

# PLOS ONE

## Continuous glucose monitoring in obese pregnant women with no hyperglycemia on glucose tolerance test --Manuscript Draft--

<b>Manuscript Number:</b>	PONE-D-20-32574
<b>Article Type:</b>	Research Article
<b>Full Title:</b>	Continuous glucose monitoring in obese pregnant women with no hyperglycemia on glucose tolerance test
<b>Short Title:</b>	Continuous glucose monitoring in obese pregnant women
<b>Corresponding Author:</b>	Daiane de Oliveira de Oliveira Pereira Vergani, MS University of Caxias do Sul Caxias do sul, Rio Grande do Sul BRAZIL
<b>Keywords:</b>	obesity; pregnancy, high-risk; hyperglycemia
<b>Abstract:</b>	<p><b>Objective:</b> The objective of the present study was to compare 24-hour glycemic levels between obese pregnant women with normal glucose tolerance and non-obese pregnant women. <b>Methods:</b> In the present observational, longitudinal study, continuous glucose monitoring was performed in obese pregnant women with normal oral glucose tolerance test with 75 g of glucose between the 24<sup>th</sup> and the 28<sup>th</sup> gestational weeks. The control group (CG) consisted of pregnant women with normal weight who were selected by matching the maternal age and parity with the same characteristics of the obese group (OG). Glucose measurements were obtained during 72 hours. <b>Results:</b> Both the groups were balanced in terms of baseline characteristics (age: 33.5 [28.7–36.0] vs. 32.0 [26.0–34.5] years, <math>p=0.5</math> and length of pregnancy: 25.0 [24.0–25.0] vs. 25.5 [24.0–28.0] weeks, <math>p=0.6</math> in the CG and in the OG, respectively). Pre-breakfast glycemic levels were <math>77.77 \pm 10.55</math> mg/dL in the CG and <math>82.02 \pm 11.06</math> mg/dL in the OG (<math>p&lt;0.01</math>). Glycemic levels at 2 hours after breakfast were <math>87.31 \pm 13.10</math> mg/dL in the CG and <math>93.48 \pm 18.74</math> mg/dL in the OG (<math>p&lt;0.001</math>). Daytime blood glucose levels were <math>87.6 \pm 15.4</math> vs. <math>93.1 \pm 18.3</math> mg/dL (<math>p&lt;0.001</math>) and nighttime blood glucose levels were <math>79.3 \pm 15.8</math> vs. <math>84.7 \pm 16.3</math> mg/dL (<math>p&lt;0.001</math>) in the CG and in the OG, respectively. The 24-hour, daytime, and nighttime values of the area under the curve were higher in the OG when compared with the CG (<math>85.1 \pm 0.16</math> vs. <math>87.9 \pm 0.12</math>, <math>65.6 \pm 0.14</math> vs. <math>67.5 \pm 0.10</math>, <math>19.5 \pm 0.07</math> vs. <math>20.4 \pm 0.05</math>, respectively; <math>p&lt;0.001</math>). <b>Conclusion:</b> The results of the present study showed that obesity in pregnancy was associated with higher glycemic levels even in the presence of normal findings on glucose tolerance test.</p>
<b>Order of Authors:</b>	Rosa Maria Rahmi Priscila de Oliveira Luciano Selistre Paulo Cury Rezende Gabriela Neuvald Pezzella Pâmela Antoniazzi dos Santos Daiane de Oliveira de Oliveira Pereira Vergani, MS Sônia Regina Cabral Madi José Mauro Madi
<b>Additional Information:</b>	
<b>Question</b>	<b>Response</b>
<b>Financial Disclosure</b>	The authors received no specific funding for this work.
Enter a financial disclosure statement that	

describes the sources of funding for the work included in this submission. Review the [submission guidelines](#) for detailed requirements. View published research articles from [PLOS ONE](#) for specific examples.

This statement is required for submission and **will appear in the published article** if the submission is accepted. Please make sure it is accurate.

#### Unfunded studies

Enter: *The author(s) received no specific funding for this work.*

#### Funded studies

Enter a statement with the following details:

- Initials of the authors who received each award
- Grant numbers awarded to each author
- The full name of each funder
- URL of each funder website
- Did the sponsors or funders play any role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript?
- **NO** - Include this sentence at the end of your statement: *The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.*
- **YES** - Specify the role(s) played.

\* typeset

#### Competing Interests

Use the instructions below to enter a competing interest statement for this submission. On behalf of all authors, disclose any [competing interests](#) that could be perceived to bias this work—acknowledging all financial support and any other relevant financial or non-financial competing interests.

This statement **will appear in the published article** if the submission is accepted. Please make sure it is accurate. View published research articles from [PLOS ONE](#) for specific examples.

The authors have declared that no competing interests exist.

**NO authors have competing interests**

Enter: *The authors have declared that no competing interests exist.*

**Authors with competing interests**

Enter competing interest details beginning with this statement:

*I have read the journal's policy and the authors of this manuscript have the following competing interests: [insert competing interests here]*

\* typeset

**Ethics Statement**

Enter an ethics statement for this submission. This statement is required if the study involved:

- Human participants
- Human specimens or tissue
- Vertebrate animals or cephalopods
- Vertebrate embryos or tissues
- Field research

Write "N/A" if the submission does not require an ethics statement.

General guidance is provided below. Consult the [submission guidelines](#) for detailed instructions. **Make sure that all information entered here is included in the Methods section of the manuscript.**

Institution: Universidade de Caxias do Sul-RS-Brazil

Approval number: 73901317.7.0000.5341

Form of consent obtained: The participants signed the informed consent document before taking part in study procedures.

**Format for specific study types**

**Human Subject Research (involving human participants and/or tissue)**

- Give the name of the institutional review board or ethics committee that approved the study
- Include the approval number and/or a statement indicating approval of this research
- Indicate the form of consent obtained (written/oral) or the reason that consent was not obtained (e.g. the data were analyzed anonymously)

**Animal Research (involving vertebrate animals, embryos or tissues)**

- Provide the name of the Institutional Animal Care and Use Committee (IACUC) or other relevant ethics board that reviewed the study protocol, and indicate whether they approved this research or granted a formal waiver of ethical approval
- Include an approval number if one was obtained
- If the study involved *non-human primates*, add *additional details* about animal welfare and steps taken to ameliorate suffering
- If anesthesia, euthanasia, or any kind of animal sacrifice is part of the study, include briefly which substances and/or methods were applied

**Field Research**

Include the following details if this study involves the collection of plant, animal, or other materials from a natural setting:

- Field permit number
- Name of the institution or relevant body that granted permission

**Data Availability**

Authors are required to make all data underlying the findings described fully available, without restriction, and from the time of publication. PLOS allows rare exceptions to address legal and ethical concerns. See the [PLOS Data Policy](#) and [FAQ](#) for detailed information.

