CHAPTER-II
REVIEW OF THE RELATED LITERATURE

The Review of related literature is an essential aspect of the research project. Every research should be based on relevant thinking and proper planning and procedure, otherwise it becomes an isolated entity bearing at best accidental relevance to what has been before. The findings of earlier experiments encourage the researcher to give importance to useful projects in research and also enable the researcher to avoid the past mistakes or defects in the procedure. This chapter is devoted to review of available literature relevant to the present study.

2.1 Zinc:

Zinc is essential trace element for all forms of life. Clinical zinc deficiency in humans was first described in 1961, when the consumption of diets with low zinc bioavailability due to high phytic acid content, was found ‘associated with nutritional dwarfism’ especially in developing countries (Prasad et al., 1961).

2.1.1 Functions:

Zinc is an essential component of several enzymes in human body e.g. carbonic anhydrase, alchohal dehydrogenase alkaline phosphatase, carboxypeptidase, superoxide dimutase (Prasad, 1985). The metal has also been found to be essential component of both DNA and RNA polymerases as well as associated with variety of hormonal activities, including thymic hormones, glucagon, insulin growth harmone and sex hormones (Smith et al., 1989). Further more, zinc is required for normal brain development, (Sandstead et al., 1985) antiviral, antibacterial, antifungal, and anticancer properties and has
been found to maintain normal levels of vitamin A in serum (Prasad, 1985).

Zinc is a critical nutrient for central nervous system (CNS) development, which occurs during pre- and postnatal life, for example: 1) zinc-dependent enzymes are involved in critical cell replication processes necessary for brain growth, 2) zinc-finger proteins provide brain structure and are important for neurotransmission, and 3) zinc-dependent neurotransmitters are involved in brain memory function. In addition, zinc is involved in extra-CNS metabolic processes that ultimately affect CNS function, including hormone transport, receptor binding and metabolism, and neurotransmitter precursor production (Golub et al., 1995). Zinc deficiency causes poor growth, loss of appetite and hypogeuria in young malnourished children Zinc is also believed to be important for proper fetal growth and development (Apgar, 1968).

2.1.2 Absorption and metabolism:

Absorption of zinc occurs in the duodenum and in proximal small intestine. The percentage of dietary zinc absorbed varies from 20 percent to 80 percent. Absorption depends partly on the existing nutritional status and partly on the level of intake. Zinc from animal sources is generally better absorbed than that from plant products. This is due to the phytate content of plants. Phytate binds with zinc in the intestinal lumen and making it unavailable. Fibre also exerts a same effect (Henkin, 1978).

2.1.3 Deficiency:

Evidences suggest that zinc deficiency is one of the important problems within the developed and developing countries. In 1991, a
report was published which emphasized the importance of zinc and also indicated that in countries such as Iran, Egypt, Turkey, China, Yugoslavia, and Canada, due to low consumption of red meat, and high consumption of fiber, zinc deficiency was seen quiet often (Sanders et al., 1991). Human zinc deficiency was first reported from Middle Eastern countries. Prasad and collaborators in 1961 described a new syndrome of dwarfism, they postulated zinc deficiency was the causative factor of the lack of growth and sexual maturation. A similar syndrome was found in Egypt, where Egyptian showed decreased zinc levels in plasma, red blood cells and hair (Prasad et al., 1963).

Pregnant women are facing zinc deficiency more than the other groups, due to having fetus which needs zinc for its proper growth (Shah et al., 2001). Higher age, lactation, alcoholism, and high consumption of iron, and folic acid, increase the risk of zinc deficiency (Burits et al., 1994 and Prasad et al., 1998). Other researches have shown that the fetus grown by zinc deficiency is end up with abnormalities in central nervous systems (Prasad, 1998 and Jamson, 1982). In an another study done on the zinc deficient pregnant women, it was indicated that congenital abnormalities, prolonged pregnancy, abnormal tasting sense, and other difficulties were seen in such subjects (Jameson, 1982). A separate study in 2001 indicated that using supplementary zinc materials by pregnant mother, increased newborn birth weight, and decreased the mortality rate (Osendarp et al., 2001).

Clinical signs of zinc deficiency include acrodermatitis (Moynahan, 1976), low immunity, diarrhoea (Sazawal, 1995) and poor healing as well as stunting, hypogonadism (Simmer, 1984), teratology (Hambidge, 1985), abortion (Jameson, 1989) and other abnormalities
of pregnancy (Cherry, 1989). In addition intrauterine growth retardation, prolonged labour, abnormal deliveries and vaginal bleeding (Jameson, 1976). An increased incidence of difficult and prolonged labour, haemorrhages, uterine dystocia had also been documented in female rats (Apgar, 1968) and Rhesus Monkeys (Golub et al., 1984) to whom zinc deficient diet was fed throughout pregnancy.

Maternal mild-to-moderate zinc deficiency has been associated with increased risk of a variety of maternal and fetal complications of labour and delivery (Mameesh et al., 1985, McMichael et al., 1982, Mukherjee et al., 1984, Hunt et al., 1985, Cherry et al., 1989 and Mohamed et al., 1989. These can be categorized into 1) abnormalities in labour and delivery, 2) maternal morbidity during pregnancy and the puerperium, and 3) perinatal morbidity. These associations likely reflect the role of zinc in maintaining immunocompetence, cell membrane integrity, prostaglandin synthesis and function, and estrogen-dependent gene expression. Inadequate zinc during prenatal period has also been particularly linked with low birth weight infants, pre-eclampsia and variety of congenital malformations (Jameson et al., 1989).

Ward et al., (1985) studied a clear correlation between low placental zinc status with intrauterine growth retardation. They also found, the lighter the birth weight and the smaller the head circumference at birth had related to inadequate central nervous system function.

