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Original Article

Impact of Hba1c Levels on Maternal and Neonatal Outcomes

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ABSTRACT

***Background and Objective**. Diabetes mellitus is a metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion, defective insulin action or both. This study aimed to assess the clinical utility of early and late trimester HbA1c level in predicting adverse pregnancy outcome in Gestational DM (GDM) and PGDM. **Methods**. This study was retrospective case series study conducted in Aljala hospital of Tripoli, Libya during the year 2014-2015. One hundred and thirty-five diabetic patients were randomly selected from the hospital files. The following data was obtained from the files: the age, gravidal history, type of DM, treatment of DM, HbA1c level in early and late pregnancy, gestational age, maternal outcomes (HTN, Preeclampsia, UTI, hypothyroid, diabetic complications) and neonatal outcomes (IUGR, NN sepsis, RDS, NN hypoglycemia, birth injury, congenital anomaly, apgar score, birth weight and NN polycythemia. **Results.** The mean age of the patients was 35.42 years. The majority of the patients were type 2 diabetes with mean HbA1c in early pregnancy of 7.8. In the late stage of pregnancy, the mean HbA1c was lower 7.2. The study revealed that there were no relations between early HbA1c and outcomes (maternal and neonatal) with p value > 0.05. The study also showed insignificant relation between the changes of HbA1c levels during the pregnancy and the outcome (maternal and neonatal) with p value > 0.05. **Conclusion.** Although HbA1c levels are important in pregnancy to monitor the compliance of the treatment, the use of HbA1c level to predict the adverse maternal and neonatal outcomes remains questionable.*

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INTRODUCTION

Diabetes mellitus (DM) is a multisystemic disease characterized by the presence of hyperglycemia due to defective insulin secretion, defective insulin action or both. The chronic hyperglycemia of diabetes is associated with relatively specific long-term microvascular complications affecting the eyes, kidneys and nerves, as well as an increased risk for cardiovascular disease (CVD). The diagnostic criteria for diabetes are based on thresholds of glycemia that are associated with microvascular disease, especially retinopathy [1]. "Prediabetes" is a practical and convenient term referring to impaired fasting glucose (IFG), impaired glucose tolerance IGT or a glycated hemoglobin (A1C) of 6.0% to 6.4%, each of which places individuals at high risk of developing diabetes and its complications [1].

Historically, glycosylated hemoglobin ((HbA1c) was discovered at the end of 1960s, and used in clinical practice was between 1970s and 1980s, and became internationally standardized in the 1990s and 2000s, this step helped in standardized diabetic patient care which include diagnosis and treatment at global level [2]. Since then, the HbA1c play a crucial role in management and follow up of diabetic patients. It reflects the measurement of blood glucose over the previous two to three months and represents for both pre-prandial and post-prandial blood sugar levels. [3,4]. So, it can be used as reliable laboratory parameter to reflect the long-term blood glucose control status and predict the risks of diabetic complications [5-7]. As a result, the international guidelines are highly recommended to measure HBA1c on regular basis for all diabetic patients [5,8,9].

Additionally, risks of adverse maternal and neonatal outcomes are strongly correlate with abnormal elevation of maternal HBA1c [10]. Due to large number of diabetic patients who follow their pregnancy at Aljala maternity diabetic clinic, and to our knowledge there was no such study used Hb1C level to predict pregnancy outcomes, as result this study was established and conducted. The current study was conducted to assess the clinical utility of early and late trimester HbA1c level in predicting adverse pregnancy outcome in Gestational diabetes Mellitus (GDM)

METHODS

Study design and setting

This is a retrospective case series study conducted in Aljala hospital of Tripoli, Libya during the year 2014-2015. A verbal consent was taken from each patient regarding their participation in the study, and a total of one hundred and thirty-five diabetic patients were randomly selected from the hospital files. The following data were obtained from the files; the age, gravidal history, types of DM, treatment of DM, HbA1c level in early and late pregnancy, gestational age, maternal outcomes (HTN, Preeclampsia, UTI, hypothyroid, diabetic com-plications) and neonatal outcomes (IUGR, NN sepsis, RDS, NN hypoglycemia, birth injury, congenital anomaly, apgar score, birth weight and NN polycythemia.

Statistical analysis

Statistical analysis was computerized using the Statistical Program for Social Sciences (SPSS version 21) for data entry and analysis. Descriptive statistics were used and all results were presented as frequencies, means ± standard deviation and percentages. Categorical data were compared using the Chi-square test and Fisher's exact test if appropriate. P-value of less than or equal to 0.05 was considered statistically significant.

