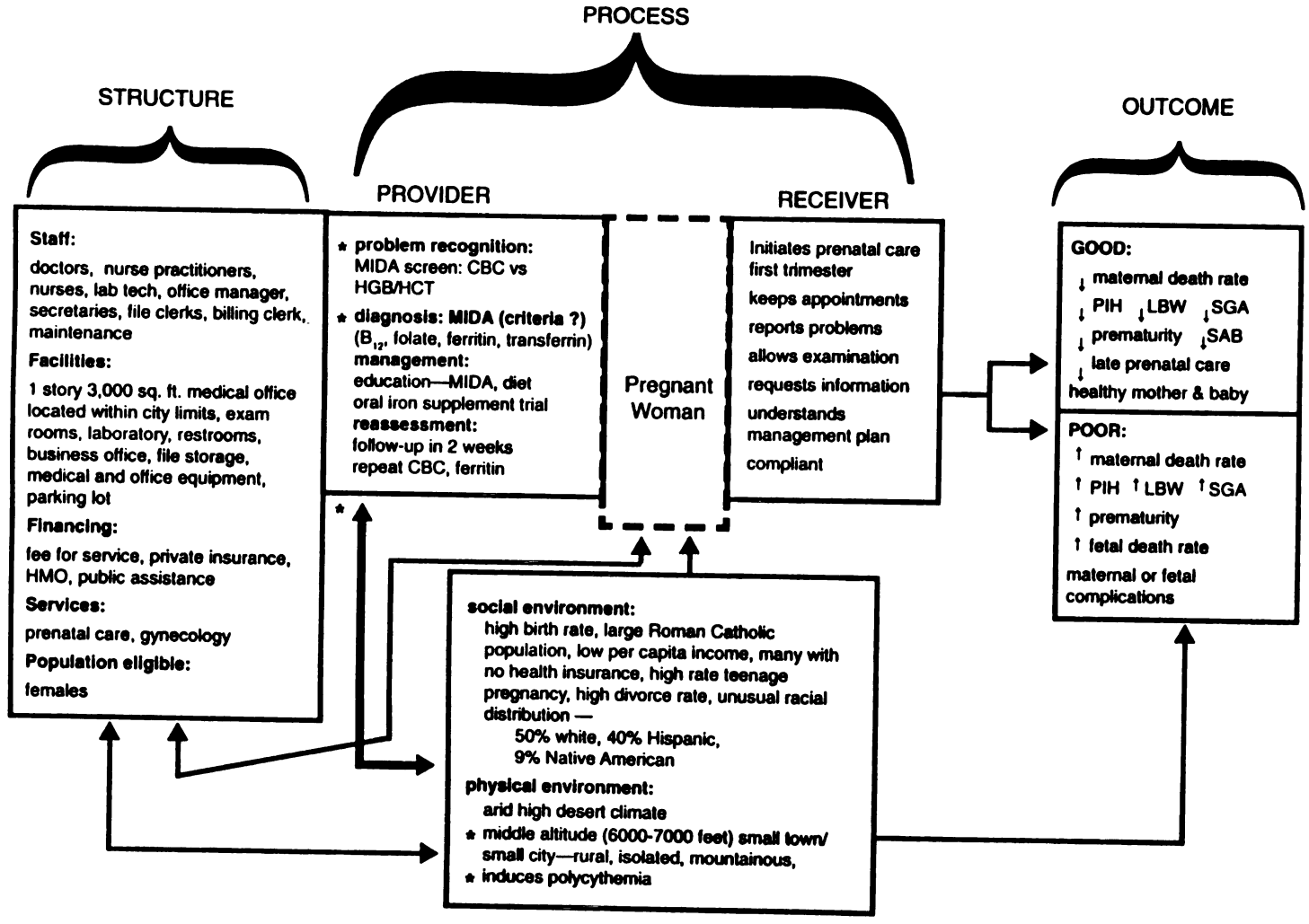

Figure 2. MIDA at Rocky Mountain Altitudes utilizing Starfield's Model.

arrow. This arrow demonstrates that physical environment (Rocky Mountain Altitudes) may so alter the appearance (usual diagnostic signs) of health problems that providers fail to recognize them using conventional assessment tools and standards of practice. When evidence of poor outcomes (i.e., maternal mortality, PIH, premature labor, and LBW) clusters in peculiar patterns (i.e., above 6,000 feet elevation), it becomes necessary to re-examine the system for flaws. In the case of MIDA at Rocky Mountain Altitudes, problem recognition and diagnosis are impaired by: a) the lack of prior research; b) an incomplete body of knowledge [altitude-adjusted reference tables to assist in differentiating normal from pathologic changes]; and c) the lack of altitude-appropriate guidelines and standards for clinical practice.

REVIEW OF THE LITERATURE

Prior MIDA Studies Above 3,000 Feet Elevation

Six prior MIDA studies at altitudes above 3,000 feet are located in the literature. Regrettably, all six are conducted in Africa more than nine years ago. Table 4 summarizes the numeric data in order of increasing altitude. Data contained on the table are not included in the presentation of each study. Discussion of findings is included in the critical remarks. A synthesis of empiric findings and general critique of the literature follows the presentation of individual studies.

Table 4.

Prior MIDA Studies at Altitude

INDICATOR	3600-4500[a] FEET	5200[b] FEET	5200[c] FEET	5400[d] FEET	7600[e] FEET	7600[f] FEET
HGB (SD) g/100ml	13.9(0.9) C 13.9(0.9)<22wLMP 13.7(1.1)>26wLMP	 13.1(1.3)tri 1 12.1(1.2)tri 2 11.7(1.2)tri 3	14.0C 12.5(1.3)tri 1 12.3(1.2)tri 2 11.1(1.2)tri 3	14.5C 11.9(1.2)primip 17.2(1.1)multip20-24yo 11.9(1.2)multip25-29yo 12.0(1.2)multip30-34yo 12.8(1.2)multip35-39yo ANEMIC GROUPS: 8.7 primips 7.5 para 3-5 9.4 para 6+	15.2(0.5)C 14.0(1.8)12wLMP 13.4(1.2)30wLMP 14.3(1.3)38+wLMP	14.2(1.0)C 12.6(1.6)28wLMP 13.1(1.1)32wLMP 13.4(0.8)36wLMP 13.8(1.2)term
HCT (SD) %	42.9(2.9) C 41.5(3.5)≤22wLMP 41.3(3.4)≥26wLMP	 39.2(3.3)tri 1 36.9(3.3)tri 2 36.2(3.5)tri 3	 37.1(3.4)tri 1 36.3(3.5)tri 2 33.8(3.6)tri 3	not given	44.2(2.5) C 41.1(3.2)12wLMP 40.1(3.3)30wLMP 42.0(3.4)≥38wLMP	46.0(3.4) C 40.9(4.3)28wLMP 42.3(3.9)32wLMP 44.2(3.4)36wLMP 45.1(2.8)term
MCV (SD) fL	not given	86.9(8.8)tri 1 90.8(7.5)tri 2 88.4(7.8)tri 3	82.5(7.6)tri 1 84.2(6.6)tri 2 80.1(9.1)tri 3	not given	not given	not given
MCH (SD) µg	not given	29.0(3.3)tri 1 29.9(2.8)tri 2 28.3(3.0)tri 3	27.8(3.1)tri 1 28.5(2.6)tri 2 26.4(3.5)tri 3	not given	not given	not given
MCHC (SD) %	not given	not given	not given	not given	34.4(1.5) C 34.0(1.9)12wLMP 33.4(1.7)30wLMP 34.3(1.5)≥38wLMP	30.9(2.0) C 31.0(2.8)28wLMP 30.7(2.2)32wLMP 30.4(2.5)36wLMP 30.6(2.0)term
MIDA DEFINED AS:	HGB < 11.0	HGB < 11.0 TS < 16% SF < 12	SF < 12	HGB < 10.0 HGB < 11.0	not given	not given

Table 4 (cont.)

INDICATOR	3600-4500[a] FEET	5200[b] FEET	5200[c] FEET	5400[d] FEET	7600[e] FEET	7600[f] FEET
RATES OF MIDA	NONE	4% tri 1 3% tri 2 9% tri 3	53% tri 1 49% tri 2 80% tri 3	8.5% HGB < 10 17% HGB < 11 11.3% primip 7.8% para 3-5 2.6% para 6+	not given	not given
RACE OF SUBJECTS	BANTU	"COLOURED"	INDIAN	14 BLACK TRIBES	NOT GIVEN	NOT GIVEN
(n) NUMBER OF SUBJECTS:						
TOTAL	150	224	100	187	497	76
CONTROL GROUP	48	47	47	25	100	49
BY TRIMESTER		1=40 2=118 3=66	1=53 2=37 3=10	1=0 2=73 3=98		
BY WEEKS LMP		≤ 22=43 ≥ 26=49			12=152 30=191 ≥38=154	28=9 32=22 36=21 TERM=24

Note. tri=trimester, C=control group, wLMP=weeks LMP, yo=years old.
[a]Gerritsen & Walker (1954). [b]Lamparelli et al. (1988a). [c]Lamparelli et al. (1988b). [d]Watson & Murray (1969). [e]Ross (1972). [f]Hofvander (1968). Complete citations are provided on the reference list.

Gerritsen and Walker

Gerritsen and Walker (1954) studied pregnant Bantu women who lived in rural areas near Johannesburg and Pretoria, South Africa. Previous studies reported extremely high daily dietary intake of iron (M=171 mg, ranging up to 200 mg per day), attributed to teff (a potato-like staple food) and the use of iron pots and utensils in food preparation. Prior postmortem examinations of this group found high incidence of abnormal iron deposits throughout the tissues of adult men and women. Gerritsen and Walker found that blood values related to iron were essentially unchanged during pregnancy, despite high altitude and dietary deficiencies of other nutrients.

The authors presented an excellent summary of the contemporary knowledge base regarding maternal iron metabolism, hemodilution and fluctuations in iron demand. The detailed presentation of dietary iron sources and consumption patterns was engaging. The mean daily iron consumption was 12 times the recommended allowance, and iron stores were pathologically high (i.e., 50% of adult females demonstrated abnormal tissue deposits at autopsy). One concludes this extraordinary population exemplifies the maximal human physiologic capacity for dietary iron absorption and iron saturation at that altitude! Since the concept of iron toxicity was not examined, it is impossible to deduce whether these data are representative of "normal" or toxic values of HGB, or if these data are appropriate to

generalize to pregnant women living at the same altitude in other parts of the world.

The investigators did not collect data for MCV, MCH or MCHC, although they remarked that hypochromic anemia was rare in this population. Data for these measures would have demonstrated the lack of microcytosis and hypochromia, supported their claim that there is no IDA, and strengthened the operational definition of anemia.

The introductory discussion reflected an understanding of hemodilution and variations in HGB as pregnancy advances. However, data were reported in peculiar groupings of 0-22 weeks LMP and 26-40 weeks LMP, thus avoiding the period of hemodilution. This grouping obscured the significant fluctuations in iron status reported by later investigators. Had data been grouped by trimester, comparison to other studies would be possible. Trimester grouped data might have furthered the understanding of HGB fluctuations throughout pregnancy.

Lamparelli et al.

In 1988, Lamparelli et al. conducted two MIDA studies in the Johannesburg area. In the first study, cross-sectional data were collected from 224 pregnant women for HGB, TS, TIBC, whole blood zinc protoporphyrin, folate, vitamin B_{12}, and serum ferritin (Lamparelli et al., 1988a). RBC counts fell significantly between the first and second trimester, but were unchanged thereafter. Serum iron, ferritin and TS decreased significantly throughout

pregnancy. Folate levels were low in 20%, but only one subject was folate deficient. Vitamin B_{12} levels showed a slight, significant drop throughout pregnancy, but no subjects had B_{12} deficiency or macrocytic anemia. Correlations of iron status with income, dietary intake, parity and method of contraception were not significant. The tabulation of data according to stage of iron deficiency revealed that only 28% had maintained normal iron status in the third trimester. Although 72% showed evidence of iron-deficiency in the third trimester, only 9% were fully anemic.