Yes - all data are fully available without restriction

A Data Availability Statement describing where the data can be found is required at submission. Your answers to this question constitute the Data Availability Statement and **will be published in the article**, if accepted.

**Important:** Stating 'data available on request from the author' is not sufficient. If your data are only available upon request, select 'No' for the first question and explain your exceptional situation in the text box.

Do the authors confirm that all data underlying the findings described in their manuscript are fully available without restriction?

**Describe where the data may be found in full sentences. If you are copying our sample text, replace any instances of XXX with the appropriate details.**

No.

- If the data are **held or will be held in a public repository**, include URLs, accession numbers or DOIs. If this information will only be available after acceptance, indicate this by ticking the box below. For example: *All XXX files are available from the XXX database (accession number(s) XXX, XXX).*
- If the data are all contained **within the manuscript and/or Supporting Information files**, enter the following: *All relevant data are within the manuscript and its Supporting Information files.*
- If neither of these applies but you are able to provide **details of access elsewhere**, with or without limitations, please do so. For example:

*Data cannot be shared publicly because of [XXX]. Data are available from the XXX Institutional Data Access / Ethics Committee (contact via XXX) for researchers who meet the criteria for access to confidential data.*

*The data underlying the results presented in the study are available from (include the name of the third party*

*and contact information or URL).*

- This text is appropriate if the data are owned by a third party and authors do not have permission to share the data.

\* typeset

Additional data availability information:

## Original article

### Full title:

# **Continuous glucose monitoring in obese pregnant women with no hyperglycemia on glucose tolerance test**

### Short title:

## **Continuous glucose monitoring in obese pregnant women**

Rosa Maria Rahmi<sup>1\*</sup>, Priscila de Oliveira<sup>2¶</sup>, Luciano Selistre<sup>3&</sup>, Paulo Cury Rezende<sup>4&</sup>, Gabriela Neuvald Pezzella<sup>5&</sup>, Pâmela Antoniazzi dos Santos<sup>6&</sup>, Daiane de Oliveira Pereira Vergani<sup>7&</sup>, Sônia Regina Cabral Madi<sup>8&</sup>, José Mauro Madi<sup>8¶</sup>

<sup>1</sup> *Department of Endocrinology, General Hospital of Caxias do Sul, Caxias do Sul University, Caxias do Sul, RS, Brazil*

<sup>2</sup> *Master degree student in Health Sciences, Caxias do Sul University, Caxias do Sul, RS, Brazil.*

<sup>3</sup> *Department of Nephrology, General Hospital of Caxias do Sul, Caxias do Sul, RS, Brazil*

<sup>4</sup> *Department of Atherosclerosis, Heart Institute of the University of São Paulo Medical School, São Paulo, SP, Brazil.*

<sup>5</sup> *Institutional Scientific Initiation Scholarship Program of Caxias do Sul University, Caxias do Sul, RS, Brazil*

<sup>6</sup> *Department of Nutrition, Caxias do Sul University, Caxias do Sul, RS, Brazil.*

<sup>7</sup> *Department of Nursing, Caxias do Sul University, Caxias do Sul, RS, Brazil.*

<sup>8</sup> *Department of Obstetrics and Gynecology, General Hospital of Caxias do Sul, Caxias do Sul University, Caxias do Sul, RS, Brazil*

25 \* *Corresponding author:*

26 **Rosa Maria Rahmi**

27 E-mail: [rmgarcia@ucs.br](mailto:rmgarcia@ucs.br) (RMR)

28 Telephone: +55 54 99931-3441 | +55 54 3218-2100

29 ¶ These authors contributed equally to this work.

30 & These authors also contributed equally to this work.

31

32 **ORCID:**

33 **Rosa Maria Rahmi** Orcid ID: <https://orcid.org/0000-0003-1547-6282>

34 **Priscila de Oliveira** Orcid ID <https://orcid.org/0000-0002-2113-143>

35 **Luciano Selistre** Orcid ID <https://orcid.org/0000-0002-0152-0636>

36 **Paulo Cury Rezende** Orcid ID <https://orcid.org/0000-0001-8625-1537>

37 **Gabriela Neuvald Pezzella** Orcid ID <https://orcid.org/0000-0001-8989-8176>

38 **Pâmela Antoniazzi dos Santos** Orcid ID: <https://orcid.org/0000-0002-1197-8739>

39 **Daiane de Oliveira Pereira Vergani** Orcid ID <https://orcid.org/0000-0003-2510-1740>

