

Maternal exposure to nutritional, chemical and environmental agents which may adversely affect the pregnancy outcome.

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Part I - Nutritional issues in pregnancy

Introduction

Modern medicine has been plagued with frequent changes in the approach to nutritional management of pregnancy. Most of the approaches in the past have been mostly cultural and without any scientific proof. The first scientific approach to dietary management of the pregnant woman was suggested by the physician Prowchownick in 1889. This was a deliberate effort to cause fetal growth retardation by restriction of caloric intake in order to avoid dystocia in patients with deformed and small pelvises. This diet was high in protein intake but restricted in calories, fluid and calcium. Since then the pendulum swung several times and some physicians even tried to prevent pre-eclampsia by applying several dietary restrictions including protein restriction as well as salt restriction.

At the present time good nutritional care during pregnancy is based on the following general premises: women are encouraged to eat to appetite, achieve adequate weight gain and breast-feed their infants after birth. This is exactly opposite to the recommendation made to their mothers.

The effect of nutrition on the outcome of the pregnancy is difficult to define due to the interrelated factors like genetic, social, cultural and economics. The nutritional physiology of human pregnancy is still poorly defined. Our inability to conduct experimental restriction studies in humans and the different metabolic physiology of animals makes it difficult to define the exact role of nutrition and the various nutritional elements to an ongoing pregnancy.

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Given the above limitations, one can see why the controversies around the effect of nutrition on the pregnancy continue. A comprehensive review of the evidence relating protein and caloric intake to birth weight found that: (1) there is no question that dietary restriction reduces birth weight and, (2) while many studies have found improvements in outcome when additional food is provided during

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pregnancy the results are not always dramatic.

A good diet during pregnancy may not be the only nutritional influence on outcome. A recent study has demonstrated that providing supplemental food to postpartum women significantly increased the birth weight of the subsequent infants, supporting the concept that pre-conception nutrition may play an

Maternal nutrition and weight prior to conception is more important for proper fetal growth than maternal weight gain during pregnancy.

important role in fetal growth. From older studies it is well known that pre-pregnancy weight is very important for the definition of the birth weight of the new offspring and that weights below ideal body weight increase dramatically the incidence of IUGR.

## WEIGHT GAIN DURING PREGNANCY

Despite the well documented influence of weight gain during pregnancy on birth weight, many pregnant women in the United States do not gain enough. The most recent national natality statistics (NCHS, 1986) indicate that low birth weight was 2.3 times more likely and fetal death 1.5 times more likely in women who gained less than 20 pounds compared with those who gained more than 20 pounds. The survey also found that in 1980 twenty percent of all black mothers gained less than 16 pounds during pregnancy. Since the high rate of low birth weight among blacks is an important public health problem, this data suggests that improving weight gain, especially in this group, may reduce the incidence of low birth weight infants.

Both maternal pre-pregnancy weight and weight-gain during pregnancy have important effects on infant birth weight. Pre-pregnancy weight below ideal body weight increases the incidence for intrauterine growth retardation (IUGR). Heavier women or those who gain a large amount of weight during pregnancy are more likely to deliver larger babies. It seems that usually there is a balance between maternal size and weight gain. When a small woman has a large weight gain during pregnancy, she usually delivers an average size infant as do large women with small weight gains during the pregnancy. Under-weight women who gain low amounts of weight are at highest risk for low birth weight, and this risk is intensified further if the mother smokes cigarettes during pregnancy. A total weight gain of approximately 24-27 pounds (10-12 kilograms) is currently recommended for all pregnant women. However, new evidence is beginning to emerge which suggests that different standards for weight gain may be appropriate on the basis of maternal factors such as age, race, pre-pregnancy weight for height, smoking habits, or multiple fetuses. Most of the research so far has focused on pre-pregnancy body mass (weight for height). It seems so far based on present knowledge that if an under-weight woman (less than 90% of ideal body weight for height) gains at least 30 pounds she reduces the likelihood of her having a baby with IUGR. On the other hand, studies suggest that for average or mildly over weight women (90-120 percent of ideal body weight) the current standard of 24 (range of 20-30) pounds appears appropriate. On the upper extreme it is known that obese women (above 20% over weight) seem to be able to deliver average size infants even with lower or no weight gain at all. Although there is no consensus as to how much weight gain should an obese woman achieve during pregnancy it is clear that there is no evidence to suggest that it is safe or appropriate to impose a restrictive diet or encourage weight loss

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during pregnancy in any pregnant woman.

