REVIEW OF LITERATURE
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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 lipids 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 hyperlipæmia occurred during pregnancy. They hypothesized that this change represented an increase in blood cholesterol as well as increase in lipid phosphorous during pregnancy. Two years later Vershow\(^2\) (1847) showed that the milky appearance of sera of some pregnant women was due to the presence of fat. The first clinical study was undertaken by Chauffard and Associates\(^3\). In 1911 who demonstrated an increase in blood cholesterol during pregnancy. In the same year Neumann & Herrmann\(^4\) studied the lipid particle 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. 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 specimen Dickmann's\(^6\) 1934 report dealt only with plasma cholesterol. Boyd found that almost no change occurred in lipid content of RBG during pregnancy, however striking changes were noted in the plasma lipids.

Different investigators have reported increased serum cholesterol level at different periods of gestation. Herrmann & Neumann (1972) analysed the serum of pregnant women and concluded that during first 6-7- months, serum cholesterol might be increased and that during the last two months an increase was the rule. Plass & Temkins\(^7\) (1923) also have given rising figures of cholesterol during pregnancy from 4th month till term. Tyler & Underhill\(^8\) 1929 determined that cholesterol and cholestrol ester increases gradually till term.
Gardner and Gainsborough\textsuperscript{9,10} (1929) reported that free cholestrol increases during pregnancy to the 30\textsuperscript{th} week with a decrease in ester cholestrol to about the same time Bugnard\textsuperscript{11}, Columbus and gwilheim . Hinglais and Covert (1940) found an increase in total cholestrol in later months of pregnancy.

Dickmann & Wagner\textsuperscript{12} (1934) found the total cholestrol to increase to 23\% above the first trimeter level , which decreases to 27\% at eighth post-partum week from the values noted at term . This rise noted by Dickmann is considerably lower than De-Alvarez\textsuperscript{13} et al (1959) findings of 54\% increase in third trimeter for total cholestrol and a 23\% decrease in the values 6-7 weeks post partum for total cholestrol and as compared to the 3\textsuperscript{rd} trimeter values. Oliver and Boyd\textsuperscript{14} (1955) after careful study of 12 normal primigravida stated that between 31\textsuperscript{st} and 33\textsuperscript{rd} week of pregnancy , there was a highly significant rise in plasma ester and total cholestrol . By the 20\textsuperscript{th} week post partum these values decreased considerably but were all higher than the level at 12\textsuperscript{th} week of pregnancy.

Mc. Eachern and Gilmour determined whole blood cholestrol in 12 pregnant women and concluded that marked elevation was found in about 30\% of normal pregnant women beginning about 6th week prior to delivery and that about 80\% had a level above normal on the first day after delivery. the figures were still higher on the 12th post partum day . Later on this increase in total serum cholestrol during pregnancy was also proved by Mullickand Bagga\textsuperscript{15} (1964) , Konttinen\textsuperscript{16} et al (1964) . Maria R . Waih et al (1975) , Kalkhoff\textsuperscript{17} (1978) , Darmandy\textsuperscript{18} et al 1982 .

Salamesh and Mastrogiannis (1994) observed that plasma lipid lipoprotein undergo both qualitative and quantitative changes during pregnancy there is a gradual two to three tfold increase in triglyceride level and they reach their peak 1200 mg/dl to 3000 mg / dl . St term & gradually falls thereafter by 36 week of gestation , VLDL and other lipoprotein particles increase their triglyceride content proportionately to each other and to increase in serum triglyceride total cholestrol level at term, changes less dramatically with only a 50-6 changes in plasma lipid and lipoproteins during pregnancy are thought to b adaptive . The rise in plasma triglyceride provide maternal fuel saving the glucose for factor . The rise in 2 DL-C appears to be necessary for placental steriodogenesis . Hypocholesterolemia caused by hypo betalipoprotein leads to decrease levels of estrogen and progesterone in affected pregnant women.
Hormones in pregnancy and their role in maintenance of pregnancy

1. Oestrogen - oestrial is the main pregnancy oestrogen which accounts for 80-90% of oestrogen formed in late pregnancy. In classic experiment Ryan\textsuperscript{19} (1959) found that there is an exceptionally high capacity of placenta to convert certain C19 steroids to oestrogen. The first proof that placenta uses plasma borne precursors as substrates for oestrogen biosynthesis shown by Baulieu and Bray (1963); Sütteri and Mac Donald\textsuperscript{20} (1963)

Effects of oestrogen on lipid profile

Eilbert (1949) found that oestrogen administration to women evoked an increase in the plasma total lipids. Russ and Associates\textsuperscript{21} (1955) found that the administration of estrogen lowered the beta lipoproteins but raised the alpha lipoprotein Devi & Sharma\textsuperscript{22} (1972), Gupta (1976). Wallace\textsuperscript{23} et al (1979) observed that total cholestrol LDL and VLDL all have been elevated in women using oral contraceptives.

