Introduction

INTRODUCTION

Bravest battle that ever was fought
Shall I tell you, where and when?
On the maps of the world you will find it not
It was fought by the mothers of children.

- Joaquin Miller

The quality of human resource of any country is largely determined by the quality of its child development which in turn is a reflection of health and nutritional status. Any developmental constraints during early childhood characterized by rapid growth rate lead to short term and long term consequences that limit human potential (UNICEF, 1994).

An unfinished task that must find top priority is nutritional care of the pregnant woman. Good nutrition is the material basis for human resource development of a country or a community and it is an issue of survival, health and development for current and succeeding generations (Chunming, 2003) Women need to attain good nutritional status before, during and after pregnancy to optimize maternal health and reduce the risk of birth defects and chronic diseases in their children in later adulthood.

Pregnancy is a period of great anabolic activity when the most rapid rate of growth takes place. It is a condition in which the foetal growth is accompanied by extensive changes in maternal body composition and metabolism (Nerlekar *et al* 1999). Maternal nutritional status not only determines the state of the offspring at birth but also, to some extent, the future course of its development (Gopalan, 1999). Based on data from different studies in a number of countries, WHO estimates that 32 per cent of new born deaths are due to infections including tetanus, 29 per cent are of inability to establish normal breathing at birth, 24 per cent due to complications of being born premature and the remaining 15 per cent from other causes such as birth defects (MOHFW, 2001).

An adverse gestational event, such as a conception culminating in spontaneous abortion or still birth, is an unwelcome, but not an unusual pregnancy outcome. Poor outcomes can also occur in pregnancies that give rise to live born infants and include preterm delivery (<37 weeks gestation) and intrauterine growth restriction (<10^{th} percentile), both of which encompass low birth weight infants (<2500g) (Ghai, 1993).

Micronutrient malnutrition represents the vicious troika of deficiencies of iodine, iron and vitamin A, with others waiting in the wings for good reason such as zinc, folic acid and n-3 fatty acid (Ramalingaswari, 1999). It is believed that micronutrient supplementation during pregnancy may improve foetal and neonatal outcome. Periconceptional folate supplementation reduced the incidence of Neural Tube Defects (NTDs). The reduction is similar for occurrent defects and for recurrent defects (Lumley *et al,* 2001).

In 1941, a substance extracted from spinach leaves was called folic acid derived from the Latin word "Folium" and found to be effective in the treatment of anemia (Linker, 2002). Folic acid, called as folate or folacin, is one of the B vitamins, also known as B_9. It is a vital raw material for the production of red blood cells, as well as nor-epinephrine and serotonin, the chemical components of the nervous system (Oakley *et al* 1996).

Folic acid is very important for women during pregnancy. Taking folic acid before conception helps to prevent the occurrence of certain birth defects during pregnancy. Folic acid also can help to synthesise the genetic material in every cell of the body and normalize the brain function (Jick *et al* 1999).

Folate is critically important for foetal development as it acts as a cofactor for many essential cellular reactions including the transfer of single carbon units and it is required for cell division (Mudd *et al* 1995). An estimated one- fourth of NTDs are attributable to the thermo labile C677T mutation in Methylene Tetra Hydro Folate Reductase(MTHFR) gene with an allele frequency of >0.3 in approximately 9-10 per cent of individuals who are homozygous, a fraction far below the 70 per cent reduction in NTDs which is associated with folic acid supplementation (Posey, 1996). In North Indian population, the 677C→ T allele of the MTHFR gene may be associated with the occurrence of a lower type of NTD. This points towards the differential roles of thermolabile MTHFR at different sites of neural tube closure (Dalal *et al* 2007).

The NTDs –anencephaly (the total or partial absence of the cranial vault, the covering skin and the brain tissue), spina bifida (non-closure of the spine resulting in herniation or exposure of the spinal cord, the meninges or both), encephalocele (herniation of meninges and brain tissue outside the cranium, covered by normal or atrophic skin) are congenital malformations which arise during the development of the brain and spinal cord (Lumley *et al* 2001) The primordial cells of neural tube usually close within the first 21 to 28 days of life. Development then rapidly progresses during the first trimester of pregnancy.

NTDs vary in severity from the mildest form such as the spina bifida aperta to the extremely severe forms such as anencephaly and rachischisis (Ellenbogen, 2002). Prognosis is usually disappointing or dismal. Neonates who are born with spina bifida can have hydrocephalus, varying degrees of paralysis and disability while babies born with anencephaly die before or shortly after birth (Green, 2002).

