Original Article

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Correlation of Maternal BMI with Foetal Liver Blood Flow and Neonatal Adiposity in Normal Pregnancies and Pregnancies Complicated by Gestational Diabetes Mellitus and Foetal Growth Restriction

Obstetrics and Gynaecology Section

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ABSTRACT

Introduction: The foetus exhibits a wide array of structural and functional adaptations in response to intrauterine conditions, towards protection of vital organs and maintaining the supply of essential nutrients. When oxygen is limited, foetal adaptations prioritise brain growth, irrespective of whether other essential nutrients are limited or not. The hypothesis for this study was that fatty acid synthesis occurs in foetal liver therefore if adaptive changes occur in the hepatic and umbilical flow it will affect fat deposition which will manifest as neonatal adiposity.

Aim: Correlation of maternal Basal Metabolic Index (BMI) with Foetal liver blood flow and neonatal adiposity in normal pregnancies and pregnancies complicated by Gestational Diabetes Mellitus (GDM) and Foetal Growth Restriction (FGR).

Materials and Methods: An observational pilot study was carried out in a tertiary care referral hospital of Northern India. Antenatal women were recruited in three groups of singleton uncomplicated pregnancies (40), Women with GDM (31) and women with FGR (29). Maternal characteristics including pre-pregnancy BMI and obstetric ultrasound doppler study were recorded at 35 weeks gestation. The time-averaged maximum velocity (TAMX) was calculated for Umbilical Vein (UV) and Ductus Venosus (DV) as (Vmax) UV and (Vmax) DV. Blood flow (Q) was calculated as $Q=h\times(D/2)^2\times p\times TAMX$. The neonatal biometry and Skin Fold Thickness (SFT) was measured. Statistical techniques used were t-tests for analyses of dichotomous outcomes, Pearson's correlation (r) and multivariate regression.

Results: In mothers with higher DV shunting neonatal adiposity was significantly lower in the FGR group. In the uncomplicated group about 46% of variation in adiposity was explained by all the study variables and overall regression equation was statistically significant (p=0.004).

Conclusion: Mothers with low BMI and normal umbilical and middle cerebral doppler flow had higher foetal hepatic flow to improve substrate deposition. DV shunting was significantly higher in hypoxic foetuses with reduced hepatic flow.

Keywords: Ductus venosus, Foetal doppler, Hepatic blood flow

INTRODUCTION

Increased flow in the UV leads to proliferation of hepatocytes in the liver of the lamb foetus. This in turn increases the production of Insulin like growth factors 1 and 2 [1]. These growth factors positively increase the growth and proliferation in these foetuses [2,3]. Various studies have compared the UV flow in growth restricted foetuses and normal uncomplicated pregnancies. They have reported that similar to lamb foetuses the human foetal hepatocyte proliferation is affected by the UV flow [4,5]. This flow affects the fat deposition in the foetus which can be detected soon after birth in the neonate [6]. It has been postulated that fat accretion in foetal life can predispose to obesity and diabetes in postnatal life in human societies which have more than adequate nutrition [4]. There is paucity of Indian data regarding comparison of foetal Doppler studies, maternal BMI and its impact as a predictor of neonatal adiposity. The authors did not find any published data on Indian women and neonates in indexed journals regarding the association of these. Hence, the pilot study was carried out to determine the further feasibility of a larger study in these groups.

Aim of the present study was to carry out a longitudinal assessment of the venous haemodynamic development of foetuses and the association of fat accretion with maternal BMI in women with uncomplicated pregnancies, GDM and FGR.

Primary Outcome

1. Foetal hepatic blood flow in uncomplicated pregnancy and those with GDM and IUGR.
2. Correlation of hepatic blood flow with neonatal adiposity in each group.

Secondary Outcome

Correlation of Maternal BMI, Foetal hepatic flow and neonatal adiposity

MATERIALS AND METHODS

This observational study was carried out in the Department of Obstetrics and Gynaecology at the All India Institute of Medical Sciences Delhi, India. It was conducted for six months, from February 2018 to August 2018. Ethical Committee approval was obtained vide letter no. IECPG-623/31.01.2018. Since a reference published study on similar protocol could not be accessed, this was a pilot study carried out with 80 women attending the Antenatal clinic.

Inclusion criteria: Women attending the antenatal clinic were recruited in three groups, after obtaining an informed consent. Group A comprised of 40 women with singleton uncomplicated pregnancies. Group B comprised of 31 women with GDM on treatment. Group C comprised of 29 women with FGR. FGR is a foetal condition where the estimated foetal weight is less than the 10th centile and Umbilical Artery Pulsatility Index (UAPI) is more than 95th centile for that period of gestation.

