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The Importance of Lipid and Lipoprotein Ratios in Interpretions of Hyperlipidaemia of Pregnancy

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1. Introduction

In spite of the fact that the hyperlipidaemia of pregnancy is usually considered physiological [1-12], all pregnant women develop hypertriglyceridaemia with subsequent formation of small, dense low-density lipoprotein(LDL) particles, both of which are an independent risk factor of coronary heart disease(CHD) [13]. By 3rd trimester most women have a lipid profile which could be considered highly atherogenic in the nonpregnant state [14]. Similarly, animal model studies showed that maternal hypercholesterolaemia during pregnancy even when temporary and limited to pregnancy triggers pathogenic events in the fetal aorta, greatly enhanced atherogenesis later in life[14, 15]. On the other hand, intrauterine growth retardation (IUGR) has been associated with pre-eclampsia [16], as a result of decreased maternal lipid transfer to the fetus secondary to placental abnormalities. IUGR has also been associated with failure of development of hyperlipidaemia during pregnancy with subsequent reduction in maternal lipid reaching the fetus in a normal placenta [17, 18]. Generally, serum lipid and lipoprotein levels in pregnancy are modulated by complex interactions between genetics, medical complications of pregnancy, co-existing medical conditions, and other maternal factors [9, 19]. This underscores the need to take a meticulous and decisive approach in interpreting hyperlipidaemia of pregnancy. In searching for an emergent or new cardiovascular risk factor, concerning lipid and lipoprotein in adult males and nonpregnant women, several lipoprotein ratios or atherogenic indices have been defined[20]. These ratios were found to provide information on risk factors difficult to quantify by routine analyses and could be a better mirror of the metabolic and clinical interactions between lipid fractions[21]. Despite findings of [22] in a registry study of heterozygous familial hypercholesterolaemia(FH) mothers, who observed no significant untoward effect of lipid-lowering drugs during pregnancy, the current trend

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is that Statins, classified by FDA as category X, should be avoided in pregnancy[23, 24]. The use of lipid and lipoprotein ratios in interpreting pregnancy associated hyperlipidaemia may provide a balanced hyperlipidaemia not only in normal pregnancy but also in the other modulators of lipid metabolism in pregnancy.

2. Pathophysiology of hyperlipidaemia of pregnancy

Pregnancy is a dynamic state consequent of the fact that normal fetal development needs the availability of essential nutrients such as glucose, free fatty acids(FFAs), long-chain polyunsaturated fatty acids(LCPUFAs), amino acids, minerals, vitamins, to be continuously supplied to the growing fetus despite intermittent maternal food intake[10,25]. The dynamism of the gestational period support fetal growth and development while maintaining maternal homeostasis and preparation for lactation. This is achieved by complex and continuously evolving adjustments in maternal nutrient metabolism occurring throughout gestation.

Many of these maternal adjustments occur in the early stages of pregnancy when the fetus is too small to make considerable metabolic demands of the mother, resulting in the maternal metabolism working from a different baseline compared with the nonpregnant state. This period is called the anabolic phase. In late pregnancy, however, the maternal metabolic processes become more complicated because of the two-way interaction between the mother and the developing fetus. This is caked the catabolic phase.

The changes in nutrient metabolism can be described by several general concepts[8]: (a) adjustments in nutrient metabolism are driven by hormonal changes, fetal demands and maternal nutrient supply; (b) more than one potential adjustment exists for each nutrient; (c) maternal behavioural changes augment physiologic adjustment; and (d) a limit exists in the physiologic capacity to adjust nutrient metabolism to meet pregnancy needs, which when exceeded, fetal growth and development are impaired. Subsequently, metabolic adaptations, during pregnancy are essential [26]: 1, To ensure adequate growth and development of the fetus; 2, to provide the fetus with adequate energy stores and substrates that are needed following birth; 3, and, to provide the mother with sufficient energy stores and substrates to cope with the demands of pregnancy as well as those of labour and lactation. One of the maternal metabolic adjustments during pregnancy includes accumulation of fat depots in maternal tissues[26]. During this anabolic phase, the number of insulin receptors on the adipocytes increases, culminating into increased insulin sensitivity, increase lipoprotein lipase(LPL) activity which hydrolyses circulating triglycerides for tissue uptake, enhanced lipogenesis and marked maternal fat deposition(about 3.5 to 6.0kg) which is used as energy sources for the mother so that glucose is spared for the developing fetus in the catabolic part of the pregnancy[27, 28]. Lean women increase their fat stores more than obese women per kg body weight, likely due to higher insulin sensitivity in them, in early pregnancy, promoting lipid uptake and de novo synthesis.

The important attributes of fat deposits during the anabolic phase in pregnant women are :(1) Hyperphagia, present in pregnant women and increases as gestational time advances. This progressive increase in the availability of exogenous substrates actively contributes to maternal accumulation of fat depots [29]; (2) Promotion of lipogenesis and suppression of lipolysis mediated by progressive increase in insulin and its sensitivity and enhanced by progesterone and cortisol [30]; (3) The proportional increase in adipose tissue lipoprotein lipase (LPL) activity [1,12,31) which hydrolyzes triglycerides(TGs) in form of TG-rich lipoproteins, chylomicron and very-low density lipoprotein(VLDL), which are respectively converted into remnant particles and intermediate-density lipoprotein (IDL). The hydrolytic products, non-esterified fatty acids(NEFA) and glycerol, are partially taken up by subjacent tissues [11, 12, 32, 33]; (4) the unique capacity of tissue to utilize intracellularly the glycerol released during lipolysis. Under normal circumstances, the negligible glycerol kinase activity in adipose tissues hampers the utilization of glycerol for glycerol-3-phosphate synthesis and its use for the synthesis of TGs [34,35]. However, an increase in glycerol kinase activity and its subsequent capacity to metabolize glycerol has been found in rodents under condition of hyperinsulinaemia and enhanced fat accumulation, such as occurs in obesity [35, 36]. The lower lipolytic activity together with the augmented capacity of the tissues for the synthesis of glycerol-3-phosphate for uses in TG synthesis from both glucose and intracellular released glycerol results in net intracellular accumulations of TGs. Since all these pathways are stimulated by insulin, it is proposed that the enhanced insulin responsiveness [37] in the presence of an augmented response of the pancreatic β-cells to the insulinotropic stimulus of glucose that has been found in early pregnant women [38] would be the principal driving forces for the net fat depot accumulation at this stage of pregnancy. These ultimately lead to maternal fat accumulations in the anabolic phase of gestation.

