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Impact of Ramadan fasting on glucose levels in women with gestational diabetes mellitus treated with diet alone or diet plus metformin: a continuous glucose monitoring study

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ABSTRACT

Objective Women with gestational diabetes mellitus (GDM) are categorized as at high risk for adverse events during Ramadan fasting. However, this is largely based on clinical opinion. In this study, we shed some light on what happens to glucose levels during Ramadan fasting.

Methods This is a prospective observational study. A total of 32 patients with GDM were recruited; 10 patients, treated with diet only (group 1), to observe their glucose levels before fasting and 22 patients who insisted on fasting the month of Ramadan, 13 treated with diet only (group 2) and nine treated with diet plus metformin 500 mg twice daily (group 3), to evaluate their glucose levels during fasting. Interstitial glucose was monitored in all by using the iPro2 Professional continuous glucose monitoring (CGM) system.

Results Mean glucose level was 116±21 mg/dL (6.16±1.16 mmol/L), 106±9 mg/dL (5.88±0.49 mmol/L) and 99±7 mg/dL (5.49±0.34 mmol/L) in groups 1, 2 and 3, respectively. Patients in group 1 had the lowest rate of hypoglycemia (50%), followed by patients in group 2 (60%), whereas patients in group 3 had the highest rate of hypoglycemia (78%).

Conclusions CGM data indicates that Ramadan fasting in women with GDM treated with diet alone or with diet plus metformin was associated with lower mean glucose levels and higher rates of hypoglycemia when compared with non-fasting glucose levels. Women with GDM should be advised against fasting during Ramadan until further data is available.

Significance of this study

What is already known about this subject?

- The vast majority of Muslim women with gestational diabetes opt to fast in the month of Ramadan despite medical/religious advice not to do so.
- Most of the medical recommendations are based on expert opinion due to the paucity of clinical studies in this field.

What are the new findings?

- Our data suggest that Ramadan fasting increases the risk of hypoglycemia in women with GDM treated with diet alone or with diet±metformin.
- The impact of metformin on the glucose changes compared with diet only is of great clinical interest. It was associated with reduced risk of hyperglycemia and lower rate of severe hypoglycemia, however, with an increased risk of mild-moderate hypoglycemia when compared with diet alone during fasting.

How might these results change the focus of research or clinical practice?

- The data is an important step in risk quantification for women with GDM wishing to fast Ramadan.
- Women with GDM should be advised against fasting during Ramadan until further data is available.
- Continuous glucose monitoring could be of good value for understanding the blood glucose changes in patients with GDM treated with diet alone or with diet±metformin pre-Ramadan and during Ramadan fasting.

INTRODUCTION

Diabetes is a growing health problem particularly in regions with a high Muslim population, such as South East Asia, Africa and the Middle East where the estimated 150 million Muslims with diabetes are expected to double in number by the year 2040.[1]

Ramadan fasting is one of the five main pillars of Islam. CREED study reported that 63.6% of people with type 2 diabetes fasted every day of Ramadan, while 94% fasted over 15 days of Ramadan.[2] Fasting during Ramadan implies no intake of food or drink, including any oral medication, from dawn to sunset. In the year 2017, Ramadan started in May, where fasting hours in most countries lasted between 15 and 19 hours and in many countries also associated with hot weather.[3] The physiological impact of changes in eating and sleep pattern during Ramadan are of

particular concern for people with medical conditions such as diabetes.[4]

While Ramadan fasting is obligatory to all healthy adult Muslims, exemptions exist for many including women during pregnancy as well as for those with medical illness.[4] Nevertheless, many studies have shown that the majority of healthy pregnant women opt to fast despite the burden of fasting while pregnant.[5–8] Some studies suggest that fasting for less than 15 hours is metabolically similar to an overnight fast for healthy pregnant woman.[9] While ketonemia and hypoglycemia frequently occur with prolonged fasting, the overall evidence does not suggest that fasting adversely affects the infant.[5 7 9–12] Furthermore, many studies on healthy women fasting during Ramadan have not demonstrated any significant impact of fasting on markers of infant well-being.[11 12]

In contrast, due to the potential risk of hypoglycemia, hyperglycemia, ketoacidosis, as well as dehydration and thrombosis, various diabetes and Ramadan guidelines have recommended that some people with diabetes, including all pregnant women with diabetes or gestational diabetes mellitus (GDM), should not fast due to the potential high risk on their health.[13–17] However, this seems not to be well enforced by healthcare professionals and many pregnant women with diabetes are not clear whether to fast or not.[18]

