OBSERVATIONAL STUDY

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

定制式孕妇营养强化似乎可降低某些常见孕产妇和新生儿并发症发生率：一项观察性研究

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), and 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-hydroxy cholecalciferol (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 .046 with 95.38% confidence interval [CI]), and PIH (SG vs PP, *P* value .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 .0154 with 98.46% CI, and CHCC *P* value .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.

摘要

我们从 2011 年 1 月 1 日至 2012 年 12 月 31 日，连续观察了一所低风险社区医院的分娩病例，通过回顾性病历审查分析了定制式营养干预对妊娠高血压综合征 (pregnancy induced hypertension, PIH)、妊娠糖尿病 (gestational diabetes, GDM)，以及小于和大于胎龄儿 (small and large for gestational age neonates, SGA、LGA) 发生率的影响。人群分为 3 组：(1) 研究组 (study group, SG)，(2) 私人诊所 (private practice, PP) 和 (3) 社区医疗诊所 (community healthcare clinic, CHCC)。各组均接受标准围产期管理，但研究组另外在干预前的妊娠早期分析了血清锌、肉毒碱、总 25 羟胆钙化醇 (25 OH-D)、亚甲基四氢叶酸还原酶和儿茶酚-O-甲基转移酶基因多态性，并随后在干预后的孕中期和产后评估了锌、肉毒碱和 25 OH-D。干预措施包括对所有 SG 患者按孕期给予营养和生活方式教育，以及补充 L-甲基叶酸、镁、必需脂肪酸和益生菌，另外还有针对性地补充锌、肉毒碱和 25 OH-D。由于单种疾病的病例发生率较低，除 GDM（SG 对比 CHCC，P 值为 0.046，置信水平为 95.38%）和 PIH（SG 对比 PP，P 值为 0.0505，置信水平为 94.95%）外，研究组各疾病的发生率仅观察到不可报告的下降。然而，相比对照人群（PP：P 值为 0.0154，置信水平为 98.46%；CHCC：P 值为 0.0265，置信水平为 97.35%），研究人群中四种疾病的总发生率显著降低。定制式营养干预似乎显著减少了不良围产期结局。需要在高危人群中开展大样本前瞻性研究，以确定定制式营养干预是否可降低单种疾病的发生率。

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) grupo del estudio (GE), (2) consulta privada (CP), y (3) clínica de atención médica general (CAMG). Todos los grupos recibieron una gestión perinatal estándar,

pero en el grupo del estudio se realizaron, además, análisis del zinc en suero, carnitina, 25-hidroxicolecalciferol (25 OH-D) total, metilentetrahidrofolato reductasa y polimorfismos en catecol-o-metil-transferasa en el primer trimestre, antes de la intervención, con las posteriores valoraciones en el segundo y tercer trimestre y postparto de zinc, carnitina y 25 OH-D tras la intervención. La intervención consistió en un proceso educativo trimestral sobre nutrición y estilo de vida, suplementos de L-metilfolato, magnesio, ácidos grasos esenciales y probióticos, para todas las pacientes del GE, con suplementos dirigidos con zinc, carnitina y 25 OH-D. Debido a las bajas tasas de incidencia de las afecciones individuales en el grupo del estudio, se encontraron reducciones que no deben comunicarse, exceptuando la DG (GE frente a CAMG, valor de P 0,046 con un nivel de confianza del 95,38 %) y la HIE (GE frente a CP, valor de P 0,0505 con un nivel de confianza del 94,95 %). Sin embargo, la tasa de incidencia agregada de las cuatro afecciones fue significativamente más baja en la población del estudio que en cualquiera de las poblaciones de comparación (CP, valor de P 0,0154 con un nivel de confianza del 98,46 %, y CAMG, valor de P 0,0265 con un nivel de confianza del 97,35 %). La intervención nutricional personalizada parece tener resultados perinatales adversos significativamente reducidos. Es necesario un estudio prospectivo con poblaciones más grandes y de riesgo, para determinar si la nutrición personalizada mejora las afecciones de forma individual.

