CHAPTER 2
REVIEW OF LITERATURE

Iron and vitamin A deficiencies are widespread during pregnancy in the world. The iron and vitamin A deficiencies in pregnancy are related to reproductive failure and high rates of mortality of offspring. Therefore, the present study entitled "Effect of Iron and Vitamin A Supplementation on Pregnancy Outcomes" has been undertaken. Before planning for the research the review of literature related to this study has been collected and presented under the following heads.

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2.1 Role of Iron in Human Body

    Iron has several vital functions in the body. It is a constitute of haemoglobin which serves as a carrier of oxygen from lungs to the tissue. Iron is also a transport medium for electrons within the cells, and is an integrated part of important enzyme systems in various tissues (Bothwell, 1979).
2.2 Iron Deficiency Anaemia (IDA)

Iron Deficiency Anaemia (IDA) is characterized by the production of small (microcytic) erythrocytes and diminished level of circulating haemoglobin.

IDA also defined as a state in which iron stores are inadequate for normal homeostasis. It is the one of the most common nutritional deficiency (Looker et al., 1997).

2.3 Prevalences of Iron Deficiency Anaemia during pregnancy

2.3.1 Global prevalences:

Iron Deficiency Anaemia is the most prevalent in the worldwide and affects over two billion people mostly in the developing countries (Rossander et al., 1996). Iron deficiency and iron deficiency anaemia are major public health problems, affecting an estimated 30 per cent of the World’s population, mostly women of reproductive age (Malee, 2008).

Anaemia affects 41.8% of pregnant women in the world and is a risk factor for maternal morbidity and mortality (Benoist et al., 2005). World Health Organization (WHO) has estimated that prevalence of anaemia in pregnant women as 14 per cent in developed and 51 per cent in developing countries and 65-75 per cent in India (WHO, 2008). The worldwide anaemia prevalence data estimated that 47% of pregnant women in Africa, 39% in Latin America, 80% in Southeast Asia, 65% in the eastern mediterranean and 40% in West Pacific are believed to be anaemic (Benoist, 2008). Occurrence of anaemia in South Asian countries is among the highest in the world. About half of the global maternal deaths due to IDA occurs in South Asian countries and India adds about 80 per cent of the Maternal deaths due to
anaemia in South Asia (WHO, 2008). The prevalence of IDA in other South Asian countries varies: Bangladesh 77%, Bhutan 59%, Nepal 65% and Sri Lanka 60%.

The incidences of anaemia in Thailand was found 19.2 per cent among 1,304 pregnant women and its occurrence was 14.8, 20.5 and 38.6 per cent in the first, second and third trimester respectively (Chotnopparatpattara et al., 2003).

In Uganda, figures of anaemia with iron deficiency was found 54.7 per cent among 96 pregnant women (Kiwanuka et al., 1999) where as in 42 villages of Bali, Indonesia the occurrence of anaemia was found 46.2 per cent in a total of 1,684 pregnant women (Suega et al., 2002).

The studies of United States revealed that iron deficiency and iron deficiency anaemia was relatively common in adolescent girls and females of childbearing age (Looker et al., 1997).

2.3.2 Prevalence of Iron Deficiency in India

Various studies from different regions of the India have reported the prevalence of anaemia between 33 and 87.6% (Agarwal et al., 1999). Dahiya et al., (1995) reported that in India, anaemia is the most common cause of maternal deaths, accounting for 20% of total maternal deaths.

About 87% of pregnant women were found to be anaemic in India. The report of second National Family Health Survey conducted between 1998-1999 (NFHS-II) indicated that 54% and 46% women of childbearing age were anaemic in rural and urban area respectively. National Family Health Survey (NFHS-III) has reported the prevalence of anaemia to be (79.2 %) in pregnant women.
The figures for anaemic women in Kerala was only 23% where as in many north-eastern states of India it was 62%. National and Regional Surveys have indicated that the prevalence of Iron Deficiency Anaemia could be as high as 85 per cent in expectant mothers. (MOHFW 1998; ICMR 2001).

Among 151 studied adolescent pregnant women of a rural block in Uttrakhand, 46 were found anaemic (Pathak, 2003). A study conducted at coimbtore revealed that out of 1,040 expectant mothers 70.4 per cent were anaemic and suffering from different degrees of anaemia (Thangleela et al., 1994).

Prevalence of anaemia is high in all the states, though there are considerable variations between States in prevalence of moderate and severe anaemia.

Data from DLHS (District Level Household & Facility Survey) showed that prevalence of moderate and severe anaemia was high even among educated and higher income groups.

2.3.3 Factors causing Iron Deficiency Anaemia (IDA)

Studies carried out in India have shown that iron deficiency is the major cause of anaemia followed by folate deficiency. The women in developing countries are always in a state of precarious iron balance during their reproductive years. Their iron stores are not well developed because of poor nutritional intake, recurrent infections, menstrual blood loss, and repeated pregnancies. Gender discrimination in a country like India results in girls lacking access to a balanced diet, adequate healthcare, and proper education. Thus the average Indian woman enters her reproductive years, particularly pregnancy, with iron and folate deficiency (Kapur et al., 2002).
In India, the prevalence of anaemia is high because of low dietary intake, poor iron (less than 20 mg/day) and folic acid intake (less than 70 micro gram/day) as well as poor bioavailability of iron (34% only) due to phytate and fibre-rich Indian diet; and chronic blood loss due to infection such as malaria and hookworm infestation (Chandar, 1992). Data from NNMB surveys revealed that iron and folic acid intake in all the age groups was very low. There has not been any increase in iron intake over the last three decades in any group. An NNMB surveys (2000-01) revealed that 50% of the iron in Indian diet is only absorbable. The surveys highlighted that the anaemia gets aggravated during adolescence and during pregnancy, assuming that the absorption of iron is 8 per cent in pregnant women and their average dietary intake will meet only 45 per cent of the requirement.

### 2.3.4 Iron Requirements During Pregnancy

During pregnancy, the total maternal needs for extra iron is about 800 mg (elemental iron), of which about 300 mg is for the foetus and the placenta and the rest is for maternal haemoglobin mass expansion (Fujimori et al., 1999). The placental and foetal requirement is obligatory and dietary intake will be diverted to this end, even if the mother is iron-deficient. Practically, all of this iron is used during the later half of pregnancy. Therefore, the iron requirement increases from a 0.8 mg/day in first trimester to 6 to 7 mg/day in the second half of pregnancy (Gopalan et al., 1993). Overall, a pregnant woman needs about 2 to 4.8 mg of iron per day. The women must consume 20 to 48 mg of dietary iron to absorb this quantity of iron daily. An average vegetarian diet does not provide more than 10 to 15 mg of iron per day. Thus, the
amount of iron absorbed from diet, coupled with that mobilized from body iron stores, is usually insufficient to meet the demands imposed by pregnancy (Taru, 2008). This is true even though the bioavailability of iron from the gastrointestinal (GI) tract is moderately increased during pregnancy and menstrual iron loss ceases. The high incidence of iron deficiency underscores the need for iron supplementation in pregnancy. Iron supplementation is especially important because the demand for iron by the mother and the foetus increases during pregnancy (Beard et al., 2000). This increased demand cannot be met without iron supplementation.

2.4 Strategies to overcome Iron deficiency

2.4.1 Iron Supplementation

Iron supplementation is the most common strategy currently used to address iron deficiency in developing countries. Iron supplementation during pregnancy is advisable in developing countries, where women often enter pregnancy with low iron stores (ICMR, 1999). Iron supplementation during pregnancy is recommended universally even in non-anaemic women (Hurrel, 1997).

There are three main strategies for correcting iron deficiency in population, which can be used alone or in combination:

(i) One of the strategy is the education combined with dietary modification or diversification to improve iron intake and bioavailability;

(ii) Iron supplementation (provision of iron, usually in higher doses, without food); and

(iii) Iron fortification of foods.
A new approach is biofortification by plant breeding or genetic engineering. Although dietary modification and diversification has been traditionally thought of as the most sustainable approach, change of dietary practices and preferences is difficult, and foods that provide highly bioavailable iron (such as meat) are expensive (Jain et al., 2001). Iron supplementation can be targeted to high-risk groups (e.g., pregnant women) and can be cost-effective (Jain et al., 2003) but the logistics of distribution and fulfillment issues are major limitations. For oral supplementation, ferrous iron salts (ferrous sulphate and ferrous gluconate) are preferred because of their low cost and high bioavailability. The standard therapy for iron-deficiency anaemia in adults is a 300-mg tablet of ferrous sulphate (60 mg of iron) 3 or 4 times per day. Although absorption is enhanced when given on an empty stomach causing nausea and epigastric pain sometimes. If these side effects occur, lower doses between meals should be attempted or iron should be provided with meals, although food reduces the absorption of medicinal iron by about two thirds (Hurrell, 1997). Alternatively, oral iron supplements can be supplied every few days; this regimen might increase fractional iron absorption. In studies supported by WHO in Southeast Asia, iron and folic acid supplementation given every week to women of childbearing age improved iron nutrition and also reduced iron deficiency anaemia (WHO, 1992). The available data from controlled trials provided clear evidence of an improvement in haematological indices in women receiving iron supplementation (Zavaleta et al., 2000). At present, there is no evidence to advice against a policy of routine iron supplementation in pregnancy. Therefore, routine
supplementation is warranted in population in which iron deficiency is common. Studies from developing countries (WHO, 1997) suggested that 120 mg elemental iron and 1mg folic acid are the optimum daily dosages needed to prevent anaemia in pregnant women. But WHO recommends, for all pregnant women, if there are no high risk factors, a combination tablet containing 60mg of elemental iron and 250µg of folate to be taken twice a day. Where this is not available, tablets such as ferrous sulphate, containing 60mg of elemental iron, should be given twice a day together with one folic acid tablet (1mg) (Tee et al., 1999). In India it is recommended that pregnant women should receive 1 adult tablet per day for 100 days where each tablet contains 100 mg of elemental iron and 500 mcg of folic acid. These tablets should be provided to pregnant after the first trimester of pregnancy (Jain et al., 2003)