The large sample size is commendable, rendering the results highly significant. The inclusion of cut-off values for TS and serum ferritin in addition to a low HGB adds strength to the operational definition, and meaning to these results. The reporting of results according to stage of iron deficiency presents a very clear picture of iron status in this population. The reporting of results by trimester aids comparison with other studies. The use of unusual units of measurement (μmol/L) for serum iron and TIBC makes it difficult to compare these results to other studies.

The control group of 47 non-pregnant female medical students may or may not be representative of the local population. There was no information for the control group regarding the variables of race, age, or duration of exposure to 5,000 feet altitude. The investigators concluded that "no adjustment for altitude was necessary"

because the control group mean and standard deviation HGB values (14 ± 2 g/dL) were not significantly different than those encountered at sea level.

In the second study, Lamparelli et al. (1988b) surveyed pregnant Indian women following reports of unusually high incidence of IDA in Indian women in a neighboring community. Cross-sectional data were collected for serum iron, TIBC, TS, serum ferritin, folate, vitamin B_{12}, CBC, RBC ZP, FEP, and HGB electrophoresis. The same control group used in Lamparelli et al. (1988a) was utilized for this study. Values of HGB, TS and serum ferritin were "corrected for hemodilution of pregnancy" using formulae developed following the previous study.

Again one questions whether the control group accurately represented the study population. One also questions the validity of the "hemodilution corrected" values for TS and serum ferritin, since these norms have been shown to be universal. Once more, serum iron and TIBC values were reported in unusual units of measurement. Data were collected for MCHC, but the table summarizing RBC indices omitted MCHC values.

Although there were 100 subjects, there was maldistribution by trimester. The first trimester was over-represented (53 subjects). Only 10 subjects represented the third trimester, where 80% had iron-deficient erythropoiesis and 20% had MIDA. This results in more reliable information

about the group with the least change and the lowest iron demand than the group at highest risk.

Except for a brief reference to serum ferritin < 12 µg/L, MIDA is not succinctly defined in the text. No definitions are provided for the labels "depleted iron stores", "iron-deficient erythropoiesis" or "IDA", although incidence rates are reported for each trimester.

Watson and Murray

Watson and Murray (1969) surveyed 187 pregnant women from 14 different tribal groups in the second and third trimester. Cross-sectional data was collected for HGB, HCT, MCHC, serum iron, and TIBC. Initially, MIDA was defined as HGB < 10.0 g/100 ml, then later as HGB < 11.0 g/100 ml. A rise in TIBC was noted as pregnancy advanced, but this rise was independent of serum iron level. Results were reported by parity groupings of primigravidae, para three to five, and para six or more. Data from multiparous women were further subdivided by age groups. Data were not reported by trimester. The investigators concluded that IDA was not a serious problem, even among pregnant multiparous women.

The most striking feature of this study is the loss of impact by grouping data by parity and age rather than by trimester. By lumping second and third trimester values into such groups, one cannot distinguish hemodilution from MIDA and the normal fluctuations between trimesters are lost. Gerritsen and Walker (1954), who suggested that there was some significant hematological phenomenon occurring in

the second trimester, were cited as references. Hemodilution in the second trimester had been reported by Scott and Pritchard (1967) two years prior to this study. Sample size was adequate and there was a good distribution of subjects representing each trimester. The failure to report results by trimester renders their data of little practical value, and impossible to compare with other studies. Had the data been grouped by trimester and subdivided by age and parity, valuable insight regarding the effects of age and parity at altitude would have been revealed.

Although data were collected for serum iron, TIBC and iron saturation, it is not evident that any of these measures were included in the operational definitional for MIDA. The stated definition consisted of WHO cut-off values for HGB. Surprisingly, data for HCT or packed cell volume was not reported.

Clearly the primiparous group, and the multiparous groups over 25 years of age had borderline mean HGB values, suggesting that subjects in the first standard deviation below the mean were highly suspicious for MIDA according to the criteria. They reported a MIDA rate of 17% when using HGB < 11.0% as a criteria, and a mean HGB of 7.5 g/dL in the anemic para three to five group (no numbers of subjects provided for this group), but concluded that MIDA "was not a serious problem". In the U.S., adult HGB values of 7.0 g/dL are often considered grounds for transfusion per usual

standards of practice, due to the increased risk of myocardial infarction.

Ross

Ross (1972) collected cross-sectional data on 497 pregnant Ethiopian women for HGB, HCT and MCHC. Previous studies indicated high daily dietary intake of iron in this low-income population. Of interest, the predominant religion observed 180 days of fasting (refraining from eating animal products) annually. Ross did not define anemia *per se*, but merely surveyed hematological values. The data revealed two surprising findings. There was very low correlation between low HGB values and high parity (mean parity was three, but parity ranged from zero to 17). There was no significant difference in HGB values for those who observed *all* the fast days versus those who observed *none* of the fast days. The empiric mean MCHC was not statistically different than sea level norms for non-pregnant women, lending support to previous findings that MCHC is not affected by altitude or pregnancy.

Although the focus of Ross' study was more on dietary analysis and nutritional status as a function of income, this is a nice presentation of maternal hematologic values at 7,600 feet elevation. Large numbers of subjects represented the control group and each of the trimesters, and data was reported by trimester. There are four basic criticisms: a) MIDA is not defined; b) racial information is not given; c) the cross-sectional design does not allow for

appreciation of individual changes in hematologic values as pregnancy progresses; and d) there is no report of microcytosis, hypochromia, or rates of MIDA provided.

Hofvander

Hofvander (1968) presented an extensive review of the IDA literature and summarized numerous small-scale studies noting high dietary iron intake in populations living at middle altitude in Ethiopia. One of the reviewed studies contained a table of various hematologic measures for a control group, several non-pregnant groups, and a group of 76 pregnant women in the latter half of pregnancy. MIDA was not defined separately from IDA and MIDA incidence was not calculated. There was only a small decrease in mean HCT in pregnant women. Surprisingly, there was an increase in serum iron in the ninth month of pregnancy that exceeded the mean value for the non-pregnant control group. The data supported earlier observations that MCHC, TIBC and serum iron norms are not affected by altitude. IDA in non-pregnant adult females was operationally defined as MCHC < 27 g/dL and HGB < 12.8 g/dL. Later, the investigators added an "altitude correction factor" of 7% to sea level HGB norms, and revised the cut-off value for HGB to 13.4 g/dL. The reported rates of IDA in non-pregnant females were 8.2% with HGB less than 12.8 g/dL, and 16.3% with HGB less than 13.4 g/dL.

Incidence of MIDA is impossible to tease out of the tabulated data. The MCHC cut-off value of 27 g/dL used to

define IDA in the non-pregnant samples surveyed simultaneously is 5% lower than today's reference range. Had MIDA been defined and rates calculated for this study, these data would be more useful.

Synthesis of Pertinent Empiric Findings

For study question number one, "what are the mean empiric maternal values for red cell indices (i.e., HGB, HCT, MCV, MCH, and MCHC) measured at the usual screening intervals during the course of pregnancy … at altitudes of 6,040, 6,400 and 7,000 feet", one would predict values close to those observed by a) Ruiz-Arguelles et al. (1980) at 6,100 and 7,280 feet, b) Robles-Gil and Gonzáles-Terán (1948) at 7,457 feet, and c) Ross (1972) and Hofvander (1968) both at 7,600 feet. One would expect to find mean HGB ranging at about 12.5 to 15.2 g/dL, mean HCT ranging between 40 and 45%, and mean MCHC values ranging between 30 and 34.5 g/dL. Ruiz-Arguelles (1980) found MCV values at these altitudes ranging between 89.7 and 91.2 fL. Unfortunately, the only data at the appropriate altitude to predict MCH values is 50 years old (Robles-Gil & Gonzáes-Terán, 1948). They found a mean MCH of 30.33 pg at 7,450 feet. Data from Lamparelli et al. (1988b) provides evidence that sea level reference values for MCH are reliable at 5,200 feet elevation. Lamparelli's third trimester group, showing a MIDA rate of 80%, was the only group with mean MCH below the reference range. In both Lamparelli studies

(1988a and 1988b), incidence of MIDA is accurately reflected in the pattern of mean values for MCH and MCV.

For study question number two, "what is the rate of MIDA when MIDA is defined as observed microcytosis (MCV < 80 fL) and hypochromia (MCH < 27 pg or MCHC < 32 g/dL)", the answer can only be obtained by data analysis. Although there have been no prior MIDA studies in New Mexico, one suspects high rates of MIDA due to high rates of poverty and LBW in two of the three sites sampled. The literature provides no precedent for utilizing this operational definition, but does provide support for using MCV, MCH and MCHC as definitional criteria. These measures have been shown to be unaffected by altitude, and appropriate for use as universal standards (Bull & Hay, 1985; Ross, 1972). The data for MCHC in the study reviewed by Hofvander (1968) was dramatically lower (3 to 4 g/dL) than Ross' (1972) values at the same altitude. One recalls that the MCHC cut-off value used to define IDA for non-pregnant groups in the Hofvander (1968) study was 5% lower than the reference range. One questions if the method used to measure MCHC introduced this level of discrepancy, or if perhaps there was a typographical error and these were actually MCH values (normal range 27-31 pg).

The answer to study question number three, "what are the mean and range values for HGB and HCT associated with MIDA at each screening interval, at each altitude", cannot be predicted on the basis of prior studies. Watson and

Murray (1969) was the only study providing mean HGB values for anemic groups. The way the data were grouped does not allow for meaningful prediction of results for this study.

The answer to study question number four, "do the 1989 CDC guidelines accurately identify MIDA in this population", cannot be predicted. No studies utilizing CDC criteria for definition of MIDA were found in the literature.

For study question number five, "is there a significant relationship between demographic variables and MIDA", one anticipates a "yes" answer for the variables of socioeconomic status, age, interconceptual time interval, and race based on evidence from prior studies. Prior outcome studies at middle and high altitudes suggest that there may be a relationship between MIDA and altitude due to high rates of premature labor and LBW. The empiric evidence is inconclusive when examining the patterns revealed on Table 4. Lamparelli et al. (1988a) found MIDA rates of 4%, 3%, and 9% in first, second and third trimesters respectively. Lamparelli et al. (1988b) found rates of 53%, 49% and 80% at the same elevation, near the same site, in a different race of people. Watson and Murray (1969) found an over-all rate of 17% in pooled samples representing second and third trimester at an altitude only 200 feet higher than the Lamparelli studies. These findings suggest that race, socioeconomic status or lifestyle factors are more important determinants of MIDA than altitude alone.

Critique of the Literature

Five of the six studies presented in detail were conducted on non-white populations (i.e., Gerritsen & Walker, 1954; Lamparelli et al., 1988a; Watson & Murray, 1969; Ross, 1972; Hofvander, 1968). All six studies were conducted in African nations. One must remember to adjust these HGB values upward by 0.5 to 1.0% for comparison to White populations, due to racial variations in HGB noted in prior studies. One must also consider the confounding variables of socioeconomic status and pre-existing nutritional status. Gerritsen and Walker (1954), and Hofvander (1968) studied populations with known patterns of high dietary iron intake, despite malnutrition of other nutrients. Lamparelli et al. (1988a), and Watson and Murray (1969) studied impoverished populations.

All six of these studies utilized a cross-sectional design. When relying on HGB as the sole indicator of iron status, it is important to show change over time in the same individual. No longitudinal MIDA studies could be located in the literature. In order to differentiate hemodilution from pathologic deterioration in iron status, PCPs at altitudes above 3,000 feet still need longitudinal data to clarify the range of acceptable values, and the range of acceptable change in individuals at routine screening intervals or from trimester to trimester.