## DIET DURING PREGNANCY

### Energy

It is true that pregnant women should get enough nutritional energy for two people but this should not be translated as double. The total caloric intake appears to be the most important nutritional factor relating to birth weight. Current estimates suggest that a typical pregnancy costs 80,000 additional calories over pre-pregnancy requirements or about 300 extra calories per day. This additional energy supplement will provide a weight gain of 10-12 kilograms at term.

Although the total energy intake may be important, nutrient density - the quantity of protein, vitamins, and minerals per 100 calories of food - is an important concept because the current recommended increase for energy is only about 17% compared to increases of 20-100 percent for vitamins and minerals. So attention should be paid for the increased energy to represent the product of a well balanced diet and rich in the above-mentioned components.

### Protein

Protein is a very important component of diet. Protein containing foods are excellent sources of vitamins and minerals such as iron, vitamin B6 and zinc. A protein intake of 75-100 grams a day or approximately 12% of total calories and as much as 20% of total calories appears to be appropriate. High levels of protein lead to fetal growth restriction much like the same way Atkins diet does to adults. This however is not healthy in fetuses. Excessive protein exerts a negative caloric effect and reduces growth in fetuses,

### Fish

Fish should be avoided in pregnancy with a few exceptions. Large predator fish should be avoided by all people, including pregnant women. Large predator fish contains large quantities of mercury and polycarbonated biphenyls (PCBs). Mercury is toxic to the brain and PCBs are carcinogens. A recent article published in the Journal of American Medical Association revealed that women who eat tuna fish twice a week, increase their risk for breast cancer by 100%. Yes, this is 100% and not a mistake. Smaller fish is also contaminated but to a much lesser degree and for this reason it is safe during pregnancy. However, small fish produced in fish farms are not healthy because they are fed the bi-products of large fish processing and thus are likewise loaded with mercury and PCBs. Small wild fish (non-farmed raised) however is safer and contains only modest amounts of the above contaminants. Some species that are still beneficial to the health of the unborn, include wild red-snapper, wild sea-bass, wild porgies, wild branzini (European sea-bass), wild striped bass, wild Alaskan salmon and of course fresh sardines and other equivalent size fish. As is evident, there are plenty of fish varieties to suit the appetite of most people. Fish is rich in omega-3 fatty oils. Omega-3 oils exert the following benefits to the mother and the unborn:

- Improve vascular endothelial function (inner lining of the vessels).
  - a. Decreased risk for clotting inside the vessels
  - b. Improved cardiovascular health

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- Decrease low density lipoproteins (LDL) and thus reduce cardiovascular risk
- Reduce the risk for preeclampsia
- Improve fetal and placental health (by means of improved placental vascular function)
- Improve fetal brain development
- Improve fetal vision
- Decrease inflammation and indirectly reduce the risk for preterm birth (preterm labor is the result of uterine / systemic inflammation).

It is therefore clear that eating fish is beneficial and pregnant women should seek opportunities to increase their intake of appropriate fish. Shrimp and other crustaceans (crab etc.) should not be considered “fish” and certainly have no relationship to fish in terms of nutritional value. Certain shellfish are rich in omega-3s and as such may be consumed during pregnancy. Caution should be exercised to assure their quality and cleanliness. Should be always cooked.

## Vegetarian Diets

Vegetarian diets that exclude animal products have become relatively popular over the last ten years and can provide adequate nutrition during pregnancy if correctly balanced. Vegetarian diets are low in vitamin B12, calcium, riboflavin and vitamin D. Attention should be paid in supplementing for the nutrients that are missing or undersupplied.

## Sodium

Dramatic changes in sodium metabolism including hormonal natriuretic effects, increased glomerular filtration rates, and increased renin activity occur during pregnancy. Sodium is extremely important in helping the pregnant cardiovascular system achieve its volume expansion in order to increase blood flow to the placenta. Sodium restriction can be detrimental on that respect. In recent years women have been encouraged to “salt to taste”. Five grams of sodium per day is appropriate and caution should be exercised to instruct women as to how much sodium is appropriate since the typical American diet has excessive salt content (8-10 grams per day). Women should cook their food and salt to taste during the preparation. This provides close to 5 grams of sodium; any additional sodium will lead to excessive consumption. Pregnant women should avoid all salty snacks because they are particularly high in sodium.