Recently a weekly iron/folate supplement was compared with a standard daily iron/folate supplement in pregnant women living in rural Malawi. Women enrolled as they attended the local antenatal clinic, then were stratified by grade of anaemia and then randomly received either 60mg iron/ 0.25 mg folic acid per day or 120 mg iron/ 0.5 mg folic acid once a week (ICMR, 2006). The results indicated that the haemoglobin values increased by similar levels in both groups with the anaemic women increasing by an average of 6.3g/L in the daily group and 5.9g/L in the weekly group for all women. The side effects of oral iron administration or women’s dislike of the tablets owing to smell or taste have often being blamed for treatment failure (ICMR, 2006). Rather, in most cases, women did not take their tablets because they never received them or received inadequate
quantities. The impact of iron supplementation could be improved by counseling on why, how and when to take iron tablets and by supplying the tablets (Sanghvi, 1996). The effectiveness of iron/folate supplementation to reduce iron deficiency and anaemia in women of reproductive age was assessed in Thyolo district. A baseline survey on iron status and haemoglobin level was conducted in June 1996. A second survey was carried out after 2 years following a 15 month intervention with iron/folate supplementation. 210 pregnant women, 210 non pregnant women (who had delivered within last 6 months) and 315 men were recruited for the survey. After the intervention, anaemia was present in 60% (baseline, 67%) of pregnant women and 51% (baseline, 61%) of women who had delivered in the last 6 months (NFHS, 2005). Moreover, severe anaemia (haemoglobin <7g/dl) was found in 1.9% (baseline, 3.3%) of pregnant women, 2.4% (baseline, 4.3%) of recently delivered women, and 1.3% (baseline, 0.3%) of men. The intervention programme was successful in increasing haemoglobin levels and decreasing the prevalence of anaemia, particularly among women who had delivered in the last 6 months.

The National Nutritional Anaemia Control Programme (NNACP) in India was launched in 1970. However, anaemia continues to be a major public health problem but the evaluation of the NNACP in various states of India revealed that the program has not achieved its objective. The main weaknesses of the programme were short supplies, poor coverage of the inadequate dose of the iron supplement, defective absorption because of intestinal infestations, problems with formulation, inadequate consumption by the beneficiaries, failure to replenish
the stocks at the beneficiary level, and lack of effective health education and supervision (Wadhwa et al., 2003).

2.4.2 Food-Based Approaches to Overcome Iron deficiency

Efforts to reduce iron deficiency should be directed toward promoting the availability of and access to iron-rich food like liver, meat, fish, poultry, and non-animal foods such as legumes, green leafy vegetables, nuts, oilseeds, jaggery, and dried fruits. In general, animal foods tend to have higher iron content than the non-animal foods (Hallberg, 1979). Bioavailability of iron-containing foods is strongly influenced by enhancers in the diet (e.g. ascorbic acid present in citrus fruits, fruit juices, green leafy vegetables, cabbage, cauliflower, tubers, and some germinated or fermented foods such as soya sauce) and inhibitors (e.g. phytates present in cereal bran, cereal grains, high-extraction flour, legumes, nut and seeds; calcium, particularly in milk and milk products; tannins present in tea, coffee, and cocoa; phosphates in egg yolk; and oxalates in vegetables) (Lechtig et al., 1975a). Iron absorption can vary from 1% to 40% depending on the mix of such elements in the meal. Typical vegetarian Indian diets can contain large quantities of inhibitors (Hallberg, 1997). Therefore, focus should also be on foods that enhance the absorption or utilization of iron. Examples of simple alterations in food habits that may improve iron bioavailability include:

- Including fresh fruits or fruit juices and other sources of vitamin C such as tomatoes, spinach, cabbage, cauliflower, potatoes, and other green leafy vegetables and tubers in the meal;
- Consuming milk, cheese, and other dairy products as between-
meal snacks rather than at mealtimes;

- Separating tea drinking from mealtime by at least 2 hours; and
- Consuming foods that contain inhibitors of iron absorption with tea or milk at those meal that are inherently low in iron such as a breakfast of a low-iron cereal (e.g. bread, cornflakes) (Hallberg, 1974).

2.5 Vitamin A

Vitamin A is particularly essential for pregnant women especially for postpartum tissue repair, as well as maintaining normal vision and helping fight off infections. A lack of vitamin A during pregnancy can cause night blindness in mother, problems in the placenta as well as low birth weight of new born (WHO, 1996). There is emerging evidence that vitamin A plays crucial roles in embryonic development and used to prevent teratogenesis under some circumstances (Christian, 2000). Because of its vital role in cell development and differentiation, it helps to ensure that the changes which occur in the cells and tissues during fatal development take place normally.

2.5.1 Pathophysiology of Vitamin A

Vitamin A is a fat-soluble vitamin ingested in the diet in two forms: as retinol itself from animal sources, such as milk, meat, fish, liver, and eggs, or as the pro-vitamin carotene from plant sources, such as green leafy vegetables, yellow fruits, and red palm oil (Azaïs et al., 2000). It is absorbed from the small intestine. Within intestinal mucosal cells, carotene is converted to retinol and, along with the directly ingested retinol, is esterified to palmitic acid. Retinyl palmitate then travels through the lymphatic system to the liver, where it is stored. Retinol (an
alcohol) and retinal (an aldehyde) are often referred to as preformed vitamin A (Christian, 2000b). Retinal can be converted by the body to retinoic acid, the form of vitamin A known to affect gene transcription. Retinol, retinal, retinoic acid, and related compounds are known as retinoids. β-carotene and other carotenoids that can be converted by the body into retinol are referred to as pro-vitamin A carotenoids. Hundreds of different carotenoids are synthesized by plants, but only about 10% of them are pro-vitamin A carotenoids (IVACG, 2001).

2.5.2 Prevalence of Vitamin A Deficiency

Vitamin A Deficiency (VAD) remains a widespread public health problem among women and children. Over 20 per cent of pre-school age children (~130 million) and nearly 6 per cent of all pregnant women (~7 million) suffer from Vitamin A Deficiency and its adverse health consequences (West, 2002; Rice et al, 2004). The countries like South Asia and Sub-Saharan Africa are also having Vitamin A deficient women and children where Vitamin A supplementation programs for children over six months of age have helped reduced high child mortality rates. The majority of studies have shown that vitamin A deficiency is widespread throughout the developing world. Vitamin A deficiency has long been recognized in much of South and Southeast Asia (India, Bangladesh, Indonesia, Vietnam, Thailand and the Philippines) by the common presentation of clinical cases of xerophthalmia or night blindness, mostly in the latter half of the pregnancies (Christian et al., 2000). Relatively recent surveys reported VAD prevalences in pregnancy follows as: 8 to 16% in rural Nepal (Katz et al., 1995); 0.6 to 2.8% in Sri Lanka (Jayasekera, 1991); and 1% in a national vitamin A survey in
Bangladesh (Helen, 1999). The prevalence of clinical VAD deficiency is estimated by combining night blindness and eye changes, primarily Bitot’s spots, to form a “total xerophthalmia” prevalence (Sommer, 1995). These clinical signs of the prevalence in Asia is quite low. The prevalence of night blindness normally increases substantially as pregnancy progresses and Night blindness further associated with a higher risk of maternal mortality and morbidity. In Nepal, the death rate was about 26/1,000 for those pregnant women who reported night blindness, compared to 3/1,000 for those who did not (Christian et al., 2001). However, subclinical VAD is much more common and is defined as the prevalence of serum retinol concentrations below 0.70 µmol/L minus the percentage of individuals with clinical VAD. The prevalence of subclinical VAD is uncertain because of very few national surveys and also there is a paucity of reliable values for serum retinol (WHO, 1996). More than 7.2 million pregnant women in the developing world are Vitamin A deficient (serum or breast-milk vitamin A concentrations < 0.70 µmol/L), and another 13.5 million have low VA status (0.70-1.05µmol/L) and more than 6 million women develop night blindness (XN) during pregnancy annually (Sommer et al., 2000). Roughly 45% of VAD and, xerophthalmic children and pregnant women with low-to-deficient VA status, live in South and Southeast Asia. These regions harbor >60% of all cases of maternal XN, three fourths of whom seem to live in India.

