The behavior of glycemic parameters during the first quarter of pregnancy in women with type 1 diabetes mellitus

Comportamiento de los parámetros glucémicos durante el primer trimestre del embarazo en mujeres con diabetes mellitus tipo 1

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Abstract
Introduction: It is known that there is a higher frequency of hypoglycemia during the first trimester of pregnancy in women with type 1 diabetes mellitus: Patients and methods: We undertook a retrospective longitudinal study of 64 pregnant women with type 1 diabetes mellitus. Four periods were defined: preconception (28 days prior to conception), first, second and third month of pregnancy. Different glycemic parameters between those 4 periods were compared. Results: Mean blood glucose level was similar in the preconception period and in the first month. Afterwards, it progressively decreased during the second and third months. HbA1c showed a similar tendency as the mean blood glucose. Both non-serious hypoglycemia as well as nocturnal hypoglycemia increased throughout the first trimester. There were no significant changes either in the number of daily blood glucose measurements or in the average daily dose of insulin. Conclusion: Together with an improved glycemic control, a tendency towards hypoglycemia –daytime as well as nocturnal– during the first quarter of pregnancy in women with type 1 diabetes is corroborated and does not seem to be attributable to the dose of insulin.

Keywords: type 1 diabetes mellitus, pregnancy, hypoglycemia, glycated hemoglobin.

Introduction
It is known from time ago that the women with type 1 diabetes mellitus (T1D) have an increased frequency of hypoglycemia during pregnancy, especially during the first quarter. This problem was especially stated from the use of intensive insulin-therapy guidelines, though it was known previously.

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List of acronyms quoted in the text:
CSII: continuous subcutaneous insulin infusion; HbA1c: glycated hemoglobin; MDI: multiple-dose insulin; NPH: neutral protamine Hagedorn insulin; T1D: type 1 diabetes mellitus.
Important changes occur during pregnancy in the mothers’ metabolism, which adapts itself to ensure an appropriate support of nutrients to the fetus. There is a “physiologic fasting” situation in the pregnant woman, due to the high consumption of nutrients by the fetus (glucose and amino acids), causing the hepatic glycogenesis to be reduced by the lack of substrates. During the pregnancy of a non-diabetic woman a progressive reduction in the fasting glycemia occurs as well as in the mean glycemia. After 28 weeks, the mean fasting glycemia in a group of 66 non-diabetic pregnant women was of 54.8 ± 6.2 mg/dL, and the daily mean glycemia of 71.9 ± 5.7 mg/dL.1

During the first three months a slight increase occurs in insulin sensitivity. In the study Diabetes in Early Pregnancy, it has been proved a reduction in the needs of insulin in the middle of the first quarter of pregnancy in diabetic women.2

It is possible that an alteration in the secretion of contra-regulating hormones contributes also to the increased hypoglycemia risk. Several studies performed in pregnant women with T1D have shown a reduced response, or even null, of the adrenalin to the hypoglycemia.3,4 In the study of Rosenn et al.4 it has been detected that the group of pregnant women with T1D did not have any response to cortisol nor glucagon to the hypoglycemia.

The frequent presence of vomit during the first quarter might contribute to the hypoglycemia tendency. However, this factor seems to be of scarce importance.5,6

On the other hand, the adequate glycemic control is fundamental during pregnancy in order to reduce the risk of congenital malformations and other obstetric-neonatal pathologies related to the diabetes. The intensification of the glycemic control contributes to the increase of hypoglycemia’s frequency.7,8

The main risk factors to show serious hypoglycemia during the first quarter of the pregnancy are the previous serious hypoglycemia history, unnoticed hypoglycemias, diabetes duration of 10 years or more, glycosylated hemoglobin (HbA1c) <6.5% and higher dose of insulin (0.1 IU/kg more in the group with serious hypoglycemia than in the group that does not show it).8,9

The hypoglycemia frequency in women with T1D, both serious and not serious, is relevantly higher during pregnancy, especially during the first three months. The values published in the literature are different; they range from 6.1 up to 71% of the women affected by a serious hypoglycemia during pregnancy.

