REVIEW OF LITERATURE
Lipid profile during normal pregnancy:

It has been known for years that an increase in circulating lipids occurs during pregnancy. Even though cholesterol and other lipid substances have been the centre of considerable lay interest and also the subject of much scientific investigations relatively few reports have dealt with serial studies of lipids during pregnancy.

Based upon virtually no information, Becquerel and Rodier\(^1\) in 1845 suggested that hyperlipaemia occurred during pregnancy. They hypothesized that this change represented an increase in blood cholesterol as well as increase in lipid phosphorus during pregnancy.

Two years later Vershow (1847)\(^2\) showed that the milky appearance of sera of some pregnant women was due to the presence of fat, this was demonstrated by shaking the sera with ether so that the fat could be extracted. Many of the early investigators felt that the hyperlipemia of pregnancy probably occurred as a result of increased fat absorption, poorly assimilated chyle, or from the mixing of milk with blood for the nourishment of the fetus.
The first clinical study was undertaken in 1911 when Chauffard and associates\(^3\) demonstrated an increase in blood cholesterol during pregnancy. In the same year Neumann and Herrmann\(^4\) studied the lipid particles in the whole blood and reported increase in cholesterol during pregnancy.

The development of micro methods made it possible to study blood lipids partitions accurately. This innovation led to some diversity of opinion as to which lipid fraction were grossly changed during pregnancy. It was not until 1934 when Boyd\(^5\) showed that the principle cause for the widely divergent results reported before that time was found to be the fact that some investigators were reporting determination performed on whole blood while other reports were based upon investigations of plasma and serum specimens. Dieckmann's\(^6\) (1934) report dealt only with plasma cholesterol. Boyd found that almost no change occurred in lipid content of red blood cells during pregnancy. However, striking changes were noted in the plasma lipids. Ever since his report all investigations has been focussed on plasma and serum lipids rather than on whole blood studies.

Different investigators have reported increased serum cholesterol level at different periods of gestation. Herrmann & Neumann (1972) analysed the serum of pregnant women in various months of gestation, thirteen of these
were under seven months. He concluded that during first 6-7 months, the serum cholesterol might be increased and that during the last two months (thirty two cases) an increase in serum cholesterol was the rule. Plass and Tempkins\textsuperscript{7} (1923) also have given figures for the blood and lipids particularly cholesterol during pregnancy. These figures indicate a gradual rise from 4th month to term.

Tyler and Underhill\textsuperscript{8} (1929) determined whole blood cholesterol in normal and pregnant women. They studied gravid uterus in each month of pregnancy beginning with the third month and reported that cholesterol and ester cholesterol increases gradually until term, at that time it was roughly one third higher than that at three months.

Gardner and Gainsborough (1929)\textsuperscript{9,10} reported that free cholesterol increases during pregnancy to the 30th week with a decrease in ester cholesterol to about the same time. In their series, there occurs then, a reversal of the curve so that at parturition, approximately a normal relationship exists again. Kaufmann & Mihlbock\textsuperscript{11} (1933) did not notice these fluctuations but they reported little variations from the second month of gestation to term. Bugnard\textsuperscript{12}, Columbus and Guilhelm, Hinglais and Coverto (1940) found an increase in total cholesterol in later months of pregnancy.
Dieckmann & Wagner (1934)\textsuperscript{13} found the total cholesterol to increase to 23 percent above the first trimester level and which decreases to 27 percent at the eighth post-partum week from the value noted at term. This rise noted by Dieckmann is considerably lower than De Alvarez et al (1959)\textsuperscript{14} findings of 54 percent increase in third trimester values above the first trimester values for total cholesterol and a 23 percent decrease in the values 6 to 7 weeks post-partum for total cholesterol and as compared to the third trimester values.

Oliver and Boyd (1955)\textsuperscript{15} after careful study of 12 normal primigravida stated that between 31st and 33rd weeks of pregnancy, there was a highly significant rise in plasma ester and total cholesterol. By the 20th post-partum week these values had decreased considerably but were all higher than the levels at the 12th week of pregnancy.