The anabolic condition of adipose tissue during early pregnancy switches to a net catabolic state during the last 1/3 of gestation. The signals responsible for this switch from lipid storage to lipid mobilization are not well understood; however, placental hormones that increase with advancing gestation, known to induce maternal insulin resistance, may play a major role. Placental growth hormone, human placental lactogen, leptin, and tumour necrosis factor-α(TNF-α) are placental hormones that induce insulin resistance. The presence of high plasma levels of placental hormones, known to have lipolytic effects, human placental lipase (HPL), an augmented production of catecholamine secondary to maternal hypoglycemia [38], and the insulin-resistant condition present at this stage [39, 40], appear to be responsible for the net breakdown of maternal fat depots, consistently causing increments of plasma nonesterified fatty acids(NEFA) and glycerol levels during the 3rd trimester of gestation. The main destination of these lipolytic products released from maternal adipose tissue is the maternal liver. They are converted in the liver into their respective active forms, acyl-CoA and glycerol-3-phosphate, to become partially re-esterified for the synthesis of triglycerides, which are transferred to native VLDL particles and released into the circulation. Acyl-CoA can also be converted throughout the β-oxidation pathway to acetyl-CoA for energy production and ketone body synthesis, whereas glycerol may also be used for glucose synthesis. Fetal-placental glucose and amino acids

utilization rates are highest at 22 to 26weeks decreasing near term. In contrast lipid transport is maximal in the 3rd trimester coincident with rapid fetal fat accretion, this spares the mother to utilize glucose during this period. Humans are born with the highest percentage of fat (12 to 15%) compared to any species and 90% deposition occurs in the last 10weeks of gestation, exponentially increasing to 7g/day near term. The preferential use of glycerol released from maternal adipose tissue for gluconeogenesis acquire greater importance during maternal fasting period, when circulating glucose levels are lower than under nonpregnant conditions[34]. Under fed condition in early gestation, plasma ketone body values are even lower in pregnant than in nonpregnant condition [41], indicating an enhanced use of these fuels by maternal tissues as alternative substrate to glucose. However, during fasting period maternal ketogenesis become highly accelerated, as indicated by the exaggerated increase in plasma ketone bodies that occur [41]. This benefit the fetus in two ways: (1) ketone bodies are used by maternal tissues, thus, saving glucose for essential function and delivery to the fetus, (2) placental transfer of ketone bodies is very efficient, attaining the same concentration in fetal plasma as in maternal circulation[42]. In addition, ketone bodies may be used by the fetus as oxidative fuels as well as substrate for brain lipid synthesis [43].

Insulin is well known to inhibits adipose tissue lipolytic activity, hepatic gluconeogenesis and ketogenesis but to increases adipose tissue LPL activity. Thus, it is not surprising that all of these pathways change in the opposite direction which is consistent with insulin resistance occurring in later part of pregnancy. These pathways become even further modified under uncontrolled gestational diabetes mellitus(GDM), where insulin resistance is further enhanced [44].

3. Maternal hyperlipidaemia of pregnancy

The enhanced net breakdown of fat depots during late pregnancy is associated with hyperlipidaemia, which chiefly corresponds to plasma rises in TGs with smaller rise in phospholipids and cholesterol [44]. The greatest increased in plasma TGs corresponds to VLDL values but TGs also accumulates in other lipoprotein fractions, which do not normally transport them, such as LDL and HDL [45]. The high TGs concentration secondary to lipolysis in the presence of increased cholesteryl ester transfer protein(CETP) activity, occurring in midgestation[45], contributes to the accumulation of TGs in the lipoprotein fractions of higher densities, LDL and HDL[44, 45]. CETP facilitates the exchange of TGs by esterified cholesterol between VLDL and either LDL or HDL. Furthermore, during late gestation the activity of hepatic lipase (HL) greatly decreased [45]. HL converts the buoyant HDL-2-TG-rich particles into small HDL-3-TG-poor particle allowing a proportional accumulation of buoyant HDL-2-TG-rich particle.

Other hormonal dynamism occurring during pregnancy contributing to maternal hypertriglyceridaemia are, **table** 1, consistently increasing oestrogen concentration almost throughout the gestation period and oestrogen has been shown to (1) increase endogenous production of VLDL-TGs [46]; (2) reduce adipose tissue LPL activity [33, 45], and (3) inhibition

of hepatic TG lipase activity [33, 44]. Thus, the oestrogenic influence over TG metabolism suggests an increased circulating VLDL-TG. Although the role of progesterone in TG metabolism is not certain, its administration in rats had a lipid neutral effect. Thus, the interaction between oestrogen and progesterone would favour hypertriglyceridaemia. Prolactin may inhibit adipose tissue LPL while stimulating breast LPL in late gestation [45]. Thus, the physiologic outcome of increasing concentration of Prolactin with advancing pregnancy would be a shift in storage from the adipocytes to the breast in preparation for lactation.

Enzymes	Activities
Adipose tissue lipoprotein lipase(LPL)	decrease
Diacylglycerol acetyltransferase	decrease
Cholesterol 7-alpha hydroxylase	decrease
Placental lipoprotein lipase (PLPL)	increase
Placental triglycerides hydroxylase	Increase
Phospholipase A2(PLA2)	Increase
Cholesterol ester transfer protein(CETP)	Increase
Hepatic lipase	Decrease
Hormones and cytokines	Concentrations
Estradiol	Increase
Insulin	Sensitivities increase during first trimester but subsequently decreases from second trimester to end of gestation
Human placental lactogen	Increase
Prolactin	Increase
Cortisol	Increase
Glucagon	Increase
Porgesterone	Increase
Leptin	Increase
Tumor Necrosis Factor-alpha(TNF-alpha)	Increase
Human chorionic somatomammotropin(HCS)	Increase

Table 1. Hormone and enzyme changes during the course of pregnancy.

The combined effects of enhanced liver production of VLDL [47, 48], decreased removal of these particles from the circulation due to low LPL activity [45,49], high CETP activity and low HL activity, would not only be responsible for the accumulation of TGs in LDL but also for the proportional accumulation of TG in buoyant TG-rich HDL-2b subfractions at the expense of the cholesterol-rich and TG-poor HDL-2a or HDL-3[45].

The increasing insulin-resistance in late gestation and continuously increasing plasma oestrogen levels occurring during pregnancy are the main hormonal factors responsible for these metabolic changes resulting into the development of maternal hypertriglyceridaemia, see table 2.

