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Folic Acid And Embryonic Development - A Literary Up-Date

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ABSTRACT

Background: Folic acid, a commonly prescribed antenatal prophylactic drug is essential for the normal development and growth of the conspectuses, and healthiness of the mother. The laxity in the seriousness of adherence to the medical advise on supplemental intake of the drug by women of reproductive age and particularly at pregnancy among the rural dwellers calls for a re-look into the dangers of such negligence and a re-emphasis of he need for compliant.

Methods: Retrospective and contemporary literature reports on the importance of folic acid and the toxicity of its deficiencies during embryonic development both clinically and experimentally were compiled and presented.

Observation: Most information obtainable on the importance of folic acid had been via experimental approach; with little efforts and emphasis at relating these to the clinical manifestations of the vitamin cum public awareness.

Conclusion: Frantic efforts at orientation to strict adherence of the supplemental dosage of 5mg daily of folic acid at pregnancy, plus fortified meals would prevent or alleviate the feto-maternal anomalies usually associated with the vitamin deficiencies.

Keywords: Folic acid; Embryonic development.

Folic acid, a B-vitamin derived its name from the experiment of Mitchel and co-workers, (1941) who reported that a concentrate prepared from spinach leaves, as a medium, stimulated the growth of a micro-organism, strepto-bacilus lactus R. Folic acid or folate, also called pteroy-glutamic acid is itself inactive. It is converted into the biologically active co-enzyme, tetra-hydrofolic acid which is important in the biosynthesis of amino and acids, protein conjugations, and hence, cell division, growth and regeneration. The formyl derivative of folic acid is folinic acid or citrovorum factor (leucovorin) and this can be used where the body fails to effect the conversion of folic acid. Reports on the effects of folic acid deficiency includes: megaloblastic erythropoiesis, thrombocytopenia, macrocytic anaemia at pregnancy and infancy with changes in bone marrow since folic acid functions involve maturation of blood cells showing increased erythroid cells and pronormoblasts, glossitis, and gastro-intestinal disturbances in man. In the embryos undergoing organogenesis, the poorest growth and differentiation occurred in the absence of folic acid. Folic acid added at various growth stages and somites development, showed significant improvement, Lawrence and Bennett, (1987); Martins et al;, (1981); Robert et al., (1946).

Absorption/Metabolism Of Folic Acid

The major source of folic acid is leafy vegetables. In plants, folic acid exists as a polyglutamate conjugate with an unusual gamma-linked polypeptide chain of 7-glutamyl acids. In the liver, the major folate is pteroyglutamyl conjugate. These unusual gama-linked glutamyl peptides chains are made resistant to hydrolysis by the usual proteolytic enzymes present in the intestine, however, they are clinked by specific group of enzymes, that is, folyglutamate hydrolases, (martins et al., 1981). Hydrolysis of pteory-hepta-glutamate to pteroymonoglutamate by intestinal enzymes is rapid, fascilitating the absorption of the folate in to mesenteric circulation. Only the monglutamate form is absorbed. Following the oral ingestion of folate, there is a transitory rise in the plasma concentration of monoglutamate, regardless of the form in which foate is administered, (Robert et al., 1946).

Folic acid promotes cell division, as seen in denovo-synthesis of purines and pyrimidines. Folic acid in the form of N^5, N10 methionine tetra bydro folate is incorporated into glycinamide riboslyl 5 phosphate which is converted to formyl glycinamide ribosyl-5-phosphate by an enzyme, formyl transferase along the de-novo synthesis pathway beginning from ribose-5-phosphates, Bethel et al., (1956); Jeffrey et al., (2000).

Folic Acid And Embryonic Development

The importance of folic acid in prenatal development has been well documented both clinically and experimentally; dossiers of published reports on the fed diet lacking folic acid and containing 1% succinyl sulfathiazole (to reduce intestinal biosynthesis of the vitamin) are available, Chrnoff (1975) Friday and Howard (1991), Farley et al. (1985), Adebisi (2002, 2003, 2004). For instance, it was observed that this chronic but apparently mild deficiency, when begun 35 days prior to mating, would increase the number of embryonic resorption by10% and the number of still born pups by 9%. Beginning the deficiency period 64 days prior to breeding and continuing through day 21 of pregnancy did not further increase the severity of the effects. There had been several earlier reports of maternal folic acid deficiency causing congenital malformations in rats. (Hurley, 1977, Preedy et al., 1990, Pierce and James, (1986). Moreso, Thierch and Philips (1940) administered aminopterin to pregnant rats as an anti-metabolite to folate.They were able to maintain their rats on a stock diet because the antagonist would counteract its contained folic acid. These workers began to treat the animals, pregnant rats shortly prior to the period of organo-genesis. The maternal decidual and embryonic placentas were reported as normal by gross anatomical inspection. Moreso, 9 methyl folate was employed to achieve folic acid deficiency on the histology of both embryo and placenta in rat. In this study, the pregnant rats were fed the deficient, antagonist containing diet on days 8 and 9 of gestation. On day 10, the embryos showed the first microscopically detectable deviation from normal development. In fact all the embryos were dead by day 13 in this experiment.

