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Correlation between Haemoglobin A1c and Umbilical Artery Doppler as Predictors for Perinatal Outcome in Pregestational Diabetic Pregnancy and Pregestational Diabetic Pregnancy Complicated By Preeclampsia In Third Trimester

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ABSTRACT

Background: Diabetes mellitus is one of the most common metabolic disorders that occur during pregnancy. It has two clinical patterns; either pregestational diabetes mellitus or gestational diabetes mellitus. Pregestational diabetes mellitus is associated with worse maternal and fetal outcomes compared to gestational diabetes mellitus. **Objectives:** To assess usefulness of using both heamoglobin A1C and umbilical artery Doppler velocity waveform analysis in predicting adverse perinatal outcomes for both pregestational diabetic pregnancies & pregestational diabetic pregnancies complicated by preeclampsia.

Methods: This comparative study was conducted on 150 pregnant women with gestational age 34 – 40 weeks who were equally divided into 3 groups; 50 pregnant women with pregesational diabetes melleitus alone and 50 pregestional diabetes melleitus complicated with preeclampsia. These two groups were compared with 50 healthy pregnant women, free from medical disease, as control group. **Results:** In pregnant women with pregestational DM, HbA1c should be kept below 7% and it is better to be less than 6.5% by proper glycemic control, as higher levels of HbA1c were associated with bad perinatal outcomes in the forms of RDS, neonatal hypoglycemia, macrosomia, IUGR, Apgar score 1 & 5min and NICU24. In addition to, bad maternal outcomes in the forms of polyhyramnios, preterm labor, PROM, prolonged labor, mode of delivery, postpartum hemorrage, puerperal sepsis, pulmonary embolism, preeclampsia and its complications as eclampsia, HELLP syndrome, renal affection, hepatic affection and retinal affection. There was no significant relation between long term maternal glycemic control (HbA1c) & the changes of blood flow velocity in the umbilical artery in pregnancy complicated with diabetes mellitus unless the pregnancy is complicated with fetal growth restriction or preeclampsia. **Conclusion:** An increased pulsatility index of umbilical Doppler was found in our study to be the important predictor of perinatal outcome in diabetic pregnancies complicated by preeclampsia but not in uncomplicated diabetic pregnancy.

Keywords: Diabetes Mellitus – Heamoglobin A1c – Umbilical Artery Doppler – Preeclampsia.

INTRODUCTION

Diabetes mellitus complicates approximately 3 to 5% of all pregnancies with 90% classified as gestational and 10% as pregestational. Pregestational diabetes prevalence continues to rise largely due to increases in Type 2 diabetes associated with obesity [(1)]. Poor glycemic control during pregnancy is associated with adverse maternal and fetal outcomes (shortened gestational period, greater risk of miscarriage, increased likelihood of operative delivery, hypoglycemia, macrosomia, and increased NICU admission). Especially at risk are those with preexisting diabetes, who would benefit from earlier diabetes consultation and tighter glycemic control before conception [(2)].

Pregestational diabetes mellitus is associated with worse maternal and fetal outcomes compared to gestational diabetes mellitus however the outcomes of pregestational diabetes mellitus are comparable to those reported from other countries except in the stillbirth rate, which could be improved by establishment of the services of preconception care [(3)].

Preeclampsia is more frequent among women with diabetes, occurring in approximately 12% as compared to 8% of the non-diabetic population. The risk of preeclampsia is also related to maternal age and the duration of preexisting diabetes. In patients who have chronic hypertension coexisting with diabetes, preeclampsia may be difficult to distinguish from near-term blood pressure elevations. The rate of preeclampsia had been found to be related to the level of glycemic control, with fasting plasma glucose (FPG) less than 105, the rate of preeclampsia was 7.8%, if FPG was greater than 105; the rate of preeclampsia was 13.8%. In this same study, pregravid body mass index was also significantly related to the development of preeclampsia [(4)].

The advances in the management of pregnancies complicated with pregestational diabetes resulted in considerable improvement in maternal and perinatal outcomes. Preconceptional glycemic control and advances in fetal surveillance have

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contributed to this improvement. The poor outcomes in diabetic patients are considered to be primarily related to poor glycemic control and this can be predicted by glycated haemoglobin A1c [(5)].

Fetal Doppler ultrasound allows the investigation of feto-placental circulation & thus providing a non-invasive monitoring tool for assessing fetal well-being. Umbilical artery Doppler reflects downstream placental vascular resistance, which is strongly correlated with intrauterine growth restriction and placental insufficiency. Fetal abnormal Doppler study combined with biophysical profile score could help in determining time of intervention in cases of preeclampsia and intrauterine growth restriction [(6)].

Antepartum fetal surveillance constitutes an essential component of the standards of care in managing pregnancies complicated by pregestational diabetes mellitus. Fetal hyperglycemia is associated with increased oxidative metabolism, hypoxemia, and increased brain and renal perfusion without any significant changes in fetoplacental perfusion. Moreover, the relationship between abnormal umbilical arterial Doppler indices and the quality of glycemic control remain unproven. However, observational studies suggest significant diagnostic efficacy of the umbilical arterial Doppler method in diabetic pregnancy complicated IUGR or hypertension [(7)].

