ORIGINAL ARTICLE

Journal of the ASEAN Federation of Endocrine Societies

Prevalence of Hypoglycaemia among Insulin-Treated Pregnant Women with Diabetes Who Achieved Tight Glycaemic Control*

Danish Ng,[1] Nurain Mohd Noor,[2] Sy Liang Yong[1]

[1]*Department of Medicine, Tengku Ampuan, Rahimah Hospital, Klang, Ministry of Health, Malaysia*
[2]*Department of Medicine, Putrajaya Hospital, Ministry of Health, Malaysia*

Abstract

Objectives. To determine the prevalence of hypoglycaemia using continuous glucose monitoring system (CGMS) among insulin-treated pregnant women with diabetes whose glycosylated haemoglobin (HbA1c) were <6.0% and identify the risk factors associated with hypoglycaemia occurrence.

Methodology. We conducted a cross-sectional study using 6-days CGMS to detect the prevalence of hypoglycaemia in 31 insulin-treated pregnant women with diabetes who achieved HbA1c <6.0%. Patients were required to log-keep their self-monitoring blood glucose (SMBG) readings and hypoglycaemia events.

Results. Eight women experienced confirmed hypoglycaemia with additional seven experienced relative hypoglycaemia, giving rise to prevalence rate of 45.2% (one had both confirmed and relative hypoglycaemia). Nine relative hypoglycaemia and 17 confirmed hypoglycaemic events were recorded. Sixteen (94%) out of 17 confirmed hypoglycaemia events recorded by CGMS were asymptomatic and were missed despite performing regular SMBG. Nocturnal hypoglycaemia events were recorded in seven women. Univariable analysis did not identify any association between conventional risk factors and hypoglycaemia events in our cohort.

Conclusion. Insulin-treated pregnant women with diabetes who achieved HbA1c <6.0% were associated with high prevalence of hypoglycaemia. Asymptomatic hypoglycaemia is common in our cohort and frequently missed despite regular SMBG. Present study did not identify any association between conventional risk factors and hypoglycaemia events in our cohort.

Key words: hypoglycaemia, continuous glucose monitoring system, pregnancy, diabetes mellitus

INTRODUCTION

Maternal hyperglycaemia is associated with increased risk of major malformations, pregnancy loss, macrosomia, birth complications, infant with excess adiposity and subsequently higher risk of developing obesity and metabolic syndrome as children.[1-4] Treatment to achieve normoglycaemia has been demonstrated to improve perinatal outcomes in numerous randomised studies.[5] The recommended glycosylated haemoglobin (HbA1C) target in pregnancy is less than 6.0% if this can be achieved without hypoglycaemia.[6] However, striving to achieve tight glycaemic control increases the risk of hypoglycaemia.[7] In a study on pregnant women with type 1 diabetes, data recording by continuous glucose monitoring system (CGMS) for 72 hours detected nocturnal hypoglycaemia (defined as interstitial glucose <2.8 mmol/L, recorded by CGMS) in up to 76% of the study population. The mean HbA1c level in their study population was 6.1±1.2%[8] Nielsen et al., in another study demonstrated that 45% of women with type 1 diabetes experienced at least one episode of severe hypoglycaemia during pregnancy. The authors defined hypoglycaemia as capillary blood glucose <4 mmol/L, and severe hypoglycaemia when the patients required help from another person to actively administer oral carbohydrate or injection of glucagon or glucose. The median HbA1c in women who experienced severe hypoglycaemia was 7.0% (interquartile range 5.9–10.9) in their study.[9] High incidence of hypoglycaemia was not only detected in women with type 1 diabetes, but also among women with gestational diabetes mellitus (GDM).[10] In the study, the authors defined hypoglycaemia as glucose <2.8 mmol/L, detected by either CGMS or glucometer. The reported incidence of hypoglycaemia differs greatly between studies mainly due to different study populations, methodological variation and used of different threshold to define hypoglycaemia.

ISSN 0857-1074 (Print) | eISSN 2308-118x (Online)
Printed in the Philippines

Received: October 14, 2018. Accepted: January 7, 2019.
Published online first: April 15, 2019.
https://doi.org/10.15605/jafes.034.01.06

Corresponding author: Danish Ng Oo Yee, MD
Department of Medicine, Tengku Ampuan, Rahimah Hospital
Jalan Langat 41200 Klang, Selangor, Ministry of Health, Malaysia
Tel. No.: +6016-6655691
E-mail: ooiyee78@hotmail.com
ORCiD: https://orcid.org/0000-0002-3454-8918

** This paper had been presented during Malaysian Endocrine and Metabolic Society Annual Congress 2017 in Kuala Lumpur, Malaysia on 20th May 2017.*

Mild hypoglycaemia may be inconvenient or frightening to patients whereas severe hypoglycaemia can lead to severe morbidity and death.[9,11] Frequent hypoglycaemia not only affect the mother, but has also been shown to be associated with intrauterine growth restriction.[6] Hence, a balance needs to be sought between achieving the targets to prevent complications due to maternal hyperglycaemia as well as avoiding maternal hypoglycaemia.