As the hormones like oestrogen and progestrone 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 & Billiwaiz (1963) they have estimated oestrial excretion in successful pregnancy and habitual abortion and shown that oestral output in successful pregnancy approximates closely to normal values which that of abortion fill week by week until 10 weeks it was less than 40% of normal\textsuperscript{24}

Progestrone :

After the first weeks of gestation very little of progestrone produced arises in the ovary (Diczfatyury and Troen\textsuperscript{25}, 1961). Daily production rate of progestrone in late normal singleton pregnancy is about 250 mg (Pearlman\textsuperscript{26}, 1957). Progestrone levels in maternal peripheral plasma increases progressively with gestation.

Workers (1957), Simpson and Colleagues (1954) found that perfusion of placenta in vitro with radiolabelled cholestrol resulted in formation of radiolabelled progestrone\textsuperscript{27}.

Hellig and associated (1970) also found that maternal plasma cholestrol was the principal precursor (upto 90%) of progestrone biosynthesis in human pregnancy\textsuperscript{28}.
Simpson and associates demonstrated that trophoblast preferentially uses how density lipoprotein cholestrol for progestrone biosynthesis. This subject was reviewed recently by casey and Colleagues\textsuperscript{20} (1992).

Effect of progesterone on lipid profile:

Corredor et al (1970) found significant rise in triglyceride levels after 6-12 months use of oral pills. Barton in 1970 found significant rise in serum triglyceride levels in females using combined pills but there was no change seen with progestin only pills\textsuperscript{30}.

Spellacy (1976) observed the effect of nonogestrel on carbohydrate and lipid metabolism there was no significant change in serum cholesterol levels.

Launtzen in 1977 observed a decreasing effect of norethisterone on cholesterol and triglyceride levels of beta lipoprotein\textsuperscript{31}. He also suggested that there is no influence of hydroxy progesterone on cholesterol level. Bradley et al (1978) found that progestins derived from 17 alpha hydroxy progesterone and others are relatively inert, while those derived from 19. Nor testosterone (levonorgestrol, norethisterone acetate and others) decreases high density lipoproteins.

Krauss et al (1983) observed effects of two different progestrone pills and found that VLDL increased with only norgestrel. LDL was significantly lower in nor ethisterone group results were variable with very low density lipoproteins.

**Lipoprotein in Toxaemic Mothers**:

The serum total cholesterol estimation was under taken in 1911 by Chauffrd and Associates\textsuperscript{32} in three eclampsia patients and normal pregnant women. They reported an increase in the blood cholesterol during pregnancy but found no consistent variation in eclampsia mothers as compared to that of the conc. in the serum of healthy Gravidac a similar conclusion was made by several other investigators (Aunyenreith & Runk; 1913, Burgert Prener; 1913; Schlimpert and Huffman, 1913; Höffmann 1955; Sléan’s & curtier; 1917 and Dickmann & Wegnar\textsuperscript{33} 1934).

Boyd in 1935\textsuperscript{34} reported plasma lipid in eclamptic mother. He observed mean value of total lipid to be 829 ± 255 mg/dl. In eclampsia and 785 ± 117 mg /dl in normal pregnancy, the mean cholesterol level was observed to be 187 ± 56 mg / dl and 179± 35 mg / dl respectively.
The pathogenesis of pre-eclampsia:

Endothelial dysfunction -

\[ \text{PG I}_2 \quad \downarrow \quad \text{EDRF} \quad \downarrow \quad \text{ Decreased synthesis} \quad \downarrow \]

\[ \text{T} \_ \text{A}_2 = \text{Platelet aggregation} \]

\[ \text{Seratonins} \quad \downarrow \quad \text{5II}_2 \]

- Vaso constriction
- Micro angiopathy
- Thrombosis

\[ \text{Systemic Blood Pressure} \uparrow \quad \text{Utero Placental flow} \downarrow \]

