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The cross-link between maternal HbA1c and neonatal outcome: A Clinical Case Report

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ABSTRACT

Introduction : Diabetes is a common condition among pregnant women, and a high glycated hemoglobin (HbA1c) level can indicate poor outcomes for both the mother and the fetus. This report presents a case of an unknown diabetic primigravida with a significantly elevated HbA1c level, which resulted in severe complications during pregnancy and adverse fetal outcomes.

Case Study: A 37-year-old primigravida was referred to the emergency obstetrics and gynecology clinic, where she reported a notable decrease in fetal movements and feelings of lethargy. Laboratory tests revealed a significantly elevated blood sugar level. After assessing fetal well-being, the decision was made to terminate the pregnancy at 33 weeks and 2 days due to severe fetal distress. Immediate treatment was initiated to control the high blood sugar levels. The outcome was the delivery of a preterm boy who presented with multiple biochemical imbalances and required admission to the neonatal intensive care unit (NICU).

Conclusion : Improving hyperglycemia and glycated hemoglobin levels to lower than the upper normal limits during both the preconception and post-conception phases can significantly reduce morbidity and mortality for mothers and their fetuses.

KEYWORDS: *Glycated hemoglobin (HbA1c), neonate outcome, gestational diabetes, congenital anomalies*

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INTRODUCTION

The impact of diabetes on pregnancy outcomes is both significant and undeniable. It presents serious risks for mothers and their unborn babies throughout pregnancy and after birth (1). Potential fetal risks include abnormal growth, shoulder dystocia, macrosomia (being large for gestational age), birth injuries, and premature labour. Additionally, babies born to mothers with uncontrolled diabetes face critical challenges such as high or low blood sugar levels, jaundice, and congenital anomalies (2). The implications of diabetes extend to mothers as well, resulting in increased rates of cesarean sections, preeclampsia, and other severe health complications (3). Glycated hemoglobin (HbA1c) is crucial for monitoring diabetes progression, as it accurately reflects long-term blood sugar levels. Clinical evidence clearly shows that elevated HbA1c levels are strongly associated with poor neonatal outcomes (1). There is no debate about the fact that diabetes jeopardizes pregnancy outcomes (8), bringing forth numerous risks for both mothers and their offspring during pregnancy and in the neonatal period (1). The risks to the fetus include abnormal growth, shoulder dystocia, macrosomia, birth injuries, and preterm labor. Furthermore, adverse effects can persist into the postnatal period, with neonates suffering from hyperglycemia or hypoglycemia, neonatal jaundice, and congenital anomalies, among other serious issues (2).

The impact of diabetes on pregnancy outcomes is indisputable. It presents significant risks for both mothers and their unborn babies, both during pregnancy and after birth (1). Potential fetal risks include abnormal growth, shoulder dystocia, macrosomia, birth injuries, and premature labor. Postnatally, babies born to uncontrolled diabetic mothers may experience issues such as high or low blood sugar, jaundice, and congenital anomalies (2). These adverse effects can also affect the mothers, leading to increased rates of caesarean sections, preeclampsia, and other serious complications (3). Glycated hemoglobin (HbA1c) has long been used to monitor the progression of diabetes as it reflects long-term blood sugar levels. Clinical evidence has shown that high HbA1c levels are associated with unfavorable neonatal outcomes (1). There is no debate on whether diabetes compromises pregnancy outcomes (8). It carries groups of adverse risks for both mothers and their offspring within the uterus and during the neonatal period (1). The fetal risks could include abnormal fetal growth, shoulder dystocia, macrosomia, being large for gestational age, birth injury, and preterm labor. However, the negative outcomes could also extend to the postnatal period, with neonates suffering from hyperglycemia or hypoglycemia, neonatal jaundice, and congenital anomalies, among others (2,15).

The adverse effects of diabetes can significantly impact mothers, leading to increased rates of cesarean sections, preeclampsia, and various other complications. Glycated hemoglobin has long been utilized to monitor the progression of the disease, as it reflects long-term blood sugar levels. Clinical evidence indicates that elevated HbA1c levels are linked to a higher incidence of unfavorable neonatal outcomes. We are reporting a clinical case involving a pregnant woman in her third trimester who was undiagnosed with diabetes. She presented at our clinic with signs of fetal compromise and exhibited a high HbA1c level, which required an emergency cesarean section. Unfortunately, this procedure resulted in multiple complications for the fetus. We have provided detailed information about this case along with a clinical review.