The tool traditionally used to treat and manage diabetes is self-monitoring of blood glucose (SMBG) using glucometer. However, intermittent SMBG using glucometer fails to provide complete insight on the pattern of glycaemia profiles with regards to the direction and recent history of the blood glucose level. A better appreciation and understanding of the effect of these two extremes, hyper- and hypoglycaemia in pregnancy, has been made possible by the advent of CGMS technology, which is able to provide a profile of glycaemic patterns throughout a 24-h period and has been shown to improve glycaemic control, reduce hypoglycaemia occurrence, lower birth weight and reduced risk of macrosomia compared to those managed using SMBG.[12-14] Continuous glucose monitoring (CGM) may also be particularly beneficial among those with hypoglycaemia unawareness, nocturnal hypoglycaemia and/or frequent hypoglycaemic episodes.[15,16]

Despite increasing numbers of investigators using this technology in pregnancy, there are limited studies that look into the occurrence of hypoglycaemia among pregnant women with diabetes.[8,10] A previous study had demonstrated an association between HbA1c level <6.5% and risk of severe hypoglycaemia during early pregnancy in type 1 diabetes.[7] Nevertheless, literature search revealed that, to date, none has looked into the prevalence of hypoglycaemia among insulin-treated pregnant women with diabetes when their HbA1c were <.6.0%. Hence, the present study aims to determine the prevalence of hypoglycaemia using CGMS among insulin-treated pregnant women with diabetes who achieved tight glycaemia control with HbA1c level <6.0%. This study also attempts to identify the risk factors associated with occurrence of hypoglycaemia.

METHODOLOGY

We conducted a cross-sectional study using CGMS (iPro™2 Professional CGM developed by Medtronic) to detect the prevalence of hypoglycaemia events among pregnant women with diabetes who achieved tight glycaemic control with HbA1c level of <6.0%. This study was carried out from June 2015 to December 2015. All pregnant women with diabetes who attended the follow up at Combined Endocrine-Obstetric Clinic Tengku Ampuan Rahimah Hospital, Klang and who had fulfilled the inclusion and exclusion criteria were recruited. The inclusion criteria were 1) diabetes in pregnancy including type 1 diabetes, type 2 diabetes and GDM, 2) on insulin therapy, of any dose, 3) HbA1C <6.0% and 4) age >18. The exclusion criteria were 1) known or suspected haemoglobinopathies, 2) renal failure with serum creatinine above the normal reference range, 3) recent blood transfusion within three months prior to the enrolment of the study, 4) not willing to check a minimum of four blood glucose readings each day and 5) decided to fast during Ramadan Month despite counselling regarding the risks.

The classification and diagnosis of diabetes followed were based on the guideline recommended by the American Diabetes Association.[17] GDM was defined as diabetes diagnosed in the second or third trimester of pregnancy that is not clearly overt diabetes, using "one-step" 75-gram oral glucose tolerance test with cut-off fasting plasma glucose values of 5.1 mmol/L and two hours of 8.5 mmol/L. HbA1c was measured using ion-exchange high performance liquid chromatography (HPLC), with National Glycohaemoglobin Standardisation Program (NGSP) and International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) reference system. No previous study has been performed to determine the prevalence of hypoglycaemia events among pregnant women with diabetes whose HbA1c's were treated to target of less than 6.0%. A relevant study was performed on 34 pregnant women with type 1 diabetes of any HbA1c levels where the prevalence of hypoglycaemia was reported as 76%.[8] In order to achieve 15% precision in estimating prevalence rate of 76%, 31 patients were recruited into present study.[18]

Out of the 229 women who were screened for eligibility of entering into the study, 46 women fulfilled the criteria. Eligible patients were informed about the study protocol and written informed consent was obtained prior to the commencement of the study. Thirty-seven women consented for the study. Patients were managed and counselled as per usual clinical practice including dietary advice, target weight gain, target glucose level, technicality of insulin injection and titration. Patients were encouraged to carry out daily usual routine during the six days of CGMS, including self-management of diabetes control. They were also oriented on frequency of capillary blood glucose testing using glucometer in order to calibrate the sensor data, log-keeping on the SMBG, food diary, physical activities, medications and other events (such as feeling of hypoglycaemic and/or hyperglycaemic symptoms, or illness). Following insertion of the CGMS device, interstitial glucose were recorded and stored every five minutes for the following six days. Upon completion of the study and after reports were generated, patients were educated regarding the effects of food, activities and medications on blood glucose levels and advised on adjustment if necessary. Six patients were excluded from the analysis because of withdrawal of consent (n=1), sensor manufacturing defect (n=1), steroid therapy (n=1) and dislodged sensor (n=3).

