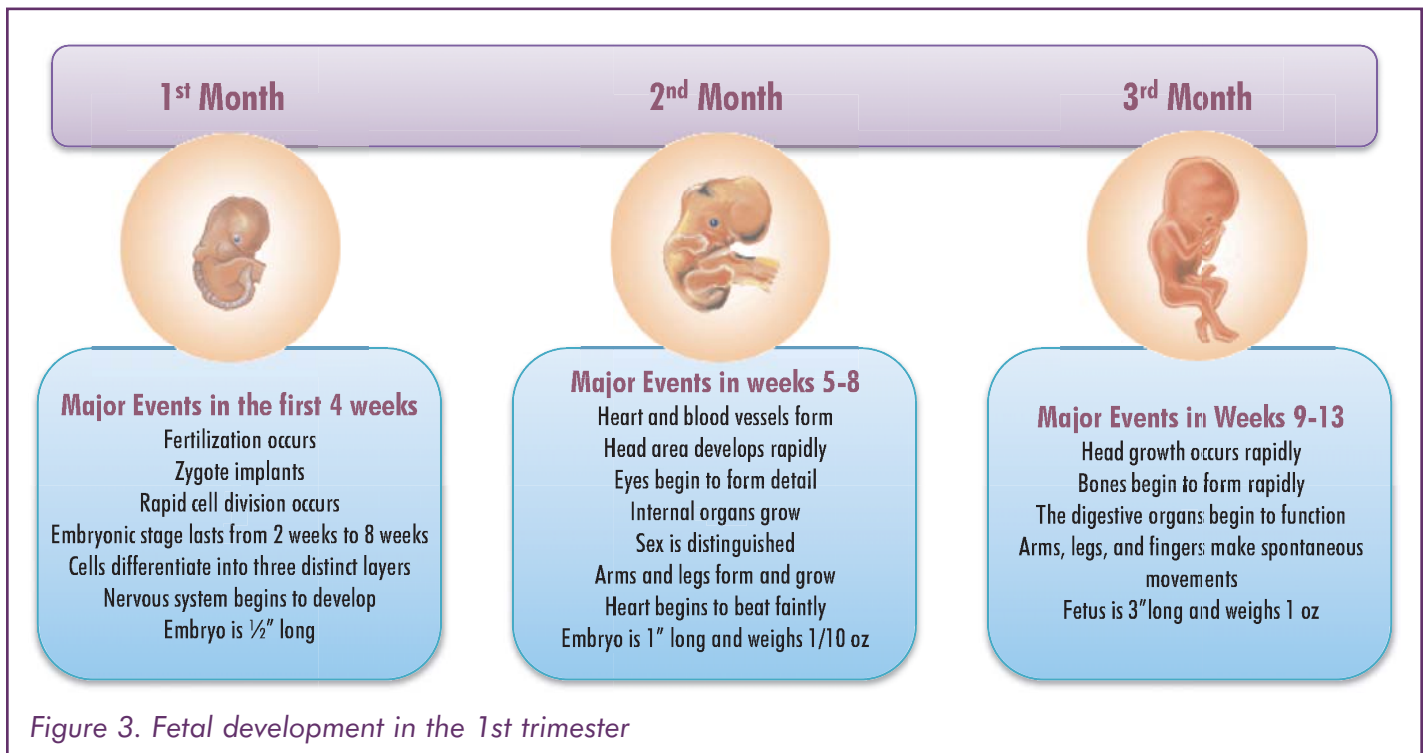


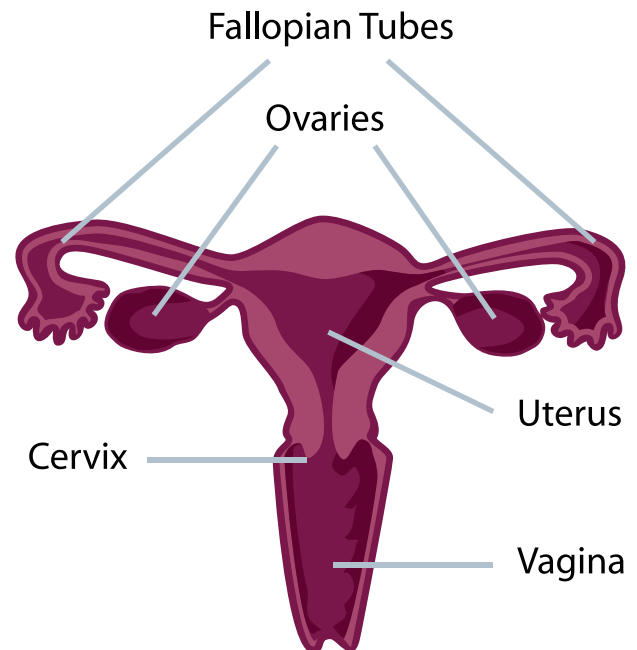
# The First Trimester

## The first 13 weeks of pregnancy



## Developmental Milestones

Everything begins with conception. Every month, during the middle of the menstrual cycle, a mature follicle is swept into one of the uterine tubes (the passage connecting the ovaries to the uterus) where it awaits the arrival of sperm. The ovum is the female reproductive cell and it matures in follicles found in the ovaries that respond to hormonal influences. The release of the mature ovum from the ovaries is brought about by a surge in luteinizing hormone. The ovum contains half the genetic material found in human cells, the other half comes from the sperm. Fertilization occurs in the uterine tubes. The sperm travels from the vagina through the cervical canal; into the uterus and finally up the uterine tube, where the egg is found. The sperm then enters the egg, and the genetic material from the sperm and the ovum are combined and develop into a morula containing several cells. Conception must occur within 24 hours of ovulation.



*Figure 4. The female reproductive system.*

The morula enters the uterus where it implants after several days and becomes a developing embryo. The embryo produces hormones that halt the menstrual cycle, permitting continued growth. The placenta, the organ that unites the mother and the child, supports embryonic growth by allowing exchanges between maternal and fetal blood. By the end of the fourth week of gestation, the heart, digestive system and spinal cord begin to develop. By the 22nd day of pregnancy, the embryonic heart begins to beat. By week 7 the embryo is the size of a raspberry. By the end of the 8th week, the eyes, the face and the teeth are developing. By two months the fetus is constantly moving and webbed fingers are clearly perceptible.

By the end of the first trimester, most of the organs are formed; arms, legs, toes and fingers are shaped and the eyes are almost completely developed.

