PREGNANCY, LACTATION AND CHILDBIRTH

Women undergo drastic physiological changes during pregnancy. More so, in fact, than at any other time except for their own birth. Pregnancy is challenging at the best of times. It is fraught with hazards and potential complications. The mother and child are at the mercy of their genetic makeup, which may be the main cause of some of these challenges. However, they are also susceptible to the environment – mainly the air, food and liquids they consume. It is especially important to void or limit exposure to toxins and teratogens (substances causing birth defects). Good general health and nutrition are important for both mother and child. Vitamins and antioxidants naturally have an important role to play. GSH wears several hats in this scenario and proves itself indispensable.

The list of pregnancy-related illnesses is very long. We cannot describe them all in this chapter but will cover those in which the role of GSH has particular relevance. Since the newborn's GSH levels greatly depend on the mothers' glutathione status, we will also discuss the brief but eventful stages of childbirth and the neonatal period (from birth to six weeks).

PRE-ECLAMPSIA, ECLAMPSIA & HYPERTENSION OF PREGNANCY

Many pregnant women are susceptible to hypertension (high blood pressure). This is caused by hormonal shifts and changes in blood volume and circulation. Some women are always Hypertensive and some experience this problem only during pregnancy. About one in twenty have a more serious condition called preeclampsia.

Symptoms of preeclampsia are hypertension, proteinurea (protein in the urine) and edema – accumulation of water in the tissues leading to swelling, particularly of the hands, feet and face. It usually occurs between the 20^{th} week of gestation and the week following birth. Its exact cause is unknown but most obstetricians (pregnancy and delivery doctors) consider it a vascular disease. It occurs most often in first-time pregnancies and in women who already have high blood pressure.

If left unchecked, one in 200 cases of preeclampsia progresses to eclampsia, a very serious condition featuring convulsive seizures and coma. If not dealt with promptly eclampsia is usually fatal, so it must be treated aggressively. Another major complication of preeclampsia is the HELLP syndrome: Hemolysis (red blood cell breakdown), Elevated Liver enzymes (indicator of liver damage), and Low Platelet count (impaired blood clotting).

Treatment for a mild case of eclampsia includes bed rest, increased fluid intake and nutritional support. Attempts to stimulate urination and stabilize fluid levels with diuretics and salt restriction have no effect. Blood pressure and neurological symptoms are best controlled with intravenous magnesium sulfate and hydralazine. The definitive solution for eclampsia patients is childbirth, which is often induced or cesarean.

PRE-ECLAMPSIA AND GSH

Many scientists have noticed that when pregnancy is complicated by preeclampsia, there is a precipitous drop in the patient's antioxidant function. This has been linked to the oxidation of circulating fats (lipid peroxidation) which damages the sensitive endothelium (lining of the blood vessels). Subsequent constriction of the muscles in the artery wall leads to narrowing of the passageways and decreased blood flow. Combined with the demands of gestation, this triggers a complex cascade of events that can lead to full-blown eclampsia.

Researchers have consistently found glutathione levels of Hypertensive pregnant mothers to be very low. G. Chen and his team at the University of Glasgow believe this depletion might account for some of the important features of pregnancy-induced hypertension – elevated intracellular calcium, decreased red blood cell deformability and endothelial damage. D.W. Branch's team at the University of Utah think the lipid peroxidation that follows may be part of the pathological process in cells of preeclamptic placentas – the foam-cell formation of deciduas. It also seems that measuring GSH levels may be a good way to determine the severity of this disease.

The HELLP syndrome is a serious complication of preeclampsia. Patients suffer liver damage, breakdown of red blood cells and loss of blood-clotting cells. GSH loss is particularly pronounced. Researchers have established a threefold correlation – severity of the preeclampsia, cell fragility and the level of GSH-oxidation.

C. Lee's obstetrical team in London, England attempted to control symptoms in a test-group of preeclampsia patients. Women with severe cases not responding to traditional therapy were given S-nitroso-glutathione. Arterial pressure, platelet activation, and uterine artery resistance all improved without further compromise of fetal well-being. In other words, it slowed or reversed the symptoms of the disorder.

GESTATIONAL DIABETES AND DIABETES IN PREGNANCY

Some women enter pregnancy with a long history of diabetes while others only suffer the disease's high blood-sugar levels when they become pregnant. This is called 'gestational diabetes' and occurs in one to three percent of pregnancies. A number of gestational diabetics will develop true diabetes later in life.

The main cause of death among newborn children of diabetic pregnancies is abnormality of the child in the uterus (congenital malformation). The causes can be traced to inadequate control of the mother's diabetes during pregnancy. Diabetic mothers run the risk of larger babies and tougher deliveries. As a result, births are usually induced if they haven't occurred by the forty-second week of pregnancy. Aside from developmental defects these babies are also at higher risk for developing jaundice, respiratory difficulties, blood sugar abnormalities, low blood calcium and other metabolic abnormalities.