For pregestational diabetic mother, appropriate antepartum fetal surveillance is needed to identify the compromised fetus that needs delivery. The efficiency of umbilical arterial Doppler ultrasound in predicting adverse perinatal outcome in diabetic pregnancies not complicated by vasculopathy, fetal growth restriction or hypertension was controversial [(7)].

Methods

This comparative study was conducted on 150 pregnant women with gestational age 34 – 40 weeks. They were equally divided into 3 groups; 50 pregnant women with pregesational diabetes melleitus alone and 50 pregestional diabetes melleitus complicated with preeclampsia and the third (control) group included 50 healthy pregnant women without any medical disease.

Inclusion criteria:

- Gestational age between 34 and 40 weeks calculated from first day of LMP or by a first trimester US.
- Singleton pregnancies.
- Living fetus.
- No other medical conditions.
- Patients were assessed less than 24 hours before delivery.
- Patients were recruited from High Risk Pregnancy Unit.

Exclusion criteria:

- Multifetal pregnancies or pregnancies with IUFD.
- Associated other medical conditions as heart diseases or rheumatological diseases apart from iron deficiency anemia.
- Prelabour rupture of membrane.
- Presence of diagnosed fetal anomalies.
- Placenta previa or antepartum hemorrhage.

All pregnant women participating in study were subjected to the following:

- ***Written consent with full History taking***: The age, parity, residence, occupation, smoking, history of diabetes, hypertension, renal disease. Past history of any medications, menstrual history, obstetric history, contraception. **The study was approved by the Ethics Board of Al-Azhar University.**
- ***Complete general examination***: (as Pulse, blood pressure, temperature, pallor and weight), puffiness of eyelids and lower limb edema.
- ***Abdominal examination*:** Inspection of abdominal contour, striae, abdominal wall edema, palpation fundal level, fundal grip, umbilical grip, 1st pelvic grip.
- ***Routine laboratory investigations*:** to assess the severity and complications of pre-eclampsia (assessment of albumin in urine, CBC, serum creatinine, complete urine analysis, fasting & 2 h postprandial blood sugar and glycated HbA1c).

☒ ***Obstetric ultrasound examination*:** was done by one obstetrician by the aid of GE LOGIQ P3 ultrasound device which made in china by the year of 2016 & will include the following :

☒ Biometric Study: Ultrasonography was performed while the pregnant woman was in a slightly tilted semifowler position with the head of the bed raised 30 degrees and with a small pillow under the right loin. Biometric measurement to assess gestational age and fetal growth through determination of the fetal biparietal diameter, abdominal circumference, femur length. Measurement of the BPD was obtained at the level of the thalamus and cavum septum pellucidum. The abdominal circumference was obtained from a transaxial view at the level of the junction of the umbilical vein and left portal vein. The femur length was measured according to the technique of ***O'Brien et al.*** [(8)]. Also placental site and grading were detected according to Grannum's classification (0, I, II, III) [(9)]. Also, estimated fetal

weight was detected according to ***Shepard*** [10]**.** Small for dates was defined as estimated fetal weight less than 10th percentile for gestational age according to the growth curves reported by ***Sabbagha & Minogue*** [11].

☒ Amniotic fluid index (AFI): The AFI was obtained by summing the measurements of the largest vertical pocket of fluid in each of four quadrants of the uterus with the transducer held perpendicular to the abdomen [12].

☒ Umbilical Artery Doppler studies: The wave forms from the UA were obtained in a free floating loop of the umbilical cord using a corresponding technique with the insonation in alignment with the direction of the vessel [13]. The patients were placed in a semirecumbent position with left lateral tilt, and then the uterine contents were quickly scanned with real time ultrasound in order to select an area of the amniotic cavity with several loops of umbilical cord. Ideally, these cord loops should not be close to the cord insertion [14]. Using pulsed wave Doppler, the characteristic sound and shape of the umbilical artery waveform were demonstrated and identified. When the screen showed several waveforms of similar height, the image was frozen and the peak systolic frequency, end diastolic frequency, S/D ratio, pulsatility index and resistant index were estimated. A minimum of 3 separate readings were averaged before the final values were obtained. Because of the potential effect of fetal breathing movements on waveform variability, recording was performed during periods of fetal apnea. Taking into consideration that the normal umbilical artery third trimester S/D ratio is 2.5 ± 0.4 with a cutoff value of 3 and PI was 0.89 ± 0.12 with a cutoff value of 1.1 [15].

☒ The patients were followed up till delivery via measuring 2h PPG/week, HbA1c on 34 week and at delivery. And through the tests of fetal wellbeing: fetal movement daily, NST/3 days, BPP & umbilical Doppler/2 weeks. All neonates were examined and checked by a neonatology specialist. Then three groups were compared according to HbA1c & umbilical Doppler results as predictors on perinatal outcomes at third trimester considering:

Fetal outcomes:

- Large for gestational age.
- Intrauterine fetal growth restriction.
- Intrauterine fetal death.

Neonatal outcomes:

- 1 minute and 5 minutes Apgar scores.
- Prematurity, RDS, hypoglycemia, hypocalcemia, hypomagnesmia, hypothermia.
- NICU admission, birth trauma, jaundice and death.
- The presence or absence of any congenital anomaly that may interfere with the results of the tests.