Lipid and lipoproteins (mg/dl)	First trimester	Second trimester	Third trimester	Nonpregnant controls
HDL-C	67±12	83±19	81±17	69±10
LDL-C	90±17	130±46	136±33	99±23
TGs	79±27	151±80	245±73	77±34
TC	173±18	243±53	267±30	183±23
ApoA-1	170±27	204±22	196±28	163±24
ApoA-2	49±7	52±6	49±5	47±6
ApoB	70±21	91±25	113±29	61±22
ApoC-11	265±13	299±18	314±21	237±11
ApoC-111	141±3	188±5	217±6	121±19
ApoE	41±12	42±9	49±19	42±20
Lp(a)	60(0-1440)	63(2-1210)	54(0-1230	86(11-473)
VLDL-1	19(12-55)	47(26-110)	109(38-170)	23(5-85)
VLDL-2	17(7-45)	36(20-77)	103946-168)	23(13-44)
IDL	26(13-54)	58(24-100)	124(79-157)	35(18-62)
Total LDL	200(135-323)	292(206-410)	353(244-534)	207(150-363)
LDL-1	33(16-52)	49(37-70)	67(27-96)	50(22-130)
LDL-11	143(95-231)	160(103-287)	201(59-316)	135(72-258
LDL-111	28(15-56)	32(24-165)	123(43-192)	31(5-68)

Table 2. The increasing lipid and lipoproteins during course of gestation(courtesy: Ahmet Basaran, MD)

4. Placental transfer of maternal lipid and lipoproteins and their metabolites to the fetus

The human placenta contains VLDL, LDL, HDL, and scavenger receptors as well as LDL receptor-related proteins. The placenta also has LPL, phospholipase-A2 (PLA-2) and intracellular lipase activities as well as plasma membrane fatty acid-binding protein (FABP/GOT2), fatty acid translocase (CD36), fatty acid transfer protein (FATP) and different cytoplasmic FABPs [29, 42,50, 51]. Thus, lipid and lipoproteins in maternal plasma can be taken up and handled by the placenta, allowing LCPUFAs associated with plasma lipoproteins to be transferred to the fetus. The human placenta is capable of transporting free fatty acids(FFAs) by diffusion and selectively increases the transport of essential fatty acids (EFAs) and their long-chain polyunsaturated fatty acids (LCPUFA) derivatives by fatty acid carrier proteins.

Although lipoprotein TGs does not directly cross the placental barrier, the placenta has mechanisms to release fatty acids(FAs) circulating in maternal plasma lipoproteins into the fetus. In addition, high levels of TGs in maternal circulation may create a steep concentration gradient across the placenta, which accelerates their transport and deposition in fetal tissues. In term human trophoblasts, insulin and fatty acids have been shown to

enhance the expression of adipophylin, which is associated with cellular lipid droplets and implicated in cellular fatty acid uptake and storage of neutral lipids

4.1. Fatty acids transfer

The supply of LCPUFA is important for fetal growth and tissue development especially for the development of the nervous system and the considerable requirements of these LCPUFAs in the fetus must be provided by their placental transfer [52]. The plasma membrane fatty acid-binding proteins present in human placental membrane [51,52] are responsible for the preferential uptake of LCPUFAs. A selective cellular membrane of certain FAs may also contributes to the placental transfer process, as would the conversion of a certain proportion of arachidonic acid(AA) to prostaglandins(PGs)[52], the incorporation of some FAs into phospholipids[50-52], the oxidation of placental fatty acids[53] and the synthesis of FAs[52,53]. Even though essential fatty acids(EFA) as well as LCPUFAs are transferred across the placenta, the fetus needs to receive substantial amounts of preformed AA and docosahexaenoic acid(DHA) which can be synthesized to a limited extent from the EFA. The two dietary EFAs are linoeic acid(18:2ω-6) and α-linolenic acid(18:3ω-3), which are precursors of the ω-6 and ω-3 LCPUFA, respectively. The synthesis of AA and DHA do not take place in the fetus or the placenta in substantial amounts, owing to the low activities of the desaturating enzymes. Both AA and DHA are abundant in the brain and the retina and their appropriate supply during pregnancy and the neonatal period is critical for proper function [1,54]. Maternal plasma NEFA, though in smaller proportion than lipoprotein TGs, is an important source of polyunsaturated fatty acids(PUFAs) for the fetus [51,52]. Maternal plasma NEFAs correlates with those in the fetus and maternal adipocytokines have been associated with fetal growth[1]. The combination of these processes determines the actual rate of placental FAs transfer and its selectivity, consequent to the proportional enrichment of certain LCPUFAs, such as AA and DHA in fetal as compared with maternal compartments [52, 54].

4.2. Cholesterols

Cholesterol plays a key role in embryonic and fetal development hence the demands for cholesterol in the embryo and fetus is relatively high. Cholesterol is an essential component of cell membrane influencing the fluidity and passive permeability by interacting with phospholipids and sphingolipids [55]. It's the precursor of bile acids and steroid hormones. It is also required for cell proliferation and development of the growing body, cell differentiation, and cell-to-cell communications, and is the precursor of oxysterol, which regulates key metabolic processes. Available cholesterol in fetus is contributed by: (1) transfer from the mother especially during the first half of the gestation and too little cholesterol due to lack of maternal cholesterol or reduced expressions of placental lipoprotein receptors is correlated with small fetuses and a trends for microcephally; and (2) Fetal synthesis especially during the last half of gestation. Too little cholesterol due to lack of synthesis leads to a spectrum of congenital defects as seen in infants with Smith-Lomli-

Opitz Syndrome(SLOS) who are unable to synthesize cholesterol at normal rate due to null/null mutations in 3β-hydroxysteriod Δ7-reductase, the enzyme that converts 7-dehydrocholesterol to cholesterol. The placental endothelial cells are capable of transporting substantial amounts of cholesterol to the fetal circulation and this mechanism is further enhanced by liver-X receptors and induced up regulation of ATP-binding cassette transporter, ABCA1 and ABCG1[56].

4.3. Glycerol

Maternal Plasma glycerol levels are consistently elevated during late pregnancy, but crosses the placenta less than glucose or L-alanine [1,25, 57] though they all have similar molecular weights. Transfer of maternal glycerol via the placenta is by simple diffusion (2). However, its effective and rapid utilization through other pathways, such as gluconeogenesis and glyceride glycerol synthesis in the mother[10,25] results in its low plasma concentration and this very active kinetics impede the formation of the adequate gradient to create the appropriate driving forces for its placental transfer.

4.4. Ketone bodies

In the 3rd trimester of pregnancy, under fed conditions, plasma ketone body concentrations remain low although are greatly increase compared to nonpregnant condition under fasting [58] consequent to enhanced adipose tissue lipolysis. The lipolysis accelerates delivery of NEFA to the liver and enhanced ketogenesis. Ketone bodies can easily cross the placenta and be used as fuels and lipogenic substrates by the fetus. The transfer of ketone bodies across the placenta occurs either by simple diffusion or by a low-specificity carrier-mediated process [25]. The activities of ketone body metabolizing enzyme are present in fetal tissues (brain, liver and kidneys)[1,25] and can be increased by conditions of maternal ketonaemia such as occurs in starvation, during late pregnancy[39] or high-fat feeding[25]. Ketone bodies are used by the fetus as oxidative fuels as well as substrates for brain lipid synthesis [25]. However, in maternal hyperketonaemia as occurs in poorly controlled diabetes patients associated with transfer of excessive arrival of ketone bodies to the fetus seems to be responsible for the major damages [10], increasing stillbirth rate, incidence of malformations, and impaired neurophysiologic development [10]. Subsequently, it could be recommended that pregnant mothers, if possible, should avoid starvation and high fat diet especially in the 3rd trimester.