CASE STUDY:

A 37-year-old woman, who had been trying to conceive for three years, presented to our facility at 33 weeks and 1 day of gestation. She was referred from an outpatient clinic due to a high HbA1c level of 12.8% and a random blood sugar (RBS) level of 278 mg/dL. The patient reported feeling exhausted and noted a decrease in fetal movement, although she had not performed proper fetal movement counting. This woman had never been diagnosed with diabetes and had not experienced elevated blood glucose levels before. She had a history of primary infertility but conceived spontaneously. During her first trimester, she faced a threatened abortion, and in the early second trimester, she suffered from a severe urinary tract infection, which was treated

with broad-spectrum antibiotics. Additionally, she received a Dexamethasone injection for fetal lung maturation after experiencing mild vaginal spotting; however, her blood glucose level was not assessed at that time. Upon seeking medical attention at 33 weeks and 1 day of pregnancy in early April 2022, she reported a significant decrease in fetal movement. The patient had an unsophisticated pregnancy with no history of amniotic membrane rupture. During routine evaluations, hyperglycemia was detected, prompting her admission to the maternity ward at Ali Omar Askar Hospital for detailed assessment. Comprehensive investigations, including fetal ultrasound, fetal Doppler, and cardiotocography (CTG), informed the decision to terminate the pregnancy. The CTG revealed concerning phases of deceleration and was non-reactive, while ultrasound findings indicated significant oligohydramnios. Once admitted, the patient received insulin treatment based on a sliding scale, and her pregnancy was ultimately terminated via cesarean section at 33 weeks and 2 days gestation. Notably, she has no prior history of hypertension or diabetes and has never faced medical issues. Furthermore, there is no family history of chronic diseases or other health concerns. As a dedicated housewife residing in Sedi Siaeh, a small village in proximity to the hospital, her situation underscores the importance of timely medical intervention in ensuring both her safety and that of her baby. Upon arrival, her random blood sugar level was 213 mg/dL, HbA1c was 14.2%, haemoglobin was 13.1 g/dL, white blood cell count (WBC) was 11 x 10^3/µL, and platelet count (PLT) was 191 x 10^3/µL. An ultrasound examination revealed a single fetus with biometry equivalent to 33 weeks of gestation, scanty amniotic fluid, and all other parameters appeared normal. The Doppler study showed a slight increase in resistance to blood flow in the umbilical artery. The outcome was the delivery of a male infant with a birth weight of 2.6 kg, who was admitted to the Nursery ICU due to tachypnea and respiratory distress, requiring nasal oxygen support. The infant also presented with hyperglycemia (326 mg/dL), neonatal jaundice necessitating phototherapy (total bilirubin level of 8.94 mg/dL), hypocalcemia (6.3 mg/dL), and a skull deformity (scaphocephaly) that required MRI scanning and further investigations to rule out any underlying pathology.

DISCUSSION:

Diabetes is a prevalent disease that can have serious consequences during pregnancy. Elevated blood glucose levels are known to contribute to poor pregnancy outcomes, as various studies have shown (4). Many researchers emphasize the importance of early detection and control of blood glucose levels to mitigate these negative outcomes (5). In this reported case, the late detection of high blood sugar levels likely explains the adverse effects on both the mother and her baby. The timing of the onset of her elevated blood glucose level is unclear due to irregular follow-up, although her blood glucose levels were within the normal range during her initial visit in early pregnancy. During early pregnancy, glucose levels change as a physiological response to hormonal changes and an increase in plasma volume, while late in pregnancy, increased fetal glucose consumption can lead to abnormal blood glucose levels, the physiological regulation of glucose levels is specifically designed to maintain normal ranges, effectively preventing complications for both the mother and the fetus (7). HbA1c serves as a crucial marker, resulting from the combination of plasma glucose and haemoglobin. It is essential for identifying undiagnosed elevated glucose levels in pregnant women over the last two to three months. This test is not only straightforward to perform and interpret but is also indispensable for monitoring the progression of gestational diabetes. Since 2010, it has been recognized as a key diagnostic tool in various medical investigations (1). A plasma glucose level of 135 mg/dL (7.5 mmol/L) is directly linked to an HbA1c level of 6.0%. Specifically, a 1% increase in HbA1c correlates with a 35 mg/dL (1.95 mmol/L) rise in plasma glucose levels (2,7). It is imperative to understand that glycated haemoglobin levels in pregnant women are significantly influenced by physiological changes, just as blood glucose levels are.