Criteria for discontinuation or withdrawal of patients were as in Supplement 1.

The following are the outcome variables and their corresponding definitions:[1,19,20]

1. Confirmed or documented hypoglycaemia was defined as blood glucose level of less than 3.0 mmol/L, recorded either by SMBG or CGMS (for at least 20 minutes).
2. Severe hypoglycaemia was defined as a hypoglycaemia event that requires assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.
3. Asymptomatic hypoglycaemia or hypoglycaemia unawareness was defined as a documented hypoglycaemia event not accompanied by typical symptoms of hypoglycaemia.

4. Relative hypoglycaemia was defined as an event during which the person with diabetes reports any of the typical symptoms of hypoglycaemia, and interprets those as indicative of hypoglycaemia, but with a measured blood glucose concentration ≥3.0 mmol/L.
5. Nocturnal hypoglycaemia was defined as a hypoglycaemia event that occurs between 00:00 and 06:00 hours.

The study had been approved by the Medical Research and Ethics Committee (MREC), Ministry of Health, Malaysia.

Statistical analysis

Demographic and baseline characteristics were expressed using mean and standard deviation (SD) for continuous variables (median with interquartile range were used for non-parametric variables). Test for normality was by using skewness and kurtosis. Numbers with proportions were used for categorical variables. Characteristics of the patients for categorical variables between group with hypoglycaemia and group without hypoglycaemia were compared using Fisher's Exact test; for continuous variables, independent-samples T test was used (Mann Whitney U test was used for non-parametric variables). Univariable analysis was used to identify the risk factors associated with occurrence of hypoglycaemia. The results were expressed as odd ratios (OD) and 95% confidence intervals (CI). The associations were considered to be significant if p value <0.05. Analyses of the data were made using the SPSS package version 23.

RESULTS

A total of 20 women with preexisting diabetes mellitus and 11 women with GDM were recruited into present study. Mean age of the overall cohort was 33.6±4.3 years. Malays formed the majority of the study cohort reflecting the ethnic composition of Malaysians' general population. The mean HbA1c at recruitment was 5.3%±0.5 (Table 1). The duration of disease was very short (≤3 years) in most of the patients except two (six and eight years respectively). Majority of the women (n=26) were on basal boluses, of these 22 women on short acting human insulin and neutral protamine hagedorn (NPH), three women on rapid acting analogues (two aspart and one lispro) and NPH, one woman on short acting human insulin and detemir . The remaining patients were on basal (n=3, all on NPH) and basal plus two (n=2, both on NPH and short acting human insulin).

During the study period, there were eight women who experienced confirmed hypoglycaemia and seven women who experienced relative hypoglycaemia with capillary glucose levels ranges from 3.3-3.8 mmol/L, giving rise to prevalence rate of 45.2% (14 women, as one had both confirmed and relative hypoglycaemia events). Nine events of relative hypoglycaemia and 17 confirmed hypoglycaemic events were recorded during the study periods with the nadir glucose level below the threshold of detection value by CGMS, i.e., <2.2 mmol/L. Of all the 17 confirmed hypoglycaemia events recorded by CMGS, almost all (94%) were asymptomatic and were missed despite performing regular SMBG daily. Patients experienced a mean of 1.9±1.1 episodes

Table 1. Baseline clinical data in 31 diabetes women according to occurrence of hypoglycaemia in pregnancy

	All (n=31)	Hypo (n=14)	No hypo (n=17)	*p* value
Age (in years)	33.6±4.3	34.5±3.7	32.8±4.6	0.283
Ethnicity				
1. Malay	17 (54.8%)	11 (78.6%)	6 (35.3%)	
2. Non-Malay (Chinese, Indian, Others)	14 (45.2%)	3 (21.4%)	11 (64.7%)	0.029
BMI (kg/m^2)	30.8 (5.9)	29.9 (4.7)	31.0 (5.1)	0.427*
Gestational age (weeks)	28.0±4.5	28.0±4.3	28.0±4.8	1.000
Trimester				
1. Second	12 (38.7%)	6 (42.9%)	6 (35.3%)	
2. Third	19 (61.3%)	8 (57.1%)	11 (64.7%)	0.724
Haemoglobin (g/L)	117±9	118±11	117±8	0.718
BP (mmHg)				
1. Systolic	117.5±12.2	119.1±8.6	116.1±14.7	0.491
2. Diastolic	74.0±9.8	73.6±8.6	74.4±10.9	0.845
Type of diabetes				
1. Preexisting #	20 (64.5%)	10 (71.4%)	10 (58.8%)	
2. Gestational	11 (35.5%)	4 (28.6%)	7 (41.2%)	0.707
Type of insulin				
1. Human insulin	27 (87.1%)	10 (71.4%)	17 (100.0%)	
2. Insulin analogue	4 (12.9%)	4 (28.6%)	0 (0%)	0.032
Total insulin dose (unit/day)	45.5±22.4	46.9±21.2	44.4±24.0	0.763
Insulin dose (unit/kg)	0.6±0.3	0.6±0.3	0.5±0.2	0.403
HbA1c (%)	5.3±0.5	5.4±0.5	5.3±0.4	0.377
HbA1c				
1. <5.0%	7 (22.6%)	2 (14.3%)	5 (29.4%)	
2. 5.0% – 5.9%	24 (77.4%)	12 (85.7%)	12 (70.6%)	0.412