40 **Sônia Regina Cabral Madi** Orcid ID <https://orcid.org/0000-0002-7039-8486>

41 **José Mauro Madi** Orcid ID <https://orcid.org/0000-0002-2345-4713>

42

43



44 **Abstract**

45 **Objective:** The objective of the present study was to compare 24-hour glycemic levels  
46 between obese pregnant women with normal glucose tolerance and non-obese pregnant  
47 women. **Methods:** In the present observational, longitudinal study, continuous glucose  
48 monitoring was performed in obese pregnant women with normal oral glucose  
49 tolerance test with 75 g of glucose between the 24<sup>th</sup> and the 28<sup>th</sup> gestational weeks. The  
50 control group (CG) consisted of pregnant women with normal weight who were  
51 selected by matching the maternal age and parity with the same characteristics of the  
52 obese group (OG). Glucose measurements were obtained during 72 hours. **Results:**  
53 Both the groups were balanced in terms of baseline characteristics (age: 33.5 [28.7–  
54 36.0] vs. 32.0 [26.0–34.5] years,  $p=0.5$  and length of pregnancy: 25.0 [24.0–25.0] vs.  
55 25.5 [24.0–28.0] weeks,  $p=0.6$  in the CG and in the OG, respectively). Pre-breakfast  
56 glycemic levels were  $77.77 \pm 10.55$  mg/dL in the CG and  $82.02 \pm 11.06$  mg/dL in the  
57 OG ( $p<0.01$ ). Glycemic levels at 2 hours after breakfast were  $87.31 \pm 13.10$  mg/dL in  
58 the CG and  $93.48 \pm 18.74$  mg/dL in the OG ( $p<0.001$ ). Daytime blood glucose levels  
59 were  $87.6 \pm 15.4$  vs.  $93.1 \pm 18.3$  mg/dL ( $p<0.001$ ) and nighttime blood glucose levels  
60 were  $79.3 \pm 15.8$  vs.  $84.7 \pm 16.3$  mg/dL ( $p<0.001$ ) in the CG and in the OG,  
61 respectively. The 24-hour, daytime, and nighttime values of the area under the curve  
62 were higher in the OG when compared with the CG ( $85.1 \pm 0.16$  vs.  $87.9 \pm 0.12$ ,  $65.6$   
63  $\pm 0.14$  vs.  $67.5 \pm 0.10$ ,  $19.5 \pm 0.07$  vs.  $20.4 \pm 0.05$ , respectively;  $p<0.001$ ). **Conclusion:**  
64 The results of the present study showed that obesity in pregnancy was associated with  
65 higher glycemic levels even in the presence of normal findings on glucose tolerance  
66 test.

67 **Keywords:** obesity; pregnancy, high-risk; hyperglycemia

68

69

70

71

## 72 **Introduction**

73 In the past few decades, the prevalence of obesity has increased, reaching the proportion of

74 a global epidemic. 2016, the World Health Organization (WHO) estimated that

75 approximately 650 million adults were obese, representing approximately 13% of the world's

76 adult population. Obesity affects all age groups and both sexes irrespective of the income

77 levels [1]. Concomitant with the global increase in obesity, the number of obese pregnant

78 women has also increased [2].

79 The association of obesity with pregnancy has been an important public health problem and

80 a major challenge for the professional team responsible for assisting this population. Maternal

81 obesity is associated with adverse pregnancy and perinatal outcomes and long-term

82 complications related to maternal and fetal health [3].

83 Current evidence supports the strong association between obesity and gestational diabetes

84 mellitus (GDM) [4,5]. Excess fat tissue releases increased amounts of unesterified fatty acids,

85 glycerol, hormones, pro-inflammatory cytokines, and other factors that participate in the

86 development of insulin resistance (IR). IR and dysfunctional beta-pancreatic cells are the

87 main factors causing hyperglycemia [6,7]. In this context, maternal obesity causes imbalance

88 in glycemc homeostasis during pregnancy, resulting in an increased risk of GDM [8].

89 Screening and diagnosis of GDM has improved in recent decades. However, there is still a

90 lack of universally accepted consensus [9-11]. In 2010, the International Association of

91 Diabetes in Pregnancy Study Group (IADPSG) [12] updated the diagnostic criteria based on

92 the results of an important study, namely the Hyperglycemia and Adverse Pregnancy

93 Outcomes (HAPO) study (13). These criteria were widely accepted by national and

94 international organizations.

95 The HAPO study suggested a strong and continuous relationship between maternal blood  
96 glucose and adverse outcomes [13]. The study proposed a lower glycemic threshold to detect  
97 GDM compared to other international guidelines [9,14-16].

98 GDM is mainly diagnosed using the oral glucose tolerance test (OGTT), which is based on a  
99 limited number of plasma glucose level readings after glucose overload [16].

100 After diagnosis, GDM needs to be treated by a multidisciplinary team. Glycemic control  
101 supervised by glycemic self-monitoring at specific time points (especially preprandial and  
102 postprandial readings) is crucial to reduce the risk of adverse maternal and fetal outcomes  
103 [17].

104 During pregnancy, the proposed range of glycemic levels to manage hyperglycemia is more  
105 limited. This rigor is believed to positively influence the adverse perinatal outcomes.  
106 However, such monitoring is based on a limited number of analyses within 24 hours and long  
107 periods between meals are not monitored. Maternal blood glucose has a dynamic variation  
108 within 24 hours and is influenced by numerous factors such as insulin sensitivity, diet,  
109 lifestyle, stress, sleep, and others [18,19].

110 Currently, with technological developments in continuous glucose monitoring (CGM), it is  
111 possible to assess daily glycemic fluctuations with greater accuracy. Several studies have  
112 been designed to allow better understanding of the effect of hyperglycemia on the temporal  
113 behavior of glycemic levels in pregnancy [20-23]. However, very few studies have analyzed  
114 the continuous evolution of glycemic levels during the period in pregnancy without glucose  
115 intolerance [24-26]. Obese women with presumably normal glucose tolerance may  
116 experience adverse perinatal complications similar to those observed in women with GDM  
117 [4,27].

118 Thus, the present study was designed to continuously assess the glycemic levels of obese  
119 pregnant women without glucose intolerance according to the criteria proposed by the  
120 IADPSG (step one) and to compare them with glycemic levels of non-obese pregnant  
121 women (step two).

122

## 123 **Materials and methods**

124 The present prospective, observational, longitudinal study involving pregnant women was  
125 followed up by the Obstetrics and Gynecology Service of the General Hospital of the  
126 University of Caxias do Sul, RS, Brazil. The study was conducted from June 2018 to July  
127 2019. We consecutively recruited pregnant women undergoing OGTT with 75 g of glucose  
128 between the 24<sup>th</sup> and the 28<sup>th</sup> gestational weeks. We included women with fasting glycemic  
129 levels below 92 mg/dL (5.1 mmol/L), 1-hour glycemic levels below 180 mg/dL (10.0  
130 mmol/L), and 2-hour glycemic levels below 153 mg/dL (8.5 mmol/L). Pregnant women with  
131 pre-gestational obesity (body mass index [BMI] range: 30–40 kg/m<sup>2</sup>) from the high-risk  
132 pregnancy clinic were included in the obese group (OG). Pregnant women from the low-risk  
133 prenatal clinic with normal pre-pregnancy weight (BMI range: 18.5–24.9 kg/m<sup>2</sup>) were  
134 included in the control group (CG). The groups were matched (1:1) by maternal age, parity,  
135 and length of pregnancy.