Exclusion criteria: Women with pre-existing medical disorders including Hypertension and Pre-pregnancy Diabetes, pregnancies complicated by Antepartum Haemorrhage/Haemolytic disorders, pregnancies with foetal congenital abnormalities or chromosomal disease, difference of >6 days in period of gestation estimated by crown rump length on ultrasound to that of calculated from last menstrual period, multiple pregnancies, pregnancy with auto immune conditions, maternal addictions like use of alcohol/tobacco during pregnancy, pregnancy with intrauterine death, neonates requiring NICU admission.

Routine antenatal data including pre-pregnancy BMI was recorded in all women. An obstetric ultrasound and Doppler study were done at 35 weeks of pregnancy. Complete biometry and Doppler parameters for Umbilical Artery (UA), Middle Cerebral Artery (MCA), DV and UV were measured, a mean of three values were calculated. Ultrasound examinations were performed with TOSHIBA Xario 200 with colour and pulsed-wave Doppler mode.

Doppler investigations were performed in the foetal quiescent phase. Maximum velocity tracings and vessel diameters were measured at two different sites: Intra hepatic UV and DV isthmus. The UV was visualised in a transverse section of the abdomen in the segment immediately upstream to the DV branching. The DV was studied in a mid-sagittal section of the abdomen. Diameters were measured in sections perpendicular to the vessels at the highest magnification possible, with callipers placed on the inner edges of the brightest image of the vessel walls. The venous Doppler samplings were performed on the same segment of the vessel where diameter measurements were obtained. Colour Doppler imaging was used to visualise the vessels at their best insonation angle as small as possible and always less than 30 degrees. The time-averaged maximum velocity was calculated for UV, and DV as (Vmax) UV and (Vmax) DV. Blood flow (Q) was calculated as $Q=h\times(D/2)^2\times p\times TAMX$ where D=vessel diameter, h=spatial blood velocity profile coefficient (UV=0.5; DV=0.7). Intraclass correlation coefficients (random-effects regression) to assess intra observer variation were 0.97 and 0.96 for the UV and DV diameter, respectively. Foetal hepatic flow was calculated as the difference between umbilical venous and DV flow i.e., HBF=UV flow-DV flow. The percentage of blood flow in the DV in relation to the umbilical flow was calculated as DV shunting. The MCA and UAPI measurements were correlated for evidence of brain sparing in relation to altered liver blood flow. Also, MCA PI, DV shunting and foetal liver blood flow was correlated with neonatal SFT. The neonate was assessed postnatally within 48 hours and following parameters were measured: Birth weight and SFT.

STATISTICAL ANALYSIS

Data analysis was carried out using STATA software version 12.0. Continuous variables were tested for normality assumptions using Kolmogorov Smirnov test. Descriptive statistics such as mean, SD and range values were calculated. Comparison of groups means were carried out using one way ANOVA test followed by Bonferroni post-hoc test. Bivariate correlation analysis was carried out to see linear association between the study variables. Multivariable linear regression analysis was carried out to explain amount of variation in adiposity by other study variables. For all statistical test a two-sided probability of $p<0.05$ was considered for statistical significance.

RESULTS

Descriptive measures such as mean and standard deviation of the study variables are presented by groups in [Table/Fig-1]. Post-hoc comparison showed that maternal BMI was moderately high in the GDM group than in FGR by 2.03 kg, however it was not statistically significant (p=0.59). HBF was significantly lower in FGR group compared to uncomplicated ($p<0.005$) group and even more strongly significant in FGR verses GDM group ($p<0.001$). DV shunting was significantly higher in FGR (p=0.002) compared to uncomplicated group (p=0.002) by 3.49 mL/min and higher by 8.54 mL/min than the GDM group (p=0.001)

Variables	Normal (n=40) Mean±SD	GDM (n=31) Mean±SD	FGR (n=29) Mean±SD	p-value (ANOVA)
Age (years)	27.22±3.56	28.74±4.12	27.21±5.64	0.285
BMI (Kg/m^2)	24.44±2.97	26.07±3.32	24.03±3.74	0.042
UA PI (number)	1.07±0.33	1.00±0.15	1.09±0.23	0.376
MCA PI (number)	2.74±0.98	3.82±0.78*	2.75±0.83	0.001
UV Flow (cms/sec)	101.86±5.95	97.80±6.14*	100.73±6.27	0.022
DV Flow (cms/sec)	34.91±4.47	28.59±4.26*	38.00±5.45*	0.001
HBF (cms/sec)	67.19±5.80	69.54±5.60	61.66±9.48*	0.001
DV shunting (%)	34.24±3.74	29.20±3.68*	37.74±5.01*	0.001
Birth wt (grams)	2653.12±421.14	2993.84±443.79*	2351.83±341.66*	0.001
SFT (mm)	16.13±1.97	17.22±2.42	15.80±2.02	0.026