5. The importance of lipid and lipoprotein ratios in hyperlipidaemia in adult male and nonpregnant females

While cholesterol is a key component of the development of atherosclerosis, LDL-C concentration has been the prime index of cardiovascular disease(CVD) risk and the main target for therapy[21]. However, currently, there is almost unanimous agreement among epidemiologists and clinicians that coronary risk assessment based exclusively on LDL-C is

not optimal[59]. Therefore in the recent past, efforts have been made in seeking emergent or new cardiovascular risk factors to improve cardiovascular disease prediction[20] and in an attempt to optimize the predictive capacity of lipid profile, several lipoprotein ratios or "atherogenic indices" have been defined. In the Framingham study, the TC:HDL-C ratio, a useful summary of the joint contribution of total cholesterol(TC) and HDL-C to coronary heart disease(CHD) risk[60], was also found to be an excellent predictor of CHD risk, with a hazard ratio of 1.21 for a 1.0 increment in ratio[60]. The value of this ratio should be emphasized when lipid profile is within desirable range. It was shown that patients with high-risk LDL-C levels >160mg/dl(4.2mmol/L) and low TC: HDL-C ratio (≤5.0) had an incidence of CHD of 4.9%. This was similar to those with low levels of both LDL-C(≤130mg/dl, 3.4mmol/L) and TC:HDL-C ratios, 4.6%[60]. By contrast, subjects with low-risk LDL-C levels(≤130mg/dl, 3.4mmol/L) and high TC:HDL-C ratio(>5.0) had a 2.5-fold higher incidence of CHD than those with similar LDL-C levels but low TC:HDL-C ratio[60]. For example, TC of 231mg/dl(5.89mmol/L) and HDL-C of 42mg/dl(1.09mmol/L) gives a TC:HDL-C ratio of 5.5, which indicate moderate atherogenic risk[61]. On the other hand, with the same level of TC, if HDL-C were 60mg/dl(1.55mmol/L), the ratio would be 3.8[61]. However, in the Helsinki Heart Study[62], it was demonstrated that the LDL-C:HDL-C ratio that paints the most relevant picture of a person's cardiovascular health risk especially when triglyceridaemia is taken into account and the risk is significantly higher in the presence of hypertriglyceridaemia. When there is no reliable calculation of LDL-C, especially when triglyceridaemia exceeds 300mg/dl(3.36mmol/L), it is preferable to use the TC:HDL-C ratio. Similarly individuals with high concentration of triglycerides, VLDL fraction shows cholesterol enrichment and thus the LDL-C:HDL-C ratio may underestimate the magnitude of the lipoprotein abnormalities in them[21]. Subsequently, both TC:HDL-C, known as the atherogenic or Castelli index, and LDL-C:HDL-C ratios are two important components and indicators of vascular risk, the predictive values of which is greater than isolated parameters used independently, particularly LDL-C. These ratios can provide information on risk factors difficult to quantify by routine analyses and could be a better mirror of the metabolic and clinical interactions between lipid fractions. Their applications therefore in interpreting hyperlipidaemia of pregnancy cannot be over emphasized.

5.1. ApoB:ApoA-1 ratio

Apolipoprotein-B(apoB) represents most of the protein contents in LDL and is also present in IDL and VLDL. ApoA-1 is the principal apolipoprotein in HDL and is believed to be a more reliable parameter for measuring HDL than cholesterol content since it is not subject to variation. Therefore, the apoB:apoA-1 ratio is also highly valuable for detecting atherogenic risk, and there is currently sufficient evidence to demonstrate that it is better for estimating vascular risk than the TC:HDL-C ratio[63-65]. The apoB:apoA-1 ratio was found to be stronger than the TC:HDL and LDL:HDL ratios in predicting risk[63]. ApoB:ApoA-1 ratio reflects the balance between two completely opposite processes. Transport of cholesterol to peripheral tissues, with its subsequent arterial internalization, and reverse transport to the liver[66]. Consequently, a larger ratio will implies higher amount of cholesterol from

atherogenic lipoprotein circulating through the plasma compartment and likely to induce endothelial dysfunction and trigger the atherogenic process. On the other hand, a lower ratio will indicate less vascular aggression by plasma cholesterol and increased more effective reverse transport of cholesterol, as well as other beneficial effects, thereby reducing the risk of CVD. However, its use is limited by the fact that apolipoprotein measurement methods are not widely used as lipoprotein methods

5.2. TG:HDL ratio

Known as the atherogenic plasma index shows a positive correlation with HDL-C estimation rate(FER$_{HDL}$) and an inverse correlation with LDL size[67]. Therefore, the phenotype of LDL and HDL particles is clearly synchronized with the FER$_{HDL}$. The simultaneous use of TG and HDL in this ratio reflects the complex interaction of lipoprotein metabolism overall and can be useful for predicting plasma atherogenecity especially in pregnant women who manifesting with hypertriglyceridaemia of pregnancy. An atherogenic plasma index[Log(TGs:HDL)] over 0.5 has been proposed as the cutoff point indicating atherogenic risk[67].

5.3. LDL-C:apoB ratio

Although apoB is not an apolipoprotein exclusive to LDL, since it is present in other atherogenic lipoproteins such as IDL and VLDL, the LDL:apoB ratio provides approximate information on LDL particle size. A ratio of <1.3 indicate the predominance of LDL particle with low cholesterol content, consistent with small, dense LDL particle[68].

Variations in plasma lipid and lipoprotein ratios in adult men and nonpregnant women have been associated with more substantial alterations in metabolic indices predictive of future consequences of hyperlipidaemia than individual components of plasma lipid profile alone[69, 70] and as discussed above. Given the physiological role of gestational hyperlipidaemia in fetal development and the fact that the adaptations in maternal lipid metabolisms taking place throughout gestation is not without consequences, an urgent establishment of reference values for lipid and lipoprotein ratios in normal pregnancy is highly recommended.