Maternal outcomes:

- Complications of DM as preeclampsia, polyhyramnios, preterm labor, PROM, prolonged labor, postpartum hemorrage, puerperal sepsis, and pulmonary embolism.
- Preeclampsia and its complications as eclampsia, HELLP syndrome, renal & hepatic & retinal affection.
- **Statistical analysis:** Data were collected, coded and entered using the statistical package SPSS version 22. Data were summarized using mean and standard deviation in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between HbA1c in different categories were done using independent sample t test. Correlations between variables were done using Pearson correlation coefficient. P-values less than 0.05 were considered as statistically significant.

RESULTS

Table (1): Comparison between; group I, group II & group III as regards age, gestational age, parity, BMI, glycemic control (FBG – 2 hsPPG – HbA1c), systolic BP and diastolic BP.

		Group I	Group II	Group III	P value
Age		29.7 ± 4.19	28.28 ± 3.72	29.88 ± 5.09	0.144 **NS**
Gestational age		36.8 ± 1.95	36.48 ± 1.77	37.02 ± 1.97	0.350 **NS**
Parity	**Primi**	12 (24%)	16 (32%)	9 (18%)	0.265 **NS**
	Multi	38 (76%)	34 (68%)	41 (82%)	
BMI		27.55 ± 1.45	28.45 ± 1.35	25.45 ± 1.25	0.2 **NS**
Glycemic Control	**FBG**	123.0 ± 8.69	126.4 ± 15.9	82.6 ± 8.03	< 0.001 **S**
	2hsPPG	173.1 ± 29.2	181.6 ± 20.2	124.2 ± 7.71	< 0.001 **S**
	HbA1c	7.50 ± 1.02	8.052 ± 0.69	5.12 ± 0.48	< 0.001 **S**
SBP		117.2 ± 7.4	151.8 ± 7.92	117.4 ± 9.15	0.001 **S**
DBP		75.8 ± 6.82	98.2 ± 4.21	76.32 ± 8.86	0.001 **S**

± = 2 standard deviations

There is no significant difference in patients' demographic characteristics between the 3 groups as regards age, gestational age & parity. There is no significant difference in patients' BMI. There is significant correlation between systolic & diastolic blood pressure in 3 groups that was high in group II & showed normal level in group I & III. There is significant correlation between HbA1c and blood glucose level (FBG – 2 hsPPG) in 3 groups which was high in both group I & II & showed normal level in group III.

Table (2): FBG, 2hsPPG, HbA1c of all groups.

	group I &II		**Group III**		**P value**
	Mean	**SD**	**Mean**	**SD**	
FBG	124.74	±12.89	82.60	±8.03	< 0.001 **S**
2hsPPG	177.39	± 25.34	124.24	±7.71	< 0.001 **S**
HbA1c	7.77	±0.909	5.12	±0.48	< 0.001 **S**

Group I &II showed higher FBG, 2hsPPG, HbA1c than in group III.

Table (3): FBG, 2hsPPG, HbA1c in groups I and II.

	group I		**Group II**		**P value**
	Mean	**SD**	**Mean**	**SD**	
FBG	123.0	±8.69	126.4	± 15.9	< 0.001 **S**
2hsPPG	173.1	±29.2	181.6	±20.2	< 0.001 **S**
HbA1c	7.50	± 1.02	8.052	±0.69	0.044 **S**

Group II showed higher FBG, 2hsPPG, HbA1c than in group I.

Table (4): SBP & DBP in the studied groups.

	group I &II		**Group III**		**P value**
	Mean	**SD**	**Mean**	**SD**	
SBP	134.54	±19.02	117.48	±9.15	< 0.001 **S**
DBP	87.05	±12.56	76.32	±8.86	< 0.001 **S**

All diabetic patients (group I & II) showed higher SBP & DBP than group III.

Table (5): SBP & DBP in groups I and II.

	group I		**Group II**		**P value**
	Mean	**SD**	**Mean**	**SD**	
SBP	117.2	± 7.4	151.8	±7.92	0.019 **S**
DBP	75.86	±6.82	98.22	±4.21	< 0.001 **S**

Group II showed higher SBP & DBP than group I.

Table (6): Comparison between groups I, II & III as regard umbilical Doppler study

	Group I		Group II		Group III		P value
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	
RI	0.629	± 0.024	0.660	± 0.040	0.623	± 0.018	0.99 **NS**
PI	1.062	± 0.065	1.411	± 0.240	0.812	± 0.010	0.02 **S**

Group II showed higher pulsatility index PI than group I & III. There was no significant difference between the 3 groups according to resistant index RI.

Table (7): Comparison between groups I, II & III as regard umbilical Doppler study

	Group I &II		**Group III**		**P value**
	Mean	**SD**	**Mean**	**SD**	
RI	0.644	±0.036	0.623	±0.018	0.892 **NS**
PI	1.237	±0.245	0.812	±0.011	< 0.001 **S**

Group I & II showed high pulsatility index more than group III & no significant difference between both groups according to resistance index.

Table (8): Comparison between groups I & II as regard umbilical Doppler study

	Group I		Group II		P value
	Mean	SD	Mean	SD	
RI	0.629	±0.024	0.660	±0.040	0.810 **NS**
PI	1.062	±0.065	1.411	±0.240	0.041 **S**

Group II showed high pulsatility index more than group I & no significant difference between both groups according to resistance index.