## Growing Pains

Baby is growing fast, and this rapid growth together with the hormonal changes required to support it are causing havoc for mom. During the first trimester, it is common for women to experience nausea and vomiting, dizzy spells, constipation, fatigue, heartburn and food cravings; most of which are related to hormonal changes. Raging hormones are also responsible for the dreaded emotional instability, mood swings and impatient tendencies.

## The Challenges of the First Trimester

The first trimester is a precarious period. It is the time where the fetus is the most susceptible to changes and disruptions to its environment. Nutritional deficiencies but also exposure to toxins and teratogens (a substance that may cause birth defects) will be most harmful during this period of rapid growth and organogenesis (the formation of organs).

Other possible problems include miscarriages. Eighty percent of miscarriages occur in the first trimester and affect 15% to 20% of all pregnancies.<sup>36</sup> Miscarriages may be related to maternal or fetal causes. Genetic anomalies affecting the fetus are the main cause of spontaneous abortions or miscarriages.

The first trimester is also likely to leave mom feeling queasy. Indeed, a Canadian study has reported nausea in 74% of pregnant participants. Roughly 80% of women will begin to feel nauseated between the fourth and seventh week post catamenia. In all but ten percent of women, the condition resolves by the 20th

week and usually remains benign. In one of every 200 pregnancies, vomiting becomes serious causing electrolyte imbalances and significant weight loss, posing a health risk to the mother and child.

## A Note about Morning Sickness

There are those who adhere to the view that morning sickness is a protective mechanism and that the safest nourishment for the fetus comes from the breaking down of maternal tissues. According to this hypothesis, morning sickness occurs during organogenesis, a time when the fetus is most fragile.