[Table/Fig-1]: Comparison of mean values of study variables among the groups.
*Significantly different from Normal group by Bonnferroni correction
BMI: Body mass index; UA PI: Umbilical artery pulsatility index; MCA PI: Middle cerebral artery pulsatility index; UV: Umbilical vein; DV: Ductus venosus; HBF: Hepatic blood flow; SFT: Skin fold thickness; wt: weight

The difference in neonatal adiposity was significantly higher ($p<0.05$) in the GDM mothers as compared to FGR. The MCA and UAPI measurements were correlated for evidence of brain sparing in relation to altered liver blood flow. Also, MCA PI, DV shunting and foetal liver blood flow was correlated with neonatal SFT. The difference in SFT was significant ($p<0.05$) between the GDM and FGR group, mean difference being 1.42%.

Multivariable linear regression analysis showed that in the GDM group, all the seven study variables together explained about 45% of variation in the birth weight. However, regression coefficient of MCA PI alone was found to be statistically significant (p=0.037) as shown in [Table/Fig-2]. Similar analysis by taking SFT as dependent variable showed that none of the seven study variables were related with SFT in the GDM group [Table/Fig-3]. In the FGR group about 78% of the variation in the neonatal birth weight was explained by the study variables in general [Table/Fig-4] and particularly the regression coefficients of BMI, MCA PI, UV flow and DV shunting were statistically significant inferring that the other two variables UAPI and HBF are not the significant predictors of birth weight in FGR group. Though an overall 74% of the variation in SFT was explained by the study variables, only two variables viz., MCA PI and DV shunting were found to be the significant predictors in the FGR group [Table/Fig-5]. Among the normal group an overall 51% of the variation in the birth weight was explained by the study variables and the significant regression coefficient due to UAPI had shown that an unit increase in UAPI is likely to reduce the birth weight by 686 grams [Table/Fig-6]. The analysis of SFT showed that the study variables explained about 46% of the variation and the variable MCA PI alone was found to be statistically significant predictor [Table/Fig-7].

Variables	Regression coefficients	Standard error	Standardised coefficients	p-values
BMI	36.03	25.68	0.27	0.174
UA PI	540.76	507.15	0.18	0.297
MCA PI	239.47	108.18	0.42	0.037
UV Flow	115.08	130.71	1.59	0.388
DV Flow	-181.83	470.06	-1.75	0.702
HBF	-72.10	44.23	-0.91	0.117
DV shunting	114.19	479.85	0.95	0.814

[Table/Fig-2]: Results of regression analysis on neonatal birth weight in GDM patients.
Overall $R^2 = 0.447$; p=0.036

Variables	Regression coefficients	Standard error	Standardised coefficients	p-values
BMI	0.06	0.16	0.08	0.718
UA PI	5.03	3.16	0.30	0.125
MCA PI	1.30	0.67	0.42	0.066
UV Flow	-0.01	0.81	-0.03	0.989
DV Flow	-0.96	2.93	-1.69	0.746
HBF	0.41	0.28	0.95	0.151
DV shunting	1.30	2.99	1.97	0.668

[Table/Fig-3]: Results of regression analysis on SFT in GDM patients.
Overall R^2=0.281; p=0.300

Variables	Regression coefficients	Standard error	Standardised coefficients	p-values
BMI	32.43	11.24	0.36	0.009
UA PI	-342.68	190.86	-0.23	0.087
MCA PI	239.49	53.71	0.58	0.000
UV Flow	-122.38	49.88	-2.25	0.023
DV Flow	323.11	135.75	5.16	0.027
HBF	1.04	4.81	0.03	0.830
DV shunting	-355.20	137.92	-5.21	0.018

[Table/Fig-4]: Results of regression analysis on neonatal birth weight in FGR patients.
Overall R^2=0.776; p<0.001