Table (9): Comparison between group I, II & III according to biophysical profile

	Group I	Group II	Group III	P value
	Median	Median	Median	
BPP	6/8	6/8	8/8	0.067 **NS**

There was no significant correlation between 3 groups (I, II & III) as regards biophysical profile.

Tables (10) & (11): Comparison between group I, II & III as regards perinatal outcome:

		Group I		Group II		Group III		P value
		Number	%	number	%	number	%	
NICU 24hrs	No	28	56.0	18	36.0	49	98.0	< 0.001 **S**
	Yes	22	44.0	32	64.0	1	2.0	
RDS	No	30	60.0	19	38.0	46	92.0	< 0.001 **S**
	Yes	20	40.0	31	62.0	4	8.0	
Neonatal hypoglycemia	No	31	62.0	22	44.0	49	98.0	< 0.001 **S**
	Yes	19	38.0	28	56.0	1	2.00	
Preterm birth	No	27	54.0	26	52.0	47	94.0	0.006 **S**
	Yes	23	46.0	24	48.0	3	6.0	
Macrosomia	No	30	60.0	34	68.0	49	98.0	< 0.001 **S**
	Yes	20	40.0	16	32.0	1	2.0	
IUGR	No	42	84.0	30	60.0	49	98.0	< 0.001 **S**
	Yes	8	16.0	20	40.0	1	2.00	
Type of delivery	Normal	20	40.0	17	34.0	30	60.0	0.023 **S**
	CS	30	60.0	33	66.0	20	40.0	

	Group I	Group II	Group III	P value
	Median	Median	Median	
Apgar 1min	6	6	8	< 0.001 **S**
Apgar 5min	7	6	9	< 0.001 **S**

There was highly significant statistical difference between the groups as regards NICU 24hrs, RDS, neonatal hypoglycemia, preterm birth, macrosomia, IUGR, mode of delivery and Apgar score 1 & 5min. Groups I, II showed higher number of NICU 24hrs admission, RDS, neonatal hypoglycemia, preterm birth, macrosomia, IUGR and CS delivery than group III.

Tables (12) & (13): Comparison between group I, II as regards perinatal outcome

		Group I		Group II		P value
		number	%	number	%	
NICU 24hrs	No	28	56.0	18	36.0	0.035
	Yes	22	44.0	32	64.0	**S**
RDS	No	30	60.0	19	38.0	0.022
	Yes	20	40.0	31	62.0	**S**
Neonatal hypoglycemia	No	31	62.0	22	44.0	0.054
	Yes	19	38.0	28	56.0	**NS**
Preterm birth	No	27	54.0	26	52.0	0.5
	Yes	23	46.0	24	48.0	**NS**
Macrosomia	No	30	60.0	34	68.0	0.266
	Yes	20	40.0	16	32.0	**NS**
IUGR	No	42	84.0	30	60.0	0.007
	Yes	8	16.0	20	40.0	**S**
Type of delivery	Normal	20	40.0	17	34.0	0.339
	CS	30	60.0	33	66.0	**NS**

	Group I	Group II	P value
	Median	Median	
Apgar 1min	6	6	< 0.001 **S**
Apgar 5min	7	6	< 0.001 **S**

There was a significant difference between the groups as regards NICU 24hrs, RDS, IUGR and Apgar score 1 & 5min. Group II showed higher number of NICU 24hrs, RDS & IUGR than group I.

Table (14): Correlation between HbA1c & perinatal outcome in group I

		HbA1c			
		Mean	Standard deviation	Median	P value
NICU 24	No	7.271	± 1.045	7.0	0.066
	Yes	7.804	± 0.928	8.0	**NS**
RDS	No	7.130	± 1.031	7.0	0.018
	Yes	8.131	± 0.873	7.95	**S**
Neonatal Hypoglycemia	No	7.183	± 0.933	7.0	0.003
	Yes	8.031	± 0.956	8.0	**S**
Preterm birth	No	7.248	± 0.988	7.0	0.052
	Yes	7.808	± 0.995	7.9	**NS**
Macrosomia	No	7.126	± 1.028	7.0	0.001
	Yes	8.075	± 0.712	8.0	**S**
IUGR	No	7.192	± 1.049	7.0	0.072
	Yes	8.100	± 0.609	8.1	**NS**
Type of delivery	Normal	6.549	± 0.510	7.0	< 0.001
	CS	8.143	± 0.735	8.0	**S**

There was a significant correlation between HbA1c and RDS, neonatal hypoglycemia, macrosomia and mode of delivery. At mean HbA1c 8.131± 0.873 there was high incidence of RDS & at mean HbA1c 7.130 ± 1.031 there was no incidence of RDS & at mean HbA1c 8.031 ± 0.956 there was high incidence of hypoglycemia & at mean HbA1c = 7.183 ± 0.933 there was no incidence of hypoglycemia. At mean HbA1c 8.075 ± 0.712 there was high incidence of macrosomia & at mean HbA1c = 7.126 ± 1.028 there was no incidence of macrosomia. At mean HbA1c = 8.143 ± 0.735 there was high incidence of CS delivery & at mean HbA1c = 6.549 ± 0.510 there was incidence of normal delivery. There is no significant correlation between HbA1c & NICU24, preterm birth and IUGR.

Table (15): Correlation between HbA1c and Apgar 1 & 5 min in group I

	HbA1c	
	Correlation coefficient	**P value**
Apgar 1 min	0.347	0.014 **S**
Apgar 5 min	0.387	0.005 **S**

There was significant correlation between HbA1c and Apgar 1min & significant correlation between HbA1c and Apgar 5 min.