Pregnant women consistently exhibit lower levels of HbA1c compared to their non-pregnant counterparts due to physiological factors such as increased maternal blood volume, higher iron demands, and decreased fasting blood glucose levels, which are managed through alterations in hemoglobin concentrations.

HbA1c levels are significantly related to the gestational stages of pregnancy (1,11). This strong correlation between HbA1c levels and pregnancy outcomes highlights the importance of accurate and regular monitoring of HbA1c with gestational age (10). Previous studies have thoroughly examined HbA1c levels in connection with the physiological changes that occur during each trimester. For example, research conducted by Connor et al. in 2012 in Ireland found that HbA1c levels significantly decreased in the first and second trimesters when compared to non-pregnant women. The HbA1c values ranged from 4.3% to 5.4% in the first trimester, 4.4% to 5.4% in the second trimester, and 4.8% to 5.5% in the third trimester. Establishing trimester-specific reference intervals is crucial for managing diabetes effectively and avoiding complications (10). While HbA1c is generally accepted as an indicator for the development of neonatal complications, various factors can influence the normal ranges, which can complicate its use in clinical settings.

In addition, HbA1c levels are connected significantly with the gestation of the pregnancy (1,11). The clear correlation between the HbA1c levels and pregnancy outcome emphasizes the essential accurate and frequent evaluation of HbA1c according to the gestational age (10). Previous studies deeply determined the levels of HbA1c with the physiological changes in each trimester. The results shown by (Connor et al, 2012) in Ireland, revealed that HbA1c was significantly decreased in the first and second trimesters compared to non-pregnant women. The values were 4.3% - 5.4%, 4.4% - 5.4% and 4.8 - 5.5% respectively. The trimester-specific reference interval is an important baseline reference that is needed to achieve good control of diabetes and avoid complications (10). HbA1c is acceptable to be used as an indicator for the development of neonatal complications but some factors could interfere with the correct ranges of levels, which is why it could interfere with its use.

Several factors and conditions can lower HbA1c results, including low red blood cell count, alcohol dependence, liver disease, certain medications and supplements, and genetic variations in hemoglobin (7). Conversely, high levels of HbA1c are associated with a higher frequency of adverse neonatal outcomes. Glycemic control, particularly during organogenesis and placentation, is crucial for improving these outcomes. HbA1c levels of 5.9% or higher in early pregnancy are regarded as challenging (6). Elevated levels before conception can lead to severe maternal morbidity and congenital fetal anomalies. In a study conducted among 105 pregnant women before 16 weeks of gestation at Parkland Memorial Hospital, the mean glycosylated hemoglobin levels were significantly lower in women who delivered normal infants compared to those with infants who had malformations. This finding supports the notion that lower HbA1c levels in early pregnancy can improve outcomes. Additionally, a cohort study of 3,459 births in Canada suggested that women who reduced their HbA1c levels during the preconception period experienced better maternal and perinatal outcomes (6), approximately 14.4% of pregnancies are affected by congenital anomalies. Research indicates that there is an increased likelihood of congenital anomalies with rising HbA1c levels; specifically, a 6.9% increase in the probability of congenital heart anomalies occurs with an adjusted relative risk of 1.09 (95% CI, 1.06-1.13) for every 0.5% increase in preconception HbA1c. Furthermore, the study found an adjusted relative risk of 1.08 (95% CI, 1.06-1.09) for perinatal mortality (1.16% CI, 1.11-1.22). Additionally, elevated HbA1c levels in the third trimester are associated with an increased risk of preeclampsia, macrosomia, and stillbirth (7). Notably, high HbA1c levels during early pregnancy, even those within the upper limits of normal ranges, are linked to adverse outcomes (14). A study examining HbA1c levels of 5.5-5.9% found a significant association with an increased risk of preterm delivery, with an

odds ratio (OR) of 2.84 (95% CI, 1.71-4.71) in pregnant women without gestational diabetes (2). Similarly, the same HbA1c levels were associated with a heightened risk of macrosomia in pregnant women with gestational diabetes, with an OR of 2.12 (95% CI, 1.13-3.97). These potential adverse effects warrant greater attention from medical staff, emphasizing the need for close and precise monitoring of pregnant women with elevated glycated hemoglobin levels. Congenital cardiac malformations are the most common type of anomaly seen in these patients (19).