## Iron

Iron demands increase significantly during pregnancy. It is estimated that at least 500 mg of iron are needed for the increase in maternal red blood cell volume and 300 mg of iron for fetal erythropoiesis (production of all new fetal red blood cells). In addition, the usual insensible losses (intestinal losses) amount to about 200 mg throughout the whole pregnancy. That comes to a total of about 1,000 mg of iron that should be supplemented throughout the pregnancy. This means that a daily supplementation of 30-60 mg of elemental iron is necessary given the fact that only up to 3-6% of elemental iron is absorbed through the intestines. Keep in mind that most of the iron supplements yield only 20-30 percent of elemental iron. That means that in order to have a yield of 30-60 mg of elemental iron we need to at least supplement the patient with 300 mg of iron. When, however, a patient is anemic and she requires additional dosages then sometimes we may have to

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supplement patients with as much as 975 mg. For example, if a patient receives iron sulfate supplements, which yield only 20% elemental iron and, only about 3-6 percent of this elemental iron is absorbed, the total daily iron intake (absorption) for such patient would be 6-12 mg. This is adequate to supply the unborn and also help the mother rebuild her deficient iron storage. Patients who require excessive iron due to anemia should receive preparations that contain ascorbic acid (vitamin C) such as Ferancee-HP, which is a combination of high yield iron gluconate with, ascorbic acid (Vitamin C). For best results the physician should always be aware of the elemental iron yield of the particular iron supplements he/she prescribes.

It is important to remind the patients that tea and coffee can bind iron in the gut and should be avoided at meals at which good sources of iron are eaten.

## Calcium

Calcium is very important in the pregnancy since the fetus is going to build up his skeleton primarily with calcium that is going to be taken by active transport across the placenta from the maternal stores. At least 1,000 to 1,200 mg. per day of calcium are recommended to meet fetal needs (total of 30 grams) and to protect the maternal skeleton which is at risk for osteoporosis. Usually most of the patient's diets are not sufficient to supplement the requirements of calcium and in such cases supplemental calcium is advised. Women who do not take supplemental calcium during pregnancy, may lose as much as 5% of their bone in the duration of each pregnancy.

## Other Nutrients

**Folic acid** is extremely important not only for the increase in the production of red cells in the fetus but also for the fetal tissue growth in general. The fetus is an ever-multiplying organism with increasing demands for RNA and DNA, which in turn requires additional amounts of folic acid. The minimum requirement for the pregnancy should be at least 800 mcg per day and it is safer if patients are supplemented by 1 mg (1000 mcg) a day along with their iron. Foods that are rich in folic acid are eggs, leafy vegetables, oranges, legumes, and wheat germ. One prenatal vitamin contains 800 mcg of folic acid.

**Zinc, vitamin B6 and magnesium** as well as **vitamin E** are essential nutrients during pregnancy and are usually removed from the grains with the usual processing. Pregnant women should be encouraged to use unrefined whole grains and flour products that are the result of limited wheat grain processing. This kind of processing usually provides sufficient fiber for the patients and this is a very welcome addition since usually the pregnancy and some of the supplemental vitamins are constipating to pregnant women.

Usually most of the above mentioned components and some additional vitamins are pretty well supplied with the usual multi vitamin preparations available today for pregnant women. Be aware, however that when additional folic acid is necessary it should be prescribed additionally because it may not be in sufficient amounts in the multi vitamin preparation that you have been prescribed.

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About 60% of your brain is made up of fat, much of which is a fatty acid called docosahexaenoic acid (DHA). DHA is important for optimal signal transmission in the brain, eyes, and nervous system. Concentrations of DHA are also found in the heart. Low levels of DHA have been correlated with changes in disposition, memory loss, visual and other neurological conditions. A nutritionally complete diet that includes important fatty acids is important to help maintain proper brain, eye and heart function. Women receiving omega-3 supplements during pregnancy have babies that score 5 points higher on average in their IQ scores in the first few years of life in comparison to babies of women who did not receive omega-3 supplements during pregnancy. Of course the best way to receive omega-3 oils is by eating appropriate fish as noted above. However, if this is not possible for any reason receiving 200 mg of DHA daily is indicated.

