INTERNATIONAL JOURNAL OF MEDICAL AND APPLIED SCIENCES
E-ISSN:2320-3137

Research Article

DYSLIPIDEMIA – A CAUSE FOR LARGE FOR GESTATIONAL AGE BABIES IN GDM WOMEN

KARTHIGA PRABHU J , ANJALAKSHI CHANDRASEKAR, ANJALAKSHI CHANDRASEKAR

1. KARTHIGA PRABHU J *,ASSISTANT PROFESSOR, DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY

2. ANJALAKSHI CHANDRASEKAR, PROFESSOR& HEAD, DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY

3. RAMYA SUNDARAM, ASSISTANT PROFESSOR, DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY

INSTITUTION: SRM MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE POTHERI, KANCHEEPURAM DISTRICT TAMILNADU

CORRESPONDENCE ADDRESS: DR. KARTHIGA PRABHU J, LOT- 45, VALLALAR STREET, CHELLI NAGAR,SELAIYUR, CHENNAI – 600073. TAMIL NADU

ABSTRACT

Though disturbances in maternal glucose metabolism and resultant fetal hyperinsulinemia are known to significantly influence fetal growth in GDM, it has been suggested that other fuels such as lipids and amino acids may also contribute to fetal growth. To compare the lipid profile in normal pregnancy and in GDM women and to determine whether mid- pregnancy (24-28 weeks) maternal serum lipid levels are predictive of large for gestational age babies in GDM women. In this prospective case control study, antenatal women were screened for GDM with non-fasting 2hour 75gm GTT (DIPSI criteria). At 24-28 weeks of pregnancy, fasting lipid profile was performed. Comparisons of lipid parameters between GDM women and the control group were done and Logistic regression analysis was performed to determine maternal parameters independently associated with birth weight. Among the lipid parameters, there was significant increase in Triglycerides (p=0.0008) and decrease in HDL cholesterol (p=0.01) in GDM women when compared to controls. Logistic regression analysis suggested that significant predictors of LGA babies were mean blood glucose levels and hypertriglyceridemia. Hypertriglyceridemia at 24–28 weeks gestation was a significant independent predictor of having a LGA infant at term (OR 5.13; P = .007) after adjusting for confounding factors. Mid –pregnancy Serum TG levels were significantly higher and HDL levels significantly lower in GDM women when compared to normal pregnant women. Maternal mid- pregnancy hypertriglyceridemia and mean blood glucose levels are the most independent variables that can predict LGA babies.

Keywords: Birth weight, Fetal Growth, GDM, Hypertriglyceridemia, LGA babies, lipid profile

INTRODUCTION:

Elevation of maternal serum lipid levels during mid to late gestation in normal pregnancy is a part of maternal adaptation to maintain stable fuel distribution to the fetus. Plasma Triglyceride (TG) levels increase continuously from early in pregnancy such that by term, a two- to threefold elevation has developed [1]. This early rise is most probably due to increased hepatic TG production from elevated estrogens. Further, increased estrogen, progesterone, and insulin favor lipid deposition and inhibit lipolysis in early pregnancy. Later in gestation, a resistance to peripheral tissue uptake of this increased hepatic TG output develops, due to the insulin resistance caused by anti-insulin effects of hormones such as placental lactogen and human chorionic somatomammotrophin on extrahepatic tissue lipoprotein lipase [2].

These metabolic changes that occur in normal pregnancy are progressive and may be accentuated in women who develop GDM. GDM is accompanied by alterations in fasting, postprandial, and integrated 24-h plasma concentrations of amino acids, glucose, and lipids. These changes include a 3-fold increase in plasma triacylglycerol concentrations towards term, elevation of plasma fatty acids, delayed postprandial clearance of fatty acids, and elevation of the branched-chain amino acids [3]. GDM induces a state of dyslipidemia consistent with insulin resistance. Lipid abnormalities associated with insulin resistance in GDM affects all lipid fractions leading to elevated triglycerides and LDL cholesterol with low HDL cholesterol.

