OBSERVATIONAL STUDY

Customized Nutritional Enhancement for Pregnant Women Appears to Lower Incidence of Certain Common Maternal and Neonatal Complications: An Observational Study

La mejora nutricional personalizada para mujeres embarazadas parece disminuir la incidencia de ciertas complicaciones maternas y neonatales frecuentes: un estudio observacional

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ABSTRACT

A retrospective chart review analyzed the effect of customized nutrition on the incidence of pregnancy-induced hypertension (PIH), gestational diabetes (GDM), small- and large-for-gestational-age (SGA, LGA) neonates, examining consecutive deliveries between January 1, 2011, and December 31, 2012, at a low-risk community hospital. The population was divided into 3 groups: (1) study group (SG), (2) private practice (PP), and (3) community healthcare clinic (CHCC). All groups received standard perinatal management, but additionally the study group was analyzed for serum zinc, carnitine, total 25-hydroxycholecalciferol (25 OH-D), methylene tetrahydrofolate reductase, and catechol-O-methyl transferase polymorphisms in the first trimester prior to intervention, with subsequent second trimester and postpartum assessment of zinc, carnitine, and 25 OH-D after intervention. Intervention consisted of trimester-by-trimester nutrition and lifestyle education, supplementation of L-methyl folate, magnesium, essential fatty acids, and probiotics for all SG patients, with targeted supplementation of zinc, carnitine, and 25 OH-D. Because of small case occurrence rates of individual conditions in the study group, unreportable reductions were found, except GDM (SG vs CHCC, P value 0.046 with 95.38% confidence interval [CI]), and PIH (SG vs PP, P value 0.0505 with 94.95% CI). The aggregated occurrence rate of the four conditions, however, was significantly lower in the study population than in either comparison population (PP P value 0.0154 with 98.46% CI, and CHCC P value 0.0265 with 97.35% CI). Customized nutritional intervention appears to have significantly reduced adverse perinatal outcomes. Prospective study within larger, at-risk populations is needed to determine whether customized nutrition improves conditions individually.

RESUMEN

En una revisión retrospectiva de historias clínicas se analizó el efecto de la nutrición personalizada sobre la incidencia de hipertensión inducida por el embarazo (HIE), diabetes gestacional (DG) y los neonatos pequeños o grandes para su edad gestacional (PEG, GED), examinando partos consecutivos entre el 1 de enero de 2011 y el 31 de diciembre de 2012 en un hospital general de bajo riesgo. La población se dividió en 3 grupos: (1) estudio (SG), (2) consulta privada (PP) y (3) clínica de atención médica general (CAMG). Todos los grupos recibieron una gestión perinatal estándar,
Observational Study

INTRODUCTION

Worldwide incidence of hypertension (HTN), obesity, cardiovascular disease (CVD), diabetes mellitus (DM), and allergic disease is rapidly rising,1 no longer sparing developing nations. Vulnerability to these chronic diseases appears rooted in the pre-conceptional and post-conceptional time periods.2 Previously presumed inevitable expressions of fixed genetic inheritance are giving way to the more hopeful realization of epigenetic modification of phenotype, first suggested by Lamarck and explored by Roseboom and others in their analysis of the chronic disease outcomes of offspring conceived during Germany’s annexation of the Netherlands, characterized by intentional and fixed-time starvation of the population.3 Lumey and others recognized a strong association between manifestations of specific chronic disease in adults and the trimester during which maternal starvation occurred and that neonates who were small for their gestational age (SGA) were at the highest risk.4 Further, the large-for-gestational-age neonates (LGA) carried increased risk for adult expression of all four of the chronic diseases noted above and that parturient under- or over-feeding also contributed to adult health risk.5

Predispositions to these morbidities, as well as osteoporosis, some cancers (CA), aging, and sex-specific disease6,7 appear malleable based on availability of micronutriute, complexity of maternal/fetal gut microbiota, dietary fatty acid and protein composition, and toxic exposure, although debate remains about the efficacy of individual nutrient levels in pregnancy. The nutrients we chose for study and intervention reflect our belief in the likelihood of maternal and fetal benefit with potential reduction of risk in the F1 and possibly F2 generations. For example, maternal carnitine insufficiency treated with 2000 mg of carnitine avoids a striking rise in free fatty acids, which are thought to be the main cause of insulin resistance and gestational diabetes.8 Because GDM is associated with LGA offspring and because these offspring experience a greater than average risk for adult disease, especially adult onset DM (AODM), it is reasonable to expect a reduced incidence of chronic disease if maternal carnitine insufficiency is recognized and treated. Iron status, more commonly assessed in pregnancy, is not only important in hematopoiesis and neurological and cognitive development9 but plays a crucial role in carnitine synthesis,10 although carnitine precursors may be more important.11