## COMMON CLINICAL DIETARY PROBLEMS IN PREGNANCY

### Adolescent Pregnancy

Adolescents themselves are growing at a fast rate. Their body is primarily in a state of anabolic metabolism and this leads to a contradiction with the demands of the pregnancy. The result of this can be several complications like IUGR with or without pre-eclampsia and increased perinatal mortality and low birth weight babies. The above problems are more likely to happen in younger patients.

For the above reasons teenage pregnancy requires particular attention and very good supervision as far as dietary management.

### Diabetes

Patients with diabetes should be managed with the help of a dietician and a diabetologist and the pregnancy diet should be adjusted accordingly. Diabetes is associated with severe pregnancy complications affecting both, the mother and the unborn and should be treated seriously under the care of a perinatologist alone or in co-operation with a medical endocrinologist experienced in treating pregnant diabetic women.

### Nausea and Vomiting

Nausea and vomiting which usually occur during the first trimester can cause discomfort and anxiety as well as weight loss, ketosis, and dehydration in more severe cases. Many patients can be helped primarily with a quick hydration on an outpatient basis and subsequently dietary advice. Frequent small meals and desirable and palatable foods should be prescribed to avoid the problem from coming back.

Medications like vitamin B6 in dosages ranging from 25 mg. to 100 mg. tid can be prescribed with or without Doxylamine in 12.5 mg. tid dosages. Sometimes psychological counseling and hospitalization may be necessary in severe cases. In more severe cases the patient may require antiemetics (Reglan or Zofran) in order to be able to keep any food and avoid dehydration and malnourishment. Occasionally, hospitalization is necessary to treat severe cases of nausea and vomiting (hyperemesis gravidarum).

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## Pica

The craving and eating of non-foods such as laundry starch and clay, is known as pica and is common during pregnancy in certain ethnic groups. Some patients crave plaster (sheet-rock) and such patients literally eat their walls. Cultural beliefs and iron deficiency anemia are both thought to contribute although the etiology is unknown. Pica can replace the ingestion of nutritious foods and may bind dietary iron, leading to anemia. There is also the possibility that the substance ingested is toxic. Appropriate management includes detection of the practice, screening for and treating iron deficiency anemia and counseling to discourage or at least minimize the ingestion of non-foods.

## Heartburn and Acid Indigestion

Heartburn and acid indigestion are common complaints during pregnancy. The usual treatment is antacid taken for relief. Attention should be paid here, however, because antacids may lead to excessive binding of iron and iron deficiency anemia. Most of the times this problem should be solved with frequent small meals and avoidance of foods that lead to excessive stimulation and over production of acid. If necessary, antacids (Maalox, Tums etc.) or acid reducing over the counter medications (Zantac, Pepsid AC etc.) are appropriate. Tagamet is contraindicated in pregnancy due to feminizing effect on male fetuses.

## Constipation

Constipation can be treated by increasing dietary fiber, fluid intake, and exercise. Good sources of dietary fiber include whole grains such as bran, legumes, and fresh fruits and vegetables. Stool softeners such as Colace are safe and may help to keep the stool soft. When the aforementioned measures fail, one or more non-medicated Fleet's enemas are appropriate. Patients should not go for more than two days without a bowel movement.

## Maternal Socio-Economic Circumstances

A diet poor in quality and quantity may be the result of an income too low to purchase enough nutritious food. Referral of the patient to local public and private agencies such as WIC (Women's, Infants and Children's special supplemental food program for financial assistance including food programs for low income, high risk pregnancies and lactating women and their children) is the first step. Counseling and education regarding low costs, nutrient dense foods such as nonfat dry milk and bean grain combinations and food budgeting, shopping and preparation techniques can also help. Frequent follow up is essential.

## Part II – Exposure to drugs and environmental agents

### Exposure to drugs

Prior to 1960, the vast majority of birth defects were regarded as genetic in origin. The fetus was believed to occupy a privileged site within the uterus, protected from the effects of environmental agents to which the mother might be exposed. Several natural experiments, however, (rubella, methyl mercury content of the Minimata Bay and the recognition of the teratogenic effects of blood sugar) have proven the opposite point.