Evidence from both human and animal studies suggests that the abnormal metabolic milieu associated with GDM can contribute, independently from genetic factors, to the development of obesity and glucose intolerance in the offspring (fetal origin of adult disease)[4]. Fetal macrosomia is one of the major complications of diabetic pregnancy. Accelerated fetal growth leads to later obesity. Earlier, the gestational diabetes was considered as a disorder of carbohydrate metabolism. Hence, monitoring of blood glucose levels remained the main determinant in directing treatment during pregnancy. However it is found strict glycemic control sometimes failed to prevent macrosomia. Significantly, higher incidence of macrosomic infants was observed in women with normal diabetic screening [5-7] . Although disturbances in maternal glucose metabolism and resultant fetal hyperinsulinemia are known to significantly impact fetal overgrowth, it has been suggested that other fuels such as lipids and amino acids may also be the determinants of fetal growth [8].

India is considered as the capital of Diabetes and the prevalence of GDM is on the increase, reported 16% in south Indian population [9]. Hence, the objective of our study is to determine the lipid profile pattern in normal pregnancy from a suburban population in south India and to compare the lipid profile with GDM women. The other objective of the study is to determine whether mid- pregnancy (24-28 weeks) maternal serum lipid levels are predictive of large for gestational age babies in GDM women.

MATERIALS AND METHODS:

This prospective case control study was conducted in SRM Medical college Hospital and Research Centre from January 2013 to December 2013. All antenatal women were universally screened for GDM with non-fasting 2hour 75gm GTT (DIPSI criteria) at their first visit, repeated again at 24-28 weeks and 32-34 weeks if the previous results were<140 mg/dl[10]. GDM was diagnosed when the 2hour 75gm GTT was ≥140mg/dl and women with the 2hour 75gm GTT <140mg/dl were considered as healthy controls. Women with

pregestational diabetes, hypertensive disorders, thyroid disorders and subjects delivered before 37 completed weeks were excluded from the study. Informed written consent was taken from all women who were willing to participate in the study.

At 24-28 weeks of pregnancy, after an overnight fast, blood samples were drawn to measure lipid parameters – total cholesterol, triglycerides, HDL- cholesterol and LDL-cholesterol. Biochemical assays on the serum were performed with Olympus AU 400 autoanalyser. The serum samples were analysed for the estimation of TC by using CHOD – PAP method, TGs by GPO – PAP enzymatic colorimetric method, HDL and LDL by direct immunoglobulin inhibition method. The atherogenic index (AI) was calculated as [(TC- HDL-C)/HDL-C]. Pre-pregnancy BMI, gestational age at diagnosis were noted. Gestational age was estimated by last menstrual period and confirmed by early fetal ultrasonographic measurements in all subjects.

All patients with a diagnosis of GDM were initially on medical nutrition therapy for 2 weeks with an aim of keeping fasting blood glucose <90 mg/dl and 2 hour postprandial blood glucose <120 mg/dl. Failure to meet these goals was indicative of insulin therapy. All subjects were followed till delivery. Neonatal birthweight, sex of the baby and mode of delivery were noted. Mean glucose levels were calculated from HbA1C at the time of delivery using the Nathan's formula (HbA1c % X 33.3 – 86). LGA babies were babies with birthweight more than 3500 g (90^{th} percentile for their gestational age). Maternal hyperlipidemia was defined as a value higher than the 75^{th} percentile value of each lipid concentration in the studied population.

The study was approved by the Institutional ethical committee (531/IEC/2013).

Statistical analysis

Lipid parameters were expressed as mean ± SD. Using student t tests. We used univariate analysis to evaluate the association between each lipid concentration and newborn weight at term. Logistic regression analysis was performed to determine maternal parameters independently associated with birth weight. All statistical tests were two-tailed, and a P value <0.05 was considered significant. Statistical analysis was done using Graphpad instat 3 and SPSS 12 software.