RESULTS

Patients' demographics

Regarding the types of diabetes, most of the patients in the study (45.2%) had type 2 diabetes, about 34.8% had gestational diabetes and 20% had type 1 diabetes. The mean age for the patients was (35.42 ± 4.6 years). The maximum age of the patients was 46 years and the minimum age was 23 years. Most of the age distribution of the patients in this study was between 36 and 40 years, which account for 39.3 %. The least percentage was patients less than 26 years (3%). Regarding the parity of the patients, about 83.7% of the patients was between nullipara and para 3. Approximately 7.4% of the patients was para 4 and 8.9% was more than para 4. About 50.4% of the patients take combination of Metformin and Insulin for the treatment, 20% take only Metformin, 28.1% take only Insulin and only 1.5% are on diet control as shown in table 1.

Table 1: Demographic Data of the patients

Characteristics	%
Age distribution of patients	
Age	
20 -25	2.96%
26 - 30	11.11%
31 - 35	34.07%
36 - 40	39.26%
>40	12.5%
Parity of patients	
Less than 4	83.7%
4	7.41%
More than 4	8.89%
Types of DM	
GDM	34.81%
Type 1 DM	20%
Type 2 DM	45.19%
Treatment of diabetes during pregnancy	
Metformin and insulin	50.37%
Insulin	28.15%
Metformin	20%
Diet control	1.48%

HbA1c level in different pregnancy stages

As depicted in table 2, regarding early pregnancy, the mean HbA1c level was 7.8 with standard deviation of 1.86. The maximum level was 15 and the minimum level was 3.5. Approximately 66.7 % of the patients have abnormal level of HbA1c (more than 7); as shown in table 2.

Table 2: HbA1c level in early and late pregnancy

HbA1c Level in Early Pregnancy	
HbA1c level	N(%)
7 and less	45(33.3%)
More than 7	90(66.7%)
Mean ± SD	7.8±1.86
Minimum and maximum levels	3.5 to 15
HbA1c Level in Late Pregnancy	
HbA1c level	N(%)
7 and less	67(49.63%)
More than 7	68(50.4%)
Mean ± SD	7.2±1.49
Minimum and maximum levels	4.5 to 15

HbA1c level in late pregnancy

During the visits of the patients to the hospital, another HbA1c test was performed in the late pregnancy near the time of delivery. The mean HbA1c level was lower than early pregnancy (7.2 with standard deviation of 1.49). The maximum level was 15 and the minimum level was 4.5. The percentage of patients with abnormal HbA1c level was lower than in early pregnancy (50.4%).

During the pregnancy, about 67 (49.63%) patients had their HbA1c level remain or decreased below 7; 30 (22.22%) patients had HbA1c decreased but the level stays above 7 and 38 (28.1%) patients had their HbA1c level remain or increased above 7, as shown in figure 1.

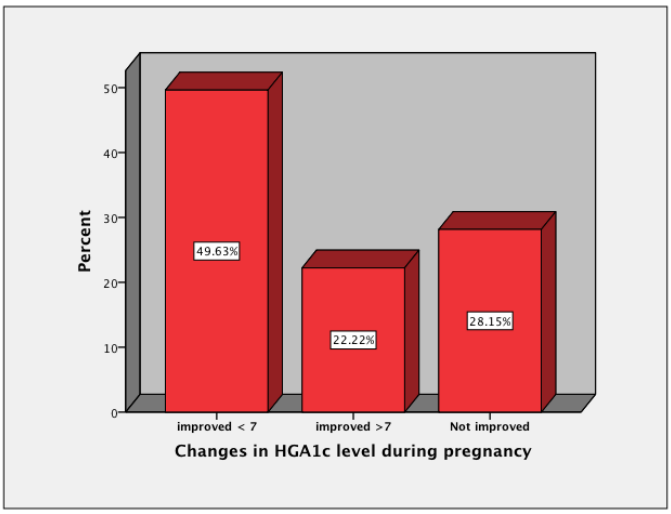

Figure 1: Changes of HbA1c levels during pregnancy

Diabetes comorbidity and complications

As shown in table 3, This study reported that 14.1% of the patients had history of hypertension, 28.9% had history of hypothyroid disease, 25.9 % had history of urinary tract infection and 5.9% had PE. Diabetic complications in the study participants were infrequent with hypoglycemia as the most common complication, which affects only 17.8%. The percentages of the other complication were as the following; nephropathy 0.7%, retinopathy 4.4%, neuropathy 0%, CAD 0.7% and DKA 2.2% (table 4).