136 Pregnant women aged 18 to 35 years and with gestational age between 24 to 32 weeks were  
137 included. The exclusion criteria were multiple pregnancies; fetal malformation; pregnant  
138 women with uncontrolled chronic diseases; smoking; alcoholism; and use of corticosteroids,  
139 beta-blockers, or hyperglycemic drugs.

140 Pregnant women were continuously monitored by the prenatal care team without any  
141 interference from the researchers.

142 The following data were collected from the medical records immediately after OGTT: age,  
143 pregestational BMI, parity, weight gain during pregnancy, gestational age at the time of  
144 OGTT, OGTT results (fasting, at 1 hour after overload, and at 2 hours after overload), family  
145 history of cardiovascular disease, and family history of diabetes. Pregestational BMI was  
146 calculated according to the WHO standards and expressed as weight (kg)/height (m)<sup>2</sup>.  
147 Maternal weight gain during pregnancy was calculated by subtracting the body weight at the  
148 time of OGTT from the pre-pregnancy weight.

149

## 150 **Continuous glucose monitoring**

151 A CGM system iPro™2 Professional CGM, by Medtronic Principal Executive Office 20  
152 Lower Hatch Street Dublin 2, Ireland), was used to measure interstitial glucose  
153 concentrations over a period of 24 hours for 3 consecutive days. The sensors were inserted  
154 in the subcutaneous tissue in the lower abdomen on the right or the left side. The sensors  
155 were connected to the transmitters attached to the skin. The sensor recorded approximately  
156 288 blood glucose level readings in each pregnant woman over 24 hours. After 72 hours, the  
157 data were stored in a database. The monitors were calibrated by inserting capillary blood  
158 glucose level measured three times a day (preprandial measurements) using the Accu-Chek  
159 Active® device (Roche, Basel, Switzerland). Concomitantly, the women were requested to  
160 record the time at the start of the main meals and the time at the start of physical exercise.  
161 The study was approved by the Ethics and Human Resources Committee of the University  
162 of Caxias do Sul (opinion No. 2,273,140). It was conducted according to the ethical principles  
163 of the Declaration of Helsinki. All participants signed an Informed Consent Form.

164 *Statistical analysis*

165 The data were expressed as mean  $\pm$  standard deviation, median [interquartile range], and  
166 percentage. Exploratory analysis of the descriptive data was performed using Student's t-test,  
167 Wilcoxon-Mann-Whitney test, and Pearson's chi-squared test.

168 Since blood glucose concentrations of nestlings from the same brood are not independent,  
169 the glucose concentrations were analyzed using mixed linear models with brood identity  
170 included as a random controlling factor. In the first step, the glucose levels were modeled  
171 according to a linear mixed model with random intercept to quantify the effect of the group  
172 (obese or non-obese). The mean values of the two groups were compared using t-test in the  
173 linear mixed model. In the second step, two models were built: a first model that included  
174 variables "group" and "time" and a second model that included an interaction between the  
175 variables "group" and "time." The second model allowed quantification of the change in the  
176 effect of the group type according to time. Analysis of variance was used to compare the two  
177 nested models and to determine the statistical significance of the interaction. The models  
178 were adjusted by the restricted maximum likelihood method using the LME function of the  
179 NLME package. Tukey's post hoc test was used for multiple comparisons.

180 The analyses were performed using R for Windows, version 3.1.1 (R-Cran project,  
181 <http://cran.r-project.org/>, The R foundation, Vienna, Austria). Nominal p-values  $<0.05$  were  
182 considered statistically significant.

183


184 **Results and discussion**

185 Altogether, 20 pregnant women were included and evaluated in this study. The baseline  
186 characteristics of the population in the OG (n=10) and in the CG (n=10) are described in  
187 Table 1. The median maternal age was 33.5 [28.7–36.0] years in the CG and 32.0 [26.0–34.5]

188 years in the OG ( $p=0.5$ ). The pregestational BMI ( $\text{kg}/\text{m}^2$ ) was 22.1 [21.7–23.8] in the CG and  
189 39.9 [35.8–41.9] in the OG ( $p<0.001$ ). Maternal weight gain until the day of OGTT tended  
190 to be greater in the OG (8.0 [5.5–10.7] kg) than in the CG (2.6 [0.00–8.6] kg) ( $p=0.09$ ).

191 The analysis of OGTT results revealed that the fasting glycemic levels tended to be higher in  
192 the OG (75.5 [72.0–79.7] mg/dL) than in the CG (81.5 [74.2–87.0] mg/dL) ( $p=0.08$ ). Blood  
193 glucose levels at 1 and 2 hours after glucose overload showed no significant differences  
194 between the groups. Moreover, no statistically significant difference was observed in parity  
195 and in family history of cardiovascular disease and diabetes between the groups (Table 1).

196 The CGM data of pregnant women from both the groups are presented in Table 2. A  
197 significant difference was observed in blood glucose levels before (77.77 mg/dl  $\pm$  10.55 vs.  
198 82.02  $\pm$  11.06,  $p<0.01$ ) and 2 hours after breakfast (87.31 mg/dl  $\pm$  13.10 vs. 93.48  $\pm$  18.74,  
199  $p<0.001$ ) between the CG and the OG. No significant difference was observed in the values  
200 within 1 hour after breakfast. No significant differences were observed in glucose levels  
201 before and after lunch and dinner between the groups.

202 Additionally, blood glucose levels during the day (between 6:00 am and 12:00 pm) were  
203 significantly higher in the OG compared to those in the CG (93.08 mg/dl  $\pm$  18.30 vs. 87.58  
204  $\pm$  15.40,  $p<0.001$ ). Similarly, blood glucose levels at night (between 12:00 pm and 6:00 am)  
205 were significantly higher in the OG compared to those in the CG (84.73 mg/dl  $\pm$  16.31 vs.  
206 79.35  $\pm$  15.76,  $p<0.001$ ) 

207 The areas under the curve (AUCs) for blood glucose levels during the day and at night were  
208 67.47 mg/dl  $\pm$  0.105 and 20.42  $\pm$  0.05, respectively in the OG and 65.56 mg/dl  $\pm$  0.144 and  
209 19.53  $\pm$  0.072, respectively in the CG ( $p<0.001$ ) (Table 2). The 24-hour AUC for blood  
210 glucose levels was 85.08 mg/dl  $\pm$  0.161 in the OG and 87.89  $\pm$  0.116 in the CG ( $p<0.001$ )  
211 (Table 2, Figure 1).