RESULTS:

During the study period from January 2013 to December 2013, 85 pregnant women with GDM and 145 pregnant women with normal 75gm OGTT were enrolled in the study. In the GDM group 54.1% were diagnosed in third trimester, 30.58% in second trimester and the remaining in first trimester. In this study, 27(31.7%) of GDM women were ≥ 30 years in contrast to 16(11%) in the controls which was statistically significant (p=0.0001). There was no significant difference in parity between the 2 groups. 55% of GDM women had pre-pregnancy BMI ≥ 25 when compared to 31.72% in the control group (p=0.0005). Family history of Diabetes was also significantly high in GDM when compared to controls (p=0.0001).

Maternal clinical and metabolic characteristics are summarized in Table 1 and Table 2.

Table 1: Clinical characteristics of GDM women and healthy controls

	GDM (85)	**Controls (145)**	**P**
Mean Age (yrs)	27.44±4.12	25.28±3.38	0.0001
Parity	0.6353 ±0.73 75	0.5655±0.6326	0.48
Weight (kg)	60.91± 10.67	58.15 ± 9.21	0.13
Height (cm)	153.15 ±6.310	156.04±5.735	0.43
Pre-pregnancy BMI (kg/m2)	25.90±3.76	23.95±3.62	0.0003
Family history of Diabetes	35(42%)	20(13.8%)	0.0001
Mean blood glucose levels at the time of delivery	110.99±13.77	92.18±9.87	0.0003
Mean Gestational age at delivery	38.03±0.74	38.51± 0.97	0.48
Mean neonatal birth weight	3063.2±424.25	2938±391.58	0.02
LGA babies (≥ 3500gm)	22(25.8%)	14(9.6%)	0.002
Caesarean delivery	58(68.2%)	85(58.6%)	0.05
Sex of the baby	51(60%)	75(51.7%)	0.27

LGA babies were significantly more in GDM when compared to controls (25.8% VS 9.6%, p=0.002).There was no significant difference in gestational age at delivery, caesarean delivery rate and sex of the baby between the two groups.

Table 2: Lipid profile between GDM and healthy pregnant women

Lipid Parameters	GDM	Healthy pregnant women	p value
Total cholesterol (mg/dl)	210.64±40.64	206.11±36.67	0.43
TGL (mg/dl)	213.62±66.02	181.67±63.13	0.0008
HDL (mg/dl)	49.94±12.53	54.19±13.13	0.01
LDL (mg/dl)	128.76±36.57	122.30±35.37	0.58
Atherogenic index	4.39±1.35	4.07±1.04	0.04

Among the lipid parameters, there was significant increase in Triglycerides (p=0.0008) and decrease in HDL cholesterol (p=0.01) in GDM patients. Due to these changes in lipid parameters, Atherogenic index was also significantly higher in GDM women (p=0.04).

Table 3: Comparison of pretreatment lipid parameters between GDM women on medical nutrition therapy and those on insulin +MNT

	GDM –insulin+ MNT (34)	GDM- Medical nutrition therapy (51)	p
TCH	209.85±23.91	203.66±62.37	0.59
TGL	219.54±86.95	199.25±83.22	0.37
HDL	51.97±9.8	52.5±13.57	0.86
LDL	123.25±27.80	115.83±60.49	0.52

Though there was increase in mean cholesterol, TGL, LDL levels in women on insulin in addition to medical nutrition therapy, it was not statistically significant.

Correlation coefficient between each variable and new born weight is summarised in Table 4.