Zinc is an important cofactor for more than 300 identified zinc metalloenzymes.12 Zinc insufficiency in late pregnancy disrupts neuronal replication and synaptogenesis,13 and maternal deficiency is associated with decreased DNA, RNA, and protein content of the F1 brain.14 Zinc deficiency affects one in five world inhabitants.14 Zinc supplementation reduces the risk of preterm birth, though not SGA.14

Vitamin D deficiency is under investigation for its role in protection against DM, CV, some CA, osteoporosis, and optimization of immune function.15 Vitamin D might be an important mediator in gut homeostasis and in signaling between microbiota and host.16 The intestinal microbiome in both newborns and lactating mothers influences infant and childhood food allergy and eczema. Supplementation with probiotics reduces incidence of these conditions in the offspring by 35% through 4 years of age17 and possibly through adolescence.18 Use of Lactobacillus rhamnosus and L reuteri appear most effective.19

Folate’s role in preventing neural-tube defects is well described. Lesser known is the commonness of single-nucleotide polymorphisms such as methylene tetrahydrofolate reductase (MTHFR) that limit methylation of folic acid and their crucial role in such disparate conditions as pregnancy-induced hypertension (PIH) and autism. MTHFR polymorphisms affect just under 50% of most ethnic groups. If B-vitamin supplementation is inadequate during the period from 3 months before conception to 1 month postconception and if the maternal genome carries MTHFR and cystathionine beta synthase (CBS) polymorphisms while the fetus is affected by catechol-O-methyl transferase, the offspring experience a 720% rise in the risk for autism.20 PIH is more common in people carrying the MTHFR C677T polymorphism,21 raising the possibility of preventive...
therapy using the methylated form of folic acid, 5-methyl-
ylene tetrahydrofolate. SGA babies are born more com-
monly to mothers with PIH-affected pregnancies, and
these neonates fall within the highest quartile of risk for
adult obesity, DM, HTN, and CVD.22

Recognizing that—in addition to these major ones—other common deficiencies such as essential fat23 and magnesium24 influence maternal/fetal health and that all nutrients work in concert, we developed a customized nutrition and lifestyle program with a supplement intended to reduce PIH and DM through epigenetic and metabolic modulation and thus reduce the frequency of LGA and SGA babies whose neonatal disadvantages place them at increased risk for chronic disease throughout their adult lives.

METHODS

All pregnant women who experienced serial con-
secutive delivery in our medical clinic between
January 1, 2011, and December 31, 2012, were evalu-
ated per our routine clinical practice. This included
assessment of vitamin D, carnitine, iron, zinc, and
MTHFR polymorphism status in the first trimester
prior to supplementation. Vitamin D, carnitine, iron,
and zinc were again assessed in the late second trimes-
ter following supplementation, and postpartum. Each
also received standard perinatal evaluations includ-
ing body mass index (BMI), weight gain, blood pres-
sure, and 1-hour non-fasting 50-gm glucose tolerance
testing. We did not test for but assumed common
insufficiencies of magnesium,24 essential fatty acids,23
and probiotics. L-methyl folate was used instead of
folic acid, and if an individual had an MTHFR poly-
morphism with conditions associated with this poly-
morphism her dosage of L-methyl folate was adjusted.
The two comparison groups were evaluated and trea-
ted for iron insufficiencies only.