Mc Eachern and Gilmour determined whole blood cholesterol in twelve pregnant women and concluded that a marked elevation was found in about 30% of normal pregnant women beginning about the sixth week prior to delivery and that about 80% had a level above normal on the first day after delivery. The figures were still high on the 12th post-partum day. Later on this increase in total serum cholesterol during pregnancy was also proved by Mullick
and Bagga\textsuperscript{16} (1964), Konttinen et al\textsuperscript{17} (1964), Maria R. Waith et al (1975), Kalkhoff\textsuperscript{18} (1978), Darmandy et al (1982)\textsuperscript{19}.

**Hormones in pregnancy and their role in maintenance of pregnancy:**

Various hormones which are important for maintenance of pregnancy and which have influence on blood lipids are as follows:

1. **Oestrogen** - Oestriol is the main pregnancy oestrogen which accounts for 80-90% of oestrogen formed in late pregnancy. It has modest biological activity relative to oestradiol, the predominant oestrogen secreted by non-gravid female.

   In classic experiment Ryan\textsuperscript{20} (1959 a) found that there is an exceptionally high capacity of placenta to convert certain C\textsubscript{19}-steroids to oestrogen. The first proof that the placenta uses plasma borne precursors as substrates for oestrogen biosynthesis shown by Baulieu and Dray (1963); Siiteri and Mac Donald (1963)\textsuperscript{21}.

   In 1966 Mac Donald and Siiteri also showed that 50% of oestradiol derived from maternal source & 50% from fetal source with 50% from fetal source in dehydroepiandrosterone sulfate precursor for which is cholesterol.
Effect of oestrogen on lipid profile:

Eilert (1949) found that oestrogen administration to women evoked an increase in the plasma total lipids. Oliver and Boyd (1955)\textsuperscript{15} stated that large physiological increase in circulating estrogen is associated with change in blood lipids of a type found in atherosclerosis while administered oestrogen can reverse such lipid changes.

Russ and associates (1955)\textsuperscript{22} found that the administration of estrogen lowered the betalipoprotein but raised the alpha lipoprotein.

Devi & Sharma (1972)\textsuperscript{23}, Gupta (1976) found that most plasma lipids and lipoprotein usually increased in women who used contraceptive that contains estrogen and progestin.

Wallace et al (1979)\textsuperscript{24} observed that total cholesterol, low density lipoprotein and very low density lipoprotein all have been elevated in women who used oral contraceptives.

As the hormones like oestrogen and progesterone are important for continuation of pregnancy. It has been shown that outcome can be predicted by the subsequent rise in pregnanediol output as pregnancy progressed (Machanghten and Michie, 1960).
In other study by Klopper and Billiwitz (1963) they have estimated oestriol excretion in successful pregnancy and habitual abortion and shown that oestriol output in successful pregnancy approximates closely to normal values which that of abortion fell week by week until 10 weeks it was less than 40% of normal\textsuperscript{25}.

**Progesterone**:

After the first few weeks of gestation, very little of progesterone produced arises in the ovary (Diczfalusy and Troen, 1961)\textsuperscript{26}. Daily production rate of progesterone in late normal singleton pregnancy is about 250 mg (Pearlman, 1957)\textsuperscript{27}.

Progesterone levels in maternal peripheral plasma increases progressively with gestation. Progesterone is formed from cholesterol in all steroidogenic tissues in a two step enzymatic reaction. Simpson and colleagues (1954) found that perfusion of placenta in vitro with radiolabelled cholesterol resulted in formation of radiolabelled progesterone\textsuperscript{28}.

Bloch (1945) and Werbin and co-workers (1957) demonstrated that after the intravenous administration of radiolabelled cholesterol to pregnant women the specific activity of urinary pregnanediol was similar to that of plasma cholesterol\textsuperscript{29}. 

Hellig and associates (1970) also found that maternal plasma cholesterol was the principal precursor (upto 90%) of progesterone biosynthesis in human pregnancy\textsuperscript{30}.

Simpson and associates demonstrated that the trophoblast preferentially uses low density lipoprotein cholesterol for progesterone biosynthesis. This subject was reviewed recently by Casey and colleagues (1992)\textsuperscript{31}.

**Effect of progesterone on lipid profile**:

Spellacy (1970) did not find any significant change in triglyceride levels when only norgestrel was used for contraception.

Corredor et al (1970) found significant rise in triglyceride levels after 6-12 months use of oral pills\textsuperscript{32}.

Barton in 1970 studied the effect of different dose regime of oral contraceptives on serum lipid levels. He found significant rise in serum triglyceride levels in females using combined pills but there was no change seen with progestin only pills.