It is important to note that categorizing women with GDM as at too high risk for adverse events during Ramadan fasting is largely based on clinical opinion rather than on empirical evidence due to the paucity of studies done in pregnant women with GDM or diabetes during Ramadan fasting, yet. A study in Saudi Arabia reported better glycemic control without adversely increasing the risk of hypoglycemia in those who fasted.[19] Improvement in fasting blood more importantly, postprandial blood glucose (BG) level, was shown in Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study to correlate with pregnancy outcomes in women with GDM.[20]

While the evidence for an impact of hyperglycemia on pregnancy outcomes seems to be strong, evidence of harm due to hypoglycemia in pregnancy seems to be more difficult to find. Indeed, Yogev *et al* have shown that pregnant women seem to have up to 20% lower BG level than non-pregnant women without having symptoms of hypoglycemia.[21] This is further supported by continuous glucose monitoring (CGM) study comparing glucose level in non-pregnant to those in pregnant women. Surprisingly, this study showed that blood levels below 60 mg/dL were frequently observed in pregnancy, both among non-diabetics and those with gestational diabetes.[22] Such levels of hypoglycemia were not seen in non-pregnant women.[22]

During pregnancy, treatment guidelines recommend BG targets to be well controlled, focusing on avoiding hyperglycemia both during fasting and postprandial,[23] aiming at the following BG levels:

- fasting ≤95 mg/dL (5.3 mmol/L) and either
- 1 hour postprandial ≤140 mg/dL (7.8 mmol/L) or
- 2 hour postprandial ≤120 mg/dL (6.7 mmol/L).

To achieve such tight glycemic control, women with gestational diabetes are recommended to self-monitor BG (SMBG) levels prebreakfast, post meals and whenever they feel symptoms of hypoglycemia or hyperglycemia. A recently published study, however, indicated that the actual frequency of monitoring in women with GDM was suboptimal and could be linked to poor pregnancy outcomes.[24]

CGM in routine care of GDM is not recommended. However, CGM could be a useful tool to add to our understanding of the impact of Ramadan fasting on glucose levels in women with GDM and ultimately lease to improve glycemic control.

METHODS

This is a prospective observational study done at Tawam Hospital Diabetes Center, Al-Ain city, UAE. The study was originally designed as an exploratory pilot study and the accurate calculation of sample size was not feasible due to paucity of data in the field. A total of 32 patients with GDM treated with diet±metformin who insisted on fasting during the lunar month of Ramadan 2017 were recruited. All participants provided written consent to participate. Before the month of Ramadan, all patients were counseled by a multidisciplinary team including endocrinologist, diabetes educators and nutritionists. They were all provided with one to one education to cover all aspects of diabetes in pregnancy as well as Ramadan focused advice. Postdiagnosis with GDM, all patients are initiated on diet±metformin or insulin according to their BG profile and/or patient preference. In our study, we report on patients treated with diet±metformin. All patients consented to wear the iPro2 Professional CGM device for a minimum of 3 days. In addition, and in order to calibrate the CGM device, patients were instructed to check their BG using a glucose meter a minimum of three, preferably six, times daily as the data of the CGM were blinded to the patient. Patients were explicitly instructed to include the late fasting hours of the day (16:00–19:00) as well as 1 hour after the two main meals (Iftar and Sohour). Hyperglycemia was defined as glucose level of more than 140 mg/dL (7.8 mmol/L) and hypoglycemia was defined as glucose level below 70 mg/dL (3.9 mmol/L). Severity of hypoglycemia was classified as mild, moderate or severe when glucose levels were 60–69 mg/dL (3.30–3.85 mmol/L), 50–59 mg/dL (2.80±3.25 mmol/L), less than 50 mg/dL (2.80 mmol/L), respectively.

The data was saved in MS Excel 2010, then uploaded to IBM SPSS V.20. For data analysis, we used descriptive analysis.

RESULTS

Ramadan 2017 started on 26 May and ended in the evening of 24June, and fasting hours started from around 04:00 am and ended around 07:00 pm. Out of 36 screened

Table 1 Rates of normoglycemia, hyperglycemia and hypoglycemia in patients' groups