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 postpartum 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 disease[6,7] appear malleable based on availability of micronutriture, 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 hematopoesis and neurological and cognitive development[9] 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 age[17] and possibly through adolescence.[18] Use of *Lactobacillus rhamnosis* 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 hypertention (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-methylene tetrahydrofolate. SGA babies are born more commonly 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 fat[23] and magnesium[24] 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 consecutive delivery in our medical clinic between January 1, 2011, and December 31, 2012, were evaluated 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 trimester following supplementation, and postpartum. Each also received standard perinatal evaluations including body mass index (BMI), weight gain, blood pressure, 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 polymorphism with conditions associated with this polymorphism her dosage of L-methyl folate was adjusted. The two comparison groups were evaluated and treated 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 trimester. Nutritional objectives for the patients in the study group are shown in Table 1. A customized nutrient packet was developed to meet the specific requirements of individual patients not being met by the educational program (Table 2). Each woman purchased her own supplements, and those unable to afford them received donation from the medical practice. The expected first and early trimester nausea that reduces adherence was mitigated by divided and nighttime dosing.

Table 1 Emphasis of Nutrition Education Classes

Nutrients	Preconception	1st Trimester	2nd Trimester	3rd Trimester	Postnatal
Protein	Adequate	Complete, carnitine, methionine, cysteine, 0.8 g/kg	Complete, adequate 1.1 g/kg	Complete, adequate 1.1 g/kg	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, zinc, calcium, selenium	Iodine, selenium	Iron, magnesium, calcium	Iron, zinc, magnesium	Iron, calcium
Vitamins	Methylation factors	Vitamins D, B_6, B_{12}, folate	Vitamins E, D, C	Vitamins C, A	B vitamins, vitamin D
Phytonutrients	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	Methylcobalamin	800 µg	Chromium (chromium niacinate)	200 µg
Vitamin C	250 mg	Biotin	100 µg	Molybdenum (molybdenum glycinate)	25 µg
Vitamin D_3	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
B_6 (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 lectis, 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 D_3 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 55[a]	4 vs 33[a]	4 vs 22[a]
	P=.0161* (CI=98.39%)	*P*=.0154* (CI=98.46%)	*P*=.0265* (CI=97.35%)
Gestational diabetes mellitus (21)	1 vs 20[b]	1 vs 10[b]	1 vs 10[b]
	P=.0678† (CI=93.22%)	*P*=.1015 (CI=89.85%)	*P*=.0465* (CI=95.38%)
Pregnancy-induced hypertension (28)	2 vs 26[a]	2 vs 18[a]	2 vs 8[a]
	P=.0827† (CI=91.78%)	*P*=.0505* (CI=94.95%)	*P*=.1966 (CI=80.34%)
Large for gestational age (6)	1 vs 5[b]	1 vs 1[b]	1 vs 4[b]
	P=.4987 (CI=50.13%)	*P*=.7855 (CI=21.45%)	*P*=.2745 (CI=72.55%)
Small for gestational age (4)	0 vs 4[c]	0 vs 4[c]	0[c]
	P=.1844 (CI=81.56%)	*P*=.1191 (CI=88.09%)	NA

Abbreviations: CI, confidence interval; NA, not available.
*$P<.05$
†$P<.1$
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

Table 4 Comparitive Characteristics of Three Clinical Groups

Characteristic	Study Group (111)	Private Practice (322)	Community Clinic (231)
Age	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%

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 .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.[25-27] 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 midwifes 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

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%[a]	6.1 %[a]
US white/non-Hispanic	5.6%	7.5%	NA	NA
US Hispanic	5.7%	4.4%	NA	NA
United States[b]	5.7%	6.7%	6.9%	7.9%
World[c-f]	<7.5%	7.5%	9%	23%

[a] Dalenius K, Bridley P, Smith B, Reinold C, Grummer-Stawn L. Pregnancy nutrition surveillance 2010 Report. Atlanta: US Department of Health and Human Services. Centers for Disease Control and Prevention; 2012.
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Abbreviation: NA, not available.

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 health benefits into adulthood and the real 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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