Table 3: Associated diseases in diabetic patients

Associated disease	Yes	No
H/O HTN	19(14.1%)	116(85.9%)
H/O hypothyroid	39(28.9%)	96(71.1%)
H/O UTI	35(25.9%)	100(74%)
PE	8(5.9%)	127(94.1%)

Table 4 Diabetes complication

Diabetes complication	Yes	NO
Nephropathy	1(0.7%)	134(99.3%)
Retinopathy	6(4.4%)	129(95.6%)
Neuropathy	0(0%)	135(100%)
CAD	1(0.7%)	134(99.3%)
H/O hypoglycemia	24(17.8%)	111(82.2%)
H/O DKA	3(2.2%)	132(97.8%)

Fetal echocardiography

The result of the echocardiography that performed to the patients shows that 63% of the patients had normal echocardiography, 1.5% had IVSH and 0.7% had VSD. About 34.8% of the patients did not have echocardiography during antenatal visits, as presented in table 5.

Table 5. Fetal echo results

Fetal Echo	N(%)
Normal	85(63%)
IVSH	2(1.5%)
VSD	1(0.7%)
Not done	47(34.8%)

Gestational age at delivery

Regarding gestational age at delivery, most of diabetic women (76.3%) had term labour. The rest of the women (23.7%) had preterm labor as shown in figure 2.

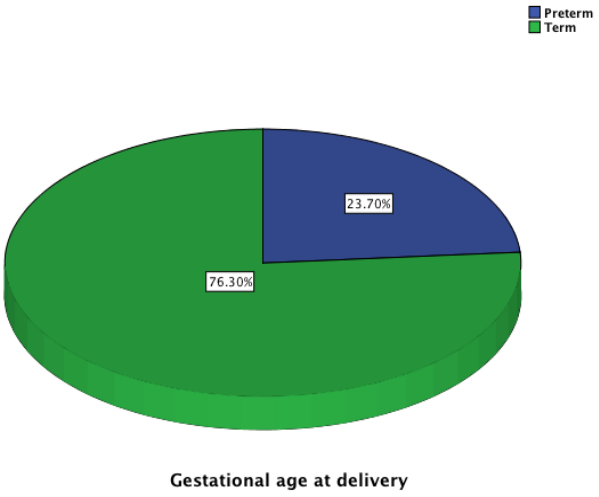

Figure 2: Gestational age at delivery

Birth weight of the babies

According to the study result, most of the diabetic women (72.6%) had normal weight babies. The percentage of low-birth-weight babies was 13.3% and the percentage of large babies was 14.1%. The mean birth weight in this study was 3.6kg with standard deviation 0.6. The birth weight ranged between 1.33 and 5.75 kg as shown in figure 3.

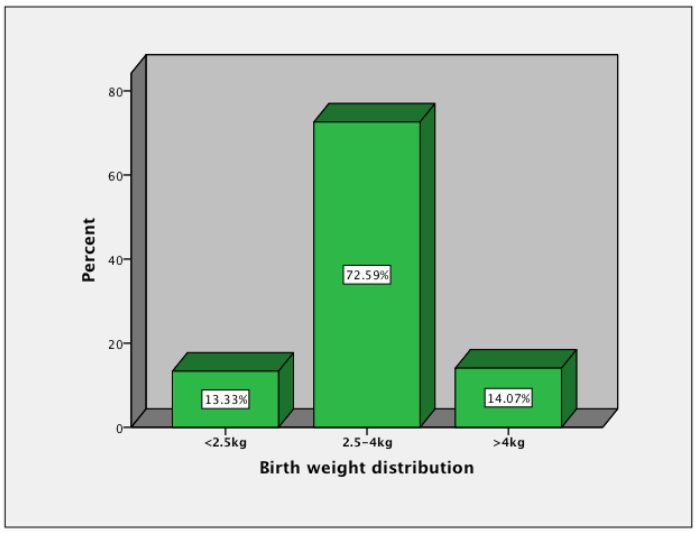

Figure 3: Birth weight of the babies

Neonatal complications

Neonatal complications in this study were as following: IUGR (2.2%), neonatal sepsis (2.2%), birth injury (2.2%), neonatal polycythemia (0.7%), congenital anomaly (3%), RDS (5.2%) and neonatal hypoglycemia (14.8%), as shown in table 6.