Recently, it has become clear that several medications, as well as environmental agents, may harm the baby in various ways.

### SOCIALLY USED SUBSTANCES

#### Alcohol

Several years ago, a specific pattern of malformation referred to as “fetal alcohol syndrome” was described in babies of alcoholic women who continued to drink alcohol during pregnancy. The principle features of the disorder include prenatal onset growth deficiency, developmental delay and a variety of structural defects including short palpebral fissures, a long philtrum with a thin, smooth upper lip, multiple joint anomalies and cardiac defects. The incidence of serious problems in the offspring of alcoholic women who continue to drink heavily during pregnancy is approximately 33%. To determine the dangerous quantity of alcohol is very difficult due to inaccuracy in reporting by the patients. For the above reasons, with respect to moderate alcohol consumption, it has been estimated that 11% of women who drink between 1 and 2 ounces of absolute alcohol a day during the first trimester of their pregnancy have babies with features consistent with the prenatal effects of alcohol. Regarding lesser amounts of alcohol, in particular “binge drinking” during pregnancy, there is no data available at the present.

#### Marijuana

To date, the vast majority of studies pertaining to the effect of marijuana on prenatal development have been conducted in experimental animals. Several studies have been conducted on patients, who use marijuana currently, but the results have been confusing and contradictory due to the several confounding factors that one has to face in such studies (use of other drugs, malnutrition, poor socioeconomic status, etc.).

In one study, however, it is worthwhile noting that the authors noted a higher frequency of neurobehavioral abnormalities in the offspring of moderate and heavy marijuana smokers including marked tremors, a pronounced response, poor self-quieting and failure to respond or habituate to light. In some cases, a cat-like cry was observed in some babies of the moderate and heavy users.

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## Amphetamines

From the known data available from two studies that were conducted in 1977 and 1980, there is no evidence that there is any increased risk to the offspring. It seems that amphetamines are most likely not teratogenic in humans.

## Cocaine

Patients who use cocaine have an increased incidence of spontaneous abortions and increased incidence of abruptio, particularly immediately after an intravenous injection of cocaine. As far as perinatal outcome, otherwise, patients who were studied prospectively had evidence of lower gestational age at delivery, increased incidence of preterm labor and delivery, lower birth weight and an increased incidence of small for gestational age infants.

It is suspected that children exposed to cocaine in utero will have increasing incidence of neuro-developmental problems. In addition, there was a case of a massive cerebral infarction developing on an infant born to a woman who took a large amount of cocaine 72 hours prior to delivery. It is clear that the placenta abruptio pathology and the hemorrhage and infarction are both consistent with the physiological action of cocaine which creates a tremendous sympathetic response with vasospasm and ischemia.

At present, no data is available on the long-term effects of prenatal cocaine exposure, although a lot of studies are in progress and they will certainly shed light to the problem.

## Lysergic Acid (LSD)

Studies in humans who were exposed to LSD failed to disclose any specific anomalies. It seems from these studies that LSD is not a human teratogen.

## Heroin

Heroin does not seem to be a human teratogen since it has not been associated with any specific structural defects. However, recent studies have shown that heroin abuse can be associated with low birth weight from both prematurity, as well as intrauterine growth retardation. It seems that chronic intrauterine exposure to heroin may affect postnatal growth and behavior, as well as perceptual and learning processes in pre-school children.

## Methadone

Methadone is not a teratogen in humans. In addition, women who have been on Methadone have neonates with higher birth weights than women who have been exposed to heroin, and there is a relationship between birth weight and length of Methadone used. The longer the patient has been on Methadone, the higher the baby's birth weight.

## Tobacco

Studies indicate a decrease in birth weight between 170 to 250 grams in the offspring of women who smoke cigarettes during the pregnancy.

It seems that the influence of smoking is greatest during the last four months of pregnancy. Patients who quit smoking before the 20 weeks of pregnancy have fetuses with weights similar to patients

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who have never smoked.