Hurley (1969) observed that zinc deficiency in rats resulted in extreme retardation of growth, congenital malformations abnormal hair and dermal lesions as well as lesions in both testes and oesophagus.
2.1.4 Prevalence of maternal zinc deficiency in India and in Abroad:

2.1.4.1 Prevalence of maternal zinc deficiency in abroad:

On the bases of intake data from several published studies, it has been estimated that 32 per cent of pregnant women worldwide may have zinc deficiency (www. Pediatriconall.com)

Population level analysis from food balance sheet had estimated that 21 percent of the world’s population is at the risk of zinc deficiency (Brown, 2004). In spite of proven benefits of adequate zinc nutrition, approximately, 2 billion people are still remaining at the risk of zinc deficiency (www.izincg.org).

Salami et al., (2004) found in Iran 49 % prevalence of zinc deficiency in pregnant women. Mean serum zinc concentration in Kenyan mothers was found to be 63.6 mcg/dl with a zinc deficiency prevalence of 52.2 %. Controlling for infection reduced prevalence to 47.5 %. Prevalence of zinc deficiency was severe with severity of anemia. Zinc deficiency was more prevalent among pregnant mothers (68.7%) than non-pregnant mothers (49.9%). Mean zinc concentration decreased by 1.79 mcg/dl per month with increase in gestation age (Mwaniki et al., 1999).

Using estimated usual intakes reported in the literature (Parr, 1996) and the estimated distribution of zinc required by women to meet their normative needs during pregnancy, Caulfield et al., (1998) have derived that 82 % of the pregnant women worldwide are likely to have inadequate usual intakes of zinc. In yet another observation, Caulfield et al., (1999) have reported that 60 % of pregnant women from an impoverished area in Lima, Peru were found to have serum zinc
concentrations less than 9.18 mmol/L indicating some degree of maternal zinc deficiency.

2.1.4.2 Prevalence of maternal zinc deficiency in India:

Pathak et al., (2003) observed that almost more than 80 percent of India’s population being vegetarian are found to be zinc deficient. In a rural block of Haryana state, India Pathak et al. (2008) studied 61.1 mcg/dL Mean serum Zinc level indicating 64.6% prevalence of zinc deficiency during pregnancy.

A community based cross sectional survey, conducted in six villages of a rural area of district Faridabad in Haryana state, India during Nov 2000 and Oct 2001 reported 73.5% prevalence of zinc deficiency in pregnant women (Pathak et al., 2004).

2.1.5 Consequences of maternal zinc deficiency on pregnancy outcomes:

Severe maternal zinc deficiency has been associated with spontaneous abortion and congenital malformations, whereas milder forms of zinc deficiency have been associated with low birth weight (LBW), intrauterine growth retardation, and preterm delivery. Importantly, milder forms of zinc deficiency have also been related to complications of labour and delivery, including prolonged or inefficient first-stage labour and protracted second-stage labour, premature rupture of membranes (PROM), and the need for assisted or operative delivery. These complications in turn impair maternal and perinatal health because they lead to increased risk of maternal lacerations, high blood loss, maternal infections, fetal distress, stillbirth, neonatal asphyxia (low Apgar scores), respiratory distress, and neonatal sepsis (Jameson, 1993)).
2.1.5.1 Fetal growth:

Women are at increased risk of zinc deficiency during pregnancy (Swanson et al., 1987) and maternal zinc deficiency has been associated with poor fetal growth in animal and human populations (Swanson et al., 1987 and Apgar et al., 1985).

Studies in India as well as abroad indicated associations between maternal serum zinc concentration and fetal growth (expressed in birth weight). Garg et al., (1995) supplemented 106 Indian mothers with 45 mg Zn/d, and observed a 300–800 g difference in birth weight to control group of 60 mothers.

Goldenberg et al., (1995) reported 580 low-income Alabaman women with low serum zinc concentrations at entry into prenatal care were randomly assigned to receive 25 mg Zn/d or placebo. Infants born to zinc supplemented women weighed 126 g more at birth, were 0.6 cm longer, and had 0.4-cm larger head circumferences than infants born to mothers receiving the placebo.

Several zinc supplementation trials reported differences in other indicators of fetal growth. Simmer et al., (1991) and Garg et al., (1993) reported 26–90% reductions in the incidence of small-for-gestational age infants and Goldenberg et al., (1995) reported a 37% reduction in the overall incidence of very LBW (<1500 g) infants associated with zinc supplementation and a 62% reduction in very LBW among nonobese women. Kynast et al., (1986) and Goldenberg et al., (1995) reported that babies born to zinc supplemented mothers were 0.5 cm longer, whereas Mohamed et al., (1989) observed babies in the zinc supplemented group to be 0.2 cm shorter than control infants at birth. Zinc-supplemented women in Alabama had infants with 0.2 cm greater
arm and femur lengths, and 1–2 mm greater triceps and subscapular skinfold thicknesses than control group (Tamura et al., 1996).

2.1.5.2 Length of gestation:

Ross et al., (1985), Cherry et al., (1989), Kynast et al., (1986), Garg et al., (1993) and Goldenberg et al., (1995) reported maternal zinc supplementation lengthened the average duration of pregnancy by 0.3–1.0. Jamson, 1993 and Goldenberg, 1995 were observed 66–85% reductions in the incidence of preterm delivery. These results indicate a consistent, effect of zinc supplementation on the average duration of pregnancy that likely explains most or all of the improvements in size at birth. Thus, it may be true that increases in average birth weight observed with zinc supplementation occur not from improvements in fetal growth rates, but rather from prolongation of time spent in uterus. However, it is also clear that maternal zinc supplementation likely results in more sizable reductions in preterm delivery, particularly in those deliveries occurring before 32 wk gestation. Finally, Kynast and Saling (1986) reported an 80% reduction in the variance of gestational age at delivery, suggesting that the incidence of preterm delivery (delivery at < 37 wk) diminished with maternal zinc supplementation.