Table 4: Correlation of clinical and metabolic parameters and neonatal birth weight

	Correlation coefficient r	p
Age	**0.22**	**0.03**
Parity	**0.31**	**0.003**
Sex of the baby	**-0.11**	**0.30**
Mean blood glucose levels at the time of delivery	**0.45**	**0.003**
BMI	**0.22**	**0.03**
TGL	**0.30**	**0.005**
LDL	**-0.06**	**0.52**
Total cholesterol	**-0.03**	**0.72**
HDL	**-0.03**	**0.71**

There was a significant positive correlation between maternal age, parity, body mass index, sex of the baby, maternal mid pregnancy serum triglyceride levels, mean blood glucose levels at the time of delivery and neonatal birth weight as shown in table 4. There was no correlation between neonatal birth weight and other lipid parameters. Mean blood glucose levels at the time of delivery among women with LGA babies was 114.67±15.39mg/dl in contrast to 95.91±8.88 mg/dl among women with AGA babies which was statistically significant.

Table 5: Lipid parameters- 75th percentile

Lipid parameters	75th percentile
Total cholesterol	244mg/dl
Triglycerides	223mg/dl
LDL	150 mg/dl
HDL	61mg/dl

Hypertriglyceridemia defined as more than the 75th percentile value was 223 mg/dl. In GDM women, Large for gestational age babies was significantly higher in mothers with hypertriglyceridemia (15 OF 34, 44.1%) than in mothers who had normal triglyceride levels (7 OF 51, 13.7%) (P = 0.002, OR=3.21). Among the LGA babies (15) with hypertriglyceridemia 6 patients required insulin in addition to medical nutrition therapy and 9 required MNT alone to control blood sugar values.

Table 6: Risk of LGA babies: logistic regression model

Variables	OR	p	95%CI
Age	0.85	0.8	0.24-2.96
Parity	0.36	0.10	0.10,1.24
Pre- pregnancy BMI (kg/m2)	0.31	0.05	0.09,1.04
Mean blood glucose levels (mg/dl)	3.35	0.03	1.07,10.44
Hypertriglyceridemia ≥223mg/dl	5.13	0.007	1.56,16.84

Multivariate analysis was done using Logistic Regression (LR) to control for potential confounding variables. Age, parity, pre-pregnancy BMI, Mean blood glucose levels at the time of delivery and hypertriglyceridemia which were significant in the univariate analysis, were included in the LR. The final model suggested that significant predictors of LGA babies

were mean blood glucose levels and hypertriglyceridemia. It was found that hypertriglyceridemia at 24–28 weeks gestation was a significant independent predictor of having a LGA infant at term (OR 5.13; 95% CI l 1.7, 18.28; P = .007) after adjusting for age, parity, pre-pregnancy BMI and mean blood glucose levels at the time of delivery.

DISCUSSION:

Maternal fat accumulation peaks in mid gestation and decreases in late gestation, whereas maternal serum lipid levels increase in mid to late pregnancy. In our study the mean fasting total cholesterol and triglyceride levels were 206.11±36.67 and 181.67± 63.13 mg/dl respectively. In contrast, the mean values were 216.8±55.1mg/dl for fasting triglyceride and 223.2±45.9 mg/dl for cholesterol in the study by Kusthagi et al from southwest India in 2009[11]. In another study from Iran, mid pregnancy Fasting serum triglyceride (mg/dl) was 213.9 ± 77.7mg/dl [7]

Hypertriglyceridemia defined as more than the 75th percentile value of all subjects was 223 mg/dl in our study nearly similar to another study from India and in contrast to 259 mg/dl from an Iranian study [7]. This probably may be due to differences in ethnicity, diet and lifestyle changes in different parts of the world.

In our study, in GDM women there is significant increase in serum triglycerides and significant decrease in HDL cholesterol similar to other studies in Ghanian and Pakisthani GDM women [12, 13]. In contrast to our findings, Sobki SH et al. reported lower levels of triglycerides in patients with gestational diabetes when compared to controls [14]. Regarding HDL, in our study levels were significantly lower than the controls similar to the studies by Asare- Anane et al and Aziz and Mahboob[12, 15].