212 Table 3 shows the isolated effect of obesity on longitudinal blood glucose variation. This  
213 effect was significant at night (78.10 mg/dl [95% confidence interval: 72.61–83.60] in the  
214 CG vs. 82.78 mg/dl [95% confidence interval: 78.60–86.96] in the OG,  $p < 0.001$ ).

215 The present study clearly showed a difference in temporal evolution of glycemic levels  
216 between obese and non-obese pregnant women without hyperglycemia according to the  
217 IADPSG criteria [12]. The national protocol in Brazil suggests that GDM screening should  
218 be performed using OGTT with 75 g of glucose between the 24<sup>th</sup> and the 28<sup>th</sup> gestational  
219 weeks in pregnant women with no previous glycemic changes. GDM is diagnosed when the  
220 following levels were reached or exceeded: fasting glucose level of 92 mg/dl, 1-hour level of  
221 180 mg/dL, and 2-hour level of 153 mg/dL [16].

222 In the studied population, the analysis of blood glucose levels at fasting, at 1 hour, and at 2  
223 hours after 75 g glucose overload confirmed that none of the pregnant women met or  
224 exceeded these criteria. However, fasting glycemic levels in the OG tended to be higher than  
225 those in the CG ( $p = 0.08$ ) at the time of screening.

226 None of the pregnant women in the study exhibited evidence of hyperglycemia. Therefore,  
227 they were routinely monitored without strict blood glucose level control until the end of  
228 pregnancy. No intervention was performed by the researchers. The objective of this study  
229 was to assess blood glucose levels without changing the routine in a population at high risk  
230 for metabolic diseases.

231 The obese pregnant women in the present study were referred to a reference center for high-  
232 risk pregnancies at the General Hospital of Caxias do Sul. There has been a significant  
233 increase in the number of women with severe obesity in recent years due to the global obesity  
234 epidemic that also affects women of reproductive age [2]. According to the study by Kim et  
235 al., the rate of GDM in a population with severe obesity (35–64.9 kg/m<sup>2</sup>) was 11.5% and the



236 relative risk of GDM was 5.0 (95% confidence interval: 3.6–6.9) even after adjustment for  
237 maternal age, race/ethnicity, parity, and marital status [8]. In addition to pregestational BMI,  
238 weight gain during pregnancy may also be associated with an increased risk for GDM  
239 [28,29].

240 In the present study population, weight gain during the study period was higher in the OG  
241 (median: 8.00 kg) when compared with that in the CG (median: 2.65 kg), which is an  
242 additional factor for increased risk of hyperglycemia. Despite the high pregestational BMI  
243 and the greater weight gain in obese pregnant women, GDM was not detected at the time of  
244 screening. Thus, there is a possibility of dysglycemia in later stages of pregnancy in risk  
245 groups with a negative GDM test. Gomes et al. showed that among 448 obese pregnant  
246 women with a negative GDM test, 30.1% (n=135) exhibited dysglycemia at the end of the  
247 third trimester, as assessed by increased hemoglobin A1c levels [30]. A secondary analysis  
248 of the HAPO study in a population of 23,316 pregnant women showed that 2,247 (9.6%)  
249 women were obese without a diagnosis of hyperglycemia and this condition showed an  
250 independent association with fetal hyperinsulinemia, growth, and adiposity, similar to the  
251 outcomes observed in GDM [4]. This subject continues being discussed due to the scarce  
252 literature on the effects of late glycemc changes and maternal lipid profile [31,32] on  
253 perinatal outcomes.

254 Blood glucose levels at specific time points (2 hours before and 2 hours after breakfast) were  
255 significantly higher in the OG. However, the levels did not exceed the recommended limits  
256 for these time points (<95 and <120 mg/dl, respectively) [17]. These are the recommended  
257 time points to monitor pregnant women with hyperglycemia. At these time points, blood  
258 glucose levels remained within the presumably normal range in both the groups. Harmon  
259 reported significant differences in glycemc levels at 1 and 2 hours after meals [26]. Stratified

260 analysis by pregestational maternal weight conducted by Yogeve et al. showed that  
261 preprandial, 1-hour postprandial, and 2-hour postprandial glycemic levels were significantly  
262 higher in obese pregnant women [25].

263 A detailed analysis of blood glucose samples repeated for 72 hours showed higher fluctuation  
264 in obese pregnant women than in non-obese pregnant women (assessed by the AUC). Similar  
265 behavior was observed when the analysis was divided into two periods (day and night). In  
266 addition, obesity was associated with a higher mean blood glucose at night. These data  
267 suggest that fetuses of the women from the OG could potentially be exposed to a blood  
268 glucose pattern that is higher than normal. These findings are consistent with the findings of  
269 Harmon et al. [26] who evaluated groups of pregnant women without hyperglycemia with  
270 and without dietary interference and reported that the AUC was always higher in obese  
271 pregnant women regardless of dietary control. In the present study, the OG included pregnant  
272 women with more severe obesity (median BMI: 39.95) and the criteria for excluding glucose  
273 intolerance in the population were different. However, Yogeve et al. [25] showed that obese  
274 women exhibited significantly lower mean glucose levels at night compared to non-obese  
275 women.

276 Differences in glycemic homeostasis between obese and non-obese pregnant women were  
277 didactically presented by analyzing temporal blood glucose variations over long periods,  
278 which is possible only with the CGM systems. Despite the few studies available in the  
279 literature, the following questions should be discussed. 1) Should the glycemic targets for  
280 obese pregnant women be individualized? 2) Could the nocturnal glycemic changes be  
281 related to increased fetal fat and/or macrosomia in obese women without GDM?

282 Increasing maternal obesity rates have challenged researchers to characterize the metabolic  
283 profile of this population in a better way. Glycemic control is not adequately addressed during

284 the follow-up in most of the obese pregnant women without GDM. On the other hand,  
285 glucose self-monitoring has limitations, as it does not include the night period. The present  
286 study suggests the need for more evidence on glycemic targets in obese women during  
287 pregnancy. The sample size in the present study did not allow correlations with perinatal  
288 outcomes. However, the use of statistical modeling and the strict composition of the two  
289 groups clearly showed distinct behaviors in dynamic changes in blood glucose levels over  
290 long periods.