A trimester-by-trimester nutrition and lifestyle-
education program was provided at no cost to meet
the general nutrient requirements of each developmental
phase, with intervention beginning in the first trimes-
ter. Nutritional objectives for the patients in the study

| Table 1 | Emphasis of Nutrition Education Classes |
|---------|-----------------------------------------|
| Nutrients | Preconception | 1st Trimester | 2nd Trimester | 3rd Trimester | Postnatal |
| Protein | Adequate | Complete, carnitine, meth-
ionine, cysteine, 0.8 g/kg | Complete, adequate | Complete, adequate | Complete, adequate |
| Fat | Essential fatty acids | Omega 3 | Omega 3 | Omega 3 | Omega 3 |
| Carbohydrate | Complex | Complex | Complex, fiber | Complex | Complex |
| Minerals | Iodine, iron, magnesium, iodine, selenium | Iron, magnesium, calcium | Iron, zinc, magnesium | Iron, calcium |
| Vitamins | Methylation factors | Vitamins D, B9, B12, folate | Vitamins E, D, C | Vitamins C, A | B vitamins, vitamin D |
| Phytoneutrients | Full range of colors of fruits and vegetables | Colors: oxidative reserve | Colors: organ growth | Colors: newborn preference | Colors: oxidant balance |
| Probiotics | | Immune balance | Immune balance | Immune balance |

| Table 2 | Prenatal Supplements Adjusted to Levels of Hemoglobin, Hematocrit, Mean Corpuscular Volume, Vitamin D, Zinc, Carnitine, and MTHFR Status |
|---------|---------------------------------------------------------------|
| Vitamin A mixed carotenoids | 5000 IU | Methylocobalamin | 800 µg | Chromium (chromium niacinate) | 200 µg |
| Vitamin C | 250 mg | Biotin | 100 µg | Molybdenum (molybdenum glycinate) | 25 µg |
| Vitamin D3 | 2000 IU | Pantothenic acid (d-calcium pantothenate) | 25 mg | Omega-3 fatty acids | 620 mg |
| Vitamin E (mixed) | 110 IU | Iron (iron bisglycinate) | 25 mg | EPA | 400 mg |
| Thiamine (mononitrate) | 5 mg | Iodine (potassium iodide) | 150 µg | DHA | 200 mg |
| Riboflavin (5 phosphate) | 5 mg | Zinc (zinc citrate) | 25 mg | Other omega-3 | 20 mg |
| Niacinamide | 25 mg | Selenium (L selenomethionine) | 100 µg | L-carnitine as 1492 mg L-carnitine tartrate | 1000 mg |
| B6 (Pyridoxal 5 phosphate) | 15 mg | Copper (copper gluconate) | 1.5 mg | Probiotic blend: Lactobacillus acidophilus | 60 B CFU |
| L-5-Methylfolate | 1000 µg | Manganese (manganese gluconate) | 5 mg | Bifidobacterium lactis, Lactobacillus plantarum, Lactobacillus salivarius, Streptococcus thermophilus | |

Abbreviations: CFU, colony-forming unit; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; MTHFR, methylenetetrahydrofolate reductase.
In all three groups, any incidence of any of the conditions under study was managed similarly, based on nationally accepted standards.

For all women giving birth at our low risk, Level 1, family practice–driven community hospital between January 1, 2011, and December 31, 2012, we retrospectively evaluated the frequency of GDM, PIH, SGA, and LGA neonates using hospital ICD-9 coding data and delivery log review. The limited resources of the low-risk hospital preclude all anticipated high-risk deliveries or preterm deliveries earlier than 36 weeks’ gestation. We compared outcomes between our study group (SG), patients of all other private practitioners (PP), and patients seen by a grant-based community healthcare clinic (CHCC), using a 2-proportion z-test. All three groups of patients received nearly identical prenatal care based on national standards, including prenatal education classes offered at low cost to all groups between the late second and early third trimesters delivering at the low risk community hospital. Six sessions over one and a half months surrounding labor and postpartum management contained a Lamaze-based training in addition to information about waterbirth and doula attended births, but contained no formal nutritional recommendations. Lifestyle instruction emphasized sleep hygiene, finding/creating a supportive community, and encouragement to use personally held spiritual practices. A formal exception from Institutional Review Board review based on retrospective observational study design was obtained.

RESULTS

The aggregated occurrence rate of the four conditions under study—GDM, PIH, SGA, and LGA—was significantly lower in our study population than in the comparison populations, with a P value of .0265 (confidence interval [CI]: 97.35%) compared to the CHCC, and a P value of .0154 (CI: 98.46%) compared to the private practice group (Table 3). The private practice group and the study group share similar age, socioeconomic status, locality, gravidity, parity, and ethnicity (Table 4). The mean BMI was similar across all populations (Table 5), however the greatest range and the highest percentage of obesity was found in the CHCC group. The federally funded community healthcare clinic and the study group differed based on socioeconomic status (very few of its patients were privately insured) and ethnicity (the CHCC saw a higher Hispanic population). Percentage of governmental payor source was consistent for the study group (50%) and the private population (46.9%). Drug use history and positive drug testing in the study group approximated the CHCC group more closely than the private practice group. The majority (86%) of the positive drug screen results revealed a predilection for marijuana use. In the study group, none of the positive drug screen results were linked to GDM, PIH, SGA, or LGA.

