European Journal of Molecular & Clinical Medicine
ISSN 2515-8260 Volume 7, Issue 07, 2020

SERUM LEPTIN LEVELS, BODY MASS INDEX AND ITS CORRELATION WITH MATERNOFETAL OUTCOME IN GESTATIONAL DIABETES MELLITUS

HARD TILVA[1], SUREKHA TAYADE[2]

1] Post Graduate Resident, Department of Obstetrics and Gynaecology, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences, Deemed to be University, Wardha.

Email- hardcrash.ht@gmail.com
Mob : +917069690999

2] Professor, Department of Obstetrics and Gynaecology, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences, Deemed to be University, Wardha.

Email- surobgy@gmail.com
Mob: +917887519832

Corresponding author's name and address: Hard Tilva
Corresponding Author's Email id: hardcrash.ht@gmail.com
Contact number: +917069690999
Type of Article: Research Protocol
Conflict of Interest: None
Funding: Nil

Abstract

BACKGROUND – Insulin resistance and profound changes in body weight are common features of pregnancy. Obesity in pregnant women and glucose intolerance due to insulin resistance, ultimately leading to Gestational Diabetes Mellitus (GDM), both can add to poor maternofetal outcome such as, macrosomia, prematurity, shoulder dystocia, preeclampsia, and even increased chances of fetal demise. Leptin is a novel potential regulator of insulin resistance. Measuring serum leptin levels in pregnant women with different BMI categories may potentially help in early detection of GDM, and predicting poor maternofetal outcome at early stages of pregnancy.

OBJECTIVES

1. ***To study serum leptin levels in women with GDM***
2. ***To study the body mass index in women with GDM and classify study subjects according to BMI***
3. ***To study the serum leptin levels in women with GDM belonging to various BMI categories and evaluate its association.***

4. ***To correlate serum leptin and BMI with materno-fetal outcome in women with GDM***

METHODOLOGY – This prospective hospital based study will be conducted in department of obstetrics and gynecology, at Acharya Vinoba Bhave Rural Hospital (AVBRH). 96 pregnant women seeking care at outpatient unit and/or in patient unit of Obstetrics & Gynaecology, in the AVBRH hospital, Sawangi, Meghe, in first trimester, will be included in the study. Screening for GDM in twice, first as soon as possible after diagnosis of pregnancy (first trimester) and second between 24-28 weeks, fasting Serum Leptin will be measured at 28 -32 weeks of gestation.

EXPECTED RESULT - It is expected that levels of Sr. Leptin will be higher in the women with GDM and will be abnormal in various BMI categories with a proportionate rise with increasing BMI.

KEYWORDS – Leptin, BMI, GDM, Maternofetal outcome.

INTRODUCTION

Metabolic disorder of glucose in pregnancy, for example, gestational diabetes mellitus(GDM), complicates pregnancy which is a significant reason for adverse pregnancy result.

Such as all types of hyperglycemia, GDM represents insufficient insulin levels

to fulfill insulin needs (1). Globally, hyperglycemia in pregnancy is prevalent in approximately 10% to 24% of all pregnancies (2) . In Asian population the burden of GDM is found to be 10.9% to 12.1% (3). Increasing trend of such cases in India is emerging as a major public health problem. Urban prevalence of GDM among Indian population is said to be around 8% to 22% of all pregnancies (4). Cause of GDM is the decreased sensitivity to insulin and the increase in anti-insulin hormones secreted by placenta during pregnancy, for example progesterone, human placental lactogen and glucocorticoid.

Novel prospective moderator of insulin resistance, such as leptin and antiobesity hormone, have been studied recently. BMI and serum leptin levels have interesting role in studying maternofetal outcome in GDM (1). Adipocytes are chief source of Leptin production which is a 16-kDa peptide hormone, but it is also produced by other tissues and organs, for example, ovary, breasts, skeletal muscle, pituitary gland, stomach, lymphoid tissue and the placenta in humans which acts upon hypothalamus which in turn decreases food consumption and increases energy utilization (5).