In several developing countries the perinatal mortality rate is higher in populations with low socio-economic status. The need of the hour is to assess the gains, analyse critically the failures, prioritize the resources and define the policies with limited short term objectives but with long time gains within a certain period. The immediate national priority is a reduction in perinatal mortality within the time frame for 2007 and 2010 (Shah *et al* 2000). A substantial proportion of foetal and neonatal morbidity and mortality in developing countries could be prevented through wider implementation of proven, affordable interventions during pregnancy, delivery and early post partum and neonatal periods (Stadt *et al* 2003).

Prevalence of NTDs shows wide variaton of geographic location, both within and between countries. Also the distribution of the types of NTDs can vary between regions (Berry *et al* 1999). For this purpose it would be useful to collect prospective data from representative areas of the country on regular basis particularly since temporal (transitory) variation in the prevalence of NTDs has been reported from other parts of the world.

Annually, world wide, an estimated 300,000 or more babies are born with spina bifida and anencephaly (Botto, 1999). Foetal deaths and still births are also more common in NTDs affected pregnancies. Nearly 2500 to 3000 children are born with these defects each year in the United States and these defects usually result in an estimated 1500 still births or pregnancy termination (England and Mills, 2001).

Recurrence of NTDs in families is possible and can occur at a rate as high as 35 per cent. The highest incidence of anencephaly can be found in Ireland, Scotland, Wales, Egypt and New Zealand while the lowest in Japan. The highest prevalence rate for spina bifida is seen among the people of Celtic origin. Females are predominantly affected which account for 60-70 per cent of children with spina bifida (Ellenbogen, 2002). Health care costs of persons with spina bifida in the United States exceed $200 million per year (CDC, 2003).

The Philippine Birth Defects Registry Project from 1999-2000 listed anencephaly and other similar malformations as the 6th most common birth defect. The rate was computed as 2.2 per 10,000 births (Padilla *et al* 2003). The total NTD incidence in the UK and Ireland (where it has been historically higher than the UK) in 1980 was 4.5 per 1000, and has fallen to 1.5 per 1000 in the 1990s, (0.66/100 in 1997 in the UK excluding Ireland (Morris and Wald,1999). However, rates of 13.8 per 1000 NTDs have been recently reported from northern China (Li *et al* 2006). Rates of anencephaly in Asia have been reported to be comparable to those of other regions outside the British Isles, while spina bifida prevalence was lower in Asia than elsewhere (Little and Elwood, 1991). However NTDs prevalence in northern China has been reported to be among the highest in the world (Moore *et al* 1997).

In general, the prevalence in northern states namely Punjab, Haryana, Delhi, Rajasthan, U.P and Bihar has been much higher (3.9-9.01 per 1000) compared to eastern, western and southern parts of the country (Verma, 2000). One exception of this statement is the reported higher incidence of NTDs from Davangere in Karnataka where the prevalence has been attributed to consanguinity (blood relationship) (Kulkarne *et al* 1989).

According to Suresh (2005) with 1.2 lakh births registered in Chennai alone every year, 2.7 per 1000 live births NTDs rate translates to nearly 300 children born with an abnormality. In Tamilnadu, Salem has been found to have a prevalence rate of 4 per 1000 live births.

NTDs may also be higher among multiple births and with lower birth weight (Whiteman *et al* 2000). The higher reported incidence of lower gestational age at delivery is often because of the NTDs (Rasmussen *et al* 2001). One investigation reported increased risk of encephalocele but not anencephaly or spina bifida with macrosomia (new born greater than 4000g of birth weight) (Waller *et al* 2001), while another found no association between large for gestational age and anencephaly, spina bifida or encephalocele (Lapunzina *et al* 2002).

Sex of the infant influences the risk for NTDs. Females are more likely to have anencephaly and spina bifida than males, with the difference greater for spina bifida. This preponderance among females appears to be influenced by the presence of additional birth defects, geographical area and other factors (Lary and Paulozzi, 2001). Potential explanations for the preponderance among females include differences between the sexes in embryonic development, susceptibility to teratogenic insult and spontaneous abortion rates (Little and Elwood , 1991).

The NTDs occur mainly due to maternal factors like excessive alcohol intake, maternal diabetes, obesity (Shaw *et al* 2003), environmental factors like use of some medications for treating epilepsy or acne (Brei, 2002), presence of MTHFR 677C>T variant depress erythrocyte folate status (Relton *et al* 2004) and dietary factors like poor nutrition, especially diet deficient in folic acid (CDC, 1995). The frequency of NTDs among spontaneously aborted foetuses is ten fold higher than the rate of NTDs at birth (Byrne and Warburton, 1986).

