I. Introduction:

Why Do Some Babies Have Fetal Alcohol Syndrome (FAS) and Others Do Not?

In 1995 a hypothesis was suggested to explain why only relatively few women who drink alcohol during pregnancy give birth to children with FAS. Epidemiological, clinical case, and basic biomedical research was evaluated, and the authors concluded that specific sociobehavioral risk factors such as Low SES (Socio-Economic Status) are permissive of FAS in that they provide a context for increased vulnerability.


Poor nutritional status of the mother is one of many environmental risk factors, and it deserves some attention because nutrition is one factor that we may be able to alter to improve the outcome of pregnancy. Poverty and poor nutritional status are clearly related, so it can be difficult to tease out any unique contribution of nutrition. However subsequent FAS research has demonstrated that there are nutrition influences on FAS in humans unrelated to poverty, and animal research has demonstrated the ability of certain nutrition deficits to exacerbate the effects of perinatal alcohol.

As one example, decreased maternal antioxidant status in conjunction with alcohol provokes FAS in vulnerable fetuses. Research in this area involves examinations of the relative availability of vitamins A and C, beta-carotene (and other antioxidant phytochemicals), zinc and selenium.

Other nutritional factors are also being found to contribute to the degree of damage induced by maternal alcohol use. These include the relative availability of a number of vitamins and minerals whose functional role in metabolism is affected by the
presence of alcohol. Significant alcohol intake alters the amount of certain nutrients required to metabolize alcohol as an energy substrate (fuel source). The B vitamins have been the focus of much interest in this area, along with mineral co-factors like magnesium and chromium.

Excessive alcohol consumption also alters the requirement for nutrients that have a role in detoxifying potentially harmful substances. In the latter scenario, alcohol dehydrogenase enzyme and the Cytochrome p40 system are examples of this “garbage disposal” function that has much more work to do when alcohol intake is excessive. Both depend significantly on the adequacy of certain nutrients such as iron and zinc, and the requirement for these nutrients may increase as well.

It is useful to remember that the usual recommended intakes of nutrients (like the RDAs, DRIs, AIs, etc.) are based on the best guess about the needs of the “healthy” population. Excessive alcohol intake can alter people’s actual nutrient requirements substantially so the usual recommendations may no longer be optimal or even adequate. This paper will focus on research into this issue.

Additionally, while it is clearly the case that avoiding alcohol abuse during pregnancy (or at any time of life) is the goal, we are a long way from reaching it. While efforts continue to be made in that direction, it seems to me that right now we should still do all we can to make maternal alcohol consumption hurt the babies less.

II. Historical Perspective on Nutrition Aspects of FAS:

Although the term FAS was not coined until the early 1970s, the damage associated with alcohol use in pregnancy has been noted at least as long ago as early Bible times. Dietary interventions have been seen as potential factors in the treatment of children of alcoholics for at least 100 years.

[1890] Over 100 years ago (in 1890) a report in the Journal of the American Medical Association made the following dietary regimen recommendations:

"No fact is more firmly established than that alcoholic ancestors will transmit to their children a defective brain and nerve power. The form and shape of this defect and its manifestations will vary widely.

The general principles which should govern in the treatment may be grouped as follows:
1) “No form of alcohols are safe, and narcotics of all kinds should be used with great care.”

2) “The diet should not include meats, because of their stimulating character; while meats contain much food force, they act as stimulants to a brain already over-stimulated and exhausted, and increase the peril of nervous disease.”

3) “The pathological tendency of all these cases is to become alcohol-takers and meat-eaters, hence the diet should always be non-stimulating and farinaceous [grain-based], and should be carried out with military regularity.”


This diet is (of course) no longer advised, although FAS does effect growth and nutritional needs.

III. ALCOHOL and NUTRITIONAL STATUS

Alcohol has its most profound negative effect on nutritional status once alcohol intake exceeds 30% of daily calories on a regular basis. At this level, intakes of protein, fat, vitamin A, vitamin C, thiamine, calcium, iron, zinc and fiber usually fall below 75% of the (non-pregnancy) RDA.

Malabsorption, alcohol-nutrient and nutrient-nutrient interactions aggravate the nutritional profile. Additionally, the “RDA” (or RDI or DRI or AI or similar recommended intake levels) no longer directly applies when the population is not a member of the “healthy” population. Deficiencies in many B-complex vitamins are frequently seen among alcoholics. Thiamine and folic acid deficiency are the most common (or at least the most commonly looked-for or recognized), leading to cardiac and neurologic complications.

[Medical and Nutritional Complications of Alcoholism: Mechanisms and Management, 1992]

Many studies have examined the role of a number of nutrients or diet features relative to:

1) alcohol use in general,
2) the effects of alcohol on the fetus, and
3) the health of children with FAS.

This paper will focus on the possibility of minimizing fetal damage from alcohol exposure with an emphasis on prenatal vitamin and mineral nutrition factors.
Evaluating the effects of alcohol on fetal development in humans is extremely difficult. Many types of studies are simply impossible for ethical reasons. Much of the research therefore involves laboratory animals and our ability to generalize study results to humans is always an issue.