Table (16): Correlation between HbA1c & perinatal outcome in group II

		HbA1c			
		Mean	**Standard deviation**	**Median**	**P value**
NICU 24	No	7.733	± 0.621	8.05	0.013 **S**
	Yes	8.231	± 0.671	8.5	
RDS	No	7.736	± 0.603	8.0	0.010 **S**
	Yes	8.245	± 0.677	8.5	
Neonatal Hypoglycemia	No	7.513	± 0.610	7.55	0.029 **S**
	Yes	8.539	± 0.702	8.5	
Preterm birth	No	7.492	± 0.677	7.7	0.089 **NS**
	Yes	8.224	± 0.676	8.3	
Macrosomia	No	7.310	± 1.00	7.2	0.379 **NS**
	Yes	7.594	± 1.02	7.350	
IUGR	No	7.606	± 0.682	8.15	0.068 **NS**
	Yes	8.270	± 0.660	8.5	
Type of delivery	Normal	7.757	± 0.653	8.1	0.017 **S**
	CS	8.232	± 0.659	8.5	

There was a significant correlation between HbA1c and NICU 24, RDS, neonatal hypoglycemia & type of delivery. At mean HbA1c = 8.231 ± 0.671 there was a high incidence of NICU admission & at mean HbA1c = 7.733 ± 0.621 there was no incidence of NICU admission while at mean HbA1c 8.245 ± 0.677 there was a high incidence of RDS & at mean HbA1c 7.736 ± 0.603 there was no incidence of RDS. At mean HbA1c 8.539 ± 0.702 there was a high incidence of hypoglycemia & at mean HbA1c = 7.513 ± 0.610 there was no incidence of hypoglycemia. At mean HbA1c = 8.232 ± 0.659 there was a high incidence of CS delivery & at mean HbA1c = 7.757 ± 0.653 there was incidence of normal delivery.

Therefore, there was significant correlation between HbA1c and NICU 24, RDS, neonatal hypoglycemia & type of delivery at mean HbA1c > 8.2 % but there was no significant correlation between HbA1c & IUGR, preterm birth, and macrosomia in group II.

Table (17): Correlation between HbA1c and Apgar 1, 5 min in group II

	HbA1c	
	Correlation coefficient	**P value**
Apgar 1 min	- 0.411	0.003 **S**
Apgar 5 min	0.365	0.009 **S**

There was significant correlation between HbA1c and Apgar 1min & significant correlation between HbA1c and Apgar 5 min.

Table (18): Correlation between Umbilical artery Doppler (RI) with perinatal outcome in group I:

		RI		P value
		Mean	SD	
NICU 24	No	0.629	± 0.028	0.882 **NS**
	Yes	0.630	± 0.019	
RDS	No	0.626	± 0.021	0.078 **NS**
	Yes	0.639	± 0.022	
Neonatal hypoglycemia	No	0.624	± 0.022	0.076 **NS**
	Yes	0.637	± 0.027	
Preterm birth	No	0.627	± 0.023	0.622 **NS**
	Yes	0.631	± 0.026	
Macrosomia	No	0.625	± 0.025	0.159 **NS**
	Yes	0.635	± 0.023	
IUGR	No	0.626	± 0.022	0. 35 **NS**
	Yes	0.646	± 0.031	
Type of delivery	Normal	0.623	± 0.027	0.173 **NS**
	CS	0.633	± 0.022	

There was no significant correlation between resistant index with NICU 24h, RDS, neonatal hypoglycemia, preterm birth, macrosomia, IUGR and mode of delivery.

Table (19): Correlation between Umbilical artery Doppler (PI) with perinatal outcome in group I

		PI		P value
		Mean	SD	
NICU 24	No	1.061	± 0.067	0.910 **NS**
	Yes	1.063	± 0.062	
RDS	No	1.056	± 0.070	0.427 **NS**
	Yes	1.071	± 0.055	
Neonatal hypoglycemia	No	1.057	± 0.068	0.558 **NS**
	Yes	1.068	± 0.058	
Preterm birth	No	1.047	± 0.071	0.130 **NS**
	Yes	1.074	± 0.054	
Macrosomia	No	1.047	± 0.068	0.055 **NS**
	Yes	1.084	± 0.053	
IUGR	No	1.055	± 0.063	0.116 **NS**
	Yes	1.095	± 0.062	
Type of delivery	Normal	1.043	± 0.076	0.090 **NS**
	CS	1.074	± 0.052	

There was no significant correlation between pulsatility index with NICU 24h, RDS, neonatal hypoglycemia, preterm birth, macrosomia, IUGR and mode of delivery.

Table (20): Correlation between Umbilical artery Doppler (PI & RI) & APGAR 1min & APGAR 5min in group I

	PI		RI	
	Correlation coefficient	P value	Correlation coefficient	P value
Apgar 1min	0.302	0.033 **S**	- 0.250	0.081 **NS**
Apgar 5min	0.331	0.019 **S**	- 0.180	0.210 **NS**

There was significant correlation between pulsatility index & APGAR 1min & APGAR 5min but there was no significant correlation between resistant index & APGAR 1min & APGAR 5min.