5.4. The hyperlipidaemia of pregnancy, a dyslipidaemia? Find out!

5.4.1. The importance of lipid and lipoprotein ratios in interpreting the hyperlipidaemia of pregnancy

In normal nonpregnant adult population, higher concentrations of plasma triglycerides are associated with preferentially higher VLDL-1 concentration [71]. This particle is secreted by the liver to supply tissues with TGs fatty acids in the post absorptive state. The concentration of VLDL-2, the principal precursor in the circulation to IDL and LDL, does not change as dramatically. In addition, in normal nonpregnant adult population, a higher

concentration of VLDL-1 is associated with a failure of insulin action and increased risk of CHD. In contrast, in pregnant women, as pregnancy progresses and high TG levels developed, VLDL-1 and VLDL-2 rose together so that the ratio, instead of increasing 2-fold, as would be predicted from population studies in the nonpregnant subjects (VLDL-1 o VLDL-2 ratio at a plasma TGs of 0.5mmol/L is 1.0 compared to 2.0 at plasma TGs of 2.5mmol/L)[71], remain constant. Sattar[33], *et al*, found a parallel increase in the small cholesterol-rich VLDL-2(17 to 103mg/dl) and the larger TG-rich VLDL-1(19 to 109mg/dl) at 35 weeks. Similarly, the relationships of VLDL constituents expressed as ratios were not significantly different comparing antepartum and postpartum observations, however, the TG/C ratio was higher at all of these times compared to controls, but the composition of these fractions was similar to that seen in a recent cross-sectional survey of healthy adults (19). The increase in VLDL-TG during gestation is likely due to an increase in VLDL synthesis rather to a compositional change in the VLDL particle, as a study showed no significant increase in VLDL TG/C ratio over time, and the ratios is similarly lower in all the trimesters compared to nonpregnant period(see table 3)

Ratios	First trimester	Second trimester	Third trimester	Nonpregnant control
TC:HDL-C	2.56	3.37	3.90	3.29
LDL-C:HDL-C	1.44	1.95	2.37	1.79
TGs:HDL-C	0.56	0.79	1.16	0.64
VLDL-TGs:CL	1.64±1.53	2.47±3.91	2.57±3.60	3.69±3.48
LDL-TG:CL	0.46±	1.24±2.68	0.56±0.29	0.14±0.08
HDL-TG:CL	0.58±0.21	0.60±0.19	0.69±0.32	0.21±0.09
HDL-TG:ApoA-1	4.09±1.55	5.24±1.43	6.13±1.28	2.73±0.71
LDL-CL:ApoB	2230±339	2222±228	2113±305	2506±167
LDL-TG:ApoB	217±59	256±41	332±60	157±32
LDL-PL:ApoB	748±123	753±66	727±109	824±64
IDL-TG:ApoB	2026±1085	1666±360	1550±202	1530±371
VLDL-TG:ApoB	6272±1924	6278±1629	5551±1416	7040±2778

Table 3. Lipid and lipoprotein ratios in the three trimesters of normal pregnancy.

Taken together, and as shown in **table 3**, although one of the consequences of pregnancy is that maternal lipid metabolism is specifically altered, using the lipid and lipoprotein ratios, the hyperlipidaemia occurring in the later part of pregnancy appears to be a balanced hyperlipidaemia. These are discussed below

During the course of normal pregnancy, plasma TGs and cholesterol rise by 200-400% and 25-50% respectively. The total LDL mass increased during gestation (median concentration increased by about 70%, 200-353mg/dl) between 10 to 35weeks, see table 4. The lipid become enriched with TGs and depleted in cholesterol. The larger, more buoyant subclasses of LDL (LDL-1 and LDL-2) predominant in healthy pregnant females and may in the reproductive

age, whereas smaller, denser LDL-3 often occur after menopause [11, 72]. Several studies showed there to be an association between elevated plasma TG concentrations, small, dense LDL [11, 73] and decreased HDL cholesterol [74], in particular HDL-2 cholesterol [73]

VARIABLES	10 WEEKS OF GESTATION	35 WEEKS OF GESTATION
Triglyceride(mean)	69.65mg/dl	227.69mg/dl
Total cholesterol(mean)	172.57mg/dl	282.38mg/dl
HDL-C(mean)	64.73mg/dl	65.50mg/dl
VLDL-1(mean)	19mg/dl	109mg/dl
VLDL-2(mean)	17mg/dl	103mg/dl
IDL(mean)	26mg/dl	124mg/dl
LDL	200mg/dl	333mg/dl
LDL-1	33mg/dl	67mg/dl
LDL-11	143mg/dl	201mg/dl
LDL-111	28mg/dl	123mg/dl
LDL-1	17% of total LDL	20% of total LDL
LDL-11	69% of total LDL	49% of total LDL
LDL-111	14% of total LDL	32% of total LDL

Table 4. Magnitude of changes in lipid and liporpotein values from first to third trimester.

In men and nonpregnant females, plasma TG is the major determinant of small, dense LDL, occurring for 40-60% of the variability of this fraction in the plasma [71,75,76]. In addition, recent cross-sectional studies [70,74] have prompted the suggestion that, within the relationship between plasma TGs and LDL subfractions profile, there is a threshold effect. At low-normal plasma TG concentrations, there is a positive association between LDL-2(the major LDL species) concentration and plasma TGs. Above a certain plasma value, however(reportedly about 1.5mmol/L in men)[71,75], LDL-2 concentration correlates negatively with plasma TGs, and LDL-3 concentration which had been relatively constant below this TG concentrations, correlates positively with plasma TG. Generally, percent LDL-3(and LDL-3 mass) changed little in early gestation despite increasing TG concentrations. However, there appeared to be considerable variation between individuals in the gestational age and plasma TGs intervals at which change in the LDL profile first manifested—the elevated TG levels already present in the first trimester may be responsible for the increased in dense LDL

In line with the alarming observations in LDL subclasses and total LDL mass, LDL-1 mass increased around 2-fold, from 33 to 67mg/dl; LDL-2 mass increased least by around 40% from a median of 143 to 201mg/dl, reaching a maximum of 218mg/dl at 30weeks gestation, whereas in sharp contrast, LDL-3 mass increased by greater than 4-fold from 23 to 123mg/dl.

However, as concentration of LDL-2 is declining, that of LDL-3 is increasing and implying that the ratio may tend towards a unit.

Towards end of second trimester to end of gestation, the concentrations of VLDL, IDL, and LDL-1/LDL-2 further increased, producing a distribution of lipoproteins dominated by buoyant lipoprotein species, in particular LDL-1. In line with this, Winkler's[11], et al data do not support the idea that the same mechanisms as those described for the atherogenic lipoprotein phenotypes govern lipid metabolism in late pregnancy.   Therefore, in uncomplicated pregnancy there appears to be a balance between potentially damaging factors such as altered lipid metabolism and as yet poorly understood protective mechanisms [11,33,75]. However, the clinical significance of gestational lipoprotein metabolisms may arise if this balance is compromised as in hypertensive disorders of pregnancy. It is in these circumstances then when the application of these ratios is very important, for example; Toescu, [77] et al while comparing lipid levels between pregnant diabetic women(types 1 and 2 and GDM) and pregnant nondiabetic counterparts did not demonstrated any significant differences among the groups according to trimesters, implying that the observed hyperlipoproteinaemia during pregnancy is independent of diabetes status[10]

Kilby,[78] *et al* although observed higher lipid levels and increased in TC, TGs, VLDL/LDL ratio, HDL-C with gestational age in type 1 DM, similarly found no significant difference from gestationally matched controls[78] in their study. Investigations are required to characterize lipid and lipoprotein profile using ratios in the other modulators, particular these will assists clinicians while dealing with hyperlipidaemia of pregnancy considering the limited quantification opportunities.