However, studies in laboratory animals are demonstrating several areas of specific interactions between nutrients and alcohol exposure that modify the developmental injury associated with the alcohol exposure. There are very likely similar relationships in humans, as has been well documented for certain nutrients such as the effect of alcoholism on vitamin B-1 (thiamin) and folic acid status, requirements and utilization.

Specific Nutrients of Interest in FAS:

Thiamin (Vitamin B-1)

A number of mechanisms may be involved in the pathogenesis of thiamin deficiency in the alcoholic:

1. inadequate dietary intake;
2. impaired intestinal transport; and especially
3. decreased conversion of the dietary or supplement form to the active coenzyme form (i.e. TPP).

In rats, both functional and structural studies showed that neurotoxic effects of developmental alcohol exposure were not reversed by thiamin administration. However, adverse effects of undernutrition following developmental alcohol exposure were suppressed by thiamin administration. **In a more recent study (2009) the results indexed thiamin deficiency related to alcohol or to dietary inadequacy as a potent risk factor for stillbirths.**


**The recommended thiamin (vitamin B-1) intake for non-pregnant chronic alcoholics is 15 mg/day (DRI = 1.4).** That is, the person who abuses alcohol benefited from taking in ten times the usual amount of thiamin. **This is a good illustration of a situation in which the usual recommended intake level is not adequate in certain “non-healthy” populations.** There is currently no specific recommendation for pregnant women who are alcoholics, but it is likely to be more because of increased need.

But how safe would it be to provide over ten times the usual amount of thiamin in pregnancy?

The Food and Nutrition Board did not set a tolerable upper level (UL) of intake for thiamin because there are no well-established toxic effects from the consumption of excess thiamin in food or through long-term oral supplementation (up to 200 mg/day).

[http://lpi.oregonstate.edu/infocenter/vitamins/thiamin/]

A recent study investigated the tolerable upper intake levels of vitamin B-1 and vitamin B-2 in weaning rats. The results showed that feeding a diet containing up to 1.0% thiamin-HCl or 1.0% riboflavin (vitamin B-2) did not induce apparent adverse effects, and the “no-observed-adverse-effect-levels” (NOAELs) for thiamin and riboflavin in rats might be 1.0% in diet, corresponding to 900 mg/kg body weight/day.


While this was not a human study or a pregnancy study, it is useful as an indicator of how unlikely it would be that providing simply generous thiamin (like the 15 mg described for non-pregnant alcoholics above) in alcoholic pregnancy would be harmful.

Consider that:

1. The current prenatal recommendation (DRI) is **1.4 mg/day of thiamin, but it is extremely unlikely to be toxic at levels far above this**, (e.g. there is no recognized upper limit of safety, as described earlier.


2. The DRI reference weight for (non-pregnant) women is 126 lbs (57 kg).

3. The “no observed effect in rats” level of 900 mg/kg/d described above would correspond to a 57 kg (~125 lb) human’s intake of **51,300 mg thiamin /day**. This makes the **15 mg thiamin /day** suggested earlier for (non-pregnant) alcoholics not look so very high.

It is well known that thiamin deficiency in pregnancy is very injurious to both mother and baby, and fetal development in the presence of both alcohol abuse and thiamin deficiency is worse than either exposure alone.

There are many reports of Wernicke’s encephalopathy (also called Wernicke-Korsakoff Syndrome) in pregnancy. This is a very serious life-threatening and neurologically damaging
condition caused by thiamin deficiency. It is one manifestation of a life-threatening condition from thiamin deficiency called beriberi – a condition unexpected in the general US population, and therefore rarely recognized when it develops.

Thiamin deficiency during pregnancy is particularly injurious to mother and baby. It has also been described as a side effect during pregnancy of hyperemesis gravidarum (very severe nausea and vomiting in early pregnancy,) history of maternal gastric bypass (bariatric) surgery, and some eating disorders. (Please see my “Prenatal Top 10” handout for more on this.)

As the most common contributing cause of thiamin deficiency in the developed world is alcohol abuse, it is reasonable to consider a person who abuses alcohol as being at significant risk of being thiamin deficient, even in the absence of any symptoms or lab tests. **When that person is pregnant or planning a pregnancy, it would be very prudent to recognize the potential for fetal damage from the relative inadequacy, and to address it.**


**Identifying alcohol-related thiamin deficiency:**

Researchers have described early diagnosis of alcohol-related thiamin deficiency as an important aspect of effective intervention and treatment. Alcohol biomarkers exist that provide a direct and indirect way of estimating the amount of alcohol being consumed, the duration of ingestion and the harmful effects that long-term alcohol use has on body functions. Appropriate use of these markers can be very helpful when considering a diagnosis of alcohol-related thiamin deficiency.

CB Note:

**However, we do not need to diagnose deficiency before recommending a generous thiamin intake in women at risk.** The simple expedient of providing a generous (safe and cheap) thiamin intake to all women with a history of alcohol abuse may help prevent fetal damage. The idea would be to prevent injury by NOT waiting until overt deficiency has caused enough serious damage to be recognizable.

Thinking further along this line, though … many women’s alcohol use/abuse goes undetected and unadmitted. Providing generous thiamin to all would provide some protection to those individuals and their infants, plus those with a history of bariatric surgery.

