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Hypoglycaemia on an oral glucose tolerance test in pregnancy – Is it clinically significant?

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ABSTRACT

Aim: During pregnancy, some women have a low glucose level on the 75 g oral glucose tolerance test (OGTT). The implications of this are unclear and there is no guideline on how to manage these women.

Method: We recruited pregnant women with a glucose level <3.5 mmol/L at 1- or 2-h during a screening antenatal OGTT. These women (Group 1) underwent self-monitoring of blood glucose (SMBG) over a two-week period. We also compared Group 1's demographic and pregnancy outcomes data with women who had normal OGTT results (Group 2) and women diagnosed with gestational diabetes mellitus (GDM) (Group 3).

Results: 52 women were recruited. Post-hoc analysis of the SMBG results revealed 50% of women experienced 2 or more elevated fasting BGLs (>5.1 mmol/L) in a week when using the Australian Diabetes in Pregnancy Society (ADIPS) criteria. A further 8% women had elevated 2-h glucose levels (above 6.7 mmol/L). Group 1 women tended to have higher booking weight. They were less likely to have a history of macrosomia or be of East or South-East Asian ethnicity. There were no differences in pregnancy outcomes between Groups 1 and 2, but Group 1 had a higher rate of congenital abnormality (6%) than Group 3 (2%).

Conclusion: A large proportion of pregnant women who had a low glucose level on OGTT had elevated glucose levels on SMBG, however their pregnancy outcomes were not significantly different to women who had a normal OGTT. Currently there is not enough evidence to advocate routine SMBG and treatment for this group of women.

1. Introduction

Untreated gestational diabetes can lead to increased maternal and fetal complications. Treatment of gestational diabetes has been shown to reduce the risk of complications [1]. There is the possibility that women who develop hypoglycaemia during a screening oral glucose tolerance test (OGTT) during pregnancy may have undiagnosed gestational diabetes.

The OGTT is regarded as the gold standard method used to diagnose gestational diabetes mellitus (GDM) [2,3]. However, there have been few studies looking at low glucose levels following OGTT during pregnancy. In our clinical practice,

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we found that some pregnant women experience hypoglycaemia during the OGTT, defined as less than 3.5 mmol/L on at least one reading during the OGTT. The level of 3.5 mmol/L was used based on our hospital's practice which was designed in part from the self-monitoring of blood glucose (SMBG) levels used in the ACHOIS study [1]. There is little guidance in the literature as to the significance of such a result, or how this should be interpreted and managed.

The insulin sensitivity in pregnancy has been shown to decline in pregnancy, with a resulting increase in insulin release in normoglycaemic women on OGTT [4]. Kuhl described that women with GDM have "impaired first-phase insulin responses" which may result in "late occurrence of peak plasma insulin concentrations during an OGTT" [5]. This may describe the phenomenon that women who experience hypoglycaemia during an OGTT may in fact have undiagnosed GDM.

Several studies have shown an association between hypoglycaemia in pregnancy and poor perinatal outcomes [6–8]. On the other hand, Weissman et al. showed that hypoglycaemia was associated with reduced risk of GDM and lower association of poor perinatal outcomes [9]. We hence devised a study to determine whether women who experience hypoglycaemia on OGTT in pregnancy in fact have gestational diabetes, and whether there are implications in pregnancy outcomes.

2. Method

We recruited pregnant women between March 2015 and August 2016 who had a screening OGTT that resulted in a serum glucose level of less than 3.5 mmol/L at one or two hours, and if they did not meet the criteria for GDM on the fasting, one or two-hour serum glucose readings. Those who consented to the study were then asked to perform SMBG as an alternative method to diagnosing GDM [10]. All women were registered for delivery at Liverpool Hospital, a large tertiary referral hospital in New South Wales, Australia, servicing a population base of approximately 900,000 [11] people, of an ethnically diverse demographic. The women underwent the screening OGTT as part of their routine antenatal blood tests performed between 24 and 28 weeks' gestation. If they were deemed to have high risk factors (previous GDM, previous hyperglycaemia, maternal age ≥40 years, family history of diabetes mellitus, BMI > 35 kg/m^2, previous macrosomia, polycystic ovarian syndrome) they would undergo an OGTT at the first opportunity as identified by the antenatal staff, and then a second screening OGTT at 24–28 weeks.