Table (21): Correlation between Umbilical artery Doppler (PI & RI) & biophysical profile in group I

	PI		RI	
	Correlation coefficient	**P value**	**Correlation coefficient**	**P value**
BPP	- 0.191	0.183 **NS**	- 0.121	0.401 **NS**

There was no significant correlation between resistant index and pulsatility index and biophysical profile.

Table (22): Correlation between Umbilical artery Doppler (RI) with perinatal outcome in group II

		RI		P value
		Mean	**SD**	
NICU 24	No	0.650	± 0.046	0.161 **NS**
	Yes	0.667	± 0.034	
RDS	No	0.654	± 0.046	0.145 **NS**
	Yes	0.669	± 0.034	
Neonatal hypoglycemia	No	0.648	± 0.042	0.075 **NS**
	Yes	0.668	± 0.035	
Preterm birth	No	0.653	± 0.031	0.273 **NS**
	Yes	0.665	± 0.046	
Macrosomia	No	0.658	± 0.038	0.765 **NS**
	Yes	0.661	± 0.041	
IUGR	No	0.654	± 0.041	0.271 **NS**
	Yes	0.667	± 0.036	
Type of delivery	Normal	0.648	± 0.044	0.126 **NS**
	CS	0.666	± 0.035	

There is no significant correlation between resistant index and NICU 24h, RDS, neonatal hypoglycemia, preterm birth, macrosomia, IUGR and mode of delivery.

Table (23): Correlation between Umbilical artery Doppler (PI) with perinatal outcome in group II

		PI		P value
		Mean	**SD**	
NICU 24	No	1.340	± 0.298	0.119 **NS**
	Yes	1.451	± 0.193	
RDS	No	1.337	± 0.297	0.090 **NS**
	Yes	1.456	± 0.188	
Neonatal hypoglycemia	No	1.338	± 0.278	0.065 **NS**
	Yes	1.468	± 0.191	
Preterm birth	No	1.394	± 0.203	0.611 **NS**
	Yes	1.429	± 0.277	
Macrosomia	No	1.406	± 0.234	0.58 **NS**
	Yes	1.429	± 0.259	
IUGR	No	1.084	± 0.249	0.034 **S**
	Yes	1.451	± 0.225	
Type of delivery	Normal	1.347	± 0.270	0.141 **NS**
	CS	1.450	± 0.214	

There was significant correlation between pulsatility index and IUGR. At mean PI = 1.451± 0.225 there was a high incidence of IUGR & at mean PI = 1.084 ± 0.249 there was no incidence of IUGR. There was no significant correlation between pulsatility index and NICU 24h, RDS, neonatal hypoglycemia, preterm birth, macrosomia and mode of delivery.

Table (24): Correlation between Umbilical artery Doppler (PI & RI) & APGAR 1min & APGAR 5min in group II

	PI		RI	
	Pearson correlation	**P value**	**Pearson correlation**	**P value**
Apgar 1min	- 0.314	0.026 **S**	0.254	0.45 **NS**
Apgar 5min	- 0.389	0.005 **S**	0.306	0.30 **NS**

There was significant correlation between pulsatility index & APGAR 1min & APGAR 5min but there was no significant correlation between resistant index & APGAR 1min & APGAR 5 min.

Table (25): Correlation between Umbilical artery Doppler (PI & RI) & biophysical profile in group II

	PI		RI	
	Correlation coefficient	**P value**	**Correlation coefficient**	**P value**
BPP	0.188	0.19 **NS**	0.259	0.069 **NS**

There was no significant correlation between resistant index and pulsatility index and biophysical profile.

Table (26): Correlation between HbA1c & Umbilical artery Doppler (PI & RI) group I

	PI		RI	
	Pearson correlation	**P value**	**Pearson correlation**	**P value**
HbA1c	0.208	0.148 **NS**	0.254	0.074 **NS**

There was no significant correlation between HbA1c and (PI & RI).

Table (27): Correlation between HbA1c & Umbilical artery Doppler (PI & RI) group II

	PI		RI	
	Pearson correlation	**P value**	**Pearson correlation**	**P value**
HbA1c	- 0.034	0.813 **NS**	- 0.050	0.728 **NS**

There was no significant correlation between HbA1c and PI & RI.

Our study results about correlation between HbA1c & perinatal outcomes showed that in group I there was significant correlation between HbA1c & RDS, neonatal hypoglycemia, macrosomia, mode of delivery, Apgar 1min and Apgar 5 min. But, there was no significant correlation between HbA1c & NICU24, preterm birth and IUGR). In group II, there was significant correlation between HbA1c & NICU 24, RDS, neonatal hypoglycemia, mode of delivery, Apgar 1min and Apgar 5 min. While, there was no significant correlation between HbA1c & IUGR, preterm birth and macrosomia. In group III, there was no significant correlation between HbA1c & NICU 24h, RDS, hypoglycemia, preterm birth, macrosomia, IUGR, mode of delivery, Apgar 1min and Apgar 5 min.