An additional advantage to this approach is that no one must be singled out as being an alcoholic, or made to admit alcohol abuse before we provide any help in this area. In populations with a high prevalence of alcohol abuse this kind of simple intervention would likely be a quite cost-effective way to minimize fetal alcohol severity to some degree, and to protect the adult drinker from serious injury as well with no harm to others. As always, this is not the official recommendation of any official health group … it’s just my best guess.

**Riboflavin (Vitamin B-2)**

Riboflavin deficiency is very common in alcoholism because of poor diet but also because alcohol impairs absorption of riboflavin in the intestine. Absorption of dietary sources is more impaired by alcohol than absorption of riboflavin in vitamin supplements. Milk is the richest dietary source. Riboflavin is involved in all energy and protein metabolism so it is important in fetal development. It may be especially important in mood.


**Niacin (Vitamin B-3)**

Chronic alcoholics are also at risk of unrecognized pellagra (niacin deficiency) which is a condition that can, if uncorrected, result in dementia, severe skin problems, and even death. Niacin is involved in many metabolic functions, so deficiency can result in a wide range of problems.

A form of niacin called nicotinamide was found to prevent some of the deleterious effects of alcohol on the developing mouse brain when given shortly after alcohol exposure. The authors concluded that nicotinamide may hold promise as a preventive therapy of FAS.

**Vitamin B6 (Pyridoxine)**

Deficiency has been reported in alcoholics and even in the general public. High alcohol intake may be associated with inadequate intake, and in addition, alcohol increases B6 destruction so one’s requirements would be higher than usual. Vitamin B-6 is a cofactor for all protein, amino acid and neurotransmitter metabolism. It can also result in an elevated homocysteine level.


**Folic Acid and Vitamin B12:**

Folic acid is a nutrient of well-documented prenatal importance. It works with vitamin B12 and vitamin B6 in certain pathways related to making DNA, which means that all three need to be adequate for fetal development to proceed normally. Lower serum folate levels have often been reported in alcoholic populations.

Since 1998 folic acid has been added to grain products in the US which has improved the birth defects rates significantly. However, the amount added for the general public is unlikely to prevent deficiency in alcohol abusers because alcohol directly impairs folate absorption in the intestine. Additionally, malnourished alcoholics do not absorb folate as well as well-nourished alcoholics do.

Once folate depletion occurs, alcohol accelerates the production of megaloblastic anemia, and suppresses the hematologic response to folate. Folic acid deficiency is also related to mental health issues (e.g. depression.) It now appears that supplementing folic acid and vitamin B12 together may help prevent some fetal damage from exposure to alcohol.


**Choline:**

Disturbances in choline metabolism cause neural tube defects in mouse embryos in vitro. Maternal choline availability is critical in the developing fetal rat brain hippocampus – an area of the brain responsible for memory and much affected by fetal alcohol exposure. Inhibitors of choline uptake and metabolism cause developmental abnormalities in mice.

Choline is an essential nutrient in methylation, acetylcholine and phospholipid biosynthesis, and in cell signaling. The demand by an embryo or fetus for choline may place a pregnant woman and, subsequently, the developing fetus at risk for choline deficiency.

Several studies have shown that providing prenatal or neonatal choline supplementation can ameliorate some of the effects of prenatal alcohol ... findings with important implications for children of women who drink alcohol during pregnancy.


What are the best sources of dietary choline?

This is a nutrient that has not been in our radar until fairly recently, and it is turning out to have important roles in a wide variety of tissues. It deserves closer attention because inadequacy is a problem for some people, and deficiency is now known to be associated with serious medical problems.

By far the richest dietary sources are:

- egg yolk ~125 mg/yolk
- beef liver ~120 mg/1oz
- wheat germ ~85mg/half cup

There is an excellent overview with references and lots of information about choline at this website: http://lpi.oregonstate.edu/infocenter/othernuts/choline/
The following excerpts are from that site:

“Most choline in foods is found in the form of phosphatidylcholine. Milk, eggs, liver, and peanuts are especially rich in choline.”

[CB note: peanut butter has only 10 mg choline per Tbsp., so I’m not sure why it was mentioned here.]

“Phosphatidylcholine, also known as lecithin, contains about 13% choline by weight.”
Presently, national surveys do not provide any information on the dietary intake of choline, but it has been estimated that the average intake by adults is between 730 and 1,040 mg/day.

Lecithins added during food processing may increase the daily consumption of choline by about 115 mg/day.

**Strict vegetarians who consume no milk or eggs may be at risk of inadequate choline intake.** …

**“ Supplements: ** Choline salts, such as choline chloride and choline bitartrate are available as supplements. Phosphatidylcholine supplements also provide choline; however, they are only 13% choline by weight. Therefore, a supplement providing 4,230 mg (4.2 grams) of phosphatidyl choline would provide 550 mg of choline. Although the chemical term, "lecithin" is synonymous with phosphatidylcholine, commercial lecithin preparations may contain anywhere from 20-90% phosphatidylcholine. Thus, lecithin supplements may contain even less than 13% choline.”