As part of the routine screening OGTT, women fasted for at least 8 h and performed an OGTT the following morning. The OGTT consisted of a baseline fasting serum blood glucose level, followed by consumption of a 75 g glucose drink, then serum blood glucose levels at 1 h and 2 h post the glucose drink. Women who obtained a serum glucose level defined as <3.5 mmol/L at either 1- or 2-h post glucose load were flagged as having hypoglycaemia. Women who obtained a fasting glucose level of <3.5 mmol/L were not included in the study. These women were then contacted and asked to attend an appointment with an endocrinologist and consented for the study. They were also to attend an information session where they were provided with a glucometer and instruction on its use by a diabetes nurse educator. They were instructed to perform SMBG levels four times a day (fasting, 2-h post breakfast, lunch and dinner) for a fortnight. They were not advised to make any changes to their existing diet or exercise patterns. After the fortnight, the pregnant women then presented their SMBG for review by an endocrinologist to determine whether a diagnosis of GDM should be made. GDM was diagnosed if the women had >20% of total SMBG above target, or ≥4/14 (28.6%) of SMBG at either the fasting or post-meal times. This measure was based on research suggesting the use of SMBG for screening of GDM, particularly in situations where OGTT was not possible, such as resource-constrained settings [10] or post-bariatric surgery [12]. The SMBG targets applied at the time of the study were according to our local district protocol, which was based on the 1998 ADIPS criteria [13]. In our post-hoc analysis we used the SMBG treatment targets based on the current ADIPS [14] guidelines, see Table 1. Although not validated, 20% of total SMBG above target was determined as the diagnostic cut off as it was deemed to be a clinically significant percentage of elevations. It was also a conservative estimate which took into account the accuracy issues of using finger-prick SMBG compared to venous blood glucose levels used in an OGTT, which have been documented to have a variance in the range of 5–16% [15–17].

Women considered to have GDM based on SMBG were then given the same treatment program as pregnant women diagnosed with GDM in the traditional manner based on OGTT diagnostic criteria. Those who did not have elevated BGLs were advised that they did not have GDM and discharged from further review by the endocrinologist. We excluded women who did not meet the inclusion criteria or were unable or chose not to provide informed consent. Women with multiple pregnancy were also excluded.

Data was also collected from pregnant women who were registered to give birth at our centre in 2015. Data was collected from antenatal and birth records as well as results of the OGTT performed at the hospital's pathology laboratory.

Descriptive statistics including means, percentages and standard deviations were calculated. Demographic and outcome means were compared using the Chi-square test of independence for categorical variables and either the independent student *t*-test or one-way analysis of variance (ANOVA) for continuous variable data. Statistical significance

Table 1 – Capillary blood glucose targets for gestational diabetes mellitus (GDM) management.

	Fasting (mmol/L)	2 h after breakfast (mmol/L)	2 h after lunch (mmol/L)	2 h after dinner (mmol/L)
ADIPS 2014 [14]	≤5.0	≤6.7	≤6.7	≤6.7

was determined to be p-value < 0.05. Statistical analysis of the data was performed using IBM® SPSS® Statistics Version 25 (IBM Corporation, Armonk, New York, US).

3. Results

We identified 66 women who experienced hypoglycaemia on screening OGTT and were eligible to participate in the study. 52 out of 66 pregnant women consented and were recruited into the study, with 14 women declining to participate in the trial. Distribution of the OGTT serum glucose results of the 52 women who consented to participate in the study are shown in Fig. 1. The majority of women experienced hypoglycaemia at the 2-h result, with only one woman recording a result of 3.1 mmol/L at 1-h. The mean serum glucose result was 4.38 (±0.27)mmol/L at fasting, 5.91 (±1.39)mmol/L at 1-h and 2.9 (± 0.45)mmol/L at 2-h. 3 women presented for an early OGTT, with the other women in the study presenting between 24 and 28 weeks. One woman was lost to follow up between SMBG and delivery, however her SMBG results are still included in our analysis.