Son et al[16] in 2010 reported that in GDM women maternal fasting serum triglyceride levels were significantly higher in mothers of LGA new borns compared with other mothers; however, no significant correlations were found between new born birth weight and maternal fasting glucose, total cholesterol, or HDL cholesterol levels. In the same study, after adjusting for confounding variables including prepregnancy body mass index, weight gain during pregnancy, age, and parity, maternal hypertriglyceridemia at 24-32 weeks' gestation remained an independent parameter for identifying term LGA new borns. Mossayebi E [17] in 2013 showed that maternal FBS and TG are the most independent variables which can predict the presence of macrosomia (Nagelkerke R-square = 0.53, $p < 0.001$). In the study by Schaefer et al, circulating maternal lipids, but not glucose (mean blood glucose levels at the time of delivery = 84.2±18.3 mg/dl) correlated with fetal growth at different time points during the 3rd trimester in a population of well-controlled GDM pregnancies [18]. In accordance with the above studies, in our study maternal fasting serum triglyceride levels at 24- 28 weeks gestation significantly and positively associated with new born weight at term.

FOR THE FUTURE:

In this study, there was a non-significant increase in pretreatment total cholesterol, triglycerides and LDL in GDM group on insulin +MNT than those on medical nutrition therapy alone. Probably this may be due to more insulin resistance in those women. In future studies with lipid profile post treatment will be required to evaluate whether insulin helps in reducing hypertriglyceredemia and in turn reduce LGA babies.

It has been shown in literature that Modified therapy using lower fasting/2-h postprandial glucose targets of 80/100 –110 mg/dl significantly reduces LGA growth by over 50%. This therapy may be most effective in pregnancies with mild initial hyperglycemia and excessive growth. When both moderate maternal glycemia and excessive growth are present, and insulin is prescribed regardless of therapy protocol, the LGA rates appear less responsive to glycemic therapy, possibly because high-risk growth may be well established before the traditional time of diagnosis of GDM [19]. So, in future we have to find out whether modified intensive therapy may reduce hypertriglyceredemia and in turn LGA babies. When both moderate maternal glycemia and excessive growth are present, and insulin is prescribed regardless of therapy protocol, the LGA rates appear less responsive to glycemic therapy, possibly because high-risk growth may be well established before the traditional time of diagnosis of GDM. So, in future we have to find out whether modified intensive therapy may reduce hypertriglyceredemia and in turn LGA babies.

Atherogenic index in our study in GDM women was 4.39±1.35 in contrast to 3.19±0.24 in the study by McGrowder[20]. The raised atherogenic index in GDM women may be risk factor in causing coronary heart disease in future. These patients should be followed up after delivery to see whether the lipid levels return to normal or these changes are permanent. Preventive measures should be aimed at improving insulin sensitivity in women predisposed to GDM.

CONCLUSIONS:

Mid – pregnancy Serum triglyceride levels were significantly higher and HDL levels significantly lower in GDM patients when compared to normal healthy pregnant women. Maternal mid - pregnancy hypertriglyceridemia and mean blood glucose levels are the most independent variables that can predict the presence of LGA babies after adjusting for age, parity and pre-pregnancy BMI.

REFERENCES:

1. Desoye G, Schweditsch MO, Pfeiffer KP, Zechner R, Kostner GM: Correlation of hormones with lipid and lipoprotein levels during normal pregnancy and postpartum. J Clin Endocrinol Metab 64:704-712,1987.

2. Herrera E, Lasuncion MA, Gomez-Coronado D, Aranda P, Lopez-Luna P, Maier I: Role of lipoprotein lipase activity on lipoprotein metabolism and the fate of circulating triglycerides in pregnancy. Am J Obstet Gynecol 158:1575-1583, 1988

3. Metzger BE, Phelps RL, Freinkel N, Navickas IA. Effects of gestational diabetes on diurnal profiles of plasma glucose, lipids, and individual amino acids. Diabetes Care 1980;3:402–9.

4.Emilio Herrera Ph.D, Henar Ortega-senovilla, Ph.D Disturbances in lipid metabolism in diabetic pregnancy-are these the cause of the problem? Best practice and research clinical endocrinology and metabolism 24(2010) 515-525.