**Here’s another good resource:**

**“Good Sources of Dietary Choline Now a Mouse Click Away**


A new specialty database is now available to help people get healthful amounts of the nutrient choline in their diets. The database can be accessed online, free of charge, at the Agricultural Research Service's Nutrient Data Laboratory (NDL) web site: [http://www.ars.usda.gov/main/site_main.htm?modecode=12-35-45-00](http://www.ars.usda.gov/main/site_main.htm?modecode=12-35-45-00)

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CB Note -- Practical application to FAS:

The cheapest and most available food to encourage pregnant women to eat to improve choline intake is clearly egg yolk. The WIC program already provides eggs as part of the food package for low income pregnant women, so the missing step is actively encouraging generous egg consumption for pregnant women in general, and those with potential alcohol issues in particular.

Remember to advise the NON-low income pregnant women about this as well. Alcohol problems are found at all levels of socio-economic status (SES.) However, women are more likely to be identified or labeled as alcohol abusers if they are from a lower income population. Similarly, the likelihood of an infant receiving a diagnosis of Fetal Alcohol Syndrome is significantly less in whites and in higher SES populations, even when alcohol use is suspected or evident.

[For people concerned that the cholesterol content of some extra egg yolks might present a problem: In our society we tend to equate the word cholesterol with serious health problems. It is important to realize that in pregnancy women actually work very hard to make a lot more cholesterol than normal. Trying to make more cholesterol available during pregnancy is physiologically normal. This is because cholesterol is required to make important perinatal substances like myelin (the greasy nerve-coating that speeds up messages), steroid hormones and the membranes of all cells. As she is trying to produce about a trillion cells, a little extra dietary cholesterol at this time is likely to actually be helpful.]

B-Vitamin Summary:

Thiamin is among the most studied vitamins affected by alcohol abuse, but as a good rule of thumb, one clearly should consider the status of all the B vitamins to be at risk as well. No B vitamin is ever found to be the only one compromised when deficiency is recognized and other co-existing B vitamin deficiencies are then looked for.

Unfortunately, at present the looking-for-other-deficiencies part is quite uncommon in actual practice. It is costly and not always even possible to do this in a patient-care setting. “Evidence Based” is a very desirable goal, but an additional problem we have is that the nature of most nutrition research is modeled on identifying the effect of an intervention with a single nutrient while holding all else constant (as much as possible.)
This research model would tend to miss any potential effect of adjusting intake of one B-vitamin. As an over-simplified analogy, it would be like concluding that giving oxygen, food and water is not beneficial because giving any one of them to a rat deprived of all three would not result in improvement in its state of health.

Research methods aside, it seems reasonable to at least attempt to assure the adequacy of as broad a scope of nutrients as possible within safe limits. **However, this requires health care professionals to become more familiar with what the safe limits actually ARE for each nutrient.** In general, in “application-to-real-people” terms it would mean something as simple as thinking about providing a multivitamin instead of just the one nutrient that was evaluated and found to be inadequate. Similarly, one might supplementation with all the B vitamins (e.g. as a B-complex supplement of whatever strength is indicated by the situation.)

Typically the broader-scope products are no more costly than single-nutrient products, the safety of the interventions described above is not an issue, and there is the potential to do more good than just focusing on providing the one nutrient known to be deficient. [And --- do I have to say this? -- of course, no supplements are truly “complete,” they don’t take the place of “eating right,” and they don’t make it OK to abuse alcohol. I am just looking for something I can do that is at least easy, safe, cheap, more helpful and actually do-able without a prescription in a very terrible situation.]

**Vitamin A and FAS:**

Vitamin A in one of its hormonal forms (RA -- retinoic acid) is a key director of the process of “differentiation” in which a fertilized egg begins to differentiate into various body parts and organs. Too little RA or too much RA are both associated with poor fetal outcome. There are many phenotypic similarities between fetal alcohol syndrome and malformations of both vitamin A toxicity and deficiency. Some vitamin A derivatives like the acne medication Accutane are also known to cause birth defects if taken during early pregnancy.

One interaction that appears to have a role in altering fetal development is that the synthesis of RA from retinol catalyzed by alcohol dehydrogenase. Researchers have suggested that excessive alcohol intake competes for this enzyme, leading to RA deficiency. In other words, using up all one’s alcohol dehydrogenase enzyme trying to protect ones body from alcohol toxicity, may result in having substantially less available to make vitamin A retinol into the key RA form.

In FAS, vitamin A metabolism is severely affected, and cell differentiation can be compromised. Hepatic (liver) stores are low in chronic alcoholics but replacement therapy may be toxic to the liver and to the fetus. Chronic alcohol use depletes hepatic vitamin A stores regardless of intake because alcohol breaks down vitamin A and promotes its mobilization from the liver. In other words, it is a big problem but the solution is not easy.


CB comment: Reminder about vitamin A interactions with alcohol abuse:

This is a metabolic interaction of alcohol and vitamin A that occurs regardless of vitamin A nutritional status. Inadequate or excessive vitamin A intake would clearly be potentially contributory, of course. However, it is important to emphasize that simply providing more than RDA levels of vitamin A in the retinol form will not correct the problem, and it could be detrimental. The beta-carotene (the precursor to vitamin A retinol) is not a problem in this regard because one controls the conversion of beta-carotene to retinol based on need.