Abbreviation: Hypo= Hypoglycaemia; N= number; HbA1c=Haemoglobin A1c; BP= blood pressure; BMI= body mass index
Categorical variables are expressed as number (percentage)
Continuous variables are expressed as means±standard deviation
* Non-parametric variables are expressed as median (interquartile range)
# All were type 2 diabetes

of hypoglycaemia during the six days study period. The mean duration of hypoglycaemia experienced by each patient during the six days study period was 48.8±29.2 minutes. None of the women had severe hypoglycaemia. Nocturnal hypoglycaemic events were recorded in seven women (three experienced both daytime and nocturnal hypoglycaemia, whereas four experienced only nocturnal hypoglycaemia). The remaining seven women experienced only daytime hypoglycaemia. There were five women who did not comply with regular SMBG necessary for calibration of the CGMS resulting in loss of some CGMS data.

There was no significant difference between women who developed hypoglycaemia compared to those who did not with regards to baseline characteristics include age, body mass index, gestational age, recruitment HbA1c level, haemoglobin level, systolic blood pressure and diastolic blood pressure (Table 1). Malay ethnicity appeared to be associated with higher proportion of hypoglycaemia rate.

None of the women was in their first trimester, 12 (38.7%) were in the second trimester and 19 were (61.3%) in the third trimester. Six out of 12 women (50.0%) in the second trimester compared to eight out of 19 women (42.1%) in the third trimester experienced hypoglycaemia (p=0.724). There was no significant difference between preexisting diabetes mellitus who experienced hypoglycaemia when compared to GDM (p=0.707). There were only four women on insulin analogue and all of them experienced hypoglycaemia during the study period. Women who experienced hypoglycaemia used higher daily insulin dose compared to those who did not. However, this difference was not statistically significant (0.6±0.3 vs. 0.5±0.2 unit/kg, p=0.403).

Univariable analysis demonstrated a crude association between ethnicity and hypoglycaemia events (OR 6.72; 95% CI 1.33-33.91; p=0.021). However, the other conventional risk factors of hypoglycaemia did not significantly relate with occurrence of hypoglycaemia (Table 2).

Table 2. Factors associated with the risk of hypoglycaemia event

	Univariable analysis	
	Crude OR (95% CI)	***p* value**
Age	1.10 (0.92-1.32)	0.277
Ethnicity		
Malay	6.72 (1.33-33.91)	0.021
Non-Malay	1.00	
BMI	0.99 (0.86-1.11)	0.740
Trimester		
Second	1.38 (0.32-5.88)	0.667
Third	1.00	
Type of diabetes		
Preexisting	1.75 (0.39-7.92)	0.467
Gestational	1.00	
Duration of diabetes	0.79 (0.48-1.30)	0.349
Mean insulin injection/day	1.42 (0.58-3.44)	0.444
Insulin dose (unit/kg)	3.46 (0.20-58.78)	0.390
HbA1c categories		
<5 %	0.4 (0.07-2.48)	0.325
5.0-5.9 %	1.00	

Abbreviation: OR = odd ratios; CI = confidence intervals; BMI= body mass index; HbA1c=Haemoglobin A1c
Type of insulin was not analysed due to zero cell count

DISCUSSION

To our knowledge, this is the first study that evaluates the prevalence of hypoglycaemia among pregnant women with diabetes who achieved a tight glycaemic control with HbA1c <6.0%. Hence, all trimesters of pregnant women and all types of diabetes were included in order to provide an overall picture of the prevalence. This study demonstrated high prevalence of hypoglycaemia among insulin-treated pregnant women with diabetes when their HbA1c levels were less than 6.0%. The prevalence rate in current study is comparable with other studies among cohort of type 1 diabetes during their early pregnancy, where the risk was well recognised to be highest.[7,9,21,22]