Three studies (i.e., Gerritsen & Walker, 1954; Lamparelli et al., 1988a; Watson & Murray, 1969) relied on

HGB cut-off values for part of the operational definition of MIDA. Authorities in the field (i.e., Bothwell, Charlton, Cook, DeMaeyer, and Yip) have commented on a) the relative uselessness of single measures of HGB or HCT as indicators of iron status, and b) the use of arbitrary cut-off values for indicators that vary widely in populations. There is strong sentiment that the only justifiable use of single HGB measures today is in large population studies or in establishing local reference ranges in healthy individuals (Johnson, 1990). The coupling of HGB values with other iron indicators (i.e., serum ferritin, TS, TIBC, FEP, and transferrin receptor) and controlling for factors that lead to misinterpretation (i.e., lead toxicity, thalassemias, folate or vitamin B_{12} deficiencies) provides a more precise evaluation of iron status, as shown in the Lamparelli studies.

It is disturbing to discover such a paucity of MIDA literature from developed countries. The bulk of MIDA research has been conducted in the public health context, heavily influenced by WHO, international nutrition groups, and nutrition surveillance groups. Most of the data come from tropical and Third World nations that are notoriously poor, malnourished, heavily populated by Blacks, and have high incidence of thalassemias, hemoglobinopathies, malaria and hookworm. It has only been within the past 25 years that the U.S. has established large scale nutrition surveillance systems which include pregnant women. These

include a) the Interagency Board for Nutrition Monitoring and Related Research, and b) the Pregnancy Nutrition Surveillance System, Division of Nutrition, National Center for Chronic Disease Prevention and Health Promotion at the Centers for Disease Control and Prevention. Historically, pregnant women were excluded from large U.S. studies because of known variations in HGB values and hemodilution in the second trimester (NHANES I and II). Three of the four MIDA studies conducted in the U.S. between 1950 and 1960 surveyed low-income populations in the South. We have more MIDA information about poor and malnourished women than we do about the "average American" woman! In an effort to fill this gap in the literature, this study sampled apparently healthy adult women who lived in an unusual environment, where little was known about normal maternal laboratory values.

METHODS

Study Design

This study utilized a descriptive, retrospective survey design. Existing demographic and longitudinal hematologic data were retrieved from medical records of adult pregnant women living at Rocky Mountain Altitudes.

Sample

The sample was the medical records of non-smoking, non-Black, adult women who delivered term infants from a singleton pregnancy between January 1 and December 31, 1996. Three primary care practices located within the altitude

interval of 6,000 to 7,000 feet above sea level served as data collection sites, one each in Taos, Las Vegas, and Santa Fe, New Mexico.

Sample Criteria

Medical records selected for inclusion in the study met the following criteria:

1. The record contained evidence that the subject: a) had been between 18 and 45 years of age at first day of LMP; b) was non-smoking for the duration of the pregnancy; c) delivered a singleton term infant in 1996; d) identified her race; and e) had a home address within city limits or on the measured plateau (i.e., domicile was at the same altitude as the data collection site).
2. Laboratory data (CBC, HGB or HCT) were available for initial and follow-up MIDA screenings at 28 and 36 weeks LMP.
3. There was absence of documentation that oral iron supplements were used in addition to prenatal vitamin formulas between the initial and 28 week LMP laboratory screenings.
4. There was absence of records transferred from another facility at a different altitude level since the first day LMP.

Field Procedures

Each site provided a list of clients who delivered singleton infants in 1996. The primary investigator

retrieved the records of clients listed, and did on-site review of each record for the sample criteria. Records meeting the criteria were selected for study. On-site data collection was done by the primary investigator only.

Data Collection

Demographic and clinical data were extracted from each record. Demographic data included age at first day LMP, race, marital status, number of pregnancies (gravida), number of previous deliveries (para), number of previous abortions and miscarriages, date of last delivery or abortion, interconceptual time interval in months, and insurance provider. Clinical data included laboratory values for HGB, HCT, MCV, MCH, and MCHC from initial, 28 and 36 week LMP screenings.

Recording of Data and Scoring

Demographic and clinical data were encoded onto scoring sheets. For demographic items, numeric codes were created. Age in years was calculated from birthdate to first day of LMP. Marital status was scored as "2" for married, "1" for single, and "0" for other or not stated. Race was scored as "1" for non-Hispanic White, "2" for Hispanic, Spanish or Mexican, "3" for Native American, "4" for Asian, and "5" for other. Gravida was scored as the number of documented pregnancies. Parity was scored as the number of documented prior deliveries. Abortions was scored as the documented number of prior miscarriages or abortions. Interconceptual time interval was the calculated number of months between

last delivery (or abortion) and LMP. A score of zero "0" was entered for cases of missing data, primiparous pregnancy, or if an interval greater than 36 months had elapsed. Insurance status was scored as "1" for none, "2" for Medicaid, "3" for health maintenance organization, and "4" for private insurance. For clinical data, numeric laboratory values were encoded exactly as they appeared on laboratory report sheets.

Altitude was encoded into the identification numbers. Case numbers ranging 101 to 119 represented Taos at 6,040 feet. Case numbers ranging from 201 to 240 represented Las Vegas at 6,400 feet. Case numbers ranging from 301 to 373 represented Santa Fe at 7,000 feet.

To indicate cases that met the operational definition criteria for MIDA (MCV < 80 fL, and either MCH < 27 pg or MCHC < 32 g/dL), labels of MIDA1, MIDA2 and MIDA 3 were utilized to indicate the screening interval in which MIDA appeared. Those meeting the criteria upon the initial screen were assigned a "1" for MIDA1. Those meeting the criteria upon the second screen at 28 weeks LMP were assigned a "1" for MIDA2. Those meeting the criteria upon the third screen at 36 weeks LMP were assigned a "1" for MIDA3. A score of zero ("0") was entered for cases not meeting the criteria, and for cases of incomplete data for each screening interval.

Similarly, labels of CDC1, CDC2, and CDC3 were utilized to a) identify cases meeting the CDC criteria for MIDA,

utilizing the cut-off values listed on Table 2 for each screening interval, at each altitude, and b) indicate the screening interval in which MIDA was identified. For the initial screen at less than 20 weeks LMP, the CDC1 label was used. For the 28 week LMP screen, CDC2 was used. For the 36 week LMP screen, CDC3. For the Taos and Las Vegas samples, cut-off values for HGB were 11.3 g/dL upon initial screen, 11.4 g/dL at the 28 week LMP screen, and 12.1 g/dL at the 36 week LMP screen. For the Taos and Las Vegas samples, cut-off values for HCT were 34.0%, 34.0% and 36.0% respectively. For the Santa Fe sample, HGB cut-off values were 11.6, 11.7, and 12.4 g/dL upon initial, 28 week LMP and 36 week LMP screens respectively. The cut-off values for HCT for the Santa Fe sample were 35.0, 35.0, and 37.0% respectively. For each screening interval, cases with HGB or HCT values below the cut-off value were identified as anemic per the CDC Criteria and were assigned a score of "1" for CDC1, CDC2, or CDC3.

Data Analysis

Scored data were entered onto an Excel 7.0 spreadsheet, converted to Excel 4.0 and then copied to SPSS (Statistical Program for Social Sciences) Base 7.5 for Windows, Graduate Professional Pack software for analysis, utilizing a PC computer.

To answer Study Question 1, "what are the mean and range empiric values for RBC indices . . .", descriptive statistical analysis was performed for each site separately,

and for the entire sample. For each screening interval, range, mean and standard deviation values were calculated for HGB, HCT, MCV, MCH, and MCHC. Results were tabulated. A sub-set of normal cases was then created by eliminating all cases identified as anemic by either the operational definition for MIDA or the CDC criteria (i.e., cases scored as "1" for MIDA1, MIDA2, MIDA3, CDC1, CDC2, or CDC3) from the sample. Descriptive analyses were repeated for the remaining "normal" cases and results were tabulated.

To answer Study Question 2, "what is the incidence of MIDA when MIDA is defined as observed microcytosis and hypochromia", frequencies were calculated for MIDA at each screening interval.

To answer Study Question 3, "what are the mean and range values for HGB and HCT associated with MIDA at each screening interval, at 6,000 to 7,000 feet elevation", descriptive analysis for mean, standard deviation and range was planned but not performed due to the very low rates of MIDA observed. Laboratory values for each case were tabulated.

To answer Study Question 4, "do the CDC Guidelines accurately identify MIDA in this population", correlations were planned but not calculated due to the small sub-sample meeting criteria for MIDA. Frequencies were calculated for cases meeting the CDC Criteria to provide comparison to rates observed when utilizing the operational definition for MIDA.

To answer Study Question 5, "is there a significant relationship between demographic variables and MIDA", correlations were planned but not calculated. The number of cases meeting the criteria for MIDA was too small to assess for relationships with demographic factors.

Confidentiality of Human Subjects

Confidentiality of subjects was strictly maintained. The primary investigator had no contact with the women represented by the medical records reviewed for the study. The list of clients provided by the data collection site, and the master list matching names and study identification numbers were destroyed at the data collection sites upon completion of the study.

This research proposal was reviewed and approved by the University Committee on Research Involving Human Subjects (UCRIHS) at Michigan State University, East Lansing, Michigan (see Appendix B).

Operational Definitions

MIDA

MIDA was operationally defined as an MCV < 80 fL (observed microcytosis) and either MCH < 27 pg or MCHC < 32 g/dL (observed hypochromia) at any time in the course of pregnancy.

Rocky Mountain Altitudes

"Rocky Mountain Altitudes" was operationally defined as the altitude interval of 6,000 to 7,000 feet above sea level. Altitude level for each data collection site was

determined utilizing U.S. Geological Survey maps of New Mexico. Confirmation of official altitude was provided verbally by the local Chamber of Commerce at each location.

Assumptions and Limitations

Assumptions

The following assumptions were made: a) sea level norms for MCV, MCH, and MCHC are reliable at Rocky Mountain Altitudes; and b) medical laboratories that performed the automated CBCs are essentially "equal", due to quality assurance standards.

Limitations

Design Factors

Due to the retrospective survey format, items of available data were limited to RBC indices and documented demographic variables. The socioeconomic environment may have had a significant impact upon the results. Insurance provider was the only retrievable datum of socioeconomic status given the study design. Study design also prohibited assessment of duration of exposure to the altitude surveyed, and assurance that subjects were fully acclimated physiologically prior to conception. Retrospective study design prohibited assurance of a full data set for each subject.

Contamination of Results

Results may have been affected by undocumented frequent travel to significantly higher or lower elevations than were ascribed to subjects for the purpose of this study. Unknown

or unidentified local factors (genetic, geologic, occupational, or cultural) may confound the interpretation of data.

RESULTS

Data sets for all three sites included cases with incomplete data for the variables studied. At Taos, marital status was not documented for approximately 25% of the sample and HCT was the only MIDA screen at the 28 and 36 week LMP visits. Although the Taos sample was small (n=19), available data were included to provide comparison to other sites. At all sites, clients without health insurance and health maintenance organization members frequently had only HGB and/or HCT screens at the 28 and 36 week LMP visits. For these cases, data for MCV, MCH and MCHC were not available. Frequently, dates of abortions and miscarriages were not documented at all three sites.

Minor difficulties were encountered in obtaining lists of potential cases for the study from primary care sites. At one site, the list could not be generated from office records. Delivery records had to be retrieved from the hospital. There were confidentiality issues involved in releasing the list directly to the primary investigator, who was not employed by the hospital. This issue was resolved by having the attending doctor retrieve the list of his own clients from the medical records department.