Antioxidant Nutrients and FAS:

Normal metabolism produces waste products called by many names but commonly called “free radicals.” Other terms are “singlet oxygen” and “reactive oxygen species (ROS).” In 25-words-or-less [could I EVER say anything that briefly? 😛], free radicals can injure cell membranes by stealing electrons from the surface. This electron theft is called “oxidation.” An antioxidant prevents that damage and protects the cell membranes … sometimes by donating an electron of its own so the free radical is “quenched.”

In nature, many different antioxidants work together. For example, inadequate vitamin E can be compensated for by a generous selenium intake … and vice versa. Similarly, after vitamin E has donated an electron to quench a free radical, vitamin C can reactivate vitamin E by giving it a brand new electron. Simplified, this means that when studying the effect of inadequacy or supplementation of vitamin E, the vitamin C and selenium status of the subjects could significantly affect the findings.

As described earlier regarding research problems with sorting out the effects of the B vitamins, this sort of complex interaction among many antioxidant substances makes it difficult to identify the specific effect of a certain amount of just one particular antioxidant. To correctly interpret the results, one would need to know about the status of other antioxidant/pro-oxidant substances at the time of the evaluation. This can make it difficult to carry out high quality research with clearly interpretable results.

Free radical injury from failure to have adequate antioxidants available is called “oxidative stress” and it is associated with a very wide range of problems such as complications of diabetes, macular degeneration, and rancid butter.
As noted, free radical production is a NORMAL part of metabolism and free radicals NORMALLY get handled by NORMAL amounts of antioxidants from foods and supplements such as:

1. Well known antioxidant vitamins like vitamins A, C, and E
2. Less well-known vitamin-related substances like alpha-lipoic acid, CoQ-10 (ubiquinone)
3. Minerals such as selenium and zinc are used to produce important antioxidant enzymes like (respectively) “glutathione peroxidase” and “zinc-copper superoxide dismutase.”
4. Some “phytochemicals” (“substances in plants”) such as the pigments called “carotenoids” are very potent antioxidants. Examples include the orange-colored pigment beta-carotene, red lycopene, green lutein, red/blue anthocyanin, and yellow zeaxanthin. For example, lycopene in tomatoes is 200 times as potent as an antioxidant the more familiar vitamin E. There are over 500 known carotenoids, so we are only just beginning to mine these vegetable/fruit treasures.
5. MANY other phytochemicals such as polyphenols, pycnogenol (from pine bark) and resveratrol (in red wine and red grapes) are being found to have important antioxidant (and other beneficial) activity. Research in this area is simply exploding.

KEY ISSUE: Any condition in which fuel (or other) metabolism is not proceeding in a standard manner will result in more free radical production, so the person will have an increased need for antioxidant protection. This is true for many health conditions such as diabetes, inflammatory diseases, and alcohol abuse as well. Obtaining a large percentage of calories from alcohol is not part of “normal” operations. This is another example of the usually adequate nutrient intake levels no longer being sufficient to meet the needs of people who are not members of the group called “the healthy population.”

Application to FAS in particular:

It appears that at least some of the fetal damage from alcohol abuse is related to the excessive production of free radicals that accompanies high alcohol use.

2005-2009


1999-2005


Zinc and Fetal Alcohol Syndrome:

The antioxidant function of zinc was described above. In addition to that role, there are more than 200 zinc-dependent enzymes that will function poorly in the presence of zinc deficiency. This includes decreased function of alcohol dehydrogenase, an enzyme described earlier as important for detoxifying alcohol and for producing retinoic acid from retinol.

Zinc is of critical reproductive importance (e.g. DNA production), and it has specific roles in immune functions. For example, the production of T-cells by the thymus gland is very zinc-dependent. The diet of alcohol abusers is often poor and lacking in zinc along with many other nutrients. There also appear to be altered requirements for zinc, due to:

1) possible impaired absorption,
2) higher metabolic requirements, and
3) increased excretion of zinc.
**Zinc Adequacy in the General Population:**

An “average” 1500 calorie diet provides about 40% of the (non-pregnancy) adult DRI for zinc. Many women regularly take in 1500-1600 kcals daily. Vegetarianism and trends toward eating less meat (and especially red meat) decrease it further. High fiber diets include phytates, which like tannins in tea and oxalates in leafy greens, decrease absorption of both zinc and iron from plant and supplement sources.

The zinc content of foods and its absorbability correspond fairly well to the naturally occurring iron content of food. However, it is not generally added to foods that are fortified with iron. We regularly check people’s iron status and iron deficiency is known to be a common health problem. However, we rarely evaluate zinc intake or labs.

**So here’s the question:**

If people’s diets are often found to be low in iron (even in spite of iron fortification of many foods), why would we assume that their zinc intake is adequate? (We do.)

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There is continuing evidence that inadequacy of zinc has the potential to exacerbate fetal damage associated with alcohol abuse.


The initial discovery of this relationship is still fascinating:
Interesting Observations:

Zinc deprived rats were noted in 1971 to “look like” rat pups with FAS. The number and severity of defects dramatically increased when the alcohol (ETOH) is administered to zinc-deprived pregnant rats.