291

## 292 **Conclusion**

293 In conclusion, the present study demonstrated that continuously assessed blood glucose  
294 levels were higher in obese pregnant women without GDM than in non-obese pregnant  
295 women and this effect was more evident at night. Additional studies correlating these  
296 changes with fetal outcomes might contribute to a more personalized care for this  
297 population.

## 298 **Acknowledgements**

299 The authors are grateful to Hospital Geral de Caxias do Sul for receive this search.

## 300 **References**

- 301 1. World Health Organization. Obesity and overweight [Internet]. World Health  
302 Organization; Geneva: 2020. [cited 2020 Jul 24]. Available from:  
303 <https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight>
- 304 2. Poston L, Caleyachetty R, Cnattingius S, Corvalán C, Uauy R, Herring S, et al.  
305 Preconceptional and maternal obesity: epidemiology and health consequences. *Lancet*  
306 *Diabetes Endocrinol.* 2016;4(12):1025–1036. doi: 10.1016/S2213-8587(16)30217-0.
- 307 3. Catalano PM, Shankar K. Obesity and pregnancy: mechanisms of short term and  
308 long term adverse consequences for mother and child. *BMJ.* 2017;356:j1.4.  
309 doi.org/10.1136/bmj.j1
- 310 4 Catalano PM, McIntyre HD, Cruickshank JK, McCance DR, Dyer AR, Metzger  
311 BE, et al. The hyperglycemia and adverse pregnancy outcome study: associations of GDM  
312 and obesity with pregnancy outcomes. *Diabetes Care.* 2012;35(4):780–786.  
313 doi.org/10.2337/dc11-1790.
- 314 5. Plows JF, Stanley JL, Baker PN, Reynolds CM, Vickers MH . The Pathophysiology  
315 of Gestational Diabetes Mellitus. *Int J Mol Sci.* 2018;19(11):3342. doi:  
316 10.3390/ijms19113342
- 317 6. Saltiel AR, Olefsky JM. Inflammatory mechanisms linking obesity and metabolic  
318 disease. *J Clin Invest.* 2017;127(1):1–4. doi.org/10.1172/JCI92035.
- 319 7. Pantham P, Aye IL, Powell TL. Inflammation in maternal obesity and gestational  
320 diabetes mellitus. *Placenta.* 2015;36(7):709–715. doi: 10.1016/j.placenta.2015.04.006.
- 321 8. Kim SY, England L, Wilson HG, C. Bish, Satten GA, et al. Percentage of  
322 gestational diabetes mellitus attributable to overweight and obesity. *Am J Public Health.*  
323 2010;100(6):1047–1052. doi.org/10.2105/AJPH.2009.172890

- 324 9. ACOG Practice Bulletin No. 190: Gestational Diabetes Mellitus. *Obstet Gynecol.*  
325 2018;131(2):e49–e64. doi.org/10.1097/aog.0000000000002501.
- 326 10. Chiefari E, Arcidiacono B, Foti D, Brunetti A. Gestational diabetes mellitus: an  
327 updated overview. *J Endocrinol Invest.* 2017;40(9):899–909. doi.org/10.1007/s40618-016-  
328 0607-5.
- 329 11. Behboudi-Gandevani S, Amiri M, Yarandi RB, Tehrani FR. The impact of  
330 diagnostic criteria for gestational diabetes on its prevalence: a systematic review and meta-  
331 analysis. *Diabetol Metab Syndr.* 2019;11:11. doi.org/10.1186/s13098-019-0406-1
- 332 12. Metzger BE. International Association of Diabetes and Pregnancy Study Groups  
333 Consensus Panel. International association of diabetes and pregnancy study groups  
334 recommendations on the diagnosis and classification of hyperglycemia in pregnancy.  
335 *Diabetes Care.* 2010;33(3):676–682. doi: 10.2337/dc09-1848
- 336 13. The HAPO Study Cooperative Research Group. Hyperglycemia and adverse  
337 pregnancy outcomes. *N Engl J Med.* 2008;358(19):1991–2002.  
338 dx.doi.org/10.2337%2Fdb08-1112.
- 339 14. National Institute for Health and Care Excellence [Internet]. National Institute for  
340 Health and Care Excellence (2015): Diabetes in pregnancy: management from  
341 preconception to the postnatal period (NG3). 2015 [published 2015 Feb 25]. Available  
342 from: <https://www.nice.org.uk/guidance/ng3>.
- 343 15. Feig DS, Berger H, Donovan L, Godbout A, Kader T, Keely E, et al. Clinical  
344 Practice Guidelines Diabetes and Pregnancy Diabetes Canada Clinical Practice Guidelines  
345 Expert Committee. *Can J Diabetes.* 2018;42:S255–S282. doi.org/10.1016/j.jcjd.2017.10.038