Our study results about correlation between umbilical artery Doppler (RI & PI) and perinatal outcomes showed that in group I there was no significant correlation between (RI & PI) and NICU 24h, RDS, neonatal hypoglycemia, preterm birth, macrosomia, IUGR and mode of delivery. While, there was significant correlation between PI and APGAR 1min & APGAR 5min and there was no significant correlation between RI and APGAR 1min & APGAR 5min. In group II, there was no significant correlation between RI and NICU 24h, RDS, neonatal hypoglycemia, preterm birth, macrosomia, IUGR and mode of delivery. Meanwhile, there was significant correlation between PI & IUGR. There was no significant correlation between PI and NICU 24h, RDS, neonatal hypoglycemia, preterm birth, macrosomia and mode of delivery. There was significant correlation between PI and APGAR 1min & APGAR 5min but there was no significant correlation between RI with APGAR 1min & APGAR 5min in group II. In group III, there was no significant correlation between (RI & PI) and NICU 24h, RDS, neonatal hypoglycemia, preterm birth, macrosomia, IUGR, mode of delivery & APGAR 1min & APGAR 5min.

Our study results about correlation between HbA1c and umbilical artery Doppler (RI & PI) in group I, group II & group III showed that there was no significant correlation between HbA1c and umbilical artery Doppler (RI & PI) regarding perinatal outcomes.

Discussion

According to our study, there was significant correlation between HbA1c in pregestational diabetic pregnant women and perinatal outcomes in

the form of RDS, neonatal hypoglycemia, macrosomia, mode of delivery, Apgar 1min and Apgar 5 min. In addition, there was significant correlation between HbA1c in pregestational diabetic pregnant women complicated with preeclampsia in the forms of NICU 24, RDS, neonatal hypoglycemia, mode of delivery, Apgar 1min and Apgar 5 min.

Our study also showed a significant correlation between umbilical artery Doppler (PI) in pregestational diabetic pregnant women and APGAR 1min & APGAR 5min. As well as, there was a significant correlation between umbilical artery Doppler (PI) in pregestational diabetic pregnant women complicated with preeclampsia and perinatal outcomes in the forms of IUGR, APGAR 1min & APGAR 5min.

Our study results about correlation between HbA1c and umbilical artery Doppler (PR & RI) in all pregnant women within the study, showed that there was no significant correlation between HbA1c and umbilical artery Doppler regarding perinatal outcomes.

HbA1c, in pregnant women with pregestational DM, was correlated with bad perinatal outcomes in the forms of preterm birth and IUGR as well as NICU24 in cases not complicated with preeclampsia and macrosomia in cases complicated with preeclampsia,

Our findings in pregestational diabetic pregnant women group, showed that there was significant correlation between HbA1c and perinatal outcomes including RDS, neonatal hypoglycemia, macrosomia, mode of delivery, Apgar 1min and Apgar 5 min. This supported a hypothesis that the excess of insulin in the fetal circulation can delay pulmonary maturation associated with the low production of surfactant leading to the respiratory distress syndrome or hyaline membrane disease. This condition was about six-fold more frequently found in newborns of women with diabetes than in non-diabetic women [(16)].

Our findings in pregestational diabetic pregnant women complicated by preeclampsia, showed that there was significant correlation between HbA1c and perinatal outcomes including NICU 24, RDS, neonatal hypoglycemia, mode of delivery, Apgar 1min and Apgar 5 min. This finding was supported by a hypothesis that pregnancies with preeclampsia or gestational hypertension that delivered between 35 and 37 weeks of gestation had higher rates of neonatal intensive care unit admission, small for gestational age, and longer neonatal stay than normotensive pregnancies, regardless of the severity of the hypertensive disease [(17)].

Our finding in pregestational diabetic pregnant women complicated by preeclampsia showed that there was significant correlation between PI with IUGR. This was supported by a hypothesis that under perfusion of the placenta caused villous damage; that was total tertiary villous capillary bed, which was reduced leading to increased placental resistance. These changes could be diagnosed by Doppler and characteristic changes were seen in the uterine, umbilical, middle cerebral arteries and ductus venosus vessels. In severe cases, delivery of the fetus with optimum intrapartum surveillance, or caesarean section was essential [(18)].

In this study, there was higher incidence of perinatal fetal morbidities including hypoglycemia, macrosomia, IUGR, NICU admission, respiratory distress syndrome and preterm labour in comparison with the control group. This agreed with the ***Milena*** [(19)] study who found that a higher incidence of perinatal fetal morbidity (hypoglycemia, jaundice, respiratory distress syndrome) in pregnant patients with type 1, type 2 as well as gestation diabetes. The complications were mainly correlated with the degree of hyperglycemia**.**

Additionally, **Abdel Aal *et al*.** [(20)] study observed a positive correlation between HbA1c & adverse perinatal outcomes when HbA1c > 7% between 34 – 36 weeks where there was an increased frequency of adverse fetal outcomes including RDS, macrosomia, polyhydramnios, prematurity and neonatal hypoglycemia.

There was a significant correlation between HbA1c and neonatal hypoglycemia that agreed with the study published by **Abdel Aal *et al*.** [(20)] who showed that the incidence of neonatal hypoglycemia was 40% & there was statistically significant relation between HbA1c and neonatal glucose level.

In this study, there was no correlation found between HbA1c & prematurity in all groups. This did not agree with **Abdel Aal *et al.*** [(20)] study that revealed positive correlation between HbA1c & adverse neonatal outcomes including prematurity. An HbA1c of 7% had sensitivity of 90% and specificity of 81% in predicting prematurity. Such difference could be attributed to our small sample size and the gestational age of our samples was at 34 – 40 weeks.