Compliance data for the study group revealed variable adherence rates for individual nutrients as follows: zinc 47%, carnitine 58.7%, vitamin D3 89.3%, iron 89.3%, and L-methyl folate 75%. Perinatal nutrition class attendance exceeded 70%. Insufficiency rates of all nutrient categories rose in our study group between first and third trimesters, testing as follows: zinc 37% to 85%, carnitine 56.7% to 97%, 25 OH D 55% to 69%, and hemoglobin 15.1% to 49.2%.

Table 3 Significant Differences in Pregnancy Complications in Clinic Populations (2-proportion z-test)

| Population (n)                  | Study vs Combined | Study vs Private | Study vs Community |
|--------------------------------|-------------------|------------------|-------------------|
| Deliveries (664)               | 111 vs 553        | 111 vs 322       | 111 vs 231        |
| Total complications (59)       | 4 vs 55a          | 4 vs 33a         | 4 vs 22a          |
| GDM (21)                       | P = .0161a        | P = .0154a       | P = .0265a        |
| Gestational diabetes mellitus | (CI = 98.39%)     | (CI = 98.46%)    | (CI = 97.35%)     |
| PIH (28)                       | 1 vs 20b          | 1 vs 10b         | 1 vs 10b          |
| Pregnancy-induced hypertension | P = .0678b        | P = .1015        | P = .0465b        |
| (28)                           | (CI = 93.22%)     | (CI = 89.85%)    | (CI = 95.83%)     |
| Large for gestational age (6)  | 1 vs 5b           | 1 vs 1b          | 1 vs 4b           |
| Small for gestational age (4)  | 0 vs 4c           | 0 vs 4c          | 0c                |
| Abbreviations: CI, confidence interval; NA, not available. | | | |

* P < 0.05
† P < 0.1
Power:

- a = all case size low, so slightly under typical prerequisites
- b = case size very low, moderately under statistic prerequisites
- c = case size nonexistent, unsuitable for meaningful statistics
Despite the small study population size and the infrequent occurrence of the test conditions, two individual test condition comparisons proved significant: (1) study group vs CHCC: GDM \( P \) value of 0.0462 (CI: 95.38%) and (2) study group vs private practice: PIH \( P \) value of 0.0505 (CI: 94.95%).

**DISCUSSION**

These results, though preliminary, suggest that the nutrition and lifestyle intervention in the study population is highly likely to be responsible for the reductions seen in PIH, DM, SGA, and LGA neonates. This is despite not reaching sufficiency in individual nutrient levels. The acting hypothesis is that rather than one nutrient level brought to sufficiency creating benefit, it is the complex interplay of all crucial nutriture that allows for functional improvement. We do not know if the other two comparison groups have similar nutrient insufficiencies. Given the similarities between the study group and the private group, it is a reasonable assumption that these insufficiencies exist in the private group as well, but additional study is needed.

In this retrospective observational study, the demographic data appear comparable with the exception of ethnicity and drug history. Several naturally occurring selection factors work toward keeping the populations comparable: (1) All providers are family practice physicians or certified nurse midwives restricting patients followed in their practices to lower-risk individuals; (2) the limited resources of a low-risk hospital preclude all anticipated high-risk deliveries or preterm deliveries earlier than 36 weeks; and (3) the ethnic and socioeconomic homogeneity of the small community in which the hospital is located.

Significance of reductions in GDM, PIH, SGA, and LGA when compared individually were limited by lack of case size in the study group (SG) but also by selection of a relatively low-risk population for treatment compared to US and world standards, suggesting the possibility that a higher-risk group such as the CHCC would experience greater reductions in morbidity (Table 6).