Spellacy (1976) observed that effect of norgestrel on carbohydrate and lipid metabolism. There was no significant change in serum cholesterol levels.

Lauritzen in 1977 observed a decreasing effect of norethisterone on cholesterol and triglyceride levels of
beta lipoproteins\textsuperscript{33}. He also suggested that there is no influence of hydroxyprogesterone on cholesterol level.

Bradley et al (1978) studied various exogenous progestins\textsuperscript{34} and found that they constitute a heterogeneous group of members which have in common the capacity to influence the endometrium. In their effect on lipoproteins however, progestins derived from 17 alpha hydroxyprogesterone (medroxy progesterone) and others are relatively innert which those derived from 19 nortestosterone (levonorgestrol, norethisterone acetate and others) decreases high density lipoprotein.

Coym (1982) studied the effect of progesterone and found that there was a significant elevation in triglyceride level from 60-71, 94-97 mg/dl in subject using 150 ug and 1 ug norethindrone and norethindrone acetate respectively. It appears that oestrogen is only responsible factor and progesteron counters its effect.

Krauss et al (1983) observed effects of two different progesterone pills and found that very low density lipoprotein increased with only noregestrel. Low density lipoprotein was significantly lower in norethisterone group. Results were variable with very low density lipoprotein levels.

\textbf{Habitual Abortions and Lipids :}

Recurrent pregnancy loss or habitual abortion is defined as three or more successive spontaneous abortions.
This subject is of special interest because its consideration raises to many unresolved problems. The aetiology is various. The cases fall into two main groups - in the larger the sequence of abortion is due to the chance occurrence in successive pregnancies of one of the random or fortuitous causes of abortion. The importance of these for fortuitous causes is shown by the high proportion of all pregnancies that end in abortion as compared with the relatively few instances of recurrent abortion. In the smaller group abortion sequence is attributable to a truly recurrent cause.

In practice, because of our ignorance of the nature of some of the recurrent causes it is not possible to discern to which of the group a given abortion sequence should be assigned and in order to segregate the truly recurrent cases an indirect approach was suggested by Malpas (1938)\textsuperscript{35}.

The accepted incidence of abortion in all pregnancies is from 18-20%. Given a general incidence of 18% it follows that of 100 women pregnant for the first time a certain number \(x\) will abort because of a fortuitous cause, a certain number \(y\) because of recurrent cause and \(x + y\) will equal 18. If the 18 women who abort become pregnant again, those in whom a recurrent factors present will abort again and the others will still be subject to the random causes of abortion and the \(x\) percent of them will abort again
In this way it is possible to draw up a table showing how many of the original 100 women will have one, two or three or more abortion in succession. Making this assumption, the chances of second pregnancy continuing one abortion is 78% after 2 abortion 62% and after 3 abortion 27% and after 4 abortion 6%. This progressive fall in the spontaneous abortion cure rate means that after three successive abortions there is an overwhelming likelihood that a truly recurrent cause is present (Malpas).

Later on Macgregor and Stewart (1939) have modified some details of this theory. They sum up their examination of the problem with the statement that in a series of cases with at least two successive abortions, but including a number with three, the expectation of the abortion in next pregnancy is 65%. The view of Malpas, MacGregor and Stewart have been widely accepted for many years and as a result an unduly gloomy prognosis has often been given. It is now an established fact that the abortion incidence predicted by this way does not confirm to what occur in practice.

Goldzieher and Benigno (1958) in a critical review of the subject attached the Malpas formula and claimed that it was only after four consecutive abortions that any appreciable alteration in the abortion rates was observed.
Mann (1959) also criticized the inaccuracy of mathematical prediction of abortion sequence. He commented on the fact that results varying from good to excellent had been achieved by many different therapies. Similar views were expressed by Stallworthy (1959)\textsuperscript{38}.

The implantation of the conceptus, the support of embryonic development and the continuation of pregnancy depends on a complex interaction of hormonal effect on the ovary and the uterus. When a woman presents with two or more first trimester spontaneous abortion, a persistent or recurrent endocrine defect must be ruled out.