2.1.5.3 Neurobehavioral development:

Because of the important role of zinc in CNS function, it is clear that maternal and early infant zinc deficiencies are likely to adversely affect fetal and infant neurologic and behavioral development (Figure2.1). Kirksey et al., (1991) observed positive associations between maternal serum zinc concentrations during pregnancy and the developmental status of Egyptian newborns assessed by using the Brazelton Neonatal Behavioral Assessment Scale (Brazelton, 1984).
Subsequently, Kirksey et al., (1994) reported that positive associations were still observed between maternal zinc status during pregnancy and infant developmental status when assessed at 6 month of age by using the Bayley Scales of Infant Development (Baylay, 1969).

**Figure 2.1 Consequences of maternal zinc deficiency on birth outcomes and maternal and neonatal health (Caulifield et al., 1998).**
2.1.5.4 Labour and delivery complications:

The relation between maternal zinc nutriture and parturition was first described by Apgar (1968). Female rats fed 1-mg Zn/g diet throughout pregnancy experienced difficult and prolonged labours as compared with control and pair-fed animals. Observational studies in humans have associated low maternal serum zinc concentrations during pregnancy or at delivery with PROM, placental abruption, inefficient uterine contractions, and prolonged or nonprogressive labour, all of which can result in cesarean delivery. Maternal zinc deficiency has been associated with a 3.5–7.0-fold increased risk for PROM (Sikorski et al., 1990 and Scholl et al., 1993) a 2.8-fold increased risk of placental abruption (Kynast et al., 1986), a 2–5-fold increased risk for a prolonged first-stage labour (both latent and active phases), a 9-fold increased risk for a protracted second-stage labour, and a 4-fold increased risk for having a labour lasting > 20 h (Lazebnik et al., 1988 and Dura et al., 1984). Lazebnik et al., (1988) also found nearly a 5-fold increased risk of third degree lacerations associated with poor maternal zinc status. The results of Simmer et al., (1991) suggested that supplementing pregnant women with zinc can lower the risk of such complications of labour and delivery; they found 60–80% reductions in the incidences of induction and caesarean delivery associated with zinc supplementation. Again, these studies had design flaws and were not conducted in zinc-deficient populations.

Prolonged labour as well as other complications of labour and delivery increase risk to both the mother and baby (Chelmow et al., 1993). Few studies have examined maternal and perinatal morbidity associated with zinc deficiency. Mukherjee et al., (1984) found that,
overall, women with low serum zinc concentrations were 20–50% more likely to suffer from a variety of maternal and fetal complications of labour and delivery, including fetal distress and maternal infections. McMichael et al., (1982) reported a 1–2-fold increased risk of perinatal morbidities (respiratory distress, fetal distress, or presence of meconium) associated with low maternal zinc status. In their quasi-experimental study, Kynast et al., (1986) found that zinc supplementation was associated with a 60% reduction in vaginal bleeding, placental abruption, and maternal haemorrhage. However, Mahomed et al., (1989), in a small supplementation trial, found no such effects.

2.1.5.5 Postnatal outcomes:

Maternal zinc deficiency during pregnancy may result in problems for the infant during postnatal life. Effects from maternal zinc deficiency on growth and development in utero likely influence growth and development during neonatal life and beyond (Figure 2.2). Zinc is also important for the transfer of many substances to target tissues. Among these substances are 2 with recognized importance for child survival: immunologic factors and vitamin A (Shankar et al., and Christian et al., 1998). The interrelations between maternal zinc deficiency, infant vitamin A status, immunologic development, and postnatal health and survival are shown in Figure 2.3.

2.1.5.5.1 Immunologic development:

A major determinant of postnatal survival is the ability of the infant to resist infection and respiratory and diarrheal disease. As discussed by Shankar and Prasad (1998), perinatal zinc deficiency can result in poor development of natural immunity and decreased
acquisition of maternal antibodies.

2.1.5.5.2 Vitamin A status:

The relation between zinc and vitamin A status is well known (Solomans et al., 1980). As reviewed by Christian and West (1998), previous studies provided some indication that maternal zinc deficiency may influence newborn vitamin A status. Mild gestational zinc deficiency in pregnant rhesus monkeys was associated with lower maternal serum retinol and a lack of association between serum retinol and retinol binding protein (Baly et al., 1984).

Figure 2.2 Interrelations between maternal zinc deficiency and pre and postnatal growth and development (Caulifield et al., 1998).

In a related study, Peters et al., (1986) found reduced vitamin A concentrations in fetuses of mothers fed a diet throughout pregnancy that was marginal in zinc, but replete in vitamin A. Furthermore, vitamin A supplementation of these mothers did not overcome the deleterious effects of zinc deficiency on maternal transfer of vitamin A to the fetus.
2.2.5.5.3 Postnatal growth:

The effect of zinc deficiency on growth has been well studied. Both animal and human studies provide evidence for the crucial role of zinc in supporting adequate growth, and results from supplementation trials in preschool and school-aged children support the public health importance of zinc deficiency in growth faltering during infancy and childhood (Allen, 1994). The work of Golub et al., (1984) in rhesus monkeys suggested that growth faltering associated with maternal zinc deficiency during fetal life lasts throughout infancy.

2.1.6 Zinc supplementation in pregnancy:

Goldenberg et al., (1995) concluded that zinc supplementation in women with relatively low plasma zinc concentration in early pregnancy, was associated with greater infant birth weight and head circumference.
Osendarp et al., (2001) in a field study with in poor Bangladeshi communities, analysed that maternal zinc supplementation was associated with reduced risk of acute diarrhea, dysentery and impetigo.

Halsted et al., (1973) reported that severe zinc deficiency can cause fetal malformation which can be reversed by supplementation with oral zinc in pregnancy.

2.2 **Vitamin A:**

Vitamin A occurs only in foods of animal origin. Beta carotene is the common precursor of vitamin A and occurs in foods such as carrots, dark green leafy vegetables (Williams, 1991), etc.

2.2.1 **Functions:**

Vitamin A plays many physiological processes, such as, normal functioning of retina, growth, immunity, epithelial tissue maintenance as well as necessary in embryonic development, reproduction and bone growth. It is also essential throughout the life span, particularly during periods when cell proliferate and differentiate rapidly i.e. during pregnancy (Strobel, 2007).