Currently the applications of lipid and lipoprotein ratios in interpreting the hyperlipidaemia of pregnancy are limited particularly in the poor developing nations. In spite of the fact that the hyperlipidaemia of pregnancy is usually considered physiological, serum lipid and lipoprotein levels in pregnancies are generally modulated by complex interactions between genetics, medical complications of pregnancy, co-existing medical conditions and other maternal factors[19], **table 5**.

Therefore the hyperlipidaemia during pregnancy could be classified according to clinical implications and future prospects as in **fig 1,** particularly where there is limited opportunity of investigations do to poverty.

In our laboratory [79] the ratios were found to be important particularly where measurement of lipid and lipoprotein is not routinely done due to poverty. In addition hyperlipidaemia in pregnancy is confounded by other conditions that may predispose to hyperlipidaemia, such as obesity, diabetes mellitus, chronic renal insufficiency, and pre-eclampsia. Similarly subfractions of lipoproteins are usually not done due to limited methodology. Without the use of lipid and lipoprotein ratios particularly considering these confounding conditions which are also likely to present with hyperlipidaemia, interpreting the hyperlipidaemia of pregnancy is encountered with difficulties.

Medical complications of pregnancy
1. Pre-eclampsia
2. Pregnancy-induced hypertension
3. Gestational diabetes mellitus
4. Intra-uterine growth restriction(retardation)
5. Prelipaemia

Co-existing medical conditions
1. Obesity
2. Types 1 and 2 diabetes mellitus
3. Hypothyroidism
4. Hypertension
5. Renal diseases, particularly nephritic syndrome
6. Alcoholism
7. Medications, eg LMWt-heparin and glucocorticoid

Other maternal factors
1. BMI(Obesity)
2. Maternal weight gain in the index pregnancy
3. Maternal nutrition
4. Pre-pregnancy lipid levels

Table 5. Factors that can also modulate lipid and lipoprotein concentrations in pregnancy (genetic factors not mentioned)

Image from courtesy of Ahmet BASARAN, MD
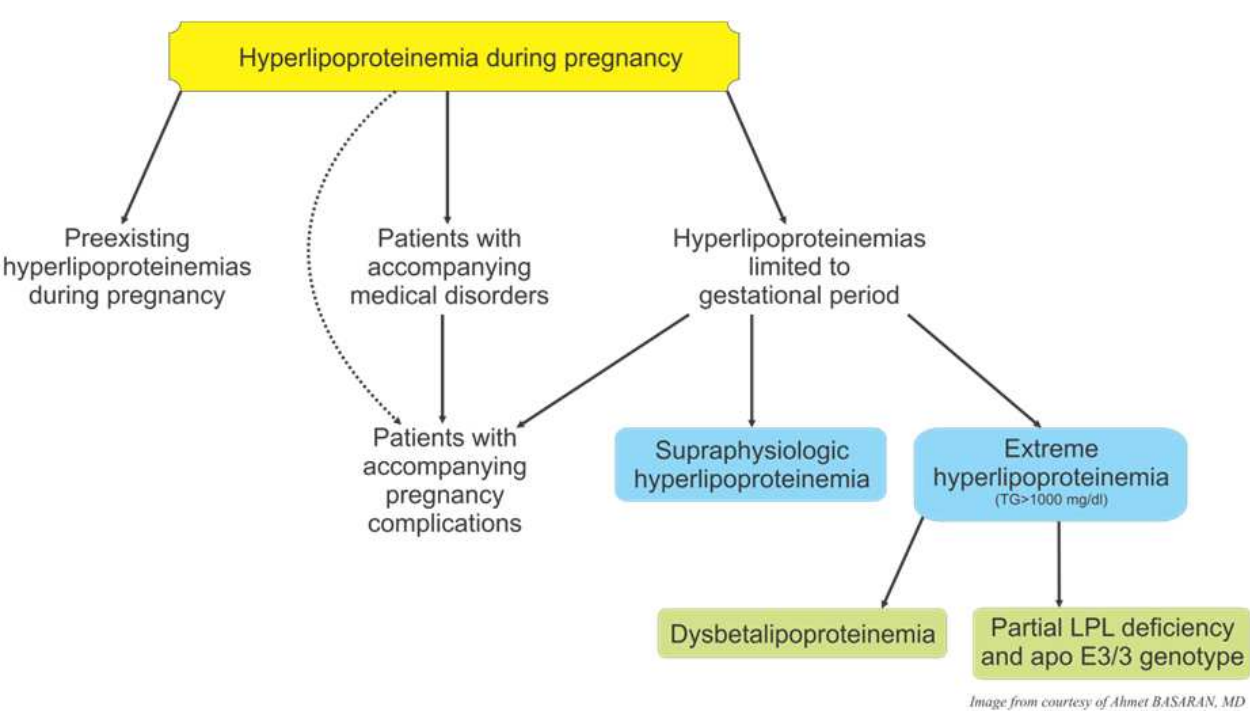
Figure 1. Classification of hyperlipidaemia of pregnancy

Whilst the hyperlipidaemia of pregnancy is considered physiological, studies have demonstrated that deviations present as a two-edged sword. On one hand, development of the physiological hyperlipidaemia out of proportion could be associated with many consequences and on the other hand failure to development the required proportion of physiological hyperlipidaemia of pregnancy could also be associated with some consequences, **Table 6** and these will be discussed subsequently

Consequences of hyperlipidaemia
Complications associated with hyperlipidaemia of pregnancy:
Cholesterol gallstones
Intrahepatic cholestasis
Acute pancreatitis
Endothelial dysfunction
Unanswered questions concerning hyperlipidaemia of pregnancy
Is hyperlipidaemia of pregnancy atherogenic?
Is hyperlipidaemia of pregnancy a dyslipidaemia?
Future effect of pregnancy-induced Supraphysiologic hyperlipidaemia
Pre-eclapmsia and hyperlipidaemia of pregnancy
Consequences of failure of development of hyperlipidaemia
IUGR—Intra-uterine growth retardation
Future development of metabolic syndrome in affected fetus

Table 6. Consequences of deviations of Hyperlipidaemia of pregnancy.

6. Is normal pregnancy atherogenic?[80]

The change in triglycerides in normal pregnancy is important in relation to lipoprotein subclasses, such as LDL. These lipoproteins contain subfractions of various sizes, densities and compositions, which differ in their ability to initiate atherogenesis [81]. One of the subfractions of LDL (LDL-3) is small, dense LDL particles which do not bind readily to the LDL receptors and therefore remain in the circulation for longer time, penetrate the arterial intima better than do larger ones[82] and are more readily oxidized, probably because they contain less vitamin E and other antioxidants[83]. Finally, their uptake into macrophages to create form cells, and initiate atherogenesis, is facilitated [84]. This may explain their identification as an independent risk factor for coronary heart disease [82-84].