GSH AND DIABETES IN PREGNANCY

All diabetic patients are subject to higher levels of free radical production and lipid peroxidation. In a diabetic environment, embryos develop a higher incidence of

malformations and developmental problems. This phenomenon is called 'embryotoxicity'. The exact mechanism of embryotoxicity in diabetes has yet to be elaborated, but it is clear that oxidative damage to cells plays an important role. Low GSH levels in these patients' embryos place the fetus at risk from the ravages of free radicals.

A Japanese study confirmed that restoring GSH status in embryo cultures normalized the growth retardation and embryo malformations seen with untreated mothers. A Swedish group had similarly positive results treating embryo cultures with NAC (N-acetylcysteine), a potent GSH-enhancing precursor.

TOXINS AND TERATOGENS IN PREGNANCY

We are all exposed to toxins from our environment. They come from the food we eat, the water we drink, the air we breathe, the medications we take, the jobs we hold and bad habits like drinking and smoking. The embryo is exposed to the same toxins as its pregnant mother, but is at much higher risk because they affect its fundamental growth and development.

The consequences range from low birth weight to malformations or even fetal death. Sometimes the consequences are so subtle that they may not appear for years – such as diminished IQ scores in later childhood. The mother is the only one who can keep these risks to a minimum. Above all, she must ensure that her built-in detoxification processes are working well.

GSH AND TOXICOLOGY IN PREGNANCY

According to recent research, the fetus seems to be low in antioxidant defenses. Perhaps it depends on its mother's good health, in which case anything that further depresses these levels could compromise fetal development. After all, the fetus grew from the embryo, and GSH levels are very high in the embryo's conceptual tissue. Conceptual tissue is the extraordinary mass of cells that differentiates and grows into the organs and systems of a human fetus. The process of organ development (organogenesis) is extremely sensitive, but at this stage is especially well protected by higher GSH levels. Researchers in toxicology are studying the possibility that elevated GSH levels may protect unborn children from foreign substances (xenobiotics). If this proves so, measuring GSH in early pregnancy may also be a way to identify possible risks of toxicity.

Some pediatric researchers have tried to match levels of antioxidant defense systems to the frequency and severity of birth defects. W.D. Graf and his associates at the University of Washington compared the frequency of neural tube defects with GSH enzyme levels and established just such a connection. In a very significant Ukrainian study, scientists collected the placentas of women from around the country. All lived in areas affected to a greater or lesser extent by radioactive pollution. As expected, the placentas from the most polluted areas had the lowest GSH levels. They were simply depleted by the overwhelming demands of an ongoing radiation threat. This group was able to show that placentas with low GSH levels were associated with more difficult

pregnancies, harder deliveries and poor postnatal health. They concluded that "glutathione status [is] a prerequisite of the detoxifying activity of the feto-placental barrier." In other words, without placental GSH the fetus is largely unprotected from toxins and other xenobiotics.

The two most common toxins found in pregnancy are alcohol and tobacco. Although most pregnant women can and do choose to avoid them, abuse of these drugs is not uncommon. The mother may have a habitual dependence on these drugs or may simply be exposed to secondhand smoke. In either case, GSH plays an important role in protecting mother and child against such toxic threats.

ALCOHOL AND TOBACCO

Most drug-induced malformations of the fetus result from alcohol abuse during pregnancy. Fetal alcohol syndrome is a clinical condition leading to a long list of possible abnormalities, the most serious being severe mental retardation. In tests on laboratory mammals, the presence of alcohol drained GSH from the liver much more quickly in the fetus than in the mother. Other studies combined alcohol with cocaine, which further magnified the fall in GSH. At the University of New Mexico researchers gave test animals GSH-depleting drugs. This increased the severity of fetal alcohol syndrome. On a more positive note, G.I. Henderson and his team at the University of Texas used antioxidants on their test animals and showed that much of the damage of fetal alcohol exposure could be avoided by maintaining adequate GSH levels.

Women who smoke during pregnancy risk many complications, including early labor, premature rupture of membranes and premature delivery. A possible cause was identified by researchers who demonstrated that cigarette smoke interferes with signals between certain white blood cells and blood platelets, thus interfering with normal blood clotting. The same researchers were able to stop this interference by raising GSH levels.

OTHER TOXINS

Many other studies have shown that antioxidant defense systems – notably the GSH system – play an indispensable role in detoxifying the newborn of numerous xenobiotics, including heavy metals such as mercury, lead, cadmium and arsenic, drugs such as hydantoin, phenytoin, and various poisons. In the lab, GSH-enhancing drugs like NAC actually diminish the toxic effects of mercury on congenital abnormalities and death. NAC is in fact recommended as an emergency measure for pregnant women who have overdosed on acetaminophen.