Among the hormonal causes hypothyroidism has been reported to cause both infertility and increased rate of fetal loss. In 1951 Jones and Delfs reported 63.5\% prevalence of hypothyroidism in habitual abortus based on the measurements of basal metabolic rate (BMR) and blood cholesterol levels\textsuperscript{39}. In 1962 Greenman and co-workers uncovered a history of spontaneous abortion or stillbirth in six of seven women with a low serum butanol extractable iodine.

Using current radio-immunoassay techniques to measure thyroid functions, Tho and colleagues in 1979\textsuperscript{40} and Harger and associates in 1983\textsuperscript{41} failed to demonstrate conclusive evidence of thyroid disease in any of the 219 women they evaluated.
Although thyroid function assessments are simple and relatively inexpensive, their utility in diagnosing recurrent abortion is so small that justification in asymptomatic women is difficult. However, the prevalence of thyroid antibodies among women having two or more consecutive spontaneous abortion justifies measurement to help to diagnose autoimmune cause of recurrent abortion.

Evidence for carbohydrate intolerance leading to recurrent miscarriages also is poorly substantiated. In fact, there is no data that support a role for subclinical or adequately controlled diabetes mellitus in cases of pregnancy wastage.

Crane and Wahl studied the overall incidence of spontaneous abortion among 154 diabetic pregnant mother from 1977 to 1980 and compared them with a matched control groups, and there was no increase incidence of recurrent abortion in diabetic patients.

For most women with recurrent first trimester spontaneous abortions the routine performance of a glucose tolerance test is therefore not indicated. For a patient with an unexplained second trimester or third trimester pregnancy loss or with clinical signs of diabetes mellitus, an investigation of carbohydrate intolerance is warranted.

So among the endocrine defects inadequate luteal phase remains the important cause for recurrent abortions.
Luteal phase defect was defined in 1949 by Jones in patients with reproductive failure \(^{43}\).

Jones and Delfs in 1951 reported a 35% incidence of luteal phase deficiency in patients with recurrent abortions \(^{39}\).

Botella Llusia (1962) found that 38% of women with three or more consecutive abortions had a poorly developed secretory endometrium, compared with a 6% incidence in infertile women \(^{44}\).

In a series heavily weighted towards genetic abnormalities, Tho et al (1979) \(^{40}\) reported that 23% of women with two or more histologically documented abortions or one or more abortions with a phenotypically abnormal child had dys-synchronous endometrial development on biopsy study.

The corpus luteum is an unusual endocrine gland, diverse in function and important for successful reproduction in all mammalian species. Luteectomy before 7 weeks of gestation causes abortion in most women (Csapo A.I., 1972). The substance secreted by the corpus luteum responsible for successful pregnancy was shown as early as 1929 by Allen and Corner to be progesterone \(^{46}\). Further evidence that corpus luteum function necessary for implantation and early embryo growth can be replaced by hormones alone, comes from
studies of women receiving donor oocytes\textsuperscript{47,48} (Sauer, M.U., 1992; Meldrum, 1993).

In 1991 Asrinbekova, Karpova & Muiashko studied the state of sex hormone reception in the endometrium of women with late habitual abortion and found that the oestrogen receptor/progesteron receptor ratio in the cytosol in the endometrium at secretory phase of menstrual cycle was higher in cases of patients with habitual abortion than in normal non-pregnant females.

In 1993 Bopp & Shoupe\textsuperscript{49} diagnosed luteal phase defect when mid luteal serum progesteron level $\leq 10$ ng/ml and advised endometrial biopsy when progesteron levels are $\geq 10$ ng/ml in patients with habitual abortion & unexplained fertility.

In 1994 Jordan Craig, O., Cliflor O.K. studied luteal phase defect and concluded that luteal phase defect is relatively uncommon but important cause of infertility and habitual abortion\textsuperscript{50}. They recommended tests for determination of LPD is a mid-luteal phase though serum progesterone level $\leq 10$ ng/ml or sum of three progesterone levels that is $\leq 30$ ng/ml. The endometrial biopsy is a second time test that is only recommended when LPD needs to be evaluated in a treated cycle (ovulation induction or supplemental progesterone).
Intra-uterine Growth Retardation:

It was not until about 30 years ago that physicians first recognized that runting or fetal growth retardation was a human as well as animal phenomenon. In 1961 Warkany and co-workers reported normal values for infant weights, lengths and head circumferences and defined fetal growth retardation.

In 1962, WHO introduced the term low birth weight for all babies weighing less than 2500 gm as a single category.