The present study adopted blood glucose level <3.0 mmol/L for definition of hypoglycaemia, as per recommendation of the International Hypoglycaemia Study Group.[20] This threshold value has been agreed to have serious clinical and health-economic consequences. A uniform hypoglycaemia definition would also permit meta-analysis of various studies as a statistical tool to increase power when comparing various interventions. Previous studies used difference threshold values ranges from 2.8 mmol/L to 3.9 mmol/L to define hypoglycaemia, making comparison between studies very challenging.[8-10,22-24]

The gold standard for the measurement of glucose traditionally is with plasma glucose using a high-precision enzymatic laboratory method (glucose oxidase, glucose dehydrogenase, or hexokinase).[25] Since 1987, however, glucometers have been standardised to report plasma-adjusted values within 15% from those obtained by a laboratory reference method and are now recognised and widely used as the standard of care for adjustment of therapy.[25,26] The current study adopted CGMS in additional to a glucometer as the method of detection for hypoglycaemia. Interstitial glucose measured by CGMS is highly correlated with meter glucose (r=0.91–0.92) with the overall mean absolute relative difference of 11.0%.[27-30]

Our study recorded 94% of hypoglycaemia unawareness including nocturnal hypoglycaemia, which were missed despite performing regular intermittent SMBG. The high incidence of hypoglycaemia unawareness during pregnancy may relate, in part, to the loss of counterregulatory hormones reported in women with preexisting diabetes, particularly growth hormone and epinephrine.[31,32] With the advent of CGMS which can reveal hypoglycaemia unrecognised by intermittent blood glucose determinations, this can provide a useful tool to guide clinicians in adjusting diabetes therapy and to guide patients to improve adherence to the management regimes. On the basis of the additional information provided by continuous monitoring that recorded hypoglycaemic events, the therapeutic regimen (insulin therapy, diet adjustment, or both) was changed in seven (88%) of the eight women. Previous studies have shown improvements in pregnancy outcomes and duration of hypoglycaemic episodes with CGM.[8,10,13,33] However, the present study was not designed to explore this.

The incidence of hypoglycaemia has been reported in previous studies to be highest in early pregnancy and lowest in the third trimester.[7,34-36] It has been suggested

that pregnancy related hyperemesis gravidarum, increased insulin sensitivity during early pregnancy, insulin independent feto-placental glucose uptake, over-insulinisation of previously poorly controlled diabetes, a transient decline in progesterone secretion during the late first trimester, luteo-placental shift in progesterone secretion, or other hormonal shifts might be the contributing factors for severe hypoglycaemia in early pregnancy.

Unexpectedly, none of the woman in current study was in their early pregnancy stage at recruitment, which could reflect the time interval needed to intensify the treatment regime before achieved target HbA1c <6.0%, i.e., most women would have surpassed the first trimester period when they have achieved their HbA1c target. Determining the prevalence rate of hypoglycaemia without including this high-risk category will definitely underestimate the actual prevalence in our patients' cohort. Besides, it also weakened the power to detect any association between gestational age and hypoglycaemia occurrence.

A HbA1c level of less than 6.5% has been shown to be associated with risk of hypoglycaemia.[7] However, in the current study, it appears that when HbA1c was below 6.0%, any further reduction of HbA1c did not predict further risk of hypoglycaemia.

Among those pregnant women with type 1 diabetes, it has been reported that a 10 years' longer diabetes duration was associated with 1.6 (95% CI 1.0-2.4) odds of developing severe hypoglycaemia.[7] However, none of our study patients had type 1 diabetes and the majority of them had very short disease duration. Hence, the present study did not demonstrate similar association.

Only four women were on insulin analogues and their insulin regimes were changed prior to the study recruitment as they experienced hypoglycaemia when they were treated with human insulin. It appeared that they continued to experience hypoglycaemia despite being shifted to insulin analogues. However, there is no data available to compare the relationship between changing treatment regime with duration and severity of hypoglycaemia. A recent randomised trial compared prandial insulin aspart with human insulin in type 1 diabetes either switching them preconceptionally or during early pregnancy demonstrated trends toward improved risk of severe hypoglycaemia in the aspart group but the difference was not statistically significant.[22,23] More importantly, switching to insulin analogues after human insulin treatment during pregnancy did not seem to worsen the risk of hypoglycaemia.[22,37]

Evers et al., demonstrated in their study that a daily insulin dose 0.1 unit/kg or higher were risk indicators predictive for severe hypoglycaemia during the first trimester.[7] The current study did not demonstrate a similar association among those women during their second and third trimesters. Besides, the mean daily insulin dose used in their study (0.7±0.3 unit/kg) was also higher compared to our study population (0.6±0.3 unit/kg), which might predispose their study cohorts to higher hypoglycaemia risk.