The critical numbers of cigarettes that may affect the baby's growth seem to be a daily usage of five cigarettes. The more cigarettes, of course, one smokes, the higher the toll on the baby's growth rate. It appears according to a recent study that some women are predisposed to the negative effects of smoking. Such women suffer from a specific gene mutation. Offspring of such women are more likely to be affected severely by smoking while offspring of women who smoke but lack the specific gene mutation are less likely to suffer the consequences of cigarette smoking. As far as neonatal intellectual performance and long-term behavioral effects, the findings are contradictory by different studies. Again, it is very difficult to distinguish between effects that may be the result of the use or abuse of nicotine and effects, which may be the result of the patient's genetic predispositions, as well as socioeconomic status.

Patients who smoke should be encouraged to stop smoking at any stage in pregnancy and advised to at least improve other habits that may counteract the effects of smoking. However, the occasional patient who is unable to stop smoking, should be encouraged to take supplemental vitamin C and E as well as 400 mg a day of omega-3 acids (preferably the pure form of DHA produced from algae). Fish oil supplements should be avoided due to the increased levels of Mercury and polycarbonate biphenyls (PCBs). These supplements reduce the oxidative damage of the endothelium (from smoking effects) and help the vascular endothelium recover from the smoking injury.

## THERAPEUTIC AND DIAGNOSTIC AGENTS

### Anti-psychotic and Tranquilizers

#### Diazepam

Diazepam has been relatively safe during pregnancy, and there is only a small increase in the risk of oral clefts. Some studies have reported that use of Diazepam during pregnancy may increase the fetus's risk for cleft lip from 0.1%, which is the general population, to 0.4%. Ultrasound evaluation of the fetus at about 20-22 weeks should exclude or diagnose the condition easily.

#### Meprobamate and Chlordiazepoxide

Some studies that were done on humans that were exposed to these medications in utero revealed that neither Meprobamate nor Chlordiazepoxide is a human teratogen.

#### Phenothiazine

The most extensive study of Phenothiazine use during pregnancy involved 12,764 pregnant Parisian women followed from 1963 to 1969. Of the 315 women who took this medication during the first trimester of pregnancy, 11 gave birth to children with malformations. It may be significant that 8 of the 11 malformed children had been prenatally exposed to one of the Phenothiazines with a 3- carbon aliphatic side chain including Acetylpromazine, Trimeprazine, Chlorpromazine, Methotrimeprazine, Methoxypromazine and Oxomemazine. It seems from the above study that Phenothiazines are probably not teratogenic in humans, although there remains some concern about

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the 3-carbon aliphatic side chain derivatives.

## Tricyclic Anti-depressants

Originally, some reports indicated that these medications may cause limb reduction abnormalities, but subsequent studies showed that Tricyclic Antidepressants are not teratogenic in humans. Nevertheless, it is advisable that if a patient has been exposed to those during the first trimester to have a detailed ultrasound evaluation at about 20-22 weeks.

## Lithium

A registry of Lithium babies has been established to permit a prospective evaluation of the prenatal effects of Lithium. As of 1975, 143 babies prenatally exposed to Lithium had been reported to the registry. 13 had malformations, 9 of which were defects in development of the heart and great vessels. Of particular significance, 4 of the 9 defects were Ebstein's anomaly of the tricuspid valve, which occurs with a frequency of only 1 in 20,000 in the general population. This data strongly suggests that Lithium is teratogenic in humans.

## Progestogens and Estrogen-Progestogen Combinations

Due to confounding factors, the effects of the above medications on human fetuses are not quite clear. A specific pattern of malformations referred to as VACTERR (vertebral, anal, cardiac, tracheoesophageal, renal and radial) was associated with the use of progestogen-estrogen compounds or a progestogen alone compound during early pregnancy. Most of the studies were retrospective and various biases make the results not very valid. As conflicting as many of these results seem to be, the following practical conclusions are warranted:

1. If progestogens and/or progestogen-estrogen combinations are teratogenic in humans, the magnitude of the teratogenic risk is extremely small and is not biologically significant.
2. Progestogen exposure during the vulnerable period may double the incidence of hypospadias in the offspring; however, it is important to recognize that the resulting risk, 140 per 10,000 male births is extremely low.

From the practical point of view, when a patient has been exposed to the above medications, it is advisable to have an ultrasound evaluation at around 22 weeks to look for specific anomalies that could be identified.