Although interesting, this view remains problematic. Indeed, it does not explain why some women remain nauseous throughout pregnancy, a phenomenon that is clearly detrimental. There is also the impasse of the vast array of clinical evidence pointing out common maternal nutritional deficiencies during pregnancy leading to unfavorable growth and negative outcomes for the fetus.

Furthermore, although the embryo is most vulnerable to contaminants during organ development, it is also most vulnerable to inadequate nutrition at this time and several clinical trials have demonstrated that supplementation during early development can reduce the incidence of congenital malformations, folate being a famous example.

## Favorable Nutrients during the First Trimester

### Vitamin D for Adult Disease Prevention

The role of vitamin D for bone health has been well studied. Unfortunately, other roles for the vitamin are poorly understood and the exact requirements have not been identified. There is, however, growing evidence that vitamin D plays a significant role in health and disease prevention that extend far beyond the skeletal system. Better vitamin D nutrition during pregnancy has recently been linked to a reduced risk of immune disorders such as multiple sclerosis,<sup>37</sup> rheumatoid arthritis and chronic disease susceptibility later in life.<sup>38</sup> It has been hypothesized that low prenatal vitamin D levels lead to fetal imprinting, increasing the risk for cancer, schizophrenia, insulin dependent diabetes, immune disorders and other adult health outcomes.<sup>39</sup> Epidemiological evidence linking multiple sclerosis and vitamin D deficiency includes an increased prevalence of the disease at

higher latitudes, an association with spring births (lower maternal sun exposure in second and third trimester) and promising results in animal models of the condition.<sup>40</sup> Vitamin D is synthesized through the skin's exposure to UV light. Higher latitudes and spring births would lead to lower sun exposure during gestation and would reduce the vitamin D available during fetal development.

Vitamin D supplementation during pregnancy may be required given the prevalence (reported at 12%) of hypovitaminosis D in women of childbearing age in the United States. Furthermore, pregnant women have higher requirements for vitamin D due to fetal requirements and a tendency to reduce outdoor activity and sun exposure.<sup>41</sup> Vitamin D supplementation during pregnancy was recommended in 1991, but received little attention.<sup>42</sup>

### **Biotin deficiency is Teratogenic**

Clinical studies have documented that biotin deficiency may be common during pregnancy.<sup>43</sup> Indeed, urinary excretion of 3-hydroxyisovaleric acid, shown to be elevated in early pregnancy, is a sign of decreased activity of a biotin dependent enzyme.<sup>44</sup> Although vitamin deficits may occur during pregnancy, biotin status may be more worrisome. Animal studies have demonstrated that biotin deficiency is teratogenic. Ninety four percent of pups born to biotin deficient dogs were malformed despite the fact that there were no observable signs indicating an abnormal pregnancy.<sup>45</sup> Similarly, all offspring of mice rendered deficient in biotin suffered from cleft palate and limb shortening.<sup>46</sup> It appears that biotin is required for cellular proliferation as demonstrated by the biotin uptake in replicating lymphocytes, which is 300-700% that of non-proliferating cells.<sup>47</sup> Biotin requirements increase during fetal development - a period of intense cellular growth. Therefore, a marginal deficiency could cause abnormal cellular replication and congenital malformations due to anomalies in fatty acid metabolism (biotin is a cofactor in fatty acid production and oxidation).

### **Too Much Vitamin A must be Avoided**

Chronic consumption of high doses of vitamin A must be avoided, especially during pregnancy. In non-pregnant adults, preformed vitamin A in amounts of roughly 5000 IU per day was shown to increase the risk of bone fracture.<sup>48-49</sup> During pregnancy, the consequences of high dose vitamin A supplementation