Others possible predictors for hypoglycaemia in pregnancy are history of severe hypoglycaemia pre-pregnancy and hypoglycaemic unawareness.[9,32,38] None of our study patients with preexisting diabetes mellitus has a history of severe hypoglycaemia pre-pregnancy.

The sample size recruited in the present study, which was calculated based on prevalence rate from the previous relevant study, was a major limiting factor due to the cost of CGMS. Consequently, the power to detect a relationship between various variables and hypoglycaemia may have been too small. For the same reason, we did not pursue with multivariable analysis. Besides, sample size calculated was based upon a study among type 1 diabetes with a different cut-off definition for hypoglycaemia. Future studies to identify the risk factors associated with hypoglycaemia in this cohort of patients should consider focusing on the very high-risk group, i.e., type 1 diabetes in their early pregnancy. Further research should also study maternal and neonatal outcomes in order to elucidate how the benefits of strict glycaemic control can be balanced with the markedly increased risk of hypoglycaemia during pregnancy. In order to maintain near-normoglycaemic state without episodes of hypoglycaemia, it is of utmost importance that besides considering to relax the strict glycaemic target, patients at risk should receive appropriate self-management education including carbohydrate counting with clear insulin dose adjustment instruction, risk of hypoglycaemia unawareness and more frequent SMBG including midnight glucose monitoring for those at risk of nocturnal hypoglycaemia. Another approach will be utilisation of CGMS technology, whenever it is feasible to discover the occurrence of hypoglycaemia especially amongst patients with preexisting diabetes mellitus. However, the cost of CGMS will be the limiting factor.

CONCLUSION

In conclusion, this study demonstrated that insulin-treated pregnant women with diabetes who achieved HbA1c <6.0% were associated with high prevalence of hypoglycaemia. Almost all (94%) of the confirmed hypoglycaemia events were asymptomatic and were missed despite performing regular SMBG. The conventional risk factors of hypoglycaemia did not significantly related with occurrence of hypoglycaemia in the current study cohort.

Acknowledgments
The authors wish to thank National Institutes of Health Malaysia for rewarding the research funding and National Clinical Research Centre for rewarding the research grant and providing statistical assistance. We also extend our sincere appreciation to the Obstetrics and Gynaecology Department for their collaboration to allow the research to be carried out.

The authors would like to thank the Director General of Health Malaysia for his permission to publish this paper. This paper had been presented during Malaysian Endocrine and Metabolic Society Annual Congress 2017.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure
The authors declared no conflict of interest.

Funding Source
The research has been funded by the National Institutes of Health Malaysia and National Clinical Research Centre.