2.5.3 Causes of Vitamin A Deficiency

Vitamin A deficiency occurs with the chronic consumption of diets that are deficient in both Vitamin A and β-carotene. The main cause of Vitamin A Deficiency is a low intake of animal
products, which contain high amounts of absorbable retinol. Liver and kidneys are the concentrated source of vitamin A. β-carotene is a form of pro-vitamin A, which readily converts to vitamin A in the body (Garfield. et al., 1994). β-carotene is the main pro-vitamin in plant sources of vitamin A, however, this is generally less well absorbed than retinol. Vitamin A deficiency is widespread and occurs when the intake of dairy products and carotene-rich vegetables and fruit is limited and, occasionally, with malabsorption syndrome. β-carotene from fruit and from some yellow and orange tubers, including sweet potatoes, is substantially better absorbed than that from leaves and from vegetables in general (Strobel et al., 2007). It has been reported by the surveys that population with the highest prevalence of VAD consumes low amount of animal products as well as fruit rich in β-carotene. In rural Nepal risk factors for night blindness in women were reported as: less frequent consumption of preformed vitamin A (in animal products), and of pro-vitamin A (in mangoes and dark green leaves); urinary or reproductive tract infections; vomiting and poor appetite; and a poor diet in general. Breast milk is the main source of vitamin A and the poor maternal vitamin A status has subsequently low breast milk retinol content, which is a risk factor for the earlier onset of VAD in infants (Ross et al., 2003). Poor absorption of vitamin A may also occur in some types of diarrhea and fever, during which there is a higher rate of utilization and disposal of the vitamin. In severe protein-energy malnutrition, retinol binding protein synthesis is impaired. Zinc and iron deficiencies also interfere with the utilization and transport of stored retinol.
2.5.4 Consequences of Vitamin A

People most at risk are children between six months to six years, pregnant women, and lactating women. There is biological evidence suggesting that vitamin A deficiency may increase mortality by increasing women's risk of pregnancy-related infections and other conditions that can lead to death (Faisel et al., 2000). For pregnant women in high-risk areas, Vitamin A deficiency occurs especially during the last trimester when demand by both the inborn child and mother is highest. The mother's deficiency is demonstrated by the high prevalence of night blindness during this period. Vitamin A deficiency in pregnancy is known to result in night blindness and to increase the risk of maternal mortality (Christian et al., 2001). There is evidence from intervention trials in vitamin A deficient populations, that VAD has other serious consequences. The results of these trials indicate that VAD causes: increased morbidity and mortality of infants, children and pregnant women; poor growth of children; and possibly increased mortality and morbidity of infants infected with HIV (Coutsoudis et al., 1999). It also contributes to anaemia, by interfering with iron transport and utilization for Haemoglobin synthesis. This also causes blindness; impaired cognitive function; impaired physical work capacity; morbidity (incidence and/or severity) due to diarrhoea, measles, acute respiratory infections, malaria and other infectious diseases; cause-specific mortality related to these diseases; and all-cause mortality. Outcomes potentially associated with vitamin A deficiency in pregnant women included intrauterine growth retardation, and antepartum hemorrhage (Sommer, 1995) due to abruptio placentae, foetal loss, low birth weight, preterm birth,
all-cause infant mortality, maternal morbidity and maternal mortality (Khatry et al., 2001). Vitamin A deficiency reduces leukocyte numbers, lymphoid tissue weights, complement, T cell functions, tumor resistance, natural killer cell numbers, antigen-specific immunoglobulins G and E, and TH2 numbers and increases interferon-γ synthesis (IVACG, 2001).

2.4.5.1 Assessment of Vitamin A deficiency

Many assessment criteria have been applied to the determination of whether VAD is a public health problem for a given population. In the last few years, it has become clear that some assessment criteria previously suggested (WHO, 1996) are difficult to apply or interpret on a population level or give results that are less precise or reliable than desired. It has also become apparent that vitamin A deficiency is widespread in developing countries, particularly those sharing similar environments. The informal consultation reviewed assessment criteria for vitamin A deficiency and made the following recommendations:

A. Ocular indicators: Ocular signs of vitamin A deficiency are associated with advanced stages of the condition. They are rare compared to the very vast problem of sub-clinical deficiency. The indicators already identified with clear cut-off points (WHO, 1996) — that is, conjunctival xerosis with Bitot’s spots; corneal xerosis, ulceration or keratomalacia; and corneal scars — are useful. Another indicator that should be added to these is night blindness in the last pregnancy, with 5% proposed as a cut-off point for determining whether vitamin A deficiency is a public health problem, using a locally familiar term for night blindness where one exists. This is an indicator of vitamin A deficiency not only among women but also among young children.
in a given population (Christian et al., 2000). A recall of night blindness during the last pregnancy provides a low-cost, widely adaptable, non-invasive way to assess risk of maternal vitamin A deficiency that does not require highly trained technical staff. Recall of maternal night blindness can be added easily to a multi-purpose household survey, once the appropriate local term(s) for the condition are identified. In a population-based study in Nepal, women with XN during pregnancy had a mean serum retinol concentration (SD) of 0.72 (0.41) µmol/L compared to a level of 1.03 (0.39) µmol/L among non-night blind pregnant women (p << 0.001) (Christian et al., 1998). As this is an indicator without a long record of use in women, a history of maternal XN should continue to be used, where possible, with serum retinol and other biochemical or functional indices of vitamin A status in the community.

B. **Biochemical indicators**: The indicator of choice is less than 0.7 µmol/litre serum retinol; a public health problem exists when more than 20% of the population has serum retinol below this cut-off. Children 6-36 months are a key group to evaluate against this criterion.

C. **Dark adaptometry**: Dark adaptometry is a useful approach for non-invasive assessment of early stages of vitamin A deficiency by objective physical criteria, and it merits more attention. There is an urgent need to accelerate research on and dissemination of this tool for population-level assessment of vitamin A status.

### 2.5.4.2 Retinol activity equivalents (RAE)

Different dietary sources of vitamin A have different potencies. For example, β-carotene is less easily absorbed than
Retinol and must be converted to retinal and retinol by the body (Mikhail, 1994). The most recent international standard of measure for vitamin A is retinol activity equivalents (RAE), which represent vitamin A activity as retinol. Two micrograms (mcg) of β-carotene in oil provided as a supplement can be converted by the body to 1 mcg of retinol giving it an RAE ratio of 2:1. However, 12 mcg of β-carotene from foods are required to provide the body with 1 mcg of retinol, giving dietary β-carotene an RAE ratio of 12:1. Other pro-vitamin A carotenoids in foods are less easily absorbed than β-carotene, resulting in RAE ratios of 24:1 (Ramirez et al., 1998). The RAE ratios for β-carotene and other pro-vitamin A carotenoids are shown in the table below. An older international standard, still commonly used, is the international unit (IU). One IU is equivalent to 0.3 mcg of retinol.

### Retinol activity equivalents (RAE) ratios for β-carotene and other pro-vitamin A carotenoids

<table>
<thead>
<tr>
<th>Quantity Consumed</th>
<th>Quantity Bioconverted to Retinol</th>
<th>RAE ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mcg of dietary or supplemental vitamin A</td>
<td>1 mcg of retinol*</td>
<td>1:1</td>
</tr>
<tr>
<td>2 mcg of supplemental β-carotene</td>
<td>1 mcg of retinol</td>
<td>2:1</td>
</tr>
<tr>
<td>12 mcg of dietary β-carotene</td>
<td>1 mcg of retinol</td>
<td>12:1</td>
</tr>
<tr>
<td>24 mcg of dietary alpha-carotene</td>
<td>1 mcg of retinol</td>
<td>24:1</td>
</tr>
<tr>
<td>24 mcg of dietary β-cryptoxanthin</td>
<td>1 mcg of retinol</td>
<td>24:1</td>
</tr>
</tbody>
</table>

*One IU is equivalent to 0.3 microgram (mcg) of retinol, and one mcg of retinol is equivalent to 3.33 IU of retinol.
2.5.5 Strategies to overcome Vitamin A deficiency

2.5.5.1 Supplementation of Vitamin A

It is now recognized that there are several benefits of maternal vitamin A supplementation during pregnancy. A double-blind, randomized, placebo-controlled trial in rural Nepal revealed that vitamin A supplementation of VAD populations during pregnancy can have a major impact on maternal mortality (Christian et al., 2000). In this study, over 20,000 pregnant women were randomly assigned to three groups prior to conception. They received weekly an oral supplement containing either 7,000 µg RE of vitamin A, or 4,000 µg RE as β-carotene, or a placebo. Maternal deaths from pregnancy-related causes per 100,000 pregnancies were 704 in the placebo group, 426 in the vitamin A group, and 361 in the β-carotene group: equivalent to reduced risks of maternal mortality of 40% and 49% in the vitamin A and β-carotene groups respectively (Mikhail, 1994). A large study from Nepal examined the effect of Vitamin A Supplementation on the reduction of pregnancy related and direct mortality occurring within 12 weeks postpartum, 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 50% in the β-carotene group). The combined effect of these two forms of Supplementation was 44% reduction in pregnancy related deaths. However, β-carotene (pro-Vitamin A) has significant anti-oxidant properties that are not present in Vitamin A.