Group and treatment	Pre-Ramadan diet	Ramadan diet	Ramadan diet and metformin
Number of patients	10	13	9
Total glucose readings	8323	19411	14076
Mean glucose±SD	116 mg/dL±21 (6.16±1.16 mmol/L)	106 mg/dL±9 (5.88±0.49 mmol/L)	99 mg/dL±7 (5.49±0.34 mmol/L)
Per cent of time glucose level in 70–140 mg/dL (7.7–10 mmol/L)±SD	78.6%±7.1%	89%±6.6%	90.2%±6.2%
Per cent of time glucose level >140 mg/dL (7.7 mmol/L)±SD	19.0%±22%	7.18%±6.3%	4.15%±2.77%
Per cent of time glucose level <70 mg/dL (3.88 mmol/L±SD	2.71%±3.86%	3.76%±4.99%	5.66%±4.74%

patients, three refused participation and one was excluded because of misdiagnosis. A total of 32 patients participated in the study. Mean age 32.9±3, prepregnancy body mass index (BMI) of 29.5±2 kg/m^2 and parity of 2.78 (0–10). Personal history of GDM was confirmed in 15 patients (47%) and family history of diabetes mellitus was present in 21 patients (66%). Patients were divided into three groups: group 1 (10 patients) on diet only, monitored before Ramadan, group 2 (13 patients) on diet only, monitored during Ramadan fasting, and group 3 (nine patients) treated with diet plus metformin 500 mg twice daily, monitored during Ramadan fasting. Mean monitoring periods were 3.0, 5.2 and 5.5 days and total glucose readings were 8323, 19 411 and 14 076 for groups 1, 2 and 3, respectively. Patients in the study monitored their BG using the glucose reading meter on average of 3.4 readings/patient/day. All patients completed their fast throughout the monitoring period with no reports of adverse events or hospital admissions.

Mean glucose level was 116±21 mg/dL (6.16±1.16 mmol/L), 106±9 mg/dL (5.88±0.49 mmol/L) and 99±7 mg/dL (5.49±0.34 mmol/L) in groups 1, 2 and 3, respectively.

Patients in group 1 (pre-Ramadan) had the highest incidence of hyperglycemia and the lowest rate of hypoglycemia, whereas patients in group 3 (on diet plus metformin fasting) had the highest rate of hypoglycemia with the highest rate of normoglycemia and lowest rate in hyperglycemia (table 1).

Analysis of postprandial hyperglycemia revealed that glucose levels of more than 180 mg/dL (10 mmol/L) occurred during 32%, 23% and 5% of hyperglycemic CGM observations in groups 1, 2 and 3, respectively (table 2).

Table 2 Severity of hyperglycemia

	Glucose level between140 and 180 mg/dL (7.7–10 mmol/L) (%)	Glucose level >180 mg/dL (10 mmol/L)(%)
Group 1	68	32
Group 2	77	23
Group 3	95	5

Further analysis of hypoglycemia revealed that hypoglycemia occurred at least once in 50%, 60% and 78% of patients in groups 1, 2 and 3, respectively. While 71% of hypoglycemia before Ramadan was in the fasting (prebreakfast) and 29% was in the prandial states; however, 100% of hypoglycemic episodes in Ramadan were encountered in the late fasting hours of the day (16:00–19:00). The severity of hypoglycemia shows that the incidence of severe hypoglycemia, a glucose level of less than 50 mg/dL (2.80 mmol/L), was 0%, 23% and 4% in groups 1, 2 and 3, respectively (table 3).

DISCUSSION

Our study has many important clinical implications despite the fact that these groups may not have been totally comparable as allocation was not random and indeed; the aim of the study was to have a better understanding of changes in BG levels during fasting and non-fasting periods for women with GDM. As mentioned above, many Muslim women with GDM insist on fasting the month of Ramadan despite medical and religious recommendations not to do so.[5–8] The CGM data in this study shed light on what happens to glucose levels during Ramadan fasting compared with pre-Ramadan. In our study, the glucose levels above 140 mg/dL were considered as high for educational purposes and those above 180 mg/dL were considered very high. Our data indicate that glucose levels were better in those women with GDM fasting in Ramadan than pre-Ramadan whether they were treated with diet plus metformin or diet only. Indeed, the average difference between the pre-Ramadan and during Ramadan glucose level of group 3 who were treated with diet and metformin was over 17 mg/dL. Furthermore, this group had the highest rate of normoglycemia in the study (90.2%). This result is similar to what was observed previously in a study from Saudi Arabia where it was noted that women with GDM who fasted during Ramadan had a better glycemic control.[19] Nevertheless, in our opinion, women with GDM should be advised against fasting until further studies on benefits and risks are conducted.