This can be explained in part by the differences in the design of the studies, as not all of them are focused on the same period of pregnancy; some of them study women with pregestational and gestational diabetes and the definition of serious hypoglycemia varies in some of them. These discrepancies also reflect differences among the different sites as regards to the glycemic control targets and education of the patients.7,13

As regards to the possible effects on the fetus, some studies performed in mice detected that the exposure to the hypoglycemia during early stages of the embryogenesis was teratogen.14 However, in the studies performed later in humans, this has not been confirmed.

During the gestation it seems that the indicative parameters of fetal welfare are not affected by mothers’ hypoglycemia. The maintenance of a relative low glucose concentration during pregnancy is associated to an increase of the risk of having a newborn of low weight for the gestational age.15

Objectives
To study the behavior of the glycemic parameters during the preconception period (28 days previous to the conception date, estimated by echography), and the first quarter of pregnancy in women with T1D, taking special interest on hypoglycemia.

Patients and methods
We conducted a longitudinal, retrospective study for which women with T1D have been enrolled who had been assisted at the Diabetes and Pregnancy Unit of Hospital “La Paz” since the preconception period until delivery. The patients who had not undertaken preconception care had been excluded and those who had abortions and multiple pregnancies. The final size of the sample was of 64 patients.

The glycemic control targets have been some pre-prandial and prandial glycemic values of 70-100 and 100-140 mg/dL, respectively. All the patients performed self-
monitoring of the glycemia using the same type of glycometer (One Touch Profile®, LifeScan, Milpitas, CA, United States). The patients were requested to perform self-analysis of the capillary glycemia between 6 and 7 times a day (pre-prandial before breakfast, lunch and dinner, postprandial 2 h after starting breakfast, lunch and dinner, and at dawn between 2 and 5 h). The registered values were downloaded to a computer during each visit (software for the handling of the diabetes: One Touch®, LifeScan, Milpitas, CA, United States). The HbA1c was measured in the preconception period and each month, using high-resolution liquid chromatography (Bio-Rad, Richmond, RA, United States).

The patients followed a treatment with intensive flexible insulin therapy: 63 of them with bolo-basal therapy (neutral protamine Hagedorn insulin [NPH] and regular), and one of them with continuous subcutaneous insulin infusion (regular). All the patients have been trained as regards to the diabetes self-care, adjusting themselves the doses of insulin in order to achieve the targets. They attended the consultation each 4 weeks during the preconception period and each 1-2 weeks according to the needs, during pregnancy. Both the patient and a member of her family have been trained in the handling of the hypoglycemia, and glucagon was indicated to all of them.

For the definition of serious hypoglycemia we adopt the one included by the American Diabetes Association at present: event that for whose resolution help of a third party was needed. Non-serious hypoglycemia is defined as any event of capillary glycemia ≤50 mg/dL that the patient could solve alone. Night hypoglycemia was considered as any event of capillary glycemia ≤50 mg/dL produced between 00.00 and 05.00 h.

The following variables were compared in the preconception period, the first, second and third month of gestation: a) daily mean number of glycemia measurements; b) mean glycemia; c) HbA1c; d) frequency of non-serious hypoglycemia; e) frequency of night hypoglycemia and f) daily mean dose of insulin adjusted by weight. The frequency of serious hypoglycemia was very low; therefore it has been compared between the preconception period and the first quarter of the gestation as a whole.

The statistical analysis was done using the SPSS program version 15.0. In order to compare the means among the quantitative variables, analysis of variance was used with the test of Bonferroni as post hoc test, or the t test of Student for dependent samples, as applicable. In order to compare qualitative variables, the χ² test has been used and the Fisher exact test. A value of p <0.05 was considered statistically relevant.

Results

The demographic characteristics of the patients are depicted in table 1.

The mean daily number of glycemia measurements was of 4.9 ± 1.3 in the preconception period, 5.3 ± 1.3 in the second month and 5.6 ± 1.3 in the third month. No statistically relevant differences were found.

Five women (7.8%) showed serious hypoglycemia during the preconception period. Likewise, five patients had it during the first quarter. The difference between both data did not reach a statistical significance. Two patients (3.1%) suffered hypoglycemia during both periods.

The mean glycemia of the first month was similar than that of the preconception period (p= 1.000) and decreased progressively throughout the first three months of pregnancy. The most stressed decrease took place between the first and the second month (figure 1).

The HbA1c was similar during the preconception period and first month (p= 1.000). Afterwards, it decreased progressively until the third month (figure 2).