With alteration in maternal lipid stores and glucose metabolism in pregnant women, serum leptin levels are increased. There is 2-3 times increment in leptin concentration of pregnant women compared to leptin concentration in non-pregnant women which peaks around 28 weeks of pregnancy (1). Evidences show that amnion cells and trophoblasts of placenta also augments the production of leptin, and maternal circulating leptin concentration is considered to have a few overlay increment above non-pregnant conditions (6). The current discoveries with respect to maternal circulating leptin levels during pregnancy in GDM women were clashing in past researches, with high, low or similar concentrations documented in women having GDM contrasted with those with normal glycemic control. Such varieties might be ascribed to the utilization of one step bio-sample together with immense contrasts within

circumstances of leptin estimation, liable to the active variations in leptin concentrations in the course of pregnancy. The state of increased leptin levels might be gainful for the implantation, creation of human chorionic gonadotropin and amino acid take-up and the peripheral leptin resistance status may likewise be engaged in the pregnancy-specific lipid regulation (6). Nonetheless, not many studies depicted the longitudinal GDM-related shifts in leptin concentration. Concentrations of maternal leptin during pregnancy, according to the level of glucose can help to increase a superior agreement with regard to development of GDM (6). Scientists have shown that leptin directly affects the response of the entire body to insulin by regulating the efficacy of insulin-interceded glucose metabolism via skeletal muscle and hepatic gluconeogenesis control. The results of some experiments indicate that leptin has an extreme inhibitory effect on insulin secretion. Wide epidemiological trials have shown that plasma leptin concentration in men and non-pregnant women are emphatically related to insulin resistance (6).

GDM and increased BMI also have a strong association(7). With an increase in BMI, a gradual increase in serum leptin concentration has been observed (8). In normal, overweight and obese subjects, major differences between leptin concentration were found in both genders (9). Obesity is defined as body fat abundance. BMI is used almost generally as a metric for obesity in huge studies that look at the relationship of obesity with morbidity and mortality yet it does not segregate among fat and lean body mass. Leptin, is delivered by adipocytes and its serum concentration seems to reflect absolute muscle to fat ratio. Maskari et al 2006 suggested that leptin levels correspond with body mass index in most obese individuals (9). Thus we can say serum Leptin will be increased in women with increased BMI having more adipose tissue.

This research is intended to investigate the association between the amount of serum leptin and the body mass index of gestational diabetes mellitus in pregnant women and the seriousness of the condition.

RATIONALE

GDM largely contributes to the morbidity and mortality of pregnant females and poor fetal outcome. Predicting GDM at early stages can help in improving maternal and fetal health. Serum leptin level and BMI measurement is an easy and affordable process. This research would continue to improve scientific understanding and analyze the relationship between serum leptin and BMI and determine its function in predicting adverse maternaofetal outcomes in patients with GDM.

AIM AND OBJECTIVES

AIM:-

The aim of this study is to establish the relationship between maternal serum leptin and BMI levels and their connection with maternofetal outcome in women with gestational diabetes mellitus in rural populations.

OBJECTIVES:-

1) Analysis of serum levels of leptin in women with GDM.
2) To study the body mass index in women with GDM and classify study subjects according to BMI

3) To research and assess the relationship of serum leptin levels in women with GDM in different categories of BMI.
4) To correlate serum leptin and BMI with maternofetal outcome in women with GDM

METHODS

Research question:

1) Are serum leptin levels high in women with GDM?
2) In women with GDM belonging to separate BMI groups, is there a substantial change in serum leptin levels?
3) Do women with high BMI and abnormal leptin levels have adverse materno-fetal outcome?

Ethical consideration: There will be no financial burden to the study subject in context of this research. For which we will be applying for funding from intramural grant, ICMR grant, and concessions. Written informed consent from all registered women will be taken and ethical permission will be received from Institutional Ethics Committee (IEC) and.

Study design: Prospective Hospital Based Study.

Duration of Study: 2 years

Study Site: Department of Obstetrics and Gynaecology, AVBRH, Dutta Meghe Institute of Medical Sciences, Sawangi (Meghe), Wardha.

Study Population - Pregnant women seeking care at outpatient unit and/or in patient unit of Obstetrics & Gynaecology, in the, AVBRH hospital, Sawangi, Meghe, in first trimester, fitting into inclusion and exclusion criteria and were amenable for follow up.

The sample size of 96 will be considered in the study

Materials: Human Leptin ELISA kit, Weight Scale and Stadiometer

Inclusion criteria:

- Consecutive, consenting, singleton pregnant women of all ages and parity will be invited to participate in this study during their first prenatal visit, in first trimester of pregnancy.
- Women with abnormal glucose screening by DIPSI method (2 hours value after 75 gram oral glucose load , irrespective of fasting status) will be added to the research.