Sample

Only 132 of approximately 700 records reviewed met the criteria for inclusion in the study. Demographic characteristics were summarized by site and for the entire sample on Table 5. There was variation by site in racial distribution, insurance provider, parity, and interconceptual time interval.

The Las Vegas sample was younger than the Taos and Santa Fe samples, had the largest percentage (60%) of single women, and displayed no ethnic diversity. Santa Fe had the largest percentage of married women (two-thirds), and had the highest number of HMO and private insurance subscribers. In Las Vegas and Taos, over two-thirds relied on Medicaid. All three sites were similar in regards to mean number of pregnancies, abortions and miscarriages but patterns for multiparous women varied by site.

Mean values for interconceptual time interval (number of months between pregnancies) were consistent with prior observations of high fertility. Las Vegas had the highest number of pregnancies occurring less than 6 months post-partum, and one-third had become pregnant within two years of their previous delivery. At all three sites, 25-33% had spaced their pregnancies less than 24 months apart, putting them at risk for MIDA due to failure to recover iron stores prior to subsequent pregnancy. Only 15-20% of women were spacing pregnancies by two years or more. Taos was

Table 5.

Sample Demographic Characteristics by Site

CHARACTERISTIC	TAOS	LAS VEGAS	SANTA FE	ALL SITES
SAMPLE SIZE	19	40	73	132
AGE IN YEARS				
M	30.7	24.5	28.1	27.4
range	20-41	18-36	18-43	18-43
MARITAL STATUS				
single (n)	26.3%(5)	60.0%(24)	32.9%(24)	40.2%(53)
married (n)	47.4%(9)	40.0%(16)	67.1%(49)	56.1%(74)
not stated (n)	26.3%(5)	(0)	(0)	3.7%(5)
RACE				
non-Hispanic White (n)	84.2%(16)	(0)	41.1%(30)	34.8%(46)
Spanish or Mexican (n)	15.8%(3)	100%(40)	54.8%(40)	62.9%(83)
Native American (n)	(0)	(0)	1.4%(1)	0.8%(1)
Asian (n)	(0)	(0)	2.7%(2)	1.5%(2)
INSURANCE PROVIDER				
none (n)	31.6%(6)	5.0%(2)	4.1%(3)	8.3%(11)
Medicaid (n)	52.6%(10)	62.5%(25)	24.7%(18)	40.2%(53)
H.M.O. (n)	(0)	5.0%(2)	30.1%(22)	18.2%(24)
private (n)	15.8%(3)	27.5%(11)	41.1%(30)	33.3%(44)

Table 5 (cont.)

CHARACTERISTIC	TAOS	LAS VEGAS	SANTA FE	ALL SITES
PREGNANCIES				
M	2.26	2.63	2.40	2.45
first (n)	26.3%(5)	20.0%(8)	24.7%(18)	23.5%(31)
second (n)	21.1%(4)	30.0%(12)	35.6%(26)	31.8%(42)
third (n)	52.6%(10)	30.0%(12)	23.3%(17)	29.5%(39)
fourth or more (n)	(0)	20.0%(8)	16.4%(12)	15.2%(20)
PREVIOUS DELIVERIES				
M	0.63	1.1	0.88	0.90
none (n)	58.0%(11)	27.5%(11)	35.7%(26)	36.4%(48)
one (n)	21.0%(4)	47.5%(19)	45.2%(33)	42.4%(56)
two (n)	21.0%(4)	20.0%(8)	10.9%(8)	15.0%(20)
three (n)	(0)	2.5%(1)	4.1%(3)	3.1%(4)
four or more (n)	(0)	2.5%(1)	4.1%(3)	3.1%(4)
ABORTIONS AND MISCARRIAGES				
M	0.68	0.5	0.6	0.57
none or not given (n)	52.6%(10)	65.0%(26)	60.3%(44)	60.6%(80)
one (n)	26.3%(5)	22.5%(9)	27.4%(20)	25.6%(34)
two (n)	21.1%(4)	10.0%(4)	10.9%(8)	12.0%(16)
three (n)	(0)	(0)	(0)	(0)
four or more (n)	(0)	2.5%(1)	1.4%(1)	1.6%(2)

Table 5 (cont.)

CHARACTERISTIC	TAOS	LAS VEGAS	SANTA FE	ALL SITES
INTERCONCEPTUAL TIME INTERVAL				
M	26.6	21.6	17.1	21.03
0-6 months	0	7.5%	6.8%	13.3%
7-12 months	0	2.5%	6.8%	4.7%
≤ 12 months	0	10.0%	13.6%	23.3%
13-18 months	0	7.5%	6.8%	6.1%
19-24 months	26.3%	15.0%	5.5%	11.3%
≤ 24 months	26.3%	32.5%	25.9%	61.7%
25-30 months	10.5%	10.0%	9.6%	9.9%
31-36 months	10.5%	10.0%	5.5%	7.7%
24-36 months	21.0%	20.0%	15.1%	22.1%

exceptional in that women were spacing pregnancies by at least 18 months.

Research Questions

For research question one, mean empiric values for red cell indices are summarized by screening interval and altitude level on Table 6. Table 7 summarizes "normal values"; the calculated mean for all remaining data after anemic cases were eliminated from the sample. Findings for each indicator follows.

HGB

Mean HGB values at all sites ranged between 12.5 and 13.9 g/dL, in agreement with prior findings (Ruiz-Arguelles et al., 1980; Robles-Gil and Gonzáles-Terán, 1948; Ross, 1972; Hofvander, 1968) of mean HGB levels ranging from 12.5 to 14.6 g/dL. There was a predictable drop from baseline of about 1.0 g/dL in mean HGB at 28 weeks LMP, and a small rise in mean HGB of 0.1-0.5 g/dL between 28 and 36 weeks LMP. This pattern is consistent with variations reported by Scott & Pritchard (1967), and well within the normal limits (drop of 2.2 g/dL at 28 weeks, then a rise of about 0.7 g/dL at 36 weeks) they described.

An interesting pattern is revealed when looking at HGB range values on Table 6. Lower limits of the range decline and ranges widen both as altitude increases and as pregnancy progresses. Perhaps this pattern suggests that physiologic adaptation to altitude (hyperactive erythropoiesis) is beginning to be taxed by pregnancy.

Table 6.

Maternal RBC Indices at Rocky Mountain Altitudes

RBC INDEX	ALTITUDE			
	TAOS 6040 feet	LAS VEGAS 6400 feet	SANTA FE 7000 feet	ALL SITES 6-7000 feet
HEMOGLOBIN (g/dL)				
≤ 20 weeks LMP				
M(SD)	13.83(1.15)	13.82(0.90)	13.67(0.83)	13.74(0.90)
range	12.2-16.3	11.5-15.4	10.7-15.7	10.7-16.3
n=	18	37	73	128
28 weeks LMP				
M(SD)	N/A	12.52(0.90)	12.64(0.81)	12.60(0.83)
range	N/A	10.9-14.2	10.6-14.8	10.6-14.8
n=	0	32	73	105
36 weeks LMP				
M(SD)	N/A	12.50(1.31)	12.96(0.88)	12.80(1.07)
range	N/A	8.7-15.2	10.6-14.6	8.7-15.2
n=	0	40	73	113

Table 6 (cont.)

RBC INDEX	TAOS 6040 feet	ALTITUDE: LAS VEGAS 6400 feet	ALTITUDE: SANTA FE 7000 feet	ALTITUDE: ALL SITES 6-7000 feet
HEMATOCRIT (%)				
≤ 20 weeks LMP				
M(SD)	40.34(3.19)	40.57(2.71)	39.54(2.38)	39.96(2.63)
range	36.3-47.2	34.3-45.0	31.4-45.5	31.4-47.2
n=	19	37	73	129
28 weeks LMP				
M(SD)	36.95(2.17)	36.99(2.68)	37.08(2.38)	37.03(2.42)
range	33.0-40.0	31.6-41.4	31.6-46.2	31.6-46.2
n=	19	32	73	124
36 weeks LMP				
M(SD)	39.16(2.49)	37.15(4.27)	38.06(2.45)	37.94(3.15)
range	34.0-45.0	25.9-45.3	32.4-43.9	25.9-45.3
n=	17	39	73	129

Table 6 (cont.)

RBC INDEX	TAOS 6040 feet	ALTITUDE: LAS VEGAS 6400 feet	ALTITUDE: SANTA FE 7000 feet	ALTITUDE: ALL SITES 6-7000 feet
MCV (fL)				
≤ 20 weeks LMP				
M(SD)	89.88(3.50)	90.10(4.21)	89.05(4.13)	89.46(4.07)
range	82.0-94.0	77.9-97.4	72.0-98.5	72.0-98.5
n=	17	36	73	126
28 weeks LMP				
M(SD)	N/A	92.79(4.19)	91.63(4.31)	91.99(4.28)
range	N/A	84.4-101.8	81.0-102.5	81.0-102.5
n=	0	32	72	104
36 weeks LMP				
M(SD)	N/A	91.43(5.87)	91.0(4.48)	91.34(5.03)
range	N/A	75.7-102.2	78.0-102.9	75.7-105.1
n=	0	32	73	105
MCH (pg)				
≤ 20 weeks LMP				
M(SD)	N/A	30.73(1.63)	30.94(1.24)	30.87(1.39)
range	N/A	26.1-34.2	28.1-34.7	26.1-34.7
n=	0	36	68	104
28 weeks LMP				
M(SD)	N/A	31.41(1.56)	31.21(1.54)	31.34(1.57)
range	N/A	27.8-35.2	26.4-35.3	26.4-35.3
n=	0	32	61	93
36 weeks LMP				
M(SD)	N/A	30.94(2.12)	31.05(1.74)	31.08(1.89)
range	N/A	25.1-34.4	26.8-35.3	25.1-35.3
n =	0	32	58	90

Table 6 (cont.)

RBC INDEX	ALTITUDE			
	TAOS 6040 feet	LAS VEGAS 6400 feet	SANTA FE 7000 feet	ALL SITES 6-7000 feet
MCHC (%)				
≤ 20 weeks LMP				
M(SD)	34.30(0.46)	34.11(0.72)	34.56(0.73)	34.40(0.72)
range	33.1-35.1	32.8-35.9	32.4-36.3	32.4-36.3
n=	17	36	72	125
28 weeks LMP				
M(SD)	N/A	33.85(0.68)	34.13(0.90)	34.03(0.84)
range	N/A	32.6-35.8	32.0-36.4	32.0-36.4
n=	0	32	72	104
36 weeks LMP				
M(SD)	N/A	33.85(1.26)	34.04(0.84)	33.97(0.99)
range	N/A	32.2-39.7	31.6-36.0	31.6-39.7
n=	0	32	73	105

Note. N/A indicates there were no data available for these variables. The laboratory in Taos did not include MCH values on hematology profiles. Missing data reflect variations in profiles between laboratories and restrictions imposed by the payor source.

Table 7.

Hematology Profiles for Healthy Pregnant Women at 6,000-7,000 Feet Altitude

	6000 Feet		6400 Feet		7000 Feet	
	n	M (SD)	n	M (SD)	n	M (SD)
≤ 20 weeks LMP						
HGB (g/dL)	14	13.98(1.17)	24	13.97(0.84)	45	13.89(0.74)
HCT (%)	15	40.70(3.24)	24	40.98(2.46)	45	40.23(2.13)
MCV (fL)	13	90.08(3.97)	23	89.95(3.60)	45	89.48(3.46)
MCH (pg)	0		23	30.71(1.34)	44	30.93(1.28)
MCHC (g/dL)	13	34.37(0.52)	23	34.16(0.77)	44	34.48(0.73)
28 weeks LMP						
HGB (g/dL)	0		21	12.92(0.64)	45	12.97(0.50)
HCT (%)	15	37.47(1.88)	21	38.19(2.04)	45	37.98(1.59)
MCV (fL)	0		21	92.62(3.70)	44	91.67(3.62)
MCH (pg)	0		22	31.37(1.58)	39	31.30(1.36)
MCHC (g/dL)	0		21	33.86(0.66)	44	34.17(0.78)
36 weeks LMP						
HGB (g/dL)	0		26	13.06(1.12)	45	13.42(0.53)
HCT (%)	13	39.91(2.12)	25	39.03(3.55)	45	39.39(1.62)
MCV (fL)	0		19	92.77(3.92)	45	91.56(3.95)
MCH (pg)	0		19	31.25(1.29)	35	31.24(1.60)
MCHC (g/dL)	0		19	33.69(0.48)	45	34.08(0.69)

Note. This healthy "normal" subsample was created by eliminating cases of MIDA as defined by (a) the operational definition (MCV < 80 fL, and MCH < 27 pg or MCHC < 32 g/dL) and (b) the CDC criteria (per Table 1).