These 52 women with hypoglycaemia on OGTT (Group 1) were compared to 1249 pregnant women who presented to our centre and were not diagnosed with GDM (Group 2), as well as 544 pregnant women diagnosed with GDM (Group 3) at our centre over the same period. Demographic data of the three groups are shown in Table 2. There were significant differences in age, parity, pre-pregnancy BMI, booking weight, history of GDM macrosomia and family history of GDM between 3 groups. There were also significant differences in the ethnicities of East/South-East Asian, South Asian, Middle Eastern and Anglo-European represented between the 3 groups. When compared to women with normal glycaemia (Group 2), women in Group 1 had a higher booking weight and lower rate of macrosomia. On the other hand, women in Group 3 were older and were more likely to have a previous history of GDM when compared to women in Group 1. The ethnic backgrounds of women in Group 1 and Group 3 were also quite different (Table 2).

When these 52 women were asked to perform SMBG over a 2-week period, BGLs were mostly elevated at fasting time, with 50% (26/52) of women experiencing at least 4 out of 14 elevated fasting BGLs according to the current ADIPS BGL targets. There was an additional 4 women (8%) who had either elevated mealtime BGLs or total BGLs > 20%, making a total of 30 women who meet the diagnosis of GDM according to the ADIPS BGL targets. In practice, however, only 8 women (15%) were treated for GDM according to the local criteria at the time, as these were based on older criteria that was less stringent than the ADIPS BGL targets. 3 of these women (6%) were then managed with insulin. No women were managed with metformin. Only one woman experienced one episode of a BGL reading of <3.5 mmol/L during SMBG. Table 3 shows a comparison of the demographics of the eight women who were treated compared to the 44 women who performed SMBG and were not treated, showing there was a significant difference in age and history of GDM. In terms of outcomes, there were no significant differences.

Table 4 highlights the three groups in relation to pregnancy outcomes. When comparing Group 1 and Group 2, there were no significant differences in pregnancy outcomes of hypertension, pre-eclampsia, caesarean section rates, gestation, birthweight, neonatal intensive care unit admission, neonatal hypoglycaemia, death or congenital abnormalities. Similarly when comparing Group 1 to Group 3, they were not significantly different except in the outcome of having a higher rate of congenital abnormality (6% v 2%).

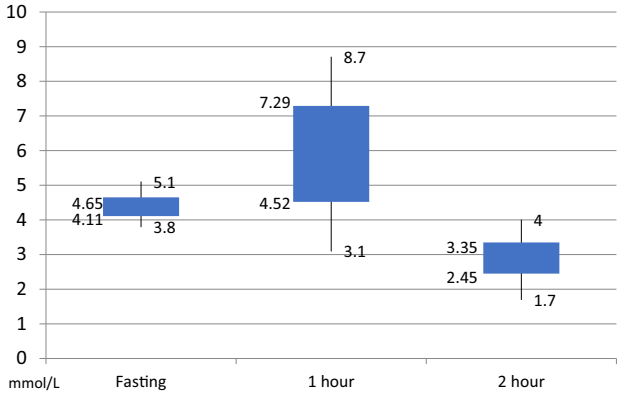

Fig. 1 – Serum glucose results of women who experience hypoglycaemia on the oral glucose tolerance test.

4. Discussion

Our findings indicate the Group 1 women appear to have similar demographic data and outcomes to Group 2 women. However, there were several differences in the characteristics between women in Group 1 and Group 3. Generally, the Group 1 women were of lower parity, and had a higher booking weight, and less likely to have a previous family history of GDM or history of macrosomia. They were more likely to be of Anglo-European or Middle Eastern and less likely to be of East or South-East Asian ethnicity.

Although women with low glucose levels on OGTT were not considered as having GDM, they could be at higher risk of developing GDM in the future given more than half went on to experience hyperglycaemic excursions during SMBG. We note that there seems to be a higher rate of congenital abnormality in Group 1 compared with the other 2 groups (6% v 1% v 2%), that was statistically significant for the Group 1 and 3 comparison, but not for the Group 1 v Group 2 comparison. The absolute number of cases for this outcome is small (3 out of the 52 births in Group 1) and may not represent a true effect. Looking at the cases in Group 1, two of them represent major congenital malformations (severe ventriculomegaly and eye opacity) with one case of a minor congenital malformation (hypospadias).

The implications of low glucose levels on OGTT in pregnant women has not been well studied nor has there been much documentation as to the management strategies that should be employed. It has been noted from some studies that insulin secretion in GDM women were higher compared to pregnant controls [18,19], but other studies have contradicted this finding [20]. In describing women with GDM, Kuhl

Table 2 – Demographic data of the three groups of pregnant women.