2.2.2 **Deficiency:**

Dannecker et al., (1991) found that Vitamin A deficiency was strongly associated with night blindness, depressed immune function and higher morbidity and mortality due to infectious diseases such as diarrhea, measles and respiratory infections.

Price (2006) reported that Vitamin A deficiency in rats, caused prolong gestation period and difficult labour. Another research quoted by price showed that lack of vitamin A in the diet of pigs resulted in abortion and disturbances in ovulation, leading to sterility.
World health Organisation indicated that 231 million children in more than 90 countries are affected clinically by vitamin A deficiency (Gosstein et al., 1994).

2.2.3 Prevalence of maternal vitamin A deficiency:

2.2.3.1 Prevalence of maternal vitamin A deficiency in abroad:

Li et al., (2002) found in China that maternal vitamin A deficiency (MVAD) in pregnancy caused learning and memory impairment of adult offspring.

Grippo et al., (1991) observed that the main consequence of poor vitamin A supply during pregnancy was associated with vitamin A status at birth and in the next few months.

Prevalence of night blindness during pregnancy and lactation was prevalent in the rural teral of Nepal (Katz et al., 1995).

In an Indonesian trial the imputed prevalence of vitamin A deficiency was 34.2%, higher than in any of the other included trials (Humphrey et al., 1998).

Samba et al., (1998) conducted a prospective cohort study of 377 HIV-negative women and their infants in Blantyre, Malawi. Serum vitamin A levels were measured during the second or third trimester of pregnancy and infants were followed during the first year of age. Mothers of infants who died had lower serum vitamin A levels during pregnancy (0.74 ± 0.13/mol/l) compared with mothers of infants who did not die (1.02 ± 0.03/mol/l) ($p = 0.055$). Infants born to women whose vitamin A levels were in the lowest quartile (< 0.32 pmol/l) had three-fold higher likelihood of mortality than infants born to women whose vitamin A levels were in the higher quartiles ($p < 0.03$). These
results suggested that maternal vitamin A deficiency during pregnancy contributed to higher infant mortality rate.

2.2.3.2 Prevalence of maternal vitamin A deficiency in India:

Dabi et al., (2006) observed in Jodhpur that clinical signs and symptoms of vitamin A deficiency (night blindness, conjunctival xerosis, Bitot’s spots, corneal xerosis) and low levels of serum vitamin A were commonly seen almost twice in mothers who delivered IUGR newborns. At least 24% mothers delivered IUGR babies and 10% mothers delivered appropriate for gestational age babies, had one or the other clinical sign of hypovitaminosis A. Clinical signs of vitamin A deficiency correlated well with serum vitamin A levels. Severe deficiency of vitamin A (serum vitamin A < 10 mg/dl) was observed in 4% mothers who delivered IUGR babies, while it was not observed in mothers of appropriate for gestational age babies. Increasing serum vitamin A levels were associated with higher birth weight when mothers had BMI of more than 18 kg/m².

The study suggested in Hyderabad that subclinical vitamin A deficiency was a problem during the third trimester of pregnancy. Serum concentration of retinol <20 μg/dl appeared to indicate a deficient status, and was associated with an increased risk of preterm delivery and maternal anaemia (Radhika et al., 2002).

In a multicentre study Toteja et al. (2002) assessed the prevalence of night blindness among 6,633 pregnant women from 15 districts. The sampling methodology followed was a “30 cluster survey”. The highest prevalence of night blindness (19.62%) among pregnant women was observed in Dibrugarh and lowest (0.59 %) was in Bishnupur.
2.2.4 Vitamin A / β-carotene supplementation during pregnancy:

Malawi (2001) investigated the effects of vitamin A supplementation on treatment of anemia in pregnancy.

In a large study conducted in Nepal, West et al., (1999) examined the effects of vitamin A supplementation on the reduction of pregnancy-related and direct mortality occurring within 12 weeks post partum, including injury-related deaths. The study reported a reduction in mortality for all cases in the supplementation groups (40% in the vitamin A group and 49% in the β-carotene group). The combined effect of these two forms of supplementation was 44% reduction in pregnancy-related deaths.

Vitamin A supplementation proved to be most beneficial for reducing infant mortality, where the prevalence of vitamin A deficiency among pregnant women was at least 22% (Deeks et al., 2010).

2.3 Interactions between zinc and vitamin A:

Zinc deficiency is thought to be interfere with vitamin A metabolism in several ways:

Zinc deficiency results in decreased synthesis of retinol binding protein (RBP), which transports retinal through the circulation to tissues and also protects the organism against potential toxicity of retinal. Zinc deficiency results in decreased activity of the enzyme that release retinal from its storage form in the liver. Zinc is also required for the enzyme that converts retinol into retinal (Christian, 1998).

Zinc participates in the absorption, mobilization, transport, and metabolism of micronutrients, including vitamin A, most likely through its involvement in protein synthesis and cellular enzyme
functions. There is also an evidences that vitamin A affects zinc absorption and utilization. Thus, fluctuation in the status of one or both micronutrients may reasonably expect to alter the metabolism of the other, with functional consequences on the health of the individual (Christian and West, 1998). Two mechanisms are most often postulated to explain a potential dependence of vitamin A on zinc. One relates to a regulatory role of zinc on vitamin A transport mediated through protein synthesis (Mejia, 1986). Zinc deficiency can depress the synthesis of retinol-binding protein (RBP) in the liver and lead to lower concentrations of RBP in the plasma (Smith, 1974 and Smith et al., 1976).

The other postulated mechanism is an interaction between vitamin A and zinc is oxidative conversion of retinol to retinaldehyde (retinal), a critical step in the metabolic pathway of vitamin A, requires the action of a zinc-dependent retinol dehydrogenase enzyme (Huber et al., 1975 and Sundaresan et al., 1977).
2.3.1 Human Studies based on interaction of zinc and vitamin A:

Kozlowski et al., (1987) observed in 3–9-y-old American children with delayed cognition, a significantly lower serum vitamin A concentration in children with low serum zinc concentration than in children with higher circulating zinc concentrations. Mean serum zinc concentrations were lower in school-aged Bangladeshi children with serum retinol concentrations <0.7 µmol/L compared with those with concentrations > 0.7 µmol/L (Ahmed et al., 1993).