HCT

Prior studies (Ruiz-Arguelles et al., 1980; Robles-Gil & Gonzáles-Terán, 1948; Ross, 1972; Hofvander, 1968) found mean HCT values ranging between 40 and 45%. The empiric data were 2.5-4% lower than expected, in slight disagreement with prior studies. For the sub-set of "normal" healthy subjects (Table 7), mean HCT ranged from 37.4 to 40.9% in this study. The observed drop between the initial and 28 week screens ranged between 2 and 3.3%. The observed rise between 28 and 36 weeks ranged between 0.8 and 2.4%.

MCV

Ruiz-Arguelles et al. (1980) found mean MCV ranging between 89.7 and 91.2 fL. Mean MCV for this study ranged between 89.4 and 92.7 fL in close agreement, and lying well within the reference range of 80-95 fL. Of note, the range of values widened and variation increased directly as altitude increased. Outliers were just as likely to represent macrocytosis as microcytosis.

MCH

The reference range for MCH is 27-31 pg (Pagana & Pagana, 1992). At 7,450 feet altitude, Robles-Gil and Gonzáles-Terán (1948) observed a mean MCH value of 30.33 pg and a range of 25-35 pg. Mean MCH values for the current study ranged from 30.71 to 31.41 pg. There was a very slight trend towards upper limits of normal or hyperchromia. The observed range of MCH values was 25.1 to 35.3 pg, identical to the Robles-Gil and Gonzáles-Terán (1948) study.

Standard deviations were less than 2.2, indicating tight clustering around the mean or small variation.

MCHC

The reference range for MCHC is 32-36% (Pagana & Pagana, 1992). All mean MCHC values fell between 33.6 and 34.6%, and standard deviations were less than 1.3%. There were very few outliers at 36 weeks LMP, again indicating tight clustering around the mean. Prior studies (Ruiz-Arguelles et al., 1980; Robles-Gil & Gonzáles-Terán, 1948) of non-pregnant women noted mean MCHC values ranging between 30 and 34.5%. Values obtained in this study were well within the reference range and, although slightly higher, in agreement with prior studies.

In answering the second research question, "What is the rate of MIDA when MIDA is defined as MCV < 80 fL and MCH < 27 pg or MCHC < 32 g/dL?", the data revealed only two cases of MIDA. Both cases occurred in Las Vegas, one upon initial screen and one at the 36 week LMP screen. The observed rates for MIDA were none at Taos, none at Santa Fe, and at Las Vegas, 0.4% at ≤ 20 weeks LMP, 0% at 28 weeks LMP, and 0.4% at 36 weeks LMP. The overall rate of MIDA for the entire sample was 0.75% at initial and 36 week LMP screens. These values were summarized on Table 8.

The third research question, "What are the mean and range values for HGB and HCT associated with MIDA?", could not be answered because of the extremely low rate of MIDA observed. The single case of MIDA at ≤ 20 weeks LMP had the

Table 8.

Rates of MIDA

SCREEN	TAOS 6040 feet	LAS VEGAS 6400 feet	SANTA FE 7000 feet	ALL SITES 6000-7000 feet
≤ 20 weeks LMP	0	0.4%(n=1)	0	0.75%
28 weeks LMP	0	0	0	0
36 weeks LMP	0	0.4%(n=1)	0	0.75%

Note. MIDA was defined as MCV < 80 fL, and either MCH < 27 pg or MCHC < 32 g/dL at any time during pregnancy.

following CBC values: HGB=11.5 g/dL, HCT=34.3 %, MCV=77.9 fL, MCH=26.1 pg, and MCHC=33.6 g/dL. The single case at 36 weeks LMP had the following CBC values: HGB=10.3 g/dL, HCT=31.1 %, MCV=75.7 fL, MCH=25.1 pg, and MCHC=33.1 g/dL. Demographic characteristics for these cases were summarized in Table 10.

For the fourth research question, "Do the 1989 CDC Guidelines (see Table 2) accurately identify MIDA in this population?", the data indicate that CDC Guidelines are more accurate in detecting iron-deficiency than identifying actual anemia. For the single case of MIDA at ≤ 20 weeks LMP, the HGB and HCT values were borderline, just above the CDC cut-off values, although the MCV and MCH were abnormally low and indicative of anemia. The CDC criteria missed this case. For the single case of MIDA at 36 weeks LMP, the CDC criteria identified this individual as anemic both at the 28 and 36 week LMP screens, indicating accuracy in detecting some stage of iron-deficiency was present, although not specific as to severity. In general, the CDC criteria identified more cases of MIDA than were actually present by this study's operational definition, and missed one case of actual MIDA. Number of cases and rates of MIDA identified by CDC Criteria were summarized on Table 9.

For research question five, "Is there a significant relationship between demographic variables and MIDA?", the rate of MIDA was too low to conduct any meaningful analyses.

Table 9.

Rates of Maternal Anemia per 1989 CDC Guidelines

SCREEN	TAOS 6040 ft	LAS VEGAS 6400 ft	SANTA FE 7000 ft	ALL SITES 6000-7000 ft
≤ 20 weeks LMP	0	0	1.37%	0.75%
n=	0	0	1	1
28 weeks LMP	10.53%	15.00%	16.44%	15.15%
n=	2	6	12	20
36 weeks LMP	10.53%	30.00%	30.14%	27.27%
n=	2	12	22	36

Note. Utilizing the CDC Criteria from Table 1, HGB cut-off values for the Taos and Las Vegas samples were 11.3, 11.4 and 12.1 g/dL for <20 weeks LMP, 28 weeks LMP and 36 week LMP screens respectively. HCT cut-off values for Taos and Las Vegas samples were 34.0, 34.0 and 36.0% respectively. For Santa Fe, HGB cut-off values were 11.6, 11.7, and 12.4 g/dL. HCT cut-off values were 35.0, 35.0, and 37.0%.

Table 10.

Case Comparison of Anemic Subjects: Demographic Characteristics

Demographic Variable	Case 1 @ ≤ 20 weeks LMP	Case 2 @ 36 weeks LMP
Age	25	21
Marital status	married	married
Race	Hispanic	Hispanic
Insurance provider	Medicaid	Private
Pregnancy #	4	2
Parity	1	0
Prior abortions/miscarriages	2	1
Interconceptual time interval	24 months	> 36 months

DISCUSSION

Of greatest importance, this study discovered normal values for red cell indices of healthy, pregnant women living at 6,000 to 7,000 feet elevation. Table 6 summarizes the raw data, and Table 7 summarizes data from the "normal" sub-set. Table 7 is the first empirically derived table of normal maternal red cell indices at 6,000 to 7,000 feet elevation to appear in the U.S. literature. Cases identified as anemic by the CDC Criteria were often borderline or had only one abnormal value for MCV, MCH or MCHC. These cases were probably representative of impaired

iron status, although not fully anemic by the operational definition. The sub-set of "normals" was created to ascertain the most reliable mean and standard deviation values for the healthiest women in the sample. In this healthy population, there was no indication of a sudden change in values between altitudes that might account for poor outcomes of pregnancy or other phenomena.

Rates of MIDA were not determined for the altitude interval of 6,000 to 7,000 feet due to the small number of cases found (two) and sampling criteria that selected for normal pregnancies. Approximately 80 percent of records reviewed did not meet the sampling criteria. Late prenatal care, age at conception (under 18 years old), smoking, premature labor, multiple fetus pregnancy (i.e., twins), change in domicile or inability to confirm the altitude of the subject's domicile from available information excluded many potential cases from the sample.

The 1989 CDC Criteria were not accurate in identifying MIDA in this sample. The criteria detected iron deficiency, but were inaccurate as to severity. One concludes that these criteria are unreliable for the detection of MIDA in populations at elevations between 6,000 and 7,000 feet. Primary care practices utilizing CDC tables may be over- or under-diagnosing MIDA, although the prudent practitioner would be alerted to borderline or suspicious values warranting further diagnostic investigation.

The Starfield Model was effective in describing the relationship between environment and the process of care, and the relationship between environment and outcome. It was also effective in giving direction to future research efforts in the primary care context. For this study, the model required a small refinement highlighting the relationship between environment and process of care (i.e., the provider features of problem recognition and diagnosis).

Retrospective survey for retrieval of existing longitudinal data was effective as a means of determining normal RBC indices for normal pregnancies with good outcomes at altitudes above 3,000 feet. Longitudinal data were important in appreciating changes in laboratory values as pregnancy progressed. Retrospective survey imposed limitations on items of data available for study (i.e., demographic variables, clinical data), sampling criteria, and upon the interpretation of findings.

Racial distribution patterns among the three sites were radically different than reported state racial distribution statistics (i.e., 50% non-Hispanic White, 40% Hispanic, 9% Native American). The Taos sample was 84% non-Hispanic White and only 16% Hispanic. There were no Native Americans in the Taos sample although a major pueblo is located less than 20 miles from the Midwifery Center. The Las Vegas sample was 100% Hispanic. The Santa Fe sample was more evenly mixed, but still reflected a higher concentration of Hispanics than expected. For the pooled sample, non-

Hispanic Whites (35%) and Native Americans (0.8%) were under-represented, and Hispanics were over-represented (63%). Surprisingly, there were more Asians (1.5%) than Native Americans in the sample. The under-representation of Native Americans in the sample is unclear, but might be explained by the provision of free prenatal services to registered Native Americans through the U.S. Public Health Service (PHS). Primary care services were available at individual pueblo PHS clinics, local public health clinics and at the PHS hospital in Santa Fe. The unusual ethnic distribution patterns in Taos and Las Vegas can be traced to historic settlement patterns.

Legal and socioeconomic factors may explain the wide differences noted in insurance provider categories from site to site. Low numbers of cases with private insurance in the Taos sample reflected the political and economic environment. Few Taos businesses provided health insurance benefits to employees. Although state Medicaid regulations permitted direct reimbursement to Certified Nurse Midwives in 1996, some third party payors did not. The absence of health maintenance organizations reflected the small size and relative isolation of the community. In 1996, the Midwifery Center was one of four prenatal care provider sites in Taos and the fee for prenatal care and delivery was 55% lower than fees charged by other providers. Certainly, economic factors influenced the selection of prenatal care provider in the Taos sample. Perhaps this finding reveals a

social phenomenon that women who opt for midwifery services or home birth are less likely to have health insurance, or that there is strong financial motivation to select midwifery services.

The Medicaid eligible statistics did not accurately reflect the high reliance on Medicaid for prenatal care in the Taos and Las Vegas samples. The State of New Mexico provided special temporary medical assistance (through Medicaid) and supplemental food programs (through W.I.C.) for infants and pregnant women. The income criteria for the temporary programs were more liberal than for the standard programs. The "Medicaid eligible statistics" were inaccurate in reflecting levels of poverty by county (especially in Taos) and did not reflect the distribution of funds for special programs targeting pregnant women.