Severe Pre-eclampsia

Patho physiological mechanism in mild and severe Pre-eclampsia 5 HT = 5 Hydroxy tryptamine
AT 11 = Angiotensin-II
PG I = Prostaglandin I2
EDRF = Endothelium derived relaxing factor

\[ \text{T} \_ \text{A}_2 = \text{Thromboxque A}_2 \]

\[ \text{RAAS} = \text{Renin angiotensin aldosterone system} \]

Auto acceleration balance compensation
Neutral fat value were 219 ± 210 mg /dl and 248 ± 63 mg /dl , phospholipids were 361 ± 102 mg /dl and 293 ± 52 mg / dl in eclampsia and normal subjects relatively . However the ratio of phospholipid and cholesterol was found to be significantly higher in eclamptic patients than in other toxic or normal pregnancy .

Calvin et al (1939) found the initial cholesterol value of Toxaemic mother at third month to be 21 mg / dl which gradually rise in a fluctuating manner to 233 mg / dl in the 7th month then dropped sharply to 194 mg /dl in 8th month and 176 mg /dl in 9th month . During the time of pregnancy the basic metabolism was rising sharply in Toxaemic subjects .

Langer Crantz (1945) , Macy (1951) and Dickmann (1952) observed an increase in both serum protein and serum lipid in Toxaemia . Smith eta l (1959) observed that cholesterol and lipid phosphorous increase as pregnancy progresses reaching their maximum at term. The percentage of lipoprotein showed a decline with progress of pregnancy specially during 3rd trimester.

De Alverz and Bratvold36 (1961) studied total lipid in 7 normal pregnant women . the average mean value for total lipid during the last four weeks of normal pregnancy was 974 ± 154 mg / dl . The mean value for mild pre-eclampsia was significantly elevated [ p.002] above the average value for normal pregnant women in third trimester . The women of severe Toxaemia were having total lipids almost 200 mg / dl above the mean level of normal pregnant level .

Arsoba and Kretowicz (1963) reported elevation in serum cholesterol , phospholipids and total lipid toxaemia of pregnancy.

Nelson36 et al (1966) observed triglyceride content of placenta . In toxaemia simply reflect that placenta is disease organ in toxaemia and found raised level of both maternal & Foetal Phospholipids and triglycerides as compared with controls . However the elevation was not statistically significant.

Mullick & Bagga (1964) found a gradual increase in Beta- lipoproteins and alpha lipoproteins ratio as pregnancy advances . Bhattacharya37 et al (1969) concluded after their extensive study over normal & abnormal pregnancy that although cholesterol levels were slightly higher in toxaemia group , the cholesterol metabolism seemed to be similar in normal toxaemia of pregnancy.

In 1978 Chaturvedi , Tandon and Singh38 observed that in toxaemia of pregnancy there was significant rise in total serum cholesterol as compared to the IIId trimester of normal pregnancy .
They also observed that in toxaemia serum cholesterol level did not return to same level as it did in the normal; pregnancy in post partum period and this was statistically significant. The level cholesterol had no significant relationship with the degree of hypertension in ante partum period. Mullick & Bugga (1964) found a gradual increase in beta lipoproteins and beta and alpha lipoprotein ratio increases as pregnancy advances.

Warren et al. 1962 observed greatest increase in triglyceride followed by phospholipids and finally cholesterol in a pregnant female.

Pregnancy is associated with significant increase in VLDL and LDL conc. HDL2 generally shows a slight decrease whereas HDL3 is markedly increased leading to a significant increase in total HDL. Studies of Oliver and Boyd showed that beta/alpha ratio is even greater than the uncomplicated pregnancy. Increased HDL3 and decreased HDL2 are still demonstrable 6-9 months post partum and the beta / alpha ratio remains 4 : 1 five months post partum period (HDL2 - Chol, page 325) Worth, Arky & Knopp. In 1975 reported a consistent increase in LDL:HDL lipoprotein ratios quantitatively greater increase in beta than in alpha function. They stated that triglyceride rises more than cholesterol and phospholipids and HDL cholesterol is not significantly reduced.

Pontis et al. (1978) observed diminished percentage concentration of alpha lipoprotein with a concomitant elevation of percentage of beta lipoprotein at the first stage of labour and in Puerperium alterations towards normal non pregnant levels.