In a group of 24 American preterm infants (with birth weight < 2000 g), randomized intravenous zinc supplementation increased plasma retinol and RBP over changes observed in control subjects, suggesting that zinc may have enhanced hepatic release of vitamin A through increased RBP production (Hustead et al., 1988).

2.3.1.1 Human Studies based on interaction of zinc and Vitamin A during pregnancy:

In pregnant women Christian et al., (2001) found that zinc supplementation resulted in larger increase in plasma zinc in women receiving either Beta carotene or Vitamin A than in those receiving placebo.

Dijkhuizen et al., (2004) observed in Indonesia that supplementation with Beta-carotene and zinc but not with Beta-carotene alone, was effective in improving vitamin A status of both mothers and infants 6 months postpartum.

2.3.2 Animal studies based on the interaction of zinc and Vitamin A:

Mobarhan et al., (1992) experimented on rats and showed lower serum retinol and cellular hepatic RBP (cRBP) concentration in zinc-deficient rats compared with groups with adequate zinc intake.
Changes in vitamin A intake affect zinc absorption, status, and function. In situ experiments in vitamin-deficient chicks showed that zinc absorption was depressed not only throughout the small intestine (by 40%), but particularly in the ileum (by 57%) (Berzin et al., 1987).

Sklan et al., (1987) observed that administration of retinyl acetate increased ileal absorption of zinc nearly 3-fold. It was noted that experimental chicks manifested severe hypovitaminosis A and their body weight was 60% of that of the controls and they had secondary zinc deficiency. A dramatic decline in zinc absorption is likely to occur in severe vitamin A deficiency. In chicks fed a vitamin A–deficient diet, plasma zinc concentrations were lower and hepatic zinc concentrations were higher than vitamin A–adequate controls.

2.3.2.1 Animal Studies based on Interaction of zinc and Vitamin A in pregnancy:

Duncan et al., (1978) examined the singular and joint effects of maternal zinc and vitamin A deficiencies on vitamin A status and pregnancy outcomes in rats fed with 3 different concentrations of zinc and vitamin A, representing adequate, marginally deficient, and deficient dietary concentrations, respectively. Marginal and deficient intakes of either zinc or vitamin A in pregnant and fetal rats had lower plasma vitamin A concentrations compared with those receiving adequate intakes of each nutrient. However, plasma retinol was lowest in pregnant and fetal rats, fed with marginal to zinc deficient diet. There was also a tendency of increased hepatic vitamin A concentrations with decreased dietary zinc, presumably reflecting impaired mobilization. Effects were observed in reproductive health outcomes i.e affected implantation sites and increased malformed
fetuses with marginal and deficient intakes of either vitamin A or zinc, but the consequences were more severe with combined deficiencies. However, only marginal and deficient intakes of zinc caused both maternal and fetal weight to decline, raising concern that dietary restriction of zinc was responsible for changes in vitamin A status and pregnancy outcomes.

2.3.3 Zinc and Vitamin A interaction via the visual cycle:

Vitamin A and zinc interact during the conversion of retinol to retinal in the retina of the eye during the visual cycle (Wald et al., 1950), as well as in other tissues such as the liver and testes (Sundaresan et al., 1977). The zinc metalloenzyme ADH is required for this oxidative process. Retina is sensitive to zinc nutriture and that zinc deficiency can impair photoreceptor function by regulating ADH activity. Rhodopsin, a photosensitive pigment required for night vision, is synthesized from retinal and a membrane protein, opsin. In zinc deficiency the formation of 13-cis-retinal is reduced, causing a decrease in rhodopsin formation and rod photosensitivity that can lead to poor dark adaptation or night blindness (Huber et al., 1975).

2.3.4 Zinc and vitamin A interaction in disease states:

There may be an interaction between zinc and vitamin A in patients suffering from various pathologic conditions that severely compromise hepatic function such as alcoholic cirrhosis, cystic fibrosis, and idiopathic hemochromatosis (Solomons and Russell, 1980). The metabolism and transport of both zinc and vitamin A appear to be affected by chronic ethanol consumption and by the functional damage of hepatic cirrhosis. Impairment in dark adaptation in alcoholic cirrhosis is associated with deficiencies of zinc or vitamin A, or both (Patek et al., 1939 and McClaim et al., 1979).
Mean serum zinc and RBP concentrations were shown to be significantly lower in Nigerian cirrhotic patients with hypogonadism than in those without this condition. Liver cirrhosis can cause hypogonadism [which is also observed in zinc deficiency (Abdu et al., 1989)], possibly because of depressed activity of zinc-dependent ADH that can also lead to lower testicular metabolism of retinol (Sundaresan et al., 1977).

In alcoholics in Sri Lanka, serum concentrations of zinc and vitamin A were lower than in healthy control subjects (Atukorala et al., 1986). Serum zinc and vitamin A were positively correlated, but only in those with cirrhosis. The presence of a zinc–vitamin A interaction was also explored in patients with cystic fibrosis, rheumatoid arthritis, and cancer of the larynx. Navarro and Desquilbet (1981) found that RBP was significantly lower in patients with cystic fibrosis and was positively correlated with plasma vitamin A concentrations.

2.3.5 **Supplementation of zinc and vitamin A/ β-carotene together during pregnancy:**

Dijkhuizen et al. (2004) observed in Indonesia that supplementation with β-carotene and zinc but not with β-carotene alone, was effective in improving vitamin A status of both mothers and infants 6 months postpartum.

In pregnant women Christian et al., (2001) found that zinc supplementation resulted in larger increase in plasma zinc in women receiving either β-carotene or Vitamin A than in those receiving placebo.