A nested case-control study with in this trial found a significant reduction in night blindness. It could be speculated that this reduced prevalence of night blindness may have
accounted for the observed reduction in material deaths from physical injuries in the trials. A cluster-randomized trial in Nepal showed that all-cause maternal mortality up to 12 weeks postpartum was reduced by weekly vitamin A (RR: 0.60; 95% CI: 0.37-0.97) and β-carotene supplementation (RR: 0.51; 95% CI: 0.30-0.86) compared with the placebo group. (Christian et al., 2001).

As this may have implications for specific pregnancy complications such as pre-eclampsia/eclampsia. Empirical evidence from a single randomized placebo-controlled field trial that included ~20,000 pregnant women living an area of southern Nepal where vitamin A deficiency is prevalent also suggests that interventions which improve women's vitamin A status can reduce maternal mortality (Dali, 1999). A substantial reduction (40 per cent) in pregnancy-related mortality was observed among the women who received vitamin A or β-carotene supplements on a weekly basis before, during, and after pregnancy (West et al., 1999). The study also showed that pregnant women who became night blind, a well-known sign of vitamin A deficiency, were several times more likely to die in the first six weeks after delivery than those who did not (Christian et al., 2000).

2.5.5.2 Supplementation protocols:

The ideal vitamin A supplementation protocol would call for frequent low-dose supplements. The supplementation guidelines prepared by WHO, UNICEF and IVACG and recently issued by WHO (WHO, 1997) take this reality into account and are appropriate. That is, preventive supplementation with higher doses of vitamin A can follow this schedule: Infants < 6 month of age only if not breastfed 50,000 IU orally (Breastfed children in
this group should be protected by post-partum supplementation of their mothers.)

Infants 6-12 months of age 100,000 IU orally, every 4-6 months

Children > 12 mo of age 200,000 IU orally, every 4-6 months

 Mothers (post-partum, lactating) 200,000 IU orally within 8 wks of delivery

The introduction or expansion of daily (5,000 to 10,000 IU) or weekly (25,000 IU) supplementation of pregnant women with vitamins and minerals in many countries may provide another occasion for testing modes of more frequent vitamin A supplementation. Weekly vitamin A supplementation (7000 µg) in Nepal reduced maternal mortality by 40%, the prevalence of subclinical vitamin A deficiency by 84% (Dreyfuss, 1998), and the risk of night blindness by 38% (Pokhrel, 1999). Vitamin A is associated with anaemia (Herrera et al., 1997) and supplementing pregnant women in their second trimester with both vitamin A (2400 mg) and iron daily for 2 mo improved haemoglobin concentrations more so than did supplementation with iron or vitamin A alone. Vitamin A therapy, in the form of cod liver oil, for women with puerperal fever reduced the severity of puerperal fever and reduced maternal mortality by about two-thirds when given with the usual treatment for sepsis (McArdle, 1986). In later studies, prophylactic cod liver oil reduced the incidence of puerperal fever (McArdle, 1986). Hakimi et al.'s preliminary data from an ongoing, randomized, placebo-controlled trial showed for the 680 women for whom data were available that the number of episodes of elevated body temperature (>38°C) on at least day 1 postpartum was reduced by 78% in women given 2400 µg vitamin
A daily during pregnancy compared with the control group who received no vitamin A supplement (RR = 0.22; 95% CI: 0.08, 0.65).

2.5.5.3 Food-Based Strategies

The Efficacy of Food-Based Strategies to Improve Vitamin A Status.

A major immediate cause of undernutrition is the habitual consumption of poor quality diets. “Poor quality” refers primarily to a low content of absorbable micronutrients (Ramakrisham et al., 1999). In addition, some people also have a low energy intake. Where low energy intake is due to lack of food availability, it is almost certain that the quality of the diet is also poor (ICNND, 1963). Typically, poverty is associated with a low intake of animal products, and subsequently low intakes of riboflavin, vitamin B12, absorbable iron and zinc, calcium, and preformed vitamin A. Intake of fruit and some vegetables may also be low, and associated with inadequate intakes of vitamin C and folic acid (ICNND, 1967). Thus a food-based strategy is important. It can increase the availability and intake not only of vitamin A and iron, but also of many other micronutrients.

2.6 Relationship Between Vitamin A and Iron

Vitamin A deficiency and anaemia due to nutritional status are major problems worldwide, and are especially significant in developing countries, with children and pregnant women most often affected. Research during the 1920s suggested an interaction between Vitamin A and Iron, and interest in this interaction has continued in recent decades. A relationship between vitamin A and iron could have relevance to the treatment of nutritional anaemia, and numerous studies have suggested that
supplemental vitamin A in addition to iron is superior to iron alone in treating nutritional anaemia.

While iron-deficiency anaemia and vitamin A deficiency are both significant problems in many countries, research establishing an interaction between iron and vitamin A could have major implications for treatment of anaemia that is due to nutritional status (Karyadi, 1996).

Numerous studies using humans have supported the notion that vitamin A has an impact on iron status and, in turn, iron-deficiency anaemia. Early research suggested that people deficient in vitamin A were prone to anaemia that was reversed when sufficient doses of vitamin A were taken. One study in Indonesia reported that 50-70% of all pregnant women in that country were anaemic due to nutritional status (Suharno, 1993). Using a double-blind, randomized design, these pregnant women were assigned to one of four groups: iron, vitamin A, iron and vitamin A, and placebo. Hematological variables were measured in a total of 251 women, and the results indicated that the group receiving both vitamin A and iron showed the most improvement (Mejia et al., 1988). Specifically, those receiving both nutrients exhibited an increase in haemoglobin that was over 50% greater than those receiving iron alone, and, using the data from the other groups, the authors state that one-third of this increase is due to vitamin A while the other two-thirds is due to iron. Furthermore, 97% of the women receiving both nutrients recovered from anaemia, while the other groups recovered as follows: iron (68%); vitamin A (35%); and placebo (16%). These results strongly support the use of vitamin A in addition to iron when treating nutritional anaemia (Ramakrisham et al., 1999).
Another study focused on a number of Guatemalan children indicated that iron intake is sufficient, yet iron-deficiency anaemia still develops (Muhilal et al., 1988). This, taken together with the prevalence of vitamin A deficiency in this region, further study have been done to determine if vitamin A would have an impact on the anaemia in these children. The study design was similar to the above study, with four groups of children receiving either vitamin A, iron, vitamin A and iron, or placebo for two months. Various hematological measures were taken, and the results supported an effect of vitamin A on iron status. In the group of children receiving vitamin A alone, the increase in haemoglobin averaged 9.3 g/L (using a daily dosage of 10,000 IU for two months). The changes were similar for the groups receiving iron alone and both vitamin A and iron (about 14 g/L), and the placebo group showed an average increase in haemoglobin of 3.2 g/L (WHO, 1997). The study report a strong effect of vitamin A on serum iron and, in turn, percent transferrin saturation. No alteration in total iron binding capacity (TIBC) was observed in the group receiving vitamin A. The major finding in this study was that vitamin A raised the level of serum iron in anaemic children could lead to greater hematopoiesis and thus recovery from anaemia. Also, the increase in serum iron is maximal when both vitamin A and iron are administered, with either alone resulting in an increase of lesser magnitude.