- 346 16. American Diabetes Association. 2. Classification and Diagnosis of Diabetes:  
347 Standards of Medical Care in Diabetes-2020. *Diabetes Care*. 2020;43(Suppl 1):S14–  
348 S31.[doi.org/10.2337/dc20-S002](https://doi.org/10.2337/dc20-S002).
- 349 17. American Diabetes Association. 14. Management of Diabetes in Pregnancy:  
350 Standards of Medical Care in Diabetes-2020. *Diabetes Care*. 2020;43(Suppl 1):S183–S192.  
351 [doi.org/10.2337/dc20-S014](https://doi.org/10.2337/dc20-S014)
- 352 18. Tan E, Scott EM. Circadian rhythms, insulin action, and glucose homeostasis. *Curr*  
353 *Opin Clin Nutr Metab Care*. 2014;17(4):343–348.  
354 [doi.org/10.1097/mco.0000000000000061](https://doi.org/10.1097/mco.0000000000000061).
- 355 19. Catalano PM, Huston L, Amini SB, Kalhan SC. Longitudinal changes in glucose  
356 metabolism during pregnancy in obese women with normal glucose tolerance and  
357 gestational diabetes mellitus. *Am J Obstet Gynecol*. 1999;180(4):903–916. [doi:](https://doi.org/10.1016/s0002-9378(99)70662-9)  
358 [10.1016/s0002-9378\(99\)70662-9](https://doi.org/10.1016/s0002-9378(99)70662-9).
- 359 20. Polsky S, Garcetti R. CGM, Pregnancy, and Remote Monitoring. *Diabetes Technol*  
360 *Ther*. 2017;19(S3):S49–S59. [doi.org/10.1089/dia.2017.0023](https://doi.org/10.1089/dia.2017.0023).
- 361 21. Scott EM, Feig DS, Murphy HR, Law G. Continuous Glucose Monitoring in  
362 Pregnancy: Importance of Analyzing Temporal Profiles to Understand Clinical Outcomes.  
363 *Diabetes Care*. 2020;43(6):1178–1184.[doi.org/10.2337/dc19-2527](https://doi.org/10.2337/dc19-2527)
- 364 22. Wei Q, Sun Z, Yang Y, YU H, Ding H, Wang. Effect of a CGMS and SMBG on  
365 Maternal and Neonatal Outcomes in Gestational Diabetes Mellitus: a Randomized  
366 Controlled Trial. *Sci Rep*. 2016 Jan 27;6:19920. [doi 10.1038/srep19920](https://doi.org/10.1038/srep19920).
- 367 23. McLachlan K, Jenkins A, O'Neal D. The role of continuous glucose monitoring in  
368 clinical decision-making in diabetes in pregnancy. *Aust N Z J Obstet Gynaecol*.  
369 2007;47(3):186–90. [doi: 10.1111/j.1479-828X.2007.00716.x](https://doi.org/10.1111/j.1479-828X.2007.00716.x)

- 370 24. Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, et al. Clinical  
371 Targets or Continuous Glucose Monitoring Data Interpretation: Recommendations From  
372 the International Consensus on Time in Range. *Diabetes Care*. 2019;42(8):1593–1603.  
373 doi.org/10.2337/dci19-0028
- 374 25. Yogev Y, Ben-Haroush A, Chen R, Rosenn B, Hod M, Langer O. Diurnal glycemc  
375 profile in obese and normal weight nondiabetic pregnant women. *Am J Obstet Gynecol*.  
376 2004;191(3):949–953. doi: 10.1016/j.ajog.2004.06.059
- 377 26. Harmon KA, Gerard L, Jensen DR, Kealey E, Hernandez T, Reece M, et al.  
378 Continuous glucose profiles in obese and normal-weight pregnant women on a controlled  
379 diet: metabolic determinants of fetal growth. *Diabetes Care*. 2011;34(10):2198–2204. doi:  
380 10.2337/dc11-0723
- 381 27. Gaudet L, Ferraro ZM, Wen SW, Walker M. Maternal obesity and occurrence of  
382 fetal macrosomia: a systematic review and meta-analysis. *Biomed Res Int*.  
383 2014;2014:640291. | doi.org/10.1155/2014/640291
- 384 28. Dutton H, Borengasser SJ, Gaudet LM, Barbour L, Keely E. Obesity in Pregnancy:  
385 Optimizing Outcomes for Mom and Baby. *Med Clin North Am*. 2018;102(1):87–106. doi:  
386 10.1016/j.mcna.2017.08.008
- 387 29. Gibson KS, Waters TP, Catalano PM. Maternal weight gain in women who  
388 develop gestational diabetes mellitus. *Obstet Gynecol*. 2012;119(3):560–565.doi:  
389 10.1097/AOG.0b013e31824758e0
- 390 30. Gomes D, von Kries R, Delius M, Mansmann U, Nast M, Stubert M et al. Late-  
391 pregnancy dysglycemia in obese pregnancies after negative testing for gestational diabetes  
392 and risk of future childhood overweight: An interim analysis from a longitudinal mother-

393 child cohort study. PLoS Med. 2018;15(10):e1002681.

394 doi.org/10.1371/journal.pmed.1002681

395 31. Calabuig-Navarro V, Haghiac M, Minium J, Glazebrook P, Ranasinghe G, Hoppel

396 C, et al. Effect of Maternal Obesity on Placental Lipid Metabolism. Endocrinology.


397 2017;158(8):2543–2555. doi.org/10.1210/en.2017-00152

398 32. Barbour LA, Hernandez TL. Maternal Lipids and Fetal Overgrowth: Making Fat

399 from Fat. Clin Ther. 2018;40(10):1638–1647. doi: 10.1016/j.clinthera.2018.08.007



400 **Table 1.** Maternal characteristics of the studied patients

	<b>CG (n=10)</b>	<b>OG (n=10)</b>	<b>p-value</b>
Age (years).	33.50 [28.75–36.00]	32.0 [26.0–34.5]	0.5 
Parity $\geq 1$ (n)	9	10	1.0
Pregestational BMI (kg/m <sup>2</sup> )	22.15 [21.70–23.82]	39.95 [35.85–41.88]	<0.001
Weight gain (kg)	2.65 [0.00–8.57]	8.00 [5.50–10.75]	0.09
Family history of CVD (%)	30	20	1.00
Family history of diabetes (%)	40	50	1.00
Length of pregnancy (weeks)*	25.0 [24.0–25.0]	25.5 [24.0–28.0]	0.6
OGTT (mg/dL)			
Fasting	75.50 [72.00–79.75]	81.50 [74.25–87.00]	0.08
1 hour	129.0 [117.0–141.0]	134.0 [120.0–161.0]	0.4
2 hours	110.00 [95.25–116.00]	109.00 [93.75–124.50]	0.9

401 \* Length of pregnancy at the time of oral glucose tolerance test,OG: obese group, CG:  
 402 control group, BMI: body mass index; OGTT: oral glucose tolerance test; wk: week; CVD:  
 403 cardiovascular disease. Data are medians, Interquartile range (IQR), and percentage. P-  
 404 values are calculated using by Wilcoxon-Mann-Whitney test and chi-squared test.