Exclusion criteria:

- Established Diabetes Mellitus (DM)
- Multiple pregnancy

- Women with other associated serious medical disorders (hypertension, renal disease, moderate to severe anemia, thyroid disorder, TORCH group of infections etc) interfering with maternal and perinatal outcome at the time of recruitment in study
- Women with Intrauterine fetal death
- Women having congenitally anomalous baby

METHODOLOGY:

METHODS

The study will be initiated after the approval from institutional ethical committee. The nature of the research will be clarified to women meeting selection requirements, and written informed consent in the local vernacular language (Marathi) will be obtained on a formal Performa before enrollment. Women willing to participate will be informed about the Biochemical test (Serum Leptin) with the help of an information sheet that will be provided to the Consecutive, consenting pregnant women in first trimester will be recruited in the study, weight of the woman will be measured and pre-pregnancy weight will be calculated by subtracting 400 grams from the first trimester weight. Height will be measured using stadiometer and pre-pregnancy BMI will be calculated.

Recruited women will be screened for GDM in twice, first as soon as possible after diagnosis of pregnancy (first trimester) and second between 24-28 weeks as per GOI guidelines (10). Single step testing, utilizing 75 gm oral glucose load will be utilized (DIPSI method). Seventy five gm. Glucose after dissolving in roughly 300 ml water will be ingested per oral whether the pregnant women are in fasting or non-fasting condition, independent of the last meal and 2 hours blood glucose level will be estimated. The starting point blood sugar level of $\geq$140 mg/dL will be taken as cut off for determining GDM (10). Those women with abnormal DIPSI test will be included in the study for further evaluation.

Detailed history regarding age, residence, literacy, economic status according to Kuppuswamy classification(11) , gravidity/ parity and obstetric events (Abortions, live births, number of living children, SBs and NNDs), family history of diabetes mellitus will be recorded. Details of pregnancy will be obtained to decide inclusion/exclusion in study. Last menstrual period will be recorded and gestational age will be calculated. Ultrasound examination will be done to confirm intrauterine, singleton, pregnancy in the first trimester. Clinical examination and antenatal investigations will be done according to routine departmental protocol.

SERUM LEPTIN TEST

The Fasting Serum Leptin concentration will be determined at 28-32 weeks of gestation using the enzyme-linked immunosorbent assay (ELISA) process. The commercially available human serum leptin ELISA kit (Biotechnica Info lab, Bangalore) will be used. The procedure for the ELISA method will be performed according to the instructions provided by the manufacture. This test will have a sensitivity margin of 9.38 pg/ml.

All enrolled women will be followed throughout during their pregnancy, intrapartum and postpartum by primary investigator. Regular follow up visits will be conducted and all study participants will be examined, evaluated and managed according to standard guidelines. Antenatal adverse effects such as preterm labour, premature rupture of membranes, pregnancy induced hypertension etc. will be noted. Decisions regarding the mode of delivery, gestational age at delivery, spontaneous versus induced delivery and any interventions needed will be decided by consultant obstetrician looking after the woman without any interference from study. Intrapartum events like gestational age at delivery, delivery mode, sex of infant, weight at birth, Apgar score at 5 minutes, need for instrumental delivery, need for caesarean section, prolonged labour, obstructed labour, shoulder dystocia etc. will be noted. Newborn resuscitation and care will be taken care of by resident pediatrician. Apgar score calculated by the attending neonatologist will be recorded. Weight in gram will be measured on digital weighing machine. Adverse fetal events such as stillbirth, need for NICU admission, birth asphyxia and neonatal death etc. will be noted. Indication for neonatal intensive care such as preterm birth, low birth weight, respiratory distress, meconium aspiration, sepsis, Hyperbilirubinemia, hypothermia, hypoglycemia and convulsions will be recorded as per diagnosis made by attending pediatrician. Postpartum complications such as postpartum hemorrhage, retained placenta, need for blood transfusion, failure of lactation, puerperal sepsis etc. will be recorded. Maternal death, if any, will be recorded. A pilot-tested data collection form will be used to access the data.

STATISTICAL ANALYSIS

In a pilot-tested data collection method, the details will be tabulated. The data will be entered in a spread sheet (Excel) and transferred to Epi Info-151 software. Student's t test will be used to test continuous variable; normally distributed and Mann Whitney test will be used to compare continuous variables with a skewed distribution. Proportions will be compared by Chi Square test. Outcome measures will be serum leptin levels in various BMI categories in GDM women and maternal-fetal outcomes. The Kolmogorov-Smirnov test will analyze the normal distribution of the data and will be reported as arithmetic means ± SD, non-normally distributed data will be represented by medians (quartiles) and categorical data will be represented by numbers and percentages(12). The chi square test and a two-level P value will compare the proportions.

EXPECTED OUTCOME/RESULTS

It is expected that levels of Sr. Leptin will be higher in the women with GDM and will be abnormal in various BMI categories with a proportionate rise with increasing BMI. It is also expected that those women with high BMI and High Serum leptin will have more chances of adverse maternal-fetal outcome.