One line of investigation into the interaction between vitamin A and iron comes from animal studies, and has allowed to better define the changes associated with vitamin A deficiency and related changes in iron indices. Inadequate vitamin A may result in volume balance alterations, with a loss of extracellular
fluid, which translates into decreased blood volume, and this could mask decreases in erythrocyte number and haemoglobin content. Nevertheless, animal studies have provided important information about vitamin A and its effects on iron status. Compared changes in iron metabolism during either vitamin A or iron deficiency in rats, in order to describe the changes in order of their occurrence (Roodenburg et al., 1994). In rats experiencing iron deficiency haemoglobin levels decreased, and iron absorption and TIBC increased as levels of tissue iron decreased. Vitamin A deficiency was initially manifest by anaemia, then increased iron absorption and increased iron level in the spleen. Eventually, packed cell volume, haemoglobin concentration, and serum iron were increased relative to control, due to hemoconcentration. Also, decreased TIBC in the vitamin A-deficient rats, coupled with increased tissue levels of iron, suggests that iron is not mobilized, which could alter hematopoiesis. A subsequent study by the same group used rats initially on diets with sufficient iron and varying levels of vitamin A. Then the diets were changed to include the same amounts of vitamin A but no iron, followed by a period of iron supplement or iron supplement plus vitamin A. The results suggested that iron in combination with vitamin A is more effective than iron alone in treating lowered iron status, which agrees with studies performed in humans. Also, the studies assert that vitamin A promotes the use of spleen and bone iron stores. While the exact mechanisms underlying the impact of vitamin A on iron and anaemia are unknown, several hypotheses exist to explain this phenomenon. One prevalent hypothesis is that vitamin A increases levels of serum iron, which allows
hematopoiesis to thrive, increasing haemoglobin and erythrocyte production (Thumham, 1993). In vitamin A deficiency, iron would not be available for erythropoiesis, and anaemia would result. The reasoning behind this hypothesis is evident in the above studies. Another hypothesis, proposed by Thumham, involves the immune function of vitamin A (Thumham, 2000). Thumham uses the following reasoning for this hypothesis. Vitamin A (specifically, retinol) and iron are bound by retinol-binding protein and transferrin, respectively. During infection, the level of these proteins is diminished, which could be beneficial for various reasons. Due to increased epithelial permeability during infection, these proteins could be lost in the urine, so suppression of these proteins would minimize such losses. Also, the potential oxidizing effects of iron would be lessened during an infection. However, decreased availability of vitamin A could disrupt the integrity of epithelial tissues, especially the eye, gastrointestinal tract, and respiratory tract. This would make this tissue susceptible to infection. Thumham suggests that the anti-infectious activity of vitamin A could have an impact on the reversal of anaemia using this nutrient. Supplementation with vitamin A could lessen infection and help release iron that is stored in the liver during infection, which would in turn stimulate hematopoiesis. One relevant point of Thumham’s hypothesis is that the anaemic subjects in vitamin A and anaemia studies may have some level of infection, which might play a role in their recovery from anaemia when vitamin A is administered. Research into the mechanism of the observed effect of vitamin A on anaemia could lead to very specific interventions for this condition, yet it is already clear that vitamin A, when used with
iron, can be beneficial in the treatment of anaemia. This relationship between vitamin A and anaemia could have an impact on how nutritional anaemia is approached from a public health perspective, and the development of the most effective treatment is a definite possibility.

2.6.1 Iron and vitamin A interrelationship

Vitamin A appears to be involved in the pathogenesis of anaemia through diverse biological mechanisms, such as the enhancement of growth and differentiation of erythrocyte progenitor cells, potentiation of immunity to infection and reduction of the anaemia of infection, and mobilization of iron stores from tissues. (Semba et al., 2002) Vitamin A appears to influence anaemia via modulation of hematopoiesis, by enhancement of immunity to infectious diseases (Thumham, 1993; Semba, 1998) and, hence, the anaemia of infection (Means, 2000), and through the modulation of iron metabolism (Bloem, 1995). In the nineteenth century, it was recognized that anaemia often occurred in individuals with night blindness, and this observation led some clinicians to conclude that anaemia was among the underlying causes of night blindness (Nozeran, 1865; Parinaud, 1881; Saltini, 1881; Lecoeuvre, 1896). Administration of cod-liver oil, a potent source of vitamins A and D, was widely used to treat anaemia in the nineteenth century Thompson, 1855; Greene, 1877; McArdle, 1896). Animal and human studies in the early twentieth century suggested that vitamin A deficiency was related to abnormalities of hematopoiesis and iron metabolism. Hemosiderosis of the liver and spleen were described in autopsy studies of vitamin A-deficient infants (Blackfan & Wolbach, 1933), thus linking vitamin A deficiency to abnormalities of iron
metabolism. 1940, Wagner noted that adults who were given an experimental vitamin A-deficient diet for 6 months developed low haemoglobin and hematocrit (Wagner, 1940). Epidemiology A close association between vitamin A deficiency and anaemia has been shown in many nutritional surveys from around the world, and perhaps this is not surprising, given the widespread prevalence of nutritional anaemia and vitamin A deficiency in developing countries (Bloem, 1995). In the nutrition survey from Paraguay, haemoglobin and plasma retinol concentrations were highly correlated, with a correlation coefficient of 0.90 (Interdepartmental Committee on Nutrition for National Defense 1967). Pooled data from surveys conducted in Vietnam, Chile, Brazil, Uruguay, Ecuador, Venezuela, Guatemala and Ethiopia showed a high correlation ($r=0.77$, $P<0.0001$) between haemoglobin and plasma retinol concentrations (Hodges et al., 1978). Vitamin A deficiency was also common among pregnant women in Malawi and Nepal and, in the same populations, a high prevalence of anaemia was found. In a study conducted in Bangladesh, women of childbearing age were randomly allocated to receive iron, vitamin A plus iron or vitamin A plus iron and zinc (Kolsteren et al., 1999). Significant increases in haemoglobin were observed only among women who received vitamin A, iron and zinc. The lack of an effect of vitamin A alone upon haemoglobin was attributed to the relative lack of vitamin A deficiency among women in this population.

Studies conducted among pregnant women suggest that vitamin A supplementation alone during pregnancy can increase haemoglobin concentrations (Suharno et al., 1993). In West Java, Indonesia, 251 anaemic pregnant women were randomly allocated
to receive iron, 60mg=day, vitamin A, 2.4mg RE=day, iron, 60mg=day plus vitamin A, 2.4mg RE=day, or placebo for 8 weeks. After supplementation, the proportion of women who were not anaemic in the iron, vitamin A, vitamin A plus iron and placebo groups was 68, 35, 97 and 16%, respectively. Other studies have also explored the use of vitamin A combined with iron and or folate (Panth et al., 1990; Chawla & Puri, 1995). In a population with a high prevalence of iron deficiency anaemia, weekly vitamin A supplementation reduced anaemia by 9% during pregnancy and postpartum compared with controls. A study conducted in Tanzania suggests that daily multivitamins, but not vitamin A, increased haemoglobin concentrations among HIV-positive pregnant women (Fawzi et al., 1998). In Indonesia, pregnant women who received weekly vitamin A and iron supplementation had a greater increase in haemoglobin than women who received weekly iron or daily iron (Muslimatun et al., 2001). There was an accompanying decrease in serum ferritin among women who received vitamin A and iron, suggesting to the investigators that vitamin A supplementation increased the utilization of iron for hematopoiesis.

2.6.2 Impact of together supplementation of Vitamin A and Iron

Vitamin A deficiency may exacerbate iron-deficiency anaemia. Vitamin A supplementation has beneficial effects on iron deficiency anaemia and improves iron nutritional status among children and pregnant women. The combination of supplemental vitamin A and iron seems to reduce anaemia more effectively than either supplemental iron or vitamin A alone.
(Hodges et al., 1978). Moreover, studies in rats have shown that iron deficiency alters plasma and liver levels of vitamin A (Corey et al., 1972).

A study in Indonesia showed that in anaemic women (Hb <11.0g/dl), supplementation reduced the prepared pregnant women with anaemia. After supplementation, the proportion of women who became anaemic was 35% in vitamin A supplementation group, 68% in the iron supplemented group the group supplemented with both vitamin A and iron, compared with 16% in the placebo group results suggest that vitamin A and iron combination may be more effective than either iron alone in treating mild anaemia in pregnancy. It has been known that vitamin A plays an important role in haematopoiesis (Suharno et al., 1996) and more recently it has been suggested that vitamin A supplementation, particularly in women with low or borderline serum retinol concentration, may improve mobilization of iron stores (Mejia, 1988). Although serum retinol is commonly used as an indicator of Vitamin A status, it is under strict homeostatic control and more accurate ways of diagnosing Vitamin A deficiency in pregnancy include dose response test. The influence of vitamin A and iron supplementation was studied in anaemic pregnant women in West Java, in a randomised, double masked placebo controlled field trial. 251 women aged 17-35 years, parity 0-4, gestation 16-24 weeks and haemoglobin between 80 and 109g/L were randomly allocated to four groups: vitamin A (2.4mg retinol) and placebo iron tablets; iron (60 mg elemental iron) and placebo vitamin A (WHO, 1999); vitamin A and iron; or both placebos, all daily for 8 weeks. Maximum haemoglobin was achieved with both vitamin A and iron supplementation.
(12.78g/L, 95% CI 10.86-14.70), with one third of the response attributable to vitamin A (3.68g/L, 95% CI 2.03-5.33) and two thirds to iron (7.71g/L, 95% CI 5.97-9.45). After supplementation the proportion of women who became non-anaemic was 35% in the vitamin A supplemented group (Panth, 1990), 68% in the iron supplemented group (Mahomed, 2000), 97% in the group supplemented with both, and 16% in the placebo group (WHO, 2000). Therefore this study concluded that improvement in vitamin A status may contribute to the control of anaemia in pregnant women.

To date, relatively few large scale surveys have been conducted to estimate the prevalence of vitamin A deficiency in women primarily in Asia and Africa. Although many surveys used the presence of night blindness as an indicator of poor vitamin A status among women, some survey data related to low serum retinol and breast milk vitamin A concentrations are also available. However, very few studies have been conducted to date that quantitatively relate the risk of vitamin A deficiency (defined by any indicator) to adverse health outcomes in women (Huang et al., 2008). After considering the availability of intervention trial data and global prevalence data for vitamin A deficiency in women, a definition related to low serum retinol concentrations among pregnant women in the 15–44-year age range emerged as the most appropriate choice for use in the CRA project. Estimates for the prevalence of vitamin A deficiency have been generated only for pregnant women in the 15–44-year age range primarily because the strongest information is available for this particular group of women (Sommer, 1998). Vitamin A
deficiency in pregnant women aged 15–44 years was operationally defined as:

- Vitamin A deficient: Serum retinol concentration <0.70mmol/l.
- Vitamin A sufficient: Serum retinol concentration ≥0.70mmol/l.