5. Orskou J, Henriksen TB, Kesmodel U. Maternal characteristics and lifestyle factors and the risk of delivering high birth weight infants. Obstet Gynecol 2003:102-115.

6. Okun N, Verma A, Mitchell BF. Relative importance of maternal constitutional factors and glucose intolerance of pregnancy in the development of newborn macrosomia. J Matern Fetal Med 1997; 6: 285–90.

7. Leila Sekhavat, Fatemah Zare, Sedighah Akhavan Karbasi. Maternal serum triglyceride at mid pregnancy and newborn weight in non diabetic and normal BMI women. NJOG 2008 May-June; 3(1): 19 – 23

8. Freinkel N. Banting lecture 1980: Of pregnancy and progeny. Diabetes 1980;29(12):1023–35.

9. Seshiah, V.; Balaji, V.; Balaji MS.; et al. (2004). Gestational diabetes mellitus in India. J Assoc Physicians India.Vol. 52, No. 9, (September 2004), pp. 707-11

10. Seshiah V, Sahay BK, Das AK, Shah S, Banerjee S, Rao PV, et al. Gestational Diabetes Mellitus - Indian Guidelines. (804-6).J Indian Med Assoc. 2009;107:799–802.

11. Kushtagi P; Arvapally S. Maternal mid-pregnancy serum triglyceride levels and neonatal birth weight. International Journal of Gynaecology and Obstetrics. 2009 Sep; 106(3) .

12. Asare-Anane H, Bawah AT, Osa-Andrews B , Adanu R, Ofori EK, Bani SA, Ateko RO, Tagoe EA, Nyarko AK. Lipid Profile In Ghanaian Women With Gestational Diabetes Mellitus. International Journal Of Scientific & Technology Research 2013; 2(4) :168-75.

13. Khan R, Ali K, Khan Z, AhmadT. Lipid profile and glycosylated hemoglobin status of gestational diabetic patients and healthy pregnant women. Indian Journal of Medical Sciences.2012 ;66 (7): 149-54

14. Sobki SH, Al-Senaidy AM, Al-Shammari TA, Inam SS, Al-Gwiser AA, Bukhari SA. Impact of gestational diabetes on lipid profiling and indices of oxidative stress in maternal and cord plasma. Saudi Med J 2004;25:876-80.

15. Aziz R, Mahboob T: Lipid profile and serum insulin levels in Gestational Diabetes. Journal of the Dow University of Health Sciences. 2008 ; 2 (3):102-106. 16. Son GH, Kwon JY, Kim YH, Park YW. Maternal serum triglycerides as predictive factors for large-for-gestational age newborns in women with gestational diabetes mellitus. Acta Obstetricia et Gynecologica Scandinavica. 2010; 89(5): 700–704.

17. Mossayebi E, Arab Z, Rahmaniyan M, Almassinokiani F, Kabir A Prediction of neonates' macrosomia with maternal lipid profile of healthy mothers. Pediatr Neonatol. 2014 Feb;55(1):28-34.

18. Schaefer-Graf UM, Graf K, Kulbacka I, et al. Maternal lipids as strong determinants of fetal environment and growth in pregnancies with gestational diabetes mellitus. Diabetes Care. 2008;31(9):1858–1863.

19. Kjos SL, Schaefer –Graf UM. Modified Therapy for Gestational Diabetes Using High-Risk and Low-Risk Fetal Abdominal Circumference Growth to Select Strict Versus Relaxed Maternal Glycemic Targets. Diabetes Care July 2007; 30(2).

20. McGrowder D, Grant K, Irving R, Gordon L, Crawford T,Lindo RA, Fraser YP. Lipid Profile and Clinical Characteristics of Women with Gestational Diabetes Mellitus and Preeclampsia. Journal of Medical Biochemistry. 2009; 28(2): 72–81.