The frequency of non-serious hypoglycemia was not different in the preconception period than in the first month (p= 1.000). Afterwards, such frequency increased progressively (figure 3).

<table>
<thead>
<tr>
<th>Table 1. Characteristics of the patients</th>
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<tr>
<td>Age (years)</td>
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<td>Body mass index (kg/m²)</td>
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<td>Duration of the diabetes (years)</td>
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<td>Patients with diabetic retinopathy (%)</td>
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<td>Patients with diabetic nephropathy (%)</td>
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<td>Patients with previous serious hypoglycemia (%)</td>
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The data are expressed as mean ± standard deviation, or number of cases and percentage between brackets.
The night hypoglycemia frequency increased progressively during the first quarter (figure 4).

There have not been relevant changes in the mean daily dose of insulin (preconception 0.62 ± 0.15 IU/kg, first month 0.65 ± 0.16 IU/kg; second month 0.68 ± 0.15 IU/kg, third month 0.64 ± 0.15 IU/kg (p> 0.05).

Discussion
In our study, only the 7.8% of the women have been affected by a serious hypoglycemia during pregnancy. This value is lower than the one usually published in the literature, where the percentage of affected women exceeds the 45% frequently. It is difficult to define the cause of these differences. We can think that it is due to the pre-
conception care. However, in the study of Evers, et al., also with preconception care, the 41% of the women suffered serious hyperglycemia. In a study in which the evolution of the two groups of patients with or without preconception care has been compared, the serious hypoglycemia frequency was not different between both.13

The finding of a reduction of the mean glycemia and the HbA1c during the first quarter is a previously known fact in non-diabetic pregnant patients, that is confirmed in our series of patients with T1D. No differences have been found in the insulin dose adjusted by weight; in other words, the decrease of the mean glycemia is associated to pregnancy by itself. According to this, it increased the hypoglycemia risk during the first quarter.

There are a few studies that assess specifically the night hypoglycemia frequency during pregnancy. In one of them, performed in 43 pregnant women with T1D, it has been found that the 37% of them had hypoglycemia throughout the night, during such time blood samples have been taken from a cannula. Only one of them registered hypoglycemia and the other hypoglycemia remained unnoticed.17

In our study, the night hypoglycemia frequency increases progressively during the first quarter, reaching the 1.1 ± 1.3% of all the measurements in the third month. Taking into account the design, it is impossible to study the quantity of unnoticed night hypoglycemias, as the patients woke up actively to perform the measurement.

Our study was done in a group of patients under treatment with human insulin (regular plus NPH), as the use of insulin analogues during pregnancy was not authorized at that moment. Both the insulin lispro and the insulin aspart have proved to reduce the frequency of serious and non-serious hypoglycemia compared to the regular insulin.18-21

Up to present, only two randomized and controlled studies have been published that compare the therapy with multiple-dose insulin (MDI) and continuous subcutaneous insulin infusion (CSII) during pregnancy. In one of them, the glycemic control level has been compared as well as the development of pregnancy in women with T1D, 30 of them under treatment with CSII and 60 under treatment with MDI. No differences have been found regarding to the frequency or seriousness of the hypoglycemia between both groups (in the group with CSII, the 72% had non serious hypoglycemia and 28% serious hypoglycemia, and in the group with MDI, the 75 and the 25%, respectively).22 Recently, a meta-analysis has been published about the topic that includes only two studies (60 women with 61 pregnancies). A relevant increase has been obtained in the mean weight at delivery associated to CSII. The authors do not consider this fact as clinically relevant, as there have not been statistically relevant differences in the macrosomy rate. No differences have been found in any of the analyzed variables, among them the frequency of serious and non-serious hypoglycemia.23 This might be due to the small number of adequate trials for the meta-analysis and the low number of participants in the described trials.

Conclusion
During the first quarter of pregnancy, in women with T1D we have found a tendency towards the hypoglycemia, which is stated during the second and third month of gestation. This tendency is linked to an improvement of the glycemic control. However, it does not seem attributable to changes in the insulin dose adjusted by weight, parameter in which no statistically relevant differences have been found.

Declaration of potential conflict of interests
M. García Domínguez, L. Herranz de la Morena, E. Moya Chimienti and L.F. Pallardo Sánchez state that there are no conflicts of interest as regards to the content of this article.

References