Both alcohol exposure and zinc deficiency result in fetal harm. But there is a synergistic teratogenic effect … the damage was much more severe when zinc deficiency and alcohol exposure occurred together. This is a very good illustration of the notion introduced at the beginning of this paper that other environmental variables clearly have a role in determining the developmental damage associated with fetal alcohol exposure.

Representative Rat Pups


Remember that “at 30% of kcals as alcohol the intake of many nutrients drops below 75% of the RDA” statement? The serious fetal effects shown above occurred at only 15-20% of calories from alcohol!

Clearly a diet that provides 75% or more of the RDA should not be our “comfort zone” when discussing FAS. Even brief periods of inadequate zinc intake during critical periods can cause birth defects, because of an inability to mobilize maternal zinc stores for use by the fetus.
In 1989 a study of the hair zinc content at birth in FAS babies showed no difference compared with controls. Did this prove that zinc status had no role in the development of fetal alcohol syndrome? This is an example of the importance of asking the right questions at the right time. This issue should be evaluated before conception if possible, and in early pregnancy at the latest. Zinc status during the critical first two months of pregnancy (when dysmorphic changes might occur) may not be reflected in zinc status of baby in later pregnancy (when the pregnancy has been recognized and prenatal vitamin/mineral supplements are often provided or the mother makes a greater effort to “eat right.”)

**Protein and Zinc Interaction in FAS:**

Protein synthesis is impaired by alcohol regardless of dietary protein intake. Zinc is also essential for protein synthesis. Alcohol clearance is decreased in individuals consuming diets with inadequate protein content. Diets with inadequate protein content are also likely to be inadequate in zinc and other nutrients.

Altered zinc metabolism contributes to the developmental toxicity of alcohol and also of the seizure-control medication valproic acid and other drugs. The developmental toxicity of certain compounds is, in part, due to maternal toxicity resulting in alterations in zinc (Zn) metabolism that affects the developing baby. As noted earlier, this may include a relative inadequacy of alcohol dehydrogenase, a key zinc-containing enzyme in the detoxification of alcohol and many drugs and an important substance in production of retinoic acid. **It appears that the teratogenic effects of several chemicals can be modulated by dietary Zn intake.**

Since the study with the rat pups shown above was published, a number of studies have attempted to improve outcomes by supplementing zinc – in general, the results are mixed – some factors seemed to be improved, and others did not. This likely reflects the huge role of zinc in many areas of metabolism … it is a cofactor for the function of over 200 enzymes in the body. It also reflects the influence of other factors (besides intake) that alter zinc metabolism in the alcoholic state. **There is no evidence that supplementing zinc at levels above the usual recommended level is beneficial, and giving more than that amount in supplement form may even be harmful.**

**However, the notion of assuring RDA/DRI level adequacy of zinc is very reasonable, since overt deficiency is clearly permissive of greater teratogenic effects from alcohol exposure.** The use of a standard multivitamin with minerals will usually provide this amount (i.e. 12-15 mg) and it will not be excessive even if the mother eats a diet rich in zinc-containing foods. The richest foods in zinc content and in zinc absorbability are meats, which also provide excellent protein and absorbable iron. [Please see my handout on “Nutrition Support of Iron Deficiency” for more details on the iron and zinc content and availability in foods and supplements.]

Iron Deficiency and Fetal Alcohol Syndrome:

Iron deficiency may play a role in increased fetal damage from alcohol exposure for several reasons beyond its well-known oxygen-carrying function. As described earlier, the Cytochrome P450 system is an iron-dependent system that can be thought of as a garbage disposal. It is responsible for breaking down many substances that would be harmful if they built up in the body. It is a factor in the disposal of many medications and potential environmental toxins like alcohol. Poor iron status can compromise the functioning of the garbage disposal. As a result, an iron deficient person may fail to metabolize alcohol (and other drugs) in a timely manner. That means that when the mother drinks alcohol, both she and her baby are exposed to alcohol longer than usual, which may increase its teratogenic effects.

The reverse may also be true. Fetal alcohol exposure produces some defects that parallel the abnormalities associated with early iron deficiency. Researchers looked at amounts of iron, transferrin and ferritin in three CNS regions in rats (cerebral cortex, subcortical forebrain and brainstem). The pattern of brain iron distribution was delayed by alcohol exposure by up to 2 weeks. Alcohol-induced alterations in iron homeostasis persisted into adulthood. The net result: timely delivery and bioavailability of iron was compromised by alcohol exposure. The defects in iron regulation are permanent and may underlie alcohol-induced abnormalities in iron dependent growth processes such as myelination.


CB question:

Mother rats in this study received normal dietary iron. What if maternal initial iron status were poor and/or the diet were inadequate in iron as well?

Could that ever happen? In any case, assuring adequacy (instead of assuming it) has the potential to benefit both mother and baby.

So what can we do to provide some protection to the fetus being exposed to alcohol.