The teratogenic response of the rat embryos to folic acid is not unique, similar effects were reported in the mouse; while hydrocephalus and skeletal defects had been observed in humans due to maternal injection of aminopterin. However, the great majority of human congenital malformations have been produced in experimental animals by a variety of means. Similarities in comparative embryology of mammalian forms provide ample explanation for both the observed differences and the considerable similarities of malformations. An excellent example was reported of cardiovascular malformations in the rat pups of vitamin A deficient dams explainable on the basis of their embryonic derivations. The same embryonic basis was implicated for the cardiovascular abnormalities induced by maternal deficiency in pteroy-glutamic acid. These investigators were able to achieve a transient deficiency in the vitamin by adding the antagonist x-methyl folate to a folate deficient diet compounded of purified foodstuffs and contain 1% succinyl-sulfathiazole. This diet was fed *ad libitum* to pregnant rats of known gestational duration and continued for a selected number of days. Then the dams were returned to a complete ration lacking the antagonist and containing 50.5mg/kg folate. This work showed that deficiency on days 7 and 8 resulted primarily in cardiac abnormalities of the great arterial vessels derived from the great aortic arches. If the maternal situational deficiency extends from day 9 through to day 10 the situation was reversed, with the larger percentage of abnormal pups having defects in the great vessels. This is a direct result of known developmental sequence of the heart and the major arteries, Johnson, (1970); Steeger-Theunisen (1995).

Such findings had been extended to many organs adversely influenced by diverse agents. It has been extended to many principles of teratology, that is, the stage of embryonic or foetal development during exposure to a teratogenic action will determine the nature of

the abnormalities produced. Development of the skeletal system was severely altered in properly timed maternal deficiency period began on day 10 and continued through term. For instance, the palatine shelves normally moved from the vertical position above ht tongue to the horizontal position above the tongue at the end of day 16. in folate-deficient embryo, the shelves did not become horizontal until day 18,by which time the skull base was too wide for the shelves to touch and fuse. (Chepenik et al., 1970, Payton et al.,1978).

The Probable Mechanism Of Action Of Folate Deficiency

One way in which folate antagonist are thought to kill cells is that theyproduce 'unbalanced growth' that is, they inhibit DNA synthesis. Some cytotoxic agents at lower dosage suppress DNA synthesis and cell division without causing cell death. Depressed proliferative activity in itself may contribute to teratogenesis by reducing the number of cells available for the formation of tissues during the organ genesis. This rate of DNA synthesis corresponds to an average 10 replications in 48 hours or an average length of the cell cycle of less than 5 hours. The majority of the cells will be in the replicating state throughout the 48 hours. Even a brief pulse of a DNA damaging agent that reduces DNA synthesis would be capable of affecting a large number of cells. Many agents that depress DNA synthesis are known to be teratogenic. Yet it is not clear that depression of DNA synthesis alone can lead to birth defects. The cell deaths that accompany inhibition of DNA synthesis are believed to be a more important correlate to dysmorpho-genesis. However, a prominent feature of a transient folic acid deficiency induced by 9-methyl folate from days 10 13 of gestation is a high malformation rate and low intra-uterine death rate. Furthermore, inspection of histological sections prepared from limbs of 13 day old treated embryos did not reveal evidence of cell death. It may well be that the embryos regulations is in response to the folate antagonist so as not to enter into undifferentiated, unbalanced growth, resulting in truly abnormal differentiation rather than absence of structures due to cell death. In preliminary studies, altered DNA synthesis had been found in embryos obtained from 9-methyl foalte treated rats on day 13 of gestation. The possibility that maternal anti-folate treatment may alter the rates of sub-cellular organelles biosynthesis in the embryos was suggested also from experiment using radiological precursor to membrane phospho-lipid. However, since teratogenic treatments with anti-folate during organo-genesis in the rat results primarily in altered calcification and ossification in developing long bones, this spurred up the beginning of investigation in to the composition fo the normal and 9-methyl folate treated embryos. (Pietrirzk and Thorand, 1997, Schmidt et al. 1977).