Congenital malformations associated with chromosomal anomalies must not be counted, as they are unrelated to glycemic control, even if they occur coincidentally. Similarly, patent ductus arteriosus should be excluded from consideration because it is linked to preterm infants, irrespective of glycemic control (14). In our current case, the absence of significant congenital malformations can be attributed to normal blood glucose levels during the early stages of pregnancy. However, the baby is suffering from other biochemical imbalances that necessitate immediate admission to the ICU (18). This case involved the termination of the pregnancy at 33 weeks due to fetal compromise. It is a well-established fact that a majority of women with diabetes during pregnancy encounter preterm births, often defined as deliveries occurring before 37 weeks, with many experiencing extreme preterm delivery before 32 weeks. These preterm births can occur spontaneously or be induced for medical reasons. Furthermore, perinatal deaths within 28 days, particularly among preterm infants, are a prevalent and significant complication associated with high levels of HbA1c (3,14). Maternal morbidity results in extended hospital stays and various antenatal and postnatal complications, as well as increased maternal mortality risk (13). Poorly controlled glycemic levels can lead to severe maternal mortality, manifesting as postpartum hemorrhage, puerperal sepsis, and severe preeclampsia. Additionally, inadequate management of diabetes is linked to an elevated rate of cesarean sections, as demonstrated by our patient (1).

In our reported case, the baby was admitted to the NICU due to multiple neonatal complications, including hyperglycemia, hypocalcemia, neonatal jaundice, tachypnea, and respiratory distress. These complications were also observed in a previous study involving 100 primigravida women, which found that a majority of newborns required admission to a neonatal ICU for various metabolic reasons similar to those in our case. Specifically, the study reported that neonatal tachycardia was present in 49.5% of cases, neonatal jaundice requiring treatment occurred in 16.5%, and electrolyte disturbances in the form of hypocalcemia may be due to impaired PTH and vitamin D metabolism in preterm neonate needing calcium supplements were observed in 12.6% of newborns. Furthermore, hypoglycemia requiring treatment was identified in 7.8% of the cases (17). The research concluded that HbA1c is not only effective for monitoring glycemic control but also serves as a good indicator of fetal compromise and outcomes. A related complication of high levels of HbA1c is the birth of macrosomic babies, which can be predicted antenatally by measuring the anterior abdominal wall thickness and abdominal circumference in pregnant women with diabetes. This combination of investigations successfully detected 80.9% of macrosomic babies. Macrosomia is particularly prevalent among women with pregestational diabetes and is closely related to the degree of glycemic control. A study conducted in Dublin, Ireland, by (O'Dwyer et al, 2022) found that an HbA1c level greater than 5.5% in early pregnancy was associated with an odds ratio of 24 for macrosomia, and around 44% of the participants exhibited an HbA1c level exceeding 7%, indicating a significant issue with glycemic control. This poor control at 36 weeks of pregnancy is directly linked to increased birth weights (16). The importance of improving perinatal outcomes for pregnant women with diabetes is undeniable when HbA1c levels are reduced during the pregestational phase and throughout early to mid-pregnancy. A compelling cohort study in Canada, involving 3,459 participants, reinforces these conclusions by clearly demonstrating a decreased risk of

congenital anomalies, preterm birth, perinatal mortality, and severe maternal morbidity (1,15).

CONCLUSION

Improving HbA1c levels before and during pregnancy can significantly reduce the risks of morbidity and mortality for both mothers and their children. This includes lower rates of congenital heart disease, premature births, and maternal health issues. The findings of this analysis highlight the critical importance of monitoring glucose levels, especially for those approaching the upper limits of normal. Additionally, better management of glycemic levels before and during pregnancy can be beneficial for both the mother and the fetus.

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