Improving the regular diet of chronic alcohol users can of course be very useful if it can be achieved. In particular, encouraging intake of brightly colored fruits and vegetables is very safe and it provides terrific antioxidants and key nutrients. However, I would be VERY surprised if women who abuse alcohol had not already heard somewhere that fruits and vegetables are “good for you.” Many may even already be eating lots of fruits and vegetables.
Others (like everybody else) may not ordinarily eat them for reasons of flavor, cost, time or whatever. **Increasing intake in this situation is most likely to occur if one could help her identify some specific key foods that she enjoys that are rich in antioxidants.** These might include things not always thought of as key providers of antioxidants, like tomato sauce, canned peaches, red grape juice, etc. Many generous-antioxidant foods like these are now being provided through the WIC Program. Other foods like ketchup are surprisingly good sources of lycopene. If money is not the problem, the grab-and-go fruits and veggies now in many grocery stores can be very helpful.

**A standard prenatal multivitamin/mineral supplement should be encouraged** (for many reasons) as well as more generous vitamins C and E. Remember that her need for antioxidants is much higher than usual, so higher than RDA/DRI intake levels would be a good idea. This concept has been studied much more in other oxidative stress-inducing conditions such as diabetes with good results. Antioxidant adequacy has been shown to help to decrease the incidence of birth defects in infants of mothers with diabetes. This situation (FAS) is quite comparable in terms of oxidative stress, but less studied.

Most multivitamin/mineral supplements have RDA/DRI levels of zinc and iron, but **iodine, vitamin K and selenium** levels are quite variable between brands. All three have great importance in pregnancy. For example, fetal alcohol syndrome is the number one cause of preventable mental retardation in the US. Iodine deficiency syndrome is the number one cause of preventable mental retardation in the WORLD.

**New concerns have recently been raised about IODINE inadequacy during pregnancy, even in the US and other areas where salt has been iodized to provide iodine.** This has prompted the World Heath Organization (WHO) to increase the recommendations for iodine during pregnancy from 200 to 250 microg/d and suggested that a median urinary iodine (UI) concentration of 150-249 microg/L indicates adequate iodine intake in pregnant women. Many multivitamins, including prenatal vitamins, contain little or now iodine. Clearly a combination of alcohol exposure plus relative iodine deficiency does not bode well for the developing fetus.

[Please see my “New Attention to an Old Problem: Iodine Deficiency in Pregnancy and Lactation,” “Top Five Easy Ways to Improve Your Family’s Nutrition” and “Top Ten Nutrition Plan for Optimizing Pregnancy Outcome” for more on these and related issues.]


Some products are missing a lot of minerals. **SELENIUM** is one that is highly variable so check the label. The usual recommendation is a daily intake of 60-70 mcg/day. The advisable upper limit is 600 mcg/day, so providing RDA-ish levels is safe and a very good idea in view of its key role as an antioxidant component and the increased requirements for
antioxidant protection in fetal alcohol exposure. If a person’s multivitamin with minerals contains inadequate selenium, 50 mcg supplements are available over the counter.

**A new “likely-to-be-inadequate-but-out-of-our-radar” vitamin is VITAMIN K.**

1. We are much more dependent on an outside source of vitamin K than was earlier believed.
2. Many people in the US are now being found to be vitamin K deficient when we check … but it is rarely checked because it has traditionally been assumed to be made in adequate amounts by intestinal bacteria.
3. It is often left out of multivitamin pills (check the label) – it is even omitted as an important nutrient to consider in the 2,000 kcal suggested meal pattern in the new Food Guide Pyramid.
4. Inadequacy of vitamin K increases risk of several problems in pregnancy, including toxemia.
5. Dark leafy greens are the richest food sources, and many folks eat very little of these foods … which of course also includes people who abuse alcohol.

**The AI for vitamin K for pregnant women is 90 mcg/day but some groups are now being found to have needs higher than AI recommended levels.** It would not surprise me to find that women who abuse alcohol are among those with different requirements. In spite of a common belief that vitamin K is potentially toxic because it is fat soluble, it is now very clear that vitamin K is extremely NOT toxic. In fact, there is no upper limit of safety established for vitamin K because no one has ever gotten into trouble from taking too much. [The business with certain anticoagulant drugs is a drug/nutrient interaction issue, and unrelated to the safety of the vitamin in people not using this kind of medication.]


[See my “Top Five Easy Ways to Improve Your Family’s Nutrition” and “Vitamin K” handouts for more on these and related issues.]

It is reasonable to identify several brands of multivitamins with minerals that are satisfactory and generally low in cost, with some attention to the problems above regarding iodine, selenium and vitamin K. However, instead of just advising her to buy and take a multivitamin, physically providing the appropriate supplement(s) is far more likely to achieve the goal of trying to protect that baby. Some places do this, but most do not.

Developing a program that provides this link in the chain would be very cost effective in protecting against fetal damage of many types … even for women who do not use alcohol! This calls for a big paradigm shift from the “just eat right” advice we are more comfortable with. [See my “Top Ten Nutrition Recommendations for Pregnancy” for more on these issues.]
Additionally, many insurance programs do not cover nutrition supplements because they are “over the counter.” For people on a tight budget, this alone can be a deal-breaker. If the mother is also addicted to drugs/nicotine/ alcohol etc., the likelihood of her limited funds being saved to buy vitamin pills seems to be unrealistic.