Another glaring confounder is the lower-than-expected compliance with individual treatment plans, which illustrates the practical difficulties facing many

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**Table 4 Comparative Characteristics of Three Clinical Groups**

| Characteristic | Study Group (111) | Private Practice (322) | Community Clinic (231) |
|---------------|------------------|------------------------|-----------------------|
| Age (Mean±SD) | 29.7±5.68        | 29.8±2.72              | 27.6±2.91             |
| Gravidity     | 2.97±1.76        | 2.72±1.58              | 2.91±1.74             |
| Parity        | 1.13±1.17        | 1.10±1.08              | 1.31±1.38             |
| Race (%)      |                  |                        |                       |
| Caucasian     | 93.3             | 90.8                   | 58.4                  |
| Hispanic      | 5.0              | 8.6                    | 41.6                  |
| Smoking, alcohol, drug history (%) | 21.7 | 9.1 | 27.2 |
| Drug screen positive at birth (%) | 5.0 | 1.2 | 7.2 |

**Table 5 Body Mass Index (BMI) Descriptive Statistics Among Three Clinical Groups**

| Statistic | Study Group | Private Practice | Community Clinic |
|-----------|-------------|------------------|------------------|
| Mean±SD   | 24.8±5.3    | 24.1±5.4         | 26.1±5.6         |
| Minimum   | 17.0        | 18.0             | 18.0             |
| First quartile | 21.0 | 20.5 | 21.0 |
| Median    | 24.0        | 22.5             | 25.0             |
| Third quartile | 26.0 | 26.0 | 30.0 |
| Maximum   | 54.0        | 42.0             | 39.0             |
| BMI ranges: |            |                   |                  |
| 25-30     | 33%         | 24%              | 27%              |
| >30       | 11%         | 10%              | 24%              |

**Table 6 Prevalence Comparisons of Gestational Diabetes Mellitus (GDM), Pregnancy-induced Hypertension (PIH), Large for Gestational Age (LGA), and Small for Gestational Age (SGA)**

| Population (n) | GDM | PIH | LGA | SGA |
|----------------|-----|-----|-----|-----|
| Study group (n=111) | 1 (0.90%) | 2 (1.80%) | 1 (0.9%) | 0 |
| Private practice (n=322) | 10 (3.1%) | 18 (5.59%) | 1 (0.31%) | 4 (1.24%) |
| Community clinic (n=231) | 10 (4.3%) | 8 (3.46%) | 4 (1.73%) | 0 |
| Oregon | NA | NA | 9.4% | 6.1% |
| US white/non-Hispanic | 5.6% | 7.5% | NA | NA |
| US Hispanic | 5.7% | 4.4% | NA | NA |
| United Statesb | 5.7% | 6.7% | 6.9% | 7.9% |
| Worldc | <7.5% | 7.5% | 9% | 23% |

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patients during their pregnancies: (1) the physical, financial, and social requirements of traveling to a classroom four times throughout the prenatal and postpartum time periods; (2) the revolutionary dietary and lifestyle changes demanded by the program; and (3) the motivation, empowerment, and tools necessary to make those changes.

The perinatal period represents a unique opportunity for real change in lasting health outcomes. There is no more amenable phase in the human lifecycle for introducing habits that will lead to healthier lives for mothers and their babies. People are open to what will improve the health of their offspring, and not too surprisingly, this time period appears to present a critical window of opportunity for epigenetic and biometabolic intervention with positive outcomes that transcend generations.28

Some of the difficulties in achieving compliance can be overcome by appropriate and engaging educational material. To that end, we converted nutritional and lifestyle lessons into easily assimilated written materials (at appropriate reading level), graphic materials, e-learning modules, and a web-based interactive application that allows the patient and provider ready access to customized food and lifestyle choices with a robust teaching glossary. These materials can be easily accessed on a computer or hand-held device by both patient and provider. Thus the program facilitates an online relationship that fosters simultaneous interactive oversight for the provider.

The direct savings in public-health costs that could be achieved by significant reduction of perinatal morbidity is highly promising and warrants further investigation. Even more promising is the potential extension of the possibility of generational reductions in chronic diseases, which could save millions of dollars as well as untold human suffering.

These data suggest that it is time to shift previous assumptions of inevitable maternal and fetal disease to assumptions that many of these conditions are preventable through targeted intervention during this critical perinatal window. Further investigations suggested by these data will need to be addressed in a prospective manner with a larger at-risk population, with educational and supplemental tools that empower patients to comply with nutritional and lifestyle regimes that positively affect maternal and fetal health. It seems reasonable that generational reductions in the chronic diseases of obesity, HTN, DM, CVD, osteoporosis, allergy, and mental illness could be achieved.28-33

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