Ronald K. Kalkhoff (1978) stated that the hyper triglyceridemia of late pregnancy is mainly due to increase in VLDL concentration, constituents are proportional; and cholesterol, triglyceride and phospholipids are unchanged. Hyper triglyceridemia also due to increase in HDL and LDL in which triglyceride is reliably more. They also stated that Oestrogen is principal hormonal factor responsible for increased synthesis and release of endogenous triglyceride.

Knopp et al 91981) stated that progressive hypertriglyceridemia of pregnancy is due to rise in VLDL triglyceride of particular interest was their finding of biphasic pattern in HDL cholesterol conc. with a peak in midgestation and then a subsequent decline towards non pregnant levels at term.

Dermandy et al. (1982) concluded that the primary changes in lipoprotein metabolism during pregnancy appears to be concerned with VLDL they observed pronounced elevation of VLDL conc. In
ultra centrifugal analysis of serum from pregnant women in 3rd trimester, compared with that from non pregnant women. After delivery the elevated serum triglyceride conc. decreases rapidly and the significantly greater utilization of serum triglyceride in lactating women could be caused by the tissue specified direction of VLDL towards the mammary glands for milk synthesis.

**Lipoprotein in IUGR (Intrauterine growth retardation)**

In 1961 Warkany and co-workers\textsuperscript{15} reported normal values for infant weights lengths & head circumferences and defined fetal growth retardation. In 1962, WHO introduced the term low birth weight for all babies weighing less than 2.5 kg as a single category.

Gruenwald\textsuperscript{16} (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 Lubchenko & co-workers\textsuperscript{17} from Denner published detailed comparison of gestational age to birth weights in an effort to derive norms for expected fetal size and therefore, growth at a given gestational week.

Battaglia and Zubchenko (1967) then classified small for gestational age (SGA) infants as those weighing below 10th percentile for their gestational age.

Kramer\textsuperscript{18} (1987) 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 no. of studies. Problems with growth retarded fetuses - Wennnergren and co-workers (1988) the neonatal performance of 160 infants defined to be growth retarded because their birth weight was a t or two standard deviation from the mean. In most cases 831 growth retardation has been suspected antenatally by birth weight less than 2 standard deviation of the mean for that period of gestation. hypoglycemia & Hypothermia occured frequently. The major hazard of growth retardation were still birth and fetal distress. Similar observations have been made by Villar & Colleagues (1990)\textsuperscript{49} for growth retardation at term and by Vesser & associates (1986) between 25 and 34 weeks.

Autopsy findings in small for gestational age (SGA) infants have revealed two basic pattern of impaired fetal growth (Gruenwald, 1963, Naye and Kelly, 966) one was designated as symmetrical growth retardation because all body organs tend stc be
proportionately reduced in size and assymetrical when some body organs are more affected than others.

Factors regulating fetal growth are mainly genetic and racial. Neonates of Indian and Chinese weigh less than those of Europeans of Africans (Ashcroft and Desai, 1976). Foetal growth is also influenced by the maternal weight, height, age, parity and duration of gestation. Social deprivation influences height & shorter women are not optimal reproduce as far as support of fetal growth is concerned (Gruenwald, 1968).

Maternal & placental causes are also important. Hypertension during pregnancy causes IUGR. It varies with mean arterial pressure at 4-6 months higher it is lower the birth weight (Page and Christiansons, 1976).

Boyd & Scott (1958) showed that compared to normal placenta in pre-eclampsia and IUGR were of a lower volume of Parenchyma and Villous surface with increased area 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) and mid arm circumference 9less than 20 cms) 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 (Hyttten, 1979) with nutritional supplements (Calories, protein, Iron < Folic acid) in the 2nd half of pregnancy there is fetal Odycst gain of over 200 gm, compared with controls. (Ven katschalam, 1962, Iyengar & Rajalakshmi, 1974; laching et al, 1975).

Biale (1983) studied lipolytic activity in the placenta of chronically deprived featurers, concluded that lipoprotein lipase activity was significantly greater in placenta of pre-eclamptic women and in placenta of intra uterine growth retarted features.

Iwaszkiewicz, Pawlowska (1986) 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 Economise & Crook showed that small for gestational age fetuses had hyper triglyceridemia and hypo glycemia and hypoinsulinemia.

Recently Berg, Ronald, Sande (1994) found that high lipoprotein (9) [ Lp (9) ] level in maternal serum can interfere with placental circulation and causes fetal growth retardation.