References

1. Kitzmiller JL, Block JM, Brown FM, et al. Managing preexisting diabetes for pregnancy: Summary of evidence and consensus recommendations for care. Diabetes Care. 2008;31(5):1060-79. PMID: 18445730. PMCID: PMC2930883. https://doi.org/10.2337/dc08-9020.
2. HAPO Study Cooperative Research Group, Metzger BE, Lowe LP, et al. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med. 2008;358(19):1991-2002. PMID: 18463375. https://doi.org/10.1056/NEJMoa0707943.
3. Group HSCR. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study: Associations with neonatal anthropometrics. Diabetes. 2009;58(2):453-9. PMID: 19011170. PMCID: PMC2628620. https://doi.org/10.2337/db08-1112.
4. Boney CM, Verma A, Tucker R, Vohr BR. Metabolic syndrome in childhood: Association with birth weight, maternal obesity, and gestational diabetes mellitus. Pediatrics. 2005;115(3):e290-6. PMID: 15741354. https://doi.org/10.1542/peds.2004-1808.
5. Hartling L, Dryden DM, Guthrie A, Muise M, Vandermeer B, Donovan L. Benefits and harms of treating gestational diabetes mellitus: A systematic review and meta-analysis for the U.S. Preventive Services Task Force and the National Institutes of Health Office of Medical Applications of Research. Ann Intern Med 2013;159(2):123-9. PMID: 23712381. https://doi.org/10.7326/0003-4819-159-2-201307160-00661.
6. American Diabetes Association. (12) Management of diabetes in pregnancy. Diabetes Care. 2015;38 Suppl:S77-9. PMID: 25537713. https://doi.org/10.2337/dc15-S015.
7. Evers IM, ter Braak EW, de Valk HW, van Der Schoot B, Janssen N, Visser GH. Risk indicators predictive for severe hypoglycemia during the first trimester of type 1 diabetic pregnancy. Diabetes are 2002;25(3):554-9. PMID: 11874946.
8. Yogev Y, Chen R, Ben-Haroush A, Phillip M, Jovanovic L, Hod M. Continuous glucose monitoring for the evaluation of gravid women with type 1 diabetes mellitus. Obstet Gynecol. 2003;101(4):633-8. PMID: 12681863.
9. Nielsen LR, Pedersen-Bjergaard U, Thorsteinsson B, Johansen M, Damm P, Mathiesen ER. Hypoglycemia in pregnant women with type 1 diabetes: Predictors and role of metabolic control. Diabetes Care. 2008;31(1):9-14. PMID: 17909091. https://doi.org/10.2337/dc07-1066.
10. Chen R, Yogev Y, Ben-Haroush A, Jovanovic L, Hod M, Phillip M. Continuous glucose monitoring for the evaluation and improved control of gestational diabetes mellitus. J Matern Fetal Neonatal Med 2003;14(4):256-60. PMID: 14738172. https://doi.org/10.1080/jmf.14.4.256.260.
11. Shafiee G, Mohajeri-Tehrani M, Pajouhi M, Larijani B. The importance of hypoglycemia in diabetic patients. J Diabetes Metab Disord. 2012;11:17. https://doi.org/10.1186/2251-6581-11-17.
12. Juvenile Diabetes Research foundation Continuous Glucose Monitoring Study group, Tamborlane WV, Beck RW, et al. Continuous glucose monitoring and intensive treatment of type 1 diabetes. N Engl J Med 2008;359(14):1464-76. PMID: 18779236. https://doi.org/10.1056/NEJMoa0805017.
13. Murphy HR, Rayman G, Lewis K, et al. Effectiveness of continuous glucose monitoring in pregnant women with diabetes: Randomised clinical trial. BMJ. 2008;337:a1680. PMID: 18818254. PMCID: PMC2563261. https://doi.org/10.1136/bmj.a1680.
14. Battelino T, Phillip M, Bratina N, Nimri R, Oskarsson P, Bolinder J. Effect of continuous glucose monitoring on hypoglycemia in type 1 diabetes. Diabetes Care. 2011;34(4):795-800. PMID: 21335621. PMCID: PMC3064030. https://doi.org/10.2337/dc10-1989.
15. Blevins TC, Bode BW, Garg SK, et al. Statement by the American Association of Clinical Endocrinologists Consensus Panel on continuous glucose monitoring. Endocr Pract. 2010;16(5):730-45. PMID: 21356637. https://doi.org/10.4158/EP.16.5.730.
16. American Diabetes A. (6) Glycemic targets. Diabetes Care. 2015;38 Suppl:S33-40. PMID: 25537705. https://doi.org/10.2337/dc15-S009.
17. American Diabetes Association. (2) Classification and diagnosis of diabetes. Diabetes Care. 2015;38 Suppl:S8-16. PMID: 25537714. https://doi.org/10.2337/dc15-S005.
18. Naing L Winn T, Rusli BN. Practical issues in calculating the sample size for prevalence studies. Arch Orofac Sci. 2006;1(1):9-14.
19. Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and diabetes: A report of a workgroup of the American Diabetes Association and the Endocrine Society. Diabetes Care. 2013;36(5):1384-95. PMID: 23589542. PMCID: PMC3631867. https://doi.org10.2337/dc12-2480.
20. International Hypoglycaemia Study G. Glucose concentrations of less than 3.0 mmol/L (54 mg/dL) should be reported in clinical trials: A joint position statement of the American Diabetes Association and the European Association for the study of diabetes. Diabetes Care. 2017;40(1):155-7. PMID: 27872155. https://doi.org/10.2337/dc16-2215.
21. Robertson H, Pearson DWM, Gold AE. Severe hypoglycaemia during pregnancy in women with type 1 diabetes is common and planning pregnancy does not decrease the risk. Diabet Med. 2009;26(8):824-6. https://doi.org/10.1111/j.1464-5491.2009.02769.x.