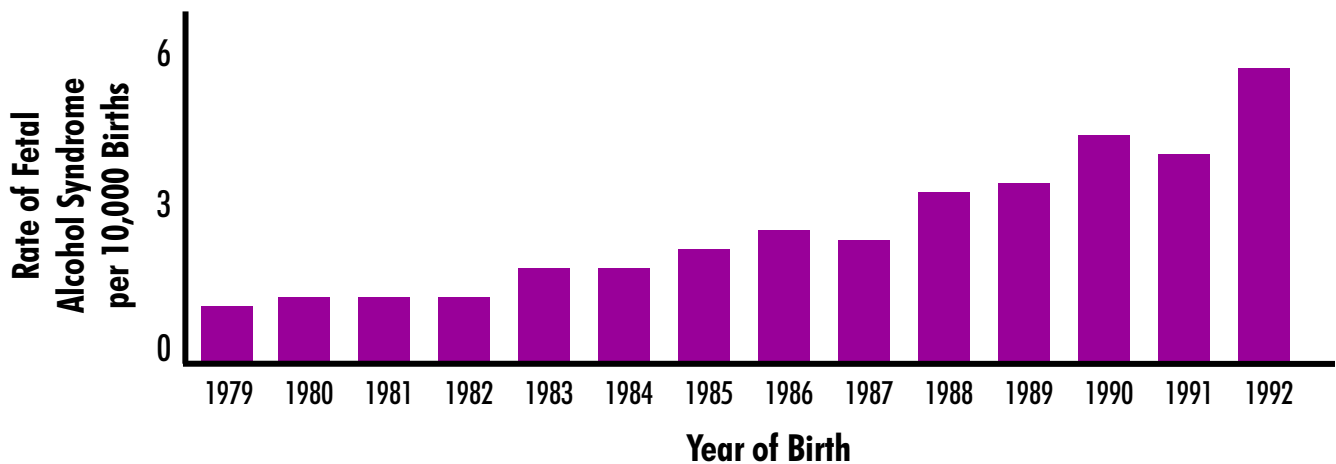
are dire with birth defects reported in one out of every 57 women taking 10,000 IU or more per day of preformed vitamin A.<sup>50</sup> Women taking more than 10,000 IU of preformed vitamin A per day are almost five times more likely to give birth to a malformed infant.<sup>51</sup> Beta-Carotene is not teratogenic and appears to be a much safer alternative to preformed vitamin A supplementation.<sup>52</sup>

There are benefits to vitamin A supplementation during pregnancy. Lower vitamin A levels are seen in habitual abortions.<sup>53</sup> Vitamin A supplementation may also prevent night blindness during and after pregnancy, a significant problem in developed countries. Night blindness is indicative of inadequate vitamin A nutrition and is associated with a two to four-fold increase in maternal mortality.<sup>54</sup>

### **Vitamin B3 Protects the Developing Brain**

Fetal exposure to alcohol is the number one cause of non-genetic mental retardation in developed countries. Maternal alcohol consumption can lead to Fetal Alcohol Syndrome, a condition with the following possible features: congenital heart disease, growth retardation, feeding problems, and disorganization of neurons<sup>55</sup> leading to serious neurological disorders such as hyperactivity, learning and memory deficits, psychosis, depression, and schizophrenia.<sup>56</sup> The incidence of Fetal Alcohol Syndrome is estimated at 1 out of every 100 newborn children in the United States.<sup>57</sup> A single episode of binge drinking leads to the death of thousands of fetal neurons<sup>58</sup> explaining the toxicity seen with ethanol consumption. It has been suggested that vitamin B3 may have neuroprotective activity in the developing brain. Research has also shown that vitamin B3 protects the nervous system from free radicals.<sup>59</sup>

In the latest study, researchers from Cornell University examined the possible benefits of vitamin B3 for the prevention of ethanol-induced neurodegeneration in mice.<sup>60</sup> The results are encouraging. Vitamin B3 reduced injuries to neurons and "inhibited the decrease in the number of neurons following ethanol exposure during early postnatal development" an effect that appears to be related to mitochondrial protection.<sup>61</sup> Most importantly, the research uncovered that vitamin B3 is capable of preventing hyperactivity and memory impairment in animals exposed to ethanol in utero making vitamin B3 the first treatment with demonstrated efficacy at the cellular, molecular and behavioral level for the prevention of ethanol induced neuronal apoptosis (cellular death).



Graph 7. Reported incidence rate of fetal alcohol syndrome, by year of birth, from the Birth Defects Monitoring Program of the Centers for Disease Control and Prevention, 1979-1992.