Though the etiology of NTDs is multi-factorial, there have been many studies highlighting the role of increasing maternal folate levels in the prevention of NTDs. Reports show that an estimated 50-70 per cent of these birth defects could be prevented with adequate folic acid intake (American Academy of Pediatrics, 1999). There are also findings that folic acid is also protective against atrial and ventricular septal defects, limb deformities, urologic anomalies, omphalocele and cleft lip or cleft palate (McDonald *et al* 2003).

A study in Metro Manila among pregnant women showed that 12.4 per cent and 43.5 per cent were folate deficient based on RBC folate and serum folate levels respectively. The prevalence of folate deficiency based on RBC folate levels was found to be higher in pregnant women in the first trimester compared to those in the second or third trimester. This finding suggests that a significant number of subjects entered pregnancy with insufficient folate stores in their bodies. The lower prevalence of folate deficiency among pregnant women in the second and third trimester may be due to prenatal supplement use. The study also reported that maternal diet was found to meet only 33.7 per cent of the recommended daily allowance for folate (Cheong *et al* 2003).

Strategies to achieve adequate levels of folic acid include, increased intake of folate-rich foods, dietary folic acid supplementation and folic acid fortification of food. Increasing the intake of foods rich in folate was shown to be a relatively ineffective way of increasing RBC folate levels compared with equivalent consumption of folic acid-fortified food since the synthetic form has better bioavailability (McNulty *et al* 2000). Only around 50 per cent of food folate is absorbed by the body while about 85 per cent of folic acid in fortified foods and 100 per cent of folic acid in vitamin supplements is absorbed. This shows that dietary folic acid or folate may not be adequate in the maximal protection against NTDs (Green, 2002).

Although adequate folate consumption from food was shown to have a protective effect against NTD affected pregnancies, it should be coupled with intake of folic acid supplements (Frey and Hauser, 2003). Dietary supplies of folic acid are in the polyglutamate form and are converted in the wall of the small intestine to the monoglutamate form before being absorbed into the blood stream. Folic acid is synthesised by intestinal bacteria in the large intestine, and absorption occurs in the upper part of the small intestine and is stored in the liver (Bronstrup and Anja, 1998). The effect of thermal processing on folate bioavailability depends to a great extent on the form of folate present in food. Availability of folate from food is also affected by inhibitory compounds known as conjugase inhibitors which prevent the digestion of folate, which is necessary for folate absorption (Brody, 1991).

One of the newly emerging areas in the field of clinical genetics is the concept of primary prevention. The prevention of the birth of an affected child prior to its occurrence in any family would be secondary. It requires targeting of preventive measures to an entire population or to high-risk individuals if the latter can be identified by suitable screening strategies. Two feasible approaches for achieving this include, screening of maternal serum alpha-fetoprotein (MSAFP) and to identify the presence of open NTDs in foetus in uterus at 16^{th} and 18^{th} week of gestation.

One of the most remarkable developments in the field of teratogenesis during last two decades has been the demonstration of efficacy of periconceptional folic acid supplementation in the prevention of NTDs. This has opened the avenue for primary prevention of NTDs except for the fact that most human pregnancies are neither pre-planned nor such compliance on mass scale appears to be feasible.

The evidence that periconceptional supplementation of folic acid may prevent the occurrence of NTDs has raised the hope of the primary prevention of NTDs in the population at large. However since pregnancies are not pre-planned, it cannot be feasible to start folic acid supplementation prior to conception for all pregnancies. Also, the compliance of such intake may not be assured. An alternative could be to carry out extensive public health education to promote greater consumption of natural foods rich in folate, but this approach too is likely to be limited by the socio-economic status of the population at large. To overcome these constraints, it has been suggested to fortify commonly used foods, such as breakfast cereals and bread as in the western countries, so that the daily intake of folic acid can be increased to effective levels in all women in the reproductive age group.

Many women know about folic acid but do not take it pre conceptionally. Women may associate folic acid with pregnancy and less with pre pregnancy. Greater emphasis is therefore necessary on periconceptional use to improve folic acid uptake. So focusing on less affluent women for folic acid promotion by general practitioners, primary care professionals and nutritionists is essential to overcome birth defects. With this background the present study entitled "Neural Tube Defects (NTDs) and the effect of counseling and folic acid supplementation" was undertaken with the following objectives to

- Study the prevalence of NTDs in Erode, a town in Tamil Nadu
- Study the possible influence of maternal factors on NTDs and the problems faced by the pregnant mothers of NTD affected pregnancies
- Counseling women planning pregnancy to prevent the occurrence of NTDs and
- Evaluate the efficacy of periconceptional supplementation of folate alone as well as in combination with multivitamin or iron in preventing the recurrence of NTDs.