To keep your eye on the prize … that is, to help protect that baby … the most likely way to achieve success is to both physically provide the vitamin/mineral, and to explain that taking it as directed may help protect the baby from some of the effects of her drinking. Of course we do not give her the impression that it will make it OK to drink … we should continue to make it plain that stopping alcohol consumption is the absolutely best thing she can do. But I have found that most women with an alcohol or other drug problem would very much prefer not to be addicted. Most of the women are also very worried about their baby’s health, even as they continue to abuse alcohol or drugs. I have found that many of these women are actually quite willing to take their vitamins (even when they have been unable to stop drinking) when strongly encouraged, the benefits to the baby are explained and they are also provided with the bottle of vitamins.

**Will she take it?**

Isn’t this just a big waste of time? Many will take supplements (especially if the supplements are provided and the women are educated about the reasons for their use.) Some won’t. Should we decide not to try with any of the women because some will not follow through? Don’t pre-judge that she “does not care about her baby” just because she is addicted to alcohol . . . many would like to quit drinking but just can’t.

One health professional actually told me at a conference that if we gave them multivitamins, the women would “just sell the vitamins on the black market.” (Hmmm … what IS the street value of generic multivitamin pills these days, especially when many other people will be receiving them for free as well?) I think this exposes an unfortunate tendency to be more ready to judge her rather than to help her. Remember to “Keep your eye on the prize:” the healthiest baby possible in spite of a suboptimal pregnancy situation. In addition to the baby’s health, there are also potential for many positive benefits in terms of the mother’s health and health care costs.

**Beyond the multivitamin-with-minerals and encouraging consumption of nutritious foods in place of the alcohol:**

**What might be helpful and won’t be harmful?**

**Consider additional:**

*Vitamin E* (e.g. 400 iu)
Vitamin C (e.g. 250-500 mg)

Selenium (e.g. add a 50 mcg tablet if her multivitamin has less than 30 mcg.)

Magnesium (e.g. RDA-ish levels of 250 mg as magnesium oxide or chloride.) Magnesium deficiency has not been studied as a particular interactive factor in FAS, but it IS recognized as suboptimally represented in the diets of the majority of even healthy Americans. Most multivitamins have only 10-25% of the recommended amount, so a person with poor diet (as is common in people wit alcohol problems) would likely not have her needs met by the amount in the multivitamin. **Inadequacy during pregnancy has serious consequences for pregnancy outcome in general.**

Iodine  Help her make sure that the salt she uses at home is the iodized kind, and check the iodine content of her multivitamin with minerals. The new WHO recommendation for iodine intake in pregnancy is 250 mcg/d

Thiamin (at least 15 mg)

Folic acid (100-800 mcg extra) Generous B vitamin supplementation in general as a “B-Complex” is a good idea, but the folic acid content of those remains at 400 mcg, and the level of thiamine suggested is higher than would be provided by most B-complex products.

Choline  Check that diet and food provide AT LEAST 450 mg (the recommended amount for a healthy pregnancy.) I would be inclined to double it in an alcohol-abuse situation, based on knowing that that intake is not at all harmful and she certainly could need more. Whether or not an additional supplement form is needed depends on things like how much is in the multivitamin and her egg yolk intake, as described earlier.

Vitamin D (1000-2000/day). There are many reasons why alcohol abusers are at risk of being overtly deficient in vitamin D, and the DRA/RDA level of 400 iu is insufficient even for maintenance in a large proportion of the general population. (This is especially true if you happen to live in North Dakota!) Ideally, one should check her vitamin D level because deficiency in pregnancy is itself looking like it has some serious damaging effects. If she is low the doctor will want to give her a much higher therapeutic dose rather than a maintenance dose.

Vitamin K (at least 100 mcg/day)

[See my “Top Five Easy Ways to Improve Your Family’s Nutrition” and “Top Ten Nutrition Plan for Optimizing Pregnancy Outcome” and “Vitamin K” for more on these and related issues.]
Identifying Whom to “Treat”

Except for the really generous thiamin, the recommendations described are not unsuitable for women in general. For example, the same interventions apply to optimize pregnancy outcome if she has diabetes. Or even if she has no medical problems. But when you want to indentify those who are specifically at risk of ETOH abuse . . .

Final thoughts:

In view of the vagaries of “detection” (at what stage of pregnancy or pre-pregnancy is she “screened,” the large variability in the likelihood of detection by current methods, the effectiveness of interventions that rely on detecting alcohol abuse in women already several months pregnant, etc.) it makes more sense to focus nutrition interventions as if all women were potentially at risk of these common nutritional inadequacies … not just those identified as alcohol abusers; both the Risk : Benefit ratio and Cost : Benefit ratios are clearly in that direction.

Also, it has often been said that alcohol abusers are rarely only using alcohol. Many are “polypharmacy” users/abusers, so there is the potential for other drug effects (nicotine, caffeine, cocaine, inhalants, etc.) whenever the population being studied is human. This can complicate interpretation of the data obtained about the effects of nutrition on fetal alcohol syndrome specifically. There is a lot more to learn, but the suggestions presented here have resonance with other abuse other substances as well.

The papers referred to in this handout (and others) can be found at no cost at www.meritcare.com

Top Five Easy Ways to Improve Your Family's Nutrition

Pregnancy

Iron Deficiency

Antioxidant Phytochemicals: Ideas for adding them to the diet

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