Plasma triglycerides are the major determinant of small, dense LDLs, accounting for 40-60% of the variability of this fraction in the plasma [75]. VLDL represents the major precursor of LDL and reflects plasma TGs levels. Two subclasses of VLDL have been defined: a large and buoyant fraction enriched with TGs (VLDL-1) and a smaller, denser fraction(VLDL-2). It follows from the association between LDL subclasses and raised TGs that VLDL-1 may be important as a vehicle in the process of neutral lipid exchange and generation of small,

dense LDLs. Cholesterol esters are transferred from LDL and HDL to VLDL-1 by cholesterol ester transfer protein(CETP) in exchange for TGs and the increased concentration of VLDL-1, due to hypersecretion by the liver promote TG transfer into LDL during pregnancy[33]. TG-enriched LDL particles subsequently undergo a size reduction through the action of hepatic lipase, resulting in the formation of small, dense LDL subfractions. In addition Lippi[2], et al demonstrated in their study that advanced pregnancy is associated with an increased prevalence of undesirable or abnormal values for total cholesterol, LDL-C and TGs in the second trimester, and total cholesterol, LDL-C, TGs TC:HDL ratio in third trimester demonstrating that physiological pregnancy is associated with a substantial modification of lipid and lipoproteins metabolism from the second trimester, providing reference ranges for traditional and emerging cardiovascular risk predictors throughout the gestational period. Therefore, is normal pregnancy atherogenic?

All pregnant women develop a transient hyperlipidaemia associated with hypertriglyceridaemia, and subsequent formation of small, dense LDL particles, both of which are an independent risk factor for CHD, and by 3rd trimester most women have a lipid profile which would be considered highly atherogenic in the non-pregnant state[13]. Increased prevalence of angina, cholesterol gallstone, and obesity in postmenopausal women who have had several pregnancies has been observed [85]. Yet the long-term consequences of multiple pregnancy, gestational diabetes or maternal obesity in LDL subfractions and lipid profile are unknown. Further studies are recommended to determine if certain women are at increased risk of CVD in later life because of effects on their lipid profile during pregnancy. In contrast, increasing suggestions are that maternal hypercholesterolaemia during pregnancy even when temporary and limited to pregnancy triggers pathogenic events in the fetal aorta, greatly enhanced fatty streak formation and that may influence atherogenesis later in life[14,15]. Fetal plasma cholesterol levels are high and are proportional to the maternal cholesterol levels [14] in second trimester, decline with increasing fetal age[14] and are even lower at term birth. This is supported by the fact that lipid levels observed in umbilical cord blood(UCB) from normal pregnancy were significantly lower than those found in maternal blood with exception of HDL-C, and that LDL:HDL ratio in neonate of normal pregnancy are much lower than the value in normal pregnant mothers[16]. The high HDL levels and a lower LDL:HDL ratio in UCB suggest that the fetus of a normal pregnancy is protected against atherogenic lipoprotein[16]. Despite these findings, studies at autopsy demonstrated that atherosclerosis progresses much faster in offsprings of hypercholesterolaemic mother than in offsprings of normocholesterolaemic mothers[86]. Same studies observed that at each time point, offsprings of hypercholesterolaemic mothers had 1.5 to 3-fold larger lesions than offsprings of normocholesterolaemic mothers, and they suggested that, pathogenic programming in utero increases the susceptibility to atherogenic risk factors later in life and maternal intervention with cholesterol-lowering agents reduce postnatal lipid peroxidation and atherosclerosis in their offsprings[87]. A registry study by Toleikyte,[22] et al, of heterozygous familial hypercholesterolaemic(FH) mothers observed that: the serum levels of cholesterol in the nonpregnant, nontreated women were 370mg/dl(9.59mmol/L); no maternal cardiovascular deaths were observed; the children of mothers with FH were no more likely than the general

population to be born prematurely, have low birth weight, or have congenital malformations; and that no congenital malformations were observed in the 19 pregnancies associated with the use of lipid-lowering drugs during pregnancy. However, the current trend is that Statins, classified by FDA as category X in pregnancy, should be avoided in pregnancy [23,24]. Although there are observations for and against the maternal hyperlipidaemia being atherogenic to the fetus and increasing tendencies of future atherosclerosis, a long-term follow-up studies of offsprings of mothers with FH who did not inherited the disease is recommended. The result will demonstrate evidence of effects of maternal hyperlipidaemia on fetal atherosclerosis and or predisposition to future atherosclerosis in these offsprings.

6.1. Fetal lipoproteins in pre-eclampsia

Successful placental development is very important for normal fetal growth, and may condition health and well being during childhood and even adulthood [88], because it forms the interface for nutrients, fluids and gas exchange between mother and fetus. Pre-eclampsia (PE), a human pregnancy specific vascular disorder, defines a pathologic condition that affects the mother and can adversely influence the feto-placental unit. PE is associated with placental dysfunction, oxidative stress[1, 89], dyslipidaemia[16,90] and endothelial cell activation, and is a major cause of maternal and fetal morbidity and mortality[88] A pro-atherogenic lipid profile, characterized by increased TG levels with reduced HDL concentration[90, 91] and increased small, dense LDL particles[90] has been described. In contrast other studies demonstrated a dominance of buoyant LDL-1 and a significant decreased of small, dense LDL, namely LDL-5 and LDL-6[92]. Notwithstanding, it has been suggested that an abnormal lipid metabolism may not only be a manifestation of PE, but dyslipidaemia may play an essential role in its pathogenesis

Apart from genetic predisposition, the second group of disorders associated with an increased risk of PE includes a variety of chronic conditions such as dyslipidaemia, diabetes mellitus, hypertension, renal diseases, and various thrombophilias[93]. These disorders can be convincingly grouped together based on their common association with vascular endothelial dysfunction, especially those which have been included in the proposed metabolic syndrome [93]. Ironically also all are associated with dyslipidaemia. Although PE is a multifactorial disorder, it is therefore tempting to ask, could dyslipidaemia be the central focal point linking these disorders into pathogenesis of PE? One of the abnormalities found in the abnormal placental bed is presence of acute atherosis in desidual vessels, characterized by accumulations of foam cells and perivascular mononuclear cell infiltration. Reduced placental perfusion and placental/fetal hypoxia may develop.