Variables	Regression coefficients	Standard error	Standardised coefficients	p-values
BMI	0.03	0.07	0.05	0.708
UA PI	-1.21	1.21	-0.14	0.329
MCA PI	1.65	0.34	0.68	<0.001
UV Flow	-0.59	0.32	-1.84	0.076
DV Flow	1.77	0.86	4.77	0.053
HBF	-0.05	0.03	-0.24	0.114
DV shunting	-1.92	0.88	-4.77	0.040

[Table/Fig-5]: Results of regression analysis on SFT in FGR patients.
Overall R^2=0.741; p<0.001

Variables	Regression coefficients	Standard error	Standardised coefficients	p-values
BMI	-18.21	19.31	-0.13	0.353
UA PI	-685.60	197.07	-0.54	0.001
MCA PI	107.50	69.72	0.25	0.133
UV Flow	34.65	98.05	0.49	0.726
DV Flow	-31.78	250.66	-0.34	0.900
HBF	-31.97	34.79	-0.44	0.365
DV shunting	11.91	251.52	0.11	0.963

[Table/Fig-6]: Results of regression analysis on neonatal birth weight in Normal patients.
Overall R^2=0.513; p=0.001

DISCUSSION

The study group comprised of women with singleton pregnancy divided in three subgroups of uncomplicated pregnancy, women with GDM and FGR. On review of literature other studies have observed the hepatic flow and neonatal adiposity only in one group only either uncomplicated pregnancy, FGR or pre-gestational diabetes.

In a study by Godfrey KM et al., 381 uncomplicated singleton pregnancies studied for hepatic flow, MCA Doppler indices at 34 and 36 weeks of gestation and neonatal adiposity were followed by determining adiposity at four years [7]. The median liver blood flow, DV shunting and PI in MCA were 150.9 (87.3-239.4) mL/min, 24.1 (12.0-42.0) % and 1.98 (1.52-2.45), respectively. The median maternal age, pre-pregnant BMI and sum of SFT and infant birthweight were 30 years (25-35), 23.8 kg/m^2 (21.9-26.5),

Variables	Regression coefficients	Standard error	Standardised coefficients	p-values
BMI	-0.07	0.10	-0.10	0.496
UA PI	-1.10	0.97	-0.19	0.267
MCA PI	0.85	0.34	0.43	0.018
UV Flow	0.15	0.48	0.45	0.758
DV Flow	0.20	1.23	0.44	0.875
HBF	-0.24	0.17	-0.70	0.176
DV shunting	-0.33	1.24	-0.64	0.789

[Table/Fig-7]: Results of regression analysis on SFT in Normal patients.
Overall R^2=0.458; p=0.004

62.4 mm (47.6-86.5) and 3485 g (2875-4160), respectively. While maternal age, pre-pregnancy BMI and MCA PI was similar to the uncomplicated study group, the hepatic flow, neonatal adiposity and birthweight were lower in the uncomplicated study group compared to study by Godfrey KM et al., [7]. This could be attributed to the differences in European and Asian population characteristics.

Belloti M et al., studied flow to the foetal liver and the DV in intrauterine growth-restricted human foetuses in relationship with dilatation of the ductal isthmic diameter [4]. The hepatic flow and DV shunting in 29 growths restricted and 137 normal foetuses were reported. In their study the hepatic flow in left lobe was 48.8 mL/min and right lobe was 40 mL/min in normal foetuses while it was reduced to 11 mL/min in left and 6.7 mL/min in right lobe in growth restricted foetuses. Foetal hepatic flow in the present study in group C (IUGR) was 61.66±9.48 mL/min which was studied at 35 weeks of gestation [Table/Fig-1]. Foetuses with growth restriction have a lower total venous flow normalised for their weight as was also observed in present study [4]. In normal human foetuses, only 15% of umbilical blood flow is shunted through the DV at term [8,9]. DV shunting was reported as 26.47% to 90.36% by Belloti M et al., in growth restricted foetuses [4]. In the present study DV shunting was significantly (p=0.002) higher in FGR compared to uncomplicated group (p=0.002) by 3.49 ml/min and higher by 8.54 mL/min than the GDM group (p=0.001). In the present study it was observed that for one unit increase in UV flow and DV shunting an average reduction in birth weight would be about 122 gm and 355 gm, respectively while the other variables held constant.

Measurement of SFT is a simple clinical method to determine the percentage of adiposity in the neonate. SFT correlates closely with Dual-energy X-ray absorptionmetry (FM_{DXA}) in new-borns and infants aged ≤4 months [10].