DISCUSSION

Pregnancy and GDM provide an unique opportunity to observe the co-relation between plasma leptin levels and changes in BMI.

The metabolism of glucose in non-GDM pregnant women is maintained by an elevated insulin release rate with reduced insulin sensitivity (13). In obese and insulin resistant pregnant woman, endogenous insulin production will be inadequate. Diabetes will be disclosed for the first time in such a scenario, particularly in late pregnancy (14).

Many studies depict that women having GDM had serum leptin concentrations on the higher side compared to non-GDM women. Kautzky-Willer reported in one such study that maternal third-trimester plasma leptin concentrations in GDM women were higher compared to the control sample. (24.9 ng/mL vs. 18.2 ng/mL; p ¼ 0.001) (15). The Vitoratus (16) and Qiu (17) experiments were both found to have identical outcomes. Evidences from GBD studies are available(18,19,20). A number of related articles were reviewed(21,22,23). Warjukar et. al. studied about microalbuminuria and uric acid in Type 2 Diabetes Mellitus(24). Gupte et. al. assessed endothelial function by FMD (Flow Mediated Dilatation) in prediabetes(25).

This research also aims to compare serum leptin and BMI levels with GDM in women and to examine whether this rise in serum leptin and BMI levels can trigger any adverse maternal-fetal outcomes.

CONCLUSION

In conclusion for pregnant women with GDM, serum leptin levels together with BMI should be incorporated to predict any adverse maternofetal outcome. Considering that their accuracy for predicting maternofetal outcome might be relatively modest, further studies should validate the clinical usefulness of serum leptin and BMI.

ETHICAL CONSIDERATIONS

The Serum leptin kit will be purchased with the help of intramural institutional grant and the study subject will not have to bear the expenses of this test. Consent will be obtained and ethical approval will be sought from institutional ethical board.

REFERENCES

[1] Soheilykhah S, Mojibian M, Rahimi-Saghand S, Rashidi M, Hadinedoushan H. Maternal serum leptin concentration in gestational diabetes. Taiwan J Obstet Gynecol. 2011 Jun;50(2):149–53.

[2] Plows J, Stanley J, Baker P, Reynolds C, Vickers M. The Pathophysiology of Gestational Diabetes Mellitus. Int J Mol Sci. 2018 Oct 26;19(11):3342.

[3] Lee KW, Ching SM, Ramachandran V, Yee A, Hoo FK, Chia YC, et al. Prevalence and risk factors of gestational diabetes mellitus in Asia: a systematic review and meta-analysis. BMC Pregnancy Childbirth. 2018 Dec;18(1):494.

[4] Siddiqui S, Waghdhare S, Panda M, Sinha S, Singh P, Dubey S, et al. Regional prevalence of gestational diabetes mellitus in North India. J Diabetol. 2019;10(1):25.

[5] Ramos-Lobo AM, Donato J. The role of leptin in health and disease. Temperature. 2017 Jul 3;4(3):258–91.

[6] Xiao W-Q, He J-R, Shen S-Y, Lu J-H, Kuang Y-S, Wei X-L, et al. Maternal circulating leptin profile during pregnancy and gestational diabetes mellitus. Diabetes Res Clin Pract. 2020 Mar;161:108041.

[7] Shah A, Stotland N, Cheng Y, Ramos G, Caughey A. The Association between Body Mass Index and Gestational Diabetes Mellitus Varies by Race/Ethnicity. Am J Perinatol. 2011 Aug;28(07):515–20.

[8] Paul RF, Hassan M, Nazar HS, Gillani S, Afzal N, Qayyum I. EFFECT OF BODY MASS INDEX ON SERUM LEPTIN LEVELS. J Ayub Med Coll Abbottabad. :4.

[9] Maskari MYA, Alnaqdy AA. Correlation between Serum Leptin Levels, Body Mass Index and Obesity in Omanis. :5.

[10] Gestational-Diabetes-Mellitus.pdf.

[11] MODIFIED KUPPUSWAMY SCALE | PSM Made Easy [Internet]. [cited 2020 Sep 7]. Available from: http://www.ihatepsm.com/blog/modified-kuppuswamy-scale

[12] Kolmogorov–Smirnov test. In: Wikipedia [Internet]. 2020 [cited 2020 Nov 28]. Available from: https://en.wikipedia.org/w/index.php?title=Kolmogorov%E2%80%93Smirnov_test&oldid=990620453

[13] Yen SS. Endocrine regulation of metabolic homeostasis during pregnancy. Clin Obstet Gynecol. 1973 Sep;16(3):130–47.