Demographic	Group 1: Hypoglycaemia on OGTT (n = 52)	SD/ %	Group 2: No GDM (n = 1249)	SD/ %	Group 3: GDM (n = 532)	SD/%	p comparing Group 1 and 2	p comparing Group 1 and 3
Age	29.92	±5.36	28.69	±5.46	31.54	±5.41	0.11	0.04
Parity	0.94	±1.07	0.98	±1.24	1.25	±1.43	0.81	0.13
Ethnicity (%)								
African	0	0%	32	3%	15	3%	0.64	0.38
East/South-East Asian	2	4%	200	16%	122	23%	0.02	<0.01
South Asian (including Indian, Pakistani, Sri Lankan)	4	8%	162	13%	111	21%	0.39	0.03
Pacific Islander	2	4%	74	6%	35	7%	0.77	0.76
Middle Eastern	18	35%	292	23%	107	20%	0.07	0.02
South/Central American	2	4%	21	2%	9	2%	0.23	0.26
Anglo-European	22	42%	442	35%	121	23%	0.31	<0.01
Aborigine	2	4%	26	2%	6	1%	0.31	0.16
Pre-pregnancy BMI	25.84	±5.59	25.41	±6.05	26.9	±6.75	0.61	0.27
Booking weight (kg)	77.69	±17.7	70.77	±18.3	70.05	±20.74	0.01	0.01
History of GDM (%)	2	4%	41	3%	134	25%	0.68	<0.001
Family history of diabetes	20	38%	542	43%	228	43%	1.00	1.00
Previous Macrosomia (%)	0	0%	92	7%	52	10%	0.046	0.01

Abbreviations: BMI = body mass index; GDM = gestational diabetes mellitus; OGTT = oral glucose tolerance test; SD = standard deviation.

Table 3 – Demographic and pregnancy outcomes between women who received treatment vs no treatment and had hypoglycaemia on OGTT.

Demographic	Women with hypoglycaemia on OGTT who received treatment (n = 8)	SD/%	Women with hypoglycaemia on GDM who did not receive treatment (n = 44)	SD/%	p
Age	33.00	±7.84	29.36	±4.69	0.04
Parity	1.38	±1.06	0.86	±1.07	0.96
Ethnicity (%)					
African	0	0%	0	0%	
East/South-East Asian	2	25%	0	0%	0.001
South Asian (including Indian, Pakistani, Sri Lankan)	0	0%	4	9%	0.38
Pacific Islander	0	0%	2	5%	0.54
Middle Eastern	2	25%	16	36%	0.54
South/Central American	0	0%	2	5%	0.54
Anglo-European	4	502%	18	41%	0.63
Aborigine	0	0%	2	5%	0.54
Pre-pregnancy BMI	24.47	±7.18	26.09	±5.31	0.89
Booking weight (kg)	77.69	±17.7	79.56	±17.27	0.43
History of GDM (%)	2	4%	0	0%	0.001
Family history of diabetes	20	38%	41	41%	0.27
Previous Macrosomia (%)	0	0%	0	0%	

Abbreviations: BMI = body mass index; GDM = gestational diabetes mellitus; OGTT = oral glucose tolerance test; SD = standard deviation.

first described the two phases of insulin secretion after an OGTT and that compared with normal pregnant controls, women with GDM had a reduced first phase insulin response, but a similar second phase insulin response. Importantly he described a "late occurrence of the peak plasma insulin concentrations" of GDM women in response to an OGTT. Kuhl also described an excessive secretion of proinsulin in women with GDM, which does not always return to normal postpartum [5]. Our hypothesis is that pregnant women who have either a delayed insulin secretory response or increased proinsulin secretion may go on to develop hypoglycaemia on an OGTT. Moreover, both Pratley [21] and Spellman [22] describe having impaired early insulin secretion as a marker of ß-cell failure and part of the pathogenesis for developing diabetes. Hence the delayed insulin secretion response causing hypoglycaemia in our study group may signal a population susceptible to developing gestational diabetes. In contrast, Cai et al. found that hypoglycaemia post OGTT in a non-pregnant Chinese population was associated with an increased insulin sensitivity and beta-cell function [23]. It would be interesting to see if these abnormalities persist post-partum, and whether these women are more likely to develop glucose intolerance in the future.