Although the Medicaid eligible statistic indicated similar levels of poverty in Taos and Santa Fe, per capita personal income and poverty level statistics did not. The discrepancies in insurance status at these two sites were dramatic. These differences are explained by: a) the dissimilar availability of health insurance benefits through employers at each location; b) a difference in the number of prenatal care options available at each location; and c) practice policies which restrict the number of new clients who rely on Medicaid. One must be mindful of differences in services provided and type of practice. The Santa Fe OB/GYN group practice routinely managed high-risk obstetric cases

and required a doctor assisted hospital delivery. The Taos midwifery practice routinely screened out (or referred out) high-risk cases and provided midwife assisted home birth or delivery in the home-like birth center. Planned hospital delivery was not offered as a service to Midwifery Center clients at that time. These features limited the clientele at each site.

In Taos, the lack of RBC indices for the 28 and 36 week LMP MIDA screens was attributed to a practice policy of utilizing HCT only, due to the financial status of the clientele. The Taos data for "insurance provider" imply that 82% were at or below poverty level. This explains why more thorough lab screening was not performed routinely.

In regards to interconceptual time interval, the literature suggests that pregnancies be spaced by 18 to 24 months to allow for full recovery of maternal iron stores. Subjects with interconceptual time intervals of more than 36 months were scored as zero ("0") for statistical analyses, as these subjects were well beyond the danger period for incomplete recovery of iron stores. The Taos sample was exemplary in spacing pregnancies at least 18 months apart. Without further research it is impossible to ascertain if these women were financially motivated, health-consciously motivated, or if this was merely a chance finding. One recalls that in Taos 32% had no health insurance and 50% relied on Medicaid. This group also had the highest percentage of non-Hispanic Whites, and displayed the highest

rate of abortion or miscarriage (47%). One might speculate that a) these women more readily utilized legal abortion for contraceptive failure or as a means of spacing pregnancies, or b) the midwives had made an impact on decisions regarding spacing of pregnancy through patient education.

There are three reasons why such low rates of MIDA were found in this study. One is that subjects were in a state of chronic hyperactive erythropoiesis pre-conceptually due to altitude adaptation. The other reasons are selective sampling, and retrospective design. Sampling criteria very effectively selected for apparently healthy women who demonstrated healthy behaviors and had normal singleton pregnancies with term deliveries. About eighty percent of records reviewed failed to meet the sampling criteria. Complicated pregnancies, unhealthy behaviors (e.g., smoking, extreme age at conception, late prenatal care) and preterm deliveries were intentionally screened out of the sample. Retrospective design assisted in ascertaining normal laboratory values utilizing pre-existing data for traditional screening measures. Determination of normal values is essential for recognition of pathologic deviation (MIDA). Unfortunately, the sampling criteria suppressed desirable information about abnormal laboratory values at middle altitude. Prospective study design and liberal sampling criteria would remedy this problem.

Although this study was unable to correlate demographic variables with incidence of MIDA due to inadequate sample

size, several prior studies have addressed this issue and identified high risk groups. High risk groups have been more aggressively studied than have normal populations in differing environments, to the detriment of the knowledge base. This study begins to address this gap in the literature. Additionally, nutrition surveillance systems are operational and one anticipates publication of the NHANES III data for pregnant women.

Implications for Advanced Practice Nursing and Primary Care

APNs are encouraged to play an active role in changing current protocols and practice policies related to MIDA screening, diagnosis and management. Table 7 will provide empiric evidence to assist APNs in justifying the need for further diagnostic testing for pregnant women that live at 6,000 to 7,000 feet elevation and have borderline or clearly abnormal values upon screening for MIDA. It is clear that several conventional screening and diagnostic tests for anemia are not valid during pregnancy or in populations living at altitudes above 3,000 feet. Until a nationally recognized authority revises standards of care and MIDA screening guidelines for populations at altitude, health maintenance organizations, Medicaid and managed care groups will continue to refuse payment for "non-standard" laboratory tests. If PCPs are limited to HGB and/or HCT screening for low-income or managed care clients, at least they will now have some basis for suspicion of impaired iron status, MIDA, and the potential for related complications.

Until standardized tables for populations above 3,000 feet are available, practitioners are encouraged to revise MIDA screens and diagnostic panels locally. Red cell indices (CBC or hematology profile) may be considered the minimum acceptable screen for populations above 3,000 feet elevation. The addition of serum ferritin is prudent. For borderline screen values (at or below the first standard deviation below the mean) differential diagnostic testing should include serum ferritin (if not included with the screen), TS, TIBC and either FEP or RBC ZP in addition to the usual folate and cyanobalamin (vitamin B_{12}). For pregnant women, serum iron can be dropped from the standard anemia profile as these values are ambiguous at best. While awaiting results from diagnostic testing, APNs can initiate a trial of oral iron supplements, confident that there is no risk for iron toxicity and its related complications.

APNs can play a significant role in reducing MIDA incidence and preventing complications related to MIDA. As primary care providers, APNs can: a) select altitude-appropriate screening and diagnostic tools; b) educate prenatal clients about MIDA; c) promote the use of effective post-partum contraception; d) promote change in local protocols for MIDA screening, diagnosis and management; and e) conduct small-scale MIDA and outcome studies for their own practice. APN entrepreneurs can specialize in preventative community education, case management, lecture presentations for the academic and professional communities,

and publication of articles in professional journals. APNs in academic settings can enhance the education of future nurses, APNs and PCPs by including MIDA education in the obstetric portion of the curriculum. APN researchers can approach local universities, state health departments, existing prenatal nutrition surveillance groups, or existing maternal and infant care projects for support of statewide prospective MIDA studies. By networking, a regional network and database could be formed in conjunction with prospective studies.

Recommendations for Further Research

Although MIDA is not currently a "hot topic" for research, the impact of managed care and outcome studies may soon spur renewed interest. MIDA research provides an excellent opportunity for multi-disciplinary cooperation in expanding the knowledge base for Primary Care. APNs are faced with a unique opportunity to take the lead in MIDA research and make important scientific contributions.

The next step for research is to determine maternal norms for red cell indices at altitudes ranging from 3,000 to 10,000 feet above sea level. Standardized tables defining normal values for the traditional screening intervals in 1,000 foot elevation intervals are greatly needed. Simultaneous measures of MCV, MCHC, serum ferritin, TS, TIBC and FEP are highly desirable. Longitudinal data for these measures would assist in fully assessing iron status and defining acceptable changes in individuals

throughout pregnancy. Prospective longitudinal studies are essential for clarifying acceptable laboratory values and defining acceptable limits of net change in laboratory values in individuals at landmark intervals throughout pregnancy. Correlations of pregnancy outcome with these laboratory measures may provide insight into causal relationships or identify early indicators for poor pregnancy outcomes. Funding for such projects may exist within state public health departments or existing national surveillance projects.

The second step is to assess the scope of the problem. It is important to determine MIDA incidence rates nationwide, by region, by state, and at various altitudes. The NHANES III data may provide some answers. Prospective longitudinal studies are still needed to assess the severity of the problem at middle altitudes. To assure significant gains in knowledge about MIDA, sampling criteria should not exclude subjects under 18 or over 45 years old, smokers, those who sought prenatal care after 20 weeks LMP, or those with multiple fetus pregnancy. These subjects need to be studied simultaneously, but separately as sub-groups. Sampling criteria should assure that subjects a) have achieved full physiologic adaptation to the specified altitude level under study, b) do not spend significant amounts of time at altitudes more than 500 feet higher or lower than their domicile, and c) can verify the location (altitude) of their domicile.

The most difficult step is to determine the underlying cause of MIDA. Is MIDA merely a phenomenon of poor nutritional status in conjunction with the physiologic stress of adaptation to pregnancy? One wonders if there is a genetic hematopoietic factor related to ethnicity or race that makes certain groups high risk for IDA, or if high incidence in particular groups really due to socioeconomic status or other underlying factors. Data from Blacks indicates a genetic difference in hemoglobin production. Why has IDA incidence in Hispanics jumped so dramatically? Is this a phenomenon of sampling, an increase in the Hispanic population, or is there a genetic reason for this finding? The isolation of demographic variables will require sophisticated research methods and complex data analysis techniques. It would be helpful to know the weighted value of particular demographic variables (i.e., socioeconomic status, interconceptual time interval, race, age).

The revision of guidelines for routine MIDA screening is long over-due. Throughout the literature, experts in the field (Bothwell, Bull & Hay, Charlton, Cook, DeMaeyer, Johnson, Yepez, Yip) agree that HGB and HCT are poor measures of maternal iron status. Considering the advances in laboratory technology in the past 25 years, it is time to abandon these crude measures. For 15 years, numerous investigators have promoted the use of serum ferritin, TS and serum transferrin receptor as more sensitive indicators

of maternal iron status, yet these measures are not addressed by nationally recognized authorities responsible for setting standards for prenatal care. There are so many variables affecting HGB values that results are ambiguous at best. In the primary care context, it is extremely cumbersome to calculate multiple "correction factors" for each patient to obtain meaningful results. The technology exists to support the formulation of new straightforward standards for evaluating iron status in pregnant women. Serum ferritin shows promise. The development of simple, inexpensive tests for serum ferritin, TS and transferrin receptor designed for use at primary care sites would be beneficial.

The challenges of revising standards of care and developing new guidelines for MIDA screening and diagnosis remains. An addendum to current standards and guidelines that addresses known variations at altitudes above 3,000 feet would be valuable. The empiric evidence in this study suggests that there is minimal variation in mean values for red cell indices within the altitude interval of 6,000 to 7,000 feet. Therefore, a single standard could be applied to the entire thousand foot interval. In these days of managed care, it will be important to substantiate the cost-effectiveness of the new screening profile. In order to encourage changes in third party payor policies, a nationally respected authority (i.e., ACOG, the American Academy of Pediatrics or perhaps the World Association of

Perinatologists) must endorse revisions for a) a consensus definition of MIDA, b) standards of practice for prenatal care, and c) guidelines for MIDA screening and diagnostic profiles MIDA that apply to populations residing between sea level and 10,000 feet elevation.

SUMMARY

Although maternal iron deficiency anemia is the most common complication of pregnancy, little research has been done at altitudes above 3,000 feet. Recognition of MIDA at elevations above 3,000 feet is complicated by compensatory relative polycythemia, presenting a dilemma for APNs in primary care. Normal elevations in RBC count, HGB and HCT in altitude acclimated individuals can potentially mask anemia when relying upon traditional screening measures to evaluate iron status, especially in pregnant women. Empirically derived altitude-adjusted reference tables for maternal norms of RBC indices and specific recommendations for MIDA screening in altitude-induced polycythemic populations could not be found in the existing literature.

The Starfield Model of the Health Services System served as a conceptual framework. Starfield's Model adequately addressed the primary care provider issues of problem recognition and diagnosis. The model required refinement regarding the impact of environmental factors which may alter conventional diagnostic indicators to the point of obscuring the suspected disease.

Existing data were extracted from 132 medical records of pregnant women that lived at altitudes ranging from 6,000 to 7,000 feet elevation. Only two cases of MIDA were found because sampling criteria selected for normal pregnancies. The 1989 CDC Criteria were unreliable in detecting MIDA. Mean, standard deviation and range values for RBC indices at the traditional prenatal screening intervals were found for healthy pregnant women upon eliminating cases of MIDA and cases of borderline or impaired iron status identified by CDC Criteria. Rates of MIDA incidence and correlations of MIDA with demographic factors could not be calculated due to the low rate of MIDA found.