Catarino[16], et al, while comparing lipid and lipoproteins in normal pregnant and PE pregnant women found an enhanced physiologic hyperlipidaemia. However, the most striking difference noted in PE women was the rise TGs that almost double the median value compared to normal pregnant women. Higher TGs value has been associated with endothelial dysfunction and may therefore play an important role in the pathogenesis of PE. Considering the placental dysfunction and lipid changes occurring in PE, fetal lipid

metabolism can be affected due to an altered placental transfer of lipids. Maternal TGs does not cross the placenta. It has to be hydrolyzed by human placental LPL into FFAs which is then transported to the fetus. Fetal TG levels are therefore dependent on maternal TGs. Moreover, the placenta also contains receptors for VLDL, LDL and HDL which also transport TGs and other esterified lipid to the fetus (23)

Catarino[16],et al observed that lipid levels observed in umbilical cord blood (UCB) from normal pregnancy were significantly lower than those found in maternal blood except for HDL, which was similar. In addition, LDL:HDL ratio in neonates of normal pregnancies are much lower than the values in normal pregnant mothers. In contrast, lower values of HDL and ApoA-1 and higher TG levels were noted in neonates of PE mothers. In addition, higher LDL:HDL ratio, a decreased HDL which is more pronounced than ApoA-1, suggest that fetal loading of ApoA-1 with cholesterol is significantly less in PE. Hence fetal HDL composition is likely to be altered due possibly to enrichment with the enhanced hypertriglyceridaemia. Also observed in the PE is a significantly higher value of TGs in UCB which is parallel with significant increased TGs in maternal blood. Since hypertriglyceridaemia is considered a maternal adaptation in order to assure fetal growth in normal pregnancy, the exaggerated hypertriglycedaemia noticed in PE mothers could be a compensation pathway to face the uteroplacental hypoperfusion in order to enhance FAs transfer to the fetus. In line with this, it seems LPL expression is also enhanced in PE as was observed in IUGR [94]. Taken together, it appears lipid transfer from maternal side in PE mothers to their fetus are altered in both quantity and quality and does not seems to be protective as noticed in neonates of normal pregnancies. In support of this PE has been associated with reduced fetal birth weight [95, 96] and the expression of lipoprotein receptors are decreased in the placenta of women with PE.

PE pregnancies is associated with an enhanced hypertriglyceridaemia, which seems to have a negative impact on fetal lipid profile, as reflected by a higher atherogenic LDL:HDL ratio, decreased HDL, disproportionate decreased in HDL and ApoA-1 and enhanced hypertriglycedaemia, children born in pregnancies associated with PE deserve a closer clinical follow-up later in life.

6.2. Role of lipid metabolism in pathogenesis of intrauterine growth restriction (IUGR)[17]

It was proposed that the abnormal lipid metabolism noted in pre-eclampsia was in an attempt to compensate for the placental insufficiency [97], given the physiological role of gestational hyperlipidaemia in supplying both cholesterol and triglycerides to the rapidly developing fetus [98]. In contrast Dabi[17], et al demonstrated that concentration of total cholesterol (TC), TGs, LDL and VLDL observed to increase with increasing gestational age in normal pregnancies, these lipids and lipoproteins decreased with increasing gestational age in pregnancies with IUGR. HDL did not change significantly. These findings certainly indicated that pregnancies complicated by IUGR are associated with an abnormal lipid profile, particularly decreased levels of TC, TGs, LDL and HDL(Dabi [17],et al Sattar[18], et al), see table 7

	Group A			Group B		
Weeks	28-31	32-36	37-40	28-31	32-36	37-40
TC	216.3+29.2	202.5+26.0	191.5+34.5	238.0+17.0	250.7+27.6	260.3+23.6
TGs	173.83+78.18	168.23+51.73	137.83+18.25	148.25+15.31	160.36+24.43	171.14+41.56
HDL-C	42.0+5.3	43.0+4.4	46.4+3.2	44.4+4.5	43.0+6.0	41.6+8.2
LDL	139.4+23.9	126.3+21.8	117.0+31.8	165.9+26.5	174.8+26.5	184.5+23.4
VLDL	34.78+15.63	33.64+10.34	27.26+3.81	29.77+3.06	32.05+4.91	34.22+8.31

Table 7. Lipid and Lipoprotein changes with advancing gestational age(Group A=Pts with IUGR and Group B=Pt with normal pregnancy)

It is well known that normal fetal development needs the availability of both essential fatty acids and long chain polyunsaturated fatty acids (LCPUFAs), thus making a persuasive case indicating a relationship between nutritional status of mother during gestation reflecting her lipid profile and fetal growth. From observations in study by Dabi[17], *et al* and similar findings in other studies, it is possible that the decreased concentrations of TC, TGs, VLDL and LDL may have decreased availability of glycerol, LCPUFAs and essential fatty acids to the fetuses of mothers with otherwise normal pregnancy ultimately leading to IUGR. In addition to above findings, Sattar[18], *et al* observed a decreased in levels of VLDL-2 and IDL in IUGR pregnancies, which are precursors of LDL. Taken together, the decreased cholesterol levels (mainly reflected as decrease LDL) may be due to decreased synthesis of LDL in women with IUGR. The HDL: apoA and apoB:apoA ratios were found to be higher in the IUGR and was suggested that blood lipid modifications in the IUGR group are partly secondary to changes in HDL metabolism and the competitive inhibition of fibrinolysis by apoB which is increased in pregnancy with IUGR. This indicated that apoA: apoB ratio could be a good marker for the early detection of IUGR. Taken together also, these findings definitely generated considerable interest in certain aspects of fetal growth and its relationship to blood lipid levels during pregnancy. However, more study is recommended aiming at analyzing the otherwise normal pregnancies associated with IUGR, particularly to elucidate the hypothesis that the decrease in TGs(and particularly LDL and VLDL-2) compromises the supply of substrates for energy production to the growing fetus resulting in IUGR. The effect of the changes in lipid profile and its translation in changes in blood viscosity needs more extensive research including detailed analyses of apoA and apoB levels in these patients.

6.3. Pregnancy-induced Supraphysiologic hyperlipidaemia

It is well known in literature that hyperlipidaemia is a normal metabolic adjustment in pregnancy benefiting both mother and the fetus. However, some women may not be able to adapt to the hyperlipidaemic stress of pregnancy. In addition, in similarity with other gestational metabolic syndromes such as gestational diabetes mellitus (GDM), pregnancy-induced hypertension (PIH), pre-eclampsia, eclampsia, etc, some of them may develop a

state of Supraphysiologic hyperlipidaemia, defined as lipid levels greater than 95th percentile for the corresponding gestational age, because of failed adaptation to requirement of pregnancy. Supraphysiologic hyperlipidaemia may serve as a marker for what is cited by Montes[99], et al, a 'prelipaemia' in the same way that GDM is a marker for pre-diabetes.

The characteristics of Supraphysiologic hyperlipidaemia, as observed by Montes[99], et al, are that, the antepartum hyperlipidaemia may return to normal levels postpartum more slowly than normal, the presence of HDL cholesterol concentrations that are persistently low antepartum and postpartum, and the patients do have hyperlipidaemic family members. In contrast, hypercholesterolemia is not greatly exaggerated in pregnancy among these women. Are there future consequences of the pregnancy-induced Supraphysiologic hyperlipidaemia? Long-term follow-up studies of women with genetically well-characterized disorders of lipoprotein metabolism are required to determine if an abnormal lipoprotein response in pregnancy can identify prelipaemic subjects and distinguish among the major disorders of lipoprotein metabolism. Identification of the prelipaemia will provide an opportunity to study prospectively the natural progression, potential for atherosclerosis, and possible treatment of hyperlipidaemia from early adulthood.

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