Christensen and Rosenblatt (1995) reported that while there is strong evidence that folate deficiency including the use of antifolate drugs in early pregnancy is teratogenic and may lead to a range of serious anomalies of the developing foetus including intra-uterine death. The mechanism for these effects have not yet been delineated, though there is increasing evidence that marginal folate status exacerbates the effects of an underlying genetic defects in the mother, the foetus or both. An abnormal relationship exists in the ingestion of folate between women who had, and those who had not been giving birth to infants with neural tube defects. However, periconceptional folate supplementation had been shown to give effective protection against the development of birth defect. Genetic counseling and prenatal diagnosis had been suggested for women who are recognized to be at risk for the occurrence of birth defects.

The Implications Of Folate At Pregnancy

The implications of diabetes in folate deficiency at pregnancy had been investigated (Kaplan et al. 1999). This study indicated no difference in folate level in the diabetic and non-diabetic pregnant women. It was concluded that folate deficiency is not an important risk factor for diabetic women exhibiting foetal anomalies

when compared to non-diabetic women. Although this does not preclude or diminish the importance of periconceptional folic acid supplementationor other possible scenarios that could restrict folate use by an embryo leading to major anomalies.

Steegers Theunisen (1995) re-echoed the lack of adequate knowledge about the importance of folate in normal foetal development and well-being. However, in man, folate acts as a substrate in the transfer of one-carbon moieties and thereby, plays an essential role in the several amino acids such as methionine and nucleic acid; and folate requirements are related to the amount of tissue growth. Moreover, epidemiological, clinical and teratological research showed that this B vitamin is particularly involved in the rpevention and pathogenesis of some birth defects.

Numerous existing research had confirmed that pregnant women are prone to becoming folate deficient because of the significant increase in folate requirement during pregnancy and folate intake of pregnant women are often insufficient. Pietrizik and Thorand (1997) reduced folate levels in blood and neutrophilic hyper segmentation reflect a negative folate balance. Possible consequences of low maternal folate status may be pregnancy complicated as seen in abortion, *abortus imminens, abruptio planenta and congenital malformations,* such as neural tube defects, and skeletal disorders. However, periconceptional folate supplementation had been recommended (Christensen and Rosenblatt 1995), though the mechanisms of the protective effects remains elusive, a relative folate shortage rather than deficiency seems to be responsible for ht malformation which can be compensated for by a higher intake. It was concluded in this wise: that maternal low folate status may in itself be the most important risk factor for congenital defects and that food fortification may be the only discovery of genetic abnormalities in folate related enzymes, which might explain the role of folate in the prevention birth defects (Kaplan et al. 1999, Malloy et al. 1999, Tell et al 1998).

Gonzalez and his colleagues (1997) agreed with the fact that folate deficiency is one of today's most common vitamin deficiencies in women, and that women who consumed low level of folate during pregnancy are at risk of poor pregnancy outcomes. They pointed out however, that other factors such as heredity, social class, maternal age, birth order, maternal diet, length of time between pregnancies, maternal zinc deficiencies, use of anticonvulsants, drugs abnormal homocysteine metabolism and the use of oral contraceptives have been implicated in the incidence of birth defects and that fetuses are highly dependent on folate of the mothers.

Although the most conspicuous symptom of folic acids is pernicious anaemia, it had been observed that the lack of folate intake during pregnancy induced birth defects, thus emphasizing the pre-conception importance of folate, and that during pregnancy, there is a much higher risk to develop folate deficiency because of a drastic increase in foeto-placenta folate transfer, and even ideal diets could not prevent folate deprivation in such situations (Maekawa et al. 1999).

In the light of this, it had been reported that bread fortified to contain a daily dose of 900mg folic acid was administered to folate deficient patients in late pregnancy. The patients subsequently showed significant rise in red cell folate concentration. They discovered that the rise was similar to that observed in women receiving a daily dose of 300mcg of folic acid in tablet form (Gregory 1997, Margo et al. 1975).

In earlier consideration of the use of supplemental folic acid, it was suggested that women of reproductive age should be advised to take 0.4mg folic acid daily while strategies be devised to increase folate among young women and inform them of the benefits of periconceptional folate supplementation. In pregnant women not taking folate supplement the incidence of folate deficiency was reported increased as pregnancy advanced, while those taking supplements achieved normal blood folate concentration (Rider 1994, Locksmith and Duff 1998, Zamrazilova and Kacovska 1997).

In conclusion, folic acid and cyano-cobalamin supplementation may be cost-effective among many population sub-groups and could have a major epidemiologic benefit for prevention of birth defects and incidence of coronary heart diseases, CHD, from the already

documented and the on going experimental works and clinical trails.

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