405 **Table 2.** Continuous glucose monitoring data in control and obese groups

	<b>CG</b>	<b>OG</b>	<b>p-value*</b>
<b>Glucose (mg/dL)</b>			
Before breakfast	77.77 ± 10.55	82.02 ± 11.06	<0.01
1 hour after breakfast	94.25 ± 15.70	97.26 ± 11.06	0.8
2 hours after breakfast	87.31 ± 13.10	93.48 ± 18.74	<0.001
Before lunch	82.77 ± 15.15	85.26 ± 15.65	0.2
1 hour after lunch	97.74 ± 13.60	97.71 ± 14.96	0.6
2 hours after lunch	93.78 ± 12.30	91.13 ± 13.65	0.15
Before dinner	82.80 ± 2.75	86.68 ± 2.04	0.08
1 hour after dinner	94.42 ± 19.05	94.02 ± 17.35	0.8
2 hours after dinner	90.65 ± 23.37	92.78 ± 20.27	0.2
Daytime	87.58 ± 15.40	93.08 ± 18.30	<0.001
Nighttime	79.35 ± 15.76	84.73 ± 16.31	<0.001
<b>AUC (mg/min/dL)</b>			
Day	65.56 ± 0.144	67.47 ± 0.105	<0.001
Night	19.53 ± 0.072	20.42 ± 0.05	<0.001
24 hours	85.08 ± 0.161	87.89 ± 0.116	<0.001

406 CG: control group, OG: obese group, AUC: area under the curve. Preprandial and  
 407 postprandial glucose level is the mean of three consecutive values before or after the  
 408 respective meal. Daytime glucose is the mean glucose level between 6:00 am and 12:00  
 409 pm. Nighttime glucose is the mean glucose level between 12:00 pm and 6:00 am. Daytime  
 410 AUC is between 6:00 am and 12:00 pm and nighttime AUC is between 12:00 pm and 6:00  
 411 am.\*The p-values (obese vs. control) are based on F statistics for comparisons test.


412 **Table 3.** The Mixed Linear Model to analyze the effect of obesity on the glucose levels.

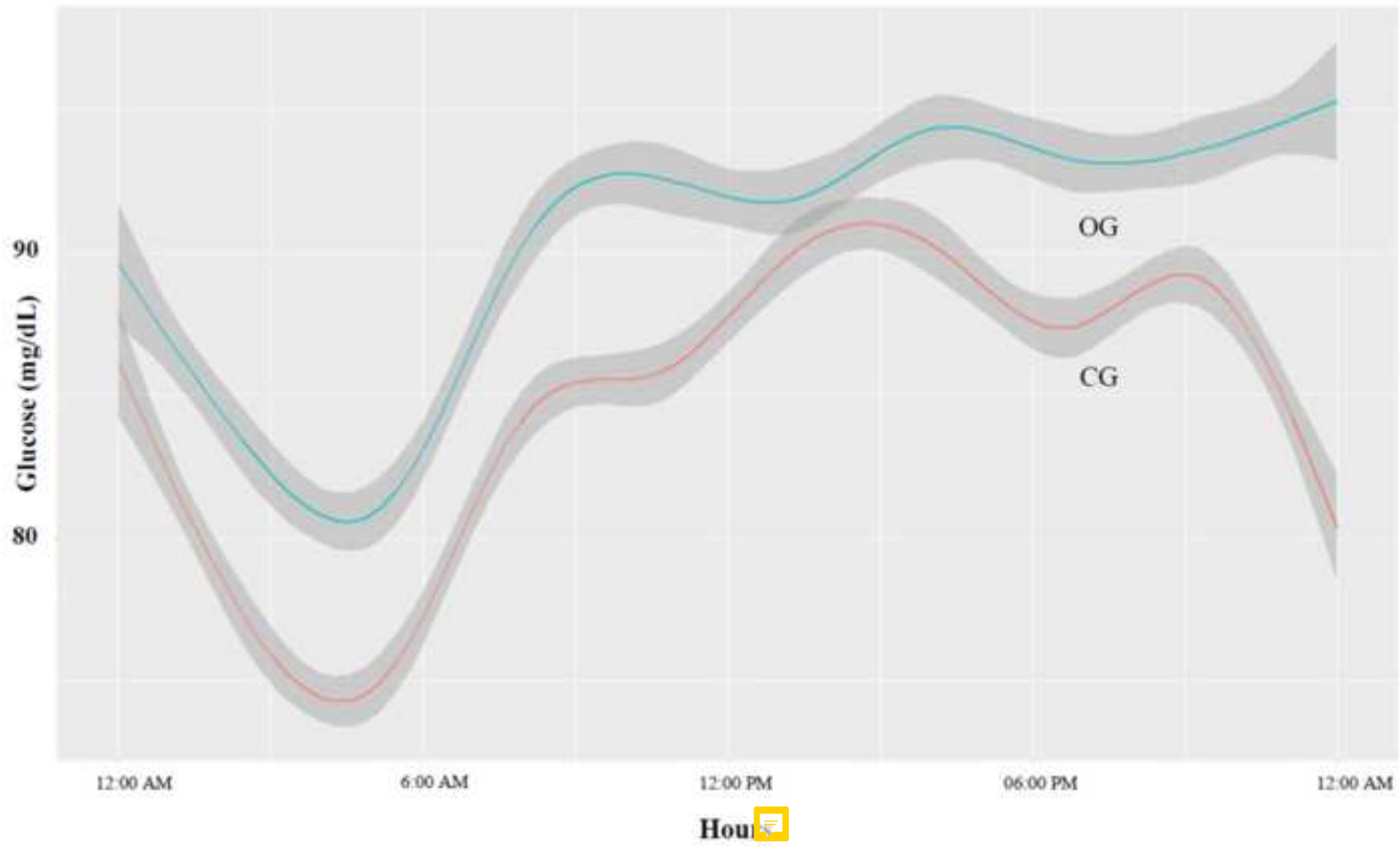
---

	<b>CG (95.0% CI)</b>	<b>OG (95.0% CI)</b>	<b>p-value</b>
Whole sample	84.94 (81.55; 88.33)	88.58 (85.43; 91.63)	0.17
Daytime	86.87 (82.90; 90.84)	90.21 (87.20; 93.24)	0.25
Nighttime	78.10 (72.61; 83.60)	82.78 (78.60; 86.96)	<0.001

---

413

**Figure 1.** Glucose profile in pregnant women with normal glucose tolerance 



Obese group (n=10) is represented by the green smooth curve ( $\lambda=1,000,000$ ) and Control group (n=10) by the red smooth curve.



Click here to access/download  
**Supporting Information**  
renamed\_20b2f.docx