Table 6: Neonatal complications

Neonatal complication	Yes	No
IUGR	3(2.2%)	132(97.8%)
NN Sepsis	3(2.2%)	132(97.8%)
Birth injury	3(2.2%)	132(97.8%)
NN polycythemia	1(0.7%)	134(99.3%)
Congenital anomaly	4(3%)	131(97%)
RDS	7(5.2%)	128(94.8%)
NN hypoglycemia	20(14.8%)	115(85.2%)

Relation of HbA1c in early and during pregnancy and maternal complication

All of nephropathy patients and all patients who suffered from DKA in this study had HbA1c level above 7. About 83.3% of patients with retinopathy had HbA1c level above 7. Regarding hypoglycemia, around 62.5% of patients who had hypoglycemia HbA1c level above 7. The association between HbA1c level in early stage of pregnancy and maternal complication was statistically insignificant with p value > 0.05 (table 7).

Table 7: Relation of HbA1c in early pregnancy and maternal and neonatal complication

Maternal outcome	HbA1c level		
	7 and less	More than 7	P value
Nephropathy	0(0%)	1(100%)	0.897
Retinopathy	1(16.7%)	5(83.3%)	0.346
Hypoglycemia	9(37.5%)	15(62.5%)	0.400
DKA	0(0%)	3(100%)	0.293
Neonatal complications			
IUGR	1(33.3%)	2(66.7%)	0.742
NN Sepsis	2(66.7%)	1(33.3%)	0.258
Birth injury	1(33.3%)	2(66.7%)	0.742
NN polycythemia	0(0%)	1(100%)	0.667
Congenital anomaly	1(25%)	3(75%)	0.593
RDS	5(71.4%)	2(28.6%)	0.059
NN hypoglycemia	8(40%)	12 (60.2%)	0.329

The relation between HbA1c changes during the pregnancy and maternalcom-plication was statistically insignificant with p value > 0.5. All of nephropathy patients and all patients who suffered DKA in this study had HbA1c decreased but the level stays above 7 (improved level but above 7). About 66.7% of patients with retinopathy had improved level of HbA1c but above than 7. More than half of patients who had hypoglycemia had their HbA1c level remain or decreased below 7 (improved level less than 7).

Relation of HbA1c in early and during pregnancy and neonatal complication:

The relation between HbA1c level in early pregnancy and neonatal complications was statistically insignificant with p value > 0.05. The result shows that 66% of the IUGR have abnormal level of HbA1c, about 33.3% of babies with NN sepsis have abnormal level of HbA1c, 66.6% of babies with birth injury have abnormal level of HbA1c, 100% of babies with polycythemia have ab-normal level of HbA1c, 75% of babies with congenital anomaly have abnormal level of HbA1c, 28.6% of babies with RDS have abnormal level of HbA1c and 60.2% of babies with hypoglycemia have abnormal level of HbA1c. shown in table 7

The relation between HbA1c changes during the pregnancy and neonatal com-plication was statistically insignificant with p value > 0.5. The result shows that 100% of neonates with IUGR their mother had HbA1c decreased but the level stays above 7 (improved level but above 7). The study reported that 66.7% of neonates with sepsis their mother had their HbA1c level remain or decreased below 7 (improved level less than 7). About 66.7% of neonates with birth injury their mother had improved level of HbA1c (less than 7). Regarding congenital anomaly, about 75% of congenital anomaly in neonate associated with HbA1c level improved level of HbA1c (less than 7). The majority of RDS cases (71.4%) occur in mother with improved level of HbA1c (less than 7). Half of neonatal hypoglycemia occurs in mother with improved level of HbA1c (less than 7). 100% of neonate with polycythemia their mother had improved level of HbA1c (less than 7), as shown in table 8

Table 8: Relation of HbA1c changes during pregnancy with maternal and neonatal complications

Maternal outcome	HbA1c level			
	Improved < 7	Improved > 7	Not improved	P value
Nephropathy	0(0%)	1(100%)	0(0%)	0.169
Retinopathy	2(33.3%)	4(66.7%)	0(0%)	0.237
Hypoglycemia	14(58.3%)	6(25%)	4(16.7%)	0.328
DKA	0(0%)	3(100%)	0(0%)	0.652
Neonatal complications				
IUGR	0(0%)	2(100%)	0(0%)	0.714
NN Sepsis	2(66.7%)	0(0%)	1(33.3%)	0.196
Birth injury	2(66.7%)	1(33.3%)	0(0%)	0.986
NN polycythemia	1(100%)	0(0%)	0(0%)	0.362
Congenital anomaly	3(75%)	1(25%)	0(0%)	0.431
RDS	5(71.4%)	2(28.6%)	0.270	0.355
NN hypoglycemia	10(50%)	6 (30%)	4(20%)	0.549