The strength of this study is to take a sample of women who have experienced hypoglycaemia and evaluate whether they are in fact experiencing hyperglycaemia or are normoglycaemic based on 2 weeks of SMBG. Furthermore this was mostly performed during the third trimester, a period which traditionally results in maximal insulin resistance [5]. Our findings showed that these women do not have worse pregnancy outcomes and hence there is no justification to recommend routine monitoring and treatment. However, these findings need to be confirmed in larger studies.

We acknowledge there are multiple limitations in this study. Firstly, capillary blood glucose testing on a glucometer is not a validated method to diagnose GDM. There are also questions as to the accuracy of using a glucometer to measure glucose levels, especially in pregnant women [16]. A study by Perera et al. on blood glucose meters in pregnancy showed that they were inaccurate when compared with plasma measurements and could vary by as much as 2 mmol/L [17]. Other limitations of using glucometers in measuring glucose levels in pregnancy as described by Negrato stem from strip factors, physical factors, patient factors and pharmacological factors [16]. In our study, Verio IQ meters were used, but the choice of the most appropriate meter during pregnancy remains contentious [24].

This study had a small sample size, and conducted in a single centre with a population that has a high GDM prevalence due to the population largely being comprised of ethnicities at high risk of GDM [25]. Furthermore, for those women who remained on target with their SMBG testing in the 2 weeks post study enrolment, we did not ascertain whether these women continued to remain normoglycaemic, or developed a similar frequency of hyperglycaemia as other women at a later stage of their pregnancy. It is also possible that the women after having performed 2 weeks of SMBGs made lifestyle changes which reduced their overall rate of outcomes.

A future area of research is whether all women with hypoglycaemia on OGTT are prone to glucose excursions compared to normoglycaemic or GDM pregnancies. For comparison we did not ask women without GDM on OGTT (i.e. Group 2) to do two weeks of SMBG. It is possible that women in Group 2 naturally have similar degrees and frequencies of SMBG level elevations compared to Group 1. A future direction of research could be to compare two weeks of SMBG in these two groups to see if there is any difference in SMBG levels.

More research is certainly required in this area to determine whether these findings are generalizable and applicable to pregnant women of a different demographic. Our results

Table 4 – Pregnancy outcomes of women with hypoglycaemia on OGTT compared with normoglycaemic and GDM pregnant women.

Outcome	Group 1 Hypoglycaemia on OGTT (n = 52)	SD/%	Group 2 No GDM (n = 1249)	SD/%	Group 3 GDM (n = 532)	SD/%	p Group 1 v Group 2	p Group 1 v Group 3
Hypertension	1	2%	36	3%	21	4%	1.00	0.35
Pre-eclampsia toxaemia	0	0%	18	1%	2	0%	1.00	0.51
Delivery mode								
Emergency caesarean section	2	4%	122	10%	56	11%	0.23	0.57
Elective caesarean section	5	10%	169	14%	106	20%	0.54	0.58
Induction	15	29%	250	20%	147	28%	0.16	0.18
Spontaneous normal vaginal delivery	29	56%	700	56%	213	40%	1.00	0.51
Death in utero	0	0%	0	0%	8	2%	n/a	n/a
Gestation	39.21	±1.75	39.37	±1.89	38.36	±3.00	0.58	0.15
Birthweight	3292	±493	3366	±548	3263	±551	0.34	0.06
Male gender	23	44%	613	49%	264	50%	0.57	0.81
Neonatal intensive care unit admission	5	10%	102	8%	83	16%	0.61	0.69
Hypoglycaemia	0	0%	20	2%	54	10%	1.00	0.49
Death	0	0%	6	0%	13	2%	1.00	0.71
Cognitive abnormality	3	6%	15	1%	13	2%	0.14	<0.001

Abbreviations: ADIPS = Australian Diabetes in Pregnancy Society; GDM = gestational diabetes mellitus; OGTT = oral glucose tolerance testing; SD = standard deviation.

seem to show that women who experience hypoglycaemia group affect a higher proportion of Anglo-European and fewer East/South-East Asian ethnicities.

5. Conclusion

Pregnant women who had hypoglycaemia following an oral glucose loading on OGTT, when asked to perform glucose monitoring, were often found to have elevated glucose readings However this group of women have no significant differences in pregnancy outcomes compared with women who had normoglycaemia on OGTT. Currently we do not have sufficient evidence to recommend routine SMBG for these women, but post-partum follow up of this group of women should be performed.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2018.11.018.

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