2.4 **Human Pregnancy:**

Pregnancy is the carrying of one or more offspring, known as a fetus or embryo, inside the womb of a female. In a pregnancy, there
can be multiple gestations, as in the case of twins or triplets. Childbirth usually occurs about 38 weeks after conception; i.e., approximately 40 weeks from the last normal menstrual period (LNMP) in humans. The World Health Organization defines normal term for delivery as between 37 weeks and 42 weeks (WHO). Pregnancy occurs when a sperm produced by a male, fuses with an ovum produced by a female.

**Figure 2.5 How pregnancy occurs:**

Source: “How pregnancy occurs” (Gynaeonline.com)

2.4.1 Progression:

**Figure 2.6 Prenatal development**

Source: “Prenatal Development” (Mikael Haggstrom, 2010).
2.4.2 Initiation:

Pregnancy occurs as the result of the female gamete or oocyte merging with the male gamete, spermatozoon, in a process referred to, in medicine, as "fertilization", or more commonly known as "conception". After the point of fertilization, it is referred to as a zygote or fertilized egg. The fusion of male and female gametes usually occurs through the act of sexual intercourse, resulting in spontaneous pregnancy. However, the advent of artificial insemination and in vitro fertilisation have also made achieving pregnancy possible in cases where sexual intercourse does not result in fertilization (e.g., through choice or male/female infertility)

Figure 2.7 Initial stages of Human Embryogenesis

Source: “The initial stages of Human Embryogenesis” (Larsen WJ, 1993).
2.4.3 Prenatal period:

Prenatal defines the period occurring "around the time of birth", specifically from 22 completed weeks (154 days) of gestation (the time when birth weight is normally 500 g) to 7 completed days after birth (WHO, 1999).

Legal regulations in different countries include gestation age beginning from 16 to 22 weeks (5 months) before birth.

2.4.4 Postnatal period:

The postnatal period begins immediately after the birth of a child and then extends for about six weeks. During this period, the mother's body returns to prepregnancy conditions as far as uterus size and hormone levels are concerned.

2.4.5 Duration:

The expected date of delivery (EDD) is 40 weeks counting from the first day of the last menstrual period (LMP), and birth usually occurs between 37 and 42 weeks. The actual pregnancy duration is typically 38 weeks after conception. Though pregnancy begins at conception, it is more convenient to date from the first day of a woman's last menstrual period, or from the date of conception if known. Starting from one of these dates, the expected date of delivery can be calculated. Forty weeks is 9 months and 6 days, which forms the basis of Naegele's rule for estimating date of delivery (Norwitz and Errol, 1939).

Fewer than 5% of births occur on the due date; 50% of births are within a week of the due date, and almost 90% within 2 weeks. It is much more useful and accurate, therefore, to consider a range of due
dates, rather than one specific day, with some online due date calculators providing this information (Tracy, 2005).

2.4.6 Terms of delivery:

Pregnancy is considered "at term" when gestation attains 37 complete weeks but is less than 42 (between 259 and 294 days since LMP). Events before completion of 37 weeks (259 days) are considered preterm; from week 42 (294 days) events are considered postterm. When a pregnancy exceeds 42 weeks (294 days), the risk of complications for woman and fetus increases significantly. As such, obstetricians usually prefer to induce labour, in an uncomplicated pregnancy, at some stage between 41 and 42 weeks (Stovall and Thomas, 2004).

Recent medical literature prefers the terminology preterm and postterm to premature and postmature. Preterm and postterm are unambiguously defined as above, whereas premature and postmature have historical meaning and relate more to the infant's size and state of development rather than to the stage of pregnancy (Rimawi, 2006)

2.4.7 Childbirth:

Childbirth is the process whereby an infant is born. It is considered by many to be the beginning of the infant's life, and age is defined relative to this event in most cultures.

A woman is considered to be in labour when she begins experiencing regular uterine contractions, accompanied by changes of her cervix — primarily effacement and dilation. While childbirth is widely experienced as painful, some women do report painless labours, while others find that concentrating on the birth helps to quicken labour and lessen the sensations. Most births are successful vaginal
births, but sometimes complications arise and a woman may undergo a cesarean section.

2.4.8 Diagnosis:

The beginning of pregnancy may be detected in a number of different ways, either by a pregnant woman without medical testing, or by using medical tests with or without the assistance of a medical professional.

2.4.9 Early signs and symptoms:

Most pregnant women experience a number of symptoms, which can signify pregnancy. The symptoms can include

- Nausea and vomiting
- Excessive tiredness and fatigue
- Craving for certain foods not normally considered a favourite
- Frequent urination particularly during the night.

2.4.10 Early medical signs and symptoms:

A number of early medical signs are associated with pregnancy. These signs typically appear, if at all, within the first few weeks after conception. Although not all of these signs are universally present, nor are all of them diagnostic by themselves, taken together they make a presumptive diagnosis of pregnancy. These signs include

- The presence of human chorionic gonadotropin (hCG) in the blood and urine.
- Missed menstrual period
- Implantation bleeding that occurs at implantation of the embryo in the uterus during the third or fourth week after last menstrual period
- Increased basal body temperature sustained for over 2 weeks after ovulation
- Chadwick's sign (darkening of the cervix, vagina, and vulva), Goodell's sign (softening of the vaginal portion of the cervix)
- Hegar's sign (softening of the uterus isthmus).
- Pigmentation of linea alba – Linea nigra, (darkening of the skin in a midline of the abdomen, caused by hyperpigmentation resulting from hormonal changes, usually appearing around the middle of pregnancy.

2.4.11 Pregnancy Tests

Pregnancy detection can be accomplished using one or more various pregnancy tests, which detect hormones generated by the newly formed placenta. Clinical blood and urine tests can detect pregnancy 12 days after implantation, which is as early as 6 to 8 days after fertilization. Blood pregnancy tests are more accurate than urine tests. Home pregnancy tests are personal urine tests, which normally cannot detect a pregnancy until at least 12 to 15 days after fertilization. Both clinical and home tests can only detect the state of pregnancy, and cannot detect the date the embryo was conceived (Qasim et al., 2006).