**Progesterone** however has none of the above effects since it is the natural hormone that supports the pregnancy and is very different than the synthetic Progestogens.

## Diethylstilbestrol (Stilbestrol)

Intrauterine exposure to Diethylstilbestrol (DES) can lead to various reproductive tract anomalies and changes in the vaginal epithelium that can lead to vaginal adeno-carcinoma. Patients who were exposed to DES in utero are likely to deliver prematurely because of incompetent cervix and should be followed as such.

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## Chlomathine

Chlomathine is not considered to be a teratogenic agent in humans.

## Adrenal Corticosteroids

Corticosteroids are potent teratogens in some rodents, but they are not considered to be teratogenic in humans.

## Anti-microbials

Penicillin has been widely used during pregnancy, and it is a safe medication. Tetracyclines should not be used during pregnancy because of structural defects in the bone development and discoloration of the teeth. In addition, tetracycline used intravenously for severe infections in the past was associated with yellow atrophy of the liver and maternal death. Sulfonamides are contraindicated when delivery of the fetus is imminent because they displace bilirubin and may lead to kernicterus. Early in pregnancy, however, they can be used safely without any problem. The prenatal use of Sulfasalazine and corticosteroids in pregnant women suffering from inflammatory bowel disease revealed no particular risks to the pregnancy. The combination of Trimethoprim-Sulfamethoxazole is likewise safe. However, caution should be exercised here because Trimethoprim is a anti-folate, and as such, it may have an effect on RNA production by the fetus, and if it is used chronically, it may affect fetal growth. However, no human studies are known to prove this point although it remains a theoretical concern. The use of anti-tuberculous drugs carries certain risks. The use of Isoniazid (INH) has been associated with some neurological damage in the offspring, but this is not quite clear. The benefit to risk ratio should be evaluated each time this medication is to be used. Streptomycin has been used in pregnancy and has been associated with increased incidence of offsprings with hearing problems secondary to damage of the eighth nerve. The use of Rifampin and Ethambutol is rather safe since it has not been found to have any specific effects on the fetus. Metronidazole is not a teratogen but a mutagen, and the theoretical risk of carcinogenesis may not be evident for the next 20, 30 or more years. This should be kept in mind, and its use throughout the pregnancy should be only restricted to absolutely necessary cases. As a rule, during pregnancy one should only use antibiotics that are known to be safe and have been around for a long time as long as such antibiotics are appropriate for the specific infection under treatment.

## Anti-convulsants

Phenylhydantoin, Trimethadione and Valproic Acid have all been associated with congenital defects. It is not clear, however, that the so-called fetal hydantoin syndrome is the result of exposure to Phenylhydantoin or the result of predisposing genetic factors that lead to epilepsy to begin with. This is suspected to be the case because epileptic patients who have never been exposed to hydantoin during pregnancy, as well as patients who were exposed to other anti-epileptic drugs (Barbiturates), have given birth to offsprings with the fetal hydantoin syndrome. Use of Trimethadione has been associated with a fetal Trimethadione syndrome with features like prenatal onset growth deficiency, mental deficiency, cardiac septal defects and typical craniofacial abnormalities consistent of a short up-turned nose with a broad and low nasal bridge, prominent

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forehead and a very unusual up-slant of the eyebrows and a poorly developed overlapping helix of the external ear. The incidence of this disorder in the offspring of women receiving Trimethadione during pregnancy is unknown at this time. To the contrary, the use of Valproic Acid has led to specific congenital defects, and it is quite clear that Valproic Acid is a potent human teratogen with primarily anomalies related to the neurological system (meningomyelocele). Because of the associated problems, the use of this medication should be avoided to the extent that the patient's condition allows it.

## Warfarin and Its Derivatives

The major features of the Warfarin embryopathy include prenatal onset growth deficiency, mental deficiency, seizures, severe hypoplasia of the nose and stippling in calcified epiphyseal regions primarily the axial skeleton, proximal femurs and calcanea. Patients who have been exposed to Warfarin during pregnancy should discontinue the medication as soon as the pregnancy is identified and be switched to treatment with Heparin. For diagnostic purposes, an ultrasound at about 20-22 weeks to rule out fetal embryopathy is advisable, and subsequently, ultrasounds every four weeks to identify any growth problems.