2.5 Pregnancy

Pregnancy, also known as gravidity or gestation, is the time during which one or more offspring develops inside a woman (Abman, 2011). A multiple pregnancy involves more than one offspring, such as with twins (Wylie, 2005). Pregnancy can occur by sexual intercourse or assisted reproductive technology. It usually lasts around 40 weeks from the last menstrual period (LMP) and ends in childbirth (Abman, 2011). This is just over 9 lunar months, where each month is about 29½ days. When measured from conception it is about 38 weeks. An embryo is the developing offspring during the first 8 weeks following conception, after which, the term foetus is used until birth. Symptom of early pregnancy may include a missed periods, tender breasts, nausea and vomiting, hunger, and frequent urination (Wylie, 2005). Pregnancy may be confirmed with a pregnancy test.

Pregnancy is typically divided into three trimesters. The first trimester is from week one through twelve and includes conception. Conception is followed by the fertilized egg traveling down the fallopian tube and attaching to the inside of the uterus, where it begins to form the foetus and placenta. The first trimester carries the highest risk of miscarriage (natural death of embryo or foetus) (Lippincott, 2012). The second trimester is from week 13 through 28. Around the middle of the second
trimester, movement of the foetus may be felt. At 28 weeks, more than 90% of babies can survive outside of the uterus if provided high-quality medical care. The third trimester is from 29 weeks through 40 weeks.

Prenatal care improves pregnancy outcomes (WHO, 2014). This may include taking extra folic acid, avoiding drugs and alcohol, regular exercise, blood tests, and regular physical examinations (WHO, 2014). Complications of pregnancy may include high blood pressure of pregnancy, gestational diabetes, iron-deficiency anaemia, and severe nausea and vomiting among others. Term pregnancy is 37 weeks to 41 weeks, with early term being 37 and 38 weeks, full term 39 and 40 weeks, and late term 41 weeks. After 41 weeks, it is known as post term. Babies born before 37 weeks are preterm and are at higher risk of health problems such as cerebral palsy. It is recommended that delivery not be artificially started with either labor induction or caesarean section before 39 weeks unless required for other medical reasons (WHO, 2014).

2.5.1 Terminology

One scientific term for the state of pregnancy is gravidity (adjective "gravid"), Latin for "heavy" and a pregnant female is sometimes referred to as a gravida. Similarly, the term parity (abbreviated as "para") is used for the number of times a female has given birth, counting twins and other multiple births as one pregnancy, and usually including stillbirths. Medically, a woman who has never been pregnant is referred to as a nulligravida, a woman who is (or has been only) pregnant for the first time as a primigravida (Robinson et al., 1939) and a woman in subsequent pregnancies as multigravida or multiparous.
Women who have never carried a pregnancy achieving more than 20 weeks of gestation age are referred to as nulliparous (MedicineNet, 2000).

### 2.5.2 Signs and symptoms

The symptoms and discomforts of pregnancy are those presentations and conditions that result from pregnancy but do not significantly interfere with activities of daily living or pose a threat to the health of the mother or baby. This is in contrast to pregnancy complications. Still, there is often no clear separation between symptoms versus discomforts versus complications, and in some cases the same basic feature can manifest as either a discomfort or a complication depending on the severity. For example, mild nausea may merely be a discomfort (morning sickness), but if severe and with vomiting causing water-electrolyte imbalance it can be classified as a pregnancy complication (hyperemesis gravidarum).

Common symptoms and discomforts of pregnancy include:

- Tiredness.
- Constipation
- Pelvic girdle pain
- Back pain
- 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.
- 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.

- Urinary tract infection.
- Varicose veins. Common complaint caused by relaxation of the venous smooth muscle and increased intravascular pressure.
- Haemorrhoids (piles) are swollen veins at or inside the anal area, resulting from impaired venous return, straining associated with constipation, or increased intra-abdominal pressure in later pregnancy (Vazquez, 2010).
- Regurgitation, heartburn, and nausea.
- Striae gravidarum, pregnancy-related stretch marks

2.5.3 Complications

Each year, ill-health as a result of pregnancy is experienced (sometimes permanently) by more than 20 million women around the world (WHO, 2009). In 2013 complications of pregnancy resulted in 293,000 deaths down from 377,000 deaths in 1990. Common causes include maternal bleeding (44,000), complications of abortion (44,000), high blood pressure of pregnancy (29,000), maternal sepsis (24,000), and obstructed labor (19,000) (GBD, 2014)

The following are some examples of pregnancy complications:

- Pregnancy induced hypertension
- Anaemia
- Postpartum depression
- Postpartum psychosis
• Thromboembolic disorders. The leading cause of death in pregnant women in the US (Blackwel, 2008)

• PUPPP skin disease that develop around the 32nd week. (Pruritic Urticarial Papules and Plaques of Pregnancy), red plaques, papules, itchiness around the belly button that spread all over the body except for the inside of hands and face.

• Ectopic pregnancy, implantation of the embryo outside the uterus.

• Hyperemesis gravidarum, excessive nausea that is more severe than morning sickness.

There is also an increased susceptibility and severity of certain infections in pregnancy.

2.5.4 Intercurrent diseases

In addition to complications of pregnancy that can arise, a pregnant woman may have intercurrent diseases, that is, other diseases or conditions (not directly caused by the pregnancy) that may become worse or be a potential risk to the pregnancy.

• Diabetes mellitus and pregnancy deals with the interactions of diabetes mellitus (not restricted to gestational diabetes) and pregnancy. Risks for the child include miscarriage, growth restriction, growth acceleration, fetal obesity (macrosomia), polyhydramnios and birth defects.

• Systemic lupus erythematosus and pregnancy confers an increased rate of fetal death in utero and spontaneous abortion (miscarriage), as well as of neonatal lupus.

• Thyroid disease in pregnancy can, if uncorrected, cause
adverse effects on fetal and maternal well-being. The deleterious effects of thyroid dysfunction can also extend beyond pregnancy and delivery to affect neurointellectual development in the early life of the child. Demand for thyroid hormones is increased during pregnancy which may cause a previously unnoticed thyroid disorder to worsen.

- Hypercoagulability in pregnancy is the propensity of pregnant women to develop thrombosis (blood clots). Pregnancy itself is a factor of hypercoagulability (pregnancy-induced hypercoagulability), as a physiologically adaptive mechanism to prevent post partum bleeding (Gresele, 2008). However, when combined with an additional underlying hypercoagulable states, the risk of thrombosis or embolism may become substantial (Gresele, 2008).

2.5.5 Physiology

The most commonly used event to mark the initiation of pregnancy is the first day of the woman's last normal menstrual period, and the resulting fetal age is called the gestational age.
This choice is a result of a lack of a convenient way to discern the point in time when the actual creation of the foetus naturally happens. In case of in vitro fertilisation, gestational age is calculated by days from oocyte retrieval + 14 days (Tunón et al., 2000).

Still, already at the initiation of the preceding menstrual period the female body goes through changes to prepare for an upcoming conception, including a rise in follicle stimulating hormone that stimulates folliculogenesis and subsequently oogenesis in order to give rise to a mature egg cell, which is the female gamete. Fertilization is the event where the egg cell fuses with the male gamete, spermatozoon. After the point of fertilization, the fused product of the female and male gamete is referred to as a zygote or fertilized egg. The fusion of male and female gametes usually occurs following the act of sexual intercourse. It can also occur by assisted reproductive technology such as artificial insemination and in vitro fertilisation, which may be undertaken as a voluntary choice or due to infertility.

The event of fertilization is sometimes used as a mark of the initiation of pregnancy, with the derived age being termed fertilization age, and is an alternative to gestational age. Fertilization usually occurs about two weeks before her next expected menstrual period, and if either date is unknown in an individual case it is a frequent practice to add 14 days to the fertilization age to get the gestational age and vice versa.

2.5.5.2 Development of embryo and foetus

The sperm and the egg cell, which has been released from one of the female's two ovaries, unite in one of the two fallopian
tubes. The fertilized egg, known as a zygote, then moves toward the uterus, a journey that can take up to a week to complete. Cell division begins approximately 24 to 36 hours after the male and female cells unite. Cell division continues at a rapid rate and the cells then develop into what is known as a blastocyst. The blastocyst arrives at the uterus and attaches to the uterine wall, a process known as implantation.

The development of the mass of cells that will become the infant is called embryogenesis during the first approximately 10 weeks of gestation. During this time, cells begin to differentiate into the various body systems. The basic outlines of the organ, body, and nervous systems are established. By the end of the embryonic stage, the beginnings of features such as fingers, eyes, mouth, and ears become visible. Also during this time, there is development of structures important to the support of the embryo, including the placenta and umbilical cord. The placenta connects the developing embryo to the uterine wall to allow nutrient uptake, waste elimination, and gas exchange via the mother's blood supply. The umbilical cord is the connecting cord from the embryo or foetus to the placenta.