2.4.11.1 Human Chorionic Gonadotropin Hormone Test

In the post-implantation phase, the blastocyst secretes a hormone named human chorionic gonadotropin, which in turn stimulates the corpus luteum in the woman's ovary to continue producing progesterone. This acts to maintain the lining of the uterus so that the embryo will continue to be nourished. The glands in the lining of the uterus will swell in response to the blastocyst, and capillaries will be
stimulated to grow in that region. This allows the blastocyst to receive vital nutrients from the woman.

Despite all the signs, some women may not realize they are pregnant until they are quite far along in their pregnancy. In some cases, a few women have not been aware of their pregnancy until they begin labour. This can be caused by many factors, including irregular periods (quite common in teenagers), certain medications (not related to conceiving children), and obese women who disregard their weight gain. Others may be in denial of their situation.

2.4.11.2 Sonograph:

An early sonograph can determine the age of the pregnancy fairly accurately. In practice, doctors typically express the age of a pregnancy (i.e., an "age" for an embryo) in terms of "menstrual date" based on the first day of a woman's last menstrual period, as the woman reports it. Unless a woman's recent sexual activity has been limited, she has been charting her cycles, or the conception is the result of some types of fertility treatment (such as IUI or IVF),

Diagnostic criteria are: Women who have menstrual cycles and are sexually active, a period delayed by a few days or weeks is suggestive of pregnancy; elevated B-hcG to around 100,000 mIU/mL by 10 weeks of gestation (Robinson et al., 1939).

2.4.12 Embryonic and fetal development

Prenatal development is divided into two primary biological stages. The first is the embryonic stage, which lasts for about two months. At this point, the fetal stage begins. At the beginning of the fetal stage, the risk of miscarriage decreases sharply, all major structures including hands, feet, head, brain, and other organs are
present, and they continue to grow and develop. When the fetal stage commences, a fetus is typically about 30 mm (1.2 inches) in length, and the heart can be seen beating via sonograph; the fetus bends the head, and also makes general movements and startles that involve the whole body (Prechtl and Heinz, 2007). Some fingerprint formation occurs from the beginning of the fetal stage (Zabinski and Mark, 2007).

Electrical brain activity is first detected between the 5th and 6th week of gestation, though this is still considered primitive neural activity rather than the beginning of conscious thought, something that develops much later in fetation. Synapses begin forming at 17 weeks, and at about week 28 begin multiply at a rapid pace which continues until 3–4 months after birth. It isn't until week 23 that the fetus can survive, albeit with major medical support, outside of the womb. It is not until then that the fetus possesses a sustainable human brain (Judy, 2006).

Figure 2.8 (A) Pregnancy progress week by week

a. Embryo at 4 weeks after fertilization
b. Fetus at 8 weeks after fertilization
c. Fetus at 18 weeks after fertilization
d. Fetus at 38 weeks after fertilization

Source: 3D Pregnancy, 2007
2.4.13 Physiology

Pregnancy is typically broken into three periods, or trimesters, each of about three months. While there are no hard and fast rules, these distinctions are useful in describing the changes that take place over time.

2.4.13.1 First trimester

Pregnancy is often defined as beginning when the developing embryo becomes implanted into the endometrial lining of a woman's uterus. Most pregnant women do not have any specific signs or symptoms of implantation, although it is not uncommon to experience minimal bleeding at implantation. Some women will also experience cramping during their first trimester. This is usually of no concern unless there is spotting or bleeding as well. After implantation the uterine endometrium is called the decidua. The placenta, which is
formed partly from the decidua and partly from outer layers of the embryo, is responsible for transport of nutrients and oxygen to, and removal of waste products from the fetus. The umbilical cord is the connecting cord from the embryo or fetus to the placenta. The developing embryo undergoes tremendous growth and changes during the process of fetal development.

2.4.13.2 Second trimester

Weeks 13 to 28 of the pregnancy are called the second trimester. Most women feel more energized in this period, and begin to put on weight as the symptoms of morning sickness subside and eventually fade away.

In the 20th week the uterus, the muscular organ that holds the developing fetus, can expand up to 20 times its normal size during pregnancy. Although the fetus begins to move and takes a recognizable human shape during the first trimester, it is not until the second trimester that movement of the fetus, often referred to as "quickening", can be felt. This typically happens in the fourth month, more specifically in the 20th to 21st week, or by the 19th week if the woman has been pregnant before. However, it is not uncommon for some women not to feel the fetus move until much later. The placenta fully functions at this time and the fetus makes insulin and urinates. The reproductive organs distinguish the fetus as male or female.

2.4.13.3 Third trimester

Final weight gain takes place, which is the most weight gain throughout the pregnancy. The fetus will be growing the most rapidly during this stage, gaining up to 28 g per day. The woman's belly will transform in shape as the belly drops due to the fetus turning in a
downward position ready for birth. During the second trimester, the woman's belly would have been very upright, whereas in the third trimester it will drop down quite low, and the woman will be able to lift her belly up and down. The fetus begins to move regularly, and is felt by the woman. Fetal movement can become quite strong and be disruptive to the woman. The woman's navel will sometimes become convex, "popping" out, due to her expanding abdomen. This period of her pregnancy can be uncomfortable, causing symptoms like weak bladder control and backache. Movement of the fetus becomes stronger and more frequent and via improved brain, eye, and muscle function the fetus is prepared for ex utero viability. The woman can feel the fetus "rolling" and it may cause pain or discomfort when it is near the woman's ribs and spine.

There is head engagement in the third trimester, that is, the fetal head descends into the pelvic cavity so that only a small part (or nothing) of it can be felt abdominally.

It is during this time that a baby born prematurely may survive. The use of modern medical intensive care technology has greatly increased the probability of premature babies surviving, and has pushed back the boundary of viability to much earlier dates than would be possible without assistance (Lams et al., 2008). In spite of these developments, premature birth remains a major threat to the fetus, and may result in ill-health in later life, even if the baby survives.