DISCUSSION

Diabetes mellitus is a common malady to complicate pregnancy. Both GDM and PGDM can adversely affect the fetal and the maternal outcomes [11]. Strict glycemic control is essential to minimize the maternal and fetal morbidity and mortality of pregnancies complicated by diabetes [12]. In addition to home blood glucose measurement, which may not always reflect the true average blood glucose level, HbA1c is a useful parameter in metabolic regulation. Thus, supplementation with HbA1c, as is common outside pregnancy, seems appropriate [12]. Elevated HbA1c (A1C) is associated with increased risk of adverse pregnancy outcomes (Maternal and fetal). However, a level of A1C below which further improvement will carry no benefit for the fetus has not been de-fined [13].

The aim of this study was to assess the clinical utility of early and late trimester HbA1c level in predicting adverse pregnancy outcome in GDM and PGDM. The result of this study shows that more than half of the patients in early pregnancy have HbA1c level more than 7% with mean of 7.8 and standard deviation of 1.86. The mean HbA1c level decreased in the late pregnancy to 7.2. This result was in agreement with the result of Krstevska et al study, which reported that in early pregnancy the mean HbA1c level was higher than 7% and the result in the late pregnancy decreased to 6.2 which is lower than the current study [14]. Another study which done by Lynn et al shows different result of HbA1c level with mean level less than 7% [15].

Unfortunately, there are few studies on the effect of the changes of HbA1c level during pregnancy on maternal and fetal outcome. This study showed that approximately half of the patients show improved level of HbA1c in late-stage pregnancy compared to early stage of pregnancy. Most of the other studies only show the levels of HbA1c during the early stage of pregnancy. Other studies such as Krstevska et al study and Lene et al study reported that in late stage of pregnancy the mean level of HbA1c improved which is similar to this study result [14,16].

Diabetic complications in this study were infrequent with hypoglycemia as the most common complication. Other diabetics complications addressed in this study include retinopathy, nephropathy, neuropathy, DKA and CAD. All of the other complications affect only few patients in this study. The result of Krstevska et al study was similar to our result, which showed that the complications of diabetes were infrequent and only affects few patients. The Krstevska et al study also showed the same percentage for some complications such as retinopathy and

nephropathy [14]. This can be related to the fact that in this study 80% of participants were type2 DM or GDM, and complications like retinopathy, nephropathy, neuropathy, and CAD are more common among those who have type 1DM for long time.

Regarding the neonatal complications the study result was in agreement with the study result of Maresh et al study, which shows that NN hypoglycemia and the need for a neonatal glucose infusion is common neonatal complication that occurs in diabetic women in addition to increase risk of large of date and risk of birth injury [17]. All of these risks are significantly increase as HbA1c level increases. However, opposite to this study result, Suhonen et al., found increase in hemoglobin A1c in early pregnancy is statistically significant association with the occurrence of congenital malformations among Type I diabetes mellitus mothers [18].

The study revealed that there are no relations between early HbA1c and out-comes (maternal and neonatal) with p value > 0.05. The study also showed insignificant relation between the changes of HbA1c levels during the pregnancy and the outcome (maternal and neonatal) with p value > 0.05. The result of Gunnar et al study showed an almost linear association between HbA1c and risk of adverse outcome (maternal and neonatal), which was in disagreement with the current study. The Gunnar L et al study also reported that an increase of HbA1c during the pregnancy associated with the increase of adverse out-come (maternal and neonatal) [13]. Similarly, Meek et al found hemoglobin A1c significantly associated with obstetric and neonatal outcomes especially in the second trimester and many alternative laboratory markers had lower predictive ability than HbA1c regarding pregnancy and neonatal outcomes. [19] Other studies reported that the risks of adverse pregnancy outcomes decrease as the level of HBA1c decrease and vasa versa [13,20-22].

CONCLUSION

Although HbA1c levels are important in pregnancy to monitor the compliance of the treatment, the use of HbA1c level to predict the adverse maternal and neonatal outcomes remains questionable.

Disclaimer

The article has not been previously presented or published, and is not part of a thesis project.

Conflict of Interest

There are no financial, personal, or professional conflicts of interest to declare.

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