After about 10 weeks of gestational age, the embryo becomes known as a foetus instead. At the beginning of the fetal stage, the risk of miscarriage decreases sharply (Lennart, 1990). When the fetal stage commences, a foetus is typically about 30 mm (1.2 inches) in length, and the heart can be seen beating via ultrasound; the foetus can be seen making various involuntary motions at this stage (Kalverboer et al., 2001). During continued fetal development, the early body systems and structures that were established in the embryonic stage continue
to develop. Sex organs begin to appear during the third month of gestation. The foetus continues to grow in both weight and length, although the majority of the physical growth occurs in the last weeks of pregnancy.

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 fetaion. Synapses begin forming at 17 weeks, and at about week 28 begin to multiply at a rapid pace which continues until 3 to 4 months after birth (Illes, 2008).

(1. Embryo at 4 weeks after fertilization) (2. Foetus at 8 weeks after fertilization) (3. Foetus at 18 weeks after fertilization) (4. Foetus at 38 weeks after fertilization)

2.5.5.3 Maternal changes

During pregnancy, the woman undergoes many physiological changes, which are entirely normal, including cardiovascular,
hematologic, metabolic, renal and respiratory changes that become very important in the event of complications. The body must change its physiological and homeostatic mechanisms in pregnancy to ensure the foetus is provided for. Increases in blood sugar, breathing and cardiac output are all required. Levels of progesterone and oestrogens rise continually throughout pregnancy, suppressing the hypothalamic axis and subsequently the menstrual cycle.

Pregnancy is typically broken into three periods, or trimesters, each of about three months. Obstetricians define each trimester as lasting for 14 weeks, resulting in a total duration of 42 weeks, although the average duration of pregnancy is actually about 40 weeks.

2.5.5.3.1 First trimester

Minute ventilation is increased by 40% in the first trimester (Campbell, 2001). The womb will grow to the size of a lemon by eight weeks. Many symptoms and discomforts of pregnancy like nausea and tender breasts appear in the first trimester.[38]

2.5.5.3.2 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. The uterus, the muscular organ that holds the developing foetus, can expand up to 20 times its normal size during pregnancy.

It is not until the second trimester that movement of the foetus, often referred to as "quickening", can be felt. During the second trimester, most women begin to wear maternity clothes.
2.5.5.3.3 Third trimester

Final weight gain takes place, which is the most weight gain throughout the pregnancy. The woman's abdomen will transform in shape as it drops due to the foetus turning in a downward position ready for birth. During the second trimester, the woman's abdomen 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 abdomen up and down. The foetus begins to move regularly, and is felt by the woman.

Head engagement, where the fetal head descends into cephalic presentation, relieves pressure on the upper abdomen with renewed ease in breathing. It also severely reduces bladder capacity, and increases pressure on the pelvic floor and the rectum.

It is also during the third trimester that maternal activity and sleep positions may affect fetal development due to restricted blood flow. For instance, the enlarged uterus may impede blood flow by compressing the lower pressured vena cava, with the left lateral positions appearing to providing better oxygenation to the infant (Stacey, 2011).

2.5.5.3.4 Determining gestational age

Since these are spread over a significant period of time, the duration of pregnancy necessarily depends on the date selected as the starting point chosen.

As measured on a reference group of women with a menstrual cycle of exactly 28-days prior to pregnancy, and who had spontaneous onset of labor, the mean pregnancy length has been estimated to be 283.4 days of gestational age as timed from
the first day of the last menstrual period as recalled by the mother, and 280.6 days when the gestational age was retrospectively estimated by obstetric ultrasound measurement of the fetal biparietal diameter (BPD) in the second trimester (Axelsson et al., 1995). Other algorithms take into account a variety of other variables, such as whether this is the first or subsequent child (i.e., pregnant woman is a primipara or a multipara, respectively), the mother's race, parental age, length of menstrual cycle, and menstrual regularity), but these are rarely used by healthcare professionals. In order to have a standard reference point, the normal pregnancy duration is generally assumed to be 280 days (or 40 weeks) of gestational age.

The best method of determining gestational age is ultrasound during the first trimester of pregnancy. This is typically accurate within seven days (Obstet, 2014). This means that fewer than 5 percent of births occur on the day of being 40 weeks of gestational age; 50 percent of births are within a week of this duration, and about 80 percent are within 2 weeks (Kieler et al., 1995) Once the estimated due date (EDD) is established, it should rarely be changed, as the determination of gestational age is most accurate earlier in the pregnancy.

The most common system used among healthcare professionals is Naegele's rule, which was developed in the early 19th century. This calculates the expected due date from the first day of the last normal menstrual period (LMP or LNMP) regardless of factors known to make this inaccurate, such as a shorter or longer menstrual cycle length. Pregnancy most commonly lasts for 40 weeks according to this LNMP-based method, assuming that the woman has a predictable menstrual
cycle length of close to 28 days and conceives on the 14th day of that cycle.

The average time to birth has been estimated to be 268 days (38 weeks and two days) from ovulation, with a standard deviation of 10 days or coefficient of variation of 3.7% (Jukic et al., 2013).

2.5.5.4 Childbirth

Childbirth is the process whereby an infant is born. 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.

2.5.5.4.1 Timing of childbirth

In the ideal childbirth labor begins on its own when a woman is "at term" (ACOG, 2013). Pregnancy is considered at term when gestation has lasted between 37 and 42 weeks. Unless there is a medical reason to do so, planned delivery of a child should not happen until after the completion of 39 weeks of pregnancy (ACOG, 2013).

Events before completion of 37 weeks are considered preterm (WHO, 2013). Preterm birth is associated with a range of risks and problems and whenever possible should be avoided in favor of giving birth when the pregnancy is at term (Saigal et al., 2008).
Sometimes if a woman's water breaks or contractions before 39 weeks, birth is unavoidable (ACOG, 2014). A natural beginning to an early term delivery is usually a physiological sign that the time is right for birth and not usually a cause for worry.[citation needed] Intentionally planning to give birth before 39 weeks by Caesarean section or labor induction, even if considered "at term", results in an increased risk of complications and harm to mother and child (ACOG, 2013). This is from factors including underdeveloped lungs of newborns, infection due to underdeveloped immune system, feeding problems due to underdeveloped brain, and jaundice from underdeveloped liver (Michele, 2011).

Babies born between 39 and 41 weeks gestation have better outcomes than babies born either before or after this range. This special time period is called "full term". Whenever possible, waiting for labor to begin on its own in this time period is best for the health of the mother and baby. Because of the likelihood of increased problems including the need for a c-section, between 39–41 weeks inducing labor without a medical indication is discouraged unless the cervix is favorable (ACOG, 2013).

Events after 42 weeks are considered postterm (Norwitz et al., 2012). When a pregnancy exceeds 42 weeks, the risk of complications for both the woman and the foetus increases significantly. Therefore, in an otherwise uncomplicated pregnancy, obstetricians usually prefer to induce labour at some stage between 41 and 42 weeks.
## Stages of Pregnancy Term

<table>
<thead>
<tr>
<th>Stage</th>
<th>Starts</th>
<th>Ends</th>
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</thead>
<tbody>
<tr>
<td>Preterm</td>
<td>-</td>
<td>at 37 weeks</td>
</tr>
<tr>
<td>Early term</td>
<td>37 weeks</td>
<td>39 weeks</td>
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<tr>
<td>Full term</td>
<td>39 weeks</td>
<td>41 weeks</td>
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<tr>
<td>Late term</td>
<td>41 weeks</td>
<td>42 weeks</td>
</tr>
<tr>
<td>Postterm</td>
<td>42 weeks</td>
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</tbody>
</table>

### 2.5.5.4.2 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 begins the return to prepregnancy conditions that includes changes in hormone levels and uterus size.

### 2.5.6 Diagnosis

The beginning of pregnancy may be detected either based on symptoms by the pregnant woman herself, or by using medical tests with or without the assistance of a medical professional. Approximately 1 in 475 women at 20 weeks, and 1 in 2500 women at delivery, refuse to acknowledge that they are pregnant, which is called denial of pregnancy (Jenkins, 2011). Some non-pregnant women have a very strong belief that they are pregnant along with some of the physical changes. This condition is known as pseudocyesis or false pregnancy (Gabbe, 2010).

#### 2.5.6.1 Physical signs

Most pregnant women experience a number of symptoms (NHS, 2010), which can signify pregnancy. The symptoms can include nausea and vomiting, excessive tiredness and fatigue, cravings for certain foods that are not normally sought
out, and frequent urination particularly during the night.

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), and 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) (Mayo, 2007). Breast tenderness is common during the first trimester, and is more common in women who are pregnant at a young age (David, 2008). Shortly after conception, the nipples and areolas begin to darken due to a temporary increase in hormones. This process continues throughout the pregnancy.