Of course, pregnant women should always avoid alcohol. Unfortunately, fetal exposure to ethanol is widespread (see Graph 7) despite the 1989 imposed label warning for all alcoholic beverages in the United States: "According to the Surgeon General, women should not drink alcoholic beverages during pregnancy because of the risk of birth defects." One explanation is that alcohol exposure may be occurring before the mother knows she is pregnant. In Project Viva which enrolled 2 128 pregnant women, 70% reported alcohol consumption after their last menstrual period but before learning they were pregnant while eight percent continued consuming alcohol once they realized they were pregnant.<sup>62</sup>

### Ginger and Vitamin B6 for Morning Sickness

More than half of pregnant women experience nausea and vomiting of pregnancy especially in the first trimester. The rapidly increasing production of the human chorionic gonadotropin (HCG) hormone by the placenta may be to blame. Indeed, it is thought that the hormone stimulates the vomiting center in the brain, triggering nausea and the vomiting reflex.



Ginger is a well-known antiemetic and several studies have documented its efficacy at reducing the symptoms of morning sickness with significant improvements in nausea and retching after four days of supplementation with 1500mg of ginger daily.<sup>63</sup> The studies have also demonstrated that ginger does not adversely affect the fetus; birth weights, gestational age and APGAR scores (a test designed to quickly evaluate a newborn's physical condition) were not affected in newborns when the mother was giving ginger as a treatment for nausea and vomiting.

Vitamin B6 is essential for neurotransmitter synthesis, lipid metabolism and protein synthesis. During pregnancy, vitamin B6 was shown to prevent dental decay<sup>64</sup> and is effective at reducing the nausea and vomiting of pregnancy.<sup>65</sup> A study looking at the comparative effectiveness of vitamin B6 and ginger found significant improvement in nausea and a reduction of vomiting episodes in both treatment groups.<sup>66</sup>

## Homocysteine levels, Folate, Vitamin B12, Inositol, Choline and Neural Tube Defects

### Homocysteine

Homocysteine is a highly toxic by-product of normal metabolism and is known to be a risk factor for vascular disorders. During pregnancy, rising homocysteine levels are associated with increasing risks of serious complications such as preeclampsia, placental abruption and thrombosis.<sup>67</sup>

Homocysteine accumulation is in some ways similar to folate deficiency as folate derivatives are required to recycle homocysteine. Therefore, elevated homocysteine levels are also indicative of deficient methylation because homocysteine is recycled through methylation. DNA also needs to be methylated throughout fetal development.<sup>68</sup> Changes to DNA methylation may be responsible for gene silencing, and thus it has been hypothesized that improper DNA methylation may be responsible for fetal programming and prolonged changes in cellular function.<sup>69</sup>

fundamental to the disorder. NTD are amongst the most common birth defects causing serious disability and mortality. About one in 33 infants born in the United States will be affected by birth defects ranging from NTD to cleft palate or lips and cardiac malformations. Studies have demonstrated that high dose folate supplementation (10 mg/day) prevented recurrence of orofacial clefts in populations at high risk for the malformation.<sup>73-74</sup> Folate also reduced the incidence of congenital heart defects.<sup>75</sup>

It is estimated that folate supplementation alone would decrease neural tube defects by 50%<sup>76</sup> and the risk of malformations by 30-60%.<sup>77</sup> However, because embryonic development including neural tube formation occurs early during gestation (neurulation occurs between the 17th and 30th post-conception days)<sup>78</sup>, folate supplementation must begin before conception. This is why it is currently recommended that all women who could become pregnant should supplement their diet with folate. By the time women realize they are pregnant, it is often too late to prevent NTD. The increased folate demands throughout pregnancy are often not met through the diet. Furthermore, supplemental folate is 1.7 times more bioavailable than food folate,<sup>79</sup> strengthening the support for folic acid supplementation throughout pregnancy.