GSH, CHILDBIRTH, AND THE PERINATAL PERIOD

One of the major complications around childbirth (the perinatal period) is inadequate oxygen supply to the baby (hypoxia). Before the separation, the baby is dependent for its oxygen on umbilical supplies, but this can be compromised during difficulties. For a number of reasons the baby might also suffer respiratory difficulties. In either case, the consequences of hypoxia are problematic and every effort is made to avoid it.

When the baby does not get enough oxygen individual cells are unable to maintain energy levels. This results in hypoxic damage. One molecule – adenosine triphosphate (ATP) – is responsible for carrying energy from the power generators (mitochondria) of individual cells. Because GSH stimulates ATP-production it can be considered anti-hypoxic. Another complication of the hypoxic child is lipid peroxidation, which is also addressed by GSH. And there is every reason to believe it would also help infants suffering from diminished liver function (jaundice).

OXYGEN – SOURCE OF LIFE AND OXIDATIVE STRESS

Premature infants often need oxygen therapy. This brings energy production up but also increases oxidative stress, explaining why visual problems are often encountered by premature infants. Excessive oxygenation causes immature tissue such as that at the margin of the retina to shut down their blood vessels. This condition is called retrolental fibroplasias or retinopathy of prematurity, and has such serious consequences as retinal detachment. Antioxidants may be a potential antidote to this side effect of oxygen therapy. A. Papp from Hungary suggests that giving mothers sulfur-containing amino acids sustains GSH levels and helps prevent this problem.

Other problems relating to high oxygen levels include developmental changes to the nervous system and oxidative lung injury. Newborn animals depleted of glutathione with BSO (a GSH inhibitor) experienced a dramatic increase in these types of damage. J. Sastre and his group from Spain conducted laboratory tests to demonstrate NAC's ability to lessen oxidative stress in newborns. The NAC was administered to the mothers. L.A. Brown of Emory University in Atlanta was able to prevent oxygen-induced lung injury in mammals with GSH supplementation. There is every reason to believe that elevated GSH levels in the mother will counteract the negative effects of many perinatal complications.

GSH AND LACTATION

Lactation and breast-feeding are usually discussed alongside pregnancy and childbirth. In this context, GSH is particularly interesting. One could say it plays a starring role.

It is impossible to overestimate the benefits of mother's milk on the health and development of newborns, especially considering its long-term effects on the immune system. Compared with bottle-fed children, those who are breast-fed suffer from fewer infectious diseases, especially ear infections and pneumonia, fewer problems with allergies, and fewer cases of childhood cancer, including leukemia, lymphoma and bone and brain tumors.

Compared to the milk of other mammals, human milk has the lowest proportion of protein. But the protein make-up is also very different. The two major protein constituents of milk are whey and casein. The whey to casein ratio is much higher in human milk, and these predominant whey proteins contain the critical precursors of glutathione, including beta-lactoglobulin, alpha-lactalbumin, serum albumin, and lactoferrin. These proteins are high in sulfur-containing amino acids such as cysteine and cysteine. The structure of these proteins as well as their content is very important.

Because the cysteine and cysteine are integrated into these larger proteins, they can survive the rigors of digestion and arrive intact in the cells of the infant. There, they are subsequently used to manufacture GSH. Breast-feeding therefore profoundly affects the baby's immune function by giving it high levels of glutathione precursors.

It is possible to extract these proteins intact from cow's milk. The extraction of whey must be carried out carefully, because these proteins are extremely fragile. Their structure easily changes to a form that is biologically inactive. In spite of its unchanged food value, denatured protein loses its capacity to delivery GSH precursors. New technologies have been developed to extract these proteins from mammalian milk without denaturization. In a sense, this is mother's milk protein for adults – a natural way to raise GSH levels. Immunocal is one such whey protein.

CONCLUSION

Glutathione's role in embryonic, fetal and placental development is crucial. It is constantly at work as a scavenger of free radicals and as a detoxifying enzyme of dozens of foreign substances and toxins. Without GSH, these substances can push the child towards an unnerving variety of developmental and health problems. Once past the stage of organogenesis, the unborn child's principal GSH protection comes from outside its own body – the placenta. There is an interesting similarity between the placenta and the liver. Among their many other functions, both act as filters for toxins and both have high levels of GSH within their tissues. It is no coincidence.

Many common complications of pregnancy including high blood pressure, preeclampsia and gestational diabetes coincide with low glutathione levels. Decreased GSH can cause many difficulties in pregnancy. A great deal of research is being carried out using GSH enhancing strategies to combat these problems. There is already some success and much optimism.

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