Table 3 Frequency and severity of hypoglycemia

	Frequency of glucose level <70 mg/dL (<3.9 mmol/L) (%)	Mild hypoglycemia glucose level 60–69 mg/dL (3.30–3.85 mmol/L) (%)	Moderate hypoglycemia glucose level 50–59 mg/dL (2.80±3.25 mmol/L) (%)	Severe hypoglycemia glucose level <50 mg/dL (<2.80 mmol/L) (%)
Group 1	50	92	8	0
Group 2	60	58	19	23
Group 3	78	74	22	4

The frequency and the severity of hypoglycemia in pregnant women is clinically important. Previous studies have indicated that BG levels in pregnant women could be up to 20% lower than those of non-pregnant women regardless of their glycemic status.[21] Indeed, previous studies in pregnant women labeled BG levels <60 to be mild hypoglycemia and showed that this is not an uncommon occurrence regardless of their glycemic status.[22] Furthermore, in another CGM study including 10 healthy pregnant women, hypoglycemia was also noted.[24] Guided by these data, we grouped hypoglycemia by severity, as mild (69–60 mg/dL), moderate (59–50 mg/dL) or severe (<50 mg/dL). In our study, utilizing CGM data, hypoglycemia was seen in all groups including 50% of patients in group 1 (pre-Ramadan) who were treated with diet only. Furthermore, our data showed that about 8% of the hypoglycemic episodes in group 1 were below 60 mg/dL; however, there were no episodes in this group with BG <50 mg/dL. These results are highly important as they corroborated previous studies in healthy pregnant women and may question the cut-off for the definition of hypoglycemia during pregnancy.

Contrary to what was observed in the Saudi study,[19] our data suggest that Ramadan fasting increases the rate of all levels of hypoglycemia as patients in groups 2 and 3, respectively, had 60% and 78% incidence of hypoglycemia compared with the 50% noted in group 1 (pre-Ramadan). More importantly, rates of severe hypoglycemia were much higher in patients in group 2 (23%) and group 3 (4%) who were fasting in the month of Ramadan, while there was no severe hypoglycemia in group 1 patients who were not fasting. The difference in rates of hypoglycemia between our study and the Saudi study could be due to our use of CGM while the Saudi study used SMBG. It is noteworthy that the hypoglycemic episodes detected during our study were all asymptomatic, and the implications of this should be further explored.

The value of CGM in women with GDM is another interesting point. In this study, the CGM data were blinded as the main objective was to understand the glucose changes that occur in GDM women during pre-Ramadan and Ramadan. In light of these data, it would be interesting to see the impact of unblinded CGM on the behaviour and on the overall glucose changes of women with GDM during fasting in Ramadan. The value of CGM was stressed on for monitoring gestational glucose variability including beyond what is simply observed by HbA1c.[24] Indeed, in this study, BG fluctuations were observed in healthy pregnant women, those with GDM as well as pregnant women with type 1 diabetes.[24] Our patients were using SMBG during the study and the frequency of their SMBG test averaged 3.4 tests/daily. This is in line with recent concerns about the low frequency of SMBG monitoring by women with GDM and its implications for the outcome of the pregnancy.[25]

Metformin use in GDM is not universally accepted as many guidelines recommend management with insulin as the gold standard of care. However, many clinicians opt for metformin as many of our patients with GDM are reluctant to start insulin therapy. The glucose levels observed in group 3 treated with diet and metformin during Ramadan fasting in GDM deserves further study, as it seems that they had the best rate of BG where their mean glucose level was 99±7 mg/dL (5.49±0.34 mmol/L) compared with group 2 who fasted and were treated with diet only and had a mean BG of 106±9 mg/dL (5.88±0.49 mmol/L). While the overall rate of hypoglycemia in group 3 was higher than group 1 or 2, this occurred with lower rates of severe hypoglycemia than group 2 (4% vs 23%).

A limitation of our study was its small size, it being designed as an exploratory study only and thus limited statistical power. More limitations include the lack of reporting adverse maternal and neonatal outcomes. Furthermore, the size of the sample did not allow analysis of other potentially confounding factors such as age, parity, BMI, personal and family history. Nevertheless, the results of our study are highly informative and call for a larger multicentre study to verify the significance of this clinically important data and to also look into pregnancy and neonatal outcomes of women with GDM insisting on Ramadan fasting.

CONCLUSIONS

CGM could be of good value for monitoring glucose in patients with GDM during Ramadan fasting as it allows better understanding of rates of hypo/hyperglycemia during fasting. Furthermore, data indicates that hypoglycemia can occur in women with GDM regardless of the type of treatment they are on and indeed, independent from their fasting status. Ramadan fasting in women with GDM treated with diet alone or with diet plus metformin was associated with lower mean glucose levels but higher

rates of hypoglycemia when compared with non-fasting glucose levels. Women with GDM should be advised against fasting during Ramadan until further data is available.

Contributors BOA planned and submitted the study for approval, researched data, wrote and edited the manuscript. MH planned the study, researched data, wrote and edited the manuscript. LM recruited and followed patients, obtained consents, contributed to discussion. NN analysed the data and edited the manuscript. BA takes full responsibility for the work. The authors have no relevant conflict of interest to disclose.

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