APNs in communities located above 3,000 feet were challenged to revise their individual practice protocols and promote local revisions of MIDA screening and diagnostic panels to reflect altitude-appropriate measures. CBC (or hematology profile) and serum ferritin were recommended as the minimal MIDA screening tools for populations at middle altitude. Nationally recognized authorities were challenged to revise the definition of MIDA, screening guidelines and standards for prenatal care to include populations residing at altitudes from sea level to 10,000 feet elevation. Research leading to the development of standardized tables for maternal norms of iron status indicators for altitudes ranging up to 10,000 feet was encouraged. Other suggestions for further research included: a) determination of efficacy and cost-effectiveness for specific maternal iron

indicators; b) determination of weighted values for demographic risk factors; and c) the development of assessment tools for serum ferritin and transferrin saturation for use in Primary Care facilities.

LIST OF REFERENCES

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American Academy of Pediatrics (AAP), & American College of Obstetricians and Gynecologists (ACOG). (1992). Guidelines for perinatal care (3rd ed.). Elk Grove Village, IL: American Academy of Pediatrics.

American College of Obstetricians and Gynecologists (ACOG). (1989). Standards for obstetric-gynecologic services (7th Ed.). Washington, DC: Author.

Athens, J.W., & Lee, G.R. (1993). Polycythemia: erythrocytosis. In G.R. Lee, T.C. Bithell, J. Foerster, J.W. Athens, & J.N. Lukens (Eds.), Wintrobe's Clinical Hematology (9th Ed.) (pp. 1245-1261). Philadelphia: Lea & Febiger.

Bently, D. (1985). Iron metabolism and anaemia in pregnancy. Clinics in Haematology, 14, 613-628.

Bhargava, M., Kumar, R., Iyer, P., Ramji, S., Kapani, V., & Bhargava, S. (1989). Effect of maternal anaemia and iron depletion on fetal iron stores, birthweight and gestation. Acta Pediatrica Scandinavica, 78, 321-322.

Brown, R. (1991). Determining the cause of anemia: General approach with emphasis on microcytic hypochromic anemias. Postgraduate Medicine, 89(6), 161-170.

Bull, B., & Hay, K. (1985). Are red blood cell indexes international? Archives of Pathology and Laboratory Medicine, 109, 604-606.

Bushnell, F. (1992). A guide to primary care of iron-deficiency anemia. Nurse Practitioner, 17(11), 68-74.

Buys de Jorge, M., Contrini, M., Miranda, C., Carrera, C., Torrejon, I., Martin, B., & Scaro, J. (1988). Maternal and fetal hematologic values at high altitude. Sangre (Barcelona), 33(2), 97-101. (In Spanish with English abstract.)

Centers for Disease Control. (1989). CDC criteria for anemia in children and child-bearing aged women. Mortality and Morbidity Weekly Report, 38(22), 400-404.

Centers for Disease Control. (1990). Anemia during pregnancy among low income women in the US. Mortality and Morbidity Weekly Report, 39(5), 73-76, 81.

Colmer, J. (1990). Anemia in pregnancy as a risk factor for infant iron deficiency-Valencia infant aenemia cohort study. Journal of Paediatric Perinatal Epidemiology, 4(2), 196-204.

Cook, J.D., & Lynch, S.R. (1986). The liabilities of iron deficiency. Blood, 68, 803-809.

Cook, J., Skikne, J., Lynch, S., & Reuser, M. (1986). Estimates of iron sufficiency in the U.S. population. Blood, 68, 726-731.

Cook, J. & Skikne, B. (1989). Iron deficiency: Definition and diagnosis. Journal of Internal Medicine, 226(5), 349-55.

Cook, J., Skikne, B., & Baynes, R. (1994). Iron deficiency: The global perspective. Advances in Experimental Medicine and Biology, 356, 219-228.

Cunningham, F., MacDonald, P., Gant, N., Leveno, K., & Gilstrap, L. III (Eds.) (1993). Williams Obstetrics (19th Ed.) (pp. 1171-1176). Norwalk, CT: Appleton & Lange.

Dainiak, N., Spielvogel, H., Sorba, S., & Cudkowicz, L. (1989). Erythropoietin and the polycythemia of high altitude dwellers. Advances in Experimental Medicine and Biology, 271, 17-21.

Dallman, P., Yip, R., & Johnson, C. (1984). Prevalence and causes of anemia in the United States, 1976-1980. American Journal of Clinical Nutrition, 39, 437-445.

Daouda, H., Galan, P., Prual, A., Sekou, H., & Hercberg, S. (1991). Iron status in Nigerian mothers and their newborns. International Journal of Vitamin and Nutrition Research, 61, 46-50.

DeCherney, A.H., & Pernoll, M.L. (Eds.) (1994). Current obstetric & gynecologic diagnosis & treatment (pp. 448-450). Norwalk, CT: Appleton & Lange.

DeMaeyer, E., & Adiels-Tegman, M. (1985). The prevalence of anaemia in the world. World Health Statistics Quarterly, 38, 302-316.

DeMaeyer, E. (1989). Preventing and controlling iron deficiency anaemia through primary health care: A guide for health administrators and programme managers. Geneva: World Health Organization.

Dimperio, D. (1988). Prenatal nutrition: Clinical guidelines for nurses. White Plains, NY: March of Dimes.

Dorland's Illustrated Medical Dictionary (28th ed.). (1994). Philadelphia: W. B. Saunders Co.

Expert Scientific Working Group (1985). Summary of a report on assessment of the iron nutritional status of the U.S. population. American Journal of Clinical Nutrition, 42, 1318-1330.

Fanelli-Kuczmarski, M., & Woteki, C. (1990). Monitoring the nutritional status of the Hispanic population: Selected findings for Mexican Americans, Cubans and Puerto Ricans. Nutrition Today, 25(3), 6-11.

Farley, P., & Foland, J. (1990). Iron deficiency anemia: How to diagnose and correct. Postgraduate Medicine, 87(2), 89-93, 96, 101.

Finch, C., & Cook, J. (1984). Iron deficiency. American Journal of Clinical Nutrition, 39, 471-477.

Fleming, A.F., Harrison, K.A., Briggs, N.D., Attai, E.D.E., Ghatoura, G.B.S., Akintunde, E.A., & Shah, N. (1989). Anaemia in young primigravidae in the guinea savanna of Nigeria: Sickle-cell trait gives partial protection against malaria. Annals of Tropical Medicine and Parasitology, 78(4), 395-404.

Food and Nutrition Board (FNB), & Institute of Medicine (IOM). Earl, R., & Woteki, C. (Eds.) (1993). Iron deficiency anemia: Recommended guidelines for the prevention, detection and management among U.S. children and women of childbearing age. Washington, DC: National Academy Press.

Frikiche, A., Cusumano, G., Senterre, J., & Lambotte, R. (1990). Fetomaternal hemorrhage: A cause of fetal morbidity and mortality. Revue Medicale de Liege (Liege), 45(10), 498-503.

Garcia, Anthony (May 13, 1997). Personal communication - citing HMGR152X (March 1997) and Population projections for the State of New Mexico by age and sex 1990-2020, Bureau of Business and Economic Research, University of New Mexico. Office of Medical Assistance, State of New Mexico. [Appendix A]

Garn, S., Ridella, S., Petzold, A., & Falkner, F. (1981). Maternal hematological levels and pregnancy outcomes. Seminars in Perinatology, 5, 155-162. [Collaborative Perinatal Project].

Gerritsen, T., & Walker, A. (1954). The effect of habitually high iron intake on certain blood values in pregnant Bantu women. Journal of Clinical Investigation, 33, 23-26.

Godfrey, K., Redman, C., Barker, D., & Osmund, C. (1991). The effect of maternal anaemia and iron deficiency on the ratio of fetal weight to placental weight. British Journal of Obstetrics and Gynaecology, 98, 886-891.

Goodlin, R., Holdt, D., & Woods, R. (1982). Pregnancy-induced hypertension associated with hypervolemia: Case report. American Journal of Obstetrics and Gynecology, 142, 114-115.

Guyatt, G., Oxman, A., Ali, M., Willan, A., McIlroy, W., & Patterson, C. (1992). Laboratory diagnosis of iron-deficiency anemia: An overview. Journal of General Internal Medicine, 7, 145-153.

Herbert, V. (1991). Diagnosis and treatment of iron disorders: Introduction and medicolegal considerations. Hospital Practice, 26(Suppl. 3, April), 4-6.

Ho, C., Yuan, C., & Yeh, S. (1987). Serum ferritin levels and their significance in normal full-term pregnant women. International Journal of Gynecology and Obstetrics, 25(4), 291-295.

Hofvander, Y. (1968). Hematological investigations in Ethiopia, with special reference to a high iron intake. Acta Medica Scandinavica, Supplement 494, S 4-74.

Hurtado, A., Merino, C. & Delgado, E. (1945). Influence of anoxemia on the hematopoietic activity. Archives of International Medicine, 75, 284-323.

Hytten, F. (1985). Blood volume changes in normal pregnancy. Clinics in Haematology, 14, 601-612.

Interagency Board for Nutrition Monitoring and Related Research [IBNMRR], (1993). Nutrition monitoring in the United States. Chartbook I: selected findings from the national nutrition monitoring and related research program. Ervin, B., & Reed, D. (Eds.). Hyattsville, MD: Public Health Service.

Isaacs, D., Altman, D.G., & Valman, H.B. (1986). Racial differences in red cell indices. Journal of Clinical Pathology, 39, 105-109.

Jackson, M., Mayhew, T., & Haas, J. (1988a). On the factors which contribute to thinning of the villous membrane in human placentae at high altitude. I: Thinning and regional variation in thickness of the trophoblast. Placenta, 9, 1-8.

Jackson, M., Mayhew, T., & Haas, J. (1988b). On the factors which contribute to thinning of the villous membrane in human placentae at high altitude. II: An increase in the degree of peripheralization of fetal capillaries. Placenta, 9, 9-18.

Johnson, M. (1990). Iron: Nutrition monitoring and nutrition status assessment. Journal of Nutrition, 120, (suppl II), 1486-1491.

Kim, I., Hungerford, D., Yip, R., Kuester, S., Zyrkowski, C., & Trowbridge, F. (1992). Pregnancy nutrition surveillance system - U.S. 1979-1990. Mortality and Morbidity Weekly Report, 41, (SS-7, November 27), 25-41.

Kitay, D. (1994). Iron deficiency. In F. Zuspan, & E. Quilligan (Eds.). Current therapy in obstetrics and gynecology, (pp. 421-424). Philadelphia: W. B. Saunders.

Klebanoff, M., Shiono, P., Selby, J., Trachtenberg, A., & Graubard, B. (1991). Anemia and spontaneous preterm birth. American Journal of Obstetrics and Gynecology, 164(Part I), 59-63.

Koller, O. (1982). The clinical significance of hemodilution during pregnancy. Obstetrical and Gynecological Survey, 37(11), 649-52.

Koller, O., Sagen, N., Ulstein, M., & Vaula, D. (1979). Fetal growth retardation associated with inadequate haemodilution in otherwise uncomplicated pregnancy. Acta Obstetrica et Gynecologica Scandinavica, 58, 9-13.

Koller, O., Sandevei, R., & Sagen, N. (1980). High hemoglobin levels during pregnancy and fetal risk. International Journal of Gynaecology & Obstetrics, 18, 53-56.

Lamparelli, R., Bothwell, T., MacPhail, A., VanDerWesthuyzen, J., Baynes, R., & MacFarlaine, B. (1988a). Nutritional anaemia in pregnant coloured women in Johannesburg. South African Medical Journal, 73(8), 477-481.

Lamparelli, R., VanDerWesthuyzen, J., Bothwell, T., Pienaar, L., and Baynes, R. (1988b). Anaemia in pregnant Indian women in Johannesburg. South African Medical Journal, 74(4), 170-173.

Lanzkowsky, P. (1985). Problems in diagnosis of iron deficiency anemia. Pediatric Annals, 14(9), 618-637.

Lazebnik, N., Kuhnert, B., & Kuhnert, P. (1989). The effect of race on serum ferritin during parturition. Journal of the American College of Nutrition, 8(6), 591-596.