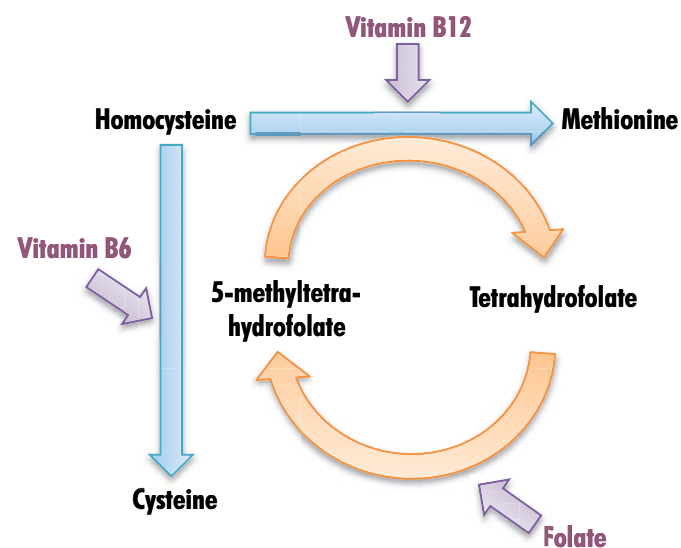


Figure 5. The Methyl Cycle. Source: Redrawn from Ray and Laskin (1999)<sup>70</sup>

The etiology behind neural tube defects (NTD) remains unclear. The process of neural tube closure is also poorly understood. The latest model suggests two sites of fusion (see Figure 6).<sup>71</sup> It is thought that inadequate folate status due to insufficient intake or irregular genes may increase the risk of abnormal cellular division leading to birth defects. It has also been observed that women carrying fetuses with NTD have mildly elevated homocysteine levels. Both homocysteine levels and NTD are influenced by genetic and nutritional factors.<sup>72</sup>

## Folate

Most pregnant women are aware of the importance of folate during pregnancy. The vitamin was examined in the 1960's and 1970's for its potential in reducing neural tube defects (NTD). NTD are a common but serious congenital defect where the neural tube of the embryo - the structure that develops into the central nervous system - does not grow normally. Although genetics are a significant contributing factor to the development of NTD, environmental factors are also

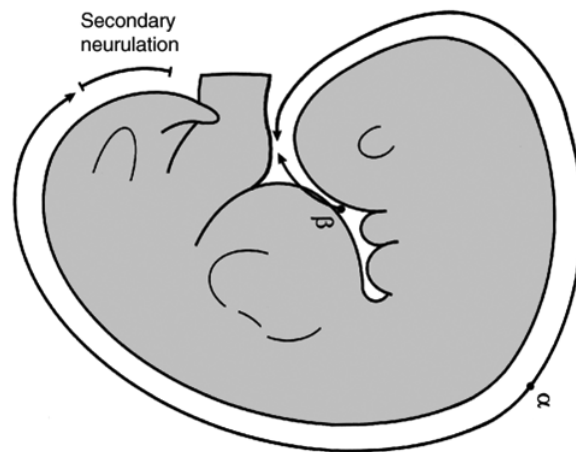


Figure 6. Fusion of the neural tube 25-27 days post-ovulation. Fusion begins at site A and then at site B. Source: Redrawn from O'Rahilly and Muller (2002)<sup>71</sup>

The influence of folic acid on NTD may well be related to homocysteine. Folic acid is a precursor to methylene tetrahydrofolate, the enzyme involved in the remethylation of homocysteine into methionine. Furthermore, of the nutritional factors that regulate homocysteine levels, folate status has the greatest influence.<sup>80</sup>

## Inositol

Other nutrients have also shown promise when it comes to congenital defects. Inositol, a lipotropic factor, helps in the metabolism of fatty acids. Approximately one gram per day of inositol is found in the diet.<sup>81</sup> Inositol is essential for cellular growth. A recent study demonstrates that maternal blood concentrations diminish during the first trimester of pregnancy after which concentrations slowly increase.<sup>82</sup>

In maternal mice with genetic anomalies leading to neural tube defects in the offspring's that do not respond to folic acid supplementation, shortcomings can be prevented through myo-inositol supplementation early in pregnancy.<sup>83</sup> Unfortunately, approximately 30% of NTD are unresponsive to folate supplementation. There is no current treatment for such situations but inositol may be an effective treatment for folate resistant NTD. Indeed, it appears that supplementation with inositol leads to the activation of a specific protein kinase C (PKC) that may be essential for embryonic development, and particularly for the normal closure of the neural tube. The effect is cancelled by the administration of a PKC inhibitor - a further indication that inositol's benefits are related to PKC activity.

