

**Dietary Supplements Health Education Act
Structure Function Claims Related to Pregnancy
Docket No: 00N-0506**

**March of Dimes Birth Defects Foundation
Donald R. Mattison, Medical Director
March 30, 2000**

Introduction

Thank you for the opportunity to comment on FDA interpretation of how structure function claims related to pregnancy will be dealt with under the Dietary Supplements Health Education Act.

The March of Dimes Birth Defects Foundation is one of the oldest public health nongovernmental agencies in the United States, with a mission devoted to improving the outcome of pregnancy. In accomplishing this mission the Foundation considers its activities against the continuum of reproductive health, which begins prior to conception.

The Foundation is a volunteer led organization with more than 3 million volunteers with all ranges of backgrounds - from physicians and scientists at highly specialized academic health centers, to health care professionals at community health centers, to nonprofessionals of all types.

The common theme linking all of these diverse volunteers is the March of Dimes mission - to improve pregnancy outcome. From that perspective this legislation, and how structure function claims are interpreted in relationship to pregnancy are critical to our foundation, especially because we believe it is essential to prohibit pregnancy related structure function claims under the Dietary Supplements Health Education Act.

In my comments, and in the written materials submitted, I will focus on the following topics

- Physiological changes associated with pregnancy
- Nausea and vomiting in pregnancy
- Leg edema in pregnancy
- Five questions posed by FDA
- Prohibit pregnancy related structure function claims under DSHEA

Physiological Changes Associated With Pregnancy

Successful adaptation to, and completion of pregnancy, requires a set of complex physiological changes in the mother as well as dynamic adaptations by the placenta and fetus.

One of the most obvious changes is the increase in maternal body weight. Over the course of pregnancy the fetus grows to approximately 8 lbs. (3400 gms.), the placenta weighs about 1 ½ lbs. (650 gms.), the uterus increases from about ¼ lbs. (75 gms.) to about 2 lbs. (970 gms.), the weight of the breasts increase about 1lbs. (405 gms.), blood weight increases about 3 lbs. (1450 gms.), and subcutaneous adipose tissue increases about 8 lbs. (3345 gms.).

In addition, there are changes in the physiology of the mother, with cardiac output increasing 50% (from 4.3 to 6.2 liters/min.), pulmonary function increasing about 40% (minute ventilation increases from 7270 to 10,340 ml), renal blood flow and glomerular filtration rate both increasing about 50%, the motility of the intestines decreasing, and other changes. All of these changes occur at different periods of pregnancy and are essential for the normal progress of pregnancy. Indeed, if these changes do not occur the outcome of pregnancy is typically worse than when they do occur.

These changes associated with pregnancy create conditions, which in a young healthy woman would be considered signs and symptoms associated with disease. For example, as a consequence of pulmonary and cardiovascular changes, it is common for a healthy pregnant woman to have leg edema and shortness of breath. In a young healthy woman, who was not pregnant, those symptoms would suggest the need for further evaluation for potential cardiovascular disease, but during pregnancy these are expected changes, and the health care provider teaches the woman that these will occur.

Nausea and vomiting of pregnancy, and leg edema of pregnancy are also conditions that usually represent normal adaptation of pregnancy, but are also symptoms of disease and cannot be distinguished between normal or disease states by the layperson. Nausea and vomiting is generally thought to represent the hormonal changes which take place over the first part of

pregnancy – explaining why it typically diminishes or resolves after the first trimester.

Leg edema is thought to be produced by a series of maternal physiological changes including; increased vascular permeability, decreased serum protein, pressure of the uterus on the veins leading from the legs toward the heart, and increased intravascular volume. As indicated earlier, these are normal adaptations of pregnancy and are more frequently found in those pregnancies that have a healthier outcome.

Pregnancy then is a dynamic evolving physiological state with both maternal as well as fetal changes necessary for a successful outcome. Indeed as a recognition of this evolving state and the potential for rapid development of disease in either the mother or fetus, authoritative bodies like the American College of Obstetricians and Gynecologists have established clinical guidelines on the frequency of visits and types of evaluations recommended.