Gruenwald (1963) reported that approximately one third of low birth weight infants were mature and their small size could be explained by chronic fetal distress probably due to placental insufficiency.

In 1963 Lubchenco and co-workers from Denner published detailed comparisons of gestational age to birth weights is an effort to derive norms for expected fetal size and therefore, growth at a given gestational week.

Battaglia and Lubchenco (1967) then classified small for gestational age (SGA) infants as those whose weights were below the 10th percentile for their gestational age.
Large for gestational age infants had weight above the 90th percentile for their gestational age. These defined as small for gestational age were shown to be at increased with for early neonatal death (Koops and associates, 1982)\textsuperscript{54}.

The impact of population differences on fetal growth standards cannot be over emphasized. Goldenberg and associates (1989 b) reviewed studies on fetal growth published in the English literature since 1963 and in part due to population differences concluded that there is currently no single national standard for fetal growth retardation.

Kramer (1987)\textsuperscript{55} reviewed 895 studies on fetal growth in English and French languages published between 1970 and 1984 and concluded that there was great confusion and controversy despite the profuse number of studies.

Problems with growth retarded fetuses - Wennergren and co-workers (1988) analysed the neonatal performance of 160 infants defined to be growth retarded because of their birth weight was at or two standard deviation from the mean. In most cases (83%) growth retardation had been suspected antenatally by birth weight less than 2 standard deviation of the mean for that period of gestation. Hypoglycemia and hypothermia occurred
frequently. The major hazard of growth retardation were stillbirth and fetal distress. Similar observations have been made by Villar and colleagues (1990)\textsuperscript{56} for growth retardation at term and by Wesser and associates (1986) between 25 and 34 weeks.

Autopsy findings in small for gestational age infants have revealed two basic pattern of impaired fetal growth (Gruenwald, 1963; Naye and Kelly, 1966). One of these is designated as symmetrical growth retardation because all body organs tends to be proportionately reduced in size and asymmetrical when some body organs are more affected and then others.

Factors regulating fetal growth are mainly genetic and racial. The neonates of the Indian and Chinese weigh less than those of Europeans or the Africans (Ashcroft and Desai, 1976)\textsuperscript{57}. The fetus growth is also influenced by the maternal weight, height, age, parity and duration of gestation. Social deprivation influences height and shorter women are not optimal reproductor as far as support of fetal growth is concerned (Gruenwald, 1968).

Apart from fetal cause of intra-uterine growth retardation maternal and placental causes are important. Hypertension during pregnancy causes intra-uterine growth retardation. It varies with mean arterial pressure at
4-6 months — higher it is, lower the birth weight (Page and Christiansson, 1976).

Boyd & Scott (1985) showed that compared to normal, the placentae in pre-eclampsia and intra-uterine growth retardation were of a lower volume of parenchyma and villous surface with increased areas of infarction.

Poor maternal nutritional status also affects fetal growth. Pregnancy weight of 40 kg or below, poor weight gain in pregnancy (less than six kg), Anaemia (Hb. less than 8 gm/dl) in pregnancy and mid-arm circumference (less than 20 cm.) were associated with low birth weight babies (Jayam et al, 1984). Acute starvation restricts fetal growth with birth weight of 300-400 gm. due to loss of body fat (Hytten, 1979) with nutritional supplements (Calories protein, iron and folic acid) in the 2nd half of pregnancy, there is fetal oocyst gain of over 200 gm. compared with controls (Venkatachalam, 1962; Iyengar & Rajalakshmi, 1974; Lachting et al, 1975). Biale (1983) studied lipolytic activity in the placenta of chronically deprived fetuses, concluded that lipoprotein lipase activity was significantly greater in placentas of pre-eclamptic women and in placenta of intra-uterine growth retarded fetuses.
Iwaszkiewicz, Pawlowska (1986)\textsuperscript{62} found that pregnancy complicated by intra uterine growth retardation, the free fatty acids concentration in amniotic fluid was almost three times higher than in normal pregnancy.

In 1980 Economide & Crook\textsuperscript{63} showed that small for gestational age fetuses had hyper-triglyceridemia and hypoglycaemia and hypoinsulinemia.

Recently Berg, Ronald, Sande (1994)\textsuperscript{64} found that high lipoprotein(a) | Lp(a) | level in maternal serum can interfere with placental circulation and causes fetal growth retardation.