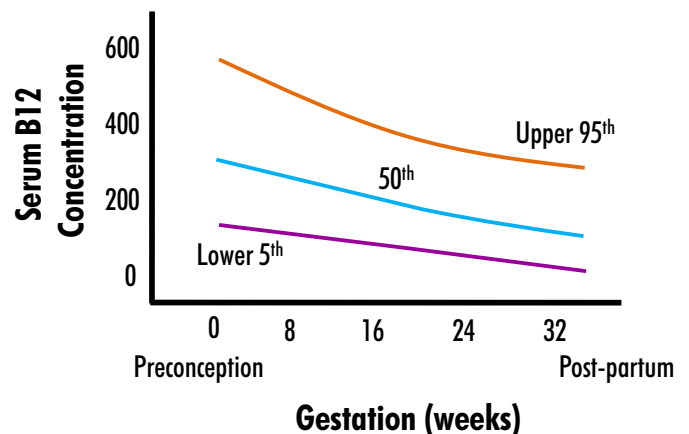
The first use of inositol supplementation in a mother with a history of folate-resistant NTD resulted in a normal pregnancy and healthy baby with no signs of toxicity for the mother or fetus.<sup>84</sup> The mother was given 500mg of inositol and 2.5mg folate daily starting three months pre-conception and continuing 60 days post-conception. A study from the Netherlands revealed that lower maternal inositol concentrations were linked to an increased risk of cleft lip or palate in the infant.<sup>85</sup> Cleft lips or palate are another common congenital defect that develops between the seventh and 14th weeks of pregnancy. Inositol is also involved in lung surfactant production<sup>86-87</sup> and may be especially beneficial in premature babies. Inositol also reduced retinopathy, death, bronchopulmonary dysplasia and intraventricular hemorrhage in premature infants.<sup>88</sup>

Inositol is beneficial for diabetic pregnancies. The rates of congenital malformations in diabetic mothers are four to five times higher than in normal pregnancies. Congenital defects account for 40% of

infant's mortality with diabetic mothers. The exact reason for the defects that affect mostly the heart and nervous system remains unclear, but free radicals, insulin and arachidonic acid deficiency have been suggested as possible underlying factors. In animal studies, inositol reduced the incidence of neural tube defects in diabetic animals by 50%<sup>89</sup>, suggesting that inositol depletion may be involved in the pathophysiology.<sup>90</sup> Inositol depletion appears to be the main mechanism behind hyperglycemia-induced embryopathy.<sup>91</sup> However, it is probably best to limit inositol supplementation later on during pregnancy, as inositol may be involved in parturition.<sup>92</sup>

## Vitamin B12

Also known as cobalamin, vitamin B12 is essential for health. Vitamin B12 is important for the maintenance of adequate methyl donors. The vitamin is required for the activation of folate, the recycling of homocysteine, fat metabolism, cellular replication and DNA synthesis. Vitamin B12 deficiency leads to neurological deficits, anemia and elevated homocysteine levels. During pregnancy, inadequate cobalamin levels increase the risk of NTD.<sup>93</sup> Vitamin B12 serum concentrations progressively decline during pregnancy (see Graph 8) leading to borderline or deficient levels<sup>94</sup>, with low vitamin B12 levels associated with neural tube defects.<sup>95</sup>



Graph 8. Vitamin B12 serum concentration throughout a healthy pregnancy. Upper or 95th, lower or 5th and 50th percentiles of the concentrations of vitamin B12 from preconception, throughout pregnancy, to 6 weeks post-partum. Source: Redrawn from Cikot (2001)<sup>1</sup>