These visits, for women with uncomplicated pregnancies, generally occur monthly over the first 28 weeks of pregnancy and increase to every 2 – 3 weeks until 36 weeks then advance to at least weekly visits at the end of pregnancy. In no other situation are healthy adults seen this frequently by highly trained and specialized health care providers. This frequency of visits has been established by expert clinicians because of the rapidity with which disease can develop during pregnancy. Unlike the normal adult, the physiological status of the mother, the placenta and the fetus are continuously changing, and from this perspective we find the binary categorization of the DSHEA (disease or structure/function claims) to be inadequate.

Nausea And Vomiting In Pregnancy

During the early part of pregnancy, and likely stimulated by hormonal changes associated with early pregnancy is a characteristic pattern of nausea and vomiting. Nausea and vomiting associated with pregnancy typically begins at about 4-8 weeks and persists until 15 – 20 weeks of gestation.

Among many women the symptoms are annoying, uncomfortable but manageable with changes in eating habits. Unfortunately, however for some women the nausea and vomiting of pregnancy is worse than annoying or uncomfortable and is certainly not time limited (ie continues beyond mid-

gestation). This continuous and unrelenting vomiting is severe and lifethreatening – and is termed by clinicians hyperemesis gravidarum – loosely translated as the excess vomiting of pregnancy. This condition produces morbidity because it prevents sufficient nutrients from being ingested by the mother and also leads to dehydration and electrolyte imbalance. Together these conditions represent physiological stressors for the mother and the fetus.

What is excess vomiting in pregnancy – is it vomiting three, four, or more times per day and how is the impact on the mother assessed or characterized – I wish that the definition were as simple as counting – unfortunately that is not the case and typically the physician will assess blood and urine chemistry to determine the impact of nausea and vomiting on the course of pregnancy. That being the case, allowing or encouraging women to use dietary supplements on the premise that they can be used to manage nausea and or vomiting in pregnancy is totally inappropriate because it assumes that the woman can distinguish the normal from the abnormal conditions of pregnancy.

Leg Edema Of Pregnancy

As described above one of the common symptoms of pregnancy is leg edema, produced by increased intravascular volume, increased pressure on the veins from the leg to the heart, decreased serum proteins, and increased vascular permeability. Unfortunately, edema is also associated with the development of hypertension or pre-eclampsia during pregnancy – both diseases that should be carefully followed and treated under the care of a physician experienced in the care of these high risk patients.

It is also unfortunate that like nausea and vomiting of pregnancy, it is difficult for a non health professional to determine if the leg edema associated with pregnancy is also associated with other serious changes as these require assessment of the pattern of blood pressure change over the course of pregnancy as well as measurement of protein and other chemicals in blood and urine.

Five Questions Posed by the FDA

In the Federal Register it was noted that the*FDA specifically seeks comments on the following points*

- 1. What are the potential hazards that may be associated with the use of dietary supplements for conditions associated with pregnancy, both to the pregnant woman and the fetus? Should these hazards be considered to be different than hazards to other potential users? If so, why and on what basis under DSHEA?*

I hope I have provided, in the time permitted, convincing evidence that pregnancy is a dynamic and evolving physiological state with the potential for rapid development of disease.

While others have previously commented, we believe that the use of dietary supplements may produce a false sense of security with respect to symptoms which may signal the rapid development of more severe conditions among pregnant women and so delay needed diagnosis and treatment.

Consider, for example, the two structure function examples cited. Leg edema may represent normal adaptation to pregnancy or a symptom of preeclampsia, renal function impairment (increased elimination of protein, sodium), hepatic function impairment (decreased production of protein), nutritional impairment (inadequate intake of protein), or other conditions which can rapidly progress to disease which impairs the life of the mother or fetus.

Similarly, nausea and vomiting in the first trimester, while commonly self-limiting may represent an early signal of hyperemesis gravidarum. Unfortunately, hyperemesis gravidarum, with altered carbohydrate or electrolyte status impairing maternal adaptation to pregnancy or fetal growth and development, may also produce maternal and fetal dehydration with increased blood viscosity and as a result impaired intervillous perfusion and increased propensity for blood clotting.