[14] Carpenter MW. Rationale and performance of tests for gestational diabetes. Clin Obstet Gynecol. 1991 Sep;34(3):544–57.

[15] Kautzky-Willer A, Pacini G, Tura A, Bieglmayer C, Schneider B, Ludvik B, et al. Increased plasma leptin in gestational diabetes. Diabetologia. 2001 Feb;44(2):164–72.

[16] Vitoratos N, Salamalekis E, Kassanos D, Loghis C, Panayotopoulos N, Kouskouni E, et al. Maternal Plasma Leptin Levels and Their Relationship to Insulin and Glucose in Gestational-Onset Diabetes. Gynecol Obstet Invest. 2001;51(1):17–21.

[17] Qiu C, Williams MA, Vadachkoria S, Frederick IO, Luthy DA. Increased maternal plasma leptin in early pregnancy and risk of gestational diabetes mellitus. Obstet Gynecol. 2004 Mar;103(3):519–25.

[18] Murray, Christopher J L, Aleksandr Y Aravkin, Peng Zheng, Cristiana Abbafati, Kaja M Abbas, Mohsen Abbasi-Kangevari, Foad Abd-Allah, et al. "Global Burden of 87 Risk Factors in 204 Countries and Territories, 1990–2019: A Systematic Analysis for the Global Burden of Disease Study 2019." *The Lancet* 396, no. 10258 (October 2020): 1223–49. https://doi.org/10.1016/S0140-6736(20)30752-2.

[19] Vos, Theo, Stephen S Lim, Cristiana Abbafati, Kaja M Abbas, Mohammad Abbasi, Mitra Abbasifard, Mohsen Abbasi-Kangevari, et al. "Global Burden of 369 Diseases and Injuries in 204 Countries and Territories, 1990–2019: A Systematic Analysis for the Global Burden of Disease Study 2019." *The Lancet* 396, no. 10258 (October 2020): 1204–22. https://doi.org/10.1016/S0140-6736(20)30925-9.

[20] Wang, Haidong, Kaja M Abbas, Mitra Abbasifard, Mohsen Abbasi-Kangevari, Hedayat Abbastabar, Foad Abd-Allah, Ahmed Abdelalim, et al. "Global Age-Sex-Specific Fertility, Mortality, Healthy Life Expectancy (HALE), and Population Estimates in 204 Countries and Territories, 1950–2019: A Comprehensive Demographic Analysis for the Global Burden of Disease Study 2019." *The Lancet* 396, no. 10258 (October 2020): 1160–1203. https://doi.org/10.1016/S0140-6736(20)30977-6.

[21] Patel, A.B., H. Kulkarni, K. Kurhe, A. Prakash, S. Bhargav, S. Parepalli, E.V. Fogleman, J.L. Moore, D.D. Wallace, and P.L. Hibberd. "Early Identification of Preterm Neonates at Birth with a Tablet App for the Simplified Gestational Age Score (T-SGAS) When Ultrasound Gestational Age Dating Is Unavailable: A Validation Study." *PLoS ONE* 15, no. 8 August (2020). https://doi.org/10.1371/journal.pone.0238315

[22] Kshirsagar, P.C., A. Tembhare, and P. Palsodkar. "Evaluation of Serum Ferritin Level in Anaemic & Nonanemic Pregnant Women & Its Correlation with Maternal and Perinatal Outcome." *International Journal of Pharmaceutical Research* 11, no. 4 (2019): 2075–79. https://doi.org/10.31838/ijpr/2019.11.04.515.

[23] Walinjkar, R.S., S. Khadse, S. Kumar, S. Bawankule, and S. Acharya. "Platelet Indices as a Predictor of Microvascular Complications in Type 2 Diabetes." *Indian Journal of Endocrinology and Metabolism* 23, no. 2 (2019): 206–10. https://doi.org/10.4103/ijem.IJEM-13-19.

[24] Warjukar, P., P. Jain, P. Kute, A. Anjankar, and S.S. Ghangale. "Study of Microalbuminuria and Uric Acid in Type 2 Diabetes Mellitus." *International Journal of Current Research and Review* 12, no. 14 Special Issue (2020): 56–65. https://doi.org/10.31782/IJCRR.2020.5665.

[25] Gupte, Y., S. Acharya, S. Kumar, and P.S. Patil. "Assessment of Endothelial Function by FMD (Flow Mediated Dilatation) in Prediabetes." *International Journal of Pharmaceutical Research* 11, no. 2 (2019): 1808–12. https://doi.org/10.31838/ijpr/2019.11.02.202.