Lee, G. R. (1993a). Microcytosis and the anemias associated with impaired hemoglobin synthesis. In G. R. Lee, T. C. Bithell, J. Foerster, J. W. Athens, & J. N. Lukens (Eds.). Wintrobe's Clinical Hematology (9th ed.) (pp. 791-807). Philadelphia: Lea & Febiger.

Lee, G. R. (1993b). Iron deficiency and iron-deficiency anemia. In G. R. Lee, T. C. Bithell, J. Foerster, J. W. Athens & J. N. Lukens (Eds.). Wintrobe's Clinical Hematology (9th ed.)(pp. 808-839). Philadelphia: Lea & Febiger.

Leshan, L., Gottleib, M. & Mark, D. (1995). Anemia is prevalent in an urban African-American adolescent population. Archives of Family Medicine, 4, 433-437.

Letsky, E. (1991). Hematologic disorders. In W. Barron, & M. Lindheimer (Eds.), Medical disorders during pregnancy (pp. 272-322). Chicago: Mosby Year Book.

Lewis, G., & Rowe, D. (1986). Can a serum ferritin estimation predict which pregnant women need iron? British Journal of Clinical Practice, 40, 15-16.

Looker, A. C., Dallman, P. R., Carroll, M. D., Gunter, E. W., & Johnson, C. L. (1997). Prevalence of iron deficiency in the United States. Journal of the American Medical Association [JAMA], 277(12), 973-976.

Looker, A. C., Johnson, C. L., McDowell, M., & Yetley, E. (1989). Iron status: Prevalence of impairment in three Hispanic groups in the United States. American Journal of Clinical Nutrition, 49, 553-558.

Marsh, W. Jr., Nelson, D., & Koenig, H. (1983). Free erythrocyte protoporphyrin [FEP] II. The FEP test is clinically useful in classifying microcytic RBC disorders in adults. American Journal of Clinical Pathology, 79(6), 661-6.

Maternal and Child Health Bureau, Health Services Division, Health and Environment Department, & The New Mexico Health Systems Agency (1986). The health of mothers & infants in New Mexico. Albuquerque, NM: Author.

McCullough, R., Reeves, J., & Liljegren, R. (1977). Fetal growth retardation and increased infant mortality at high altitude. Archives of Environmental Health, 32, 36-39.

Meyers, L., Habicht, J-P., Johnson, C. L. & Brownie, C. (1983). Prevalences of anemia and iron deficiency anemia in black and white women in the United States estimated by two methods. American Journal of Public Health, 73(9), 1042-1049.

Moore, L., Hershey, D., Jahnigen, D., & Bowes, W. Jr. (1982). The incidence of pregnancy-induced hypertension is increased among Colorado residents at high altitude. American Journal of Obstetrics and Gynecology, 144(4), 423-429.

Murphy, J., Newcombe, R., O'Riordan, J., Coles, E., & Pearson, J. (1986). Relationship of hemoglobin levels in first and second trimesters to outcome of pregnancy. Lancet, 1(8488), 992-994. [Cardiff Birth Survey, Wales, UK].

National Center for Health Statistics (NCHS), & Department of Health and Human Services (DHHS), (1985). Plan and operation of the Hispanic Health and Nutrition Examination Survey (HHANES), 1982-1984. Series 1 (plan), No. 191. and Series 11 (results). Hyattsville, MD: Public Health Service.

New Mexico Department of Health [NMDH], Public Health Division, Bureau of Vital Records & Health Statistics, (June 1996). 1994 New Mexico: selected health statistics - annual report. Santa Fe, NM: Author.

New Mexico Department of Health [NMDH], Public Health Division, Office of Information Management, New Mexico Vital Records & Health Statistics, (October 1997). 1995 New Mexico selected health statistics - annual report. Santa Fe, NM: Author.

New Mexico Prenatal Care Network, & University of New Mexico, School of Medicine, Maternity and Infant Care Project (1992). A better start for a better future 1988-1990: Prenatal care in New Mexico - a state and county analysis (2nd ed.). Albuquerque, NM: New Mexico Prenatal Care Network.

Olmas, J., Figueroa, J., Rodriguez, L., Halac, E., & Irrazabal, D. (1988). Altitude and birthweight [letter]. Journal of Pediatrics, 113, 786-787.

Pagana, K. D., & Pagana, T. J. (1992). Mosby's diagnostic and laboratory test reference. Chicago: Mosby Year Book.

Perry, G., Byers, T., Yip, R., & Margen, S. (1992). Iron nutrition does not account for the hemoglobin differences between blacks and whites. Journal of Nutrition, 122, 1417-1424.

Piedras, J., Loria, A., & Galvan, I. (1995). Red blood cell indices in a high altitude hospital population. Archives of Medical Research, 26, 65-68.

Pilch, S., & Senti, F. (Eds.)(1984). Assessment of the iron nutritional status of the United States population based on data collected in the Second National Health and Nutrition Examination Survey, 1976-1980. Bethesda, MD: Life Sciences Research Office of the Federation of American Societies for Experimental Biology.

Reshetnikova, O., Burton, G., Milovanov, A., & Fokin, E. (1996). Increased incidence of placental chorioangioma in high-altitude pregnancies: Hypobaric hypoxia as a possible etiologic factor. American Journal of Obstetrics & Gynecology, 174, 557-561.

Reynafarje, C., Lozano, R., & Valdivieso, J. (1958). The polycythemia of high altitude: Iron metabolism and related aspects. Blood, 14, 433-455.

Robles-Gil, J., & Gonzáles-Terán, D. (1948). Determination of the number of erythrocytes, volume of packed red cells, hemoglobin and other hematologic standards in Mexico City (altitude 7,457 feet). Blood, 3, 660-681.

Ross, S. (1972). Haemaglobin and haematocrit values in pregnant women on a high iron intake and living at high altitude. Journal of Obstetrics and Gynaecology, British Commonwealth, 79, 1103-1107.

Ruiz-Arguelles, G., Sanchez-Medal, L., Loria, A., & Cordova, M. (1980). Red cell indices in normal adults residing at altitudes from sea level to 2670 meters. American Journal of Hematology, 8, 265-271.

Sanchez, C., Merino, C., & Figallo, M. (1970). Simultaneous measurement of plasma volume and cell mass in polycythemia of high altitude. Journal of Applied Physiology, 28, 775-778.

Schifman, R., Thomasson, J., & Evers, J. (1987). Red blood cell zinc protoporphyrin testing for iron-deficiency anemia in pregnancy. American Journal of Obstetrics and Gynecology, 157, 304-307.

Scholl, T., Hediger, M., Fischer, R., & Shearer, J. (1992). Anemia vs. iron deficiency: Increased risk of preterm delivery in a prospective study. American Journal of Clinical Nutrition, 55, 985-988.

Scott, D., & Pritchard, J. (1967). Iron deficiency in healthy young college women. Journal of the American Medical Association, 199(12), 147-150.

Skikne, B., Flowers, C., & Cook, J. (1990). Serum transferrin receptor: A quantitative measure of tissue iron deficiency. Blood, 75, 1870-1876.

Starfield, B. (1973). Health services research: a working model. New England Journal of Medicine, 289, 132-136.

Starfield, B. (1992). Primary care: concept, evaluation, and policy (pp. 3-21). New York: Oxford University Press.

Starfield, B. (1996). A framework for primary care research. Journal of Family Practice, 42(2), 181-185.

Ulmer, H., & Goepel, E. (1988). Anemia, ferritin and pre-term labor. Journal of Perinatal Medicine, 16(5-6), 459-465.

Unger, C., Weiser, J., McCullough, R., Keefer, S., & Moore, L. (1988). Altitude, low birthweight and infant mortality in Colorado. Journal of the American Medical Association, 259, 3427-3432.

Viteri, F. (1994). The consequences of iron deficiency and anemia in pregnancy. Advances in Experimental Medicine and Biology, 352, 127-139.

Watson, W., & Murray, E. (1969). Serum iron and haemoglobin levels in pregnant East African women of mixed tribal origin. Journal of Obstetrics and Gynaecology (British Commonwealth), 76, 366-369.

Williams, M. D., & Wheby, M. S. (1992). Anemia in pregnancy. Medical Clinics of North America, 76, 631-647.

Winslow, R., Chapman, K., Gibson, C., Samaja, M., Monge, C., Goldwasser, E., Sherpa, M., Blume, F., & Santolaya, R. (1989). Different hematologic responses to hypoxia in Sherpas and Quechua indians. Journal of Applied Physiology, 66, 1561-1569.

World Health Organization, (1972). Nutritional anaemias: Report of a WHO group of experts. Technical Report Series No. 503. Geneva: Author.

Yancey, M., Moore, J., Brady, K., Milligan, D., & Strampel, W. (1992). The effect of altitude on umbilical cord blood gases. Obstetrics & Gynecology, 79, 571-574.

Yancey, M., & Richards, D. (1994). Effect of altitude on the amniotic fluid index. Journal of Reproductive Medicine, 39, 101-104.

Yepez, R., Estevez, E., Galan, P., Chauliac, M., Davila, M., Calle, A., Estrella, R., Masse-Raimbault, A-M., & Hercberg, S. (1994). Anémie en altitude: validité du critère de définition [Anemia at altitude: validity of definitional criteria]. Cahiers Santé, 4, 9-13 (in French with summary in English).

Yip, R. (1987). Altitude and birth weight. Journal of Pediatrics, III (6, Pt 1), 869-876.

Yip, R., Johnson, C., & Dallman, P. (1984). Age-related changes in laboratory values used in the diagnosis of anemia and iron deficiency. The American Journal of Clinical Nutrition, 39, 427-436.

Zamudio, S., Palmer, S., Dahms, T., Berman, J., McCullough, R. G., McCullough, R. E., & Moore, L. (1993). Blood volume expansion, preeclampsia, and infant birth weight at high altitude. Journal of Applied Physiology, 75, 1566-1573.

APPENDIX A

MICHIGAN STATE
UNIVERSITY

October 27, 1997

TO: Rachel F. Schiffman
A230 Life Sciences

RE: IRB#: 97-667
TITLE: MATERNAL IRON DEFICIENCY ANEMIA AT ROCKY MOUNTAIN ALTITUDES
REVISION REQUESTED: N/A
CATEGORY: 1-E
APPROVAL DATE: 10/20/97

The University Committee on Research Involving Human Subjects'(UCRIHS) review of this project is complete. I am pleased to advise that the rights and welfare of the human subjects appear to be adequately protected and methods to obtain informed consent are appropriate. Therefore, the UCRIHS approved this project and any revisions listed above.

RENEWAL: UCRIHS approval is valid for one calendar year, beginning with the approval date shown above. Investigators planning to continue a project beyond one year must use the green renewal form (enclosed with the original approval letter or when a project is renewed) to seek updated certification. There is a maximum of four such expedited renewals possible. Investigators wishing to continue a project beyond that time need to submit it again for complete review.

REVISIONS: UCRIHS must review any changes in procedures involving human subjects, prior to initiation of the change. If this is done at the time of renewal, please use the green renewal form. To revise an approved protocol at any other time during the year, send your written request to the UCRIHS Chair, requesting revised approval and referencing the project's IRB # and title. Include in your request a description of the change and any revised instruments, consent forms or advertisements that are applicable.

PROBLEMS/ CHANGES: Should either of the following arise during the course of the work, investigators must notify UCRIHS promptly: (1) problems (unexpected side effects, complaints, etc.) involving human subjects or (2) changes in the research environment or new information indicating greater risk to the human subjects than existed when the protocol was previously reviewed and approved.

If we can be of any future help, please do not hesitate to contact us at (517)355-2180 or FAX (517)432-1171.

Sincerely.

David E. Wright, Ph.D.
UCRIHS Chair

DEW:bed

cc: Cynthia D. Anderson

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