Additionally, **Milena** [(19)] showed that preterm delivery was associated with poor glycemic control reflected through higher values of HbA1c in third trimester in diabetic pregnant women that suggest the difference between the results and the others could be attributed to the difference in sample size.

If a larger sample size was used perhaps such results would have been reproduced.

In this study, there was significant correlation between HbA1c and birth weight. This agreed with the study published by ***Abdel Aal et al.*** [20] where a positive correlation between HbA1c & neonatal weight was found & HbA1c greater than 7% had a sensitivity of 82% and specificity of 63% in predicting macrosomia.

In this study, there was no correlation between umbilical artery Doppler (PI, RI) & adverse neonatal outcomes in diabetic patients. This agreed with the study published by ***Wong et al.*** [21] that umbilical artery Doppler velocimetry was not a good predictor of adverse perinatal outcomes in diabetic pregnancies.

In our study, elevated pulsatility index in diabetic patients complicated by preeclampsia agreed with ***Reece et al.*** [22] who found that abnormal Doppler flow velocity waveform analysis was associated with diabetic pregnancy complicated by diabetic vasculopathy and preeclampsia.

There was no correlation between elevated PI & RI with preterm birth that disagreed with ***Wong et al.*** [21] who observed an increase in the iatrogenic premature delivery rate, which is not related to spontaneous preterm labour. One might argue that the increase in elective premature delivery might be related to the finding of abnormal umbilical Doppler results. However, in our patients the decision of elective delivery was not only taken after abnormal Doppler indices that were noted but also other parameters as non-stress testing, biophysical profile scoring and fetal kick count were taken into consideration.

In this study, there was correlation between elevated pulsatility index & IUGR in diabetic patients with preeclampsia that agreed with ***McIntyre*** [23] who reported that birth weights of babies in the abnormal Doppler group were significantly lower ($P < 0.01$). This was a result of increased incidence of preterm births as there was no significant difference between the Z-scores for study group birthweight and birthweight for term newborns (3476 vs 3661 g) for the two groups. In diabetic pregnancies with abnormal umbilical Doppler velocimetry, there was a higher incidence of SGA babies ($P < 0.05$).

In our study, there was significant correlation between elevated PI & Apgar score at 1 & 5 minute in DM with preeclampsia. This agreed with ***Maulik*** [24] who showed that abnormally elevated umbilical artery Doppler indices have been associated with low Apgar score, fetal distress (late and severe variable decelerations), absent variability, low fetal scalp and umbilical cord arterial pH, presence of thick meconium and admission to the neonatal intensive care unit.

Wong et al. [21] concluded that there was no difference in median 1 – min Apgar score (7 vs 7), median 5 – min Apgar score (9 vs 9), cord blood pH and incidence of spontaneous preterm birth between abnormal and normal Doppler group. This did not agree with our study, which concluded that there was significant correlation between PI and APGAR 1 & 5min in pregestational diabetes melleitus and pregestational diabetes melleitus complicated with preeclampsia. Such difference could be attributed to our small sample size and the gestational age of our samples was at 34 – 40 weeks.

In the present study, there was no correlation between HbA1c and umbilical artery Doppler in diabetic pregnant women. This agreed with ***Landon et al.*** [25] who found no significant correlation between mean 3rd trimester umbilical artery S/D & glycosylated hemoglobin or mean blood glucose levels. While, it agreed with ***Abdel Aal et al.*** [20] who reported that there was no significant relationship between HbA1c & Doppler indices.

Strengths of the study included the prospective collection of quantitative data and it is population-based design. So the study can be replicated in different areas or over time with the production of comparable findings. Our data were consistent, precise and reliable.

However multivariate analysis techniques of our quantitative data were generally complex and required the use of specialized statistical software, which was generally expensive and represented a limitation. A small proportion of the pregnant women was appropriate for the representation of the target population and this small sample size affects the ability to generalize study findings to wider populations. Small-scale quantitative studies may be less reliable because of the low quantity of data. It was difficult to control the effects of external variables that might result in misleading interpretations of causality for example; the attendance of many pregestational diabetic pregnant women to the antenatal care unit was irregular so there was interruption of their follow up.

If we were to design this study again, there will be a number of changes we would do. We would use a large sample size for more accurate analysis & more reliable and make sure that the patients would attend for the follow up regularly by providing appropriate facilities.

CONCLUSION

In pregnant women with pregestational DM, HbA1c should be kept below 7% and it is better to be less than 6.5% by proper glycemic control as higher levels of HbA1c were associated with bad perinatal outcomes in the forms of RDS, neonatal hypoglycemia, macrosomia, IUGR, Apgar score 1 & 5min and NICU24. In addition, there were bad maternal outcomes in the forms of polyhyramnios, preterm labor, PROM, prolonged labor, mode of delivery, postpartum hemorrage, puerperal sepsis, pulmonary embolism, preeclampsia and its complications as eclampsia, HELLP syndrome, renal & hepatic & retinal affection.

There was no significant relation between long term maternal glycemic control (HbA1c) & the changes of blood flow velocity in the umbilical artery in pregnancy complicated with diabetes mellitus unless the pregnancy is complicated with fetal growth restriction or preeclampsia.

An increased pulsatility index of umbilical Doppler was found in our study to be the important predictor of perinatal outcome in diabetic pregnancies complicated by preeclampsia but not in uncomplicated diabetic pregnancy.

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