2.4.14 Weight gain

Caloric intake must be increased to ensure proper development of the fetus. The amount of weight gained during pregnancy varies among women. The National Health Service recommends that overall
weight gain during the 9 month period for women who start pregnancy with normal weight be 10 to 12.5 kilograms (22–28 lb) (Klusmann et al., 2005). During pregnancy, insufficient weight gain can compromise the health of the fetus. Likewise, excessive weight gain can pose risks to both the woman and the fetus.

2.4.15 Nutrition

A balanced, nutritious diet is an important aspect of a healthy pregnancy. Eating a healthy diet, balancing carbohydrates, fat, and proteins, and eating a variety of fruits and vegetables, usually ensures good nutrition (Stevenson et al., 2000).

Several micronutrients are important for the health of the developing fetus, especially in areas of the world where insufficient nutrition is prevalent (Haider and Bhutta, 2006). Iron, Zinc folic acid vitamin A, D and calcium, required for normal Hb, reproductive functions, cell formation and bone development, may need supplementation during pregnancy (Basile et al., 2007).

2.4.16 Complications

Each year, according to the WHO, ill-health as a result of pregnancy is experienced (sometimes permanently) by more than 20 million women around the world. Furthermore, the "lives of eight million women are threatened, and more than 500,000 women are estimated to have died in 1995 as a result of causes related to pregnancy and childbirth" (WHO, 2009).

The following are complications that may occur during pregnancy:

**Back pain.** A particularly common complaint in the third trimester when the patient's center of gravity has shifted.
**Constipation.** A complaint that is caused by decreased bowel mobility secondary to elevated progesterone (normal in pregnancy), which can lead to greater absorption of water.

**Braxton Hicks contractions.** Occasional, irregular, and often painless contractions that occur several times per day.

**Edema (swelling).** Common complaint in advancing pregnancy. Caused by compression of the inferior vena cava (IVC) and pelvic veins by the uterus leads to increased hydrostatic pressure in lower extremities.

**Regurgitation, heartburn, and nausea.** Common complaints that may be caused by Gastroesophageal Reflux Disease (GERD); this is determined by relaxation of the lower esophageal sphincter (LES) and increased transit time in the stomach (normal in pregnancy), as well as by increased intra-abdominal pressure, caused by the enlarging uterus.

**Haemorrhoids.** Complaint that is often noted in advancing pregnancy. Caused by increased venous stasis and IVC compression leading to congestion in venous system, along with increased abdominal pressure secondary to the pregnant space-occupying uterus and constipation.

**Pelvic girdle pain.** PGP disorder is complex and multi-factorial and likely to be represented by a series of sub-groups with different underlying pain drivers from peripheral or central nervous system (O’Sullivan and Beales, 2007), altered laxity/stiffness of muscles (Vleeming et al., 2008), laxity to injury of tendinous/ligamentous structures (Vleeming et. al., 2002) to ‘mal-adaptive’ body mechanics (O’Sullivan and Bealesa, 2006). Musculo-Skeletal Mechanics involved
in gait and weight bearing activities can be mild to grossly impaired. PGP can begin pre or postpartum. There is pain, instability or dysfunction in the symphysis pubis and/or sacroiliac joints.

**Increased urinary frequency:** A common complaint referred by the gravida, caused by increased intravascular volume, elevated GFR (glomerular filtration rate), and compression of the bladder by the expanding uterus.

**Varicose veins:** Common complaint caused by relaxation of the venous smooth muscle and increased intravascular pressure.

**Miscarriage** or spontaneous abortion is the spontaneous end of a pregnancy at a stage where the embryo or fetus is incapable of surviving, generally defined in humans at prior to 24 weeks of gestation. Miscarriage is the most common complication of early pregnancy (Petrozza and John, 2006). The most common symptom of a miscarriage is bleeding. Bleeding during pregnancy may be referred to as a threatened abortion (Everett, 1997)

**Figure 2.9 Time frame of pregnancy outcomes**

Source: Miscarriage- pregnancy-timeline (David Ruben, 2008).
Pre-eclamptic Toxaemia (PET) is also called Toxemia of pregnancy or pregnancy induced hypertension. This is a syndrome that develops after the 20th week of pregnancy. It is characterized by:

- Persistent high blood pressure at or above 140/90mmHg.
- Edema or swelling of the feet and ankles.
- Proteinuria or presence of protein in the urine.

Edema is usually the first sign to occur followed by high blood pressure and then by proteinuria.

The exact cause is unknown but it is believed to be associated with a defect of the immunological mechanism involved in normal fetomaternal host response. Caesarian section has to be done if blood pressure cannot be controlled or there is risk of developing complications like eclampsia or eye changes (Stevenson, 1971).

Caesarian delivery: Risk of complications for the mother is somewhat greater in a cesarean birth than in a vaginal birth. Overall, the risk of maternal death from a cesarean birth (4 per 10,000 births) is four times greater than from a vaginal birth (Hankins et al., 1995).

2.4.17 New born outcomes:

- Birth weight is the body weight (more technically "mass") of a baby at birth. The duration of gestation prior to birth, that is, the gestational age at which the child is born. The prenatal growth rate, generally measured in relation to what weight is expected for any gestational age.

- Head circumference: Also called Occipital-frontal circumference. Head circumference is a measurement of a child' s head around its largest area, it measures the distance from above the eyebrows and
ears and around the back of the head (Kimmer et al., 2007).

- **Preterm birth:** Preterm birth refers to the birth of a baby of less than 37 weeks gestational age (Goldenberg et al., 2008). The shorter the term of pregnancy, the greater the risks of mortality and morbidity for the baby primarily due to the related prematurity. Preterm-premature babies ("premmies") have an increased risk of death in the first year of life (infant mortality), with most of that occurring in the first month of life (neonatal mortality). Worldwide, prematurity accounts for 10% of neonatal mortality, or around 500,000 deaths per year (Smith et al., 2003).

**Figure 2.10 Birth weight versus gestational age**

Source: Weight vs gestational age (Yehudamalul, 2010)