## Choline

Choline is an essential nutrient involved in the synthesis of phospholipids and neurotransmitters. Choline is also a methyl donor implicated in the metabolism of homocysteine. Animal studies have shown that choline requirements during pregnancy may be difficult to attain through dietary means.<sup>96</sup> Fetal choline requirements are extremely high with plasma concentrations that are three times higher than maternal levels<sup>97-98</sup>, which may lead to a diminution of maternal choline stores.<sup>99</sup> Worrisome findings as a study published in the American Journal of Epidemiology revealed that higher dietary intake of choline before conception reduced the risk of NTD, and other congenital defects affecting the nervous system.<sup>100</sup> This explains why the dietary reference intake for choline during gestation was set relatively high at 450 mg per day.

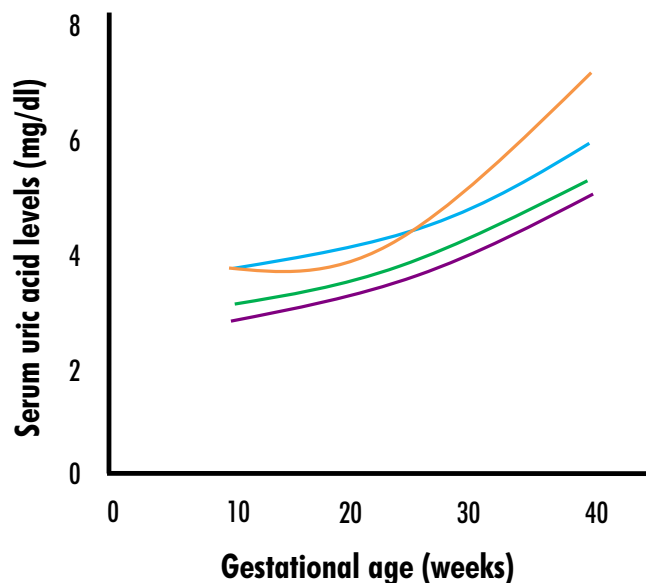
## Trimethylglycine

Trimethylglycine (TMG) is another methyl donor inversely related to homocysteine levels, emphasizing its role in pregnancy.<sup>101</sup>

## The Dangers of Elevated Uric Acid Levels

Uric acid is a metabolite of protein breakdown. Uric acid is present in the blood and is eliminated via the urine. Associations between elevations of uric acid concentration and preeclampsia were first reported in 1917. Hypotheses behind elevations of serum uric acid levels during pregnancy have revolved around kidney dysfunction and reductions in glomerular filtration rates. Animal studies have revealed that uric acid is an independent risk factor for cardiovascular disease and hypertension<sup>102</sup> suggesting that the molecule itself may play a significant role in fetal and maternal pregnancy related complications. Evidence

showing that elevations in uric acid precede the development of preeclampsia<sup>103</sup> supports the view that uric acid leads to preeclampsia and not vice versa. The unfavorable effects of imbalanced uric acid levels go beyond preeclampsia, with studies showing a strong correlation between early pregnancy fetal loss and a diminution of the normal uric acid decline seen in the first trimester of pregnancy. However, this apparent lack of diminution of uric acid levels may simply be due to an inadequate blood volume expansion in early pregnancy.<sup>104</sup>



Graph 9. Predicted mean serum uric acid concentrations after adjusting for serum creatinine.

Purple line: control pregnancy. Green line: women with gestational hypertension and proteinuria without evidence of hyperuricemia at delivery. Blue line: women with gestational hypertension, proteinuria, and hyperuricemia at delivery. Orange line: women with gestational hypertension and hyperuricemia at delivery. Source: Redrawn from Powers (2006)

The advertisement features a white bottle of BioFolate supplement on the left. The bottle label includes the text: 'advanced series', 'A NATURAL FORM OF FOLATE', 'UNE FORME NATURELLE DE FOLATE', 'BioFolate', '5-METHYLTETRAHYDROFOLATE', '1 mg', and '100% VEGETARIAN'. The background is dark blue with glowing yellow and red circular patterns. Large white text on the right reads: 'Folate in its most Bioavailable Form'.