## Aminopterin and Its Methyl Derivative

When Aminopterin is taken before 40 days of gestation, it is always lethal to the embryo. Serious malformations as well as intrauterine growth deficiency have been recorded in association with Aminopterin ingestion later in the first trimester. Most of the fetuses that have been exposed to the above two medications have been developing severe problems, and patients who are pregnant should never be exposed to these drugs. If exposure has happened because of lack of knowledge about the pregnancy, then certainly abortion may be a choice for the patients.

## Bendectin and Debendox

The above two medications have been used on patients with hyperemesis gravidarum or nausea associated with pregnancy. They are primarily a combination of Doxylamine Succinate and Pyridoxine Hydrochloride (Vitamin B6). Unfortunately, because of some poorly designed studies and litigation problems, this medication (Bendectin) has been discontinued in this country, and a lot of patients are suffering because of that. The associated anomalies that were reported were the result of bias on recollection of the mothers who were exposed to the medication. Fortunately, subsequent studies have shown that there is no increased teratogenicity on patients who were exposed to Bendectin. Since the medication is unavailable, whenever its use is deemed appropriate by the physician, the patient could be prescribed Vitamin B6 anywhere from 25 to 100 mgs. t.i.d. and a separate prescription for Doxylamine Succinate in dosages of 12.5 mgs. t.i.d.

## Isotretinoin (13-Cis-Retinoic Acid)

This medication has been licensed in the United States under the name Accutane, and it was recognized as a human teratogen one year later. A characteristic pattern of malformations has been delineated including ear deformities, cardiovascular anomalies, severe defects in central nervous system development and thymic anomalies. Its use during pregnancy should be completely avoided. The use of the same compound as a local cream may be "risky" but so far there have been

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no reports of damaged fetuses of mothers who were exposed to the medication by local external application. It is worth noting here that even for years after the patient has been exposed to oral Accutane, the pregnancy is at risk for the above anomalies.

## Diagnostic and Therapeutic Radiation

Radiation exposure in excess of 5 RADS may be teratogenic. However, from a practical standpoint, serious risk to the fetus does not occur until the absorbed dose is 10 RADS or more. Most of the diagnostic x-rays deliver amounts in less than 1 RAD quantities, and even a series of x-rays including fluoroscopy (for example, barium enema) do not have more than a total of 800 millirads exposures. When x-rays for diagnostic purposes are necessary, they can be performed as long as exposure is kept to lowest necessary for good imaging.

## Exposure to environmental agents

### Occupational Chemicals and Pesticides

Whenever a patient has been exposed to any occupational chemicals or pesticides, they should be referred to a prenatal diagnostic center for genetic counseling and for specific search in an effort to identify the patient's exposures and the potential risks to her pregnancy. This can be a very tedious job, but most of the patients can be reassured that their pregnancies will continue well. Usually, the pregnancies of these patients are followed up with serial ultrasounds not only for anomalies but also for fetal growth.

### Hyperthermia

Hyperthermia has been associated with growth deficiency, central nervous system defects including mental deficiency and macrocephaly, hypertonia and microphthalmia and variable dysmorphismogenesis of the first and second branchial arches resulting in mid-face hypoplasia, micrognathia, cleft lip with or without cleft palate and malformed ears. It is believed that it is not the infectious agent that causes the hyperthermia, but the increased temperature that leads to these congenital defects since patients who were exposed to hyperthermia because of sun bathing or hot tub use showed evidence of these anomalies on their offspring. Therefore, although conclusive evidence does not exist regarding the teratogenicity of hyperthermia in humans, legitimate concerns have been raised, particularly about generalized defects in central nervous system development and closure of the neural tube in prenatally exposed offspring.

## CONCLUSION

It is important to emphasize that the teratogenic potential of most agents is unknown at this time. Whereas only a few agents have been shown to be teratogenic in humans, the majority have not been adequately tested, creating an obvious dilemma for the physician attempting to provide optimum care for pregnant women. Although no easy answers seem forthcoming, it would seem

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prudent to provide all pregnant women with all the facts available regarding the teratogenic potential of any drug, chemical or environmental agent to which they are exposed. In most of the incidences, the medications are not teratogens, and a simple ultrasound can be reassuring.