22. Heller S, Damm P, Mersebach H, et al. Hypoglycemia in type 1 diabetic pregnancy: Role of preconception insulin aspart treatment in a randomized study. Diabetes Care. 2010;33(3):473-7. PMID: 20007944. PMCID: PMC2827491. https://doi.org/10.2337/dc09-1605.
23. Mathiesen ER, Kinsley B, Amiel SA, et al. Maternal glycemic control and hypoglycemia in type 1 diabetic pregnancy: A randomized trial of insulin aspart versus human insulin in 322 pregnant women. Diabetes Care. 2007;30(4):771-6. PMID: 17392539. https://doi.org/10.2337/dc06-1887.
24. Ringholm L, Pedersen-Bjergaard U, Thorsteinsson B, Damm P, Mathiesen ER. Hypoglycaemia during pregnancy in women with type 1 diabetes. Diabet Med. 2012;29(5):558-66. PMID: 22313112. https://doi.org/10.1111/j.1464-5491.2012.03604.x.
25. Sacks DB, Arnold M, Bakris GL, et al. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Diabetes Care. 2011;34(6):e61-99. PMID: 21617108. PMCID: PMC3114322. https://doi.org/10.2337/dc11-9998.
26. American Diabetes Association. Standards of medical care in diabetes--2008. Diabetes Care. 2008;31(Suppl 1):S12-54. PMID: 18165335. https://doi.org/ 10.2337/dc08-S012.
27. Medtronic MiniMed I. iPro2 user guide, 2016. Available from https://www.medtronicdiabetes.com/sites/default/files/library/download-library/user-guides/iPro2-with-Enlite-User-Guide.pdf.
28. Kovatchev B, Anderson S, Heinemann L, Clarke W. Comparison of the numerical and clinical accuracy of four continuous glucose monitors. Diabetes Care. 2008;31(6):1160-4. PMID: 18339974. PMCID: PMC4607511.NIHMSID: NIHMS725705.https://doi.org/10.2337/dc07-2401.
29. Gross TM, Bode BW, Einhorn D, et al. Performance evaluation of the MiniMed continuous glucose monitoring system during patient home use. Diabetes Technol Ther. 2000;2(1):49-56. PMID: 11467320. https://doi.org/ 10.1089/152091500316737.
30. Gross TM, Ter Veer A. Continuous glucose monitoring in previously unstudied population subgroups. Diabetes Technol Ther. 2000;2(Suppl 1):S27-34. PMID: 11469629.
31. Rossi G, Lapaczewski P, Diamond MP, Jacob RJ, Shulman GI, Sherwin RS. Inhibitory effect of pregnancy on counterregulatory hormone responses to hypoglycemia in awake rat. Diabetes. 1993;42(10):1440-5. PMID: 8375583.
32. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, Thompson D, Berger H, et al. Diabetes and pregnancy. Can J Diabetes 2013;37 (Suppl 1):S168-83. PMID: 24070943. https://doi.org/10.1016/j.jcjd.2013.01.044.
33. Bode B, Gross K, Rikalo N, et al. Alarms based on real-time sensor glucose values alert patients to hypo- and hyperglycemia: The guardian continuous monitoring system. Diabetes Technol Ther. 2004;6(2):105-13. PMID: 15117576. https://doi.org/10.1089/152091504773731285.
34. Keely E, Barbour LA. Management of diabetes in pregnancy. Available from https://www.ncbi.nlm.nih.gov/books/NBK279010/. Accessed 14 August 2015. Endotext [Internet]. South Dartmouth (MA):2000.
35. Rosenn BM, Miodovnik M, Holcberg G, Khoury JC, Siddiqi TA. Hypoglycemia: The price of intensive insulin therapy for pregnant women with insulin-dependent diabetes mellitus. Obstet Gynecol. 1995;85(3):417-22. PMID: 7862383. https://doi.org/10.1016/0029-7844(94)00415-A.
36. Jovanovic L, Knopp RH, Brown Z, et al. Declining insulin requirement in the late first trimester of diabetic pregnancy. Diabetes Care. 2001;24(7):1130-6. PMID: 11423491.
37. Garg SK, Frias JP, Anil S, Gottlieb PA, MacKenzie T, Jackson WE. Insulin lispro therapy in pregnancies complicated by type 1 diabetes: Glycemic control and maternal and fetal outcomes. Endocr Pract. 2003;9(3):187-93. PMID: 12917059. https://doi.org/10.4158/EP.9.3.187.
38. Nielsen LR, Pedersen-Bjergaard U, Thorsteinsson B, Boomsma F, Damm P, Mathiesen ER. Severe hypoglycaemia during pregnancy in women with type 1 diabetes: Possible role of renin-angiotensin system activity? Diabetes Res Clin Pract. 2009;84(1):61-7. PMID: 19188000. https://doi.org/10.1016/j.diabres.2009.01.006.

SUPPLEMENT 1

Criteria for discontinuation or withdrawal of a patient

1. Experience local irritation such as redness, pain or swelling at the site of sensor insertion and iPro™2 attachment site
2. Experience allergic reaction to adhesive tape
3. Lost to follow up. The patient did not return to the clinic and attempts to contact the patient were unsuccessful.
4. Voluntary withdrawal. The patient wishes to withdraw from the study. The reason of withdrawal, if provided, will be recorded.
5. Patient goes into labour, regardless of stage of labour
6. Patient admitted to hospital for reasons that deems likely to affect glucose control such as infection, poor oral intake, treatment with steroid
7. Miscarriage or intrauterine demise

Note: Data from discontinued or withdrawn women were not interpreted. Discontinued or withdrawn women were followed up as their routine clinic visit as per scheduled. Discontinued or withdrawn women were replaced.