Are these different than hazards to other potential users – yes, because of the complex maternal adaptation to pregnancy which are necessary for successful pregnancy as well as the potential for harm to the embryo or fetus

during development - a period which may be especially vulnerable to interruption.

If so, why and on what basis under DSHEA? Unfortunately, the Foundation believes that the two state nature of the Dietary Supplement Health Education Act (disease or structure function claims) is not well suited to the dynamic state which occurs over the nine months of pregnancy. Therefore, we argue that all pregnancy related structure function claims should be prohibited. Note however that there are health claims that we believe should be left intact. These relate to deficiency states, which are associated with abnormal pregnancy outcome. One notable example is the benefit derived from folic acid in decreasing the risk of neural tube defects.

2. Are there certain conditions associated with pregnancy (in addition to those already identified in the final rule) for which structure/function claims should not be permitted? If so, why and on what basis?

We believe that structure function claims should not be permitted at all during pregnancy - because both mother and fetus are continuously changing to adapt to pregnancy and to grow and develop.

As previously noted, there is a set schedule of visits which occur over the course of pregnancy which have been designed by the American College of Obstetricians and Gynecologists, an authoritative body of experts in woman's health care. This schedule of visits has been established in recognition of the increasing risk for the rapid development of disease in the mother or fetus across the course of pregnancy. Because of the complex pattern of anatomic and physiological changes during pregnancy we believe that structure function claims should not be permitted in relationship to pregnancy under the Dietary Supplements Health Education Act.

3. What is the potential for harm that may be associated with the use of dietary supplements during pregnancy for conditions unrelated to pregnancy?

As suggested by the question, women who are pregnant may also have other diseases that are unrelated to the pregnancy. Unfortunately, it has been shown that the interaction between pregnancy and other diseases found in women are complex, and may in some cases act to modify adaptations to pregnancy. As a result, these diseases increase maternal morbidity or

produce stress for the fetus. These intercurrent diseases may therefore act during pregnancy to increase risk and decrease the time needed to develop maternal or fetal disease. As a consequence, for some of these conditions, for example hypertension or diabetes, the American College of Obstetricians and Gynecologists, have suggested preconception visits to optimize maternal health status and an increased frequency of visits during the course of pregnancy to follow more closely the health of the mother and fetus.

4. Are there means to address safety concerns associated with dietary supplement use during pregnancy, for example a requirement to conduct animal studies or collect human safety information?

We believe that with the exception of vitamins and minerals that are used in preventing deficiency states, dietary supplements should not be used during pregnancy. For that reason we have no comment about the means to address safety concerns associated with use of dietary supplements during pregnancy.

5. Should dietary supplements with a specific recommended use during pregnancy be required to bear specific warnings about use during pregnancy? Should all dietary supplements be required to bear such warnings?

We believe all dietary supplements marketed to women of childbearing age should contain the following warning – *Women of childbearing age should consult with a physician before taking this product because dietary supplements are exempt from many aspects of Food and Drug Administration oversight.* However, as noted above there are classes of products, which are used in preventing deficiency states that have been shown to be beneficial during pregnancy. These products should be excluded from that advisory statement.

Conclusions

Thank you for the opportunity to participate in this important analysis of the DSHEA and present the views of the March of Dimes on how structure function claims related to pregnancy will be interpreted. In closing let me briefly reiterate perspective of the Foundation

I hope the material I have summarized provides the information needed to conclude that the complex set of changes which occur over the course of pregnancy can represent normal adaptations or disease processes and that the distinction can be difficult and require the evaluation of a trained health professional.

In addition, as described by the American College of Obstetricians and Gynecologists the risk for rapid development of disease in the mother or the fetus increases as pregnancy progresses. This is reflected in the increasing frequency of visits suggested by this authoritative body as pregnancy progresses.

As a result, pregnancy does not fit neatly within the framework of the Dietary Supplement Health Education Act. For these reasons the March of Dimes Birth Defects Foundation requests that FDA prohibit pregnancy related structure function claims under DSHEA.