2.5.6.2 Biomarkers

Pregnancy detection can be accomplished using one or more various pregnancy tests (NHS, 2010), which detect hormones generated by the newly formed placenta, serving as biomarkers of pregnancy. Blood and urine tests can detect pregnancy 12 days after implantation (Qasim, 2010). Blood pregnancy tests are more sensitive than urine tests. Home pregnancy tests are urine tests, and normally detect a pregnancy 12 to 15 days after fertilization.
2.5.6.3 Ultrasound

Obstetric ultrasonography can detect some congenital diseases at an early stage, estimate the due date as well as detecting multiple pregnancy (Whitworth et al., 2010). The resultant estimated gestational age and due date of the foetus are slightly more accurate than methods based on last menstrual period (Nguyen, 1999). In those who are at low risk it is unclear if obstetric ultrasound before 24 weeks makes a significant difference in outcomes.

2.5.7 Management

2.5.7.1 Attending prenatal care

Prenatal medical care is the medical and nursing care recommended for women before and during pregnancy. The aim of good prenatal care is to identify any potential problems early, to prevent them if possible (through recommendations on adequate nutrition, exercise, vitamin intake etc.), and to manage problems, possibly by directing the woman to appropriate specialists, hospitals, etc. if necessary.

2.5.7.2 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.

Adequate periconceptional folic acid (also called folate or Vitamin B9) intake has been shown to decrease the risk of fetal neural tube defects such as spina bifida, a serious birth defect. The neural tube develops during the first 28 days of pregnancy, explaining the necessity to guarantee adequate periconceptional
folic acid (Klusmann, 2005). Folate (from folia, leaf) is abundant in spinach (fresh, frozen, or canned), and is found in green leafy vegetables e.g. salads, beets, broccoli, asparagus, citrus fruits and melons, chickpeas (i.e. in the form of hummus or falafel), and eggs. In the United States and Canada, most wheat products (flour, noodles) are fortified with folic acid (CDC, 2008).

DHA omega-3 is a major structural fatty acid in the brain and retina, and is naturally found in breast milk. It is important for the woman to consume adequate amounts of DHA during pregnancy and while nursing to support her well-being and the health of her infant. Developing infants cannot produce DHA efficiently, and must receive this vital nutrient from the woman through the placenta during pregnancy and in breast milk after birth (Salem, 2001).

Several micronutrients are important for the health of the developing foetus, especially in areas of the world where insufficient nutrition is prevalent. (Theobald, 2007). In developed areas, such as Western Europe and the United States, certain nutrients such as Vitamin D and calcium, required for bone development, may require supplementation (Basile et al., 2007).

Dangerous bacteria or parasites may contaminate foods, including Listeria and Toxoplasma gondii. Careful washing of fruits and raw vegetables may remove these pathogens, as may thoroughly cooking leftovers, meat, or processed meat. Soft cheeses may contain Listeria; if milk is raw, the risk may increase. Cat feces pose a particular risk of toxoplasmosis. Pregnant women are also more prone to Salmonella infections.
from eggs and poultry, which should be thoroughly cooked. Practicing good hygiene in the kitchen can reduce these risks (Tarlow, 1994).

2.5.7.2.1 Weight gain

The amount of healthy weight gain during a pregnancy varies (Viswanathan et al., 2008). Weight gain is only partly related to the weight of the baby and growing placenta, and includes extra fluid for circulation, and the weight needed to provide nutrition for the growing foetus. Most needed weight gain occurs later in pregnancy.

The Institute of Medicine recommends an overall pregnancy weight gain for those of normal weight (body mass index of 18.5–24.9), of 11.3–15.9 kg (25–35 pounds) having a singleton pregnancy. Women who are underweight (BMI of less than 18.5), should gain between 12.7–18 kg (28–40 lbs), while those who are overweight (BMI of 25–29.9) are advised to gain between 6.8–11.3 kg (15–25 lbs) and those who are obese (BMI>30) should gain between 5–9 kg (11–20 lbs).

During pregnancy, insufficient or excessive weight gain can compromise the health of the mother and foetus. The most effective interventions for weight gain in underweight women is not clear. Being or becoming very overweight in pregnancy increases the risk of complications for mother and foetus, including cesarean section, gestational hypertension, pre-eclampsia, macrosomia and shoulder dystocia (Viswanathan et al., 2008). It can make losing weight after the pregnancy difficult (Thangaratinam et al., 2012).
2.5.7.3 Medication use

Drugs used during pregnancy can have temporary or permanent effects on the foetus. Therefore, many physicians would prefer not to prescribe for pregnant women, the major concern being over teratogenicity of the drugs.

2.5.7.3.1 Use of recreational drugs

Use of recreational drugs in pregnancy can cause various pregnancy complications.

- **Ethanol** during pregnancy can cause fetal alcohol syndrome and fetal alcohol spectrum disorder. A number of studies have shown that light to moderate drinking during pregnancy might not pose a risk to the foetus, although no amount of alcohol during pregnancy can be guaranteed to be absolutely safe (Ornoy, 2010).

- **Tobacco smoking** and pregnancy, when combined, can cause a wide range of behavioral, neurological, and physical difficulties. Smoking during pregnancy causes twice the risk of premature rupture of membranes, placental abruption and placenta previa (Hackshaw, 2011). Also, it causes 30% higher odds of the baby being born prematurely.

- **Prenatal cocaine exposure** is associated with, for example, premature birth, birth defects and attention deficit disorder.

- **Prenatal methamphetamine exposure** can cause premature birth and congenital abnormalities. Other investigations have revealed short-term neonatal outcomes to include small deficits in infant neurobehavioral function and growth restriction when compared to control infants. Also, prenatal
methamphetamine use is believed to have long-term effects in terms of brain development, which may last for many years.

- Cannabis in pregnancy is possibly associated with adverse effects on the child later in life.

2.5.7.4 Exposure to environmental toxins

Intrauterine exposure to environmental toxins in pregnancy has the potential to cause adverse effects on the prenatal development of the embryo or foetus, as well as pregnancy complications. Potential effects of toxic substances and pollution include congenital abnormalities. Also, neuroplastic effects of pollution can give rise to neurodevelopmental disorders for the child later in life. Conditions of particular severity in pregnancy include mercury poisoning and lead poisoning.

2.5.7.6 Exercise

Regular aerobic exercise during pregnancy appears to improve (or maintain) physical fitness; however, the quality of the research is poor and the data was insufficient to infer important risks or benefits for the mother or infant (Kramer, 2006). Physical exercise during pregnancy does appear to decrease the risk of Caeserian section (C-section).

The Clinical Practice Obstetrics Committee of Canada recommends that "All women without contraindications should be encouraged to participate in aerobic and strength-conditioning exercises as part of a healthy lifestyle during their pregnancy". Although an upper level of safe exercise intensity has not been established, women who were regular exercisers before pregnancy and who have uncomplicated, healthy pregnancies
should be able to engage in high intensity exercise programs, such as jogging and aerobics for less than 45 minutes, with no adverse effects if they are mindful of the possibility that they may need to increase their energy intake and are careful to not become overheated. In the absence of either medical or obstetric complications, they advise an accumulation of 30 minutes a day of exercise on most if not all days of the week.

2.5.7.7 Sleep

It has been suggested that shift work and exposure to bright light at night should be avoided at least during the last trimester of pregnancy to decrease the risk of psychological and behavioral problems in the newborn. A proposed underlying mechanism is that the circadian rhythm of the mother programs the developing rhythm of the foetus (Reiter et al., 2014).

2.5.8 Society and Culture

In most cultures, pregnant women have a special status in society and receive particularly gentle care (Womack, 2010). At the same time, they are subject to expectations that may exert great psychological pressure, such as having to produce a son and heir. In many traditional societies, pregnancy must be preceded by marriage, on pain of ostracism of mother and (illegitimate) child.

2.5.8.1 Arts

Due to the important role of the Mother of God in Christianity, the Western visual arts have a long tradition of depictions of pregnancy (Rossi et al., 2005).

Pregnancy, and especially pregnancy of unmarried women, is also an important motif in literature.
2.5.8.2 Infertility

Modern reproductive medicine offers many forms of assisted reproductive technology for couples who stay childless against their will, such as fertility medication, artificial insemination, in vitro fertilization and surrogacy.

2.5.8.3 Abortion

An abortion is the termination of an embryo or foetus, either naturally or via medical methods. When done electively, it is more often done within the first trimester than the second, and rarely in the third. Not using contraception, contraceptive failure, poor family planning or rape can lead to undesired pregnancies. Legality of socially indicated abortions varies widely both internationally and through time.

2.5.8.4 Legal protection

Many countries have various legal regulations in place to protect pregnant women and their children. Maternity Protection Convention ensures that pregnant women are exempt from activities such as night shifts or carrying heavy stocks. Maternity leave typically provides paid leave from work during roughly the last trimester of pregnancy and for some time after birth. Notable extreme cases include Norway (8 months with full pay) and the United States (no paid leave at all except in some states). Moreover, many countries have laws against pregnancy discrimination.