The errors reported between in vivo and non-invasive measurement of adiposity in a group of infants seems to be acceptable [10]. It also compared favourably with those presented by Koo WWK and Walters JC [11]. In the present study Mean±SD of neonatal adiposity based on SFT and whole-body length was 16.13±1.97 in group A, 17.22±2.42 in group B and 15.80±2.02 in group C (p=0.026). The correlation between SFT and neonatal adiposity improved when body length was included in the model. This can be explained from another study which reported that postnatal fat accumulation occurs at the extremities predominantly [12].

The SFT was significantly higher (p<0.05) in the GDM compared to the FGR group, mean difference being 1.42%. However, in case where MCA PI was low suggestive of cerebral redistribution/foetal hypoxia as in FGR group there was more DV shunting, the hepatic flow was lower and neonatal adiposity was decreased. Regression coefficients of MCA PI and DV shunting were statistically significant (p<0.05) in the FGR group. A unit increase in MCA PI was found to increase the SFT value by 1.65, while DV shunting was found to decrease the SFT by 1.92. The difference in neonatal adiposity was significantly higher (p<0.05) in the GDM mothers as compared to FGR. Godfrey KM et al., reported that mothers with greater pre-pregnancy body fat have both higher foetal hepatic blood flow and increased neonatal adiposity [7]. Multivariable linear regression

analysis showed that in the GDM group, all the seven study variables together explained about 45% of variation in the birth weight. However, regression coefficient of MCA PI alone was found to be statistically significant (p=0.037) as shown in [Table/Fig-2]. In the uncomplicated group Regression coefficient of MCA PI alone was statistically significant (p=0.018). One unit increase in MCA PI would result in 0.85 increase in SFT value, while the other variables were constant, lower foetal MCA PI was, however, associated with lower neonatal sub scapular SFT (r=0.24, p=0.001).

Godfrey KM et al., also reported that foetuses with higher distribution of DV shunting had thinner SFT of subscapsular skin than the foetuses with lesser DV shunting [7]. They also reported significant association between neonatal subcapsular SFT, higher hepatic blood flow and greater neonatal adiposity [7]. Foetal liver also receives venous blood flow not only from the UV but also from the portal vein, the flow of which was not evaluated in the present study. Portal vein contributes only a small proportion of the foetal hepatic blood flow and does not contribute as a source of placental nutrient substrates [13]. Dietary supply of amino acids such as glycine and long chain fatty acids such as docohexaenoic acid are essential for metabolism and growth. These conditionally essential nutrients can be generated by conversion of other nutrients in the liver if dietary supply is inadequate. However, in conditions of reduced essential nutrients which cannot be synthesised in the liver like oxygen the hepatic flow is compromised to increase the cerebral redistribution [14]. HBF was significantly lower in FGR group compared to uncomplicated (p<0.005) group and even more strongly significant in FGR verses GDM group. HBF was not significantly altered in GDM group as compared to the uncomplicated group. However, the difference in neonatal adiposity was significantly higher (p<0.05) in the GDM mothers as compared to FGR. In overweight/obese mothers, obesity-related elevations of 20 maternal triglycerides, fatty acids, and placental fatty acid transporters result in higher foetal triglycerides that, in turn can be a major source of foetal fat deposition.

The strength of this study is in it being prospective and a pilot attempt to compare three different groups. Due to multiple variables relevant statistical analysis was applied.

Limitation(s)

Limitation of the study is the lack of strength due to small number of subjects and only one fixed period of gestation for interrogation.

CONCLUSION(S)

Maternal BMI had no association with hepatic flow or neonatal adiposity in uncomplicated pregnancies and GDM. MCA PI can be a positive predictor for neonatal birth weight in women with GDM. Higher body fat percentage in neonates of diabetic mothers could be due to increased levels of fatty acids and triglycerides in the maternal blood transported to the foetus via the placenta.

Foetal hepatic flow is significantly altered in women with low BMI and growth restricted foetuses. Maternal BMI, MCA PI, UV flow and DV shunting are positive predictors for neonatal weight in the FGR group. UA PI is a significant predictor for neonatal weight in uncomplicated pregnancies however neonatal adiposity is positively correlated with MCA PI in these pregnancies. Therefore, this study supports the hypothesis that neonatal adiposity is significantly higher in foetuses with higher MCA PI and lower DV flow in uncomplicated pregnancies and FGR groups. Such foetuses can be identified to have the propensity to develop adiposity later in life. This study strengthens the association of foetal origin of adult disease wherein foetal doppler can identify foetal propensity to develop adiposity. Further research is needed with larger number of women which can further establish how to the identify foetuses with propensity for adiposity in adult life so as to begin interventions in early childhood.

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